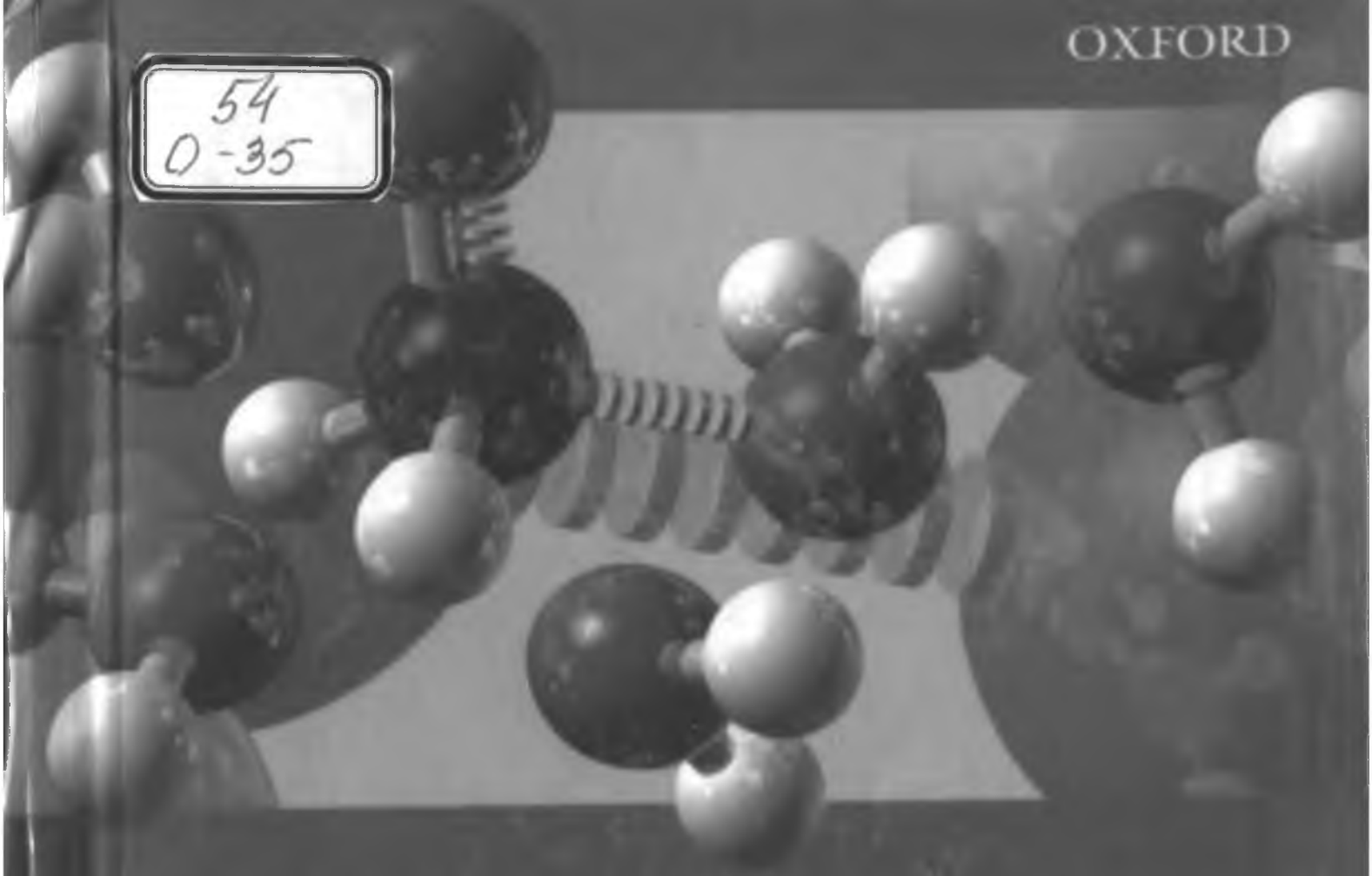
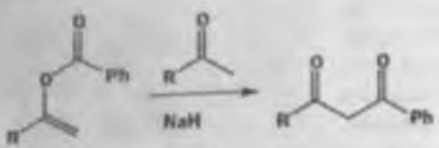
OXFORD

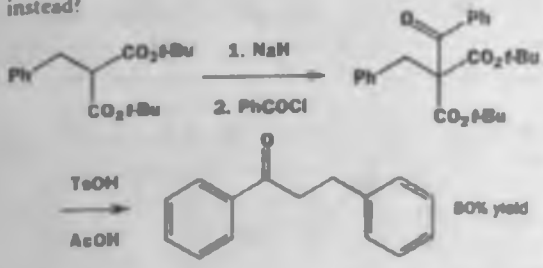


Clayden, Greeves, Warren
and Wothers

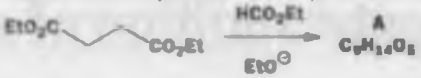
ORGANIC CHEMISTRY



12. This is a *C*-acylation route to a simple ketone. Why was NaH chosen as the base? Why did *O*-acylation not occur? Why were *t*-butyl esters used? What would probably have happened if the more obvious Friedel–Crafts (Chapter 22) route were tried instead?



13. Base-catalysed reaction between these two esters allows the isolation of one product in 82% yield. Predict its structure.



The NMR spectrum of the product shows that two species are present. Both show two 3H triplets at about δ_H = 1 p.p.m. and two 2H quartets at about δ_H = 3 p.p.m. One has a very low field proton and an ABX system at 2.1–2.9 p.p.m. with J_{AB} 16 Hz, J_{AX} 8 Hz, and J_{BX} 4 Hz. The other has a 2H singlet at 2.28 p.p.m. and two protons at 5.44 and 8.86 p.p.m. coupled with *J* 13 Hz. One of these protons exchanges with D_2O. Any attempt to separate the mixture (for example, by distillation or chromatography) gives the same mixture. Both compounds, or the mixture, on treatment with ethanol in acid solution give the same product. What are these compounds?

Compound B has IR 1740 cm^{-1}, δ_H 1.15–1.25 p.p.m. (four t, each 3H), 3.45 p.p.m. (2H, q), 3.62 p.p.m. (2H, q), 4.1 p.p.m. (two 2, each 2H), 2.52 p.p.m. (2H, ABX system, J_{AB} 16 Hz), 3.04 p.p.m. (1H, X of ABX split into a further doublet by *J* 5 Hz), and 4.6 p.p.m. (1H, d, *J* 5 Hz). The couplings between A and X and between B and X are not quoted in the paper. Nevertheless, you should be able to work out a structure for compound B.

ɔnjugate addition of enolates

29

nnections

ilding on:

- **arbonyl chemistry ch2, ch12, & ch14**
- **onjugate addition ch10**
- **ols and enolates ch21**
- **ucleophilic attack on electrophilic arbons ch23**
- **ynthesis in action ch25**
- **hemistry of enol(ate)s ch26–ch29**

Arriving at:

- **Convergent plans for synthesis**
- **Thermodynamic control**
- **Selection of reagents for enol(ate) conjugate addition**
- **Tandem reactions and Robinson annelation**
- **Substitution may be elimination–conjugate addition in disguise**
- **Nitriles and nitro compounds**

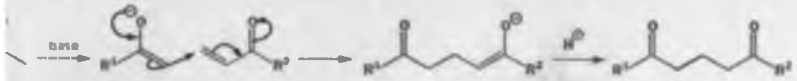
Looking forward to:

- **Synthesis and retrosynthesis ch30**
- **Diastereoselectivity ch33–ch34**
- **Saturated and unsaturated heterocycles ch42 & ch44**
- **Main group chemistry ch46–ch47**
- **Asymmetric synthesis ch45**
- **Natural products ch51**

ʻoduction: conjugate addition of enolates is a powerful thetic transformation

■ Conjugate addition is also called 1,4-chain addition and is described in Chapters 10 and 23

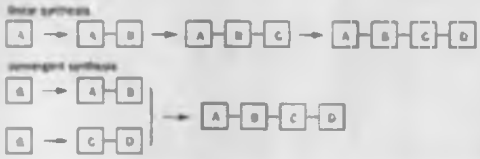
roduct of a conjugate addition of an enolate or enol equivalent to an α,β-unsaturated carbonyl ound will necessarily be a dicarbonyl compound or an equivalent derivative. As the carbonyl occupies such a central position in synthesis it will come as no surprise that these intermedi- vith two carbonyl groups, are very widely used.



e other important feature of this conjugate addition reaction is that the two carbonyl groups in oduct are reasonably far apart while the newly formed bond is in the middle of the molecule. neans that Michael addition can be a *convergent* route to the product—a feature that usually nizes synthetic efficiency.

ar vs. convergent syntheses

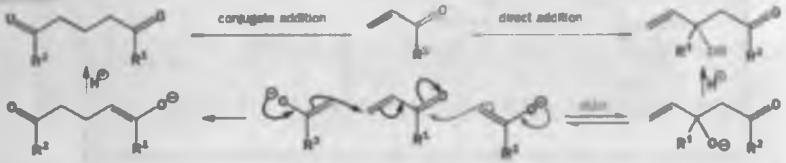
vergent synthesis joins fragments that have been rated beforehand rather adding together many fragments in a linear n. The overall yield will ally be higher



ıjugate addition of enolates is the result of thermodynamic trol

le nucleophiles have exactly the same opportunity to attack the carbonyl group directly as do mple nucleophiles discussed in Chapter 10 and the same factors govern the eventual outcome

of the reaction. Thermodynamic control leads to conjugate addition but kinetic control leads to direct addition. The key to successful conjugate addition is to ensure that direct addition to the carbonyl (an aldol reaction, Chapter 28) is reversible. This enables the conjugate addition to compete and, as its product is more stable, it eventually becomes the sole product. This is thermodynamic control at its best!

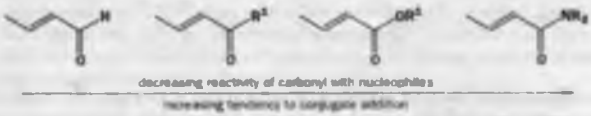


The aldol product is more sterically hindered than the conjugate addition product so increased branching on the nucleophile tends to accelerate the retro-aldol process, which releases steric strain and favours equilibration to the thermodynamic product. Perhaps more important is the stability of the enolate: the more stable the starting enolate, the easier it is to reverse both reactions and this favours the more stable conjugate addition product. One of the most important ways of stabilizing an enolate—using another electron-withdrawing group such as CO_2Et—achieves both of these enhancements at the same time as branching inevitably accompanies the extra anion stabilization.

There is also a frontier orbital effect that assists conjugate addition over the aldol reaction. You will recall that the carbonyl carbon is a relatively hard centre, whereas the β carbon of an enone is soft. As the nucleophilic enolate becomes more stabilized with extra electron-withdrawing groups, it becomes increasingly soft and hence more likely to attack the β carbon.

The unsaturated component plays an important role

The nature of the carbonyl group in the α,β-unsaturated electrophile is also important as the more electrophilic carbonyl groups give more direct addition and the less electrophilic carbonyl groups (esters, amides) give more conjugate addition. Aldehydes are unhindered and very reactive and thus very prone to direct addition but, if the enolate equivalent is carefully chosen, conjugate addition works well. Ketones are borderline and can be pushed towards either the aldol or conjugate addition pathways by choice of enolate equivalent as we shall see. Esters and amides are much less electrophilic at the carbonyl carbon and so are good substrates for conjugate addition.

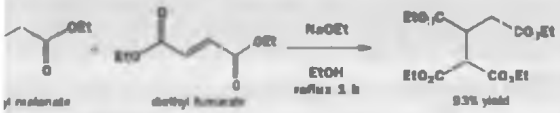


njugate addition is *thermodynamically* controlled; direct addition is *inetically* controlled

able enolates promote conjugate addition by:
making the aldol reaction more reversible
making the enolate anion softer
ss reactive Michael acceptors promote conjugate addition by:
making the aldol reaction more reversible
making the carbonyl group less electrophilic

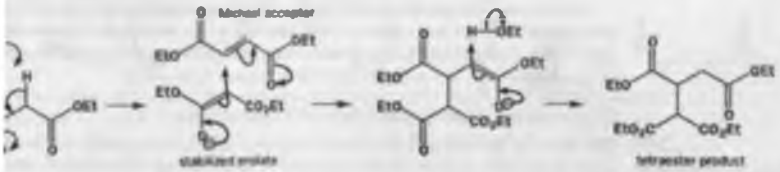
are excellent anion-stabilizing groups on enolate or Michael acceptors

ers (malonates and substituted derivatives) combine three useful features in conjugate addi-ctions: they form stable enolate anions that undergo clean conjugate addition; if required, he ester groups can be removed by hydrolysis and decarboxylation; and, finally, the remain-or ester is ideal for conversion into other functional groups.

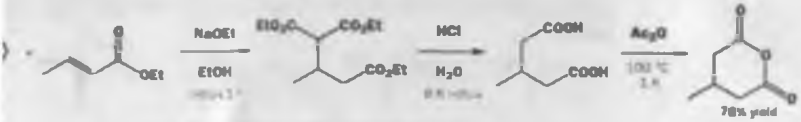


yl malonate diethyl fumarate

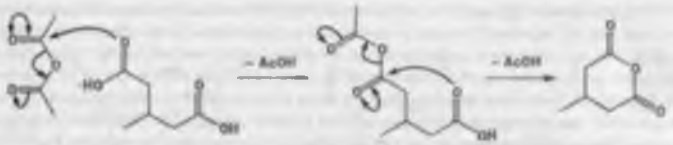
hyl malonate adds to diethyl fumarate in a conjugate addition reaction promoted by sodium le in dry ethanol to give a tetraester. Diethyl fumarate is an excellent Michael acceptor because er groups withdraw electrons from the alkene. The mechanism involves deprotonation of the ate, conjugate addition, and reprotonation of the product enolate by ethanol solvent. In this n two ester groups stabilize the enolate and two more promote conjugate addition.



value of malonate esters is illustrated in this synthesis of a substituted cyclic anhydride by ate addition to ethyl crotonate, hydrolysis, and decarboxylation, followed by dehydration cetic anhydride. This route is very general and could be used to make a range of anhydrides ifferent substituents simply by choosing an appropriate unsaturated ester.



mechanism of the conjugate addition is the same as that in the previous example and the nism for ester hydrolysis was covered in Chapter 12. The key step in the dehydration reaction formation and cyclization of the mixed anhydride formed from the diacid and acetic anhy-Both steps have the same mechanism, attack of an acid on an anhydride, but the second step is nolecular. Like most cyclizations the reaction is entropically favoured as two molecules react to ree—the cyclic anhydride and two molecules of acetic acid.



● **Use of electron-withdrawing groups to favour conjugate addition**

Conjugate addition of enolates is promoted by electron-withdrawing groups (for example, CO_2Et), especially by:

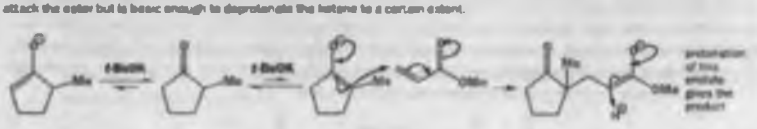
- two electron-withdrawing groups stabilizing the enolate
- two electron-withdrawing groups conjugated with the alkene

It is not necessary to have both features in the same reaction.

Alkali metal (Li, Na, K) enolates can undergo kinetic conjugate addition

It is not essential to have two anion-stabilizing groups for successful conjugate addition and it is even possible with simple alkyl metal (Li, Na, and K) enolates. Lithium enolates are not ideal nucleophiles for thermodynamically controlled conjugate addition. Better results are often observed with sodium or potassium enolates, which are more dissociated and thus more likely to revert. Lithium binds strongly to oxygen and so tends to prevent reversible aldol addition, which leads to loss of conjugate addition product. Potassium hydroxide is the ideal base for this example as it is hindered and so will not attack the ester but is basic enough to deprotonate the ketone to a certain extent.

Two enolates are possible but, under the equilibrating conditions, the more stable and more reactive enolate is the important intermediate leading to the more interesting product with a quaternary carbon atom.



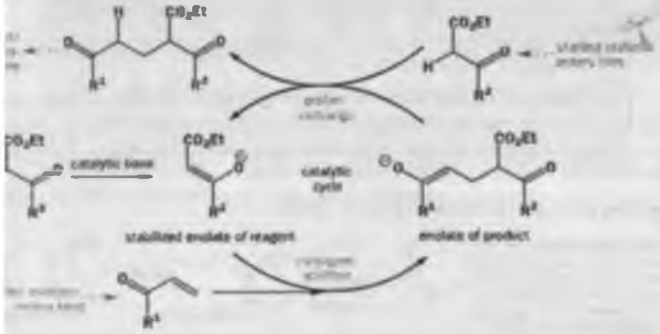
If the conditions are right, good yields are sometimes observed from kinetically controlled conjugate addition even with lithium enolates. This unlikely outcome is favoured by hindered nucleophiles and conjugated or hindered carbonyls. In these cases the lack of reversibility is not an issue as the aldol product is never formed. In this example the enolate of the ketyl ketone is the hindered nucleophile and the conjugated ketone is rather unreactive.

However, most successful conjugate additions use stable enol or enolate equivalents and we shall continue to discuss them in the next section.

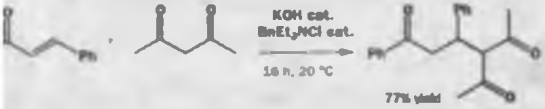
Conjugate addition can be catalytic in base

As the penultimate product in a conjugate addition is an enolate anion, if the pK_a of the nucleophile is appropriate, only a catalytic quantity of base is required to initiate the reaction. The enolate anion of the product is protonated by a molecule of starting material to give the neutral final product and another enolate anion of starting material. The reversible reaction sequence, including the unwanted aldol equilibrium, can be forced over towards the conjugate addition product. The balance of pK_as is likely to be right for nucleophiles with two electron-withdrawing groups when adding to a double bond conjugated to a single carbonyl group.

is proton exchange sets up a catalytic cycle. The cycle is started by an external base removing a
n from the most acidic species present in the reaction mixture at the start which is the nucle-
. This is an important condition for success of the catalytic method and the reason that all the
nts can be mixed together at the start of the reaction with no adverse effects. There is no need
m the nucleophilic enolate quantitatively; more is formed as the reaction proceeds. The advan-
af this way of running a conjugate addition are that strongly basic conditions are avoided so
ilild bases such as tertiary amines (for example, Et_3N) or fluorides (for example, Bu_4NF) can be
yed successfully.



ie catalytic approach to conjugate addition is illustrated by the addition of a β-diketone to an
atic enone catalysed by potassium hydroxide and benzyltriethylammonium chloride, which is a
: transfer catalyst. Once again, the catalytic cycle is initiated by deprotonation of the most acidic
onent in the reaction mixture, acetyl acetone, which is followed by a cycle of conjugate addi-
nd proton exchange leading inexorably to the product.



ls are more likely than enolates to undergo direct conjugate addition

catalysis is not required for conjugate addition. If the nucleophile is sufficiently enolized under
eaction conditions then the enol form is perfectly able to attack the unsaturated carbonyl com-
nd. Enols are neutral and thus soft nucleophiles favouring conjugate attack, and β-dicarbonyl
ounds are enolized to a significant extent (Chapter 21). Under acidic conditions there can be
lutely no base present but conjugate addition proceeds very efficiently. In this way methyl vinyl
se (butenone) reacts with the cyclic β-diketone promoted by acetic acid to form a quaternary
e. The yield is excellent and the triketone product is an important intermediate in steroid syn-
s as you will see later in this chapter.

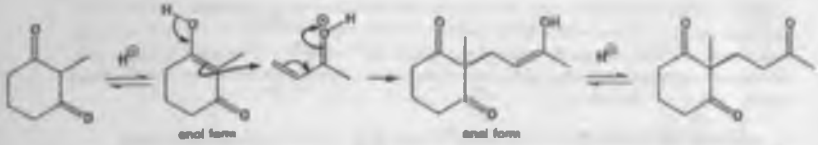
he mechanism involves acid-catalysed conversion of the keto form of the cyclic β-diketone
the enol form, which is able to attack the protonated enone. The mechanistic detail is precisely
gous to the attack of an enolate shown above; the only difference is that both reactants are

▶ Hydrogen fluoride is a weak acid in aqueous solution, $pK_a = 3.45$, due to the strength of the H–F bond. This bond strength also accounts for the basicity of the fluoride ion.

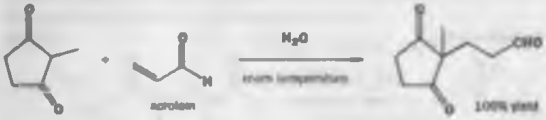
▶ Diagrams of catalytic cycles are not always easy to understand. The main cycle rotates anticlockwise round the centre of the diagram with the starting materials entering top right and bottom left with the product emerging top left. The first molecules of enolate enter middle left. It would be helpful if you were to follow the formation of one molecule of product on the diagram and see how it sets off the next cycle. It is very important that you do not allow catalytic cycles to replace mechanisms in your understanding of chemical reactions.

■ The origins of the benefits of phase transfer catalysis (PTC) were presented in Chapters 23 and 28.

protonated. The product is the enol form of the triketone, which rapidly tautomerizes to the more stable keto form.

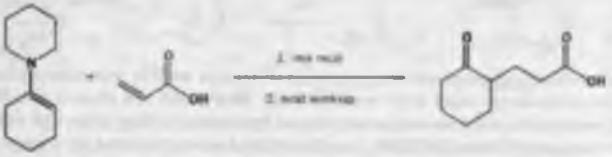


The thermodynamic control of conjugate addition allows even enals that are very electrophilic at the carbonyl carbon to participate successfully. Any aldol reaction, which must surely occur, is reversible and 1,4-addition eventually wins out. Acrolein combines with this five-membered diketone under very mild conditions to give a quantitative yield of product. The mechanism is analogous to that shown above.

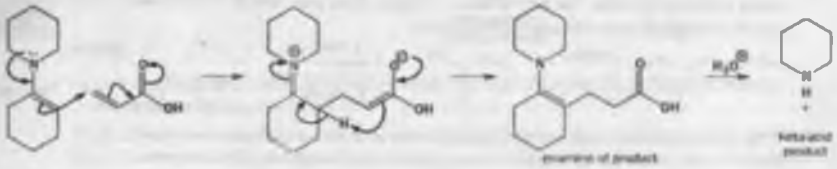


Enamines are convenient stable enol equivalents for conjugate addition

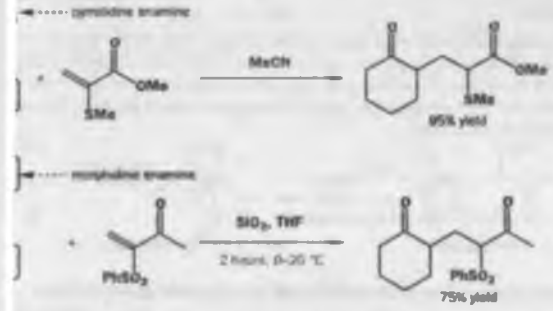
If you want to do a conjugate addition of a carbonyl compound without having a second anion-stabilizing group, you need some stable and relatively unreactive enol equivalent. In Chapters 27 and 28 you saw how enamines are useful in alkylation reactions. These neutral species are also perfect for conjugate addition as they are soft nucleophiles but are more reactive than enols and can be prepared quantitatively in advance. The reactivity of enamines is such that heating the reactants together, sometimes neat, is all that is required. Protic or Lewis acid catalysis can also be used to catalyse the reaction at lower temperature.



The mechanism is rather like enol addition. The differences are that the enamine is more nucleophilic because of the nitrogen atom and that the product is an enamine, which can be converted into the corresponding carbonyl by mild acidic hydrolysis. This is usually performed during the work-up and so does not really constitute an extra step. The amine is washed out as the hydrochloride salt so isolation is straightforward. After conjugate addition the resulting enolate-iminium ion undergoes proton transfer rapidly to produce the more stable carbonyl-enamine tautomer. This is shown as an intramolecular process but it could just as easily be drawn with an external base and source of protons. The resulting enamine is then stable until aqueous acid is added at the end of the reaction. Hydrolysis occurs via the iminium ion to reveal the second carbonyl group and release the secondary amine.



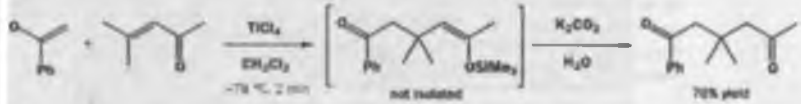
ngs of secondary amines can be used to form the enamines but those formed from piperidine, lline, and morpholine combine reduced steric demands at the reactive double bond with good ility of the nitrogen lone pair. The electronic nature of the other substituents on the key dou- nd can vary without affecting the success of the conjugate addition. In these two examples om from cyclohexanone formed with pyrrolidine and morpholine add in good yield to an α,β- nated carbonyl compound with an extra electron-withdrawing methylthio or phenylsulfonyl



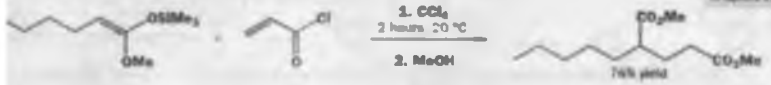
ugate addition of silyl enol ethers leads to the silyl enol ether of the product

ost alternatives to enamines for conjugate addition of aldehyde, ketone, and acid derivative are silyl enol ethers. Their formation and some uses were discussed in Chapters 21 and 26–28, ese stable neutral nucleophiles also react very well with Michael acceptors either spontaneous- ith Lewis acid catalysis at low temperature.

he 1,5-dicarbonyl compound is required, then an aqueous work-up with either acid or base s the silicon–oxygen bond in the product but the value of silyl enol ethers is that they can go synthetically useful reactions other than just hydrolysis. Addition of the silyl enol ether d from acetophenone (PhCOMe) to a disubstituted enone promoted by titanium tetra- de is very rapid and gives the diketone product in good yield even though a quaternary carbon is created in the conjugate addition. This is a typical example of this very powerful class of con- addition reactions.



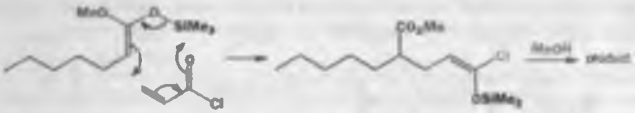
yl ketene acetals are even more nucleophilic than ordinary silyl enol ethers and react sponta- ly with acyl chlorides. The intermediate enol ether of the acid chloride was not isolated but ated directly into a methyl ester with methanol.



The synthesis and reactivity of silyl ketene acetals are discussed in Chapters 21, 26, and 27.

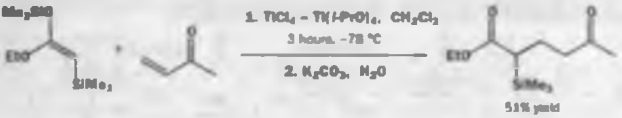
e mechanism, in the absence of a catalyst, can be written as a cyclic process involving direct er of silicon from the nucleophile to the electrophile but it might actually be stepwise. The soft

nature of the silyl enol ether is demonstrated by the choice of soft double bond over hard carbonyl carbon as the electrophilic partner even though the carbonyl compound is an acid chloride.

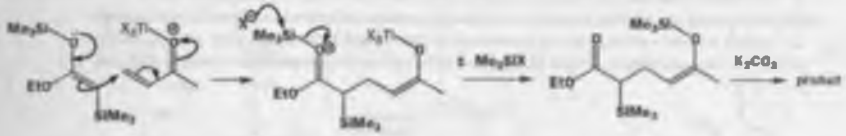


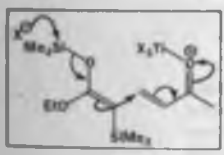
Lewis acid catalysis ($TiCl_4$) is normally required for silyl enol ether reactions

Conventional Lewis acid catalysis using a mixture of titanium tetrachloride and titanium isopropoxide is used to promote the addition of the silyl ketene acetal to methyl vinyl ketone. The key step in the mechanism is the conjugate addition of the silyl ketene acetal to the enone to form the bond shown in black in the product. The catalysis allows the reaction to proceed at much lower temperature, –78 °C. Do not be confused by the second $SiMe_3$ group. This is not an *O*-$SiMe_3$ group but a *C*-$SiMe_3$ group and plays no active part in the reaction.



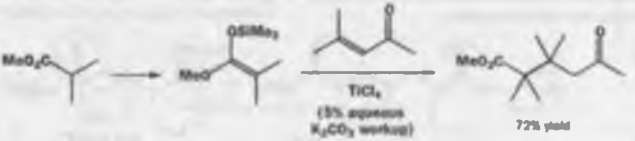
The electrophile coordinates to the Lewis acid first producing an activated enone that is attacked by the silylated nucleophile. It is difficult to determine at what stage the trimethylsilyl group moves from its original position and whether it is transferred intramolecularly to the product. In many cases the anion liberated from the Lewis acid (Cl^-, RO^-, Br^-) is a good nucleophile for silicon so it is reasonable to assume that there is a free trimethylsilyl species (Me_3SiX) that captures the titanium enolate (Chapter 28).





The mechanism can be drawn in a more concise form as shown in the frame. This gives the essence of the reaction but the details of the transfer of the TiX_3 and $SiMe_3$ groups are not shown and are in any case uncertain. The *C*-$SiMe_3$ group survived the mild basic treatment that cleaved the silyl enol ether formed by initial conjugate addition.

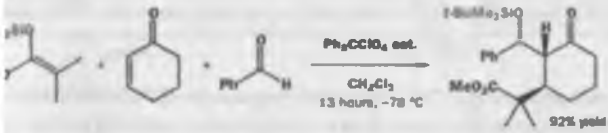
It is even possible to use a silyl enol ether to create a new C–C bond that joins two new quaternary centres. In this example the silyl ketene acetal does conjugate addition on an unsaturated ketone catalysed by the usual Lewis acid ($TiCl_4$) for such reactions.

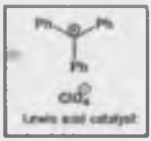


Sequential (tandem) conjugate additions and aldol reactions build complex molecules in a few steps

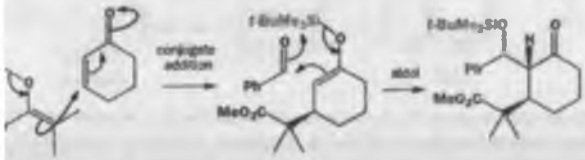
The silyl enol ether that is the initial product from conjugate addition of a silyl enol ether or silyl ketene acetal need not be hydrolysed but can also be used in aldol reactions. This example uses trityl perchlo

yl = Ph_3C), which is a convenient source of the trityl cation, as catalyst rather than a metal-
ıın acid. The very stable Ph_3C^+ cation carries a full positive charge and presumably functions
ıns way as a Lewis acid. The combination of a silyl ketene acetal, cyclohexenone, and benzalde-
as a highly chemoselective and stereoselective conjugate addition–aldol sequence.



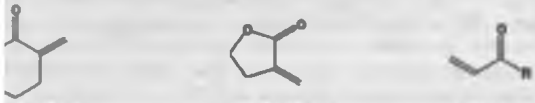


chemoselective (Chapter 24) conjugate addition of the silyl ketene acetal on the enone is
d to direct aldol reaction with the aldehyde. Then an aldol reaction of the intermediate silyl
er on the benzaldehyde follows. The stereoselectivity results, firstly, from attack of benzalde-
the less hindered face of the intermediate silyl enol ether, which sets the two side chains *trans*
ycloheranone, and, secondly, from the intrinsic diastereoselectivity of the aldol reaction (this
d in some detail in Chapter 34). This is a summary mechanism.

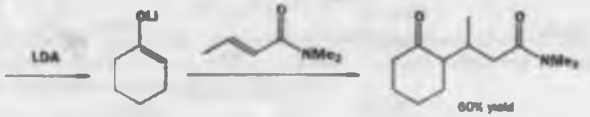


iety of electrophilic alkenes will accept enol(ate) ophiles

plest and best Michael acceptors are those α,β-unsaturated carbonyl compounds with exposed ated β carbon atoms, such as *exo*-methylene ketones and lactones and vinyl ketones, and we in the next section that these need to have their high reactivity moderated in most applications.

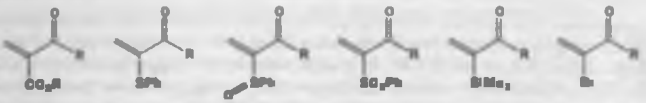


e Michael acceptors react with most enol equivalents to give good yields of conjugate addi-
ducts. Before discussing them we shall first briefly discuss other good Michael acceptors that
ıs important but have their uses. Esters are good Michael acceptors because they are not very
philic. Unsaturated amides are even less electrophilic and will even give conjugate addition
s with lithium enolates.



■
The fact that this is an *N,N*-dimethyl amide should remind you of the use of this kind of saturated amide in carbonyl substitution reactions with R_2Li in Chapter 12.

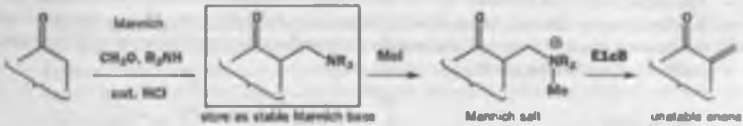
else fails, the trick to persuade a stubborn enolate to do conjugate rather than direct substitu-
ı add an extra anion-stabilizing substituent in the α position. Here is a selection of reagents
hus. In each case the extra group (CO_2Et, SPh, SOPh, SO_2Ph, $SiMe_3$, and Br) can be removed
conjugate addition is complete.



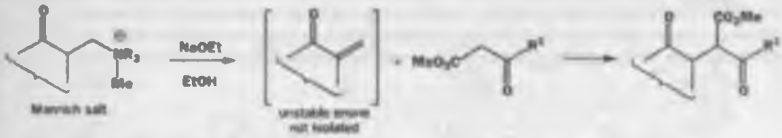
However, most α,β-unsaturated *ketones* can be made to do conjugate addition by suitable choice of enol(ate) equivalent and conditions. Now we need to look at the best Michael acceptors, their reactions, and how to make them.

The Mannich reaction provides stable equivalents of *exo*-methylene ketones

The key substrates for conjugate addition are the α,β-unsaturated carbonyl compounds. When the double bond is inside a chain or ring these compounds are available via a wide variety of routes including the aldol reaction and are generally stable intermediates that can be stored for use at will. When the double bond is *exo* to the ring or chain (*exo*-methylene compounds), the unhindered nature of the double bond makes them especially susceptible to attack by nucleophiles (and radicals). This reactivity is needed for conjugate additions but the compounds are unstable and polymerize or decompose rather easily.

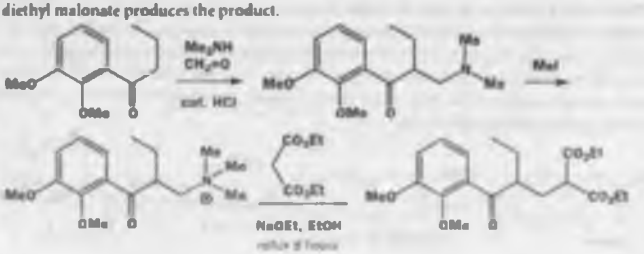


The preferred synthetic route to these important intermediates is the Mannich reaction (Chapter 27). The compound is stored as the stable Mannich base and the unstable enone released by elimination of a tertiary amine with mild base. The same conditions are right for this elimination and for conjugate addition. Thus the *exo*-methylene compounds can be formed in the flask for immediate reaction with the enol(ate) nucleophile. The overall reaction from β-amino carbonyl to 1,5-dicarbonyl appears to be a substitution but the actual mechanism involves elimination and conjugate addition.

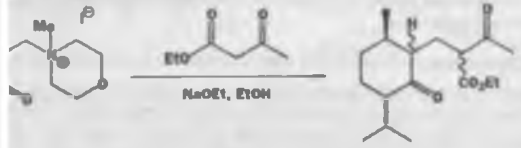


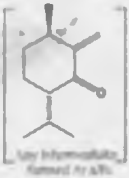
Using the Mannich reaction in conjugate addition

Either the tertiary amine or the quaternary ammonium salt can be stored as a stable equivalent of the *exo*-methylene compound. In our first example, the Mannich base with dimethylamine is first methylated with methyl iodide and then added to the conjugate addition reaction. Elimination of trimethylamine, which escapes from the refluxing ethanol as a gas, reveals the *exo*-methylene ketone in which the methylene group is *exo* to a chain. Fast conjugate addition of the stabilized enolate of diethyl malonate produces the product.



ε ketones with *exo* cyclic methylenes can be prepared in just the same way and used *in situ*. line is often used as a convenient secondary amine for the Mannich reaction and the result- un-ketones can be methylated and undergo elimination–addition reactions with stabilized nuch as that derived from ethyl acetoacetate. This starting material was prepared from nat- rthone and the mixture of diastereoisomers produced is unimportant because the product is al in a Robinson annelation (see below).



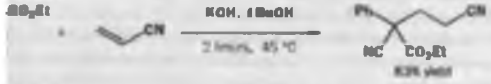


unsaturated nitriles are ideal for conjugate addition

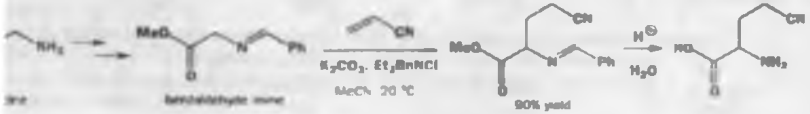
ile group is not as reactive towards direct attack by nucleophiles as its carbonyl cousins but is able to stabilize an adjacent negative charge in the style of enolates. Alkenes conjugated with re thus activated towards nucleophilic attack without the complications of competing direct n to the activating group.

regioselectivity of enolate formation is governed by the usual factors so that methyl ketone forms the more stable enolate with sodium metal. This undergoes smooth and onjugate addition to acrylonitrile, which is unsubstituted at the β position and so very

yanide group can also act as an anion-stabilizing group in the nucleophile. In combination ester group, the enolizable proton is acidified to such an extent that potassium hydroxide can as base.

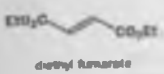


simplest amino acid, glycine, would be an ideal starting material for the synthesis of more ted amino acids but it does not easily form enols or enolates. The methyl ester of the ben- de imine has two electron-withdrawing groups to help stabilization of the enolate and conju- ition of acrylonitrile is now possible. The base used was solid potassium carbonate with a ary ammonium chloride as phase transfer catalyst. Simple hydrolysis of the alkylated prod- s to the extended amino acid.



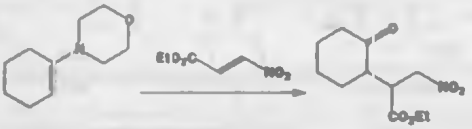
▶ Acrylonitrile CH_2=CHCN is one of the best Michael acceptors for enol(ate)s. The reaction is known as **cyanoethylation** as H adds a $-CH_2CH_2CN$ group to the enol(ate).

Nitro is more powerful than carbonyl in directing conjugate addition



diethyl fumarate

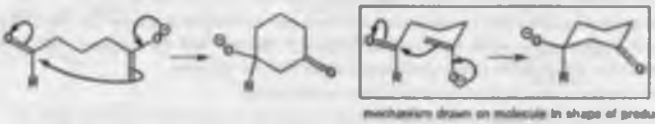
We have seen how two ester groups in fumarate diesters encourage conjugate addition, but what if there are two *different* groups at the ends of the Michael acceptor? Then you must make a judgement as to which is more electron-withdrawing. One case is clear-cut. The nitro group is worth two carbonyl groups (p. 000) so that conjugate addition occurs β to the nitro group in this case.



Conjugate addition followed by cyclization makes six-membered rings

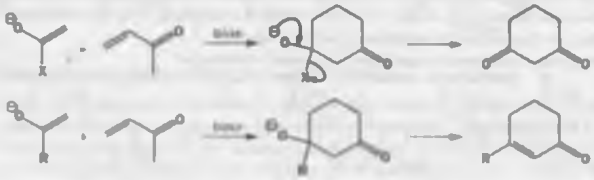
The product of Michael addition of an enolate to an α,β-unsaturated carbonyl compound will normally be a 1,5-dicarbonyl compound. The two reactive carbonyl groups separated from one another by three carbon atoms present the opportunity for ring formation by intramolecular aldol condensation. If one of the carbonyls acts as an electrophile while the other forms a nucleophilic enolate, this cyclization gives a six-membered ring.

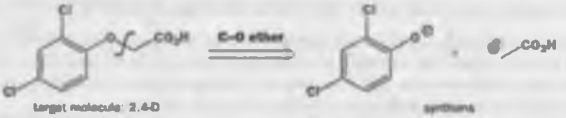
Drawing out the curly arrows for the formation is not easy as the chain has to fold back on itself which is hard to represent in two dimensions. However, remembering that the actual structure of a six-membered ring is a chair is extremely helpful. By using the structure of the product as a template for the transition state and reactive conformation of the starting material a clear representation is achieved.



mechanism drawn on molecule in shape of product

The precise nature of the carbonyl groups determines what happens next. If R is a leaving group (OR, Cl, etc.), the tetrahedral intermediate collapses to form a ketone and the product is a 1,3-diketone. The synthesis of dimedone (later in this chapter) is an example of this process where an alkoxy group is the leaving group. Alternatively, if R is an alkyl or aryl group, loss of R is not an option and the cyclization is an intramolecular aldol reaction. Dehydration produces an α,β-unsaturated ketone, which is a stable final product.

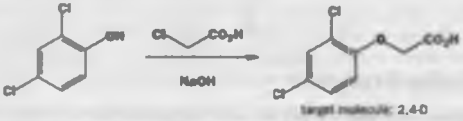




We can apply these ideas to the synthesis of the herbicide 2,4-D (2,4-dichlorophenoxyacetic acid). The most reasonable disconnection of an ether is the C–O bond because we know that ethers can be made from alkyl halides by substitution with an alkoxide anion. We don't at this stage need to decide exactly which alkyl halide or alkoxide to use, so we just write the synthons.

Once the retrosynthetic analysis is done, we can go back and use our knowledge of chemistry to think of reagents corresponding to these synthons. Here, for example, we should certainly choose the anion of the phenol as the nucleophile and some functionalized acetic acid molecule with a leaving group in the α position.

We can then write out a suggested synthesis in full from start to finish. It isn't reasonable to try to predict exact conditions for a reaction: to do that you would need to conduct a thorough search of the chemical literature and do some experiments. However, all of the syntheses in this chapter are real examples and we shall often give full details of conditions to help you become familiar with them.



Some definitions of terms used in synthesis

• target molecule (or TM)	the molecule to be synthesized
• retrosynthetic analysis or retrosynthesis	the process of mentally breaking down a molecule into starting materials
• retrosynthetic arrow	an open-ended arrow, ⇒ , used to indicate the reverse of a synthetic reaction
• disconnection	an imaginary bond cleavage, corresponding to the reverse of a real reaction
• synthon	idealized fragments resulting from a disconnection. *Synthons* need to be replaced by *reagents* in a suggested synthesis
• reagent	a real chemical compound used as the equivalent of a synthon

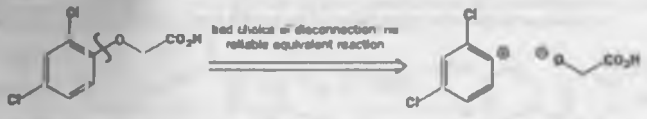
Choosing a disconnection

The hardest task in designing a retrosynthetic analysis is spotting where to make the disconnections. We shall offer some guidelines to help you, but the best way to learn is through experience and practice. The overall aim of retrosynthetic analysis is to get back to starting materials that are available from chemical suppliers, and to do this as efficiently as possible.

● Guideline 1

Disconnections must correspond to known, reliable reactions

We have already mentioned that disconnections must correspond to known reliable reactions and it's the most important thing to bear in mind when working out a retrosynthesis. When we disconnected the ether 2,4-D we chose to disconnect next to the oxygen atom because we know about the synthesis of ethers. We chose *not* to disconnect on the aryl side of the oxygen atom because we know of no reliable reaction corresponding to nucleophilic attack of an alcohol on an unactivated aromatic ring.



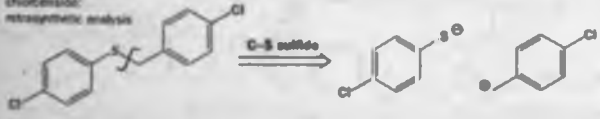
● We talked about nucleophilic aromatic substitution is possible in Chapter 23.

● Guideline 2

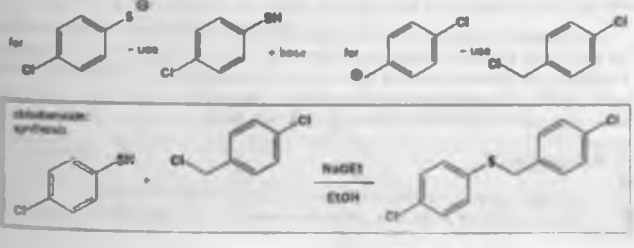
For compounds consisting of two parts joined by a heteroatom, disconnect next to the heteroatom

In all the retrosynthetic analyses you've seen so far there is a heteroatom (N or O) joining the rest of the molecule together, and in each case we made the disconnection next to that N or O. This guideline works for esters, amides, ethers, amines, acetals, sulfides, and so on, because these compounds are often made by a substitution reaction.

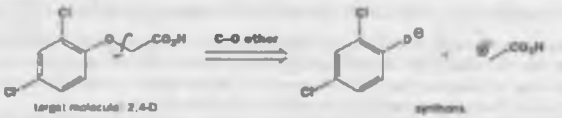
Chlorbenside is used to kill ticks and mites. Using Guideline 2 we can suggest a disconnection next to the sulfur atom: using Guideline 1 we know that we must disconnect on the alkyl and not on the aryl side.



We can now suggest reagents corresponding to the synthons, and propose a synthetic scheme.



▶ You shouldn't have expected to predict that sodium ethoxide would be the base used for this reaction, but you should have been aware that a base is needed, and have had some idea of the base strength required to deprotonate a thiol.



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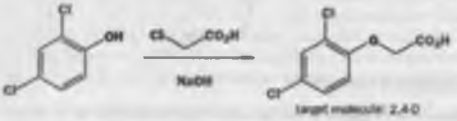

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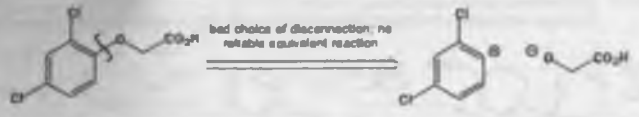
Disconnections must correspond to known, reliable reactions

We have already mentioned that disconnections must correspond to known reliable reactions and it's the most important thing to bear in mind when working out a retrosynthesis. When we disconnected the ether 2,4-D we chose to disconnect next to the oxygen atom because we know about the synthesis of ethers. We chose *not* to disconnect on the aryl side of the oxygen atom because we know of no reliable reaction corresponding to nucleophilic attack of an alcohol on an unactivated aromatic ring.

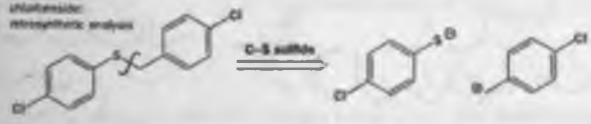


● Guideline 2

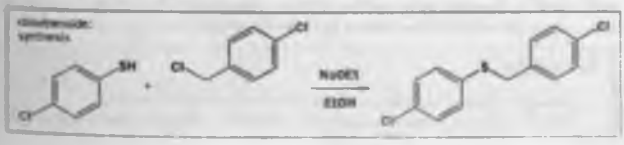
For compounds consisting of two parts joined by a heteroatom, disconnect next to the heteroatom

In all the retrosynthetic analyses you've seen so far there is a heteroatom (N or O) joining the rest of the molecule together, and in each case we made the disconnection next to that N or O. This guideline works for esters, amides, ethers, amines, acetals, sulfides, and so on, because these compounds are often made by a substitution reaction.

Chlorbenside is used to kill ticks and mites. Using Guideline 2 we can suggest a disconnection next to the sulfur atom; using Guideline 1 we know that we must disconnect on the alkyl and not on the aryl side.



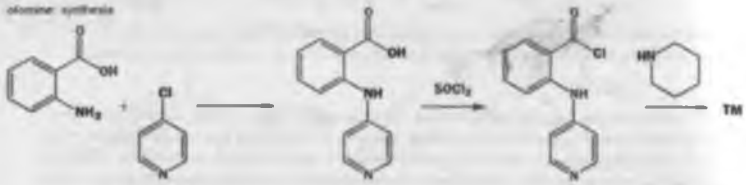
We can now suggest reagents corresponding to the synthons, and propose a synthetic scheme.



▶ We talked about cases where nucleophilic aromatic substitution is possible in Chapter 23.

▶ You shouldn't have expected to predict that sodium ethoxide would be the base used for this reaction, but you should have been aware that a base is needed, and have had some idea of the base strength required to deprotonate a thiol.

The retrosynthetic transformation of an acyl chloride to a carboxylic acid is not really a disconnection because nothing is being disconnected. We call it instead a **functional group interconversion**, or FGI, as written above the retrosynthetic arrow. Functional group interconversions often aid disconnections because the sort of reactive functional groups (acyl chlorides, alkyl halides) we want in starting materials are not desirable in compounds to be disconnected because they pose chemoselectivity problems. They are also useful if the target molecule contains functional groups that are not easily disconnected.



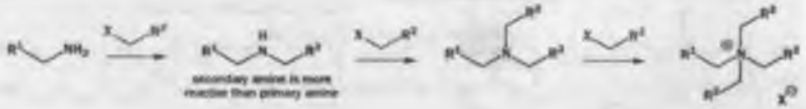
By using an appropriate reagent or series of reagents, almost any functional group can be converted into any other. You should already have a fair grasp of reasonable functional group interconversions. They mostly fall into the categories of oxidations, reductions, and substitutions (Chapters 12, 14, 17, and 24).

Amine synthesis using functional group interconversions

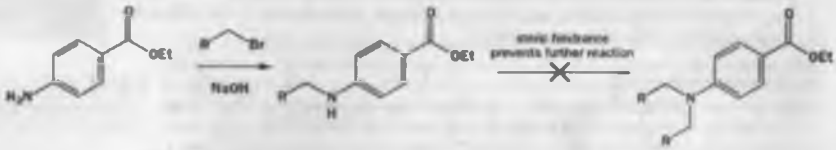
The synthesis of amines poses a special problem because only in certain cases is the obvious disconnection successful.

We discussed this in Chapters 14 and 24

The problem is that the product is usually more reactive than the starting material and there is a danger that multiple alkylation will take place.

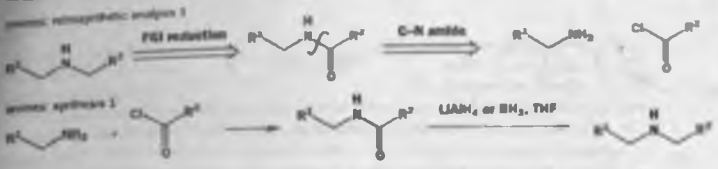


The few successful examples you have seen so far in this chapter have been exceptions, either for steric or electronic reasons, and from now on we advise you to avoid disconnecting an amine in this way. Sometimes further alkylation is made unfavourable by the increased steric hindrance that would result: this is probably the case for the cetaben ethyl ester we made by this reaction.



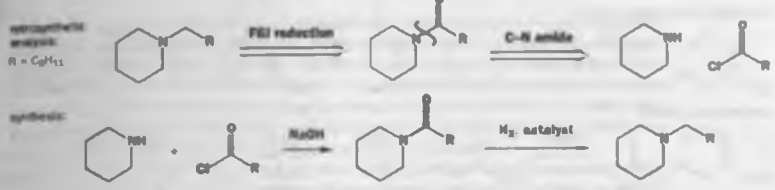
If the alkylating agent contains an inductive electron-withdrawing group, the product may be less reactive than the starting material — benzylamine was only alkylated once by the alkyl bromide in the synthesis of ICI-D7114 on p. 000 because of the electron-withdrawing effect of the aryloxy group.

What are the alternatives? There are two main ones, and both involve functional group interconversion, with the reactive amine being converted to a less reactive derivative before disconnection. The first solution is to convert the amine to an amide and then disconnect that. The reduction of amide to amine is quite reliable, so the FGI is a reasonable one.

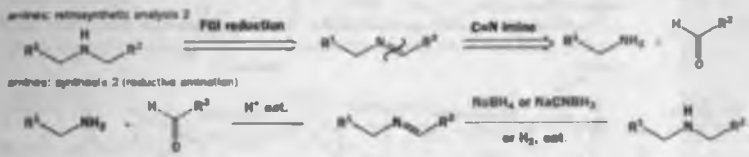


▶ Notice that we wrote 'FGI reduction' above the arrow because we are talking about the forward reaction we are going to do at this step.

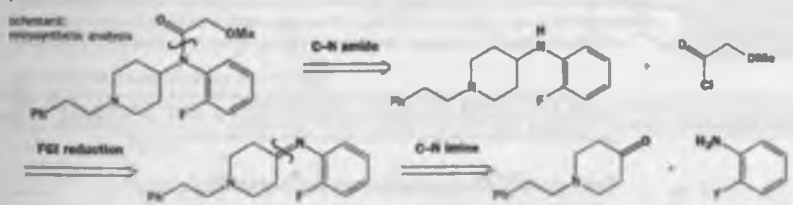
This approach was used in a synthesis of this amine, though in this case catalytic hydrogenation was used to reduce the amide.



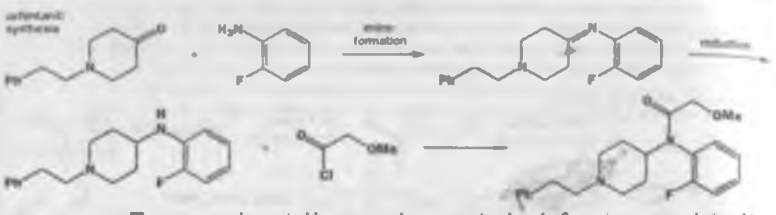
The second alternative is to convert to an imine, which can be disconnected to amine plus carbonyl compound. This approach is known as **reductive amination**, and we discussed it in detail in Chapter 14.



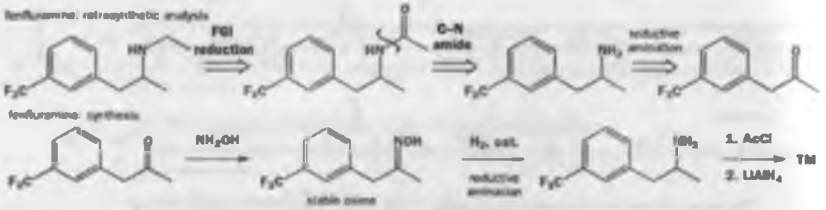
Ocfentanil is an opioid painkiller that lacks the addictive properties of morphine. Disconnection of the amide gives a secondary amine that we can convert to an imine for disconnection to a ketone plus 2-fluoro aniline.



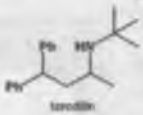
The synthesis is straightforward: a reductive amination followed by acylation of the only remaining NH group. The tertiary amine in the left-hand ring interferes with neither of these reactions.



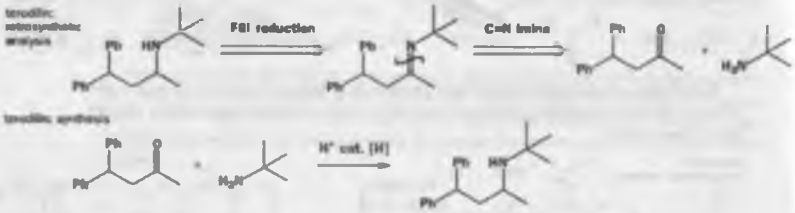
There are several conceivable routes to the neuroactive drug fenfluramine—one analysis, which uses both the amide and the imine FGI methods, is shown below and this was the route used to make the drug. Notice that the oxime was used instead of the imine. *N*-unsubstituted imines are very unstable, and the much more stable, indeed isolable oxime serves the same purpose. Oximes are generally reduced with $LiAlH_4$.



You should now be able to suggest a plausible analysis of the secondary amine terodilin. This is the structure; write down a retrosynthetic analysis and suggested synthesis before looking at the actual synthesis below.



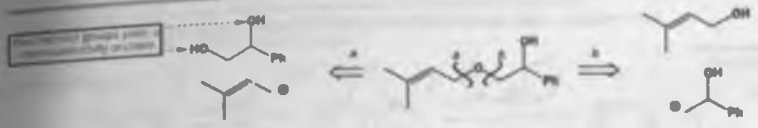
You should find yourself quite restricted in choice: the amide route clearly works only if there is a CH_2 group next to the nitrogen (this comes from the C=O reduction), so we have to use an imine.



In the synthesis of terodilin, it was not necessary to isolate the imine—reduction of imines is faster than reduction of ketones, so formation of the imine in the presence of a mild reducing agent (usually $NaCNBH_3$ or catalytic hydrogenation) can give the amine directly.

Two-group disconnections are better than one

This compound was needed for some research into the mechanisms of rearrangements. We can disconnect on either side of the ether oxygen atom, but (*b*) is much better because (*a*) does not correspond to a reliable reaction: it might be hard to control selective alkylation of the primary hydroxyl group in the presence of the secondary one.

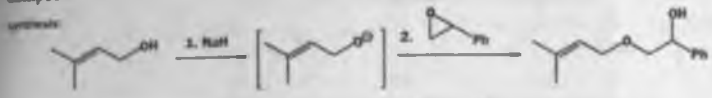


You might think that the best reagent to use as the equivalent of the synthon:

would be

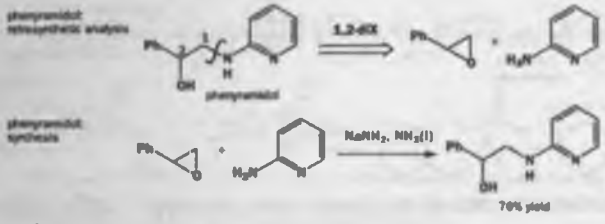
Be more ingenious! A much better solution is to use an epoxide

Nucleophile attack on the less hindered terminal carbon atom of the epoxide gives us the type of compound we want, and this was how the target molecule was made.



In using the epoxide we have gone one step beyond all the disconnections we have talked about so far, because we have *used one functional group to help disconnect another*—in other words, we noticed the alcohol adjacent to the ether we wanted to disconnect, and managed to involve them both in the disconnection. Such disconnections are known as **two-group disconnections**, and you should always be on the look-out for opportunities of using them because they are an efficient way of getting back to simple starting materials. We call this epoxide disconnection a **1,2-disconnection** because the two functional groups in the two-group disconnection are in a 1,2-relationship.

Drug molecules often have 1,2-related functional groups: 2-amino alcohols form one important class. Phenyramidol, for example, is a muscle relaxant. A simple two-group disconnection takes it straight back to 2-amino pyridine and styrene oxide.

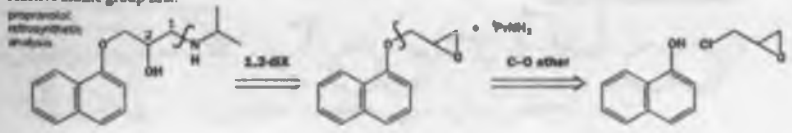


Notice that we have written '1,2-diX' above the arrow to show that it's a two-group ('diX') disconnection—we've also numbered the carbon atoms in the starting material to show the 1,2-relationship. It may seem trivial in such a simple example, but it's a useful part of the process of writing retrosynthetic analyses because it helps you to spot opportunities for making two-group disconnections.

▶ The observant among you may now be questioning why this synthesis is successful—after all, we have made a secondary amine by alkylating a primary one with an epoxide—exactly the sort of thing we advised against on p. 000. Alkylations with epoxides usually stop after the first step because the inductively electron-withdrawing hydroxyl group in the product makes it less nucleophilic than the starting material. In the synthesis of ICI-D7114 on p. 000, it's this same effect that prevents the amine being multiply alkylated.

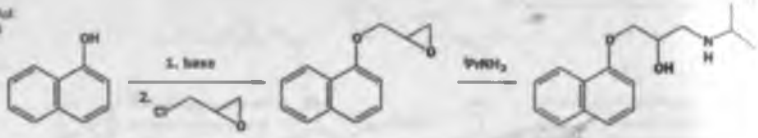
Propranolol is one of the top heart drugs

The Zeneca drug propranolol is a beta-blocker that reduces blood pressure and is one of the top drugs worldwide. It has two 1,2-relationships in its structure but it is best to disconnect the more reactive amine group first.



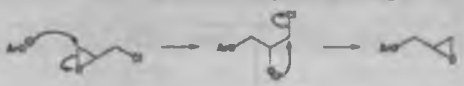
The second disconnection can't make use of an epoxide, but a simple ether disconnection takes us back to 1-naphthol and epichlorohydrin, a common starting material for this type of compound.

propranolol synthesis



▶

Epichlorohydrin is a useful starting material for 1,2,3-substituted compounds. The epoxide is more electrophilic than the C–Cl bond, and the mechanism of the first step of the synthesis is surprising.

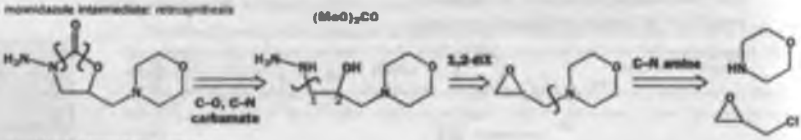


How would you verify this experimentally? Think about what would happen if the epichlorohydrin were enantiomerically pure.

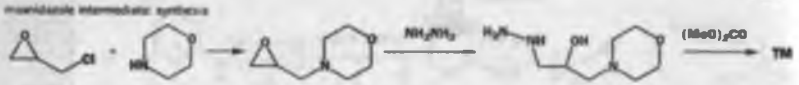
Moxnidazole can be made with epichlorohydrin

Moxnidazole is an antiparasitic drug, and our next target molecule is an important intermediate in its synthesis. The obvious first disconnection is of the carbamate group, revealing two 1,2 relationships. A 1,2-diX disconnection gives an epoxide that can be made by alkylation of morpholine with epichlorohydrin.

moxnidazole intermediate: retrosynthesis



moxnidazole intermediate: synthesis



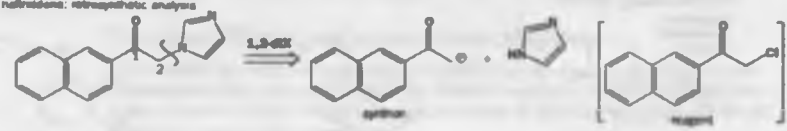
At the carbonyl oxidation level another synthon is needed for 1,2-diX disconnections

Just as epoxides are useful reagents for this synthon:  α halocarbonyl compounds are useful reagents for the carbonyl equivalent: 

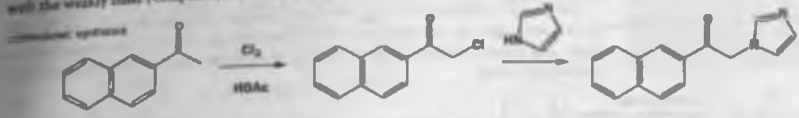
We can consider disconnection to this synthon to be a two-group disconnection because the α halocarbonyl equivalents are easily made by halogenation of a ketone, ester, or carboxylic acid (see Chapter 21) and the carbonyl group adjacent to the halide makes them extremely reactive electrophiles (Chapter 17).

Nafimidone is an anticonvulsant drug with an obvious two-group disconnection of this type.

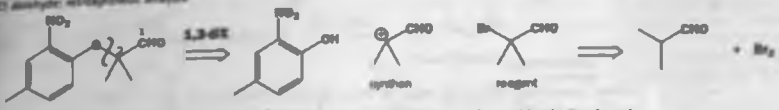
nafimidone: retrosynthetic analysis



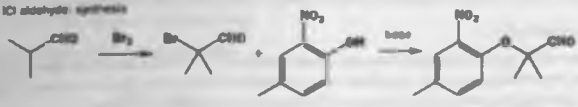
The α-chloroketone is simply made by chlorination, and substitution is rapid and efficient even with the weakly basic (Chapter 8) heterocyclic amine.



The aldehyde below was needed by ICI when they were developing a thromboxane antagonist. Two-group disconnection gives a 2-halo-aldehyde that can be made from isobutyraldehyde.



The synthesis requires a normal bromination of a carbonyl compound in acid solution but the next step is a most unusual S_N2 reaction at a *tertiary* centre. This happens because of the activation by the aldehyde group (Chapter 17) and is further evidence that the functional groups must be thought of as working together in this type of synthesis.

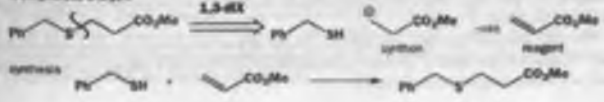


1,3-Disconnections

In Chapter 10 you saw how α,β-unsaturated carbonyl compounds undergo conjugate additions—reactions like this.

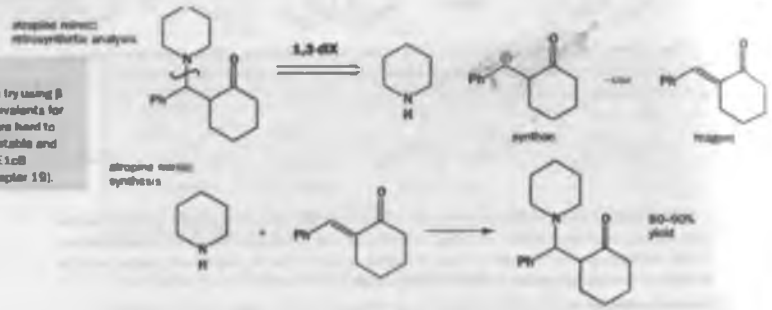
Two-group 1,3-disconnections are therefore possible because they correspond to this forward reaction. These Michael acceptors have an electrophilic site two atoms away from the carbonyl group, and are therefore the reagents corresponding to this synthon.

This type of reaction is available only when the alkene is conjugated to an electron-withdrawing group—usually carbonyl (Chapter 10) but it can be nitro, cyanide, etc. (Chapter 23). This disconnection is available only at this oxidation level unlike the last. We can do a two-group 1,3-disconnection on this sulfide, for example.



Remember that not all nucleophiles will successfully undergo Michael additions—you must bear this in mind when making a 1,3-disconnection of this type. Most reliable are those based on nitrogen, sulfur, and oxygen (Chapter 10).

Our second example is an amine structurally similar to the 'deadly nightshade' drug, atropine, which has the ability to calm involuntary muscle movements. There is a 1,3-relationship between the amine and ketone functional groups, and 1,3-disconnection takes us back to piperidine and an unsaturated ketone.



To summarize...

Before we leave C–X disconnections and go on to look at C–C disconnections we should just review some important points. We suggested three guidelines for choosing disconnections and now that you have met the principle of two-group disconnections, we can add a fourth:

● Guidelines for good disconnections

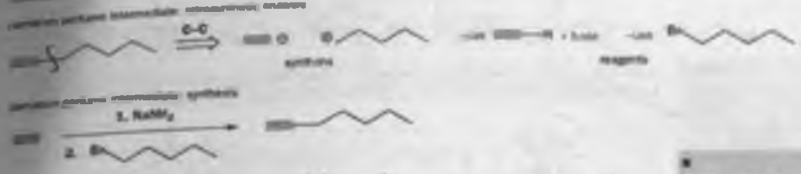
1. **Disconnections must correspond to known, reliable reactions**
2. **For compounds consisting of two parts joined by a heteroatom, disconnect next to the heteroatom**
3. **Consider alternative disconnections and choose routes that avoid chemoselectivity problems—often this means disconnecting reactive groups first**
4. **Use two-group disconnections wherever possible**

Two-group disconnections reduce the complexity of a target molecule more efficiently than one-group disconnections, and you should always be on the look-out for them. You will meet more two-group disconnections in the next section, which deals with how to disconnect C–C bonds.

C–C disconnections

The disconnections we have made so far have all been of C–O, C–N, or C–S bonds, but, of course, the most important reactions in organic synthesis are those that form C–C bonds. We can analyse C–C disconnections in much the same way as we've analysed C–X disconnections. Consider, for example, how you might make this simple compound, which is an intermediate in the synthesis of a carnation perfume.

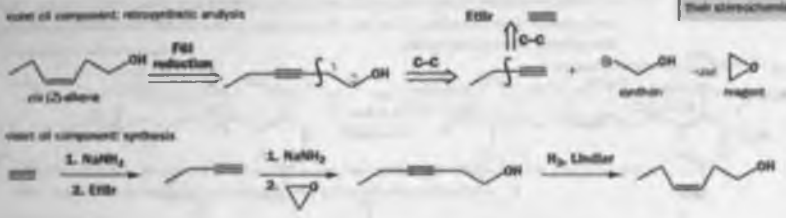
The only functional group is the triple bond, and we shall want to use the chemistry of alkynes to show us where to disconnect. You know that alkylation of alkynes is a reliable reaction, so a sensible disconnection is next to the triple bond.



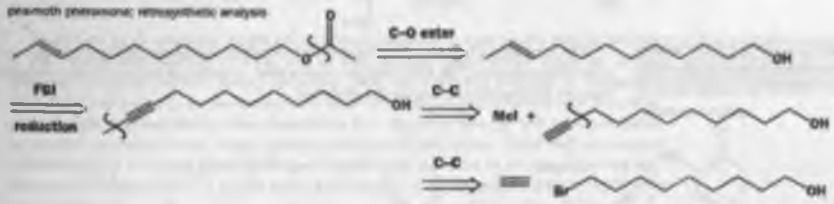
Alkynes are particularly valuable as synthetic intermediates because they can be reduced either to *cis* or to *trans* double bonds.

It's often a good idea to start retrosynthetic analysis of target molecules containing isolated double bonds by considering FGI to the alkyne because C–C disconnections can then become quite easy.

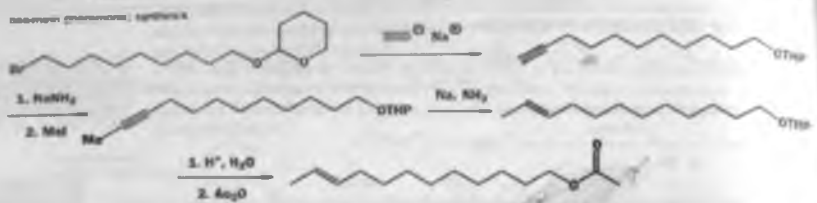
This *cis*-alkene is a component of violet oil, and is an intermediate in the synthesis of a violet oil component. FGI to the alkyne reveals two further disconnections that make use of alkyne alkylations. The reagent we need for the first of these is, of course, the epoxide as there is a 1,2-relationship between the OH group and the alkyne.



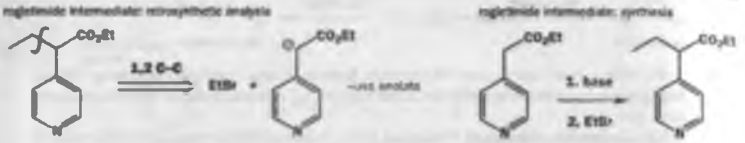
The next example is the pheromone of the pea-moth, and can be used to trap the insects (see the introduction to Chapter 24). After disconnecting the ester, FGI on the *trans* double bond gives an alkyne.



Disconnection on either side of the alkyne leads us back to a bromo-alcohol alkylating agent. In the synthesis of the pheromone, it turned out to be best if the hydroxyl group was protected as its THP ether. You should be able to think of other alkylation-type reactions that you have met that proceed reliably and therefore provide a good basis for a disconnection—the alkylation of enolates of esters or ketones, for example (Chapter 26).

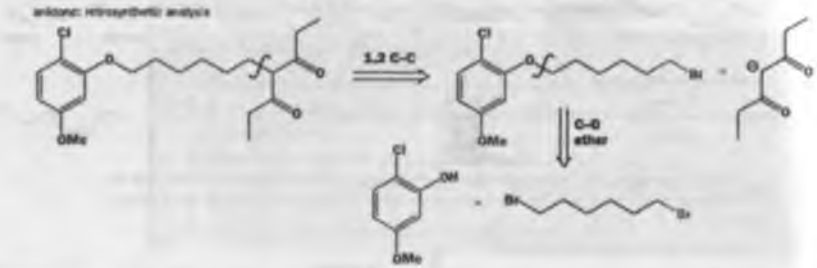


This next ester was needed for a synthesis of the sedative roglutimide (see later for the full synthesis). The ethyl group is disconnected because it can be readily introduced by alkylation of the ester enolate.



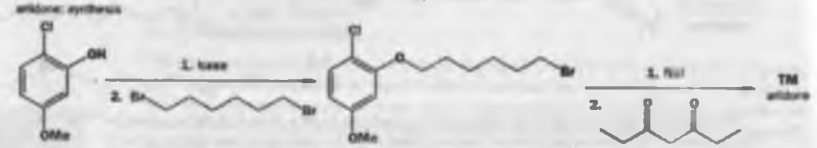
We have labelled the disconnection '1,2 C–C' because the new C–C bond is forming two atoms away from the carbonyl group. To spot disconnections of this sort, you need to look for alkyl groups in this 2-position.

Aridone is a drug that prevents polio and herpes simplex viruses from 'unwrapping' their DNA, and renders them harmless. It has just the structural characteristic you should be looking for: a branch next to a carbonyl group.



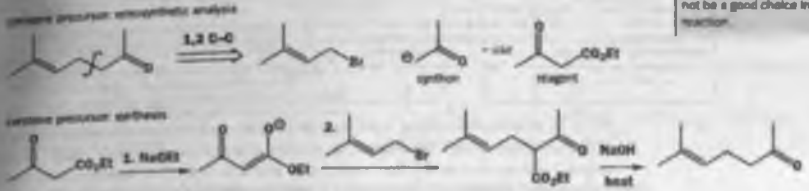
Look back to Chapter 26 if you don't understand why.

With two carbonyl groups, the alkylation should be particularly straightforward since we can use a base like methoxide. The ether disconnection is then immediately obvious. In the synthesis of aridone the alkyl iodide was used for the alkylation.

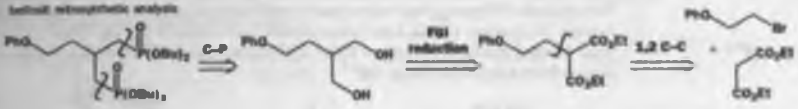


We introduced the chemistry of malonate esters in Chapters 21 and 26 as a useful way of controlling the enolization of carbonyl compounds. Alkylation followed by decarboxylation means that we can treat acetoacetate and malonate esters as equivalent for these synthons.

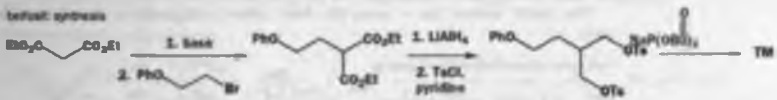
This unsaturated ketone is an important industrial precursor to β-carotene, vitamin A, and other similar molecules. Disconnection using the carbonyl group gives a synthon for which a good reagent will be acetoacetate.



This organophosphorus compound, belfosil, is a Ca^{2+} channel blocker. You haven't met many phosphorus compounds yet, but you should be able to reason that a good disconnection will be the C–P bond by analogy with the sulfides you met earlier in the chapter. We could use bromide as a leaving group, but alkyl bromides are inconvenient to disconnect further, so we go back to the more versatile diol—in the forward synthesis we shall need a way of making the OH groups into good leaving groups. There is still no obvious disconnection of the diol, but FGI to the ester oxidation level reveals a malonate derivative.



In the synthesis, the diol was converted to the bis-tosylate (see Chapter 17 if you've forgotten about tosylates and mesylates) and reacted with a phosphorus nucleophile.



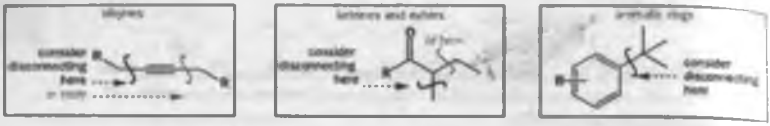
Notice how we disconnected the phosphorus-based functional groups straight back to alcohols in the retrosynthetic analysis, and not, say, to alkyl halides. Oxygen-based functional groups (alcohols, aldehydes, ketones, esters, and acids) have one important property in common—versatility. They are easily converted into each other by oxidation and reduction, and into other groups by substitution. What is more, many of the C–C disconnections you will meet correspond to reactions of oxygen-based groups, and particularly carbonyl groups. Faced with an unusual functional group in a target molecule the best thing to do is convert it to an oxygen-based group at the same oxidation level—it usually makes subsequent C–C disconnections simpler. So we add a new guideline.

● Guideline 5

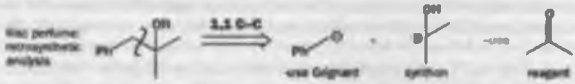
Convert to oxygen-based functional groups to facilitate C–C disconnections

Looking for 1,2 C–C disconnections

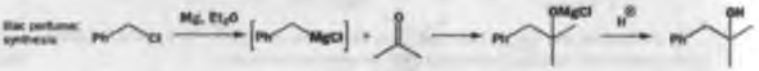
In each of the cases you have met so far, we have used a functional group present in the molecule to help us to disconnect the C–C bond using a 1,2 C–C disconnection. You can look for 1,2 C–C disconnections in alkynes, carbonyl compounds, and alkylated aromatic rings. And, if the target isn't a carbonyl compound, consider what would be possible if functional groups such as hydroxyl groups were converted to carbonyl groups (just as we did with belfosdil).



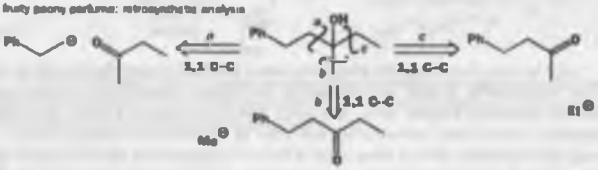
All of these disconnections relied on the reaction of a carbon electrophile with a nucleophilic functional group. The alternative, reaction of a carbon nucleophile (such as a Grignard reagent) with an electrophilic functional group, allows us to do C–C disconnections on alcohols. For example, this compound, which has a fragrance reminiscent of lilac, is a useful perfume for use in soap because (unlike many other perfumes that are aldehydes or ketones) it is stable to alkali.



We look to the one functional group, the hydroxyl, to tell us where to disconnect, and disconnection next to the OH group gives two synthons for which sensible reagents are a Grignard reagent and acetone. The perfume is made from benzyl chloride and acetone in this way. Notice that we label these disconnections 1,1 C–C because the bond being disconnected is attached to the same carbon atom as the hydroxyl functional group.



This similar alcohol has a 'peony-like fruity odour' and could be disconnected in three ways.



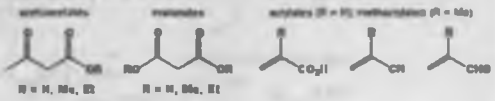
■ The synthesis of this starting material involves an aldol reaction between acetone and benzaldehyde of the sort discussed in Chapter 27 followed by hydrogenation of the double bond.

Disconnection (c) leads back to a ketone, which is cheaply made starting from acetone and benzaldehyde, and this was the route that was chosen for the synthesis.

Available starting materials

Although any of the above routes to the fruity peony perfume ester give an acceptable synthesis, the key factor in choosing route (c) was the ease of synthesis of the starting materials from available compounds. But how can you know which materials will be available? So far in this chapter we have avoided this question, and often our retrosynthetic analyses have been incomplete because the suggested starting materials must themselves be synthesized in the laboratory. From now on, though, we will take every analysis back to available starting materials to help you get a feel for what is, and is not, available.

The only way to be absolutely sure what you can buy is to look up a compound in a supplier's catalogue, and this is what a chemist would do when assessing possible alternative synthetic routes. A good rule of thumb is that **compounds with up to about six carbon atoms and with one functional** group (alcohol, aldehyde, ketone, acid, amine, double bond, or alkyl halide) are usually available. This is less true for heavily branched compounds, but most straight-chain compounds with these functional groups are available up to eight or more carbon atoms. Cyclic compounds with one functional group from five- to eight-membered are also available. Of course, many other compounds are available too, including some difunctional compounds. Here are a few of them:

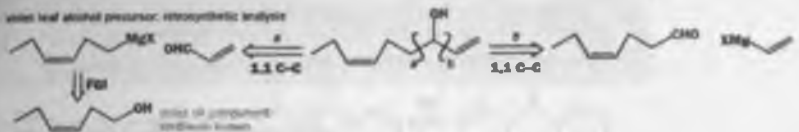


You will soon start to appreciate what is available as you see which compounds we use as starting materials. Supplier's catalogues are available free for the asking and make quite useful bedtime reading. You could consider getting one. In addition, on-line and CD catalogues are available in most chemistry departments and can be searched by structure.

Some starting materials become available because other chemists have made them

Our next target is an allylic alcohol that produces the perfumery compound 'violet leaf alcohol' by a rearrangement step. Two disconnections are possible, but one of them, (a), leads back to a Grignard reagent that can be made by FGI on the violet oil component whose synthesis we described on p. 000.

violet leaf alcohol precursor: retrosynthetic analysis

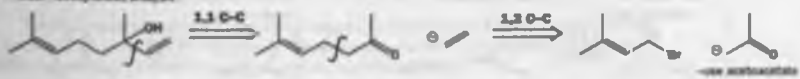


The synthesis was best carried out using the alkylmagnesium iodide and the iodide was made from the alcohol via the chloride.

violet leaf alcohol precursor: synthesis

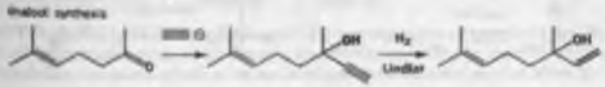
Linalool is another perfumery compound. Disconnection of the vinyl group leads to the ketone you met on p. 000, best made by alkylation of acetoacetate, an acetone enolate equivalent.

linalool: retrosynthetic analysis



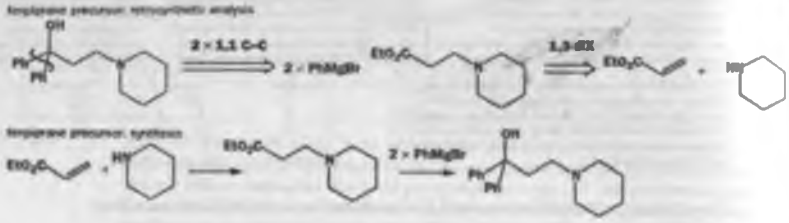
On an industrial scale it was best to introduce the vinyl anion synthon as acetylene and then hydrogenate the alkyne. The unsaturated ketone was chosen as the starting material because its synthesis was already known.

linalool: synthesis



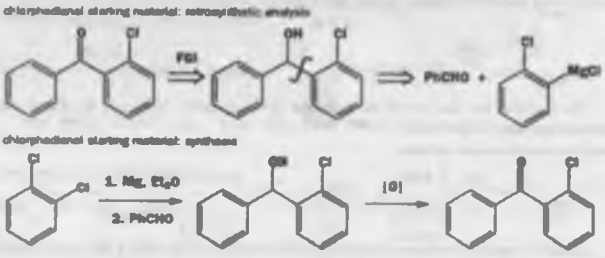
Double disconnections can be a short cut

Tertiary alcohols with two identical groups next to the hydroxyl group are often made by attack of two equivalents of a Grignard reagent on an ester. The synthesis of the antihistamine compound fenpipramine provides an example: the tertiary alcohol is a precursor to the drug and can be disconnected to ester + Grignard reagent because of the two Ph groups. The ester required has a 1,3 functional group relationship, and can be disconnected to amine plus Michael acceptor.

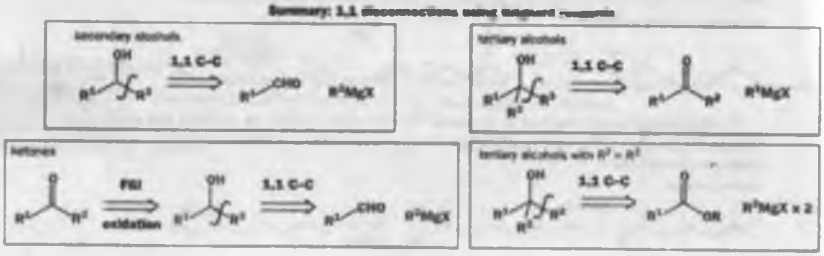


The fact that Grignard reagents add twice to esters means that disconnection of a *ketone* in this way is often not reliable. We talked about a few ways of doing this type of reaction in Chapter 12.

An alternative is to first convert to the alcohol oxidation level, then disconnect. This was the method chosen for this starting material for the synthesis of chlorphedianol.



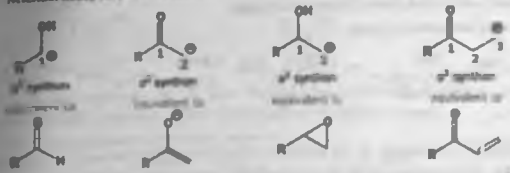
Summary: 1,1 disconnections using Grignard reagents



Donor and acceptor synthons

You've now met a variety of synthons and it's useful to be able to classify them as donor or acceptor synthons. We call a negatively polarized synthon a **donor** synthon and give it the symbol 'd'. Positively polarized synthons are called acceptor synthons and are given the symbol 'a'.

We can classify the synthons further according to where the functional group is in relation to the reactive site. The first synthon in the diagram below, which corresponds to an aldehyde, we call an a^1 synthon, because it is an acceptor that carries a functional group on the same carbon as its reactive centre. The second is a d^2 synthon because it is a donor whose reacting site is in the 2-position relative to the carbonyl group. Earlier you met two other types of synthon, corresponding to epoxide and Michael acceptor, and we can now classify these as a^2 and a^3 synthons.



This terminology is useful because it reduces synthons to the bare essentials: what polarity they are and where the polarity is sited. The actual functional group they carry is, as you now appreciate, less important because FGI will usually allow us to turn one FG into another.

● Synthons are classified as a (acceptor) or d (donor)

- A number shows the position of the acceptor or donor site relative to a functional group
- An a^1 synthon is a carbonyl compound and a d^2 synthon an enolate

Two-group C–C disconnections

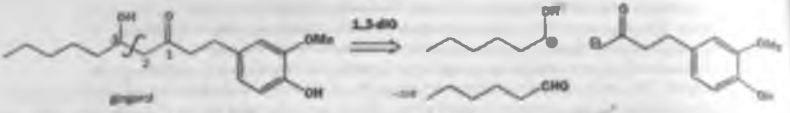
1,3-Difunctionalized compounds

It's not only Grignard reagents that will react with aldehydes or ketones to make alcohols: enolates will too—we spent Chapters 27 and 28 discussing this reaction, the aldol reaction, its variants, and ways to control it.

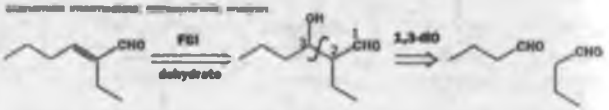
The aldol reaction is extremely important in organic synthesis because it makes compounds with two functional groups in a 1,3-relationship. Whenever you spot this 1,3-relationship in a target molecule—think aldol! In disconnection terms we can represent it like this.

We call this disconnection a **two-group C–C disconnection**, because we are using the OH and the C=O groups together to guide our disconnection. The disconnection gives us a d^2 synthon for which we shall use an enolate equivalent, and an a^1 synthon, for which we shall use an aldehyde or a ketone.

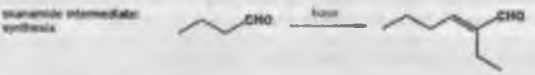
Chapter 27 has many examples and perhaps gingerol is the best. As soon as you see the 1,3-relationship, the disconnection should be obvious.



The β-hydroxy carbonyl products of aldol reactions are often very easily dehydrated to give α,β-unsaturated carbonyl compounds and, if you spot an α,β-unsaturated carbonyl group in the molecule, you should aim to make it by an aldol reaction. You will first need to do an FGI to the β-hydroxy carbonyl compound, then disconnect as before.

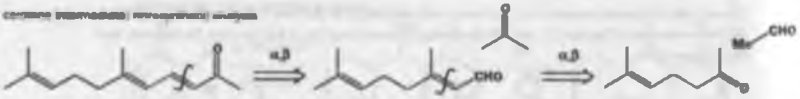


This aldehyde is an intermediate in the synthesis of the tranquillizer oxanamide. Because both components of the aldol reaction are the same, no special precautions need to be taken to prevent side-reactions occurring. In the synthesis, the dehydration happened spontaneously.



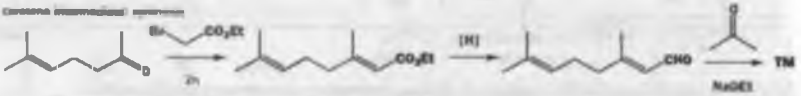
Because this disconnection of unsaturated carbonyl compounds is so common, it's often written using a shorthand expression.

The next compound was needed for an early synthesis of carotene. Again, it's an α,β-unsaturated ketone so we can disconnect using the same 'α,β' disconnection.



The aldehyde generated by this first disconnection is also α,β-unsaturated, so we can do another α,β disconnection, back to a ketone whose synthesis we have already discussed (p. 000).

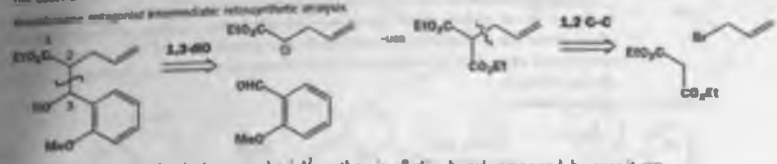
An aldol reaction using the enolate of acetaldehyde and requiring it to react with a ketone is doomed to failure: acetaldehyde itself is far too good an electrophile. In the forward synthesis, therefore, this first step was carried out at the ester oxidation level (using a Reformatsky reaction), and the ester was subsequently converted to the aldehyde by a reduction of the kind discussed in Chapter 24.



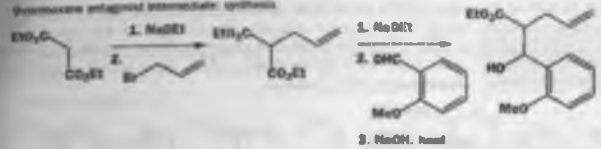
There was no problem with selectivity in the second aldol reaction because the aldehyde is not enolizable. The Reformatsky reaction in this sequence illustrates the fact that, of course, aldol-type

reactions happen at the ester oxidation level as well, and you should equally look to disconnect β-hydroxy or α,β-unsaturated esters, acids, or nitriles in this way. Just remember to look for 1,3-relationships, convert the functional groups to oxygen-based ones, and disconnect them to d^1 plus a^1 synthons.

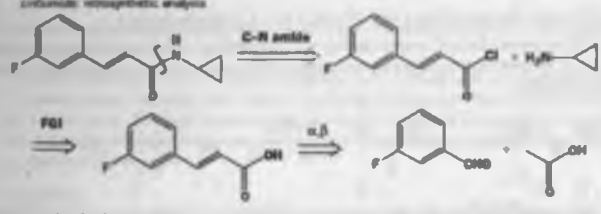
The next compound was needed by ICI when chemists there were developing a thromboxane antagonist to inhibit blood clot formation. You can immediately spot the 1,3-relationship between the ester and the hydroxyl group, so 1,3-diO disconnection is called for.



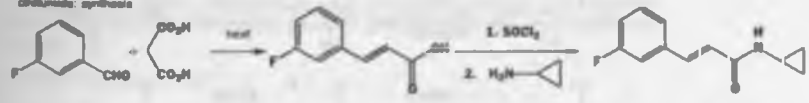
A good equivalent for the 'ester enolate' d^2 synthon is a β-dicarbonyl compound, because it can easily be disconnected to diethyl malonate and an alkylating agent.



This unsaturated amide is known as cinfluminde and is a muscle relaxant. Disconnection of the amide gives an acid chloride that we can make by FGI from the acid. You should then spot the α,β-unsaturated carbonyl disconnection, a masked 1,3-diO disconnection, back to *m*-fluorobenzaldehyde.

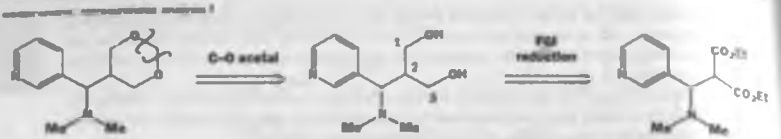


Again, the forward reaction was best done using malonate chemistry but the variant with malonic acid was used. The cyclopropyl amine unit (here as an amide) is present in many biologically active compounds and the free amine is available.

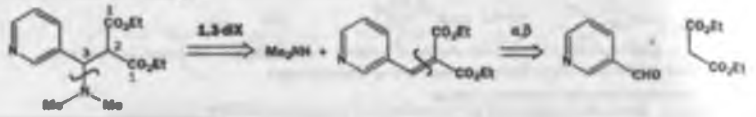


Functional group relationships may be concealed by protection

The analgesic dextpicomine is a more difficult problem than those you have seen so far. At first sight it has no useful disconnections especially as there are no carbonyl groups. However, removal of the acetal reveals a 1,3-diol that could be formed by reduction of a much more promising diester.

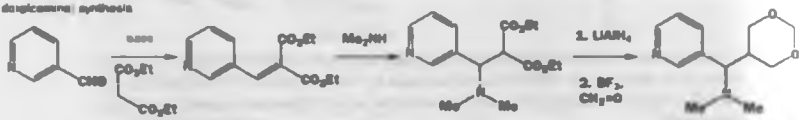


The diester has a 1,3-diCO relationship and could be disconnected but we have in mind using malonate so we would rather disconnect the alternative 3-amino carbonyl compound (the Me_2N group has a 1,3-relationship with both ester groups) by a 1,3-diX disconnection giving an unsaturated ester. This α,β-unsaturated ester disconnects nicely to a heterocyclic aldehyde and diethyl malonate.



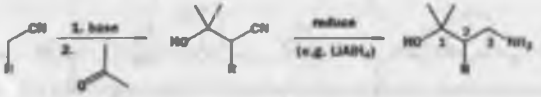
▶
It is interesting to note that acetals, usually employed for protection, can be useful in their own right as in this drug.

The synthesis is shorter than the retrosynthetic analysis and involves only three steps. Good retrosynthetic analysis, using two-group disconnections, should lead to short syntheses.

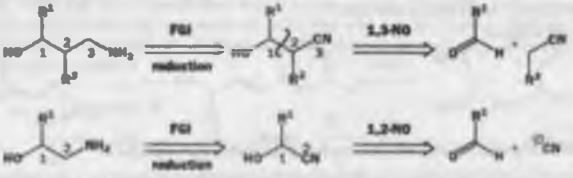


Aldol-style disconnections with N and O in a 1,3-relationship: I

Another important class of compounds that undergo aldol-type additions to aldehydes and ketones is nitriles. Because nitriles can be reduced to amines, this reaction provides another useful route to 3-amino-alcohols.

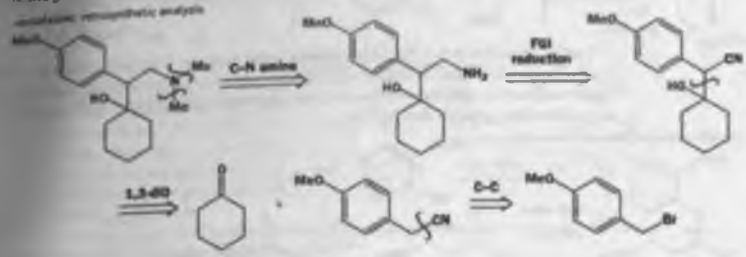


This reaction, coupled with the reduction of cyanohydrins (Chapter 6), means that compounds with either a 1,3- or a 1,2-relationship between N and O can be made from cyanides.

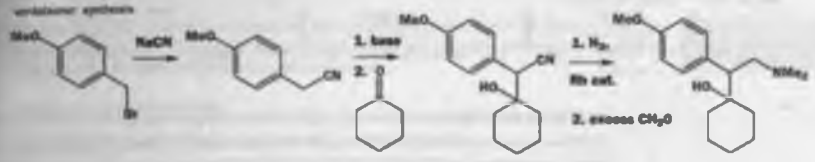


Venlafaxine is an antidepressant and, like many neuroactive agents, it is an amino-alcohol. In this case, the two functional groups are 1,3-related, so we aim to use a 1,3-diX disconnection. Usually,

you would convert the amine to an alcohol to simplify the disconnection, but by spotting the opportunity for using a nitrile you can avoid the need for this extra step. A preliminary removal of the two *N*-Me groups is necessary.

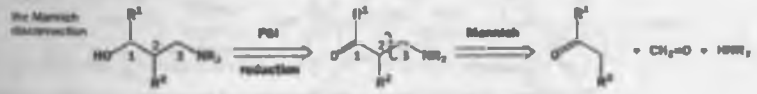


In the forward synthesis, it turned out that the nitrile reduction was best done using hydrogen and a metal (Rh) catalyst. The final methylation of the primary amine had to be done via the imine and iminium ion (see Chapter 24) to prevent further unwanted alkylations. The reagent was an excess of formaldehyde (methanal $CH_2{=}O$). Problem 22 offers a chance to try this mechanism.

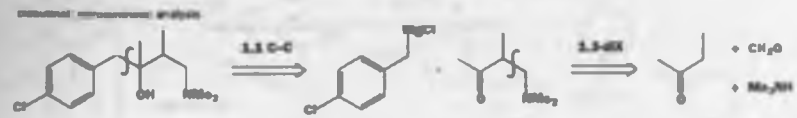


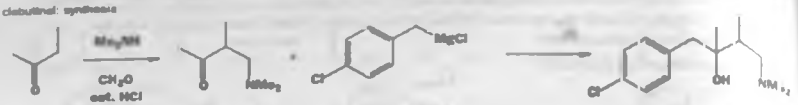
Aldol-style disconnections with N and O in a 1,3-relationship: II—the Mannich reaction

Another important reaction for making amines with a 1,3-relationship to a carbonyl group is the Mannich reaction. You met this in Chapter 27 as a way of doing otherwise unreliable aldol additions to formaldehyde. Because the amine is introduced directly and not by reduction of a nitrile, it can have two alkyl groups from the start. Compare this scheme with the one above using a nitrile group as the source of the amine.

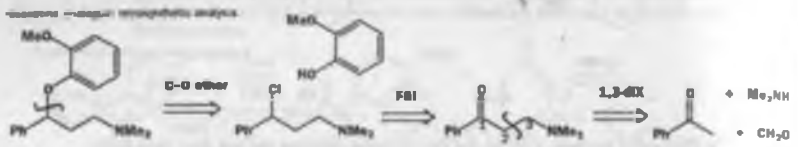


Our example is clobutinol—an antitussive (cough medicine). A preliminary 1,1 C–C disconnection of the tertiary alcohol is necessary to provide a 3-amino ketone that we can make by a Mannich reaction.

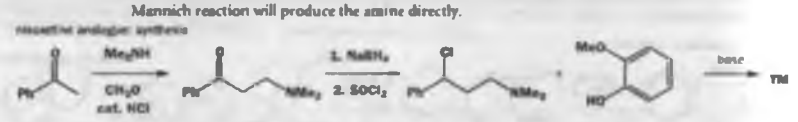




You can immediately spot the 1,3 relationship in this analogue of the antidepressant, nisoxetine, but, unfortunately, it can't be disconnected straight back to an amino-alcohol because that would require nucleophilic substitution on an electron-rich aromatic ring. We have to disconnect the ether on the other side, giving an alkyl chloride.

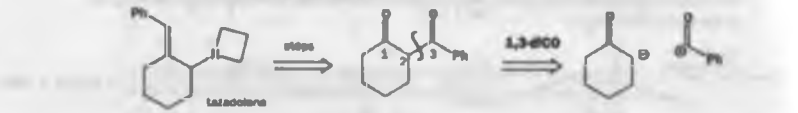


Using guideline 5 (p. 000) we want to convert the halide to an oxygen-based group, and a sensible solution is to choose the ketone. 1,3-Disconnection of this compound corresponds to a Mannich reaction. This is another case where FGI of the amine to an alcohol is not desirable, because the Mannich reaction will produce the amine directly.

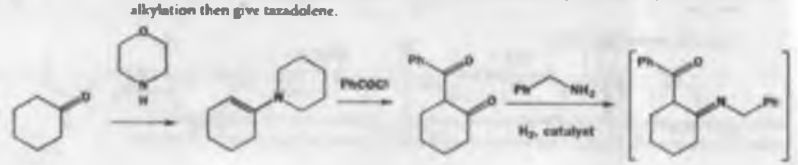


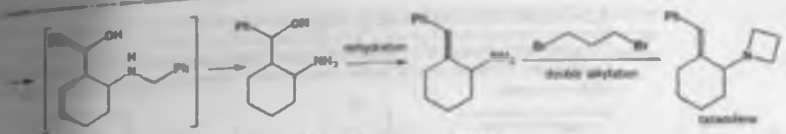
The Claisen ester disconnection: a 1,3-diO relationship needing two carbonyl groups

1,3-Diketones can be disconnected in a similar way: this time the disconnection corresponds to a Claisen condensation, but it's still 1,3-diO, and again you need to look out for the 1,3 relationship. The synthons are still d^2 plus a^1 but the a^1 synthon is used at the ester oxidation level. This diketone is the starting material for the synthesis of the antidepressant tazadolene. With 1,3-diketones, there's always a choice where to disconnect, and you should be guided by which disconnection (1) corresponds to the most reliable reaction and (2) gives the simplest starting materials. In this case, it's much better to disconnect back to cyclohexanone.

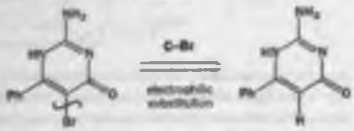


The synthesis is interesting because, after the acylation of the enamine, the amino group is introduced by a clever reductive amination with benzylamine ($PhCH_2NH_2$) that forms the C–N bond, reduces the ketone, and hydrogenolyses the N–benzyl bond (Chapter 24). Dehydration and double alkylation then give tazadolene.





The 1,3-dicarbonyl relationship may not be revealed in the target molecule and C–heteroatom disconnections or FGIs may be needed before the 1,3-diO C–C disconnection. Bropirimine is a bromine-containing antiviral and anticancer drug. The bromine atom can be put in last of all by electrophilic bromination.



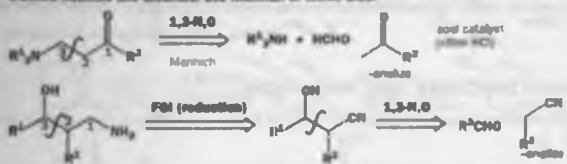
Disconnection of two C–N bonds removes a molecule of guanidine and reveals a 1,3-dicarbonyl relationship with a straightforward disconnection.

In the event, the 1,3-dicarbonyl was made using malonate chemistry with an unusual twist: the lithium derivative gave *C*-acylation in good yield. Simply refluxing the product with guanidine formed the heterocycle and bromination gave bropirimine.

Summary: 1,3-diO disconnections

3-hydroxy carbonyls and α,β-unsaturated carbonyls: use the aldol reaction

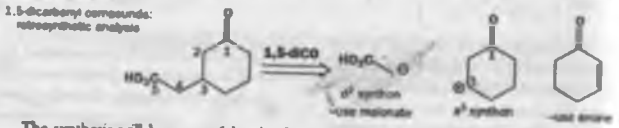
3-amino ketones and alcohols: use Mannich or nitrile aldol



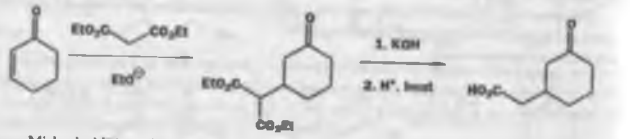
1,3-diketones: use the Claisen condensation

1,5-Related functional groups

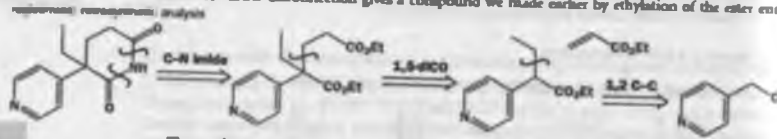
This compound has a 1,5 rather than a 1,3 relationship between two carbonyl groups. Disconnection to give an enolate as one reagent therefore requires an a^3 rather than an a^1 synthon: in other words a Michael acceptor.



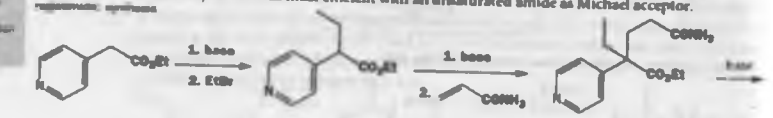
The synthesis will be successful only if (1) the right reagent enolizes and (2) the nucleophile undergoes conjugate (and not direct 1,2-) addition to the unsaturated carbonyl compound (Chapter 29). Malonate derivatives enolize easily and do Michael additions and are therefore a good choice for this type of reaction.



Michael addition of enolates to α,β-unsaturated compounds is a good way of making 1,5-difunctionalized compounds, and you should look for these 1,5-relationships in target molecules with a view to making them in this way. Our example is reglemitide, a sedative that can be disconnected to a 1,5-diester. Further 1,5-diCO disconnection gives a compound we made earlier by ethylation of the ester enolate.

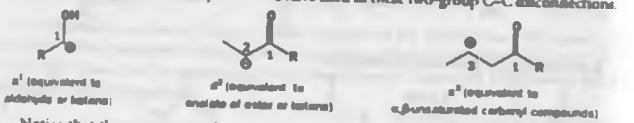


The synthesis was most efficient with an unsaturated amide as Michael acceptor.



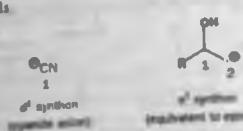
'Natural reactivity' and 'umpolung'

Cast your mind back over the synthons we have used in these two-group C–C disconnections.



Notice that the acceptor synthons have odd numbers; the donor synthon has an even number. donor and acceptor properties alternate along the chain as we move away from a carbonyl group. This 'natural reactivity' of carbonyl compounds explains why we find it easy to discuss ways of making 1,3- and 1,5-difunctionalized compounds, because they arise from $a^1 + d^2$ and from $a^3 + d^2$. Reagents corresponding to synthons like d^1 or a^2 are rarer, and therefore compounds with 1,2- or 1,4- related functional groups require special consideration retrosynthetically.

You have in fact met one example of each of the 'unnatural' synthons with a^2 and d^1 reactivity. Such synthons are given the German name *Umpolung*, meaning 'inverse polarity' because their natural reactivity is reversed, and umpolung reagents are the key to the synthesis of 1,2- and 1,4-difunctionalized compounds.

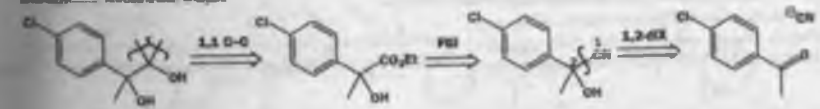


We shall finish this chapter by looking at disconnections of 1,2- and 1,4-difunctionalized compounds because these require us to use reagents with umpolung equivalent to d^1, d^3, a^2, and a^4 synthons. There are very many reagents for these synthons—if you are interested to learn more, consult a specialized book.

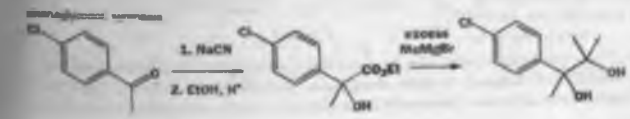
1,2-Difunctional compounds

You met ways of making 1,2-difunctionalized compounds when we first talked about two-group disconnections, and we used an epoxide as an a^2 synthon. Epoxides are, of course, also 1,2-functionalized, and in fact this is often the key to making 1,2-functionalized compounds: use something with the 1,2 relationship already in place. You saw lots of examples of this type of strategy earlier in this chapter. Perhaps the simplest approach is electrophilic addition to alkenes. If the alkene is made by a Wittig reaction, the disconnection is (eventually) between the two functionalized carbon atoms in the target molecule. This example shows dihydroxylation as the electrophilic addition but there is also epoxidation, bromination, and bromination in water to give Br and OH as the functional groups.

A normal C–C disconnection is also a possibility, but disconnection to the 'natural' a^1 synthon and the umpolung d^1 is necessary. One very useful umpolung reagent is cyanide, and you can see it in action in this synthesis of the tranquillizer phenaglycodol. The tertiary alcohol with two R groups the name should prompt you to think of doing a double Grignard addition to an ester. FGI then reveals the nitrile functional group necessary for a 1,2-diX disconnection to cyanide plus ketone.

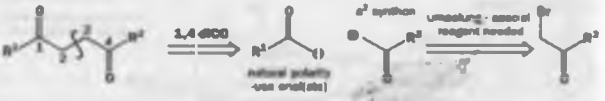


The starting material is obviously available by a Friedel–Crafts acylation of chlorobenzene and the rest of the synthesis follows. Note that the nitrile can be converted directly into the ester with acidic ethanol and that an excess of Grignard reagent is needed because the free OH group destroys some of it.

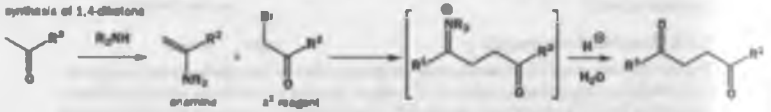


1,4-Difunctional compounds

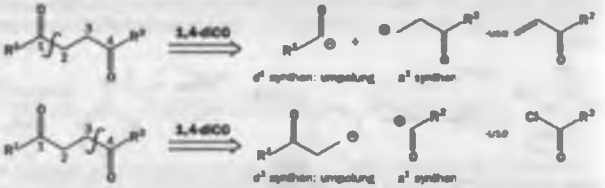
There are more possibilities here and we shall finish this chapter with a brief analysis of them to show you how much of this subject lies beyond what we can do in this book. If we start with a 1,4-dicarbonyl compound we might consider first disconnection of the central bond.



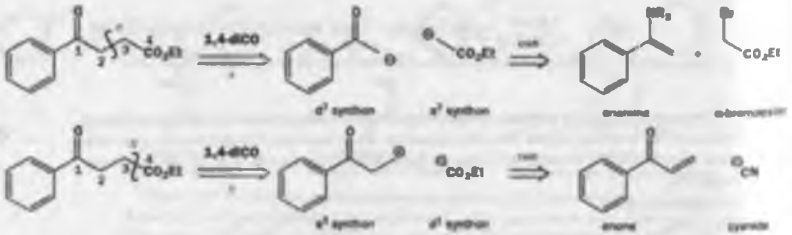
We can use an enolate for one reagent but the other will have to have umpolung. This is not a very serious kind of umpolung as an α-bromo carbonyl compound will do the job nicely if we select our enol(ate) equivalent carefully. In Chapter 26 we suggested enamines for this job. The synthesis becomes:



If we attempt the disconnection of one of the other bonds, two possibilities are available because the two fragments are different. We can use either a $d^1 + a^3$ strategy or an $a^1 + d^3$ strategy. In each case we have one natural synthon and one with umpolung.

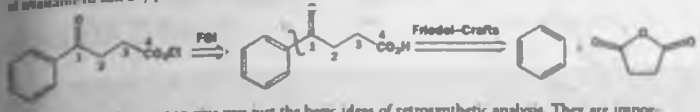


These strategies are more difficult to realize with the reagents you have met so far but conjugate addition of a cyanide to an unsaturated carbonyl compound would be an example of the $d^1 + a^3$ strategy. We have included these to try to convince you that there is no escape from umpolung in the synthesis of a 1,4-dicarbonyl compound. If you were making this keto-ester you would have to understand two of the three strategies.



There is one way to avoid umpolung and that is to make the disconnection outside the 1,4 relationship. As it happens, we have already seen this strategy in action (p. 000). It involves a Friedel–Crafts acylation of benzene (Chapter 22) with a cyclic anhydride and leads directly to this

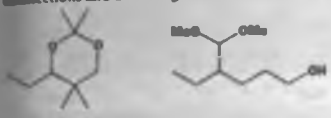
product by quite a short route. This strategy is available only if there happens to be a starting material available to suit any particular case.



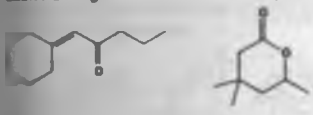
This chapter is meant to give you just the basic ideas of retrosynthetic analysis. They are important because they reinforce the concept that the combination of electrophile and nucleophile is the basis for the understanding of organic reactions. Synthesis and reactions are two sides of the same coin. From now on we shall use the methods introduced in this chapter when we think that they will help you to develop your understanding.

Problems

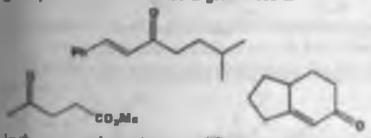
1. Suggest ways to make these two compounds. Show your disconnections and don't forget to number the relationships.



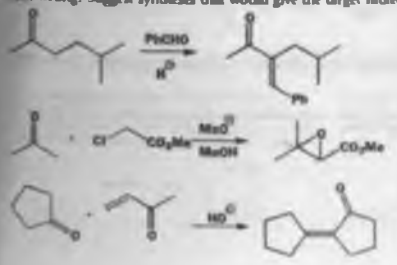
2. Propose syntheses of these two compounds, explaining your choice of reagents and how the necessary selectivity is achieved.



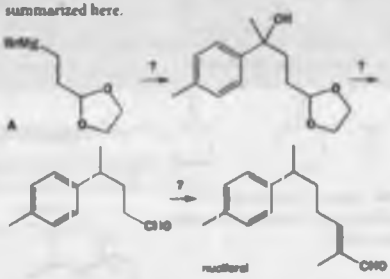
3. The reactions to be discussed in this problem were planned to give syntheses of these three target molecules.



In the event, each reaction gave a different product shown below. What went wrong? Suggest syntheses that would give the target molecules.



4. The natural product nuciferal was synthesized by the route summarized here.



(a) Suggest a synthesis of the starting material A.

(b) Suggest reagents for each step.

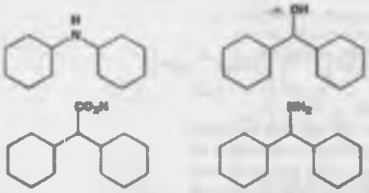
(c) Draw out the retrosynthetic analysis giving the disconnections that you consider the planners had in mind and label them suitably.

d) What synthon does the starting material A represent?

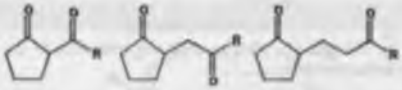
5. A synthesis of the enantiomerically pure ant pheromone is required. One suitable starting material might be the enantiomerically pure alkyl bromide shown. Suggest a synthesis of the pheromone based on this or another starting material.

6. Show how the relationship between the alkene and the carboxylic acid influences your suggestions for a synthesis of these unsaturated acids.

7. How would you make these compounds?

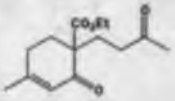


8. Show how the relationship between the two functional groups influences your suggestions for a synthesis of these diketones.

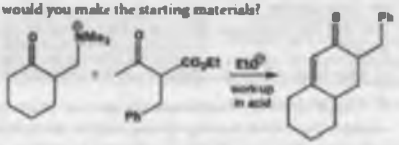


9. Suggest syntheses for these compounds. (*Hint.* Look out for a 1,4-dicarbonyl intermediate.)

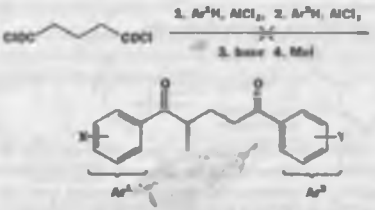
10. Suggest a synthesis of this diketo-ester from simple starting materials.



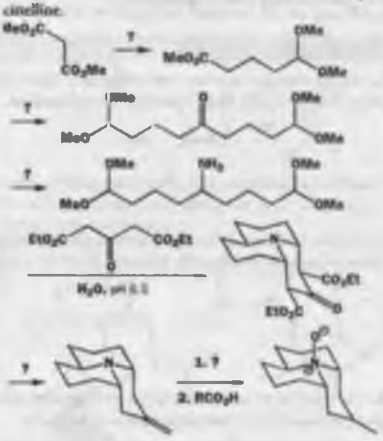
11. Explain what is happening in this reaction. Draw a scheme of retrosynthetic analysis corresponding to the synthesis. How would you make the starting materials?



12. These diketones with different aryl groups at the ends were needed for a photochemical experiment. The compounds could be prepared by successive Friedel–Crafts acylations with a dioic dichloride but the yields were poor. Why is this a bad method? Suggest a better synthesis.

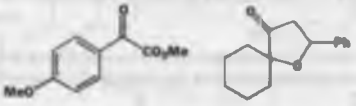


13. This is a synthesis for the ladybird defence compound coccinelline.



Suggest reagents for the reactions marked '?' (several steps may be needed) and give mechanisms for those that are not.

14. Suggest syntheses for these compounds.



Controlling the geometry of double bonds

31

Connections

Building on:

- Carbonyl chemistry ch8, ch12, & ch14
- Kinetic and thermodynamic control ch1.13
- Wittig reaction ch14
- Conjugate addition ch10
- Stereochemistry ch16
- Elimination reactions ch19
- Reduction ch24
- Chemistry of enol(ate)s ch28–ch29

Arriving at:

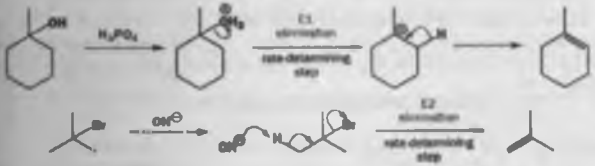
- What makes *E* and *Z* alkenes different?
- Why *E*/*Z* control matters
- Eliminations are not stereoselective
- Cyclic alkenes are *cis*
- Equilibration of alkenes gives *trans*
- Effects of light and how we see
- Julia olefination and the Wittig reaction at work
- Reliable reduction of alkynes

Looking forward to:

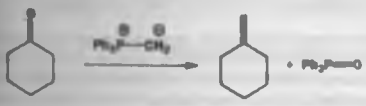
- Diastereoselectivity ch33–ch34
- Pericyclic reactions ch35–ch36
- Fragmentations ch38
- Radicals and carbenes ch39–ch40
- Main group chemistry ch46–ch47
- Asymmetric synthesis ch48
- Polymerization ch52
- Organic synthesis ch53

The properties of alkenes depend on their geometry

You have met alkenes participating in reactions in a number of chapters, but our discussion of how to *make* alkenes has so far been quite limited. Chapter 19 was about elimination reactions, and there you met E1 and E2 reactions.



In Chapter 14, you met an important reaction known as the Wittig reaction, which also forms alkenes.



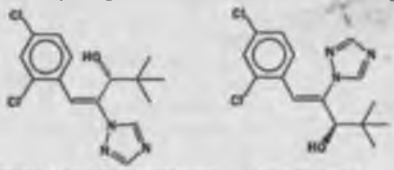
Different physical properties: maleate and fumarate

These two compounds, (*Z*)- and (*E*)-dimethyl but-2-enedioate, are commonly known as dimethyl maleate and dimethyl fumarate. They provide a telling example of how different the physical properties of geometrical isomers can be. Dimethyl maleate is a liquid with a boiling point of 202 °C (it melts at –19 °C), while dimethyl fumarate is a crystalline compound with a melting point of 103–104 °C.

In this chapter we shall talk about reactions similar to the ones on the previous page and we shall be interested in *how to control the geometry of double bonds*. Geometrical isomers of alkenes are different compounds with different physical, chemical, and biological properties. They are often hard to separate by chromatography or distillation, so it is important that chemists have methods for making them as single isomers.

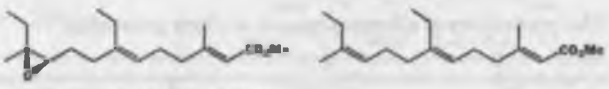
Why is double bond control important?

The activity of the fungicide diniconazole is dependent on the geometry of its double bond: the *E*-isomer disrupts fungal metabolism, while the *Z*-isomer is biologically inactive.



diniconazole: *E*-isomer has fungicidal activity *Z*-isomer is inactive

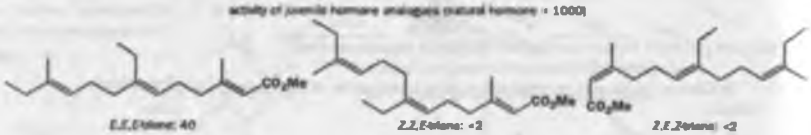
If insect pests can be prevented from maturing they fail to reproduce and can thus be brought under control. Juvenile insects control their development by means of a 'juvenile hormone', one of which is the monoepoxide of a triene.



isomeric juvenile hormone: activity = 1000 the *2, E, E*-triene: activity = 100

Synthetic analogues of this compound, such as the trienes, are also effective at arresting insect development, *providing that the double bond geometry is controlled*. The *Z,E,E* geometrical isomer of the triene is over twice as active as the *E,E,E*-isomer, and over 50 times as active as the *E,Z,Z*- or *Z,E,Z*-isomers.

activity of juvenile hormone analogues (natural hormone = 1000)

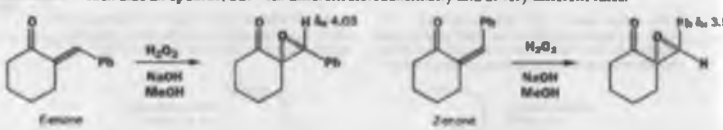


E,E,E-triene: 40 *Z,Z,E*-triene: <2 *Z,E,Z*-triene: <2

These are, of course, just two out of very many examples of compounds where the *E*- and *Z*-isomers have sufficiently different properties that it's no good having one when you need the other.

▶ We shall see later how to make these isomers.

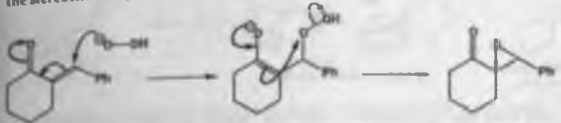
Chemical reactions on *E*- and *Z*-isomers usually give the same type of product, though often with different stereochemistry. The two geometrical isomers may also react at very different rates. For example, the reaction of these conjugated *E*- and *Z*-enones with alkaline hydrogen peroxide gives in each case an epoxide, but with different stereochemistry and at very different rates.



E-enone *Z*-enone

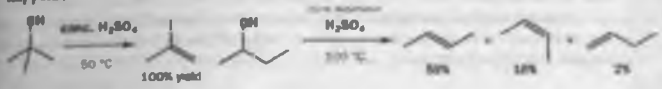
Epoxidation of the *E*-enone is complete in 2 hours and the epoxide can be isolated in 78% yield. The reaction on the *Z*-enone is very slow—only 50% is converted to the epoxide under the same

conditions in 1 week. The mechanism involves conjugate addition and ring closure with cleavage of the weak O–O bond (Chapter 23). The closure of the three-membered ring is fast enough to preserve the stereochemistry of the intermediate enolate.



Elimination reactions are often unselective

You saw in Chapter 19 that elimination reactions can be used to make alkenes from alcohols using acid or from alkyl halides using base. The acid-catalysed dehydration of tertiary butanol works well because the double bond has no choice about where to form. But the same reaction on 2-butanol is quite unselective—as you would expect, the more substituted alkene is formed (almost solely, as it happens) but even then it's a mixture of geometrical isomers.



In Chapter 19 we explained why more substituted double bonds are formed preferentially (p. 000) and why *E*-alkenes are more stable than *Z*-alkenes (p. 000).

How, then, can we use elimination reactions to give single geometrical isomers? You have, in fact, already met one such reaction, on p. 000, and in this chapter we shall cover other reactions that do just this. These reactions fall into four main classes, and we shall look at each in turn before summarizing the most important methods at the end of the chapter.

Some people call geometrical isomers diastereoisomers, which they are in a sense: they are stereoisomers that are not mirror images. However, we shall avoid this usage in the chapter since for most chemists the word diastereoisomer carries implications of three-dimensional stereochemistry.

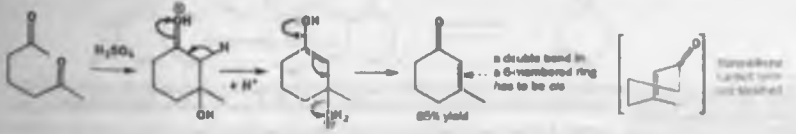
● Ways of making single geometrical isomers of double bonds

1. Only one geometrical isomer is possible (for example, a *cis* double bond in a six-membered ring)
2. The geometrical isomers are in equilibrium and the more stable (usually *E*) is formed
3. The reaction is stereoselective and the *E*-alkene is formed as the main product by kinetic control
4. The reaction is stereospecific and the alkene geometry depends on the stereochemistry of the starting materials and the mechanism of the reaction

In three- to seven-membered rings, only *cis*-alkenes are possible

These reactions fall into class (1) of the list above.

In Chapter 28 you met the Robinson annelation as a method of making cyclohexenones. The product of the elimination step contains a double bond, but there is no question about its geometry because in a six-membered ring only a *cis* double bond can exist—a *trans* one would be far too strained.

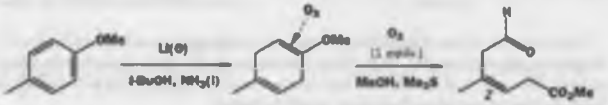


The same is true for three-, four-, five-, and seven-membered rings, though *trans*-cycloheptene has been observed fleetingly. An eight-membered ring, on the other hand, is just about large enough

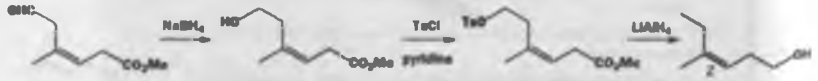
to accommodate a *trans* double bond, and *trans*-cyclooctene is a stable compound, though still less stable than *cis*-cyclooctene.

You may think that this method is rather too trivial to be called a method for controlling the geometry of double bonds, as it's only of any use for making cyclic alkenes. Well, chemists are more ingenious than that! Corey needed this *cis*-alkene as an intermediate in his synthesis of the juvenile hormone we talked about above (it forms the left-hand end of the structure as shown there).

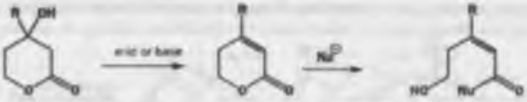
He realized that the *Z* double bond would be easy to make if he were to start with a cyclic molecule (in which only *cis* double bonds are possible) which could be ring-opened to the compound he needed. This is how he did it.



Birch reduction (Chapter 24) of a simple aromatic ether generated two *cis* double bonds (notice that one of these is actually *E*). The more reactive (because it is more electron-rich) of these reacts first with ozone to give an aldehyde-ester in which the *Z* geometry is preserved. $NaBH_4$ reduces the aldehyde group to a hydroxyl group, which needs to be got rid of: a good way to do this is to tosylate and reduce with $LiAlH_4$, which substitutes H for OTs. The $LiAlH_4$ also does the job of reducing the ester to an alcohol, giving the compound that Corey needed.



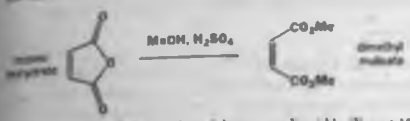
It is not necessary to have an all-carbon ring to preserve the *cis* geometry of a double bond. Lactones (cyclic esters) and cyclic anhydrides are useful too. A double bond in a five- or six-membered compound must have a *cis* configuration and compounds like these are readily made. Dehydration of this hydroxylactone can give only a *cis* double bond and ring-opening with a nucleophile (alcohol, hydroxide, amine) gives an open-chain compound also with a *cis* double bond. The next section starts with an anhydride example.



Equilibration of alkenes to the thermodynamically more stable isomer

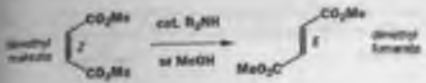
Acyclic *E*-alkenes are usually more stable than acyclic *Z*-alkenes because they are less sterically hindered. Yet *Z*-alkenes do not spontaneously convert to *E*-alkenes because the π bond prevents free rotation: the energy required to break the π bond is about 260 kJ mol^{-1} (rotation about a σ bond

requires about 10 kJ mol^{-1}). You may therefore find the following result surprising. Dimethyl maleate is easily made by refluxing maleic anhydride in methanol with an acid catalyst.



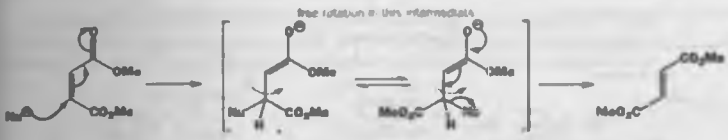
▶ This reaction is, of course, another simple example of the type we have just been discussing: the *Z*-alkene arises from the cyclic starting material.

If the product is isolated straight away, a liquid boiling at 199–202 °C is obtained. This is dimethyl maleate. However, if the product is left to stand, crystals of *dimethyl fumarate* (the *E*-isomer of dimethyl maleate) form. How has the geometry been inverted so easily?

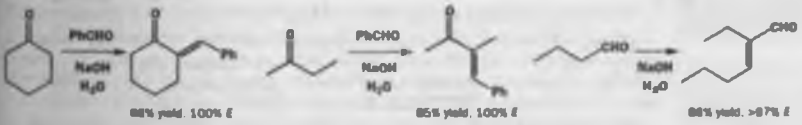


A clue is that the process is accelerated enormously by a trace of amine. Michael addition of this amine, or of methanol, or any other nucleophile, provides a chemical mechanism by which the π bond can be broken. There is free rotation in the intermediate, and re-elimination of the nucleophile can give either *E*- or *Z*-alkene. The greater stability and crystallinity of the *E*-alkene means that it dominates the equilibrium. Michael addition therefore provides a mechanism for the equilibration of *Z*-alkenes to *E*-alkenes.

▶ For this reason, it can be very difficult to make *Z* alkenes conjugated to reactive electrophilic groups such as aldehydes.



Similar mechanisms account for the double bond geometry obtained in aldol reactions followed by dehydration to give α,β-unsaturated carbonyl compounds. Any *Z*-alkene that is formed is equilibrated to *E* by reversible Michael addition during the reaction.



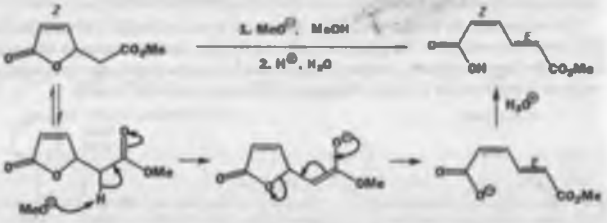
The double aldol product from acetone and benzaldehyde, known as dibenzylidene acetone (dba), is a constituent of some sun-protection materials and is used in organometallic chemistry as a metal ligand. It is easily made geometrically pure by a simple aldol reaction—again, reversible Michael addition equilibrates any *Z* product to *E*.

Equilibration of alkenes not conjugated with carbonyl groups requires different reagents

Iodine will add reversibly not only to Michael acceptors but also to most other alkenes. It can therefore be a useful reagent for equilibrating double bond geometrical isomers.

However, in neither this E2 reaction nor the E1 reaction on p. 000 is the stereoselectivity very good, and in this reaction the regioselectivity is bad too. The root of the problem is that one of the groups lost is always H (either as HBr or H_2O in these cases), and in most organic molecules there are lots of Hs to choose from!

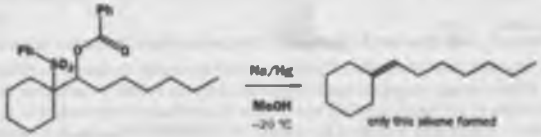
Both stereo- and regioselectivity are better in E1cB reactions, such as the opening of this unsaturated lactone in base. The double bond inside the ring remains *Z* but the new one, formed as the ring opens, prefers the *E* geometry. The transition state for the elimination step already has a product-like shape and prefers this for simple steric reasons.



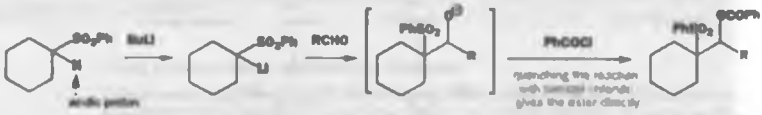
The Julia olefination is regiospecific and connective

This reaction is an elimination—the phenylsulfonyl ($PhSO_2$) and benzoate ($PhCO_2$) groups in the starting material are lost to form the double bond—but it is completely regioselective. Only the alkene shown is formed, with the double bond joining the two carbons that carried the $PhSO_2$ and $PhCO_2$ groups. This elimination is promoted by a reducing agent, usually sodium amalgam (a solution of sodium metal in mercury) and works for a variety of compounds providing they have a phenylsulfonyl group adjacent to a leaving group. It is called the **Julia olefination** after Marc Julia (1922–) who did his PhD at Imperial College, London, with Sir Derek Barton and now works at the École Normale in Paris and is best known for his work on sulfones.

▶ Olefin is an alternative name for alkene and olefination simply means alkene synthesis, usually by the formation of both σ and π bonds.



The most common leaving groups are carboxylates such as acetate or benzoate, and the starting materials are very easily made. As you will see in Chapter 46, sulfones are easily deprotonated next to the sulfur atom by strong bases like butyllithium or Grignard reagents, and the sulfur-stabilized anion will add to aldehydes. A simple esterification step, which can be done in the same reaction vessel as the addition, introduces the acetate or benzoate group. This is how the starting material for the elimination above was made.

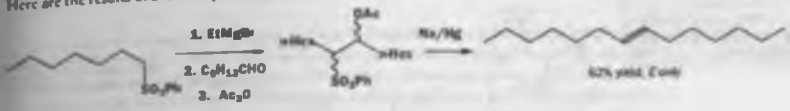


The short sequence of steps (starting with sulfone plus aldehyde and leading through to alkene) is known as the Julia olefination. It is our first example of a **connective double bond synthesis**—in other words, the double bond is formed by joining two separate molecules together (the aldehyde

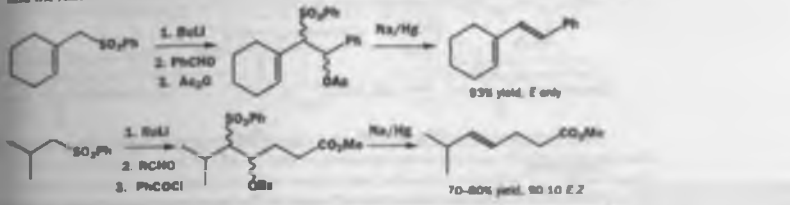
and sulfone). You will be reminded of the most important connective double-bond forming reaction, the Wittig reaction, later in the chapter.

The Julia olefination is stereoselective

Here are the results of a few simple Julia olefinations.

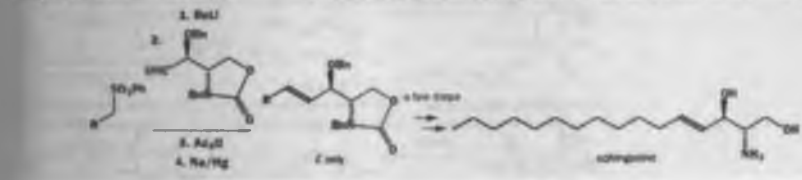


Notice that deprotonations can be with BuLi or EtMgBr and that the acylation step works with acetic anhydride or with benzoyl chloride. As you can see, they are all highly stereoselective for the *E*-isomer, and the Julia olefination is one of the most important ways of making *E* double bonds connectively.



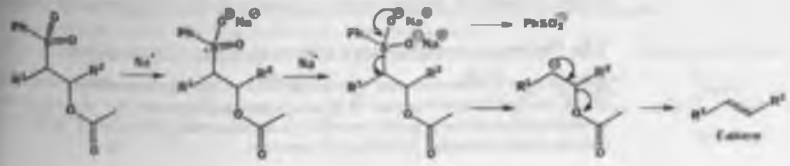
Further example—preparation of sphingosine

In 1987, American chemists were studying the synthesis of some biological molecules using enzymes. One of the compounds they were interested in was sphingosine, an amino alcohol that forms the backbone of sphingolipids (fat-like molecules found in cell membranes). They wanted to compare the enzyme-produced material with an authentic sample, which they made by using a Julia olefination to introduce the *E* double bond.



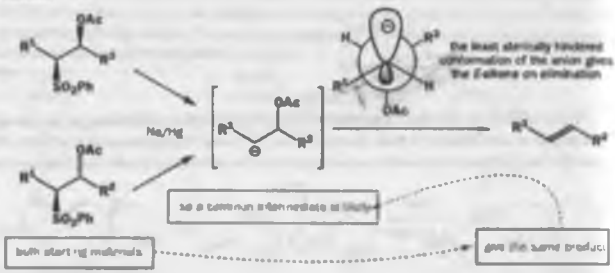
The Julia olefination is stereoselective and not stereospecific

The reason for the *E* selectivity lies in the mechanism of the elimination. The first step is believed to be two successive electron transfers from the reducing agent (sodium metal) to the sulfone. Firstly, a radical anion is formed, with one extra unpaired electron, and then a dianion, with two extra electrons and therefore a double negative charge. The dianion fragments to a transient carbanion that expels acetate or benzoate to give the double bond.



▶ A single-step E2 elimination would have to go via an anti-periplanar transition state and would be stereospecific. You will be able compare this stereoselective Julia olefination with the stereospecific Peterson elimination shortly.

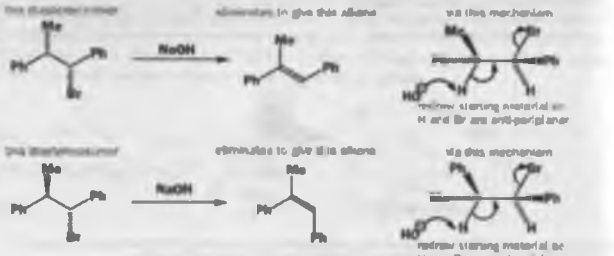
We know that there must be an anion intermediate because the elimination is *not* stereospecific—in other words, it doesn't matter which diastereoisomer of the starting material you use (all of the examples in this section have been mixtures of diastereoisomers) you always get the *E*-alkene product. The intermediate anion must have a long enough lifetime to choose its conformation for elimination.



Stereospecific eliminations can give pure single isomers of alkenes

■ These reactions fall into class (4) of the list on p. 000.

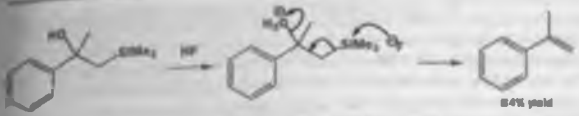
You met a stereospecific elimination in Chapter 19. The requirement for the H and the Br to be anti-periplanar in the E2 transition state meant that the two diastereoisomers of this alkyl bromide eliminated to alkenes with different double bond geometries (p. 000).



However, reactions like this are of limited use—their success relies on the base's lack of choice of protons to attack: provide an alternative H and we are back with the situation in the reaction on p. 000. Logic dictates, therefore, that only trisubstituted double bonds can be made stereospecifically in this way, because the reaction must not have a choice of hydrogen atoms to participate in the elimination. The answer is, of course, to move away from eliminations involving H, as we did with the Julia olefination. We shall look at this type of reaction for much of the rest of this chapter.

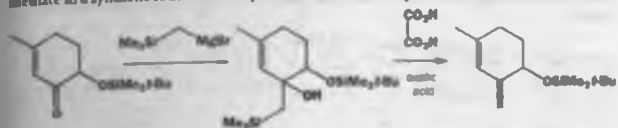
The Peterson reaction is a stereospecific elimination

There are many reactions in organic chemistry in which an Me_3Si group acts like a proton—Chapter 47 will detail some more reactions of silicon-containing compounds. Just as acidic protons are removed by bases, silicon is readily removed by hard nucleophiles, particularly F^- or RO^-, and this can promote an elimination. An example is shown here.

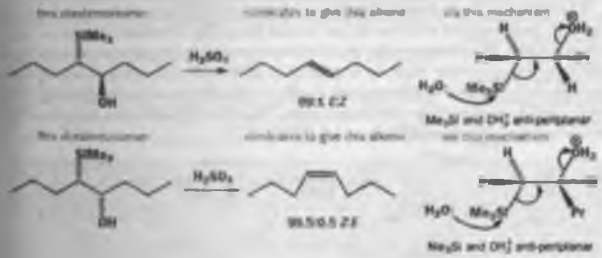


84% yield

The reaction is known as the **Peterson reaction**. It is rather like those we discussed right at the beginning of this chapter—eliminations of alcohols under acidic conditions to give alkenes. But, unlike those reactions, it is fully regioselective (like the Julia olefination), and so is particularly useful for making double bonds where other elimination methods might give the wrong regioisomer or mixtures of regioisomers. In this next example only one product is formed, in high yield, and it has an exocyclic double bond. Just think what would have happened without the silicon atom (ignore the one attached to the oxygen—that's just a protecting group). This compound is, in fact, an intermediate in a synthetic route to the important anticancer compound Taxol.

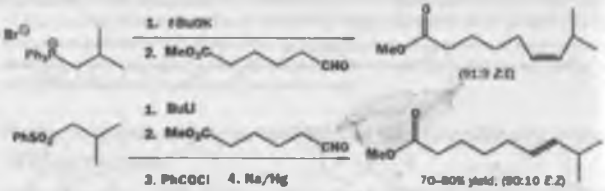


You've probably spotted that this is another connective alkene synthesis. The Peterson reaction is particularly useful for making terminal or exocyclic double bonds connectively because the starting material (the magnesium derivative shown above) is easily made from available Me_3SiCH_2Br. The reaction is also stereospecific, because it is an E2 elimination proceeding via an anti-periplanar transition state. In principle, it can therefore be used to make single geometrical isomers of alkenes, the geometry depending on the relative stereochemistry of the starting material. However, this use of the Peterson reaction is limited by difficulties in making diastereoisomerically pure starting materials.

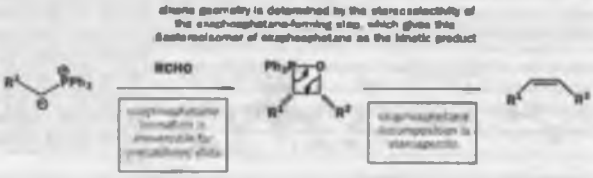


There is another, complementary version of the Peterson reaction that uses base to promote the elimination. The starting materials are the same as for the acid-promoted Peterson reaction. When base (such as sodium hydride or potassium hydride) is added, the hydroxyl group is deprotonated, and the oxyanion attacks the silicon atom *intramolecularly*. Elimination takes place this time via a *syn-periplanar* transition state—it has to because the oxygen and the silicon are now bonded together, and it is the strength of this bond that drives the elimination forward.

The key intermediates in the synthesis of the *E*- and the *Z*-isomers of capsaicin were the *E* and *Z* unsaturated esters shown below. By using a Wittig reaction with an unstabilized ylid it was possible to make the *Z*-isomer selectively, whilst the Julia olefination gave the *E*-isomer.

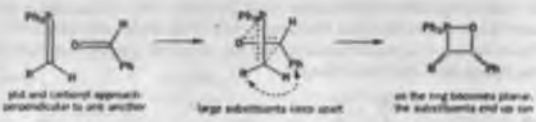


How can the *Z* selectivity in Wittig reactions of unstabilized ylids be explained? We have a more complex situation in this reaction than we had for the other eliminations we considered, because we have two separate processes to consider: formation of the oxaphosphetane and decomposition of the oxaphosphetane to the alkene. The elimination step is the easier one to explain—it is stereospecific, with the oxygen and phosphorus departing in a syn-periplanar transition state (as in the base-catalysed Peterson reaction). Addition of the ylid to the aldehyde can, in principle, produce two diastereomers of the intermediate oxaphosphetane. Provided that this step is irreversible, then the stereospecificity of the elimination step means that the ratio of the final alkene geometrical isomers will reflect the stereoselectivity of this addition step. This is almost certainly the case when R is not conjugating or anion-stabilizing; the *syn* diastereoisomer of the oxaphosphetane is formed preferentially, and the predominantly *Z*-alkene that results reflects this. The *Z* selective Wittig reaction therefore consists of a kinetically controlled stereoselective first step followed by a stereospecific elimination from this intermediate.



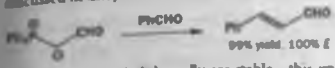
Why is formation of the *syn* oxaphosphetane favoured?

This question is the subject of much debate, because the mechanism by which the oxaphosphetane is formed is not entirely understood. One possible explanation relies on rules of orbital symmetry, which you will meet in Chapters 35 and 36—we need not explain them in detail here but suffice it to say that there is good reason to believe that, if the ylid and carbonyl compound react together to give the oxaphosphetane in one step, they will do so by approaching one another at right angles. Keeping the large substituents apart produces a transition state like that shown below, which (correctly) predicts that the oxaphosphetane will have *syn*

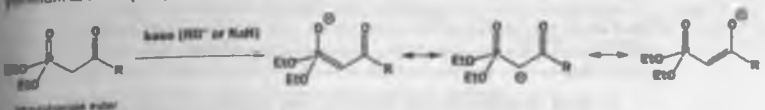


The *E* selective Wittig reaction

Stabilized ylids, that is ylids whose anion is stabilized by further conjugation, usually within a carbonyl group, give *E*-alkenes on reaction with aldehydes. These ylids are also enolates and were discussed in Chapter 27.

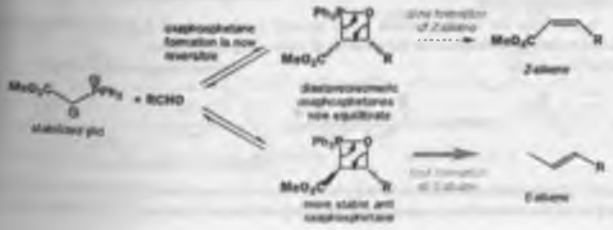


These stabilized ylids really are stable—this one, for example, can be recrystallized from water. This stability means though that they are not very reactive, and often it is better not to use the phosphonium salt but a phosphonate instead.



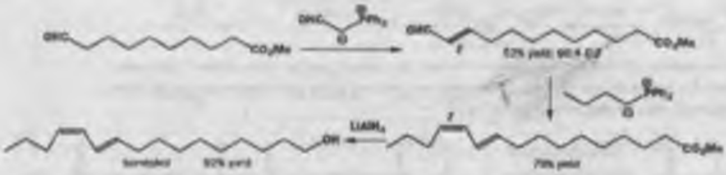
Phosphonate esters can be deprotonated with sodium hydride or alkoxide anions to give enolate-type anions that react well with aldehydes or ketones to give *E*-alkenes. Alkene-forming reactions with phosphonates are called Horner–Wadsworth–Emmons (or Horner–Emmons, Wadsworth–Emmons, or even Horner–Wittig) reactions. This example is a reaction that was used by some Japanese chemists in the synthesis of polyzonimine, a natural insect repellent produced by millipedes.

So why the change to *E* stereoselectivity when the ylid is stabilized? Again, chemists disagree about the details but a likely explanation is that the extra stability given to the ylid starting materials makes the reaction leading to the oxaphosphetane reversible. Stereoselectivity in this step is therefore no longer kinetically controlled but is thermodynamically controlled: reversal to starting materials provides a mechanism by which the oxaphosphetane diastereoisomers can interconvert. Providing the rate of interconversion is faster than the rate of elimination to alkene, the stereospecific step will no longer reflect the initial kinetic ratio of oxaphosphetane diastereoisomers. It is not unreasonable to suppose that the thermodynamically more stable of the oxaphosphetanes is the *trans*-diastereoisomer, with the two bulky groups on opposite sides of the ring, and that elimination of this gives *E*-alkene. What is more, the rate of elimination to give an *E*-alkene ought to be significantly faster than the rate of elimination to give a *Z*-alkene, simply by virtue of steric crowding in their respective transition states. The *anti* diastereoisomer is therefore 'siphoned off' to give *E*-alkene more rapidly than the *syn* diastereoisomer gives *Z*-alkene. Meanwhile equilibration of the two oxaphosphetane diastereomers via starting material replenishes the supply of *anti* diastereoisomer, and virtually only *E*-alkene is produced.



An E,Z-diene by two successive Wittig reactions

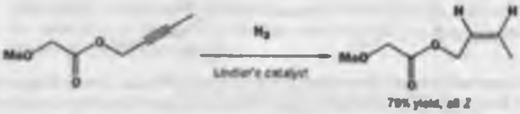
The [illegible] moth [illegible] by producing a pheromone known as bombykol. Bombykol is an E,Z-diene, and in this synthesis (dating from 1977) two successive Wittig reactions exploit the stereoselectivity obtained with stabilized and unstabilized ylids, respectively, to control the stereochemistry of the product.



E- and Z-alkenes can be made by stereoselective addition to alkynes

In this last section of the chapter we shall leave elimination reactions to look at addition reactions. Alkynes react with some reducing agents stereoselectively to give either the Z double bond or the E double bond. Some of these reactions were described briefly in Chapter 24.

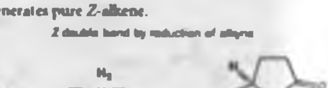
Z selective reduction of alkynes uses Lindlar's catalyst



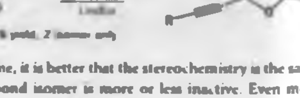
Lindlar's catalyst = Pd, $CaCO_3$, $Pb(OAc)_2$

This pure Z-alkene was needed for studies on the mechanism of a rearrangement reaction. In Chapter 24 you met catalytic hydrogenation as a means of reducing alkenes to alkanes, and we introduced Lindlar's catalyst (palladium and lead acetate on a support of calcium carbonate) as a means of controlling chemoselectivity so that *alkynes* could be reduced to *alkenes*. What we did not emphasize then was that the two hydrogen atoms add to the alkyne in a *syn* fashion and the alkene produced is a Z-alkene. The stereoselectivity arises because two hydrogen atoms, bound to the catalyst, are delivered simultaneously to the alkyne.

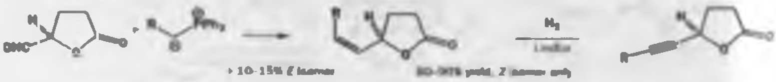
The reason that catalytic hydrogenation often results in syn addition of hydrogen to alkenes was discussed in Chapter 24.



You can compare this method of forming Z-alkenes directly with the Wittig reaction in these two syntheses of another insect pheromone, that of the Japanese beetle.



In this case, the Wittig reaction is not entirely Z-selective, and it generates some E-isomer. Lindlar-catalysed reduction, on the other hand, generates pure Z-alkene.

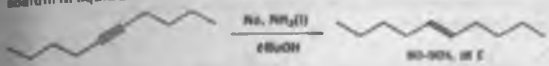


For a biologically active sample of this pheromone, it is better that the stereochemistry is the same as that of the natural compound—the E double bond isomer is more or less inactive. Even more

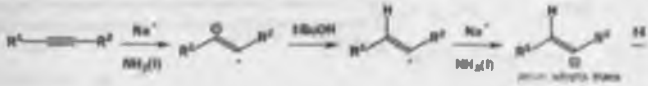
important is the configuration at the chiral centre in the pheromone—the wrong enantiomer is not only inactive, but it also inhibits the male beetles' response to the natural stereoisomer. In Chapter 43 we shall talk about ways of making single enantiomers selectively.

E selective reduction of alkynes uses sodium in liquid ammonia

The best way of ensuring *anti* addition of hydrogen across any triple bond is to treat the alkyne with sodium in liquid ammonia.

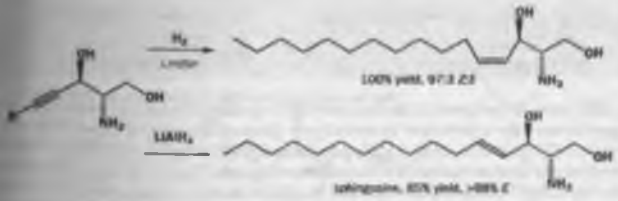


The sodium donates an electron to the LUMO of the triple bond (one of the two orthogonal π* orbitals). The resulting radical anion can pick up a proton from the ammonia solution to give a vinyl radical. A second electron, supplied again by the sodium, gives an anion that adopts the more stable *trans* geometry. A final proton quench by a second molecule of ammonia or by an added proton source (*t*-butanol is often used, as in the Birch reduction) forms the *E*-alkene.



An alternative, and more widely used, method is to reduce alkynes with $LiAlH_4$. This reaction works only if there is a hydroxy or an ether functional group near to the alkyne, because it relies on delivery of the reducing agent to the triple bond through complexation to this oxygen atom.

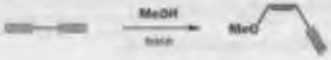
Making alkenes by addition to alkynes offers two distinct advantages. Firstly, although the reaction is not connective in the sense that the Wittig and Julia reactions are, the starting materials can often be made straightforwardly by alkylation of alkynyl anions. Secondly, the same alkyne can be used to make either *E*- or *Z*-alkene—an advantage shared with the Peterson reaction but here the starting material is much easier to make. In some early work on sphingosine (a constituent of cell membranes), some Swiss chemists needed to make both *E*- and *Z*-isomers of the naturally occurring compound. This was an easy task once they had made the alkyne.



Addition of nucleophiles to alkynes

This rarer, and rather surprising, approach to *Z*-alkenes sometimes gives excellent results particularly in the addition of nucleophiles to butadiyne. The base-catalysed addition of methanol gives an

excellent yield of *Z*-1-methoxybut-1-en-3-yne. This reaction is so easy to do that the product is available commercially.



Notice that methanol adds once only: you would not expect nucleophiles to add to a simple alkyne and it is the conjugation that makes addition possible. Methoxide ion adds to one of the alkynes to give a conjugated anion.

The anion is linear with the negative charge delocalized along the conjugated system and the charge is therefore in a p orbital in the plane of the molecule. The other p orbital is involved in π bonding as well but at right angles to the plane of the molecule. When the anion reacts with a molecule of methanol, protonation occurs on the lobe of the p orbital away from the MeO group and the *Z*-alkene is formed. This product is mentioned in other chapters of the book: now you know why it is available.

● Summary of methods for making alkenes stereospecifically

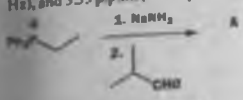
Here is a summary of the most important methods for making double bonds stereoselectively.

To make *cis* (*Z*)-alkenes	To make *trans* (*E*)-alkenes
• Wittig reaction of *unstabilized* ylid	• Wittig reaction of *stabilized* ylid
• Constrain the alkene in a ring	• Equilibration to the more stable isomer
	• Julia olefination
	• Simple unselective elimination reactions
• *syn* addition of hydrogen across an alkyne	• *trans* selective reduction of alkyne
• Peterson elimination	• Peterson elimination

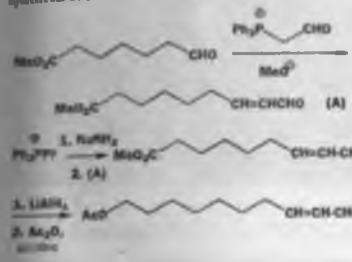
In this chapter we have dealt for the first time with the problem of producing compounds as single stereoisomers—the stereoisomers concerned were geometrical isomers of alkenes. The next two chapters will look in more detail at making stereoisomers, but we shall move out of two dimensions into three and consider reactions that have diastereoselectivity. The two subjects are closely related since often single diastereoisomers are made by addition reactions of single geometrical isomers of double bonds and, as you saw with the Peterson and Wittig reactions, single diastereoisomers can lead stereospecifically to single geometrical isomers.

Problems

1 Deduce the structure of the product of this reaction from the spectra and explain the stereochemistry. Compound A has δ_H 0.95 p.p.m. (6H, d, *J* 7 Hz), 1.60 p.p.m. (3H, d, *J* 5 Hz), 2.65 p.p.m. (1H, double septuplet, *J* 4 and 7 Hz), 5.10 p.p.m. (1H, dd, *J* 10 and 4 Hz), and 5.35 p.p.m. (1H, dq, *J* 10 and 5 Hz).



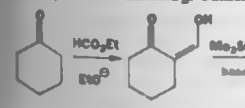
2 A single diastereoisomer of an insect pheromone was prepared in the following way. Which isomer is formed and why? Outline a synthesis of one other isomer.



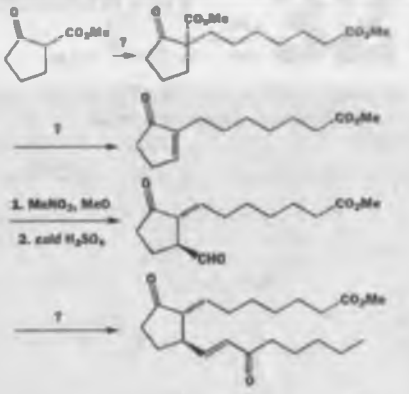
3 How would you prepare samples of both geometrical isomers of this compound?

4 Decomposition of this diazocompound in methanol gives an unstable alkene A ($C_8H_{14}O$) whose NMR spectrum contains these signals: δ_H 3.50 p.p.m. (3H, s), 5.50 p.p.m. (1H, dd, *J* 17.9 and 7.9 Hz), 5.80 p.p.m. (1H, ddd, *J* 17.9, 9.2, and 4.3 Hz), 4.20 p.p.m. (1H, m), and 1.3–2.7 p.p.m. (8H, m). What is its structure and geometry? You are not expected to work out a mechanism for the reaction.

5 Why do these reactions give different alkene geometries?

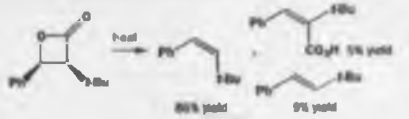


6 Here is a synthesis of a prostaglandin analogue. Suggest reagents for the steps marked '?', give mechanisms for those not so marked, and explain any control of alkene geometry.

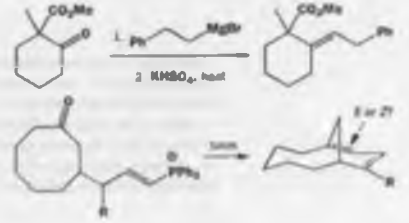


7 Isoeugenol, the flavouring principle of cloves, occurs in the plant in both the *E* (solid) and *Z* (liquid) forms. How would you prepare a pure sample of each and how would you purify each from any of the other isomer?

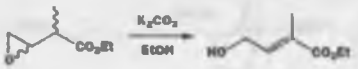
8 Thermal decomposition of this lactone gives mainly the *Z*-alkene shown with minor amounts of the *E*-alkene and an unsaturated acid. Suggest a mechanism for the reaction that explains these results.



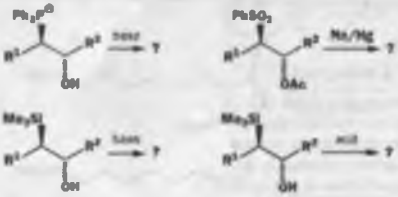
9 What controls the double bond geometry in these examples? In the second example, one alkene is not defined by the drawing.



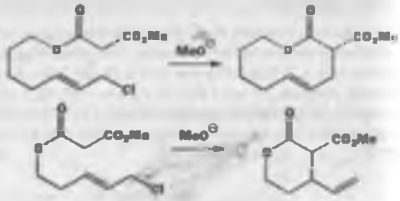
20 Treatment of this epoxide with base gives the same *E*-alkene regardless of the stereochemistry of the epoxide. Comment.



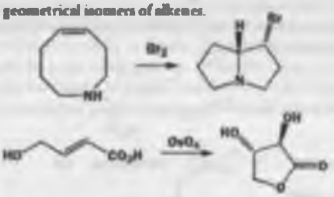
21 Which alkene would be formed in each of the following reactions? Explain your answer mechanistically.



22 Comment on the difference between these two reactions.



23 Give mechanisms for these stereospecific reactions on single geometrical isomers of alkenes.



Determination of stereochemistry by spectroscopic methods

32

Connections

Building on:

- Determining organic structures ch3
- Proton NMR spectroscopy ch11
- Review of spectroscopic methods ch15
- Stereochemistry ch16
- Conformation ch18
- Controlling double bond geometry ch31

Arriving at:

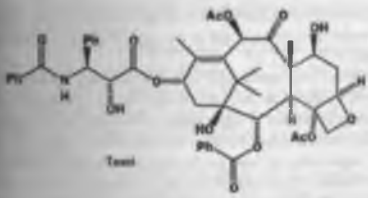
- How coupling varies with the angle between bonds
- How ring size affects coupling
- How electronegative atoms reduce coupling
- How π systems increase geminal coupling
- How protons attached to the same carbon can be different, and can couple to one another
- What homotopic, enantiotopic, and diastereotopic mean
- The nuclear Overhauser effect: what it is and how to exploit it

Looking forward to:

- Controlling stereochemistry with rings ch33
- Diastereoselectivity ch34
- Saturated heterocycles ch42
- Asymmetric synthesis ch45
- Organic synthesis ch 53

Introduction

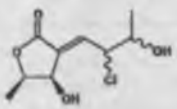
From time to time throughout the book we have spread before your eyes some wonderful structures. Some have been very large and complicated (such as palytoxin, p. 000) and some small but difficult to believe (such as tetra-*t*-butyl tetrahedrane, p. 000). They all have one thing in common. Their structures were determined by spectroscopic methods and everyone believes them to be true. Among the most important organic molecules today is Taxol, an anticancer compound from yew trees. Though it is a 'modern' compound, in that chemists became interested in it only in the 1990s, its structure was actually determined in 1971.



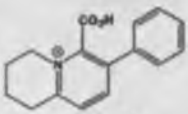
Taxol

No one argued with this structure because it was determined by reliable spectroscopic methods—NMR plus an X-ray crystal structure of a derivative. This was not always the case. Go back another 25 years to 1946 and chemists argued about structures all the time. An undergraduate and an NMR spectrometer can solve in a few minutes structural problems that challenged teams of chemists for years half a century ago. In this chapter we will combine the knowledge presented systematically in Chapters 3, 11, and 15, add your more recently acquired knowledge of stereochemistry (Chapters 16, 18, and 31), and show you how structures are actually determined in all their stereochemical detail using all the evidence available.

two recently discovered simple natural products



chlorocarolide A



isethionic A

It would be wise to review Chapter 28 now if what we said there is not fresh in your mind.

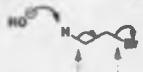
In general, we will not look at structures as complex as Taxol. But it is worth a glance at this stage to see what was needed. The basic carbon skeleton contains one eight- and two six-membered rings. These can be deduced from proton and carbon NMR. There is a four-membered heterocyclic ring—a feature that caused a lot of argument over the structure of penicillin. The four-membered cyclic ether in Taxol is easily deduced from proton NMR as we will see soon. There are ten functional groups (at least—it depends on how you count) including six carbonyl groups. These are easily seen in the carbon NMR and IR spectra. Finally, there is the stereochemistry. There are eleven stereogenic centres, which were deduced mostly from the proton NMR and the X-ray crystal structure of a closely related compound (Taxol itself is not crystalline).

New structures are being determined all the time. A recent issue of one important journal (*Tetrahedron Letters* No. 14 of 1996) has a paper on Taxol but also reports the discovery and structure determination of the two new natural products in the margin. Both compounds were discovered in ocean sponges, one from Indonesia and one from a fungus living in a sponge common in the Pacific and Indian oceans. Both structures were determined largely by NMR and in neither case was an X-ray structure necessary. You should feel a bit more in tune with the chemists who deduced these structures as they look much simpler than Taxol or even than penicillin. We hope you will feel by the end of this chapter that you can tackle structural problems of this order of complexity with some confidence. You will need practice, and in this area above all it is vital that you try plenty of problems. Use the examples in the text as worked problems: try to solve as much as you can before reading the answer—you can do this only the first time you read because next time you will have your memory as a prompt.

The stereochemistry at two of the stereogenic centres of chlorocarolide was unknown when this structure was published—stereochemistry is one of the hardest aspects of structure to determine. Nonetheless, NMR is second only to X-ray in what it tells us of stereochemistry, and we shall look at what coupling constants (*J* values) reveal about configuration, conformation, and reactivity. The first aspect we consider is the determination of conformation in six-membered rings.

^3J values vary with H–C–C–H dihedral angle

best arrangement for E2 elimination



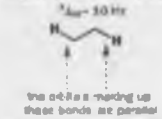
the orbitals making up these bonds are parallel

● Remember

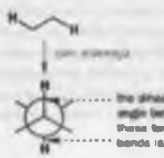
Parallel orbitals interact best.

In the last chapter, we looked at some stereospecific eliminations to give double bonds, and you know that E2 elimination reactions occur best when there is an anti-periplanar arrangement between the proton and the leaving group.

largest ^3J from parallel orbitals



the orbitals making up these bonds are parallel



the dihedral angle between these two C–H bonds is 180°

In the NMR spectrum, coupling between protons arises from through-bond and not through-space interactions: *trans* coupling in alkenes is *bigger* than *cis* coupling (see Chapter 11, p. 000). So the same arrangement that leads to the best reaction ought also to lead to the largest coupling constant. In other words, if we replace 'Br' in the diagram with a second hydrogen atom but keep the orbital alignment the same, we ought to get the biggest possible coupling constant for a saturated system.

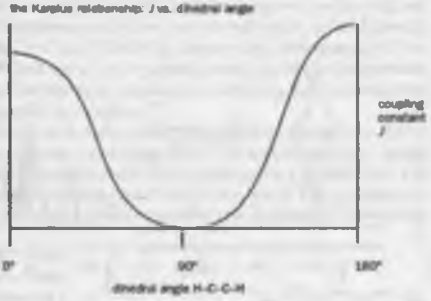
The usual description of this situation is in terms of the dihedral angle between the H–C–C–H bonds. The dihedral angle is obvious in the Newman projection as it is the angle between the two C–H bonds projected on a plane orthogonal to the C–C bond. In a Newman projection this plane is the plane of the paper and here the angle is 180°.

When the dihedral angle is zero, the two C–H bonds are again in the same plane but not perfectly parallel. The coupling constant is again large, but not so large as in the previous case. In fact, the two arrangements are very like *cis* and *trans* double bonds, but the C atoms are tetrahedral not trigonal.

You may guess that, when the dihedral angle is 90°, the coupling constant is zero. What happens in between these extremes was deduced by Karplus in the 1960s and the relationship is usually known as the **Karplus equation**. It is easiest to understand from a graph of J against dihedral angle.

Examine this graph carefully and note the basic features as you will need them as we go through the chapter. These features are:

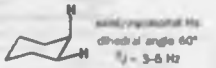
- Coupling is largest at 180° when the orbitals of the two C–H bonds are perfectly parallel
- Coupling is nearly as large at 0° when the orbitals are in the same plane but not parallel
- Coupling is zero when the dihedral angle is 90°—orthogonal orbitals do not interact
- The curve is flattened around 0°, 90°, and 180°—J varies little in these regions from compound to compound



- The curve slopes steeply at about 60° and 120°—J varies a lot in this region with small changes of angle and from compound to compound
- Numerical values of J vary with substitution, ring size, etc., but the Karplus relationship still works—it gives good *relative* values

These ideas come to life in the determination of conformation in six-membered rings. *Trans* diaxial hydrogen atoms are aligned with a dihedral angle of 180° and give the largest J values.

The other two situations, where one or both hydrogen atoms are equatorial, both have angles of about 60°, though axial/equatorial couplings are usually slightly larger than equatorial/equatorial ones.

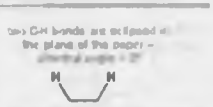


Now for some illustrations. The simple cyclohexyl ester has just one substituent, which we expect to be equatorial (Chapter 18). The black hydrogen therefore has four neighbours—two axial Hs and two equatorial Hs. We expect to see a triplet from each and that the axial/axial coupling constant will be large. In fact, there is a 1H signal at δ 4.91, it is a tt (triplet of triplets) with J = 8.8 and 3.8 Hz. Only an axial H can have couplings as big as 8.8 Hz, so now we *know* that the ester is equatorial.

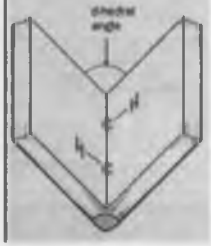
By contrast, the next ester, which also has only one substituent, has a 1H signal at δ 4.0 p.p.m. which is a simple triplet with J = 3.2 Hz. With no large couplings this cannot be an axial proton and the substituent must now be axial. It so happens that the small equatorial/axial and equatorial/equatorial couplings to the green hydrogens are the same. This is not so surprising as the dihedral angles are both 60°

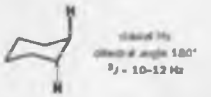
None of the dihedral angles in a six-membered ring are 90°, but in some bicyclic systems they are. Norbornane-type structures (bicyclo[2.2.0]heptanes), for example, typically have couplings of 0 Hz between the protons shown in black and green because the H–C–C–H dihedral angle is 90°.

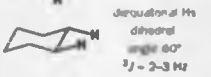
The determination of *conformation* by NMR may more importantly allow us to

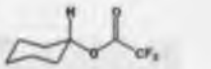


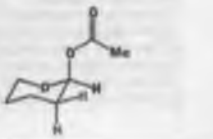
As a reminder, the dihedral angle is most easily visualized by imagining the C–C bond lying along the spine of a partially-opened book. If the C–H bonds are written one on one page and the other on the other, then the dihedral angle is the angle between the pages of the book.



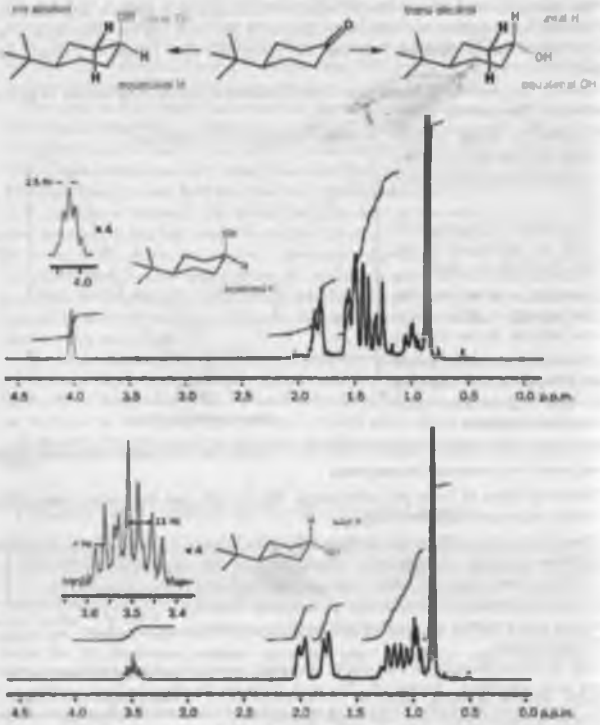








determine *configuration* at the same time. This often occurs when there are two or more substituents on the ring. Here is a simple example: you saw in Chapter 18 that the reduction of 4-*t*-butylcyclohexanone can be controlled by choice of reagent to give either a *cis* or a *trans* alcohol. It is easy to tell them apart as the *t*-butyl group will always be equatorial.



▶ You can draw a general conclusion from this observation: an NMR signal is roughly as wide as the sum of all its couplings. In any given compound, an axial proton will have a much wider signal than an equatorial proton.

The NMR spectrum of the green H is quite different in the two cases. Each has two identical axial neighbours and two identical equatorial neighbours (two are shown in black—there are two more at the front!). Each green H appears as a triplet of triplets. In the *cis* alcohol both couplings are small (2.72 and 3.00 Hz) but in the *trans* alcohol the axial/axial coupling is much larger (11.1 Hz) than the axial/equatorial (4.3 Hz) coupling.

Hydrogenation of the double bond in this unsaturated acetal gives the saturated compound as a single isomer. But which one? Are the two substituents, Me and OEt, *cis* or *trans*?

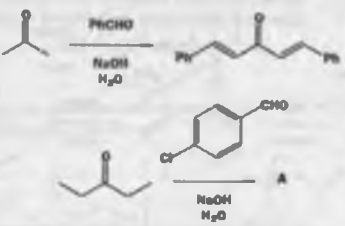
The appearance of the two black hydrogens in the NMR spectrum reveals the answer and also shows what conformation the molecule adopts. There is a 1H signal at 3.95 p.p.m. (which is therefore next to oxygen) and it is a double quartet. It must be the hydrogen next to the methyl group because of the quartet coupling. The quartet coupling constant has the 'normal' J value of 6.5 Hz. The doublet coupling is 9 Hz and this is too large to be anything other than an axial/axial coupling. This hydrogen is axial.

There is another 1H signal at 4.40 p.p.m. (next to *two* oxygens) which is a double doublet with J = 9 and 2 Hz). This must also be an axial proton as it shows an axial/axial (9 Hz) and an axial/equatorial coupling. We now know the conformation of the molecule.

Both black hydrogens are axial so both substituents are equatorial. That also means in this case that they are *cis*. But note that this is because they are both on the same, upper side of the ring, not because they are both equatorial! The hydrogen at the front has two neighbours—an axial (brown) H, J = 9, and an equatorial (green) H, J = 2 Hz. All this fits the Karplus relationship as expected. You may have spotted that the H at the back appears to be missing a small coupling to its equatorial neighbour. No doubt it does couple, but that small coupling is not noticed in the eight lines of the double quartet. Small couplings can easily be overlooked.

When this compound is allowed to stand in slightly acidic ethanol it turns into an isomer. This is the *trans* compound and its NMR spectrum is again very helpful. The proton next to the methyl group is more or less the same but the proton in between the two oxygen atoms is quite different. It is at 5.29 p.p.m. and is an unresolved signal of width about 5 Hz. In other words it has no large couplings and must be an equatorial proton. The conformation of the *trans* compound is shown in the margin.

Now for a surprising product, whose structure and stereochemistry can be determined by NMR. Normally, reaction of a symmetrical ketone such as acetone with an aromatic aldehyde and base gives a double aldol condensation product in good yield.



But in one particular case, the reaction between pentan-2-one and 4-chlorobenzaldehyde, a different product is formed. The mass spectrum shows that two aldehydes have reacted with one ketone as usual, but that only one molecule of water has been lost. Some of what we know about this compound is shown in the scheme.

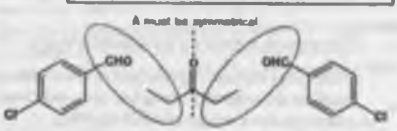
A = $C_{20}H_{18}Cl_2O_2$

m.p. 189–190 °C

IR: 1705, 1600 cm^{-1}

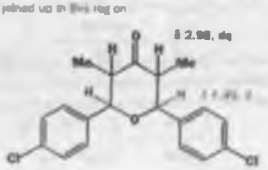
δ_H 7.73 (2H, s)
4.40 (2H, d, J 10.4)
2.98 (2H, dq, J 10.4, 6.6)
1.08 (6H, d, J 6.6)

The ^{13}C NMR spectrum shows that there is one ketone carbonyl group, as expected, but no alkene carbons. There is only one set of ^{13}C signals for the 4-Cl-phenyl ring and only two other carbons. This must mean that the molecule is symmetrical.



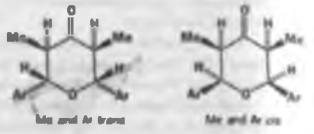
The three molecules must be joined up somewhere in the region marked. But how can we lose only one molecule of water and keep the symmetry?

The proton NMR spectrum gives the answer. Both methyl groups are still there, and they are identical, so we have two identical MeCH fragments. These CH protons (black) are *double* quartets so they have another neigh-

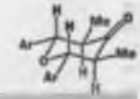


hour, the only remaining aliphatic proton (actually again two identical protons, in green) at δ_H 4.49 p.p.m. These protons must be next to both oxygen and the aromatic ring to have such a large shift. But there is only one spare oxygen atom so the protons at 4.49 p.p.m. must be next to the same oxygen atom—the structure is shown on the previous page.

All that remains is the stereochemistry. There are four stereogenic centres but because of the symmetry only two structures are possible. Both methyl groups must be on the same side and both aryl rings must be on the same side.

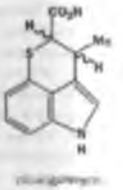


The coupling constant between the hydrogen atoms is 10.4 Hz and so they must both be axial. This means that the molecule has this structure and it is the *trans* compound: all the substituents are equatorial so it is the most stable structure possible.

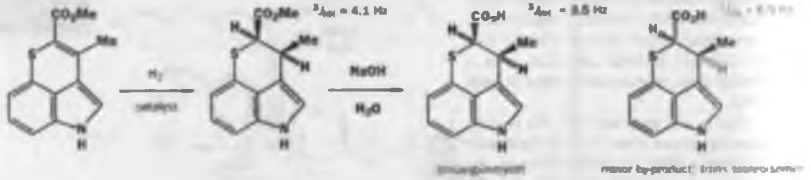


We looked at the conformations of cyclohexanes and cyclohexene oxides in Chapter 10, and we will look again at the stereochemistry of reactions of six-membered rings containing double bonds in Chapter 33.

Only fully saturated six-membered rings are really chairs or boats. Even with one double bond in the ring, the ring is partly flattened: here we will look at an even flatter example. A unique antibiotic has been discovered in China and called 'chuangxinmycin' (meaning 'a new kind of mycin' where mycin = antibiotic). It is unique because it is a sulfur-containing indole: few natural products and no other antibiotics have this sort of structure.



The structure itself was easy to elucidate, but the stereochemistry of the two black hydrogens was not so obvious. The coupling constant (^3J) was 3.5 Hz. During attempts to synthesize the compound, Kozikowski hydrogenated the alkene ester below to give an undoubted *cis* product.

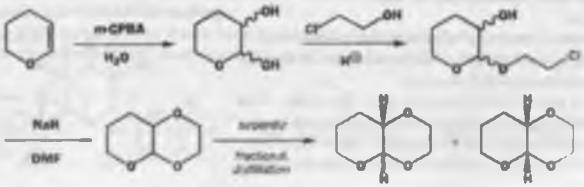


Hydrogenation is cis-selective: see Chapter 24.

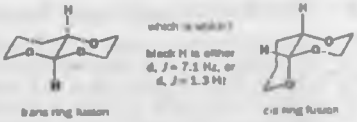
The ^3J coupling between the black hydrogens in this compound was 4.1 Hz, much the same as in the antibiotic and, when the ester group was hydrolysed in aqueous base, the main product was identical to natural chuangxinmycin. However, there was a minor product, which was the *trans* isomer. It had ^3J 8.0 Hz. Note how much smaller this value is than the axial/axial couplings of 10 Hz or more in saturated six-membered rings. The flattening of the ring reduces the dihedral angle, reducing the size of J.

Stereochemistry of fused rings

Where rings are fused together (that is, have a common bond) determination of conformation may allow the determination of ring junction stereochemistry as well. Both isomers of this bicyclic ether were formed as a mixture and then separated.

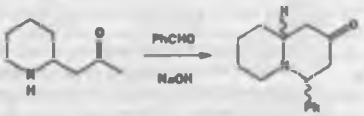


One proton at the ring junctions appears clearly in the NMR spectrum as it is next to two oxygen atoms (shown in black on the conformational diagrams alongside). In one compound it is a doublet, $J = 7.1$ Hz, and in the other a doublet $J = 1.3$ Hz. Which is which?

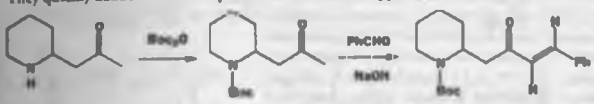


The coupling is to the green proton in each case and the dihedral angles are 180° for the *trans* compound but only 60° for the *cis* one, so the smaller coupling belongs to the *cis* compound. We shall discuss below why the *absolute* values are so low: this example illustrates how much easier stereochemical determination is if you have both stereoisomers to compare.

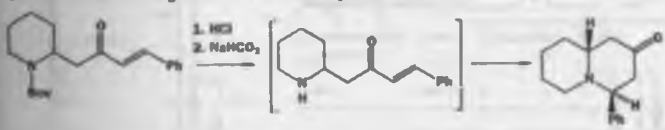
In the next example, unlike the last one, it eventually proved possible to make both compounds in high yield. But first the story: reaction of an amino-ketone with benzaldehyde in base gave a mixture of diastereoisomers of the product.



In unravelling the mechanism of the reaction, chemists protected the nitrogen atom with Boc (Chapter 25) before the reaction with benzaldehyde and found that a new product was formed that was clearly an *E*-alkene as its NMR spectrum contained δ_H 6.73 (1H, d, J 16). This is too large a coupling constant even for axial/axial protons and can be only *trans* coupling across a double bond. They quickly deduced that a simple aldol reaction had happened.



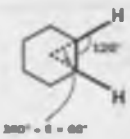
When the Boc protecting group was removed, the cyclization reaction occurred under very mild conditions but now a *single* diastereoisomer of the product was formed.



This isomer had one proton that could be clearly seen at δ_H 4.27 p.p.m.—well away from all the rest. This is the proton marked in black between nitrogen and the phenyl group. It was a double doublet with $J = 6$ and 4 Hz. Neither of these is large enough to be an axial/axial coupling but 6 Hz is within the range for axial/equatorial and 4 Hz for equatorial/equatorial coupling. The compound must have the conformation shown in the margin.

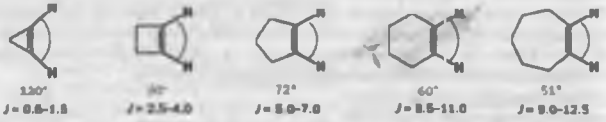
Treatment of this product with stronger base (NaOH) isomerized it to a compound in which the same proton, now at δ_H 3.27 p.p.m., was again a double doublet but with $J = 10$ and 5 Hz. It is now an axial proton so the new conformation is this.

Notice that we have confidently assigned the configuration of these compounds without ever being able to 'see' the yellow proton at the ring junction. Since nitrogen can invert rapidly, we know that this decalin-like structure will adopt the more stable *trans* arrangement at the ring junction.



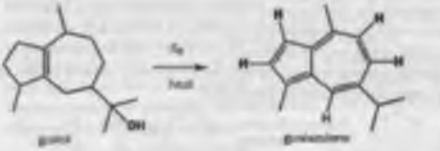
The dihedral angle is not the only angle worth measuring

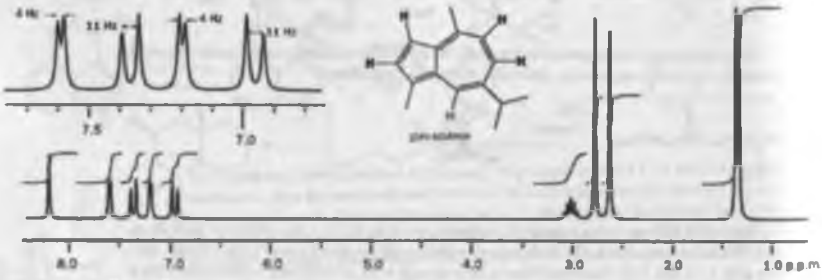
We should also consider how the two C–H bonds are spread out in space. The dihedral angle is what we see when we look down the spine of the book in our earlier analogy (p. 000)—now we want to look at the pages in the normal way, at right angles to the spine, as if we were going to read the book. We can show what we mean by fixing the dihedral angle at 0° (the C–H bonds are in the same plane) and looking at the variation of J with the ring size of cyclic alkenes.

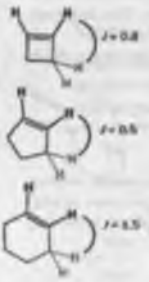


120°	90°	72°	60°	51°
J = 0.5–1.5	J = 2.5–4.0	J = 5.0–7.0	J = 8.5–11.0	J = 9.0–12.5

The wider apart the hydrogens are spread, the smaller the coupling constant. Remember, the dihedral angle stays the same (0°)—we are just varying the angle in the plane. A dramatic illustration of this comes with the product of dehydrogenation of the natural product guaiol with elemental sulfur. From the brown, smelly reaction mixture, guaiazulene, a deep blue oil, can be distilled.





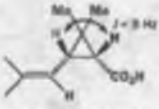


Some assignments are clear. The 6H doublet and the 1H septuplet are the isopropyl group and the two 3H singlets belong to the two methyl groups—we can't really say which belongs to which. The 1H singlet must be the green hydrogen as it has no neighbours and that leaves us with two coupled pairs of protons. One pair has J = 4 Hz and the other J = 11 Hz. We expect to find larger coupling where the H–C–C–H angle is smaller, so we can say that the 4 Hz coupling is between the pair on the five-membered ring and the 11 Hz coupling is between the pair on the seven-membered ring.

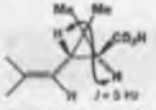
When protons on a double bond in a ring have neighbours on saturated carbon, the coupling constants are all small and for the same reason—the angles in the plane of the ring are approaching 90° even though the dihedral angles are 45–60° in these examples. A bizarre result of this is that the ^3J coupling between the red and black hydrogens is often about the same as the allylic (^4J) coupling between the red and the green hydrogens. An example follows in a moment.

Vicinal (^3J) coupling constants in other ring sizes

The 'spreading out' effect also affects vicinal (^3J) couplings in simple saturated rings. No other ring size has as well defined a conformation as that of the six-membered ring. We can still note useful trends as we move from 6 to 5 to 4 to 3. Briefly, in five-membered rings, *cis* and *trans* couplings are about the same. In four- and three-membered rings, *cis* couplings are larger than *trans*. But in all cases the absolute values of J go down as the ring gets smaller and the C–H bonds are 'spread out' more. Indeed, you can say that *all* coupling constants are smaller in small rings, as we shall see. We need to examine these cases a bit more.



cis chrysanthemic acid



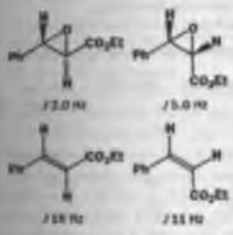
trans chrysanthemic acid

Three-membered rings

Three-membered rings are flat with all bonds eclipsed so the dihedral angle is 0° for *cis* Hs and 104° for *trans* Hs. Looking at the Karplus curve, we expect the *cis* coupling to be larger, and it is. A good example is chrysanthemic acid, which is part of the pyrethrin group of insecticides found in the pyrethrum plant. Both *cis* and *trans* chrysanthemic acids are important.

In both isomers the coupling between the green proton on the ring and its red neighbour on the double bond is 8 Hz. In the *cis* compound, the green proton is a triplet so the *cis* coupling in the ring is also 8 Hz. In the *trans* compound it is a double doublet with the second coupling, *trans* across the ring to the black H, of 5 Hz.

The most important three-membered rings are the epoxides. You saw in Chapter 11 (p. 000) that electronegative atoms reduce coupling constants by withdrawing electron density from the bonds that transmit the coupling 'information'. This means that epoxide couplings are very small—much smaller than those of their closely related alkenes, for example. Compare the four coupling constants in the diagram: for the epoxide, all couplings are small, but *cis* coupling is larger than *trans* coupling. In alkenes, *trans* coupling is larger (Chapter 11, p. 000). The table summarizes the coupling constants for alkenes, epoxides, and cyclopropanes.



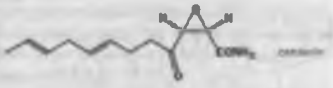
Coupling constants *J*, Hz

Stereochemistry	Alkene	Cyclopropane	Epoxide
cis	10–12	8	5
trans	14–18	5	2

▶ The epoxides have much smaller coupling constants because: (1) the C–C bond is longer; (2) there is an electronegative element; and (3) the 'spreading out' effect of the small ring comes into play.

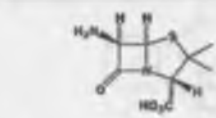
Cerulenin

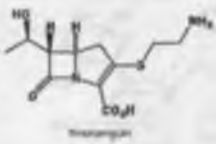
The natural product cerulenin is an antibiotic containing a cis epoxide. The coupling constant between the black hydrogens is 5.5 Hz.


cerulenin

The compound has been made from an unsaturated ketone by epoxidation and ring opening. Follow what happens to the coupling constant between the black hydrogens as this sequence develops.

The *cis* coupling in the alkene is small because it is in a five-membered ring. It gets smaller in the bicyclic epoxide because the black Hs are now in both five- and three-membered rings and both are next to oxygen, but it gets larger in cerulenin itself because the five-membered ring has been opened.





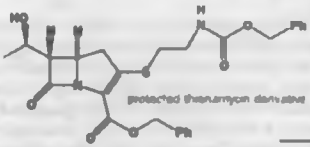
thienamycin

Four-membered rings

A similar situation exists with four-membered rings—the *cis* coupling is larger than the *trans* but they are generally both smaller than those in larger rings. A good example is the amino acid in the margin, the skeleton of the penicillins. The NMR spectrum contains three 1H signals in the middle regions. There is a singlet at δ_H 4.15 p.p.m. that clearly belongs to the isolated green proton and two doublets at δ_H 4.55 and 5.40 p.p.m. that must belong to the black protons. The coupling constant between them is 5 Hz and they are *cis*-related.

There are now large numbers of β-lactam antibiotics known and one family has the opposite (*trans*) stereochemistry around the four-membered ring. The typical member is thienamycin. We will analyse the spectrum in a moment, but first look at the differences—apart from stereochemistry—between this structure and the last. The sulfur atom is now outside the five-membered ring, the acid group is on a double bond in the same ring, and the amino group has gone from the β-lactam to be replaced by a hydroxyalkyl side chain.

Turning to the spectrum and the key question of stereochemistry, this is what the Merck discoverers said in their original article: '^{1}H NMR spectra of thienamycin (and derivatives) ... show small vicinal coupling constants $J \leq 3$ Hz for the two β-lactam hydrogens. Past experience with penicillins ... shows the *cis* relationship of the β-lactam hydrogens to be always associated with the larger coupling.' As we have just seen penicillins have $J = 5$ Hz for these hydrogens.



protected thienamycin derivative

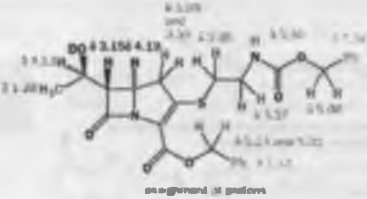
The NMR spectrum of a thienamycin derivative with protecting groups on the amine and carboxylic acids is shown below. Try your hand at interpreting it before you read the explanation below. Your aim is to find the coupling constant across the four-membered ring.

NMR spectrum of thienamycin derivative in CD_3OD

Shift (δ_H), p.p.m.	Integration	Multiplicity	Coupling constants (J), Hz
1.28	3H	d	6.5
2.96	2H	m	not resolved
3.08	1H	dd	9, 18
3.15	1H	dd	2.5, 7
3.38	1H	dd	9, 18
3.37	2H	m	not resolved
4.13	1H	dq	7, 6.5
4.19	1H	dt	2.5, 9
5.08	2H	s	—
5.23 and 5.31	2H	AB system[a]	12.5
5.80	1H	broad	—
7.34	10H	m	not resolved

[a] See p. 000 for discussion of AB systems.

The simple answer is 2.5 Hz. The signals at 3.15 and 4.19 p.p.m. are the protons on the β-lactam ring and the 9 Hz extra coupling is to the CH_2 in the five-membered ring. If you went into this spectrum in detail you may have been worried about the 12.5 and especially the 18 Hz couplings. These are ^2J (geminal) couplings and we will discuss them in the next section.



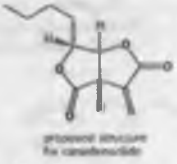
The full assignment is shown above.

We should emphasize that a coupling constant of 5 or 2.5 Hz in isolation would not allow us to assign stereochemistry across the four-membered ring but, when we have both, we can say with confidence that the larger coupling is between *cis* Hs and the smaller coupling between *trans* Hs.

Five-membered rings

You can visualize this conformation of a five-membered ring simply as a chair cyclohexane with one of the atoms deleted. But this picture is simplistic because the five-membered ring flexes (rather than flips) and any of the carbon atoms can be the one out of the plane. All the hydrogen atoms are changing positions rapidly and the NMR spectrum 'sees' a time-averaged result. Commonly, both *cis* and *trans* couplings are about 8–9 Hz in this ring size.

The best illustration of the similarity of *cis* and *trans* couplings in five-membered rings is a structure that was incorrectly deduced for that very reason. Canadensolide is an antifungal compound found in a *Penicillium* mould. The gross structure was quite easy to deduce from the mass spectrum, which gave the formula $C_{11}H_{14}O_4$ by exact mass determination; the infrared, which showed (at 1780 and 1667 cm^{-1}) a conjugated 5-ring lactone; and some aspects of the proton NMR. The proposed structure is shown alongside.

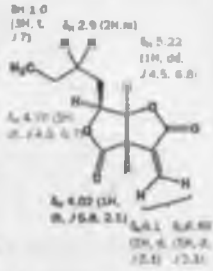


The stereochemistry of the ring junction Hs (shown in black and green) is not in question. They are certain to be *cis* as it is virtually impossible for two five-membered rings to be fused *trans*. The stereochemistry in question involves the third stereogenic centre on the left-hand ring. The coupling constant between the black and green Hs is 6.8 Hz, while that between the green and brown Hs is 4.5. Is this different enough for them to be *trans*? The original investigators decided that it was.

The mistake emerged when some Japanese chemists made this compound by an unambiguous route. The NMR spectrum was quite like that of canadensolide, but not the same. In particular, the coupling between the green and brown Hs was 1.5 Hz—quite different! So they also made the other possible diastereoisomer and found that it was identical to natural canadensolide. The details are in the margin.

a

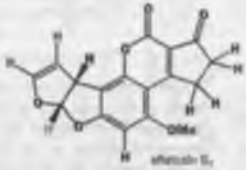
You can convince yourself of this by making a model.



An example of vicinal coupling in structural analysis: aflatoxins

We can bring together a lot of these points in the structure of one compound, the dreaded aflatoxin. Aflatoxin B_1 is an example.

The four red protons on saturated carbons in the five-membered ring in the margin appear as two triplets: δ_H 2.61 (2H, t, *J* 5 Hz) and δ_H 3.42 (2H, t, *J* 5 Hz). The *cis* and *trans* couplings are the same. The yellow proton on the left, on the junction between the two five-membered cyclic ethers, is a doublet δ_H 6.89 (1H, d, *J* 7 Hz). This is, of course, the *cis* coupling to the black hydrogen. The black hydrogen has this coupling too, but it appears as a doublet of triplets with a triplet coupling of 2.5 Hz: δ_H 4.81 (1H, dt, *J* 7, 2.5, 2.5 Hz). These small couplings can only be to the two green hydrogens: the ^3J and ^4J couplings are indeed the same.



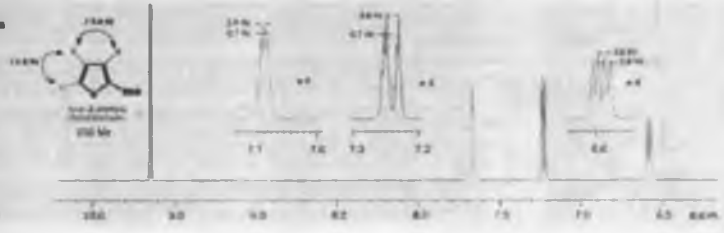
b Aflatoxins

Aflatoxins were mentioned in Chapter 20: they occur in moulds, including those that grow on some foods, and cause liver cancer. These slow-acting poisons are among the most toxic compounds known.

Finally there is another strange coincidence—each green hydrogen appears as a triplet with 2.5 Hz couplings. Evidently, the *cis* coupling across the double bond is also 2.5 Hz. We expect *cis* coupling in a cyclopentene to be small (it was 4 Hz in the azulene on p. 000), but not that small—it must be the electronegative oxygen atom that is reducing the value still further.

Coupling in furans

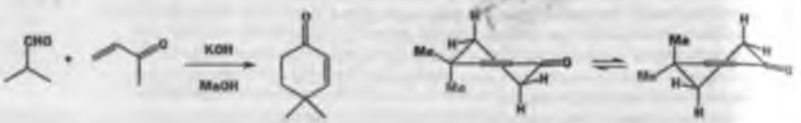
The size of coupling constants in five-membered rings containing oxygen is illustrated clearly in furfuraldehyde (furan-2-aldehyde): note how small the couplings are.



Geminal (^2J) coupling

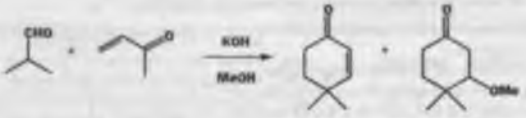
For coupling to be seen, the two hydrogen atoms in question must have different chemical shifts. For ^2J couplings the two hydrogen atoms are on the same carbon atom, so in order to discuss geminal coupling we must first consider what leads the two hydrogens of a CH_2 group to have different shifts.

To introduce the topic, an example. It may seem to you that any six-membered ring might show different chemical shifts for axial and equatorial groups. But this doesn't happen. Consider the result of this Robinson annelation reaction.



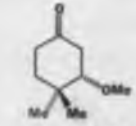
The two methyl groups at C4 give rise to a single signal in the ^{13}C NMR at 27.46 p.p.m. Even though one of them is (pseudo)axial and one (pseudo)equatorial, the molecule exists in solution as a rapidly equilibrating mixture of two conformations. The axial green methyl in the left-hand conformer becomes equatorial in the right-hand conformer, and vice versa for the black methyl group. This exchange is rapid on the NMR time scale and the equilibrium position is 50:50. Time averaging equalizes the chemical shifts of the two methyl groups, and the same is true for the CH_2 groups around the back of the ring.

However, the enone is not the only product of this reaction. A methanol adduct is also formed by Michael addition of methanol to the conjugated enone.

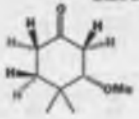


This product has two methyl signals at 26.1 and 34.7 p.p.m. If we examine the molecule by conformational analysis as we did for the first product we see a similar situation.

Similar but not the same. This time, the two conformations are not identical. One has the OMe group equatorial and the other has it axial. Even the two methyl groups do not entirely change places in the two conformations. True, the green methyl is axial on the left and equatorial on the right, but it has a gauche (dihedral angle 60°) relationship with the OMe group in *both* conformations. The black Me group is gauche to OMe on the left but anti-periplanar to the OMe group on the right. When two different conformations, in each of which the black and green methyl groups are different (that is, they don't just change places), are averaged, the two methyl groups are not equalized.



green: syn to OMe
black: anti to OMe



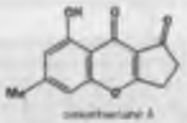
Perhaps a simpler way to discover this is to use a configurational, rather than a conformational, diagram. The green methyl group is on the same face of the molecule as the MeO group, while the black methyl group is on the other face. No amount of ring flipping can make them the same. They are *diastereotopic*, a term we shall define shortly. And so are all three CH_2 groups in the ring. The green Hs are on the same face of the molecule as the MeO group while the black Hs are on the other face.

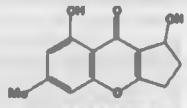
A proton NMR example confirms this, and here is one from an odd source. There are fungi that live on animal dung, called coprophilous fungi. They produce antifungal compounds, presumably to

fight off competition! Anyway, in 1995 two new antifungal compounds were discovered in a fungus living on lemming dung. They were named coniochaetones A and B and their structures were deduced with the usual array of mass and NMR spectra. The proton spectra, run on a 600 MHz machine, are shown below, and they reveal considerable detail.

Coniochaetone A		Coniochaetone B	
δ_H, p.p.m.	Coupling	δ_H, p.p.m.	Coupling
2.41 (3H)	s	2.38 (3H)	s
		5.43 (1H)	ddd, J 1.4, 3.3, 7.8 Hz
2.70 (2H)	m	2.49 (1H)	m
		2.03 (1H)	m
3.07 (2H)	m	3.10 (1H)	dddd, J 1.4, 5.1, 9.4, 18 Hz
		2.81 (1H)	ddd, J 5.1, 9.3, 18 Hz
6.77 (1H)	broad s	6.70 (1H)	broad s
6.89 (1H)	broad s	6.82 (1H)	broad s
12.21 (1H)[a]	s	12.28 (1H)[a]	s

[a] Exchanges with D_2O

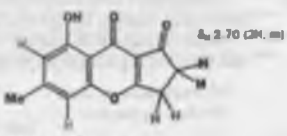


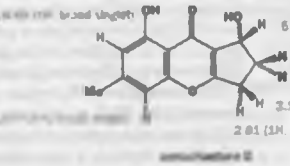


Some of the spectrum is essentially the same for the two compounds, but other parts are quite different. Coniochaetone A has a very simple spectrum, very easily assigned.

Coniochaetone B is rather more interesting. The spectrum is much more complicated, even though it has only one more C–H than coniochaetone A. The reason is that addition of that H atom creates a stereogenic centre and makes the top and bottom faces of the molecule different. Both CH_2 groups become diastereotopic.

The green Hs are coupled to each other (J = 18 Hz) and to each of the black Hs with a different coupling constant. One of the green hydrogens also shows a long-range (^4J = 1.4 Hz) W-coupling to the red H. The black Hs are too complex to analyse, even at 600 MHz, but the different couplings to the red hydrogen are shown by the signal at 5.43 p.p.m.

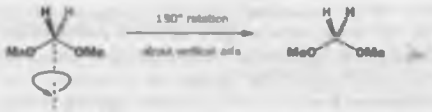




Diastereotopic CH_2 groups

The green protons in the last example couple to one another, so they must be different. Until this chapter, you may have thought it self-evident that two protons attached to the same carbon would be identical, but you have now seen several examples where they are not. It is now time to explain more rigorously the appearance of CH_2 groups in NMR spectra, and you will see that there are *three* possibilities. To do this, we shall have to discuss some aspects of symmetry that build on what you learned in Chapter 1a.

First, an example in which the two hydrogens are indeed the same. We may draw one hydrogen coming towards us and one going away, but the two Hs are the same. This is easy to demonstrate. If we colour one H black and one green, and then rotate the molecule through 180°, the black H appears in the place of the green H and vice versa. The rotated molecule hasn't changed because the other two substituents (OMe here) are also the same.



If we had given out uncoloured models of this molecule with this book, and asked each reader to paint one H green and one H black, we would have no way at all of giving instructions about which to paint what colour. But it wouldn't matter because, even without these instructions, every reader would produce an identical model, whichever way they painted their Hs.

The correct description for this pair of hydrogen atoms is **homotopic**. They are the same (*homo*) topologically and cannot be distinguished by chemical reagents, enzymes, NMR machines, or human beings. The molecule is achiral—it has no asymmetry at all.

● Homotopic groups

Homotopic groups cannot be distinguished by any means whatsoever: they are chemically entirely identical.

What happens when the other two substituents are different? At first sight the situation does not seem to have changed. Surely the two hydrogens are still the same as one another?

In fact, they aren't—not quite. If we had given out uncoloured models of this molecule and just said 'paint one H green and one H black', we would not have got just one type of model.

We would have got about 50% looking like this:

and 50% looking like this:

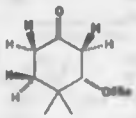
▶ To understand this discussion, it is very important that you appreciate points such as this which we covered in Chapter 16. You may need to refresh your memory of the stereochemical points there before you read further.

But this time, we *could* give instructions about which H we wanted which colour. To get the first of these two, we just need to say 'Take the MeO group in your *left* hand and the Ph group in your *right*, kink the carbon chain upwards. The hydrogen coming towards you is to be painted black.' All the models produced by readers would then be identical—*as long as the readers knew their left from their right*. This is a very important point: the green and black hydrogens in this molecule (unlike the first one) can be described only in phrases incorporating the words 'left' or 'right', and are distinguishable only by a system that knows its left from its right.

Human beings are such a system: so are enzymes, and the asymmetric reagents you will meet in Chapter 45. But NMR machines are not. NMR machines cannot distinguish right and left—the NMR spectra of two enantiomers are identical, for example. It is not a matter of enantiomers in the molecule in question—it has a plane of symmetry and is achiral. Nonetheless, the relationship between these two hydrogens is rather like the relationship between enantiomers (the two possible ways of colouring the Hs are enantiomers—mirror images) and so they are called **enantiotopic**. Enantiotopic protons appear identical in the NMR spectrum.

● Enantiotopic groups

Enantiotopic groups can be distinguished by systems that can tell right from left, but are still magnetically equivalent and appear identical in the NMR spectrum.



The third situation usually arises when the molecule has a stereogenic centre. As an example we can take the Michael product from the beginning of this section.

It is now very easy to distinguish the two hydrogens on each ring carbon atom and, if we want to give instructions on how to paint a model of this molecule, we can just say 'Make all the Hs on the same side of the ring as OMe green, and the ones on the opposite side to OMe black.' We do not need to use the words 'right' or 'left' in the instructions, and it is not necessary to

know your right from your left to tell the two types of Hs apart. Ordinary chemical reagents and NMR machines can do it. These Hs are different in the way that diastereoisomers are different and they are diastereotopic. We expect them to have different chemical shifts in the proton NMR spectrum.

The same is true of the methyl groups: they too are diastereotopic and we expect them to have different shifts.

Diastereotopic groups

Diastereotopic groups are chemically different: they can be distinguished even by systems that cannot tell right from left, and they appear at different chemical shifts in the NMR spectrum.

How to tell if protons are homotopic, enantiotopic, or diastereotopic

What we have said so far explains to you why homotopic and enantiotopic groups appear identical in the NMR spectrum, but diastereotopic protons may not. Now we will give a quick guide to determining what sort of pair you are dealing with in a given molecule.

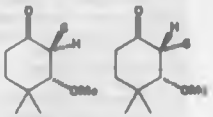
The key is to turn your molecules into two molecules. Replace one of the Hs (we'll assume we're looking at Hs, but the argument works for other groups too—Me groups, for example, as in the last example above) with an imaginary group 'G'. Write down the structure you get, with stereochemistry shown. Next, write down the structure you get by replacing the other H with the group G. Now the more difficult bit: identify the stereochemical relationship between the two molecules you have drawn.

- If they are identical molecules, the Hs are homotopic
- If they are enantiomers, the Hs are enantiotopic
- If they are diastereoisomers, the Hs are diastereotopic

This is really just a simpler way of doing what we did with black and green above, but it is easy to do for any molecule. Take the first of our examples, and replace each H in turn by G.

These two molecules are identical, because just turning one over gives the other: the protons are homotopic. Now for the next example.

The two molecules are not identical: to make one into the other you need to reflect in the plane of the paper, so they are enantiomers, and the Hs are *enantiotopic*. There is another term we must introduce you to in relation to this molecule, which will become useful in the next chapter, and that is 'prochiral'. The molecule we started with here was not chiral—it had a plane of symmetry. But by changing just one of the Hs to a different group we have made it chiral. Molecules that are achiral but can become chiral through one simple change are called prochiral.



Now we will choose one of the three pairs of Hs in the cyclohexanone example. The starting molecule is, of course, now chiral, and the two molecules we get when we replace each H by G are now diastereoisomers: one has G and OMe *anti*, the other *syn*, and the pairs of hydrogens are diastereotopic.

Finally, one last look at symmetry in the three molecules. We will consider two planes as potential planes of symmetry—the plane that bisects the H–C–H angle of the two Hs we are interested in (this is the plane of the paper as we have drawn all three molecules), and a plane at right angles to that plane, passing through the carbon atom and both hydrogen atoms. This second plane is marked on the diagrams in yellow.

This molecule, the most symmetrical of the three, is achiral. The central carbon atom is completely nonstereogenic. Both planes are planes of symmetry and the hydrogens are homotopic. They are chemically and magnetically equivalent.

NMR machines can tell the difference, but it does not follow that they will. There are many examples of protons that are different but have the same chemical shift (toluene, PhMe, shows a singlet in the NMR for all its aromatic protons even though they are of three different kinds). Sometimes diastereotopic protons have the same chemical shift, sometimes slightly different chemical shifts, and sometimes very different chemical shifts.

This slightly less symmetrical molecule is not chiral but *prochiral*. The carbon atom is a pro-chiral (or prostereogenic) centre. The plane of the paper is still a plane of symmetry, but the yellow plane containing the two H atoms is not and the hydrogen atoms are enantiotopic. They are magnetically equivalent and can be distinguished only by humans, enzymes, and other asymmetric reagents.

This least symmetrical molecule is chiral as it has a chiral (stereogenic) centre. The carbon atom we are discussing is not a stereogenic centre but is again a prochiral centre. Neither plane is a plane of symmetry and the hydrogen atoms are diastereotopic. They are chemically and magnetically different and can be distinguished by NMR or by chemical reagents.

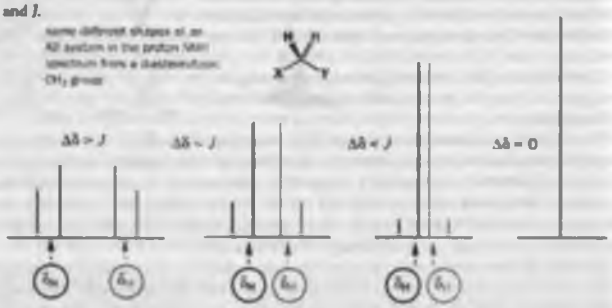
Look back at the structures we have just been discussing and you should see that both the enone used to produce this molecule and coriochaetone A have a plane of symmetry bisecting their CH_2 groups while coriochaetone B does not. This gives another easy way of telling if a pair of groups will appear different in the NMR spectrum. If the plane passing through the carbon atom and bisecting the H–C–H bond angle (the plane of the paper in these diagrams) is a plane of symmetry, then the two Hs (which are reflected in that plane) are magnetically equivalent. (If they also lie in a plane of symmetry, they are homotopic; if they don't, they are enantiotopic.)

The shape of the NMR signal

A prochiral CH_2 group with diastereotopic Hs isolated from any other Hs will give rise to two signals, one for each H, and they will couple to each other so that the complete signal is a pair of doublets. You would expect geminal coupling constants to be larger than vicinal ones simply because the Hs are closer—we are talking about ^2J instead of ^3J couplings. A typical vicinal (^3J) coupling constant for a freely rotating open-chain system without nearby electronegative atoms would be 7 Hz. A typical geminal (^2J) coupling constant is just twice this, 14 Hz.

■ The shape of NMR signals when J and the chemical shift difference are of the same order of magnitude were discussed in Chapter 13. The arguments apply to any coupled protons of similar chemical shift—there we used disubstituted aromatic rings as the example—but are particularly relevant here.

The chemical shift differences ($\Delta\delta$) between Hs on the same carbon atom tend to be small—usually less than 1 p.p.m.—and the coupling constants J tend to be large so the signals usually have $\Delta\delta \sim J$ and are distorted into an AB pattern. The signal may have any of the forms indicated here, depending on the relative sizes of $\Delta\delta$ (the chemical shift difference between the peaks) and J.

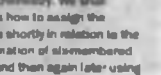


▶ It is not usually easy to decide which proton gives rise to which signal. This is not important in assigning the structure, but may be important in assigning stereochemistry. We shall discuss how to assign the protons shortly in relation to the conformation of six-membered rings, and then again later using the nuclear Overhauser effect.

The coupling constant is always the difference in Hz between the two lines of the same colour in these diagrams, but the chemical shifts are not so easily measured. The chemical shift of each proton is at the weighted mean of the two lines—the more distorted the signal, the nearer the chemical shift to that of the larger inner line.

Examples of AB systems from diastereotopic CH_2 groups

It is time to look at some examples. The insect pheromone frontalin can be drawn like this.

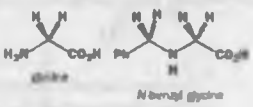


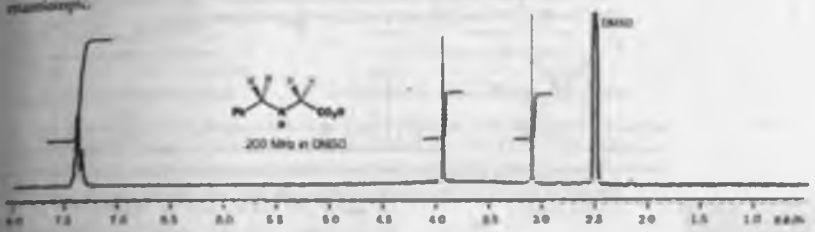
There is nothing wrong with this drawing except that it fails to explain why the black and green hydrogens are different and give a pair of doublets at δ_H 3.42 and 2.93 p.p.m., each 1H, J 7 Hz (an AB

system) in the proton NMR. These protons must be diastereotopic. A conformational diagram should help.

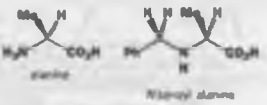
The vital H atoms are on a diaxial bridge across the six-membered ring. Under the black H is an oxygen atom, while under the green H is a three-carbon link. If there were a plane of symmetry between these two Hs, it would have to be the plane marked by the dashed yellow lines in the second diagram. This is *not* a plane of symmetry and the two Hs *are* diastereotopic. They have no neighbours, so they give a simple AB system. The coupling constant here is small for ^2J—only 7 Hz—but that should not surprise you since we have a five-membered ring and a nearby oxygen atom.

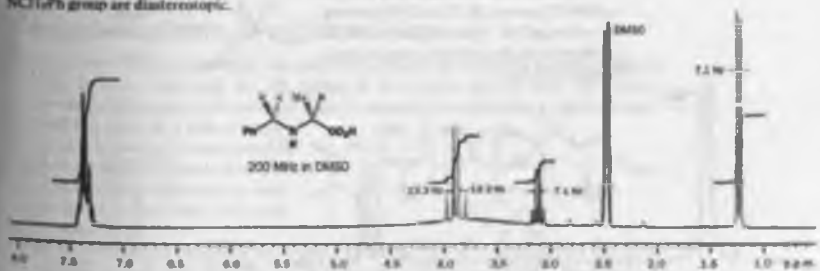
The same principles apply to open-chain compounds, such as amino acids. All of the amino acids in proteins except glycine are chiral. Glycine has a prochiral CH_2 group that gives a singlet in the NMR spectrum as the Hs are enantiotopic. Similarly, the *N*-benzyl derivative of glycine has a second prochiral CH_2 group (NCH_2Ph) that gives another singlet in the NMR spectrum as these Hs too are enantiotopic.





The plane of the paper is a plane of symmetry for both these CH_2 groups in the way they are drawn here. The *N*-benzyl derivatives of the other amino acids are quite different. Each shows an AB signal for the NCH_2Ph group because these molecules have stereogenic centres and there are no planes of symmetry. The Hs of the NCH_2Ph group are diastereotopic.



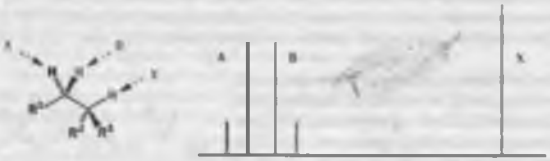


In the way in which the molecule is drawn, the brown H is on the same side as the Me group and the yellow H on the other. It does not matter that there is free rotation in this molecule—there is no conformation you can draw in which the important plane, passing between the diastereotopic Hs through their carbon atom, is a plane of symmetry.

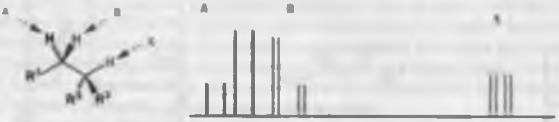
See p. 000 for the use of A, B, X, etc. to describe protons.

The ABX system

It is more common to find diastereotopic CH_2 groups with neighbours, and the most common situation is that in which there is one neighbour, giving an **ABX** system. We will outline diagrammatically what we expect. Let's start with the AB system for the diastereotopic CH_2 group and the single line for the neighbour, which we call 'X' because it's at a quite different chemical shift.



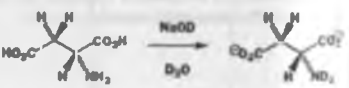
Now we must add the coupling between A and X and between B and X. Since A and B are different, there is no reason why J_{AX} and J_{BX} should be the same. One is normally larger than the other, and both are normally smaller than J_{AB}, since J_{AX} and J_{BX} are vicinal ^3J couplings while J_{AB} is a geminal ^2J coupling. We shall arbitrarily put $J_{AX} > J_{BX}$ in this example.

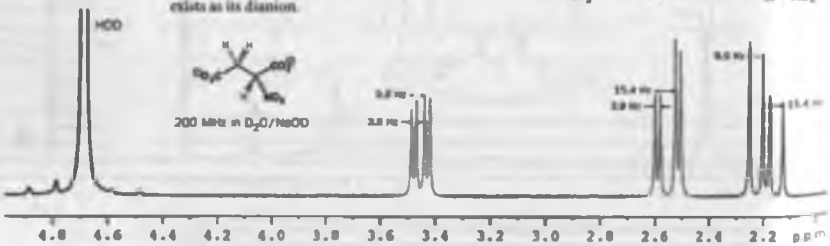


You can read J_{AX} and J_{BX} from the AB part of the signal quite easily by measuring the distance between each pair of lines, in Hz. If you want to read them from the X part, remember that it is made up like this.

In the signal for X, the larger coupling, J_{AX}, is the spacing between lines 1 and 3 or between lines 2 and 4 while the smaller coupling, J_{BX}, is the spacing between lines 1 and 2 or 3 and 4. Naturally, J_{AX} and J_{BX} are the same whether you measure them in the AB signal or in the X signal.

When aspartic acid is dissolved in D_2O with NaOD present, all OH and NH_2 protons are exchanged for deuterium atoms and do not show up in the spectrum—the molecule exists as its dianion.

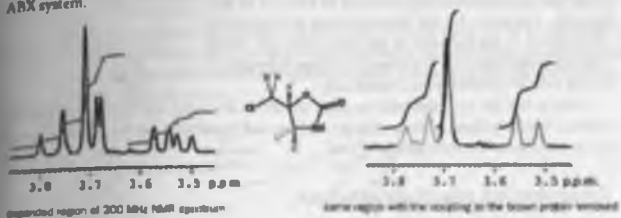




The spectrum consists of a beautiful ABX system with the brown proton as a double doublet at δ_H 3.45 p.p.m. and the black and green protons as an AB pair between 2 and 3 p.p.m. The coupling between red and green is typical: 15 Hz.

More complex examples

We have stressed all along that diastereotopic CH_2 groups may be separated in the proton NMR but need not be. It may just happen that the chemical shift difference is zero giving an A_2 system. It is not possible to predict which diastereotopic CH_2 groups will be revealed in the NMR spectrum as AB systems and which as A_2. Both may even appear in the same molecule. As an example, consider the compound shown below. The brown hydrogen has a very complicated signal, coupling to four other hydrogens. The spectrum for these four hydrogens is also complicated but may be simplified by irradiating the brown hydrogen to remove any coupling to it. Then we can clearly see that one CH_2 group shows itself as diastereotopic while the other does not. From the chemical shifts we may guess that the CH_2Cl group is the A_2X system at 3.7 p.p.m. and that it is the one in the ring that gives the ABX system.



expanded region of 200 MHz NMR spectrum — same region with the coupling to the brown proton removed

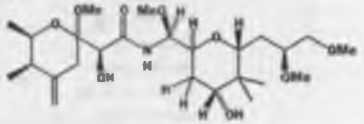
As a general guide, CH_2 groups close to a stereogenic centre are more likely to be revealed as diastereotopic, but it is more likely that the ones next to the stereogenic centre, whether in the ring or in the open chain, will show up as AB systems in the NMR. The remote CH_2 group at the end of the chain is more likely to be A_2 in the NMR, but one cannot be sure. You must be able to recognize diastereotopic CH_2 groups and to interpret AB and ABX systems in the NMR. You must also not be surprised when a diastereotopic CH_2 group appears in the NMR spectrum as an A_2 or A_2X system.

■

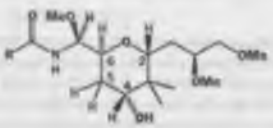
For another example, look back at the compound on p. 800. It contains the two CH_2OH groups, both have a diastereotopic CH_2 pair but one appears as a singlet and one as an AB system.

Geminal coupling in six-membered rings

While we were discussing coupling in rings earlier in the chapter we avoided the question of geminal coupling by never considering the CH_2 groups in the ring. In practice there will often be diastereotopic CH_2 groups in six-membered rings. As an example, we will look at a problem in structure determination of a rather complex molecule. It is pederin, the toxic principle of the blister beetle *Paederus fuscipes*. After some incorrect early suggestions, the actual structure of the compound was eventually deduced.

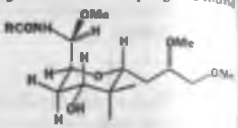


We are not going to discuss the full structure elucidation, but will concentrate on the stereochemistry of the right-hand ring. You can see that there is a CH_2 group in this ring and it has, of course, diastereotopic Hs. At first the OH group was placed at the wrong position on the ring, but a careful analysis of the NMR spectrum put this right and also gave the stereochemistry. The five (green) protons on the ring gave these signals (left-hand part of the molecule omitted for clarity).



δ_H 1.85 (1H, ddd, *J* 5, 10, 12)
2.10 (1H, ddd, *J* 3, 4, 12)
3.75 (1H, dd, *J* 4, 10)
3.85 (1H, ddd, *J* 3, 5, 8)
4.00 (1H dd, *J* 3, 7)

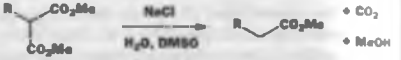
Three of the protons have shifts δ_H 3–4 p.p.m. and are obviously on carbons attached to oxygen atoms. The other two, δ_H about 2 p.p.m., must be the diastereotopic pair at C5. The coupling of 12 Hz, which appears in both signals, must be the geminal coupling and the other couplings are found in the signals at δ_H 3.75 and 3.85 p.p.m. The signal at δ_H 3.75 p.p.m. has no other couplings and must be from C4 so that leaves δ_H 3.85 p.p.m. for the hydrogen atom at C6 which is also coupled to the hydrogen in the side chain. The 10 Hz coupling is axial/axial but the others are all much smaller so we can draw the conformation immediately.



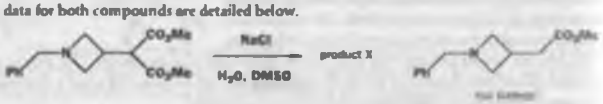
There is just the one axial/axial coupling and so the left-hand side chain must occupy an axial position. This is perhaps a bit surprising—it's large and branched—but the molecule has no choice but to place one of the two side chains axial.

A surprising reaction product

Chapter 26 revealed that sodium chloride can be a surprisingly powerful reagent. It removes ester groups from malonate derivatives, like this.

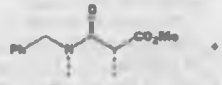


However, using this reaction to decarboxylate the malonate shown here did not merely remove the CO_2Me group. Instead, a compound was formed with a much more complicated NMR spectrum than that of the expected product (which was known as it could be made another way). The NMR data for both compounds are detailed below.



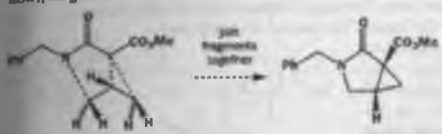
product X		product X			
$C_{14}H_{15}NO_2$		$C_{14}H_{15}NO_2$			
δ_H	7.35–7.25 (3H, m)	δ_C	169.1	δ_H	7.2–7.4 (5H, m, Ph)
	7.2 (2H, d, *J* 7)		169.0		3.65 (3H, s, OMe)
	4.45 (1H, d, *J* 14)		138.2		3.45 (2H, t, *J* 7)
	4.3 (1H, d, *J* 14)		128.8		2.95–2.85 (2H, m)
	3.8 (3H, s, OMe)		128.1		2.85–2.75 (1H, m)
	3.45 (1H, dd, *J* 7, 10)		127.8		2.6 (2H, t, *J* 7)
	3.1 (1H, d, *J* 10)		52.4		
	2.35–2.25 (1H, m)		46.45		
	1.9 (1H, dd, *J* 5, 10)		46.4		
	1.1 (1H, t, *J* 5		31.5		
			22.8		
			20.7		

The unknown product has lost MeOH but retained both carbonyl groups (δ_C 169.1, 169.0 p.p.m. typical for acid derivatives). In the ^{1}H NMR, the phenyl ring and one OMe group are still there. The other striking thing about the ^{1}H NMR is the presence of so many couplings. It looks as if all the hydrogens are magnetically distinct. Indeed we can see one diastereotopic CH_2 at 4.45 and 4.3 p.p.m. with ^2J = 14 Hz. This is the 'normal' value and would fit well for the NCH_2Ph group. But note the chemical shift! For δ_H to be so large the nitrogen atom must be part of an amide, which would also explain the two acid derivative C=O groups. So we have the partial structure on the right.



All that is left is C_3H_5 and this must be fitted in where the dotted lines go. One reasonable interpretation from the NMR would be two diastereotopic CH_2 groups, one with ^2J = 10 and one with ^2J = 5 Hz, linked by a CH group.

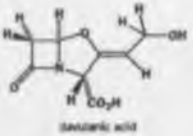
If this is the case, what has brought the values of ^2J down from 14 to 10 and even 5 Hz? Electronegative elements can't be the culprits as the only one is nitrogen, but small rings could. If, in fact, we simply join these two fragments together in rather a surprising way (the dotted lines show how), we get the correct structure.



In this case, the geminal couplings do not help to assign the stereochemistry—the three- and five-membered rings can only be fused *cis* (just try making a model of the *trans* compound!)—but they do help in assigning the structure.

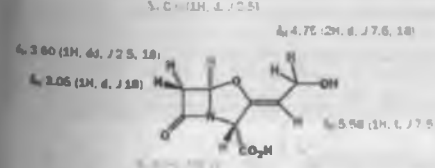
We should at this point just recap what we have done here—we made no attempt to work out the structure by thinking about what the mechanism of the reaction might be. We used, purely and simply, NMR to work out fragments of the structure which we then put together in a logical way. Considering reasonable mechanisms can be a help in structure determination—but it can also be a hindrance. If the product is unexpected, it follows that the mechanism is unexpected too.

For an example with a four-membered ring, we go back to β-lactams. A serious problem with β-lactam antibiotics is that bacteria develop resistance by evolving enzymes called β-lactamases, which break open the four-membered ring. In 1984, a team from Beechams reported the exciting discovery of some very simple inhibitors of these enzymes all based on the core structure named clavulanic acid. This too was a β-lactam but a much simpler one than the penicillins we saw earlier.



clavulanic acid

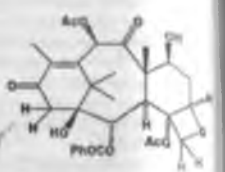
The structure elucidation used all the usual spectroscopic techniques as well as X-ray crystallography, but it is the ^{1}H NMR that is particularly interesting to us here. Here it is, with the assignments shown.



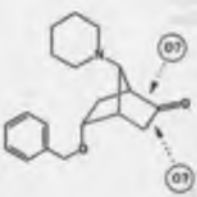
Notice the very large geminal coupling between the red and the black hydrogens (more of this later) and the fact that the green hydrogens, though actually diastereotopic, resonate at the same chemical shift. The *cis* coupling across the four-membered ring is larger (2.5 Hz) than the *trans* coupling (0 Hz) as expected.

The π contribution to geminal coupling

We began this chapter with a diagram of Taxol. This molecule is rather too complex for us to analyse in detail, but the geminal couplings of an important closely related compound are worth noting. Here are the details.

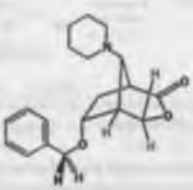


The coupling between the black Hs is 20 Hz while that between the green Hs is 6 Hz. This is a rather extreme example as the green Hs are in a four-membered ring and next to an oxygen atom, so they are expected to show a small J value, while the black Hs are in a six-membered ring and not next to an electronegative element. Nevertheless, 20 Hz is a very large coupling constant. The reason is the adjacent π bond. If a CH_2 group is next to an alkene, aromatic ring, C=O group, CN group, or any other π-bonded functional group, it will have a larger geminal coupling constant. This effect is quite clear in both Taxol and clavulanic acid.

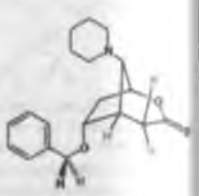


The oxidation of the bicyclic amino-ketone shown in the margin demonstrates how useful this effect can be. This is the Baeyer–Villiger rearrangement, which you will meet in Chapter 37. The mechanism is not important here: all you need to know is that it inserts an oxygen atom on one side or the other of the ketone C=O group. The question is—which side?

In fact, both lactones were isolated and the problem then became—which was which? In both NMR spectra there were AB systems at 4.6–4.7 for diastereotopic CH_2 groups isolated from the rest of the molecule, with ^2J = 11.8 Hz. These are clearly the black and green hydrogens on the benzyl groups. The coupling constant is reduced by the oxygen atom and increased by the phenyl's π contribution, so it ends up about average.



product A



product B

Both lactones also had clear ABX systems in the NMR corresponding to the yellow, brown, and orange protons. In one compound ^2J = 10.8 Hz and in the other ^2J = 18.7 Hz. The smaller value has been reduced by neighbouring oxygen and this must be compound A. The larger value has been increased by the π contribution from the carbonyl group and this must be compound B.

● The size of ^2J and ^3J coupling constants

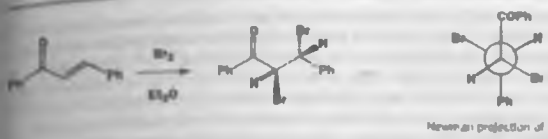
We have now covered all of the important influences on the size of coupling constants. They are:

- dihedral angle: ^3J greatest at 180° and 0°; about 0 Hz at 90°
- ring size, which leads to 'spreading out' of bonds and lower ^2J and lower ^3J in small rings
- electronegative atoms, which decrease ^2J and ^3J coupling constants between protons
- π systems, which increase ^2J coupling constants between protons

The nuclear Overhauser effect

■ We looked at the stereochemistry of elimination reactions in double bonds in Chapter 30.

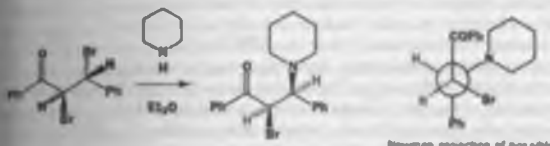
Many occasions arise when even coupling constants do not help us in our quest for stereochemical information. Consider this simple sequence. Bromination of the alkene gives as expected *trans* addition and a single diastereoisomer of the dibromide.



Newman projection of product

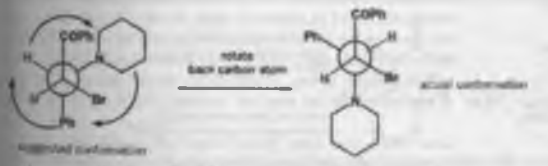
The vicinal (^3J) coupling constant between the two black Hs is 11 Hz. This is rather large and can be explained by a predominant conformation shown in the Newman projection, with the two large groups (PhCO and Ph) as far from each other as possible, the two medium groups (Br) as distant as possible, and the two black Hs in the places which are left. The dihedral angle between the black Hs is then 180° (they are anti-periplanar) and a large J is reasonable.

But now see what happens when we react the dibromide with piperidine. A single diastereoisomer of an amine is formed, and there is good evidence that it has the opposite configuration from the dibromide; in other words, replacement of Br by N has occurred with inversion.

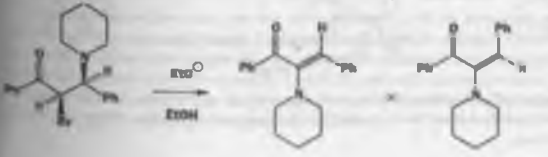


Newman projection of possible conformation of product

We might expect that the conformation would now be different and that, since inversion has occurred, the two green Hs would now be gauche instead of anti-periplanar. With a dihedral angle of 60° the coupling constant would be much less. But it isn't. The coupling constant between the green Hs is exactly the same (11 Hz) as the coupling constant between the black Hs in the starting material. Why? The new substituent (piperidine) is very big, much bigger than Br and probably bigger in three dimensions than a flat Ph group. The conformation must change (all we are doing is rotating the back carbon atom by 120°) so that the two green Hs also have a dihedral angle of 180°.



A more serious situation arises when we treat this product with base. An unusual elimination product is formed, in which the amine group has moved next to the ketone. The reaction is interesting for this point alone, and one of the problems at the end of the chapter asks you to suggest a mechanism. But there is added interest, because the product is also formed as a single geometrical isomer, E or Z. But which one? There is a hydrogen atom at one end of the alkene but not at the other so we can't use ^3J coupling constants to find out as there aren't any.



What we need is a method that allows us to tell which groups are close to one another in space (through not necessarily through bonds) even when there are no coupling constants to help out. Very fortunately, an effect in NMR known as the nuclear Overhauser effect allows us to do this.

The details of the origin of the nuclear Overhauser effect are beyond the scope of this book, but we can give you a general idea of what the effect is. As you learned from Chapter 11, when a proton NMR spectrum is acquired, a pulse of radiofrequency electromagnetic radiation jolts the spins of the protons in the molecule into a higher energy state. The signal we observe is generated by those spins dropping back to their original states. In Chapter 11 it sufficed to assume that the drop back down was spontaneous, just like a rock falling off a cliff. In fact it isn't—something needs to 'help' the protons to drop back again—a process called **relaxation**. And that 'something' is other nearby magnetically active nuclei—usually more protons. Notice *nearby*—nearby in space not through bonds. With protons, relaxation is fast, and the number of nearby protons does not affect the appearance of the NMR spectrum.

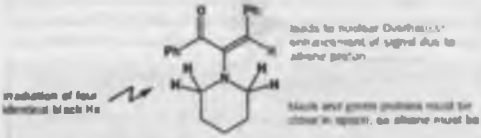
We find that, although peak intensity is independent of the number of nearby protons, by using methods whose description is beyond the scope of this book, it is possible to make the intensity respond, to a small extent, to those protons that *are* nearby. The idea is that as certain protons (or groups of identical protons) are irradiated selectively (in other words, they are jolted into their higher energy state and held there by a pulse of radiation at exactly the right frequency—not the broad pulse needed in a normal NMR experiment). Under the conditions of the experiment, this causes protons that were relying on the irradiated protons to relax them to appear as a slightly more intense (up to a few per cent) peak in the NMR spectrum. This effect is known as the nuclear Overhauser effect, and the increase in intensity of the peak the nuclear Overhauser enhancement. Both are shortened to 'NOE'.

▶ Why you can't integrate ^{13}C NMR spectra

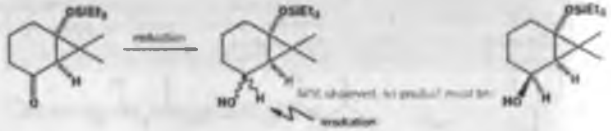
Relaxation is the real reason why you can't integrate ^{13}C signals. Relaxation of ^{13}C is slow, but is fastest with lots of nearby protons. This is the reason that you will often find that $-CH_2$ groups show strong signals in the ^{13}C NMR, while quaternary carbons, with no attached protons, show weak ones. quaternary carbons relax only slowly, so we don't detect such an intense peak. Allowing plenty of time for all ^{13}C atoms to relax between pulses gives more proportionally sized peaks, but at the expense of a very long NMR acquisition time.

All you need to be aware of at this stage is that irradiating protons in an NOE experiment gives rise to enhancements at other protons that are nearby in space—no coupling is required, and NOE is *not* a through-bond phenomenon. The effect also drops off very rapidly: the degree of enhancement is proportional to $1/r^6$ (where r is the distance between the protons) so moving two protons twice as far apart decreases the enhancement one can give to the other by a factor of 64. NOE spectra are usually presented as differences: the enhanced spectrum minus the unenhanced, so that those protons that change in intensity can be spotted immediately.

Applying NOE to the problem in hand solves the structure. If the protons next to the nitrogen atom in the piperidine ring are irradiated, the signal for the alkene proton increases in intensity, so these two groups of protons must be near in space. The compound is the *E*-alkene.

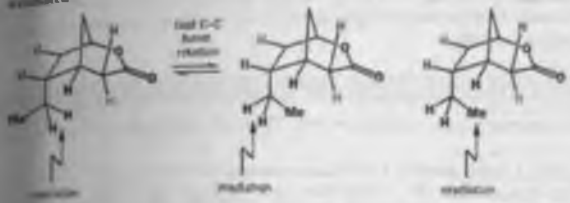


Data from NOE experiments nicely supplement information from coupling constants in the determination of three-dimensional stereochemistry too. Reduction of this bicyclic ketone with a bulky hydride reducing agent gives one diastereoisomer of the alcohol, but which? Irradiation of the proton next to the OH group leads to an NOE to the green proton.



This suggests that the two protons are on the same side of the molecule and that reduction has occurred by hydride delivery to the face of the ketone opposite the two methyl groups on the [illegible] membered ring.

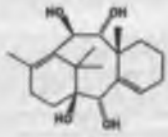
For a more complex example we can return to a lactone (shown in the margin) obtained by oxidation of a bicyclic ketone similar to the one we mentioned earlier (p. 000). When this compound was made, two questions arose. What was the stereochemistry of the ethyl group, and which signal in the NMR spectrum belonged to which hydrogen atom? In particular, was it possible to distinguish the signals of the diastereotopic brown and yellow Ha? Three experiments were carried out, summarized in the diagrams below. First the CH_2 and then the CH_3 protons of the ethyl group were irradiated and the other protons were observed. Finally, the green proton was irradiated.



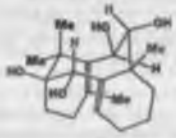
In the first experiment, enhancement of the signals of the black, yellow, and green Ha was observed. The ethyl group can rotate rapidly on the NMR time-scale so all the enhancements can be explained by the first two conformations. An NOE effect to the yellow but not to the brown H is particularly significant. Irradiation of the methyl group led to enhancement of the yellow proton but not the brown. Clearly, the ethyl group is in the position shown.

Irradiation of the green proton, whose stereochemistry is now clear, enhanced the orange proton and allowed its chemical shift to be determined. Previously, it had been lost in the many CHs in the range.

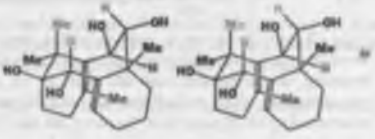
We shall finish this chapter by returning to Taxol once more. The tricyclic compound drawn here was made in 1996 as an intermediate for Taxol synthesis. The stereochemistry and the conformation of the molecule were deduced by a series of NOE experiments.



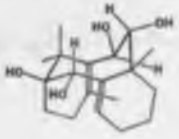
Four NOE experiments were carried out, summarized two at a time in the diagrams on the right. Irradiation of the methyl groups established that the black pair were on the same carbon atom and hence allowed assignment of the spectrum. Then irradiation of the remaining methyl group on saturated carbon established the geometry of the green hydrogens and gave the stereochemistry at three centres.



Next irradiation of the brown methyl group on a double bond showed it was close to the brown hydrogen and gave the stereochemistry at that centre. Finally, irradiation at one of the two methyl groups of the CMe_2 group (yellow) showed that it was close to the two green hydrogens and hence all these three groups were clustered in the centre of the molecule. It's important here to draw a conformational diagram as they do not look very close in the flat diagram shown.



These experiments fixed not only the stereochemistry at all the stereogenic centres but also allowed the conformation of the central eight-membered ring to be deduced. This ring is outlined in black on the diagram in the margin and has two chair-like sections. It is no trivial matter to work out such conformations without X-ray data and the NOE result tells us about the most important conformation *in solution*, rather than in the crystal. The alliance between coupling constants and NOE gives us a powerful method for structural determination.



To conclude...

As you leave this chapter, you should carry the message that, while X-ray crystallography is the 'final appeal' with regard to determining configuration, NMR can be a very powerful tool too. Analysis of coupling constants and nuclear Overhauser effects allows:

- determination of configuration, even in noncrystalline compounds
- determination of conformation in solution

As you embark on the next two chapters, which describe how to make molecules stereoselectively, bear in mind that many of the stereochemical outcomes were deduced using the techniques we have described in this chapter.

Problems

Note. All NMR shifts are in p.p.m. and coupling constants are quoted in hertz. The usual abbreviations are used: d = doublet; t = triplet; and q = quartet.

1 A revision problem to start you off easily. A Pacific sponge contains 2.8% dry weight of a sweet-smelling oil with the following spectroscopic details. What is its structure and stereochemistry?

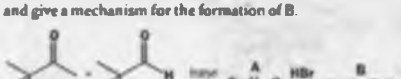
Mass spectrum gives formula: $C_9H_{15}O$

IR 1680, 1635 cm^{-1}

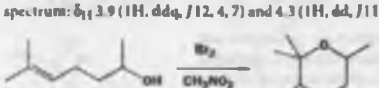
δ_H 0.90 (6H, d, *J* 7), 1.00 (3H, t, *J* 7), 1.77 (1H, m), 2.09 (2H, t, *J* 7), 2.49 (2H, q, *J* 7), 5.99 (1H, d, *J* 16), and 6.71 (1H, dt, *J* 16, 7)

δ_C 8.15 (q), 22.5 (two qs), 28.3 (d), 33.1 (t), 42.0 (t), 131.8 (d), 144.9 (d), and 191.6 (s)

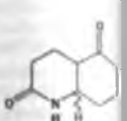
2 Reaction between this aldehyde and ketone in base gives a compound A with the ^1H NMR spectrum: δ 1.10 (9H, s), 1.17 (9H, s), 6.4 (1H, d, *J* 15) and 7.0 (1H, d, *J* 15). What is its structure? (Don't forget stereochemistry!) When this compound reacts with HBr it gives compound B with this NMR spectrum: δ 1.08 (9H, s), 1.13 (9H, s), 2.71 (1H, dd, *J* 1.9, 17.7), 3.25 (dd, *J* 10.0, 17.7), and 4.38 (1H, dd, *J* 1.9, 10.0). Suggest a structure, assign the spectrum, and give a mechanism for the formation of B.



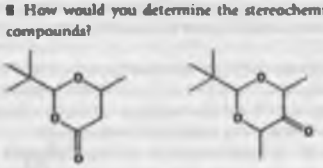
3 In Chapter 20 we set a problem asking you what the stereochemistry of a product was. Now we can give you the NMR spectrum of the product and ask: how do we *know* the stereochemistry of the product? You need only the partial NMR spectrum: δ_H 3.9 (1H, ddq, *J* 12, 4, 7) and 4.3 (1H, dd, *J* 11, 3).



4 Two diastereoisomers of this cyclic keto-lactam have been prepared. The NMR spectra have many overlapping signals but the proton marked in green can clearly be seen. In isomer A it is δ_H 4.12 (1H, q, *J* 3.5), and isomer B has δ_H 3.30 (1H, dt, *J* 4, 11, 11). Which isomer has which stereochemistry?



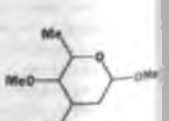
5 How would you determine the stereochemistry of these two compounds?



6 The structure and stereochemistry of the antifungal antibiotic ambruticin was in part deduced from the NMR spectrum of this simple cyclopropane. Interpret the NMR spectrum and show how it gives definite evidence on the stereochemistry.

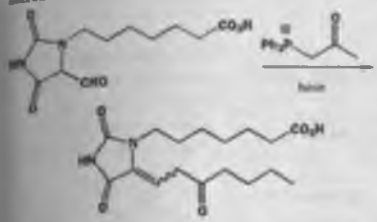
δ_H 1.13 (3H, d, *J* 8), 1.32 (3H, t, *J* 7), 1.47 (9H, s), 1.71 (1H, t, *J* 5), 2.2 (1H, ddq, *J* 5, 12, 7), 4.3 (2H, q, *J* 8), 6.05 (1H, d, *J* 17), and 6.75 (1H, dd, *J* 17, 12)

7 One of the sugar components in the antibiotic kijanimycin has the gross structure and NMR spectrum shown below. What is its stereochemistry? All couplings in Hz, signals marked * exchange with D_2O.

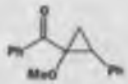


δ_H 1.33 (3H, d, *J* 6), 1.61* (1H, broad s), 1.87 (1H, ddd, *J* 14, 3, 3.5), 2.21 (1H, ddd, *J* 14, 3, 1.5), 2.87 (1H, dd, *J* 10, 3), 3.40 (1H, s), 3.47 (3H, s), 3.99 (1H, dq, *J* 10, 6), 1.33 (3H, d, *J* 6), 4.24 (1H, ddd, *J* 3, 3, 3.5), and 4.79 (1H, dd, *J* 3.5, 1.5)

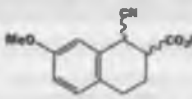
8 The structure of a Wittig product intended as a prostaglandin model was established by the usual methods—except for the geometry of the double bond. Irradiation of a signal at 3.54 (2H, t, *J* 7.5) led to an enhancement of another signal at δ_H 5.72 (1H, t, *J* 7.1) but not to a signal at δ_H 3.93 (2H, d, *J* 7.1). What is the stereochemistry of the alkene? How is the product formed?



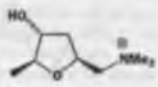
9 How would you determine the stereochemistry of this cyclopropane? The NMR spectra of the three protons on the ring are given: δ_H 1.64 (1H, dd, *J* 6, 8), 2.07 (1H, dd, *J* 6, 10), and 2.89 (1H, dd, *J* 10, 8).



10 A chemical reaction produces two diastereoisomers of the product. Isomer A has δ_H 3.08 (1H, dt, *J* 4, 9, 9) and 4.32 (1H, d, *J* 9, 4) while isomer B has δ_H 4.27 (1H, d, *J* 4). The other protons overlap. Isomer B is converted into isomer A on treatment with base. What is the stereochemistry of A and B?

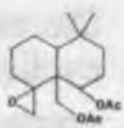


11 Muscarine, the poisonous principle of the death cap mushroom, has the following structure and proton NMR spectrum. Assign the spectrum. Can you see definite evidence for the stereochemistry? All couplings in Hz; signals marked * exchange with D_2O.



δ_H 1.16 (3H, d, *J* 6.5), 1.86 (1H, ddd, *J* 12.5, 9.5, 5.5), 2.02 (1H, ddd, *J* 12.5, 2.0, 6.0), 3.36 (9H, s), 3.54 (1H, dd, *J* 13, 9.0), 3.74 (1H, dd, *J* 13, 1.0), 3.92 (1H, dq, *J* 2.5, 6.5), 4.03 (1H, m), 4.30* (1H, d, *J* 3.5), and 4.68 (1H, m).

12 An antifeedant compound that deters insects from eating food crops has the gross structure shown below. Some of the NMR signals that can clearly be made out are also given. Since NMR coupling constants are clearly useless in assigning the stereochemistry, how would you set about it?



δ_H 2.22 (1H, d, *J* 4), 2.99 (1H, dd, *J* 4, 2.4), 4.36 (1H, d, *J* 12.3), 4.70 (1H, dd, *J* 4.7, 11.7), 4.88 (1H, d, *J* 12.3)

13 The seeds of the Costa Rican plant *Ateleia herbert smithii* are avoided by all seed eaters (except a weevil that adapts them for its defence) because they contain two toxic amino acids (IR spectra like other amino acids). Neither compound is chiral. What is the structure of these compounds? They can easily be separated because one (A) is soluble in aqueous base but the other (B) is not.

A is $C_6H_{14}NO_4$ (mass spectrum) and has δ_C 34.0 (d), 40.0 (t), 56.2 (s), 184.8 (s), and 186.0 (s). Its proton NMR has three exchanging protons on nitrogen and one on oxygen and two complex signals at δ_H 2.68 (4H, A_2B_2 part of A_2B_2X system) and 3.37 (X part of A_2B_2X system) with J_{AB} 9.5, J_{AX} 9.1, and J_{BX} small.

B is $C_6H_9NO_2$ (mass spectrum) and has δ_C 38.0 (d), 41.3 (t), 50.4 (t), 75.2 (s), and 173.0 (s). Its proton NMR spectrum contains two exchanging protons on nitrogen and δ_H 1.17 (2H, ddd, *J* 2.3, 6.2, 9.5), 2.31 (2H, broad m), 2.90 (1H, broad t, *J* 3.2), and 3.40 (2H, broad s).

Because the coupling pattern did not show up clearly as many of the coupling constants are small, decoupling experiments were used. Irradiation at δ_H 3.4 simplifies the δ_H 2.3 signal to (2H, ddd, *J* 5.8, 3.2, 2.3), sharpens each line of the ddd at 1.17, and sharpens the triplet at 2.9.

Irradiation at 2.9 sharpens the signals at 1.17 and 2.9 and makes the signal at 2.31 into a broad doublet, *J* about 6. Irradiation at 2.31 sharpens the signal at 3.4 slightly and reduces the signals at 2.9 and 1.17 to broad singlets. Irradiation at 1.17 sharpens the signal at 3.4 slightly so that it is a broad doublet, *J* about 1.0, sharpens the signal at 2.9 to a triplet, and sharpens up the signal at 2.31 but irradiation here had the least effect.

This is quite a difficult problem but the compounds are so small (C_6 only), have no methyl groups, and have some symmetry so you should try drawing structures at an early stage.

Stereoselective reactions of cyclic compounds

33

Connections

Building on:

- Stereochemistry ch16
- Conformational analysis ch18
- Determination of stereochemistry by spectroscopy ch32

Arriving at:

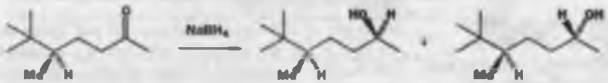
- Stereoselectivity in cyclic systems is easy to understand
- Flattened four- and five-membered rings are attacked *anti* to large substituents
- Flattened six-membered rings are attacked from an axial direction
- Bicyclic structures are attacked on the *exo* side face
- Tethering together nucleophile and electrophile forces one stereochemical outcome
- Hydrogen-bonding can reverse the normal stereochemical outcome of a reaction

Looking forward to:

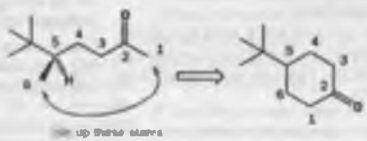
- Diastereoselectivity ch34
- Asymmetric synthesis ch45
- Organic synthesis ch53
- Pericyclic reactions ch35–ch36

Introduction

This chapter is about rings and stereochemistry. Stereochemistry is easier to understand in cyclic compounds and that alone might make a separate chapter worthwhile. But there is something much more fundamental behind this chapter. Stereochemistry is better behaved in cyclic compounds. Suppose you were to reduce this ketone to one of the corresponding alcohols.



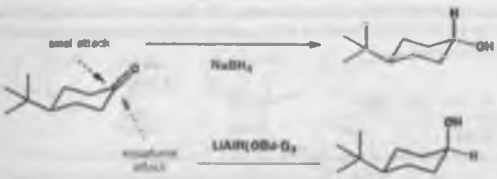
There would be very little chance of any control of stereochemistry at the new stereogenic centre (shown in black). A more or less 50:50 mixture of the two diastereoisomers would be expected. However, if we join up the molecule into a ring, things are suddenly quite different. (This is not, of course, a chemical reaction—just a thought process!)



The cyclic ketone has a fixed conformation controlled by the determination of the *t*-butyl group to be equatorial. Reduction can be controlled to give almost exclusively either the axial or the equatorial alcohol as we explained in Chapter 18. Large reagents prefer to approach equatorially while small reagents like to put the new OH group into an equatorial position. These are *stereoselective* reactions, and, because the two different outcomes are diastereoisomers, we can call them **diastereoselective**.

■

If your memory of Chapter 18's discussion of axial and equatorial attack on cyclohexanones is dim, you should refresh it now. We shall use several examples that build on what we said there (p. 000).



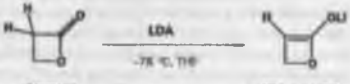
The key to the difference is in the conformations. The cyclic ketone has one conformation and the two approaches to the faces of the ketone are very different. The open-chain compound has an indefinite number of conformations as rotation about all the C–C bonds is possible. In any one conformation, attack on one face of the ketone or the other may happen to be preferred, but on average there will be very little difference. There is all the difference in the world between cyclic and open-chain compounds when it comes to stereoselective reactions. This is why we have made this topic into two chapters: this one (33) dealing with rings, the next (34) with what happens without rings.

In this chapter we shall look at reactions happening to cyclic compounds, reactions that close rings (cyclizations), and reactions with cyclic intermediates and with cyclic transition states. We shall investigate what happens to stereochemistry when two (or even more) rings are joined together at a bond or at an atom. We shall see how stereochemical effects change as the ring size increases from three atoms to eight or more. You will find that you have met some of the reactions before in this book. This chapter collects them together and explains the principles of stereochemical control in cyclic systems as well as introducing some new reactions.

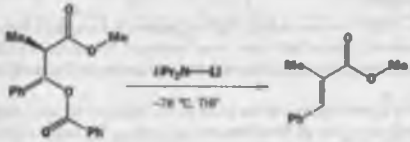
Reactions on small rings

Four-membered rings can be flat

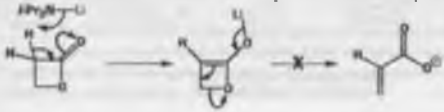
The smallest ring that we can conveniently work on is four-membered. Saturated four-membered rings have a slightly bent conformation but four-membered lactones are flat. The enolates of these lactones can be made in the usual way with LDA at –78 °C and are stable at that temperature.



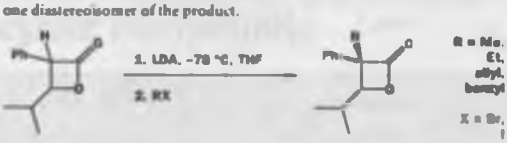
The formation of the lithium enolate is straightforward but it might be expected to be unstable because of a simple elimination reaction. It is not possible to make open-chain lithium enolates with β oxygen substituents like this because they do undergo elimination.



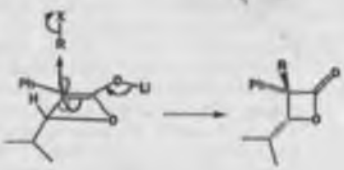
But, in the four-membered ring, the p orbitals of the enolate and the C–O single bond are orthogonal (see drawing in margin) so that no interaction between them, and no elimination, can occur. The enolate can be combined with electrophiles in the usual way (Chapters 26 and 27).



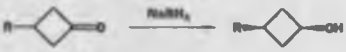
If the β-lactone has a substituent already then there may be a choice as to which face of the enolate is attacked by an electrophile. Simple alkylation with a variety of alkyl halides gives essentially only one diastereoisomer of the product.



The enolate, as we have seen, is planar, the phenyl group is in the plane (so it doesn't matter which of the two possible diastereoisomers of the starting material is used), and the isopropyl group is the only thing out of the plane. The electrophile simply adds to the face of the enolate not blocked by the isopropyl group. This is a very simple case of a diastereoselective reaction.



Reduction of substituted four-membered ring ketones is usually reasonably stereoselective. If the substituent is in the 3-position and small reagents like $NaBH_4$ are used, the *cis* isomer is favoured.



This result sounds very like the results already noted for six-membered rings and the explanation is similar. Saturated four-membered rings—even the ketones—are slightly puckered to reduce eclipsing interactions between hydrogen atoms on adjacent carbon atoms, and 'axial' attack by the small nucleophile gives the more stable *cis* product having both substituents 'equatorial'.

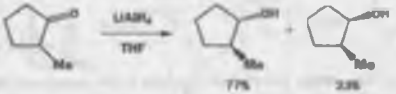
Five-membered rings are flexible

We discussed the conformation of some five-membered rings in Chapter 32: a saturated five-membered ring has a conformation variously called a 'half-chair' or an 'envelope'. It does look a bit like an opened envelope with one atom at the point of the flap, or it looks like most of (five-sixths rather than half?) a chair cyclohexane.

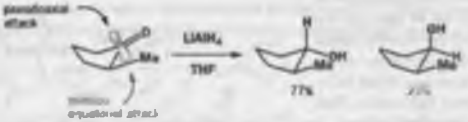
At any one moment, one of the carbon atoms is at the point of the envelope but rapid ring flipping equilibrates all these conformers so that all five atoms are, on average, the same. Substituted cyclopentanes can have substituents in pseudoaxial or pseudoequatorial positions or on the point position, like this.

[illegible] substituents on cyclopentanes.

The result is a very flexible system that often behaves in stereoselective reactions as if the two positions on any carbon atom are the same.



As you can see, reduction of 2-substituted cyclopentanones may not be very stereoselective. The substituent probably occupies a pseudoequatorial position and the two faces of the ketone are very similar.

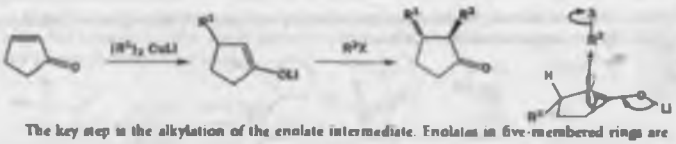


What selectivity there is (about 3:1) favours pseudoaxial attack in the conformation drawn as is reasonable for a small nucleophile. The use of a much more bulky reducing agent such as $LiBH(s\text{-}Bu)_3$ dramatically reverses and increases the stereoselectivity. Essentially only the *cis* compound is formed because the bulky reagent attacks the side of the carbonyl opposite to the methyl group.

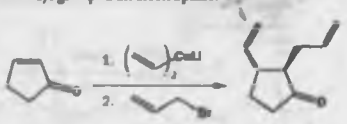
When there are two or three trigonal carbons in the ring, the ring is flatter, and reactions such as enolate alkylation and conjugate addition give excellent stereoselectivity even with a simple cyclopentane ring. Unsaturated five-membered lactones ('butenolides') give a very clear illustration of stereochemically controlled conjugate addition. There is only one possible stereogenic centre and the ring is almost planar so we expect nucleophilic attack to occur from the less hindered face. Cuprates are good nucleophiles for this reaction and here Me_2CuLi adds to the unsaturated lactone.

The starting material was a single enantiomer and hence so is the product—an insect pheromone.

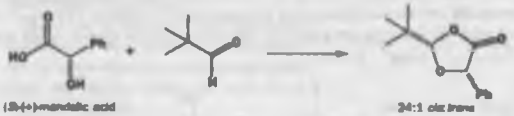
It is not even necessary to have a stereogenic centre in an unsaturated ring if we want to create stereochemistry. A tandem conjugate addition and alkylation creates two new stereogenic centres in one operation. The conjugate addition of a lithium cuprate makes a lithium enolate, which will react in turn with an alkyl halide. The product is usually *trans*.



The key step is the alkylation of the enolate intermediate. Enolates in five-membered rings are almost flat and the incoming alkyl halide prefers the less hindered face away from the recently added group R. The example below shows that, if both new groups have double bonds in their chains, it is easier to add a vinyl group as the nucleophile and an allyl group as an electrophile.



Our main example of enolate reactions in five-membered rings is one of some general importance. It illustrates how stereochemical information can be transmitted across a ring even though the original source of that information may be lost during the reaction. That may sound mysterious, but all will become clear. The first reaction is to make a five-membered cyclic acetal from an optically active hydroxy-acid. Our example shows (*S*)-(+)-mandelic acid reacting with *t*-BuCHO.



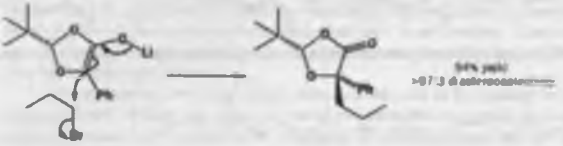
(*S*)-(+)-mandelic acid

24:1 *cis*:*trans*

Acetal formation involves nucleophilic attack of the OH group on the aldehyde so there is no change at the stereogenic centre. The stereochemistry of the new (acetal) centre may surprise you—why should the *cis*-isomer be so favoured? This is a conformational effect as both substituents can occupy pseudoequatorial positions.

Now, if we make the lithium enolate with LDA, the original stereogenic centre is destroyed as that carbon becomes trigonal. The only stereogenic centre left is the newly introduced one at the acetal position.

The ring is now flattened by the alkene and reaction of the enolate with an electrophile is again a simple matter of addition to the face of the enolate opposite to the *t*-butyl group.

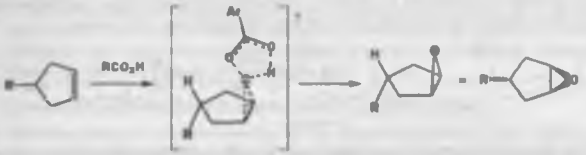


If the acetal is now hydrolysed, the new stereogenic centre is revealed as an alkylated version of the starting material. It may appear that the alkylation has happened stereospecifically with retention, but what has really happened is that the new stereogenic centre in the acetal intermediate has relayed the stereochemical information through the reaction.

Five-membered rings also allow us to explore electrophilic attack on alkenes. A simple 4-substituted cyclopentene has two different faces—one on the same side as the substituent and one on the opposite side. Epoxidation with a peroxy-acid occurs preferentially on the less hindered face.

Make sure this reaction is stereoselective—but neither starting material nor products are chiral. Diastereoselectivity never figures nothing to do with chirality!

The mechanism of S_N2 ring opening was discussed on p. 000

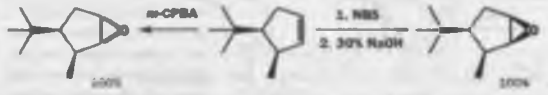


In the transition state (marked ‡) the peroxyacid prefers to be well away from R, even if R is only a methyl group. The selectivity is 76:24 with methyl. The opposite stereoselectivity can be achieved by bromination in water. The bromonium ion intermediate is formed stereoselectively on the less hindered side and the water is forced to attack stereospecifically in an S_N2 reaction from the more hindered side.

Treatment of the product with base (NaOH) gives an epoxide by another S_N2 reaction in which oxygen displaces bromide. This is again stereospecific and gives the epoxide on the same side as the group R.

Two substituents on the *same side* of a five-membered ring combine to dictate approach from the other side by any reagent, and the two epoxides can be formed each with essentially 100% selectivity.

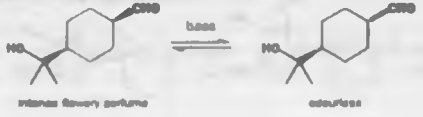
Bromohydrin—NBS acts as a source of electrophilic bromine see p. 000 of Chapter 20.



Stereochemical control in six-membered rings

From five-membered rings we move on naturally to six-membered rings. As well as the opportunity for more stereogenic centres around the larger ring, we have the additional prospect of conformational control—something special to six-membered rings because of their well-defined conformational properties. We shall start with simple reactions occurring on the opposite face to existing substituents and move on to conformational control, particularly to one theme—axial addition.

First, something about thermodynamic control. Because of the strong preference for substituents to adopt the equatorial position, diastereoisomers may equilibrate by processes such an enolization. For example, this fine perfumery material is made worthless by enolization.



The situation is bad because the worthless compound is preferred in the equilibrium mixture (92:8). This is because the two substituents are both equatorial in the *trans*-isomer.

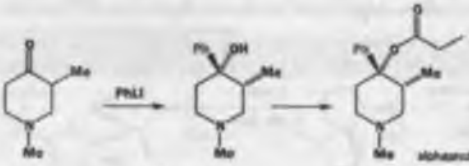
Although a disadvantage here, in other cases equilibration to the more stable all-equatorial conformation can be a useful source of stereochemical control. You will very shortly see an example of this.

Stereoselectivity in reactions of six-membered rings

We discussed the reduction of cyclohexanones in Chapter 18 and established that reducing agents prefer the equatorial approach while small reagents may prefer to put the OH group in the more stable equatorial position. If the nucleophile is not H but something larger than OH then we can expect equatorial attack to dominate both because of ease of approach and because of product stability.

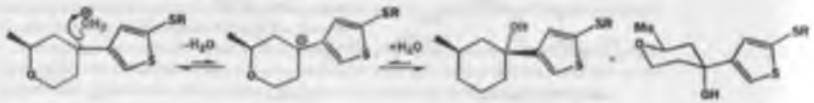
A simple example is the addition of PhLi to the heterocyclic ketone below which has one methyl group next to the carbonyl group. This methyl group occupies an equatorial position and the incoming phenyl group also prefers the equatorial approach so that good stereoselectivity is observed.

This product was used in the preparation of the analgesic drug alphaprodine. We shall represent the reaction now in configurational terms. It is important for you to recognize and be able to draw both configurational (as below) and conformational (as above) diagrams.



When the stereogenic centre is further away from the site of attack, the stereoselectivity may not be so good. Zeneca have announced the manufacture of a drug by the addition of a lithiated thiophene to another heterocyclic ketone, which initially gave a mixture of diastereoisomers.

Such a mixture is no good for manufacture of a pure drug, but the compound can be equilibrated in dilute acid by repeated S_N1 formation of a tertiary benzylic cation and recapture by water so that the required product (which is more stable as it has both Me and the thiophene equatorial) dominates by 92:8 and can be purified by crystallization. The unwanted isomer can be recycled in the next batch.



In these reactions the molecule has a free choice whether to place a substituent in an axial or equatorial position and this is the only consideration because the starting materials in the reactions—ketones or carbocations—have six-membered rings that are already in the chair conformation even though they have one trigonal (sp^2) atom in the ring.

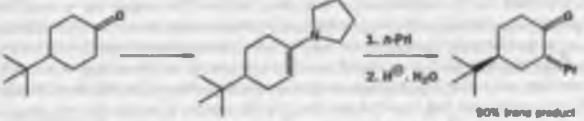
Axial attack is preferred with unsaturated six-membered rings

When the starting material for a reaction has two or more trigonal (sp^2) atoms in the ring, it is no longer in the chair conformation. In these cases, the stereochemistry of the reaction is likely to be driven by the need for the transition state and product to have a chair rather than a boat conformation. This can override the preference for substituents to go into equatorial positions. This is the basis for axial attack on enolates, cyclohexenes, and enones.

● The number of trigonal carbon atoms in the ring is important

- Six-membered rings with one trigonal (sp^2) carbon atom can undergo axial or equatorial attack
- Six-membered rings with two or more trigonal carbon atoms undergo *axial attack* in order to form chairs rather than boats. The final product may end up with axial or equatorial substitution, but this is not a consideration in the reaction itself

Alkylations of enolates, enamines, and silyl enol ethers of cyclohexanone usually show substantial preference for axial attack. The enamine of 4-*t*-butylcyclohexanone, which has a fixed conformation because of the *t*-butyl group, gives 90% axial alkylation and only 10% equatorial alkylation with *n*-PrI.

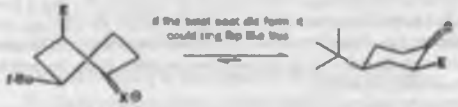


It is a simple matter to show that the preferred product has the new propyl group in the axial position because both the starting ketone and the product have chair conformations with the *t*-butyl equatorial.

To get at the explanation we need to look at the conformation of the enamine intermediate. At this point we shall generalize a bit more and write a structure that represents any enol derivative where X may be OH, O^-, $OSiMe_3$, NR_2, and so on. The conformation has a double bond in the ring, and is a partially flattened chair, as described in Chapter 18.

The *t*-butyl group is in an equatorial position at the back of the ring. The electrophile must approach the enol derivative from more or less directly above or below because only then can it attack one of the lobes of the p orbital at the enol position shown in yellow. The top of the molecule looks to be more open to attack so we shall try that approach first.

As the electrophile bonds to the trigonal carbon atom, that atom must become tetrahedral and it does so by forming a vertical bond upwards. The result is shown in the diagram—the ring turns into a twist-boat conformation. Now, of course, after the reaction is over, the ring can flip into a chair conformation and the new substituent will then be equatorial, but that information is not present in the transition state for the reaction. We could say that, at the time of reaction, the molecule doesn't 'know' it can later be better off and get the substituent equatorial: all it sees is the formation of an unstable twist boat with a high-energy transition state leading to it.

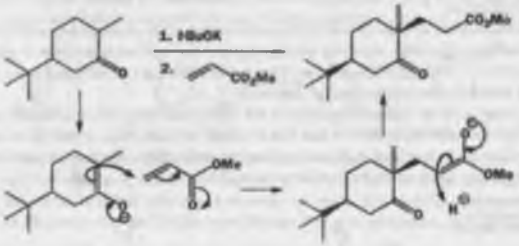


Attack from the apparently more hindered bottom face makes the trigonal carbon atom turn tetrahedral in the opposite sense by forming a vertical bond to the electrophile downwards. The ring goes directly to a chair form with the electrophile in the axial position.

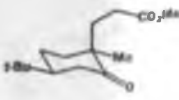
When the carbonyl group is restored by hydrolysis (if necessary—X may be O already) the ring need not flip: it's already a chair with the *t*-butyl equatorial, and the new substituent is axial on the chair. This is the observed product of the reaction.

It's important that you understand what is going on here. The reagent *has* to attack from an axial direction to interact with the p orbital. If it attacks from above, the new substituent is axial on an unstable twist boat. If it attacks from below, the new substituent is axial on a chair—granted, this is not as good as equatorial on a chair, but that's not an option—it has to be axial on something, and a chair is better than a twist boat. So this is the product that forms. It's just hard luck for the substituent that it can't know that *if it did* weather it out on the twist boat it could later get equatorial—it plumps for life on the easy chair and so has to be content with ending up axial.

Here is an example with an unsaturated carbonyl compound as an electrophile: the reaction is Michael addition. The ketone here is slightly *different*—it has the *t*-butyl group in the 3- rather than the 4-position and the reacting centre becomes quaternary during the Michael reaction. But the result is still axial attack.



This result is more impressive because the large electrophile ends up on the *same* side of the ring as the *t*-butyl group, so the stereoselectivity cannot be based on any simple idea of reaction on the less hindered side of the ring. It is genuine axial attack, as the conformational diagram of the product confirms.

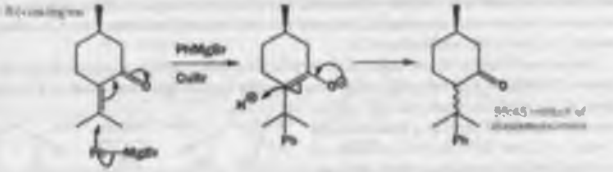


Cyclohexenones are even flatter than cyclohexenes, but it is convenient to draw them in a similar conformation. Conjugate addition to this substituted cyclohexenone gives the *trans* product.

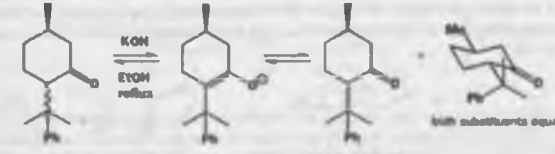
This is also axial addition to form a chair directly (rather than a twist boat) with the nucleophile approaching from the bottom. We must draw the ring as a flattened chair.

The 5-alkyl cyclohexenone that we have chosen as our example gives the best results. The mechanism suggests that the enolate intermediate is protonated on the top face (axial addition again) though we cannot tell this. But, if we carry out a tandem reaction with the enolate trapped by a different electrophile, the product is again that of axial attack.

We shall end this section on conformational control in six-membered rings with the preparation of a useful chiral molecule 8-phenylmenthol from the natural product (*R*)-(+)-pulegone. The first step is a conjugate addition to an exocyclic alkene. A new stereogenic centre is formed by protonation of the enolate intermediate but with virtually no stereoselectivity.

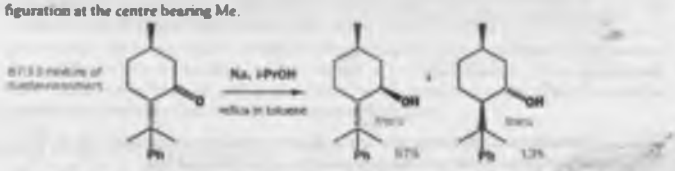


Now thermodynamic control can be brought into play. The position next to the ketone can be epimerized via the enolate to give the more stable isomer with both substituents equatorial. This improves the ratio of diastereoisomers from 55:45 to 87:13.



Now the ketone can be reduced with a small reagent—Na in *i*-PrOH works well—to put the hydroxyl group equatorial. This means that all the product has OH *trans* to the large group next to

the ketone, though it is still an 87:13 mixture of diastereoisomers with respect to the relative configuration at the centre bearing Me.



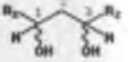
These alcohols can be separated (they are, of course, diastereoisomers and not enantiomers) and the major, all-equatorial one is the useful one (see Chapter 45). This is an impressive example of conformational control by thermodynamic and by kinetic means using only a distant methyl group in a six-membered ring.

Conformational control in the formation of six-membered rings

In Chapter 32 we solved a structural problem from the aldol reaction of pentan-3-one and 4-chlorobenzaldehyde in basic solution. The product turned out to be a six-membered cyclic keto-ether.

Once you know the gross structure of the product, the stereochemistry should be no surprise. This is a typical thermodynamically controlled formation of a six-membered ring with all the substituents equatorial.

Any reaction that is reversible and that forms a six-membered ring can be expected to put as many substituents as possible in the thermodynamically favourable equatorial position. This principle can be used in structure determination too. Suppose you have one diastereoisomer of a 1,3-diol and you want to find out which stereoisomer it is.



Having read Chapter 32 you might think of using the NMR coupling constants of the two black protons. But that will do no good because the molecule has no fixed conformation. Free rotation about all the σ bonds means that the Karplus equation cannot be used as a time-averaged J value of about 6–7 Hz will probably be observed for both protons regardless of stereochemistry. But suppose we make an acetal from the 1,3-diol with benzaldehyde.

This may not seem to help much. But acetal formation is under thermodynamic control, so the most stable possible conformation will result with the large phenyl group equatorial and the two R groups either both equatorial or one equatorial and one axial, depending on which diastereoisomer you started with.

Now the molecule has a fixed conformation and the coupling constants of the black Hs to the neighbouring CH_2 group can be determined—an axial H will show one large J value, an equatorial H only small J values.

This section has been strong on thermodynamic control but weak on the more common kinetic control. This will be remedied in Chapter 35 where you will meet the most important cyclisation reaction of all—the Diels–Alder reaction. It is under kinetic control and there is a great deal of stereochemistry associated with it.

Stereochemistry of bicyclic compounds

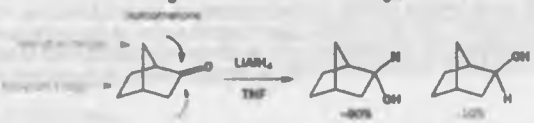
There are broadly three kinds of bicyclic compounds, some of which you have met before (Chapter 18, for example). If we imagine adding a new five-membered ring to one already there, we could do this in a bridged, fused, or *spiro* fashion. Bridged bicyclic compounds are just what the name implies—a bridge of atom(s) is thrown across from one side of the ring to the other. Fused bicyclic compounds have one *bond* common to both rings, while *spiro* compounds have one *atom* common to both rings.

You will notice that these three types of bicyclic compounds with five-membered rings have different numbers of atoms added to a 'parent' five-membered ring. The bridged compound has two extra atoms, the fused compound three, and the *spiro* compound four. These are marked in green with the original five-membered ring in red. We shall consider stereoselectivity in each of these types of bicyclic ring systems, starting with bridged structures.

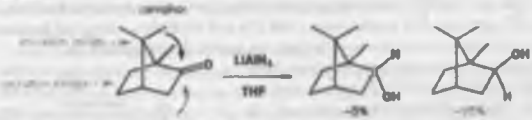
A selection of important bridged bicyclic compounds is shown below, with the various ring sizes indicated in black.

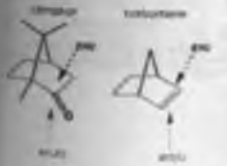
Bridged structures (sometimes called cage structures) are generally very rigid—the only exception among these examples is the bottom right-hand portion of cocaine. This rigidity is reflected in the stereochemistry of their reactions.

Attack on this unsubstituted bridged ketone—norbornenone—occurs predominantly from the side of the one-atom bridge rather than the two-atom bridge.



This selectivity is completely reversed in camphor because the one-atom bridge then carries two methyl groups. One of these must project over the line of approach of the hydride reducing agent.

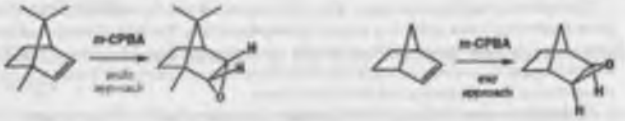




The two methyl groups on the bridge of the camphor molecule are key features in stereoselective reactions—take them away and the result often changes dramatically. This bicyclic system, with and without methyl groups, has been so widely used to establish stereochemical principles that the two faces of, say, the ketone group in camphor, or the alkene in norbornene, have been given the names *endo* and *exo*. These refer to inside (*endo*) and outside (*exo*) the boat-shaped six-membered ring highlighted in orange.

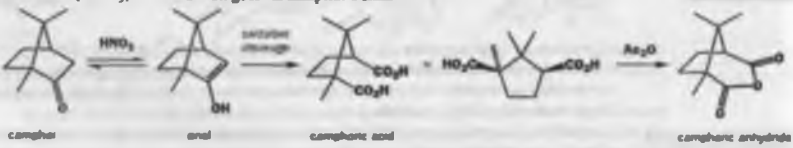
Like $LiAlH_4$ reduction, addition of a Grignard reagent to camphor occurs almost entirely from the *endo* face, but almost entirely from the *exo* face with norbornanone.

In a similar style, epoxidation of the two alkenes is totally stereoselective, occurring *exo* in norbornene and *endo* when methyl groups are present on the bridge. These stereoselectivities would be remarkable in a simple monocyclic compound, but in a rigid bridged bicyclic structure they are almost to be expected.



Reactions that break open bridged molecules preserve stereochemistry

Some powerful oxidizing agents are able to cleave C–C bonds, as you will see in Chapter 35. Oxidation of camphor in this way produces a diacid known as camphoric acid. The usual reagent is nitric acid (HNO_3) and oxidation goes via camphor's enol.



Because the bridge holds the molecule in a fixed conformation, the cleaved diacid has to have a specific stereochemistry. There is no change at the stereogenic centres, so the reaction must give retention of configuration. We can confidently write the structure of camphoric acid with *cis*-CO_2H groups, but any doubt is dispelled by the ability of camphoric acid to form a bridged bicyclic anhydride.

▶ Note that only one enol can form—enolization the other way would lead to an impossible planar carbon at the bridgehead position. See p. 000.

▶ Anhydride formation with acetic anhydride goes via attack of one acid group on Ac_2O to form a mixed anhydride, followed by displacement of AcOH by the other acid group.

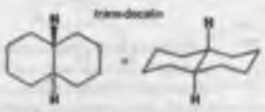
Fused bicyclic compounds

trans-Fused rings

The ring junction of a fused 5/6-membered ring system can have *cis* or *trans* stereochemistry, and so can any pair of larger rings. For smaller rings, *trans* 5/5- and 4/6-ring junctions can be made, with difficulty, but with smaller rings *trans* ring junctions are essentially impossible.

5,6 can be *trans* or *cis*

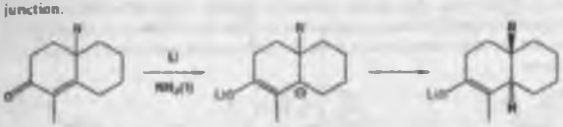
The *trans*-fused 6/6 systems—*trans*-decalins—have been very widely studied because they appear in steroids (Chapter 51). Their conformation is discussed in Chapter 18 and conformational control simply extends what we saw with simple six-membered rings.



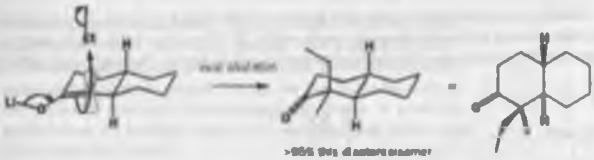
5,6 can be *trans* or *cis*, but getting *trans*

A 6/6 fused system will prefer a *trans* ring junction as *trans*-decalins (Chapter 18) have all-chair structures with every bond staggered from every other bond, as you can see from the diagram alongside. We can show

this by giving a 6/6 system the choice: reducing this enone with lithium metal gives a lithium enolate (Chapter 26). Protonation of this anion with the solvent (liquid ammonia) gives a *trans* ring junction.



The lithium enolate remains and can be alkylated with an alkyl halide in the usual way. When there are hydrogen atoms at both ring junction positions, axial alkylation occurs just as you should now expect, and a new ketone with three stereogenic centres is formed with >95% stereoselectivity.



>95% this diastereoisomer

However, if there is anything else—even a methyl group—at the ring junction, so that axial approach would give a bad 1,3 diaxial interaction in the transition state, the stereoselectivity switches to >95% equatorial alkylation. This unexpected reversal of normal stereoselectivity is a result of the extra rigidity of the *trans*-decalin system.

>95% this diastereoisomer

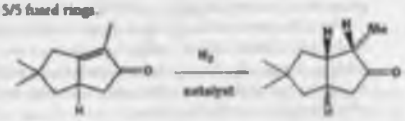
In most reactions of *trans*-decalins, the conformational principles of simple six-membered rings can be used, but you may expect tighter control from the greater rigidity. If you wish to design a molecule where you are quite certain of the conformation, a *trans*-decalin is a better bet than even a *t*-butyl cyclohexane as *trans*-decalins cannot flip.

cis-Fused rings

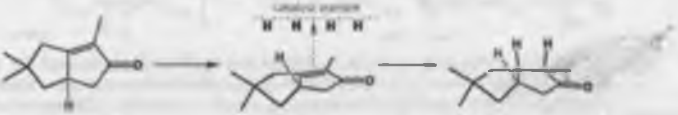
Almost any *cis*-fused junction from 3/3 upwards can be made. Bicyclo[1.1.0]butane exists, though it is not very stable. *cis*-Fused 4/5, 4/6, and 5/5 systems are common and are much more stable than their *trans*-isomers.

Any method of making such bicyclic compounds will automatically form this stereochemistry. An important method of stereochemical control that we have not used so far in this chapter is catalytic hydrogenation of alkenes, which adds a molecule of hydrogen stereospecifically *cis*. If the reaction also makes a fused ring system, it may show stereoselectivity too. Here is an example with 5/5 fused rings.

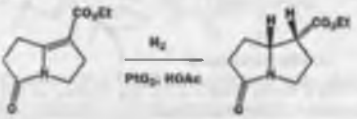
The two new hydrogen atoms (shown in black) must, of course, add *cis* to one another: this is a consequence of the stereospecificity of the reaction. What is interesting is that



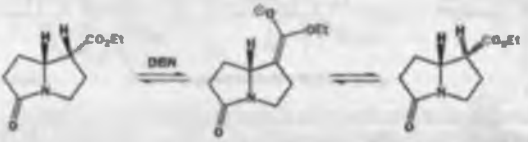
they have also added *cis* to the green hydrogen atom that was already there. This approach does give the more stable *cis* ring junction but the stereochemistry really arises because the other ring hinders approach to the other face of the alkene. Think of it this way: the alkene has two different faces. On one side there is the green hydrogen atom, and on the other the black parts of the second ring. To get hydrogenated, the alkene must lie more or less flat on the catalyst surface and that is easier on the top face as drawn.



If one of the ring junctions is a nitrogen atom, we might think that there is no question of stereochemistry because pyramidal nitrogen inverts rapidly. So it does, but if it is constrained in a small ring, it usually chooses one pyramidal conformation and sticks to it. The next case is rather like the last.



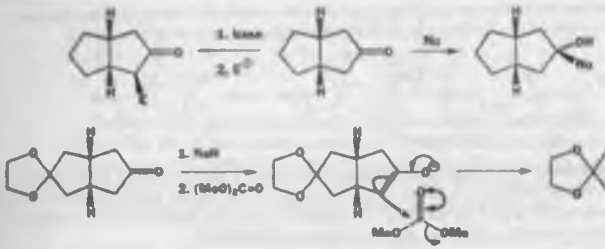
Here again the two black hydrogens have added stereospecifically *cis*, but there is no stereogenic centre in the starting material to control stereoselectivity. So what is there to discuss? If the product is treated with a tertiary amine base (actually DBN is used), it equilibrates to the other diastereoisomer via the ester enolate.



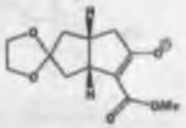
It is easy to see *how* the equilibration happens as the enolate can be protonated at the front or the back, but *why* should it prefer the second structure? This is thermodynamic control and results from the 'disguised' *cis* ring junction. Because it is more stable to have two five-membered rings *cis*-fused, the nitrogen atom is slightly (only slightly, because it is part of an amide) pyramidalized in that direction.

The molecule folds along the C–N bond common to both rings so that it looks rather like that half-opened book that you put face downwards on the table while you answered the phone. The ester group much prefers to be in free space outside the folded rings and not cramped inside them.

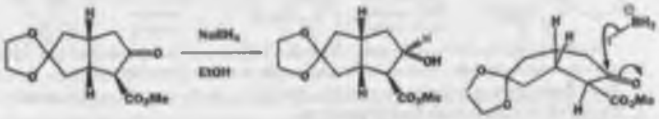
This is the key to *cis*-fused bicyclic rings—everything happens on the outside (on the cover of the book). Nucleophiles add to carbonyl groups from the outside, enolates react with alkyl halides or Michael acceptors on the outside, and alkenes react with peroxyacids on the outside. Notice that this means the same side as the substituents at the ring junction. The rings are folded away from these substituents that are on the outside.



A real example comes in the acylation (Chapter 28) of the enolate from the keto-acetal above and alongside. The molecule is folded downwards and the enolate is essentially planar. Addition presumably occurs entirely from the outside, though the final stereochemistry of the product is controlled thermodynamically because of reversible enolization of the product: whatever the explanation, the black ester group prefers the outside.

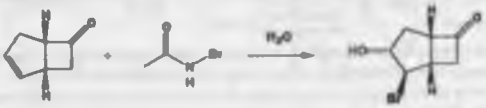


Reduction of the ketone product also occurs exclusively from the outside and this has the ironic effect of pushing the new OH group into the inside position. Attack from the inside is very hindered in this molecule because one of the acetal oxygen atoms is right on the flight path. You will see more in a moment on how to force groups into the inside.



A simple example of epoxidation occurs on a cyclobutane fused to a five-membered ring. This is a very rigid system and attack occurs exclusively from the outside to give a single epoxide in good yield.

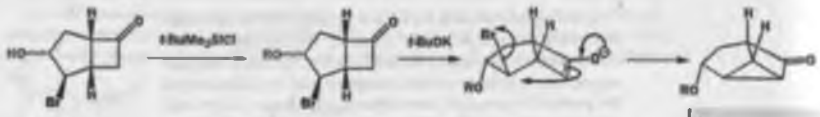
Epoxidation is stereospecific and *cis*—both new C–O bonds have to be on the same face of the old alkene. But Chapter 20 introduced you to several electrophilic additions to alkenes that were stereospecific and *trans*, many of them proceeding through a bromonium ion. If stereospecific *trans* addition occurs on a *cis*-fused bicyclic alkene, the electrophile will first add to the outside of the fold, and the nucleophile will then be forced to add from the inside. A telling example occurs when the 4/5 fused unsaturated ketone below is treated with *N*-bromoacetamide in water.



The bromonium ion is formed on the outside of the rigid structure and the water is then forced to add from the inside to get *trans* addition. As well as exhibiting stereospecificity (*trans* addition) and stereoselectivity (bromonium forms on outside), this reaction also exhibits regioselectivity in the

attack of water on the bromonium ion. Water must come from inside, but it attacks the less hindered end of the bromonium ion, keeping as far from the 'spine of the half-open book' as possible.

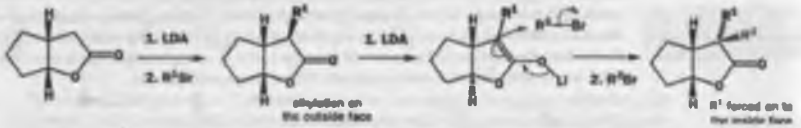
After protection of the OH group, treatment with base closes a three-membered ring to give a remarkably strained molecule. The ketone forms an enolate and the enolate attacks the alkyl bromide intramolecularly to close the third ring. This enolate is in just the right position to attack the C–Br bond from the back, precisely because of the folding of the molecule.



Inside/outside selectivity may allow the distinction between two otherwise similar functional groups. The *cis*-fused bicyclic diester below may look at first rather symmetrical but ester hydrolysis leaves one of the two esters alone while the other is converted to an acid.

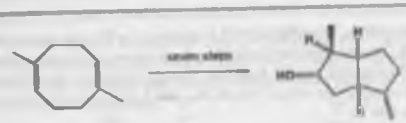
Only the outside ester—on the same side as the ring junction H—is hydrolysed. In the mechanism for ester hydrolysis, the rate-determining step is the attack by the hydroxide ion so the functional group increases in size in the vital step. This will be much easier for the free outside CO_2Et group than for the one inside the half-open book.

The end result is that the larger of the two groups is on the inside! There are other ways to do this too. If we alkylate the enolate of a bicyclic lactone, the alkyl group (black) goes on the outside as expected. But what will happen if we repeat the alkylation with a different alkyl group? The new enolate will be flat and the stereochemistry at the enolate carbon will be lost. When the new alkyl halide comes in, it will approach from the outside (green) and push the alkyl group already there into the inside.

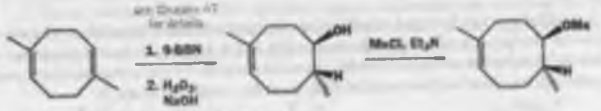


Should you wish to reverse the positions of the two groups, you simply add them in the reverse order. Whichever group is added first finishes on the inside; the other finishes on the outside.

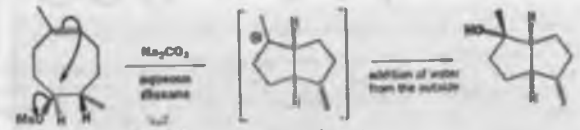
Before we move on to *cis*-decalins, here is a sequence of reactions that starts with a symmetrical eight-membered ring with no stereogenic centres and ends with two fused five-membered rings with five stereogenic centres, all controlled by stereospecific reactions, some with stereoselective aspects controlled by *cis*-fused rings.



The first step is a reaction you haven't yet met—it comes in Chapter 47. All you need to know now is that the reagent, a boron-containing compound called 9-borabicyclononane (9-BBN), hydrates one of the double bonds in the reverse fashion to what you would expect with acid or Hg^{2+} (Chapter 20) and stereospecifically (H and OH go in *cis*). The resulting alcohol is mesylated (p. 000) in the usual way. This puts in H and OMs stereospecifically *cis* to each other.

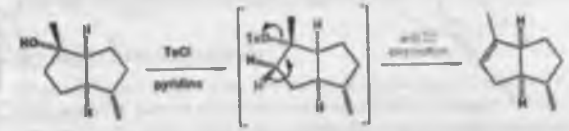


Now comes the first really interesting step. The other alkene does an intramolecular S_N2 reaction to displace the mesylate with inversion and form two fused five-membered rings. The ring junction is *cis*, of course.

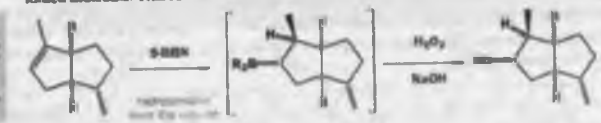


The resulting tertiary cation is not isolated but quenched in the reaction mixture with water. One new stereogenic centre is set up in the cyclization and another in the reaction with water. In the cyclization the molecule prefers to fold in such a way that the new ring junction is *cis*.

Addition of water to the cation occurs from the outside—but, in fact, this is unimportant as that stereogenic centre is about to be lost anyway. Treatment with TsCl causes an E2 *anti* elimination. The only proton *anti* to the OTs group is away from the ring junction, so this is where the new double bond goes.



Finally, a second hydroboration with 9-BBN occurs regiospecifically and on the outside of the folded molecule. This reaction adds the last two centres making five in all.

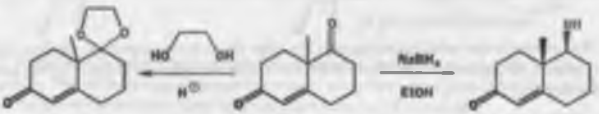


cis-Decalins: *cis*-fused six-membered rings

First a brief reminder of the conformation of *cis*-decalins (see Chapter 18). Unlike *trans*-decalins, which are rigid, they can flip rapidly between two all-chair conformations. During the flip, all

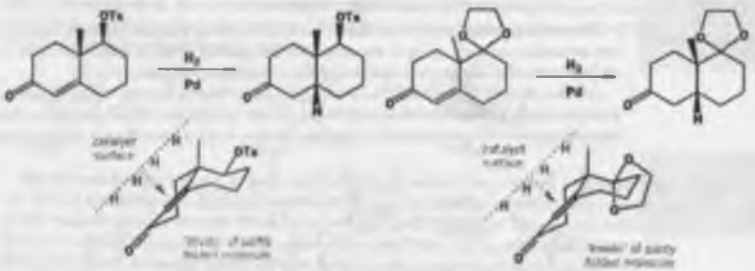
substitutents change their conformation. The substituent R is axial on ring B in the first conformation but equatorial in the second. The ring junction Hs are always axial on one ring and equatorial on the other. The green hydrogen is equatorial on ring A and axial on ring B in the first conformation and vice versa in the second. Of course, they are *cis* in both. Because R gets equatorial, the second conformation is preferred in this case.

A standard reaction that gives substituted decalins is the Robinson annelation (Chapter 29). A Robinson annelation product available in quantity is the keto-enone known sometimes as the **Wieland–Miescher ketone** and used widely in steroid synthesis. The nonconjugated keto group can be protected or reduced without touching the more stable conjugated enone.

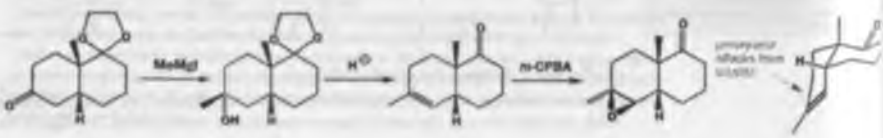


'Wieland–Miescher ketone'

If either of these products is reduced with hydrogen and a Pd catalyst (the alcohol is first made into a tosylate), the *cis*-decalin is formed. We saw a few pages back that the same kind of enones can be reduced with lithium metal in liquid ammonia and that then the more stable *trans*-decalin results.



The *cis*-decalin is formed because the enone, though flattened, is already folded to some extent. A conformational drawing of either molecule shows that the top surface is better able to bind to the flat surface of the catalyst. Each of these products shows interesting stereoselective reactions. The ketal can be converted into an alkene by Grignard addition and E1 elimination and then epoxidized. Everything happens from the outside as expected with the result that the methyl group is forced inside at the epoxidation stage.



Treatment of the other product, the keto-tosylate, with base leads to an intramolecular enolate alkylation—a cyclization on the inside of the folded molecule that actually closes a four-membered ring. The reaction is easily seen in conformational terms and the product cannot readily be drawn in conventional diagrams.

A similar reaction happens on the epoxide to produce a beautiful cage structure. This time it is a five-membered ring that is formed, but the principle is the same—the molecule closes across the fold rather easily. The new stereogenic centres can only be formed the way they are.

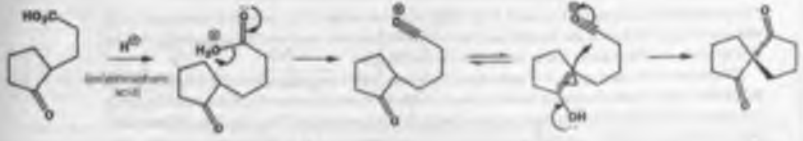
A summary of stereoselective reactions that occur on the *cis*-fused rings

1. Reactions on the outside
   - Nucleophilic additions to carbonyl groups in the ring
   - Reactions of enolates of the same ketones with electrophiles: alkyl halides, aldols, Michael additions
   - *cis*-Additions to cyclic alkenes: hydrogenation, hydroboration, epoxidation
2. Reactions on the outside and the inside
   - *trans*-Additions to cyclic alkenes: bromination, epoxide openings
3. Reactions on the inside
   - Bond formation across the ring(s)

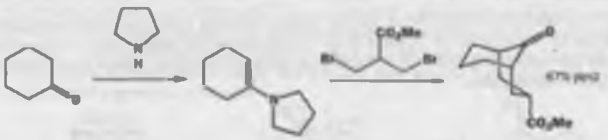
Spirocyclic compounds

These rings meet at an atom alone. This means that the two rings are orthogonal about the tetrahedral atom that is common to both. Even symmetrical-looking versions are unexpectedly chiral. The compound in the margin, for example, is not superimposable on its mirror image, and its chirality is rather similar to that of an allene.

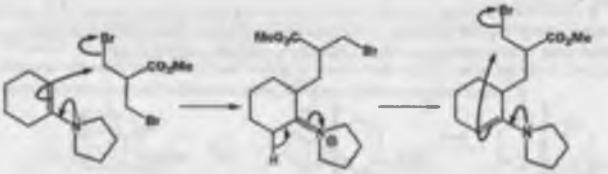
These sorts of compounds may look rather difficult to come by, but some simple ones are simply made. Cyclization of this keto-acid with polyphosphoric acid leads to a spirocyclic diketone.



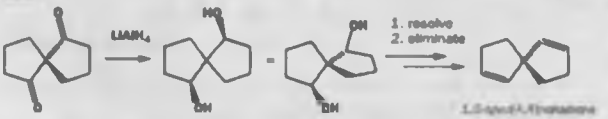
The *spiro* compound is formed because the more substituted enol is preferred in acid solution. In a different case, with an enamine, a bridged product is preferred.



After the first alkylation, the enamine prefers to re-form on the less substituted side so that the second alkylation occurs on the other side of the ketone from the first. The spirocyclic compound is further disfavoured as it would have a four-membered ring in this case.



It is much more difficult to pass stereochemical information from one ring to the other in spirocyclic compounds because each ring is orthogonal to the other. Nonetheless, some reactions are surprisingly stereoselective—one such is the reduction of the spirocyclic diketone that we made a moment ago. Treatment with $LiAlH_4$ gives one diastereoisomer of the spirocyclic diol.



The diol was resolved and used to make the very simple *spiro*-diene as a single enantiomer. It is chiral even though it has no chiral centre because it does not have a plane of symmetry.

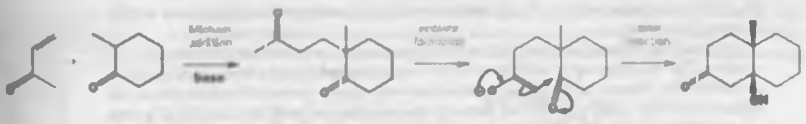
Reactions with cyclic intermediates or cyclic transition states

Rings are so good at controlling stereochemistry (as you have seen) that it's well worth introducing them where they are not really necessary in the final product, simply in order to enjoy those high levels of stereochemical control. In the rest of this chapter we shall consider the use of temporary rings in stereochemical control: these might be cyclic intermediates in a synthetic pathway, or cyclic reaction intermediates, or even merely cyclic transition states. All aid good stereocontrol. We shall concentrate on examples where the ring reverses the normal stereoselectivity so that some different result is possible.

Tethered functional groups can reach only one side of the molecule

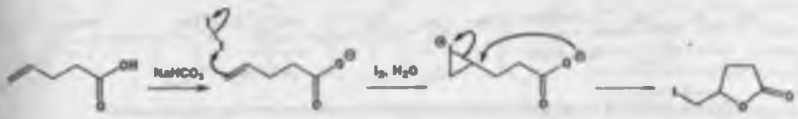
The proverbial donkey starved to death in the field with two heaps of hay because it could not decide which one to go for first. If the donkey had been tethered to a stake near one heap it would have been able to reach that heap alone and it could have feasted happily.

This principle is often applied to molecules. If a nucleophile is joined to the carbonyl group it is to attack by a short chain of covalent bonds, it may be able to reach only one side of the carbonyl group. An example from a familiar reaction concerns the Robinson annelation. The first step, Michael addition, creates a stereogenic centre but no relative stereochemistry. It is in the second step—the aldol cyclization—that the stereochemistry of the ring junction is decided.

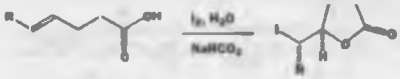


The enolate is tethered to the atom next to the ketone in the other ring. It can attack easily from the side to which it is attached through a stable chair-like transition state. Attacking the other face of the ketone (to give a *trans*-decalin) is much more difficult, even though it would give the thermodynamically more stable product.

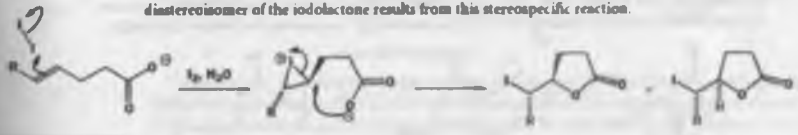
In fact, this is not such a good example because the aldol product is normally dehydrated and the second stereogenic centre is lost. More important examples are those in which a ring is formed but can later be cleaved, and among the best of this type of reaction are iodolactonizations, which you first met in Chapter 20. To remind you, iodolactonization involves treating a nonconjugated unsaturated acid with iodine in aqueous $NaHCO_3$. The product is an iodolactone.



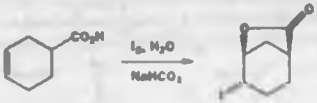
The cyclization reaction is a typical two-stage electrophilic addition to an alkene (Chapter 20) with attack by the nucleophile at the more substituted end of the intermediate halonium ion. The iodonium ring opening is a stereospecific S_N2 and, in the simplest cases where stereochemistry can be observed, the stereochemistry of the alkene will be reproduced in the product.



The starting acid contains an *E*-alkene that gives a *trans* iodonium ion. Inversion occurs in the attack of the carboxylate anion on the iodonium ion and we have shown this by bringing the nucleophile in at 180° to the leaving group with both bonds in the plane of the paper. A single diastereoisomer of the iodolactone results from this stereospecific reaction.

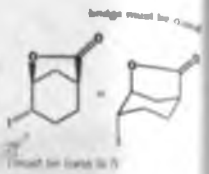


The following cyclic example illustrates the stereoselective aspect of iodolactonization.

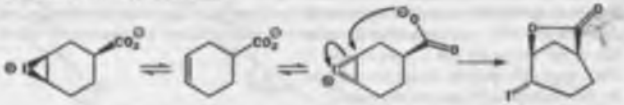


The relationship between the two stereogenic centres on the old alkene is not an issue—that aspect of the reaction is stereospecific. A more interesting question is the relationship with the third centre. One way to look at this question would be to say that the structure shown is the only possible

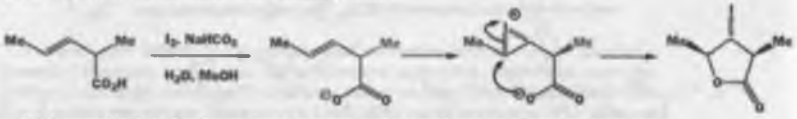
one. The lactone bridge has to be diaxial (and hence *cis*) if it is to exist and the O and I atoms have to be *trans*. End of story.



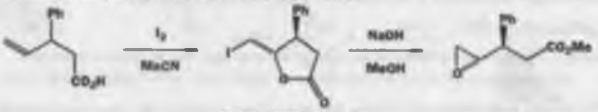
But it is still interesting to see how the product arises as it gives us insight into other less clear-cut reactions. The $-CO_2H$ group is too far away for us to argue seriously that the two faces of the alkene are sufficiently different for the iodine to attack one only. A more reasonable explanation is that iodine attacks both faces reversibly but that only the iodonium ion with the I and CO_2H groups *trans* to each other can cyclize. This turns out to be a general rule—iodolactonizations are reversible and under thermodynamic control.



One of the simplest open-chain examples is 2-methylhut-3-enoic acid, which cyclizes in >95% yield to a single iodolactone with three stereogenic centres. Two come from stereospecific *trans* addition to the *E*-alkene but the third reveals that iodine attacked the face of the alkene opposite the green methyl group in the conformation that can cyclize.

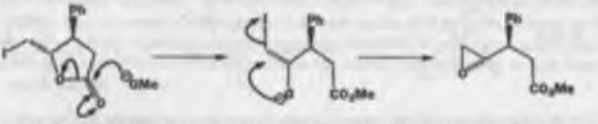


We have said little in this chapter about the stereospecific transformation of one ring into another but we now have an opportunity to remedy that defect. Iodolactonization of a terminal alkene with a stereogenic centre next to it is as stereoselective as (if not more than) the example we have just seen. The two side chains on the ring end up *trans* to one another as we should expect. This is a purely stereoselective process as the alkene has no geometry.

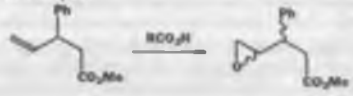


57% yield, 10:1 *trans*:*cis*

Reaction of the iodolactone product with alkaline methanol transforms it stereospecifically into the methyl ester of an epoxy acid. There is no change in stereochemistry here: methoxide opens the lactone and the oxyanion released carries out an internal S_N2 reaction on the primary alkyl iodide.

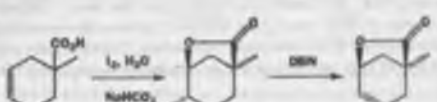


The more obvious way to make this epoxide would be by epoxidation of the ester of the original unsaturated acid. However, the stereoselectivity in that reaction is nowhere near as good as in the iodolactonization. We shall return to this subject when we discuss reactions in acyclic systems in the next chapter.



A general problem in the synthesis of steroid compounds is the construction of a diketone with 5/6 *trans*-fused rings and a quaternary carbon atom at the ring junction. Tethering can solve this problem, and we will present two strategies—one using a lactone derived from an iodolactonization reaction, and one using a sulfur atom.

A lactone makes a good temporary tether because it can be hydrolysed or reduced to break the ring at the C–O bond and reveal new stereogenic centres on the old structure. In this sequence a lactone, formed by iodolactonization, controls all the subsequent stereochemistry of the molecule in two ways: it fixes the conformation rigidly in one chair form—hence forcing the iodide to be axial—and it blocks one face of the ring. The iodolactonization is very similar to one you saw on p. 000. Next, an alkene is introduced by E2 reaction on the iodide. This stereospecific reaction requires an anti-periplanar H atom so it has to take the only available neighbouring axial hydrogen atom—furthermore, reaction the other way would produce a bridgehead alkene.



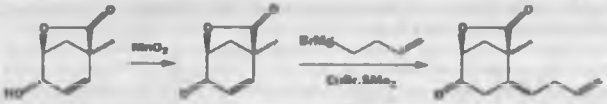
The resulting alkene has its top face blocked by the bridge so a *cis* addition reaction, such as epoxidation, will occur entirely from the bottom face.

Now the epoxide is opened with HBr to give the only possible *trans* diaxial product (Chapter 18). The role of the bridge in fixing the conformation of the ring is more important in this stereospecific reaction because the bromide ion is forced to attack from the top face. The alcohol is protected as a silyl ether.

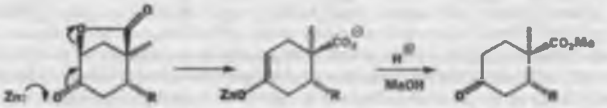
Do you see how the functional groups are being pushed round the ring? This process is extended further by a second elimination also with DBN, which this time really does have to seek out the only neighbouring axial hydrogen: there's no bridgehead to take the decision for it. Acid removes the silyl protecting group.

The next important reaction is a Michael addition so the alcohol must first be oxidized to a ketone. As it is an allylic alcohol, it can be oxidized by manganese dioxide. The ring is further flattened as three atoms are now trigonal. But-3-enyl Grignard reagent is next added with Cu(I)

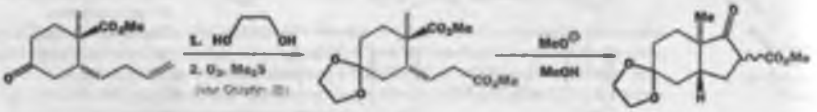
catalysis to make sure that conjugate addition occurs. Conjugate addition normally gives the axial product as we saw earlier and fortunately this is not the direction blocked by the bridge.



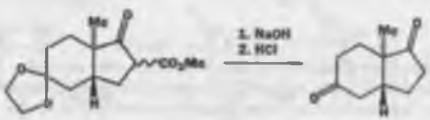
The bridge has now done its work and is removed by zinc metal reduction. This reaction removes leaving groups on the atoms next to carbonyl groups. In this case it is the axial carboxylate that is driven out by the zinc. The released carboxyl group is esterified.



The last stages are shown below. The ketone is protected, and the alkene oxidized to a carbonyl group, cleaving off one of the C atoms (you will meet this reaction—ozonolysis—in Chapter 35). The diester can be cyclized by a Claisen ester condensation. The stereogenic centres in the ring are not affected by any of these reactions so a *trans* ring junction must result from this reaction.

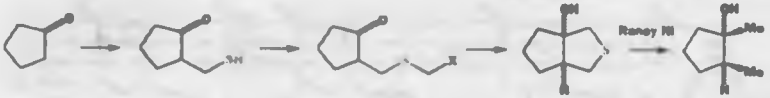


Finally, after ester hydrolysis, HCl decarboxylates the product and removes the protecting group. As we saw earlier, it is not easy to get a *trans*-fused 5/6 system. In this sequence the molecule is effectively tricked into making the *trans* ring junction by the work done with the blocking lactone bridge.

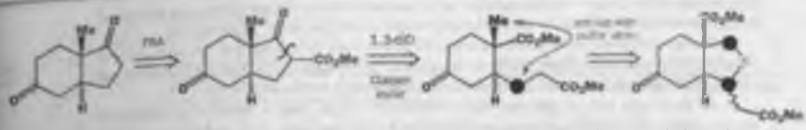


Sulfur as a tether

An even more versatile tether is a sulfur atom, which can be removed completely with Raney nickel (which reduces C–S to C–H). The sulfur atom makes the tether easy to assemble too. Here is the essence of the idea.

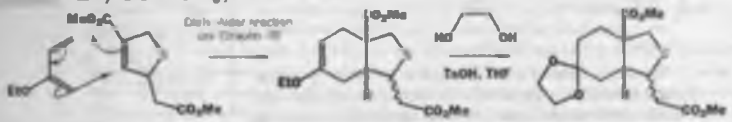


In this second synthesis of the problematic steroid *trans* ring junction, the idea is to make the five-membered ring by a Claisen ester condensation and to direct the stereochemistry by tethering the CH groups with a sulfur atom. We can represent this easily in disconnection terms (Chapter 31). The *cis*-carbons to be joined through sulfur are shown in black.

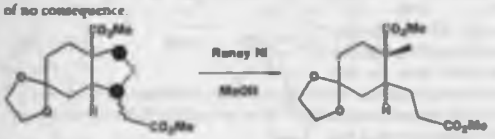


The preparation of the sulfur heterocycle uses reactions you have met before—first a five-membered ring ketone is formed, which is reduced, lactonized, and eliminated.

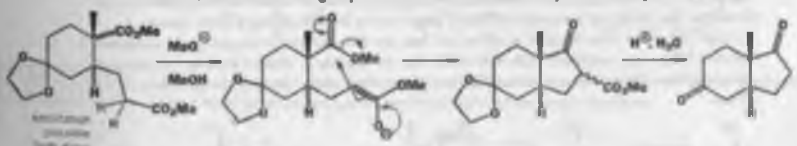
The next steps involve the Diels–Alder reaction, which you will meet in Chapter 35, so we will have no detailed discussion here, just giving the reactions, and pointing out that the product necessarily has a *cis* 6/5 ring junction.



Now the ring has done its work, the two necessary stereogenic centres are fixed, and the sulfur atom can be removed with Raney nickel. The third, undefined, stereogenic centre becomes a CH_2 group in this operation, so the lack of stereocontrol at this centre during the Diels–Alder reaction is of no consequence.



The Claisen ester condensation involves the only possible enolate attacking the only possible electrophilic carbonyl group. The stereochemistry of the ring junction cannot be changed by the reaction, and the two ester groups that started *trans* must end up *trans* in the product.



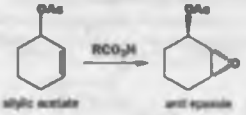
Cyclic transition states can reverse normal stereoselectivity

We have considered what happens when there is a ring present in the starting material, or where we encourage formation of a ring in an intermediate as a means of controlling stereochemistry. In this

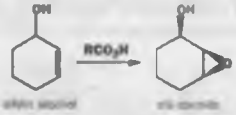
final section of this chapter we shall consider some examples where stereoselectivity arises because of a ring formed only transiently during a reaction in a cyclic transition state.

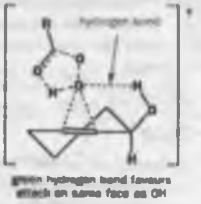
We'll start with some epoxidation reactions. Of course these *form* rings, and you have seen, in Chapter 20, epoxidations of alkenes such as cyclohexene. We said in Chapter 20 that epoxidation was stereospecific because both new C–O bonds form to the same face of the alkene.

If we block one face of the ring with a substituent—even quite a small one, such as an acetate group—epoxidation becomes stereoselective for the face *anti* to the substituent already there.



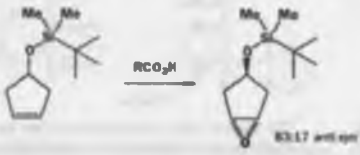
With one exception—when the substituent is a hydroxyl group. When an allylic alcohol is epoxidized, the peroxy-acid attacks the face of the alkene *syn* to the hydroxyl group, even when that face is more crowded. For cyclohexenol the ratio of *syn* epoxide to *anti* epoxide is 24:1 with *m*-CPBA and it rises to 50:1 with CF_3CO_3H.





The reason is shown in the transition state: the OH group can hydrogen bond, through the H of the alcohol, to the peroxy-acid, stabilizing the transition state when the epoxidation is occurring *syn*. This hydrogen bond means that peroxy-acid epoxidations of alkenes with adjacent hydroxyl groups are much faster than epoxidations of simple alkenes, even when no stereochemistry is involved.

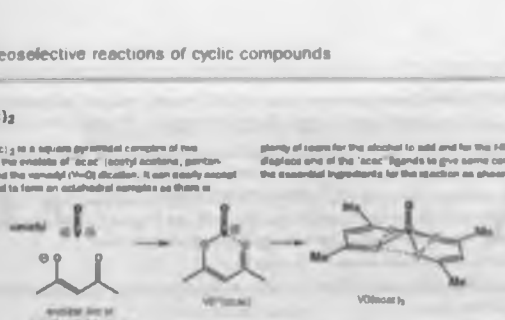
Peroxy-acids work for epoxidizing allylic alcohols *syn* to the OH group, but another reagent is better when the OH group is further from the alkene. 4-Hydroxycyclopentene, for example, can be converted into either diastereomer of the epoxide. If the alcohol is protected with a large group such as TBDMS (*t*-butyldimethylsilyl) it becomes a simple blocking group and the epoxide is formed on the opposite face of the alkene. The selectivity is reasonable (83:17) given that the blocking group is quite distant.



If the OH group is not blocked at all but left free, and the epoxidation reagent is the vanadium complex $VO(acac)_2$ combined with *t*-BuOOH, the *syn* epoxide is formed instead. The vanadyl group chelates reagent and alcohol and delivers the reactive oxygen atom to the same face of the alkene.

$VO(acac)_2$

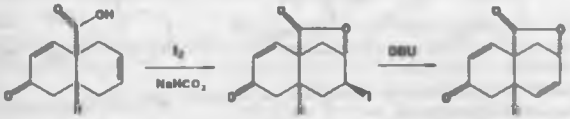
Vanadyl (acac)$_2$ is a square pyramidal complex of two molecules of the enolate of 'acac' (acetyl acetone, pentan-2,4-dione) and the vanadyl (V=O) dication. It can easily accept another ligand to form an octahedral complex as there is plenty of room for the alcohol to add and for the Me_3COOH to displace one of the 'acac' ligands to give some complex with the essential ingredients for the reaction as shown above.



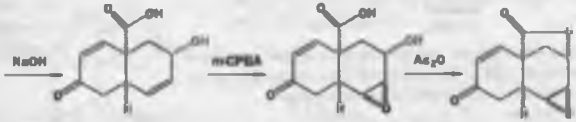
The delivery of an oxygen atom through a cyclic transition state by vanadyl complexes is also particularly effective with allylic alcohols. Here is a simple example—the green arrow shows merely the directing effect and is not a mechanism. Delivery of oxygen from OH through a VO complex is particularly effective when the OH group is pseudoaxial and the *t*-Bu group ensures this.

In both epoxidation examples, the stereoselectivity is due to the cyclic nature of the transition state: the fact that there is a hydrogen bond or O–metal bond 'delivering' the reagent to one face of the alkene. This is a very important concept, and we revisit it in the next chapter: cyclic transition states are the key to getting good stereoselectivity in reactions of acyclic compounds.

Before we move on, we leave you with one final example. Stereoselectivity in the epoxidation of lactone-bridged alkenes related to those we saw earlier (p. 000) can be completely reversed if the lactone is hydrolysed, revealing a hydroxyl group. In this bicyclic example, the hydroxyl group delivers the peroxy-acid from the bottom face of the alkene. First, the lactone bridge is used to introduce the alkene as before.

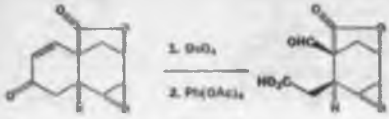


Now the critical steps—the lactone bridge is hydrolysed, the epoxide added from the bottom face by a peroxy-acid hydrogen bonded to the OH group, and the lactone bridge reinstated.



▶
You have met several methods for cleaving C=C bonds in this chapter, including this one and also ozone. These reactions will be discussed in Chapter 35.

The second ring in these compounds is actually a tether, and it enables two more functional groups to be introduced in a *cis* fashion by oxidation of the remaining alkene.



To conclude...

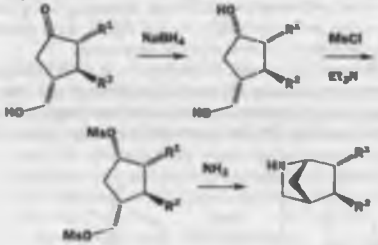
Diastereoselectivity in rings generally follows a few simple principles:

- Flattened three-, four-, or five-membered rings, especially ones with two or more trigonal carbons in the ring, are generally attacked from the less hindered face
- Flattened six-membered rings with two or more trigonal carbons in the ring (that is, which are not already a chair—so six-membered rings with one trigonal C atom don't count here) react in such a way that the product becomes an axially substituted chair
- Bicyclic compounds react on the outside face
- Reaction on the more hindered face can be encouraged by: (1) tethered nucleophiles, or (2) cyclic transition states

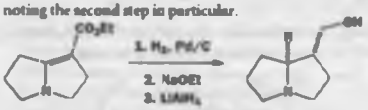
Diastereoselectivity in compounds without rings is different: it is less well controlled, because there are many more conformations available to the molecule. But even in acyclic compounds, rings can still be important, and some of the best diastereoselectivities arise when there is a ring formed temporarily in the transition state of the reaction. With or without cyclic transition states, in some cases we have good prospects of predicting which diastereoisomer will be the major reaction product, or explaining the diastereoselectivity if we already know this. That is the subject of the next chapter.

Problems

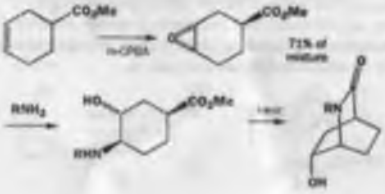
1. Comment on the control over stereochemistry achieved in this sequence.



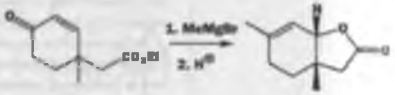
2. Explain the stereochemistry of this sequence of reactions, noting the second step in particular.



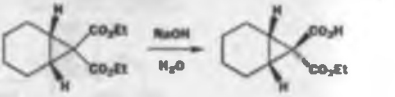
3. Explain how the stereo- and regiochemistry of these compounds are controlled. Why is the epoxidation only moderately stereoselective, and why does the amine attack where it does?



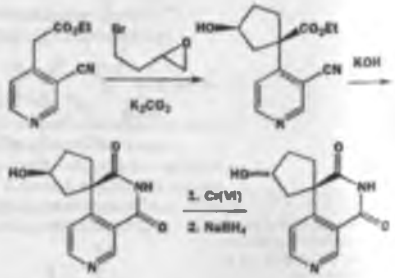
4. What controls the stereochemistry of this product? You are advised to draw a mechanism first and then consider the stereochemistry.



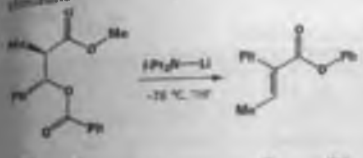
5. Why is one of these esters more reactive than the other?



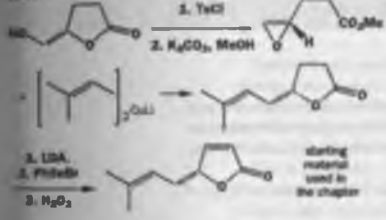
6. Explain the stereoselectivity in these reactions.



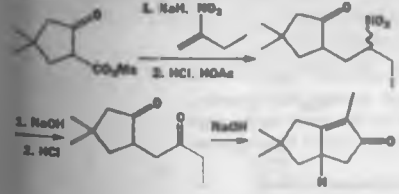
7. A problem from the chapter. Draw a mechanism for this reaction and explain why it goes so much better than the elimination on a β-lactone.



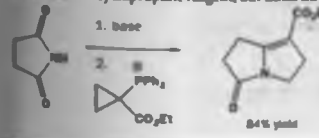
8. Another problem from the chapter. The syntheses of the starting material for this reaction is a good example of how cyclic compounds can be used in a simple way to control stereochemistry. Draw mechanisms for each reaction and explain the stereochemistry.



9. A revision problem. Suggest mechanisms for the reactions used to make this starting material used in the chapter.



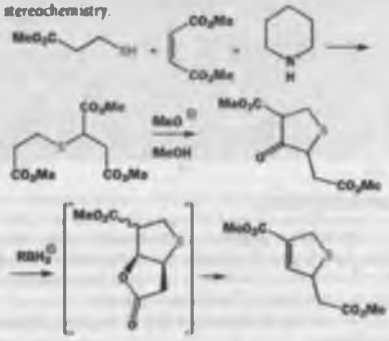
10. And another problem from the chapter. Here also draw a mechanism for the formation of the starting material. You have never seen the cyclopropane reagent, but think how it might react ....



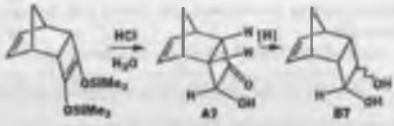
Stuck? The first step opens the three-membered ring and the second step is a well-known alkene-forming reaction ...

11. In the chapter we introduced the selective reduction of the Wieland–Miescher ketone. The problem is: can you suggest a reason for this stereoselectivity?

12. We warned you in the chapter that this would appear as a problem: suggest mechanisms for these reactions and explain the stereochemistry.



13. Hydrolysis of a bis-silylated ene-diol gives a hydroxy-ketone A whose stereochemistry is supposed to be as shown. Reduction of A gives a diol B. The ^{13}C NMR spectrum of B has five signals: one in the 100–150 p.p.m. range, one in the 50–100 p.p.m. range, and three below 50 p.p.m. The proton NMR of the three marked hydrogens in A is given below with some irradiation data. Does this information give you confidence in the stereochemistry assigned to A? You may wish to consider the likely stereochemical result of the reduction of A.



A has δ_H 4.46 p.p.m. (1H, dd, *J* 9.0, 3.8 Hz), 3.25 p.p.m. (1H, ddd, *J* 9.0, 7.5, 4.5 Hz), and 3.48 p.p.m. (1H, ddd, *J* 7.5, 5.5, 3.8 Hz). Irradiation at 3.48 p.p.m. collapses the signal at 4.46 p.p.m. to (d, *J* 9.0 Hz) and the signal at 3.25 p.p.m. to (dd, *J* 9.0, 4.5 Hz). Irradiation at 4.46 p.p.m. collapses the signal at 3.48 p.p.m. to (dd, *J* 7.5, 5.5) and the signal at 3.25 p.p.m. to (dd, *J* 7.5, 4.5).

Diastereoselectivity

34

Connections

Building on:

- Stereochemistry ch16
- Conformation ch18
- Controlling double bond stereochemistry ch31
- Determining stereochemistry by NMR ch32
- Controlling stereochemistry in cyclic compounds ch33

Arriving at:

- How to make single diastereoisomers from single geometrical isomers
- How to predict and explain the reactions of chiral carbonyl compounds
- How chelation to metal ions can change stereoselectivity
- How to predict and explain the reactions of chiral alkenes
- Stereoselectivity in the aldol reaction
- How to make *syn* aldol products
- How to make *anti* aldol products

Looking forward to:

- Saturated heterocycles ch42
- Asymmetric synthesis ch45
- Organic synthesis ch52

Looking back

You have had three chapters in a row about stereochemistry: this is the fourth, and it is time for us to bring together some ideas from earlier in the book. We aim firstly to help you grasp some important general concepts, and secondly to introduce some principles in connection with stereoselective reactions in acyclic systems. But, first, some revision.

We introduced the stereochemistry of structures in Chapter 16. We told you about two types of stereoisomers.

Enantiomers and diastereoisomers

- **Enantiomers**—stereoisomers that are mirror images of one another
- **Diastereoisomers**—stereoisomers that are not mirror images of one another

In this chapter we shall talk about how to make compounds as single diastereoisomers. Making single enantiomers is treated in Chapter 45. Chapter 33 was also about making single diastereoisomers, and we hope that, having read that chapter, you are used to thinking stereochemically.

In this chapter we shall talk about two different ways of making single diastereoisomers.

Reactions that make single diastereoisomers

- **Stereospecific reactions**—reactions where the mechanism means that the stereochemistry of the starting material determines the stereochemistry of the product and there is no choice involved
- **Stereoselective reactions**—reactions where one stereoisomer of product is formed predominantly because the reaction has a choice of pathways, and one pathway is more favourable than the other

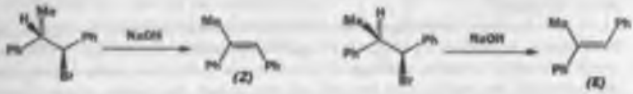
These terms were introduced in Chapter 19 in connection with elimination reactions, and many of the reactions we mention will be familiar from earlier chapters (particularly Chapters 17–20 and 26–27).

Making single diastereoisomers using stereospecific reactions of alkenes

The essence of the definition we have just reminded you of is much easier to grasp with some familiar examples. Here are two.

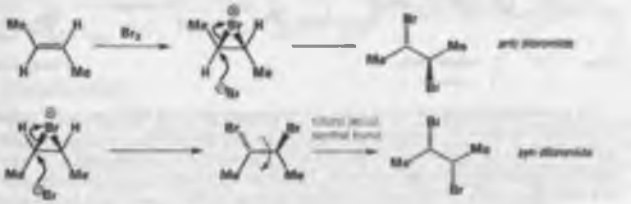
- S_N2 reactions are stereospecific: they proceed with inversion so that the absolute stereochemistry of the starting material determines the absolute stereochemistry of the product

- E2 reactions are stereospecific: they proceed through an anti-periplanar transition state, with the relative stereochemistry of the starting material determining the geometry of the product

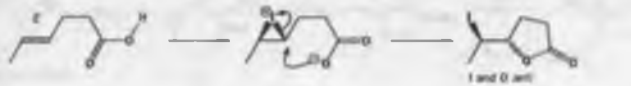


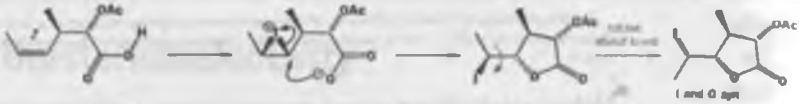
Both of these examples are very interesting because they show how, once we have some stereochemistry in a molecule, we can change the functional groups but keep the stereochemistry—this is the essence of a stereospecific reaction. In the second example, we change the bromide to a double bond, but we keep the stereochemistry (or 'stereochemical information') because the geometry of the double bond tells us which bromide we started with.

This is a good place to begin if we want to make single diastereoisomers, because we can reverse this type of reaction: instead of making a single geometry of alkene from a single diastereoisomer, we make a single diastereoisomer from a single geometry of double bond. Here is an example of this—again, one you have already met (Chapter 19). Electrophilic addition of bromine to alkenes is stereospecific and leads to *anti* addition across a double bond. So if we want the *anti* dibromide we choose to start with the *trans* double bond; if we want the *syn* dibromide we start with the *cis* double bond. The geometry of the starting material determines the relative stereochemistry of the product.



Iodolactonization has a similar mechanism; notice how in these two examples the geometry of the double bond in the starting material defines the relative stereochemistry highlighted in black in the product.

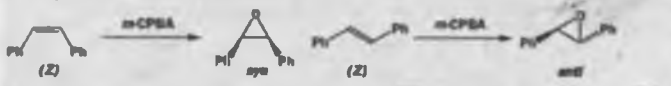




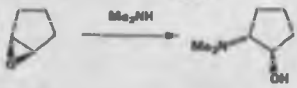
1 and 0 syn

For a stereospecific alkene transformation, choose the right geometry of the starting material to get the right diastereoisomer of the product. Don't try to follow any 'rules' over this—just work through the mechanism.

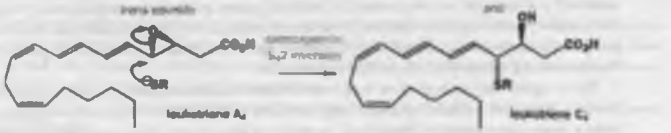
Now for some examples with epoxides. Epoxides are very important because they can be formed stereospecifically from alkenes: *cis*-alkenes give *cis* (or *syn*) -epoxides and *trans*-alkenes give *trans* (or *anti*) -epoxides.



Epoxides also react stereospecifically because the ring-opening reaction is an S_N2 reaction. A single diastereoisomer of epoxide gives a single diastereoisomer of product.

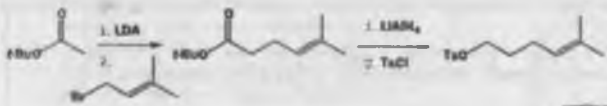


We have mentioned leukotrienes before: they are important molecules that regulate cell and tissue biology. Leukotriene C_4 (LTC_4) is a single diastereoisomer with an *anti* 1,2 S,O functional group relationship. In nature, this single diastereoisomer is made by an epoxide opening: since the opening is S_N2 the epoxide must start off *anti* and, indeed, the epoxide precursor is another leukotriene, LTA_4.



When Corey was making these compounds in the early 1980s he needed to be sure that the relative stereochemistry of LTC_4 would be correctly controlled, and to do this he had to make a *trans* epoxide. Disconnecting LTA_4 as shown led back to a simpler epoxide.

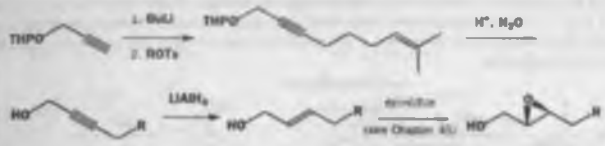
The *trans* allylic alcohol needed to make this compound was made using one of the methods we introduced in Chapter 31: reduction of an alkynyl alcohol with $LiAlH_4$. Here is the full synthesis: alkylation of an ester enolate with prenyl bromide gives a new ester, which itself is turned into an alkylating agent by reduction and tosylation. The alkyne is introduced as its lithium derivative with the alcohol protected as a THP acetal. Hydrolysis of the acetal with aqueous acid gives the hydroxy-alkyne needed for reduction to the *E* double bond, which is then epoxidized.



continued overleaf

Chapter 20, p. 000.

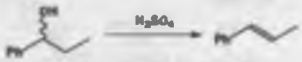
Chapters 17 (p. 000) and 19 (p. 000).



Stereoselective reactions

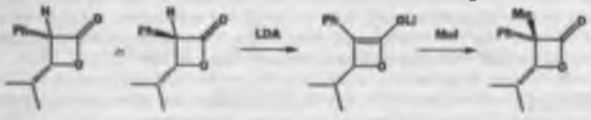
For most of the rest of the chapter we shall discuss stereoselective reactions. You have already met several examples and we start with a summary of the most important methods.

- E1 reactions are stereoselective: they form predominantly the more stable alkene

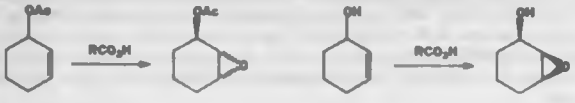


- Nucleophilic attack on six-membered ring ketones is stereoselective: small nucleophiles attack axially and large ones equatorially

- Alkylation of cyclic enolates is stereoselective, with reaction taking place on the less hindered face (four- or five-membered rings) or via axial attack (six-membered rings)

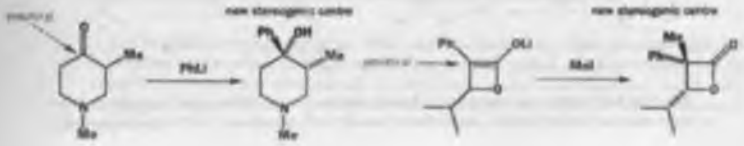


- Epoxidation of cyclic alkenes is stereoselective, with reaction taking place on the less hindered face, or directed by hydrogen bonding to a hydroxyl group

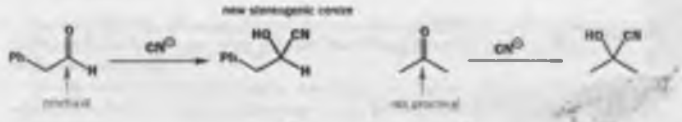


Prochirality

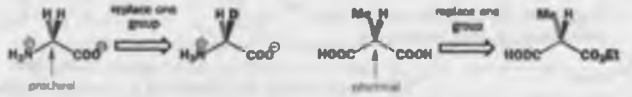
Take another look at all the reactions in the chapter so far—in particular those that give single diastereoisomers (rather than single enantiomers or geometrical isomers)—in other words, those that are diastereoselective. They all involve the creation of a new, tetrahedral stereogenic centre at a carbon that was planar and trigonal. This leads us to our first new definition. Trigonal carbons that aren't stereogenic (or chiral) centres but can be made into them are called prochiral.



At the very start of Chapter 17, we introduced stereochemistry by thinking about the reactions of two sorts of carbonyl compounds. They are shown again here: the first has a prochiral carbonyl group. The second, on the other hand, is not prochiral because no stereogenic centre is created when the compound reacts.



Tetrahedral carbon atoms can be prochiral too—if they carry two identical groups (and so are not a chiral centre) but replacement of one of them leads to a new chiral centre, then the carbon is prochiral.

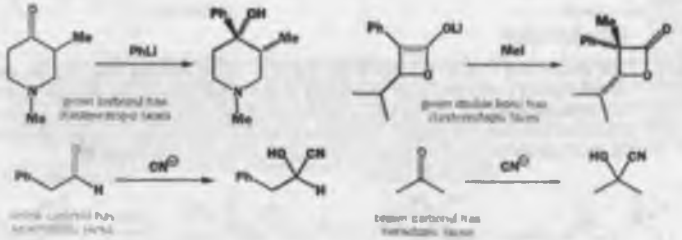


Glycine is the only α amino acid without a chiral centre, but replacing one of the two protons on the central carbon with, say, deuterium creates one: the CH_2 carbon is prochiral. Similarly, converting malonate derivative into its monoester makes a chiral centre where there was none: the central C is prochiral.

Now, does this ring any bells? It should remind you very much of the definitions in Chapter 32 of **enantiotopic** and **diastereotopic** in connection with NMR spectra. Replacing one of two enantiotopic groups with another group leads to one of two enantiomers; replacing one of two diastereotopic groups with another group leads to one of two diastereoisomers. Diastereotopic groups are chemically different; enantiotopic groups are chemically identical.

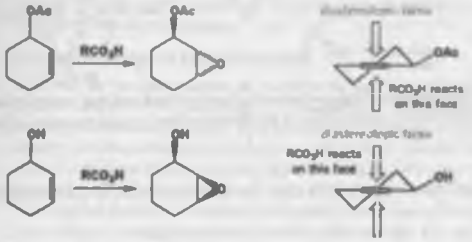
Enantiotopic and diastereotopic protons and groups are discussed in Chapter 32, p. 000.

Exactly the same things are true for the faces of a prochiral carbonyl group or double bond. If reaction on one of two faces of the prochiral group generates one of two enantiomers, the faces are enantiotopic; if the reaction generates one of two diastereoisomers, the faces are diastereotopic. We will now apply this thinking to the first few reactions in this chapter: they are shown again below. The first two examples have prochiral C=C or C=O bonds with diastereotopic faces: choosing which face of the double bond or carbonyl group to react on amounts to choosing which diastereoisomer to form. In the third example, the faces of the prochiral carbonyl group are enantiotopic: choosing which face to attack amounts to choosing which enantiomer to form. In the fourth example, the two faces of C=O are homotopic: an identical product is formed whichever face is attacked.



Knowing this throws some new light on the last chapter. Almost without exception, every stereoselective reaction there involved a double bond (usually C=C; sometimes C=O) with diastereotopic

faces. The diastereotopic faces were distinguished by steric hindrance, or by a nearby hydrogen-bonding group, and so were able to react differently with an incoming reagent.

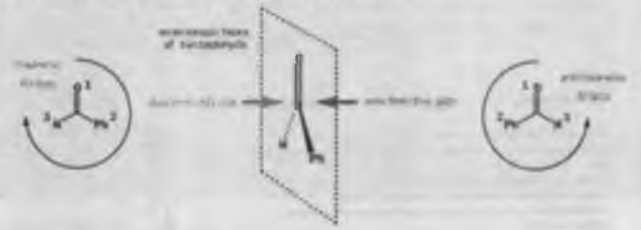


Using an *R*/*S*-type system to name prochiral faces and groups

Just as stereogenic centres can be described as *R* or *S*, it is possible to assign labels to the enantiotopic groups at prochiral tetrahedral carbon atoms or the enantiotopic faces of prochiral trigonal carbon atoms. The basis of the system is the usual *R*,*S* system for stereogenic centres, but *pro-R* and *pro-S* are used for groups and *Re* and *Si* for faces.

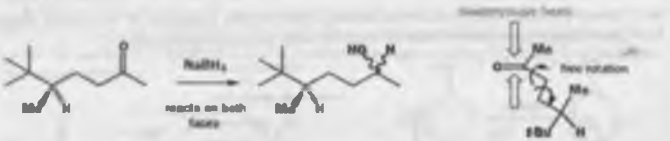
Pro-R and *pro-S* can be assigned to a pair of enantiotopic groups simply by using the usual rules to assign *R* or *S* to the centre created if the group in question is artificially elevated to higher priority than its enantiotopic twin. We'll use G to replace H as we did in Chapter 32: just assume that G has priority immediately higher than H. The method is illustrated for glycine.

Faces of a prochiral trigonal carbon atom are assigned *Re* and *Si* by viewing the carbon from that side and counting down the groups in priority 1–3. Counting round to the right (clockwise) means the face is *Re*; counting round to the left (anticlockwise) means it's *Si*. Remember our advice from Chapter 16: think of turning a steering wheel in the direction of the numbers: does the cargo go to the right or the left?



Like *R* and *S*, these stereochemical terms are merely labels: they are of no consequence chemically.

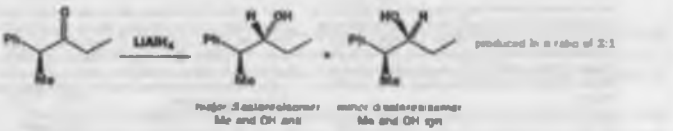
Just like diastereotopic signals in an NMR spectrum, diastereotopic faces are always different in principle, but sometimes not so in practice. The very first reaction of Chapter 33 is a case in point: this C=O group has two diastereotopic faces, which, due to free rotation about single bonds, average out to about the same reactivity, so we cannot expect any reasonable level of diastereoselectivity.



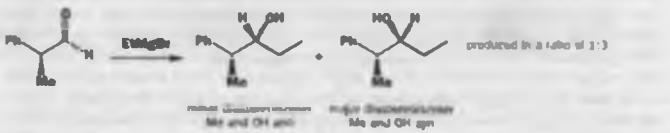
We put Chapter 33 first because in rings conformation is well defined, and this 'averaging' effect is held at bay. We are about to let it out again, but we will show you how it can be turned to surprisingly good effect.

Additions to carbonyl groups can be diastereoselective even without rings

What happens if we bring the stereogenic centre closer to the carbonyl group than it was in the last example? You might expect it to have a greater influence over the carbonyl group's reactions. And it does. Here is an example.

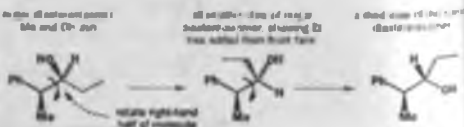


There is three times as much of one of the two diastereoisomeric products as there is of the other, and the major (*anti*) diastereoisomer is the one in which the nucleophile has added to the front face of the carbonyl group as drawn here. We can make these same two diastereoisomers by addition of an organometallic to an aldehyde. For example, this Grignard reagent gives three times as much of the *syn* diastereoisomer as the *anti* diastereoisomer. The major product has changed, but the product still arises from attack on the front face of the carbonyl as shown.



Drawing diastereoisomers of acyclic molecules

If you find it hard to see that these are still the same two diastereoisomers, try mentally rotating the right-hand half of the molecule about the bond shown below. The next three structures all show the same diastereoisomer (the major product from the last reaction), but in three different conformations (we are just rotating about a bond to get from one to another).



Which is the best? A good guideline, which we suggested in Chapter 16, is to place the longest carbon chain zig-zagging across the page in the plane of the paper, and show all the smaller substituents to attend above or below that chain. The first structure here is drawn like that. But this is only a guideline, and the second structure here is a bit more informative regarding the reaction because, when it is drawn like this, you can clearly see from which direction the vinyl group has attacked the carbonyl. Our advice would be that you first of all draw the product of any reaction in more or less the same conformation as the starting material to ensure you make no mistakes, and then rotate about a single bond to place the longest chain in the plane of the paper.

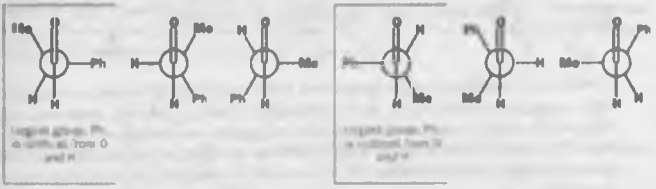
If you have problems manipulating structures mentally—for an exam, if you find it hard to work out whether the substituents that aren't in the plane should be in front of or behind the page—build some models.

These two reactions are not nearly as diastereoselective as most of the reactions of cyclic compounds you met in the last chapter. But we do now need to explain why they are diastereoselective at all, given the free rotation possible in an acyclic molecule. The key, as much with acyclic as with cyclic molecules, is conformation.

The conformation of a chiral aldehyde

What will be the conformation of the aldehyde in the margin? Using the principles we outlined in Chapter 17, we can expect it to be staggered, with no eclipsing interactions, and also with large substituents as far apart from one another as possible. A Newman projection of one of the possible conformers might look like the one shown in the margin. There are no eclipsing interactions, and the large phenyl group is held satisfactorily far away from the O and the H atoms of the aldehyde.

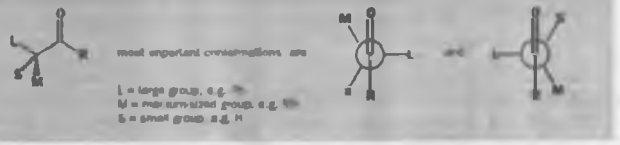
By rotating about the central bond of the aldehyde (the one represented by a circle in the Newman projection) we can suggest a series of possible conformations. Provided we move in 60° steps, none of them will have any eclipsing interactions. The full set of six conformers is shown here. Look at them for a moment, and notice how they differ.



Only two of them, boxed in yellow, place the large Ph group perpendicular to the carbonyl group. These yellow boxed conformations are therefore the lowest-energy conformers and, for the purpose of the discussion that follows, they are the only ones whose reactions we need to consider.

● Lowest energy conformations of a carbonyl compound

The most important conformations of a carbonyl compound with a stereogenic centre adjacent to the carbonyl group are those that place the largest group perpendicular to the carbonyl group.

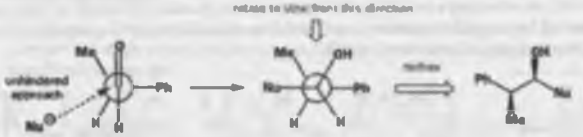


The major product arises from the most reactive conformer

Now that we have decided which are the important conformations, how do we know which gives the product? We need to decide which is the *most reactive*. All we need to do is to remember that any nucleophile attacking the carbonyl group will do so from the Bürgi–Dunitz angle—about 107° from the C=O bond. The attack can be from either side of C=O, and the following diagrams show the possible trajectories superimposed on the two conformations we have selected, which are in equilibrium with one another.

the black flight path is the best

Not all four possible 'flight paths' for the nucleophile are equally favourable. For the three shown in brown, the nucleophile passes within 30° or so of another substituent. But, for the one shown in black, there is no substituent nearby except H to hinder attack: the conformation on the left is the most reactive one, and it reacts to give the diastereoisomer shown below.



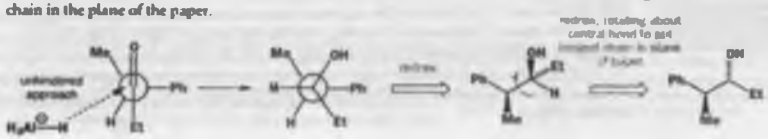
With Nu = Et we have the right product and, more importantly, we can be pretty sure it is for the right reason: this model of the way a nucleophile attacks a carbonyl compound, called the Felkin–Anh model, is supported by theoretical calculations and numerous experimental results. Notice that we don't have to decide which is the lower energy of the two conformations: this is not necessary because the attack in black will occur even if the conformer on the left is the minor one in the mixture.

Cram's rule

You may hear 'Cram's rule' used to explain the outcome of reactions involving attack on chiral carbonyl compounds. Cram was the first to realize that these reactions could be predicted, but we now know why these compounds react in a predictable way. We will not describe Cram's rule because, although it often does predict the right product, in this case it does so for the wrong reason. Explanations and other logical thinking are more important than rules, and you must be able to account for and predict the reactions of chiral aldehydes and ketones using the Felkin–Anh model.

The same reasoning accounts for the diastereoselectivity of the reduction on p. 000: first we need to draw the two important conformers of the ketone; the ones that have the large group (Ph) perpendicular to the C=O group.

Now choose the angle of attack that is the least hindered, and draw a Newman projection of the product. Finally, redraw the Newman projection as a normal structure, preferably with the longest chain in the plane of the paper.

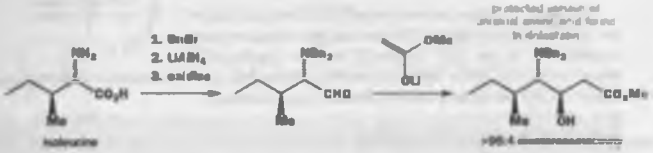


Remember our guideline: draw the product in a conformation similar to that of the starting material; then redraw to put the longest chain in the plane of the paper. Here, this just means drawing the view from the top of the Newman projection—there is no need to rotate any bonds in this case.

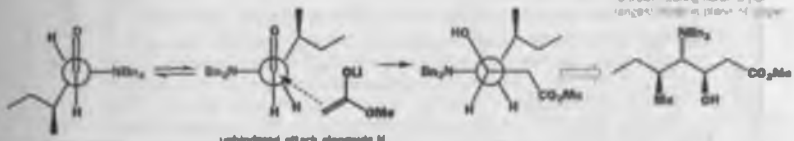
This is an example of the Curtin–Hammett principle, which says that it is the relative energies of the transition states that control selectivity, not the relative energies of the starting materials. It's a really useful reminder not to make a mistake than a principle.

The effect of electronegative atoms

One of the most powerful anticancer agents known is dolastatin, isolated from the sea-hare *Dolabella*. Dolastatin contains an unusual amino acid, with three stereogenic centres, and chemists in Germany managed to exploit Felkin–Anh control very effectively to make it from the much more widespread amino acid isoleucine. This is the sequence of reactions



The key step is the aldol reaction of the enolate of methyl acetate with the protected amino aldehyde. To rationalize the stereoselectivity, we first need to draw the two most important conformations of this aldehyde with the large group perpendicular to C=O. The trouble is—which do we choose as 'large': the $-NBn_2$ group or the branched alkyl group? Since we know which diastereoisomer is produced we can work backwards to find that it must be the NBn_2 group that sits perpendicular to C=O in the reactive transition state, and not alkyl.



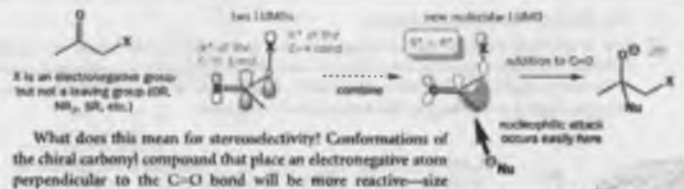
unhindered attack alongside H

Now look at the diastereoselectivity of the reaction: it is much greater than the 3:1 we saw before—more like 20:1. This really does suggest that there is a further factor at work here, and that further factor is the electronegative N atom.

Carbonyl groups increase the reactivity of adjacent leaving groups towards nucleophilic substitution by several orders of magnitude. This was an effect that we noted in Chapter 17, where we showed that the ketone below reacts by the S_N2 mechanism 5000 times as fast as methyl chloride itself.

We explained this effect by saying that the π^* of the C=O and the σ^* of C–Cl overlap to form a new, lower-energy (and therefore more reactive) LUMO. What we did not note then, because it was not relevant, is that this overlap can only occur when the C–Cl bond is perpendicular to the C=O bond, because only then are the π^* and σ^* orbitals aligned correctly.

The same thing happens even with electronegative atoms X that are not leaving groups in the S_N2 reaction (for example, X = OR, NR_2, SR, etc.). The π^* and σ^* orbitals add together to form a new, lower-energy molecular orbital, more susceptible to nucleophilic attack. But, if X is not a leaving group, attack on this orbital will result not in nucleophilic substitution but in addition to the carbonyl group. Again, this effect will operate only when the C–X and C=O bonds are perpendicular so that the orbitals align correctly.



What does this mean for stereoselectivity? Conformations of the chiral carbonyl compound that place an electronegative atom perpendicular to the C=O bond will be more reactive—size doesn't matter. So, in the dolastatin amino acid example, the conformations with NBn_2 perpendicular to C=O are the only conformations we need to consider.

Using the Felkin–Anh model

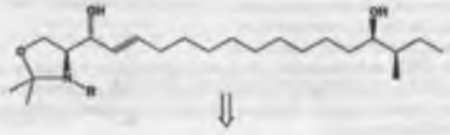
To predict or explain the stereoselectivity of reactions of a carbonyl group with an adjacent stereogenic centre, use the Felkin–Anh model.

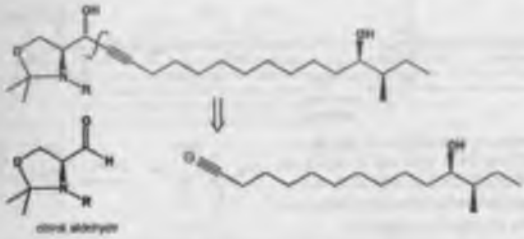
- Draw Newman projections of the conformations of the starting material that place a large group or an electronegative group perpendicular to C=O
- Allow the nucleophile to attack along the least hindered trajectory, taking into account the Bürgi–Dunitz angle
- Draw a Newman projection of the product that arises from attack in this way
- Carefully flatten the Newman projection on to the page to produce a normal structure, preferably with the longest chain of C atoms in the plane of the page. Check that you have done this last step correctly: it is very easy to make mistakes here. Use a model if necessary, or do the 'flattening out' in two stages—first view the Newman projection from above or below and draw that; then rotate some of the molecule about a bond if necessary to get the long chain into the plane of the page.

As an illustration of two sorts of diastereoselectivity, our next example is a natural product called penaresidin A. It was isolated from a Japanese sponge in 1991, and has the structure shown below

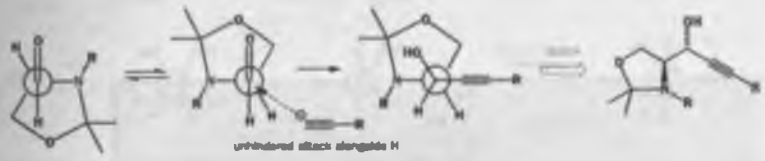
penaresidin A

or something like this, because at the time of writing the relative stereochemistry between the two remotely related groups of chiral centres is still not known for sure. What is sure is the stereochemistry around the ring: NMR (the methods of Chapter 32) gives that. What Mori and his co-workers set out to do was to make, using unambiguous stereoselective methods, all the possible diastereoisomers of penaresidin A to discover which was the same as the natural product. It was fairly straightforward to get to the target molecule from the structure below and overleaf, so that's the compound whose synthesis we need to consider. If we imagine getting the *E*-alkene by stereoselective reduction of the alkyne, disconnection to an alkynyl anion equivalent reveals an aldehyde with a chiral centre next to the carbonyl group.

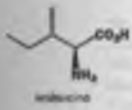


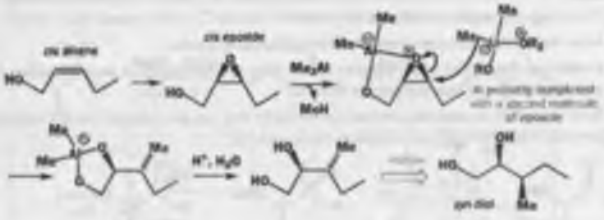


How will this aldehyde (which can be made from the amino acid serine) react with nucleophiles such as lithiated alkynes? Consider a Felkin–Anh transition state: again, we know that the nitrogen, being electronegative, will lie perpendicular to the carbonyl group in the most reactive conformation, so we need only consider these two. The least hindered direction of attack is shown, and that indeed gives the required product.



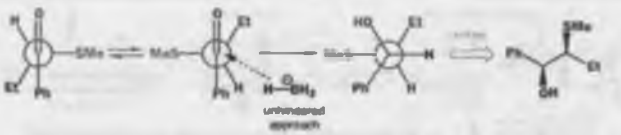
The other two chiral centres need to be controlled separately. The *trans* relative configuration could be obtained from another amino acid, which itself has two stereogenic centres—isoleucine. The *cis* was harder. The chemists decided to make it by starting with the *cis* diol shown, which could come from ring opening of an epoxide with an aluminium reagent. Since the ring opening goes with inversion, the epoxide needs to be *cis*, so the ultimate starting material was chosen to be a *cis* allylic alcohol. It turned out that the *cis* stereochemistry was right.



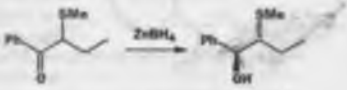


Chelation can reverse stereoselectivity

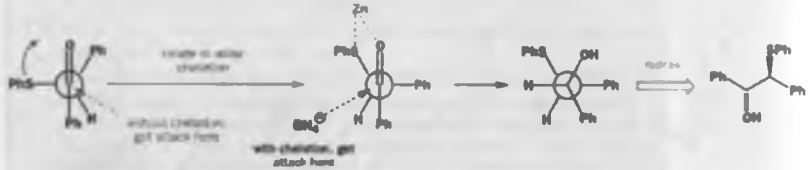
You should now be in a position to explain the outcome of this reaction without much difficulty. Sulfur is the electronegative atom, so the conformations we need to consider are the two following. Unhindered attack on the second gives the diastereoisomer shown.



But, from what we have told you so far, the next reaction would present a problem: changing the metal from sodium to zinc has reversed the stereoselectivity. Using the simple Felkin–Anh model now does not work; it gives the wrong answer.



The reason is that zinc can chelate sulfur and the carbonyl group. Chelation is the coordination of two heteroatoms carrying lone pairs to the same metal atom, and here it changes the conformation of the starting material. No longer does the most reactive or most populated conformation place the electronegative S atom perpendicular to C=O; instead it prefers S to lie as close to the carbonyl oxygen as possible so that Zn can bridge between S and O, like this.



When chelation is possible, this is the conformation to consider—the one with the carbonyl O and the other chelating atom almost eclipsing one another. It is the most populated, because it is stabilized by the chelation, and it is also the most reactive, because the Lewis-acidic metal atom increases the reactivity of the carbonyl group. Attack is still along the less hindered pathway, but this now leads to the other face of the carbonyl group, and the stereochemical outcome is reversed.

Two things are needed for chelation to occur:

- a heteroatom with lone pairs available for coordination to a metal
- a metal ion that prefers to coordinate to more than one heteroatom at once. These are mainly more highly charged ions as shown in the table

Metals commonly involved in chelation	Metals not usually involved in chelation
Li^+ sometimes	Li^+ often
Mg^{2+}	Na^+
Zn^{2+}	K^+
Cu^{2+}	
Ti^{4+}	
Ce^{3+}	
Mn^{2+}	

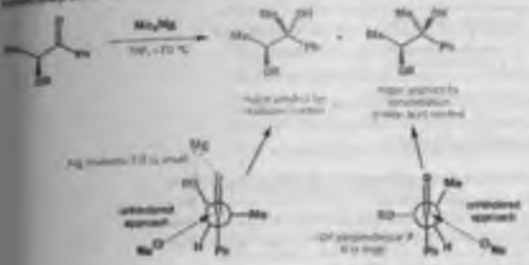
Here is another example of a reversal in selectivity that can be explained using a nonchelated Felkin–Anh model with Na^+ and a chelated model with Mg^{2+}.

$NaBH_4$ (Nu = H)	73%	27%
Me_2Mg (Nu = Me)	1%	99%

Not only does chelation control reverse the stereoselectivity, but it gives a much higher degree of stereoselectivity. Stereoselectivities in chelation-controlled additions to C=O groups are typically >95:5. But this fits in nicely with the ideas we presented at the end of the last chapter: stereoselectivity is likely to be high if a cyclic transition state is involved. Chelation involves just such a transition state, so it should be no surprise that it lets us achieve much higher levels of control than the acyclic Felkin–Anh model does.

Chelation, rate, and stereoselectivity

The connection of rate of addition with diastereoselectivity was demonstrated in a series of experiments that involved reacting Me_2Mg with a ketone with a hydroxy substituent. As the protecting group was changed from a methyl ether to a trimethylsilyl ether and then through a series of increasingly bulky alkyl ethers, both the rate of the reaction and the diastereoselectivity decreased. With small protecting groups, the reaction takes place through the chelated transition state—the selectivity shows this—and the rate is faster because of the activating effect of the Lewis-acidic magnesium ion. But with larger protecting groups, chelation of Mg^{2+} between the two oxygen atoms is frustrated, the rate drops off, and the selectivity becomes more what would be expected from the Felkin–Anh model.

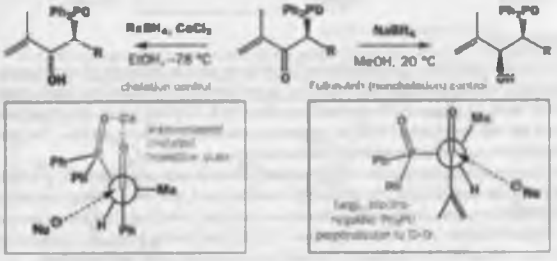


R	Ratio	Relative rate
Me	>99:1	1000
$SiMe_3$	99:1	100
$SiEt_3$	96:4	8
$SiMe_2tBu$	88:12	2.5
$SiPh_2tBu$	83:17	0.82
$Si(iPr)_3$	42:58	0.45

Chelation

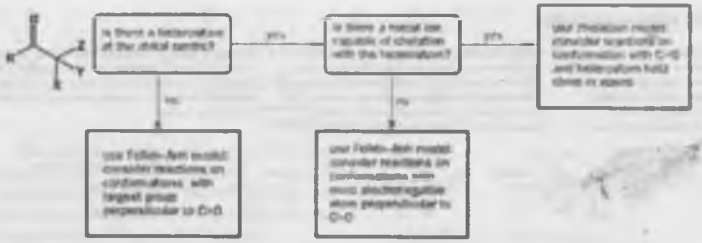
- may change the direction of diastereoselectivity
- leads to high levels of diastereoselectivity
- increases the rate of the addition reaction

Chelation is possible through six- as well as five-membered rings, and the reduction of the ketone below is a nice example of the reversal of diastereoselectivity observed when chelating Ce^{3+} ions are added to a normal sodium borohydride reduction. The products were important for making single geometrical isomers of alkenes in a modification of the Wittig reaction (Chapter 31). Notice too how the rate must change: with Ce^{3+} the reaction can be done at –78 °C.



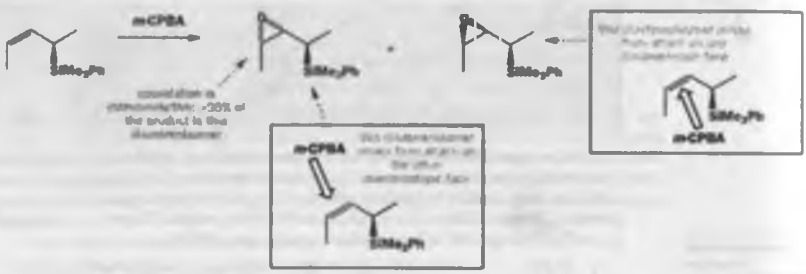
Attack on α chiral carbonyl compounds: summary

The flow chart summarises what you should consider when you need to predict or explain the stereochemical outcome of nucleophilic attack on a chiral carbonyl compound.



Stereoselective reactions of acyclic alkenes

Earlier in the chapter we discussed how to make single diastereoisomers by stereospecific additions to double bonds of fixed geometry. But if the alkene also contains a chiral centre there will be a stereoselective aspect to its reactions too: its faces will be diastereotopic, and there will be two possible outcomes even if the reaction is fully stereospecific. Here is an example where the reaction is an epoxidation.

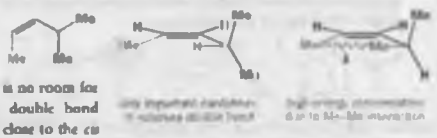


The Houk model

In order to explain reactions of chiral alkenes like this, we need to assess which conformations are important, and consider how they will react, just as we have done for chiral carbonyl compounds. Much of the work on alkene conformations was done by K.N. Houk using theoretical computer models, and we will summarize the most important conclusions of these studies. The theoretical studies looked at two model alkenes, shown in the margin.

The calculations found that the low-energy conformations in each case were those in which a substituent eclipses the double bond. For the simple model alkene 1, the lowest-energy conformation is the one that has the proton in the plane of the alkene. Another low-energy conformation—only 3.1 kJ mol^{-1} higher—has one of the methyl groups eclipsing the double bond, so that when we start looking at reactions of this type of alkene, we shall have to consider both conformations.

For the model alkene 2, with a *cis* substituent, the conformation is more predictable and the only low-energy conformer is the one with the hydrogen eclipsing the double bond. There is no room for a methyl group to eclipse the double bond because if it did it would get too close to the *cis* substituent at the other end of the double bond.



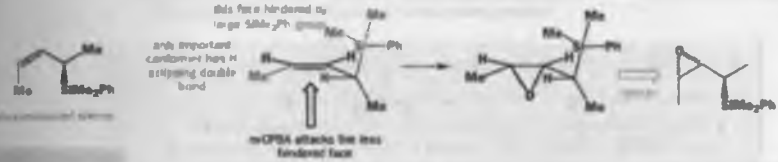
The message from the calculations is this:

- The lowest-energy conformation of a chiral alkene will have H eclipsing the double bond
- If there is a *cis* substituent on the alkene, this will be the only important conformation; if there is no *cis* substituent, other conformations may be important too

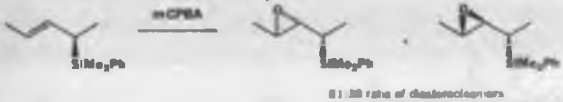
Now we can apply the theoretical model to some real examples.

Stereoselective epoxidation

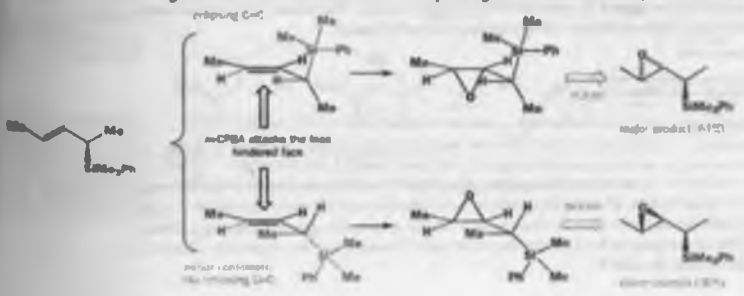
We started this section with a diastereoselective epoxidation of an alkene. The alkene was this one, and it has a substituent *cis* to the stereogenic centre. We can therefore expect it to have one important conformation, with H eclipsing the double bond. When a reagent—*m*-CPBA here—attacks this conformation, it will approach the less hindered face, and the outcome is shown.



Without the *cis* substituent, selectivity is much lower.



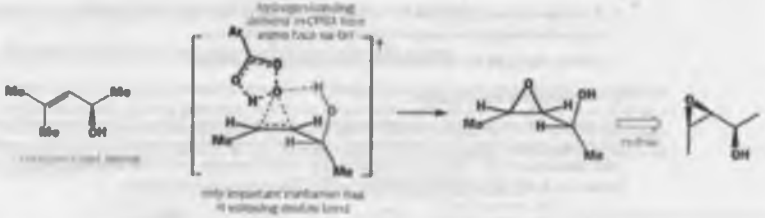
m-CPBA still attacks the less hindered face of the alkene, but with no *cis* substituent there are two low-energy conformations: one with H eclipsing the double bond, and one with Me eclipsing. Each gives a different stereochemical result, explaining the low stereoselectivity of the reaction.



You saw at the end of the last chapter that the reactions of *m*-CPBA can be directed by hydroxyl groups, and the same thing happens in the reactions of acyclic alkenes. This allylic alcohol epoxidizes to give a 95:5 ratio of diastereoisomers.

95:5 ratio of diastereoisomers

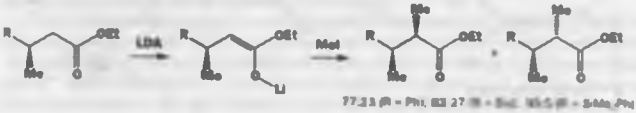
Drawing the reactive conformation explains the result. The thing that counts is the *cis* methyl group: the fact that there is a *trans* one too is irrelevant as it is just too far away from the stereogenic centre to have an effect on the conformation.



- **To explain the stereoselectivity of reactions of chiral alkenes:**
  - **Draw the conformation with H eclipsing the double bond**
  - **Allow the reagent to attack the less hindered of the two faces or, if co-ordination is possible, to be delivered to the face *syn* to the coordinating group**
  - **Draw the product in the same conformation as the starting material**
  - **Redraw the product as a normal structure with the longest chain in the plane of the paper**

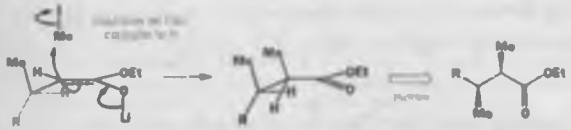
Stereoselective enolate alkylation

Chiral enolates can be made from compounds with a stereogenic centre β to a carbonyl group. Once the carbonyl is deprotonated to form the enolate, the stereogenic centre is next to the double bond and in a position to control the stereoselectivity of its reactions. The scheme below shows stereoselectivity in the reactions of some chiral enolates with methyl iodide.

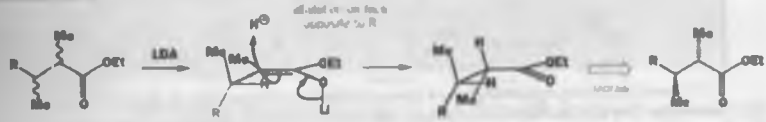


77:23 (R = Ph), 82:27 (R = Bu), 95:5 (R = SiMe$_2$Ph)

The enolate is a *cis*-substituted alkene, because either O$^-$ or OEt must be *cis* to the stereogenic centre, so that to explain the stereoselectivity, we need consider only the conformation with H eclipsing the double bond. Notice how the diastereoselectivity increases as the group R gets bigger, because there is then more contrast between the size of Me and R. In each case, the electrophile adds to the less hindered face, opposite R.

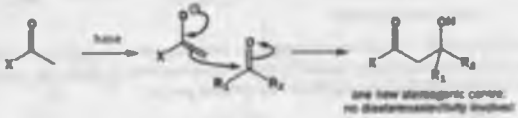


The other diastereoisomer can be made just by having the methyl group in place first and then protonating the enolate. The selectivities are lower (because a proton is small), but this does illustrate the way in which reversing the order of introduction of two groups can reverse the stereochemical outcome of the reaction.

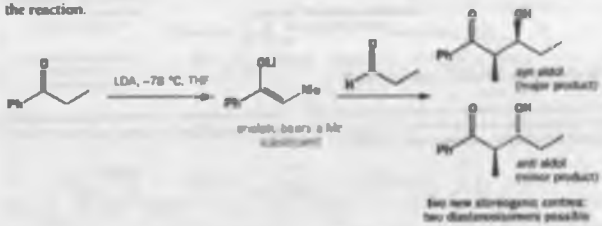


Aldol reactions can be stereoselective

In Chapter 27 you met the **aldol reaction**: reaction of an enolate with an aldehyde or a ketone. Many of the examples you saw approximated to this general pattern.



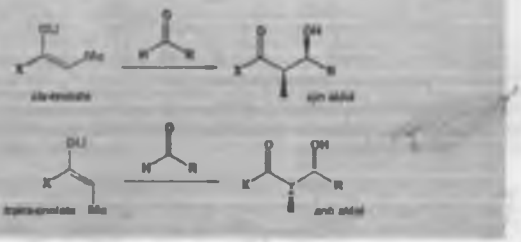
Only one new stereogenic centre is created, so there is no question of diastereoselectivity. But with substituted enolates, two new stereogenic centres are created, and we need to be able to predict which diastereoisomer will be formed. Here is an example from p. 000. We did not consider stereochemistry at that stage, but we can now reveal that the *syn* diastereoisomer is the major product of the reaction.



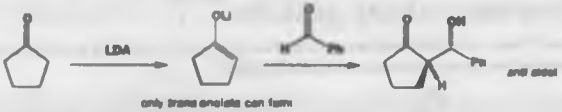
The important point about substituted enolates is that they can exist as two geometrical isomers, *cis* or *trans*. Which enolate is formed is an important factor controlling the diastereoselectivity because it turns out that, in many examples of the aldol reaction, *cis*-enolates give *syn* aldols preferentially and *trans*-enolates give *anti* aldols preferentially.

● Diastereoselectivity in aldol reactions

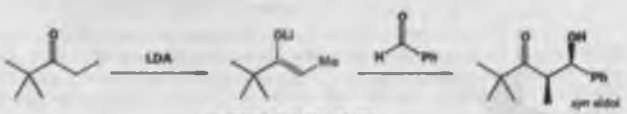
Generally (but certainly not always!) in aldol reactions:



Let's start by showing some examples and demonstrating how we know this to be the case. Some enolates can only exist as *trans*-enolates because they are derived from cyclic ketones. This enolate, for example, reacts with aldehydes to give only the *anti* aldol product.



If we choose the group 'X', next to the carbonyl group, to be large, then we can be sure of getting just the *cis*-enolate. So, for example, the lithium enolate of this *t*-butyl ketone forms just as one geometrical isomer, and reacts with aldols to give only the *syn* aldol product.



cis-enolate avoids Me and tBu coming into contact

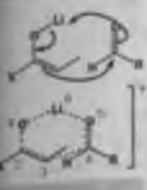
cis and *trans*, *E* and *Z*, *syn* and *anti*

Before going further, there are two points we must clarify. The first is a problem of nomenclature, and concerns the enolates of esters. There are two closely related ester enolate equivalents, drawn with the same double bond geometry. Is it *E* or *Z*?

The answer is both! For the Li enolate, the usual rule makes OLi of lower priority than OMe, so it's *E*, while the silyl enol ether (an 'silyl ketene acetal') has OSi of higher priority than OMe, so it's *Z*. This is merely a nomenclature problem, but it would be irritating to have to reverse all our arguments for lithium enolates simply because lithium is of lower atomic number than carbon. So, for the sake of consistency, it is much better to avoid the use of *E* and *Z* with enolates and instead use *cis* and *trans*, which then always refer to the relationship between the substituent and the anionic oxygen (bearing the metal).

The other point concerns *syn* and *anti*. We said earlier that there is no precise definition of these terms. They are a useful way of distinguishing two diastereoisomers provided the structure of at least one of them is presented in diagrammatic form. For aldol products the convention is that *syn* or *anti* refers to the enolate substituent (the green Me in the last example) and the new hydroxyl group, provided the main chain is in the plane of the paper, the way we have encouraged you to draw molecules.

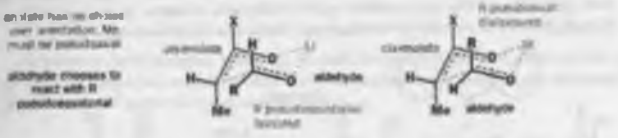
The aldol reaction has a chair-like transition state



The Zimmerman–Traxler ring transition state for the aldol reaction was proposed by Zimmerman and Traxler and is sometimes called the Zimmerman–Traxler transition state.

These are the experimental facts: how can we explain them? Aldol reactions are another class of stereoselective process with a cyclic transition state. During the reaction, the lithium is transferred from the enolate oxygen to the oxygen of the carbonyl electrophile. This is represented in the margin both in curly arrow terms and as a transition state structure.

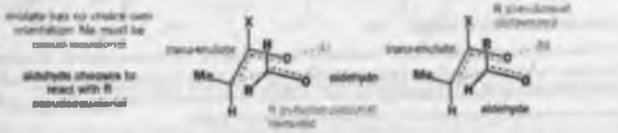
A six-membered ring is involved, and we can expect this ring to adopt more or less a chair conformation. The easiest way to draw this is first to draw the chair, and then convert atoms to O or Li as necessary. Here it is.



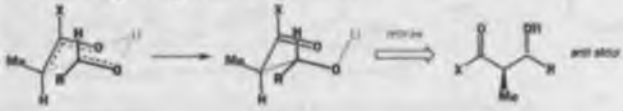
In drawing this chair, we have one choice: do we allow the aldehyde to place R equatorial or axial? Both are possible but, as you should now expect, there are fewer steric interactions if R is equatorial. Note that the enolate doesn't have the luxury of choice. If it is to have three atoms in the six-membered ring, as it must, it can do nothing but place the methyl group pseudoaxial.

The aldol formed from the favoured transition state structure, with R pseudoequatorial, is shown below—first in the conformation of the transition state, and then flattened out on to the page, and it is *syn*.

We can do the same for a *trans*-enolate. The enolate has no choice but to put its methyl substituent pseudoequatorial, but the aldehyde can choose either pseudoequatorial or pseudoaxial. Again, pseudoequatorial is better



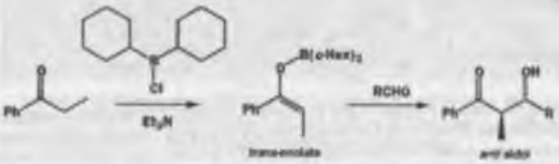
and the reaction gives the product shown—the *anti* aldol.



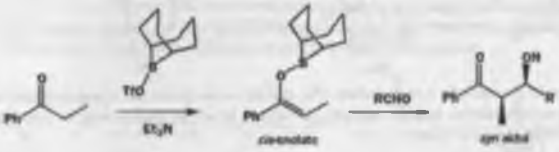
Stereoselective enolization is needed for stereoselective aldols

The cyclic transition state explains how enolate geometry controls the stereochemical outcome of the aldol reaction. But what controls the geometry of the enolate? For lithium enolates of ketones the most important factor is the size of the group that is not enolized. Large groups force the enolate to adopt the *cis* geometry; small groups allow the *trans*-enolate to form. Because we can't separate the lithium enolates, we just have to accept that the reactions of ketones with small R will be less diastereoselective.

With *boron* enolates, we don't have to rely on the structure of the substrate—we choose the groups on boron—and we can get either *cis* or *trans* depending on which groups these are. Boron enolates are made by treating the ketone with an amine base (often Et_3N or *i*-Pr_2NEt) and R_2B–X, where X^- is a good leaving group such as chloride or triflate ($CF_3SO_3^-$). With bulky groups on boron, such as two cyclohexyl groups, a *trans*-enolate forms from most ketones. The boron enolate reacts reliably with aldehydes to give *anti* aldol products through the same six-membered transition state that you saw for lithium enolates.

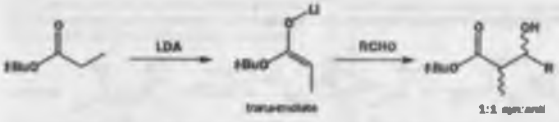


With smaller B substituents, the *cis*-enolate forms selectively. Here, the boron is part of a bicyclic structure known as 9-BBN (9-borabicyclononane—you will meet this in Chapter 47). The bicyclic part may look large but, as far as the rest of the molecule is concerned, it's 'tied back' behind the boron, and the methyl group can easily lie *cis* to oxygen. The *cis*-enolate then gives *syn* aldol products. Di-*n*-butylboron triflate (Bu_2BOTf) also gives *cis*-enolates.

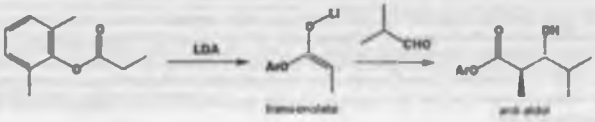


Stereoselective ester aldols

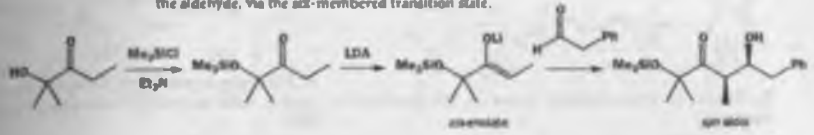
We have talked mainly about aldol reactions of ketones (as the enolate component). Esters usually form the *trans* lithium enolates quite stereoselectively. You might therefore imagine that their aldol reactions would be stereoselective for the *anti* product. Unfortunately, this is not the case, and even pure *trans*-enolate gives about a 1:1 mixture of *syn* and *anti* aldols.



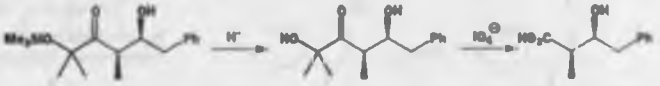
There is one important exception, and that is a class of esters of hindered phenols. The *trans*-enolates of these compounds react selectively with aldehydes to give the *anti* aldol products.



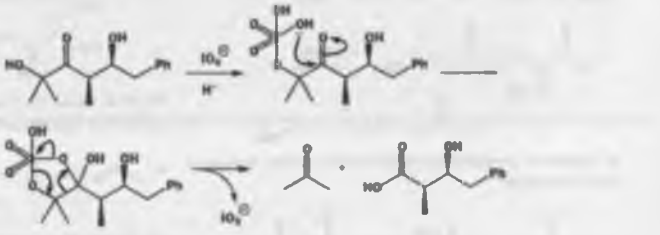
An ingenious way of getting a *syn* ester aldol product is to do the more reliable ketone *syn* aldol with a bulky group (to ensure the *cis*-enolate is formed) and then to oxidize off the bulky group. Here's what we mean. The starting material is very like the *t*-butyl ketone that you saw enolize stereoselectively above: only the *cis*-enolate can form. The enolate reacts highly *syn* selectively with the aldehyde, via the six-membered transition state.



At this point, the bulky group is no longer needed. The oxygen is deprotected in acid and, in the same step, periodate ions oxidatively cleave the C–C bond between the two oxygen substituents. The product is the acid parent of a *syn* ester aldol product.



We shall show you the mechanism of the cleavage, because it leads us nicely into the next chapter. The first step is rather like the first step of many oxidations—formation of an inorganic ester (here a periodate). The periodate can form a cyclic ester by attack on the carbonyl group. Next, we can push the arrows round the ring to reduce the iodine from I(VII) to I(V), cleave the double bond, and generate acetone and the acid.



You will see many more cyclic mechanisms in the next two chapters, including some more C–C cleavage reactions.

Summary: How to make *syn* and *anti* aldols

To make *syn* aldols of ketones:

- with a ketone RCOEt with bulky R, use lithium enolate
- use boron enolate with 9-BBN-OTf or Bu_2BOTf

To make *syn* aldols of esters:

- use a bulky 2-alkoxyketone and cleave to an acid

To make *anti* aldols of ketones:

- with a cyclic ketone, use lithium enolate
- use boron enolate with dicyclohexylboron chloride

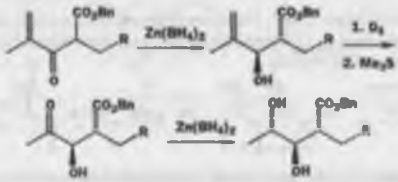
To make *anti* aldols of esters:

- use the ester of a hindered phenol

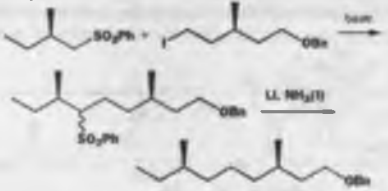
Problems

1. How would you make each diastereoisomer of this product from the same alkene?

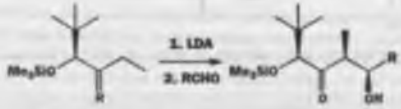
2. Explain the stereoselectivity shown in this sequence of reactions.



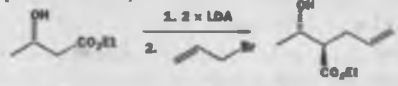
3. How is the relative stereochemistry of this product controlled? Why was this method chosen?



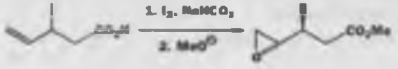
4. Explain the stereochemical control in this reaction, drawing all the intermediates.



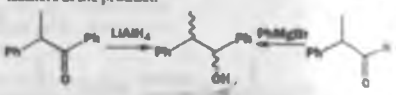
5. When this hydroxy-ester is treated with a twofold excess of LDA and then alkylated, one diastereoisomer of the product predominates. Why?



6. Explain how the stereochemistry of this epoxide is controlled.

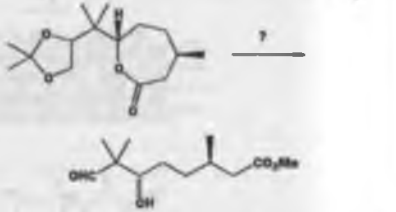


7. Explain how these two reactions give different diastereoisomers of the product.



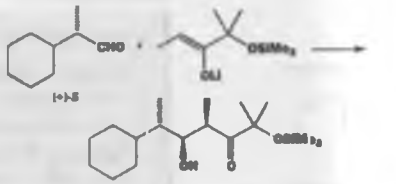
8. Explain the stereoselectivity in this reaction. What isomer of the epoxide would be produced on treatment of the product with base?

9. How could this cyclic compound be used to produce the open-chain compound with correct relative stereochemistry?

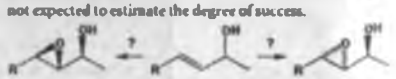


10. How would you transform this alkene stereoselectively into either of the diastereoisomers of the amino-alcohol?

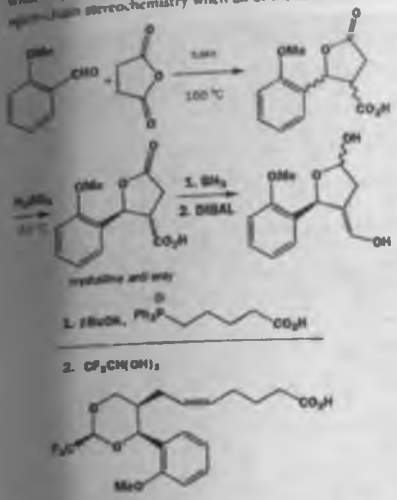
11. Explain the formation of essentially one stereoisomer in this reaction.



12. How would you attempt to transform this allylic alcohol into both diastereoisomers of the epoxide stereoselectively? You are not expected to estimate the degree of success.



34. Revision. Here is an outline of the AstraZeneca synthesis of a tricyclic melatonin analogue. Explain the reactions, giving mechanisms for each step, and explain how the stereochemistry is controlled. In what way could this be considered an example of the control of epimeric stereochemistry when all of the molecules are cyclic?



Pericyclic reactions 1: cycloadditions

35

Connections

Building on:

- Structure of molecules ch4
- Reaction mechanisms ch5
- Conjugation and delocalization ch7

Arriving at:

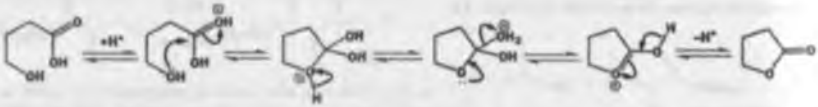
- In cycloadditions electrons move in a ring
- In cycloadditions more than one bond is formed simultaneously
- There are no intermediates in cycloadditions
- Cycloadditions are a type of pericyclic reaction
- The rules that govern cycloadditions: how to predict what will and will not work
- Photochemical reactions: reactions that need light
- Making six-membered rings by the Diels–Alder reaction
- Making four-membered rings by [2 + 2] cycloaddition
- Making five-membered rings by 1,3-dipolar cycloaddition
- Using cycloaddition to functionalize double bonds stereospecifically
- Using ozone to break C=C double bonds

Looking forward to:

- Electrocyclic reactions and sigmatropic rearrangements ch36
- Radical reactions ch39
- Aromatic heterocycles ch43–ch44
- Asymmetric synthesis ch45
- Organic synthesis ch53

A new sort of reaction

Most organic reactions are ionic. Electrons move from an electron-rich atom towards an electron-poor atom: anions or cations are intermediates. Formation of a cyclic ester (a lactone) is an example.



The reaction involves five steps and four intermediates. The reaction is acid-catalysed and each intermediate is a cation. Electrons flow in one direction in each step—towards the positive charge. This is an ionic reaction.

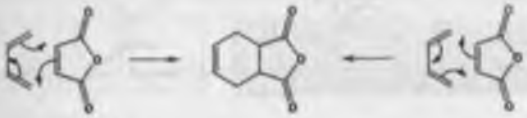
This chapter is about a totally different reaction type. Electrons move round a circle and there are no positive or negative charges on any intermediates—indeed, there are no intermediates at all. This type of reaction is called **pericyclic**. The most famous example is the Diels–Alder reaction.

▶ In Chapter 38 you will meet a third category—radical reactions—in which one electron instead of two is on the move.

■ Otto Diels (1876–1954) and his research student Kurt Alder (1902–58) worked at the University of Kiel and discovered this reaction in 1928. They won the Nobel Prize in 1950. Diels also discovered the existence of carbon suboxide, C_3O_2 (see p. 000).

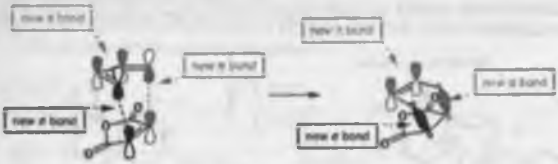
This reaction goes in a single step simply on heating. We can draw the mechanism with the electrons going round a six-membered ring.

Each arrow leads directly to the next, and the last arrow connects to the first. We have drawn the electrons rotating clockwise, but it would make no difference at all if we drew the electrons rotating anticlockwise.

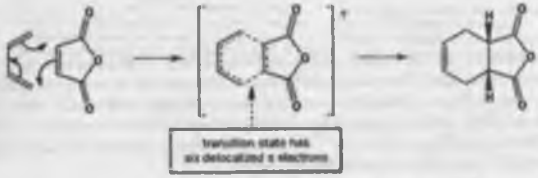


Both mechanisms are equally correct. The electrons do not really rotate at all. In reality two π bonds disappear and two σ bonds take their place by the electrons moving smoothly out of the π orbitals into the σ orbitals. Such a reaction is called a **cycloaddition**. We must spend some time working out how this could happen.

First, just consider the orbitals that overlap to form the new bonds. Providing the reagents approach in the right way, nothing could be simpler.

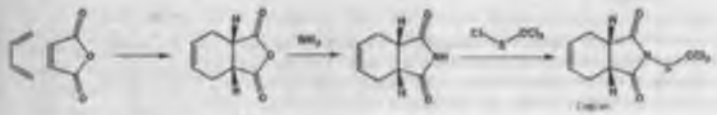


The black p orbitals are perfectly aligned to make a new σ bond as are the two green orbitals, while the two brown orbitals are exactly right for the new π bond at the back of the ring. As this is a one-step reaction there are no intermediates but there is one transition state looking something like this.



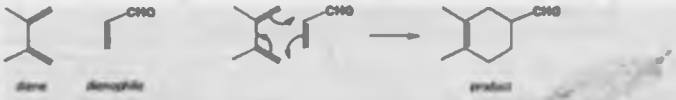
One reason that the Diels–Alder reaction goes so well is that the transition state has six delocalized π electrons and thus is aromatic in character, having some of the special stabilization of benzene. You could look at it as a benzene ring having all its π bonds but missing two σ bonds. This simple picture is fine as far as it goes, but it is incomplete. We shall return to a more detailed orbital analysis when we have described the reaction in more detail.

Cephalosporin



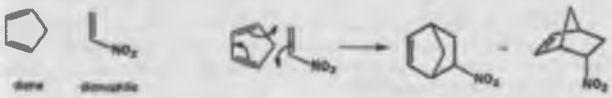
General description of the Diels–Alder reaction

Diels–Alder reactions occur between a conjugated diene and an alkene, usually called the dienophile. Here are some examples: first an open-chain diene with a simple unsaturated aldehyde as the dienophile.



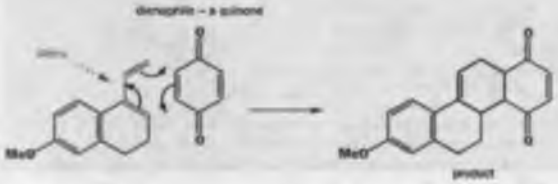
diene dienophile product

The mechanism is the same and a new six-membered ring is formed having one double bond. Now a reaction between a cyclic diene and a nitroalkene.



diene dienophile

The mechanism leads clearly to the first drawing of the product but this is a cage structure and the second drawing is better. The new six-membered ring is outlined in black in both diagrams. Now a more elaborate example to show that quite complex molecules can be quickly assembled with this wonderful reaction.

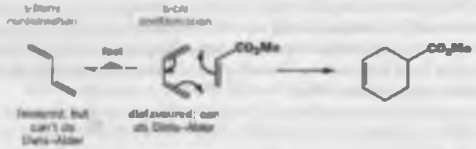


product

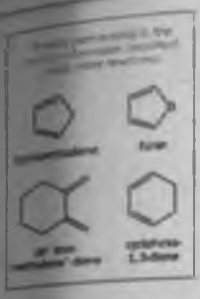
The diene

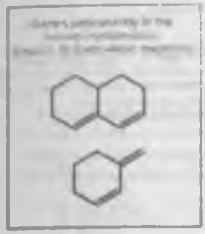
The diene component in the Diels–Alder reaction can be open-chain or cyclic and it can have many different kinds of substituents. There is only one limitation: it must be able to take up the conformation shown in the mechanism. Butadiene normally prefers the *s-trans* conformation with the two double bonds as far away from each other as possible for steric reasons. The barrier to rotation about the central σ bond is small (about 30 kJ mol^{-1} at room temperature: see Chapter 18) and rotation to the less favourable but reactive *s-cis* conformation is rapid.

▶ The 's' in the terms 's-cis' and 's-trans' refers to a σ bond and indicates that these are conformations about a single bond and not configurations about a double bond.



Cyclic dienes that are permanently in the *s-cis* conformation are exceptionally good at Diels–Alder reactions—cyclopentadiene is a classic example—but cyclic dienes that are permanently in the *s-trans* conformation and cannot adopt the *s-cis* conformation will not do the Diels–Alder reaction at all. The two ends of these dienes cannot get close enough to react with





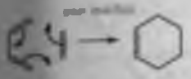
an alkene and, in any case, the product would have an impossible *trans* double bond in the new six-membered ring. (In the Diels–Alder reaction, the old σ bond in the centre of the diene becomes a π bond in the product and the conformation of that σ bond becomes the configuration of the new π bond in the product.)

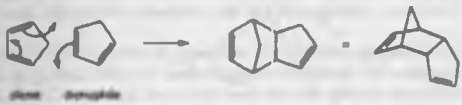
● The diene

The diene must have the *s-cis* conformation.

The dienophile

The dienophiles you have seen in action so far all have one thing in common. They have an electron-withdrawing group conjugated to the alkene. This is a common though not exclusive feature of Diels–Alder dienophiles. There must be some extra conjugation—at least a phenyl group or a chlorine atom—or the cycloaddition does not occur. You will often see the reaction between butadiene and a simple alkene (even ethylene) given in books as the basic Diels–Alder reaction. This occurs in only poor yield. Attempts to combine even such a reactive diene as cyclopentadiene with a simple alkene lead instead to the dimerization of the diene. One molecule acts as the diene and the other as the dienophile to give the cage structure shown.



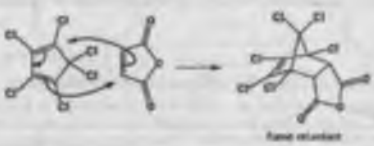


diene dienophile

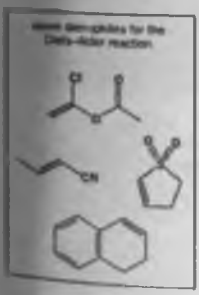
Cyclopentadiene

Cyclopentadiene is formed in considerable amounts during the cracking of petroleum. It exists as its dimer at room temperature but can be dissociated into the monomer on heating—the effect of the increased importance of entropy at higher temperatures (Chapter 13). It can be chlorinated to give hexachlorocyclopentadiene, and the Diels–Alder product of this diene with maleic anhydride is a flame retardant.

high b.p. b.p. 41 °C



flame retardant

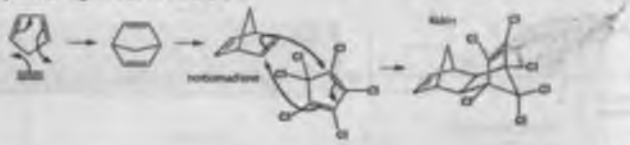


Simple alkenes that do undergo the Diels–Alder reaction include conjugated carbonyl compounds, nitro compounds, nitriles, sulfones, aryl alkenes, vinyl ethers and esters, haloalkenes, and dienes. In addition to those you have seen so far, a few examples are shown in the margin. In the last example it is the isolated double bond in the right-hand ring that accepts the diene. Conjugation with the left-hand ring activates this alkene. But what exactly do we mean by 'activate' in this sense? We shall return to that question in a minute.

Dieldrin and Aldrin

In the 1950s two very effective pesticides were launched and their names were 'Dieldrin' and 'Aldrin'. As you may guess they were made by the Diels–Alder reaction. Aldrin is derived from two consecutive Diels–Alder reactions. In the first, cyclopentadiene reacts with acetylene to give a simple symmetrical cage molecule 'norbornadiene'.

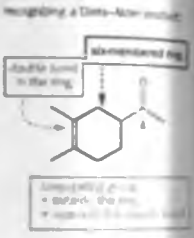
(bicyclo[2.2.1]heptadiene). Norbornadiene is not conjugated and cannot take part in a Diels–Alder reaction as a *diene*. However, it is quite strained because of the cage and it reacts as a *dienophile* with perchlorocyclopentadiene to give Aldrin.



This is quite a complex product but we hope you can see how it is made up by looking at the two new bonds marked in black. Dieldrin is the epoxide of Aldrin. The use of these compounds, like that of many organochlorine compounds, was eventually banned when it was found that chlorine residues were accumulating in the fat of animals high up in the food chain such as birds of prey and humans.

The product

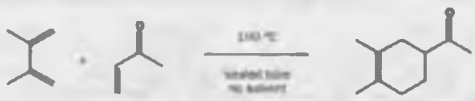
Recognizing a Diels–Alder product is straightforward. Look for the six-membered ring, the double bond inside the ring, and the conjugating group outside the ring and on the opposite side of the ring from the alkene. These three features mean that the compound is a possible Diels–Alder product.



The simplest way to find the starting materials is to carry out a disconnection that is closer to a real reaction than most. Just draw the reverse Diels–Alder reaction. To do this, draw three arrows going round the cyclohexene ring starting the first arrow in the middle of the double bond. It doesn't, of course, matter which way round you go.

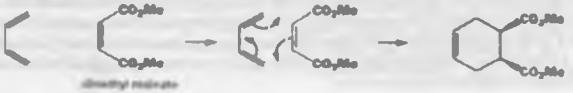
the disconnection is the imaginary reverse Diels–Alder reaction

The reaction couldn't be simpler—just heat the components together without solvent or catalyst. Temperatures of around 100–150 °C are often needed and this may mean using a sealed tube if the reagents are volatile, as here.

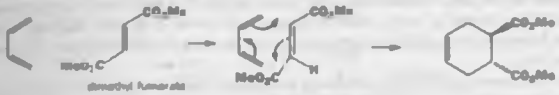


Stereochemistry

The Diels–Alder reaction is stereospecific. If there is stereochemistry in the dienophile, then it is faithfully reproduced in the product. Thus *cis* and *trans* dienophiles give different diastereoisomers of the product. Esters of maleic and fumaric acids provide a simple example.

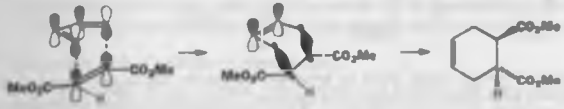


dimethyl maleate

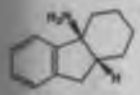


dimethyl fumarate

In both cases the ester groups simply stay where they are. They are *cis* in the dienophile in the first reaction and remain *cis* in the product. They are *trans* in the dienophile in the second reaction and remain *trans* in the product. The second example may look less convincing—may we remind you that the diene actually comes down on top of the dienophile like this.

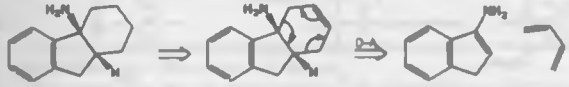


One of the CO_2Me groups is tucked under the diene in the transitions state and then, when the product molecule is flattened out in the last drawing, that CO_2Me group appears underneath the ring. The orange hydrogen atom remains *cis* to the other CO_2Me group.

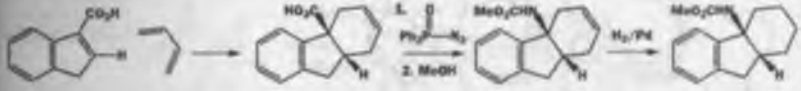


potential drugs to treat stroke

The search by the Parke–Davis company for drugs to treat strokes provided an interesting application of dienophile stereochemistry . The kinds of compound they wanted were tricylic amines. They don't look like Diels–Alder products at all. But if we insert a double bond in the right place in the six-membered ring, Diels–Alder (D–A) disconnection becomes possible.



Butadiene is a good diene, but the enamine required is not a good dienophile. An electron-withdrawing group such as a carbonyl or nitro group is preferable; either would do the job. In the event a carboxylic acid that could be converted into the amine by a rearrangement with Ph_2PON_3 (see Chapter 40) was used.

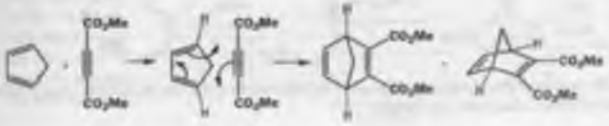


The stereochemistry at the ring junction must be *cis* because the cyclic dienophile can have only a *cis* double bond. Hydrogenation removes the double bond in the product and shows just how useful the Diels–Alder reaction is for making saturated rings, particularly when there is some stereochemistry to be controlled.

▶ You can add the Diels–Alder reaction to your mental list of reactions to consider for making a single diastereoisomer from a single geometrical isomer of an alkene: see Chapter 34.

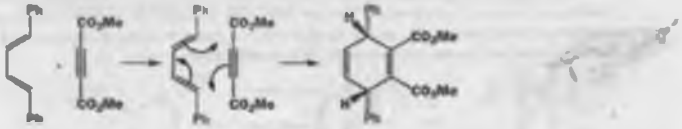
Stereochemistry of the diene

This is slightly more complicated as the diene can be *cis, cis*, or *cis, trans* (there are two of these if the diene is unsymmetrical) or *trans, trans*. We shall look at each case with the same dienophile, an acetylenedicarboxylate, as there is then no stereochemistry in the triple bond! Starting with *cis, cis*-dienes is easy if we make the diene cyclic.

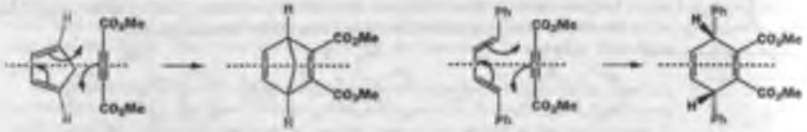


The diene has two sets of substituents—inside and outside. The inside one is the bridging CH_2 group and it has to end up on one side of the molecule (above in the last diagram) while the two green hydrogens are outside and remain so. In the final diagram they are below the new six-membered ring.

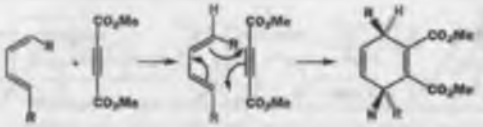
With a *trans, trans*-diene we simply exchange the two sets of substituents, in this example putting Ph where H was and putting H where the bridging CH_2 group was. This is the reaction.



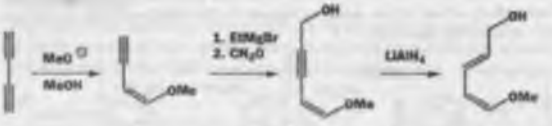
The green Ph groups end up where the hydrogens were in the first example—beneath the new six-membered ring—and the hydrogens end up above. It may seem puzzling at first that a *trans, trans*-diene gives a product with the two phenyls cis. Another way to look at these two reactions is to consider their symmetry. Both have a plane of symmetry throughout and the products must have this symmetry too because the reaction is concerted and no significant movement of substituents can occur. The black dotted line shows the plane of symmetry, which is at right angles to the paper.



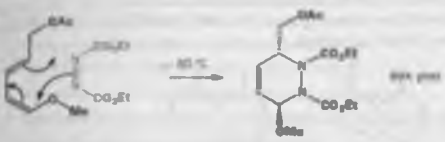
The remaining case—the *cis, trans*-diene—is rarer than the first two, but is met sometimes. This is the unsymmetrical case and the two substituents clearly end up on opposite sides of the new six-membered ring.



The red R group may seem to get in the way of the reaction but, of course, the dienophile is not approaching in the plane of the diene but from underneath. It is difficult to find a convincing example of this stereochemistry as there are so few known, partly because of the difficulty of making *E,Z*-dienes. One good approach uses two reactions you met in Chapter 31 for the control of double bond geometry. The *cis* double bond is put in first by the addition of methanol to butadiyne and the *trans* double bond then comes from $LiAlH_4$ reduction of the intermediate acetylenic alcohol.



The acetate of this alcohol is used in a Diels–Alder reaction with the interesting dienophile DEAD (diethyl azodicarboxylate—in orange).

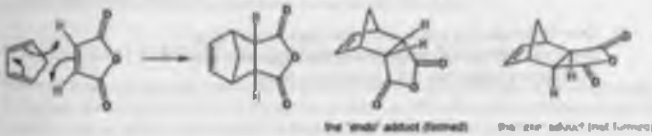


The product is formed in excellent yield and has the *trans* stereochemistry that was predicted. Do not be misled into thinking that DEAD is being shown with stereochemistry—it has none—and in the product the amide nitrogen atoms are planar and there is no stereochemistry there.

Now to the most interesting cases of all, when both the diene and the dienophile have stereochemistry.

The *endo* rule for the Diels–Alder reaction

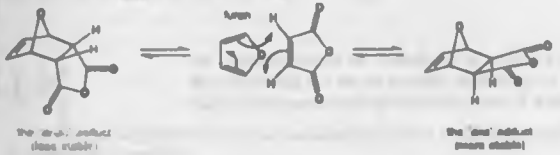
It is probably easier to see this when both the diene and the dienophile are cyclic. All the double bonds are *cis* and the stereochemistry is clearer. In the most famous Diels–Alder reaction of all time, that between cyclopentadiene and maleic anhydride, there are two possible products that obey all the rules we have so far described.



the 'endo' adduct (formed) the 'exo' adduct (not formed)

The two green hydrogen atoms must be *cis* in the product but there are two possible products in which these Hs are *cis*. They are called *exo* and *endo*.

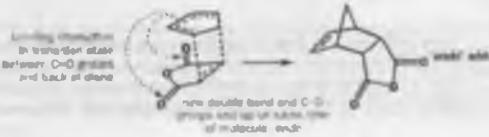
The product is, in fact, the *endo* compound. This is impressive not only because only one diastereoisomer is formed but also because it is the less stable one. How do we know this? Well, if the Diels–Alder reaction is reversible and therefore under thermodynamic control, the *exo* product is formed instead. The best known example results from the replacement of cyclopentadiene with furan in reaction with the same dienophile.



the 'endo' product (less stable) the 'exo' adduct (more stable)

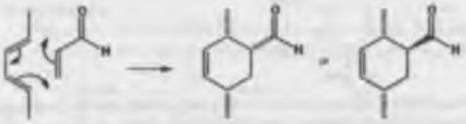
Why is the *exo* product the more stable? Look again at these two structures. On the left-hand side of the molecules, there are two bridges across the ends of the new bonds (highlighted in black): a one-C-atom bridge and a two-C-atom bridge. There is less steric hindrance if the smaller (that is, the one-atom) bridge eclipses the anhydride ring.

The *endo* product is less stable than the *exo* product and yet it is preferred in irreversible Diels–Alder reactions—it must be the kinetic product of the reaction. It is preferred because there is a bonding interaction between the carbonyl groups of the dienophile and the developing π bond at the back of the diene. (The black bonds are the new σ bonds between the two reagents.)



'endo' adduct

The same result is found with noncyclic dienes and dienophiles—normally one diastereoisomer is preferred and it is the one with the carbonyl groups of the dienophile closest to the developing π bond at the back of the diene. Here is an example.



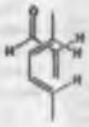
From our previous discussion we expect the two methyl groups to be *cis* to each other and the only question remaining is the stereochemistry of the aldehyde group—up or down? The aldehyde will be *endo*—but which compound is that? The easiest way to find the answer is to draw the reagents coming together in three dimensions. Here is one way to do this.

1. Draw the mechanism of the reaction and diagrams of the product to show what you are trying to decide. Put in the known stereochemistry if you wish

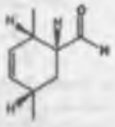
■
Title we have just done

2. Draw both molecules in the plane of the paper with the diene on top and the carbonyl group of the dienophile tucked under the diene so it can be close to the developing π-bond

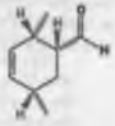
3. Now draw in all the hydrogen atoms on the carbon atoms that are going to become stereogenic centres, that is, those shown in green here



4. Draw a diagram of the product. All the substituents to the right in the previous diagram are on one side of the new molecule. That is, all the green hydrogen atoms are *cis* to each other



5. Draw a final diagram of the product with the stereochemistry of the other substituents shown too in the usual way. This is the *endo* product of the Diels–Alder reaction



If you prefer, you may draw a three-dimensional representation of the reagents coming together, rather like the ones we have been drawing earlier in the chapter. You may indeed prefer to invent a method of your own—it does not matter which method you choose providing that you can quickly decide on the structure of the *endo* adduct in any given Diels–Alder reaction.

Time for some explanations

We have accumulated rather a lot of unexplained results

- Why does the Diels–Alder reaction work so well?
- Why must we have a conjugating group on the dienophile?
- Why is the stereochemistry of each component retained so faithfully?
- Why is the *endo* product preferred kinetically?

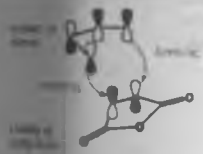
There is more. The simpler picture we met earlier in this chapter also fails to explain why the Diels–Alder reaction occurs simply on heating while attempted additions of simple alkenes (rather than dienes) to maleic anhydride fail on heating but succeed under irradiation with UV light.

We shall now explain all this in one section using frontier molecular orbitals. Of all the kinds of organic reactions, pericyclic ones are the most tightly controlled by orbitals, and the development of the ideas we are about to expound is one of the greatest triumphs of modern theoretical chemistry. It is a beautiful and satisfying set of ideas based on very simple principles.

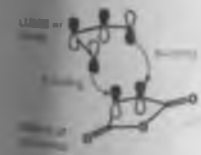
The frontier orbital description of cycloadditions

When an ionic cyclization reaction occurs, such as the lactonization at the head of this chapter, one important new bond is formed. It is enough to combine one full orbital with one empty orbital to make the new bond. But in a cycloaddition two new bonds are formed at the same time. We have to arrange for two filled p orbitals and two empty p orbitals to be available at the right place and with the right symmetry. See what happens if we draw the orbitals for the reaction above. We could try the HOMO (π) of the alkene and the LUMO (π^*) of the double bond in the anhydride.

This combination is bonding at one end, but antibonding at the other so that no cycloaddition reaction occurs. It obviously doesn't help to use the other HOMO/LUMO pair as they will have the same mismatched symmetry.

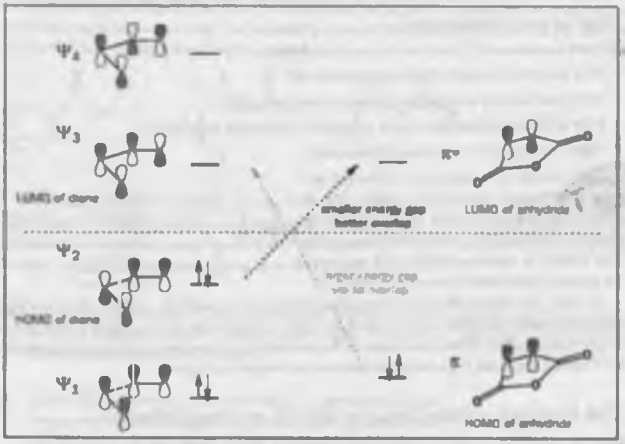


Now see what happens when we replace the alkene with a diene. We shall again use the LUMO of the electron-poor anhydride.



Now the symmetry is right because there is a node in the middle of the HOMO of the diene (the HOMO is Ψ_2 of the diene) just as there is in the LUMO of the dienophile. If we had tried the opposite arrangement, the LUMO of the diene and the HOMO of the dienophile, the symmetry would again be right.

Now the LUMO of the diene has two nodes and gives the same symmetry as the HOMO of the dienophile, which has no nodes. So either combination is excellent. In fact most Diels–Alder reactions use electron-deficient dienophiles and electron-rich dienes so we prefer the first arrangement. The electron-deficient dienophile has a low-energy LUMO and the electron-rich diene has a high-energy HOMO so that this combination gives a better overlap in the transition state. The energy levels will be like this.



This is why we usually use dienophiles with conjugating groups for good Diels–Alder reactions. Dienes react rapidly with electrophiles because their HOMOs are relatively high in energy, but simple alkenes have relatively high-energy LUMOs and do not react well with nucleophiles. The most effective modification we can make is to lower the alkene LUMO energy by conjugating the double bond with an electron-withdrawing group such as carbonyl or nitro. These are the most common type of Diels–Alder reactions—between electron-rich dienes and electron-deficient dienophiles.

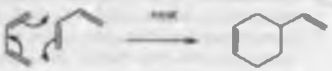
A rarer type is the reverse electron-demand Diels–Alder reaction in which the diene has electron-donating groups and the diene has a conjugated electron-withdrawing group. These reactions use the HOMO of the dienophile and the LUMO of the diene. This combination still has the right orbital symmetry.

Dimerizations of dienes by cycloaddition reactions

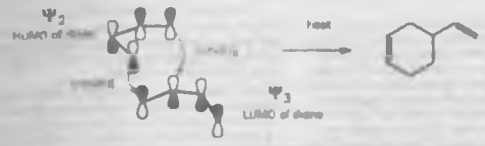
Because dienes have relatively high-energy HOMOs and low-energy LUMOs they should be able to take part in cycloadditions with themselves. And they do. What they cannot do is form an eight-membered ring in one step (though this is possible photochemically or with transition metal catalysis as we shall see later).

You should have expected this failure because the ends of the required orbitals must again have the wrong symmetry, just as they had when we tried the alkene dimerization.

Dienes do dimerize, but by a Diels–Alder reaction.



One molecule of the diene acts as a dienophile. Now the symmetry is correct again.



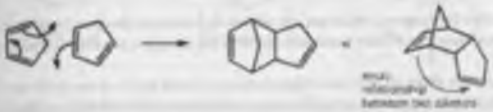
Count the number of π electrons

- The cycloadditions that *do* occur thermally, for example, the Diels–Alder reaction, have $(4n + 2\pi)$ electrons in their 'aromatic' transition states
- The cycloadditions that do *not* occur thermally, for example the dimerization of alkenes and of dienes, have $4n\pi$ electrons in their 'anti-aromatic' transition states

The Diels–Alder reaction in more detail

The orbital explanation for the *endo* rule in Diels–Alder reactions

We are going to use a diene as dienophile to explain the formation of *endo* products. The diene serves as a good model for the very wide variety of dienophiles because the one thing they all have in common is a conjugating group and a second alkene is the simplest of these. To make matters even easier we shall look at the dimerization of a cyclic diene; we might almost say *the* cyclic diene—cyclopentadiene. We introduced this reaction above where we simply stated that there was a favourable electronic interaction between the conjugating group on the dienophile and the back of the diene in the *endo* product though we did not explain it at the time.



If we now draw the frontier orbitals in the two components as they come together for the reaction, we can see first of all that the symmetry is correct for bond formation.

Now we shall look at that same diagram again but replace with orange dashed lines the orbitals that are overlapping to form the new σ bonds so that we can see what is happening at the back of the diene.

The symmetry of the orbitals is correct for a bonding interaction at the back of the diene too. This interaction does not lead to the formation of any new bonds but it leaves its imprint in the stereochemistry of the product. The *endo* product is favoured because of this favourable interaction across the space between the orbitals even though no bonds are formed.

Entropy and the *endo* rule

Another way to look at the result comes from considering the special entropy problem involved in cycloaddition reactions. A very precise orientation of the two molecules is required for two bonds to be formed at once. These reactions have large negative entropies of activation (Chapter 41)—order must be created at the transition state as the two components align with one another. The through-space attractive HOMO/LUMO interaction between the two molecules can lead to an initial association that can be compared to a squishy sandwich with too much mayonnaise. The cyclopentadiene rings are the slices of bread and the electrons are the filling that holds them together but still allows them to rotate until the right atoms come together for bonding.

Rotation about a vertical axis through the centre of the sandwich eventually brings the right atoms together for bond formation. At that moment the backs of the rings are still stuck together by the "mayonnaise" and the *endo* product results.

The solvent in the Diels–Alder reaction

We discussed some effects of varying the solvent in Chapter 13, and we shall now introduce a remarkable and useful special solvent effect in the Diels–Alder reaction. The reaction does not need a solvent and often the two reagents are just mixed together and heated. Solvents can be used but, because there are no ionic intermediates, it seems obvious that which solvent is unimportant—any solvent that simply dissolves both reagents will do. This is, in general, true and hydrocarbon solvents are often the best.

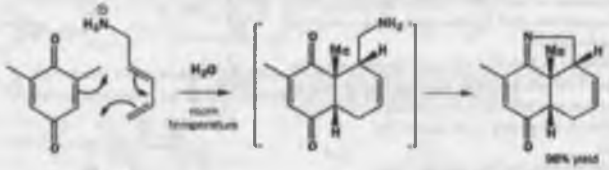
However, in the 1980s an extraordinary discovery was made. Water, a most unlikely solvent for most organic reactions, has a large accelerating effect on the Diels–Alder reaction. Even some water added to an organic solvent accelerates the reaction. And that is not all. The *endo* selectivity of these reactions is often superior to those in no solvent or in a hydrocarbon solvent. Here is a simple example.

endo product *exo* product

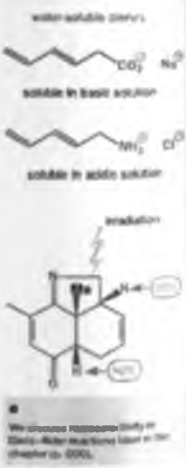
Solvent	Relative rate	*endo*:*exo* ratio
hydrocarbon (isooctane)	1	80:20
water	700	96:4

The suggestion is that the reagents, which are not soluble in water, are clumped together in oily drops by the water and forced into close proximity. Water is not exactly a solvent—it is almost an anti-solvent!

Water-soluble dienes are also used in Diels–Alder reactions in water and they too work very well. Sodium salts of carboxylic acids and protonated amines both behave well under these conditions. Presumably, the soluble tail is in the water but the diene itself is inside the oily drops with the dienophile. In this example an aminodiene reacts with a quinone dienophile.



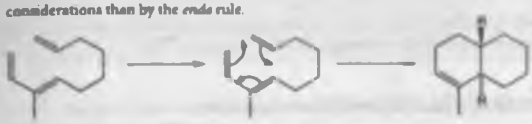
A single regio- and stereoisomer was formed in essentially quantitative yield and the stereochemistry was easily proved by NMR using NOE (Chapter 32). Irradiation at the black methyl group in the middle of the molecule gave strong NOEs to the two green hydrogen atoms, which must therefore be on the same side of the molecule as the methyl group.

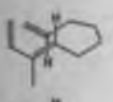


Intramolecular Diels–Alder reactions

When the diene and the dienophile are already part of the same molecule it is not so important for them to be held together by bonding interactions across space and the *exo* product is often preferred.

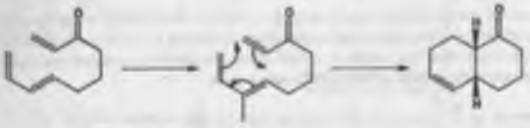
Indeed, it seems that intramolecular Diels–Alder reactions are governed more by normal steric considerations than by the *endo* rule.



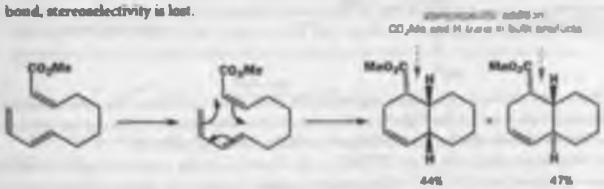


This reaction happens only because it is intramolecular. There is no conjugating group attached to the dienophile and so there are no orbitals to overlap with the back of the diene. The molecule simply folds up in the sterically most favourable way (as shown in the margin, with the linking chain adopting a chair-like conformation) and this leads to the *trans* ring junction.

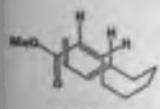
In the next example there is a carbonyl group conjugated with the dienophile. Now the less stable *cis* ring junction is formed because the molecule can fold so that the carbonyl group can enjoy a bonding overlap with the back of the diene. This time the linking chain has to adopt a boat-like conformation.



If, on the other hand, we give the dienophile a conjugating group at the other end of the double bond, stereoselectivity is lost.

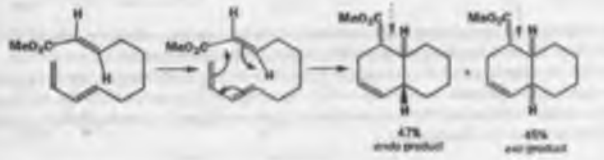


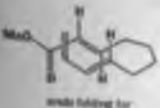
The *cis*-alkene dienophile gives stereospecific addition—in each product the CO_2Me is *cis* to the alkyl chain (and therefore *trans* to the H atom). But we get about a 50:50 mixture of *endo* and *exo* products. This does not seem to be because there is anything wrong with the transition state for *endo* addition, which leads in this case to *cis*-fused rings.



endo folding for the cis-alkene

Similarly, with the *trans*-alkene, two products are formed and both retain the *trans* geometry of the dienophile. But once again a nearly 50:50 mixture of *endo* and *exo* products is formed.





endo folding for the trans-alkene

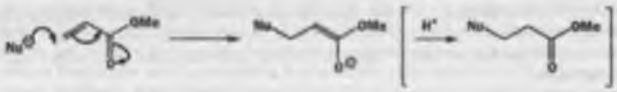
Folding the molecule so that the *endo* product would be formed does not again seem to present any problem. Presumably, either the carbonyl group of the ester is too far away from the diene to be effective or else it is simply that the advantage of the *endo* arrangement is not worth having in intramolecular Diels–Alder reactions.

● Intramolecular Diels–Alder

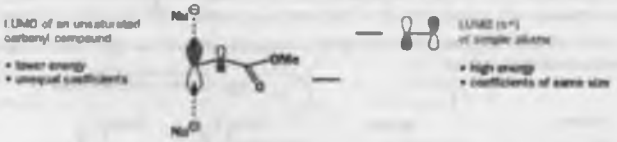
Intramolecular Diels–Alder reactions may give the *endo* product or they may not! Be prepared for either *exo* or *endo* products or a mixture.

Regioselectivity in Diels–Alder reactions

The compounds that we are now calling dienophiles were the stars of Chapters 10, 23, and 29 where we called them Michael acceptors as they were the electrophilic partners in conjugate addition reactions. Nucleophiles always add to the β carbon atoms of these alkenes because the product is then a stable enolate. Ordinary alkenes do not react with nucleophiles.



In frontier orbital terms this is because conjugation with a carbonyl group lowers the energy of the LUMO (the π* orbital of the alkene) and at the same time distorts it so that the coefficient on the β carbon atom is larger than that on the α carbon atom. Nucleophiles approach the conjugated alkene along the axis of the large p orbital of the β carbon atom.



These same features can ensure regioselective Diels–Alder reactions. The same orbital of the dienophile is used and, if the HOMO of the diene is also unsymmetrical, the regioselectivity of the reaction will be controlled by the two largest coefficients bunding together.

So what about distortion of the HOMO in the diene? If a diene reacts with an electrophile, the largest coefficient in the HOMO will direct the reaction. Consider the attack of HBr on a diene. We should expect attack at the ends of the diene because that gives the most stable possible cation—an allyl cation as an intermediate.

In orbital terms attack occurs at the ends of the diene because the coefficients in the HOMO are larger there. We need simply to look at the HOMO (Ψ_2) of butadiene to see this.

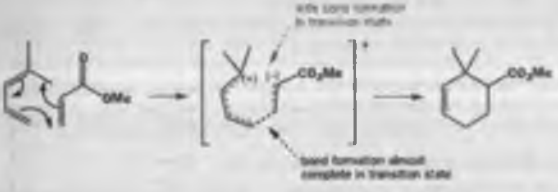
HOMO of butadiene

Ψ_2

So it is not surprising that the dienes react in the Diels–Alder reaction through their end carbons. But supposing the two ends are different—which reacts now? We can again turn to the reaction with HBr as a guide. Addition of HBr to an unsymmetrical diene will give the more stable of the two possible allyl cations as the intermediate.

In orbital terms, this clearly means that the HOMO of the diene is distorted so that the end that reacts has the larger coefficient.

When the unsymmetrical diene and the unsymmetrical dienophile combine in a Diels–Alder reaction, the reaction itself becomes unsymmetrical. It remains concerted but, in the transition state, bond formation between the largest coefficients in each partner is more advanced and this determines the regioselectivity of the reaction.

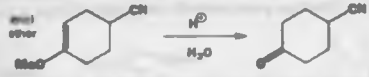


The simplest way to decide which product will be formed is to draw an 'ionic' stepwise mechanism for the reaction to establish which end of the diene will react with which end of the dienophile. Of course this stepwise mechanism is not completely correct but it does lead to the correct orientation of the reagents and you can draw the right mechanism afterwards. As an example we shall look at a diene with a substituent in the middle. This is the reaction.

First decide where the diene will act as a nucleophile and where the diene will act as an electrophile.

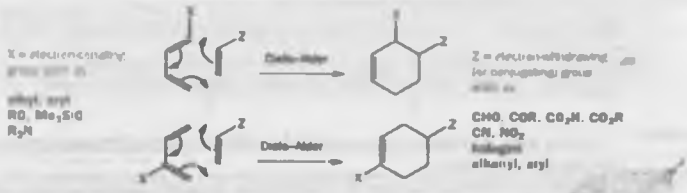
Now draw the reagents in the correct orientation for these two ends to combine and draw a concerted Diels–Alder reaction.

This is an important example because an enol ether functional group is present in the product and this can be hydrolysed to a ketone in aqueous acid (see Chapter 21).



Summary of regioselectivity in Diels–Alder reactions

The important substitution patterns are: a diene with an electron-donating group (X) at one end or in the middle and a dienophile with an electron-withdrawing group (Z) at one end. These are the products formed.



A useful mnemonic

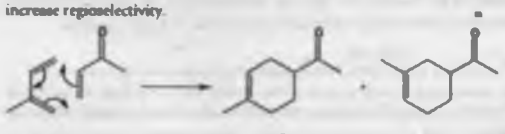
If you prefer a rule to remember, try this one.

- The Diels–Alder reaction is a cycloaddition with an aromatic transition state that is *ortho* and *para* directing

You can see that this mnemonic works if you look at the two products above: the first has the two substituents X and Z on neighbouring carbon atoms, just like *ortho* substituents on a benzene ring, while the second has X and Z on opposite sides of the ring, just like *para* substituents.

Lewis acid catalysis in Diels–Alder reactions

Where the reagents are unsymmetrical, a Lewis acid that can bind to the electron-withdrawing group of the dienophile often catalyses the reaction by lowering the LUMO of the dienophile still further. It has another important advantage: it increases the difference between the coefficients in the LUMO (a Lewis-acid complexed carbonyl group is a more powerful electron-withdrawing group) and may increase regioselectivity.



heat in toluene at 120 °C in a sealed tube	71:	29
with $SnCl_4 \cdot 5H_2O$ at 0 °C	93	:7

This Diels–Alder reaction is useful because it produces a substitution pattern ('*para*') common in natural terpenes (Chapter 51). But the regioselectivity introduced by one methyl group on the diene is not very great—this reaction gives a 71:29 mixture when the two compounds are heated together at 120 °C in a sealed tube. In the presence of the Lewis acid ($SnCl_4$) the reaction can be carried out at lower temperatures (below 25 °C) without a sealed tube and the regioselectivity improves to 93:7.

Regioselectivity in intramolecular Diels–Alder reactions

Just as the stereoselectivity may be compromised in intramolecular reactions, so may the regioselectivity. It may be simply impossible for the reagents to get together in the 'right' orientation. The examples below have a very short chain—just three carbon atoms—joining diene to dienophile and so the same regioselectivity is found regardless of the position of the conjugating carbonyl group.

The first example has the 'right' orientation ('*ortho*') but the second has the 'wrong' orientation ('*meta*'). In real life there is no prospect of any other orientation and, as the reaction is intramolecular, it goes anyway. Notice the lower temperature required for the Lewis acid ($ROAlCl_2$)-catalysed reaction.

The Woodward–Hoffmann description of the Diels–Alder reaction

Kenichi Fukui and Roald Hoffmann won the Nobel prize in 1981 (Woodward died in 1979 and so couldn't share this prize: he had already won the Nobel prize in 1965 for his work on synthesis) for the application of orbital symmetry to pericyclic reactions. Theirs is an alternative description to the frontier orbital method we have used and you need to know a little about it. They considered a more fundamental correlation between the symmetry of all the orbitals in the starting materials and all the orbitals in the products. This is rather too complex for our consideration here, and we shall concentrate only on a summary of the conclusions—the **Woodward–Hoffmann rules**. The most important of these states:

> **● Woodward–Hoffmann rules**
>
> **In a thermal pericyclic reaction the total number of $(4q + 2)_s$ and $(4r)_a$ components must be odd.**

▶ We have already seen the significance of $4n$ and $4n + 2$ numbers in aromaticity.

This needs some explanation. A component is a bond or orbital taking part in a pericyclic reaction as a single unit. A double bond is a $_\pi 2$ component. The number 2 is the most important part of this designation and simply refers to the number of electrons. The prefix π tells us the type of electrons. A component may have any number of electrons (a diene is a $_\pi 4$ component) but may not have mixtures of π and σ electrons. Now look back at the rule. Those mysterious designations $(4q + 2)$ and $(4r)$ simply refer to the number of electrons in the component where q and r are integers. An alkene is a $_\pi 2$ component and so it is of the $(4q + 2)$ kind while a diene is a $_\pi 4$ component and so is of the $(4r)$ kind.

Now what about the suffixes 's' and 'a'? The suffix 's' stands for suprafacial and 'a' for antarafacial. A suprafacial component forms new bonds on the same face at both ends while an antarafacial component forms new bonds on opposite faces at both ends. See how this works for the Diels–Alder reaction. Here is the routine.

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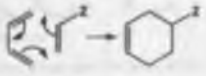
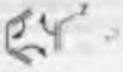
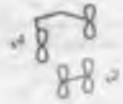


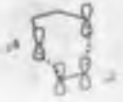
2. Choose the components. All the bonds taking part in the mechanism must be included and no others



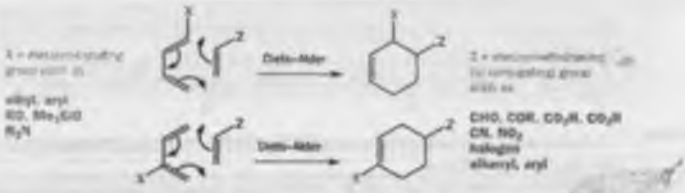
3. Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals at the ends of the components (only!)



4. Join up the components where new bonds are to be formed. Coloured dotted lines are often used



▶ Please note—these orbitals are not p-orbitals, and do not make up HOMOs or LUMOs or any particular molecular orbital. Do not attempt to mix frontier orbital and Woodward–Hoffmann descriptions of pericyclic reactions.



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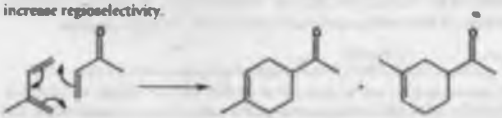

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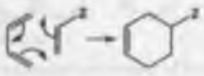

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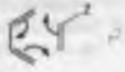

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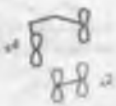
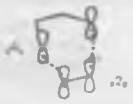


4. Join up the components where new bonds are to be formed. Coloured dotted lines are often used

5. Label each component a or s depending on whether new bonds are formed on the same or on opposite sides.



6. Count the number of $(4q + 2)_s$ and $(4r)_a$ components. If the total count is odd, the reaction is allowed

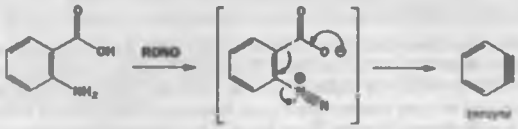
■ There is one $(4q + 2)_s$ component (the alkene) and no $(4r)_a$ components. Total = 1 so it is an allowed reaction

▶ Components of the other symmetry, that is $(4q + 2)_a$ and $(4r)_s$ components, do not count. You can have as many of these as you want!

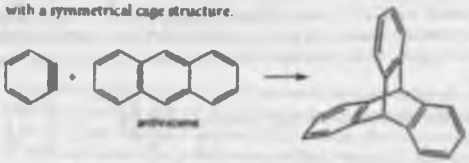
You may well feel that there is very little to be gained from the Woodward–Hoffmann treatment of the Diels–Alder reaction. It does not explain the *endo* selectivity nor the regioselectivity. However, the Woodward–Hoffmann treatment of other pericyclic reactions (particularly electrocyclic reactions, in the next chapter) is helpful. You need to know about this treatment because the Diels–Alder reaction is often described as an all-suprafacial [4 + 2] cycloaddition. Now you know what that means.

Trapping reactive intermediates by Diels–Alder reactions

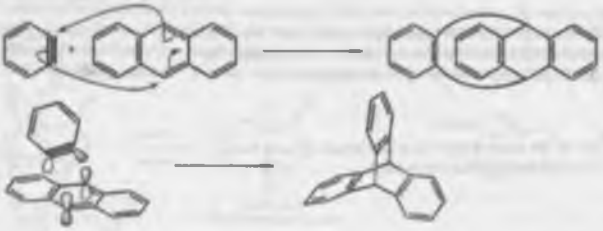
In Chapter 23 we met the remarkable intermediate benzyne and mentioned that convincing evidence for its existence was the trapping by a Diels–Alder reaction. An ideal method for generating benzyne for this purpose is the diazotization of anthranilic acid (2-aminobenzoic acid).



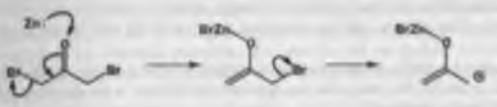
Benzyne may not look like a good dienophile but it is an unstable electrophilic molecule so it must have a low-energy LUMO (π^* of the triple bond). If benzyne is generated in the presence of a diene, efficient Diels–Alder reactions take place. Anthracene gives a specially interesting product with a symmetrical cage structure.



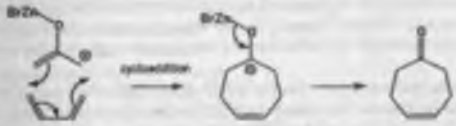
It is difficult to draw this mechanism convincingly. The two flat molecules approach each other in orthogonal planes, so that the orbitals of the localized π bond of benzyne bond with the p orbitals on the central ring of anthracene.



Another intermediate for which Diels–Alder trapping provided convincing evidence is the oxyallyl cation. This compound can be made from α,α'-dibromoketones on treatment with zinc metal. The first step is the formation of a zinc enolate (compare the Reformatsky reaction), which can be drawn in terms of the attack of zinc on oxygen or bromine. Now the other bromine can leave as an anion. It could not do so before because it was next to an electron-withdrawing carbonyl group. Now it is next to an electron-rich enolate so the cation is stabilized by conjugation.

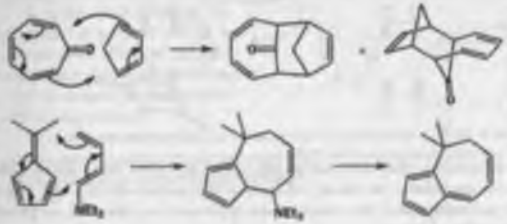


The allyl cation has three atoms but only two electrons so it can take part in cycloadditions with dienes—the total number of electrons is the required six. This is one of the few reactions that works only to produce a seven-membered ring.



Other thermal cycloadditions

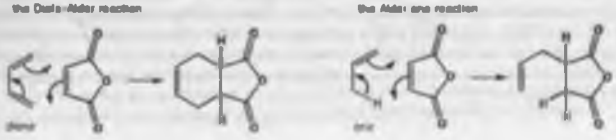
Six is not the only (4n + 2) number and there are a few cycloadditions involving ten electrons. These are mostly diene + triene, that is, ${}_4d_6 + {}_4e_6$, cycloadditions. Here are a couple of examples.



In the first case, there is an *endo* relationship between the carbonyl group and the back of the diene—this product is formed in 100% yield. In the second case Et_2NH is lost from the first product under the reaction conditions to give the hydrocarbon shown. This type of reaction is more of an oddity: by far the most important type of cycloaddition is the Diels–Alder reaction.

The Alder 'ene' reaction

The Diels–Alder reaction was originally called the 'diene reaction' so, when half of the famous team (K. Alder) discovered an analogous reaction that requires only one alkene, it was called the Alder ene reaction and the name has stuck. Compare here the Diels–Alder and the Alder ene reactions.



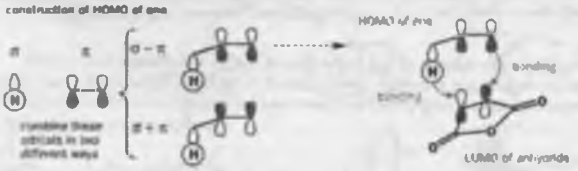
The simplest way to look at the ene reaction is to picture it as a Diels–Alder reaction in which one of the double bonds in the diene has been replaced by a C–H bond (green). The reaction does not form a new ring, the product has only one new C–C bond (shown in black on the product), and a hydrogen atom is transferred across space. Otherwise, the two reactions are remarkably similar.

The ene reaction is rather different in orbital terms. For the Woodward–Hoffmann description of the reaction we must use the two electrons of the C–H bond to replace the two electrons of the double bond in the Diels–Alder reaction, but we must make sure that all the orbitals are parallel, as shown.

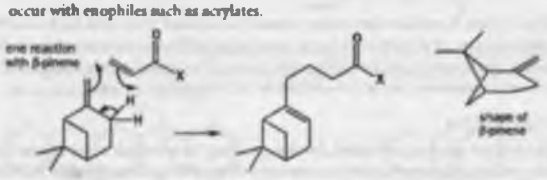
The C–H bond is parallel with the p orbitals of the ene so that the orbitals that overlap to form the new π bond are already parallel. The two molecules approach one another in parallel planes so that the orbitals that overlap to form the new σ bonds are already pointing towards each other. Because the electrons are of two types, π and σ, we must divide the ene into two components, one $_{\pi}2$ and one $_{\sigma}2$. We can then have an all-suprafacial reaction with three components.

All three components are of the $(4q + 2)_s$ type so all count and the total is three—an odd number—so the reaction is allowed. We have skipped the step-by-step approach we used for the Diels–Alder reaction because the two are so similar, but you should convince yourself that you can apply it here.

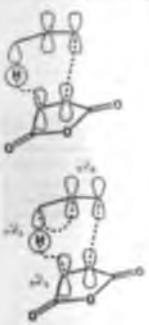
In frontier orbital terms we shall want again to use the LUMO of the anhydride so we need to construct the HOMO of the ene component. This must be the HOMO of the π bond and σ bond (C–H) combined. These two bonds can combine in a bonding way (σ + π) or in an antibonding fashion (σ – π). The second is higher in energy than the first and since there are a total of four electrons (two in the σ bond and two in the π bond), it is the molecular HOMO. The HOMO of the ene is bonding at both ends with the LUMO of the anhydride and the reaction is favourable.



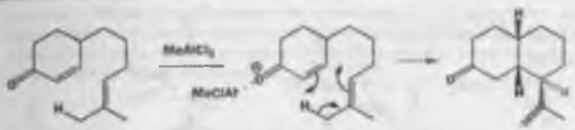
Now for some real examples. Most ene reactions with simple alkenes are with maleic anhydride. Other dienophiles—or enophiles as we should call them in this context—do not work very well. However, with one particular alkene, the natural terpene β-pinene from pine trees, reaction does occur with enophiles such as acrylates.

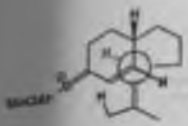


The major interaction between these two molecules is between the nucleophilic end of the exocyclic alkene and the electrophilic end of the acrylate. These atoms have the largest coefficients in the HOMO and LUMO, respectively, and, in the transition state, bond formation between these two will be more advanced than anywhere else. For most ordinary alkenes and enophiles, Lewis acid catalysis to make the enophile more electrophilic, or an intramolecular reaction (or both!), is necessary for an efficient ene reaction.



▶ We discuss in more detail in Chapter 38 how to assign signs with d bonds. Here the π bond reacts suprafacially because the 1s orbital of H has no nodes.

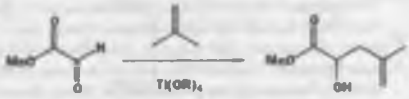




The ene is delivered to the bottom face of the enone, as its tether (Chapter 33) is too short for it to reach the top face, and a *cis* ring junction is formed. The stereochemistry of the third centre is most easily seen by a Newman projection of the reaction. In the diagram in the margin we are looking straight down the new C–C bond and the colour coding should help you to see how the stereochemistry follows.

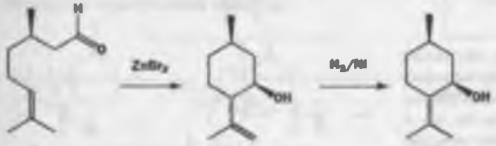
Since the twin roles of the enophile are to be attacked at one end by a C=C double bond and at the other by a proton, a carbonyl group is actually a very good enophile. These reactions are usually called **carbonyl ene reactions**.

The important interaction is between the HOMO of the ene system and the LUMO of the carbonyl group—and a Lewis-acid catalyst can lower the energy of the LUMO still further. If there is a choice, the more electrophilic carbonyl group (the one with the lower LUMO) reacts.

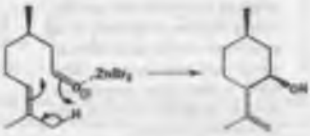


It is not obvious that an ene reaction has occurred because of the symmetry of the ene. The double bond in the product is not, in fact, in the same place as it was in the starting material.

One carbonyl ene reaction is of commercial importance as it is part of a process for the production of menthol used to give a peppermint smell and taste to many products. This is an intramolecular ene reaction on another terpene derivative.



It is not obvious what has happened in the first step, but the movement of the alkene and the closure of the ring with the formation of one (not two) new C–C bonds should give you the clue that this is a Lewis-acid-catalysed carbonyl ene reaction.



The stereochemistry comes from an all-chair arrangement in the conformation of the transition state. The methyl group will adopt an equatorial position in this conformation, fixing the way the other bonds are formed. Again, colour coding should make it clearer what has happened.

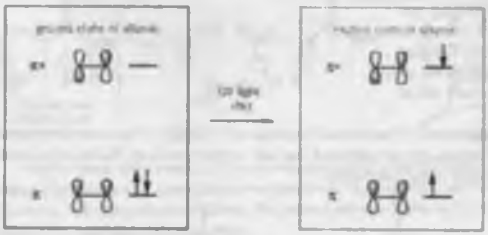
Menthol manufacture

It may seem odd to you to have a chemical process to produce menthol, which would be available naturally from mint plants. This process is now responsible for about half the world's menthol production as it must make some sort of sense! The truth is that menthol cultivation is wasteful in good land that could produce food crops such as rice

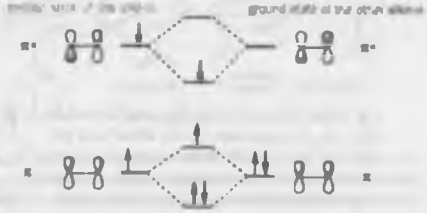
while the starting material for menthol manufacture is the same β-pinene we have just met. This is available in large quantities from pine trees grown on poor land for paper and furniture. The early stages of the process are discussed in Chapter 48.

Photochemical [2 + 2] cycloadditions

We shall now leave six-electron cycloadditions such as the Diels–Alder and ene reactions and move on to some four-electron cycloadditions. Clearly, four is not a $(4n + 2)$ number, but when we told you in the box on p. 000 that only cycloadditions with $(4n + 2)$ electrons are allowed we used the term 'thermally'. Cycloadditions with $4n$ electrons *are* allowed if the reaction is not thermal (that is, driven by heat energy) but **photochemical** (that is, driven by light energy). All the cycloadditions that are not allowed thermally are allowed photochemically. The problem of the incompatible symmetry in trying to add two alkenes together is avoided by converting one of them into the excited state photochemically. First, one electron is excited by the light energy from the π to the π* orbital.

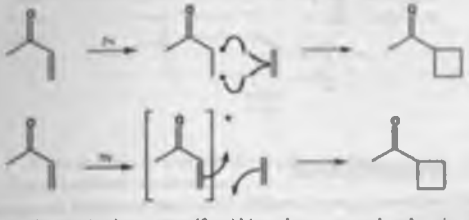


Now, combining the excited state of one alkene with the ground state of another solves the symmetry problem. Mixing the two π orbitals leads to two molecular orbitals and two electrons go down in energy while only one goes up. Mixing the two π* orbitals is as good—one electron goes down in energy and none goes up. The result is that three electrons go down in energy and only one goes up. Bonding can occur.

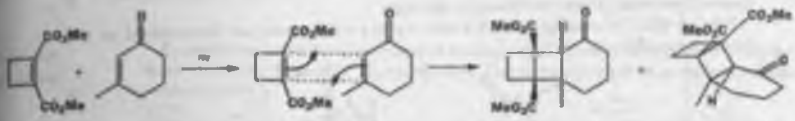


Alkenes can be dimerized photochemically in this way, but reaction between two different alkenes is more interesting. If one alkene is bonded to a conjugating group, it alone will absorb UV light and

be excited while the other will remain in the ground state. It is difficult to draw a mechanism for these reactions as we have no simple way to represent the excited alkene. Some people draw it as a diradical (since each electron is in a different orbital); others prefer to write a concerted reaction on an excited alkene marked with an asterisk.



The reaction is stereospecific within each component but there is no *endo* rule—there is a conjugating group but no 'back of the diene'. The least hindered transition state usually results.

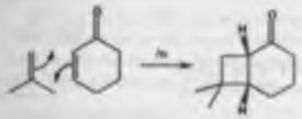


The dotted lines on the central diagram simply show the bonds being formed. The two old rings keep out of each other's way during the reaction and the conformation of the product looks reasonably unhindered.

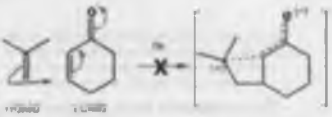
You may be wondering why the reaction works at all, given the strain in a four-membered ring: why doesn't the product just go back to the two starting materials? This reverse reaction is governed by the Woodward–Hoffmann rules, just like the forward one, and to go back again the four-membered ring products would have to absorb light. But since they have now lost their π bonds they have no low-lying empty orbitals into which light can promote electrons (see Chapter 7). The reverse photochemical reaction is simply not possible because there is no mechanism for the compounds to absorb light.

Regioselectivity in photochemical [2 + 2] cycloadditions

The observed regioselectivity is of this kind.



If we had combined the HOMO of the alkene with the LUMO of the enone, as we should in a thermal reaction, we would expect the opposite orientation so as to use the larger coefficients of the frontier orbitals and to maximize charge stabilization in the transition state.

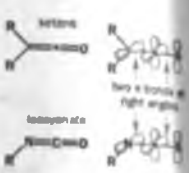


But we are not doing a thermal reaction. If you look back at the orbital diagram above, you will see that it is the HOMO/HOMO and LUMO/LUMO interactions that now matter in the reactions of the excited state. The sizes of the coefficients in the LUMO of the alkene are the other way round to those in the HOMO. There is one electron in this pair of orbitals—in the LUMO of the enone in fact, as the enone has been excited by the light—so overlap between the two LUMOs (shown in the frame)

is bonding and leads to the observed product. The easiest way to work it out quickly is to draw the product you do *not* expect from a normal HOMO/LUMO or curly arrow controlled reaction.

Thermal [2 + 2] cycloadditions

Despite what we have told you, there are some thermal [2 + 2] cycloadditions giving four-membered rings. These feature a simple alkene reacting with an electrophilic alkene of a peculiar type. It must have two double bonds to the *same* carbon atom. The most important examples are ketenes and isocyanates. The structures have two π bonds at right angles.

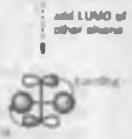


Here are typical reactions of dimethyl ketene to give a cyclobutanone and chlorosulfonyl isocyanate to give a β-lactam.

To understand why these reactions work, we need to consider a new and potentially fruitful way for two alkenes to approach each other. Thermal cycloadditions between two alkenes do not work because the HOMO/LUMO combination is antibonding at one end.

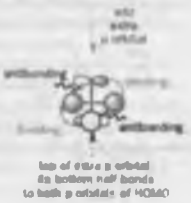
If one alkene turns at 90° to the other, there is a way in which the HOMO of one might bond at both ends to the LUMO of the other. First we turn the HOMO of one alkene so that we are looking down on the p orbitals.

Now we add the LUMO of the other alkene on top of this HOMO and at 90° to it so that there is the possibility of bonding overlap at both ends.

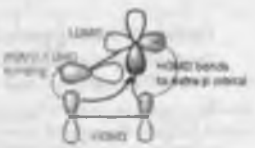


This arrangement looks quite promising until we notice that there is antibonding at the other two corners! Overall there is no net bonding.

We can tilt the balance in favour of bonding by adding a p orbital to one end of the LUMO and at a right angle to it so that both orbitals of the HOMO can bond to this extra p orbital. There are now four bonding interactions but only two antibonding. The balance is in favour of a reaction. This is also quite difficult to draw!



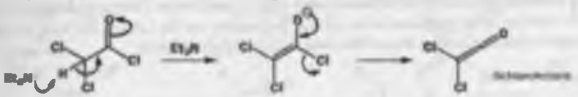
If you find this drawing difficult to understand, try a three-dimensional representation.



Ketenes have a central sp carbon atom with an extra π bond (the C=O) at right angles to the first alkene—perfect for thermal [2 + 2] cycloadditions. They are also electrophilic and so have suitable low-energy LUMOs.

Ketene [2 + 2] cycloadditions

Ketene itself is usually made by high-temperature pyrolysis of acetone but some ketenes are easily made in solution. The very acidic proton on dichloroacetyl chloride can be removed even with a tertiary amine and loss of chloride ion then gives dichloroketene in an E1cB elimination reaction.

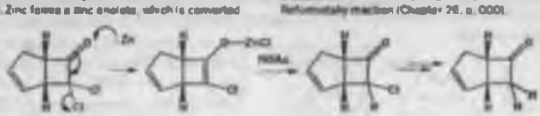


If the elimination is carried out in the presence of cyclopentadiene a very efficient regio- and stereospecific [2 + 2] cycloaddition occurs.

The most nucleophilic atom on the diene adds to the most electrophilic atom on the ketene and the *cis* geometry at the ring junction comes from the *cis* double bond of cyclopentadiene. It is impressive that even this excellent diene undergoes no Diels–Alder reaction with ketene as dienophile. The [2 + 2] cycloaddition must be much faster.

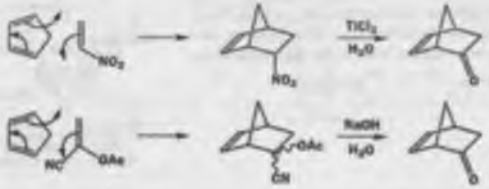
Using the products

Dichloroketene is convenient to use, but the two chlorine atoms are not usually needed in the product. Fortunately, these can be removed by zinc metal in acetic acid solution. Zinc forms a zinc enolate, which is converted into the ketone by the acid. Regiochemistry removes both chlorine atoms. You saw the reductive formation of a zinc enolate earlier in the chapter (p. 000) and in the Reformatsky reaction (Chapter 21, p. 000).



But what do we do if we *want* the product of a ketene [4 + 2] cycloaddition? We must use a compound that is not a ketene but that can be transformed into a ketone afterwards—a masked ketene or

a ketene equivalent. The two most important types are nitroalkenes and compounds such as the 'cyanohydrin ester' in the second example.



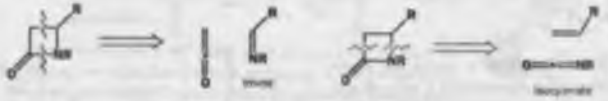
Finding the starting materials for a cyclobutane synthesis

The disconnection of a four-membered ring is very simple—you just split it in half and draw the two alkenes. There may be two ways to do this.

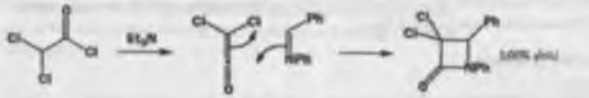
Both sets of starting materials look all right—the regiochemistry is correct for the first and doesn't matter for the second. However, we prefer the second because we can control the stereochemistry by using *cis*-butene as the alkene and we can make the reaction work better by using dichloroketene instead of ketene itself, reducing out the chlorine atoms with zinc.

Synthesis of β-lactams by [2 + 2] cycloadditions

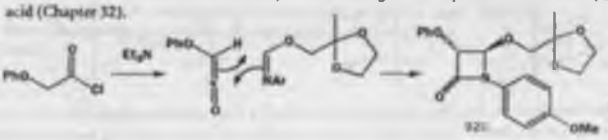
Now the disconnections are really different—one requires addition of a ketene to an imine and the other the addition of an isocyanate to an alkene. Isocyanates are like ketenes, but have a nitrogen atom instead of the end carbon atom. Otherwise the orbitals are the same.

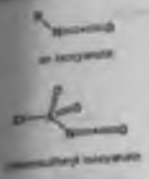


And the good news is that both work, providing we have the right substituents on nitrogen. The dichloroacetyl chloride trick works well with imines and, as you ought to expect, the more nucleophilic nitrogen atom attacks the carbonyl group of the ketene so that the regioselectivity is right to make β-lactams.



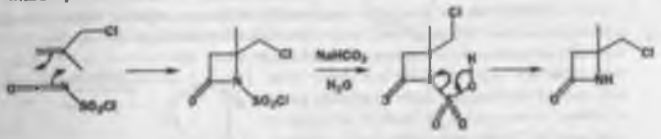
If both components have one substituent, these will end up *trans* on the four-membered ring just to keep out of each other's way. This example has more functionality and the product could be used to make β-lactams with antibiotic activity, such as analogues of the β-lactamase inhibitor, clavulanic acid (Chapter 32).





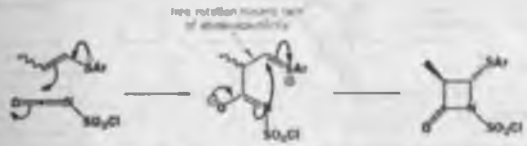
You will notice that in both of these examples there is an aryl substituent on the nitrogen atom of the imine. This is simply because imines are rather unstable and cannot normally be prepared with a hydrogen atom on the nitrogen. *N*-Aryl imines are quite stable (Chapter 13, p. 000).

When we wish to make β-lactams by the alternative addition of an isocyanate to an alkene, a substituent on nitrogen is again required, but for quite a different reason. Because alkenes are only moderately nucleophilic, we need a strongly electron-withdrawing group on the isocyanate that can be removed after the cycloaddition, and the most popular by far is the chlorosulfonyl group. The main reason for its popularity is the commercial availability of chlorosulfonyl isocyanate. It reacts even with simple alkenes.



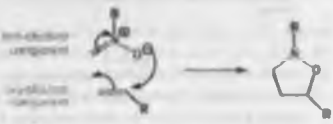
The alkene's HOMO interacts with the isocyanate's LUMO, and the most electrophilic atom is the carbonyl carbon so this is where the terminal carbon atom of the alkene attacks. The chlorosulfonyl group can be removed simply by hydrolysis under mild conditions via the sulfonic acid.

With a more electron-rich alkene—an enol ether, for example, or the following example with its sulfur analogue, a vinyl sulfide—the reaction ceases to be a concerted process and occurs stepwise. We know this must be the case in the next example because, even though the starting material is an *E*/*Z* mixture, the product has only *trans* stereochemistry: it is stereoselective rather than stereospecific, indicating the presence of an intermediate in which free rotation can take place.



Making five-membered rings—1,3-dipolar cycloadditions

We have seen how to make four-membered rings by [2 + 2] cycloadditions and, of course, how to make six-membered rings by [4 + 2] cycloadditions. Now what about five-membered rings? It sounds at first impossible to make an odd-numbered ring in this way. However, all we need is a three-atom, four-electron 'diene' and we can do a Diels–Alder reaction. Impossible! Not at all—the molecules are called 1,3-dipoles and are good reagents for cycloadditions. Here is an example.

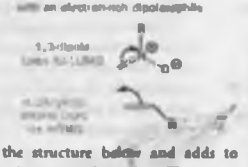


The molecule containing N and O atoms labelled 'four-electron component' is the 1,3-dipole. It has a nucleophilic end (O^-) and an electrophilic end—the end of the double bond next to the central N^+. These are 1,3-related so it is indeed a 1,3-dipole. This functional group is known as a nitrone. You could also think of it as the *N*-oxide of an imine.

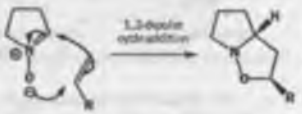
The nitrone gets its four electrons in this way: there are two π electrons in the N=C double bond and the other two come from one of the lone pairs on the oxygen atom. The two-electron component is a simple alkene in this example. In a Diels–Alder

reaction it would be called the dienophile. Here it is called the **dipolarophile**. Simple alkenes (which are bad dienophiles) are good dipolarophiles and so are electron-deficient alkenes.

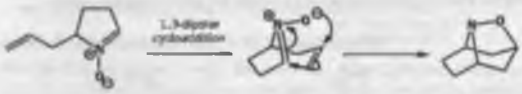
The difference between dienes and 1,3-dipoles is that dienes are nucleophilic and prefer to use their HOMOs in cycloadditions with electron-deficient dienophiles while 1,3-dipoles, as their name implies, are both electrophilic and nucleophilic. They can use either their HOMOs or their LUMOs depending on whether the dipolarophile is electron-deficient or electron-rich.



One important nitrone is a cyclic compound that has the structure below and adds to dipolarophiles (essentially any alkene!) to give two five-membered rings fused together. The stereochemistry comes from the best approach with the least steric hindrance, as shown. There is no *endo* rule in these cycloadditions as there is no conjugating group to interact across space at the back of the dipole or dipolarophile. The product shown here is the more stable *exo* product.

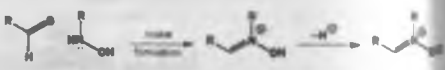


If the alkene is already joined on to the nitrone by a covalent bond so that the dipolar cycloaddition is an intramolecular reaction, one particular outcome may be dictated by the impossibility of the alternatives. Here is a simple case where an allyl group is joined to the same ring as in the previous example. The product has a beautifully symmetrical cage structure and the mechanism shows the only way in which the molecule can fold up to allow a 1,3-dipolar cycloaddition to occur.

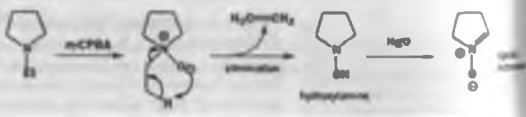


Making nitrones

There are two important routes to nitrones; both start from hydroxylamines. Open-chain nitrones are usually made simply by imine formation between a hydroxylamine and an aldehyde.

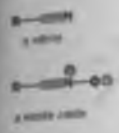


The cyclic nitrones are made from simple tertiary amines by oxidation and then cyclic elimination to give a hydroxylamine. This is oxidized again with HgO to give the nitrone.



The importance of the Diels–Alder reaction is that it makes six-membered rings with control over stereochemistry. The importance of 1,3-dipolar cycloadditions is not so much in the heterocyclic products but in what can be done with them. Almost always, the first formed heterocyclic ring is broken down in some way by carefully controlled reactions. The nitrone adducts we have just seen contain a weak N–O single bond that can be selectively cleaved by reduction. Reagents such as $LiAlH_4$ or zinc metal in various solvents (acetic acid is popular) or hydrogenation over catalysts such as nickel reduce the N–O bond to give NH and OH functionality without changing the structure or stereochemistry of the rest of the molecule. From the examples above, we get these products.

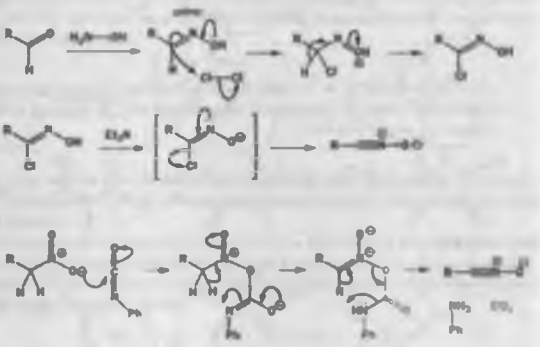
In each cycloaddition, one permanent C–C and one C–O bond (shown in orange) were made. These were retained while the N–O bond present in the original dipole was discarded. The final product is an amino-alcohol with a 1,3-relationship between the OH and NH groups.

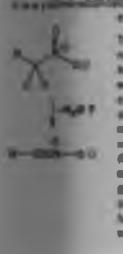


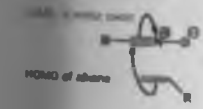
Linear 1,3-dipoles

In the Diels–Alder reaction, the dienes had to have an *s*-*cis* conformation about the central single bond so that they were already in the shape of the product. Many useful 1,3-dipoles are actually linear and their 1,3-dipolar cycloadditions look very awkward. We shall start with the nitrile oxides, which have a triple bond where the nitrone had a double bond.

Making nitrile oxides



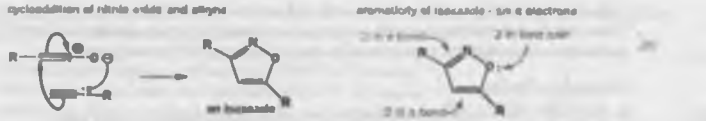




The dipolarophile (here a simple alkene) has to approach uncomfortably close to the central nitrogen atom for bonds to be formed. Presumably, the nitrile oxide distorts out of linearity in the transition state. As you should expect, this is a reaction between the HOMO of the alkene and the LUMO of the nitrile oxide so that the leading interaction that determines the structure of the product is the one in the margin.

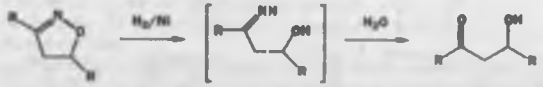
If there is stereochemistry in the alkene, it is faithfully reproduced in the heterocyclic adduct as we should expect for a concerted cycloaddition.

Both partners in nitrile oxide cycloadditions can have triple bonds—the product is then a stable aromatic heterocycle called an isoxazole.

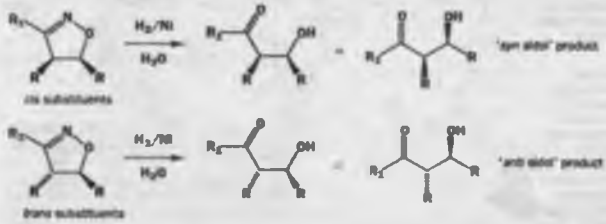


Though isoxazoles have some importance, the main interest in nitrile oxide cycloadditions lies again in the products that are formed by reduction of the N–O bond and by the C=N double bond. This produces amino-alcohols with a 1,3-relationship between the two functional groups.

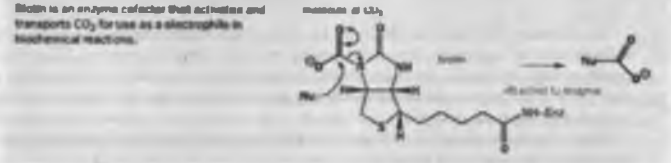
The N–O bond is the weaker of the two and it is possible to reduce that and leave the C=N bond alone. This leaves an imine that usually hydrolyses during work-up.



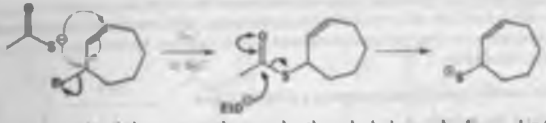
Any stereochemistry in the adduct is preserved right through this reduction and hydrolysis sequence: you might like to compare the products with the products of the stereoselective aldol reactions you saw in Chapter 34.



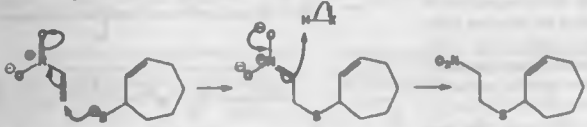
Biotin



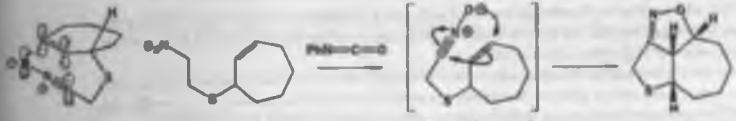
We shall end this section with a beautiful illustration of an intramolecular 1,3-dipolar cycloaddition of a nitrile oxide that was used in the synthesis of the vitamin biotin. Starting at the beginning of the synthesis will allow you to revise some reactions from earlier chapters. The starting material is a simple cyclic allylic bromide that undergoes an efficient S_N2 reaction with a sulfur nucleophile. In fact, we don't know (or care!) whether this is an S_N2 or S_N2' reaction as the product of both reactions is the same. This sort of chemistry was discussed in Chapter 23 if you need to check up on it. Notice that it is the sulfur atom that does the attack—it is the soft end of the nucleophile and better at S_N2 reactions. The next step is the hydrolysis of the ester group to reveal the thiolate anion.



This step is strictly an ester exchange rather than a hydrolysis and is discussed in Chapter 12. Next the nucleophilic thiolate anion does a conjugate addition (Chapters 10 and 29) on to a nitroalkene.

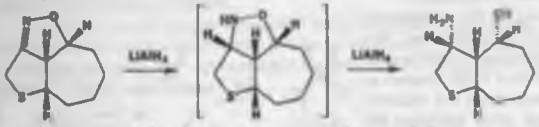


Now comes the exciting moment. The nitroalkene gives the nitrile oxide directly on dehydration with PhN=C=O and the cycloaddition occurs spontaneously in the only way it can, given the intramolecular nature of the reaction.

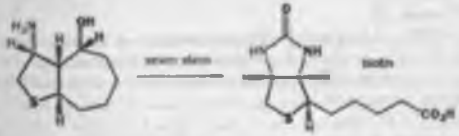


We have drawn the reaction with the nitrile oxide coming up from the underside of the seven-membered ring, pushing all the hydrogen atoms at the ring junctions upwards and making all the rings join up in a *cis* fashion.

Next the cycloadduct is reduced completely with $LiAlH_4$ so that both the N–O and C=N bonds are cleaved. This step is very stereoselective as the C=N reduction probably precedes the N–O cleavage and the hydride has to attack from the outside (top) face of the molecule. These considerations are explored more thoroughly in Chapter 35.



The sulfur-containing ring, and the stereochemistry, of biotin are already defined and, in the seven steps that follow, the most important is the breaking open of the seven-membered ring by a Beckmann rearrangement, which you will meet in Chapter 37.



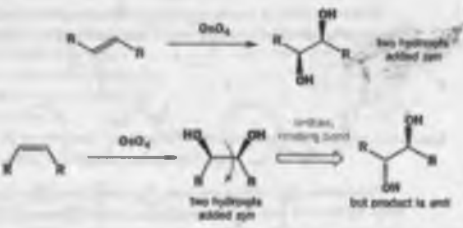
Two very important synthetic reactions: cycloaddition of alkenes with osmium tetroxide and with ozone

We shall end this chapter with two very important reactions, both of which we have alluded to earlier in the book. These reactions are very important not just because of their mechanisms, which you must

be aware of, but even more because of their usefulness in synthetic chemistry, and in that regard they are second only to the Diels–Alder reaction when considering all the reactions in this chapter. They are both oxidations—one involves osmium tetroxide (OsO_4) and one involves ozone (O_3) and they both involve cycloaddition.

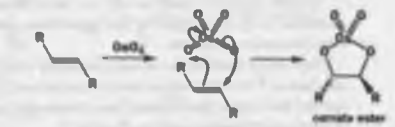
OsO_4 adds two hydroxyl groups *syn* to a double bond

We emphasized the fact that cycloadditions, being concerted, are stereospecific with regard to the geometry of the double bond. One very important example of this is the stereospecific reaction of an alkene with OsO_4. First, we give you the result of the reaction—the overall outcome is that two hydroxyl groups are added *syn* to the double bond.

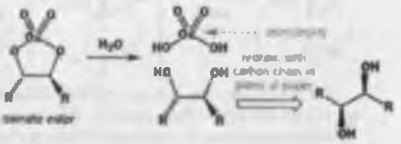


They add *syn* whether the double bond is *E* or *Z*, and, by redrawing the second example in a different conformation, you can see how defining the geometry of the starting material defines which diastereoisomer of the product is obtained.

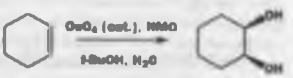
Now for the mechanism. We must admit before we start that this is a reaction about which there is still some controversy, and we give you the simplest reasonable view of the mechanism. Future results may show this mechanism to be wrong, but it will certainly do to explain any result you might meet. The first step is a cycloaddition between the osmium tetroxide and the alkene. You can treat the OsO_4 like a dipole—it isn't drawn as one because osmium has plenty of orbitals to accommodate four double bonds.

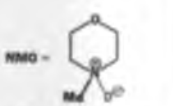


The product of the stereospecific cycloaddition is an 'osmate ester'. This isn't the required product, and the reaction is usually done in the presence of water (the usual solvent is a *t*-BuOH–water mixture), which hydrolyses the osmate ester to the diol. Because both oxygen atoms were added in one concerted step during the cycloaddition, their relative stereochemistry must remain *syn*.



The osmium starts as Os(VIII) and ends up as Os(VI)—the reaction is, of course, an oxidation, and it's one that is very specific to C=C double bonds (as we mentioned in Chapter 24). As written, it would involve a whole equivalent of the expensive, toxic, and heavy metal osmium, but it can be made catalytic by introducing a reagent to oxidize Os(VI) back to Os(VIII). The usual reagent is *N*-methylmorpholine-*N*-oxide (NMO) or Fe(III), and typical conditions for an osmylation, or dihydroxylation, reaction are shown in the scheme alongside.



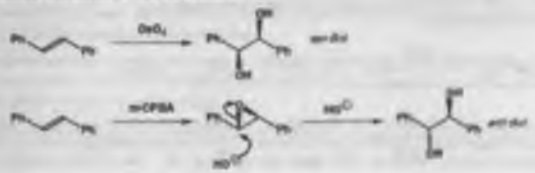


In behaviour that is typical of a 1,3-dipolar cycloaddition reaction, OsO_4 reacts almost as well with electron-poor as with electron-rich alkenes. OsO_4 simply chooses to attack the alkene HOMO

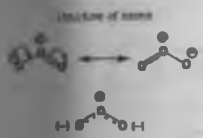
or its LUMO depending on which gives the best interaction. This is quite different from the electrophilic addition of *m*-CPBA or Br_2 to alkenes.

syn and *anti* addition of hydroxyl groups

It is important that you note the link between the OsO_4 reaction and the stereospecific trans-annular ring we highlighted at the beginning of Chapter 34. In particular, you now know ways to add two hydroxyl groups both *syn* and *anti* across a double bond; the *syn* addition uses OsO_4 and the *anti* addition uses epoxidation followed by ring opening with HO^-.



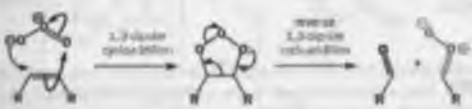
A cycloaddition that destroys bonds—ozonolysis



Our last type of cycloaddition is most unusual. It starts as a 1,3-dipolar cycloaddition but eventually becomes a method of cleaving π bonds in an oxidative fashion so that they end up as two carbonyl groups. The reagent is ozone, O_3.

Ozone is a symmetrical bent molecule with a central positively charged oxygen atom and two terminal oxygen atoms that share a negative charge. It is a 1,3-dipole and does typical 1,3-dipolar cycloadditions with alkenes.

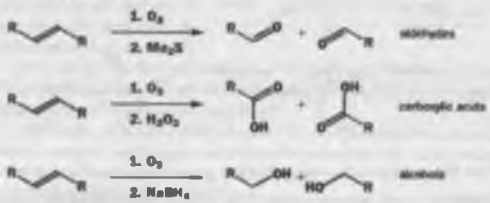
The product is a very unstable compound. The O–O single bond (bond energy 140 kJ mol^{-1}) is a very weak bond—much weaker than the N–O bond (180 kJ mol^{-1}) we have been describing as weak in previous examples—and this heterocycle has two of them. It immediately decomposes—by a *reverse* 1,3-dipolar cycloaddition.



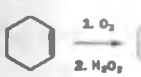
The products are a simple aldehyde on the left and a new, rather unstable looking molecule—a 1,3-dipole known as a carbonyl oxide—on the right. At least it no longer has any true O–O single bonds (the one that looks like a single bond is part of a delocalized system like the one in ozone). Being a 1,3-dipole, it now adds to the aldehyde in a third cycloaddition step. It might just add back the way it came, but it much prefers to add in the other way round with the nucleophilic oxygen attacking the carbon atom of the carbonyl group like this.

This compound—known as an ozonide—is the first stable product of the reaction with ozone. It is the culmination of two 1,3-dipolar cycloadditions and one reverse 1,3-dipolar cycloaddition. It is still not that stable and is quite explosive, so for the reaction to be of any use it needs decomposing. The way this is usually done is with dimethylsulfide, which attacks the ozonide to give DMSO and two molecules of aldehyde.

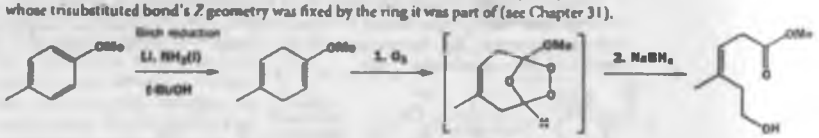
The ozonide will also react with oxidizing agents such as H_2O_2 to give carboxylic acids, or with more powerful reducing agents such as $NaBH_4$ to give alcohols. Here are the overall transformations—each cleaves a double bond—it is called an ozonolysis.



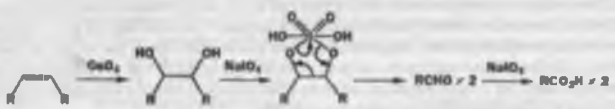
Ozonolysis of cyclohexenes is particularly useful as it gives 1,6-dicarbonyl compounds that are otherwise difficult to make. In the simplest case we get hexane 1,6-dioic acid (adipic acid) a monomer for nylon manufacture.



More interesting cases arise when the products of Birch reduction (Chapter 24) are treated with ozone. Here it is the electron-rich enol ether bond that is cleaved, showing that ozone is an electrophilic partner in 1,3-dipolar cycloadditions. If the ozonide is reduced, a hydroxy ester is formed whose trisubstituted bond's *Z* geometry was fixed by the ring it was part of (see Chapter 31).



An alternative method of cleaving C=C bonds is to use OsO_4 in conjunction with $NaIO_4$. The diol product forms a periodate ester, which decomposes to give two molecules of aldehyde. These are themselves oxidized by the periodate to carboxylic acids.



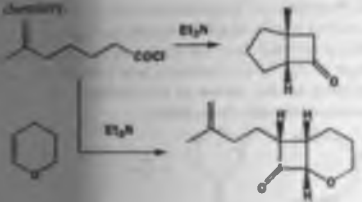
Summary of cycloaddition reactions

- A cycloaddition is a one-step ring-forming reaction between two conjugated π systems in which two new σ bonds are formed joining the two reagents at each end. The mechanism has one step with no intermediates, and all the arrows start on π bonds and go round in a ring.

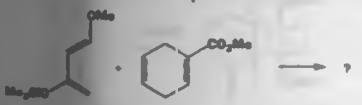
- The cycloadditions are supra-facial—they occur on one face only of each π system—and for a thermally allowed reaction there should be 4*n* + 2 electrons in the mechanism, but 4*n* in a photochemical cycloaddition. These rules are dictated by orbital symmetry.
- Cycloaddition equilibria generally lie over on the right-hand side in a thermal reaction because C–C σ bonds are stronger than C–C π bonds. In a photochemical cycloaddition, the product loses its π bonds and therefore its means of absorbing energy. It is the kinetic product of the reaction even if it has a strained four-membered ring.
- The stereochemistry of each component is faithfully reproduced in the product—the reactions are stereospecific—and the relationship between their stereochemistries may be governed by orbital overlap to give an *endo* product.

Problems

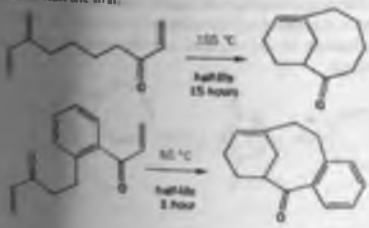
1. Give mechanisms for these reactions, explaining the stereochemistry.



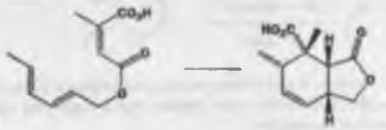
2. Predict the structure of the product of this Diels–Alder reaction.



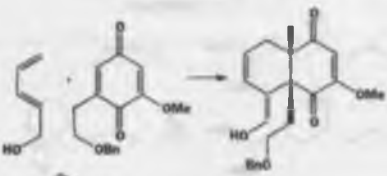
3. Comment on the difference in rate between these two reactions. It is estimated that the second goes about 10^5 times faster than the first.

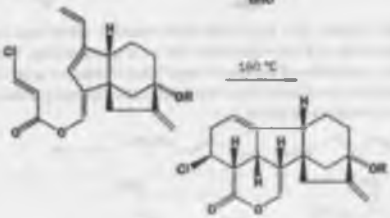


4. Justify the stereoselectivity in this intramolecular Diels–Alder reaction.

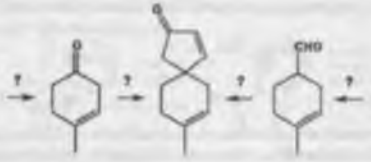


5. Explain the formation of single adducts in these reactions.

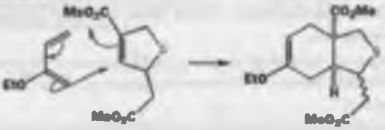




6. Revision elements. Suggest two syntheses of this spirocyclic ketone from the starting materials shown. Neither starting material is available.

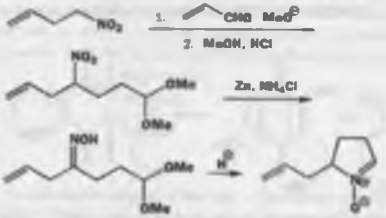


7. This reaction appeared in Chapter 33. Account for the selectivity.

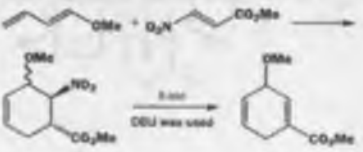


8. Draw mechanisms for these reactions and explain the stereochemistry.

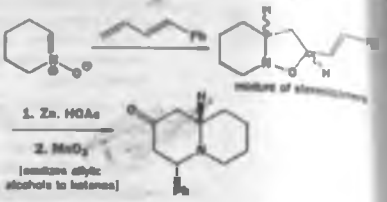
9. Revision. One of the nitrones used as an example in the chapter was prepared by this route. Explain what is happening and give details of the reactions.



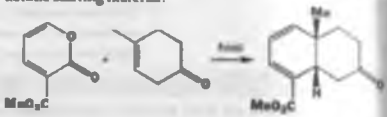
10. Explain why this Diels–Alder reaction gives total regioselectivity and stereospecificity but no stereoselectivity. What is the mechanism of the second step? What alternative route might you have considered if you wanted to make this final product and why would you reject it?



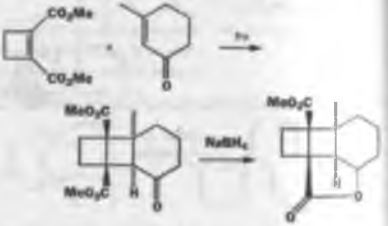
11. Give mechanisms for these reactions and explain the regio- and stereochemical control (or the lack of it).



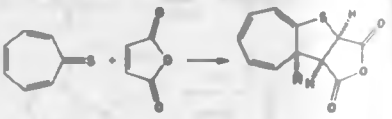
12. Suggest a mechanism for this reaction and explain the stereo- and regiochemistry. How would you prepare the unsaturated ketone starting material?



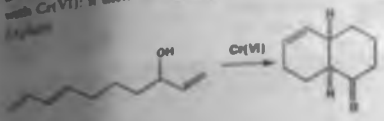
13. Photochemical cycloaddition of these two compounds is claimed to give the single diastereoisomer shown. The chemists who did this work claim that the stereochemistry of the adduct is simply proved by its conversion into a lactone on reduction. Comment on the validity of this deduction and explain the stereochemistry of the cycloaddition.



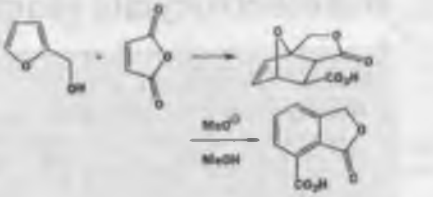
14. Thioketones, with a C=S bond, are not usually stable as we shall see in Chapter 44. However, this thioketone is quite stable and undergoes reaction with maleic anhydride to give the product shown. Comment on the stability of the starting material, the mechanism of the reaction, and the stereochemistry of the product.



35. This unsaturated alcohol is perfectly stable until it is oxidized with Cr(VI): it then immediately cyclizes to the product shown. Explain.



36. Suggest mechanisms for these reactions and comment on the stereochemistry of the first product.



Pericyclic reactions 2: Sigmatropic and electrocyclic reactions

36

Connections

Building on:

- Cycloadditions and the principles of pericyclic reactions (essential reading!) ch35
- Acetal formation ch14
- Conformational analysis ch18
- Elimination reactions ch19
- Controlling alkene geometry ch31

Arriving at:

- The second and third types of pericyclic reaction
- Stereochemistry from chair-like transition states
- Making γ,δ-unsaturated carbonyl compounds
- What determines whether these pericyclic reactions go 'forwards' or 'backwards'
- Special chemistry of N, S, and P
- Why substituted cyclopentadienes are unstable
- What 'con'- and 'dis'-rotatory mean
- Reactions that open small rings and close larger rings

Looking forward to:

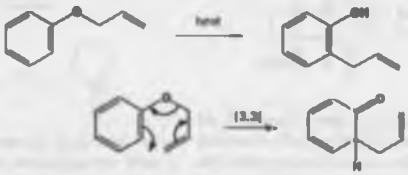
- Rearrangements ch37
- Synthesis of aromatic heterocycles ch44
- Main group chemistry ch46–ch47
- Asymmetric synthesis ch48
- Natural products ch51

Cycloadditions, the subject of the last chapter, are just one of the three main classes of pericyclic rearrangement. In this chapter, we consider the other two classes—sigmatropic rearrangements and electrocyclic reactions. We will analyse them in a way that is similar to our dealings with cycloadditions.

Sigmatropic rearrangements

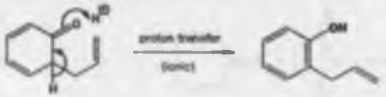
The Claisen rearrangement was the first to be discovered

The original sigmatropic rearrangement occurred when an aryl allyl ether was heated without solvent and an *ortho*-allyl phenol resulted. This is the **Claisen rearrangement**.



The first step in this reaction is a pericyclic reaction of a type that we will learn to call a **[3,3]-sigmatropic rearrangement**.

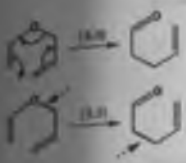
This is a one-step mechanism without ionic intermediates or any charges, just like a cycloaddition. The arrows go round in a ring. The difference between this and a cycloaddition is that one of the arrows starts on a σ bond instead of on a π bond. The second step in the reaction is a simple ionic proton transfer to regenerate aromaticity.



How do we know that this is the mechanism? If the allyl ether is unsymmetrical, it turns 'inside-out' during Claisen rearrangement, as required by the mechanism. Check for yourself that this is right.

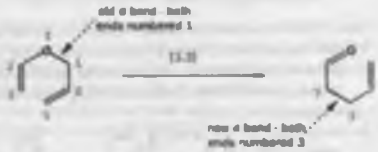
The aliphatic Claisen rearrangement also occurs

It was later found that the same sort of reaction occurs without the aromatic ring. This is called either the aliphatic Claisen rearrangement or the Claisen–Cope rearrangement. Here is the simplest possible example.

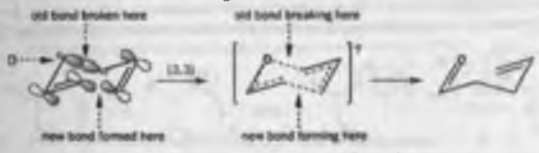


These reactions are called sigmatropic because a σ bond appears to move from one place to another during the reaction. The important bonds are coloured black here.

This particular reaction is called a [3,3]-sigmatropic rearrangement because the new σ bond has a 3,3 relationship to the old σ bond. You can see this if you number the ends of the old σ bond '1' and '1' and count round to the ends of the new σ bond in the product. You will find that the ends of the new σ bond both have the number '3'.



These [3,3]-sigmatropic rearrangements happen through a chair-like transition state, which allows us both to get the orbitals right and to predict the stereochemistry (if any) of the new double bond. The orbitals look something like this.



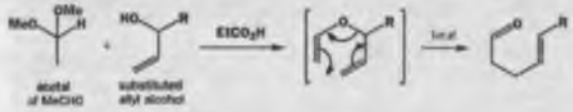
Note that these do not represent any specific frontier orbitals, they simply show that, in this conformation, the new σ bond is formed from two p orbitals that point directly at each other and that the two new π bonds are formed from orbitals that are already parallel.

Alkene stereochemistry in the Claisen rearrangement comes from a chair-like transition state

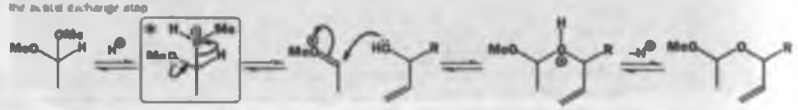
Stereochemistry may arise if there is a substituent on the saturated carbon atom next to the oxygen atom. If there is, the resulting double bond strongly favours the *trans* (*E*) geometry. This is because the substituent prefers an equatorial position on the chair transition state.

The substituent R prefers an equatorial position as the molecule reacts and R retains this position in the product. The new alkene bond is shown in black and the substituents in green. Notice that the *trans* geometry of the alkene in the product is already there in the conformation chosen by the starting material and in the transition state.

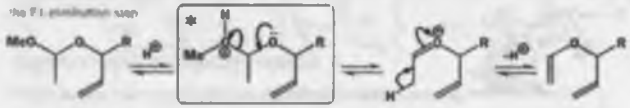
The starting material for these aliphatic Claisen rearrangements consists of ethers with one allyl and one vinyl group. We need now to consider how such useful molecules might be made. There is no problem about the allyl half—allylic alcohols are stable easily made compounds. But what about the vinyl half? 'Vinyl alcohols' are just the enols of aldehydes (MeCHO). The solution is to use an acetal of the aldehyde in an acid-catalysed exchange process with the allylic alcohol.



It is not necessary to isolate the allyl vinyl ether as long as some of it is formed and rearranges into the final product. The acid catalyst usually used, propanoic acid, has a conveniently high boiling point so that the whole mixture can be equilibrated at high temperature. The first step is an acetal exchange in which the allylic alcohol displaces methanol.



The methanol is distilled off as it is the most volatile of the components in this mixture. A second molecule of methanol is now lost in an acid-catalysed elimination reaction to give the vinyl group.

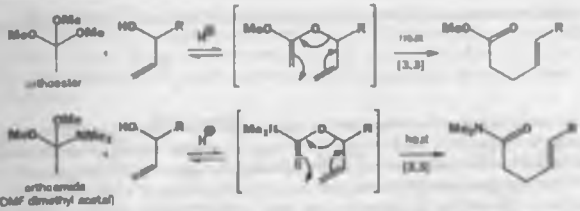


▶ Note that the first molecule of methanol was displaced in an S_Ni reaction and the second lost in an E1 reaction. The chemistry of acetals is dominated by the loss of protonated OR or OH groups as in the steps marked *. Never be tempted to use S_N2 mechanisms with acetals.

The Claisen rearrangement is a general synthesis of γ,δ-unsaturated carbonyl compounds

Finally, the [3,3]-sigmatropic rearrangement can be carried out by heat as part of the same step or as a separate step depending on the compounds. This is a very flexible reaction sequence and can be used for aldehydes (as shown above), ketones, esters, or amides. In each case acetal-like compounds are used—acetals themselves for aldehydes and ketones; orthoesters and orthoamides for the other two (though the orthoamides are often called 'amide acetals').

(continued overleaf)



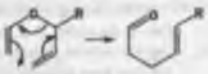
The common feature in the products of these Claisen rearrangements is a γ,δ-unsaturated carbonyl group. If this is what you need in a synthesis, make it by a Claisen rearrangement.

Orbital descriptions of [3,3]-sigmatropic rearrangements

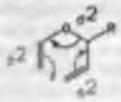
It is possible to give a frontier orbital description of a [3,3]-sigmatropic rearrangement but this is not a very satisfactory treatment because two reagents are not recognizing each other across space as they were in cycloadditions. There are *three* components in these reactions—two non-conjugated π bonds that do have to overlap across space and a σ bond in the chain joining the two π bonds.

The Woodward–Hoffmann rules give a more satisfying description and we shall follow the routine outlined for cycloadditions. Note that for stage 3, we can use the three-dimensional diagram we have already made.

1 Draw the mechanism for the reaction (we shall stay with a familiar one)



2 Choose the components. All the bonds taking part in the mechanism must be included and no others



3 Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals at the ends of the components (only!)

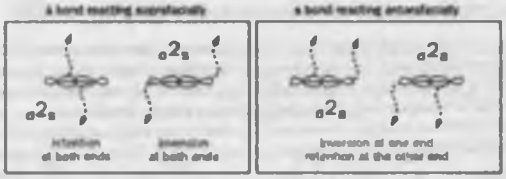
4 Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds

5 Label each component s or a depending whether new bonds are formed on the same or on opposite sides. See below for the σ bond symmetry

6 Add up the number of $(4q + 2)_s$ and $(4r)_a$ components. If the sum is *odd*, the reaction is allowed

One new aspect of orbital symmetry has appeared in this diagram—how did we deduce a or s symmetry in the way the σ bond reacted? For π bonds it is simple—if both bonds are formed on the same side of the old π bond, it has reacted *suprafacially*; if on opposite sides, *antarafacially*.

With a σ bond the symmetry is not so obvious. We want to know if it does the *same* thing at each end (s) or a *different* thing (a). But what is the 'thing' it does? It reacts using the large lobe of the sp^3 orbital (retention) or the small lobe (inversion). If it reacts with retention at both ends or inversion at both ends, it reacts *suprafacially*, while if it reacts with retention at one end and inversion at the other, it reacts *antarafacially*. There are four possibilities.



In the routine above, we chose to use our σ bond so that we got inversion at one end and retention at the other. That was why we identified it as an antarafacial component. If we had chosen another style we should have got different descriptions of the components, but the reaction would still have been allowed—for example, changing just one connecting line.

This changes the symmetry of the σ bond so that it becomes a $_s2_s$ component but it also changes the symmetry of one of the π bonds so that it becomes a $_s2_a$ component. The net result is still only one component of the Woodward–Hoffmann symmetry, the sum is still one, and the reaction still allowed.

The direction of [3,3]-sigmatropic rearrangements

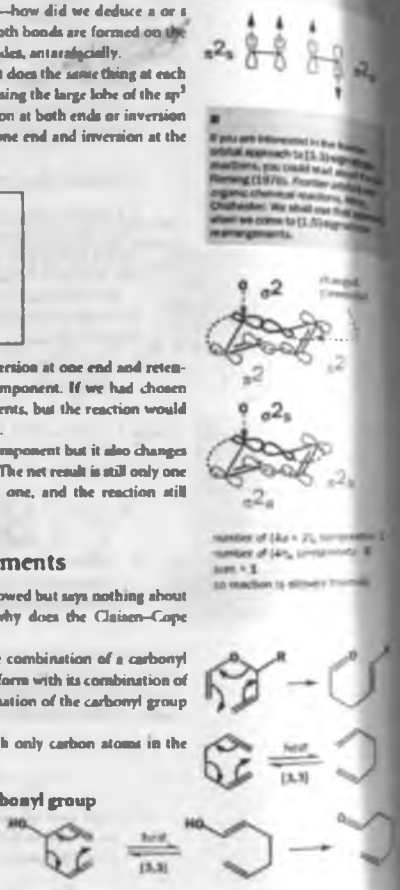
Orbital symmetry tells us that [3,3]-sigmatropic rearrangements are allowed but says nothing about which way they will go. They are allowed in either direction. So why does the Claisen–Cope rearrangement always go in this direction?

Think back to our discussion on enols and you may recall that the combination of a carbonyl group and a C–C σ bond made the keto form more stable than the enol form with its combination of a C=C π bond and a C–O σ bond. The same is true here. It is the formation of the carbonyl group that drives the reaction to the right.

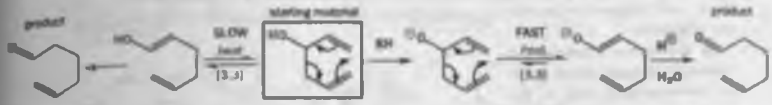
The **Cope rearrangement** is a [3,3]-sigmatropic rearrangement with only carbon atoms in the ring. In its simplest version it is not a reaction at all.

Directing the Cope rearrangement by the formation of a carbonyl group

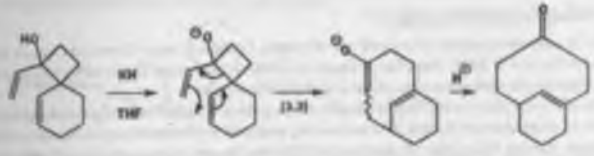
The starting material and the product are the same. We can drive this reaction too by the formation of a carbonyl group if we put an OH substituent in the right place.



The product of the sigmatropic step is the enol of the final product. It turns out that the reaction is accelerated if the starting alcohol is treated with base (KH is the best) to make the alkoxide. The product is then the potassium enolate, which is more stable than the simple potassium alkoxide starting material. As the reaction proceeds, conjugation is growing between O^- and the new π bond.

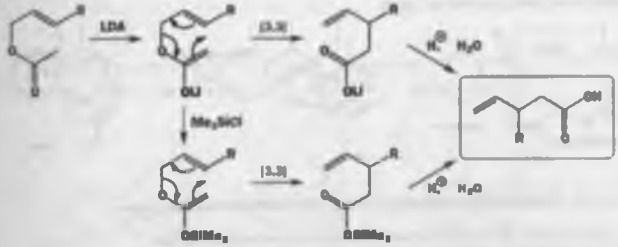


Some remarkable compounds can be made by this method. One of the strangest—a 'bridgehead' alkene—was made by a potassium-alkoxide-accelerated Cope rearrangement in which a four-membered ring was expanded into an eight-membered ring containing a *trans* double bond.

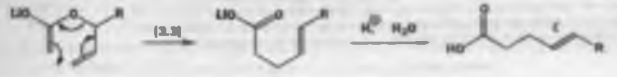


A combination of an oxygen atom in the ring and another one outside the ring is very powerful at promoting [3,3]-sigmatropic rearrangements and easy to arrange by making the lithium enolate of an ester of an allylic alcohol.

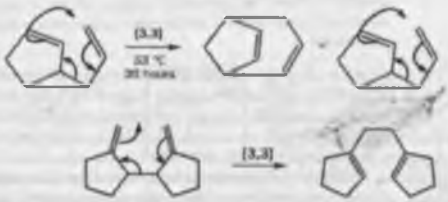
Sometimes it is better to convert the lithium enolate into the silyl enol ether before heating to accomplish the [3,3]-sigmatropic rearrangement. In any case, both products give the unsaturated carboxylic acid on work-up.



This reaction is known as the Ireland–Claisen rearrangement as it was a variation of the Claisen rearrangement invented by R.E. Ireland in the 1970s and widely used since. If the substituents are suitably arranged, it shows the same *E* selectivity as the simple Claisen rearrangement and for the same reason.



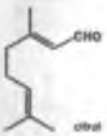
In some cases simple Cope rearrangements without any oxygen atoms at all can be directed by an unstable starting material or a stable product. The instability might be strain and the stability might simply be more substituents on the double bonds. In this case the driving force is the breaking of a weak σ bond in a three-membered ring. This reaction goes in 100% yield at only just above room temperature, so it is very favourable.



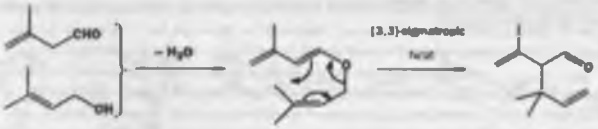
In this second example, the trisubstituted double bonds inside the five-membered rings of the product are more stable than the exomethylene groups in the starting material.

An industrial synthesis of citral

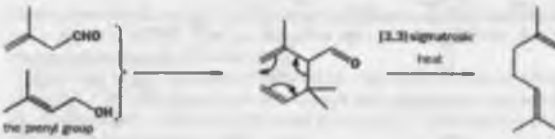
'Citral' is a key intermediate in the synthesis of vitamin A, and in Chapter 31 you had a go at designing a synthesis of it. BASF manufacture citral by a remarkable process that involves two successive [3,3]-sigmatropic rearrangements, a Claisen followed by a Cope.



The allyl vinyl ether needed for the Claisen rearrangement is an enol ether of an unsaturated aldehyde with an unsaturated alcohol. The two starting materials are themselves derived from a common precursor, making this a most efficient process! Heating the enol ether promotes [3,3]-sigmatropic rearrangement propelled by the formation of a carbonyl group.



But the product of this rearrangement is now set up for a second [3,3]-sigmatropic rearrangement, this time made favourable by a shift into conjugation and the formation of two trisubstituted double bonds from two terminal ones. Overall, the prenyl group walks from one end of the molecule to the other, inverting twice as it goes.



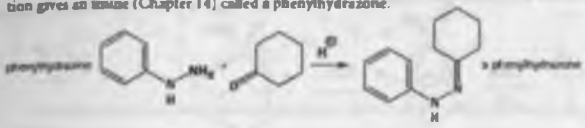
Sex for seaweeds censored by a [3,3]-sigmatropic rearrangement

In order to reproduce, the female gametes of marine brown algae must attract motile male gametes. They do by releasing a pheromone, long thought to be the cyclooctatetraene ectocarpene. In 1995 results were published that suggested that, in fact, the pheromone was a cyclopropene, and that ectocarpene was ineffective as a pheromone.

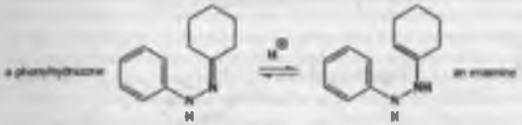
How had the confusion arisen? Well, the remarkable thing is that the cyclopropyl pheromone inactivates itself, with a half-life of several minutes at ambient temperature, by [3,3]-sigmatropic rearrangement to the cycloheptadiene, driven by release of strain from the three-membered ring. This not only confused the earlier pheromone chemists, but it also provides a marvellously precise way for the algae to signal their presence and readiness for reproduction without saturating the sea water with meaningless pheromone.

Applications of [3,3]-sigmatropic rearrangements using other elements

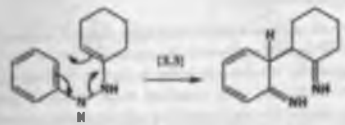
There is no need to restrict our discussion to carbon and oxygen atoms. We shall finish this section with two useful reactions that use other elements. The most famous synthesis of indoles is a nineteenth century reaction discovered by Emil Fischer—the Fischer indole synthesis—and it would be a remarkable discovery even today. Reaction of phenylhydrazine with a ketone in slightly acidic solution gives an imine (Chapter 14) called a phenylhydrazone.



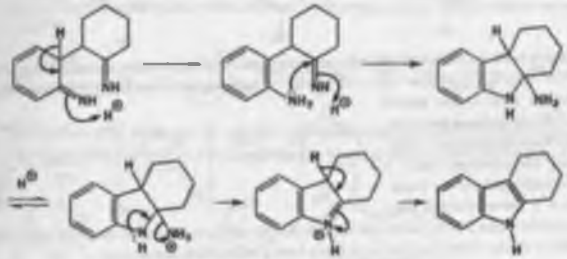
If the ketone is enolizable, this imine is in equilibrium with the corresponding enamine. The important bonds are given in black in the diagram.



The enamine is ideally set up for a [3,3]-sigmatropic rearrangement in which the σ bond to be broken is the weak N–N σ bond and one of the π bonds is in the benzene ring.



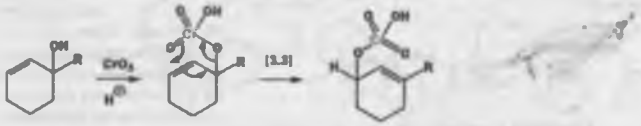
The product is a highly unstable double imine. Aromaticity is immediately restored and a series of proton shifts and C–N bond formation and cleavage give the aromatic indole. In the last diagram the ten-π-electron indole is outlined in black.



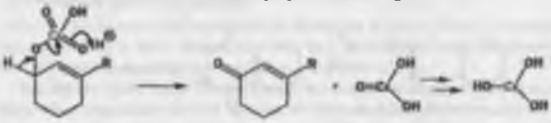
Indoles are of some importance in biology and medicine and the Fischer indole synthesis is widely used. Sometimes the complete reaction occurs, as in this example, under the slightly acidic conditions needed to make the phenylhydrazone. More commonly, the phenylhydrazone is isolated and converted into the indole with a Lewis acid such as $ZnCl_2$.

That was a [3,3]-sigmatropic reaction involving two nitrogens. There follows one with two oxygens and a chromium atom. When tertiary allylic alcohols are oxidized with CrO_3 in acid solution, no direct oxidation can take place, but a kind of conjugate oxidation occurs.

The first step in Cr(VI) oxidations can take place to give a chromate ester (Chapter 24) but this intermediate has no proton to lose so it transfers the chromate to the other end of the allylic system where there is a proton. The chromate transfer can be drawn as a [3,3]-sigmatropic rearrangement.

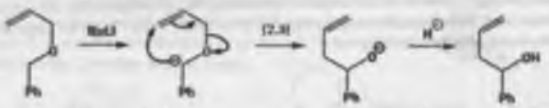


The final step is the normal oxidation (Chapter 24) in which chromium drops down from orange Cr(VI) to Cr(IV) and eventually by disproportionation to green Cr(III).



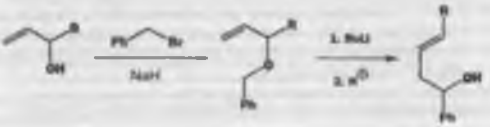
[2,3]-Sigmatropic rearrangements

All [3,3]-sigmatropic rearrangements have six-membered cyclic transition states. It is no accident that the size of the ring is given by the sum of the two numbers in the square brackets as this is universally the case for sigmatropic rearrangements. We are now going to look at [2,3]-sigmatropic rearrangements so we will be needing five-membered cyclic transition states. There is a problem here. You cannot draw three arrows going round a five-membered ring without stopping or starting on an atom. One way to do this is to use a carbanion.



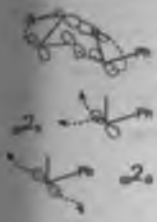
The starting material is a benzyl allyl ether and undergoes [2,3]-sigmatropic rearrangement to make a new C–C σ bond at the expense of a C–O σ bond—a bad bargain this as the C–O bond is stronger. The balance is tilted by the greater stability of the oxyanion in the product than of the carbanion in the starting material. The new bond has a 2,3 relationship to the old and the transition state is a five-membered ring.

The transition state can be quite chair-like so that the new π bond will be *trans* if it has a choice. There will be a choice if the ether has been made from a substituted allyl alcohol.



We cannot draw a complete chair as we would need a six-membered ring for that (see discussion of [3,3]-sigmatropic rearrangements above), but the part that is to become the new π bond can be in a chair-like part of the five-membered ring. The substituent R prefers an equatorial position and the resulting *trans* arrangement of the groups is outlined in black.

We can use the same conformational diagram to show how the orbitals overlap as the new bond is formed.

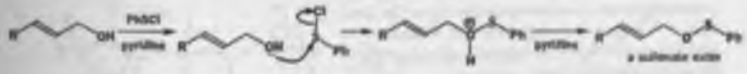


When we come to use the Woodward–Hoffmann rules on these [2,3]-sigmatropic rearrangements, we find something new. We have a π bond and a σ bond and a carbanion. How are we to represent a carbanion (or a carbocation) that is just a p orbital on an atom? The new symbol we use for a simple p orbital is ω. A carbanion is an $_{\omega}2$ component and a carbocation is an $_{\omega}0$ component as it has zero electrons. If the two new bonds are formed to the same lobe of the p orbital of the carbanion, we have an $_{\omega}2_s$ component but, if they are formed to different lobes, we have an $_{\omega}2_a$ component.

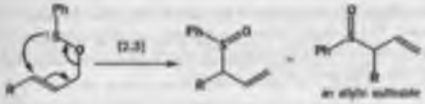
Without going through the whole routine again, the [2,3]-sigmatropic rearrangement we have been discussing can be described as an $_{\pi}2_s + {}_{\sigma}2_s + {}_{\omega}2_s$ reaction. There is one $(4q + 2)_s$ and no $(4r)_a$ components so the reaction is thermally allowed.

Sulfur is good at [2,3]-sigmatropic rearrangements

There are many [2,3]-sigmatropic rearrangements involving a variety of heteroatoms as well as carbon. We shall describe just one more because it involves no ions at all. The key is an element that is prepared to change its oxidation state by two so that we can start and finish an arrow on that element. The element is sulfur, which can form stable compounds at three oxidation states: S(II), S(IV), or S(VI).

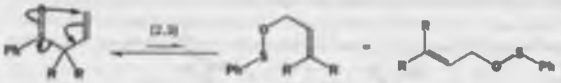


Reaction of an allylic alcohol with PhSCl gives an unstable sulfenate ester that rearranges on heating to an allylic sulfoxide by a [2,3]-sigmatropic rearrangement involving both O and S.

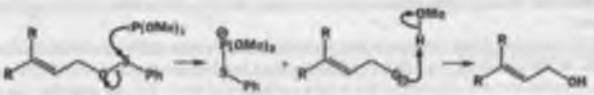


Notice that arrows both start and stop on the sulfur atom, which changes from S(II) to S(IV) during the reaction. The new functional group with an S=O bond is called a **sulfoxide**. This is a good preparation of allylic sulfoxides. The product forms an anion stabilized by sulfur, which can be alkylated.

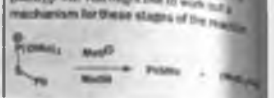
We have said that all these sigmatropic rearrangements are reversible but now we can prove it. If this product is heated in methanol with a nucleophile such as $(MeO)_3P$, which has a liking for sulfur, the [2,3]-sigmatropic rearrangement runs backwards and a sulfenate ester is again formed.



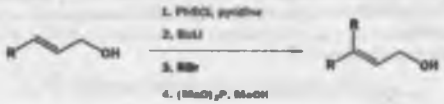
This is an unfavourable reaction, because the equilibrium lies over on the sulfoxide side. But the nucleophile traps the sulfenate ester and the methanol ensures that the alkoxide ion formed is immediately protonated so that we get another allylic alcohol.



The other products are actually Ph$_3$P and $(MeO)_3P{=}O$. You might like to work out a mechanism for these stages of the reaction.



So what is the point of going round in circles like this? The net result is the alkylation of an allylic alcohol in a position where alkylation would not normally be considered possible.

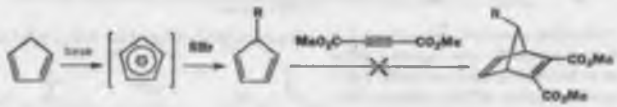


[1,5]-Sigmatropic hydrogen shifts

When one of the numbers in square brackets is '1', the old and new σ bonds are to the same atom, so we are dealing with the migration of a group around a conjugated system. In the case of a [1,5] shift the transition state is a six-membered ring (remember—just add together the numbers in square brackets). Here is an important example.

Let us first check that this is indeed a [1,5]-sigmatropic rearrangement by numbering the position of the new σ bond with respect to the old. Note that we must go the long way round the five-membered ring because that is the way the mechanism goes.

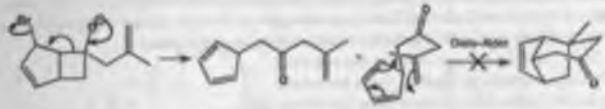
It is a [1,5]-sigmatropic rearrangement. The figure '1' in the square brackets shows that the same atom is at one end of the new σ bond as was at one end of the old σ bond. One atom has moved in a 1,5 manner and these are often called [1,5]-sigmatropic *shifts*. This is often abbreviated to [1,5]H shift to show which atom is moving. This particular example is important because sadly it prohibits a most attractive idea. The cyclopentadiene anion is very stable (Chapter 8) and can easily be alkylated. The sequence of alkylation and Diels–Alder reaction looks very good.



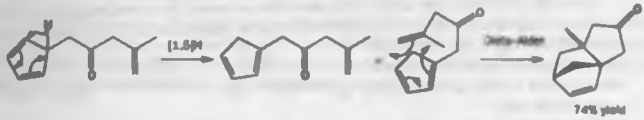
Sadly this sequence is, in fact, no good at all. A mixture of three Diels–Alder adducts is usually obtained resulting from addition to the three cyclopentadienes present in solution as the result of

rapid [1,5]H shifts. The one drawn above is a minor product because there is more of the other two dienes, which have an extra substituent on the double bonds.

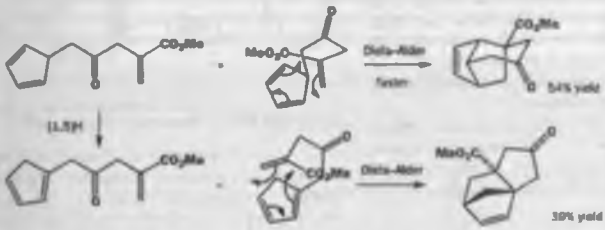
An excellent example comes from the intramolecular Diels–Alder reactions explored by Dreiding in 1983. One particular substituted cyclopentadiene was made by a fragmentation reaction (see Chapter 38). It might have been expected to give a simple Diels–Alder adduct.



There is nothing wrong with this reaction; indeed, the product looks beautifully stable, but it is not formed because the [1,5]H shift is too quick and gives a more stable cyclopentadiene with more substituents on a double bond. *Then* it does the Diels–Alder reaction.



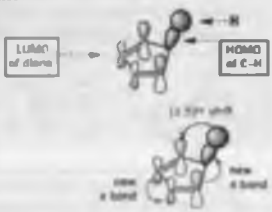
Notice that in these compounds the ketone is not conjugated to any of the alkenes and so does not influence the reaction. If we increase the reactivity of the dienophile by putting an ester group in conjugation with it, most of the compound does the Diels–Alder reaction *before* it does the [1,5]H shift.



Orbital description for the [1,5]H sigmatropic shift

It is equally satisfactory to use frontier orbitals or the Woodward–Hoffmann rules for these reactions. We can take the diene as one component (HOMO or LUMO or $_{\pi}4$) and the C–H bond as the other (LUMO or HOMO or $_{\sigma}2$). Let us start by using the LUMO of the diene and the HOMO of the C–H bond.

If the circle around the H atom surprised you, perhaps it will also remind you that hydrogen has only a 1s orbital which is spherical. You can probably see already that all the orbitals are correctly lined up for the reaction.

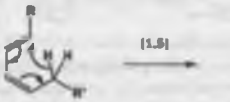


The hydrogen atom slides across the top face of the planar cyclopentadiene ring. We call this a suprafacial migration. This name has got nothing to do with the components in the Woodward–Hoffmann rules—it just means that the migrating group leaves from one face of the π system and rejoins that same face (the top face in this example). Antarafacial migration would mean leaving the top face and rejoining the bottom face—a clear impossibility here.

If you use the Woodward–Hoffmann rules, you need to note that the hydrogen atom must react with retention. The 1s orbital is spherically symmetrical and has no node, so wherever you draw the dotted line from that orbital it always means retention. Choosing the components is easy—the diene is a $_{\pi}4_{s}$ and the C–H bond a $_{\sigma}2_{s}$ component.

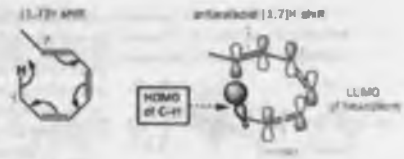
The easiest way to join them up is to link the hydrogen atom's 1s orbital to the top lobe of the p orbital at the back of the diene and the black sp^3 orbital to the top lobe at the front of the diene. This gives us $_{\pi}4_{s}$ and $_{\sigma}2_{s}$ components and there is one $(4q + 2)_{s}$ and no $(4r)_{a}$ components so the sum is odd and the reaction is allowed. Both approaches give us the same picture—a suprafacial migration of the hydrogen atom with (inevitably) retention at the migrating group.

These [1,5]-sigmatropic shifts are not restricted to cyclopentadienes. In Chapter 35 we bemoaned the lack of Diels–Alder reactions using *E,Z*-dienes. One reason for this dearth is that such dienes undergo [1,5]H shifts rather easily and mixtures of products result.



The complete rules for sigmatropic hydrogen shifts are simple. In thermal reactions, [1,3]H shifts occur suprafacially but [1,3]H and [1,7]H shifts must be antarafacial. It is just as well that antarafacial [1,3]H shifts are impossible (though allowed) as otherwise double bonds would wander about organic molecules like this.

Antarafacial [1,3]H shifts are impossible because a rigid three-carbon chain is too short to allow the H atom to transfer from the top to the bottom—the H atom just can't reach. When we come to [1,7]H shifts, the situation is different. Now the much longer chain is just flexible enough to allow the transfer.



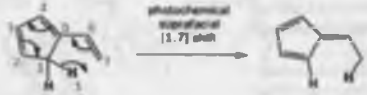
The hydrogen atom leaves the top side of the triene and adds back in on the bottom side. Antarafacial migration is allowed and possible.

Summary of thermal sigmatropic hydrogen shifts

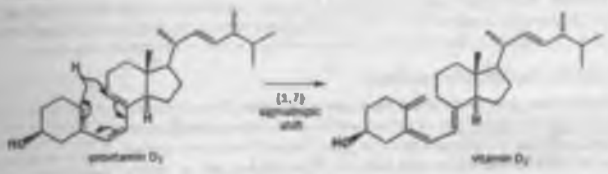
	[1,3]H shift	[1,5]H shift	[1,7]H shift
stereochemistry	antarafacial	suprafacial	antarafacial
feasibility	impossible	easy	possible

Photochemical [1,*n*]H sigmatropic shifts follow the opposite rules

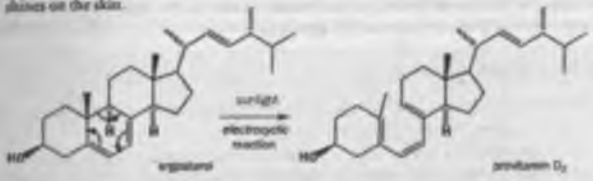
As you should by now expect (p. 000), all this is reversed in photochemical reactions. Here is an example of a [1,7]H shift that cannot occur antarafacially because the molecule is a rigid ring, but that can and does occur photochemically.



A [1,7]H shift occurs in the final stages of the human body's synthesis of vitamin D from cholesterol. Here is the last step of the biosynthesis.



This step happens spontaneously, without the need for light, so the shift must be antarafacial. The reason the body *does* need light to make vitamin D is the previous step, which only occurs when light shines on the skin.

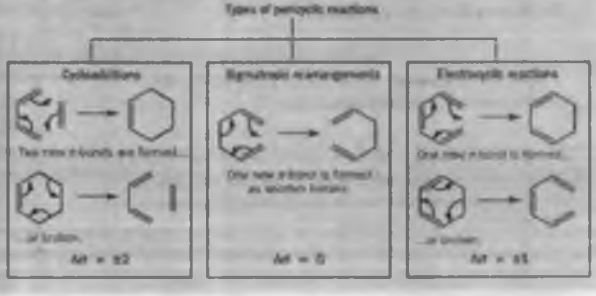


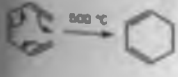
This ring opening is clearly pericyclic—the electrons go round in a ring, and the curly arrows could be drawn either way—but it is neither a cycloaddition (only one π system is involved) nor a sigmatropic rearrangement (a σ bond is broken rather than moved). It is, in fact, a member of the third and last kind of pericyclic reaction, an *electrocyclic reaction*.

Electrocyclic reactions

In an **electrocyclic reaction** a ring is always broken or formed. Rings may, of course, be formed by cycloadditions as well, but the difference with electrocyclic reactions is that just one new σ bond is formed (or broken) across the ends of a single conjugated π system. In a cycloaddition, two new σ bonds are always formed (or broken), and in a sigmatropic rearrangement one σ bond forms while one breaks.

● The types of pericyclic reactions are distinguished by the number of σ bonds made or broken





One of the simplest electrocyclic reactions occurs when hexatriene is heated to 500 °C.

It is a pericyclic reaction because the electrons go round in a ring (you could equally draw the arrows going the other way); it's electrocyclic because a new σ bond is formed across the ends of

a π system. The reaction goes because the σ bond that is formed is stronger than the π bond that is lost. The opposite is true for the electrocyclic reaction shown in the margin—ring strain in the four-membered ring means that the reverse (ring-opening) reaction is preferred to ring closure.

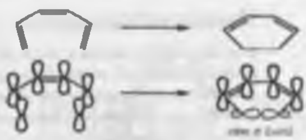
Rules for electrocyclic reactions

Whether they go in the direction of ring opening or ring closure, electrocyclic reactions are subject to the same rules as all other pericyclic reactions—you saw the same principle at work in Chapter 35 where we applied the Woodward–Hoffmann rules both to cycloadditions and to reverse cycloadditions. With most of the pericyclic reactions you have seen so far, we have given you the choice of using either HOMO–LUMO reasoning or the Woodward–Hoffmann rules. With electrocyclic reactions, you really have to use the Woodward–Hoffmann rules because (at least for the ring closures) there is only one molecular orbital involved.

▶ In one famous case, the release of ring strain is ... counterbalanced by the formation of a π bond at ... a σ bond. Cycloheptatriene exists in equilibrium with a ... isomer known as norcaradiene. Usually cycloheptatriene ... major component of the equilibrium, but the norcaradiene structure is favoured if R is an electron-withdrawing ...

> **● Electrocyclic reactions**
>
> - **An electrocyclic reaction is the formation of a new σ bond across the ends of a conjugated polyene or the reverse**
>
> **It is important that you do not confuse electrocyclic reactions with pericyclic reactions. Pericyclic is the name for the family of reactions involving no charged intermediates in which the electrons go round the outside of the ring. *Electrocyclic* reactions, *cycloadditions*, and *sigmatropic* rearrangements are the three main classes of *pericyclic* reactions.**

Let's start with the hexatriene ring closure, first looking at the orbitals, and then following the same procedure that we taught you for cycloadditions and sigmatropic rearrangements to see what the Woodward–Hoffmann rules have to say about the reaction. As a preliminary, we should just note that hexatriene is, of course, a 6 π electron ($_{\pi}6$) conjugated system and, on forming cyclohexadiene, the end two orbitals have to form a σ bond.

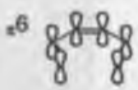


▶ Reminder. In a thermal per... reaction the total number ... $(4q+2)_s$ and $(4r)_a$ compon... must be odd.

So, now for the Woodward–Hoffmann treatment.

1 Draw the mechanism for the reaction

2 Choose the components. All the bonds taking part in the mechanism must be included and no others

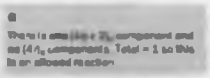


3 Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals at the ends of the components (only!)

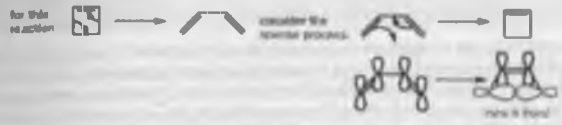
4 Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds

5 Label each component s or a depending on whether new bonds are formed on the same or on opposite sides

6 Add up the number of $(4q + 2)_s$ and $(4r)_a$ components. If the sum is *odd*, the reaction is allowed



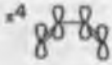
Notice that we called the reaction 's' because the top halves of the two π orbitals were joining together. We can give the same treatment to the cyclobutene ring-opening reaction—the Woodward–Hoffmann rules tell us nothing about which way the reaction will go, only if the reaction is allowed, and it is invariably easier with electrocyclic reactions to consider the ring-closing reaction even if the ring opening is favoured thermodynamically. This is the process we need to consider.



And the Woodward–Hoffmann treatment again.

1 Draw the mechanism for the reaction

2 Choose the components. All the bonds taking part in the mechanism must be included and no others

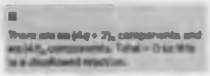


3 Make a three-dimensional drawing of the way the components come together for the reaction, putting in orbitals *at* the ends of the components (only!)

4 Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds

5 Label each component s or a depending whether new bonds are formed on the same or on opposite sides

6 Add up the number of $(4q + 2)_s$ and $(4r)_a$ components. If the sum is *odd*, the reaction is allowed.



Oh dear! We know that the reaction works, so something must be wrong. It certainly isn't Woodward and Hoffmann's Nobel-prize-winning rules—it's our way of drawing the orbital overlap that is at fault. We were fine till stage 3 (we had no choice till then)—but look at what happens if we make the orbitals overlap in a different way.

1 As before

2 As before

3 Make a three-dimensional drawing of the way in which the components come together for the reaction, putting in orbitals at the ends of the components (only!)

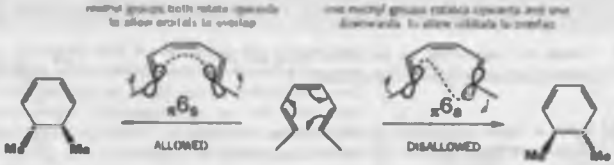
4 Join up the components where new bonds are to be formed. Make sure you join orbitals that are going to form new bonds

5 Label each component s or a depending on whether new bonds are formed on the same or on opposite sides

6 Add up the number of $(4q + 2)_s$ and $(4r)_a$ components. If the sum is *odd*, the reaction is allowed.

There are no $(4q + 2)_s$ components and one $(4r)_a$ component. Total = 1 so the reaction is an allowed reaction.

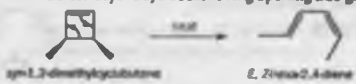
Now it works! In fact, extension of this reasoning to other electrocyclic reactions tells you that they are *all* allowed—provided you choose to make the conjugated system react with itself *supra*facially for $(4n + 2)$ π systems and *antara*facially for $(4n)$ π systems. This may not seem particularly informative, since how you draw the dotted line has no effect on the reaction product in these cases. But it can make a difference. Here is the electrocyclic ring closure of an octatriene, showing the product from (a) suprafacial reaction and (b) antarafacial reaction.



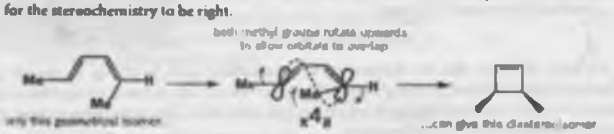
The meanings of con- and disrotation

Whether the reaction is supra- or antarafacial ought to be reflected in the relative stereochemistry of the cyclized products—and indeed it is. This reaction gives solely the diastereoisomer on the left, with the methyl groups syn—clear proof that the reaction is suprafacial. This is a difficult result to explain without the enlightenment provided by the Woodward–Hoffmann rules!

This electrocyclic cyclobutene ring opening also gives the product as a single stereoisomer.



Again, if we draw the reverse reaction, we can see that the reaction required has to be antarafacial for the stereochemistry to be right.



We have drawn little green arrows on the two diagrams to show how the methyl groups move as the new σ bonds form. For the allowed suprafacial reaction of the 6π electron system they rotate in

▶ The green arrows in this and subsequent diagrams are merely mechanical devices to show the way in which the substituents move. They are not rigorous, real, mechanistic curly arrows.

opposite directions so the reaction is called disrotatory (yes, they both go up, but one has to rotate clockwise and one anticlockwise) while for the allowed antarafacial reaction of the 4π electron system they rotate in the same direction so the reaction is called conrotatory (both clockwise as drawn, but they might equally well have both gone anticlockwise). We can sum up the course of all electrocyclic reactions quite simply using these words.

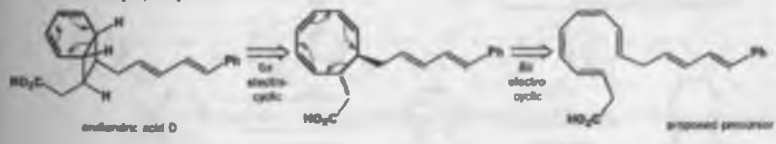
Rules for electrocyclic reactions

- **All electrocyclic reactions are allowed**
- **Thermal electrocyclic reactions involving $(4n + 2)$ π electrons are *disrotatory***
- **Thermal electrocyclic reactions involving $(4n)$ π electrons are *conrotatory***
- **In *conrotatory* reactions the two groups rotate in the *same* way; *both* clockwise or *both* anticlockwise**
- **In *disrotatory* reactions, *one* group rotates *clockwise* and *one anticlockwise***

This rotation is the reason why you must carefully distinguish electrocyclic reactions from all other pericyclic reactions. In cycloadditions and sigmatropic rearrangements there are small rotations as bond angles adjust from 109° to 120° and vice versa, but in electrocyclic reactions, rotations of nearly 90° are required as a planar polyene becomes a ring, or vice versa. These rules follow directly from application of the Woodward–Hoffmann rules—you can check this for yourself.

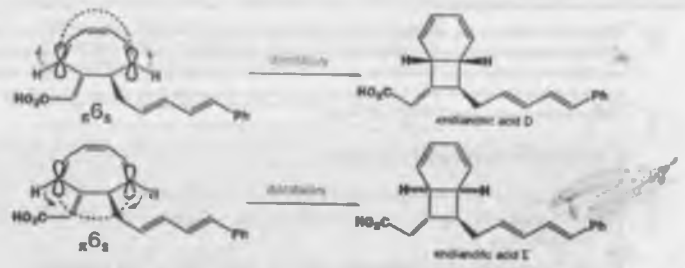
Electrocyclic reactions occur in nature

A beautiful example of electrocyclic reactions at work is provided by the chemistry of the endiandric acids. This family of natural products, of which endiandric acid D is one of the simplest, is remarkable in being racemic—most chiral natural products are enantiomerically pure (or at least enantiomerically enriched) because they are made by enantiomerically pure enzymes (we discuss all this in Chapter 45). So it seemed that the endiandric acids were formed by non-enzymatic cyclization reactions, and in the early 1980s their Australian discoverer, Black, proposed that their biosynthesis might involve a series of electrocyclic reactions, starting from an acyclic polyene precursor.

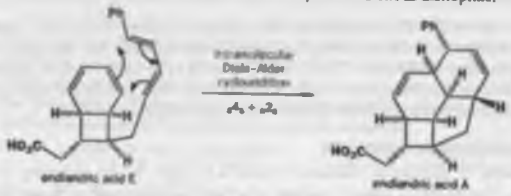


What made his proposal so convincing was that the stereochemistry of the endiandric acid D is just what you would expect from the requirements of the Woodward–Hoffmann rules. The first step from the precursor is an 8π electrocyclic reaction, and would therefore be conrotatory.

This sets up a new 6π system, which can undergo an electrocyclic reaction in disrotatory fashion. Because there are already chiral centres in the molecule, there are, in fact, two possible diastereoisomeric products from this reaction, both arising from disrotatory cyclization. One is endiandric acid D; one is endiandric acid E.



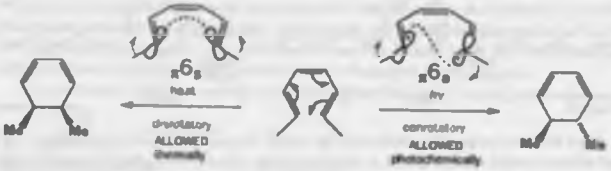
Of course, this was only a theory—until in 1982 K.C. Nicolaou's group synthesized the proposed endiandric acid precursor polyene—and in one step made both endiandric acids D and E, plus endiandric acid A, which arises from a further pericyclic reaction, an intramolecular Diels–Alder cycloaddition of the acyclic diene on to the cyclohexadiene as dienophile.



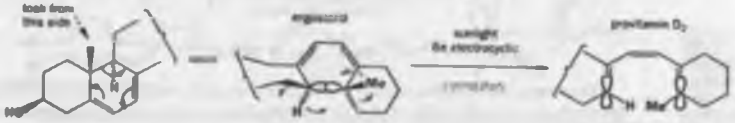
Endiandric acid A has four rings and eight stereogenic centres and yet is formed as a single diastereoisomer in one step from an acyclic polyene! And it's all controlled by pericyclic reactions.

Photochemical electrocyclic reactions

After your experience with cycloadditions and sigmatropic rearrangements, you will not be surprised to learn that, in photochemical electrocyclic reactions, the rules regarding conrotatory and disrotatory cyclizations are reversed.



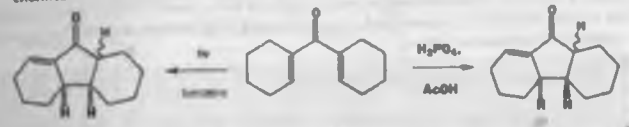
We can now go back to the reaction that introduced this section—the photochemical electrocyclic ring opening of ergosterol to give provitamin D_2. By looking at the starting material and product we can deduce whether the reaction is conrotatory or disrotatory.



It's clearly conrotatory, and a little more thought will tell you why it has to be—a disrotatory thermal 6π cyclization would put an impossible *trans* double bond into one of the two six-membered rings. Vitamin D deficiency is endemic in those parts of the world where sunlight is scarce for many months of the year—and all because of orbital symmetry.

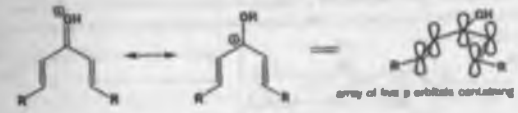
Cations and anions

What we have just been telling you should convince you that the two reactions below are electrocyclic reactions, not least because the stereochemistry reverses on going from thermal to photochemical reaction.

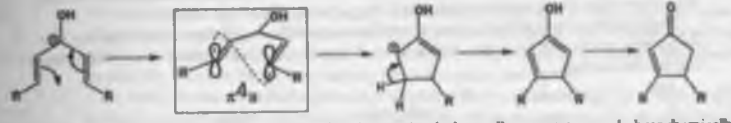


They are examples of what is known, after its Russian discoverer, as the Nazarov cyclization. In its simplest form, the Nazarov cyclization is the ring closure of a doubly α,β-unsaturated ketone to give a cyclopentenone.

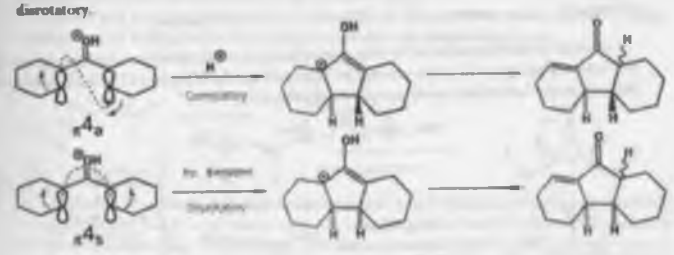
Nazarov cyclizations require acid, and protonation of the ketone sets up the conjugated π system required for an electrocyclic reaction.



One of the five π orbitals involved is empty—so the cyclization is a 4π electrocyclic reaction, and the orbitals forming the new σ bond must interact antarafacially. Loss of a proton and tautomerism gives the cyclopentenone.



The real example above confirms that the reaction is thermally conrotatory and photochemically disrotatory.



Dienyl cations and dienyl anions both undergo electrocyclic ring closure—a nice example occurs when cyclooctadiene is deprotonated with butyllithium.

There are still five p orbitals involved in the cyclization, but now there are six π electrons, so the reaction is disrotatory.

In this case, it is the conrotatory *photochemical* cyclization that is prevented by strain (it was tried—cyclooctadienyl anion is stable for at least a week at –78 °C in broad daylight) as the product would be a 5,5 *trans*-fused system. The same strain prevents thermal electrocyclic ring closure of cyclooctadienyl cations.

● All electrocyclic reactions are allowed

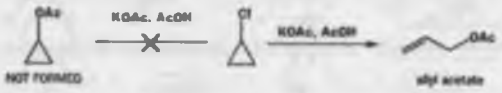
It would be a good point here to remind you that, although all electrocyclic reactions are allowed both thermally and photochemically providing the rotation is right, the steric requirements for con- or disrotatory cyclization or ring opening may make one or both modes impossible.

Small rings are opened by electrocyclic reactions

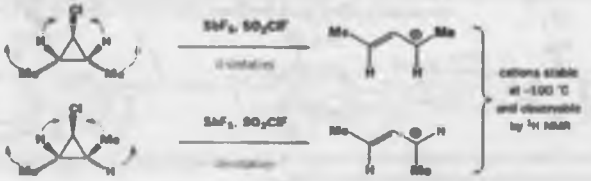
Ring strain is important in preventing a reaction that would otherwise change your view of a lot of the chemistry you know. Allyl cations are conjugated systems containing 2π electrons, so if you knew no other chemistry than what is in this chapter you might expect them to cyclize via disrotatory electrocyclic ring closure.

The product would be a cyclopropyl cation. Now, in fact, it is the cyclopropyl cations that undergo this reaction (very readily indeed—cyclopropyl cations are virtually unobservable) because ring strain encourages them to undergo electrocyclic ring opening to give allyl cations.

The instability of cyclopropyl cations means that, even as they start to form as intermediates, they spring open to give allyl cation-derived products. Try nucleophilic substitution on a cyclopropane ring and this happens.



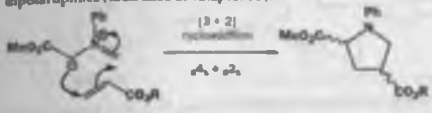
Although the initial product of the ring opening is a cation, and therefore a hard-to-observe reactive intermediate, some nice experiments in 'superacid' media (Chapters 17 and 22) have proven that cyclopropyl cation ring openings are indeed disrotatory.



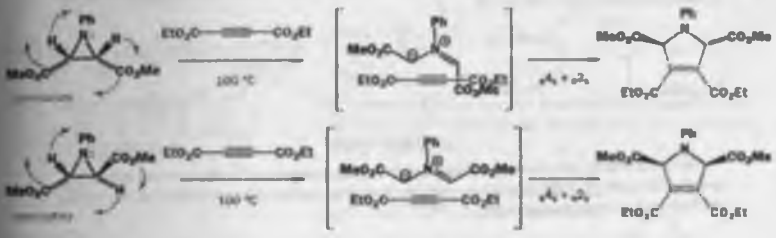
The stereochemistry of aziridine opening is predictable

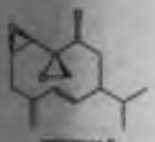
One last type of three-membered ring whose electrocyclic ring opening does tell us about the stereochemistry of the process is the aziridine. Many aziridines are stable compounds, but those bearing electron-withdrawing groups are unstable with respect to electrocyclic ring opening.

The products are azomethine ylids, and can be trapped by [3+2] cycloaddition reactions with dipolarophiles (look back at Chapter 35).



Because the cycloaddition is stereospecific (suprafacial on both components), the stereochemistry of the products can tell us the stereochemistry of the intermediate ylid, and confirms that the ring opening is conrotatory (the ylid is a 4π electron system).





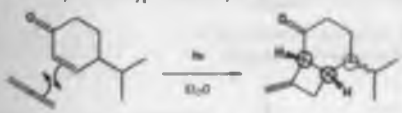
periplanone B

The synthesis of a cockroach pheromone required pericyclic reactions

We finish this pair of chapters about pericyclic reactions with a synthesis whose simplicity is outclassed only by its elegance. Periplanone B is a remarkable bis-epoxide that functions as the sex pheromone of the American cockroach. Insect sex pheromones often have economic importance because they can form the key to remarkable effective traps for insect pests.

In 1984, Schreiber published a synthesis of the pheromone in which the majority of steps involve pericyclic reactions. Make sure you understand each one as it appears—re-read the appropriate part of Chapter 35 or this chapter if you have any problems.

The first step is a photochemical [2+2] cycloaddition. You could not have predicted the regiochemistry, but it is typical of the cycloaddition of allenes with unsaturated ketones.

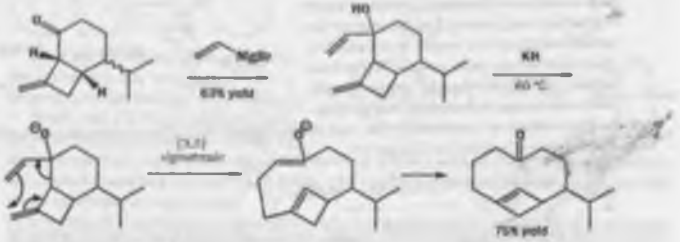


[2 + 2] cycloaddition

72% yield

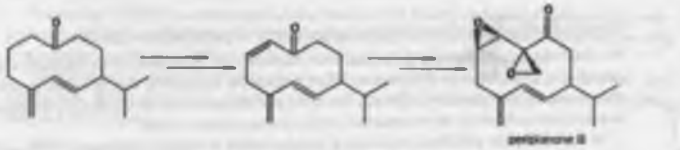
The product is a mixture of diastereoisomers because of the chiral centre already in the molecule (ringed in green), but it is, of course, fully stereospecific for the two new black chiral centres in the four-membered ring. The next step adds vinylmagnesium bromide to the ketone—again a mixture of diastereoisomers results. Now all the carbons in the 12-membered ring are present, and they are sorted out by the two steps that follow. The first is a Cope rearrangement: a [3,3]-

sigmatropic rearrangement, accelerated as we have described (p. 000) by the presence of an alkoxide substituent.



The six-membered ring has expanded to a ten-membered ring. Now for a second ring-expansion step—heating the compound to 175 °C makes it undergo electrocyclic ring opening of the four-membered ring, giving the 12-membered ring we want. Or rather not quite—the new double bond in the ring is formed as a mixture of *cis* and *trans* isomers, but irradiation isomerizes the less stable *cis* to the more stable *trans* double bond.

The remaining steps in the synthesis use chemistry not yet introduced in this book but involve the insertion of another (*Z*) alkene and two epoxides. Pericyclic reactions are particularly valuable in the synthesis and manipulation of rings.

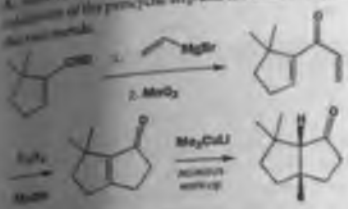


We must now take our leave of this trio of pericyclic reactions and move on to two reaction classes that have appeared frequently in these two chapters, but that involve mechanisms other than pericyclic ones and deserve chapters of their own: *rearrangements* and *fragmentations*.

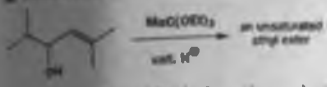
▶ There are two things to note here—firstly, the geometry of the double bond is nothing to do with whether the reaction is suprafacial or disrotatory. As you know, this 4*n* electron electrocyclic ring opening must be conrotatory, but as there is no substituent on the other end of the diene product we can't tell. Secondly, notice that, in this 12-membered ring, a *trans* double bond is not only possible, but probably preferred. We introduced irradiation as a means of interconverting double bond isomers in Chapter 31.

Problems

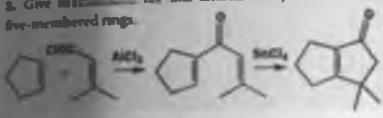
4. Give mechanisms for these steps, commenting on the regiochemistry of the pericyclic step and the different regioselectivity of the two methods.



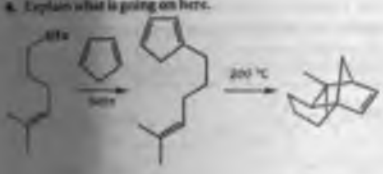
5. Predict the product of this reaction.



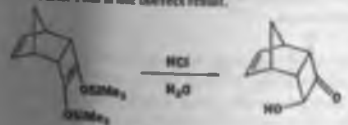
6. Give mechanisms for this alternative synthesis of two fused five-membered rings.



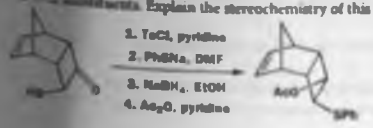
7. Explain what is going on here.



8. In Chapter 33, Problem 13, we used a tricyclic hydroxy-ketone whose stereochemistry had been wrongly assigned. Now we are going to show you how it was used and you are going to interpret the results. This is the correct result.



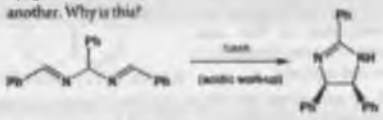
The hydroxy-ketone was first converted into a compound with PhS and OAc substituents. Explain the stereochemistry of this process.



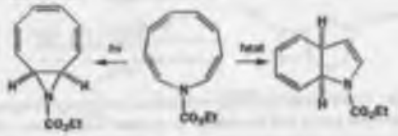
Pyrolysis of this compound at 460 °C gave a diene whose NMR spectrum included δ_H (p.p.m.) 6.06 (1H, dd, *J* 10.3, 12.1 Hz), 6.23 (1H, dd, *J* 10.3, 14.7 Hz), 6.31 (1H, d, *J* 14.7 Hz), and 7.32 (1H, d, *J* 12.1 Hz). Does this agree with the structure given? How is this diene formed and why does it have that stereochemistry?

9. Careless attempts to carry out a Claisen rearrangement on this allyl ether often give the compound shown instead of the expected product. What is the expected product? How is the unwanted product formed? Addition of a small amount of a weak base, such as $PhNMe_2$ helps to prevent the unwanted reaction. How?

10. Treatment of this imine with base followed by an acidic work-up gives a cyclic product with two phenyl groups *cis* to one another. Why is this?

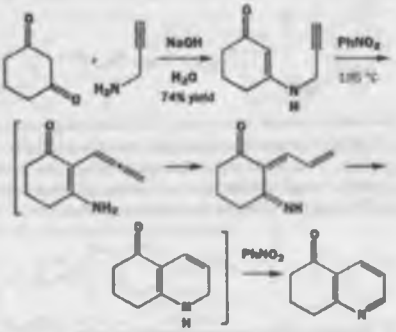


11. This question concerns the structure and chemistry of an unsaturated nine-membered ring. Comment upon its structure. Explain its different behaviour under thermal or photochemical conditions.

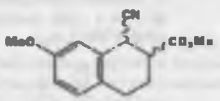


12. Propose a mechanism for this reaction that accounts for the stereochemistry of the product.

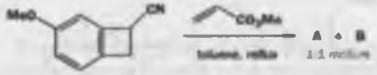
10. Treatment of cyclohexa-1,3-dione with this acetylenic amine gives a stable enamine in good yield. Refluxing this enamine in nitrobenzene gives a pyridine after a remarkable series of reactions. Fill in the details: give mechanisms for the reactions, structures for any intermediates, and suitable explanations for each pericyclic step. A mechanism is not required for the last step (nitrobenzene acts as an oxidant).



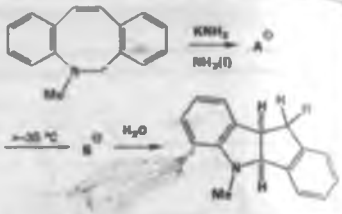
11. Problem 11 in Chapter 32 was concerned with two diastereoisomers of this compound that were formed in 'a chemical reaction'.



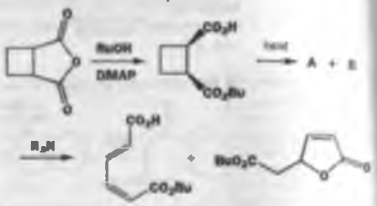
We can now let you into the secret of that 'chemical reaction'. A benzocyclobutene was heated with methyl acrylate to give a 1:1 mixture of the two isomers. What is the mechanism of the reaction and why is only one regioisomer but a mixture of stereoisomers formed? Isomer B is converted into isomer A on treatment with base. What is the stereochemistry of A and B?



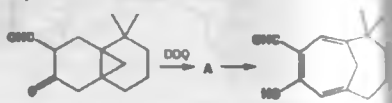
12. Treatment of this amine with base at low temperature gives an unstable anion that isomerizes to another anion above –35 °C. Aqueous work-up gives a bicyclic amine. What are the two anions? Explain the stereochemistry of the product. Revision of NMR. In the NMR spectrum of the product the two green hydrogens appear as an ABX system with J_{AB} 15.4 Hz. Comment.



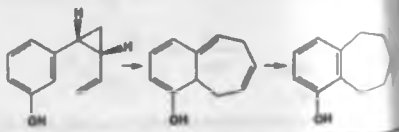
13. How would you make the starting material for these reactions? Treatment of the anhydride with butanol gives an acid that gives two inseparable compounds on heating. One [illegible] with an amine, an easily separable mixture of an acidic and a neutral compound is formed. What are the components of the mixture and how are they formed?



14. Treatment of this keto-aldehyde (which exists largely as an enol) with the oxidizing agent DDQ (a quinone—see p. [illegible]) gives an unstable compound that converts into the product shown. Explain the reactions and comment on the stereochemistry.



15. Explain the following observations. Heating this [illegible] brings it into rapid equilibrium with a bicyclic compound [illegible] does not spontaneously give the final aromatic product until treated with acid.



Rearrangements

37

Connections

Building on:

- Nucleophilic substitution at saturated carbon ch17
- Conformational analysis ch18
- Formation reactions ch19
- Electrophilic aromatic substitution ch22
- Controlling stereochemistry ch18, ch33, & ch34
- Pericyclic rearrangements ch31

Arriving at:

- Participation: nucleophiles are more efficient if they are already part of the molecule
- Participation means acceleration and retention of stereochemistry and may mean rearrangement
- Participating groups can have lone pairs or π electrons
- Carbocations often rearrange by alkyl migration
- How to work out the mechanism of a rearrangement
- Ring expansion by rearrangement
- Controlling rearrangements
- Using rearrangements in synthesis
- Insertion of O, N, or C next to a ketone

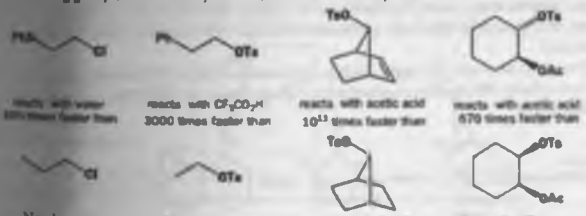
Looking forward to:

- Fragmentations ch38
- Carbene chemistry ch40
- Determination of mechanism ch41
- Stereoelectronics ch42
- Main group chemistry ch46–ch47
- The chemistry of life ch49–ch51

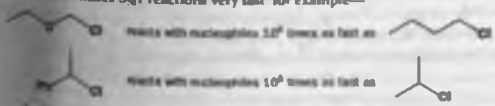
Neighbouring groups can accelerate substitution reactions

Compare the rates of the following substitution reactions. Each of these reactions is a substitution of the leaving group (OTs or Cl) by solvent, known as a solvolysis.

■ A solvolysis was defined in Chapter 17 as 'a reaction in which the solvent is also the nucleophile'.



Nearby groups can evidently increase the rate of substitution reactions significantly. Now, you may be thinking back to Chapter 17 and saying 'yes, yes, we know that'—when we were discussing the mechanisms of substitution reactions we pointed out that a cation-stabilizing group at the reaction centre makes S_N1 reactions very fast: for example—

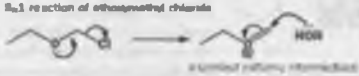


In the four examples above, though, it is not at the reaction centre itself that the functional groups change but at the carbon next to the reaction centre, and we call these groups neighbouring groups.

▶ Neighbouring group participation is occasionally called **anchimeric assistance** (Greek *anchi* = neighbouring; *meir* = part).

The mechanism by which they speed up the reactions is known as neighbouring group participation. Compare the reaction of this ether and this sulfide with an alcohol.

S_N1 reaction of ethoxymethyl chloride



a cyclic oxonium intermediate

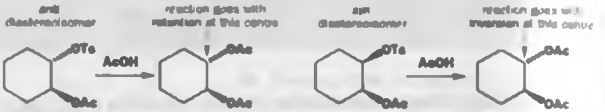
neighbouring group participation of a sulfide

three-membered ring intermediate

In both cases, ionization of the starting material is assisted by the lone pair of an electron-rich functional group. The ether in the first example assists by forming a π bond, the sulfide assists by forming a three-membered ring, and a common feature of all mechanisms involving neighbouring group participation is the formation of a cyclic intermediate.

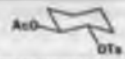
Stereochemistry can indicate neighbouring group participation

How do we know that neighbouring group participation is taking place? Well, the first bit of evidence is the *increase in rate*. The neighbouring groups will become involved only if they can increase the rate of the substitution reaction—otherwise the mechanism will just follow the ordinary S_N1 pathway. But more important information comes from reactions where stereochemistry is retained, and one of these is the last of the four examples above. Here it is again in more detail. Not only does the first of these reactions go faster than the second—its stereochemical course is different too.



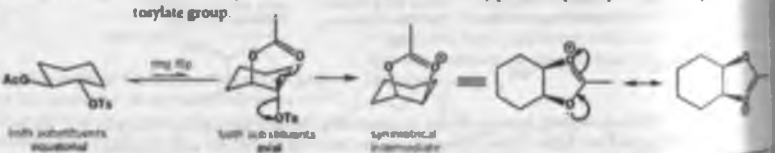
■ If you are unsure what we are talking about, go back and read Chapter 10 now!

Although one starting material has *syn* and the other *anti* stereochemistry, the products have the same (*anti*) stereochemistry: one substitution goes with retention and one goes with inversion. Again, neighbouring group participation is the reason. To explain this, we should first draw the six-membered rings in their real conformation. For the *anti* compound, both substituents can be equatorial.



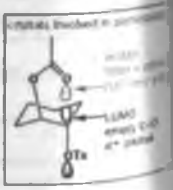
both substituents equatorial

However, not much can happen in this conformation—but, if we allow the ring to flip, you can see immediately that the acetate substituent is ideally placed to participate in the departure of the tosylate group.

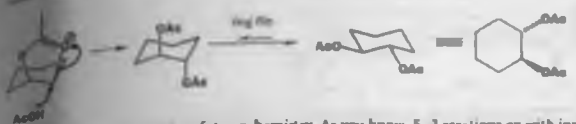


▶ While the mechanism of this first step of the substitution reaction is S_N2 in appearance—a nucleophile (the acetate group) arrives just as a leaving group (the tosylate group) departs—it is also, of course, only unimolecular.

What results is an entirely symmetrical intermediate—the positive charge on one of the oxygens is, of course, delocalized over both of them. The intramolecular S_N2 reaction takes place with inversion, as required by the orbitals, so now the junction of the two rings is *cis*.

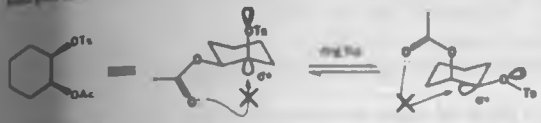


The next step is attack of acetic acid on the intermediate. This is another S_N2 reaction, which also proceeds with inversion and gives back a *trans* product.



Overall, we have *retention* of stereochemistry. As you know, S_N2 reactions go with inversion, and S_N1 reactions with loss of stereochemical information—so this result is possible only if we have two sequential S_N2 reactions taking place—in other words neighbouring group participation.

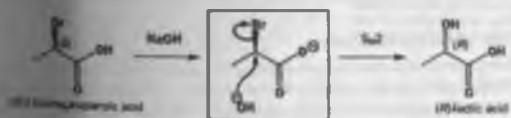
Why, then, does the other diastereoisomer react with inversion of stereochemistry? Well, try drawing the mechanism for intramolecular displacement of the tosyl group. Whether you put the complex or the acetate group equatorial doesn't matter; there is no way in which the acetate oxygen's lone pair can reach the σ* orbital of the tosylate C–O bond.



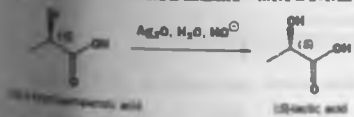
Neighbouring group participation is impossible, and substitution goes simply by intermolecular displacement of OTs by AcOH. Just one S_N2 step means overall inversion of configuration, and no participation means a slower reaction.

Retention of configuration is an indication of neighbouring group participation

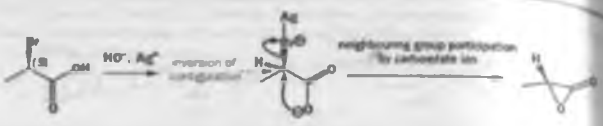
Enantiomerically pure (*S*)-2-bromopropanoic acid reacts with concentrated sodium hydroxide to give (*R*)-lactic acid. The reaction goes with inversion and is a typical S_N2 reaction—and a good one too, since the reaction centre is adjacent to a carbonyl group (see Chapter 17).



If, on the other hand, the reaction is run using Ag_2O and a low concentration of sodium hydroxide, (*S*)-lactic acid is obtained—there is overall *retention* of stereochemistry.



Nucleophilic substitution reactions that go with retention of stereochemistry are rather rare and usually go through two successive inversions with neighbouring group participation, like the example you saw in the last section. This time the neighbouring group is carboxylate; the silver oxide is important because it encourages the ionization of the starting material by acting as a halogen-selective Lewis acid.



A three-membered ring intermediate forms, which then gets opened by hydroxide in a second S_N2 step.

● Retention suggests participation

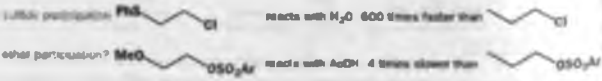
If you see a substitution reaction at a stereogenic saturated carbon atom that goes with retention of stereochemistry, look for neighbouring group participation!

Why does the carboxylate group participate only at low HO^- concentration and in the presence of Ag^+? You can think of the situation in these two reactions in terms of the factors that favour S_N1 and S_N2 reactions. In the first, we have conditions suited to an S_N2 reaction: a very good nucleophile (HO^-) and a good leaving group (Br^-). Improve the leaving group by adding Ag^+ (Ag^+ assists Br^-'s departure much as H^+ assists the departure of OH^- by allowing it to leave as H_2O) and worsen the nucleophile (H_2O instead of HO^-, of which there is now only a low concentration) and we have the sorts of conditions that would favour an S_N1 reaction. The trouble is, without neighbouring group participation, the cation here would be rather unstable—right next to a carbonyl group. The carboxylate saves the day by participating in the departure of the Br^- and forming a stable ion. The key thing to remember is that a reaction always goes by the mechanism with the fastest rate.

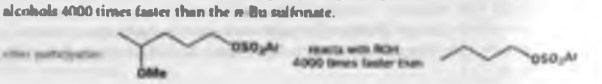
● Neighbouring groups participate only if they speed up the reaction.

What sorts of groups can participate?

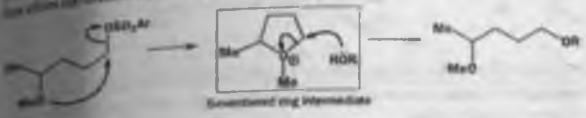
You've already met the most important ones—sulfides, esters, carboxylates. Ethers and amines (you will see some of these shortly) can also assist substitution reactions through neighbouring group participation. The important thing that they have in common is an electron-rich heteroatom with a lone pair that can be used to form the cyclic intermediate. Sulfides are rather better than ethers—thus a sulfide reacts with water much faster than *n*-PrCl but the ether reacts with acetic acid four times more *slowly* than *n*-$PrOSO_2Ar$.



The OMe group slows the reaction down just because it is electronegative more than it accelerates it by participation. A more distant OMe group can participate: this 4-MeO alkyl sulfonate reacts with alcohols 4000 times faster than the *n*-Bu sulfonate.



Again neighbouring group participation is involved, but this time through a five- rather than a three-membered ring. Participation is most commonly through three- and five-membered rings, less often six-membered ones, and very rarely four- or more than seven-membered ones.



Seven-membered ring intermediate

▶ Why these ring sizes? Well, the underlying reasons are the same as those we discussed in Chapter 1.3 when we talked about the kinetics (rates) of formation and thermodynamics (stability) of different ring sizes: three- and five-membered rings form particularly rapidly in any reaction. See also Chapter 42.

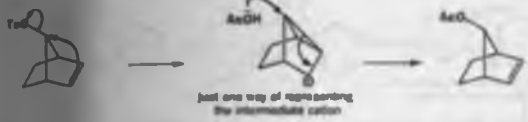
Mustard gas

Cyclization of sulfides through seven-membered rings was used to gruesome effect in the development of mustard gas during the Second World War. Mustard gas itself owes its toxicity to the neighbouring group participation of sulfur, which accelerates its elimination reactions.

mustard gas

Not all participating groups have lone pairs

Another of the four examples we started with shows that even the π electrons of a C=C double bond can participate. Retention of stereochemistry in the product (the starting tosylate and product acetate are both anti to the double bond) and the extremely fast reaction (10^{11} times that of the saturated analogue) are tell-tale signs of neighbouring group participation.



Just one way of representing the intermediate cation

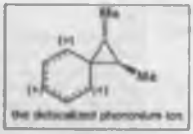
What is the structure of the intermediate?

During the 1950s and 1960s, this sort of question aroused a great deal of controversy, which we have no intention of stirring up, and all we will do is point out that the intermediate in this reaction is not fully represented by the structure we have here: it is symmetrical and could be represented by two structures with three-membered rings or by a delocalized structure in which two electrons are shared between three atoms. The difference need not concern us.

Aryl participation is more common than simple alkene participation

Finally, an example with a neighbouring phenyl group. Participation is hinted at by the retention of relative stereochemistry.

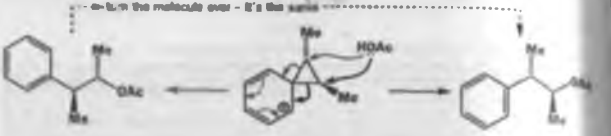
Again, π electrons are involved, but the reaction is now electrophilic aromatic substitution (Chapter 22) rather like an intramolecular Friedel–Crafts alkylation with a delocalized intermediate often termed a phenonium ion.



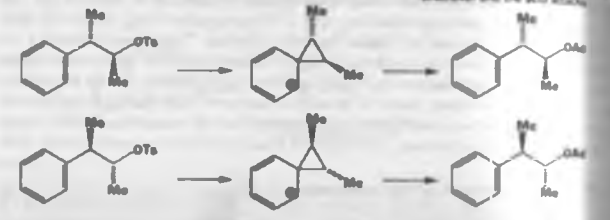
the delocalized phenonium ion

More stereochemical consequences of neighbouring group participation

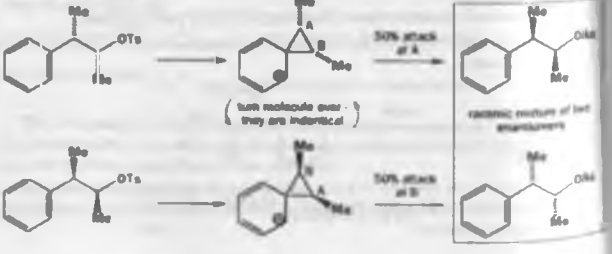
The phenonium ion is symmetrical. The acetic acid can attack either atom in the three-ring to give the same product.



The phenonium ion is nonetheless still chiral, since it has an axis (and not a plane of symmetry, so if we use an enantiomerically pure starting material we get an enantiomerically pure product.



Not so with the other diastereoisomer of this compound! Now, the phenonium ion is symmetrical with a plane of symmetry—it is therefore achiral, and the same whichever enantiomer we start from. Attack on each end of the phenonium ion gives a different enantiomer, whichever enantiomer of starting material we use we get the same racemic mixture of products. You can compare this reaction with the loss of stereochemical information that occurs in an S_N1 reaction of enantiomerically pure compounds. Both reactions pass through an achiral intermediate.

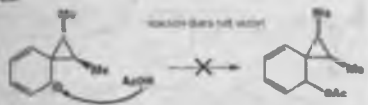


▶

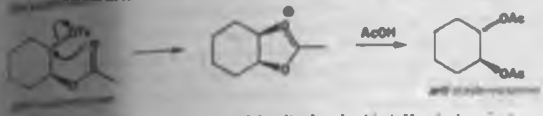
There is a subtlety here that you should not overlook and that makes this study, which was carried out by Cram in 1949, exceedingly elegant. Both of these reactions are stereospecific: the relative stereochemistry of the products depends on the relative stereochemistry of the starting materials. Yet, while the absolute stereochemistry of the starting materials is retained in one case (we get a single enantiomer of a single diastereoisomer), it is lost in the other (we get a racemic mixture of both enantiomers of a single diastereoisomer). These are important distinctions, and if you are in any doubt about them, re-read Chapters 16 and 34.

Donald Cram (1919–) of UCLA was awarded the Nobel prize in 1987 jointly with Jean-Marie Lehn (1939–) of Strasbourg and Paris and Charles Pedersen (a Norwegian born in Korea in 1904) of DuPont for 'their development and use of molecules with structure-specific interactions of high selectivity'.

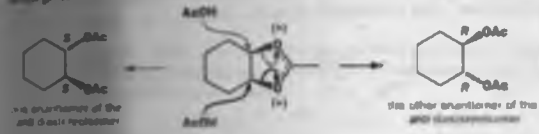
Product carbon trapping is not observed



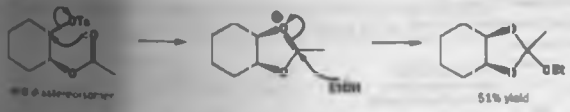
The same loss of absolute stereochemical information (but retention of relative stereochemistry) occurs in another reaction that you met at the start of this chapter. We then emphasized two features: the acceleration in rate and the retention of stereochemistry.



The intermediate oxonium ion is delocalized and achiral. If a single enantiomer of the starting material is used, racemic product is formed through this achiral intermediate. Attack at one carbon atom gives one enantiomer; attack at the other gives the mirror image.



In this case the neighbouring group can be caught in the act—when the rearrangement is carried out in ethanol, the intermediate is trapped by attack at the central carbon atom. It is as though someone switched the light on while the acetate's fingers were in the biscuit tin (the cookie jar).

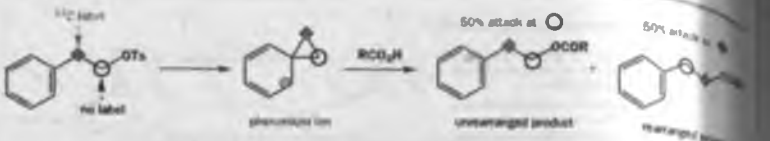


The product is an orthoester and is achiral too. This chemistry should remind you of the formation of acetals as described in Chapter 14.

Rearrangements occur when a participating group ends up bonded to a different atom

Because the intermediates in these examples are symmetrical, 50% of the time one substituent ends up moving from one carbon atom to another during the reaction. This is clearer in the following example: the starting material is prepared such that the carbon atom carrying the phenyl group is an unusual isotope—carbon-14. This doesn't affect the chemistry, but means that the two carbon atoms are easily distinguishable. Reacting the compound with trifluoroacetic acid scrambles the label between the two positions: the intermediate is symmetrical and, in the 50% of reactions with the nucleophile that take place at the labelled carbon atom, the phenyl ends up migrating to the unlabelled carbon atom in a rearrangement reaction.

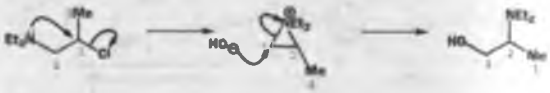
▶ Labelling an atom with an unusual isotope is a standard way to probe the details of a reaction. Radioactive ^{3}H (tritium) or ^{14}C used to be used but, with the advent of high-field NMR, non-radioactive ^{2}H (deuterium) and ^{13}C have become more popular. These methods are treated more thoroughly in Chapter 41.



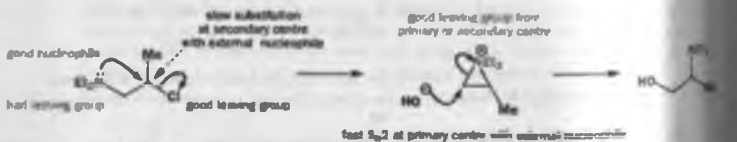
Now, consider this substitution reaction in which OH replaces Cl but with a change in the molecular structure. The substitution goes with complete rearrangement—the amine ends up attached to a different carbon atom.

We can easily see why if we look at the mechanism. The reaction starts off looking like a neighbouring group participation of the sort you are now familiar with (the carbon atoms are numbered for identification).

The intermediate is an aziridinium ion (aziridines are three-membered rings containing nitrogen—the nitrogen analogues of epoxides). The hydroxide ion chooses to attack only the less hindered terminal carbon 1, and a rearrangement results—the amine has migrated from carbon 1 to carbon 2.



We should just pause here for a moment to consider why this rearrangement works. We start with a secondary alkyl chloride that contains a very bad leaving group (Et_2N) and a good one (Cl⁻)—but the good one is hard for HO^- to displace because it is at a secondary centre (remember secondary alkyl halides are slow to react by S_N1 or S_N2). But the NEt_2 can participate to make an aziridinium intermediate—now there is a good leaving group ($RNEt_2$ without the negative charge) at the primary as well as the secondary carbon, so HO^- does a fast S_N2 reaction at the primary carbon.

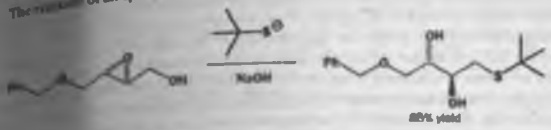


Another way to look at this reaction is to see that the good internal nucleophile Et_2N will compete successfully for the electrophile with the external nucleophile HO^-. Intramolecular reactions are usually faster than bimolecular reactions.

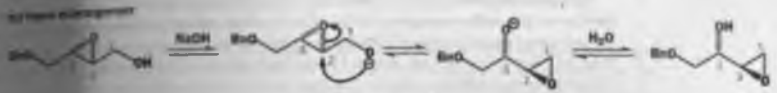
● **Intramolecular reactions, including participation, that give three-, five-, or six-membered rings are usually faster than intermolecular reactions.**

The Payne rearrangement

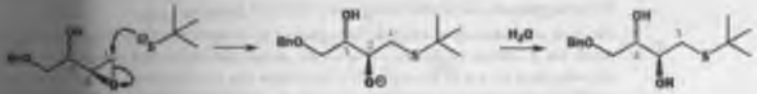
The reaction of an epoxy alcohol in base does not always give the expected product.



The thiolate nucleophile has not opened the epoxide directly, but instead *appears* to have displaced HO^-—a very bad leaving group. Almost no nucleophile will displace OH^-, so we need an alternative explanation. This comes in the form of another rearrangement, this time involving oxygen, but otherwise rather similar to the ones you have just met. Again, our epoxide, though reactive as an electrophile, suffers from being secondary at both electrophilic centres. *t*-BuS^- is a bulky nucleophile, so direct attack on the epoxide is slow. Instead, under the basic conditions of the reaction, the neighbouring alkoxide group attacks intramolecularly to make a new, rearranged epoxy alcohol. This rearrangement is called the **Payne rearrangement**.

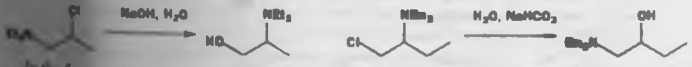


Now we do have a reactive, primary electrophilic site, which undergoes an S_N2 reaction with the *t*-BuS^- under the conditions of the rearrangement. Notice how the black OH, which started on the carbon labelled 1, has ended up on carbon 2.

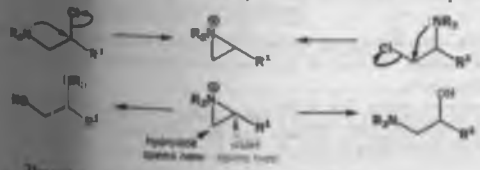


The direction of rearrangement can depend on the nucleophile

Compare these reactions: you saw the first on p. 000 but the second is new.



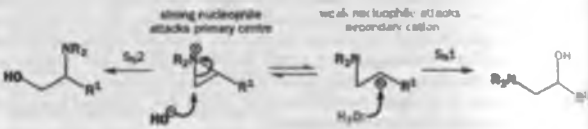
In the first reaction, the amine migrates from the primary to the secondary position; in the other it migrates from secondary to primary. Both go through very similar aziridinium intermediates, so the difference must be due to the regioselectivity with which this aziridinium opens in each case.



The only important difference is the nucleophile used in the reaction. Hydroxide opens the aziridinium at the less hindered end; water opens the aziridinium ion at the more hindered (more substituted) end. Why?

When a group migrates from a primary to a secondary carbon, we say the rearrangement has a **primary migration origin** and a **secondary migration terminus**. The migrating group moves from the migration origin to the migration terminus.

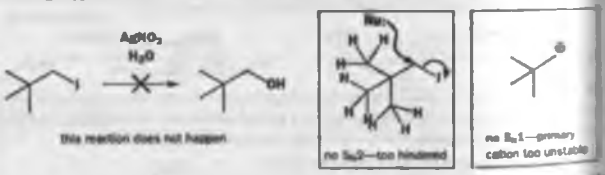
We can think of the aziridinium ion as a compound containing two alternative leaving groups, one from a primary centre and one from a secondary one. Primary centres can take part in S_N2 reactions, but cannot undergo S_N1. Secondary centres can undergo either S_N1 or S_N2 reactions, but in general, do neither very well. Now, the rate of an S_N2 reaction depends on the nucleophile: a good nucleophile (like HO^-) can do fast S_N2 reactions, while a bad one (like H_2O) cannot. The fastest reaction HO^- can do then is S_N2 at the primary centre (remember: you see only the product that goes by the fastest mechanism). Water, on the other hand, takes part only reluctantly in substitution reactions—but this does not matter if they are S_N1 reactions because their rates are independent of nucleophile. H_2O waits until the leaving group has left of its own accord, to grow a cation which rapidly grabs *any* nucleophile—water will do just as well as HO^-. This can happen only at a secondary centre because the primary cation is too unstable to form.



All the rearrangements you have met so far occurred during substitution reactions. All [illegible] because reaction *with* rearrangement is faster than reaction *without* rearrangement—in other words, rearrangement occurs because of a kinetic preference for the rearrangement pathway. You could call these reactions as 'special case' examples of neighbouring group participation—in both participation and rearrangement, the neighbouring group speeds up the reaction, but in rearrangement reactions the neighbouring group gets rather more than it bargained for, and ends up elsewhere in the molecule. Both proceed through a cyclic transition state or intermediate, and it is simply the way in which that transition state or intermediate collapses that determines whether rearrangement occurs.

Rearrangement can involve migration of alkyl groups

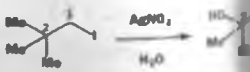
You have seen reactions in which the lone pairs of N, O, and S atoms participate, and reactions in which the π orbitals of alkenes and aromatic groups participate, and participation can lead to rearrangement for any of these groups. Alkyl groups too may rearrange. This example is a nucleophilic substitution under conditions (Ag^+, H_2O) designed to encourage S_N1 reactions (excellent leaving group, poor nucleophile). First of all, this is what does not happen (and indeed without Ag^+ *nothing happens at all*).



▶ The *t*-butylmethyl group is also called 'neopentyl'.

Compounds like this, with a *t*-butyl group next to the electrophilic centre, are notorious for [illegible] undergo substitution reactions. They can't do S_N2, they are too hindered; they can't do S_N1, the cation you would get is primary.

In fact, a rearrangement occurs. One of the methyl groups moves ('migrates') from carbon 2 to carbon 1, the new OH group taking its place at carbon 2.



How has this happened? Well, firstly, our principle (p. 000) tells us that it has happened because S_N1 and S_N2 are both so slow that this new rearrangement mechanism is faster than either. Adding Ag^+ makes I^- desperate to leave, but unassisted this would mean the formation of a primary

carbocation. The molecule does the only thing it can to stop this happening, and uses the electrons in an adjacent C–C bond to assist the departure of I^-.

Having participated, the methyl group continues to migrate to carbon 1 because by doing so it allows the formation of a stable tertiary carbocation, which then captures water in a step reminiscent of the second half of an S_N1 reaction.

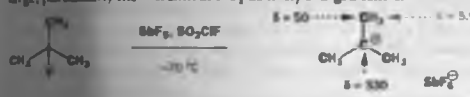
In the migration step we used a slightly unusually curved curly arrow to represent the movement of a group (Me) along a bond taking its bonding electrons with it. We shall use this type of arrow when a group migrates from one atom to another during a rearrangement.

Often, you will see this rearrangement represented in a different way. Both are correct, but we feel that the first is more intuitively descriptive.

▶ Some of the cyclic species you have seen so far (three-membered rings, epoxides) are intermediates: this cyclic species is probably only a transition state.

Carbocations readily rearrange

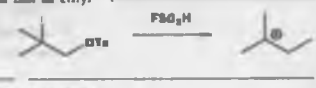
In Chapter 17 we showed you that it is possible to run the NMR spectra of carbocations by using a polar but non-nucleophilic solvent such as liquid SO_2 or SOClF. Treating an alkyl halide RX with the powerful Lewis acid SbF_5 under these conditions gives a solution of carbocation: the carbocation reacts neither with solvent nor the SbF_5X^- counterion because neither is nucleophilic. We know, for example, that the chemical shifts in both the ^{13}C and ^1H NMR spectra of the *t*-butyl cation are very large, particularly the ^{13}C shift at the positively charged centre.

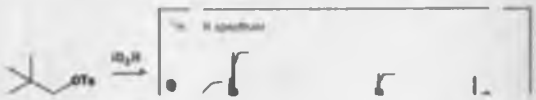


NMR can be used to follow the course of rearrangement reactions involving carbocations too. We can illustrate this with an experiment that tries to make the neopentyl cation by the substitution reaction you have just seen. This time the starting material and solvent are slightly different, but the outcome is nonetheless most revealing. Dissolving neopentyl tosylate in fluorosulfonic acid (a strong, non-nucleophilic acid) at −77 °C gives a 77% yield of a cation whose spectrum is shown below. Assigning the peaks is not hard once you know that the same spectrum is obtained when 2,2-dimethyl-2-butanol is dissolved in fluorosulfonic acid with SbF_5 added.

Clearly, both spectra are of the tertiary 2-methylbutyl cation and the neopentyl cation never saw the light of day. The reaction is the same rearrangement that you saw in the substitution reaction of neopentyl iodide, but here the rate of rearrangement can be measured and it is extremely fast. Neopentyl tosylate reacts to form a cation under these conditions about 10^4 times as fast as ethyl tosylate, even though both tosylates are primary. This massive rate difference shows that if migration of an alkyl group can allow rearrangement to a more stable carbocation, it will happen, and happen rapidly.

▶ In fact, all seven possible isomers of pentyl alcohol ($C_5H_{11}OH$) give this same spectrum under these conditions at temperatures greater than −30 °C.





▶ The distinction here is quite subtle and need not detain us long. We know that a secondary cation is formed in the case because we can see it by NMR; it subsequently rearranges to a tertiary cation. As we can never see primary cations, we don't know that they are ever formed, and the most reasonable explanation for rearrangements of the type you saw on p. 000 is that migration of the alkyl group begins before the leaving group is fully gone. This has been proven in a few cases, but we will from now on not distinguish between the two alternatives.

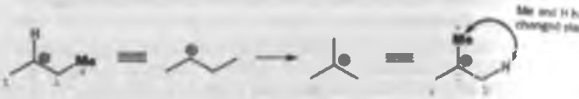
Primary cations can never be observed by NMR—they are too unstable. But secondary cations can, provided the temperature is kept low enough. *sec*-Butyl chloride in SO_2ClF at −78 °C gives a stable, observable cation. But, as the cation is warmed up, it rearranges to the *t*-butyl cation. So this rearrangement truly is a carbocation rearrangement: the starting material is an observable carbocation, and so is the product, and we should just look at the mechanism in a little more detail.

unstable secondary cation → methyl migrates to give → stable tertiary cation

With rearrangements like this it is best to number the C atoms so you can see clearly what moves where. If we do this, we see that the methyl group we have labelled 4 and the H on C3 have changed places. (Note that C3 starts off as a CH_2 group and ends up as CH_3.)

● Top tip for rearrangements

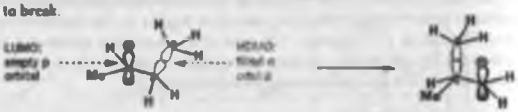
Number the carbon atoms in starting material and product before you try to work out the mechanism.



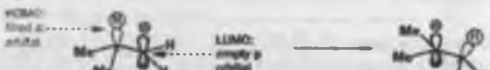
▶ You will see why Me has to migrate first if you try drawing the mechanism out with H migrating first instead.

Using the sort of arrows we introduced on p. 000, we can draw a mechanism for this in which first the Me migrates, and then the hydride. We say **hydride** migration rather than *hydrogen* (or *proton*) because the H atom migrates *with* its pair of electrons.

As these rearrangements are a new type of reaction, we should just spend a moment looking at the molecular orbitals that are involved. For the first step, migration of the methyl group, the LUMO must clearly be the empty p orbital of the cation, and the HOMO is the C–C σ bond, which is about to break.



The methyl group migrates smoothly from one orbital to another—there are bonding interactions all the way. The next step, migration of H, is just the same—except that the HOMO is now a C–H σ bond. The methyl migration is unfavourable as it transforms a secondary cation into an unstable primary cation but the hydride migration puts that right as it gives a stable tertiary cation. The whole reaction is under thermodynamic control.



Wagner–Meerwein rearrangements

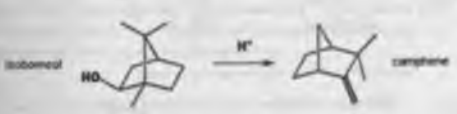
Carbocation rearrangements involving migration of H or alkyl groups don't just happen in NMR machines. They happen during normal reactions too. For example, acid-catalysed dehydration of

natural product camphenilol gives the alkene santene (a key component of the fragrance of sandalwood oil) in a reaction involving migration of a methyl group.

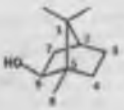
The mechanism shows why the rearrangement happens: the first-formed cation cannot eliminate H^+ in an E1 reaction because loss of the only available proton would give a very strained alkene (make a model and see!).

However, migration of a methyl group both stabilizes the cation—it becomes tertiary instead of secondary—and allows E1 elimination of H^+ to take place to give a stable alkene.

The migration of an alkyl group to a cationic centre is known as a **Wagner–Meerwein rearrangement** or **Wagner–Meerwein shift**, and this migration is, of course, a synthetic manifestation of the rearrangement we have just been looking at in NMR spectra. Wagner–Meerwein shifts have been studied extensively in the class of natural products to which both of these natural products belong—terpenes—and we will come back to them in Chapter 51 (natural products). For the moment, though, we will just illustrate this type of reaction with one more example—another acid-catalysed dehydration, of isoborneol to give camphene.



This one seems much more complicated—but, in fact, only one alkyl migration is involved. To see what has happened, remember the 'top tip'—number the carbons. You can number the starting material any way you choose—we've started with the gem-dimethyl group because it will be easy to spot in the product. The numbers just follow round the ring, with C8 being the methyl group attached to C5.



Now for the hard bit—we need to work out which carbon in the starting material becomes which carbon in the product. The best thing is just have a go—mistakes will soon become obvious, and you can always try again.

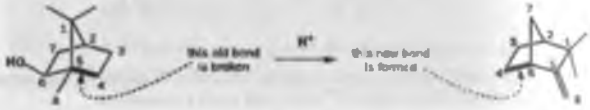
- Use the substituents to help you—some will have changed, but most will be the same or similar—for example, C1 is still easy to spot as the carbon carrying the gem-dimethyl group.

- Use connectivity to help you—again, a C–C bond or two may have broken or formed, but most of the C–C bonds in the starting material will be there in the product. C1 and C2 will probably still be next door to one another—C2 was a bridgehead carbon in the starting material, and there is a bridgehead C attached to C1 in the product; assume that's C2.

- C3 and C4 were unsubstituted carbons in the starting material, and are identifiable in the product too. The other easily spotted atom is C7—an unsubstituted C attached to C2

- C5, C6, and C8 are harder. We can assume that C8 is the $=CH_2$ carbon—it was a methyl group but perhaps has become involved in an elimination. C5 was attached to C1, C4, C6, and C8: one of the remaining carbons is attached to C1 and C8, so that seems more likely to be C5, which leaves C6 as the bridgehead, attached as before to C7 and C5

Now we have the whole picture and we can assess what has happened in the reaction—which bonds have been broken and which new bonds have been formed.



Numbering the atoms this way identifies the likely point of rearrangement—the only bond that is broken is between C4 and C5. Instead we have a new one between C5 and C6: C4 appears to have migrated from C5 to C6. Now for the mechanism. The first step will, of course, be loss of water to generate a secondary cation at C6. The cation is next to a quaternary centre, and migration of any of the three bonds could generate a more stable tertiary carbocation. But we know that the new bond in the product is between C4 and C6, so let's migrate carbon 4. Manipulating the diagrams a bit turns out to be a structure remarkably similar to our product, and all we need to do is lose a proton from C8.

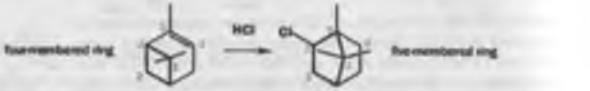
▶ If you are observant, you may ask why the alkyl group migrated in this example and not the methyl group, or the other alkyl group—all three possibilities give similar tertiary carbocations. The reason involves the alignment of the orbitals involved, which we will discuss at the end of the chapter.

Although migration of an alkyl group that forms part of a ring leads to much more significant changes in structure than simple migration of a methyl group, the reason why it happens is still just the same.

Alkyl migrations occur in order to make a carbocation more stable.

Ring expansion means rearrangement

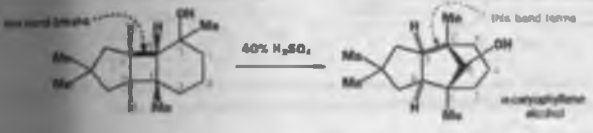
'More stable' usually means 'more substituted', but cations can also be made *more stable* if they become *less strained*. So, for example, four-membered rings adjacent to cations readily rearrange to five-membered rings in order to relieve ring strain.



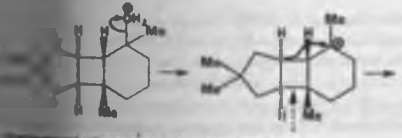
This time the cation is formed by protonation of an alkene, not departure of a leaving group, but working a mechanism should now be a straightforward matter to you.

Though the rearrangement step transforms a stable tertiary cation into a less stable secondary cation, relief of strain in expansion from a four- to a five-membered ring makes the alkyl migration favourable. In 1964, E.J. Corey published a synthesis of the natural product α-caryophyllene alcohol that made use of a similar ring expansion. Notice the photochemical [2+2] cycloaddition (Chapter 35) in the synthesis of the starting material.

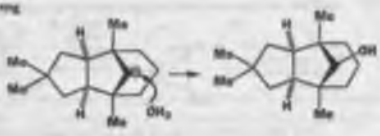
Rearrangement of this tertiary alcohol in acid gives the target natural product. The four-membered ring has certainly disappeared but it may not be obvious at first what has taken its place.



As usual, numbering the atoms makes clear what has happened: carbon 7 has migrated from carbon 6 to carbon 5. Loss of water gives a tertiary carbocation that undergoes rearrangement to a secondary carbocation with expansion of a four- to a five-membered ring.



Rearrangement relieves strain in the 4-membered ring.

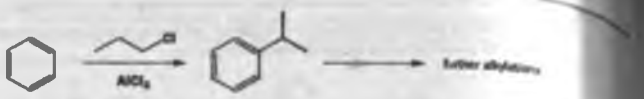


Carbocation rearrangements: blessing or curse?

Well, that depends. You have now seen a few useful carbocation rearrangements that give single products in high yield. But you have also met at least one reaction that *cannot* be done because of carbocation rearrangements: Friedel–Crafts alkylation using primary alkyl halides.

▶

Most compounds are kinetically stable precisely because spontaneous rearrangements to more thermodynamically stable compounds do not occur—the kinetic barrier to rearrangement is too high. You did meet a few exceptions in the last chapter—cyclopentadienes, for example, undergo rapid [1,5]-sigmatropic shifts of hydrogen, and are unstable with respect to the position of the double bonds. Carbocations are probably the most important class of species that *habitually* undergo rearrangement reactions, even at low temperature.



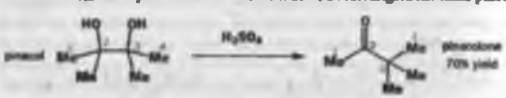
The Friedel–Crafts alkylation illustrates the problems of trying to use carbocation rearrangements to make single products in high yield. We can give three guidelines to spotting this kind of reaction.

1. The rearrangement must be fast so that other reactions do not compete
2. The product cation must be sufficiently more stable than the starting one so that the rearrangement happens in high yield
3. Subsequent trapping of the product cation must be reliable: cations are high-energy intermediates, and are therefore unselective about how they react

A reaction is no good if the cation reacts in more than one way—it may react with a nucleophile, eliminate, or undergo further rearrangement—but it must do only one of these! For the rest of this chapter, we will address only reactions that, unlike this Friedel–Crafts reaction, follow these guidelines. The reactions we will talk about all happen in good yield.

The pinacol rearrangement

When the 1,2-diol 'pinacol' is treated with acid, a rearrangement takes place.

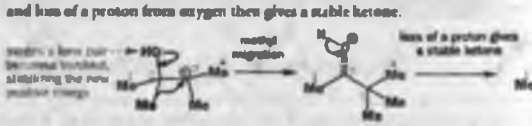


Pinacol, the trivial name for the starting material, which is made from acetone by a reaction you will meet in Chapter 39, gives its name to this class of rearrangements, and to the product, 'pinacolone'.

Wherever you see a rearrangement, you should now think 'carbocation'. Here, protonation of one of the hydroxyl groups allows it to leave as water, giving the carbocation.

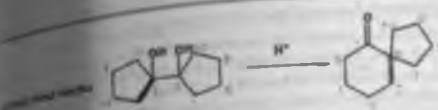
You now know that carbocations rearrange by alkyl shifts to get as stable as they can be—but this carbocation is already tertiary, and there is no ring strain, so why should it rearrange? Well, here we have another source of electrons to stabilize the carbocation: lone pairs on an oxygen atom. We pointed out early in the chapter that oxygen is very good at stabilizing a positive charge on an adjacent atom, and somewhat less good at stabilizing a positive charge two atoms away. By rearranging the first-formed carbocation gets the positive charge into a position where the oxygen can stabilize it, and loss of a proton from oxygen then gives a stable ketone.

Unlike sulfur, which stabilizes a charge 2 atoms away better than it stabilizes a charge on an adjacent atom.

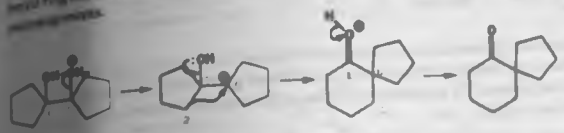


You can view the pinacol as a rearrangement with a 'push' and a 'pull'. The carbocation left by the departure of water 'pulls' the migrating group across at the same time as the oxygen's lone pair 'pushes' it. A particularly valuable type of pinacol rearrangement forms spirocyclic ring systems. You may find this one harder to follow, though the mechanism is identical with that of the last example. Our 'top tip' of numbering the atoms should help you to see what has happened: atom 2 has migrated from atom 1 to atom 6.

Spirocycles are pairs of rings joined at a single carbon atom (Chapter 33).



When drawing the mechanism it doesn't matter which hydroxyl group you protonate: or which adjacent C–C bond migrates—they are all the same. One five-membered ring expands to a six-membered ring but the reason this reaction happens is the formation of a carbonyl group, as in all pinacol rearrangements.

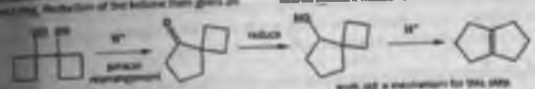


Of course, it doesn't matter how you number the atoms, but the numbering must be consistent. Usually, your initial impression of a greatly changed molecule will come down to just one or two atoms changing their substitution pattern, and numbering will help you to work out which ones they are.

The pinacol reactions in synthesis

A key synthesis of the tricyclic alkene on the right starts with a pinacol reaction.

The first step is straightforward—just like the one you worked out. The 'pinacol' dimer from cyclobutanone rearranges with the expansion of one of the rings to give a cyclopentanone fused cleanly to the remaining four-membered ring. Reduction of the ketone then gives an alcohol that rearranges to the alkene in acid. Try working out a mechanism for this transformation—start by protonating of the alcohol and allowing water to leave to give a cation. You might also like to think about why the rearrangement happens—for a clue go back to p. 000.



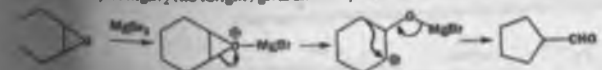
work out a mechanism for this step

Epoxides rearrange with Lewis acids in a pinacol fashion

The intermediate cation in a pinacol rearrangement can equally well be formed from an epoxide, and treating epoxides with acid, including Lewis acids such as $MgBr_2$, promotes the same type of reaction.

Rearrangement of epoxides with magnesium salts means that opening epoxides with Grignard reagents can give surprising results.

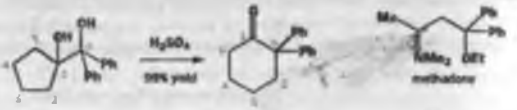
The alkyllithium reaction is quite straightforward as long as the alkyllithium is free of lithium salts. A clue to what has happened with the Grignard reagents comes from the fact that treating this epoxide with just $MgBr_2$ (no RMgBr) gives an aldehyde.



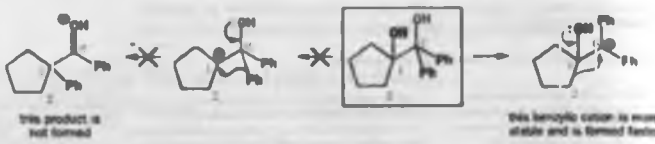
With a Grignard reagent, rearrangement occurs faster than addition to the epoxide, and then the Grignard reagent adds to the aldehyde.

Some pinacol rearrangements have a choice of migrating group

With these symmetrical diols and epoxides, it does not matter which hydroxyl group is protonated and leaves, nor which end the epoxide opens, nor which group migrates. When an unsymmetrical diol or epoxide rearranges, it is important which way the reaction goes. Usually, the reaction leaves behind the more stable cation. So, for example, this unsymmetrical diol gives the ring-expanded ketone, a starting material for the synthesis of analogues of the drug methadone.



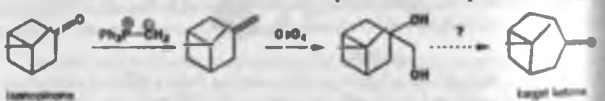
This product is formed because the green OH group leaves more readily than the black hydroxyl, the carbocation stabilized by two phenyl groups forms more readily than the carbocation stabilized by two alkyl groups. The migration step follows without selectivity as both alkyl groups on the black alcohol are the same.



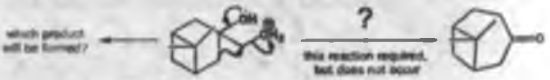
Most unsymmetrical diols or epoxides give mixtures of products upon rearrangement. The problem is that there is a choice of two leaving groups and two alternative rearrangement directions, and only for certain substitution patterns is the choice clear-cut.

Semipinacol rearrangements are pinacol reactions with no choice about which way to go

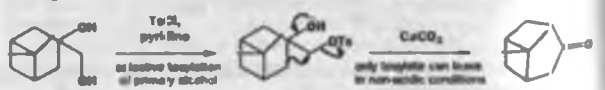
In 1971, French chemists needed this seven-membered cyclic ketone. A reasonable starting material to use is this diol, because it can be made in two steps from the natural product isonopinone.



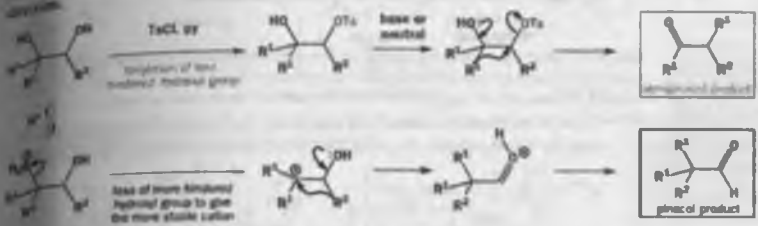
The reaction they needed for the last stage is a pinacol rearrangement—the *primary* hydroxyl group needs persuading to leave as the ring expands. The problem is, of course, that the tertiary hydroxyl group is much more likely to leave since it leaves behind a more stable carbocation.



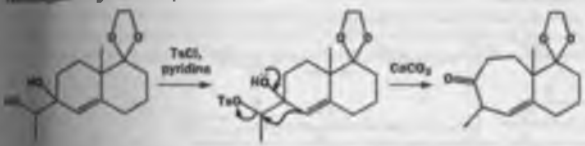
The solution to this problem is to force the primary hydroxyl group to be the leaving group by making it into a tosylate. The primary hydroxyl group reacts more rapidly with TsCl than the tertiary one because it is less hindered. A weak base is now all that is needed to make the compound rearrange in what is known as a semipinacol rearrangement.



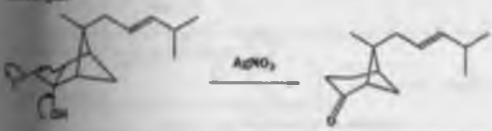
Semipinacol rearrangements are rearrangements in which a hydroxyl group provides the electrons to 'push' the migrating group across, but the 'pull' comes from the departure of leaving groups other than water—tosylate in this example, but typically also halide or nitrogen (N_2). Since tosylation occurs at the less hindered hydroxyl group of a diol, not only can semipinacol rearrangements be more regioselective than pinacol rearrangements, but their regioselectivity may be in the opposite direction.



Corey exploited this in a synthesis of the natural product longifolene. He needed to persuade an easily made 6,6-fused ring system to undergo rearrangement to a ring-expanded ketone. Again, a normal acid-catalysed pinacol rearrangement is no good—the tertiary, allylic hydroxyl group is much more likely to ionize, and the acid-sensitive protecting group would be hydrolysed too. Tosylation of the secondary alcohol in the presence of the tertiary is possible, and semipinacol rearrangement gives the required ketone.



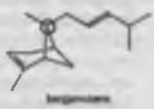
The leaving group need not be tosylate: in the following example, part of a synthesis of bergamotene (a component of valerian root oil and the aroma of Earl Grey tea), a 2-iodo alcohol rearranges.



▶ Treating 2-halo alcohols with base is, of course, a good way to make epoxides. Using $AgNO_3$ to remove iodide is a leaving ability without increasing the nucleophilicity of the hydroxyl group favours rearrangement at the expense of epoxide formation. There would certainly be a danger of epoxide formation in strong base.

The structure of bergamotene

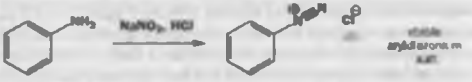
The structure of bergamotene was, for some years during the 1980s, a matter of debate. The difficult question was the configuration of the chiral centre singled in black. With modern spectroscopic techniques, we can now solve this type of problem simply, but the only solution then was to synthesize the two isomers and compare them with the natural material. There is more about bergamotene in Chapter 46.



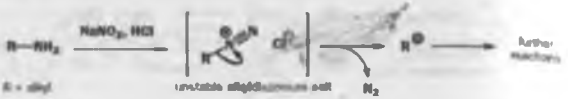
Semipinacol rearrangements of diazonium salts

You saw in Chapter 22 how aromatic amines can be converted to diazonium salts by treatment with nitrous acid (sodium nitrite, $NaNO_2$, and HCl).

▶ It might be an idea to review pp. 000–00 of Chapter 22 to be sure you understand the mechanism of this reaction.

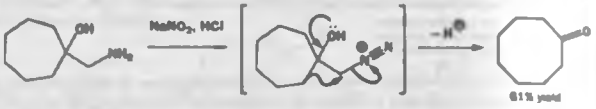


Aryldiazonium salts are stable but alkyldiazonium salts are not: nitrogen gas is the world's best leaving group, and, when it goes, it leaves behind a carbocation.

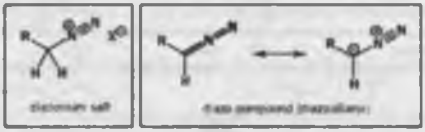


▶ Semipinacol rearrangements of diazonium salts derived from 2-amino alcohols are sometimes called **Tiffeneau–Demjanov rearrangements**.

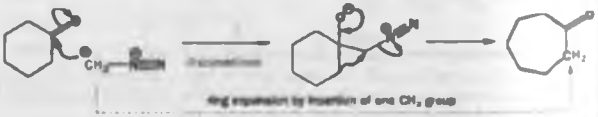
One of the 'further reactions' this carbocation can undergo is rearrangement. If the starting amine is a 2-amino alcohol, the cation can be stabilized by a semipinacol rearrangement.



While alkyldiazonium salts are unstable, their conjugate bases, diazoalkanes, are stable enough to be prepared and are nucleophilic towards carbonyl compounds. Diazoalkanes are neutral compounds having one fewer proton than diazonium salts and are delocalized structures with a central sp nitrogen atom.



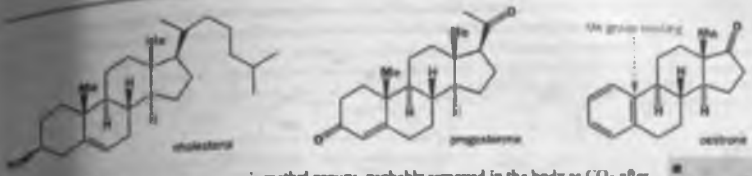
When diazomethane (a compound we will investigate in more detail in Chapter 40) adds to a ketone, the product undergoes a ring expansion by rearrangement of the same type of intermediate.



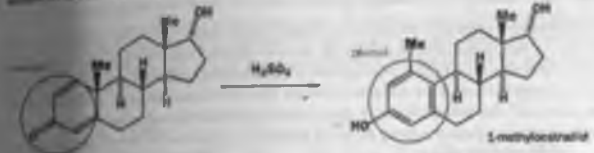
The problem with reactions like this is that both the starting material and product are ketones, so they work cleanly only if the starting material is more reactive than the product. Cyclohexanone is more reactive as an electrophile than either cyclopentanone or cycloheptanone, so it ring expands cleanly to cycloheptanone. But expansion of cyclopentanone to cyclohexanone is messy and gives a mixture of products. We shall come back to diazo compounds in more detail in Chapter 40; diazonium salts will reappear in Chapter 38 where their decomposition will provide the driving force for fragmentation reactions.

The dienone–phenol rearrangement

The female sex hormone oestrone is the metabolic product of another hormone, progesterone, itself made in the body from cholesterol.

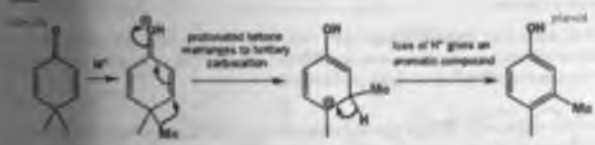


Oestrone lacks one of progesterone's methyl groups, probably removed in the body as CO_2 after oxidation. In 1986, Carl Djerassi, a man whose work led directly to the invention of the contraceptive pill, showed that another derivative of cholesterol could be rearranged to the oestrone analogue 3-methylestradiol—notice how the methyl group has this time migrated to an adjacent carbon atom. At the same time, the dienone has become a phenol.



Carl Djerassi, an Austrian born in Vienna in 1923, worked mainly at CIBA, Syntex in Mexico, and at Stanford. He developed synthesis of human hormones from compounds in plants, was a pioneer of mass spectrometry, and is a colourful campaigner for peace and disarmament.

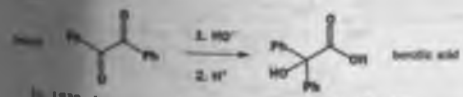
This type of rearrangement is known helpfully as a **dienone–phenol rearrangement**, and we can consider it quite simply as a type of reverse pinacol rearrangement. Pinacol and semipinacol rearrangements are driven by the formation of a carbonyl group. The rearranged cation is stabilized by being next to oxygen, and it can rapidly lose H^+ to give a carbonyl compound. In the key step of a dienone–phenol rearrangement, a protonated carbonyl compound rearranges to a tertiary carbocation.



The reaction is driven from dienone to phenol because the product cation can rapidly undergo elimination of H^+ to become aromatic.

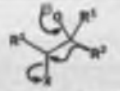
The benzilic acid rearrangement

You have seen rearrangements in which carbonyl groups form at the migration origin: the migrating group in the pinacol and semipinacol rearrangements is 'pushed' by the oxygen's lone pair as it forms the new carbonyl group. You have also seen carbonyl groups being destroyed at the migration terminus: the migrating group in the dienone–phenol rearrangement is 'pulled' towards the protonated carbonyl group. The first rearrangement reaction ever to be described has both of these at once.



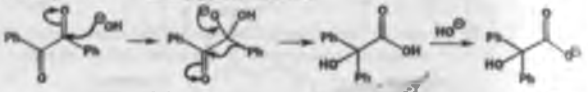
In 1838, Justus von Liebig found that treating 'benzil' (1,2-diphenylethan-1,2-dione) with hydroxide gave, after acid quench, 2-hydroxy-2,2-diphenylacetic acid, which he called 'benzilic acid'.

▶ You may find it helpful to think of the benzilic acid rearrangement as a semipinacol rearrangement, in which we have a breaking C=O π bond instead of a leaving group.



compare the migration step with this semipinacol rearrangement

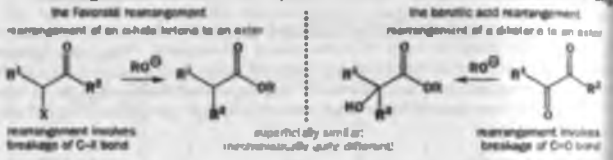
The mechanism of this **benzilic acid rearrangement** starts with attack of hydroxide on one of the carbonyl groups. The tetrahedral intermediate can collapse in a reaction reminiscent of a semipinacol rearrangement.



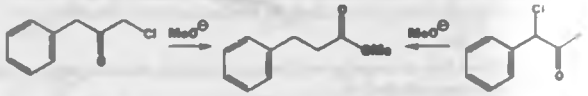
With alkoxides, the benzilic acid rearrangement can lead directly to esters by the same sort of mechanism.

The Favorskii rearrangement

We hope you have appreciated the smooth mechanistic progression so far in this chapter, from Wagner–Meerwein to pinacol and semipinacol through dienone–phenol to benzilic acid. Our aim is to help you gain an overall view of the types of rearrangements that take place (and why) and not to present you with lots of disconnected facts. It is at this point, however, that our mechanistic journey takes a hairpin bend. A surprising one, too, because, when we show you the Favorskii rearrangement, you would be forgiven for wondering what the fuss is about: surely it's rather like a variant of the benzilic acid rearrangement.

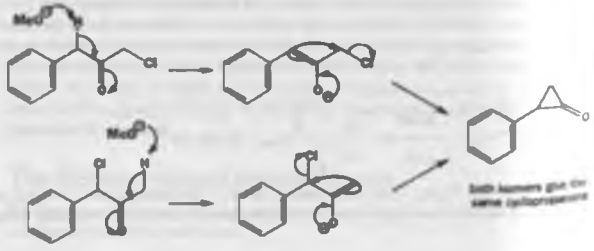


Well, this is what chemists thought until 1944, when some Americans found that two isomeric α-chloro ketones gave exactly the same product on treatment with methoxide. They suggested that both reactions went through the same intermediate.

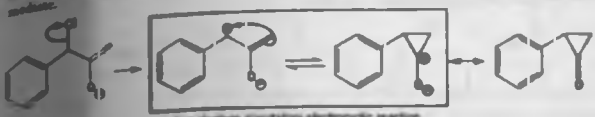


That intermediate is a three-membered cyclic ketone, a cyclopropanone: the alkoxide acts not as a nucleophile (its role in the benzilic acid rearrangement) but as a base, enolizing the ketone. The enolate can alkylate itself intramolecularly in a reaction that looks bizarre but that many chemists think is not unreasonable. The product is the same cyclopropanone in each case.

■ A full discussion of this point requires Bürgi–Dunitz's rules, which appear in Chapter 11.

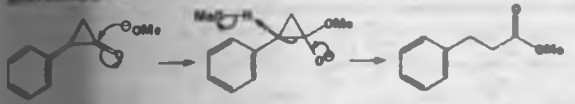


Other chemists prefer a pericyclic description of the ring-closure step. The same enolate simply loses chloride to give an 'oxyallyl cation'—a dipolar species with an oxygen and a delocalized allylic cation. This species can cyclize in a two-electron disrotatory electrocyclic reaction (Chapter 30) to give the same cyclopropanone. We shall return to this discussion in the next chapter but, whatever the mechanism, there is no doubt that a cyclopropanone is an intermediate.

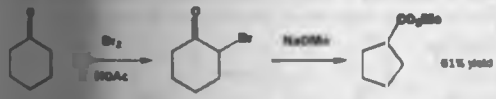


two-electron disrotatory electrocyclic reaction

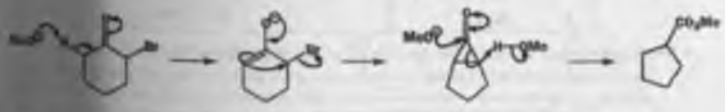
Cyclopropanones are very reactive towards nucleophiles, and the tetrahedral intermediate arising from the attack of methoxide springs open to give the ester product. The more stable carbanion shown, though the carbanion is not actually formed as a free species, there must be considerable negative charge at the carbon atom as the three-membered ring opens. Here the benzyl group is the more leaving group.



Favorskii rearrangement of cyclic 2-bromoketones leads to ring contraction and this has become one of the most fruitful uses of the rearrangement in synthesis. Bromination of cyclohexanone is a simple reaction (Chapter 21) and treatment with methoxide gives the methyl ester of cyclopentane carboxylic acid in good yield.



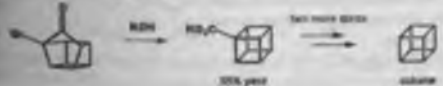
Enolization occurs on the side of the ketone away from the bromine atom and the enolate cyclizes as before but the cyclopropanone intermediate is symmetrical so that the product is the same whichever C–C bond breaks after nucleophilic attack by the methoxide ion.

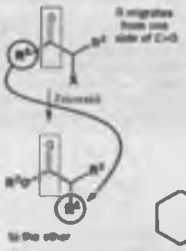


▶ Cyclopropanones and cyclobutanones are very reactive, rather like epoxides, because, while the 60° or 90° angle in the ring is nowhere near the tetrahedral angle (109°), it is nearer 109° than the 120° preferred by the sp^2 C of the C=O group. Conversely, the small ring ketones are resistant to enolization, because that would place two sp^2 carbon atoms in the ring.

Heading

[illegible] two American chemists synthesized for the first time a complicated molecule, cubane. Two of the key steps were Favorskii rearrangements, which allowed the chemists to contract five-membered rings to four-membered rings. Here is one of them. Two more steps decarboxylate the product to give cubane itself.





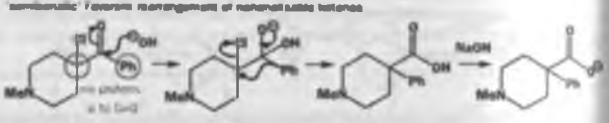
The overall consequence of the Favorskii rearrangement is that an alkyl group is transferred from one side of a carbonyl group to the other.

This means that it can be used to build up heavily branched esters and carbaxylic acids—that are hard to make by alkylation because of the problems of hindered enolates and unreactive ondary alkyl halides. Heavily substituted acids, where CO_2H is attached to a tertiary carbon would be hard to make by any other method. And the Favorskii rearrangement is a key step in synthesis of the powerful painkiller Pethidine.

The Favorskii mechanism will help you understand the Ramberg–Bäcklund reaction in Chapter 46—the two reactions have quite similar mechanisms.

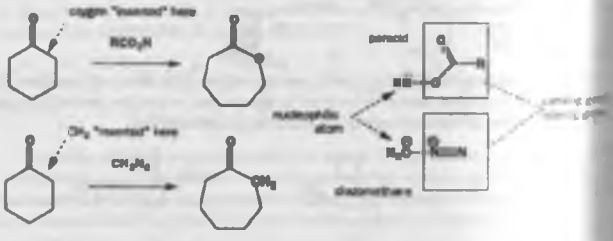
compare the migration step with this benzilic acid rearrangement

Try writing a mechanism for this last reaction and you run into a problem—there are no acidic protons so the ketone cannot be enolized! Yet the Favorskii rearrangement still works. Despite warnings against confusing the mechanisms of the Favorskii and benzilic acid rearrangements, the Favorskii rearrangement may, in fact, follow a benzilic (or 'semibenzilic', by analogy with the semi-pinacol) rearrangement mechanism, *if* there are no acidic hydrogens available.

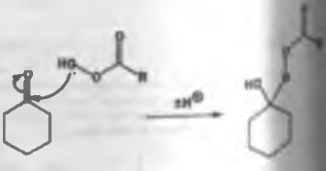


Migration to oxygen: the Baeyer–Villiger reaction

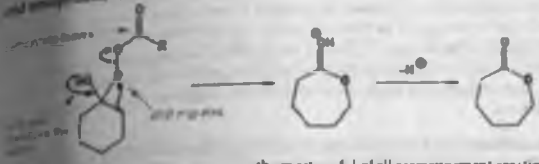
In 1899, the Germans, A. Baeyer and V. Villiger, found that treating a ketone with a peroxyacid (RCO_3H) can produce an ester. An oxygen atom is 'inserted' next to the carbonyl group.



Now, you saw a similar 'insertion' reaction earlier in the chapter, and the mechanism here is not dissimilar. Both peracids and diazomethane contain a nucleophilic centre that carries a good leaving group, and addition of peracid to the carbonyl group gives a structure that should remind you of a semipinacol intermediate with one of the carbon atoms replaced by oxygen.



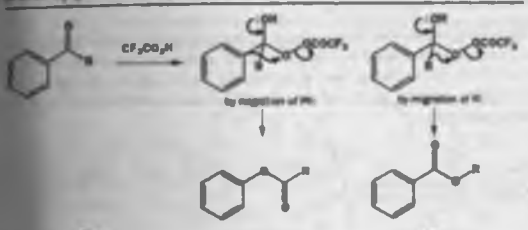
Carboxylates are not such good leaving groups as nitrogen, but the oxygen–oxygen single bond is very weak and [illegible] oxygen cannot bear to carry a positive charge so that, once the peroxide



Baeyer–Villiger reactions are among the most useful of all rearrangement reactions, and the most common reagent is *m*-CPBA (*meta*-chloroperbenzoic acid) because it is commercially available.

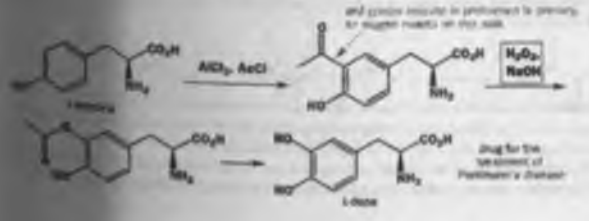
Which group migrates? (I)—the facts

A question we have deliberately avoided up to this point is this: when there is a competition between two migrating groups, *which group migrates*? This question arises in pinacol, semipinacol, and dienone–phenol rearrangements and in Baeyer–Villiger reactions (in the benzilic acid and Favorskii rearrangements, there is no choice) and the awkward fact is that the answer is different in each case! However, let's start with the Baeyer–Villiger reaction, because here the question is always valid except when the ketone being oxidized is symmetrical. Here are some examples, and you can probably begin to draw up guidelines for yourself.



R =	Yield for II (%)	Yield for III (%)
Me	90	0
Et	87	6
iPr	33	63
tBu	2	77

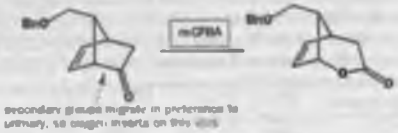
The order, with *t*-alkyl the best at migrating, then *s*-alkyl closely followed by Ph, then Et, then Me, very roughly follows the order in which the groups are able to stabilize a positive charge. Primary groups are much more reluctant to undergo migration than secondary ones or aryl groups, and this makes regioselective Baeyer–Villiger reactions possible.



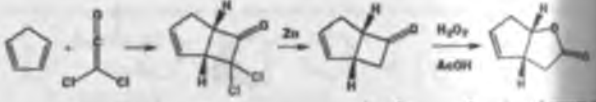
The Baeyer–Villiger reaction has solved a regioselectivity problem here. L-tyrosine, a cheap amino acid, can be converted to the important drug L-dopa provided it can be hydroxylated *ortho* to the OH group. This is where electrophilic substitutions of the phenol take place, but electrophilic substitutions with 'HO$^+$' are not possible. However, after a Friedel–Crafts acylation the acyl group can be converted to hydroxyl by the Baeyer–Villiger reaction and hydrolysis. The Baeyer–Villiger reaction means that $MeCO^+$ can be used as a synthetic equivalent for 'HO$^+$'. Note the unusual use of the less reactive H_2O_2 as oxidizing agent in this reaction. This is possible when the migrating group is an electron-rich aromatic ring. These reactions are sometimes called Dakin reactions.

Unsaturated ketones may epoxidize or undergo Baeyer–Villiger rearrangement

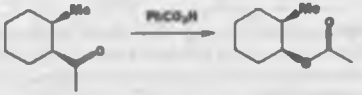
Peracids may epoxidize alkenes faster than they take part in Baeyer–Villiger reactions, so unsaturated ketones are not often good substrates for Baeyer–Villiger reactions. The balance is rather delicate. The two factors that matter are: how *electrophilic* is the ketone and how *nucleophilic* is the alkene? You might like to consider why this reaction *does* work, and why the C=C double bond here is particularly unreactive.



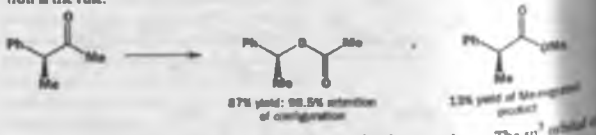
Small-ring ketones can relieve ring strain by undergoing Baeyer–Villiger reactions—this with butanone (an intermediate in a synthesis of the perfumery compound *cis*-jasmone) is made by ketene [2+2] cycloaddition, and is so reactive that it needs only H_2O_2 to rearrange. Unlike CF_3CO_3H or *m*-CPBA, H_2O_2 will not epoxidize double bonds (unless they are electron-deficient—see Chapter 23).



One point to note about both of the last two reactions is that the insertion of oxygen gives rise to retention of stereochemistry. You may think this is unsurprising in a cyclic system like this one, but indeed, the first of the two cannot possibly go with inversion. However, this is a general feature of Baeyer–Villiger reactions, even when inversion would give a more stable product.



Even when you might imagine that racemization would occur, as in this benzylic ketone, retention is the rule.



By looking at the orbitals involved, you can see why this must be so. The sp^3 orbital of the migrating carbon just slips from one orbital to the next with the minimum amount of

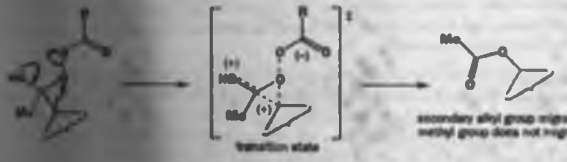
reorganization. The large lobe of the sp^3 orbital is used as the new bond forms to the same face of the migrating group as the old one, and stereochemistry is retained.

The orbital interactions in all 1,2-migrations are similar, and the migrating group retains its stereochemistry in these too. In the more familiar S_N2 reaction, inversion occurs because the anti-bonding σ* orbital rather than the bonding σ orbital is used. In the S_N2 reaction, carbon undergoes nucleophilic attack with *inversion*; in rearrangements the migrating carbon atom undergoes electrophilic attack with *retention* of configuration.

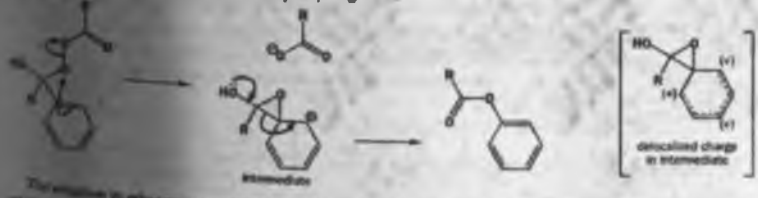
● In 1,2-migrations, the migrating group retains its stereochemistry.

Which group migrates? (II)—the reasons

Why does the more substituted group migrate in the Baeyer–Villiger reaction? The transition state has a positive charge spread out over the molecule as the carboxylate leaves as an anion. If the migrating group can take some responsibility for the positive charge the transition state will be more stable. The more stable the charge, the faster the rearrangement.

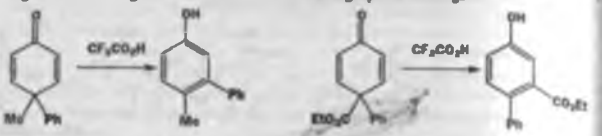


When a benzene ring migrates, π participation is involved as the benzene ring acts as a nucleophile and the positive charge can be spread out even further. Note that the Ph is stabilizing the charge here in the way that it stabilizes the intermediate in an electrophilic aromatic substitution reaction—like a pentadienyl cation rather than like a benzylic cation. What was a transition state in alkyl migration becomes an intermediate in phenyl migration.

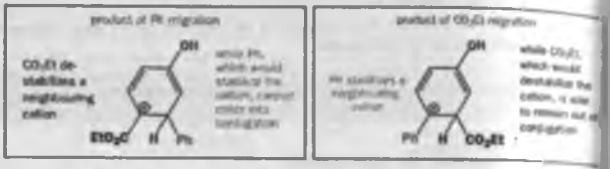


The situation in other rearrangements is much more complicated—and indeed more complicated than most textbooks would have you believe. We shall look just briefly at the dienone–phenol rearrangement again, this time considering reactions in which there is a competition between two different migrating groups. As in the Baeyer–Villiger reaction, the transition state is cationic, so you would expect cation-stabilizing groups to migrate more readily. This appears to be true for Ph versus

Me, but is most definitely not true for Ph versus CO_2Et. The cation-destabilizing group CO_2Et migrates even though Ph is much better at stabilizing a positive charge!

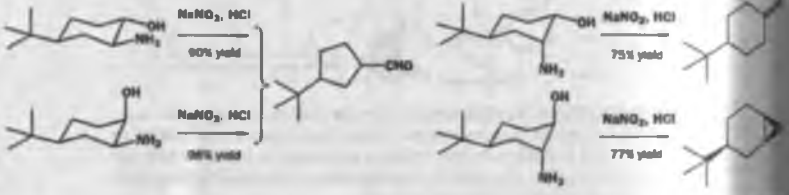


The reason is that CO_2Et is so cation-*destabilizing* that it prefers to migrate rather than be left behind next door to a cation. In this case, then, it is the cation-stabilizing ability of the group that *does not* migrate that matters most.

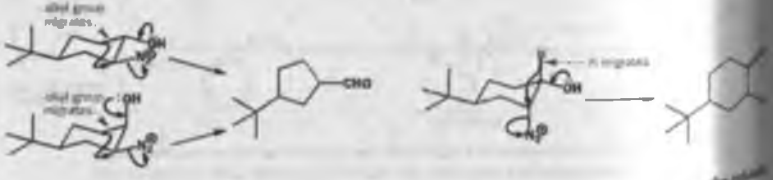


Which group migrates? (III)—stereochemistry matters too

Selectivity in rearrangement reactions is affected by the electronic nature of *both* the group that migrates *and* the group that is left behind. But there is more! *Stereochemistry* is important too. The outcome of diazotization and semipinacol rearrangement (Tiffeneau–Demjanov rearrangement) of this amino-alcohol depends entirely on the diastereoisomer you start with. There are four diastereoisomers, and we have drawn each one in the only conformation it can reasonably adopt with the *t*-butyl group equatorial.



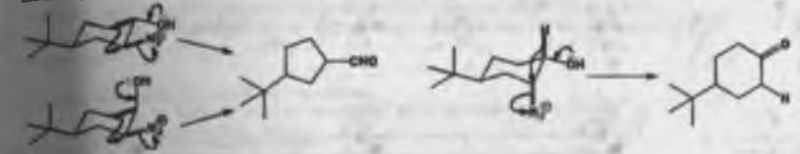
In all of these reactions, the OH group provides the electronic 'push'. In the first two reactions the ring contracts by an alkyl migration from the secondary alcohol, while in the third it is H that migrates from the same position.



The only difference between the compounds is stereochemistry and, if we look at the molecules involved in the reactions, we can see why this is so important. As the N_2 leaving group departs, electrons in the bond to the migrating group have to flow into the C–N σ^* orbital—we discuss this in

p. 660. But what we didn't talk about then was the fact that best overlap between these two orbitals (σ and σ*) occurs if they are anti-periplanar to one another—just as in an E2 elimination reaction.

For the first two compounds, with the $-N_2^+$ group equatorial, the group best placed to migrate is the alkyl group that forms the ring; for the third reaction, there is a hydrogen atom anti-periplanar to the leaving group, so H migrates.

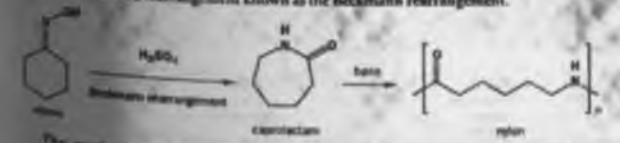


The fourth reaction has, rather than a group that might migrate, the hydroxyl group ideally placed to displace N_2 and form an epoxide—another example of participation.

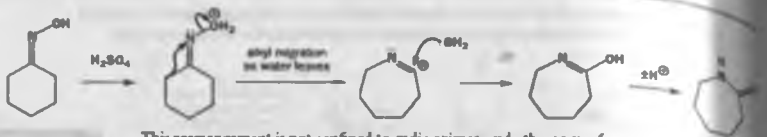
The requirement for the migrating group to be anti-periplanar to the leaving group is quite general in rearrangement reactions. The reason we haven't noticed its effect before is that most of the compounds we have considered have not been conformationally constrained in the way that these are. Free rotation means that the right geometry for rearrangement is always obtainable—stereochemistry is not a factor in the Baeyer–Villiger reaction, for example. We will come back to some more aspects of stereochemical control in the next chapter, on fragmentation reactions. Before then, we will consider one last rearrangement reaction, in which stereochemistry again plays an important controlling role.

The Beckmann rearrangement

The commercial manufacture of nylon relies upon the alkaline polymerization of a cyclic amide known trivially as caprolactam. Caprolactam can be produced by the action of sulfuric acid on the oxime of cyclohexanone in a rearrangement known as the Beckmann rearrangement.



The mechanism of the Beckmann rearrangement follows the same pattern as a pinacol or Baeyer–Villiger reaction—acid converts the oxime OH into a leaving group, and an alkyl group migrates on to nitrogen as water departs. The product cation is then trapped by water to give an amide.

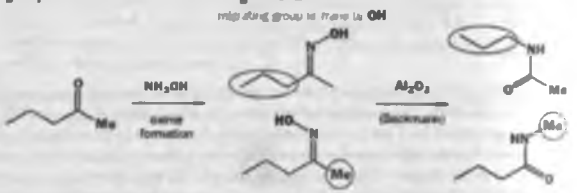


▶ A linear system like this was impossible in the seven-membered ring of the last example.

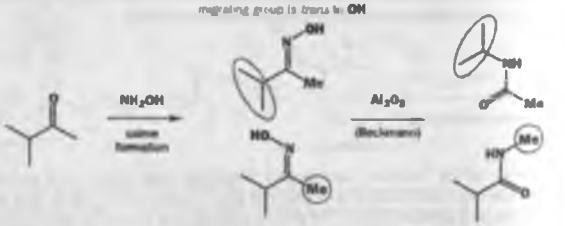
This rearrangement is not confined to cyclic oximes, and other ways of converting OH to a leaving group also work, such as PCl_5, $SOCl_2$, and other acyl or sulfonyl chlorides. In an acyclic Beckmann rearrangement, the product cation is better represented as the nitrilium ion. When we write the mechanism we can then involve the nitrogen's lone pair to 'push' the migrating group back on to the

Which group migrates in the Beckmann rearrangement?

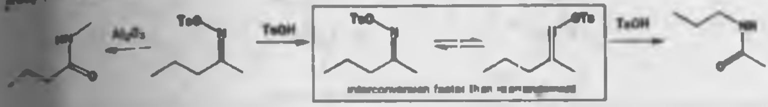
In the Beckmann rearrangement of unsymmetrical ketones there are two groups that could migrate. There are also two possible geometrical isomers of an unsymmetrical oxime: C=N double bonds can exhibit *cis*/*trans* isomerism just as C=C double bonds can. When mixtures of geometrical isomers of oximes are rearranged, mixtures of products result, but the ratio of products mirrors exactly the ratio of geometrical isomers in the starting materials—the group that has migrated is in each case the group *trans* to the OH in the starting material.



We have already touched on the idea that, for migration to occur, a migrating group has to be able to interact with the σ^* of the bond to the leaving group, and this is the reason for the specificity here. In the example a couple of pages back the stereospecificity of the reaction was due to the starting material being constrained in a conformationally rigid ring. Here it is the C=N double bond that provides the constraint. If one of the alkyl chains is branched, more of the oxime with the OH group *anti* to that chain will be formed and correspondingly more of the branched group will migrate.



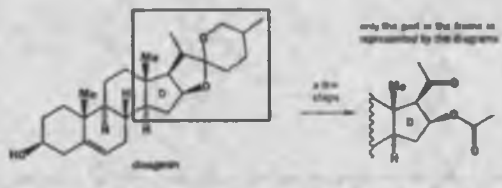
Conditions that allow those double isomers to interconvert can allow either group to migrate—which does so will then be decided, as in the Baeyer–Villiger reaction, by electronic factors. Most protic acids allow the oxime isomers to equilibrate—so, for example, this tosylated oxime rearranges with full stereospecificity in Al_2O_3 (the *anti* methyl group migrates), but with TsOH, equilibration of the oxime geometrical isomers means that either group could migrate—in the event, the propyl group (which is more able to support a positive charge) migrates faster.



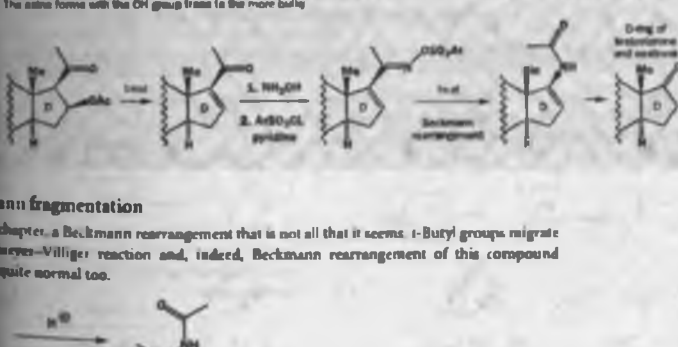
Notice that the effect of the Beckmann rearrangement is to insert a *nitrogen* atom next to the carbonyl group. It forms a useful trio with the Baeyer–Villiger *oxygen* insertion and the diazoalkane carbon insertion.

The diosgenin story: steroids from vegetables

Many of the human steroid hormones are available by 'semisynthesis'—in other words synthesis starting from a natural product similar in structure to the target molecule. One very important starting material for semisynthesis routes to these hormones is diosgenin, a plant steroid which makes up 1% of the dry mass of the roots of Mexican yams. Most of the chemical manipulation necessary to turn diosgenin into human steroids concerns the top right five-membered ring (the 'D' ring). A few steps convert the acetal group of the natural steroid into a simpler methyl ketone, present in cortisone and progesterone.



But for hormones such as oestrone and testosterone two carbon atoms need removing to make a cyclopentanone. This is accomplished using a Beckmann rearrangement. The oxime forms with the OH group trans to the more bulky cyclic substituent. Tosylation and Beckmann rearrangement gives an enamide which hydrolyses to the required cyclopentanone.

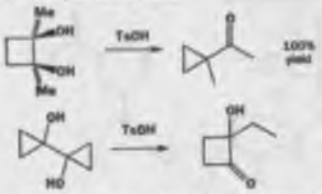


The Beckmann fragmentation

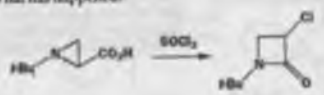
To finish this chapter, a Beckmann rearrangement that is not all that it seems. *t*-Butyl groups migrate well in the Baeyer–Villiger reaction and, indeed, Beckmann rearrangement of this compound appears to be quite normal too.

But, when this compound and another compound with a tertiary centre next to the oxime are mixed together and treated with acid, it becomes apparent that what is happening is not an intramolecular reaction.

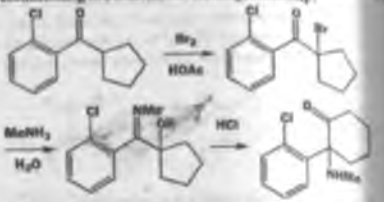
11. Suggest mechanisms for these reactions that explain any selectivity in the migration.



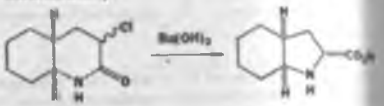
12. Attempts to produce the acid chloride from this unusual amino acid by treatment with $SOCl_2$ gave instead a β-lactam. What has happened?



13. Revision content. Suggest mechanisms for these reactions, commenting in detail on the rearrangement step.



14. Suggest a mechanism for this rearrangement, comparing it with a reaction discussed in the chapter. What controls the stereochemistry?



Fragmentation

38

Connections

Building on:

- Nucleophilic substitution at saturated carbon ch17
- Conformational analysis ch18
- Elimination reactions ch19
- Controlling stereochemistry ch16, ch22 & ch24
- Rearrangements ch37

Arriving at:

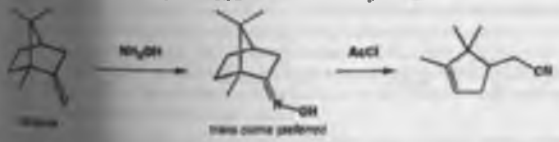
- Electron donation and electron withdrawal combine to create molecules that fragment
- Fragmentation literally means the breaking of a molecule into three by the cleavage of a C–C bond
- Reactive groups should have a 1,4 relationship
- Anti-periplanar conformation is essential
- Small rings are easy to fragment
- Medium and large rings can be made in this way
- Double bond geometry can be controlled
- Using fragmentations in synthesis

Looking forward to:

- Carbene chemistry ch40
- Determination of mechanism ch41
- Stereoselectronics ch42
- Main group chemistry ch46–ch47

Polarization of C–C bonds helps fragmentation

We finished the last chapter with an attempted migration that went wrong because the migrating group stabilized a cation too well. Here is a more convincing example of the same reaction: again, the conditions for, but not the result of, a Beckmann rearrangement.



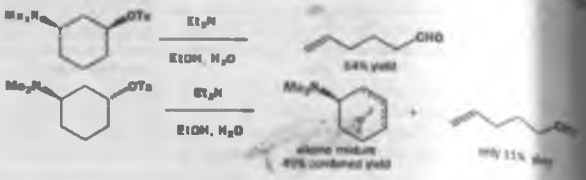
trans-ozone preferred

The starting material is bicyclic, the product monocyclic, so we have broken a C–C bond: the reaction is a fragmentation. The mechanism is straightforward once you know what happens to Beckmann rearrangements when the migrating group is tertiary—but hard to follow unless you remember the atoms!

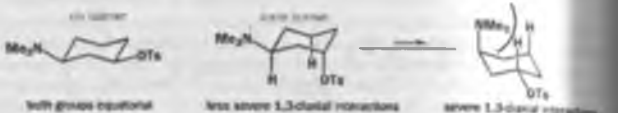
You have met few fragmentation reactions—reactions in which C–C bonds are broken—largely

▶ Beckmann rearrangements that go with fragmentation are sometimes called 'anomalous' or 'second-order' Beckmann rearrangements. You should not use the second of these names and, in any case, Beckmann fragmentation is much better than either.

Before we extend these ideas any further, consider these two quite different reactions of similar compounds.

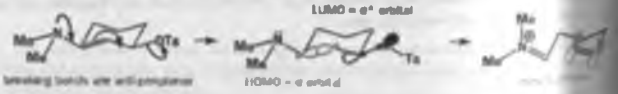


Just as with the rearrangements we looked at on p. 000, we need to draw these compounds in reasonable chair conformations in order to understand what is going on. In the *cis* isomer, both substituents can be equatorial; in the *trans* isomer one has to be axial, and this will be mainly the OTs group, since the two methyl groups of NMe_2 suffer greater 1,3-diaxial interactions.



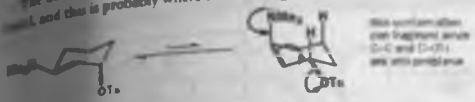
Now, the *cis* isomer has clearly undergone a fragmentation reaction and, as usual, numbering the atoms can help to identify the bond that breaks. The nitrogen lone pair pushes, the leaving group pulls, and the resulting iminium ion hydrolyses to the product aldehyde.

Yet the *trans* isomer only does this in very low yield. Mostly it eliminates TsOH to give a mixture of alkenes. Why? Well, notice that, in the *cis* isomer, the fragmenting bond is *trans* to the leaving group—indeed, it is both parallel and *trans*: in other words anti-periplanar to the leaving group. Electrons can flow smoothly from the breaking σ bond into the σ* of the C–OTs bond, forming π as they do so, a new π bond.

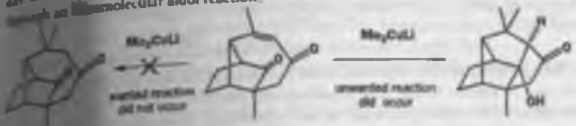


For the *trans* isomer, fragmentation of the most populated conformation is impossible because the leaving group is not anti-periplanar to any C–C bond. The only bonds anti-periplanar to OTs are C–H bonds, making this compound ideally set up for another reaction whose requirement for anti-periplanarity you have already met—E2 elimination.

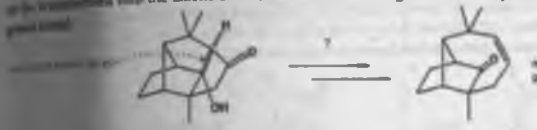
The other conformation can fragment because now the OTs is anti-periplanar to the right C–C bond, and this is probably where the 11% fragmentation product comes from.



When McMurry was making longifolene in the early 1970s, a fragmentation reaction saved the day when a conjugate addition reaction using a cuprate gave an unexpected cyclization product through an intramolecular aldol reaction.

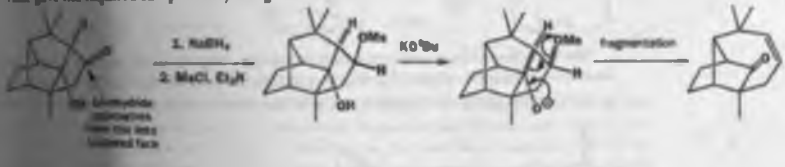


The desired compound McMurry wanted had the framework of the molecule on the left, but was to be transformed into the alkene below, so he needed to fragment the unexpected product at the green bond.



Another synthesis of longifolene is summarized later in this chapter.

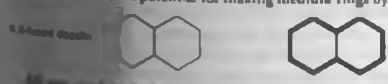
Fortunately, reducing the carbonyl group gave a hydroxyl group anti-periplanar to the green bond and therefore set up for fragmentation. Making the hydroxyl a leaving group and treating with base gave the required compound by a fragmentation reaction.



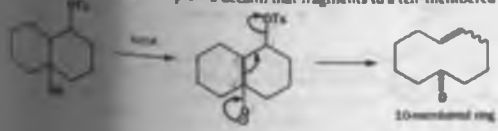
Ring expansion by fragmentation

Rings of ten or greater than eight are hard to make. Yet five- and six-membered rings are easy to make. Once you realize that a fused pair of six-membered rings is really a ten-membered ring with a bond across the middle, the potential for making medium rings by fragmentation becomes apparent.

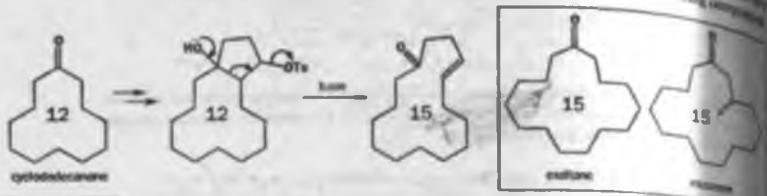
This point was discussed in Chapter 18.



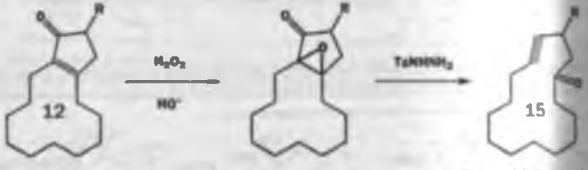
All you need to do is to make the bond to be broken the 2–3 bond in a 1, 2, 3, 4 electron cyclohexene arrangement and the ten-membered ring should appear out of the wreckage of the fragmentation. Here is an example—a decalin that fragments to a ten-membered ring.



Muscone and exaltone are important perfumery compounds with hard-to-make 15-membered ring structures. Cyclododecanone is commercially available: addition of a fused five-membered ring and fragmentation of the 12,5-ring system is a useful route to these 15-membered ring compounds.

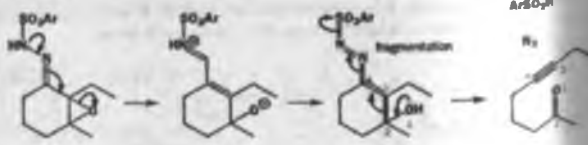


In the late 1960s, the Swiss chemist Albert Eschenmoser discovered an important reaction that can be used to achieve similar ring expansions and that now bears his name, the Eschenmoser fragmentation. The starting material for an Eschenmoser fragmentation is the epoxide of an α,β-unsaturated ketone. The fragmentation happens when this epoxy-ketone is treated with toluenesulfonyl hydrazine, and one of the remarkable things about the product is that it is an alkyne. The fragmentation happens across the epoxide (shown in black), and the product contains both a ketone (in a different place to the ketone in the starting material) and an alkyne. You can see how in this example hydrogenation of the triple bond can again give muscone (R = Me) or exaltone (R = H).



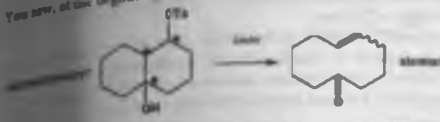
The Eschenmoser fragmentation does not have to be a ring expansion, and it is a useful synthetic method for making keto-alkynes. The following reaction, which we will use to discuss the fragmentation mechanism, was used to make an intermediate in the synthesis of an insect pheromone, *exo*-brevicomin.

The reaction starts with formation of the tosylhydrazone from the epoxy-ketone. The tosylhydrazone is unstable with respect to opening of the epoxide in an elimination reaction, and it is this elimination that sets up the familiar 1, 2, 3, 4 system ready for fragmentation. The 'push' comes from the newly created hydroxyl group, and the 'pull' from the irresistible concerted loss of a good leaving group (Ts^-) and an even better one (N_2). Notice how all the (green) bonds that break are parallel to one another, held anti-periplanar by two double bonds. Perfect!



More on stereochemistry and fragmentations

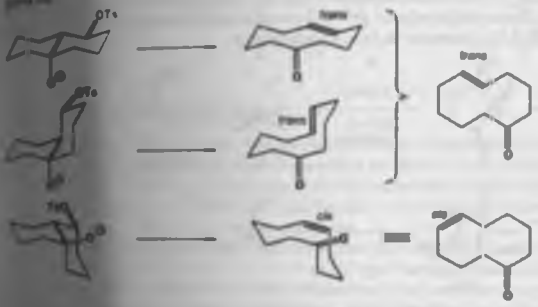
You saw, at the beginning of the last section, a ring expansion reaction of a decalin.



Now, the story of this ring expansion is a little more complex than we led you to believe, because the starting material has three stereogenic centres (*) and hence can exist as four diastereoisomers: two trans-decalins and two *cis*-decalins. What is more, the product has a double bond in a ten-membered ring: will it be *cis* or *trans*? (Both are possible—see Chapter 31.)

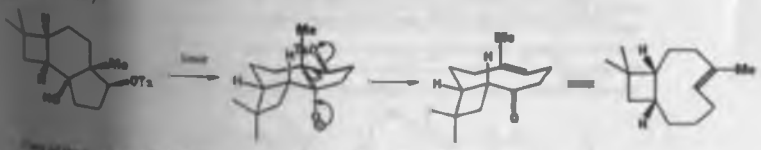
One of the four diastereoisomers of starting material cannot place the tosylate anti-periplanar to the ring-fusion bond, so it can't fragment.

The other three diastereoisomers all can, but two of them give a *trans* double bond while the third gives *cis*.

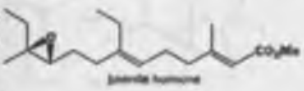


Looking at the alignment of the bonds that end up flanking the double bond in the product shows you where the geometrical isomers come from: these are the black bonds in the starting material, and are *trans* across the forming π system in the first two isomers and *cis* in the third. Fragmentations are stereospecific with regard to double bond geometry, much as E2 elimination reactions are.

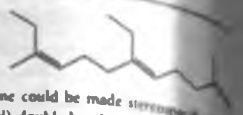
Corey applied this stereospecificity in conjunction with a ring expansion reaction to make the natural product caryophyllene. Caryophyllene is a bicyclic molecule with a nine-membered ring containing an *E*-trisubstituted double bond. The right relative stereochemistry in the starting material leads both to fragmentation of the right bond and to formation of the alkene with the right stereochemistry.



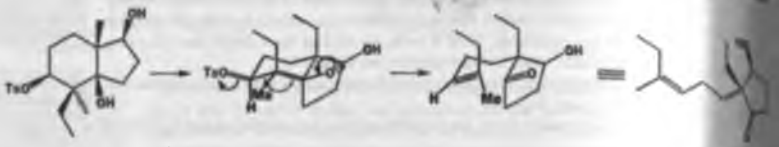
One of the most spectacular demonstrations of the use of fragmentation was the 1968 synthesis of juvenile hormone (a compound you met in Chapter 31) by chemists at Zoecon, an American pharmaceutical company.



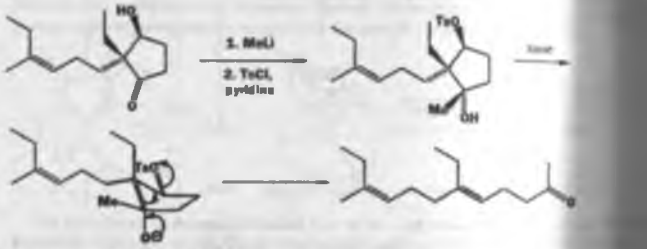
The major challenge in making juvenile hormone is the three trisubstituted double bonds (one of which ends up as an epoxide), and the initial target was to make the related aldehyde, which contains two of them.



The Syntex chemists reasoned that, if this methyl ketone could be made stereospecifically by fragmenting a cyclic starting material, the (hard-to-control) double bond stereochemistry would derive directly from the (easier-to-control) relative stereochemistry of the cyclic compound. The starting material they chose was a 5/6-fused system, which fragments to give one of the double bonds.



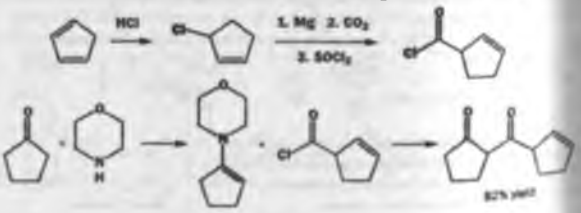
The product of this reaction is prepared for another fragmentation by addition of methyl (you might like to consider why you get this diastereoisomer) and tosylation of the less hindered secondary alcohol. Base promotes the second fragmentation.



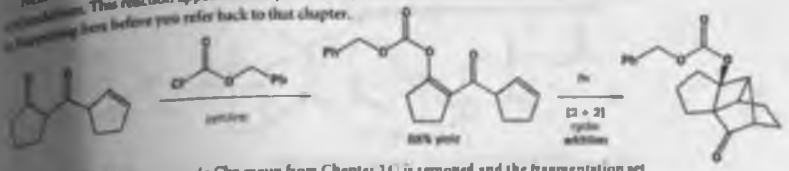
In the next chapter you will meet, among many other reactions, more fragmentations, but they will be radical fragmentations rather than ionic fragmentations, and involve homolytic cleavage of C–C bonds.

A second synthesis of longifolene

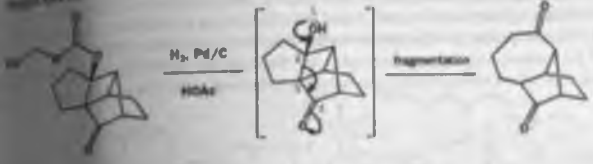
In Chapters 28 and 35 we introduced parts of Oppolzer's synthesis of longifolene. We now revisit those reactions and bring the synthesis a stage further forward with a fragmentation reaction different from the one used earlier in the chapter for the same molecule. McMurry used a fragmentation to escape from a disaster. Oppolzer had planned to use one right from the start. The first stage in the synthesis involves the building of two five-membered rings into a 1,3-diketone.



Next the enol ester of the 1,3-diketone forms a new four-membered ring by a [2 + 2] photocycloaddition. This reaction appears in Chapter 15 but you are invited to work out for yourself what is happening here before you refer back to that chapter.

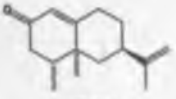


Finally the protecting group (a Cbz group from Chapter 24) is removed and the fragmentation set in motion. The four-membered ring is cleaved and the ring system of longifolene revealed. You might like to compare this route with McMurry's route described earlier in this chapter.



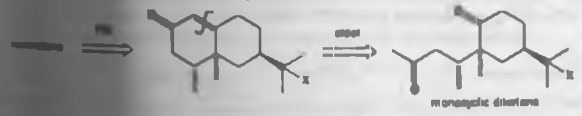
The synthesis of nootkatone

In the 1970s it was supposed that the characteristic sharp fruity scent and flavour of grapefruit came mainly if not entirely from a simple bicyclic enone called nootkatone. There was quite a rush to synthesize this compound in various laboratories and a remarkable feature of many successful syntheses was the use of fragmentation reactions. We shall describe parts of three syntheses involving the fragmentation of a six-, a four-, and a three-membered ring.



nootkatone
supposed flavour
principle of grapefruit

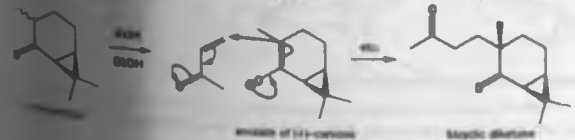
Most syntheses make the side-chain alkene by an elimination reaction so the first 'disconnection' is an FGI adding HX back onto the alkene. The last C–C bond-forming operation in most syntheses is an intramolecular aldol reaction to make the enone so that can be disconnected next. It is the starting material for the aldol, a simple monocyclic diketone, which is usually made by a fragmentation reaction because this is a good way to set up the stereochemistry.



monocyclic diketone

Fragmentation of a three-membered ring

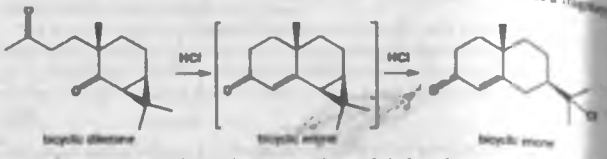
The synthesis does not look as though it will lead to nootkatone because the fragmentation product contains a great deal of development. It has the advantage that the stereochemistry is correct at one centre in the end. The synthesis starts from natural (+)-carvone; conjugate addition of the enolate to but-3-en-2-one (methyl vinyl ketone) leads to a bicyclic diketone with one extra stereogenic centre. The enone adds to the less hindered face of the enolate opposite the dimethylcyclopropane ring as the methyl group is forced upwards.



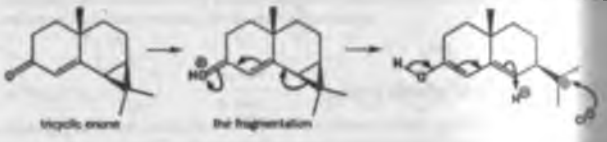
enolate of (+)-carvone

bicyclic diketone

Now the diketone is cyclized in HCl to give a bicyclic enone. A new six-membered ring has been formed but the old three-membered ring has disappeared. First, an intramolecular aldol reaction closes the new six-membered ring to form an enone and then the stage is set for a fragmentation.



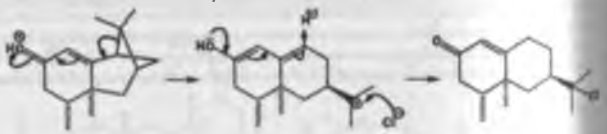
The fragmentation is pulled by the enone (with some help from the acid) and pushed by the stability of the tertiary carbocation as well as the release of strain as the single bond that is fragmented is in a three-membered ring. The fragmentation product is an enol on the left and a carbocation on the right. Addition of a proton to the end of the enol and a chloride ion to the cation gives the bicyclic enone. The chloroalkyl side chain must be on the top of the molecule because only one of the C–Cl bonds in the three-membered ring has been broken and the remaining bond cannot change its stereochemistry. The further development of this compound into nootkatone is beyond the scope of this book.



Fragmentation of a four-membered ring

This approach leads directly to the enone needed for nootkatone. A diketone prepared from a natural terpene (Chapter 51) is also treated with HCl and much the same reactions ensue except that the fragmentation now breaks open a four-membered ring. First, the intramolecular aldol reaction to make the second six-membered ring.

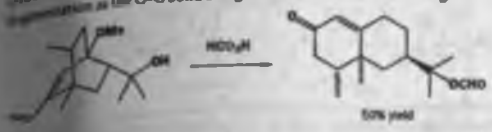
Now the fragmentation, which follows much the same course as the last one: the enone again provides the electron pull while the cleavage of a strained C–C single bond in a four-membered ring to give a tertiary carbocation provides the electron push. A simple elimination is all that is needed to make nootkatone from this bicyclic chloroenone.



Fragmentation of a six-membered ring

This chemistry is quite different from the examples we have just seen. The starting material has a bridged bicyclic structure and was made by a Diels–Alder reaction (Chapter 48). Fragmentation

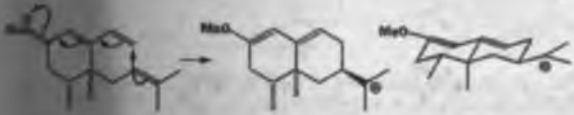
initiated by formic acid (HCO_2H), which protonates the tertiary alcohol and creates a tertiary carbocation. The ether provides the push. More serious electronic interactions are needed in this fragmentation as the C–C bond being broken is not in a strained ring.



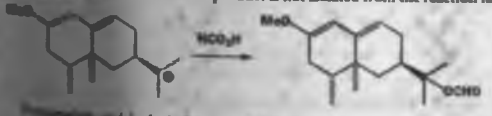
50% yield

The yield of 50% is not wonderful but there is obviously a lot of chemistry going on here so it is remarkable when so much is being achieved. The first stage is the fragmentation itself. Drawing the product first of all in the same shape as the starting material and then redrawing, to ensure that we don't make a mistake, we discover that we are well on the way to nootkatone. Note that the stereochemistry of the two methyl groups comes directly from the stereochemistry of the starting material and no new stereogenic centres are created in the fragmentation. Though one six-membered ring is fragmented, another remains.

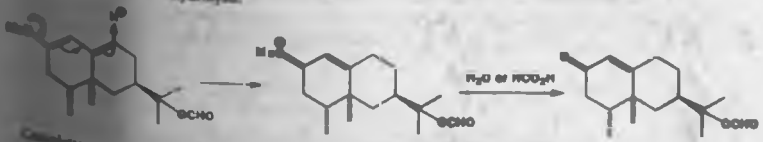
The first formed product now cyclizes to form the second six-membered ring. This recreates a carbocation at the tertiary centre like the one that set off the fragmentation as the more nucleophilic end of the isolated alkene attacks the end of the conjugate electrophile. This is a thermodynamically controlled reaction with the new stereogenic centre choosing an equatorial substituent.



The cation picks up the only nucleophile available—the very weak formic acid. This gives the product of the fragmentation, which contains two unstable functional groups—a tertiary formate ester and an enol ether—and this product is not isolated from the reaction mixture.

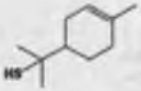


Protonation and hydrolysis of the extended enol ether to release the enone may occur during work-up and the stable enone is the first compound that can be isolated. The 50% yield of this compound represents a much better yield in four steps: fragmentation, olefin cyclization, addition of formic acid, and enol ether hydrolysis.



Completion of the synthesis of nootkatone simply requires pyrolysis of the formate ester in

refluxing 2,4,6-trimethyl pyridine (b.p. 172 °C). The reaction is a *syn* elimination by a [illegible] mechanism and it gives nootkatone in 79% yield.



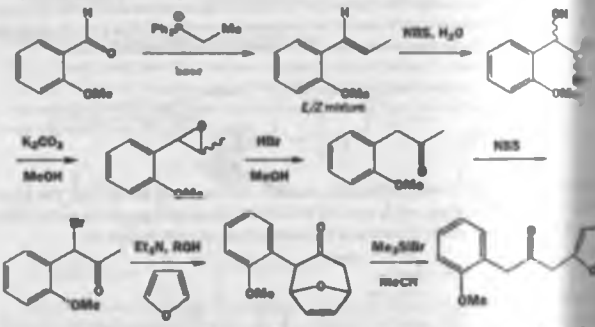
true flavouring principle of grapefruit

We first encountered this intense taste in Chapter 1 and we will discuss sulfur compounds in Chapter 46.

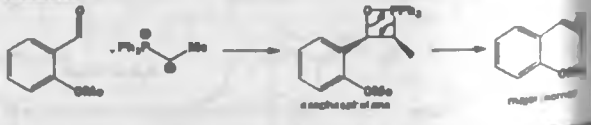
The synthesis of nootkatone occupied many chemists for some years and has given us some excellent examples of fragmentation reactions. However, the synthetic samples of nootkatone failed to deliver the intense grapefruit taste and smell of the material from grapefruits. The reason is simple: that nootkatone is not the flavour principle of grapefruit! The samples of nootkatone [illegible] grapefruit contained minute traces of the true flavour principle—a simple thiol. Humans can detect 2×10^{-5} p.p.b. (yes, parts per *billion*) of this compound, so even the tiniest trace is very powerful. At least the syntheses allowed chemists to correct an error.

A revision example: rearrangements and fragmentation

We shall end this chapter with an example that involves many of the reactions we have been discussing in recent chapters. It culminates in a fragmentation but takes in two different rearrangements (Chapter 37) on the way as well as a cycloaddition (Chapter 35) and an electrocyclic reaction (Chapter 36). Here is the whole scheme with the main changes in each step highlighted in black. You might cast your eye over the scheme and see in general terms what sort of reaction happens at each step (substitution, rearrangement, etc.).

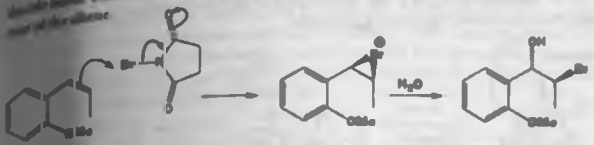


The first step is a simple Wittig reaction with an unstabilized ylid (Chapter 31), which we expect to favour the *Z*-alkene. It does but, as is common with Wittig reactions, an *E*/*Z* mixture is formed but not separated as both isomers eventually give the same compound. The reaction is [illegible] controlled and the decomposition of the oxaphosphetane intermediate is in some ways like a fragmentation.

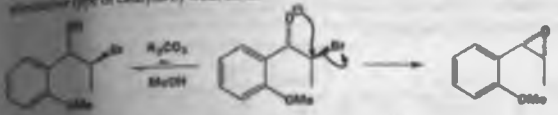


Now the alkene is converted into an epoxide by a slightly unusual sequence. Bromination with NBS (*N*-bromosuccinimide) in water gives a mixture of bromohydrins by electrophilic addition to the

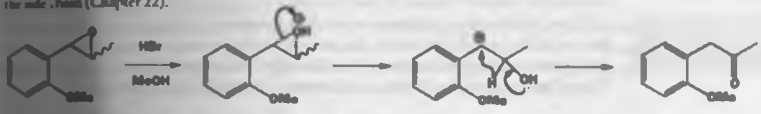
dioxide insert. The reaction occurs through a bromonium ion and is stereospecifically anti on each isomer of the alkene.



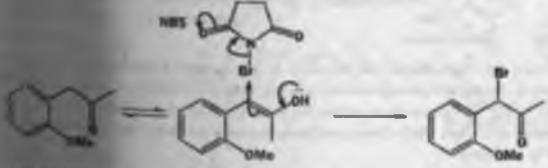
Next, the bromohydrin is treated with base and an intramolecular S_N2 reaction (Chapter 17) closes the epoxide ring. This too is stereospecific and the major isomer only is shown. The mixture of epoxides is a result of the *E*/*Z*-alkene mixture. Potassium carbonate is too weak a base to generate much of the phenolate anion but the cyclization may still go this way in methanol. In Chapter 41 you will learn of an alternative type of catalysis by weak bases.



We saw some epoxide rearrangements in Chapter 37 but this reaction seems rather tame by comparison. The epoxide opens in acid to give the more stable (secondary and benzylic) of the two possible carbocations and then a hydrogen atom migrates with the pair of electrons from the C–H bond ('hydride shift') to give a ketone. The rearrangement is useful because it allows the synthesis of aryl ketones, which cannot easily be made by a Friedel–Crafts reaction since the carbonyl group is in the wrong position on the side chain (Chapter 22).

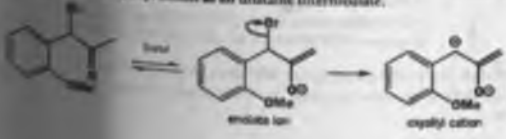


The ketone is then brominated, also with NBS, in a regioselective manner. The more conjugated enol is formed between the carbonyl group and the aromatic ring and this is attacked electrophilically by the bromine atom of the NBS (Chapter 20).

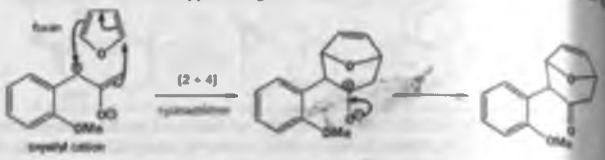


Cycloaddition and rearrangement

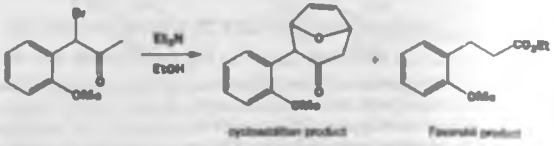
Now comes the most interesting step in the whole process—a step that unites a cycloaddition and a rearrangement and sets the scene for a fragmentation. The idea was to treat the bromoketone with base to make an oxyallyl cation as an unstable intermediate.



The oxyallyl cation with its two electrons delocalized over the allylic system would add to the double bond in a [2 + 4] cycloaddition to give a new cation stabilized by the oxyanion or, in more familiar terms, a ketone. The reaction was supposed to go like this.

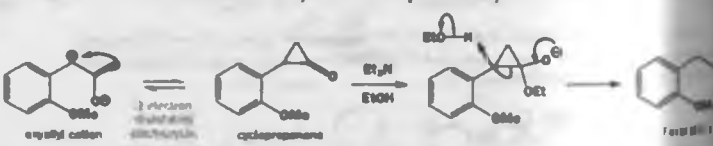


The best base turned out to be the tertiary amine Et_3N and the reaction had to be performed in alcoholic solution as alcohols were the only solvents able to keep the organic and ionic materials in solution. However, a substantial amount of a by-product was formed in ethanol—evidently the product of a Favorskii rearrangement.

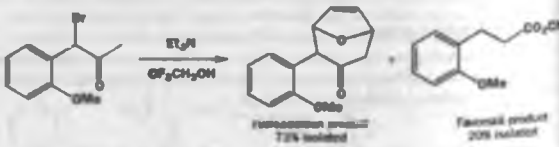


What is happening here is that the oxyallyl cation is in equilibrium with the cyclopropanone by an electrocyclic reaction (Chapter 36) and the alcohol is capturing this unstable ketone by nucleophilic addition. Hemiacetals of cyclopropanones form spontaneously in alcoholic solution (Chapter 18) because of the strain in the ketone. The anion of the hemiacetal decomposes by cleavage of a C–C bond to release what would be the more stable of the two carbanions, that is, the benzylic carbanion. This carbanion is not actually formed as it is protonated by the alcohol as it leaves.

■ This is an example of GAC (general acid catalysis) as explained in Chapter 41.



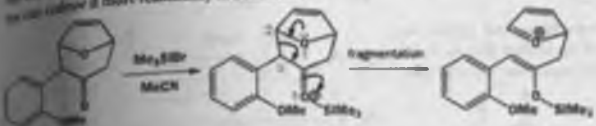
So how can the cycloaddition be promoted at the expense of the Favorskii rearrangement? Nothing can be done about the equilibrium between the oxyallyl anion and the cyclopropanone—that's a fact of life. The answer is to reduce the nucleophilicity of the alcohol by using trifluoroethanol instead of ethanol. Under these conditions the major product is the cycloadduct, which can be isolated in 73% yield.



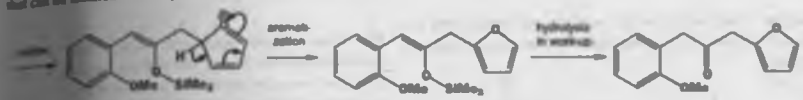
The two compounds can easily be separated as they have completely different structures and are not stereoisomers or indeed isomers of any kind. Now it is time for the fragmentation reaction of the cycloadduct.

The fragmentation reaction

The cyclobutanol is fragmented with Me_3SiBr in acetonitrile. The electrophilic silicon atom attacks the ketone and the furan oxygen atom provides the electronic push. These two groups have the 1,4 relationship necessary for a fragmentation. First of all, we shall draw the product in the same way as the starting material—this is a good tip in a complicated mechanism. The product may look odd but we can redraw it more realistically in a moment.



The redrawn product is a silyl enol ether (Chapter 21) at one end and an oxonium ion at the other. Simple proton removal and hydrolysis of the silyl enol ether in the work-up reveals a furan that can be isolated in 81% yield as the true product.

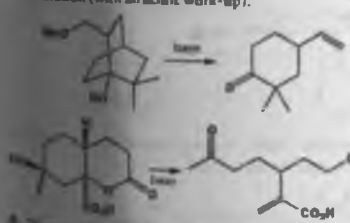


This product is worth a close look. The three-atom chain joining the two aromatic rings has the ketone on the middle carbon atom and it is therefore on C2 (β) with respect to *both* rings. This is the difficult position for a carbonyl group and so this product cannot be made by a Friedel–Crafts reaction on either ring.

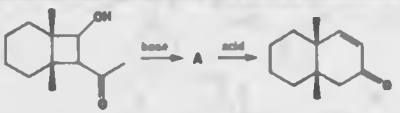
Fragmentation reactions cleave C–C single bonds by a combination of electron push and electron pull so that both electrons in the bond move in the same direction as the bond breaks. In the next chapter we shall see reactions that break C–C bonds in a quite different way. No electron push or pull is required because one electron goes one way and one the other. These are radical reactions.

Problems

1. Just to check your skill at finding fragmentations by numbers, draw a mechanism for each of these one-step fragmentations in base solution (with an acidic work-up).

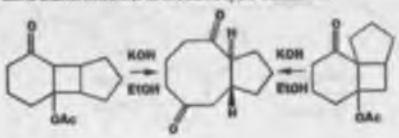


2. Treatment of this hydroxy-ketone with base followed by acid gives the enone shown. What is the structure of the intermediate A that is formed, and what is the mechanism of the formation of the final product?

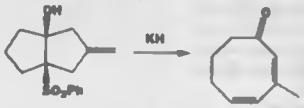


3. Suggest a mechanism for this reaction that involves a fragmentation as a key step.

4. Explain why both of these tricyclic ketones fragment to the same diastereoisomer of the same cyclo-octadione.

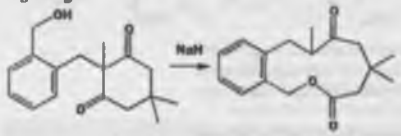


5. Suggest a mechanism for this ring expansion in which fragmentation is one step.

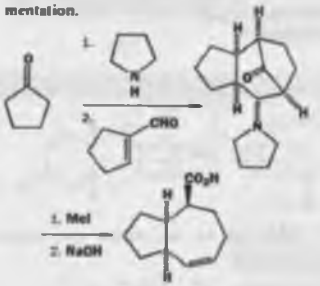


6. Suggest a mechanism for this fragmentation and explain the stereochemistry of the double bonds in the product. This is a tricky problem but find the mechanism and the stereochemistry will follow.

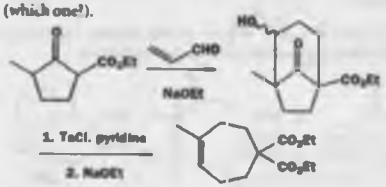
7. Suggest a mechanism for this reaction and explain why the molecule is prepared to abandon a stable six-membered ring for a larger ring.



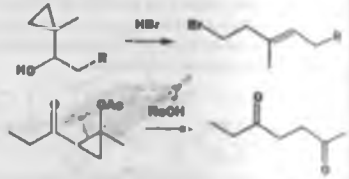
8. Give mechanisms for these reactions, commenting on the fragmentation.



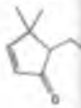
9. Propose mechanisms for the synthesis of the bicyclic intermediate and explain why only one diastereoisomer fragments (which one?).



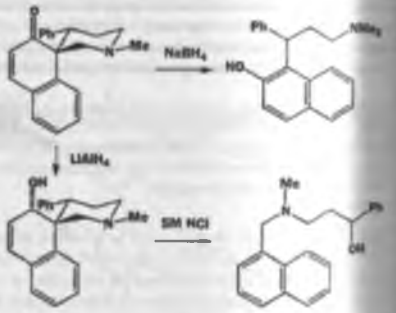
10. Suggest mechanisms for these reactions, explaining the alkene geometry in the first case. Do you consider these fragmentations?



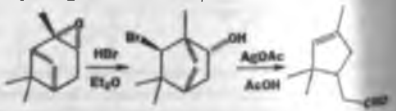
11. What steps would be necessary to carry out an Eschenmoser fragmentation on this ketone and what products would be formed?



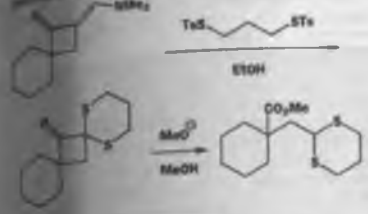
12. These related spirocyclic compounds give alkenyl naphthalenes when treated with sodium borohydride or with HCl. Each reaction starts with a different fragmentation. Give mechanisms for the reactions and explain why the fragmentations are different. Treatment of the starting ketone with $LiAlH_4$ instead of $NaBH_4$ gives the alcohol below without fragmentation. Comment on the difference between the two reagents and the stereochemistry of the alcohol.



13. Revision content. Suggest mechanisms for these reactions, explaining the stereochemistry.



14. You might not think that these reactions are truly fragmentations, but give the mechanisms anyway.



Radical reactions

39

Connections

Building on:

- Conjugate addition ch10 & ch23
- Energy profile diagrams ch13
- Nucleophilic substitution ch17
- Conformational analysis ch18
- Elimination reactions ch19
- Controlling stereochemistry ch18, ch33, & ch34
- Retrosynthetic analysis ch30
- Diastereoselectivity ch33–ch34

Arriving at:

- Radicals are species with unpaired electrons
- Radical reactions follow different rules to those of ionic reactions
- Bond strength is very important
- Radicals can be formed with Br, Cl, Sn, and Hg
- Efficient radical reactions are chain reactions
- Tin(IV) hydrides are electrophilic and nucleophilic radicals
- Radicals favour conjugate addition
- Cyclization is easy with radical reactions

Looking forward to:

- Carbene chemistry ch40
- Determination of mechanism ch41
- Stereoelectronics ch42
- Main group chemistry ch48–ch49
- Natural products ch51
- Polymerization ch52

Radicals contain unpaired electrons

You may remember that at the beginning of Chapter 8 we said that the cleavage of H–Cl into H^+ and Cl^- is possible in solution only because the ions that are formed are solvated: in the gas phase, the reaction is endothermic with $\Delta G = +1347\ kJ\,mol^{-1}$, a value so vast that even if the whole universe were made of gaseous HCl at 273 K, not a single molecule would be dissociated into H^+ and Cl^- ions.

$$HCl \longrightarrow H^{\oplus} + Cl^{\ominus}$$

(8 electrons in outer shell)

At temperatures above about 200 °C, however, HCl does begin to dissociate, but not into ions. Instead of the chlorine atom taking both bonding electrons with it, leaving a naked proton, the electron pair forming the H–Cl bond is shared out between the two atoms. ΔG for this reaction is a much more reasonable $+431\ kJ\,mol^{-1}$ and, at high temperatures (above about 200 °C, that is), HCl gas can be dissociated into H and Cl atoms.

$$HCl \xrightarrow{>200\ ^\circ C} H^{\bullet} + Cl^{\bullet}$$

(one electron) (7 electrons in outer shell)

▶ The single, unpaired electron possessed by each atom is represented by a dot. The Cl atom, of course, has seven (three pairs of electrons and one not shown).

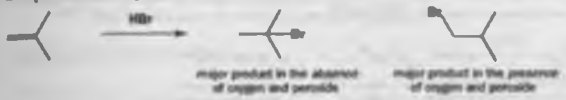
- **Heterolysis and homolysis**
  - When bonds break and one atom gets both bonding electrons, the process is called **heterolysis**

    The products of heterolysis are, of course, **ions**.
  - When bonds break and the atoms get one bonding electron each, the process is called **homolysis**

    The products of homolysis are **radicals**, which may be atoms or molecules, and contain an **unpaired electron**.

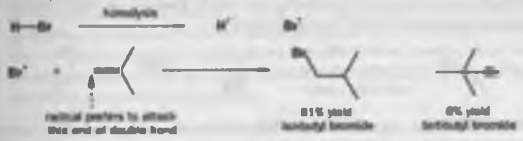
It was, in fact, a reaction of a closely related molecule, hydrogen bromide, that was among the first to alert chemists to the possibility that radicals can be formed in chemical reactions even at ambient

temperatures, and that they have a distinct pattern of reactivity. In the 1930s, Morris Kharasch found that the regioselectivity of addition of H–Br to isobutene was dependent on whether or not oxygen and peroxides were present in the reaction mixture.



It turns out that in the *absence* of peroxides the addition takes place by the type of (ionic) mechanism that you have already met. The tertiary bromide is formed because the intermediate, a tertiary cation, is more stable than the alternative primary cation.

In the *presence* of peroxides, the mechanism is quite different. Homolysis of the H–Br takes place, and bromine radicals then attack the C=C double bond at its less hindered end are formed. Mostly isobutyl bromide is formed.



What does the peroxide do? Why does its presence change the mechanism? The peroxide undergoes homolysis of the weak O–O bond extremely easily, and because of this it initiates a radical chain reaction. We said that H–Cl in the gas phase undergoes homolysis in preference to heterolysis: other types of bond are even more susceptible to homolysis. You can see this for yourself by looking at this table of bond dissociation energies (ΔG for X–Y → X˙ + Y˙).

Bond X–Y	ΔG for X–Y → X˙ + Y˙, kJ mol^{-1}	Bond X–Y	ΔG for X–Y → X˙ + Y˙, kJ mol^{-1}
H–OH	498	CH_3–Br	293
H_3C–H	435	CH_3–I	234
H_3C–OH	383	Cl–Cl	243
H_3C–CH_3	368	Br–Br	192
H–Cl	431	I–I	151
H–Br	366	HO–OH	213
H–I	298	MeO–OMe	151
CH_3–Cl	349		

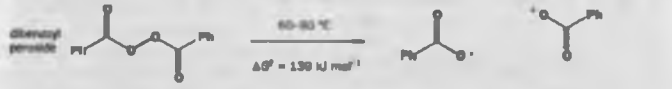
Dialkyl peroxides (dimethyl peroxide is shown in the table) contain the very weak O–O bond. The radicals formed by homolytic cleavage of these bonds, stimulated by a little heat or light, initiate what we call a 'radical chain reaction', which results in the formation of the Br˙ radicals, which add to the alkene's C=C double bond. We shall return to radical chain reactions and their mechanisms in detail later in this chapter.

Radicals form by homolysis of weak bonds

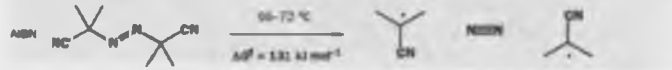
You've just met the most important way of making radicals: unpairing a pair of electrons by homolysis, making two new radicals. Temperatures of over 200 °C will homolyse most bonds; on the other hand, some weak bonds will undergo homolysis at temperatures little above room temperature. Light is a possible energy source for the homolysis of bonds too. Red light has associated with it 167 kJ mol^{-1}; blue light has about 293 kJ mol^{-1}. Ultraviolet (200 nm), with an associated energy of 586 kJ mol^{-1}, will decompose many organic compounds (including the DNA in skin cells: sunbathers beware!).

There are a number of compounds whose homolysis is particularly important to chemists, and the most important ones are discussed in turn below. They all have weak σ bonds, and generate radicals that can be put to some chemical use. The halogens are quite readily homolysed by light. These process are important in radical halogenation reactions that we shall discuss later.

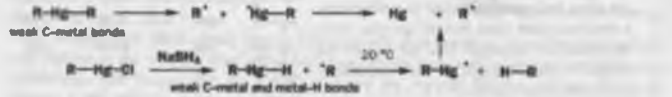
Dibenzoyl peroxide is an important compound because it can act as another initiator of radical reactions; we'll see why later. It undergoes homolysis simply on heating.



Another compound that is often used in synthetic reactions for the same reason (though it reacts with a different set of compounds) is AIBN (azobisbutyronitrile).



Some organometallic compounds, for example organomercuries or organocobalts, have very weak carbon–metal bonds, and are easily homolysed to give carbon-centred radicals. Alkyl mercury hydrides are formed by reducing alkyl mercury halides, but they are unstable at room temperature because the Hg–H bond is very weak. Bonds to hydrogen never break to give radicals spontaneously because H• is too unstable to exist, but interaction with almost any radical removes the H atom and breaks the Hg–H bond. This is the process of hydrogen abstraction, which forms the next section of the chapter.

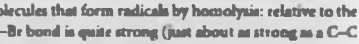


Radicals in cars

Radicals generated from another organometallic compound, tetraethyllead Et_4Pb, were the reason for adding this compound to petrol. These radicals react with other radical species involved in the pre-ignition of petrol vapour in internal combustion engines, and prevent the phenomenon known as 'knocking'. Nowadays simple organic compounds such as MeOBu^t are used instead in 'green' petrol.

Radicals form by abstraction

Notice that we didn't put HBr on the list of molecules that form radicals by homolysis: relative to the weak bonds we have been talking about, the H–Br bond is quite strong (just about as strong as a C–C bond). Yet we said that Br• radicals were involved in the addition reaction we talked about on p. 000. These radicals are formed by the action of the alkoxy radicals (generated by homolysis of the peroxide) on HBr—a process known as radical abstraction. Here is the mechanism.

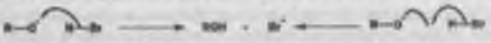


The peroxy radical RO• 'abstracts' H• from the HBr to give ROH, leaving behind a new radical Br•. We have described this process using arrows with 'half-heads' (also known as 'fish-hook arrows').

They indicate the movement of single electrons among orbitals, by analogy with our normal curly arrows, which indicate the movement of electron pairs.

Writing radical mechanisms

There is often more than one correct way of drawing a radical mechanism using half-headed arrows. For example, we could have represented the abstraction reaction shown above in either of these alternative ways.



The full story shows that the odd electron on RO• pairs with one of the electrons in the H–Br bond while the other moves on to the bromine atom.

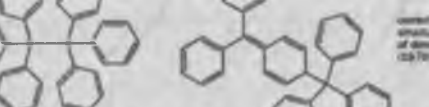
But some radical reactions always involve the reorganization of electron pairs, we can choose whether to show what happens to either or both of the members of each pair. In most examples in this book, we will draw arrows only in one direction.

The ability of radicals to propagate by abstraction is a key feature of radical chain reactions, which we shall come to later. There is an important difference between homolysis and abstraction as a way of making radicals: homolysis is a reaction of a spin-paired molecule that produces two radicals; abstraction is a reaction of a radical with a spin-paired molecule that produces one new radical and a new spin-paired molecule. Radical abstractions like this are therefore examples of your first radical reaction mechanism: they are in fact substitution reactions at H and can be compared with proton removal or even with an S_N2 reaction.

Radical substitutions differ considerably from S_N1 or S_N2 reactions: importantly, *radical substitutions almost never occur at carbon atoms*. We shall come back to radical substitutions, or abstractions (depending on whether you take the point of view of the H atom or the Br atom), later in the chapter.

First radical detected

The very first radical to be detected, the triphenylmethyl radical, was made in 1900 by abstract on of Cl• from Ph_3CCl by Ag metal.



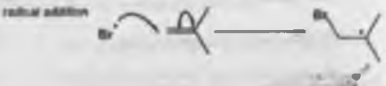
This radical is relatively stable (we shall see why shortly), but reacts with itself reversibly in solution. The product of the dimerization of triphenylmethyl was for 70 years believed to be hexaphenyl ethane but, in 1970, NMR showed that it was, in fact, an unsymmetrical dimer.

original suggested structure of triphenylmethyl dimer (1900)

correct structure of dimer (1970)

Radicals form by addition

The key step in the radical reaction with which we started the chapter is the formation of a radical by radical addition. The $Br^{\bullet}$ radical (which, you will remember, was formed by abstraction of $H^{\bullet}$ from HBr by $RO^{\bullet}$) adds to the alkene to give a new, carbon-centred radical. This is the mechanism: again, notice that half-headed arrows are used to indicate the movement of single electrons.

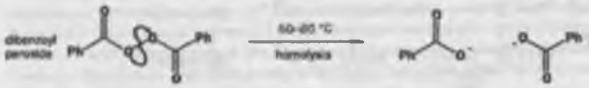


Just as charge must be conserved through a chemical reaction, so must be the spin of the electrons involved. If a reactant carries an unpaired electron, then so must a product. Addition of a radical to a spin-paired molecule always generates a new radical. Radical addition is therefore a second type of radical-forming reaction.

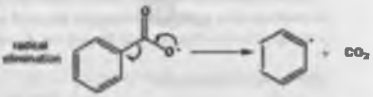
The simplest radical addition reactions occur when a single electron is added to a spin-paired molecule. This process is a reduction. You have already met some examples of single-electron reductions: Birch reductions (Chapter 24) use the single electron formed when a group I metal (sodium, usually) is dissolved in liquid ammonia to reduce organic compounds. Group I metals are common sources of single electrons: by giving up their odd s electron they form a stable M^{+} ion. They will donate this electron to several classes of molecules; for example, ketones can react with sodium to form ketyl radicals.

Radicals form by homolytic cleavage of weak bonds

A fourth class of radical-forming reaction is homolytic cleavage. For an example, we can go back to dibenzoyl peroxide, the unstable compound we considered earlier in the chapter because it readily undergoes homolysis.



The radicals formed from this homolysis are unstable and each breaks down by cleavage of a C–C bond, generating CO_2 and a phenyl radical. These homolytic bond cleavages are elimination reactions and are the reverse of radical addition reactions.



To summarize methods of radical formation

Radicals form from spin-paired molecules by:

- homolysis of weak σ bonds, e.g.
- electron transfer, that is, reduction (addition of an electron), e.g.

Radicals form from other radicals by:

- substitution (abstraction)
- addition
- elimination (homolysis)

Most radicals are extremely reactive...

Unpaired electrons are desperate to be paired up again. This means that radicals usually have a very short lifetime; they don't survive long before undergoing a chemical reaction.

Chemists are more interested in radicals that are reactive, because they can be persuaded to do interesting and useful things. However, before we look at their reactions, we shall consider some radicals that are unreactive so that we can analyse the factors that contribute to radical reactivity.

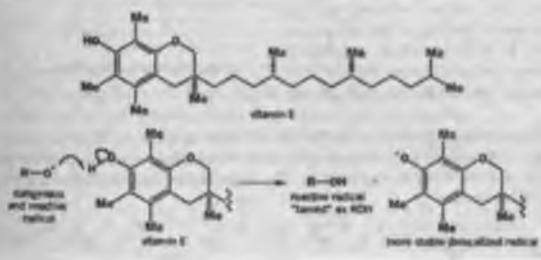
...but a few radicals are very unreactive

Whilst simple alkyl radicals are extremely short-lived, some other radicals survive almost indefinitely. Such radicals are known as **persistent radicals**. We mentioned the triphenylmethyl radical on p. 000: this yellow substance exists in solution in equilibrium with its dimer, but it is persistent enough to account for 2–10% of the equilibrium mixture.

Persistent radicals with the single electron carried by an oxygen or a nitrogen atom are also known: these three radicals can all be handled as stable compounds. The first, known as TEMPO, is a commercial product and can even be sublimed.

There are two reasons why some radicals are more persistent than others: (1) steric hindrance and (2) electronic stabilization. In the four extreme cases above, their exceptional stability is conferred by a mixture of these two effects. Before we can analyse the stability of other radicals, however, we need to look at what is known about the shape and electronic structure of radicals.

Vitamin E famous radicals

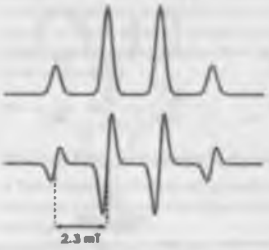


How to analyse the structure of radicals: electron spin resonance

For the last few pages we have been discussing the species we call radicals without offering any evidence that they actually exist. Well, there is evidence, and it comes from a spectroscopic technique known as **electron spin resonance**, or ESR (also known as EPR, electron paramagnetic resonance). ESR not only confirms that radicals do exist, but it can also tell us quite a lot about their structure.

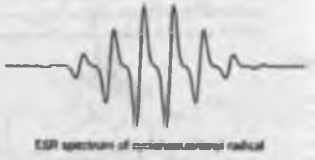
Unpaired electrons, like the nuclei of certain atoms, have a magnetic moment associated with them. Proton NMR probes the environment of hydrogen atoms by examining the energy difference between the two possible orientations of their magnetic moments in a magnetic field: ESR works in a similar way for unpaired electrons. The magnetic moment of an electron is much bigger than that of a proton, so the difference in energy between the possible quantum states in an electron field is also much bigger. This means that the magnets used in ESR spectrometers can be weaker than those in NMR spectrometers: usually about 0.3 tesla; even at this low field strength, the resonant frequency of an electron is about 9000 MHz (for comparison, the resonant frequency of a proton at 9.5 tesla is 400 MHz; in other words, a 400 MHz NMR machine has a magnetic field strength of 9.5 tesla).

But there are strong similarities between the techniques. ESR shows us, for example, that unpaired electrons couple with protons in the radical. The spectrum below is that of the methyl radical, $CH_3^{\bullet}$. The 1:3:3:1 quartet pattern is just what you would expect for coupling to three equivalent protons; coupling in ESR is measured in millitesla (or gauss; 1 gauss = 0.1 mT), and for the methyl radical the coupling constant (called a_H) is 2.3 mT.



▶ Notice that, for historical reasons, ESR spectra are recorded in a different way from NMR spectra: the diagram shows the first derivative of the absorption spectrum. The ESR spectrum you would get from a proton NMR machine is

ESR hyperfine splittings (as the coupling patterns are known) can give quite a lot of information about a radical. For example, here is the hyperfine splitting pattern of the cycloheptatrienyl radical. The electron evidently sees all seven protons around the ring as equivalent, and must therefore be fully delocalized. A localized radical would see several different types of proton, resulting in a much more complex splitting pattern.

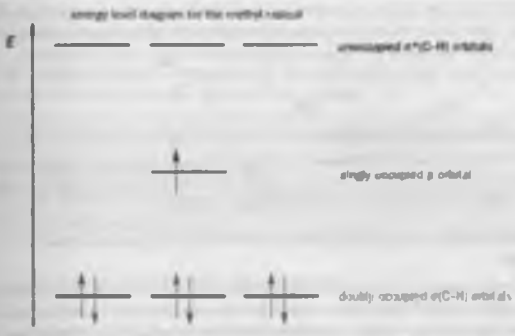


ESR spectrum of cycloheptatrienyl radical

Even the relatively simple spectrum of the methyl radical tells us quite a lot about the radical. For example, the size of the coupling constant a_H indicates that the methyl radical is planar; the trifluoromethyl radical is, on the other hand, pyramidal. The oxygenated radicals $^{\bullet}CH_2OH$ and $^{\bullet}CMe_2OH$ lie somewhere in between.

Radicals have singly occupied molecular orbitals

ESR tells us that the methyl radical is planar: the carbon atom must therefore be sp^2 hybridized, with the unpaired electron in a p orbital. We can represent this in an energy level diagram.

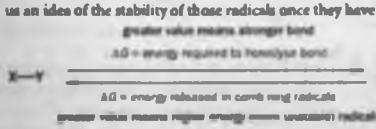


In Chapter 4 we talked about the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of organic molecules. $CH_3^{\bullet}$ (like all radicals) has an orbital containing one electron, which we call a **Singly Occupied Molecular Orbital (SOMO)**.

As with all molecules, it is the energy of the electrons in the molecular orbitals of the radical that dictate its stability. Any interaction that can decrease the energy levels of the filled molecular orbitals increases the stability of the radical (in other words, decreases its reactivity). Before we use this energy level diagram of the methyl radical to explain the stability of radicals, we need to look at some experimental data that allow us to judge just how stable different radicals are.

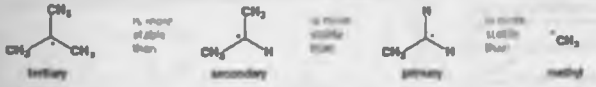
Radical stability

On p. 000 we used bond strength as a guide to the likelihood that bonds will be homolysed by heat or light. Since bond energies give us an idea of the ease with which radicals can form, they can also give us an idea of the stability of those radicals once they have formed.

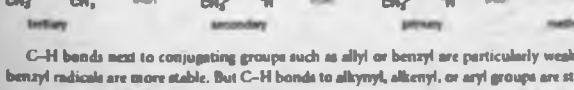


This is particularly true if we compare the strengths of bonds between the same atoms, for example, carbon and hydrogen, in different molecules; the table does this.

A few simple trends are apparent. For example, C–H bonds decrease in strength in R–H when R goes from primary to secondary to tertiary. Tertiary alkyl radicals are therefore the most stable; methyl radicals the least stable.



C–H bonds next to conjugating groups such as allyl or benzyl are particularly weak, so allyl and benzyl radicals are more stable. But C–H bonds to alkynyl, alkenyl, or aryl groups are strong.



	Dissociation energy, kJ mol^{-1}
	439
	423
	410
	397
	544
	431
	464
$H_2C{=}CHCH_2{-}H$	364
	372
	394
	385
	368
	465

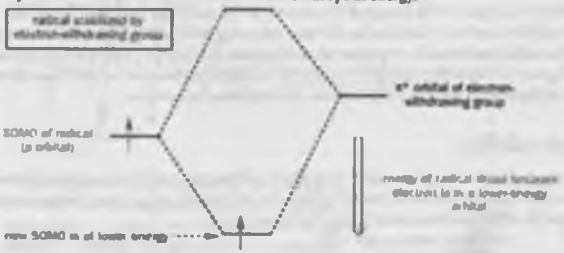
Adjacent functional groups appear to weaken C–H bonds: radicals next to carbonyl, nitrile, or ether functional groups, or centred on a carbonyl carbon atom, are more stable than even tertiary alkyl radicals.

radicals stabilized by functional groups

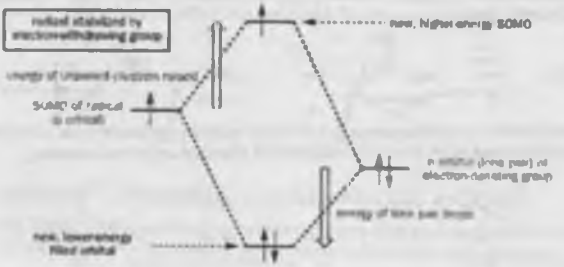
Whether the functional group is electron-withdrawing or electron-donating is clearly irrelevant here: both types seem to stabilize radicals. We can explain all of this if we look at how the different groups next to the radical centre interact electronically with the radical.

Radicals are stabilized by conjugating, electron-withdrawing, and electron-donating groups

Let's consider first what happens when a radical centre finds itself next to an electron-withdrawing group. Groups like C=O and C≡N are electron-withdrawing because they have a low-lying empty π* orbital. By overlapping with the (usually p) orbital containing the radical (the SOMO), two new molecular orbitals are generated. One electron (the one in the old SOMO) is available to fill the two new orbitals. It enters the new SOMO, which is of lower energy than the old one, and the radical experiences stabilization because this electron drops in energy.



We can analyse what happens with electron-rich groups, such as RO groups, in a similar way. Ether oxygen atoms have relatively high-energy filled π orbitals, their lone pairs. Interacting this with the SOMO again gives two new molecular orbitals. Three electrons are available to fill them. The SOMO is now higher in energy than it was to start with, but the lone pair is lower. Because two electrons have dropped in energy and only one has risen, there is an overall stabilization of the system, even though the new SOMO is of higher energy than the old one. We shall see later what effect the energy of the SOMO, rather than the overall energy of the radical, has on its reactivity.



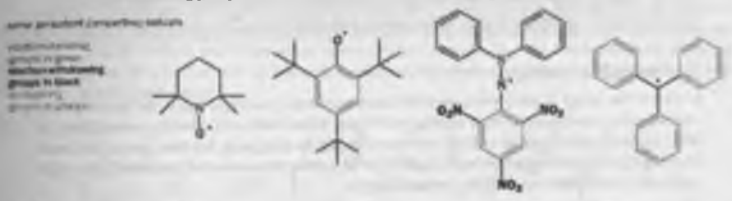
In Chapter 17, you saw how the electrons in C–H σ bonds stabilize cations: they stabilize radicals in the same way, which is why tertiary radicals are more stable than primary ones.

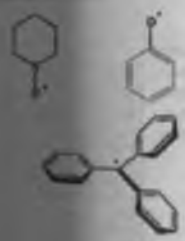
Conjugation, too, is effective at stabilizing radicals. We know that radicals next to double bonds are delocalized from their ESR spectra (p. 000); that they are more stable is evident from the bond dissociation energies of allylic and benzylic C–H bonds.

- **Anything that would stabilize an anion *or* a cation will stabilize a radical:**
  - **electron-withdrawing groups**
  - **electron-donating groups (including alkyl groups with C–H σ bonds)**
  - **conjugating groups**

Steric hindrance makes radicals less reactive

On p. 000 we showed you some radicals that are remarkably stable (persistent): some can even be isolated and purified. You should now be able to see at least part of the reason for their exceptional stability: two of them have adjacent powerful electron-donating groups and one has a powerful electron-withdrawing group as well, and three of the four are conjugated.

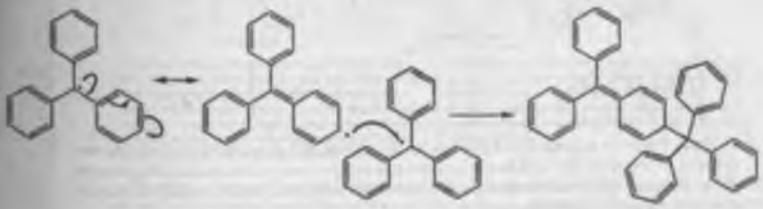




But electronic factors alone are not sufficient to explain the exceptional stability of all four radicals, since the next two radicals (in the margin) receive just about the same electronic stabilization as the first two above, but are much more reactive.

In fact, the stability of the triphenylmethyl radical we know to be due mainly to steric, rather than electronic, factors. X-ray crystallography shows that the three phenyl rings in this compound are not coplanar but are twisted out of a plane by about 30°, like a propeller. This means that the delocalization in this radical is less than ideal (we know that there is some delocalization from the ESR spectrum) and, in fact, it is little more delocalized than the diphenylmethyl or even the benzyl radical.

Yet it is much more stable than either. This must be because the central carbon, which bears most of the radical character, is sterically shielded by the twisted phenyl groups, making it very hard for the molecule to react. And when it does dimerize, we know that it does so through one of its least hindered carbon atoms.



Further evidence for the role of steric effects in helping to stabilize radicals comes from triphenyl-

methyl derivatives with *ortho* substituents: these force the phenyl rings to twist even more (at 50° or more), decreasing still further the extent of electronic stabilization through delocalization. Yet these *ortho*-substituted radicals are more stable than triphenylmethyl: this must be a steric effect. The rest of this chapter is devoted to the reactions of radicals, and you will see that the two effects we have talked about—electronic stabilization and steric hindrance—are key factors that control these reactions.

How do radicals react?

A reactive radical has a choice: it can either find another radical and combine to form a spin-paired molecule (or more than one spin-paired molecule), or it can react with a spin-paired molecule to form a new radical. Both are possible, and we shall see examples of each. A third alternative is for a radical to decompose in a unimolecular reaction, giving rise to a new radical and a spin-paired molecule.

Three possibilities

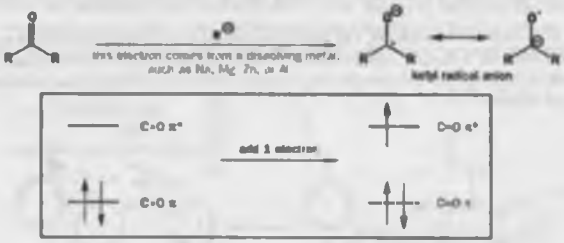
- Radical + radical → spin-paired molecule
- Radical + spin-paired molecules → new radical + new spin-paired molecule
- Radical → new radical + spin-paired molecule

Radical–radical reactions

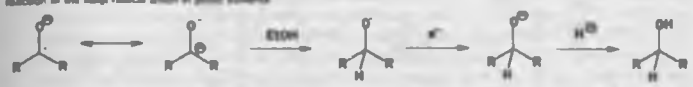
In view of the energy released when unpaired electrons pair up, you might expect this type of radical reaction to be more common than reaction with a spin-paired molecule, in which no net pairing of electrons takes place. Radical–radical reactions certainly do take place, but they are not the most important type of reaction involving radicals. We shall see why they are not as common as you might expect shortly, but first we can look at some examples.

The pinacol reaction is a radical dimerization

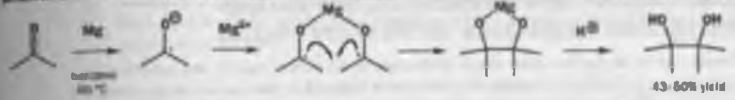
We outlined on p. 000 a way of making radicals by single electron transfer: effectively, the addition reaction of a single electron to a spin-paired molecule. The types of molecules that undergo this reaction are those with low-lying antibonding orbitals for the electron to go into, in particular, aromatic systems and carbonyl compounds. The radical anion formed by addition of an electron to a ketone is known as a ketyl. The single electron is in the π^* orbital, so we can represent a ketyl with the radical on oxygen or on carbon and the anion on the other atom.



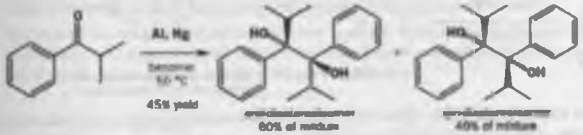
Ketyls behave in a manner that depends on the solvent that they are in. In protic solvents (ethanol, for example), the ketyl becomes protonated and then accepts a second electron from the metal (sodium is usually used in these cases). An alkoxide anion results, which, on addition of acid at the end of the reaction, gives an alcohol.



In aprotic solvents, such as benzene or ether, no protons are available so the concentration of ketyl radical builds up significantly and the ketyl radical anions start to dimerize. As well as being a radical–radical process, this dimerization process is an anion–anion reaction, so why doesn't electrostatic repulsion between the anions prevent them from approaching one another? The key to success is to use a metal such as magnesium or aluminium that forms strong, covalent metal–oxygen bonds and that can coordinate to more than one ketyl at once. Once two ketyls are coordinated to the same metal atom, they react rapidly.

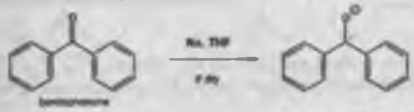


The example shows the dimerization of acetone to give a diol (2,3-dimethylbutane-2,3-diol) whose trivial name, pinacol, is used as a name for this type of reaction using any ketone. Sometimes pinacol reactions create new chiral centres: in this example, the two diastereoisomeric diols are formed in a 60:40 mixture. If you want to make a single diastereoisomer of a diol, a pinacol reaction is not a good choice!



Benzophenone as an indicator in THF stills

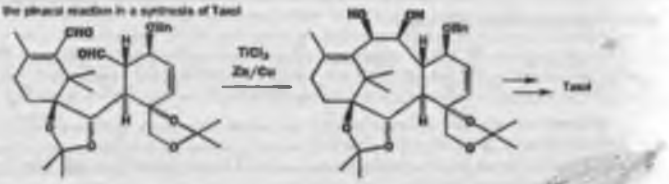
As you should have gathered by now, THF is an important organic solvent in which many low-temperature, inert atmosphere reactions are conducted. It has a drawback, however: it is quite hygroscopic, and often the reactions for which it is used as a solvent must be kept absolutely free of water. It is therefore always distilled immediately before use from sodium metal, which reacts with any traces of water in the THF. However, it is necessary to have an indicator to show that the THF is dry and that the sodium has done its job. The indicator used is a ketone, benzophenone.



When the THF is dry, the distilling liquid containing the benzophenone becomes bright purple. The colour is due to the ketyl of benzophenone, the formation of which under these conditions should not surprise you. It should also come as no surprise that this ketyl, being stabilized by conjugation and quite hindered, is pure stand-alone (long-lived)—it does not undergo pinacol dimerization (as we explained above, you would not normally choose sodium to promote pinacols anyway). However, if water is present, the ketyl is rapidly quenched in the manner of the reduction described above to give the (colourless) alkoxide anion; only when all the water is consumed does the colour return.

Pinacol reactions can be carried out intramolecularly, from compounds containing two carbonyl groups. In fact, the key step of one of the very first syntheses of Taxol® (the important anticancer compound) was an intramolecular pinacol reaction using titanium as the source of electrons.

the pinacol reaction in a synthesis of Taxol

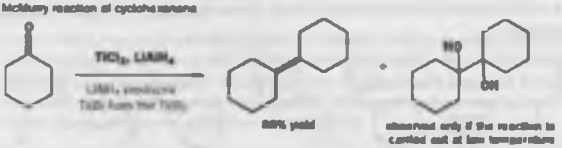


The titanium metal that is the source of electrons is produced during the reaction by reduction of $TiCl_3$ using a zinc–copper mixture. This reaction is, in fact, unusual because, as we shall see below, pinacol reactions using titanium do not normally stop at the diol, but give alkenes.

Titanium promotes the pinacol coupling and then deoxygenates the products: the McMurry reaction

Titanium can be used as the metal source of electrons in the pinacol reaction and, provided the reaction is kept cold and not left for too long, diols can be isolated from the reaction (see the example at the end of the previous section). However, unlike magnesium or aluminium, titanium reacts further with these diol products to give alkenes in a reaction known as the McMurry reaction, after its inventor.

McMurry reaction of cyclohexanone



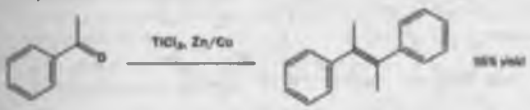
Notice that the titanium(0), which is the source of electrons in the reaction, is produced during the reaction by reacting a Ti(III) salt, usually $TiCl_3$, with a reducing agent such as $LiAlH_4$ or Zn/Cu. The reaction does not work with, say, powdered titanium metal. The McMurry reaction is believed to be a two-stage process involving firstly a pinacol radical–radical coupling. Evidence for this is that the pinacol products (diols) can be isolated from the reaction under certain conditions (you've just seen how this was done during the synthesis of Taxol).

first step of the McMurry reaction

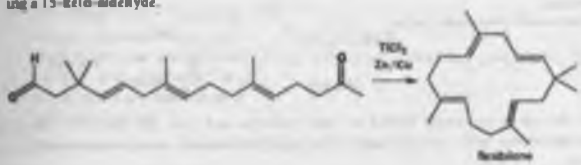
The Ti(0) then proceeds to deoxygenate the diol by a mechanism not fully understood, but thought to involve binding of the diol to the surface of the Ti(0) particles produced in the reduction of $TiCl_3$.

second step of the McMurry reaction: deoxygenation on the surface of a Ti(0) particle

We expect you to be mildly horrified by the inadequacy of the mechanism above. But, unfortunately, we can't do much better because no-one really knows quite what is happening. The McMurry reaction is very useful for making tetrasubstituted double bonds—there are few other really effective ways of doing this. However, the double bonds really need to be symmetrical (in other words, have the same substituents at each end) because McMurry reactions between two different ketones are rarely successful.

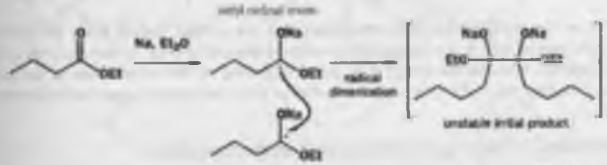


McMurry reactions also work very well intramolecularly, and turn out to be quite a good way of making cyclic alkenes, especially when the ring involved is medium or large (over about eight members). For example, the natural product flexibilene, with a 15-membered ring, can be made by cyclising a 15-keto-aldehyde.

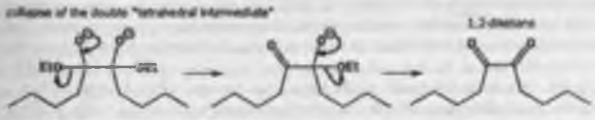


Esters undergo pinacol-type coupling: the acyloin reaction

You've seen examples of pinacol and McMurry reactions of ketones and aldehydes. What about esters? You would expect the ketyl radical anion to form from an ester in the same way, and then to undergo radical dimerization, and this is indeed what happens.



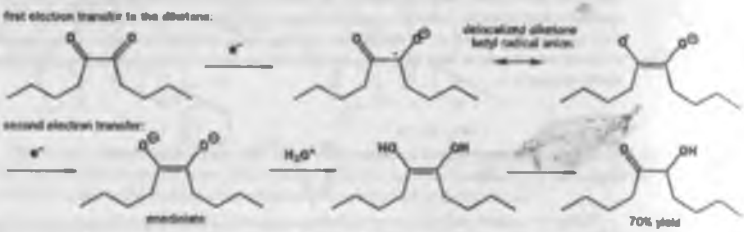
The product of the dimerization looks very much like a tetrahedral intermediate in a carbonyl addition–elimination reaction, and it collapses to give a 1,2-diketone.



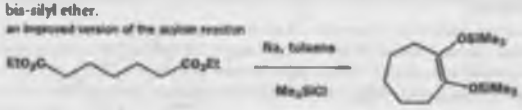
The diketone is however still reducible—in fact, 1,2-diketones are more reactive towards electrophiles and reducing agents than ketones because their π^* is lower in energy and straight away two electron transfers take place to form a molecule, which we could term an enediolate.

On quenching the reaction with acid, this dianion is protonated twice to give the enol of an α-hydroxy-ketone, and it is this α-hydroxy-ketone that is the final product of the acyloin reaction. The yield in this example is a quite respectable 70%. However, in many other cases, this usefulness of the acyloin reaction is hampered by the formation of by-products that arise because of the reactivity of the enediolate dianion. It is, of course, quite nucleophilic, and is likely to be formed in the presence

of the highly electrophilic diketone. It is also basic, and often catalyses a competing Claisen condensation of the esters being reduced.



The solution to these problems is to add trimethylsilyl chloride to the reaction mixture. The silyl chloride silylates the enediolate as it is formed, and the product of the acyloin reaction becomes a bis-silyl ether.



The silyl ethers are rarely desired as final products, and they can easily be hydrolysed to α-hydroxy-ketones with aqueous acid. This improved version makes four-membered rings efficiently.

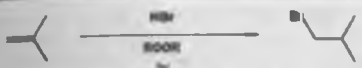
It's not by accident that these two examples of the acyloin reaction show the formation of cyclic compounds. It is a particularly powerful method of making carbocyclic rings of from four members upwards: the energy to be gained by pairing up the two electrons in the radical–radical reaction step more than compensates for the strain that may be generated in forming the ring.

The pinacol, McMurry, and acyloin reactions are exceptional

We've already said that this type of reaction, in which two radicals dimerize, is relatively uncommon. Most radicals are simply too reactive to react with one another! This may sound nonsensical, but the reason is simply that highly reactive species are unselective about what they react with. Although it might be energetically favourable for them to find another radical and dimerize, they are much more likely to collide with a solvent molecule, or a molecule of some other compound present in the mixture, than another radical. Reactive radicals are only ever present in solution in very low concentrations, so the chances of a radical–radical collision are very low. Radical attack on spin-paired molecules is much more common and, because the product of such reaction is also a radical, they give rise to the possibility of radical chain reactions.

Radical chain reactions

In looking at how radicals form, you've already seen examples of how radicals react. In fact, we've already dealt (if only very briefly) with every step of the sequence of reactions that makes up the mechanism of the radical reaction you met at the beginning of the chapter.



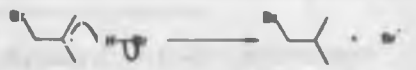
Let's now consider each step in turn and in more detail.

1 The dialkyl peroxide is homolysed (by heat or light) to give two alkoxy radicals

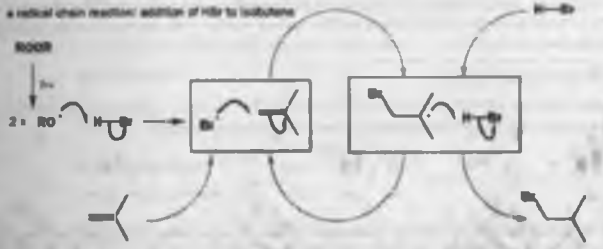
2 $RO^{\bullet}$ abstracts H from HBr (radical substitution) to give $Br^{\bullet}$

3 $Br^{\bullet}$ adds to isobutene to give a carbon-centred radical

4 The carbon-centred radical abstracts a hydrogen atom from H–Br to form the final addition product and regenerate $Br^{\bullet}$, which can react with another molecule of alkene



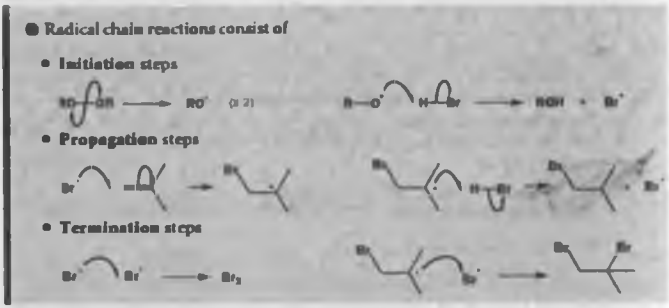
The whole process can conveniently be represented cyclically.



In each step in the cycle a radical is consumed and a new radical is formed. This type of reaction is therefore known as a **radical chain reaction**, and the two steps that form the cyclic process that keeps the chain running are known as the **chain propagation steps**. Only one molecule of peroxide **initiator** is necessary for a large number of product molecules to be formed and, indeed, the peroxide needs to be added in only catalytic quantities (about 10 mol%) for this reaction to proceed in good yield.

Any less than 10 mol%, however, and the yield drops. The problem is that the chain reaction is not 100% efficient. Because the concentration of radicals in the reaction mixture is low, radical–radical reactions are rare, but nonetheless they happen often enough that more peroxide keeps being needed to start the chain off again.

Reactions like this are known as **termination steps** and are actually an important part of any chain reaction; without termination steps the reaction would be uncontrollable.

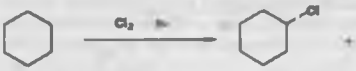


Selectivity in radical chain reactions

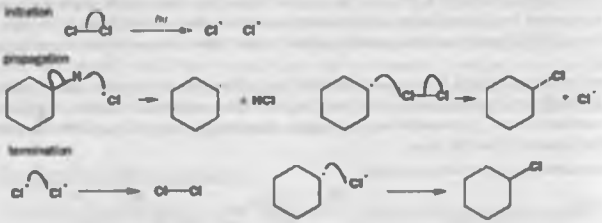
In the radical–radical reactions we looked at earlier, there was never any question of what would react with what: only one type of radical was formed and the radicals dimerized in identical pairs. Look at this chain reaction though—there are three types of radical present, $Br^{\bullet}$, $BrCH_2Me_2CH^{\bullet}$, and $RO^{\bullet}$, and they all react specifically with a chosen spin-paired partner: $Br^{\bullet}$ with the alkene, and $BrCH_2Me_2CH^{\bullet}$ and $RO^{\bullet}$ with HBr. We need to understand the factors that govern this chemoselectivity. In order to do so we shall look at another radical reaction with chemoselectivity and regioselectivity that is *measurable*.

Chlorination of alkanes

Alkanes will react with chlorine to give alkyl chlorides. For example, cyclohexane plus chlorine gas, in the presence of light, gives cycloheryl chloride and hydrogen chloride.

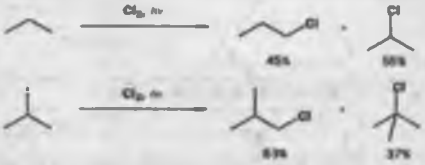


This type of reaction is important industrially since it is one of the few that allows compounds containing functional groups to be made from alkanes. As you might guess, since it needs light for initiation, the process is another example of a radical chain reaction. As with the radical addition of HBr to alkenes, we can identify initiation, propagation, and termination steps in the mechanism.



In this case, the termination steps are much less important than in the last case we looked at, and typically the chain reaction can continue for 10^6 steps for each initiation event (photolysis of chlorine). Be warned: reactions like this can be explosive in sunlight.

When the chlorine radical abstracts a hydrogen atom from the cyclohexane, only one product can be formed because all 12 hydrogen atoms are equivalent. For other alkanes, this may not be the case, and mixtures of alkyl chlorides can result. For example, propane is chlorinated to give a mixture of alkyl chlorides containing 45% 1-chloropropane and 55% 2-chloropropane, and isobutane is chlorinated to give 63% *iso*-butyl chloride and 37% *tert*-butyl chloride.



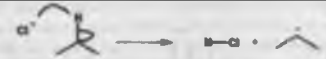
How can we explain the ratios of products that are formed? The key is to look at the relative stabilities of the radicals involved in the reaction and the strengths of the bonds that are formed and broken. First, the chlorination of propane. A chlorine radical, produced by photolysis, can abstract either a primary hydrogen atom, from the end of the molecule, or a secondary hydrogen atom, from the middle. For the first process, we have these energy gains and losses.

First process:

	ΔH, kJ mol^{-1}
one H–Cl bond formed	−431
one primary C–H bond broken	+423
total	−8

For the second process, the energies are given in the table.

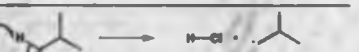
Second process:



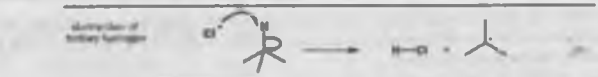
	ΔH, kJ mol^{-1}
one H–Cl bond formed	−431
one secondary C–H bond broken	+410
total	−21

Abstraction of the secondary hydrogen atom is more exothermic than abstraction of the primary hydrogen atom, for the related reasons that: (1) secondary C–H bonds are weaker than primary ones; and (2) secondary radicals are more stable than primary ones. So, we get more 2-chloropropane than 1-chloropropane. But in this case, that isn't the only factor involved: remember that there are six primary hydrogen atoms and only two secondary ones, so the relative reactivity of the primary and secondary positions is even more different than the simple ratio of products from the reaction suggests. This statistical factor is more evident in the second example we gave above, the chlorination of isobutane. Now the choice is between formation of a tertiary radical and formation of a primary one.

Abstraction of primary hydrogen:



	ΔH, kJ mol^{-1}
one H–Cl bond formed	−431
one primary C–H bond broken	+423
total	−8



	ΔH, kJ mol^{-1}
one H–Cl bond formed	−431
one tert-alkyl C–H bond broken	+397
total	−34

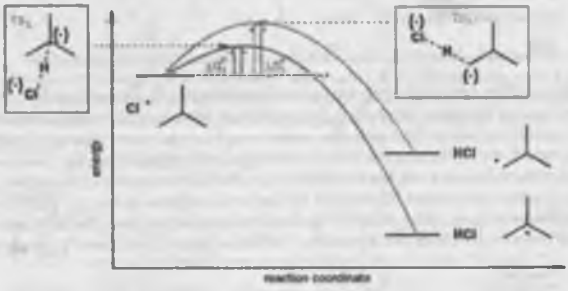
Tertiary radical formation is more exothermic, yet more primary alkyl chloride is formed than tertiary alkyl chloride. However, once the 9:1 ratio of primary to tertiary hydrogen atoms is taken into account, the relative reactivities, as determined experimentally, turn out to be as shown in the table.

ratio of products formed (tertiary:primary)	37:63
number of hydrogen atoms (tertiary:primary)	1:9
relative reactivity of each C–H bond (tertiary:primary)	37/1:63/9 = 37:7 = ca. 5:1

● Bond strength is all-important in radical reactions

These reactions illustrate a key point about radical reactions—a very important factor affecting selectivity is the strength of the bonds being formed and broken.

The rate of attack by Cl˙ on a tertiary C–H bond, then, is about five times the rate of attack by Cl˙ on a primary C–H bond. We said that this is because the formation of the tertiary radical is more exothermic than the formation of the primary radical. But the rate of a reaction depends not on ΔH for that reaction but on the activation energy of the reaction; in other words, the energy needed to reach the transition state for the reaction. But we can still use the stability of the product radicals as a guide to the stability of the transition state, because the transition state must have significant radical character.

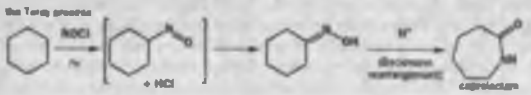


The energy diagram above illustrates this point. As the reactants (Cl˙ plus isobutane) move towards the products, they pass through a transition state (TS_1 for formation of the primary radical, TS_2 for formation of the tertiary) in which the radical character of the Cl˙ starting material is spread over both the Cl and the C centres. The greater stability of a tertiary radical compared with a primary one must be reflected to a lesser degree in these transition states: a radical shared between Cl and a tertiary centre will be more stable than a radical shared between Cl and a primary centre. The

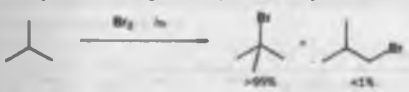
transition state TS_3 for the reaction at the tertiary C–H bond is therefore of lower energy than the transition state TS_1 for reaction at the primary C–H bond. In other words, the activation energy $\Delta G_3^{\ddagger}$ is smaller than $\Delta G_1^{\ddagger}$, so reaction at the tertiary C–H bond is faster.

The Toray process

A variant of this reaction, known as the Toray process, is used on an industrial scale in Japan to produce caprolactam, a precursor to nylon. Instead of chlorine, nitrosyl chloride is used to form a nitroso compound that rapidly tautomerizes to an oxime. As you saw in Chapter 27, this oxime undergoes a Beckmann rearrangement under acid conditions to form caprolactam.



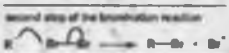
Bromine will also halogenate alkanes, and it does so much more selectively than chlorine. For example, the following reaction yields *tert*-butyl bromide with less than 1% of the primary isomer.



In this case, the first step of the radical chain reaction, the abstraction of H by $Br^{\bullet}$, is endothermic for both the primary and tertiary hydrogen atoms.

	ΔH, kJ mol^{-1}		ΔH, kJ mol^{-1}
one H–Br bond formed	−366	one H–Br bond formed	−366
one primary C–H bond broken	+423	one tertiary C–H bond broken	+397
total	+57	total	+31

The second step, trapping of the alkyl radical by Br_2, is, however, sufficiently exothermic for the reaction to be exothermic overall.

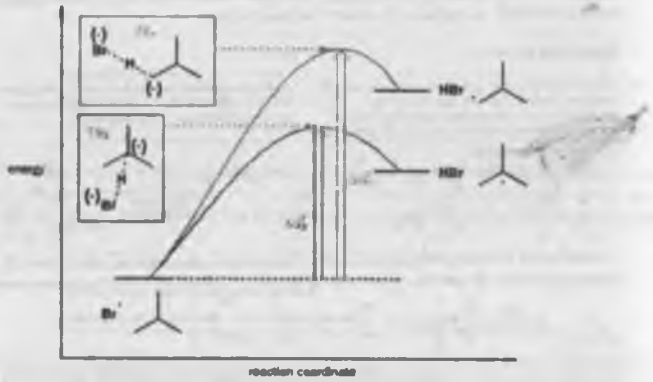


	ΔH, kJ mol^{-1}
one C–Br bond formed	−293
one Br–Br bond broken	+192
total	−101

Why is bromination so much more selective than the chlorination of alkanes? This is a good example of how the Hammond postulate applies to real chemistry. Because the products of the first step of the bromination ($R^{\bullet}$ plus HBr) are higher in energy than the starting materials, the transition state must be similar in structure and energy to that product radical; the difference in energies of the primary and tertiary product radicals should therefore be markedly reflected in the different energies of the transition states TS_1 and TS_3, and $\Delta G_3^{\ddagger}$ will be significantly larger than $\Delta G_1^{\ddagger}$. For the chlorination reaction, the products were just slightly lower in energy than the starting materials, so the transition states for the two possible reactions both resembled the starting materials rather more and the products rather less. These are the same for both tertiary and primary hydrogen abstractions, of course, so the difference in

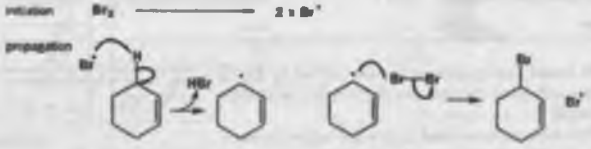
▶ The Hammond postulate gives information about the structure of transition states. It says that two states that interconvert directly (are directly linked in a reaction profile diagram) and that are close in energy are also similar in structure. So a transition state will be most like the starting material, the intermediate, or the product if it is close in energy to one of these observable structures.

energy of the product radicals exerts a less pronounced effect on the difference in energy of the transition states.

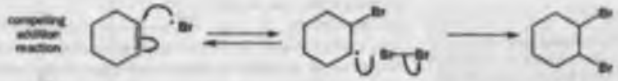


Selective radical bromination: allylic substitution of H by Br

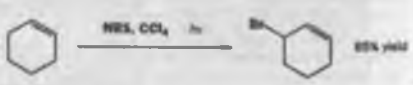
Because radical brominations are so selective, they can be used successfully in the lab to make alkyl bromides. There are relatively few ways of functionalizing an unfunctionalized centre, but radical allylic bromination is one of these. Just as tertiary radicals are more stable than primary ones, so allylic radicals are even more stable than tertiary ones (see the table on p. 000). In the presence of a suitable initiator, bromine will therefore selectively abstract an allylic hydrogen atom to give an allylic radical that can then be trapped by a molecule of bromine to regenerate a bromine radical (chain propagation) and produce the allylic bromide.



However, there is a problem with this reaction if bromine itself is used, because an alternative radical addition reaction can compete with radical abstraction.

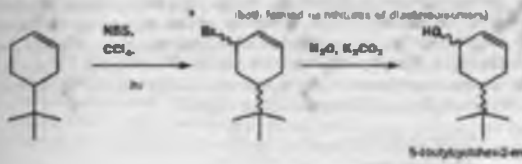


The first step of this competing addition reaction is, in fact, reversible: the reaction is driven forward by the participation of a second molecule of bromine that traps the product alkyl radical. This side-reaction can be prevented if the concentration of Br_2 in the reaction is kept very low. One possibility is to add Br_2 very slowly to the reaction mixture, but it is better not to use bromine itself, but a compound that releases molecular bromine slowly during the reaction. That compound is *N*-bromosuccinimide, or NBS.



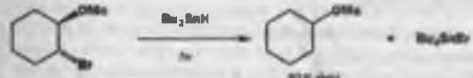
The HBr produced in the substitution reaction reacts with the NBS to maintain the low concentration of bromine.

While radical halogenation of alkanes is used only rarely in the laboratory, radical allylic bromination of alkenes is a versatile and commonly used way of making allylic bromides. Nucleophilic substitution reactions can then be used to convert the bromide to other functional groups. For example, some chemists in Manchester needed to make the two diastereoisomers of 5-*tert*-butylcyclohex-2-en-1-ol to study their reactions with osmium tetroxide. *tert*-Butyl cyclohexene is readily available, so they used a radical allylic bromination to introduce the functional group in the allylic position, which they converted to a hydroxyl group using aqueous base. Steric effects play a role here in the regioselectivity of the reaction: only the less hindered allylic hydrogen atoms further from the *t*-butyl group are removed.



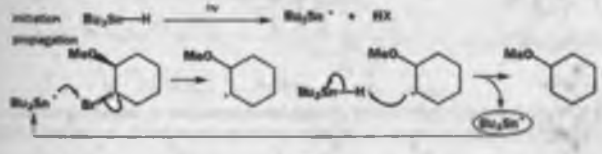
Reversing the selectivity: radical substitution of Br by H

Radical substitution reactions can also be used to *remove* functional groups from molecules. A useful reagent for this (and, as you will see, for other radical reactions too) is tributyltin hydride, Bu_3SnH. The Sn–H bond is weak and Bu_3SnH will react with alkyl halides to replace the halogen atom with H, producing Bu_3SnHal as a by-product.



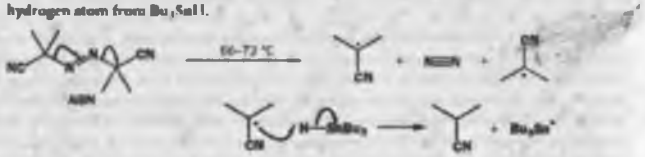
Clearly, for this reaction to be energetically favourable, new bonds formed (Sn–Br and C–H) must be stronger than the old bonds broken (Sn–H and C–halogen). Look at that table of average bond energies and you will see that this is indeed so.

The use of a tin hydride is crucial to this reaction: Sn–H bonds are weaker than Sn–Br bonds, while, for carbon, C–H bonds are stronger. Bu_3SnH is therefore an effective source of $Bu_3Sn^{\bullet}$ radicals, and the $Bu_3Sn^{\bullet}$ radical will abstract halogens, particularly I or Br, but also Cl, from organic halides, breaking a weak C–halogen (C–Hal) bond and forming a strong Sn–Hal bond. The complete mechanism of the reaction reveals a chain reaction.

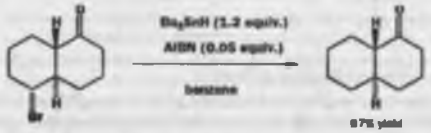


Homolysis of Bu_3SnH is promoted by the initiator AIBN

As you would imagine, the weakest C–Hal bonds are the easiest to cleave, so alkyl bromides are reduced more rapidly than alkyl chlorides, and alkyl fluorides are unreactive. With alkyl iodides and bromides, daylight can be sufficient to initiate the reaction, but with alkyl chlorides, and often with alkyl bromides as well, it is generally necessary to produce a higher concentration of $Bu_3Sn^•$ radicals by adding an initiator to the reaction. The best choice is usually AIBN, which you met on p. 000. This compound undergoes thermal homolysis at 60 °C to give nitrile-stabilized radicals that abstract the hydrogen atom from Bu_3SnH.



Why use AIBN; why not a peroxide? (You came across peroxides as initiators of the addition of H–Br to alkenes.) Since we want to cleave only a weak Sn–H bond, we can get away with using a relatively unreactive, nitrile-stabilized radical. Peroxides, on the other hand, generate RO$^•$ radicals. These are highly reactive and will abstract hydrogen from almost any organic molecule, not just the weakly bonded hydrogen atom of Bu_3SnH, and this would lead to side-reactions and lack of selectivity. AIBN is needed only in sufficient quantities to be an initiator of the reaction; it is the Bu_3SnH that provides the hydrogen atoms that end up in the product, so usually you need only 0.02 to 0.05 equivalents of AIBN and a slight excess (1.2 equivalents) of Bu_3SnH.

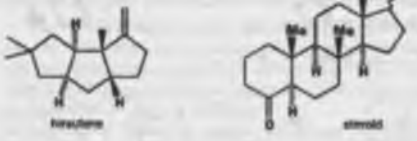


Controlling radical chains

You have now met two examples of radical chain reactions:

1. radical addition of halogens to double bonds
2. radical substitution of hydrogen by halogens, or of halogens by hydrogen

You have seen how the selectivity of these reactions depends upon the bond strengths of the bond being formed or broken. Until about 1975, these reactions, with a few exceptions, were all that were expected of radicals. Since that date, however, the use of radicals in synthetic chemistry has increased tremendously, to the point where highly complex ring structures such as the natural product hirsutene and steroids can be made from simple acyclic precursors in one radical-promoted step.



What has made this all possible is that chemists have learned how to understand the selectivity of radical reactions to such a degree that they can design starting materials and reagents to define

precisely the bonds that will break and form during the reactions. We shall now go on to look at the most important consequence of this ability to control radical reactions: they can be used to make carbon–carbon bonds.

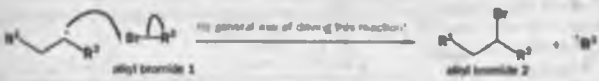
Carbon–carbon bond formation using radicals

The following radical reaction forms a new carbon–carbon bond. The mechanism is quite similar to that of the very first radical reaction we showed you, right at the beginning of the chapter. Now, with your additional appreciation of the role of bond strength in the selectivity radical reactions, you should be able to understand why each step proceeds in the way that it does.

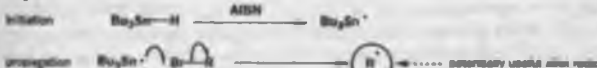
Firstly, the weakest bond, C–Br, is broken by the light being shone on to the reaction. Two radicals form, CCl_3 and Br', and it is the CCl_3 that adds to the (less hindered) unsubstituted end of the alkene to produce a (more stable) secondary benzylic radical.

This radical abstracts a Br, atom from the $BrCCl_3$, breaking the (weakest) C–Br bond, forming the product and regenerating $'CCl_3$, which adds to another molecule of alkene. Notice that the carbon-centred radical abstracts Br' and not $'CCl_3$ from $BrCCl_3$—to abstract $'CCl_3$ would require a radical substitution at carbon—remember, radicals want the easy pickings from the front of the display; they don't go nosing round the back to see if there's anything better to be had.

This reaction works quite well, giving 78% of the product, but it relies on the fact that the starting material, $BrCCl_3$, has an unusually weak C–Br bond (the $'CCl_3$ radical is highly stabilized by those three chlorine atoms). You can't use most other alkyl bromides for a number of reasons, not least of them being that the product is also an alkyl bromide and, without the selectivity provided by the CCl_3 group, the result would be an awful mixture of polymers. The problem is that we want the product radical to abstract Br from the starting alkyl bromide to make a new alkyl bromide and a new starting radical, and there is no energetic driving force behind this transformation.

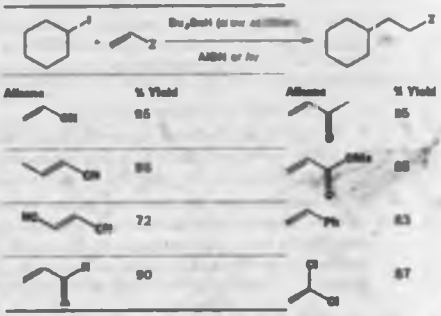


For a way of overcoming this problem, let's go back to the reaction we looked at a few pages ago, the dehalogenation of alkyl halides by Bu_3SnH. The mechanism involves formation of an alkyl (carbon-centred) radical by abstraction of Br by Bu_3Sn'. This alkyl radical then just abstracted H' from Bu_3SnH.



Is it not possible to use this alkyl radical more constructively, and encourage it to react with another molecule (an alkene, say, like $'CCl_3$ did)? The answer is a qualified yes: look at this reaction.

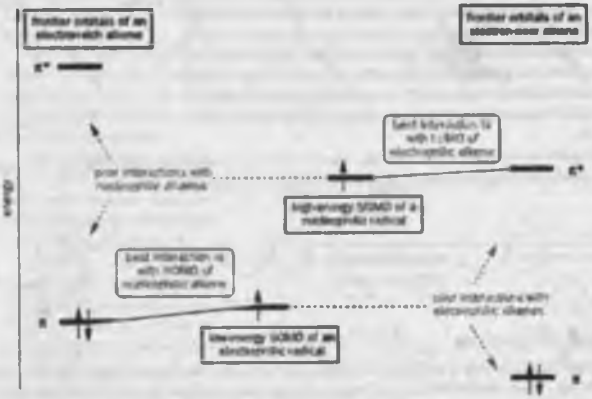
To explain why, we have to go back to our analysis (on p. 000) of the electronic structure of radicals and the energy of SOMOs. We said there that, while both electron-withdrawing groups and electron-donating groups will stabilize radicals, electron-withdrawing groups tend to lower the energy of the SOMO, while electron-donating groups tend to raise the energy of the SOMO.



Electrophilic and nucleophilic radicals

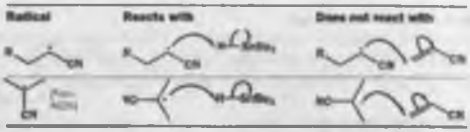
- *Low-energy* SOMOs are more willing to accept an electron than to give one up; radicals adjacent to electron-withdrawing groups are therefore *electrophilic*
- *High-energy* SOMOs are more willing to give up an electron than to accept an electron; radicals adjacent to electron-donating groups are therefore *nucleophilic*

Hence the preferred reactivity of these alkyl radicals: they are relatively nucleophilic and therefore prefer to react with electrophilic alkenes. Reaction between a nucleophilic alkyl radical and an unfunctionalized (and therefore nucleophilic) alkene is much slower. Similarly, radicals adjacent to electron-withdrawing groups do not react well with electrophilic alkenes. We can represent all this on an energy level diagram.



We will now consider a third type of radical—cyanide-stabilized alkyl radicals.

The diagram above explains the third aspect of radical chemoselectivity in this reaction: why both the product radical and the radicals produced by AIBN choose to react with Bu_3SnH and not with acrylonitrile. These radicals are electrophilic—they have an electron-withdrawing nitrile group attached to the radical centre so reaction with an electron-poor alkene is slow.



Electrophilic radicals

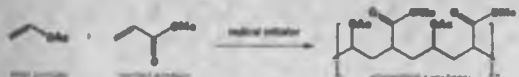
Having seen the energy diagram above, you will not be surprised to learn that the malonate radical adds readily not to electrophilic alkenes, but to nucleophilic alkenes, such as this vinyl ether, which carries an electron-donating oxygen substituent. This electrophilic radical can also be formed by H-abstraction and by oxidation.

This difference in reactivity applies to non-carbon-centred radicals too. For example, the methyl radical $CH_3^{\bullet}$ and the chlorine radical $Cl^{\bullet}$ will both abstract a hydrogen atom from propanoic acid. As you would expect, the methyl radical abstracts the hydrogen atom from next to the carbonyl group to form a carbonyl stabilized radical. Perhaps surprisingly (in view of what we said earlier about the selectivity of radical chlorinations), the chlorine radical abstracts a hydrogen atom from the terminal methyl group of the acid, despite the fact that this C–H bond is stronger. The reason has to be to do with HOMO–LUMO interactions. The methyl radical is nucleophilic, with a high-energy SOMO. It therefore attacks the C–H bond with the lowest LUMO, in other words, α to the carbonyl group. The chlorine atom, on the other hand, is electrophilic: it has a low-energy SOMO (because it is an electronegative element) and attacks the C–H bonds of the terminal methyl group because they have the highest-energy HOMO. Chlorination of functionalized compounds is not as simple as we implied earlier!

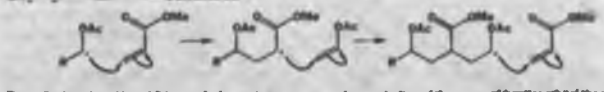
Summary of requirements for the successful use of the tin method

• Bu_3SnH	must be added or generated slowly
• R–X starting material	must contain a weak C–X bond (C–I or C–Br)
• Radical trap	must be an electrophilic alkene
	must be present in a concentration at least 10 times that of Bu_3SnH

Copolymerization



Copolymerization—continued



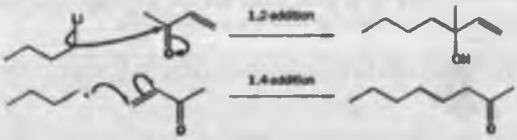
The radical produced by addition to vinyl acetate is nucleophilic, so it adds to methyl acrylate; the radical produced by addition to methyl acrylate is electrophilic, so it adds to vinyl acetate. This re addition is a clear demonstration of the power of frontier orbital theory to explain the reactivity of organic molecules—it would be hard to come up with any other convincing explanation.

The reactivity pattern of radicals is quite different from that of polar reagents

The first reaction that you met in this book, in Chapter 2, was the nucleophilic addition to a carbonyl group. Yet we have shown you no examples of radicals adding to carbonyl groups. This typical reaction of polar reagents is really quite rare with radicals.

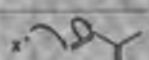
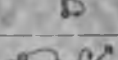
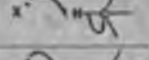
In Chapter 8 we introduced the concept of pK_a in which we saw acids and bases exchanging protons. Among the strongest organic acids are those containing O–H bonds. Yet you have seen no radical reactions in which an O–H bond is broken—in fact the reaction on p. 000 used ethanol as a solvent! Carbon acids tend to be much weaker—yet you've seen plenty of examples of C–H bonds being broken by radical attack.

In Chapter 17 we introduced nucleophilic substitution at saturated carbon, using as an example some alkyl bromides. Now, radicals do react with alkyl halides—but not at carbon! You've seen how alkyl halides undergo substitution at bromine with tin radicals. The difference in reactivity between, say, organolithiums and radicals, both of them highly reactive, is nicely illustrated by the way in which they react with enones.



We introduced the terms *hard* and *soft* in Chapters 10 and 17. From all these reactions it's evident that radicals are very soft species: their reactions are driven not by the charge density on an atom but by the coefficient and energy of the frontier orbitals at that atom.

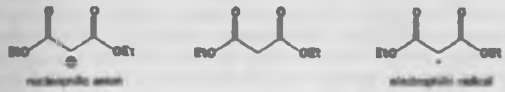
Summary of typical reactivity patterns

With	Polar nucleophiles typically react like this	Radicals typically react like this
unsaturated C=O compounds		
X–H bonds		
alkyl halides		

Umpolung

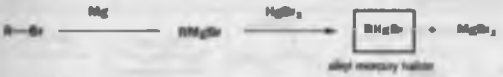
In Chapter 30, you came across the idea of umpolung, the inversion of the usual reactivity pattern of a molecule. You may have already noticed that radicals often have an umpolung reactivity pattern. Alkyl halides are electrophiles in polar reactions; yet they generate nucleophilic radicals that react with electrophilic alkenes.

Similarly, we consider the carbon atoms α to carbonyl groups to be nucleophilic, because enolization creates a partial negative charge there (in other words, ketones are a^1 reagents). Yet carbonyl-stabilized radicals are electrophilic.

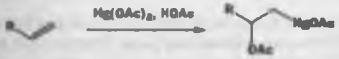


An alternative way of making alkyl radicals: the mercury method

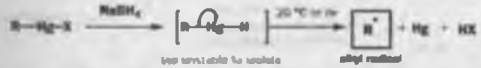
Although the tin hydride + alkyl halide method is probably the most important way of making alkyl radicals, we should mention some other methods that are useful. We said at the beginning of the chapter that carbon–metal bonds, particularly carbon–transition metal bonds, are weak and can homolyse to form radicals. Alkyl mercuries are useful sources of alkyl radicals for this reason. They can be made by a number of routes, for example, from Grignard reagents by transmetallation.



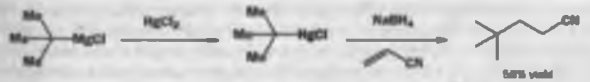
Addition of mercury acetate to a double bond gives an alkyl mercury bearing a functional group.



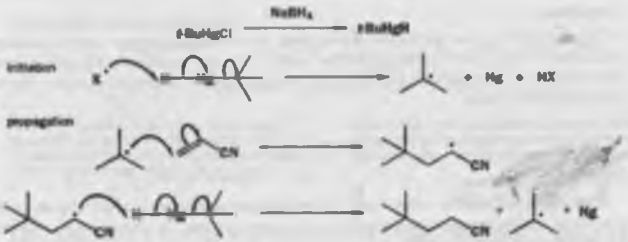
Alkyl mercury halides and alkyl mercury acetates are quite stable, but reduction with sodium borohydride leads to highly unstable alkyl mercury hydrides, which collapse at room temperature or in the presence of light to yield alkyl radicals. One other product is mercury metal and you might think you would get H^- as well but this is too unstable to be formed and is captured by something else (X)—you will see what X is in a moment. This initial decomposition of RHgH initiates the chain but its propagation is by the different mechanism shown below.



In this example a *t*-butyl radical does conjugate addition on to acrylonitrile.



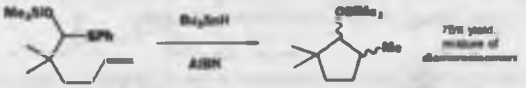
The key propagation step in the mechanism is abstraction of hydride from the starting alkyl mercury. In the propagation step anything will do to cleave the weak Hg–H bond but once the chain is running it is an alkyl radical that does this job, just as in tin hydride chemistry.



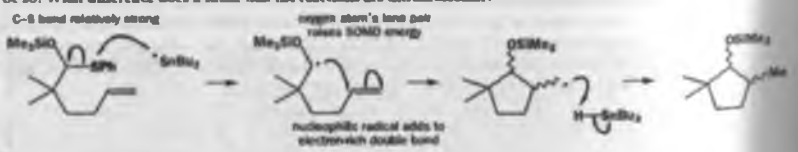
Unfortunately, radicals derived from alkylmercuries are even more limited in what they will react with than radicals made from alkyl halides by the tin hydride method. Styrene, for example, cannot be used to trap alkylmercury-derived radicals efficiently because the radicals react more rapidly with the mercury hydride (which has an even weaker metal–H bond than Bu_3SnH) than with the styrene.

Intramolecular radical reactions are more efficient than intermolecular ones

All of the reactions you have met so far involve radical attack between two molecules. We've pointed out some of the drawbacks when C–C bonds are made in this way: the radical trap has to be activated (that is, electrophilic to capture nucleophilic radicals) and must often be present in excess; and the radical starting material must contain very weak C–X bonds (such as C–Br, C–I, C–Hg). The requirements are much less stringent, however, if the radical reaction is carried out intramolecularly. For example, this reaction works.



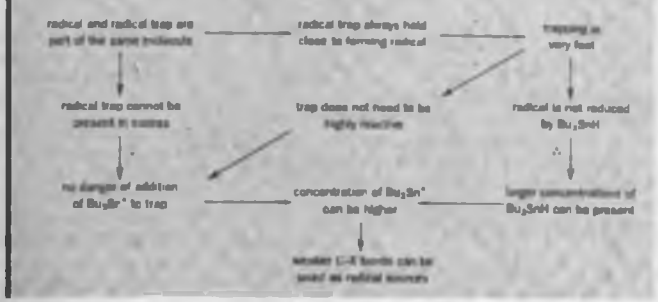
Notice that the double bond is not activated: in fact, it is nucleophilic, and the reaction still works even though the radical is also substituted with an electron-donating group. The C–S bond that is broken is also relatively strong, yet nonetheless a high yield of product is obtained. Why should this be so? What difference does it make that the reactions are intramolecular?



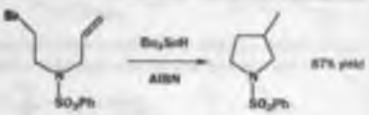
The key is that the intramolecular cyclization of the radical is now enormously favoured over other possible courses of action for the radical. Remember that when we were carrying out radical reactions *intermolecularly*, addition to the radical trap was encouraged by increasing the concentration of radical trap and decreasing the concentration of Bu_3SnH to avoid radical reduction. For *intramolecular* reactions, the double bond that acts as the radical trap is always held close to the radical, and cyclization takes place extremely rapidly, even on to unactivated double bonds. The hydride donor (Bu_3SnH) doesn't get a look in, and can be present in higher concentrations than would otherwise be possible. Moreover, as there is only one equivalent of radical trap, and the trap need not be highly reactive, there is little danger of high concentrations of $Bu_3Sn^{\bullet}$ reacting with it, so

the concentration of $Bu_3Sn^{\cdot}$ can build up to levels where the rate of abstraction of groups like Cl, SPh, and SePh is acceptable, despite their stronger C–X bonds.

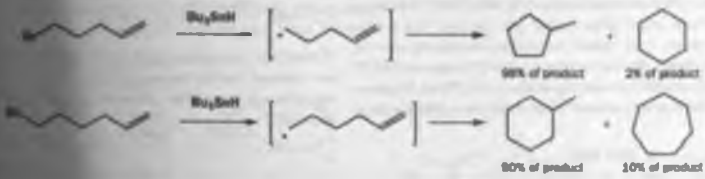
Why are intramolecular radical reactions so good?



Overall then, intramolecular radical reactions are very powerful, and are often used to make five-membered rings.



It is possible to make other ring sizes also, but the range is rather limited. Because of ring strain, three- and four-membered rings cannot be formed by radical reactions. Otherwise, smaller rings form faster than larger ones: look at these selectivities.

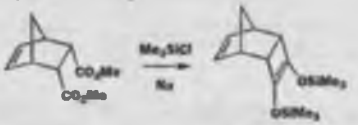


The preference for formation of a smaller ring is a very powerful one: in this reaction, the five-membered ring forms and not the six-membered one, even though cyclization to give a six-membered ring would also give a stabilized radical.

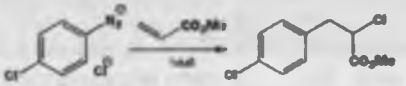
Radicals are important because they react in ways difficult to achieve with anions and cations and with different selectivity. Though radical reactions are less important than ionic reactions you need to understand their mechanisms because they are widespread in an atmosphere of the oxygen diradical. In the next chapter we will move on from carbon atoms carrying seven valence electrons to carbon atoms carrying only six valence electrons called *carbenes*.

Problems

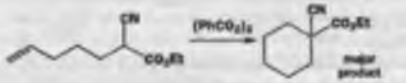
1. In Chapter 33, Problem 13, we used a silylated ene–diol that was actually made in this way. Give a mechanism for the reaction and explain why the Me_3SiCl is necessary.



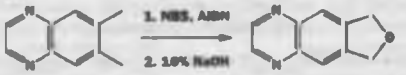
2. Heating the diazonium salt below in the presence of methyl acrylate gives a reasonable yield of a chloroacid. Why is this unlikely to be nucleophilic aromatic substitution by the S_NI mechanism (Chapter 22)? Suggest an alternative mechanism that explains the regioselectivity.



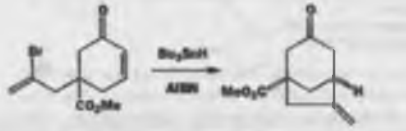
3. Suggest a mechanism for this reaction and comment on the ring size formed. What is the minor product likely to be?



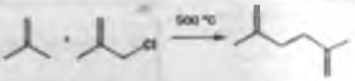
4. Treatment of this aromatic heterocycle with NBS (*N*-bromosuccinimide) and AIBN gives mainly one product but this is difficult to purify from minor impurities containing one or three bromine atoms. Further treatment with 10% aqueous NaOH gives one easily separable product in modest yield (50%). What are the mechanisms for the reactions? What might the minor products be?



5. Propose a mechanism for this reaction accounting for the selectivity. Include a conformational drawing of the product.



6. An ICI (now AstraZeneca) process for the manufacture of the diene used to make pyrethroid insecticides involves heating these compounds to 500 °C in a flow system. Propose a radical chain mechanism for the reaction.

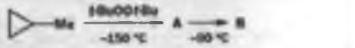


7. Heating this compound at 560°C gives two products with spectroscopic data shown below. What are these products and how are they formed?

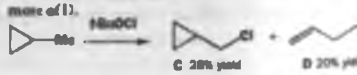
A has IR 1640 cm^{-1}; *m/z* 138 (100%), 140 (33%); δ_H 7.1 p.p.m. (4H, s), 6.5 p.p.m. (1H, dd, *J* 17, 11 Hz), 5.5 p.p.m. (1H, dd, *J* 17 Hz), and 5.1 p.p.m. (1H, dd, *J* 11, 2 Hz).

B has IR 1700 cm^{-1}; *m/z* 111 (45%), 113 (15%), 139 (50%), 140 (100%), 141 (20%), and 142 (33%); δ_H 9.9 p.p.m. (1H, s), 7.70 p.p.m. (2H, d, *J* 9 Hz), and 7.43 (p.p.m. 2H, d, *J* 9 Hz).

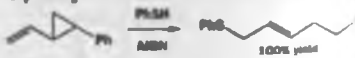
8. Treatment of methylcyclopropane with peroxides at very low temperature (–150 °C) gives an unstable species whose ESR spectrum consists of a triplet with coupling 20.7 gauss and each line splitting showing dtt coupling of 2.0, 2.6, and 3.0 gauss. Warming to a mere –90 °C gives a new species whose ESR spectrum consists of a triplet of triplets with coupling 22.2 and 28.5 gauss and each line splitting showing small ddd coupling of less than 1 gauss.



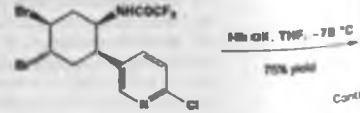
If methylcyclopropane is treated with *t*-BuOCl, various products are obtained, but the two major products are C and D. At lower temperatures more of C is formed and at higher temperatures more of D.



Treatment of the more highly substituted cyclopropane with PhSH and AIBN gives a single product in quantitative yield. Account for all of these reactions, identifying A and B and explaining the differences between the various experiments.



9. The last few stages of Corey's epibatidine synthesis are shown here. Give mechanisms for the first two reactions and suggest a reagent for the last step.



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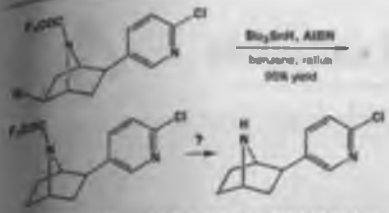
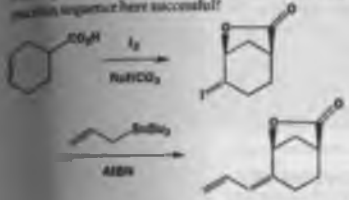
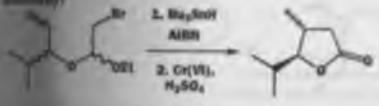


10. How would you make the starting material for this sequence of reactions? Give a mechanism for the first reaction that explains its regio- and stereoselectivity. Your answer should include a conformational drawing of the product. What is the mechanism of the last step? Attempts to carry out this last step by iodine–lithium exchange and reaction with allyl bromide fail. Why? Why is the reaction sequence here successful?

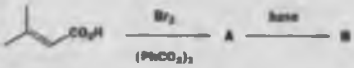


11. Suggest a mechanism for this reaction explaining why a mixture of diastereoisomers of the starting material gives a single diastereoisomer of the product. Is there any other form of selectivity?

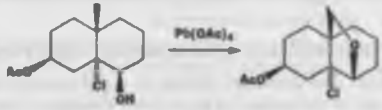


12. On the other hand, why does a single diastereoisomer of this organomercury compound give a mixture of diastereoisomers (68:32) on reduction with borohydride in the presence of acrylonitrile?

13. Reaction of this carboxylic acid ($C_5H_6O_2$) with bromine in the presence of dibenzoyl peroxide gives an unstable compound ($C_5H_6Br_2O_2$) that gives a stable compound ($C_5H_5BrO_2$) on treatment with base. The stable compound has IR 1735 and 1645 cm^{-1} and ^1H NMR δ_H 6.18 p.p.m. (1H, s), 5.00 p.p.m. (2H, s), and 4.18 p.p.m. (2H, s). What is the structure of the stable product? Deduce the structure of the unstable compound and mechanisms for the reactions.



14. The product formed in Problem 9 of Chapter 20 was actually used to make this cyclic ether. What is the mechanism?



Synthesis and reactions of carbenes

40

Connections

Building on:

- Conjugate addition ch10 & ch23
- Energy profile diagrams ch13
- Elimination reactions ch19
- Controlling stereochemistry ch16 & ch33–ch34
- Retrosynthetic analysis ch30
- Diastereoselectivity ch33–ch34
- Rearrangements ch37
- Radicals ch38

Arriving at:

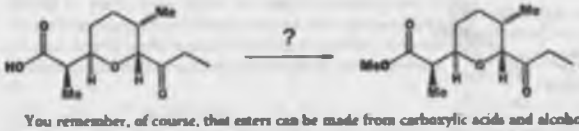
- Carbenes are neutral species with only six electrons
- Carbenes can have paired or unpaired electrons
- Carbenes are normally electrophilic
- Typical reactions include insertion into C=C bonds
- Insertion into C–H and O–H bonds is possible
- Intramolecular insertion is stereospecific
- Carbenes rearrange easily
- Carbenes are useful in synthesis

Looking forward to:

- Determination of mechanism ch41
- Heterocycles ch42–ch44
- Main group chemistry ch46–ch47
- Organometallic chemistry ch48

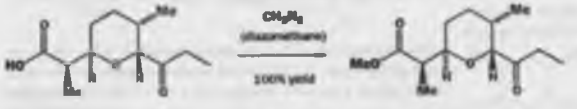
Diazomethane makes methyl esters from carboxylic acids

In 1981, some chemists in Pennsylvania needed to convert this carboxylic acid into its methyl ester as part of the synthesis of an antibiotic compound. What reagent did they choose to do the reaction?

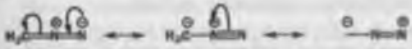


You remember, of course, that esters can be made from carboxylic acids and alcohols under acid catalysis, so you might expect them to use this type of method. On a small scale, it's usually better to convert the acid to an acyl chloride before coupling with an alcohol, using pyridine (or DMAP + Et_3N) as a base; this type of reaction might have been a reasonable choice too.

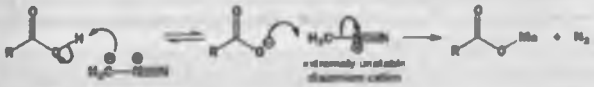
But, in fact, they chose neither of these methods. Instead, they simply treated the carboxylic acid with a compound called diazomethane, CH_2N_2, and isolated the methyl ester.



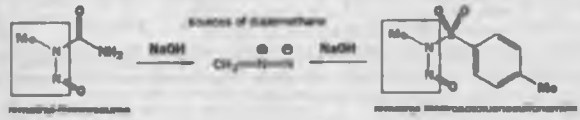
Diazomethane, CH_2N_2, is a rather curious compound that has to be drawn as a dipole. There are several different ways of expressing its structure.



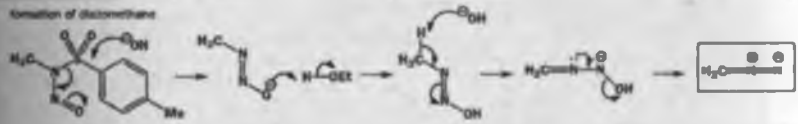
Diazomethane methylates carboxylic acids because carboxylic acids readily protonate it, giving an extremely unstable diazonium cation. This compound is desperate to lose N_2, the world's best leaving group, and so it does, with the N_2 being substituted by the carboxylate anion. The carboxylate anion is in exactly the right position to carry out an S_N2 reaction and that is what we have drawn.



Diazomethane methylation is a good way of making methyl esters from carboxylic acids on a small scale because yields are excellent and the only by-product is nitrogen. However, there is a drawback: diazomethane has a boiling point of –24 °C, and it is a toxic and highly explosive gas. It therefore has to be used in solution, usually in ether; the solution must be dilute, because concentrated solutions of diazomethane are also explosive. It is usually produced by reaction of *N*-methyl-*N*-nitrosourea or *N*-methyl-*N*-nitrosotoluenesulfonamide with base, and distilled out of that reaction mixture as an azeotrope with ether, straight into a solution of the carboxylic acid.

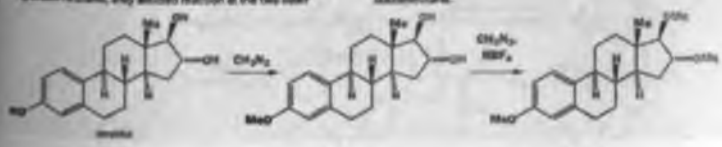


The mechanism of the reaction that forms diazomethane is shown below. The key step is base-catalysed elimination, though the curly arrows we have to draw to represent this are rather tortuous!



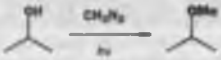
Diazomethane will also methylate phenols, because they too are acidic enough to protonate it. Ordinary alcohols, though, are not methylated because they are not strong enough acids to protonate diazomethane.

Selective methylation



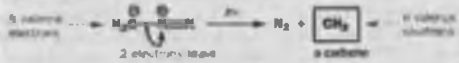
Photolysis of diazomethane produces a carbene

Alcohols can be methylated by diazomethane if the mixture is irradiated with light.

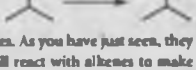


The mechanism is now totally different, because the light energy promotes loss of nitrogen (N_2) from the molecule *without protonation*. This means that what is left behind is a carbon atom carrying just two hydrogen atoms (CH_2), and having only six electrons. Species like this are called **carbenes**, and they are the subject of this chapter.

> ● **Carbenes are neutral species containing a carbon atom with only six valence electrons.**



Carbenes have six electrons: two in each bond and two nonbonding electrons, which are often represented as $:CR_2$ (as though they were a lone pair). As you will see later, this can be misleading, but $:CR_2$ is a widely used symbol for a carbene. This carbene is trapped by the alcohol to make an ether.

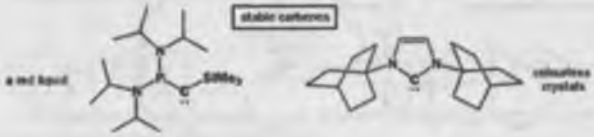


Like the radicals in Chapter 39, carbenes are extremely reactive species. As you have just seen, they are trapped by alcohols to make ethers, but more importantly they will react with alkenes to make cyclopropanes, and they will also insert into C–H bonds.

> ● **Typical carbene reactions**
>
> • **The carbene inserts itself into a σ bond or a π bond.**
>
> 
>
>
> **We will discuss the mechanisms of these three important reactions shortly, but we have introduced them to you now because they demonstrate that the reactions of carbenes are dominated by *insertion reactions* (here, insertion into O–H, C=C, and C–H) driven by their extreme *electrophilicity*. A carbon atom with only six electrons will do almost anything to get another two!**

How do we know that carbenes exist?

The best evidence for the existence of carbenes comes from some very few examples that are stable compounds. An X-ray crystal structure of the second example shown the bond angle at the carbene carbon to be 102°—we will come back to the significance of this later.



But these stable carbenes are very much the exception: most carbenes are too reactive to be observed directly. Electronic and, more importantly, steric effects make these two compounds so stable.

Even reactive carbenes can be observed, however, if they are formed by irradiating precursors (often diazo compounds like diazomethane, which we have just been discussing) trapped in frozen argon at very low temperatures (less than 77 K). IR and ESR spectroscopy can then be used to determine their structure.

How are carbenes formed?

Carbenes are usually formed from precursors by the loss of small, stable molecules. We will discuss some of the most important methods in turn, but you have already seen one in action: the loss of nitrogen from a diazo compound.

Naming azo compounds

Don't confuse diazonium salts with azo compounds. Diazomethane has twice as many nitrogen atoms per

diazomethane azomethane ketone alkyl azide

You met diazonium salts in Chapter 23. Aryne diazonium salts are stable compounds, but alkyl diazonium salts, which are formed by protonation of diazo compounds, are not. They decompose rapidly to carbocations—this was how the carboxylic acid got methylated at the beginning of

methyl group as azomethane.

the chapter. Other relatives of the azo and diazo compounds are alkyl azides. Alkyl azides have three nitrogen atoms and are usually stable but may explode on impact or heating.

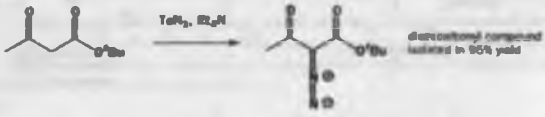
Carbenes from diazo compounds

We showed you the formation of a carbene from diazomethane to illustrate how this reaction was different from the (ionic) methylation of carboxylic acids. But this is not a very practical way of generating carbenes, not least because of the explosive nature of diazoalkanes. However, diazocarbonyl compounds are a different matter.

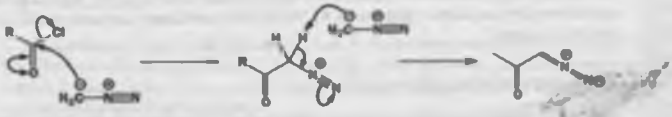
They are much more stable, because the electron-withdrawing carbonyl group stabilizes the diazo dipole, and are very useful sources of carbenes carrying a carbonyl substituent. There are two main ways of making diazocarbonyl compounds:

1 by reacting an acyl chloride with diazomethane

2 by reacting the parent carbonyl compound with tosyl azide, TsN_3, in the presence of base.



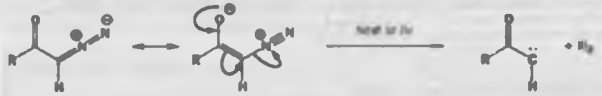
The reaction of diazomethane with acyl chlorides starts as a simple acylation to give a diazonium compound. If there is an excess of diazomethane, a second molecule acts as a base to remove a rather acidic proton between the carbonyl and the diazonium groups to give the diazocarbonyl compound.



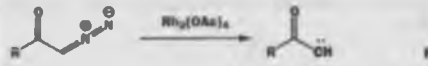
What happens to that second molecule of diazomethane? By collecting a proton it turns into the very reactive diazonium salt, which collects a chloride ion, and MeCl is given off as a gas. The second method uses tosyl azide, which is known as a diazo transfer reagent—it's just N_2 attached to a good leaving group.

tosyl azide, TsN_3

Diazocarbonyl compounds can be decomposed to carbenes by heat or light. The formation of very stable gaseous nitrogen compensates for the formation of the unstable carbene.



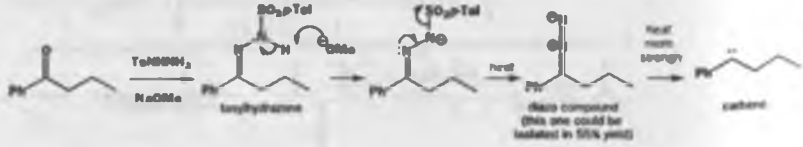
But it is much more common in modern chemistry to use a transition metal such as copper or rhodium, to promote formation of the carbene.



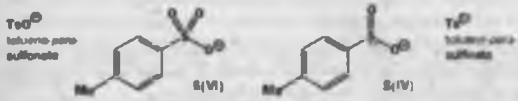
Carbenes formed in this way are, in fact, not true carbenes because it appears that they remain complexed with the metal used to form them. They are known as **carbenoids**, and their reactions are discussed later in the chapter.

Carbenes from tosylhydrazones

Many more carbenes can be made safely from diazoalkanes if the diazoalkane is just an intermediate in the reaction and not the starting material. Good starting materials for these reactions are tosylhydrazones, which produce transient diazo compounds by base-catalysed elimination of toluenesulfinate. The diazo compound is not normally isolated, and decomposes to the carbene on heating.



Notice that the leaving group from nitrogen is not the familiar tosylate (toluene-*p*-sulfonate TsO^-) but the less familiar toluene-*p*-sulfinate (Ts^-).



Carbenes are formed in a number of other similar reactions—for example, loss of carbon monoxide from ketenes or elimination of nitrogen from aziridines—but these are rarely used as a way of deliberately making carbenes.

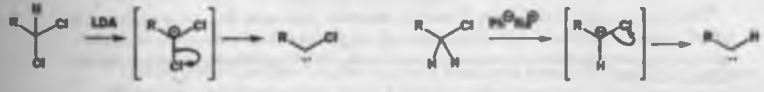
Carbene formation by α elimination

In Chapter 19 we discussed **β elimination** in detail, reactions in which a hydrogen atom is removed from the carbon atom β to the leaving group.

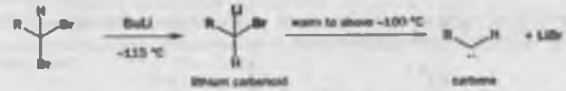
α Eliminations (eliminations in which both the proton and the leaving group are located on the same atom) are also possible—in fact, the reaction we've just been talking about (elimination of toluenesulfinate from tosylhydrazones) is an α elimination. α Eliminations follow a mechanism akin to an E1cB β elimination—a strong base removes an acidic proton adjacent to an electron withdrawing group to give a carbanion. Loss of a leaving group from the carbanion creates a carbene.

One of the best known α elimination reactions occurs when chloroform is treated with base. This is the most important way of making dichlorocarbene, $:CCl_2$, and other dihalocarbenes too, although it must be said that the widespread use of dichlorocarbene in chemistry is due mainly to the ease with which it can be made using this method!

Hydroxide and alkoxide anions are strong enough bases to promote α elimination from chloroform, and from other trihalomethanes. Carbenes can be formed from dihaloalkanes by deprotonation with stronger bases such as LDA, and even from primary alkyl chlorides using the extremely powerful bases phenylsodium or *t*-BuLi/*t*-BuOK (weaker bases just cause β elimination).

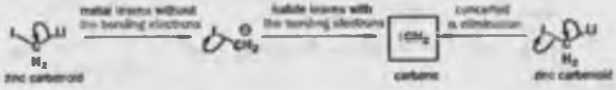


When geminal dibromoalkanes are treated with BuLi, a halogen–metal exchange reaction produces a lithium carbenoid, with a metal atom and a halogen attached to the same carbon atom. Lithium carbenoids are stable at very low temperatures—they can be observed by NMR, but they decompose to carbenes at about −100 °C.

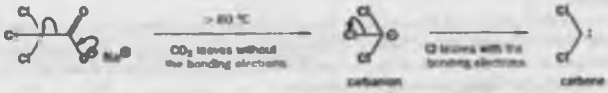


While lithium carbenoids have limited applicability in chemistry, an analogous zinc carbenoid, which can be formed by insertion of zinc into diiodomethane, is a reagent in one of the most widely used carbenoid reactions in chemistry—the Simmons–Smith reaction.

The essence of this type of carbenoid is that it should have a leaving group, such as a halogen, that can remove a pair of electrons and another, usually a metal, that can donate a pair of electrons. If the metal leaves first, a carbanion is created that can lose the halogen to make a carbene. They might also leave together. Both are α eliminations.



The problem with many of these reactions is that they require strong bases—either the organometallic compound itself is basic or a base must be used to create the carbanion. Carbenes are so unstable that they must be formed in the presence of the compound they are intended to react with, and this can be a problem if that compound is base-sensitive. For dichlorocarbene, a way round the problem is to make the carbanion by losing CO_2 instead of a metal or a proton. Decarboxylation of sodium trichloroacetate is ideal as it happens at about 80 °C in solution.

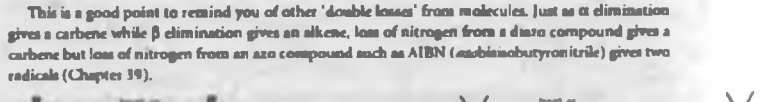


Summary: the most important ways of making carbenes

Carbenes are neutral species containing a carbon atom with only six valence electrons.

Type of carbene	Method of formation
	metal (rhodium or copper)-catalysed decomposition of diazocarbonyl compound
	thermal decomposition of diazo compound, often derived from tosylhydrazone
	α elimination of chloroform with base

This is a good point to remind you of other '*double losses*' from molecules. Just as α elimination gives a carbene while β elimination gives an alkene, loss of nitrogen from a diazo compound gives a carbene but loss of nitrogen from an azo compound such as AIBN (*azobisisobutyronitrile*) gives two radicals (Chapter 39).



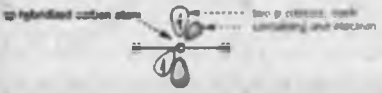
Carbenes can be divided into two types

We made two important observations earlier regarding the structure of carbenes that we will now return to and seek an explanation for: firstly, we said that the X-ray crystal structure of this stable, crystalline carbene shown that the bond angle at the carbene C is 102° and, secondly, we said that many carbenes can be observed by ESR—in other words, they have unpaired electrons.

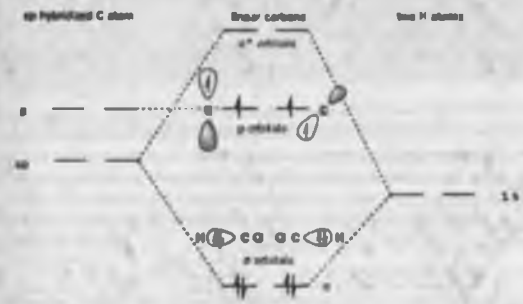
Spectroscopic investigations of a number of carbenes of differing structures have shown that they fall broadly into two groups: (1) those (which you will learn to call 'triplets') that ESR spectroscopy demonstrates have unpaired electrons and whose bond angles are 130–150°; and (2) those (like the stable crystalline carbene above which you will learn to call a 'singlet') that have bond angles of 100–110° but cannot be observed by ESR. Many carbenes, like CH_2 itself, can be found in either style, though one may be more common.

Type 1: triplet carbenes	Type 2: singlet carbenes
bond angle 130–150°	bond angle 100–110°
observable by ESR	all electrons paired
$:CH_2$	$:CCl_2$
$:CHPh$	$:CHCl$
$:CHR$	$:C(OMe)_2$
$:CPh_2$	

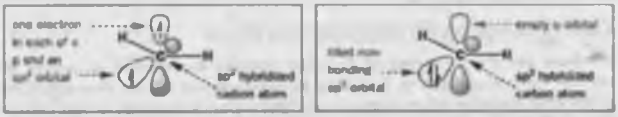
All these observations can be accounted for by considering the electronic structure of a carbene. Carbenes have 2-coordinate carbon atoms: you might therefore expect them to have a linear (diagonal) structure—like that of an alkyne—with an sp hybridized carbon atom.



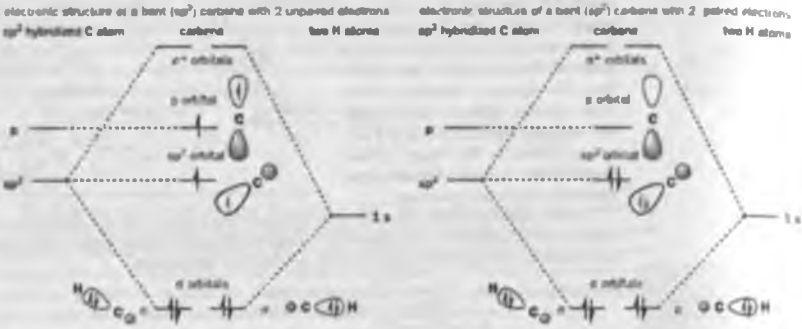
Such a linear carbene would have six electrons to distribute amongst two σ orbitals and two (higher-energy) p orbitals. The two electrons in the degenerate p orbitals would remain unpaired because of electron repulsion in the same way as in molecular oxygen -O–O-.



Yet few carbenes are linear: most are bent, with bond angles between 100° and 150°, suggesting a trigonal (sp^2) hybridization state. An sp^2 hybridized carbene would have three (lower-energy) sp^2 orbitals and one (high-energy) p orbital in which to distribute its six electrons. There are two ways of doing this. Either all of the electrons can be paired, with each pair occupying one of the sp^2 orbitals, or two of the electrons can remain unpaired, with one electron in each of the p orbitals and one of the sp^2 orbitals.



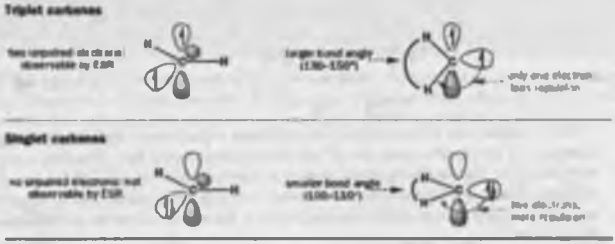
These two possibilities explain our two observed classes of carbene, and the two possible arrangements of electrons (spin states) are termed triplet and singlet. The orbitals are the same in both cases but in triplet carbenes we have one electron in each of two molecular orbitals and in singlet carbenes both electrons go into the sp^2 orbital.



● Singlet and triplet carbenes

Triplet carbenes have two unpaired electrons, one in each of an sp^2 and a p orbital, while **singlet carbenes** have a pair of electrons in a nonbonding sp^2 orbital and have an empty p orbital.

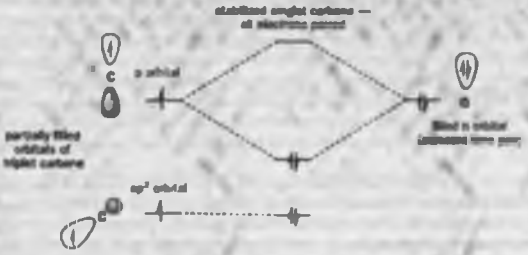
The existence of the two spin states explains the different behaviour of triplet and singlet carbenes towards ESR spectroscopy; the orbital occupancy also explains the smaller bond angle in singlet carbenes, which have an electron-repelling lone pair in an sp^2 orbital.



In the table on p. 000 we saw that the substituents on the carbene affect which of the two classes (which we now call singlet and triplet) it falls into. Why? Most type of carbenes are more stable as triplets because the energy to be gained by bringing the electron in the p orbital down into the sp^2 orbital is insufficient to overcome the repulsion that exists between two electrons in a single orbital.

All carbenes have the potential to exist in either the singlet or the triplet state, so what we mean when we say that a carbene such as $:CH_2$ is a 'triplet carbene' is that the triplet state for this carbene is lower in energy than the singlet state, and vice versa for $:CCl_2$. For most triplet carbenes the singlet spin state that would arise by pairing up the two electrons lies only about 40 kJ mol^{-1} above the ground (triplet) state: in other words, 40 kJ mol^{-1} is required to pair up the two electrons. When a carbene is actually formed in a chemical reaction, it may not be formed in its most stable state, as we shall see.

Carbenes that have singlet ground states (such as $:CCl_2$) all have electron-rich substituents carrying lone pairs adjacent to the carbene centre. These lone pairs can interact with the p orbital of the carbene to produce a new, lower-energy orbital which the two electrons occupy. This stabilization of the lone pair provides the incentive that the electron in the p orbital needs to pair up in the sp^2 orbital.



This molecular orbital formation moves electrons localized on oxygen into orbitals shared between carbon and oxygen. We can represent this in curly arrow terms as a delocalization of the lone pair electrons.

As these arrows suggest, carbenes that have heavily electron-donating substituents are less electrophilic than other carbenes: indeed, diamino carbenes can be quite nucleophilic. The division of carbenes into two types explains their structure. It also helps to explain some of their reactions, especially those that have a stereochemical implication. We will spend the rest of this chapter discussing how carbenes react.

The structure of carbenes depends on how they are made

So far we have considered only the most stable possible structure, singlet or triplet, of a given carbene. In real life, a carbene will be formed in a chemical reaction and may well be formed as the less stable of the alternatives. If a reaction occurs by an ionic mechanism on a molecule with all electrons paired (as most molecules are!) then it must be formed as a singlet. Follow the α elimination mechanism, for example.

The starting material, a normal molecule of chloroform $CHCl_3$, has all paired electrons. The C–H σ bond breaks and the two paired electrons from it form the lone pair of the carbanion. The carbanion also has all paired electrons. The two paired electrons of one of the C–Cl bonds leaves

the carbanion and the carbene is formed. It has two paired electrons in each of the two remaining C–Cl bonds and the lone pair, also paired. It is formed as a singlet. As it happens, the singlet version of CCl_2 is also the more stable. If the carbene were instead CH_2 and if it reacted rapidly, it might not have a chance to change into the more stable triplet state. And carbenes are very reactive. In explaining their reactions in the next section we shall need to consider:

- how the carbene was formed
- how rapidly it reacts
- whether it can change into the other state (singlet or triplet)

How do carbenes react?

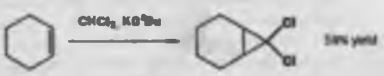
Carbenes are desperate to find another pair of electrons with which to complete their valence shell of electrons. In this respect they are like carbocations. Like carbocations, they are electrophilic but, unlike carbocations, they are uncharged. This has consequences for the type of nucleophiles carbenes choose to react with. Carbocations attack nucleophiles with high charge density—those carrying a negative or partial negative charge (think of the type of nucleophiles that will take part in S_N1 or Friedel–Crafts reactions). Carbenes, on the other hand, attack compounds we'd normally never consider as nucleophiles—even simple alkanes—by taking electrons from their HOMO. Of course, a carbocation will usually react with the HOMO of a molecule, but it will be much more selective about which HOMOs will do—usually these have to be lone pairs or electron-rich alkenes. For carbenes, any HOMO will do—a lone pair, a C=C double bond (electron-rich or -poor), or even a C–H bond.

▶ In this respect, a carbene is like an electrophilic radical—very reactive and very soft.

As you will see (and as we generalized at the beginning of the chapter), many of these reactions can be considered as insertion reactions—overall the carbene appears to have found a bond and inserted itself in the middle of it. It's important to remember that the term 'insertion reaction' describes the outcome of the reaction, though it isn't always an accurate description of the reaction's mechanism.

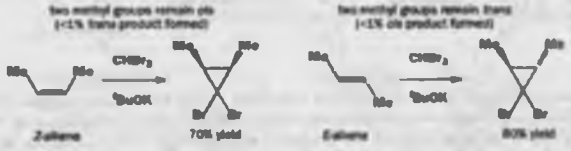
Carbenes react with alkenes to give cyclopropanes

This reaction is the most important way of making cyclopropanes, and is probably the most important reaction of carbenes.

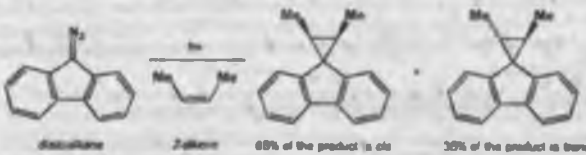


The mechanism of this type of reaction depends on whether the carbene is a singlet or a triplet, and the outcome of the reaction can provide our first chemical test of the conclusions we came to in the previous section. Singlet carbenes, like this one here (remember that electron-rich substituents stabilize the singlet spin state), can add to alkenes in an entirely concerted manner: the curly arrows for the process can be written to show this.

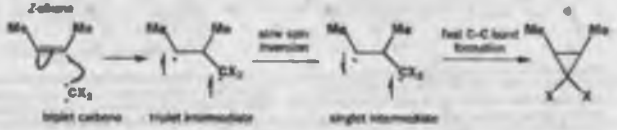
Because the process is concerted, we expect that the geometry of the alkene should be preserved in the product—the reaction ought to be *stereospecific*. The two examples below show that this is indeed the case. It is more impressive that the *Z*-alkene gives the *cis* cyclopropane as this is less stable than the *trans* cyclopropane and would change if it could.



The alkene insertion reaction is stereospecific only for singlet carbenes. For triplet carbenes, the reaction is nonstereospecific. Though carbenes formed thermally from diazoalkenes must initially be singlets, photochemistry is one way to provide the energy needed for their transformation to the more stable triplet.

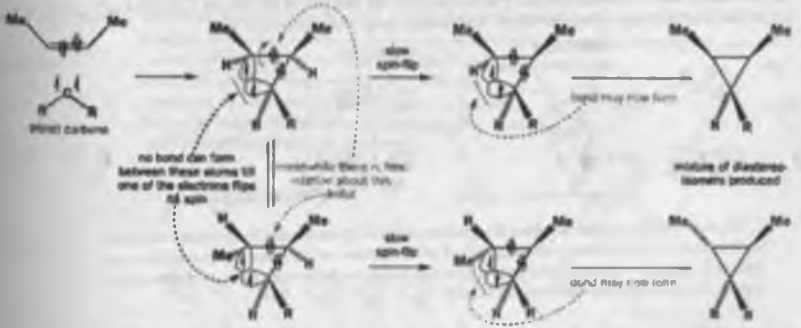


The mechanism of this nonspecific reaction must be different. In fact, a concerted reaction is impossible for triplet carbenes because of the spins of the electrons involved. After the carbene adds to the alkene in a radical reaction, the diradical (triplet) intermediate must wait until one of the spins inverts so that the second C–C bond can be formed with paired electrons. This intermediate also lives long enough for C–C bond rotation and loss of stereochemistry.



A cyclopropane has three σ bonds—in other words, six electrons, all spin-paired (three up, three down). One of these was the σ bond in the starting material; the other two electron pairs come from the π bond and from the carbene. The electrons in the π bond must have been paired, and thus they can form one of the new σ bonds. A singlet carbene (whose electrons are also paired) can then provide the second electron pair.

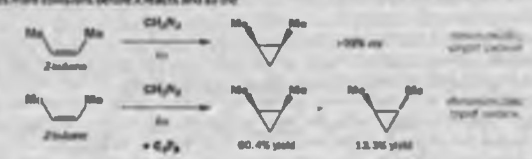
But a triplet carbene cannot, because its electrons are not paired. The second bond can only form once one of the two electrons has flipped its spin. Spin-flipping, which can only occur through collisions with another molecule (of solvent, say), is relatively slow on the time-scale of molecular rotations and, by the time the electrons are in a fit state to pair up, the stereochemistry of the starting material has been scrambled by free rotation in the intermediate.



A reminder. The same constraints arising from the need for conservation of electron spin apply to the formation as well as to the reaction of carbenes. When a carbene forms by α elimination, say, from a molecule with all electrons paired, it must be formed as the singlet, whether or not the triplet state is lower in energy. Only later may the carbene undergo spin-flipping to the triplet state. Since most carbene reactions are very rapid, this means that carbenes that are known to have triplet ground states may, in fact, react in their first-formed singlet state because they don't have time to spin-flip to the triplet. This is true for $:CH_2$ produced from CH_2N_2, which adds stereospecifically to double bonds because it is formed as a singlet and because the singlet state is more reactive than the triplet.

Some evidence for triplet carbenes in cyclopropane formation

If the reaction is diluted with a large amount of an inert solvent such as C_3F_8 (perfluoropropane) then $:CH_2$ undergoes more collisions before it reacts and so the chances of spin-flipping of singlet $:CH_2$ to triplet $:CH_2$ is increased. Addition to alkenes is then less stereospecific.

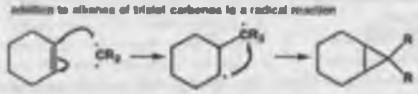


Stereospecificity (or lack of it) in the addition of a carbene to an alkene can be a good test of whether the carbene reacts as a singlet or triplet: lack of stereospecificity in a carbene addition almost certainly indicates that a triplet carbene is involved, but the fact that an addition is stereospecific doesn't mean that the carbene must be a singlet. In some cases, bond rotation may be quite slow, and spin-flipping rapid, leading to stereospecific addition. Notice that in this example the less stable cis (Z) alkene was used: the reaction will give trans-cyclopropane if it can.

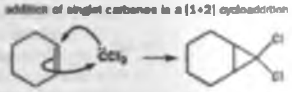
The addition of a triplet carbene to an alkene can be considered to be rather like a radical addition to a double bond. The concerted addition of a singlet carbene, on the other hand, is a pericyclic reaction, and from Chapter 35 you should be able to classify it as a [1 + 2] cycloaddition.

▶ Cycloadditions in which one of the components is a single atom (in other words, [1 + n] cycloadditions) are sometimes called cheletropic reactions.

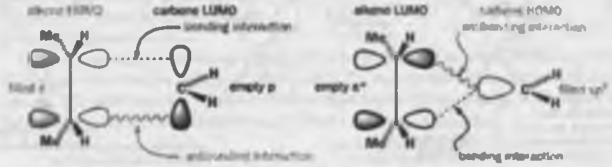
addition to alkenes of triplet carbenes is a radical reaction



addition of singlet carbenes is a [1+2] cycloaddition



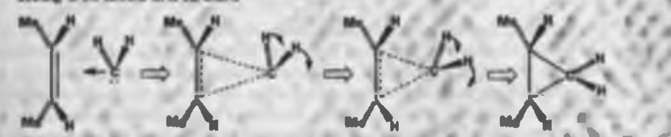
As a cycloaddition, singlet carbene addition to an alkene must obey the rules of orbital symmetry discussed in Chapters 35 and 36. We might consider the empty p orbital of the carbene (LUMO) interacting with the π bond (HOMO) of the alkene or the lone pair of the carbene in its filled sp^2 orbital (HOMO) interacting with the π* antibonding orbital of the alkene (LUMO).



You can immediately see that there is a problem when we try to interact these orbitals constructively to build two new bonds—direct approach of the carbene to the alkene is impossible because there is always an antibonding interaction. Two new bonds can be formed, however, if the carbene approaches the alkene in a 'sideways-on' manner.

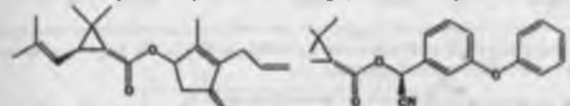
The cyclopropane product must, of course, have a more or less tetrahedral arrangement about the carbon atom that was the carbene so that, even if the carbene approaches in a sideways-on manner, it must then swing round through 90° as the bonds form.

'docking' of the carbene on to the alkene



Making cyclopropanes

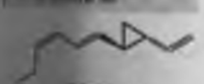
Many natural products and biologically active compounds contain cyclopropane rings: we shall feature just a few. First, a most important natural insecticide, a pyrethrin from the East African pyrethrum daisy, and its synthetic analogue decamethrin, now the most important insecticide in agriculture (see Chapter 1). Very low doses of this highly active and nonpersistent insecticide are needed.



pyrethrin I decamethrin

Ever heard of the 'ozone' or 'iodine' smell of the sea? Well, the smell of the sea is characteristic but has nothing to do with O_3 or I_2. It's more likely to be a dictyopterene, a family of volatile cyclopropanes used by female brown algae to attract male gametes. There is an example in the margin.

▶ They said John Betjeman: 'Breathe in the ozone, John. It's iodine.' Summoned by Bells, Murray, 1960, p. 30.

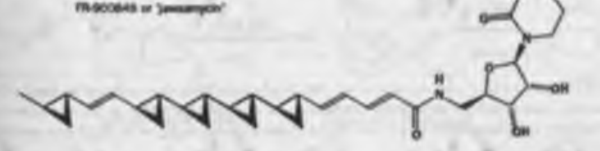


Now for two natural but highly unusual amino acids. Hypoglycidin is a blood sugar level lowering agent from the unripe fruit of the ackee tree; the causative agent of Jamaican vomiting sickness. Don't eat the green ackee. Nature makes not only strained cyclopropanes but this even more strained methylene cyclopropane with an sp^2 atom in the ring. The second and simpler amino acid is found in apples, pears, and grapefruit and encourages fruit ripening by degradation to ethylene.

Our last and most extraordinary example is an antifungal antibiotic first synthesized in 1996 and containing no less than five cyclopropanes. It has the prosaic name FR-900848 but is known unofficially in the chemical world as 'jawsamycin'.

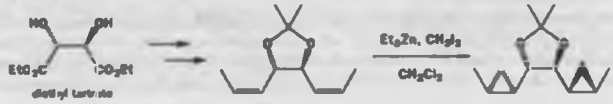
hypoglycin

FR-900848 or 'jawsamycin'

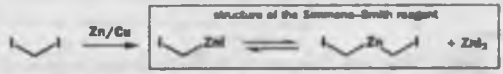


Because of these and other useful molecules containing three-membered rings, methods to make them are important as well as interesting. Most chemical syntheses of compounds containing cyclopropyl groups make use of the addition of a carbene, or carbene equivalent, to an alkene. What do we mean by carbene equivalent? Usually, this is a molecule that has the potential to form a carbene, though it may not actually react via a carbene intermediate. One such example is a zinc carbenoid formed when diiodomethane is reacted with zinc metal: it reacts with alkenes just as a carbene would—it undergoes addition to the π bond and produces a cyclopropane.

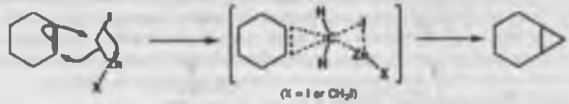
The reaction is known as the Simmons–Smith reaction, after the two chemists at the DuPont chemical factory who discovered it in 1958. Even after several decades, it is the most important way of making cyclopropane compounds, though nowadays a variant that uses more easily handled starting materials is often used. Diethyl zinc replaces the Zn/Cu couple of the traditional Simmons–Smith reaction. In this example, a double cyclopropanation on a C_2 symmetric diene derived from tartaric acid gives very good stereoselectivity for reasons we will soon discuss.



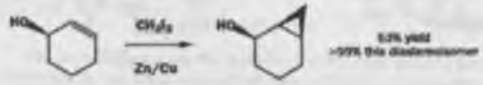
The reaction does not involve a free carbene: the zinc is still associated with the carbon atom at the time of the reaction, and the reacting species is a probably a complex of zinc that we can represent as an equilibrium between two zinc carbenoids.



The mechanism of the Simmons–Smith reaction appears to be a carbene transfer from the metal to the alkene without any free carbene being released. It may look something like this.



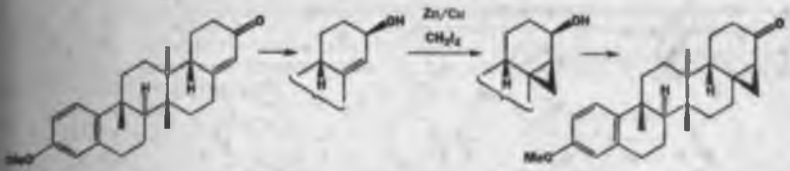
Some of the evidence for this comes from a reaction that not only throws light on to the mechanism of Simmons–Smith cyclopropanations, but makes them of even greater value in synthesis. When an allylic alcohol is cyclopropanated, the new methylene group adds stereoselectively to the same face of the double bond as the alcohol group.



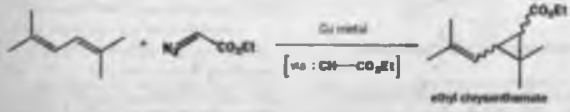
Allylic alcohols also cyclopropanate over 100 times faster than their unfunctionalized alkene equivalents. Coordination between the zinc atom and the hydroxyl group in the transition state explains both the stereoselectivity and the rate increase. Unfortunately, while the Simmons–Smith

reaction works well when a methylene (CH_2) group is being transferred, it is less good with substituted methylenes (RCH: or R_2C:).

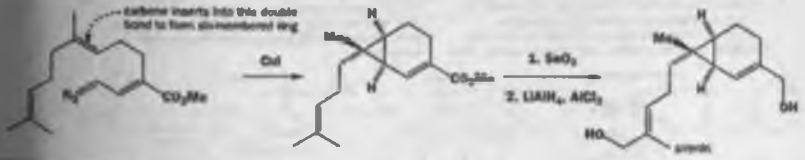
When Ireland wanted to introduce a cyclopropane ring stereoselectively into a pentacyclic system containing an enone, he first reduced the ketone to an alcohol (DIBAL gave only the equatorial alcohol) that controlled the stereochemistry of the Simmons–Smith reaction. Oxidation with Cr(VI) put back the ketone.



The carbene derived by metal-catalysed decomposition of ethyl diazoacetate attacks alkenes to introduce a two-carbon fragment into a cyclopropane—an industrial synthesis of ethyl chrysanthemate, a precursor to the pyrethrin insecticides (see p. 000), uses this reaction. The diene in the starting material is more nucleophilic (higher-energy HOMO; see Chapter 20) than the single alkene in the product, so the reaction can be stopped after one carbene addition.



The intramolecular version of this reaction is more reliable, and has often been used to make compounds containing multiply substituted cyclopropanes. Corey made use of it in a synthesis of sirenin, the sperm-attractant of a female water mould.

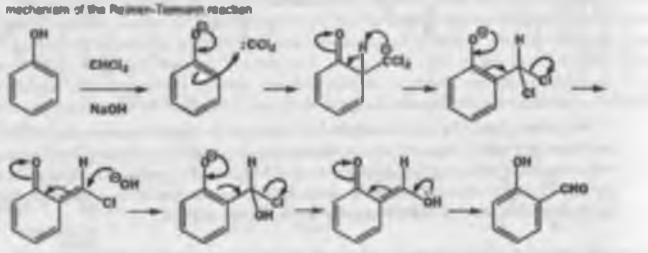


As you might imagine, carbenes like this, substituted with electron-withdrawing carbonyl groups, are even more powerful electrophiles than carbenes like $:CCl_2$, and will even add to the double bonds of benzene. The product is not stable, but immediately undergoes electrocyclic ring opening.

Dichlorocarbene :CCl_2 will not add to benzene, but does attack the electron-rich aromatic ring of phenol: the product is not a cyclopropane, but an aldehyde.

The Reimer–Tiemann reaction used to be an important way of making *ortho*-substituted phenols, but the yields are often poor, and modern industry is wary of using large quantities of chlorinated solvents. On a small, laboratory scale it has largely been superseded by ortholithiation (Chapter 9) and by modern methods outside the scope of this book. The mechanism probably goes something like this.

mechanism of the Reimer–Tiemann reaction

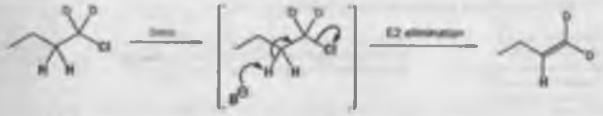


Comparison of '-enoid' reagents

Before we leave this section on cyclopropanes, we want you to take a step back from simply thinking about carbenes, and consider the types of reagents that form three-membered rings generally. They all have something in common, which we could call '-enoid' character. Cyclopropanes form when a carbene (which, in the singlet state, has an empty, electrophilic p orbital and a full, nominally nucleophilic sp^2 orbital) attacks alkenes. The Simmons–Smith carbenoid is not a carbene, but nonetheless has a carbon atom with joint nucleophilic (alkyl zinc) and electrophilic (alkyl iodide) character. When you think about it, the same is true for peracid epoxidation, which forms the oxygen analogue of a cyclopropane by attacking an alkene with an oxygen atom bearing both a lone pair (nucleophilic) and a carboxylate leaving group (electrophilic). It's an '-oxenoid'. In Chapter 46 you will meet more reagents that form cyclopropanes and epoxides by transferring CH_2—sulfonium ylids. These yet again have a nucleophilic carbon atom—carrying a negative charge and a leaving group—and, when you meet them, you can consider them to be particularly stable sulfonoids.

Insertion into C–H bonds

We said that the formation of cyclopropanes by addition of substituted carbenes to alkenes was rare—in fact, alkyl-substituted carbenes undergo very few intermolecular reactions at all because they decompose very rapidly. When primary alkyl halides are treated with base, alkenes are formed by elimination. Having read Chapter 19, you should expect the mechanism of this elimination to be E2 and, if you started with a deuterated compound like this, the alkene product would be labelled with two deuterium atoms at its terminus.

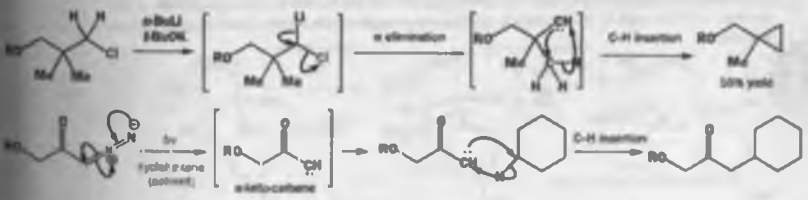


This is indeed what happens if the base is sodium methoxide (pK_a 16). If, however, it is phenylsodium (pK_a about 50), only 6% of the product is labelled in this way while 94% of the product has only one deuterium atom.

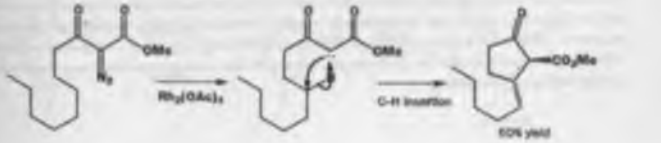
A hydrogen atom has 'migrated' from the 2-position to the 1-position. The overall mechanism of the elimination with very strong bases like phenylsodium is believed to be: (1) formation of a carbene by α elimination and then (2) 1,2-migration of a hydrogen atom on to the carbene centre. Carbenes with β hydrogens undergo extremely rapid 1,2-migration of hydrogen to the carbene centre, giving alkenes.

The reason for the rapid migration is that the electrophilic carbene has found a nearby source of electrons—the HOMO of the C–H bond—and it has grabbed the electrons for itself, 'inserting' into the C–H bond.

This type of reaction is better demonstrated by two examples in which the 'insertion reaction' is a bit more obvious: when there are no β hydrogens, the carbene inserts into C–H bonds a little further away in the same molecule or even in the solvent (cyclohexane in the second example). In the first case, the carbene is formed by α elimination and, in the second case, by photolysis of a diazoketone.

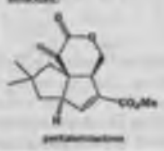


Because these insertion reactions create new bonds at completely unfunctionalized centres, they can be very useful in synthesis. This next carbene is created between two carbonyl groups from a diazocompound with rhodium catalysis and selectively inserts into a C–H bond five atoms away to form a substituted cyclopentanone.

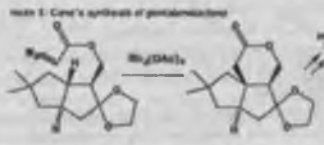


Pentalenolactone synthesis using carbenes

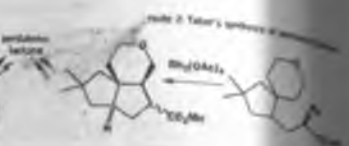
Pentalenolactone is the name given to an antibiotic extracted from *Streptomyces* fungi with an interesting tricyclic structure.



Two groups of chemists, within one year of each other, published syntheses of this compound using rhodium-promoted carbene insertions into C–H bonds. Cane's

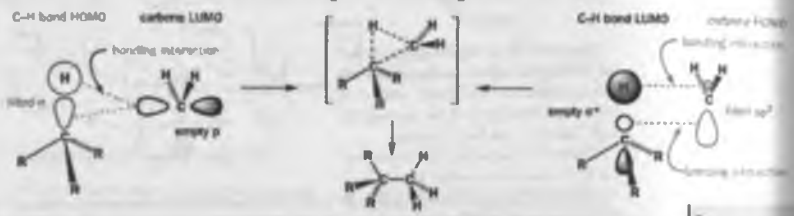


Intramolecular reaction (route 1) proceeds ... retention of stereochemistry). This ... concerted singlet carbene reaction.

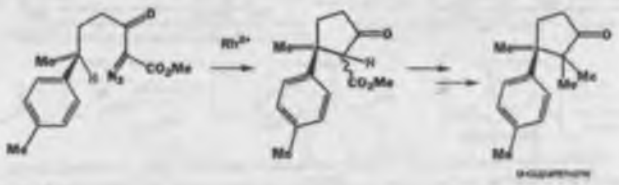


In these C–H insertion reactions, the similarity with cyclopropane formation by intramolecular cycloadditions to alkenes is clear, and the mechanisms mirror one another quite closely. As with the cyclopropanation reactions, the path of the reaction differs according to whether the carbene is a singlet or triplet. Singlet carbenes can insert in a concerted manner, with the orbitals overlapping constructively provided the carbene approaches side-on.

orbital interactions during the insertion of a singlet carbene into a C–H bond



This mechanism implies that, if the C–H bond is at a stereogenic centre, the stereochemistry at that centre will be retained through the reaction, as in Cane's synthesis of pentalenolactone. A nice example of this result is the ingenious synthesis of α-cuparenone using a stereospecific carbene insertion.

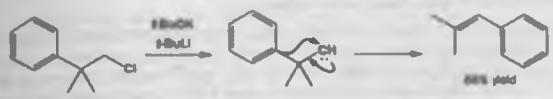


▶ In principle, triplet carbene insertions should follow a two-step radical pathway analogous to their insertion into alkenes. However, very few triplet carbene insertions into C–H bonds have been observed, and the stereochemical consequences of the two step mechanism would should result in mixtures of stereoisomers on insertion into a C–H bond at a stereogenic centre has never been verified.

▶ The migration of aryl groups to carbene centres has much in common with the migration of alkyl groups to electron-deficient carbon discussed in Chapter 27. ... all, both carbenes and carbocations are electron-deficient species with a carbon atom carrying only six electrons in its outer shell.

Rearrangement reactions

We talked just at the beginning of this section about migration reactions of hydrogen on to carbenes to give alkenes, and said that these reactions can be viewed as insertion reactions of carbenes into adjacent C–H bonds. Carbenes with no β hydrogens often insert into other C–H bonds in the molecule. However, carbenes with no β-hydrogen atoms can also undergo rearrangement reactions with alkyl or aryl groups migrating.

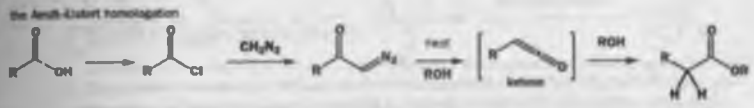


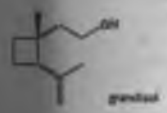
The most common example of this type of migration is that in which the carbene is adjacent to a carbonyl group. The initial product of what is known as the Wolff rearrangement is a ketene, which cannot be isolated but is hydrolysed to the ester in the work-up. Wolff rearrangement is a typical reaction of diazoketones on heating, though these species do also undergo intramolecular C–H insertion reactions.

the Wolff rearrangement

One important application of this reaction is the chain extension of acyl chlorides to their homologous esters, known as the Arndt–Eistert reaction. Notice that the starting material for the Wolff rearrangement is easily made from RCO_2H by reaction of the acyl chloride with diazomethane; the product is RCH_2CO_2H—the carboxylic acid with one more carbon atom in the chain. A CH_2 group, marked in black, comes from diazomethane and is inserted into the C–C bond between R and the carbonyl group.

the Arndt–Eistert homologation

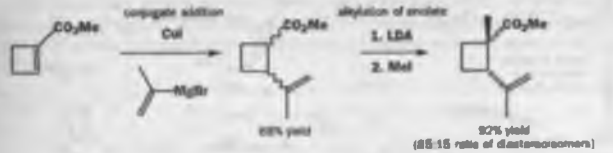




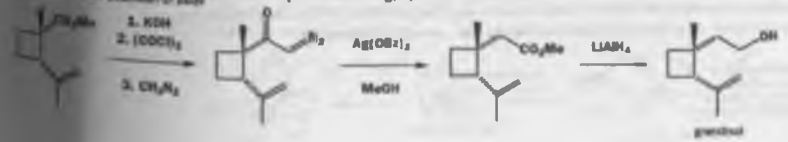
A synthesis of grandisol using Arndt–Eistert chain extension

The boll weevil is a serious pest of cotton bushes, and it produces a sex pheromone known as grandisol.

Chemists soon showed that it was an easy matter to synthesize a related ester by a conjugate addition of an organocopper derivative (Chapter 10) and then the alkylation of an ester enolate (Chapter 26). The enolate reacts with MeI on the face opposite the propenyl side chain—a good example of stereochemical control with cyclic compounds (Chapter 33).

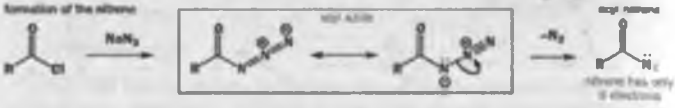


This ester is one carbon atom short of the full side chain of grandisol, so an Arndt–Eistert reaction was used to lengthen the chain by one atom. First, the ester was converted into the diazoketone with diazomethane and, then, the Wolff rearrangement was initiated by formation of the carbene with a silver compound at the Ag(II) oxidation state



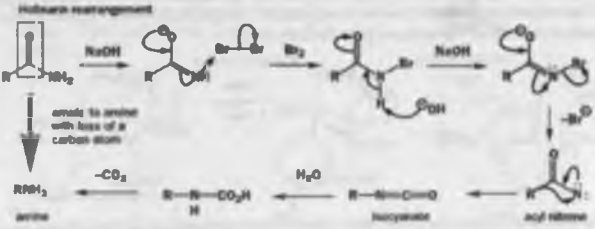
Nitrenes are the nitrogen analogues of carbenes

The Wolff rearrangement has some important cousins that we must now introduce to you—they deserve a mention because they bear a family likeness even though they do not, in fact, involve carbenes. They are a group of reactions that proceed through an intermediate nitrene—the nitrogen analogue of a carbene. The simplest to understand, because it is the direct nitrogen analogue of the Wolff rearrangement, is the Curtius rearrangement. It starts with an acyl azide—which can be made by nucleophilic substitution on an acyl chloride by sodium azide. The acyl azide is what you would get if you just replaced the $-CH=N_2$ of a diazoketone with $-N-N_2$. And, if you heat it, it is not surprising that it decomposes to release nitrogen (N_2), forming the nitrene. The nitrene has two bonds fewer (1) than a normal amine and has two lone pairs making six electrons in all.



Nitrenes, like carbenes, are immensely reactive and electrophilic, and the same Wolff-style migration takes place to give an isocyanate. The substituent R migrates from carbon to the electron-deficient nitrogen atom of the nitrene. Isocyanates are unstable to hydrolysis: attack by water on the carbonyl group gives a carbamic acid which decomposes to an amine.

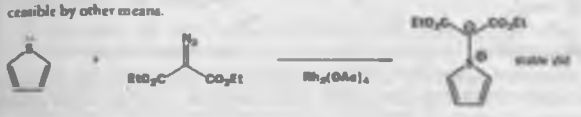
Overall, then, the Curtius rearrangement converts an acid chloride to an amine with loss of a carbon atom—very useful. Also useful is the related Hofmann rearrangement, which turns an amide into an amine with loss of a carbon atom. This time we start with a primary amide and make a nitrene by treatment with base and bromine. Notice how close this nitrene-forming reaction is to the carbene-forming reactions we talked about on p. 000. The nitrene rearranges just as in the Curtius reaction, giving an isocyanate that can be hydrolysed to the amine.



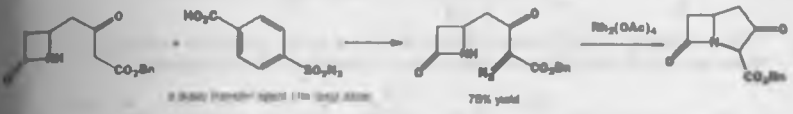
Attack of carbenes on lone pairs

Wolff rearrangements, involving shifts of alkyl groups, are effectively intramolecular insertions into C–C bonds. Carbenes will also insert into other bonds, especially O–H and N–H bonds, though the mechanism in these cases involves initial attack on the lone pair of the heteroatom.

Carbene attack is followed by proton transfer to generate a neutral molecule from the first formed zwitterion (or 'ylid'). However, if the heteroatom does not carry a hydrogen, attack on its lone pair generates an ylid that cannot rearrange in this way. Reaction of a carbene with a neutral nucleophile forms an ylid. This type of reaction is, in fact, a very useful way of making reactive ylids that are inaccessible by other means.

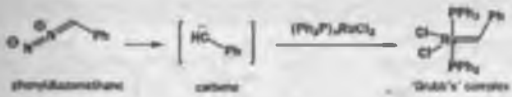


As carbonyl-substituted carbenes (like carbonyl-substituted radicals) are electrophilic, their insertion into O–H and N–H bonds can be a useful way of making bonds in an umpolung sense. Because of the difficulties in forming β-lactams (the four-membered rings found in the penicillin classes of antibiotics), Merck decided to design a synthesis of the class of compounds known as carbapenems around a rhodium-catalysed carbene insertion into an N–H bond, building the five-membered ring on to the side of the four-membered ring.

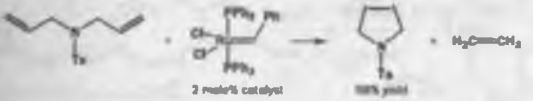


Alkene (olefin) metathesis

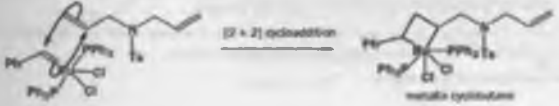
Carbenes can be stabilized as transition metal complexes: decomposition of phenyldiazomethane in the presence of a ruthenium(II) complex gives a carbene complex stable enough to be isolated and stored for months. These complexes are among the most important of carbene-derived reagents because of a remarkable reaction known as alkene (or more commonly olefin) metathesis.



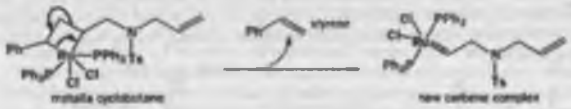
The reaction is most easily understood when a simple diene reacts with a very small amount (in this case 2 mole per cent) of the catalyst. A cyclization reaction occurs and the product is also an alkene. It contains no atoms from the catalyst: indeed, it has lost two carbon atoms, which are given off as ethylene.



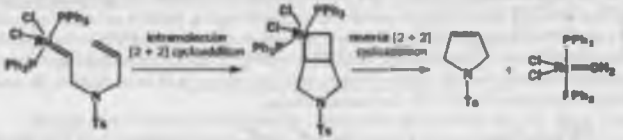
Any reaction that makes new bonds so efficiently and with so little reagent and so little waste is obviously very important. The yield is also rather good! What happens is a metathesis—an exchange of groups between the two arms of the molecule. First, the carbene complex adds to one of the alkenes in what can be drawn as a [2 + 2] cycloaddition (Chapter 35) to give a four-membered ring with the metal atom in the ring.



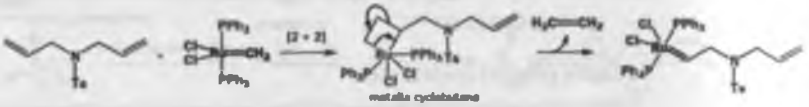
Now the same reaction happens in reverse (all cycloadditions are, in principle, reversible), either to give the starting materials or, by cleavage of the other two bonds, a new carbene complex and styrene.



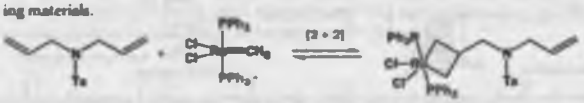
Next, an intramolecular [2 + 2] cycloaddition joins up the five-membered ring and produces a second metalla cyclobutane, which decomposes in the same way as the first one to give a third carbene complex and the product.



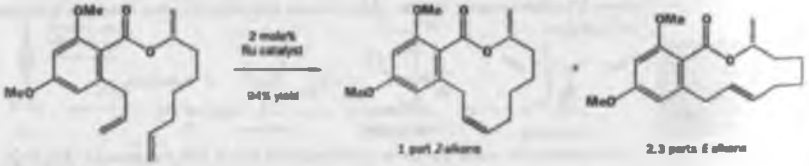
This new carbene complex then attacks another molecule of starting material and the cycle is repeated except that ethylene (ethene) is now lost instead of styrene in all the remaining cycles.



You will have noticed that the carbene complex appears to exhibit a remarkable selectivity: the ruthenium atom adds to the more substituted end of the first alkene but to the less substituted end of the second. In fact, there is no particular need for selectivity: if the second cycloaddition occurs with the opposite selectivity the metalla cyclobutane has symmetry and can decompose only to the starting materials.



One example that makes a number of points about olefin metathesis is the cyclization of this ester.



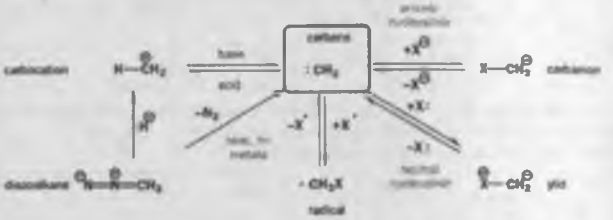
The main points are:

- Olefin metathesis is an excellent way to make difficult ring sizes—here a 12-membered ring
- It is compatible with many functional groups—here just an ester and an ether but amines, alcohols, epoxides, and many other carbonyl groups are all right
- The reaction is *E*-selective. In the previous example only a *Z*-alkene could be formed but an *E*-alkene is possible in a 12-membered ring and is the major product
- Stereogenic centres are not racemized

Alkene metathesis is one of the more important of the many new useful reactions that use transition metal complexes as catalysts. You will see more in Chapters 45 and 48.

Summary

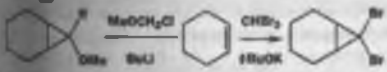
We have seen in this chapter how carbenes can be formed from many other reactive intermediates such as carbanions and diazoalkanes and how they can react to give yet more reactive intermediates such as ylids. Here is a summary of the main relationships between carbenes and these other compounds. Note that not all the reactions are reversible. Diazoalkanes lose nitrogen to give carbenes but the addition of nitrogen to carbenes is not a serious reaction.



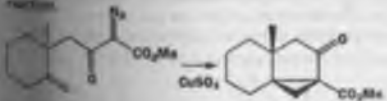
In the last few chapters we have concentrated a lot on what we call reactive intermediates, species like radicals, carbenes, or carbocations that are hard to observe but that definitely exist. Much of the evidence for their existence derives from the study of the mechanisms of reactions—we have discussed some aspects of this as we have met the species concerned, but in the next chapter we will look in detail at how mechanisms are elucidated and the methods used to determine more precisely the structure of reactive intermediates.

Problems

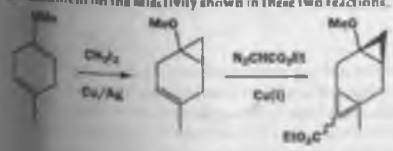
1. Suggest mechanisms for these reactions.



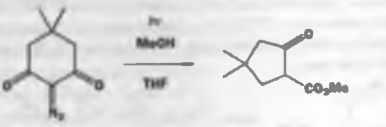
2. Suggest a mechanism and explain the stereochemistry of this reaction.



3. Comment on the selectivity shown in these two reactions.



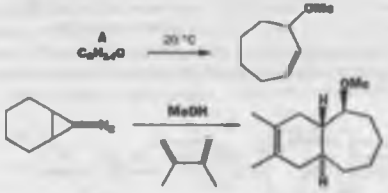
4. Suggest a mechanism for this ring contraction.



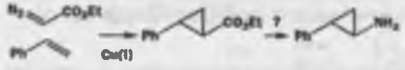
5. Suggest a mechanism for the formation of this cyclopropane.

6. Problem 4 in Chapter 32 asked: 'Decomposition of this diazo compound in methanol gives an alkene A ($C_6H_{14}O$) whose NMR spectrum contains two signals in the alkene region: δ_H 3.50 p.p.m. (3H, s), 5.50 p.p.m. (1H, dd, *J* 17.9, 7.9 Hz), 5.80 p.p.m. (1H, ddd, *J* 17.9, 9.2, 4.3 Hz), 4.20 p.p.m. (1H, m), and 1.3–2.7 p.p.m. (8H, m). What is its structure and geometry?'

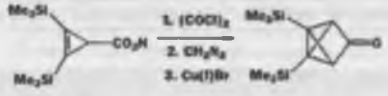
In order to work out the mechanism of the reaction you might like to take these additional facts into account. Compound A is unstable and even at 20 °C isomerises to B. If the diazo compound is decomposed in methanol containing a diene, compound A is trapped as an adduct. Account for all of these reactions.



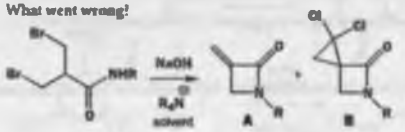
7. Give a mechanism for the formation of the three-membered ring in the first of these reactions and suggest how the ester might be converted into the amine with retention of configuration.



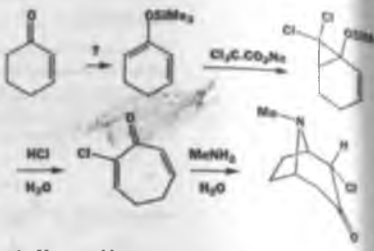
8. Explain how this highly strained ketone is produced, albeit in very low yield, by these reactions. How would you attempt to make the starting material?



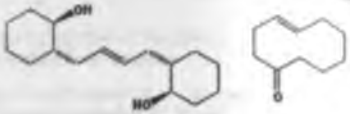
9. Attempts to prepare compound A by a phase-transfer-catalysed cyclization required a solvent immiscible with water. When chloroform ($CHCl_3$) was used, compound B was formed instead and it was necessary to use the more toxic CCl_4 for success. What went wrong?



10. Revision content. How would you carry out the first step in this sequence? Propose mechanisms for the remaining steps, explaining any selectivity.

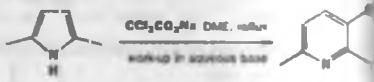


11. How would you attempt to make these alkenes by metathesis?



12. Heating this acyl azide in dry toluene under reflux for 3 hours gives a 90% yield of a heterocyclic product. Suggest a mechanism emphasizing the involvement of any reactive intermediates.

13. Give mechanisms for the steps in this conversion of a five- to six-membered aromatic heterocycle.



Determining reaction mechanisms

41

Connections

Building on:

- Mainly builds on ch13
- Acidity and basicity ch8
- Carbonyl reactions ch6, ch12, & ch14
- Nucleophilic substitution at saturated carbon ch17
- Controlling stereochemistry ch16, ch33, & ch34
- Eliminations ch19
- Electrophilic and nucleophilic aromatic substitution ch22–ch23
- Cycloadditions ch35
- Rearrangements ch36–ch37
- Fragmentations ch38

Arriving at:

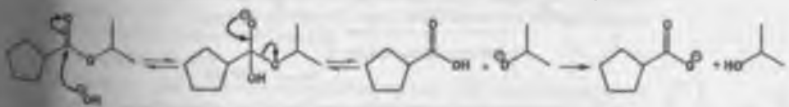
- Classes and types of mechanisms
- Importance of proposing a mechanism
- Structure of the product is all-important
- Labelling and double labelling
- Systematic structure variation and electronic demand
- The Hammett correlation explained
- Nonlinear correlations
- Deuterium isotope effect (kinetic and solvent)
- Specific acid and specific base catalysis
- General acid and general base catalysis
- Detecting and trapping intermediates
- A network of related mechanisms
- Why stereochemistry matters

Looking forward to:

- Saturated heterocycles and stereoelectronics ch42
- Heterocycles ch43–ch44
- Asymmetric synthesis ch45
- Chemistry of S, B, Si, and Sn ch46–ch47
- The chemistry of life ch49–ch51

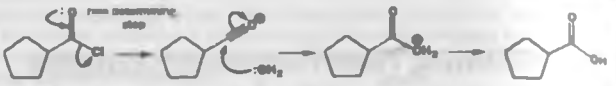
There are mechanisms and there are mechanisms

If you were asked to draw the mechanism of an ester hydrolysis in basic solution you should have no trouble in giving a good answer. It wouldn't matter if you had never seen this particular ester before or even if you knew that it had never actually been made, because you would recognize that the reaction belonged to a class of well known reactions (carbonyl substitution reactions, Chapter 12) and you would assume that the mechanism was the same as that for other ester hydrolyses. And you would be right—nucleophilic attack on the carbonyl group to form a tetrahedral intermediate is followed by loss of the alkoxide leaving group and the formation of the anion of the carboxylic acid.

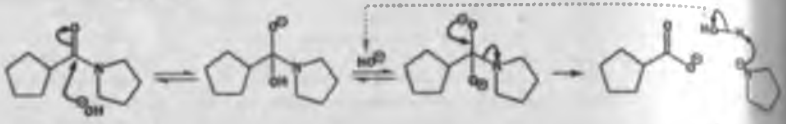


But someone at some time had to determine this mechanism in full detail. That work was done in the 1940s to 1960s and it was done so well that nobody seriously challenges it. You might also recall from Chapter 13 that, if we change the carbonyl compound to an acid chloride, the mechanism may change to an S_N1 type of reaction with an acylium ion intermediate because the leaving group is now much better: Cl^- is more stable (less basic) than RO^-. It would not be worth using hydroxide for this reaction, as the first step is the slow step, water will do just as well. Again someone had to determine this mechanism, had to show which was the slow step, and had to show that leaving group ability depended on pK_{aH}.

The link between leaving group ability and pK_{aH} was discussed in Chapter 12.

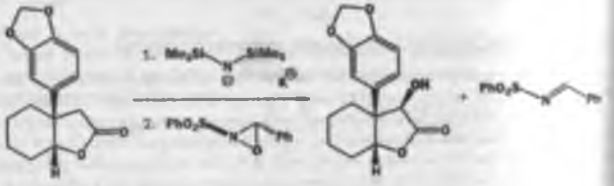


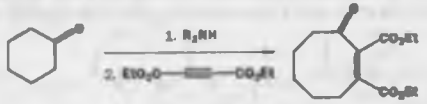
If the reaction were the hydrolysis of an amide, you might remember from Chapter 13 that third-order kinetics are often observed for the expulsion of such bad leaving groups and that this extra catalysis makes it worthwhile using concentrated base. Again, someone had to find out that, (1) the slow step is now the decomposition of the tetrahedral intermediate, (2) there are third-order kinetics involving two molecules of hydroxide; and (3) the first molecule acts as a nucleophile and the second as a base.



These reactions are versions of the same reaction. For you, writing these mechanisms chiefly means recognizing the type of reaction (nucleophilic substitution at the carbonyl group) and evaluating how good the leaving group is. For the original chemists, determining these reaction mechanisms meant: (1) determining exactly what the product is (that may sound silly, but it is a serious point); (2) discovering how many steps there are and the structures of the intermediates; (3) finding out which is the slow (rate-determining) step; and (4) finding any catalysis. This chapter describes the methods used in this kind of work.

Supposing you were asked what the mechanisms of the next two reactions might be. This is a rather different sort of problem as you probably don't recognize any of these reagents and you probably cannot fit any of the reactions into one of the classes you have seen so far. You probably don't even see at once which of the three main classes of mechanism you should use: ionic, pericyclic or radical.



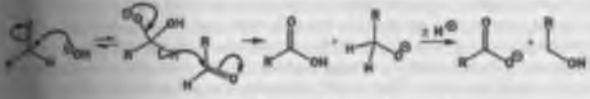


There are two types of answer to the question: 'What is the mechanism of this reaction?' You may do your best to write a mechanism based on your understanding of organic chemistry—moving the electrons from nucleophiles to electrophiles, choosing sensible intermediates, and arriving at the right products. You would not claim any authority for the result, but you would hope, as an organic chemist, to produce one or more reasonable mechanisms. This process is actually an essential preliminary to answering the question in the second way—'What is the real, experimentally verified, mechanism for the reaction?' This chapter is about the second kind of answer.

Determining reaction mechanisms—the Cannizzaro reaction

So how do we know the mechanism of a reaction? The simple answer is that we don't for certain. Organic chemists have to face situations where the structure of a compound is initially thought to be one thing but later corrected to be something different. The same is true of mechanisms. It is the nature of science that all we can do is try to account for observations by proposing theories. We then test this theory by experiment and, when the experiment does not fit the theory, we must start again with a new theory. This is exactly the case with mechanisms. When a new reaction is discovered, one or more mechanisms are proposed; evidence is then sought for and against these mechanisms until one emerges as the best choice and that remains the accepted mechanism for the reaction until fresh evidence comes along that does not fit the mechanism.

We are going to look at one reaction, the Cannizzaro reaction, and use this to introduce the different techniques used in elucidating mechanisms so that you will be able to appreciate the different information each experiment brings to light and how all the pieces fit together to leave us with a probable mechanism. Under strongly basic conditions, an aldehyde with no α hydrogens undergoes disproportionation to give half alcohol and half carboxylate. Disproportionation means one half of the sample is oxidized by the other half, which is itself reduced. In this case, half the aldehyde reduces the other half to the primary alcohol and in the process is oxidized to the carboxylic acid. Before the discovery of $LiAlH_4$ in 1946, this was one of the few reliable ways to reduce aldehydes and so was of some use in synthesis.



The mechanism we have drawn here is slightly different from that in Chapter 27 where we showed the dianion as an intermediate. The two reactions are related by base catalysis as we shall see. Now for some of the evidence and some of the alternative mechanisms that have been proposed for the Cannizzaro reaction. Most of these have been eliminated, leaving just the ones you have already met. Finally, we will see that even these mechanisms do not explain everything absolutely.

Proposed mechanism A—a radical mechanism

Early on it was thought that the hydrogen transfer might be taking place via a radical chain reaction. If this were the case, then the reaction should go faster if radical initiators are added and it should slow down when radical inhibitors are added. When this was tried, there was no change in the rate, so this proposed mechanism was ruled out.

Kinetic evidence for an ionic mechanism

The first piece of evidence that must be accounted for is the rate law. For the reaction of benzaldehyde with hydroxide, the reaction is first-order with respect to hydroxide ions and second-order with respect to benzaldehyde (third-order overall).

$$\text{rate} = k_a[\text{PhCHO}]^2[\text{HO}^-]$$

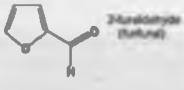
For some aldehydes, such as formaldehyde and furfural, the order with respect to the concentration of hydroxide varies between one and two depending on the exact conditions. In high concentrations of base it is fourth-order.

$$\text{rate} = k_b[\text{HCHO}]^2[\text{HO}^-]^2$$

At lower concentrations of base it is a mixture of both third- and fourth-order reactions.

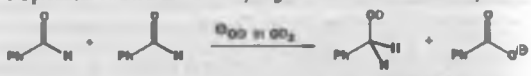
$$\text{rate} = k_a[\text{HCHO}]^2[\text{HO}^-] + k_b[\text{HCHO}]^2[\text{HO}^-]^2$$

Just because the overall order of reaction is third- or fourth-order, it does not mean that all the species must simultaneously collide in the rate-determining step. You saw in Chapter 13 that the rate law actually reveals all the species that are involved *up to and including* the rate-determining step.



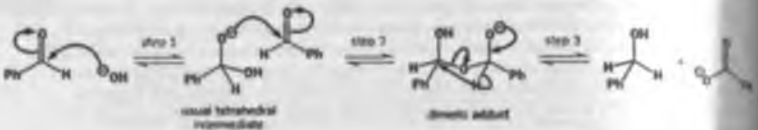
Isotopic labelling

When the reaction is carried out in D_2O instead of in H_2O it is found that there is are no C–D [illegible] the products. This tells us that the hydrogen must come from the aldehyde and not from the [illegible]



Proposed mechanism B—formation of an intermediate dimeric adduct

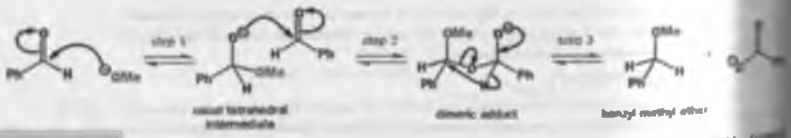
A possible mechanism that fits all the experimental evidence so far involves nucleophilic attack [illegible] usual tetrahedral intermediate on another aldehyde to give an intermediate adduct. This [illegible] could then form the products directly by hydride transfer. You may not like the look of this last step but the mechanism was proposed and evidence is needed to disprove it.



Which step would be rate-determining for this mechanism? It could not be step 1 since, if this were the case, then the rate law would be first-order with respect to the aldehyde rather than the observed second-order relationship. Also, if the reaction is carried out in water labelled with oxygen-18, the oxygen in the benzaldehyde exchanges with the ^{18}O from the solvent much faster than the Cannizzaro reaction takes place. This can only be because of a *rapid* equilibrium in step 1 and so step 1 cannot be rate-determining.

So, for mechanism B, either step 2 or step 3 could be rate-determining—either case would fit the observed rate law. Step 2 is similar to step 1; in both cases an oxyanion nucleophile attacks the aldehyde. Since the equilibrium in step 1 is very rapid, it is reasonable to suggest that the equilibrium in step 2 should also be rapid and thus that the hydride transfer in step 3 must be rate-determining. So mechanism B can fit the rate equation.

How can mechanism B be ruled out? One way is to change the attacking nucleophile. The Cannizzaro reaction works equally well if methoxide is used in a mixture of methanol and water. If mechanism B were correct, the reaction with methoxide would be as follows.



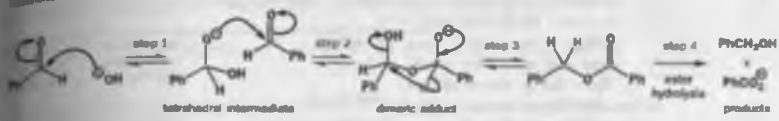
■ We shall discuss this kind of isotopic [illegible] as well as other evidence used to evaluate [illegible] towards the end of this chapter.

One of the products would be different by this mechanism: benzyl methyl ether would be formed instead of benzyl alcohol. None is observed experimentally. Under the conditions of the experiment benzyl methyl ether does not react to form benzyl alcohol, so it cannot be the case that the ether is formed but then reacts to form the products. Mechanism B can therefore be ruled out.

Proposed mechanism C—formation of an ester intermediate

This mechanism is like mechanism B but the hydride transfer in the adduct formed in step 2 displaces OH^- to form an ester (benzyl benzoate) that is then hydrolysed to the products. [illegible]

one time held to be the correct mechanism for the Cannizzaro reaction. One piece of evidence for this, and at first glance a very good one, is that by cooling the reaction mixture and avoiding excess alkali, some benzyl benzoate could be isolated during the reaction. An important point is that this does not mean that the ester *must* be an intermediate in the reaction—it might be formed at the end of the reaction, for example. However, it does mean that any mechanism we propose must be able to account for its formation. For now though we want to try and establish whether the ester is an *intermediate* rather than a by-product in the Cannizzaro reaction.



An early objection to mechanism C was that the ester would not be hydrolysed fast enough. When someone actually tried it under the conditions of the experiment, they found that benzyl benzoate is very rapidly hydrolysed (the moral here is 'don't just think about it, try it!'). However, just because the ester *could* be hydrolysed, it still did not show that it actually was an intermediate in the reaction. How this was eventually shown was rather clever. The argument goes like this. We can measure the rate constant for step 4 by seeing how quickly pure benzyl benzoate is hydrolysed to benzyl alcohol and benzoate under the same conditions as those of the Cannizzaro reaction. We also know how quickly these products are formed during the Cannizzaro reaction itself. Since, if this mechanism is correct, the only way the products are formed is from this intermediate, it is possible to work out how much of the intermediate ester must be present at any time to give the observed rate of formation of the products. If we can measure the amount of ester that is actually present and it is significantly less than that which we predict, then this cannot be the correct mechanism. It turned out that there was never enough ester present to account for the formation of the products in the Cannizzaro reaction and mechanism C could be ruled out.

The correct mechanism for the Cannizzaro reaction

The only mechanism that has not been ruled out and that appears to fit all the evidence is the one we have already given (p. 000). The fact that the rate law for this mechanism is overall third- and sometimes fourth-order depending on the aldehyde and the conditions can be explained by the involvement of a second hydroxide ion deprotonating the tetrahedral intermediate to give a dianion. When methoxide is used in a methanol/water mix, some methyl ester is formed. This does not stay around for long—under the conditions of the experiment it is quickly hydrolysed to the carboxylate.

Even this mechanism does not quite fit all the evidence

We said earlier that we can never prove a mechanism—only disprove it. Unfortunately, just as the 'correct' mechanism seems to be found, there are some observations that make us doubt this mechanism. In Chapter 39 you saw how a technique called electron spin resonance (ESR) detects radicals and gives some information about their structure. When the Cannizzaro reaction was carried out with benzaldehyde and a number of substituted benzaldehydes in an ESR spectrometer, a radical was detected. For each aldehyde used, the ESR spectrum proved to be identical to that formed when the aldehyde was reduced using sodium metal. The radical formed was the radical anion of the aldehyde.

Our mechanism does not explain this result but small amounts of radicals are formed in some reactions in which the products are actually formed by simple ionic processes. Detection of a species in a reaction mixture does not prove that it is an intermediate. Only a few chemists believe that radicals are involved in the Cannizzaro reaction. Most believe the mechanism we have given.

Variation in the structure of the aldehyde

Before leaving the Cannizzaro reaction, look at these rates of reactions for aromatic aldehydes with different substituents in the *para* position. These aldehydes may be divided into two classes: those that react faster than unsubstituted benzaldehyde and those that react more slowly. Those that go slower all have something in common—they all have substituents on the ring that donate electrons.

Aldehyde	Rate relative to benzaldehyde at 25 °C	Rate relative to benzaldehyde at 100 °C
benzaldehyde	1	1
p-methylbenzaldehyde	0.2	0.2
p-methoxybenzaldehyde	0.05	0.1
p-(dimethylamino)benzaldehyde	very slow	0.0004
p-nitrobenzaldehyde	230	2200

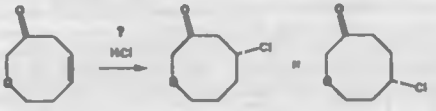
We have already seen how substituents on a benzene ring affect the rate of electrophilic substitution (Chapter 22). Electron-donating groups such as MeO– and Me_2N– dramatically speed up the rate at which an aromatic ring is attacked by an electrophile, whereas electron-withdrawing groups, particularly nitro groups, slow the reaction down. The Cannizzaro reaction is not taking place on the benzene ring itself, but substituents on the ring still make their presence known. The fact that the Cannizzaro reaction goes much slower with electron-donating groups and faster with electron-withdrawing groups tells us that, for this reaction, rather than a positive charge developing as in the case of electrophilic substitution on an aromatic ring, there must be negative charge accumulating somewhere near the ring. Our mechanism has mono- and dianion intermediates that are stabilized by electron-withdrawing groups. Later in the chapter you will see a more quantitative treatment of this variation of structure.

The rest of the chapter is devoted to discussions of the methods we have briefly surveyed for the Cannizzaro reaction with examples of the use of each method. We give examples of many different types of reaction but we cannot give every type. You may rest assured that all of the mechanisms we have so far discussed in this book have been verified (not, of course, proved) by these sorts of methods.

Be sure of the structure of the product

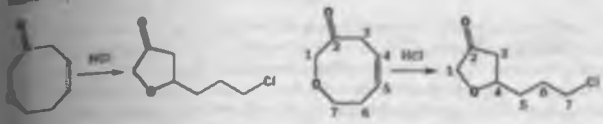
This seems a rather obvious point. However, there is a lot to be learned from the detailed structure of the product and we will discuss checking which atom goes where as well as the stereochemistry of the product. You will discover that it may be necessary to alter the structure of the starting material in subtle ways to make sure that we know exactly what happens to all its atoms by the time it reaches the product.

Suppose you are studying the addition of HCl to this alkene. You find that you get a good yield of a single adduct and you might be a bit surprised that you do not get a mixture of the two obvious adducts and wonder if there is some participation of the ether oxygen or whether perhaps the ketone enolizes during the reaction and controls the outcome.

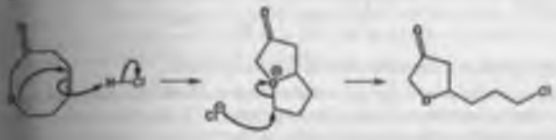


If you are cautious you might check on the structure of the product before you start a mechanistic investigation. The NMR spectrum tells you at once that the product is neither of these suggestions. It contains a $(CH_2)_3Cl$ unit and can no longer have an eight-membered ring. A ring

reaction has given a five-membered ring and a mechanistic investigation is hardly needed. Simply knowing what the product is allows us to propose a mechanism. A rearrangement has occurred and we could use the method suggested in Chapter 37, of numbering the atoms in the starting material and finding them in the product. This is quite easy as only one numbering system makes any sense.



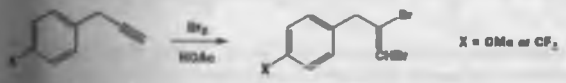
This numbering suggests that the carbon skeleton is unaffected by the reaction, that protonation has occurred at C5, that the ether oxygen has acted as an internal nucleophile across the ring at C4, and that the chloride ion has attacked C7. The mechanism is straightforward.



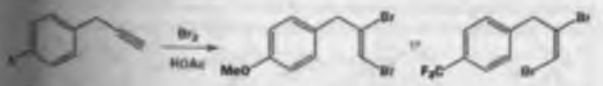
It may be disappointing to find that every step in this mechanism is well known and that the reaction is exactly what we ought to have expected with an eight-membered ring as these rings are famous for their transannular (across-ring) reactions to form 5/5 fused systems. However, it is good that a prolonged investigation is not necessary.

> ● Find out for sure what the structure of the product is before you start a mechanistic investigation.

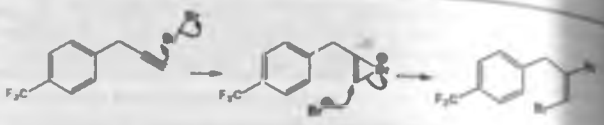
A more subtle distinction occurred in a study of the bromination of alkynes. Bromination of benzyl alkynes in acetic acid gave the products of addition of one molecule of bromine—the 1,2-dibromoalkenes. The reaction was successful with a variety of *para* substituents and there seems at first to be no special interest in the structure of the products.



Closer investigation revealed an extraordinary difference between them, not at all obvious from their NMR spectra: the compound from X = OMe was the *Z*-dibromoalkene from *cis* addition of bromine while the product from X = CF_3 was the *E*-alkene from *trans* addition. What mechanism could explain this difference?

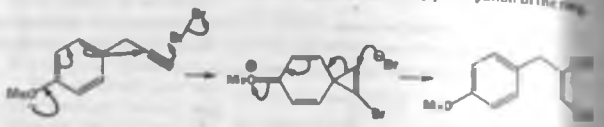


The *trans* addition is more easily explained: it is the result of formation of a bromonium ion, similar, in fact, to the normal mechanism for the bromination of alkenes. Bromine adds from one side of the alkene and the bromide ion must necessarily form the *E*-dibromo product regardless of which atom it attacks.



A similar acid-participation in saturated compounds to give a 'phenonium ion' intermediate appears in Chapter 37, p. 000.

So why does the *p*-MeO– compound behave differently? It cannot react by the same mechanism and a reasonable explanation is that the much more electron-donating ring participates in the reaction to give a carbocyclic three-membered ring intermediate that is attacked in an anti fashion to the *Z*-alkene. Both intermediates are three-membered ring cations and both are attacked with inversion but the *p*-MeO– compound undergoes double inversion by participation of the ring.



Labelling experiments reveal the fate of individual atoms

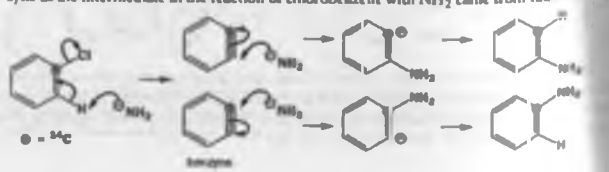
It often happens that the atoms in starting material and product cannot be correlated without some distinction being made by isotopic labelling. The isomerization of *Z*-1-phenylbutadiene to the *E*-diene in acid looks like a simple reaction. Protonation of the *Z*-alkene would give a stabilized secondary benzylic cation that should last long enough to rotate. Loss of the proton would then give the more stable *E*-alkene.

However, reaction with D^+ in D_2O reveals that this mechanism is incorrect. The product contains substantial amounts of deuterium at C4, not at C2 as predicted by the proposed mechanism. Protonation must occur at the end of the conjugated system to produce the more stable conjugated cation, which rotates about the same bond and loses H or D from C4 to give the product. More H than D will be lost, partly because there are two Hs and only one D, but also because of the kinetic isotope effect, of which more later.

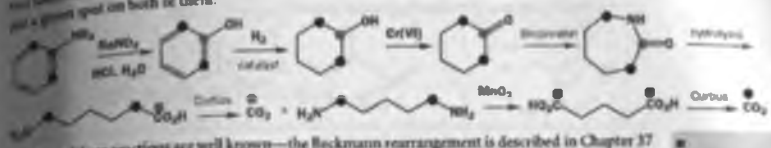
Tritium and ^{14}C are β emitters—they give off electrons—having half-lives of 12 and over 5000 years, respectively. Tritium is made on a large scale by neutron irradiation of ^6Li in a nuclear reactor.

Benzyne is discussed in Chapter 23 as an intermediate in nucleophilic aromatic substitution.

The easiest labels to use for this job are D for H, ^{13}C, and ^{18}O. None of these is radioactive; all can be found by mass spectrometry, while D and ^{13}C can be found by NMR. Old work on mechanisms used radioactive tracers such as T (tritium) for H and ^{14}C. These are isotopes of hydrogen and carbon having extra neutrons. They are, of course, more dangerous to use but they can at least always be found. The real disadvantage is that, to discover exactly where they are in the product, the molecule must be degraded in a known fashion. These radioactive isotopes are not much used nowadays except in determining biological mechanisms as you will see in Chapters 49–51. The first evidence for benzyne as the intermediate in the reaction of chlorobenzene with NH_2^- came from radioactive labelling



If benzyne is an intermediate, the product should have 50% label at C1 and 50% at the two identical ortho carbons. The labelled aniline was degraded by the reactions shown here, which you must agree was a lot of work for the chemists concerned. Each potentially labelled carbon atom had to be isolated from any other labelled atom and the radioactivity measured. We shall follow the fate of the two labelled atoms with black and green spots. Since the two *ortho* positions are identical, we must put a green spot on both of them.

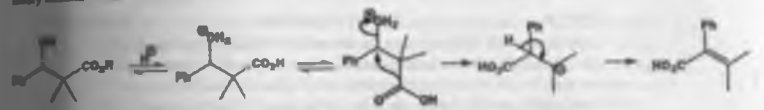


Most of these reactions are well known—the Beckmann rearrangement is described in Chapter 37 and the Curtius reaction in Chapter 40—but the oxidation of the diamine to the dicarboxylic acid is not a standard procedure and is not recommended. All the label came out in the CO_2 and almost exactly half of it was from the black and half from the green labelled carbons. This was the original evidence that convinced organic chemists in 1953 that benzyne was involved in the reaction. The evidence presented in Chapter 23 is more modern.

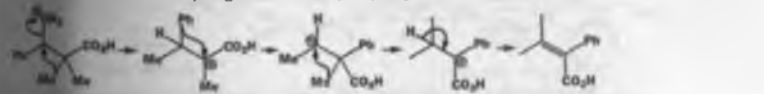
Other spectroscopical intermediates originally identified by radioactive labelling include the cyclopropanone in the Favorskii rearrangement in Chapter 37, p. 000, and a spirocyclic intermediate in electrophilic substitution on an indole in Chapter 43, p. 000.

The value of double labelling experiments

An altogether more modern approach to a labelling study was used in the surprising rearrangement of a hydroxy-acid in acidic solution. The structure of the product suggests a CO_2H migration as the most likely mechanism. This mechanism resembles closely the cationic rearrangements of Chapter 37.

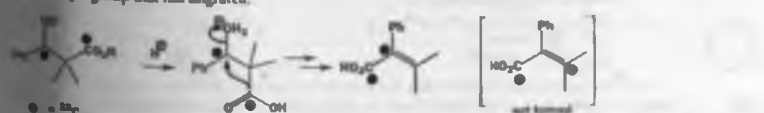


Received wisdom (Chapter 37) objects that the best migrating group in cationic rearrangements is the one best able to bear a positive charge, so that the more familiar Ph and Me migrations ought to be preferred and that a more elaborate mechanism should be sought. Such a mechanism can be written: it involves two methyl migrations and one phenyl migration and is acceptable.



These mechanisms can be tested by finding out whether the CO_2H group remains attached to its original position or becomes attached to the other carbon in the skeleton of the molecule. This can be done by double labelling. If a compound is prepared with two ^{13}C labels, one on the CO_2H group itself and one on the benzylic carbon, the NMR spectrum of the product will show what has happened. In fact, the two ^{13}C labels end up next to each other with a coupling constant $^1J_{CC}$ = 71 Hz. It is the CO_2H group that has migrated.

This style of double labelling with NMR analysis will be seen again in Chapters 49–51.

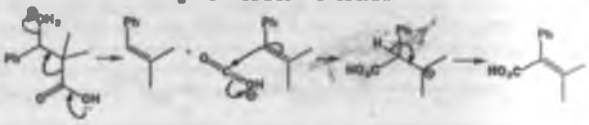


So why does the CO_2H group migrate? It does so not because it is a good migrating group but because it cannot bear to be left behind. The rearranged cation from CO_2H migration is a stable tertiary alkyl cation. The cation from Me migration is a very unstable cation with the positive charge

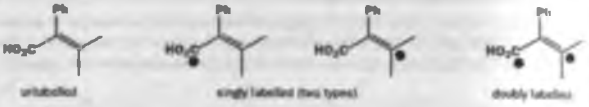
next to the CO_2H group. Such cations are unknown as the carbonyl group is very ... drawing. Received wisdom needs to be amended.

'Crossover' experiments

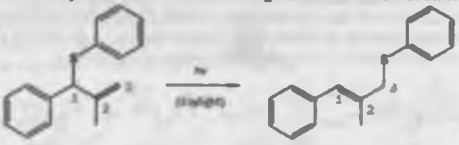
There is still one tiny doubt. Supposing the reaction is not intramolecular at all, but ... The CO_2H group might be lost from one molecule as protonated CO_2 and be picked up by ... molecule of alkene. No migration would be involved at all.



This mechanism can be checked by using a 50:50 mixture of doubly labelled and unlabelled ... ing material. The molecule of alkene that captures the roving protonated labelled CO_2 might ... to be labelled too but equally well it might be unlabelled. If this last mechanism is correct, we ... get a mixture of unlabelled, singly labelled, and doubly labelled product in the ratio 1:2:1 as ... two types of singly labelled product. The two singly labelled compounds are called the ... products and the experiment is called a crossover experiment as it discovers whether any ... one molecule cross over to another.

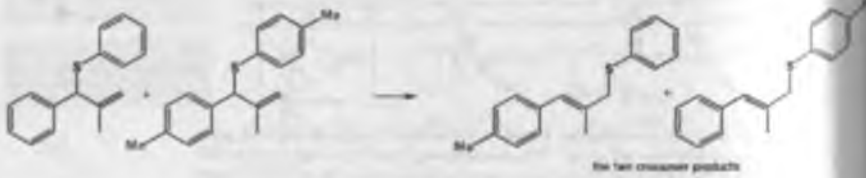


In fact, no singly labelled compounds were found: NMR analysis showed that the product ... ed entirely of unlabelled or doubly labelled molecules. The CO_2H group remains attached to the ... molecule (though not to the same atom) and the first mechanism is correct. Crossover ... demand some sort of double labelling, which does not have to be isotopic. An example ... crossover products are observed is the light-initiated isomerization of allylic sulfides.



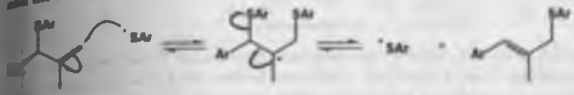
This is formally a [1,3] sigmatropic shift of sulfur (Chapter 36) but that is an unlikely ... and a crossover experiment was carried out in which the two molecules had either two phenyl ... or two *para*-tolyl groups.

The mixture was allowed to rearrange in daylight and the products were examined by ... troscopy. There was a roughly 1:2:1 mixture of products having two phenyl groups, one ... one *para*-tolyl group, and two *para*-tolyl groups. The diagram shows the starting materials and ... two crossover products only.



There is an example of a crossover experiment proving that an S_N2 reaction is intramolecular in Chapter 43, p. 1090.

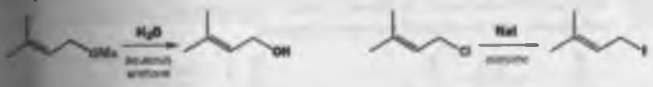
Clearly, the ArS group had become separated from the rest of the molecule and the most likely explanation was a radical chain reaction (Chapter 19) with the light producing a small amount of $ArS^{\bullet}$ to initiate the chain. The *para*-methyl group acts as a label. The whole system is in equilibrium and the more highly substituted alkene is the product.



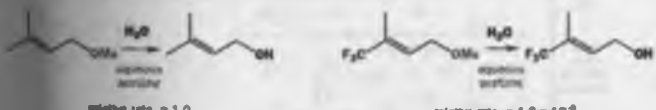
Systematic structural variation

In this last example, the hope is that the *para*-methyl group will have too weak an electronic or steric effect and in any case will be too far away to affect the outcome. It is intended to make nearly as slight a change in the structure as an isotopic label. Many structural investigations have exactly the opposite hope. Some systematic change is made in the structure of the molecule in the expectation of a predictable change in rate. A faster or slower reaction will lead to some definite conclusion about the charge distribution in the transition state.

Allylic compounds can react efficiently with nucleophiles by either the S_N1 or S_N2 mechanisms (Chapter 17) as in these two examples.

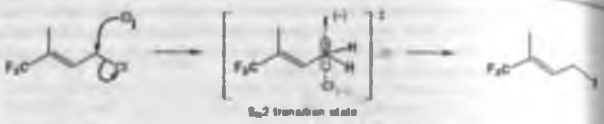


The carbon skeleton is the same in both reactions but the leaving groups and the nucleophiles are different. These reaction might both go by S_N1 or S_N2 or one might go by S_N1 and the other by S_N2. One way to find out is to make a large change in the electronic nature of the carbon skeleton and see what happens to the rate of each reaction. In these experiments one of the methyl groups was changed for a CF_3 group—exchanging a weakly electron-donating group for a strongly electron-withdrawing group. If a cation is an intermediate, as in the S_N1 reaction, the fluorinated compound will react much more *slowly*. Here is the result in the first case.



The fluorinated compound reacts half a million times more slowly so this looks very much like an S_N1 mechanism. The slow step in an S_N1 mechanism is the formation of a carbocation so any group that destabilizes the positive charge would have (and evidently does have) a large effect on the rate. Rate ratios of several powers of ten are worth noticing and a rate ratio of nearly 10^{-6} is considerable. In the second case the rate difference is much less.

A rate ratio of 11 is not worth noticing. The point is not that the fluorinated compound reacts faster but that the two compounds react at about the same rate. This strongly suggests that no charge is generated in the transition state and an S_N1 mechanism is not possible. The S_N2 mechanism is also good sense with its concerted bond formation and bond breaking requiring no charge on the carbon skeleton.



S_N2 transition state

The CF_3 group works well here as a mechanistic probe because it is held well out of the way of the reaction site by a rigid π system but is connected electronically by that same allylic system. Steric effects should be minimized and electronic effects clearly seen. This approach is clearly dominated by the small number of groups having properties like those of the CF_3 group and the small number of reactions having such favourable carbon skeletons. We will now present the most important [illegible] correlation between structure and reactivity.

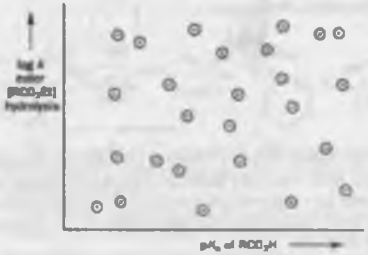
The Hammett relationship

Louis P. Hammett (1894–1987) [illegible] physical organic chemistry and at Columbia University in 1935 devised the Hammett σ/ρ relationship. The impact was enormous and in the 1940s chemists were still working out more such correlations.

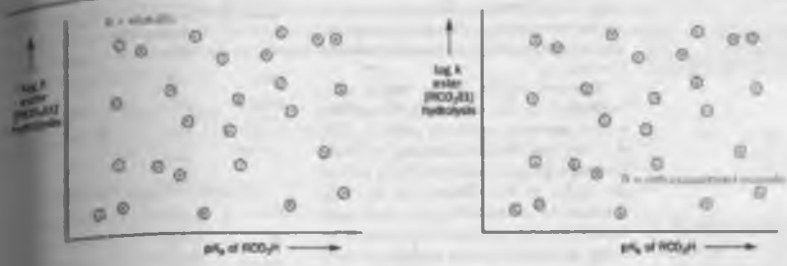
What we would ideally like to do is find a way to quantify the effects that electron-donating or -withdrawing groups have on the transition state or intermediate during the course of a reaction. This will then give us an idea of what the transition state is really like. The first question is: can we determine exactly how efficient a given group is at donating or withdrawing electrons? Hammett took the [illegible] decision to use the pK_a of an acid as a guide. For example, the rate of hydrolysis of esters [illegible] well correlate with the pK_a of the corresponding acid.

substituent on R is mechanistic probe — reaction to be investigated

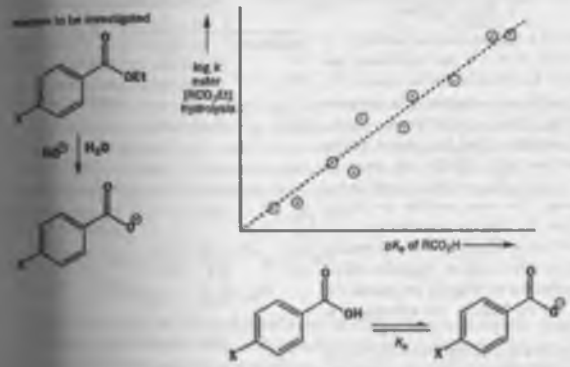
When Hammett plotted the rates of ethyl ester hydrolyses (as log k since pK_a has a log in it) against the pK_as of the corresponding acids, the initial results were not very encouraging as there was a random scatter of points over the whole graph.



Hammett had used some aliphatic acids (substituted acetic acids) and some aromatic acids (substituted benzoic acids) and he noticed that many of the points towards the top of the graph belonged to the substituted acetic acids. Removing them (brown points) made the graph a lot better. He then noticed that the remaining aromatic compounds were in two classes: the *ortho*-substituted esters reacted more slowly than their *meta*- and *para*-isomers and came towards the bottom of the graph (orange points). Removing them made the graph quite good (remaining green points).



It was not a perfect correlation but Hammett had removed the examples where steric hindrance was important. Aliphatic compounds can adopt a variety of conformations (Chapter 18) and the substituent in some of them will interfere with the reaction. Similarly, in *ortho*-substituted aromatic compounds the nearby substituent might exert steric hindrance on the reaction. Only with *meta*- and *para*-substituted compounds was the substituent held out of the way, on a rigid framework, and in electronic communication with the reaction site through the flat but conjugated benzene ring. The diagrams show the *para* substituent.



Notice that the straight line is not perfect. This graph is an invention of the human mind. It is a correlation between things that are not directly related. If you determine a rate constant by plotting the right function of concentration against time and get an imperfect straight line, that is your fault because you haven't done your measurements carefully enough. If you make a Hammett plot and the points are not on a straight line (and they won't be) then that is *not* your fault. The points really don't fit on a perfectly straight line. As you will see soon, this does not matter. We need to look at the Hammett correlation in more detail.

▶ If you plot a graph to correlate the number of miles travelled by planes jet against the percentage of births outside of marriage over the twentieth century you will get a sort of straight line. This does not imply a direct causative link!

The Hammett substituent constant σ

A quick glance at the pK_as of some substituted benzoic acids will show how well they correlate electron donation with pK_a. The substituents at the top of the table are electron-donating and the anions of the benzoic acids are correspondingly less stable so these are the weakest acids. At the bottom of the table we have the electron-withdrawing groups, which stabilize the anion and

▶ You cannot push arrows from the negative charge or the carboxylate into the ring. Try it.

make the acid stronger. The whole range is not that great, only one pH unit or so, because the carboxylate anion is not conjugated with the ring.

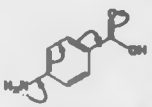
Hammett decided not to use the pK_as themselves for his correlation but defined a new parameter, which he called σ. This σ shows how electron-donating or -withdrawing a group is relative to H as a ratio of the logK_as or the difference of the pK_as between the substituent and benzoic acid itself. If the acid required to determine σ for a new substituent was not available, σ could be determined by correlation with other reactions. Here are the equations and the table of σ values for the most important substituents. A different value of σ for any given substituent was needed for the *meta* and the *para* positions and these are called σ_m and σ_p, respectively.

Substituent, X	pK_a of p-XC_6H_4COOH	pK_a of m-XC_6H_4COOH
NH_2	4.82	4.20
OCH_3	4.48	4.09
CH_3	4.37	4.26
H	4.20	4.20
F	4.15	3.86
I	3.97	3.85
Cl	3.98	3.83
Br	3.97	3.80
CO_2CH_3	3.75	3.87
$COCH_3$	3.71	3.83
CN	3.53	3.58
NO_2	3.43	3.47

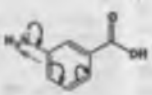
$$\sigma_X = \log\left(\frac{K_a(X\text{–}C_6H_4COOH)}{K_a(C_6H_5COOH)}\right) = pK_a(C_6H_5COOH) - pK_a(X\text{–}C_6H_4COOH)$$

You need a general idea as to what a σ value means. If σ = 0 the substituent has no effect: it is electronically the same as H. If σ is positive, the substituent is electron-withdrawing. This is unfortunate perhaps, but just remember that the comparison is with acid strength. Positive σ means a stronger acid so the substituent is electron-withdrawing. The more positive the charge induced on the ring by a substituent, the larger its σ value. Negative σ means weaker acid and electron donation. Inductive effects from polarization of σ bonds are greater for σ_m than for σ_p because the substituent is nearer.

Substituent, X	σ_p	σ_m	Comments
NH_2	−0.62	0.00	groups that donate electrons have negative σ
OCH_3	−0.29	0.11	
CH_3	−0.17	−0.06	
H	0.00	0.00	there are no values for ortho substituents
F	0.06	0.34	
I	0.23	0.35	
Cl	0.22	0.37	$\sigma_p < \sigma_m$ for inductive withdrawal
Br	0.23	0.40	
CO_2CH_3	0.45	0.33	
$COCH_3$	0.49	0.37	$\sigma_p > \sigma_m$ for conjugating substituents
CN	0.67	0.62	
NO_2	0.77	0.73	groups that withdraw electrons have positive σ



strong conjugation into carbonyl group: large negative σ_p

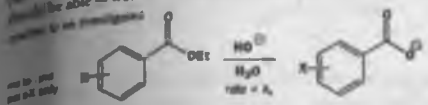


conjugation into ring not carbonyl group: balances weak effect of electronegative N: zero negative σ_m

Conjugation is generally more effective in the *para* position (see Chapter 22) so $\sigma_p > \sigma_m$ for conjugating substituents. Indeed, the NH_2 group has a large negative σ_p and a zero σ_m. The NH_2 group donates electrons strongly to the carbonyl group of benzoic acid from the *para* position but does not conjugate in the *meta* position where its donation happens just to balance the effect of electronegative nitrogen.

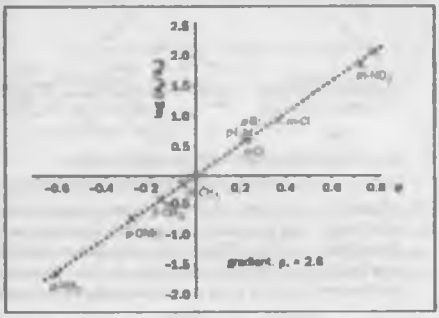
The OMe group has a negative σ_p but a positive σ_m because a weaker electron donation from the lone pairs is more important in the *para* position but the effect of very elec-

...on the σ framework of the ring in the *meta* position is more important than lone pair donation that doesn't reach the carbonyl group. You do not need to learn any σ values but you should be able to work out the sign of σ for well known substituents and estimate a rough value.



The Hammett reaction constant ρ

Now we can return to our reaction: the alkaline hydrolysis of *meta*- and *para*-substituted ethyl benzoates. The rate constants for this second-order reaction have been measured and shown here is a graph of log (k_X/k_H) versus σ, where k_X is the rate constant for the reaction with the substituted benzoate and k_H is that for the unsubstituted reaction (X = H).



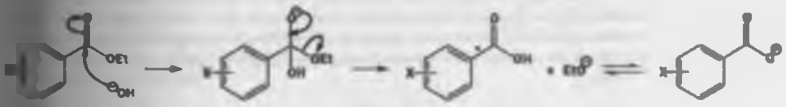
We can see straight away that there is a good correlation between how fast the reaction goes and the value of σ; in other words, the points lie more or less on a straight line. The gradient of this best fit line, given the symbol ρ (rho), tells us how sensitive the reaction is to substituent effects in comparison with the ionization of benzoic acids. The gradient is ρ = +2.6. This tells us that the reaction responds to substituent effects in the same way (because it is +) as the ionization of benzoic acids but by much more ($10^{1.6}$ times more) because it is 2.6 instead of 1.0. We already know what the mechanism of this reaction is.

▶ **Getting to grips with logs**

A difference between two values of *x* log units means the values actually differ by a factor of 10^x. From the graph for the hydrolysis of ethyl benzoates we can see that the pNO_2 benzoate hydrolyses some 10^2 times faster than the unsubstituted benzoate, while the pNH_2 benzoate hydrolyses some 10^2 times slower.

▶

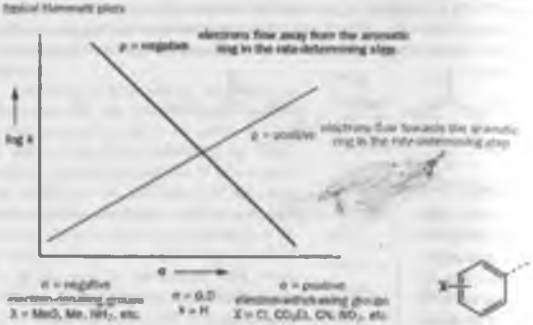
Hammett chose σ (Greek s) for substituent and ρ (Greek r) for reaction.



The first step is quite like the ionization of benzoic acid. A negative charge is appearing on the carbonyl oxygen atom and that negative charge will be stabilized by electron-withdrawing X groups. Provided that the first step is rate-determining, a positive ρ is fine. We cannot say much as yet about the value as we are comparing a reaction rate (for the hydrolysis) with an equilibrium position (for the ionization). It will help you a great deal if you think of *positive* ρ values as meaning an increase in electron density near to or on the benzene ring. They may mean the appearance of a negative charge but they may not. We need now to look at some other reactions to get a grasp of the meaning of the value of the Hammett ρ.

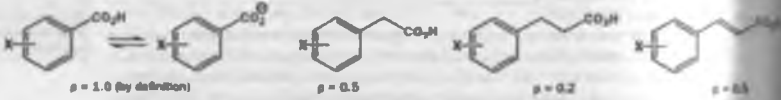
The Hammett reaction constant ρ measures the *sensitivity* of the reaction to electronic effects.

- A *positive* ρ value means *more* electrons in the transition state than in the starting material
- A *negative* ρ value means *fewer* electrons in the transition state than in the starting material

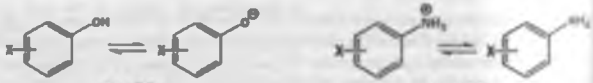


Equilibria with positive Hammett ρ values

We can compare these directly with the ionization of benzoic acids. If we simply move the carboxylic acid away from the ring, the ρ value for ionization gets less. This is just the effect of a more distant substituent. When there are two saturated carbons between the benzene ring and the carboxylic acid there is almost no effect. When we are using the aromatic ring as a probe for a reaction mechanism, it must be placed not too far away from the reaction centre. However, if we restore electronic communications with a double bond, ρ goes back up again to a useful value.

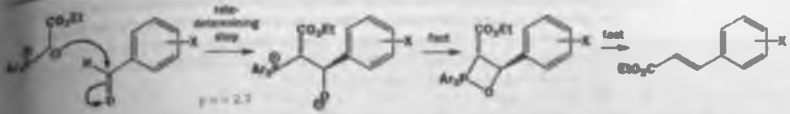


If the negative charge on the anion can actually be delocalized round the ring, as with substituted phenols, we should expect the size of ρ to increase. Both the phenol and the anion are delocalized but it is more important for the anion. The effect is larger for the ionization of anilinium salts as the acid ($ArNH_3^+$) does not have a delocalized lone pair but the conjugate base ($ArNH_2$) does.

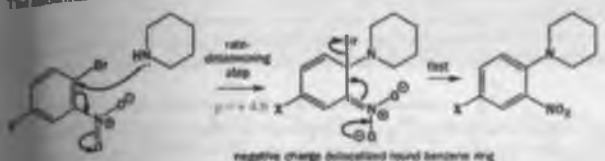


Reactions with positive Hammett ρ values

Any reaction that involves nucleophilic attack on a carbonyl group as the rate-determining step is going to have a ρ value of about 2–3, the same as for the hydrolysis of esters that we have already seen. Examples include the Wittig reaction of stabilized ylids (Chapters 14 and 31). Though there is some dispute over the exact mechanism of the Wittig reaction, the ρ value of 2.7 strongly suggests that nucleophilic attack on the aldehyde by the ylid is involved with stabilized ylids and aromatic aldehydes at least. In addition, there is a small variation of rate with the aryl group on phosphorus. If Ar = p-$MeOC_6H_4$ the reaction goes about six times faster than if Ar = p-ClC_6H_4. These groups are a long way from the reaction site but electron donation would be expected to accelerate the donation of electrons from the ylid.

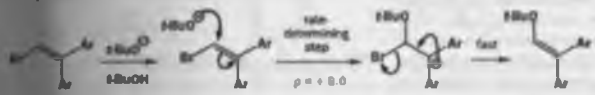


Large positive ρ values usually indicate extra electrons in the transition state delocalized into the ring itself. A classic example is nucleophilic aromatic substitution by the addition–elimination mechanism (Chapter 23). The ρ value is +4.9, but even this large value does not mean a complete anion on the benzene ring as the nitro group, present in all cases, takes most of the negative charge. The substituent X merely helps.



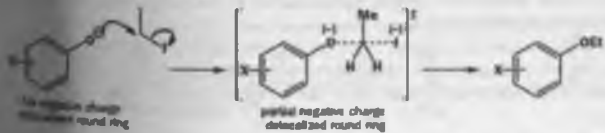
negative charge delocalized round benzene ring

We get the full value when there are no nitro groups to take the brunt of the negative charge. This vinylic substitution (an unusual reaction!) has a ρ value of +9.0. It cannot be an S_N2 reaction or it would have a small ρ value and it cannot be an S_N1 reaction or it would have a negative ρ value (fewer electrons in the transition state). It must be an addition–elimination mechanism through a benzylic anion delocalized round both benzene rings.



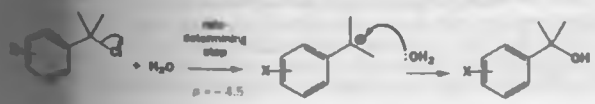
Reactions with negative Hammett ρ values

Negative ρ values mean electrons flowing away from the ring. A useful example is the S_N2 displacement of iodide from EtI by phenoxide anions. This has a ρ value of exactly –1.0. Though the transition state has a negative charge, that charge is decreasing on the aromatic ring as the starting material approaches the transition state.

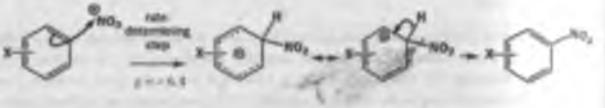


partial negative charge delocalized round ring

An S_N1 reaction on the carbon atom next to the ring has a large negative ρ value. In this example, a tertiary benzylic cation is the intermediate and the rate-determining step is, of course, the formation of the cation. The cation is next to the ring but delocalized round it and the ρ value is –4.5, about the same value, though negative, as that for the nucleophilic substitution on nitrobenzenes by the addition–elimination mechanism that we saw in the last section.

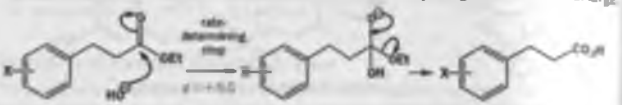


The largest negative ρ values come from electrophilic aromatic substitution (Chapter 22) in which the electrons of the ring are used in the reaction leaving a positive charge on the ring itself in the intermediate. Some of this charge is already there in the transition state. Negative ρ values mean electrons flowing out of the ring. This simple nitration has ρ = – 6.4 and ρ values for electrophilic aromatic substitution are usually in the range –5 to –9.



Reactions with small Hammett ρ values

Small Hammett ρ values arise in three ways. The aromatic ring being used as a probe for the mechanism may simply be too far away for the result to be significant. This trivial case of the alkaline hydrolysis of the 3-aryl propionate ester has a ρ value of +0.5 and it is surprising that it is even that large.



The second case is the informative one where the reaction is not dependent on electrons flowing into or out of the ring. Pericyclic reactions are important examples and the Diels–Alder reaction of arylbutadienes with maleic anhydride shows a small negative ρ value of –0.6. The small value is consistent with a mechanism not involving charge accumulation or dispersal but the sign is interesting. We explained this type of Diels–Alder reaction in Chapter 35 by using the HOMO of the diene and the LUMO of the dienophile. The negative sign of ρ, small though it is, supports this view.

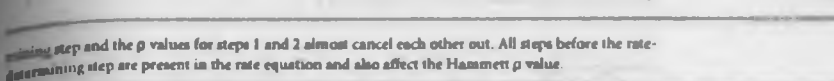
The third case is in many ways the most interesting. We have seen that the alkaline hydrolysis of ethyl esters of benzoic acids ($ArCO_2Et$) has a ρ value of +2.6 and that this is a reasonable value for a reaction involving nucleophilic attack on a carbonyl group conjugated with the aromatic ring. The hydrolysis of the same esters in acid solution, which also involves nucleophilic attack on the same carbonyl group, has a ρ value of +0.1. In other words, all these esters hydrolyse at the same rate in acid solution. Neither of the previous explanations will do. We need to see the full mechanism to explain this remarkable result.

Steps 1, 3, and 5 cannot be slow as they are just proton transfers between oxygen atoms (Chapter 13). That leaves only steps 2 and 4 as possible rate-determining steps. The bimolecular addition of the weak nucleophile water to the low concentration of protonated ester (step 2) is the most attractive candidate, as step 4—the unimolecular loss of ethanol and re-formation of the carbonyl group—should be fast. What ρ value would be expected for the reaction if step 2 were the rate-determining step? It would be made up of two parts. There would be an equilibrium ρ value for the protonation and a reaction ρ value for the addition of water. Step 1 involves electrons flowing out of the molecule and step 2 involves electrons flowing in so the ρ values for these two steps would have opposite charges. We know that the ρ value for step 2 would be about +2.5 and a value of about –2.5 for the equilibrium protonation is reasonable. This is indeed the explanation: step 2 is the rate-deter-

rate-determining step and the ρ values for steps 1 and 2 almost cancel each other out. All steps before the rate-determining step are present in the rate equation and also affect the Hammett ρ value.

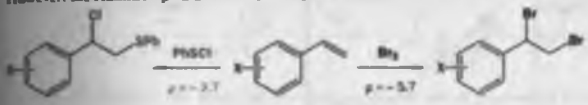
The meaning of Hammett ρ values

This then is the full picture. You should not, of course, learn these numbers but you need an idea of roughly what each group of values means. You should see now why it is unimportant whether the Hammett correlation gives a good straight line or not. We just want to know whether ρ is + or – and whether it is, say, 3 or 6. It is meaningless to debate the significance of a r value of 3.4 as distinct from one of 3.8.

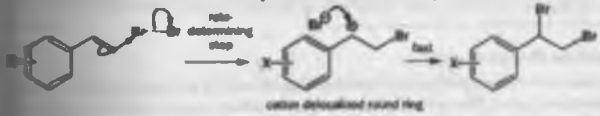


Using the Hammett ρ values to discover mechanisms

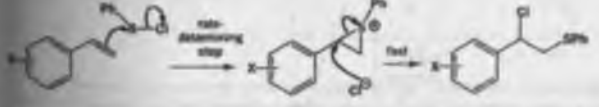
Electrophilic attack on alkenes by bromine often goes through three-membered ring cyclic bromonium ions and we can sometimes tell that this is so by studying the stereochemistry. Here are two reactions of styrenes that look very similar—a reaction with bromine and one with PhSCl. With no further information, we might be tempted to assume that they both go by the same mechanism. However, the Hammett ρ values for the two reactions are rather different.



The ρ value for bromination is definitely in the 'large' range and can only mean that a positive charge is formed that is delocalized round the benzene ring. Bromine evidently does not form a bromonium ion with these alkenes but prefers to form a secondary benzylic cation instead.



The sulfenylation, on the other hand, has a moderate negative ρ value. No cation is formed that is delocalized round the ring, but electrons flow out of the ring and we suspect some loss of conjugation. All this fits well with the formation of a three-membered ring intermediate. From experiments like this we learn that PhSCl is much more likely than bromine to react stereospecifically with alkenes through cyclic cation intermediates.

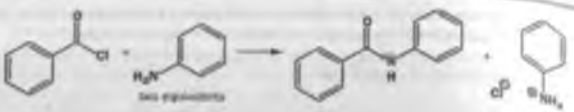


A complete picture of the transition state from Hammett plots

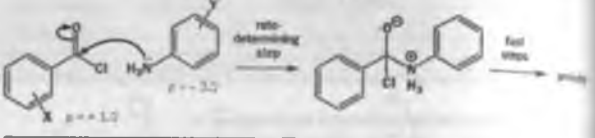
More information can be gained on the mechanism of the reaction if two separate experiments can be carried out with the mechanistic probe inserted at two different sites on the reagents. If we are studying a reaction between a nucleophile and an electrophile, it may be possible to make Hammett plots from the variation of substituents on both reagents. The acylation of amines with acid chlorides is an example.

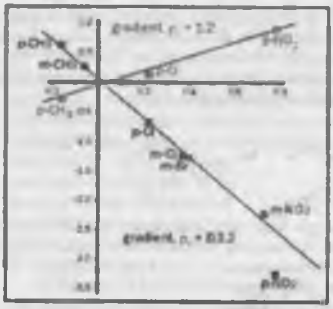
Chapter 20 gives a full description of these mechanisms.

There is more about these sulfenyl chlorides in Chapter 46.



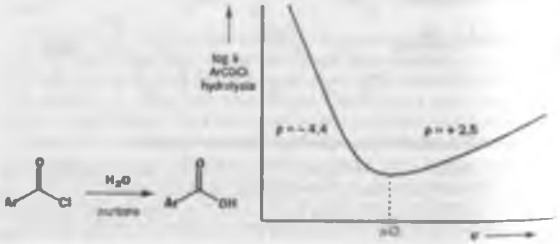
If we vary the structure of the acid chloride we get a ρ value of +1.2, suitable for nucleophilic attack on the carbonyl group. If we vary the amine we get a ρ value of –3.2, again suitable for electrons that were conjugated round the ring moving away to form a new bond. The simpler answer is correct but the rate depends on the nucleophilicity of the amine 100 times more than on the electrophilicity of the acid chloride.



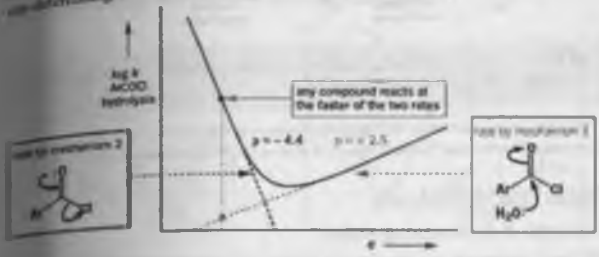


Nonlinear Hammett plots

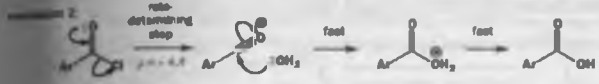
If we look at the hydrolysis of the acid chlorides of benzoic acids in aqueous acetone, we see a wavy line Hammett plot indeed. You know that Hammett plots need not be perfectly linear but this one is clearly made up of two intersecting straight lines. This might look like disaster at first but, in fact, it gives us extra information. The right-hand part of the curve, for the more electron-withdrawing substituents, has a slope of +2.5: just what we should expect for rate-determining attack of water on the carbonyl group. As we go to less electron-withdrawing substituents, the rate of the reaction suddenly starts to increase as we pass the *para*-chloro compound and the left-hand part of the curve has a slope of –4.4



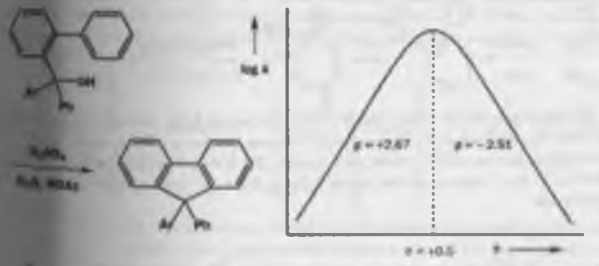
What can this mean? If the reaction becomes faster as we pass the discontinuity in the curve—and it must faster whether we go from right to left or left to right—there must be a change in mechanism. If there is a choice between two mechanisms, the faster of the two will operate. Mechanism 1 is the rate-determining nucleophilic attack by water on the carbonyl group.



The new mechanism goes faster for more electron-donating substituents and has quite a large negative ρ value suggesting the formation of a cation in the rate-determining step. This mechanism (mechanism 1) must surely be the S_N1-like process of preliminary formation of an acylium ion by loss of chloride ion.



When the Hammett plot bends the other way, so that the rate of the reaction decreases as it passes the discontinuity, we have a single mechanism with a change in rate-determining step. A reaction goes by the fastest possible mechanism but its rate is limited by the slowest of the steps in that mechanism. An example is the intramolecular Friedel–Crafts alkylation of a diphenyl derivative where the alkylating agent is a diarylmethanol attached to one of the benzene rings in the *ortho* position.



The carbocation intermediate in the Friedel–Crafts reaction (Chapter 22) is rather stable, being tertiary and benzylic, and the formation of the cation, normally the rate-determining step, with normally a negative ρ value, goes faster and faster as the electron-donating power of the substituents increases until it is faster than the cyclization which becomes the rate-determining step. The cyclization puts electrons back into the carbocation and has a positive ρ value. As the two steps have more or less the reverse electron flow to and from the same carbon atom, it is reasonable for the size of ρ to be about the same but of opposite sign.

● A reaction occurs by the faster of two possible mechanisms but by the slower of two possible rate-determining steps.

We shall see more examples of Hammett ρ values used in conjunction with other evidence as the chapter develops but now it is time to look at what other evidence is available.

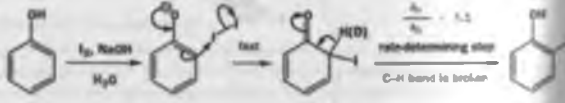
Other kinetic evidence

The kinetic deuterium isotope effect

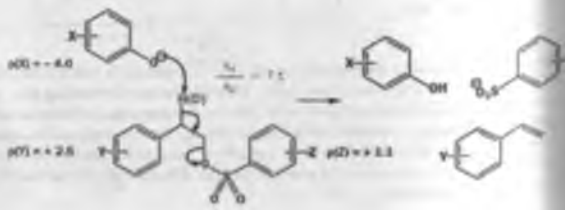
▶ Other kinetic isotope effects are known but they are very small: D is twice as heavy as H but ^{13}C only slightly heavier than ^{12}C.

The kinetic isotope effect was introduced in Chapter 19. If a bond to deuterium is formed or broken in the rate-determining step of a reaction, the deuterated compound will react more slowly, usually by a factor of about 2–7. This effect is particularly valuable when C–H bonds are being formed or broken. In Chapter 22 we told you that the rate-determining step in the nitration of benzene was the attack of the electrophile on the benzene ring. This is easily verified by replacing the hydrogen atoms round the benzene ring with deuteriums. The rate of the reaction stays the same.

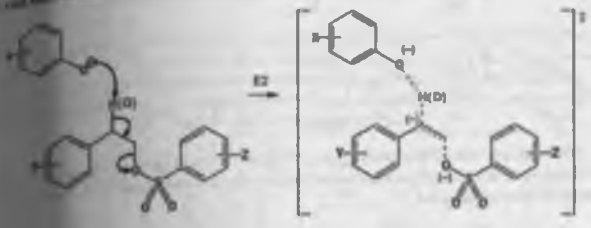
If the second step, which does involve the breaking of a C–H bond, were the rate-determining step it would go more slowly if the H were replaced by D. In this case the deuterium isotope effect is $k_H/k_D = 1.0$. If the reaction is the iodination of phenol in basic solution, there is a deuterium isotope effect of $k_H/k_D = 4.1$. Clearly, the other step must now be the rate-determining step—the phenolate ion reacts so rapidly that the first step is faster than the second.



The deuterium isotope effect can add to the information from Hammett plots in building up a picture of a transition state. Three separate Hammett ρ values can be measured for this elimination reaction and this information is very valuable. But it would be sadly incomplete without the information that a large deuterium isotope effect $k_H/k_D = 7.1$ is observed for the hydrogen atom under attack.

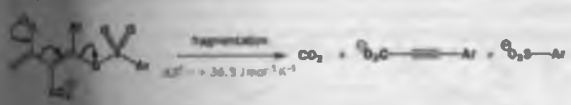


In this E2 reaction, it is no surprise that the base (ArO^-) donates electrons and the leaving group (ArO^-) accepts them. But the large deuterium isotope effect and moderate positive $\rho(Y)$ value for an aromatic ring that might have done nothing suggest some build-up of negative charge in the transition state on that carbon atom as well as on the two oxygen atoms.

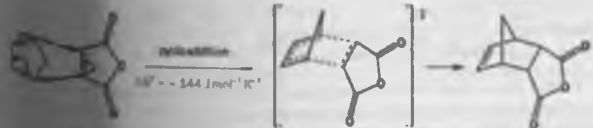


Entropy of activation

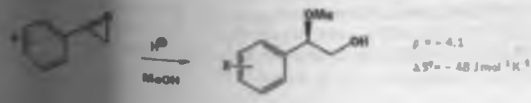
Of all the enthalpies and entropies that we introduced in Chapter 13, the entropy of activation, $\Delta S^\ddagger$, is by far the most useful. It tells us about the increase or decrease in order in a reaction as the starting material goes to the transition state. A positive $\Delta S^\ddagger$ means an increase in entropy or a decrease in order and a negative $\Delta S^\ddagger$ means an increase in order. Normally, unimolecular reactions in which one molecule gives two products have a positive $\Delta S^\ddagger$ and bimolecular reactions have a negative $\Delta S^\ddagger$. Fragmentations (Chapter 38) such as this decarboxylation in which one molecule fragments to three have positive $\Delta S^\ddagger$s. It has $\Delta S^\ddagger = +36.8\ J\ mol^{-1}\ K^{-1}$.



At the other extreme are cycloadditions (Chapter 35) such as the Diels–Alder reaction we examined a few pages back. Not only do two reagents become one product but a very precise orientation is required in the transition state usually meaning a large negative $\Delta S^\ddagger$. Diels–Alder reactions usually have $\Delta S^\ddagger$ of about −120 to −160 $J\ mol^{-1}\ K^{-1}$. The classic cyclopentadiene addition to maleic anhydride has $\Delta S^\ddagger = -144\ J\ mol^{-1}\ K^{-1}$.

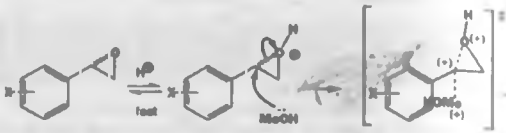


These numbers give you the range of entropies of activation you may expect to find. Large negative numbers are common but only small positive numbers are found. The largest negative numbers apply to bimolecular reactions where neither reagent is in great excess. Smaller negative numbers may mean a bimolecular reaction with solvent or some other reagent in large excess. The acid-catalysed opening of styrene oxides in methanol is a good example.



▶ Entropies of activation are measured in units of $J\ mol^{-1}\ K^{-1}$. All the values in this book are in $J\ mol^{-1}\ K^{-1}$ but in older books you will see 'entropy units' (e.u.), which are $cal\ mol^{-1}\ K^{-1}$. Values in e.u. should be multiplied by about

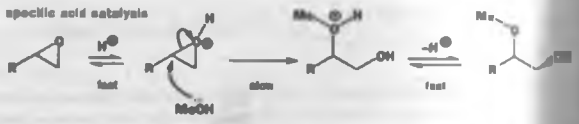
The Hammett ρ value of –4.1 suggests a carbocation intermediate as does the [illegible] the reaction (MeOH attacks the benzylic position) but the stereochemistry (the reaction [illegible] inversion) and a modest negative entropy of activation ($\Delta S^{\ddagger} = -48$ J mol^{-1} K^{-1}) suggest [illegible] S_N2 reaction with a loose transition state having substantial positive charge at the [illegible]. Neither piece of evidence alone would be enough to define the mechanism.



This example with its acid catalyst brings us to the subject of catalysis. We must now analyse the different sorts of acid and base catalysis and see how the mechanisms can be distinguished using the methods we have discussed.

Acid and base catalysis

Acids and bases provide the best known ways of speeding up reactions. If you want to make an ester—add some acid. If you want to hydrolyse an ester—add some base. It may all seem rather simple. However, there are actually two kinds of acid catalysis and two kinds of base catalysis and this section is intended to explain the difference in concept and how to distinguish which operates. When we talk about acid catalysis we normally mean specific acid catalysis. This is the kind we have just seen—epoxides don't react with methanol but, if we protonate the epoxide first, then it reacts. Specific acid catalysis protonates electrophiles and makes them more electrophilic.



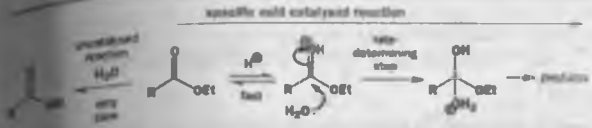
We could, on the other hand, have argued that methanol is not a good enough nucleophile but if deprotonated with a base it becomes the much more nucleophilic methoxide. This is specific base catalysis.

We shall discuss these two types first because they are straightforward. You need to appreciate their characteristics, their strengths, and their weaknesses. We hope you will get into the habit of recognizing these types of catalysis so that you hardly have to think about it—it should become second nature.

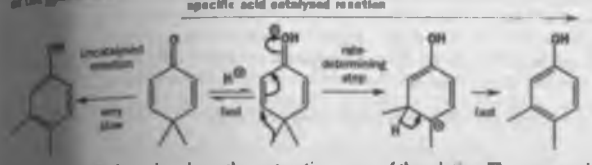
Specific acid catalysis

Specific acid catalysis (SAC) involves a rapid protonation of the compound followed by a slow step, which is accelerated in comparison with the uncatalysed reaction because of the greater reactivity of the protonated compound. You have just seen an example with an epoxide. Ester hydrolysis (ester formation) is another. Water attacks esters very slowly: it attacks protonated esters much more quickly. This is just the ordinary mechanism for acid-catalysed ester hydrolysis [illegible] in Chapter 12.

► SAC is the usual method by which acids make reactions go faster and, if you think about the acid-catalysed reactions you already know, you will see that you have been using it all along without realizing it.

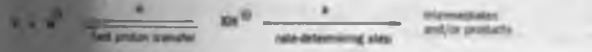


A more interesting reaction is the dienone–phenol rearrangement (Chapter 37). Rearrangement in the absence of acid is very slow but, once the ketone oxygen is protonated, it occurs very rapidly. Again we have fast equilibrium protonation followed by a rate-determining step involving a reaction of the protonated species and again this is the ordinary mechanism that you now know to call S_AC^*.



This catalysis depends only on the protonating power of the solution. The compound must be protonated to react so the catalyst must be a strong enough acid to do the job. It is not necessary that every molecule is protonated, just enough to set the reaction going as the acid is regenerated at the end. So the (log of the) rate of the reaction is inversely proportional to the pH of the solution and significant only in the region of, and of course below, the pK_{aH} of the substrate.

There is one special experimental indication of this mechanism. If the reaction is carried out in a deuterated solvent (D_2O instead of H_2O) the rate of the reaction increases. This is a solvent isotope effect rather than a kinetic isotope effect and needs some explanation. If you examine the three examples of S_AC in the previous pages you will see that they share these characteristics: a fast proton exchange is followed by a rate-determining step that does *not* involve the making or breaking of any bonds to hydrogen. In general terms:



The rate of the reaction is the rate of the rate-determining step: rate = $k[XH^+]$. The concentration of the intermediate $[XH^+]$ is related to the pH and to the concentration of the substrate by the equilibrium constant, K, of the protonation. So we have: rate = $kK[H^+][X]$. We know that k does not change when hydrogen is replaced by deuterium so K must increase in D_2O.

You will sometimes see in books the statement that D_3O^+ is a stronger acid than H_3O^+. This is rarely true. The full truth is that D_3O^+ as D_2O is a stronger acid than H_3O^+ in H_2O. Water (H_2O) is a better deuteron acceptor than D_2O is for D_3O^+, simply because it forms stronger hydrogen bonds due to the greater O–H vibration frequency. So D_3O^+ in D_2O is less well solvated than H_3O^+ in H_2O and is a stronger acid. You need an example.

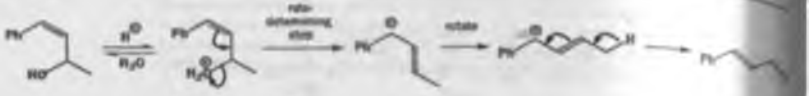
The Z-allylic alcohol below dehydrates in acid solution to the E-diene. We have lots of data on this mechanism, all summarized in the diagrams. You may like to note as well that the product contains no deuterium after dehydration in D_2O.

The Hammett ρ value of –6.0 suggests a carbocation intermediate and the positive entropy of activation suggests a rate-determining step in which disorder increases, perhaps one molecule breaking into two. The inverse solvent deuterium isotope effect (faster reaction in D_2O than in H_2O) strongly suggests S_AC. Putting all this together we have a mechanism—a simple example of S_AC with no protonation at carbon.

▶ A normal kinetic isotope effect has $k_H/k_D > 1$. Deuterium is often put into compounds by exchange with the cheapest source, D_2O, so reactions in D_2O often go slower than reactions in H_2O. Reactions with $k_H/k_D < 1$ have inverse deuterium isotope effects so a reaction that goes faster in D_2O than in H_2O (even when that is the expected pattern) has an inverse solvent deuterium isotope effect.

▶ It is not, of course, possible to use D_3O^+ in H_2O as H and D exchange very quickly. The solvent determines which acid is present.

■ You might like to compare this mechanism with the isomerization of the same diene described earlier in this chapter.



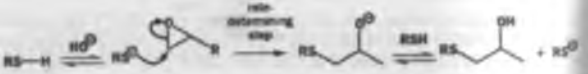
One more thing about this example. The rate-determining step is the second step in the whole reaction. The kinetic data, the Hammett ρ value and the entropy of activation, also refer to the combination of H and A. The equilibrium ρ value for the protonation will be fairly small and negative as a positive charge is being created some way from the benzene ring. The kinetic ρ value for the loss of water will be large and negative because a positive charge is being created that is delocalized into the ring. A combined value of –6 looks fine. The equilibrium entropy ΔS° for the protonation will probably be small and negative as $ROH + H_3O^+ \rightleftharpoons ROH_2^+ + H_2O$ represents little change in order (two molecules going to two) and the $\Delta S^\ddagger$ for the loss of water will be large and positive (one molecule going to two) so a small positive value is about right. It doesn't do to interpret these numbers too closely.

● Summary of features of specific acid catalysis

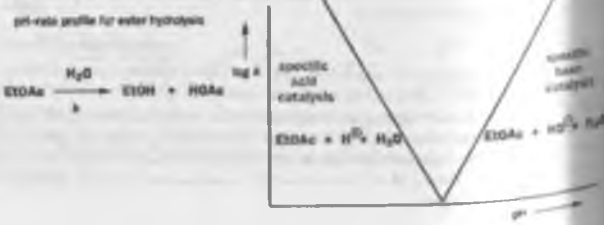
1. Only H_3O^+ is an effective catalyst; pH alone matters
2. Usually means rate-determining reaction of protonated species
3. Effective only at pHs near or below the pK_{aH} of the substrate
4. Proton transfer is not involved in the rate-determining step
5. Only simple unimolecular and bimolecular steps—moderate +ρ or $-\Delta S^\ddagger$
6. Inverse solvent isotope effect $k(H_2O) < k(D_2O)$

Specific base catalysis

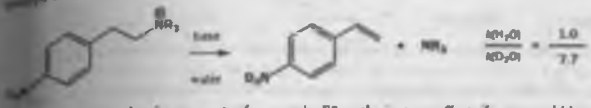
The other side of the coin is specific base catalysis (SBC) which usually involves the removal of a proton from the substrate in a fast pre-equilibrium step followed by a rate-determining reaction of the anion. Most of the base-catalysed reactions you are familiar with work by SBC. Examples include opening of epoxides with thiols.



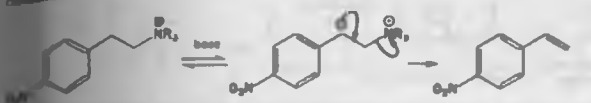
The rate of the reaction depends on the pH of the solution. If it is around or higher than the pK_a of the thiol, thiolate anion will be formed and this opens the epoxide much faster than does the unionized thiol. The nucleophile is regenerated by the oxyanion produced in the rate-determining step. A more familiar example is the base-catalysed hydrolysis of esters we have mentioned several times in this chapter. The full pH–rate profile (Chapter 13) for the hydrolysis of a simple ester such as ethyl acetate shows just two straight lines meeting each other (and zero rate) at about neutrality. Ethyl acetate hydrolysis occurs by SAC or SBC only.



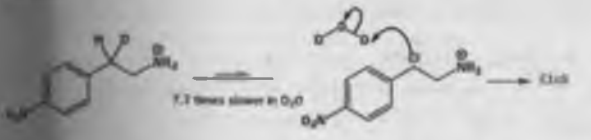
Removal of a proton from heteroatoms by heteroatom bases is always a fast step but removal of a proton from carbon can be the rate-determining step. A remarkably large inverse solvent deuterium isotope effect was found with this elimination of a tertiary amine in basic solution.



The detailed mechanism cannot, of course, be E2 or the isotope effect, if any, would be the other way round. If it is SBC, the mechanism then becomes the well-known E1cB (Chapter 19) having a carbanion as intermediate.



But 1/7.7 is too large to be a solvent isotope effect and looks much more like a normal kinetic isotope effect. And so it is. The tertiary amine is not a very good leaving group in spite of its positive charge (pK_{aH} about 10) so the carbanion mostly reverts to starting materials. The isotope effect is a hostile isotope effect on this reverse step—the protonation of the carbanion. This reaction involves a proton transfer from H_2O or D_2O and will be much faster (could be 7.7 times) in H_2O by the ordinary kinetic isotope effect. The *elimination* reaction goes faster in D_2O because the back reaction goes more slowly and more of the carbanion goes on to product.



▶ Microscopic reversibility

There is only one least-energy pathway between two interconverting compounds such as the starting material and the intermediate here. Every microscopic detail of the back reaction is exactly the same as that for the forward reaction. This is the principle of microscopic reversibility. Here we use evidence from the back reaction (slow proton transfer from water to the carbanion) to tell us about the forward reaction. This principle will be useful in Chapter 42.

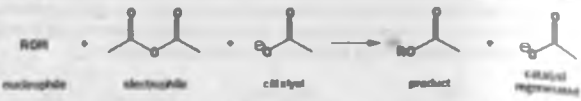
● Summary of features of specific base catalysis

1. Only HO^- is an effective catalyst; pH alone matters
2. Usually means rate-determining reaction of deprotonated species
3. Effective only at pHs near or above the pK_a of the substrate
4. Proton transfer is not involved in the rate-determining step, unless C–H bonds are involved
5. Only simple unimolecular and bimolecular steps—moderate + or $-\Delta S^{\ddagger}$
6. Inverse solvent isotope effect $k(H_2O) < k(D_2O)$

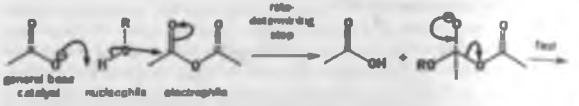
General acid/base catalysis

The other kind of acid/base catalysis is called 'general' rather than 'specific' and abbreviated GAC or GBC. As the name implies this kind of catalysis depends not only on pH but also on the concentration of undissociated acids and bases other than hydroxide ion. It is a milder kind of catalysis and is used in living things. The proton transfer is not complete before the rate-determining step but occurs during it. A simple example is the catalysis by acetate ion of the formation of esters from alcohols and acetic anhydride.

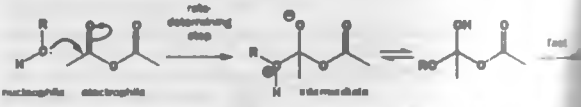
● There was some discussion of this reaction in Chapter 13. Chapter 12 refers to the difficulty of transferring protons from oxygen to oxygen, involving the carbonyl group.



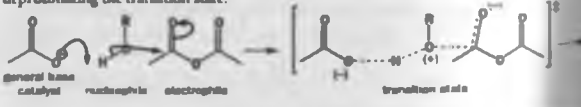
How can this catalysis work? At first sight there seems to be no mechanism available. Acetate cannot act as a specific base—it is far too weak (pK_{aH} 4.7) to remove a proton from an alcohol (pK_a about 15). If it acted as a nucleophile (Chapters 12 and 13) there would be no catalysis as nucleophilic attack on acetic anhydride would be a non-reaction simply regenerating starting material. The only thing it can do is to remove the proton from the alcohol *as the reaction occurs*.



You will see at once that there is a great disadvantage in this mechanism: the rate-determining step is termolecular and this is really termolecular—three molecules colliding—and not just some mathematical kinetic trick. This comes out most clearly in the entropy of activation which is an enormous negative value, around $\Delta S^{\ddagger} = -168\ J\ mol^{-1}\ K^{-1}$ for this reaction. There will also be a normal kinetic isotope effect for ROD against ROH as a bond to hydrogen is being formed and broken in the rate-determining step: it is $k_H/k_D = 2.4$ here. These GBC or GAC reactions are normally effective only if one of the three molecules is present in large excess—this reaction might be done in ROH as a solvent, for example, so that ROH is always present. In understanding how this GBC works it is helpful to look at the mechanism without catalysis.



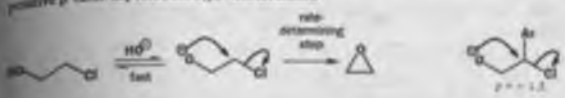
The acetate catalyst cannot remove a proton from the starting material but it can easily remove a proton from the intermediate, which has a complete positive charge on the alcohol oxygen atom. The starting material has a pK_a above the pK_{aH} of acetate but the product has a pK_a well below it. Somewhere in the middle of the rate-determining step, the pK_a of the ROH proton passes through the pK_{aH} of acetate and then acetate is a strong enough base to remove it. The GBC is effective in deprotonating the transition state.



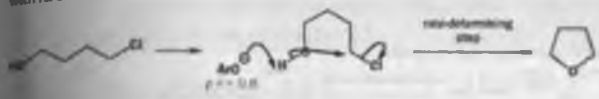
So how do we find GAC or GBC? Normally, general species catalysis is a weak substitute for specific catalysis. We must remove that more powerful style of catalysis by working at a specific pH because SAC or SBC depends on pH alone. If we find that the rate of the reaction changes with the concentration of a weak base at constant pH, we have GBC. Note that, if the proton transfer is between heteroatoms, as in this example, some other bond-making or bond-breaking steps must be happening too as proton transfer between heteroatoms is always a fast process. Proton transfer to or from carbon can be slow.

The formation of three- and five-membered cyclic ethers shows the contrast between GBC and SBC. The formation of epoxides is straightforward SBC with a simple linear dependency on pH between pH 8 and 12 and no acceleration at constant pH by carbonate (CO_3^{2-}) ions. There is no

inverse solvent isotope effect and an aryl substituent at the electrophilic carbon atom gives the small positive ρ value expected for S_N2 with an anion.



Formation of tetrahydrofuran (THF) is also faster at higher pH but, by contrast, is also accelerated by various bases at constant pH. If anions of phenols (ArO^-) are used as catalysts, a Hammett ρ value of +0.8 shows that electrons are flowing away from the aromatic ring. There is a small normal kinetic isotope effect $k_H/k_D = 1.4$. There is SBC and GBC in this reaction. Here is the mechanism with ArO^- as GBC.



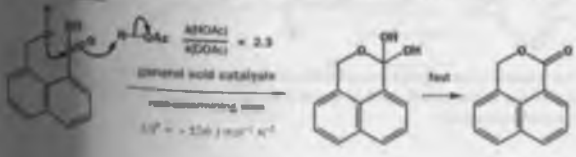
Why are the two different? The THF is easy to form, the transition state is unstrained, and only a little help is needed to make the reaction go. The epoxide is very strained indeed and the starting material needs to be raised in energy before cyclization will occur. Only the most powerful catalysis is good enough.

Summary of features of general base catalysis

1. Any base is an effective catalyst; pH also matters
2. Proton transfer is involved in the rate-determining step
3. Effective at neutral pHs even if below the pK_a of the substrate
4. Catalyst often much too weak a base to deprotonate reagent
5. Catalyst removes proton, which is becoming more acidic in the rate-determining step
6. Some other bond-making or bond-breaking also involved unless proton is on carbon
7. Often termolecular rate-determining step: large $-\Delta S^\ddagger$
8. Normal kinetic isotope effect $k(H) > k(D)$

General acid catalysis

We have already discussed this in general terms so a couple of examples will be enough. First, the termolecular problem can be avoided if the reaction is intramolecular. The catalysis is then bifunctional as in the cyclization of this hydroxy-acid. Normally, ester formation and hydrolysis are specifically acid-catalysed only but here there is catalysis by acetic acid: $k(HOAc)/k(DOAc)$ is 2.3 showing that proton transfer occurs in the rate-determining step and there is a large negative $\Delta S^\ddagger = -156$ J mol^{-1} K^{-1}. This is general acid catalysis of nucleophilic attack on a carbonyl group, admittedly in a mixed molecule.

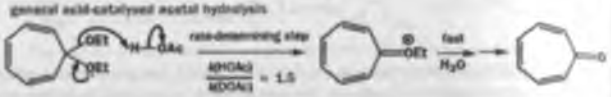


Earlier in the book (Chapter 14) we emphasized the importance of the mechanism for the [illegible] tion and hydrolysis of acetals. These are SAC reactions: alcohols are bad leaving groups and usually need to be fully protonated by strong acids before they will go, even with the help of a lone pair on another oxygen atom.

specific acid-catalysed acetal hydrolysis

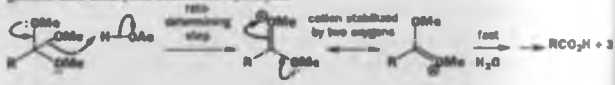
If we speed up the slow step by adding to the molecule some feature that stabilizes the cation intermediate, general acid catalysis may be found. One example is the aromatic cation formed in the hydrolysis of cycloheptatrienone acetals. The normal kinetic isotope effect produced by GAC.

general acid-catalysed acetal hydrolysis



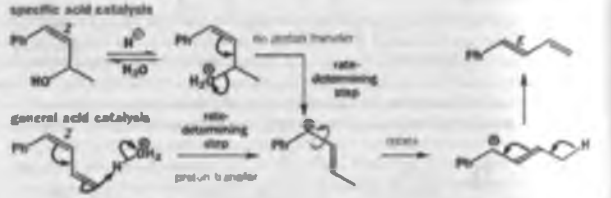
Even adding one extra alkoxy group so that we have an orthoester instead of an acetal is enough. These compounds show catalysis with a variety of weak acids at not very acidic pHs (5–6). As one OMe group is protonated, two others are pushing it out and they both help to stabilize the intermediate cation. Nature prefers these milder methods of catalysis as we will see in Chapter 50.

general acid-catalysed orthoester hydrolysis



For another contrast between SAC and GAC we need only refer you back to the two *Z*/*E* isomerizations earlier in the chapter. Isomerization of the diene in GAC—protonation at carbon is the slow step—and isomerization of the allylic alcohol is SAC. What we didn't tell you earlier was that the GAC reaction has a normal kinetic isotope effect of $k(H)/k(D) = 2.5$ and a negative entropy of activation $\Delta S^{\ddagger} = -36\ J\ mol^{-1}\ K^{-1}$—just what we should expect for a bimolecular reaction involving rate-determining proton transfer from oxygen to carbon. Notice that the intermediate cation is the same whichever the route; only the ways of getting there, including the rate-determining steps, are different.

specific acid catalysis



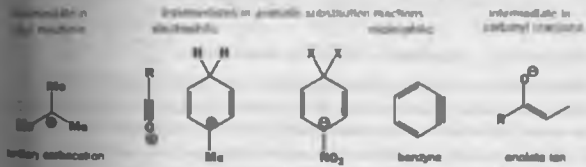
These examples show you that general acid catalysis is possible with strong acids, especially when protonation is at carbon and that, when protonation is at carbon, no other bond-making or -breaking steps need be involved.

Summary of features of general acid catalysis

1. Any acid is an effective catalyst; pH also matters
2. Proton transfer is involved in the rate-determining step
3. Effective at neutral pHs even if above the pK_{aH} of the substrate
4. Catalyst often much too weak an acid to protonate reagent
5. Catalyst adds proton to a site that is becoming more basic in the rate-determining step
6. Some other bond-making or bond-breaking also involved unless proton is on carbon
7. Often termolecular rate-determining step: large $-\Delta S^{\ddagger}$
8. Normal kinetic isotope effect $k(H) > k(D)$

The detection of intermediates

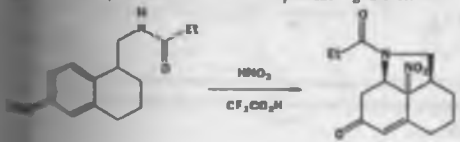
In earlier chapters we revealed how some reactive intermediates can be prepared, usually under special conditions rather different from those of the reaction under study, as a reassurance that some of these unlikely looking species can have real existence. Intermediates of this kind include the carbocation in the S_N1 reaction (Chapter 17), the cations and anions in electrophilic (Chapter 22) and nucleophilic (Chapter 23) aromatic substitutions, and the enols and enolates in various reactions of carbonyl compounds (Chapters 21 and 26–29). We have also used labelling in this chapter to show that symmetrical intermediates are probably involved in, for example, nucleophilic aromatic substitution with a benzyne intermediate (Chapter 23).



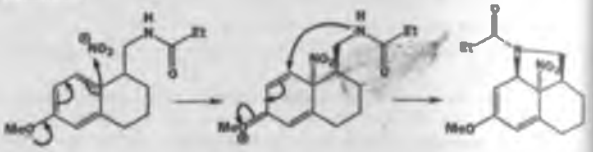
We have hedged this evidence around with caution since the fact that an intermediate can be prepared does not by any means prove that it is involved in a reaction mechanism. In this section we are going to consider other and better evidence for intermediates and at the same time revise some of the earlier material.

Trapping reactions

A more impressive piece of evidence is the design of a molecule that has built into it a functional group that could react with the intermediate in a predictable way but could not reasonably react with other species that might be present. For example, aromatic ethers react with nitrating agents in the *ortho* and *para* positions (Chapter 22). The intermediate has a positive charge delocalized over three of the carbon atoms in the benzene ring. If a nucleophilic group is built into the structure in the right way it might trap this intermediate and stop it reacting further.



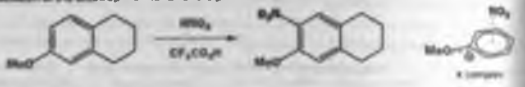
The trapping group is the amide and it has trapped a cation formed by addition of NO_2^+ to the aromatic ring. We are faced with the problem of drawing a mechanism for the formation of this remarkable compound and, when we discover that a necessary intermediate is also an intermediate in our preferred mechanism for aromatic nitration, we feel more confident about that mechanism.



This mechanism explains everything including the stereochemistry. The NO_2^+ attacks the aromatic ring *para* to the OMe group and on the opposite side to the amide. The amide is now in the perfect position to capture the cation at the meta position and, because the tether is short, it must form a *cis* bridge.

π complexes in electrophilic aromatic substitution

The weakness in the experiment in that nitration does not occur in that position without the trap but occurs in the ortho position. Nevertheless, many chemists believe that aromatic electrophilic substitution actually starts with a loose association of the electrophile with all of the p orbitals of the benzene ring so that here the NO_2^+ group would initially sit at right angles to the plane of the ring in a 'π complex' and would move afterwards to form a bond with one part of the carbon atom.



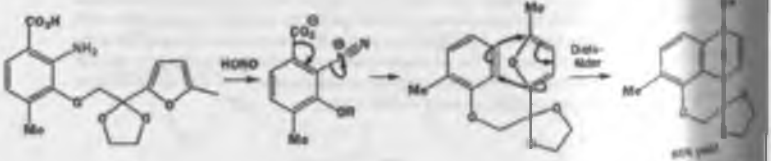
■ You will meet the related π complexes of metals in Chapter 46.

To be convincing, evidence for an intermediate should include:

- detection of the intermediate in the reaction mixture, perhaps by a trapping reaction
- a demonstration that the intermediate gives the product when added to the reaction mixture (this also means that it must be prepared as an at least reasonably stable compound)
- kinetic evidence that the rate of formation and rate of disappearance are adequate
- other suitable evidence of the kind that we have been discussing in this chapter

■ What is the cyclic acetal for? It is there to make the conformation more crowded by the Thorpe–Ingold effect: see Chapter 42.

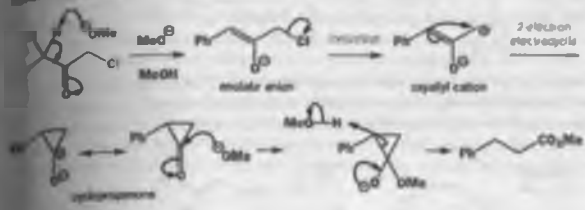
A neat intramolecular trap for benzyne works in this way. A standard benzyne-generating reaction—the diazotization of an *ortho*-amino benzoic acid (Chapter 23) gives a zwitterion that loses nitrogen and CO_2 to release the benzyne. A furan tethered to the next *ortho* position traps the benzyne in an intramolecular Diels–Alder reaction. The yield is impressive and the trap is very efficient.



The argument is that this reaction cannot really be explained without a benzyne intermediate. This same method of making benzyne is used on other *o*-amino benzoic acids and so they probably create benzynes too.

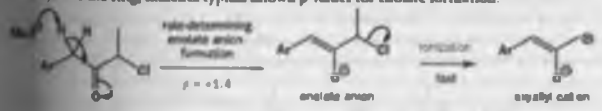
A collection of reactions linked by a common intermediate

Particularly convincing evidence can develop when a number of chemists suggest the same intermediate for a number of different reactions and show that it is possible to trap the intermediate from one reaction, put it into the others, and get the normal products. We are going to describe one set of such related reactions. In Chapter 37 we suggested a mechanism for the Favorskii rearrangement involving a series of remarkable intermediates. Here is an example.

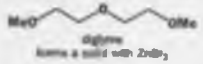


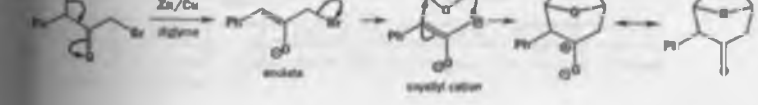
A quick summary of the evidence on this particular example. If the reaction is run in MeOD instead of MeOH, the starting material becomes deuterated at the site of enolate formation suggesting that this is a fast and reversible step. The entropy of activation for the reaction is $\Delta S^{\ddagger} = +64$ J mol^{-1} K^{-1}, suggesting that the slow step is one molecule breaking into two. There is only one such step—the second, ionization step. If various substituted phenyl groups are used, the Hammett ρ value is −5. This large negative value also suggests that the ionization is the slow step as the cation is delocalized into the benzene ring.

So there is some evidence for the first intermediate—the exchange of deuterium from the solvent. The formation of the enolate can even become the rate-determining step! If we merely add an extra methyl group to the chloroketone the reaction becomes 220 times faster and the rate-determining step changes. There is no longer any exchange of deuterium from the solvent and the Hammett ρ value changes from −5 to +1.4. This small positive value, showing some modest increase in electron density near the ring, matches typical known ρ values for enolate formation.

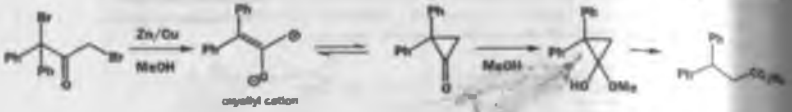


However, we are not surprised that an enolate ion is formed from a ketone in basic solution. The oxyallyl cation is much more surprising. How can we be convinced that it really is an intermediate? There are several alternative ways to make the same intermediate. If basic nucleophiles such as the methoxide ion are avoided and reaction of zinc with an α,α'-dibromoketone in a nonnucleophilic solvent like diglyme is used instead, the oxyallyl cation can be trapped in a Diels–Alder reaction. This is the basis for a good synthesis of seven-membered rings.

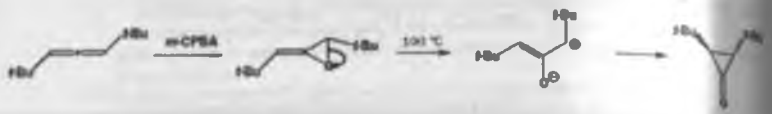




But does the oxyallyl cation go on to give cyclopropanones? In fact, there is good evidence that the two are in equilibrium. If the same method is used to create the diphenyl oxyallyl cation in methanol instead of in diglyme, the normal Favorskii product is produced. Evidently, methoxide is needed only to produce the enolate—methanol is enough to decompose the cyclopropanone.

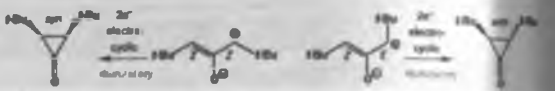


If a suitable (1,3-di-*t*-butyl) allene is epoxidized with *m*-CPBA the unstable allene oxide can actually be isolated. On heating, this epoxide gives a stable *trans*-di-*t*-butylcyclopropanone. It is very difficult to see how this reaction could happen except via the oxyallyl cation intermediate.

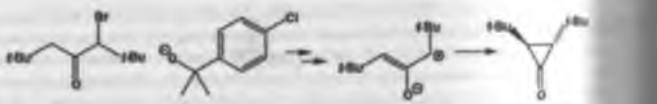


Why draw the oxyallyl cation with this stereochemistry?

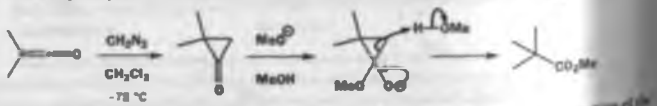
If the closure to the cyclopropanone is electrocyclic then it will be disrotatory (Chapter 38). The *E,E*-isomer so have drawn gives the *anti* cyclopropanone while either the *E,E*- or the *Z,Z*-oxyallyl cation gives the *syn*-di-*t*-butylcyclopropanone.



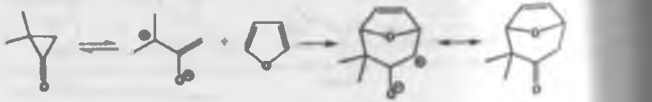
But is the same cyclopropanone an intermediate in the Favorskii reaction? If the bromoketone is treated with methoxide in methanol, it gives the Favorskii product but, if it is treated with a much more hindered base, such as the potassium phenoxide shown, it gives the same cyclopropanone with the same stereochemistry.



Other, less stable cyclopropanones, such as the 2,2-dimethyl compound, can be made by carbene addition (Chapter 40) to ketenes. This compound did the Favorskii reaction with methoxide in methanol: the only product came from the expected loss of the less unstable carbanion. This will, of course, be general acid-catalysed by methanol as no free carbanion can be released into an alcoholic solvent.



The same cyclopropanone gives a cycloadduct with furans—this must surely be a reaction of the oxyallyl cation and we can conclude that the three isomeric reactive intermediates (allene oxide, cyclopropanone, and oxyallyl cation) are all in equilibrium and give whichever product is appropriate for the conditions.

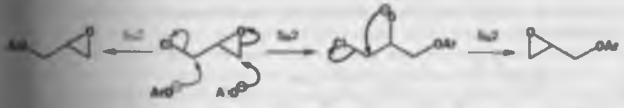


Though it is never possible to prove a mechanism, this interlocking network of intermediates, all known to be formed under the reaction conditions, all being trapped in various ways, and all known to give the products, is very convincing. If any part of the mechanism were not correct, that would throw doubt on all the other reactions as well. Nevertheless, this mechanism is not accepted by all chemists.

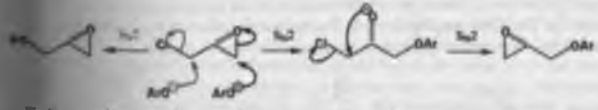
Stereochemistry and mechanism

This chapter ends with a survey of the role of stereochemistry in the determination of mechanism. Though we have left stereochemistry to the last, it is one of the most important tools in unravelling complex mechanisms. You have already seen how inversion of configuration is a vital piece of evidence for an S_N2 mechanism (Chapter 17) while retention of configuration is the best evidence for participation (Chapter 37). You have seen the array of stereochemical evidence for pericyclic mechanisms (Chapters 35 and 36). The chapters devoted to diastereoselectivity (33 and 34) give many examples where the mechanism follows from the stereochemistry. We shall not go over that material again, but summarize the types of evidence with new examples. The first example looks too trivial to mention.

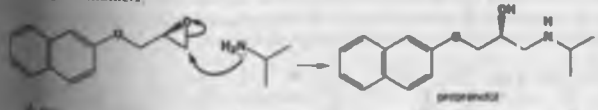
Though this reaction looks like a simple S_N2 displacement by the naphthyloxide anion on the primary alkyl chloride, there is, in fact, a reasonable alternative—the opening of the epoxide at the less hindered primary centre followed by closure of the epoxide the other way round. The electrophile is called 'epichlorohydrin' and has two reasonable sites for nucleophilic attack.



It looks difficult to tell these mechanisms apart since both involve the same kind of reaction. Stereochemistry is the answer. If enantiomerically pure epichlorohydrin is used, the two mechanisms give different enantiomers of the product. Though each S_N2 reaction takes place at a primary centre and the stereogenic centre remains the same, from the diagrams the two products are obviously enantiomers.

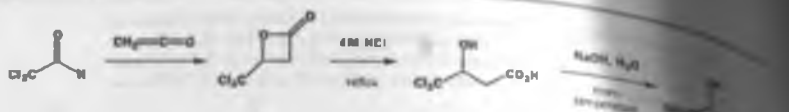


Finding out the mechanism of this process is not idle curiosity as a group of drugs used to combat high blood pressure and heart disease, such as propranolol, are made from epichlorohydrin and it is essential to know which enantiomer to use to get the right enantiomer of the drug. In fact, the more complicated mechanism shown in black is correct. This is an example of determination of mechanism by using enantiomers.

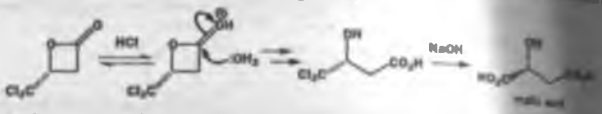


A more complicated example arises from the strange reactions used to make malic acid from chloral and ketene. An initial [2 + 2] cycloaddition (Chapter 35) is followed by acid treatment and then treatment with an excess of aqueous NaOH. Neutralization gives malic acid, an acid found naturally in apples (*Malus* spp.).

The full synthesis of propranolol is given in Chapter 38.



The mechanism of this reaction also looks straightforward: normal ester hydrolysis by hydrolysis of the CCl_3 group to CO_2H. Caution suggests investigation [illegible] membered lactones sometimes hydrolyse by S_N2 displacement at the saturated [illegible] than by attack on the carbonyl group, like the three-membered lactones discussed [illegible] (p. 000). The solution was urgently needed when it was found that enantiomerically pure [illegible] could be prepared by asymmetric synthesis (Chapter 45). The sequence was repeated with enantiomerically pure lactone: lactone hydrolysis occurred with retention of configuration and must be normal ester hydrolysis by attack of water at the carbonyl group. But the hydrolysis of the CCl_3 group occurred with inversion of configuration.



You will see in Chapter 42 that this reaction is governed by 'Baldwin's rules' and why attack on even a CCl_3 group is unfavourable.

The answer must be a mechanism related to the one we have just seen for epichlorohydrin: [illegible] by hydroxide on CCl_3 is almost unknown and it is much more likely that [illegible] by alkoxide to give an epoxide should occur. The carboxylate anion can then invert the [illegible] centre by intramolecular S_N2 displacement at the central carbon atom. Notice that the [illegible] attack at the central atom. The second four-membered lactone also hydrolyses by attack at the carbonyl group.

The Ritter reaction was introduced in Chapter 17 and the Beckmann fragmentation in Chapter 38.

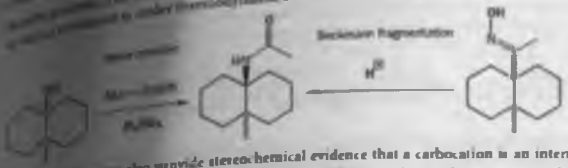
The Ritter reaction and the Beckmann fragmentation

Another collection of related intermediates occurs in the Ritter reaction and the Beckmann fragmentation. The **Ritter reaction** involves the combination of a tertiary alcohol and a nitrile in acid solution and the proposed mechanism involves a series of intermediates.

The **Beckmann fragmentation** also occurs in acid solution upon the fragmentation of an oxime with a *tertiary* alkyl group *anti* to the OH of the oxime. The fragmentation step gives the same cation and the same nitrile together with a molecule of water and these three combine in the same way to give the same amide. We need evidence that the carbocation and the nitrilium ion are genuine intermediates and that the same sequence is found in both reactions.

Evidence that the two reactions are intimately related comes from the formation of the same amide from two different starting materials: a tertiary alcohol and an oxime, both based on the

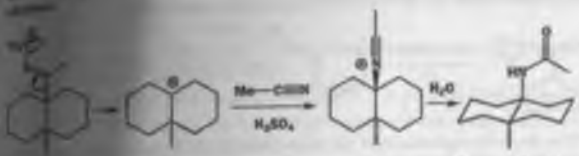
...reaction. The oxime has its OH group *anti* to the ring junction to minimize steric hindrance ... control (Chapter 14).



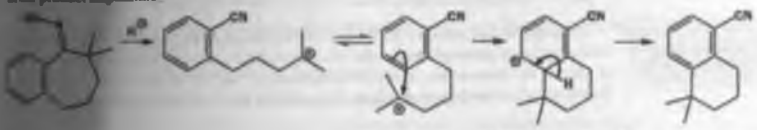
■ Decalins are widely used in conformational experiments: see Chapter 10.

...also provide stereochemical evidence that a carbocation is an intermediate in ... Both starting materials are *cis*-decalins but the product is a *trans*-decalin. The ... intermediate has no stereochemistry and can react with the nitrile from either face. ... is preferred and it gives the stable *trans*-decalin. The formation of the carbocation is ... by the Beckmann fragmentation: formation from the alcohol by the S_N1 mechanism is ...

▶ None of these compounds is chiral as there is a plane of symmetry running vertically through each molecule. We are discussing diastereoisomers only.

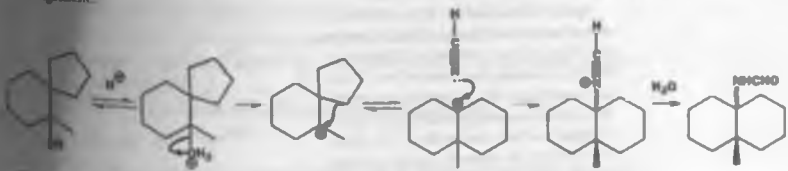


Trapping the carbocation is also possible. The Beckmann fragmentation on this oxime of an aryl seven-membered ring ketone gives a tertiary carbocation that might be expected to cyclize to give an amide. However, this reaction would give an unfavourable eight-membered ring (see Chapter 42) and does not happen. Instead, the chain twists round the other way and forms a much more stable six-membered ring by intramolecular Friedel–Crafts alkylation. Note that the regioselectivity is *meta* to CN and *ortho* to alkyl. These are both favourable but the main factor is the C_4 tether making any other product impossible.



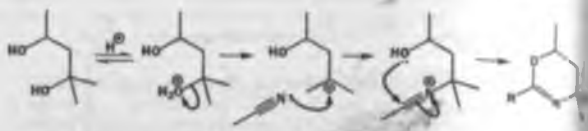
In the Ritter reaction a rather different kind of evidence for the cation is the fact that families of isomeric alcohols all give the same product. In all these cases, rearrangements of the first formed carbocation (Chapter 37) can easily account for the products. Another example in the decalin series is this Ritter reaction with KCN as the nitrile in acidic solution so that HCN is the reagent. The ... material is a spirocyclic tertiary alcohol but the product is a *trans*-decalin formed by rearrangement.

▶ This would be a dangerous experiment to carry out and is not recommended.

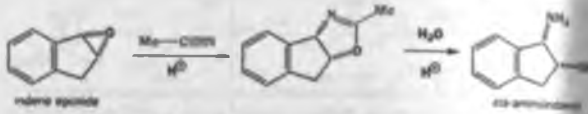


Trapping the nitrilium cation is also possible. The most famous example is probably the heterocycle ... mazine, Chapter 42) produced by intramolecular capture of the nitrilium ion with a hydrox-

yl group. Note that the tertiary alcohol reacts to give the cation while the secondary alcohol adds to the nucleophilic trap.



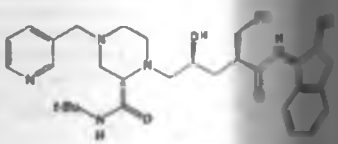
An important example in which the diastereoisomer produced was critical in determining the mechanism is the synthesis of *cis*-aminoindanol, a part of Merck's anti-HIV drug Crixivan® (Indinavir). The reaction involves treatment of indene epoxide with acetonitrile (MeCN) in acidic solution. The product is a *cis* fused heterocycle. It is easy to see which atoms have come from the nitrile (green) but the substitution of nitrogen for oxygen at one end of the epoxide has occurred with retention of configuration as the *cis*-epoxide has given the *cis* product. Clearly, we have some sort of Ritter reaction and the nitrilium ion has been trapped with an OH group.



What about the regioselectivity? The obvious explanation is that a cation is formed from the epoxide in a specific acid-catalysed ring opening. But why should the nitrile attack the bottom face of the cation? We should expect it to attack the top face preferentially as the hydroxyl group protonated blocks the bottom face.

A reasonable mechanism is that in which the nitrile adds reversibly to the cation. Every time it adds to the top face, it drops off again as the OH group cannot reach it to form the heterocycle. Every time it adds to the bottom face, it is quickly captured by the OH group because 5/5 fused rings are favourable when the ring junction is *cis*. Eventually, all the compound is converted to the heterocycle.

Again, the mechanism of this reaction is of great importance because it is the foundation stone of the synthesis of Crixivan—a drug that is saving thousands of lives. These last examples are of reactions that you would find difficult to classify into any of the familiar types we have met so far in the book. Nevertheless, the organic chemist needs to be able to propose mechanisms for new reactions and to have a general idea of the methods available to test these proposals.



Summary of methods for the investigation of mechanism

This brief summary is for guidance only and the figures quoted are approximate ranges only. The full text above should be used for detail. All methods would not be used in one investigation.

1. Make sure of the structure of the product

- Basic structure (Chapters 4 and 11) and stereochemistry (Chapter 32) by spectroscopic methods
- Detail of fate of individual atoms by labelling with D, ^{13}C, and ^{18}O. Double labelling may help
- Stereochemical course of the reaction (enantio- or diastereoselectivity) may be critical

2. Kinetic methods

- Rate equation gives composition of main transition state
- Deuterium isotope effect: $k_H > k_D$ shows bond to H formed and/or broken in transition state. Values k_H/k_D 2–7 typical
- Entropy of activation shows increase ($\Delta S^\ddagger$ positive) or decrease ($\Delta S^\ddagger$ negative) in disorder. Typical values and deductions:
  - $\Delta S^\ddagger$ positive (rarely larger than $+50$ J mol^{-1} K^{-1}): one molecule breaks into two or three
  - Moderate negative values: no change in number of molecules (one goes to one etc.) or bimolecular reaction with solvent
  - Large negative values: two molecules go to one or unimolecular reaction with ordered $TS^\ddagger$ (cycloaddition, etc.)

3. Correlation of structure and reactivity

- Replace one group by another of similar size but different electronic demand (CF_3 for CH_3 or OMe for CH_3)
- Systematic Hammett σ/ρ correlation with *m*- and *p*-substituted benzenes:
  - Sign of ρ: $+\rho$ indicates electrons flowing into and $-\rho$ electrons flowing out of ring in transition state
  - Magnitude of ρ shows effect on the benzene ring:
    - large (around 5), charge on ring ($+\rho$, anion; $-\rho$, cation)
    - moderate (around 2–4), charge on atom next to ring—may be gain or loss of conjugation
    - small (<1), ring may be distant from scene of action or ρ may be balance of two ρs of opposite sign

4. Catalysis

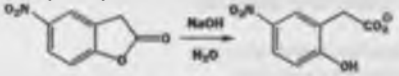
- pH–rate profile reveals specific acid or base catalysis
- Rate variation with [HA] or [B] at constant pH reveals GAC or GBC
- Deuterium isotope effect: normal ($k_H > k_D$) shows GA/BC, inverse solvent $k(D_2O) > k(H_2O)$ shows EA/BC
- GA/BC is termolecular and has large negative entropy of activation

5. Intermediates

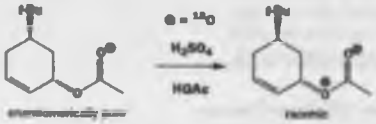
- Independent preparation or, better, isolation from or detection in reaction mixture helps
- Must show that intermediate gives product under reaction conditions
- Designed trapping experiments often most convincing

Problems

1. Propose three fundamentally different mechanisms (other than variations of the same mechanism with different kinds of catalysis) for this reaction. How would (a) D labelling and (b) ^{18}O labelling help to distinguish the mechanisms? What other experiments would you carry out to eliminate some of these mechanisms?

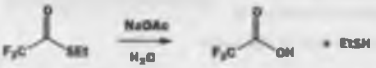


2. Explain the stereochemistry and labelling pattern in this reaction.

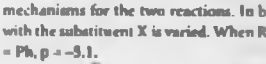


3. The Hammett ρ value for migrating aryl groups in the acid-catalysed Beckmann rearrangement is –2.0. What does this tell us about the rate-determining step?

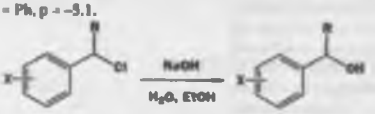
4. Between pH 2 and 7, the rate of hydrolysis of this thiol ester is independent of pH. At pH 5 the rate is proportional to the concentration of acetate ion [AcO^-] in the solution and the reaction goes twice as fast in D_2O as in H_2O. Suggest a mechanism for the pH-independent hydrolysis. Above pH 7, the rate increases with pH. What kind of change is this?



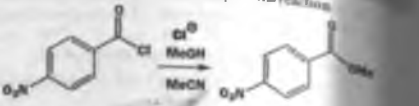
5. In acid solution, the hydrolysis of this carbodiimide has a Hammett ρ value of –0.8. What mechanism might account for this?



6. Explain the difference between these Hammett ρ values by mechanisms for the two reactions. In both cases the ring marked with the substituent X is varied. When R = H, ρ = –0.3 but, when R = Ph, ρ = –5.1.

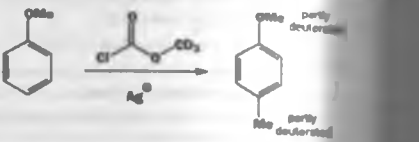


7. Explain how chloride ion catalyses this reaction.



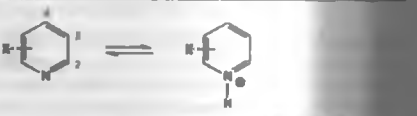
8. The hydrolysis of this oxaziridine in 0.1 M sulfuric acid has $k(H_2O)/k(D_2O) = 0.7$ and an entropy of activation of $\Delta S^{\ddagger} = -20$ J mol^{-1} K^{-1}. Suggest a mechanism for the reaction.

9. Explain how both methyl groups in the product of this reaction come to be labelled. If the starting material is re-isolated at the reaction, its methyl group is also labelled.



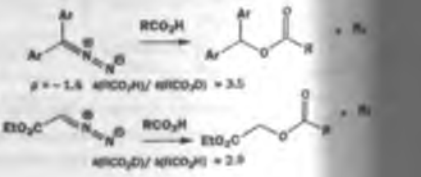
10. The pK_{BH} values of some substituted pyridines are as follows.

X	H	3-Cl	3-Me	4-Me	3-MeO	4-MeO	3-NO_2
pK_{BH}	5.2	2.84	5.68	6.02	4.88	6.62	0.81

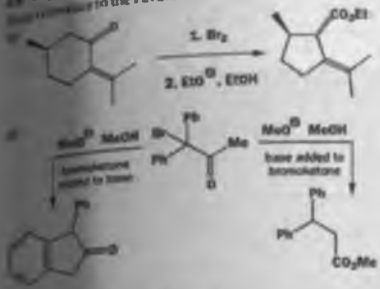


Can the Hammett correlation be applied to pyridines using the σ values for benzenes? What equilibrium ρ value does it give and how do you interpret it? Why are no 2-substituted pyridines included in the list?

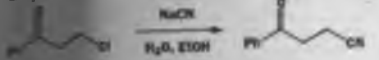
11. These two reactions of diazo compounds with carboxylic acids give gaseous nitrogen and esters as products. In both cases the rate of the reaction is proportional to [diazo compound] [RCO_2H]. Use the data for each reaction to suggest mechanisms and comment on the difference between them.



14. Suggest mechanisms for these reactions and comment on their resemblance to the Favorskii family of mechanisms.



15. If you believed that this reaction went by elimination followed by conjugate addition, what experiment would you carry out to try and prove that the enone is an intermediate?



16. This question is about three related acid-catalysed reactions: (a) the isomerization of *Z*-cinnamic acids to *E*-cinnamic acids; (b) the dehydration of the related hydroxy-acids; (c) the racemization of the same hydroxy-acids. You should be able to use the information provided to build up a complete picture of the interaction of the various compounds and the intermediates in the reactions.

(a) Data determined for the acid-catalysed isomerization of *Z*-cinnamic acids in water include the following.

(I) The rate is faster in H_2O than in D_2O: $k(H_2O)/k(D_2O) = 2.5$.

(II) The product contains about 80% D at C2.

(III) The Hammett ρ value is −5.

Suggest a mechanism for the reaction that explains the data.

(b) The dehydrations of the related hydroxy-acids also gives *E*-cinnamic acids at a greater rate under the same conditions but the products for the reaction are rather different.

(I) Hydroxy-acid deuterated at C2 shows a kinetic isotope effect: $k_H/k_D = 2.5$.

(c) If the dehydration reaction is stopped after about 10% conversion to products, the remaining starting material is completely racemized. Data for the racemization reaction include the following.

(I) The rate is slower in H_2O than in D_2O.

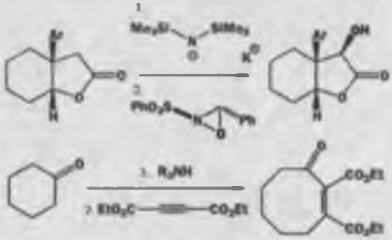
(II) Hydroxy-acid deuterated at C2 shows practically no kinetic isotope effect.

(III) The Hammett ρ value is −4.5.

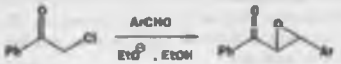
What conclusions can you draw about the dehydration?

Recalling that the dehydration goes faster than the isomerization, what would be present in the reaction mixture if the isomerization were stopped at 50% completion?

17. Propose mechanisms for the two reactions at the start of the chapter. The other product in the first reaction is the imine $PhCH{=}NSO_2Ph$.



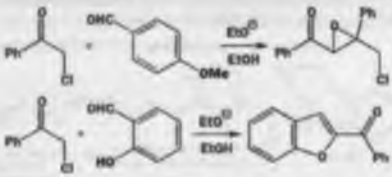
18. A typical Darzens reaction involves the base-catalysed formation of an epoxide from an α-haloketone and an aldehyde. Suggest a mechanism for the Darzens reaction consistent with the results shown below.



(a) The rate expression is:
rate = k_3[PhCO CH_2Cl][ArCHO][EtO^-]

(b) When Ar is varied, the Hammett ρ value is +2.5.

(c) The following attempted Darzens reactions produced unexpected products.



Saturated heterocycles and stereoelectronics

42

Connections

Building on:

- Acetals and hemiacetals ch14
- Stereochemistry ch16
- The conformation of cyclic molecules ch18
- Stereospecific elimination reactions ch19
- Protecting groups ch24
- NMR and stereochemistry—how orbital overlap affects coupling (the Karplus relationship) ch32
- How rings affect stereoselective reactions ch33
- Ring closing and opening by cycloadditions ch35
- Electrocyclic ring closing and opening ch36
- How alignment of orbitals affects reactivity ch37–ch38
- Determining organic mechanisms ch41

Arriving at:

- Putting a heteroatom in a ring changes the reactivity of the heteroatom
- Ring-opening reactions: the effect of ring strain
- Lone pairs in heterocycles have precise orientations
- Some substituents prefer to be axial on some six-membered saturated heterocycles
- Interactions of lone pairs with empty orbitals can control conformation
- Ring-closing reactions: why five-membered rings form quickly and four-membered rings form slowly
- Baldwin's rules: why some ring closures work well while others don't work at all

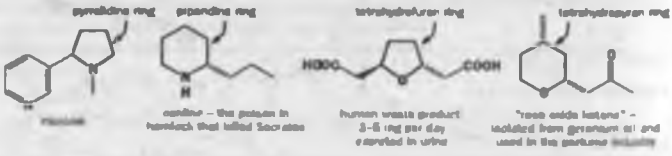
Looking forward to:

- Structure and reactions of aromatic heterocycles ch43
- Synthesis of aromatic heterocycles ch44
- Asymmetric synthesis ch45
- Chemistry of life ch49
- Mechanisms in biological chemistry ch50
- Natural products ch51

Introduction

Rings in molecules make a difference, and we have already devoted the whole of one chapter (33) and most of another (18) just to the structure and reactions of rings. In those chapters, the message was that rings have well-defined conformations, and that well-defined conformations allow reactions to be stereoselective.

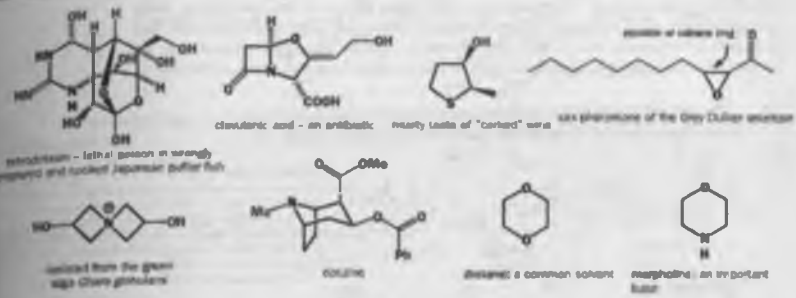
This chapter and the next two will revisit the ring theme, but the rings will all be heterocycles: rings containing not just carbon atoms, but oxygen, nitrogen, or sulfur as well. It may seem strange that this rather narrowly defined class of compounds deserves three whole chapters, but you will soon see that this is justified both by the sheer number and variety of heterocycles that exist and by their special chemical features. Chapters 43 and 44 cover heterocycles that are aromatic, and in this chapter we look at heterocycles that are saturated and flexible. Some examples, a few of which may be familiar to you, are shown below and overleaf.



nicotine – the poison in hemlock that killed Socrates

human waste product 3–5 mg per day excreted in urine

"rose oxide ketone" – isolated from geranium oil and used in the perfume industry



But what are the 'special chemical features' of saturated heterocycles? Putting a heteroatom into a ring does two important things, and these lead to the most important new topics in this chapter. Firstly, the heteroatom makes the ring easy to make by a ring-closing reaction, or (in some cases) easy to break by a ring-opening reaction. Closing and opening reactions of rings are subject to constraints that you will need to know about, and the principles that govern these reactions are discussed in the second half of the chapter.

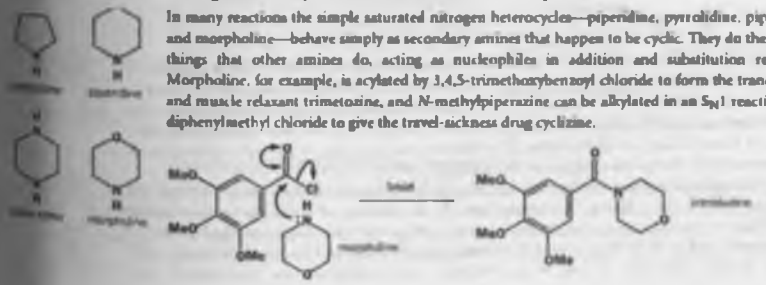
Secondly, the ring fixes the orientation of the heteroatom—and, in particular, the orientation of its lone pairs—relative to the atoms around it. This has consequences for the reactivity and conformation of the heterocycle which can be explained using the concept of **stereoelectronics**.

> **Stereoelectronic effects are chemical consequences of the arrangement of orbitals in space.**

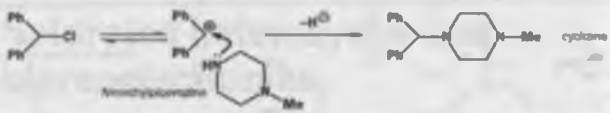
Although this is the only chapter in which stereoelectronics appears in the title, you will soon recognize the similarity between the ideas we cover here and concepts like the stereospecificity of E2 elimination reactions (Chapter 19), the Karplus relationship (Chapter 32), the Felkin–Anh transition state (Chapter 33), and the conformational requirements for rearrangement (Chapter 37) and fragmentation (Chapter 38) reactions.

Reactions of heterocycles

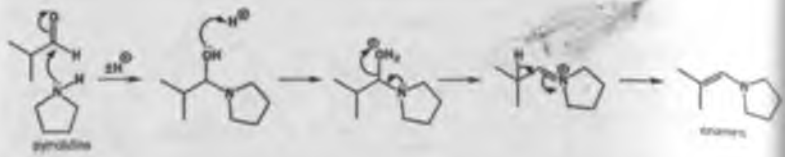
Nitrogen heterocycles: amines, but more nucleophilic



In many reactions the simple saturated nitrogen heterocycles—piperidine, pyrrolidine, piperazine, and morpholine—behave simply as secondary amines that happen to be cyclic. They do the sorts of things that other amines do, acting as nucleophiles in addition and substitution reactions. Morpholine, for example, is acylated by 3,4,5-trimethoxybenzoyl chloride to form the tranquillizer and muscle relaxant trimetozine, and *N*-methylpiperazine can be alkylated in an S_N1 reaction with diphenylmethyl chloride to give the travel-sickness drug cyclizine.



The addition of pyrrolidine to aldehydes and ketones is a particularly important reaction because it leads to enamines, the valuable enol equivalents discussed in Chapter 26.



Enamines formed from pyrrolidine and piperidine are particularly stable, because pyrrolidine and piperidine are rather more nucleophilic than comparable acyclic amines such as diethylamine. This is a general feature of cyclic amines (and cyclic ethers, too, as you will see shortly), and is a steric effect. The alkyl substituents, being tied back into a ring, are held clear of the nucleophilic lone pair, allowing it to approach an electrophile without hindrance. This effect is well illustrated by comparing the rates of reaction of methyl iodide with three amines—tertiary this time. The two cyclic compounds are bridged—quinuclidine is a bridged piperidine while the diamine known as 'DABCO' (1,4-DiAzaBiCyclo[2.2.2]Octane) is a bridged piperazine. Table 42.1 shows the relative rates, along with pK_{aH} values, for triethylamine, quinuclidine, and DABCO.

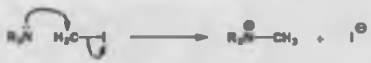
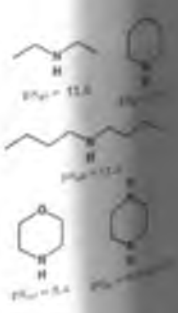


Table 42.1 Rates of reaction of amines with methyl iodide

			
	triethylamine	quinuclidine	DABCO
relative rate of reaction*	1	63	40
pK_{aH}	10.7	11.0	8.8 (and 3.0)

*Relative rate of reaction with MeI in MeCN at 20 °C.

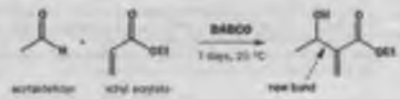


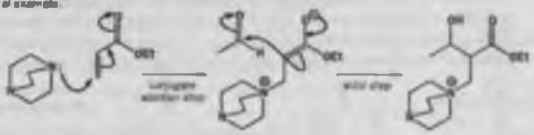
Quinuclidine and DABCO are 40–60 times more reactive than triethylamine. This is again due to the way the ring structures keep the nitrogen's substituents away from interfering with the lone pair as it attacks the electrophile. You should contrast the effect that the cyclic structure has on the pK_{aH} of the amines: none! Triethylamine and quinuclidine are equally basic and, as you can see in the margin, so (more or less) are diethylamine, dibutylamine, and piperidine. A proton is so small that it cares very little whether the alkyl groups are tied back or not.

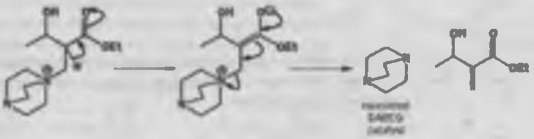
Much more important in determining pK_{aH} is how electron-rich the nitrogen is, and this is the cause of the glaring discrepancy between the basicity of quinuclidine and that of DABCO, or between the basicities of piperidine (pK_{aH} 11.2) and morpholine (pK_{aH} 8.8) or piperazine (pK_{aH} 8.4). The extra heteroatom, through an inductive effect, withdraws electron density from the nitrogen atom, making it less nucleophilic and less basic. In this

sense, morpholine can be a very useful base, less basic than triethylamine but somewhat more so than pyridine (pK_{aH} 5.2). Notice how much lower is the second pK_{aH} (that is, the pK_{aH} for protonation of the second nitrogen) of the diamines DABCO and piperazine: the protonated nitrogen of the monoprotonated amine withdraws electrons very effectively from the unprotonated one.

The Baylis–Hillman reaction



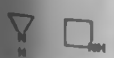




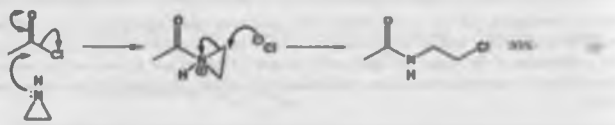
relatively low pK_{aH}, ensuring that it leaves easily in the last step. As you have seen before, good nucleophiles are usually bad leaving groups, though there are many exceptions. DABCO's combination of nucleophilicity and leaving group ability is perfect here.

The exposed nature of the nitrogen atom in cyclic amines means that nitrogen heterocycles are very frequently encountered in drug molecules, particularly those operating on the central nervous system (cocaine, heroin, and morphine all contain nitrogen heterocycles, as do codeine and many tranquillizers such as Valium). But the ring can also be used as a support for adding substituents that hinder the nitrogen's lone pair. Just as the nitrogen atom of piperidine is permanently exposed, the nitrogen atom of 2,2,6,6-tetramethylpiperidine (TMP) nestles deep in a bed of methyl groups. The lithium salt of TMP (LiTMP) is an analogue of LDA—a base that experiences enormous steric hindrance that can be used in situations where the selectivity even of LDA fails.

Aziridine: ring strain promotes ring opening



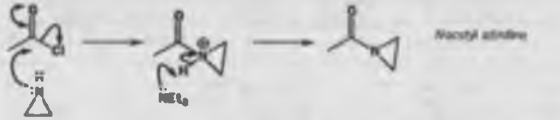
Aziridine and azetidine are stable, if volatile, members of the saturated nitrogen heterocycle family, and aziridine has some interesting chemistry of its own. Like pyrrolidine and piperidine, aziridine can be acylated by treatment with an acyl chloride, but the product is not stable. The ring opens with attack of chloride, a relatively poor nucleophile, and an open-chain secondary amide results.



Saturated heterocycles and systematic nomenclature

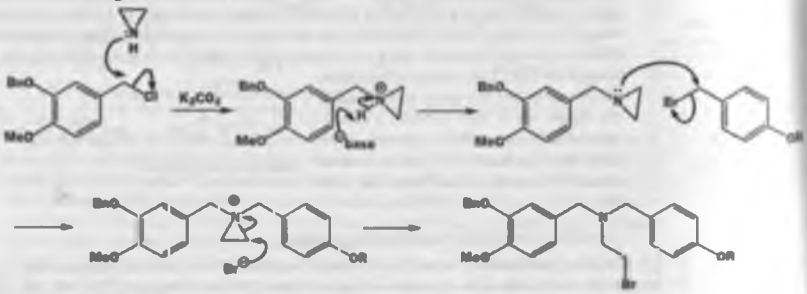
The names aziridine and azetidine are derived from a reasonably logical system of nomenclature, which assigns three-part heterocycle names according to: (a) the heteroatom ('az-' = nitrogen, 'ox-' = oxygen, 'thi-' = sulfur); (b) the ring size ('-ir-' = 3, from tet; '-et-' = 4, from tetra; '-ol-' = 5; nothing for 6; '-ep-' = 7, from hepta; '-oc-' = 8, from octa; etc.); and (c) the degree of saturation ('-ene' or '-ine' for unsaturated, '-idine' or '-ane' for saturated). Hence az-ir-idine, az-et-idine, ox-et-ane, and az-ir-ane.

You can view this ring opening as very similar to the ring opening of an epoxide (Chapter 20)—in particular, a *protonated* epoxide, in which the oxygen bears a positive charge. The positive charge is very important for aziridine opening because, when the reaction is done in the presence of a base, removal of the proton leads immediately to the neutral acyl aziridine, which is stable.



The ring opening of aziridine is a useful way of making larger heterocycles: anything that puts a positive charge on nitrogen encourages the opening by making N a better leaving group, whether it's protonation, as shown below, or alkylation.

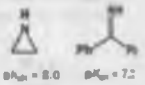
Alkylation of aziridine in base gives the *N*-substituted aziridine as you might expect, but a second alkylation leads to a positively charged aziridinium salt that opens immediately to the useful bromoamine. In this case, the product is an intermediate in the synthesis of two natural products, sandaverine and corgoine.



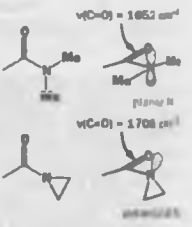
We have just mentioned the protonation of aziridine, and you might imagine from what we said earlier about the comparative nucleophilicity and basicity of nitrogen heterocycles and their acyclic counterparts that aziridine will be even more nucleophilic than pyrrolidine, and about as basic. Well,

it isn't. The idea that 'tying back' the alkyl groups increases nucleophilicity is only valid for 'normal-sized' (five- or six-membered) rings: with small rings another effect takes over.

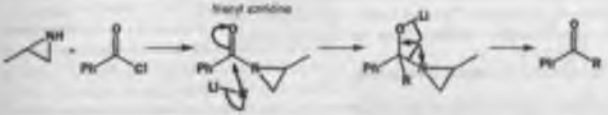
Aziridine is, in fact, much less basic than pyrrolidine and piperidine: its pK_{aH} is only 8.0. This is much closer to the pK_{aH} of a compound containing an sp^2 hybridized nitrogen atom—the imine in the margin, for example. This is because the nitrogen's lone pair is in an orbital with much more *s* character than is typical for an amine, due to the three-membered ring. This is an effect we have discussed before, in Chapter 15, and you should re-read pp. 000–000 if you need to refresh your memory. There we compared three-membered rings with alkynes, explaining that both could be deprotonated relatively easily. The anion carries a negative charge in a low-energy orbital with much *s* character: the same type of orbital carries aziridine's lone pair.



The *s* character of the aziridine nitrogen's lone pair has other effects too. The lone pair interacts very poorly with an adjacent carbonyl group, so *N*-acyl aziridines such as the one you saw on p. 000 behave not at all like amides. The nitrogen atom is pyramidal and not planar, and the stretching frequency of the C–O bond (1706 cm^{-1}) is much closer to that of a ketone (1710 cm^{-1}) than that of an amide (1650 cm^{-1}).



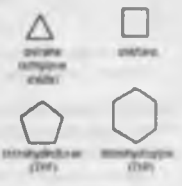
Lack of conjugation leads to increased reactivity, and *N*-acyl aziridines are useful in synthesis because they react with organolithium reagents only once to give ketones. No further reactions of the product ketone occur because the *N*-acyl aziridine is reactive enough to compete with it for the organolithium reagent.



The *s* character of the lone pair means that the nitrogen atom inverts very slowly, rather like a phosphine (which also carries its lone pair in an *s* orbital: see Chapter 4, p. 000). Usually it is not possible for nitrogen to be a stereogenic centre because inversion is too rapid—the transition state for nitrogen inversions (in which the lone pair is in a *p* orbital) is low in energy. But with an aziridine, getting the lone pair into a *p* orbital would require an awful lot of energy, so nitrogen can be stereogenic and, for example, these two stereoisomers of an *N*-substituted aziridine can be separated and isolated

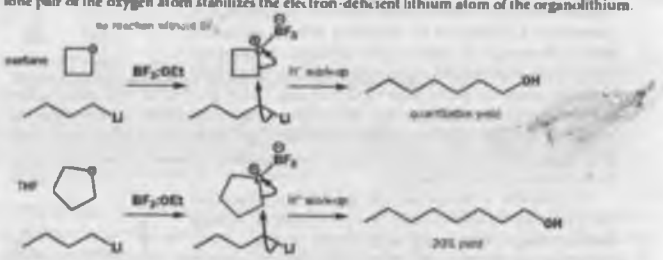
Oxygen heterocycles

Ring-opening chemistry is characteristic of oxygen heterocycles too, and there is no need for us to revisit epoxide opening here. Epoxides are particularly reactive because ring opening releases ring strain, driving the reaction forward. However, we can tell you about some chemistry of the most important simple oxygen heterocycle, THF. You may be surprised that THF does any real chemistry: after all, the very reason it is used as a solvent is precisely because it is so unreactive. Oxygen heterocycles are cyclic ethers, and ethers are the least reactive of all the common functional groups.

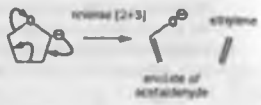


To make ethers more reactive, they must be complexed with strong Lewis acids. BF_3 is commonly used with cyclic ethers, and even with epoxides it increases the rate and yield of the reaction when organometallic reagents are used as nucleophiles. BF_3 is most easily handled as its complex with diethyl ether, written BF_3:OEt. BuLi does not react with oxetane, for example, unless a Lewis acid, such as BF_3, is added, when it opens the four-membered ring to give a quantitative yield of *n*-heptanol.

The same reaction happens with THF, but only in much lower yield. Nonetheless, just as cyclic amines are more nucleophilic than acyclic ones, so cyclic ethers are more nucleophilic than acyclic ones. This is one of the reasons why THF is such a good solvent for organolithiums—the nucleophilic lone pair of the oxygen atom stabilizes the electron-deficient lithium atom of the organolithium.



A more important reaction between BuLi and THF is not nucleophilic attack, but deprotonation. You will have noticed that reactions involving BuLi in THF are invariably carried out at temperatures of 0 °C or below—usually –78 °C. This is because, at temperatures above 0 °C, deprotonation of THF begins to take place. You might think that this would not be a problem, if BuLi were being used as a base, because the deprotonated THF could still itself act as a base. The trouble is that deprotonated THF is unstable, and it undergoes a reverse [2+3] cycloaddition. Here is the mechanism (we have represented the organolithium as an anion to help with the arrows). The products are: (1) the (much less basic) enolate of acetaldehyde and (2) ethylene. The first tends to polymerize, and the second usually evaporates from the reaction mixture.



The case of the extra ethyl group

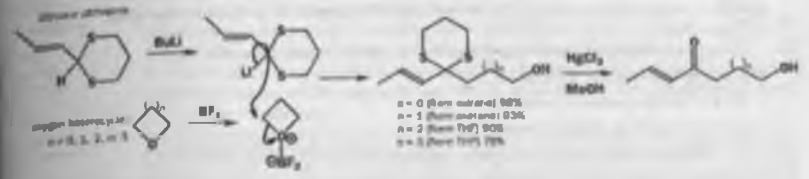
Some chemists in Belgium were studying the reactions of the organolithium shown here to find out whether the anionic centre would attach the double bond to form a five-membered ring (like a radical would: see Chapter 39). The reaction was slow, and they stirred the organolithium in THF for 8 hours at 0 °C. When they worked the reaction up they found no five-membered ring products. Instead they got a compound with an extra ethyl group attached! They showed that this ethyl group, in fact, comes from THF: the organolithium did not add to the double bond in the same molecule, but it did add slowly and in low yield to the double bond of the ethylene that is formed by decomposition of THF.

The most common use of tetrahydropyran derivatives is as protecting groups: you met this in Chapter 24 and you can see an example later in the chapter, on p. 000.

Sulfur heterocycles

The ability of sulfur to stabilize an adjacent anion will be discussed in Chapter 46, and it means that sulfur heterocycles are much easier to deprotonate than THF. The most important of these contains two sulfur atoms: dithiane. Deprotonation of dithiane occurs in between the two heteroatoms, and you can see some chemistry that arises from this on p. 000. For the moment, we will just show you series of reactions that illustrate nicely both dithiane chemistry and the ring opening of oxygen heterocycles in the presence of BF_3. This substituted derivative of dithiane is deprotonated by BuLi in the same way to give a nucleophilic organolithium that will

attack electrophiles—even oxygen heterocycles—provided BF_3 is present. The products are formed in excellent yield, even when the electrophile is THP, with no ring strain to drive the reaction. After the addition reaction the dithiane ring can be hydrolysed with mercuryl(II) (see Chapters 46 and 50 for an explanation) to give a ketone carrying other useful functional groups.

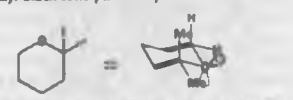


Conformation of saturated heterocycles: the anomeric effect

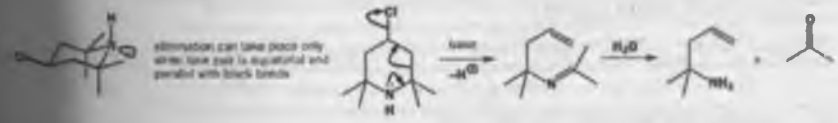
Heteroatoms in rings have axial and equatorial lone pairs

To a first approximation, the conformation of five- and six-membered saturated heterocycles follows very much the same principles as the conformation of carbocyclic compounds that we detailed in Chapter 18. If you feel you need to re-read the parts of that chapter dealing with rings—chairs and boats, or axial and equatorial substituents—now would be a good time to do it. Sticking with dithiane for the moment, then, this is the conformation. Since the sulfur atoms have lone pairs, they too occupy axial and equatorial positions. The same is true of dioxane or of piperidine.

We have coloured the lone pairs green or black according to whether they are axial or equatorial, but you can also consider the colour coding in a different way: black lone pairs are parallel with C–C or C–heteroatom bonds in the ring; green lone pairs are parallel with axial C–H bonds outside the ring, or, if the ring has substituents, with the bonds to those substituents. This substituted tetrahydropyran illustrates all this. Notice that the equatorial substituents next to the heteroatom are parallel with neither the green nor the black lone pair.



Why is this important? Well, if you cast your mind back to Chapter 38, you will remember that the overlap of parallel orbitals was very important in fragmentation reactions. Here, for example, is a fragmentation reaction that goes very well, but that can take place only if the nitrogen's lone pair is equatorial, because only an equatorial (black) lone pair can overlap with the antibonding orbital of the C–C bond that breaks. The chloride leaving group must be equatorial as well.



This is not a problem in this example, because flipping of the ring and inversion of the nitrogen are fast, and enough of the starting material is in this conformation at any one time for the reaction to take place. But compare this bicyclic acetal whose 'fragmentation' (actually just an acetal hydrolysis) looks possible by this mechanism.

Yet when we try and draw the conformation of the lone pairs we run into a problem: neither over-

laps with the C–O bond that is breaking and so neither can donate its electron density into the C–O σ*. (Another way of looking at this is to say that the intermediate oxonium ion—with a C=O double bond formed by one of the oxygen's lone pairs—would be extremely strained.) Not surprisingly, the rate of hydrolysis of this acetal is extremely slow compared with similar ones in which overlap between the oxygen lone pair and the C–O σ* is possible. The acetal in the margin hydrolyses about 10^{10} times faster.

Other situations you have met where overlap between parallel orbitals is important are:

- E2 elimination reactions (Chapter 19)
- NMR coupling constants (Chapter 32)
- reactions of cyclic molecules (Chapter 33)
- the Felkin–Anh transition state conformation (Chapter 34)

Together, these effects are called **stereoelectronic effects**, because they depend on the shape and orientation of orbitals. Most of the examples we have presented you with have been stereoelectronic effects on reactivity, but the next section will deal with how stereoelectronic effects affect conformation.

Some substituents of saturated heterocycles prefer to be axial: the anomeric effect

Some of the most important saturated oxygen heterocycles are the sugars. Glucose is a cyclic hemiacetal—a pentasubstituted tetrahydropyran if you like—whose major conformation in solution is shown on the right. About two-thirds of glucose in solution exists as this stereoisomer, but hemiacetal formation and cleavage is rapid, and this is in equilibrium with a further one-third that carries the hemiacetal hydroxyl group axial (<1% is in the open-chain form).

Having read Chapter 18 you will not be surprised that glucose prefers all its substituents to be equatorial. For four of them, of course, there is no choice: they are either all-equatorial or all-axial, and the only way they can get from one to the other is by ring-flipping. But for the fifth substituent, the hydroxyl group next to the ring oxygen (known as the **anomeric hydroxyl**), the choice of axial or equatorial is made available by hemiacetal cleavage and re-formation—it can invert its configuration. What is perhaps surprising is that the equatorial preference of this hydroxyl group is so small—only 2:1. Even more surprising is that, for most derivatives of glucose, the anomeric substituents *prefer* to be axial rather than equatorial.

Move away from glucose, and the effect is still there. Here, for example, is the NMR spectrum of this chloro compound. There are now only two possible conformations (no configurational changes are possible because this is not a hemiacetal)—both shown—and from the NMR spectrum you should be able to work out which one this compound has.

δ			J, Hz	
5.78	1H	t	2.0	H1
5.03	2H	m		H2, H3
4.86	1H	m		H4
4.37	1H	dd	12.9, 3.0	H5a
3.75	1H	ddd	12.9, 3.7, 0.6	H5b
2.10	9H	s		OAc × 3

The key point is that axial–axial couplings are large (>8 Hz, say), even with adjacent electronegative atoms (which do tend to lower coupling constants). So if H1 were an axial proton, you would expect it to have a large coupling to H2. But it doesn't—it couples to H2 with J of only 2.0 Hz. (The other coupling is a W-coupling to H3, also of 2.0 Hz: see p. 000.) Similarly, we know that the 12.9 Hz coupling shared by the two H5 protons must be a geminal (^2J) coupling. One of H5a or H5b must be axial; yet both couple to H4 with J < 4 Hz. So H4 cannot be axial. With this evidence, we have to conclude that H1 and H4 (and therefore H2 and H3) are equatorial, so the compound must exist mainly in the all-axial conformation. (The 0.6 Hz coupling to H5b is another W-coupling, and shows that H5b is the equatorial proton, and H5a therefore the axial one.)

● The anomeric effect

In general, any tetrahydropyran bearing an electronegative substituent in the 2-position will prefer that substituent to be axial. This is is known as the anomeric effect.

But why? This goes against all of what we said in Chapter 18 about axial substituents being more hindered, making conformations carrying axial substituents disfavoured. The key again is stereoelectronics, and we can now link up with the message we left you with at the end of the last section: eliminations and fragmentations can work only when the orbitals involved are parallel.

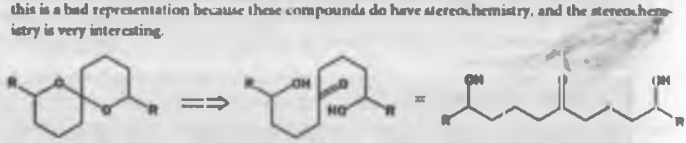
An amide is more stable (less reactive) than a ketone because the p orbital of the N and the low-lying C=O π* of the carbonyl can lie parallel—they can overlap and electron density can move from nitrogen into the C=O bond, weakening C–O. (Evidence for this comes from the lower IR stretching frequency of an amide C=O, among other things.) But C–X bonds also have low-lying antibonding orbitals—the C–X σ*—so we would expect a molecule to be stabilized if an adjacent heteroatom could donate electrons into this orbital in the same way. Take the generalized tetrahydropyran in the box above, for example, with X = Cl, say. This molecule is most stable if an oxygen lone pair can overlap with C–Cl σ*, like this.

But it can do this only if the chlorine is axial! Remember what we pointed out earlier: the oxygen's equatorial lone pairs are parallel with nothing but bonds in the ring, so the oxygen's axial lone pair is the only one that can help stabilize the molecule, and it can only do this when the Cl is axial. Only the axial conformation benefits from the stabilization, and this is the origin of the anomeric effect.

How shall we represent the stabilization? Comparing again with the amide stabilization, you might think about how to represent it with curly arrows: this is straightforward with the amide and you have seen it many times. But it looks odd with our heterocycle: electron density moves from O to Cl, and the C–Cl bond is weakened. If the process carried right on, Cl^- would leave. This is exactly what did happen in the acetal we presented you with as an example on p. 000: only the axial OAr could leave, however, because of the same requirement for overlap with an oxygen lone pair. In the real structure that we are now looking at, the Cl is still there: the C–Cl bond is weaker, and some of the oxygen's electron density is delocalized on to Cl. This can be seen in crystal structures: compounds exhibiting an anomeric effect have a longer (and therefore weakened) bond outside the ring and a shorter, stronger C–O bond within the ring.

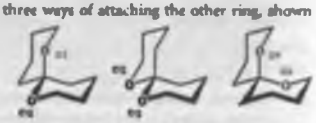
The anomeric effect in some other compounds

Now that you know about the anomeric effect, you should add it to your mental array of ways of explaining 'unexpected' results. Here is an example. Many fruit flies have pheromones based around a 'spiroketal' structure, which we could represent without stereochemistry as shown below. You can imagine the spiroketal (that is, an acetal of a ketone made of two rings joined at a single atom) being made from a dihydroxyketone—and, indeed, this is very often how they are made synthetically. But this is a bad representation because these compounds do have stereochemistry, and the stereochemistry is very interesting.

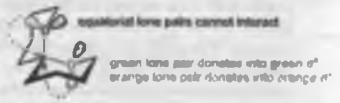


spiroketal structure of some insect pheromones

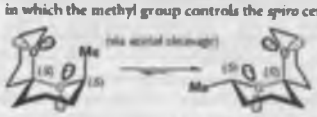
Let's start with the simplest example, with R = H (a pheromone of the olive fly). Once you have drawn one ring in its chair conformation, there are three ways of attaching the other ring, shown here. If you think they all look the same, consider the orientation of each C–O bond with respect to the ring that it is not part of: you can have each C–O axial or equatorial, and there are three possible arrangements (three conformations).



Without knowing about the anomeric effect, you would find it hard to predict which conformation is favoured, and, indeed, you might expect to get a mixture of all three. But NMR tells us that this compound exists entirely in one conformation: the last one here, in which each oxygen is axial on the other ring. Only in this conformation can both C–O bonds benefit from the anomeric effect—this is often known as the **double anomeric effect**.

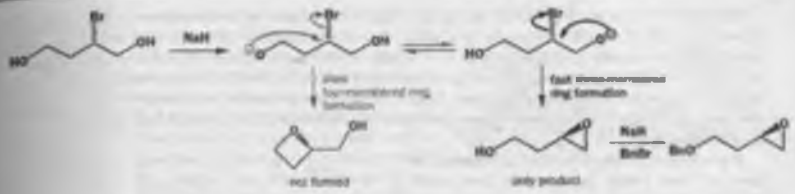


Things become even more interesting when the spiroketal carries substituents. The pheromone of *Epochus crucifer*, for example, carries one additional methyl group at a centre with (*S*) configuration. The spiroketal centre is now a chiral centre, and also exists in a single configuration. Only one possible conformation allows the methyl substituent to be equatorial and the two oxygens to be axial, and that conformation defines the configuration at the spiroketal. Only one diastereoisomer is formed, in which the methyl group controls the *spiro* centre.



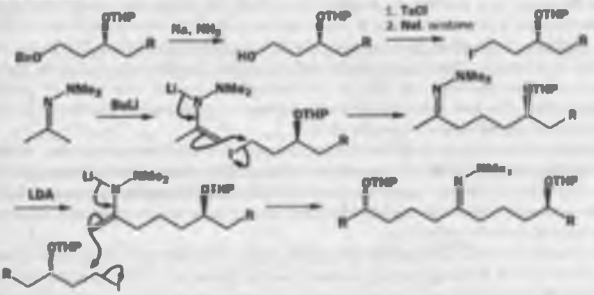
The fact that the substituents on the side chains can control the conformation of the spiroketal centre means that it is not necessary to worry about that centre in a synthesis, provided you are trying to make the spiroketal that has the double anomeric stabilization (both oxygens axial) and that has any substituents equatorial on the rings. A recent (1997) synthesis of a single enantiomer of some fruit-fly pheromones from an aspartic acid-derived bromodiol is shown overleaf. It involves three different-sized oxygen heterocycles.

The diol is made into an epoxide by an intramolecular substitution reaction that is S_N2 and so goes with inversion. There are two possible rings that could form, depending on which hydroxyl group attacks, but (as you will shortly see) three-membered rings form faster than four-membered ones, and the reaction gives none of the oxetane. The other hydroxyl group can now be protected as a benzyl ether.

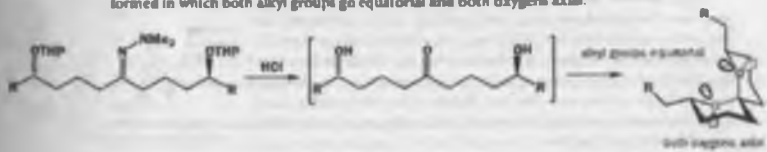


The epoxide opens well with either a copper derivative (RMgBr + CuI) or simply $NaBH_4$, and the resulting alcohol needs to be protected. A good, and in this instance topical, choice is a THP group, added using dihydropyran in the presence of acid. The disadvantage of THP protecting groups is that they introduce an unwanted chiral centre: this will not be controlled and we expect a mixture of both (*R*) and (*S*) configurations at this centre. However, you should now have no problem predicting the *conformation* of the THP rings, even if it is irrelevant to the synthesis.

Now the benzyl ether can be deprotected, and the hydroxyl group substituted for iodide via its tosylate. This iodide is an alkylating agent, and is used for two successive alkylations of a hydrazone's aza-enolate.



The product is still a hydrazone, and it needs hydrolysing to the ketone with 1 M HCl. These conditions cause immediate hydrolysis of the THP protecting groups and then cyclization to the spiroacetal, which forms with complete control over stereochemistry— a single diastereoisomer is formed in which both alkyl groups go equatorial and both oxygens axial.



Remember that the key requirement for the anomeric effect is that there is a heteroatom with a lone pair (O, N, S usually) adjacent to (that is, in a position to interact with) a low-lying antibonding orbital—usually a C–X σ^* (where X = halogen or O). The C–X bond doesn't have to be within the ring—for example, this nitrogen heterocycle prefers to have the R group axial so that the nitrogen gets an equatorial lone pair. Equatorial lone pairs are parallel with bonds within the ring, one of which is C–O, and this conformation is therefore stabilized by an N lone pair/C–O σ^* interaction.

It would be a bit much for this 1,3,5-triazine to have all three *t*-butyl groups axial (too much steric hindrance), but it can get away with having one of them axial, benefiting from the resulting equatorial lone pair, which can overlap with two C–N σ^*s in the ring.

Related effects in other types of compounds

● Any conformation in which a lone pair is anti-periplanar to a low-energy antibonding orbital will be stabilized by a stereoelectronic interaction.

As you will probably realize, it's not only in six-membered rings that stereoelectronic interactions between filled and unfilled orbitals stabilize some conformations more than others. Stereoelectronic effects control the conformations of many types of molecules. We shall look at three common compounds that are stabilized by stereoelectronic effects: in two cases, the stabilization is specific to one conformation, and we can use stereoelectronics to explain what would otherwise be an unexpected result.

But we start with a compound that is so simple that it has only one conformation because it has no rotatable bonds: dichloromethane. You may have wondered why it is that, while methyl chloride (chloromethane) is a reactive electrophile that takes part readily in substitution reactions, dichloromethane is so unreactive that it can be used as a solvent in which substitution reactions of other alkyl halides take place. You may think that this is a steric effect: indeed, Cl is bigger than H. But CH_2Cl_2 is much less reactive as an electrophile than ethyl chloride or propyl chloride: there must be more to its unreactivity. And there is: dichloromethane benefits from a sort of 'permanent anomeric effect'. One lone pair of each chlorine is always anti-periplanar to the other C–Cl bond so that there is always stabilization from this effect.

Among the most widespread classes of acyclic compounds to exhibit stereoelectronic control over conformation are acetals. Take the simple acetal of formaldehyde and methanol, for example: what is its conformation? An obvious suggestion is to draw it fully extended so that every group is fully anti-periplanar to every other—this would be the lowest-energy conformation of pentane, which you get if you just replace the Os with CH_2s.

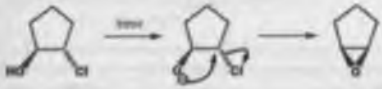
The trouble is, in this conformation none of the oxygen lone pairs get the chance to donate into the C–O σ^* orbitals. Although putting the bonds anti-periplanar to one another makes steric sense, electronically, the molecule much prefers to put the lone pairs anti-periplanar to the C–O bonds, so the bonds themselves end up gauche (synclinal) to one another. This is known as the gauche effect, but is really just another way in which the stereoelectronic effects that give rise to the anomeric effect turn up in acyclic systems.

Finally, an even more familiar example that you may never have thought about. You are well aware now that amides are planar, with partially double C–N bonds, and that tertiary amides have one alkyl group *cis* to oxygen and one *trans*. But what about esters? Esters are less reactive than acyl chlorides because of donation from the oxygen p orbital into the carbonyl π^*, so we expect them to be planar too, and they are. But there are two possible planar conformations for an ester: one with R *cis* to oxygen and one with R *trans*. Which is preferred?

Here are the two conformations drawn out for ethyl acetate. When the ethyl group (= R) and O are *cis*, not only can one oxygen lone pair interact with the C=O π^*, but the other lone pair can also donate into the σ^* of the C–O bond. This is not possible when Et and O are *trans*: they are no longer anti-periplanar. The *cis* conformation of esters is generally the preferred one, even in formate esters, where the alkyl group ends up in what is clearly a more sterically hindered orientation.

Making heterocycles: ring-closing reactions

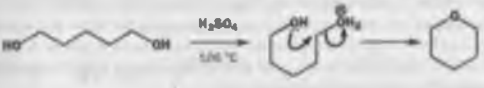
We have talked about the structure of saturated heterocycles, particularly with regard to stereoelectronic control over conformation, and before that we looked at some of their reactions. In this last section of the chapter we will look at how to make saturated heterocycles. By far the most important way of making them is by ring-closing reactions, because we can usually use the heteroatom as the nucleophile in an intramolecular substitution or addition reaction. Ring-closing reactions are, of course, just the opposite of the ring-opening reactions we talked about earlier in the chapter, and we can start with a reaction that works well in both directions: ring closure to form an epoxide. You know well that epoxides can be formed using *m*-CPBA and an alkene, but you have already seen examples (including one earlier in the chapter) where they form by an intramolecular substitution reaction such as this.

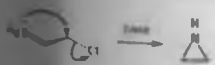


The same method can also be used to generate larger cyclic ethers. Oxetane, for example, is conveniently made by adding 3-chloropropyl acetate to hot potassium hydroxide.

The first step in this reaction is the hydrolysis of the ester. The alkoxide produced then undergoes an intramolecular substitution reaction to yield oxetane.

Tetrahydropyran was prepared as early as 1890 by a ring closure that occurs when a mixture of 1,5-pentanediol with sulfuric acid is heated.



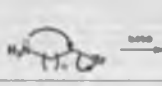


These are all S_N2 reactions, so you will not be surprised that nitrogen heterocycles can be prepared in the same way. Aziridine itself, for example, was first prepared in 1888 from 2-chloroethylamine.

This method works well to form three-, five-, and six-membered nitrogen heterocycles, but does not work well to form four-membered rings. In fact, four-membered rings are generally among the

hardest of all to form. To illustrate this, the first two columns of Table 42.2 show the rates (relative to six-membered ring formation = 1) at which bromoamines of various chain lengths cyclize to saturated nitrogen heterocycles of three to seven members.

Table 42.2 Rates of ring-closing reactions



Ring size	Product	Relative rate[a]	Product[b]	Relative rate[a]	Assessment
3		0.07			moderate
4		0.001		0.58	slow
5		100		833	very fast
6		1		1	fast
7		0.002		0.0087	slow
8				0.00015	very slow

[a] Relative to the six-membered ring formation (= 1).

[b] E = CO_2Et.

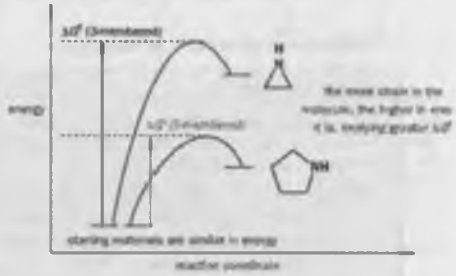
The first thing that strikes you perhaps is that the figures in the third column have been produced by a random number generator! There seems to be no rhyme or reason to them, and no consistent trend. To convince you that these numbers mean something, Table 42.2 also shows, in its next two columns, the relative rates for a quite different ring-closing reaction, this time forming four- to seven-membered rings that are not even heterocycles by intramolecular alkylation of a substituted malonate. Though the numbers are quite different in the two cases, the ups and downs are the same, and the final column summarizes the relative rates. Put another way, a rough guide (only rough!—it doesn't work in all cases) to the rate of ring formation is this.

● Rough guide to the rate of formation of saturated rings

5 > 6 > 3 > 7 > 4 > 8–10

We show the numbers in colour to highlight the fact that this seemingly illogical ordering of numbers actually conceals two superimposed trends. Once you get to five-membered rings, the rate of formation drops consistently as the ring size moves from 'normal' to 'medium', 'Small' (three- and four-membered) rings insert into the sequence below six.

The reason for the two superimposed trends is two opposing factors. Firstly, small rings form slowly because forming them introduces ring strain. This ring strain is there even at the transition state, raising its energy and slowing down the reaction. $\Delta G^\ddagger$ is very large for a three-membered ring (due to strain) but decreases as the ring gets larger. This explains why three- and four-membered rings don't fit straightforwardly into the sequence.

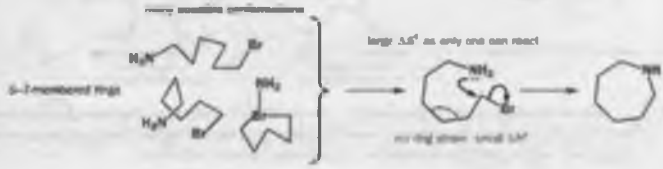


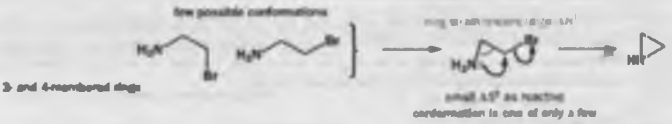
But, if the reaction rate simply depended on the strain of the product, the slowest reaction would be the formation of the three-membered ring, and six-membered rings (which are essentially strain-free) would form fastest. But as it is, four-membered rings form more slowly than three-membered ones, and five-membered ones faster than six-membered ones. To explain this, we need to remind you of an equation we presented in Chapter 13.

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

The activation energy barriers $\Delta G^\ddagger$ of our reactions are made up of two parts: an enthalpy of activation $\Delta H^\ddagger$, which tells us about the energy required to bring atoms together against the strain and repulsive forces they usually have, and an entropy of activation $\Delta S^\ddagger$, which tells us about how easy it is to form an ordered transition state from a wriggling and randomly rotating molecule.

$\Delta G^\ddagger$ for three- and four-membered ring formation is large because $\Delta H^\ddagger$ is large: energy is needed to bend the molecule into the strained small-ring conformation. $\Delta H^\ddagger$ for five-, six-, and seven-membered rings is smaller: this is the quantifiable representation of the 'ring strain' factor we have just introduced. The second factor is one that depends on $\Delta S^\ddagger$: how much order must be imposed on the molecule to get it to react. Think of it this way: a long chain has a lot of disorder, and to get its ends to meet up and react means it has to give up a lot of freedom. So, for the formation of medium and large rings, $\Delta S^\ddagger$ is large and negative, contributing to a large $\Delta G^\ddagger$ and slow reactions. For three-membered rings, on the other hand, the reacting atoms are already very close together and almost no order needs to be imposed on the molecule to get it to cyclize: rotation about just one bond is all that is needed to ensure that the amine group is in the perfect position to attack the σ^* of the C–Br bond in our example above. $\Delta S^\ddagger$ is very small for three-membered rings so, while $\Delta H^\ddagger$ is large, there is little additional contribution from the $T\Delta S^\ddagger$ term and cyclization is relatively fast. Four-membered rings suffer the worst of both worlds: forming a four-membered ring introduces ring strain ($\Delta H^\ddagger$) *and* requires order ($\Delta S^\ddagger$) to be imposed on the molecule. They form very slowly as a result.





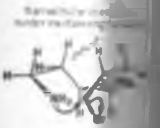
These results are summarized in the following box.

● Ring formation

- Three-membered ring formation is fast—the product is strained so $\Delta H^{\ddagger}$ is large but this is offset by the reacting atoms being as close as they can get in a freely rotating chain
- Four-membered rings form slowly—the product is still significantly strained but the reacting atoms are now not right next to each other to offset this
- Five-membered ring formation is often fastest of all. Significantly less strain and the ends are still not too far apart
- Six-membered ring formation experiences no strain but neither does it have the advantage of the ends being close
- Seven-membered rings and beyond form more slowly as $\Delta S^{\ddagger}$ increases

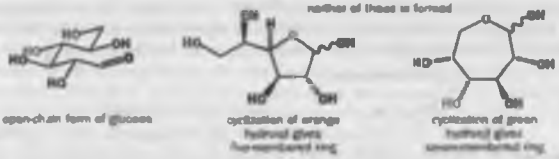
Medium and large rings

Beyond seven-membered rings, the rates stay low, but begin to level off, and may start to rise again when the rings have 10 or 11 members. These are the 'medium rings', of about 8–12 members, and they suffer from a different sort of strain, evident in the graph on p. 000 (Chapter 18), due to interactions between C–H bonds across the ring (transannular interactions). These are worst for rings of 8 and 9 members, and begin to be relieved once there are 10 or 11 atoms in the ring. For 14-membered rings and above, there is no transannular strain, and the rates of ring-closure remain essentially constant at about the 7-membered ring mark. Rates of reactions in ring sizes of 14 and above are essentially little different from those in acyclic compounds. To get large rings to form, it is often necessary to carry out the cyclization reaction in very dilute solution to discourage competing intermolecular reactions.

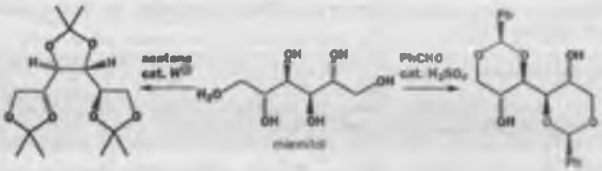


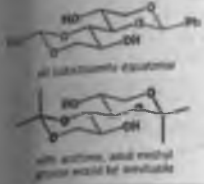
Thermodynamic control

In this section we have discussed the rate at which rings form: in other words the kinetics of ring formation. However, there are many ring-forming reactions that are under thermodynamic and not kinetic control. For example, you have already seen that glucose exists predominantly as a six-membered ring in solution. It could also exist as a five-membered ring: it doesn't because, although five-membered rings form faster than six-membered ones, they are usually less stable (remember, a six-membered ring is essentially strain-free). For similar thermodynamic reasons, it doesn't exist as a seven-membered ring, even though you can draw a reasonable structure for it.



Thermodynamic control is important in other ways in carbohydrate chemistry, because control over ring size allows selective protection of the hydroxyl groups of sugars. Compare these two reactions. Both of them give acetals from the same starting material, mannitol.





Don't be put off by the way in which we have had to twist half the molecule round to draw the left-hand structure: the stereochemistry hasn't changed. The important thing is that acetone reacts with mannitol to form three five-membered acetals (dioxolanes) while benzaldehyde forms only two six-membered acetals. This is quite a common result: when there is a choice, acetone prefers to react across a 1,2-diol to give a five-membered ring, while aldehydes prefer to react across a 1,3-diol to form a six-membered ring. Drawing a conformational diagram of the product on the right helps to explain why. All of the substituents are equatorial, making this a particularly stable structure. Now imagine what would happen if acetone formed this type of six-membered ring acetal. There would always be an axial methyl group, and the six-membered rings would be less stable.

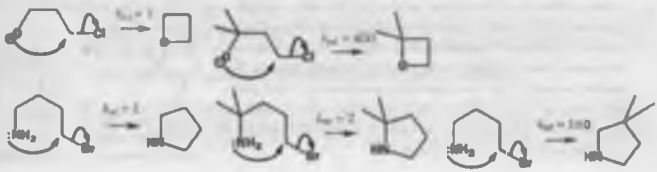
Aminals are another class of saturated heterocycles that form very readily under thermodynamic control: aminals are nitrogen analogues of acetals. They are usually made by refluxing a 1,2-diamine with an aldehyde in toluene (no acid catalyst is needed because the nitrogens are very nucleophilic), and this makes a very useful way of forming a chiral derivative of an achiral aldehyde. Here is an example: the diamine is made from the amino acid proline. The product has a new chiral centre, and it forms as a single diastereoisomer because the phenyl ring prefers to be on the *exo* face of the bicyclic system (see Chapter 33).

Refluxing in toluene removes the water as an azeotrope (see p. 000), but, in fact, the aminal forms so readily that, if you do this reaction in cold dichloromethane (in which water is insoluble), the solution becomes cloudy as droplets of water are produced!

Combatting $\Delta S^{\ddagger}$—the Thorpe–Ingold effect

Compare the following relative rates for epoxide-forming cyclization reactions. The second looks as though it suffers more steric hindrance but it is tens of thousands of times faster!

Adding substituents to other ring-forming reactions makes them go faster too: in the next two examples the products are oxetanes and pyrrolidines.

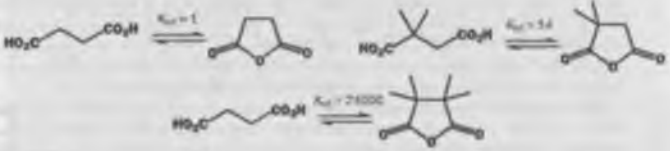


This effect is quite general, and is known as the **Thorpe–Ingold effect** after the first chemists to note its existence, in 1915.

The Thorpe–Ingold effect

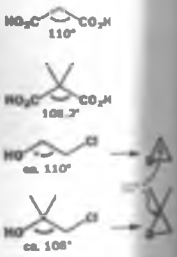
The Thorpe–Ingold effect is the way in which substituents on the ring increase the rate, or equilibrium constant, for ring-forming reactions.

As the box says, it's not only rate that can be affected by additional substitution. Here are the relative equilibrium constants for the formation of an anhydride from a 1,4-dicarboxylic acid (the unsubstituted acid is called succinic acid, and the values are scaled so that K_{rel} for the formation of succinic anhydride is 1). More substituents mean more cyclized product at equilibrium. The Thorpe–Ingold effect is both a kinetic and a thermodynamic phenomenon.



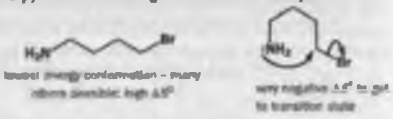
Now we need to explain why this is. The explanation comes in two parts, one of which may be more important than the other, depending on the ring being formed. The first part is more applicable to the formation of small rings, such as the first example we gave you.

If you measure the bond angles of chains of carbon atoms, you expect them to be close to the tetrahedral angle, 109.5°. The crystal structure of the 1,3-dicarboxylic acid in the margin, for example, shows a C–C–C bond angle of 110°. Now, imagine adding substituents to the chain. They will repel the carbon atoms already there, and force them a little closer than they were, making the bond angle slightly less. X-ray crystallography tells us that adding two methyl groups to our 1,3-dicarboxylic acid decreases the bond angle by about 4°.



We can assume that the same is true in the alcohol starting materials for the epoxide-forming reactions (we can't measure the angle directly because the compounds aren't crystalline). Now consider what happens when both of these alcohols form an epoxide. The bond angle has to become about 60°, which involves about 50° of strain for the first diacid, but only 46° for the second. By distorting the starting material, the methyl groups have made it slightly easier to form a ring.

This part of the argument works only for small rings. For larger rings, we need another explanation, and it involves entropy. We'll use the pyrrolidine-forming reaction as an example. We have explained the effect of $\Delta S^\ddagger$ (entropy of activation) on the rate of ring formation: as larger rings form they have to lose more entropy at the transition state, and this contributes to a less favourable $\Delta G^\ddagger$.

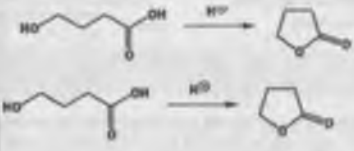


But, when the starting material has more substituents, it starts off with less entropy anyway. More substituents mean that some conformations are no longer accessible to the starting material—the green arcs below show how the methyl groups hinder rotation of the N and Br substituents into that region of space. Of those fewer conformations, many approximate to the conformation in the transition state, and moving from starting material to transition state involves a small loss of entropy: $\Delta S^\ddagger$ is less negative so $\Delta G^\ddagger$ ($= \Delta H^\ddagger - T\Delta S^\ddagger$) is more negative and the ring forms faster.

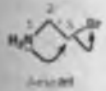
Because the same arguments apply to $\Delta S^{\ddagger}$ for the reaction as a whole (the difference in entropy between starting material and products), increased substitution favours ring closure even under thermodynamic control.

Baldwin's rules

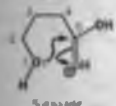
Nearly all of the cyclization reactions that we have discussed have been intramolecular S_N2 reactions where one end of the molecule acted as the nucleophile displacing the leaving group on the other end. We kept to this sort of reaction in order to make valid comparisons between different ring sizes. But you can imagine making saturated heterocycles in plenty of other ways—intramolecular substitution at a carbonyl group, for example, such as happens in this lactonization reaction, or intramolecular addition on to an alkyne.



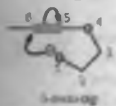
Cyclization reactions can be classified by a simple system involving: (1) the ring size being formed; (2) whether the bond that breaks as the ring forms is inside (*endo*) or outside (*exo*) the new ring; and (3) whether the electrophile is an sp (digonal), sp^2 (trigonal), or sp^3 (tetrahedral) atom. This system places three of the cyclizations just shown in the following classes.



1. The ring being formed has three members; the breaking C–Br bond is outside the new ring (*exo*); the C carrying Br is a tetrahedral (sp^3) atom (*tet*)



2. The ring being formed has five members; the breaking C=O bond is outside the new ring (*exo*); the C being attacked is a trigonal (sp^2) atom (*trig*)



3. The ring being formed has six members; the breaking C≡C bond is inside the new ring (*endo*); the C being attacked is a digonal (sp) atom (*dig*)

The classes of cyclization reactions are important, not because we have a compulsive Victorian desire to classify everything, but because which class a reaction falls into determines whether or not it is likely to work. Not all cyclizations are successful, even though they may look fine on paper! The guidelines that describe which reactions will work are known as **Baldwin's rules**: they are not really rules in the Woodward–Hoffmann sense of the term, but more empirical observations backed up by some sound stereoelectronic reasoning. To emphasize this, the rules are couched in terms of 'favoured' and 'disfavoured', rather than 'allowed' and 'forbidden'. We will deal with the rules step by step and then summarize them in a table at the end.

Firstly, and not surprisingly (because we have been talking about them for much of this chapter):

- All *exo-tet* cyclizations are favoured.

and, similarly (again you can find many examples in this book):

- All *exo-trig* cyclizations are favoured.

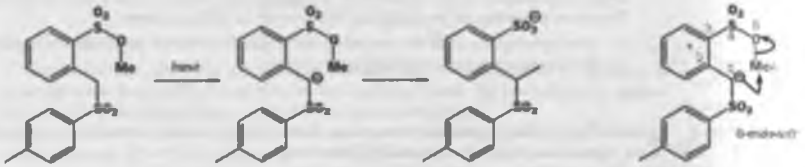
Despite the variation in rate we have described for this type of reaction, *exo-tet* cyclizations have no stereoelectronic problems: the lone pair and the C–X σ* (X is the leaving group) can overlap successfully irrespective of ring size. The ring closures in Table 42.2 all fall into this category.

The same is true for *exo-trig* reactions: it is easy for the nucleophilic lone pair to overlap with the C=X π* to form a new bond. Examples include lactone formation such as the one on p. 000.

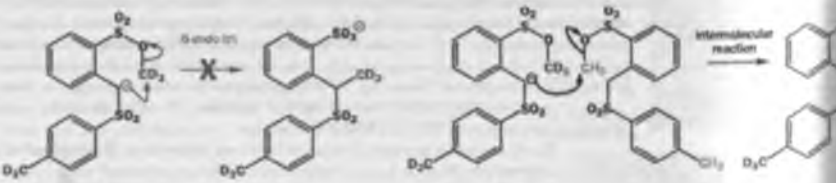
Endo-tet reactions are rather different. For a start:

● 5- and 6-*endo-tet* are disfavoured.

Endo-tet reactions would not actually make a ring, but they fall conveniently into the system and we will look at them here. Here is a reaction that looks as though it contradicts what we have just said. The arrows in the reasonable-looking mechanism on the right describe a 6-*endo-tet* process, because the breaking Me–O bond is within the six-membered ring transition state (even if no ring is formed).



But Eschenmoser showed that, for all its appeal (intramolecular reactions usually outpace all alternatives), this mechanism is wrong. He mixed together the starting material for the reaction above with the hexadeuterated compound shown below, and re-ran the reaction. If the reaction had been intramolecular, the products would have contained either no deuterium, or six deuteriums. In the event, the product mixture contained about 25% of each of these compounds, with a further 50% containing three deuteriums. The products cannot have been formed intramolecularly, and this distribution is exactly what would be expected from an intermolecular reaction.

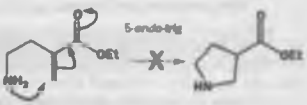


With *endo-trig* reactions, whether they work or not depends on the ring size.

● 3-, 4-, and 5-*endo-trig* are disfavoured; 6- and 7-*endo-trig* are favoured.

The most important reaction of the *endo-trig* class is the disfavoured 5-*endo-trig* reaction and, if there is one message you take away from this section, it should be that 5-*endo-trig* reactions are

disfavoured. The reason we say this is that 5-*endo-trig* cyclizations are reactions that look perfectly fine on paper, and at first sight it seems quite surprising that they won't work. This intramolecular conjugate addition, for example, appears to be a reasonable way of making a substituted pyrrolidine.

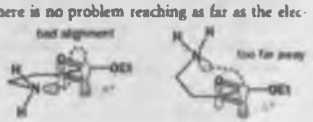


But this reaction doesn't happen: instead, the amine attacks the carbonyl group in a (favoured) 5-*exo-trig* cyclization.

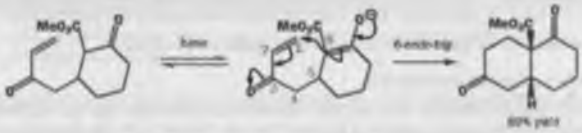
Amines usually undergo conjugate addition to unsaturated esters: see Chapter 10.

It's easier to see this with a model, and if you have a set of Dreiding or models you should use one to see for yourself.

Why is 5-*endo-trig* so bad? The problem is that the nitrogen's lone pair has problems reaching round to the π^* orbital of the Michael acceptor. There is no problem reaching as far as the electrophilic carbon in the plane of the substituents but, if it bends out of this plane, which it must if it is to overlap with the π^* orbitals, it moves too far away from the methylene carbon to react. It's like a dog chained just out of reach of a bone.

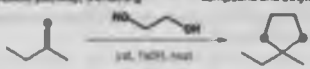


Lengthen the chain, though, and the dog gets his dinner. Here's a perfectly straightforward 6-*endo-trig*, for which orbital overlap presents no problem.

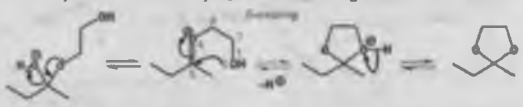


Exceptions to Baldwin's rules

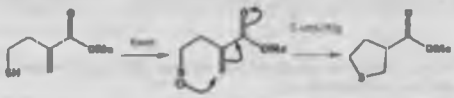
Baldwin's rules are only guidelines and, when a reaction is thermodynamically very favourable (Baldwin's rules, of course, describe the *kinetic* favourability of a reaction) and there is no other possible pathway, 5-endo-trig reactions can take place. The most striking example is one that you met quite early on in this book (Chapter 14): the formation of a cyclic acetal (dioxolane) from a carbonyl compound and ethylene glycol.



We don't need to give again the full mechanism here, but you should check that you can still write it. The key step with regard to Baldwin's rules is shown with a green arrow. It is a 5-endo-trig reaction but it works!



In fact, cations frequently disobey Baldwin's rules. Other well-defined exceptions to Baldwin's rules include pericyclic reactions and reactions in which second-row atoms such as sulfur are included in the ring. The 5-endo-trig reaction, the sulfur analogue of the amine cyclization that didn't work, is fine. C–S bonds are long, and the empty 3d orbitals of sulfur may play a role by providing an initial interaction with the C–C π orbital.



With *tet* and *trig* cyclizations, *exo* is better than *endo*; with *dig* cyclizations, the reverse is true.

● All *endo-dig* cyclizations are favoured.

Move from 5-*endo-trig* to 5-*endo-dig*, and the reactions become much easier: even 4-*endo-dig* reactions work. Here is an example of 5-*endo-dig*.

We warned you to look out for 5-*endo-trig* reactions because they are disfavoured even though on paper they look fine. Now the alert is the other way round! We expect you'd agree that these *endo-dig* reactions look awful on paper: the linear alkyne seems to put the electrophilic carbon well out of reach of the nucleophile, even further away than in the 5-*endo-trig* reaction. The important thing with *endo-dig* cyclizations, though, is that the alkyne has two π* orbitals, one of which must always lie in the plane of the new ring, making it much easier for the nucleophile to get at.

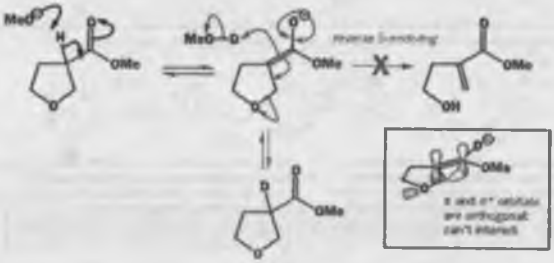
Conversely:

● 3- and 4-*exo-dig* are disfavoured; 5- to 7-*exo-dig* are favoured.

These reactions are less important and we will not discuss them in detail.

Baldwin's rules and ring opening

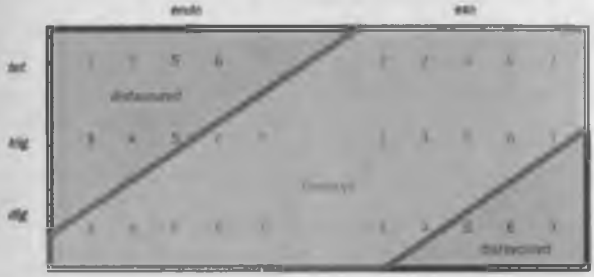
Baldwin's rules work because they are based on whether or not orbital overlap can be readily achieved in the conformation required at the transition state. You met in the last chapter the principle of microscopic reversibility, which says that, if a reaction goes via a certain mechanism, the reverse reaction must follow exactly the same path in the opposite direction. So Baldwin's rules also work for ring-opening reactions. This is where the unfavourability of 5-*endo-trig* really is important: this tetrahydrofuranyl ester, for example, looks set up to do an E1cB elimination in base. Indeed, when it is treated with methoxide in deuterated methanol it exchanges the proton α to the ester for deuterium, proving that the enolate forms. But is does not eliminate: elimination would be a reverse 5-*endo-trig* process and is disfavoured.



Whenever you think about a ring-opening reaction, consider its reverse, and think whether it is favoured according to Baldwin's rules.

To summarize

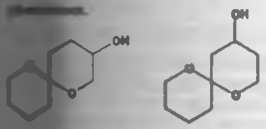
We shall end by summarizing Baldwin's rules in a chart. You should note the general outline of this chart: commit to memory that, broadly speaking, *endo-tet* and *endo-trig* are disfavoured; *exo-tet* and *exo-trig* are favoured, and the reverse for *dig*. Then you just need to learn the cut-off points that indicate the exceptions to this broad-brush view: 6-*endo-trig* falls into the favoured category while 5-*exo-dig* falls into the disfavoured one. And, if you really can remember only one thing, it should be that 5-*endo-trig* is disfavoured!



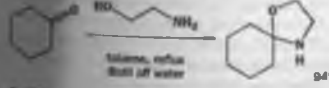
In the next two chapters, we continue with heterocycles, but move from saturated ones to flat, aromatic ones. Conformation and stereoelectronics are no longer issues, but molecular orbitals certainly are. In Chapter 44 you will meet many cyclization reactions: you will find that not a single one is Baldwin-disfavoured.

Problems

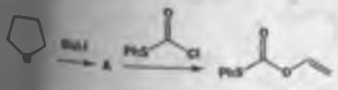
1. Predict the most favourable conformations of these insect pheromones.



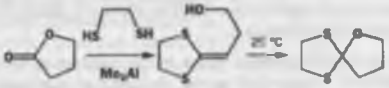
2. Refluxing cyclohexanone with ethanolamine in toluene with a Dean Stark separator to remove the water gives an excellent yield of this bicyclic. What is the mechanism, and why is acid catalysis (or any other kind) unnecessary?



3. What is A in the following reaction scheme and how does it react to give the final product?



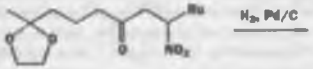
4. Give mechanisms for the formation of this *spiro* heterocycle. Why is the product not formed simply on reacting the starting materials in acid solution without Me_3Al?



5. The *Lolium* alkaloids have a striking skeleton of saturated heterocycles. One way to make this skeleton is shown below. Explain both the mechanism and the stereochemistry.

a *Lolium* alkaloid

6. Explain the stereochemical control in this synthesis of a fused bicyclic saturated heterocycle—the trail pheromone of an ant.



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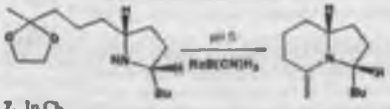
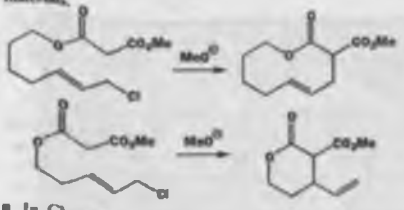
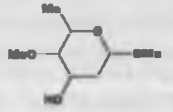


7. In Chapter 31, one of the problems asked you to comment on the difference between these two reactions. Now would you like to comment again and add comments on the way we drew the starting materials.

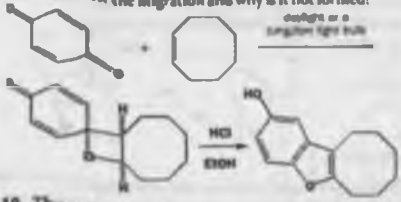


8. In Chapter 32, Problem 6, we asked you to work out the stereochemistry of a sugar. One of the sugar components in the antibiotic kijanimycin has the gross structure and NMR spectrum shown below. What is its stereochemistry? Signals marked * exchange with D_2O.

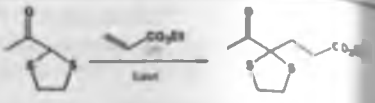


δ_H 1.33 p.p.m. (3H, d, *J* 6 Hz), 1.61* p.p.m. (1H, broad s), 1.87 p.p.m. (1H, ddd, *J* 14, 3, 3.5 Hz), 2.21 p.p.m. (1H, ddd, *J* 14, 3, 1.5 Hz), 2.87 p.p.m. (1H, dd, *J* 10, 3 Hz), 3.40 p.p.m. (3H, s), 3.47 p.p.m. (3H, s), 3.99 p.p.m. (1H, dq, *J* 10, 6 Hz), 1.33 p.p.m. (3H, d, *J* 6 Hz), 4.24 p.p.m. (1H, ddd, *J* 3, 3, 3.5 Hz), and 4.79 p.p.m. (1H, dd, *J* 3.5, 1.5 Hz). When you did this problem, you probably thought about the conformation but now draw it and say why you think the molecule prefers that conformation.

9. Revisions of Chapters 35 and 37. Give mechanisms for these reactions, commenting on the formation of that particular saturated heterocycle in the first reaction. What is the alternative product from the migration and why is it not formed?

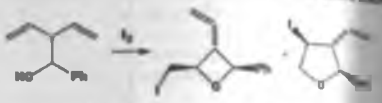


10. Though the anion of dithiolane decomposes as described in the chapter and cannot be used as a d^1 reagent, the example shown here works well without any decomposition. Explain and comment on the regioselectivity of the reaction. Anions of dithianes are notorious for preferring direct to conjugate addition.

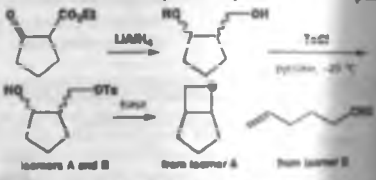


11. Propose a mechanism for this reaction. It does not occur in the absence of an *ortho*- or a *para*-OH group.

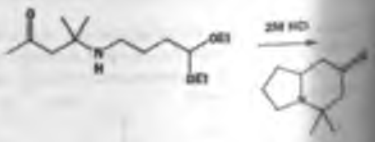
12. Explain why this cyclization gives a preponderance (3:1) of the oxetane though the tetrahydrofuran is much more stable.



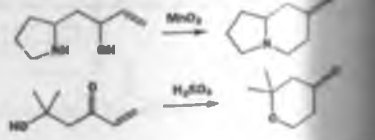
13. Reduction of this keto-ester with $LiAlH_4$ gives a mixture of diastereoisomers of the diol. Treatment with TsCl and pyridine at −25 °C gives a monotosylate from each. Treatment of these with base leads to the two very different products shown. Explain.



14. Draw a mechanism for the following multistep reaction. Do the cyclization steps follow Baldwin's rules? What other stereoelectronic effects are involved?



15. Consider the question of Baldwin's rules for [illegible] reactions. Why do you think they are successful?



Aromatic heterocycles 1: structures and reactions

43

Connections

Building on:

- Aromaticity ch7
- Electrophilic aromatic substitution ch22
- Nucleophilic attack on aromatic rings ch23
- Saturated heterocycles ch42

Arriving at:

- Aromatic systems conceptually derived from benzene: replacing CH with N to get pyridine
- Replacing CH=CH with N to get pyrrole
- How pyridine reacts
- How pyridine derivatives can be used to extend pyridine's reactivity
- How pyrrole reacts
- How furan and thiophene compare with pyrrole
- Putting more nitrogens in five- and six-membered rings
- Fused rings: indole, quinoline, isoquinoline, and indolizine
- Rings with nitrogen and another heteroatom: oxygen or sulfur
- More complex heterocycles: porphyrins and phthalocyanines

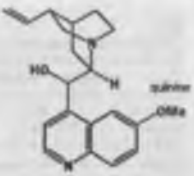
Looking forward to:

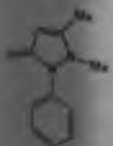
- Synthesis of aromatic heterocycles ch44
- Biological chemistry ch49–ch51

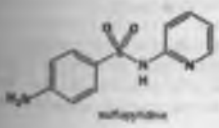
Introduction

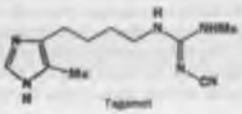
Benzene is aromatic because it has six electrons in a cyclic conjugated system. We know it is aromatic because it is exceptionally stable and it has a ring current and hence large chemical shifts in the proton NMR spectrum as well as a special chemistry involving substitution rather than addition with electrophiles. This chapter and the next are about the very large number of other aromatic systems in which one or more atoms in the benzene ring are replaced by heteroatoms such as N, O, and S. There are thousands of these systems with five- and six-membered rings, and we will examine just a few.

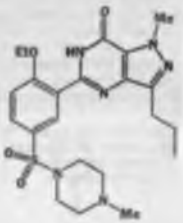
Our subject is aromatic heterocycles and it is important that we treat it seriously because most—probably about two-thirds of—organic compounds belong to this class, and they number among them many of the most significant compounds for human beings. If we think only of drugs we can define the history of medicine by heterocycles. Even in the sixteenth century quinine was used to prevent and treat malaria, though the structure of the drug was not known. The first synthetic drug was antipyrine (1887) for the reduction of fevers. The first effective antibiotic was sulfapyridine (1938). The first multi-million pound drug (1970s) was Tagamet, the anti-ulcer drug, and among the most topical of current drugs is Viagra (1997) for treatment of male impotence.









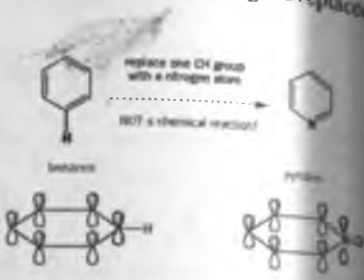


Sir James Black, discoverer of Tagamet, worked on medicinal chemistry at Smith Kline French. Later Smithkline Beecham, and was awarded the Nobel Prize for his analysis of drug receptors in 1988.

All these compounds have heterocyclic aromatic rings shown in black. Three have single rings, five- or six-membered, two have five- or six-membered rings fused together. The number of heterogens in the rings varies from one to four. We will start by looking at the simple six-membered ring with one nitrogen atom. This is pyridine and the drug sulfapyridine is an example.

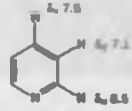
Aromaticity survives when parts of benzene's ring are replaced by nitrogen atoms

There is no doubt that benzene is aromatic. Now we must ask: how can we insert a heteroatom into the ring and retain aromaticity? What kind of atom is needed? If we want to replace one of the carbon atoms of benzene with a heteroatom, we need an atom that can be trigonal to keep the flat hexagonal ring and that has a p orbital to keep the six delocalized electrons. Nitrogen is ideal so we can imagine replacing a CH group in benzene with a nitrogen atom.



The orbitals in the ring have not changed in position or shape and we still have the six electrons from the three double bonds. One obvious difference is that nitrogen is trivalent and thus there is no NH bond. Instead, a lone pair of electrons occupies the space of the C–H bond in benzene.

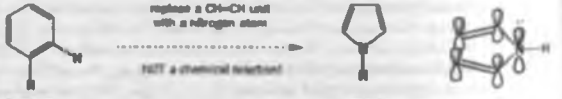
In theory then, pyridine is aromatic. But is it in real life? The most important evidence comes from the proton NMR spectrum. The six protons of benzene resonate at δ_H 7.27 p.p.m., some 2 p.p.m. downfield from the alkene region, clear evidence for a ring current (Chapter 11). Pyridine is not as symmetrical as benzene but the three types of proton all resonate in the same region.



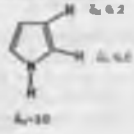
^{1}H NMR spectrum of pyridine

As we will see, pyridine is also very stable and, by any reasonable assessment, pyridine is aromatic. We could continue the process of replacing, on paper, more CH groups with nitrogen atoms, and would find three new aromatic heterocycles—pyridazine, pyrimidine, and pyrazine:

There is another way in which we might transform benzene into a heterocycle. Nitrogen has a lone pair of electrons so we could replace a CH=CH unit in benzene by a nitrogen atom; provided that we can use the lone pair in the delocalized system. This means putting it into a p orbital.



We still have the four electrons from the remaining double bonds and, with the two electrons of the lone pair on nitrogen, that makes six in all. The nitrogen atom must still be trigonal with the lone pair in a p orbital so the N–H bond is in the plane of the five-membered ring.

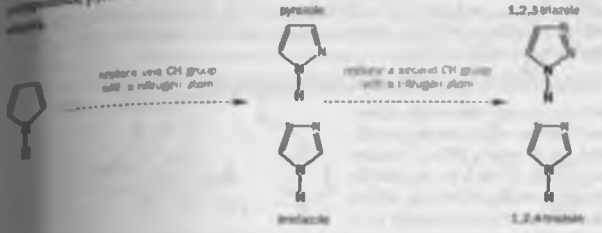


The NMR of pyrrole is slightly less convincing as the two types of proton on the ring resonate at higher field (6.5 and 6.2 p.p.m.) than those of benzene or pyridine but they still fall in the aromatic rather than the alkene region. Pyrrole is also more reactive towards electrophiles than benzene or

One of the most annoying things about heterocyclic chemistry is the mass of what appear to be illogical names. You should not, of course, attempt to learn them all, but a basic idea of how they are designed will help you. We will give you a guide on which names to learn shortly. For the moment accept that 'amine' ends in 'ine' and any heterocyclic compound whose name ends in '-ine' is a nitrogen heterocycle. The syllable 'azo-' also implies nitrogen and 'yl' (usually) implies a six-membered ring, (except in pyrrole!)

pyridine, but it does the usual aromatic substitution reactions (Friedel–Crafts, nitration, halogenation) rather than addition reactions: pyrrole is also aromatic.

Inserting heterocycles by further replacement of CH groups by nitrogen in pyrrole leads to two compounds, pyrazole and imidazole, after one replacement and to two triazoles after two replacements.

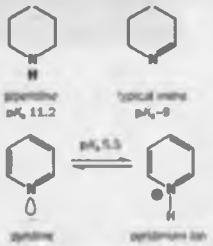


All of these compounds are generally accepted as aromatic too as they broadly have the NMR spectra and reactivities expected for aromatic compounds. As you may expect, introducing heteroatoms into the aromatic ring and, even more, changing the ring size actually affect the chemistry a great deal. We must now return to pyridine and work our way more slowly through the chemistry of these important heterocycles to establish the principles that govern their behaviour.

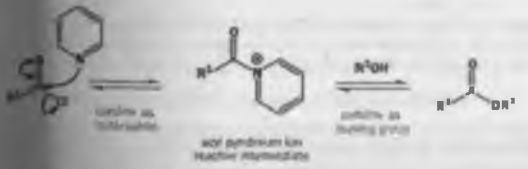
▶ The ending '-ole' is systematic and refers to a five-membered heterocyclic ring. All the five-membered aromatic heterocycles with nitrogen in the ring are sometimes called 'the azoles'. Strictly speaking, pyrrole is 'azole', pyrazole is '1,2-diazole', and imidazole is '1,3-diazole'. These names are not used but oxazole and thiazole are used for the oxygen and sulfur analogues of imidazole.

Pyridine is a very unreactive aromatic imine

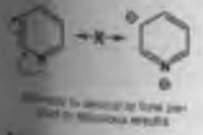
The nitrogen atom in the pyridine ring is planar and trigonal with the lone pair in the plane of the ring. This makes it an imine. Most of the imines you have met before (in Chapter 14, for example), have been unstable intermediates in carbonyl group reactions, but in pyridine we have a stable liquid—stable because of its aromaticity. All imines are more weakly basic than saturated amines and pyridine is a weak base with a pK_a of 5.5. This means that the pyridinium ion as about as strong an acid as a carboxylic acid.



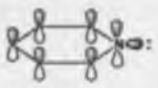
Pyridine is a reasonable nucleophile for carbonyl groups and is often used as a nucleophilic catalyst in acylation reactions. Esters are often made in pyridine solution from alcohols and acid chlorides (the full mechanism is on p. 000 of Chapter 12).



▶ Pyridine is also toxic and has a foul smell—so there are disadvantages in using pyridine as a solvent. But it is cheap and remains a popular solvent in spite of the problems.



Pyridine is nucleophilic at the nitrogen atom because *the lone pair of electrons on nitrogen cannot be delocalized around the ring*. They are in an sp^2 orbital orthogonal to the p orbitals in the ring and there is no interaction between orthogonal orbitals. Try it for yourself, drawing arrows. All attempts to delocalize the electrons lead to impossible results!

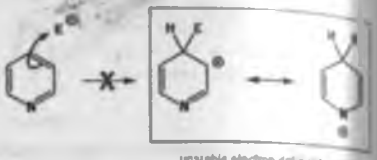


● The lone pair of pyridine's nitrogen atom is not delocalized.

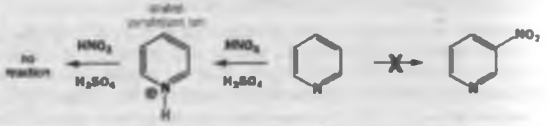
Our main interest must be this: what does the nitrogen atom do to the rest of the ring? The important orbitals—the p orbitals of the aromatic system—are superficially the same as in benzene, but the more electronegative nitrogen atom will lower the energy of all the orbitals. Lower-energy filled orbitals mean a less reactive nucleophile but a lower-energy LUMO means a *more* reactive electrophile. This is a good guide to the chemistry of pyridine. It is less reactive than benzene in electrophilic aromatic substitution reactions but nucleophilic substitution, which is difficult for benzene, comes easily to pyridine.

Pyridine is bad at electrophilic aromatic substitution

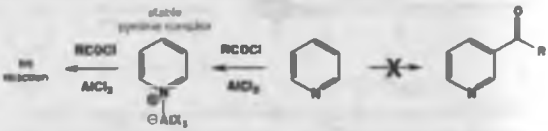
The lower energy of the orbitals of pyridine's π system means that electrophilic attack on the ring is difficult. Another way to look at this is to see that the nitrogen atom destabilizes the cationic would-be intermediate, especially at the 2- and 4-positions.



An equally serious problem is that the nitrogen lone pair is basic and a reasonably good nucleophile—this is the basis for its role as a nucleophilic catalyst in acylations. The normal reagents for electrophilic substitution reactions, such as nitration, are acidic. Treatment of pyridine with the usual mixture of HNO_3 and H_2SO_4 instantly protonates the nitrogen atom. Pyridine itself is not very reactive towards electrophiles: the pyridinium ion is totally unreactive.



Other reactions, such as Friedel–Crafts acylations, require Lewis acids and these too react at nitrogen. Pyridine is a good ligand for metals such as Al(III) or Sn(IV) and, once again, the complex with its cationic nitrogen is completely unreactive towards electrophiles.



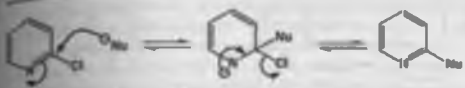
▶ Contrast the unstable electron deficient cationic intermediate with the stable pyridinium ion. The nitrogen lone pair is used to make the pyridinium ion but is not involved in the unstable intermediate. Note that reaction at the 3-position is the best option but still doesn't occur. Reaction at the 2- and 4-positions is worse.

● Pyridine does not undergo electrolytic substitution

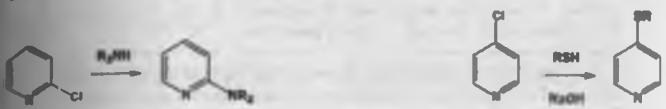
Aromatic electrophilic substitution on pyridine is not a useful reaction. The ring is unreactive and the electrophilic reagents attack nitrogen making the ring even less reactive. Avoid nitration, sulfonation, halogenation, and Friedel–Crafts reactions on simple pyridines.

Nucleophilic substitution is easy with pyridines

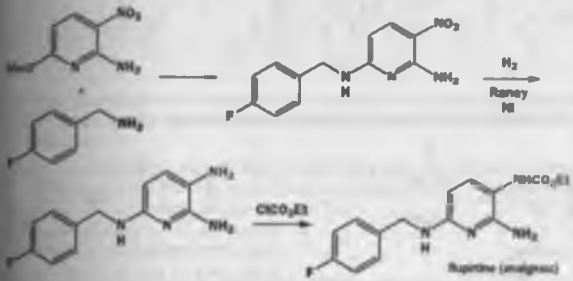
By contrast, the nitrogen atom makes pyridines *more* reactive towards nucleophilic substitution, particularly at the 2- and 4-positions, by lowering the LUMO energy of the π system of pyridine. You can see this effect in action in the ease of replacement of halogens in these positions by nucleophiles.



The intermediate anion is stabilized by electronegative nitrogen and by delocalization round the ring. These reactions have some similarity to nucleophilic aromatic substitution (Chapter 23) but are more similar to carbonyl reactions. The intermediate anion is a tetrahedral intermediate that loses the best leaving group to regenerate the stable aromatic system. Nucleophiles such as amines or thiolate anions work well in these reactions.



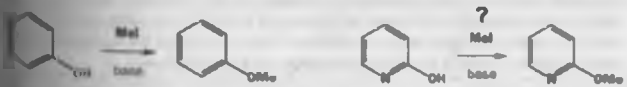
The leaving group does not have to be as good as chloride in these reactions. Continuing the analogy with carbonyl reactions, 2- and 4-chloropyridines are rather like acid chlorides but we need only use less reactive pyridyl ethers, which react like esters, to make amides. The 2- and 4-methoxypyridines allow the completion of the synthesis of flupirtine.



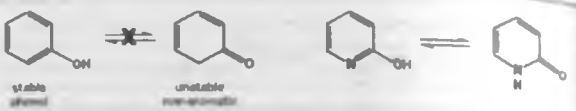
The first step is a nucleophilic aromatic substitution. In the second step the nitro group is reduced to an amino group without any effect on the pyridine ring—another piece of evidence for its aromaticity. Finally, one amino group is acylated in the presence of three others.

Pyridones are good substrates for nucleophilic substitution

The starting materials for these nucleophilic substitutions (2- and 4- chloro or methoxypyridines) are themselves made by nucleophilic substitution on pyridones and we need now to discuss these interesting molecules. If you were asked to propose how 2-methoxypyridine might be made, you would probably suggest, by analogy with the corresponding benzene compound, alkylation of a phenol. Let us look at this in detail.

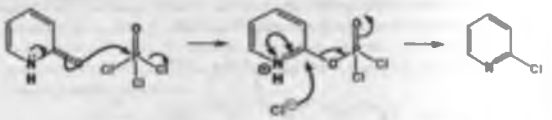


The starting material for this reaction is a 2-hydroxypyridine that can tautomerize to an amide-like structure by the shift of the acidic proton from oxygen to nitrogen. In the phenol series there is no doubt about which structure will be stable as the ketone is not aromatic; for the pyridine both structures are aromatic.



In fact, 2-hydroxypyridine prefers to exist as the 'amide' because that has the advantage of a strong C=O bond and is still aromatic. There are two electrons in each of the C–C double bonds and two also in the lone pair of electrons on the trigonal nitrogen atom of the amide. Delocalization of the lone pair in typical amide style makes the point clearer.

Pyridones are easy to prepare (see Chapter 44) and can be alkylated on oxygen as predicted by their structure. A more important reaction is the direct conversion to chloropyridines with $POCl_3$. The reaction starts by attack of the oxygen atom at phosphorus to create a leaving group, followed by aromatic nucleophilic substitution. The overall effect is very similar to acyl chloride formation from a carboxylic acid.



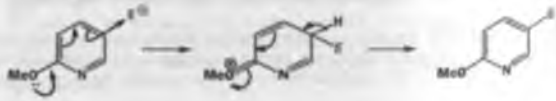
The same reaction occurs with 4-pyridone, which is also delocalized in the same way and exists in the 'amide' form; but not with 3-hydroxypyridine, which exists in the 'phenol' form.

● Pyridines undergo nucleophilic substitution

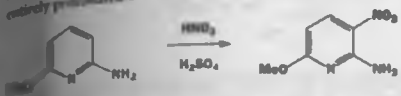
Pyridines can undergo *electrophilic* substitution only if they are activated by electron-donating substituents (see next section) but they readily undergo *nucleophilic* substitution without any activation other than the ring nitrogen atom.

Activated pyridines will do electrophilic aromatic substitution

Useful electrophilic substitutions occur only on pyridines having electron-donating substituents such as NH_2 or OMe. These activate benzene rings too (Chapter 22) but here their help is vital. They supply a nonbonding pair of electrons that becomes the HOMO and carries out the reaction. Simple amino- or methoxypyridines react reasonably well *ortho* and *para* to the activating group. These reactions happen in spite of the molecule being a pyridine, not because of it.

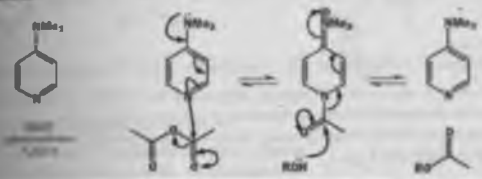


A practical example occurs in the manufacture of the analgesic flupirtine where a doubly activated pyridine having both MeO and NH_2 groups is nitrated just as if it were a benzene ring. The nitro group goes in *ortho* to the amino group and *para* to the methoxy group. This sequence is completed in the next section. The activation is evidently enough to compensate for the molecule being almost entirely protonated under the conditions of the reaction.



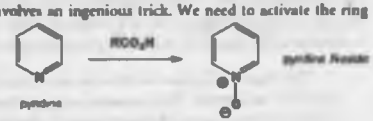
DMAP

One particular amino pyridine has a special role as a more effective acylation catalyst than pyridine itself. This is 4-(dimethylamino)pyridine in which the amino group is primed to increase the nucleophilic nature of the nitrogen atom. Whereas acylations "catalysed" by pyridine are normally carried out in solution in pyridine, only small amounts of DMAP in other solvents are needed to do the same job.

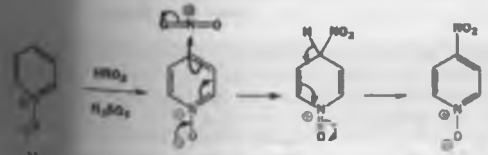


Pyridine *N*-oxides are reactive towards both electrophilic and nucleophilic substitution

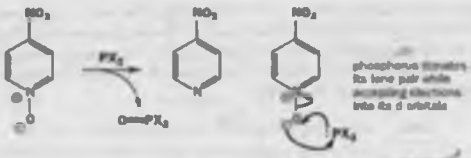
This is all very well if the molecule has such activating groups, but supposing it doesn't? How are we to nitrate pyridine itself? The answer involves an ingenious trick. We need to activate the ring with an electron-rich substituent that can later be removed and we also need to stop the nitrogen atom reacting with the electrophile. All of this can be done with a single reagent.



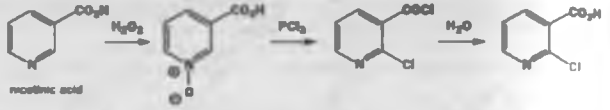
Because the nitrogen atom is nucleophilic, pyridine can be oxidized to pyridine *N*-oxide with reagents such as *m*-CPBA or just H_2O_2 in acetic acid. These *N*-oxides are stable dipolar species with the electrons on oxygen delocalized round the pyridine ring, raising the HOMO of the molecule. Reactions with electrophiles occurs at the 2- ('*ortho*') and 4- ('*para*') positions, chiefly at the 4-position to keep away from positively charged nitrogen.



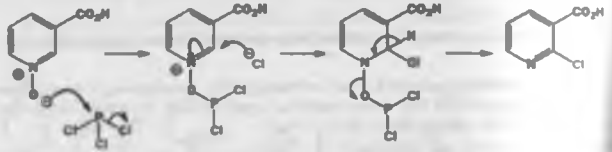
Now the oxide must be removed and this is best done with trivalent phosphorus compounds such as $(MeO)_3P$ or PCl_3. The phosphorus atom detaches the oxygen atom in a single step to form the very stable P=O double bond. In this reaction the phosphorus atom is acting as both a nucleophile and an electrophile, but mainly as an electrophile since PCl_3 is more reactive here than $(MeO)_3P$.



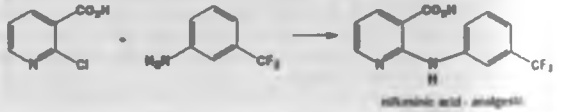
The same activation that allowed simple electrophilic substitution—oxidation to the *N*-oxide—can also allow a useful nucleophilic substitution. The positive nitrogen atom encourages nucleophilic attack and the oxygen atom can be turned into a leaving group with PCl_3. Our example is nicotinic acid whose biological importance we will discuss in Chapter 50.



The *N*-oxide reacts with PCl_3 through oxygen and the chloride ion released in this reaction adds to the most electrophilic position between the two electron-withdrawing groups. Now a simple elimination restores aromaticity and gives a product looking as though it results from chlorination rather than nucleophilic attack.



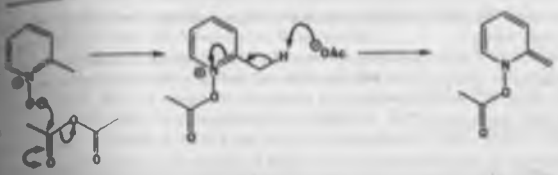
The reagent PCl_3 also converts the carboxylic acid to the acyl chloride, which is hydrolysed back again in the last step. This is a useful sequence because the chlorine atom has been introduced into the 2-position from which it may in turn be displaced by, for example, amines.



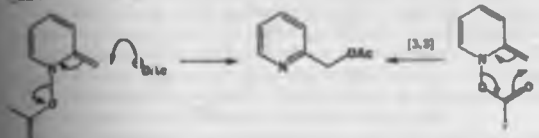
● Pyridine-*N*-oxides

Pyridine *N*-oxides are useful for both electrophilic and nucleophilic substitutions on the same carbon atoms (2-, 4-, and 6-) in the ring.

Nucleophilic addition at an even more distant site is possible on reaction with acid anhydrides if there is an alkyl group in the 2-position. Acylation occurs on oxygen as in the last reaction but now a proton is lost from the side chain to give an uncharged intermediate.



This compound rearranges with migration of the acetate group to the side chain and the restoration of aromaticity. This may be an ionic reaction or a [3,3] sigmatropic rearrangement.



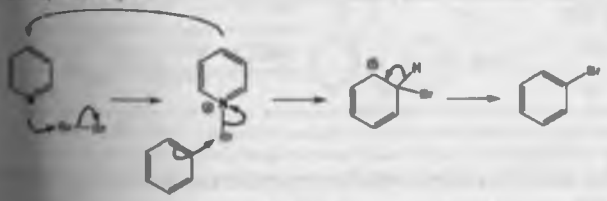
Since pyridine is abundant and cheap and has an extremely rich chemistry, it is not surprising that it has many applications.

Some applications of pyridine chemistry

One of the simplest ways to brominate benzenes is not to bother with the Lewis acid catalysts recommended in Chapter 22 but just to add liquid bromine to the aromatic compound in the presence of a small amount of pyridine. Only about one mole per cent is needed and even then the reaction has to be cooled to stop it getting out of hand.

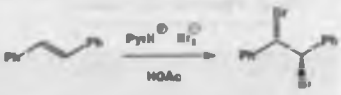
As we have seen, pyridine attacks electrophiles through its nitrogen atom. This produces the reactive species, the *N*-bromo-pyridinium ion, which is attacked by the benzene. Pyridine is a better nucleophile than benzene and a better leaving group than bromide. This is another example of nucleophilic catalysis.

■ Nucleophilic catalysis is discussed on p. 000.



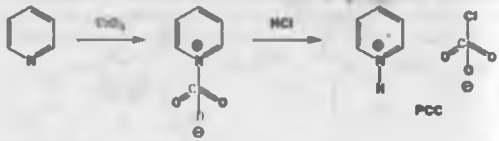
Another way to use pyridine in brominations is to make a stable crystalline compound to replace the dangerous liquid bromine. This compound, known by names such as pyridinium tribromide, is simply a salt of pyridine with the anion Br_3^-. It can be used to brominate reactive compounds such as alkenes (Chapter 20).

Both of these methods depend on the lack of reactivity of pyridine's π system towards electrophiles such as bromine. Notice that, in the first case, both benzene and pyridine are

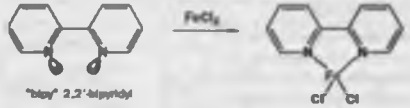


present together. The pyridine attacks bromine only through nitrogen (and reversibly at that) and never through carbon.

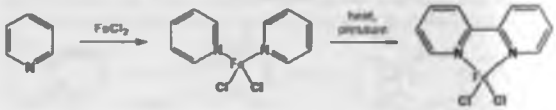
Oxidation of alcohols is normally carried out with Cr(VI) reagents (Chapter 24) but these, like the Jones' reagent ($Na_2Cr_2O_7$ in sulfuric acid), are usually acidic. Some pyridine complexes of Cr(VI) compounds solve this problem by having the pyridinium ion (pK_a 5) as the only acid. The two most famous are 'PDC' (Pyridinium DiChromate) and 'PCC' (Pyridinium Chlorochromate). Pyridine forms a complex with CrO_3 but this is liable to burst into flames. Treatment with HCl gives PCC, which is much less dangerous. PCC is particularly useful in the oxidation of primary alcohols to aldehydes as overoxidation is avoided in the only slightly acidic conditions (Chapter 24).



The ability of pyridine to form metal complexes is greatly enhanced in a dimer—the famous ligand 'bipy' or 2,2'-bipyridyl. It is bidentate and because of its 'bite' it is a good ligand for many transition metals but shows a partiality for Fe(II).

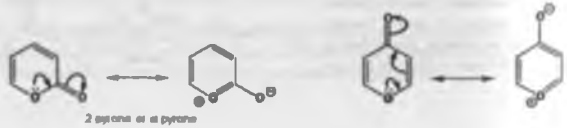


It looks like a rather difficult job to persuade two pyridine rings to join together in this way to form bipy. It is indeed very difficult unless you make things easier by using a reagent that favours the product. And what better than Fe(II) to do the job? ICI manufacture bipy by treating pyridine with $FeCl_2{\cdot}4H_2O$ at high temperatures and high pressures. Only a small proportion of the pyridine is converted to the Fe(II) complex of bipy (about 5%) but the remaining pyridine goes back in the next reaction. This is probably a radical process (Chapter 39) in the coordination sphere of Fe(II).



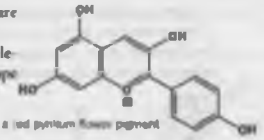
Six-membered aromatic heterocycles can have oxygen in the ring

Though pyridine is overwhelmingly the most important of the six-membered aromatic heterocycles there are oxygen heterocycles, pyrones, that resemble the pyridones. The pyrones are aromatic, though α-pyrone is rather unstable.



The pyrilium salts are stable aromatic cations and are responsible as metal complexes for some flower colours.

Heterocycles with six-membered rings based on other elements (for example, P) do exist but they are outside the scope of this book.



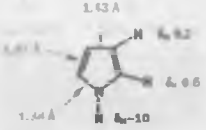
a red pyrilium flower pigment

the pyrilium cation

Five-membered heterocycles are good nucleophiles

but almost everything is the other way round with pyrrole. Electrophilic substitution is much easier than it is with benzene—almost too easy in fact—while nucleophilic substitution is more difficult. Pyrrole is not a base nor can it be converted to an *N*-oxide. We need to find out why this is.

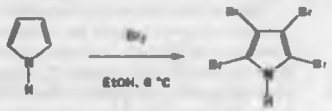
The big difference is that the nitrogen lone pair is delocalized round the ring. The NMR spectrum suggests that all the positions in the ring are about equally electron-rich with chemical shifts about 1 p.p.m. smaller than those of benzene. The ring is flat and the bond lengths are very similar, though the bond opposite the nitrogen atom is a bit longer than the others.



The delocalization of the lone pair can be drawn equally well to any ring atom because of the five-membered ring and we shall soon see the consequences of this. All the delocalization pushes electrons from the nitrogen atom into the ring and we expect the ring to be electron-rich at the expense of the nitrogen atom. The HOMO should go up in energy and the ring become more nucleophilic.

An obvious consequence of this delocalization is the decreased basicity of the nitrogen atom and the increased acidity of the NH group as a whole. In fact, the pK_a of pyrrole acting as a base is about −4 and protonation occurs at carbon. The NH proton can be removed by much weaker bases than those that can remove protons on normal secondary amines.

The nucleophilic nature of the ring means that pyrrole is attacked readily by electrophiles. Reaction with bromine requires no Lewis acid and leads to substitution (confirming the aromaticity of pyrrole) at all four free positions.



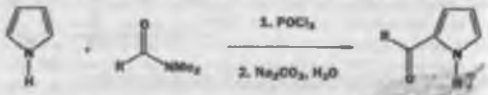
This is a fine reaction in its way, but we don't usually want four bromine atoms in a molecule so one problem with pyrrole is to control the reaction to give only monosubstitution. Another problem is that strong acids cannot be used. Though protonation does not occur at nitrogen, it does occur at carbon and the protonated pyrrole then adds another molecule like this.

reaction continues to give polymer

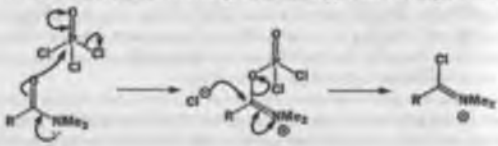
● Pyrrole polymerizes!

Strong acids, those such as H_2SO_4 with a pK_a of less than −4, cannot be used without polymerization of pyrrole.

Some reactions can be controlled to give good yields of monosubstituted products. One is the Vilsmeier reaction in which a combination of an *N,N*-dimethylamide and $POCl_3$ is used to make a carbon electrophile in the absence of strong acid or Lewis acid. It is a substitute for the Friedel–Crafts acylation, and works with aromatic compounds at the more reactive end of the scale (where pyrrole is).



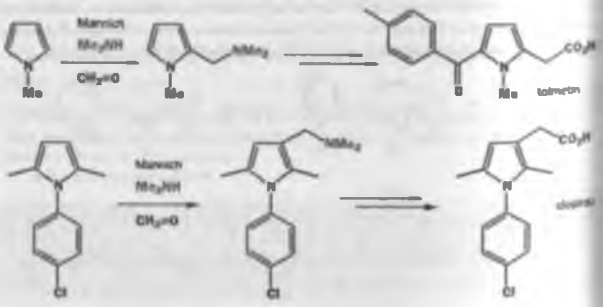
In the first step, the amide reacts with $POCl_3$ which makes off with the amide oxygen atom and replaces it with chlorine. This process would be very unfavourable but for the formation of the strong P–O bond, and is the direct analogy of the chloropyridine-forming reaction you have just seen.



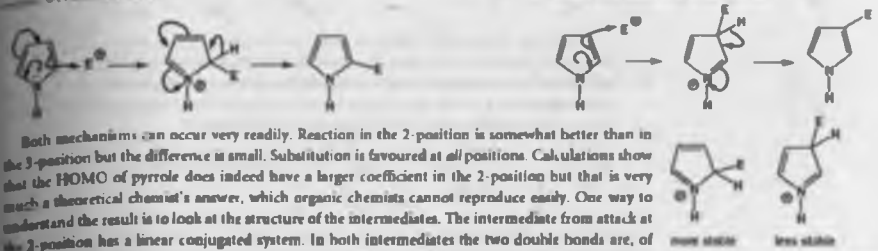
The product from this first step is an iminium cation that reacts with pyrrole to give a more stable iminium salt. The extra stability comes from the conjugation between the pyrrole nitrogen and the iminium group.

The work-up with aqueous Na_2CO_3 hydrolyses the imine salt and removes any acid formed. This method is particularly useful because it works well with Me_2NCHO (DMF) to add a formyl (CHO) group. This is difficult to do with a conventional Friedel–Crafts reaction.

You may have noticed that the reaction occurred only at the 2-position on pyrrole. Though all positions react with reagents like bromine, more selective reagents usually go for the 2- (or 5-) position and attack the 3- (or 4-) position only if the 2- and 5-positions are blocked. A good example is the Mannich reaction (Chapter 27). In these two examples *N*-methylpyrrole reacts cleanly at the 2-position while the other pyrrole with both 2- and 5-positions blocked by methyl groups reacts cleanly at the 3-position. These reactions are used in the manufacture of the non-steroidal anti-inflammatory compounds, tolmetin and clopirac.

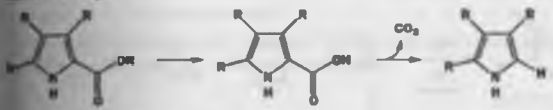


Now we need an explanation. The mechanisms for both 2- and 3-substitutions look good and we will draw both, using a generalized E^+ as the electrophile.



Both mechanisms can occur very readily. Reaction in the 2-position is somewhat better than in the 3-position but the difference is small. Substitution is favoured at *all* positions. Calculations show that the HOMO of pyrrole does indeed have a larger coefficient in the 2-position but that is very much a theoretical chemist's answer, which organic chemists cannot reproduce easily. One way to understand the result is to look at the structure of the intermediates. The intermediate from attack at the 2-position has a linear conjugated system. In both intermediates the two double bonds are, of course, conjugated with each other, but only in the first intermediate are both double bonds conjugated with N^+. The second intermediate is 'cross-conjugated', while the first has a more stable linear conjugated system.

Since electrophilic substitution on pyrroles occurs so easily, it can be useful to block substitution with a removable substituent. This is usually done with an ester group. Hydrolysis of the ester (this is particularly easy with *t*-butyl esters—see Chapter 24) releases the carboxylic acid, which decarboxylates on heating.

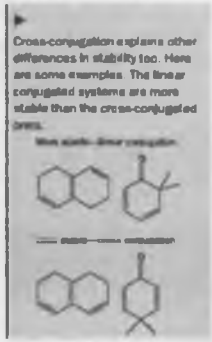


The decarboxylation is a kind of reverse Friedel–Crafts reaction in which the electrophile is a proton (provided by the carboxylic acid itself) and the leaving group is carbon dioxide. The protonation may occur anywhere but it leads to reaction only if it occurs where there is a CO_2H group.

Furan and thiophene are oxygen and sulfur analogues of pyrrole

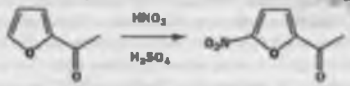
The other simple five-membered heterocycles are furan, with an oxygen atom instead of nitrogen, and thiophene with a sulfur atom. They also undergo electrophilic aromatic substitution very readily, though not so readily as pyrrole. Nitrogen is the most powerful electron donor of the three, oxygen the next, and sulfur the least. Thiophene is very similar to benzene in reactivity.

You may be surprised that thiophene is the least reactive of the three but this is because the p orbital of the lone pair of electrons on sulfur that conjugates with the ring is a 3p orbital rather than the 2p orbital of N or O, so overlap with the 2p orbitals on carbon is less good. Both furan and thiophene undergo more or less normal Friedel–Crafts reactions though the less reactive anhydrides are used instead of acid chlorides, and weaker Lewis acids than $AlCl_3$ are preferred.



Cross-conjugation explains other differences in stability too. Here are some examples. The linear conjugated systems are more stable than the cross-conjugated ones.

Notice that the regioselectivity is the same as it was with pyrrole—the 2-position is more reactive than the 3-position in both cases. The product ketones are less reactive towards electrophiles than the starting heterocycles and deactivated furans can even be nitrated with the usual reagents used for benzene derivatives. Notice that reaction has occurred at the 5-position in spite of the presence of the ketone. The preference for 2- and 5-substitution is quite marked.



So far, thiophenes and furans look much the same as pyrrole but there are other reactions in which they behave quite differently and we shall now concentrate on those.

Electrophilic addition may be preferred to substitution with furan

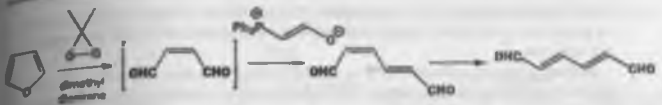
Furan is not very aromatic and if there is the prospect of forming stable bonds such as C–O single bonds by addition, this may be preferred to substitution. A famous example is the reaction of furan with bromine in methanol. In nonhydroxylic solvents, polybromination occurs as expected, but in MeOH no bromine is added at all!

Bromination must start in the usual way, but a molecule of methanol captures the first formed cation in a 1,4-addition to furan.

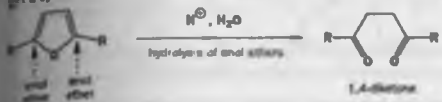
The bromine atom that was originally added is now pushed out by the furan oxygen atom to make a relatively stable conjugated oxonium ion, which adds a second molecule of methanol.

This product conceals an interesting molecule. At each side of the ring we have an acetal, and if we were to hydrolyse the acetals, we would have 'maleic dialdehyde' (*cis*-butenedial)—a molecule that is too unstable to be isolated. The furan derivative may be used in its place.

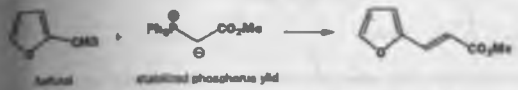
The same 1,4-dialdehyde can be made by oxidizing furan with the mild oxidizing agent dimethyldioxirane, which you met on p. 000. In this sequence, it is trapped in a Wittig reaction to give an *E,E*-diene, which is easily isomerized to *E,E*.



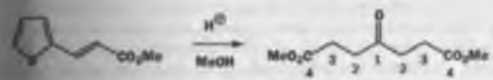
We can extend this idea of furan being the origin of 1,4-dicarbonyl compounds if we consider that furan is, in fact, an enol ether on both sides of the ring. If these enol ethers were hydrolysed we would get a 1,4-diketone.



This time the arrow is solid, not dotted, because this reaction really happens. You will discover in the next chapter that furans can also be made from 1,4-diketones so this whole process is reversible. The example we are choosing has other features worth noting. The cheapest starting material containing a furan is furan-2-aldehyde or 'furfural', a by-product of breakfast cereal manufacture. Here it reacts in a typical Wittig process with a stabilized ylid.

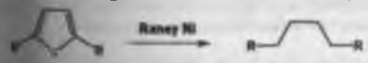


Now comes the interesting step: treatment of this furan with acidic methanol gives a white crystalline compound having two 1,4-dicarbonyl relationships.

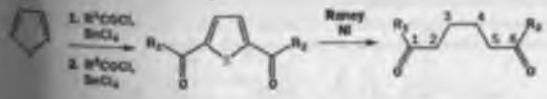


You should try to draw a mechanism for this reaction.

The thiophene ring can also be opened up, but in a very different way. Reductive removal of the sulfur atom with Raney nickel (Chapter 24) reduces not only the C–S bonds but also the double bonds in the ring and we are left with a saturated alkyl chain.

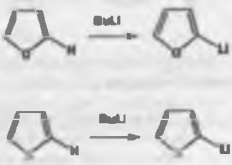


If the reduction follows two Friedel–Crafts reactions on thiophene the product is a 1,6-diketone instead of the 1,4-diketones from furan. Thiophene is well behaved in Friedel–Crafts acylations, and reaction occurs at the 2- and 5-positions unless these are blocked.



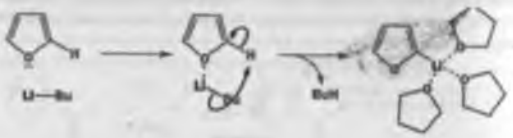
Lithiation of thiophenes and furans

A reaction that furans and thiophenes do particularly well and that fits well with these last two reactions is metallation, particularly lithiation, of a C–H group next to the heteroatom and we will discuss this next. Lithiation of benzene rings (Chapter 9) is carried out by lithium–halogen (Br or I) exchange—a method that works well for heterocycles too as

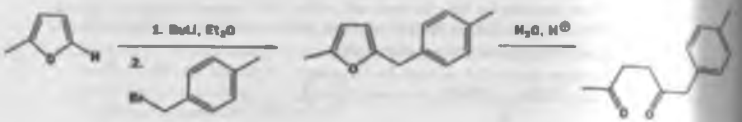


we will see later with pyridine—or by directed ('*ortho*') lithiation of a C–H group next to an activating group such as OMe. With thiophene and furan, the heteroatom in the ring provides the necessary activation.

Activation is by coordination of O or S to Li followed by proton removal by the butyl group so that the by-product is gaseous butane. These lithium compounds have a carbon–lithium bond and are soluble in organic solvents with the coordination sphere of Li completed by THF molecules.



These lithium compounds are very reactive and will combine with most electrophiles—in this example the organolithium is alkylated by a benzylic halide. Treatment with aqueous acid gives the 1,4-diketone by hydrolysis of the two enol ethers.



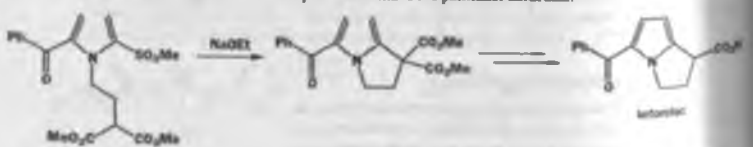
Treatment of this diketone with *anhydrous* acid would cause recyclization to the same furan (see Chapter 44) but it can alternatively be cyclized in base by an intramolecular aldol reaction (Chapter 27) to give a cyclopentenone.

This completes our exploration of chemistry special to thiophene and furan and we now return to all three heterocycles (pyrrole in particular) and look at nucleophilic substitution.

More reactions of five-membered heterocycles

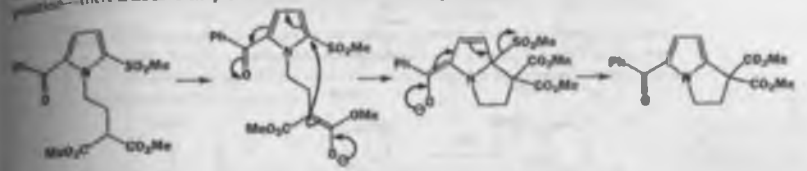
Nucleophilic substitution requires an activating group

Nucleophilic substitution is a relatively rare reaction with pyrrole, thiophene, or furan and requires an activating group such as nitro, carbonyl, or sulfonyl, just as it does with benzene (Chapter 23). Here is an intramolecular example used to make the painkiller ketorolac.



The nucleophile is a stable enolate and the leaving group is a sulfinate anion. An intermediate must be formed in which the negative charge is delocalized on to the carbonyl group on the ring just as you saw in the benzene ring examples in Chapter 23. Attack occurs at the 2-position because the

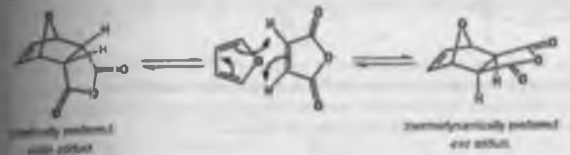
leaving group is there and because the negative charge can be delocalized on to the ketone from that position—there is no inherent preference for attack at the 2- or 5-position.



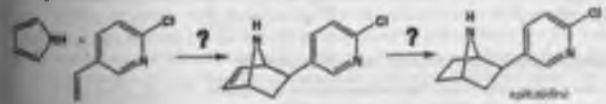
So far, all of the reactions we have discussed have been variations on reactions of benzene. These heterocycles also do reactions totally unlike those of benzene and we are now going to explore two of them.

Five-membered heterocycles act as dienes in Diels–Alder reactions

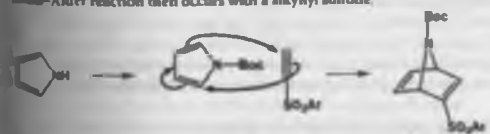
Furan is particularly good at Diels–Alder reactions but it gives the thermodynamic product, the *exo* adduct, because with this aromatic diene the reaction is reversible (Chapter 35).



If pyrrole would do a similar thermodynamically controlled *exo* Diels–Alder reaction with a vinyl pyridine, a short route to the interesting analgesic epibatidine could be imagined, with just a simple reduction of the remaining alkene left to do. The reaction looks promising as the pyridine makes the dienophile electron-deficient and pyrrole is an electron-rich 'diene'.

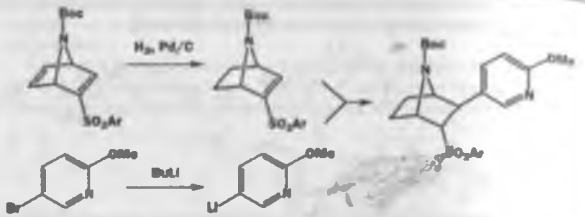


The trouble is that pyrrole will not do this reaction as it is no good at electrophilic substitution. What happens instead is that pyrrole acts as a nucleophile and attacks the electron-deficient alkene. The answer is to make pyrrole less nucleophilic by acylating the nitrogen atom with the famous 'Boc' protecting group (Chapter 24). We will see in the next section how this may be done. A good Diels–Alder reaction then occurs with a alkynyl sulfone.

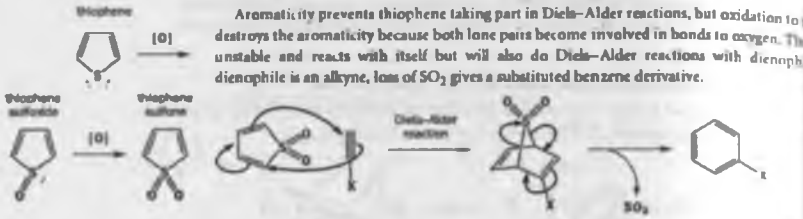


It is then possible to reduce the nonconjugated double bond chemoselectively and add a pyridine nucleophile to the vinyl sulfone. Notice in this step that a lithium derivative can be prepared from a bromopyridine. In general, heterocycles form lithium derivatives rather easily. The skeleton of epibatidine is now complete and you will find some further reactions from the rest of the synthesis in the problems at the end of this chapter.

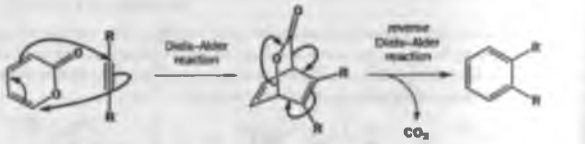
Epibatidine was discovered in the skin of Ecuadorian frogs in 1992. It is an exceptionally powerful analgesic and works by a different mechanism from that of morphine so there is hope that it will not be addictive. The compound can now be synthesized as there is no need to kill the frogs to get it—indeed, they are a protected species.



Aromaticity prevents thiophene taking part in Diels–Alder reactions, but oxidation to the sulfone destroys the aromaticity because both lone pairs become involved in bonds to oxygen. The sulfone is unstable and reacts with itself but will also do Diels–Alder reactions with dienophiles. If the dienophile is an alkyne, loss of SO_2 gives a substituted benzene derivative.



Similar reactions occur with α-pyrones. These are also rather unstable and barely aromatic and they react with alkynes by Diels–Alder reactions followed by reverse Diels–Alder reactions to give benzene derivatives with the loss of CO_2 rather than SO_2.

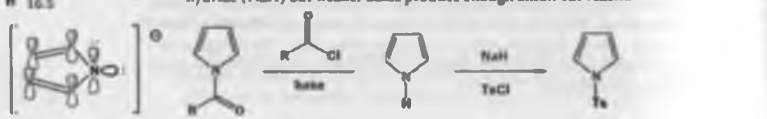


Nitrogen anions can be easily made from pyrrole

Pyrrole is much more acidic than comparable saturated amines. The pK_a of pyrrolidine is about 35, but pyrrole has a pK_a of 16.5 making it some 10^{23} times more acidic! Pyrrole is about as acidic as a typical alcohol so bases stronger than alkoxides will convert it to its anion. We should not be too surprised at this as the corresponding hydrocarbon, cyclopentadiene, is also extremely acidic with a pK_a of 15. The reason is that the anions are aromatic with six delocalized π electrons. The effect is much greater for cyclopentadiene because the hydrocarbon is not aromatic and much less for pyrrole because it is already aromatic and has less to gain.

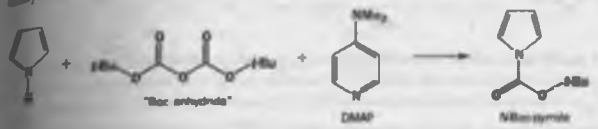
In all of the reactions of pyrrole that we have so far seen, new groups have added to the carbon atoms of the ring. The anion of pyrrole is useful because it reacts at nitrogen. The nitrogen atom has two lone pairs of electrons in the anion: one is delocalized around the ring but the other is localized in an sp^2 orbital on nitrogen. This high-energy pair is the new HOMO and this is where the molecule reacts.

N-acylated derivatives in general can be made in this way. A commonly used base is sodium hydride (NaH) but weaker bases produce enough anion for reaction to occur.



● Anions of pyrroles react with electrophiles at the *nitrogen* atom.

This is how the *N*-Boc pyrrole was made for use in the synthesis of epibatidine. The base used was the pyridine derivative DMAP, which you met earlier in the chapter. It has a pK_{aH} of 9.7 and so provides small, equilibrating amounts of the anion as well as acting as a nucleophilic catalyst. 'Boc anhydride' is used as the acylating agent.

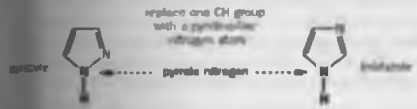


Anion formation is important in the next main section of this chapter, which is about what happens when we insert more nitrogen atoms into the pyrrole ring.

Five-membered rings with two or more nitrogen atoms

Imidazole

At the beginning of this chapter we imagined adding more nitrogen atoms to the pyrrole ring and noticed then that there were two compounds with two nitrogen atoms: pyrazole and imidazole.



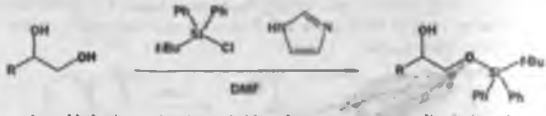
Only one nitrogen atom in a five-membered ring can contribute two electrons to the aromatic sextet. The other replaces a CH group, has no hydrogen, and is like the nitrogen atom in pyridine. The black nitrogens are the pyrrole-like nitrogens; the green ones are pyridine-like. The lone pairs on the black nitrogens are delocalized round the ring; those on the green nitrogens are localized in sp^2 orbitals on nitrogen. We can expect these compounds to have properties intermediate between those of pyrrole and pyridine.

Imidazole is a stronger base than either pyrrole or pyridine—it has a pK_{aH} of almost exactly 7, meaning that it is 50% protonated in neutral water. It is also more acidic than pyrrole, with a pK_a of 14.5.

These curious results are a consequence of the 1,3 relationship between the two nitrogen atoms. Both the (protonated) cation and the (deprotonated) anion share the charge equally between the two nitrogen atoms—they are perfectly symmetrical and unusually stable.

Another way to look at the basicity of imidazole would be to say that both nitrogen atoms can act as base on the proton being attacked. It has to be the pyridine-like nitrogen that actually captures the proton but the pyrrole nitrogen can help by using its delocalized electrons like this.

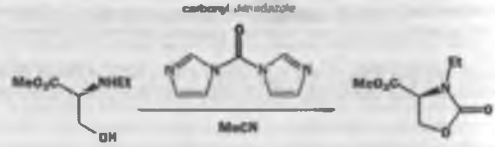
Nature makes use of this property by having imidazole groups attached to proteins in the form of the amino acid histidine and using them as nucleophilic, basic and acidic catalytic groups in enzyme reactions (this will be discussed in Chapters 49 and 50). We use this property in the same way when we add a silyl group to an alcohol. Imidazole is a popular catalyst for these reactions.



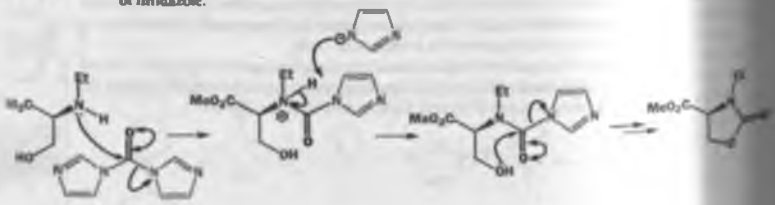
A weakly basic catalyst is needed here because we want to discriminate between the primary and secondary alcohols in the diol. Imidazole is too weak (pK_{aH} 7) to remove protons from an alcohol (pK_a ~ 16) but it can remove a proton after the OH group has attacked the silicon atom.

In fact, the imidazole is also a nucleophilic catalyst of this reaction, and the first step is substitution of Cl by imidazole—that is why the leaving group in the last scheme was shown as 'X'. The reaction starts off like this.

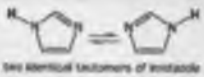
The same idea leads to the use of Carbonyl Diimidazole (CDI) as a double electrophile when we want to link two nucleophiles together by a carbonyl group. Phosgene ($COCl_2$) has been used for this but it is appallingly toxic (it was used in the First World War as a poison gas with dreadful effects). CDI is safer and more controlled. In these reactions imidazole acts (twice) as a leaving group.



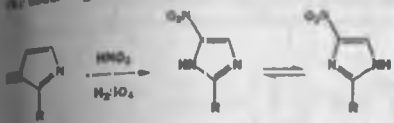
The amino group probably attacks first to displace one imidazole anion, which returns to deprotonate the ammonium salt. The alcohol can then attack intramolecularly displacing the second imidazole anion, which deprotonates the OH group in its turn. The other product is just two molecules of imidazole.



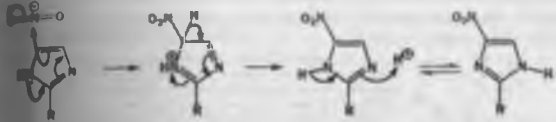
The relationship between the delocalized imidazole anion and imidazole itself is rather like that between an enolate anion and an enol. It will come as no surprise that imidazole tautomerizes rapidly at room temperature in solution. For the parent compound the two tautomers are the same, but with unsymmetrical imidazoles the tautomerism is more interesting. We will explore this question alongside electrophilic aromatic substitution of imidazoles.


two identical tautomers of imidazole

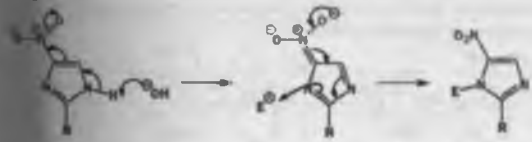
Imidazoles with a substituent between the two nitrogen atoms (position 2) can be nitrated with the usual reagents and the product consists of a mixture of tautomers.



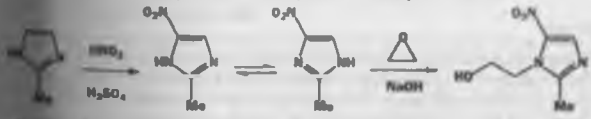
The initial nitration may occur at either of the remaining sites on the ring with the electrons coming from the pyrrole-like nitrogen atom. Tautomerism after nitration gives the mixture.



The tautomerism can be stopped by alkylation at one of the nitrogen atoms. If this is done in basic solution, the anion is an intermediate and the alkyl group adds to the nitrogen atom next to the nitro group. Again, it does not matter from which tautomer the anion is derived—there is only one anion delocalized over both nitrogen atoms and the nitro group. One reason for the formation of this isomer is that it has the linear conjugated system between the pyrrole-like nitrogen and the nitro group (see p. 000).



Important medicinal compounds are made in this way. The antiparasitic metronidazole comes from 2-methyl imidazole by nitration and alkylation with an epoxide in base.

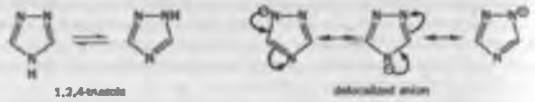


The triazoles

There are two triazoles, and each has one pyrrole-like nitrogen and two pyridine-like nitrogens. Both triazoles have the possibility of tautomerism (in 1,2,3-triazole the tautomers are identical) and both give rise to a single anion.

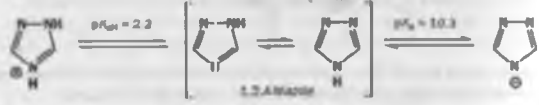

1,2,3-triazole

delocalized anion



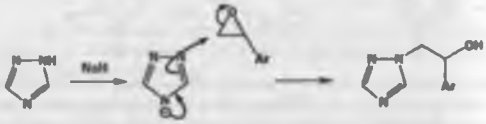
1,2,4-triazole

The 1,2,4-triazole is more important because it is the basis of the best modern agricultural fungicides as well as drugs for fungal diseases in humans. The extra nitrogen atom makes it weaker like pyridine and so more weakly basic, but it increases the acidity so that the anion is now easy to make.

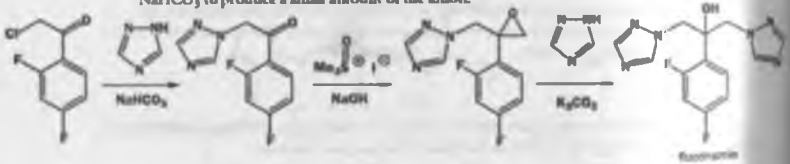


1,2,4-triazole

The fungicides are usually made by the addition of the triazole anion to an epoxide or other carbon electrophile. The anion normally reacts at one of the two linked nitrogen atoms (it does not matter which—the product is the same).

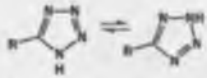


A modern example of an agent used against human fungal infections is Pfizer's fluconazole, which actually contains two triazoles. The first is added as the anion to an α-chloroketone and the second is added to an epoxide made with sulfur ylid chemistry (you will meet this in Chapter 46). Note that weak bases were used to catalyse both of these reactions. Triazole is acidic enough for even $NaHCO_3$ to produce a small amount of the anion.



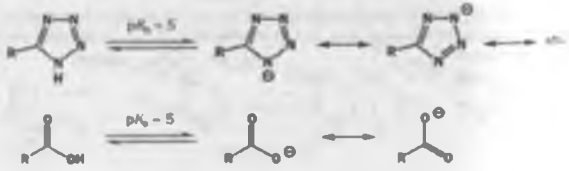
fluconazole

Tetrazole

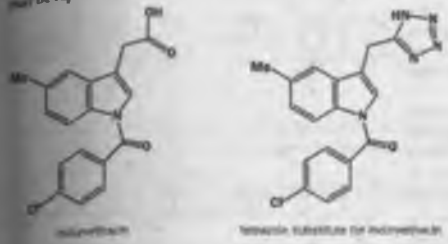


two tautomers of tetrazole

There is only one isomer of tetrazole or of substituted tetrazoles, as there is only one carbon atom in the ring, though there are two tautomers. The main interest in tetrazoles is that they are rather acidic: the pK_a for the loss of the NH proton to form an anion is about 5, essentially the same as that of a carboxylic acid. The anion is delocalized over all four nitrogen atoms (as well as the one carbon atom), and four nitrogen atoms do the work of two oxygen atoms.



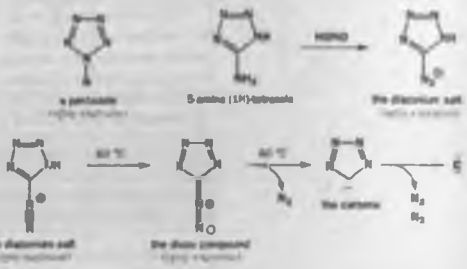
Because tetrazoles have similar acidities to those of carboxylic acids, they have been used in drugs as replacements for the CO_2H unit when the carboxylic acid has unsatisfactory properties for human medicine. A simple example is the anti-arthritis drug indomethacin whose carboxylic acid group may be replaced by a tetrazole with no loss of activity.



indomethacin — tetrazole substitute for indomethacin

Nitrogen atoms and explosions

Compounds with even two or three nitrogen atoms joined together, such as diazomethane (CH_2N_2) or azides (RN_3), are potentially explosive because they can suddenly give off stable gaseous nitrogen. Compounds with more nitrogen atoms, such as tetrazoles, are likely to be more dangerous and few people have attempted to prepare pentazoles. The first is reached with 5-aminotetrazole, with the amazing formula CN_6H_4. It is made by diazotization of 1-aminotetrazole, which first gives a diazonium salt.



The diazonium salt is extremely dangerous. It should be emphasized that [the diazonium salt] is extremely [illegible] and should be handled with great care. We recommend that no more than 0.75 mmol be isolated at one time. Ethereal solutions are somewhat more stable but explosions have occurred after standing at −78 °C for 1 hr. The stash for that, but what about the diazo compound? It is [illegible] unstable and decomposes to a carbene with loss of one molecule of nitrogen and then loses two more to give....

All that is left is a carbon atom and this is one of very few ways to make carbon atoms chemically. The carbon atoms have remarkable reactions and these have been briefly studied, but the hazardous preparation of the starting materials discourages too much research. However, you will see in the next chapter that 1-amino tetrazole is a useful starting material for making an anti-allergic drug.

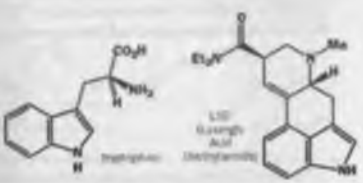
Benzo-fused heterocycles

Indoles are benzo-fused pyrroles

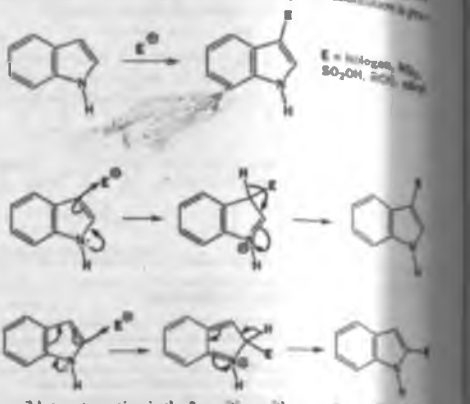
Indomethacin and its tetrazole analogue contain pyrrole rings with benzene rings fused to the side. Such bicyclic heterocyclic structures are called **indoles** and are our next topic. Indole itself has a benzene ring and a pyrrole ring sharing one double bond, or, if you prefer to look at it this way, it is an aromatic system with 10 electrons—eight from four double bonds and the lone pair from the nitrogen atom.

Though the first representation is more accurate, you will often see the second used in books and papers.

Indole is an important heterocyclic system because it is built into proteins in the form of the amino acid tryptophan (Chapter 49). Because it is the basis of important drugs such as indomethacin, and because it provides the skeleton of the indole alkaloids—biologically active compounds from plants including strychnine and LSD (alkaloids are discussed in Chapter 51).



In many ways the chemistry of indole is that of a reactive pyrrole ring with a relatively unreactive benzene ring standing on one side—electrophilic substitution almost always occurs on the pyrrole ring, for example. But indole and pyrrole differ in one important respect. In indole, electrophilic substitution occurs preferred in the 3-position with almost all reagents. Halogenation, nitration, sulfonation, Friedel–Crafts acylation, and alkylation all occur cleanly at that position.



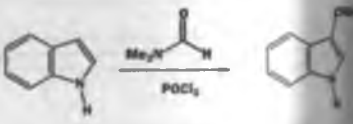
This is, of course, the reverse of what happens with pyrrole. Why should this be? A simple explanation is that reaction at the 3-position simply involves the rather isolated enamine system in the five-membered ring and does not disturb the aromaticity of the benzene ring.

The positive charge in the intermediate is, of course, delocalized round the benzene ring, but it gets its main stabilization from the nitrogen atom. It is not possible to get reaction in the 2-position without seriously disturbing the aromaticity of the benzene ring.

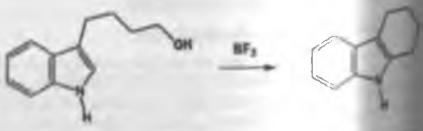
● Electrolytic substitution on pyrrole and indole

Pyrrole reacts with electrophiles at all positions but prefers the 2- and 5-positions, while indole much prefers the 3-position.

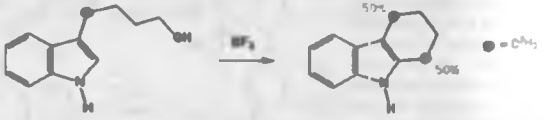
A simple example is the Vilsmeier formylation with DMF and $POCl_3$, showing that indole has similar reactivity, if different regioselectivity, to pyrrole.



If the 3-position is blocked, reaction occurs at the 2-position and this at first seems to suggest that it is all right after all to take the electrons the 'wrong way' round the five-membered ring. This intramolecular Friedel–Crafts alkylation is an example.

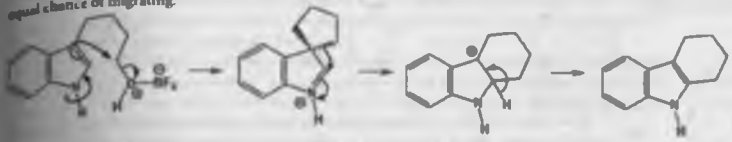


An ingenious experiment showed that this cyclization is not as simple as it seems. If the starting material is labelled with tritium (radioactive ^3H) next to the ring, the product shows exactly 50% of the label where it is expected and 50% where it is not.



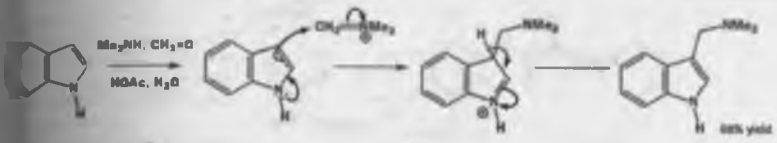
To give this result, the reaction must have a symmetrical intermediate and the obvious candidate

arises from attack at the 3-position. The product is formed from the intermediate *spiro* compound, which has the five-membered ring at right angles to the indole ring—each CH_2 group has an exactly equal chance of migrating.

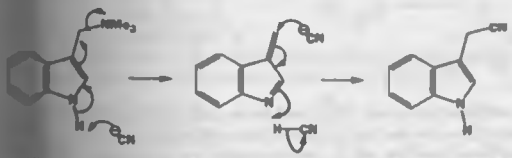


The migration is a pinacol-like rearrangement similar to those in Chapter 37. It is now thought that most substitutions in the 2-position go by this migration route but that some go by direct attack with disruption of the benzene ring.

A good example of indole's 3-position preference is the Mannich reaction, which works as well with indole as it does with pyrrole or furan.



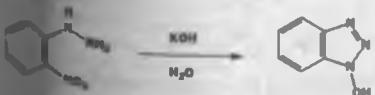
The electron-donating power of the indole and pyrrole nitrogens is never better demonstrated than in the use to which these Mannich bases (the products of the reaction) are put. You may remember that normal Mannich bases can be converted to other compounds by alkylation and substitution (see p. 000). No alkylation is needed here as the indole nitrogen can even expel the Me_2N group when NaCN is around as a base and nucleophile. The reaction is slow and the yield not wonderful but it is amazing that it happens at all. The reaction is even easier with pyrrole derivatives.



All of the five-membered rings we have looked at have their benzo-derivatives but we will concentrate on just one, 1-hydroxybenzotriazole, both because it is an important compound and because we have said little about simple 1,2,3-triazoles.

HOBt is an important reagent in peptide synthesis

1-Hydroxybenzotriazole (HOBt) is a friend in need in the lives of biochemists. It is added to many reactions where an activated ester of one amino acid is combined with the free amino group of another (see Chapter 25 for some examples). It was first made in the nineteenth century by a remarkably simple reaction.



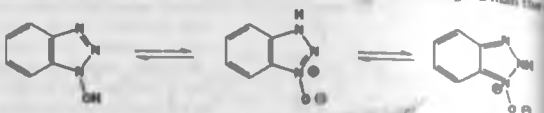
HOBt, 1-hydroxybenzotriazole

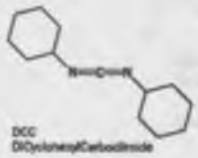
The structure of HOBt appears quite straightforward, except for the unstable N–O single bond, but we can easily draw some other tautomers in which the proton on oxygen—the only one in the

The conclusion of this reaction forms one of the problems at the end of the chapter.

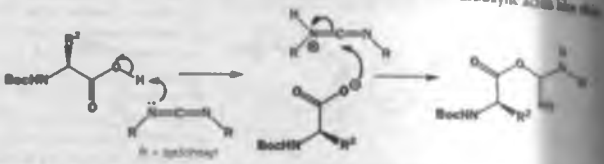
■ You met some nitrone chemistry in Fleather 36.

heterocyclic ring—can be placed on some of the nitrogen atoms. These structures are all [illegible] the second and third are nitrones, and the third structure looks less good than the other two.

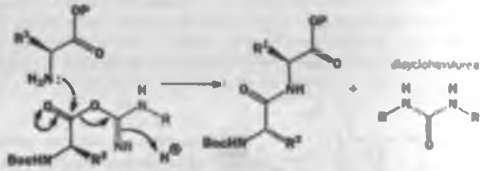




HOBt comes into play when amino acids are being coupled together in the lab. The reaction is an amide formation, but in Chapter 25 we mentioned that amino-acyl chlorides cannot be used to make polypeptides—they are too reactive and they lead to side-reactions. Instead, activated esters (with good RO^- leaving groups) are used, such as the phenyl esters of Chapter 25. It is also common to form the activated ester in the coupling reaction, using a coupling reagent, the most common being 'DCC', dicyclohexylcarbodiimide. DCC reacts with carboxylic acids like this:

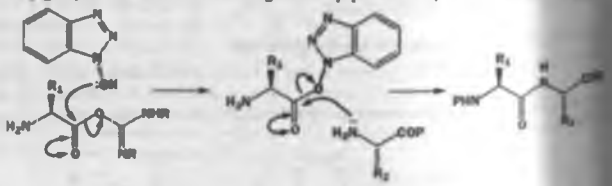


The product ester is activated because substitution with any nucleophile expels this very stable urea as a leaving group.



▶ You saw in Chapter 28 that the most electrophilic carboxylic acid derivatives are also the most enolizable.

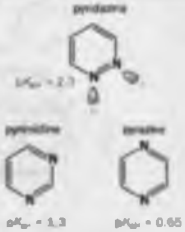
The problem with attacking this ester directly with the amino group of the second amino acid is that some racemization of the active ester is often found. A better method is to have plenty of HOBt around. It intercepts the activated ester first and the new intermediate does not racemize, mainly because the reaction is highly accelerated by the addition of HOBt. The second amino acid, protected on the carboxyl group, attacks the HOBt ester and gives the dipeptide in a very fast reaction without racemization.



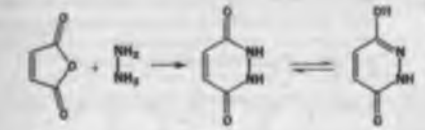
Putting more nitrogen atoms in a six-membered ring

At the beginning of the chapter we mentioned the three six-membered aromatic heterocycles with two nitrogen atoms—pyridazine, pyrimidine, and pyrazine. In these compounds both nitrogen atoms must be of the pyridine sort, with lone pair electrons not delocalized round the ring.

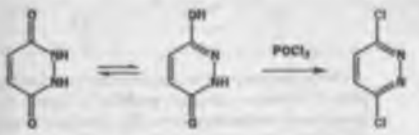
We are going to look at these compounds briefly here. Pyrimidine is more important than either of the others because of its involvement in DNA and RNA—you will find this in Chapter 49. All three compounds are very weak bases—hardly basic at all in fact. Pyridazine is slightly more basic than the other two because the two adjacent lone pairs repel each other and make the molecule more nucleophilic (the α effect again: see p. 000 of Chapter 23).



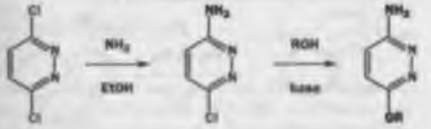
The chemistry of these very electron-deficient rings mostly concerns nucleophilic attack and displacement of leaving groups such as Cl by nucleophiles such as alcohols and amines. To introduce this subject we need to take one heterocyclic synthesis at this point, though these are properly the subject of the next chapter. The compound 'maleic hydrazide' has been known for some time because it is easily formed when hydrazine is acylated twice by maleic anhydride.



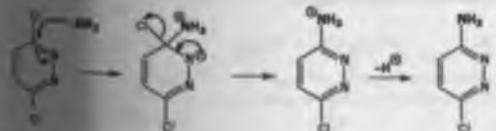
The compound actually prefers to exist as the second tautomer, which is 'more aromatic'. Reaction with $POCl_3$ in the way we have seen for pyridine gives the undoubtedly aromatic pyridazine dichloride.



Now we come to the point. Each of these chlorides can be displaced in turn with an oxygen or nitrogen nucleophile. Only one chloride is displaced in the first reaction, if that is required, and then the second can be displaced with a different nucleophile (see reaction on the right).

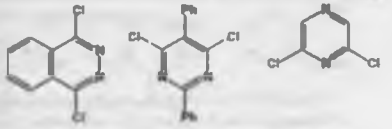


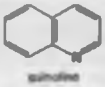
How is this possible? The mechanism of the reactions is addition to the pyridazine ring followed by loss of the leaving group, so the first reaction must go like this.



Notice the second nucleophile attacks it is forced to attack a less electrophilic ring. An electron-withdrawing group (Cl) has been replaced by a strongly electron-donating group (NH_2) so the rate-determining step, the addition of the nucleophile, is slower.

The same principle applies to other easily made symmetrical dichloro derivatives of these rings and their benzo-analogues. The nitrogen atoms can be related 1,2, 1,3, or 1,4 as in the examples alongside. The dark blue are used to link the pyridine-derived ligands required for the Sharpless asymmetric dihydroxylations, which will be described in Chapter 45.




quinoline

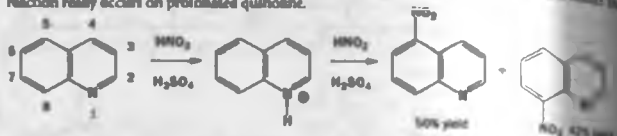

isoquinoline

Fusing rings to pyridines: quinolines and isoquinolines

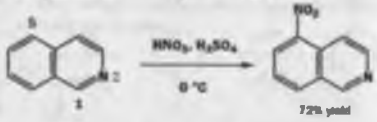
A benzene ring can be fused on to the pyridine ring in two ways giving the important heterocyclic quinoline, with the nitrogen atom next to the benzene ring, and isoquinoline, with the nitrogen atom in the other possible position.

Quinoline forms part of quinine (structure at the head of this chapter) and isoquinoline forms the central skeleton of the isoquinoline alkaloids, which we will discuss at some length in Chapter 51. In this chapter we need not say much about quinoline because it behaves rather as you would expect—its chemistry is a mixture of that of benzene and pyridine. Electrophilic substitution favours the benzene ring and nucleophilic substitution favours the pyridine ring. So nitration of quinoline gives two products—the 5- and 8-nitroquinolines—in about equal quantities (though you will realize that the reaction really occurs on protonated quinoline.

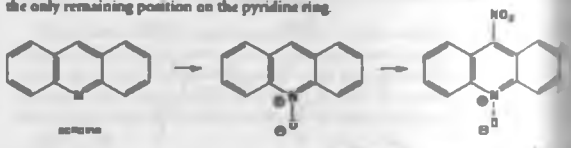
▶ Quinoline numbering, for nomenclature purposes, is shown on this structure.



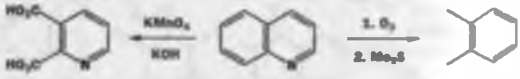
This is obviously rather unsatisfactory but nitration is actually one of the better behaved reactions. Chlorination gives ten products (at least!), of which no fewer than five are chloroquinolines of various structures. The nitration of isoquinoline is rather better behaved, giving 77% of one isomer (5-nitroisoquinoline) at 0 °C.



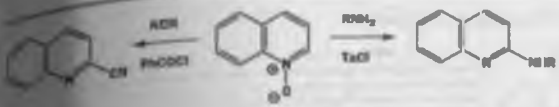
To get reaction on the pyridine ring, the *N*-oxide can be used as with pyridine itself. A good example is acridine, with two benzene rings, which gives four nitration products, all on the benzene rings. Its *N*-oxide, on the other hand, gives just one product in good yield—nitration takes place at the only remaining position on the pyridine ring.



In general, these reactions are of not much use and most substituents are put into quinoline during ring synthesis from simple precursors as we will explain in the next chapter. There are a couple of quinoline reactions that are unusual and interesting. Vigorous oxidation goes for the more electron-rich ring, the benzene ring, and destroys it leaving pyridine rings with carboxyl groups in the 2- and 3-positions.



A particularly interesting nucleophilic substitution occurs when quinoline *N*-oxide is treated with acylating agents in the presence of nucleophiles. These two examples show that nucleophilic substitution occurs in the 2-position and you may compare these reactions with those of pyridine *N*-oxide. The mechanism is similar.



In maintaining quinolines and indoles with their fused rings we kept the benzene and heterocyclic rings separate. Yet there is a way in which they can be combined more intimately, and that is to have a nitrogen atom at a ring junction.

A nitrogen atom can be at a ring junction

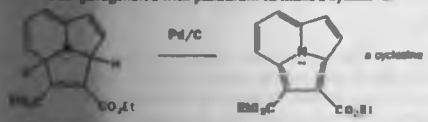
It has to be a pyrrole-type nitrogen as it must have three σ bonds, so the lone pair must be in a p orbital. This means that one of the rings must be five-membered and the simplest member of this interesting class is called **indolizine**—it has pyridine and pyrrole rings fused together along a C–N bond.

indolizine

If you examine this structure you will see that there is definitely a pyrrole ring but that the pyridine ring is not all there. Of course, the lone pair and the π electrons are all delocalized but this system, unlike indole and quinoline, is much better regarded as a ten-electron outer ring than as two six-electron rings joined together.

Indolizine reacts with electrophiles on the five-membered rings by substitution reactions as expected but it has one special reaction that leads dramatically to a more complex aromatic system. It does a cycloaddition with diethyl acetylenedicarboxylate to give a tricyclic molecule.

The dienophile is the usual sort of unsaturated carbonyl compound—but count the electrons used from the indolizine. The nitrogen lone pair is not used but all the other eight are, so this is a most unusual [2 + 8] cycloaddition. The first formed product is not aromatic (it is not fully conjugated) but it can be dehydrogenated with palladium to make a cyclazine.



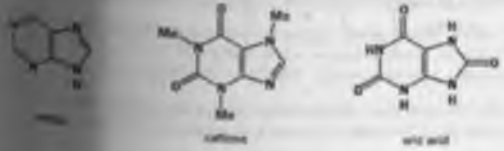
a cyclazine

Now count the electrons in the cyclazine—there are ten electrons round the outer edge and the nitrogen lone pair is not part of the aromatic system. Cyclazines have NMR spectra and reactions that suggest they are aromatic.

▶ Notice that this is the reverse of a hydrogenation: the catalyst is the same but H_2 is lost, not gained.

Fused rings with more than one nitrogen

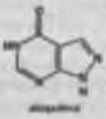
It is easily possible to continue to insert nitrogen atoms into fused ring systems and some important compounds belong to these groups. The purines are part of DNA and RNA and are treated in Chapter 29, but simple purines play an important part in our lives. Coffee and tea owe their stimulant properties to caffeine, a simple trimethyl purine derivative. It has an imidazole ring fused to a pyrimidine ring and is aromatic in spite of the two carbonyl groups.



caffeine

uric acid

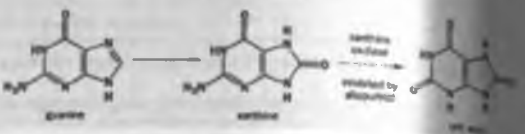
Uric acid, gout, and allopurinol



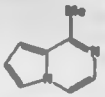
allopurinol

Another purine, uric acid, occurs widely in nature—it is used by birds, and to some extent by humans, as a way to excrete excess nitrogen—but it causes much distress in humans when crystalline uric acid is deposited in joints. We call the pain 'gout' and it isn't funny. The solution to a specific inhibitor of the enzyme producing uric acid ... and it is no surprise that a compound closely resembling uric acid, allopurinol, is the best ...

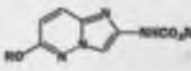
Two of the carbonyl groups have gone and the nitrogen ring has been replaced by a pyrazole ring. Purines like DNA are degraded in the body to ammonia, which is oxidized to uric acid. Allopurinol binds to the enzyme xanthine oxidase but inactivates it by not releasing, even a competing substrate. This enzyme plays a central part in human metabolism so inhibiting it is not ... but prevents overproduction of uric acid.



guanine xanthine uric acid



smell of roast meat



useful medicinal compounds

Other fused heterocycles have very attractive flavour and odour properties. Pyrazines, as ... are important in many strong food flavours: a fused pyrazine with a ring junction nitrogen ... one of the most important components in the smell of roast meat. You can read about the ... pyrazine that provides green peppers with their flavour in the Box on the next page.

Finally, the compounds in the margin form a medicinally important group of ... which includes antitumour compounds for humans and anthelmintics (compounds that get rid of ... worms) for animals. They are derived from a 6/5 fused aromatic ring system that resembles the ... electron system of the indolizine ring system but has three nitrogen atoms.

All this multiple heteroatom insertion is possible only with nitrogen and we need to look briefly at what happens when we combine nitrogen with oxygen or in heterocycles.

Heterocycles can have many nitrogens but only one sulfur or oxygen in any ring

oxazole

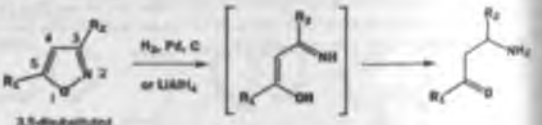
thiazole

isoxazole

isothiazole

A neutral oxygen or sulfur atom can have only two bonds and so it can never be like the nitrogen atom in pyridine—it can only be like the nitrogen atom in pyrrole. We can put as many ... nitrogens as we like in an aromatic ring, but never more than one pyrrole-like nitrogen. ... can put only one oxygen or sulfur atom in an aromatic ring. The simplest examples are ... thiazoles and their less stable isomers.

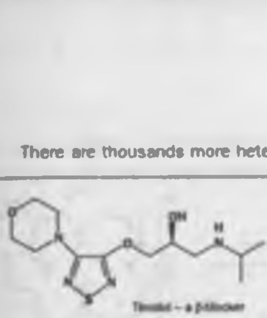
The instability of the 'iso-' compounds comes from the weak O–N or S–N bond. These bonds can be cleaved by reducing agents, which then usually reduce the remaining functional group ... The first product from reduction of the N–O bond is an unstable imino-enol. The enol tautomerizes to the ketone and the imine may be reduced further to the amine. We used this sort of chemistry on the products of 1,3-dipolar cycloadditions in Chapter 35 and isoxazoles are usually formed in such reactions.



3,5-disubstituted isoxazole

Such heterocycles with even more nitrogen atoms exist but are relatively ... and we shall mention just one, the 1,2,5-thiadiazole, because it is part of a useful drug, timolol.

1,2,5-thiadiazole



Timolol – a β-blocker

Timolol is a β-blocker that blocks the action of adrenaline (epinephrine) and keeps heart disease at bay by counteracting high blood pressure.

The flavour of green peppers

[illegible] spectroscopy we shall describe the discovery of the compound [illegible] for the flavour of green peppers. This powerful compound was [illegible] from the oil of the green pepper (*Capsicum annuum* var. *grossum*) [illegible] about 0.0001% of the mass of the peppers and the main [illegible] comes from one compound which is 30% of the oil. It had an [illegible] ion at 166 and looks like a compound without nitrogen [illegible] $C_{11}H_{18}O$. But a high-resolution mass spectrum revealed that M^+ [illegible] 166.1102 which corresponds almost exactly to $C_9H_{14}N_2O$ [illegible]

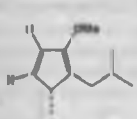
[illegible] OH, NH, or C=O peaks, and the proton NMR [illegible]

δ_H, p.p.m.	Integral	Shape	J, Hz	Comments
[illegible]	6H	d	6.7	Me_2CH-
[illegible]	1H	m	?	
[illegible]	2H	d	7.0	CH_2CH-
[illegible]	3H	s	—	-OMe?
[illegible]	1H	d	2.4	aromatic
[illegible]	1H	d	2.4	aromatic

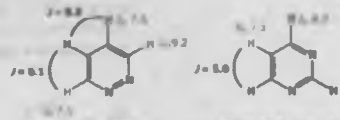
[illegible] in the Me_2CH and CH_2CH [illegible] same CH and it must be [illegible] 1.1–2.4 p.p.m. described as a [illegible] the only one showing [illegible] it will be a septuplet of [illegible] 21 lines. We can easily [illegible] part of the molecule because it has two methyl groups and a CH_2 [illegible] to the same CH group.

[illegible] of green pepper flavour compound

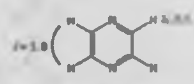
[illegible] group (only oxygen is [illegible] enough) to take a methyl group to [illegible] adds up to $C_9H_{17}O$. What is [illegible]—and no clue yet as to the [illegible]. We also have an aromatic ring [illegible] in it (because there are only [illegible] enough for a benzene ring!) [illegible] constant between the two aromatic hydrogens is 2.4 Hz. So [illegible] a pyrrole ring? Well, no, and for two reasons. If we try and [illegible], we can't fit in the last nitrogen! If we put it on the end [illegible] it would have to be an NH_2 group, and there isn't one.



A better reason is that the chemical shifts are all wrong. The protons on an electron-rich pyrrole ring come at around 6–6.5 p.p.m., upfield from benzene (7.27 p.p.m.). But these protons are at 7.8–8.0 p.p.m., downfield from benzene. We have a deshielded (electron-poor) ring, not a shielded (electron-rich) ring. From what you now know of heterocyclic chemistry, the ring must be a six-membered one, and we must put both nitrogen atoms in the ring. There are three ways to do this.



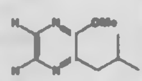
pyridazine (1,2-nitrogens) pyrimidine (1,3-nitrogens)



pyrazine (1,4-nitrogens)

The small coupling constant really fits the pyrazine alone and the chemical shifts are about right for that molecule too, though not as far downfield. But we have a MeO group on the ring feeding electrons into the aromatic system and that will increase the shielding slightly and move the protons upfield. This gives us a unique structure.

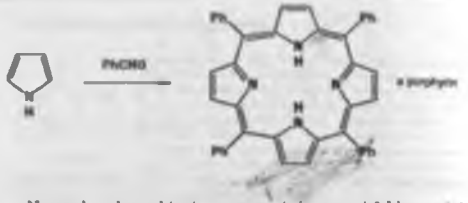
correct structure of the main flavour compound from green peppers



There is only one way to be sure and that is to make this compound and see if it is the same as the natural product in all respects including biological activity. The investigators did this but then wished that they hadn't! The structure was indeed correct but the biological activity—the smell of green peppers—was so intense that they had to seal up the laboratory where the work was done as no one would work there. Human beings can detect 2 parts in 10^{12} of this compound in water.

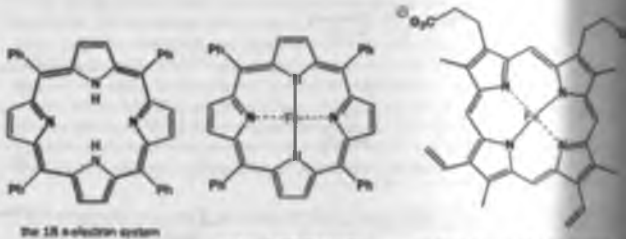
There are thousands more heterocycles out there

[illegible] going to discuss them and we hope you're grateful. In fact, it's about time to stop, [illegible] you with a hint of the complexity that is possible. If pyrrole is combined [illegible] a good yield of a highly coloured crystalline compound is formed. This is a [illegible]

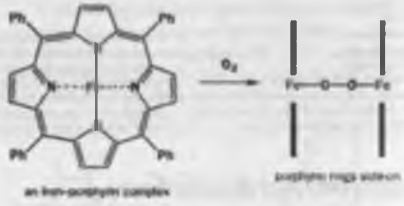


Now, what about this ring system—is it aromatic? It's certainly highly delocalized and [illegible] answer to the question clearly depends on whether you include the nitrogen electrons or not. To [illegible] if you ignore the pyrrole-like nitrogen atoms but include the pyridine-like nitrogens and [illegible] round the periphery, you have nine double bonds and hence 18 electrons—a 4n + 2 number. Most people agree that these compounds are aromatic.

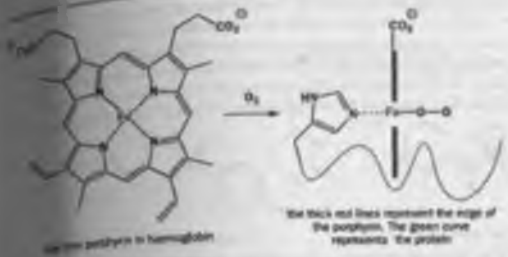
They are also more than curiosities. The space in the middle with the four inward-pointing nitrogen atoms is just right for complex formation with divalent metals such as Fe(II). With other varied substituents, this structure forms the reactive part of haemoglobin, and the iron atom in the middle transports the oxygen in blood.



Iron prefers to be octahedral with six bonds around it and in one of these spare places in haemoglobin that is occupied by oxygen. If you try and make an oxygen complex of the [illegible] porphyrin with four phenyl groups around the edge you get a sandwich dimer that [illegible] itself.



The porphyrin in blood avoids this problem by having another heterocycle to [illegible] Haemoglobin consists of the flat porphyrin bound to a protein by coordination between an imidazole in the protein (a histidine residue: see Chapter 49) and the iron atom. This leaves one face free to bind oxygen and makes the molecule far too big to dimerize.



Iron–porphyrin to haemoglobin

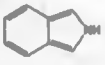
The thick red lines represent the edge of the porphyrin. The green curve represents the protein

Iron–metal complexes are strongly coloured—the iron complex is literally blood red. Some related compounds provide the familiar blue and green pigments used to colour plastic shopping bags. These are the phthalocyanine–metal complexes, which provide intense pigments in these ranges. The basic ring system resembles a porphyrin.

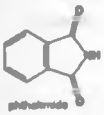
a simple phthalocyanine

a phthalocyanine–copper complex

The differences are the four extra nitrogen atoms between the rings and the fused benzene rings. These compounds are derivatives of phthalimide, an isoindole derivative that has a nonaromatic five-membered ring. The metal most commonly used with phthalocyanines is Cu(II), and the range of colours is achieved by halogenating the benzene rings. The biggest producer is ICI at Grangemouth in Scotland where they do the halogenation and the phthalocyanine formation to make their range of Procyon™ dyes.

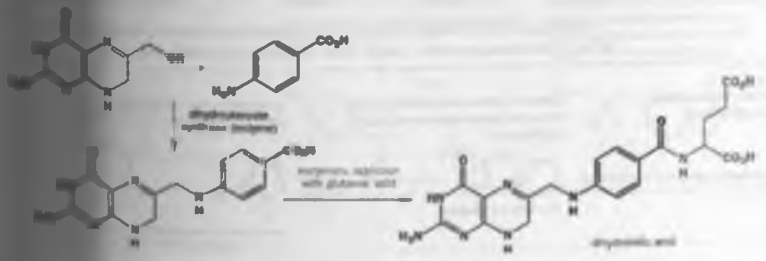


unstable isoindole



phthalimide

Some heterocycles are simple, some very complex, but we cannot live without them. We shall end this chapter with a wonderful story of heterocyclic chemistry at work. Folic acid is much in the news today as a vitamin that is particularly important for pregnant mothers, but that is involved in the metabolism of all living things. Folic acid is built up in nature from three pieces: a heterocyclic starting material (red), *p*-aminobenzoic acid (black) and the amino acid glutamic acid (brown). Here you see the precursor, dihydrofolic acid.

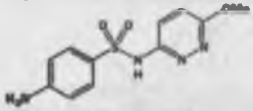


dihydropteroate synthase (enzyme)

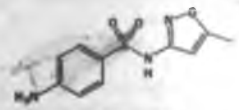
enzyme, reaction with glutamic acid

dihydrofolic acid

Although folic acid is vital for human health, we don't have the enzymes to make it, it's a vitamin, which means we must take it in our diet or we die. Bacteria, on the other hand, do make folic acid. This is very useful, because it means that if we inhibit the enzymes of folic acid synthesis we can kill bacteria but we cannot possibly harm ourselves as we don't have those enzymes. The sulfa drugs, such as sulfamethoxypyridazine or sulfamethoxazole, imitate *p*-aminobenzoic acid and inhibit the enzyme dihydropteroate synthase. Each has a new heterocyclic system added to the sulfonamide part of the drug.

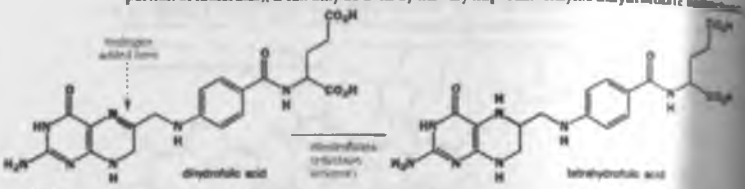


sulfamethoxypyridazine



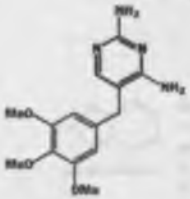
sulfamethoxazole

The next step in folic acid synthesis is the reduction of dihydrofolate to tetrahydrofolate. This can be done by both humans and bacteria and, although it looks like a rather trivial reaction (see blue portion of molecules), it can only be done by the very important enzyme dihydrofolate reductase.



dihydrofolic acid

tetrahydrofolic acid



trimethoprim

Though both bacteria and humans have this enzyme, the bacterial version is different enough for us to attack it with specific drugs. An example is trimethoprim—yet another heterocyclic compound with a pyrimidine core (black on diagram). These two types of drugs that attack the folic acid metabolism of bacteria are often used together.

We will see in the next chapter how to make these heterocyclic systems and, in Chapters 49–51, other examples of how important they are in living things.

Which heterocyclic structures should you learn?

This is, of course, mainly a matter of personal choice. Every chemist really must know the names of the simplest heterocycles and we give those below along with a menu of suggestions.

First of all, those every chemist must know:

pyridine

pyrrole

thiophene

furan

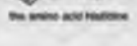
Now the table gives a suggested list of five ring systems that have important roles in the chemistry of life and in human medicine—many drugs are based on these five structures.

1 imidazole

the most important five-membered ring with two nitrogen atoms

imidazole

part of the amino acid histidine, occurs in proteins and is important in enzyme mechanisms



the amino acid histidine

a substituted imidazole is an essential part of the antiulcer drug cimetidine

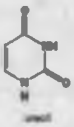
the antiulcer drug cimetidine (Tagamet), a selective histidine mimic

2 Pyrimidine

the most important aromatic ring with two nitrogen atoms

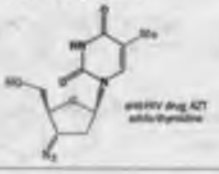
pyrimidine

three functionalized pyrimidines are part of DNA and RNA structure, e.g. uracil



uracil

many antiviral drugs, particularly anti-HIV drugs, are modified pieces of DNA and contain pyrimidines



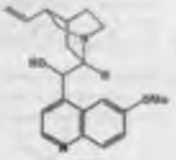
anti-HIV drug AZT
azido-thymidine

4 Quinoline

one of two benzo-pyridines with many applications

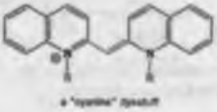
quinoline

occurs naturally in the important antimalarial drug quinine



quinine

'cyanine' dyestuffs used as sensitizers for particular light wavelengths in colour photography



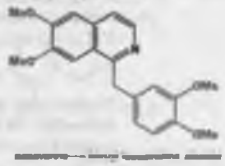
a "cyanine" dyestuff

5 Isoquinoline

the other benzo-pyridine with many applications

isoquinoline

occurs naturally in the benzyl isoquinoline alkaloids like papaverine



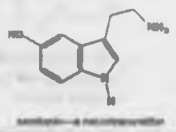
papaverine — a weak vasodilator, smooth

3 Indole

the most important benzo-pyrrole

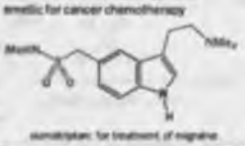
indole

occurs in proteins as tryptophan and in the brain as the neurotransmitter serotonin (5-hydroxy-tryptamine)



serotonin—a neurotransmitter

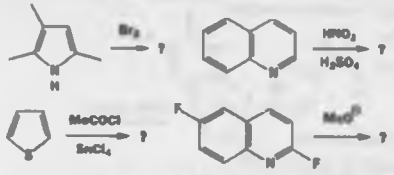
important modern drugs are based on serotonin including sumatriptan for migraine and ondansetron, an anti-emetic for cancer chemotherapy



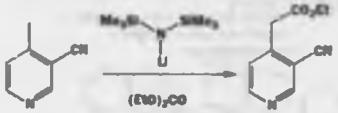
sumatriptan, for treatment of migraine

Problems

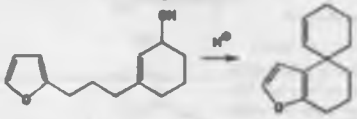
1. For each of the following reactions: (a) state what kind of substitution it suggests; (b) suggest what product might be formed if monosubstitution occurs.



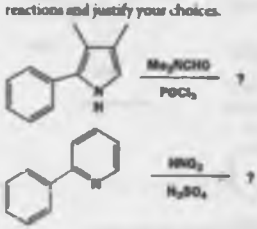
2. Give a mechanism for this side-chain extension of a pyridine.



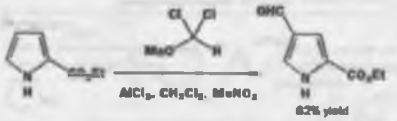
3. Give a mechanism for this reaction, commenting on the position on the furan ring that reacts.



4. Suggest which product might be formed in each of these reactions and justify your choices.

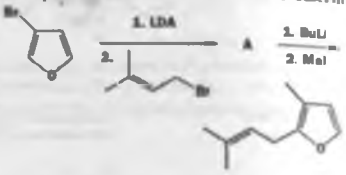


5. Comment on the mechanism and selectivity of this reaction of a pyrrole.

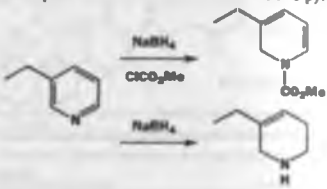


6. Explain the formation of the product in this Friedel–Crafts alkylation of an indole.

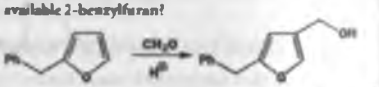
7. Explain the order of events and choice of bases in this sequence.



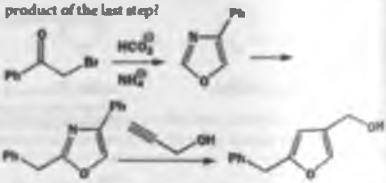
8. Explain the difference between these two pyridine reductions.



9. Why can this furan not be made by the direct route from available 2-benzylfuran?

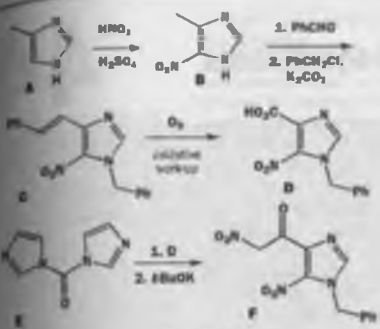


The same furan can be made by the route described below. Suggest mechanisms for the first and the last step. What is the other product of the last step?



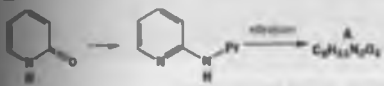
10. What aromatic system might be based on the skeleton given below? What sort of reactivity might it display?

11. The reactions outlined in the chart below describe the early steps in a synthesis of an antiviral drug by the Parke–Davis company.



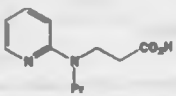
Consider how the reactivity of imidazoles is illustrated in these reactions, which involve not only the skeleton of the molecule but also the reagent E. You will need to draw mechanisms for the reactions and explain how they are influenced by the heterocycles.

12. Suggest how 2-pyridone might be converted into the amine shown. This amine undergoes mononitration to give compound A with the NMR spectrum given. What is the structure of A? Why is this isomer formed?

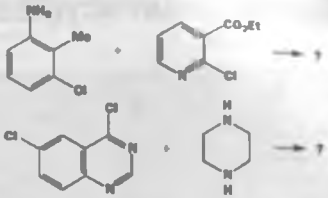


δ_H 1.0 p.p.m. (3H, t, *J* 7 Hz), 1.7 p.p.m. (2H, sextet, *J* 7 Hz), 3.3 p.p.m. (2H, q, *J* 7 Hz), 5.9 p.p.m. (1H, broad s), 6.4 p.p.m. (1H, d, *J* 8 Hz), 8.1 p.p.m. (1H, d, *J* 2 Hz), and 8.9 p.p.m. (1H, d, *J* 2 Hz).

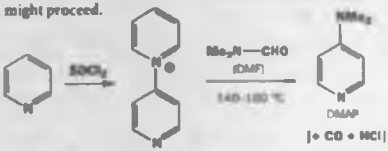
Compound A was needed for conversion into the potential enzyme inhibitor below. How might this be achieved?



13. Suggest what the products of these nucleophilic substitutions might be.



14. The synthesis of DMAP, the useful acylation catalyst mentioned in Chapters 8 and 12, is carried out by initial attack of thionyl chloride ($SOCl_2$) on pyridine. Suggest how the reactions might proceed.



Aromatic heterocycles 2: synthesis

44

Connections

Building on:

- Aromaticity ch7
- Enols and enolates ch21
- The aldol reaction ch27
- Acylation of enolates ch28
- Michael additions of enolates ch29
- Retrosynthetic analysis ch30
- Cycloadditions ch35
- Reactions of heterocycles ch43

Arriving at:

- Thermodynamics is on our side
- Disconnecting the carbon–heteroatom bonds first
- How to make pyrroles, thiophenes, and furans from 1,4-dicarbonyl compounds
- How to make pyridines and pyridones
- How to make pyridazines and pyrazoles
- How to make pyrimidines from 1,3-dicarbonyl compounds and amidines
- How to make thiazoles
- How to make isoxazoles and tetrazoles by 1,3-dipolar cycloadditions
- The Fischer indole synthesis
- Making drugs: Viagra, sumatriptan, ondansetron, indomethacin
- How to make quinolines and isoquinolines

Looking forward to:

- Biological chemistry ch49–ch52

In this chapter you will revisit the heterocyclic systems you have just met and find out how to make them. You'll also meet some new heterocyclic systems and find out how to make those. With so many heterocycles to consider, you'd be forgiven for feeling rather daunted by this prospect, but do not be alarmed. Making heterocycles is easy—that's precisely why there are so many of them. Just reflect . . .

- Making C–O, C–N, and C–S bonds is easy
- Intramolecular reactions are preferred to bimolecular reactions
- Forming five- and six-membered rings is easy
- We are talking about aromatic, that is, very stable molecules

If we are to use those bullet points to our advantage we must think strategy before we start. When we were making benzene compounds we usually started with a preformed simple benzene derivative—toluene, phenol, aniline—and added side chains by electrophilic substitution. In this chapter our strategy will usually be to build the heterocyclic ring with most of its substituents already in place and add just a few others, perhaps by electrophilic substitution, but mostly by nucleophilic substitution.

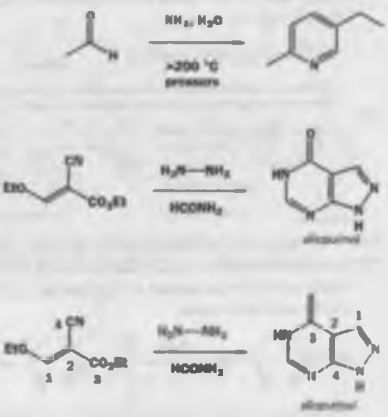
We will usually make the rings by cyclization reactions with the heteroatom (O, N, S) as a nucleophile and a suitably functionalized carbon atom as the electrophile. This electrophile will almost always be a carbonyl compound of some sort and this chapter will help you revise your carbonyl chemistry from Chapters 6, 12, 14, 21, 23, and 26–29 as well as the approach to synthesis described in Chapter 30.

Thermodynamics is on our side

Some of the syntheses we will meet will be quite surprisingly simple! It sometimes seems that we can just mix a few things together with about the right number of atoms and let thermodynamics do the rest. A commercial synthesis of pyridines combines acetaldehyde and

ammonia under pressure to give a simple pyridine.

The yield is only about 50%, but what does that matter in such a simple process? By counting atoms we can guess that four molecules of aldehyde and one of ammonia react, but exactly how is a triumph of thermodynamics over mechanism. Much more complex molecules can sometimes be made very easily too. Take allopurinol, for example. One synthesis of this gout remedy goes like this.



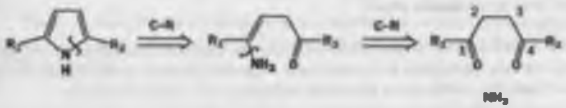
It is not too difficult to work out where the atoms go—the hydrazine obviously gives rise to the pair of adjacent nitrogen atoms in the pyrazole ring and the ester group must be the origin of the carbonyl group (see colours and numbers on the right)—but would you have planned this synthesis?

We will see that this sort of 'witch's brew' approach to synthesis is restricted to a few basic ring systems and that, in general, careful planning is just as important here as elsewhere. The difference here is that heterocyclic synthesis is very forgiving—it often 'goes right' instead of going wrong. We'll now look seriously at planning the synthesis of aromatic heterocycles.

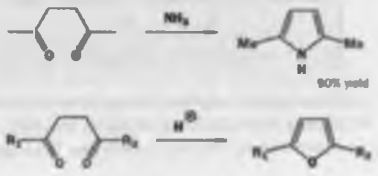
Disconnect the carbon–heteroatom bonds first

The simplest synthesis for a heterocycle emerges when we remove the heteroatom and see what electrophile we need. We shall use pyrroles as examples. The nitrogen forms an enamine on each side of the ring and we know that enamines are made from carbonyl compounds and amines.

If we do the same disconnection with a pyrrole, omitting the intermediate stage, we can repeat the C–N disconnection on the other side too:



What we need is an amine—ammonia in this case—and a diketone. If the two carbonyl groups have a 1,4 relationship we will get a pyrrole out of this reaction. So hexane-2,5-dione reacts with ammonia to give a high yield of 2,5-dimethyl pyrrole.



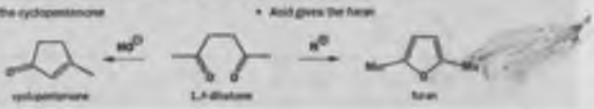
Making furans is even easier because the heteroatom (oxygen) is

already there. All we have to do is to dehydrate the 1,4-diketone instead of making enamines from it. Heating with acid is enough.

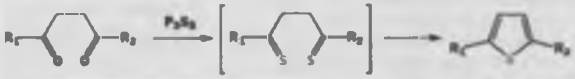
Avoiding the aldol product

1,4-Diketones also self-condense rather easily in an intramolecular aldol reaction to give a cyclopentenone with an alkyl chain. Represented ring. This too is a useful reaction but we need to know how to control it. The usual rule is:

- Base gives the cyclopentenone
- Acid gives the furan



For thiophenes we could in theory use H_2S or some other sulfur nucleophile but, in practice, an electrophilic reagent is usually used to convert the two C=O bonds to C=S bonds. Thioketones are much less stable than ketones and cyclization is swift. Reagents such as P_2S_5 or Lawesson's reagent are the usual choice here.



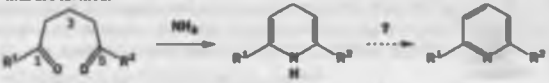
Lawesson's reagent

▶ Sulfur chemistry is discussed in Chapter 46, all we will say here about the mechanisms of these reactions is that phosphorus is commonly used to remove oxygen and replace it by another element; remember the Mitsunobu reaction?

● Making five-membered heterocycles

Cyclization of 1,4-dicarbonyl compounds with nitrogen, sulfur, or oxygen nucleophiles gives the five-membered aromatic heterocycles pyrrole, thiophene, and furan.

It seems a logical extension to use a 1,5-diketone to make substituted pyridines but there is a slight problem here as we will introduce only two of the required three double bonds when the two enamines are formed.



To get the pyridine by enamine formation we should need a double bond somewhere in the chain between the two carbonyl groups. But here another difficulty arises—it will have to be a *cis* (*Z*) double bond or cyclization would be impossible.

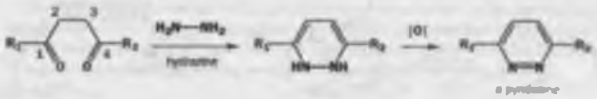
On the whole it is easier to use the saturated 1,5-diketone and oxidize the product to the pyridine. As we are going from a nonaromatic to an aromatic compound, oxidation is easy and we can replace the question mark above with almost any simple oxidizing agent, as we shall soon see.

● Making six-membered heterocycles

Cyclization of 1,5-dicarbonyl compounds with nitrogen nucleophiles leads to the six-membered aromatic heterocycle pyridine.

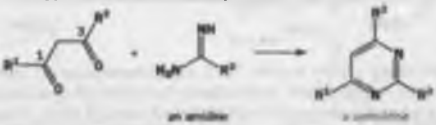
Heterocycles with two nitrogen atoms come from the same strategy

Reacting a 1,4-diketone with hydrazine (NH_2NH_2) makes a double enamine again and this is only an oxidation step away from a pyridazine. This is again a good synthesis.



If we use a 1,3-diketone instead we will get a five-membered heterocycle and the imine and enamine formed are enough to give aromaticity without any need for oxidation. The product is a pyrazole.

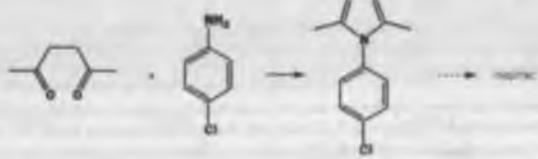
The two heteroatoms do not, of course, need to be joined together for this strategy to work. If an amidine is combined with the same 1,3-diketone we get a six-membered heterocycle. As the nucleophile contains one double bond already, an aromatic pyrimidine is formed directly.



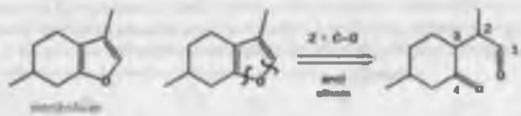
Since diketones and other dicarbonyl compounds are easily made by enolate chemistry (Chapters 26–30) this strategy has been very popular and we will look at some detailed examples before moving on to more specialized reactions for the different classes of aromatic heterocycles.

Pyrroles, thiophenes, and furans from 1,4-dicarbonyl compounds

We need to make the point that pyrrole synthesis can be done with primary amines as well as with ammonia and a good example is the pyrrole needed for clopirac, a drug we discussed in Chapter 43. The synthesis is very easy.

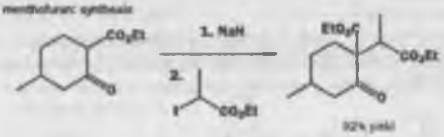


For an example of furan synthesis we choose menthofuran, which contributes to the flavour of mint. It has a second ring, but that is no problem if we simply disconnect the enol ethers as we have been doing so far.

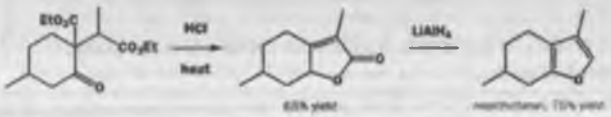


The starting material is again a 1,4-dicarbonyl compound but as there was no substituent at C1 of the furan, that atom is an aldehyde rather than a ketone. This might lead to problems in the synthesis so a few changes (using the notation you met in Chapter 30) are made to the intermediate before further disconnection.

Notice in particular that we have 'oxidized' the aldehyde to an ester to make it more stable—all the synthesis reduction will be needed. Here is the alkylation step of the synthesis, which does indeed go very well with the α-iodo-ester.



Cyclization with acid now causes a lot to happen. The 1,4-dicarbonyl compound cyclizes to a lactone, not to a furan, and the redundant ester group is lost by hydrolysis and decarboxylation. Notice that the double bond moves into conjugation with the lactone carbonyl group. Finally, the reduction gives the furan. No special precautions are necessary—as soon as the ester is partly reduced, it loses water to give the furan whose aromaticity prevents further reduction even with $LiAlH_4$.

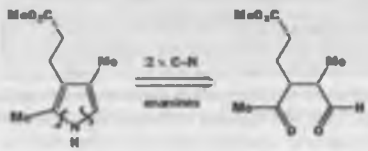


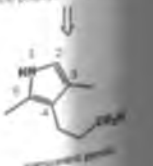
A reminder

Cyclization of 1,4-dicarbonyl compounds with nitrogen, sulfur, or oxygen nucleophiles gives the five-membered aromatic heterocycles pyrrole, thiophene, and furan.

Now we need to take these ideas further and discuss an important pyrrole synthesis that follows this strategy but includes a cunning twist. It all starts with the porphyrin found in blood. In Chapter 43 we gave the structure of that very important compound and showed that it contains four pyrrole rings joined in a macrocycle. We are going to look at one of those pyrroles.

Porphyrins can be made by joining together the various pyrroles in the right order and what is needed for this one (and also, in fact, for another—the one in the north-east corner of the porphyrin) is a pyrrole with the correct substituents in positions 3 and 4, a methyl group in position 5, and a hydrogen atom at position 2. Position 2 must be free. Here is the molecule drawn somewhat more conveniently together with the disconnection we have been using so far.

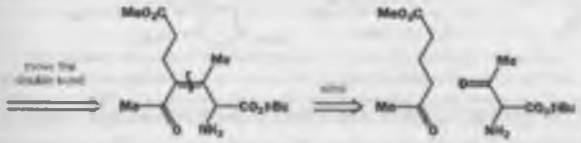




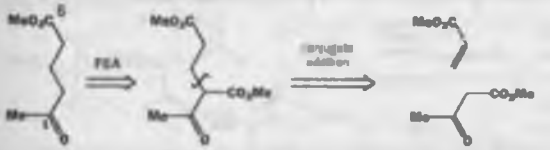
No doubt such a synthesis could be carried out but it is worth looking for alternatives for a number of reasons. We would prefer not to make a pyrrole with a free position at C2 as that would be very reactive and we know from Chapter 43 that we can block such a position with a *t*-butyl ester group. This gives us a very difficult starting material with four different carbonyl groups.

We have made a problem for ourselves by having two carbonyl groups next to each other. Could we escape from that by replacing one of them with an amine? We should then have an ester of an α amino acid, an attractive starting material, and this corresponds to disconnecting just one of the C–N bonds.

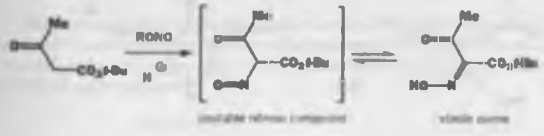
At first we seem to have made no progress but just see what happens when we move the double bond round the ring into conjugation with the ketone. After all, it doesn't matter where the double bond starts out—we will always get the aromatic product.



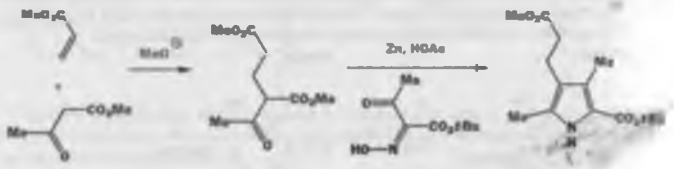
Each of our two much simpler starting materials needs to be made. The keto-ester is a 1,5-dicarbonyl compound so it can be made by a conjugate addition of an enolate, a process greatly assisted by the addition of a second ester group (Chapter 29).



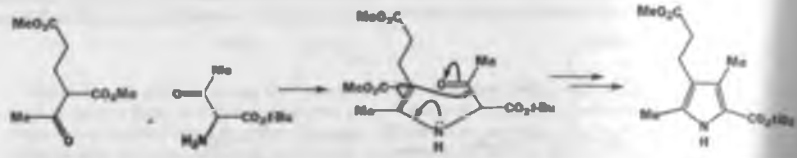
The other compound is an amino-keto-ester and will certainly react with itself if we try to prepare it as a pure compound. The answer is to release it into the reaction mixture and this can be done by nitrosation and reduction (Chapter 21) of another stable enolate.



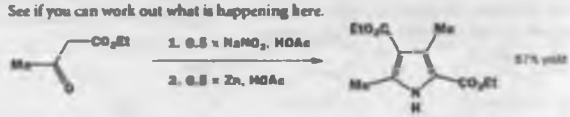
Zinc in acetic acid (Chapter 24) reduces the oxime to the amine and we can start the synthesis by doing the conjugate addition and then reducing the oxime in the presence of the keto-diester.



This reaction forms the required pyrrole in one step! First, the oxime is reduced to an amine; then the amino group forms an imine with the most reactive carbonyl group (the ketone) in the keto-diester. Finally, the very easily formed enamine cyclizes on to the other ketone.

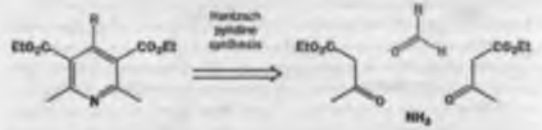


This pyrrole synthesis is important enough to be given the name of its inventor—it is the **Knorr pyrrole synthesis**. Knorr himself made a rather simpler pyrrole in a remarkably efficient reaction. See if you can work out what is happening here.



How to make pyridines: the Hantzsch pyridine synthesis

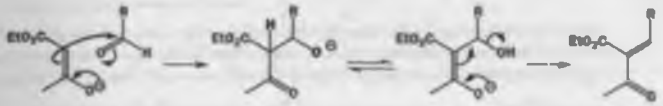
The idea of coupling two keto-esters together with a nitrogen atom also works for pyridines except that an extra carbon atom is needed. This is provided as an aldehyde and another important difference is that the nitrogen atom is added as a nucleophile rather than an electrophile. These are features of the **Hantzsch pyridine synthesis**. This is a four-component reaction that goes like this.



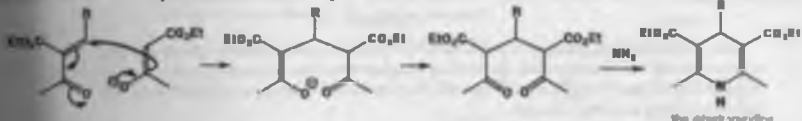
You are hardly likely to understand the rationale behind this reaction from that diagram so let's explore the details. The product of the reaction is actually the dihydropyridine, which has to be oxidized to the pyridine by a reagent such as HNO_3, Ce(IV), or a quinone.

The reaction is very simply carried out by mixing the components in the right proportions in ethanol. The presence of water does not spoil the reaction and the ammonia, or some added amine, ensures the slightly alkaline pH necessary. Any aldehyde can be used, even formaldehyde, and yields of the crystalline dihydropyridine are usually very good.

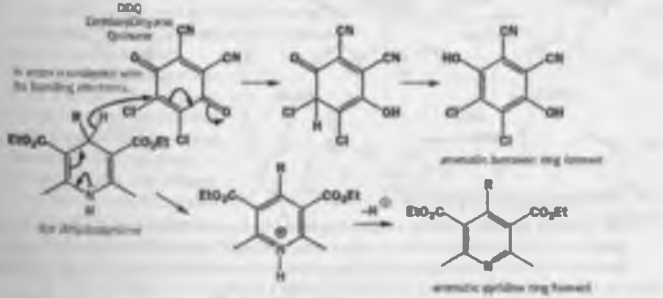
This reaction is an impressive piece of molecular recognition by small molecules and writing a detailed mechanism is a bold venture. We can see that certain events have to happen. The ammonia has to attack the ketone groups, but it would prefer to attack the more electrophilic aldehyde so this is probably not the first step. The enol or enolate of the keto-ester has to attack the aldehyde (twice!) so let us start there.



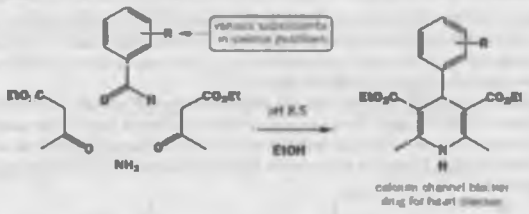
This adduct is in equilibrium with the stable enolate from the keto-ester and elimination now gives an unsaturated carbonyl compound. Such chemistry is associated with the aldol reactions we discussed in Chapter 27. The new enone has two carbonyl groups at one end of the double bond and is therefore a very good Michael acceptor (Chapter 29). A second molecule of enolate does a conjugate addition to complete the carbon skeleton of the molecule. Now the ammonia attacks either of the ketones and cyclizes on to the other. As ketones are more electrophilic than esters it is to be expected that ammonia will prefer to react there.



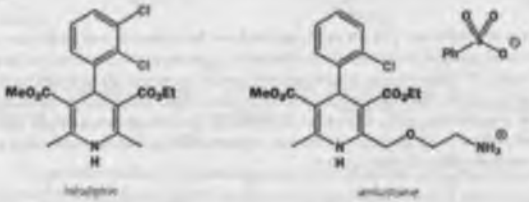
The necessary oxidation is easy both because the product is aromatic and because the nitrogen atom can help to expel the hydrogen atom and its pair of electrons from the 4-position. If we use a quinone as oxidizing agent, both compounds become aromatic in the same step. We will show in Chapter 50 that Nature uses related dihydropyridines as reducing agents in living things.



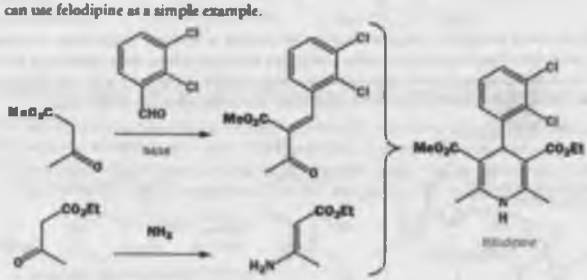
The Hantzsch pyridine synthesis is an old discovery (1882) which sprang into prominence in the 1980s with the discovery that the dihydropyridine intermediates prepared from aromatic aldehydes are calcium channel blocking agents and therefore valuable drugs for heart disease with useful effects on angina and hypertension.



So far, so good. But it also became clear that the best drugs were unsymmetrical—some in a trivial way such as felodipine but some more seriously such as Pfizer's amlodipine. At first sight it looks as though the very simple and convenient Hantzsch synthesis cannot be used for these compounds.

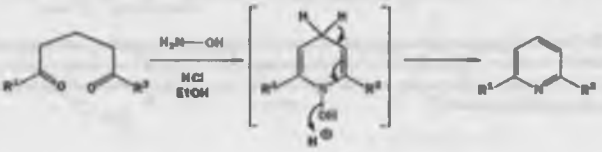


Clearly, a modification is needed in which half of the molecule is assembled first. The solution lies in early work by Robinson who made the very first enamines from keto-esters and amines. One half of the molecule is made from an enamine and the other half from a separately synthesized enone. We can use felodipine as a simple example.

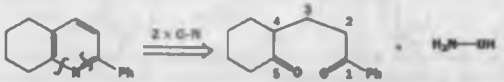


Other syntheses of pyridines

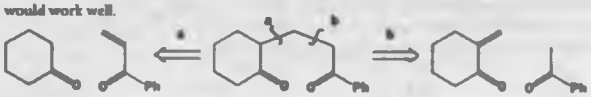
The Hantzsch synthesis produces a reduced pyridine but there are many syntheses that go directly to pyridines. One of the simplest is to use hydroxylamine (NH_2OH) instead of ammonia as the nucleophile. Reaction with a 1,5-diketone gives a dihydropyridine but then water is lost and no oxidation is needed.



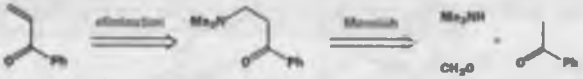
The example below shows how these 1,5-diketones may be quickly made by the Mannich (Chapter 27) and Michael (Chapter 29) reactions. Our pyridine has a phenyl substituent and a fused saturated ring. First we must disconnect to the 1,5-diketone.



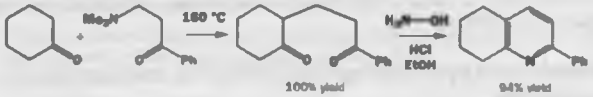
Further disconnection reveals a ketone and an enone. There is a choice here and both alternatives would work well.

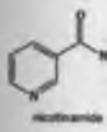


It is convenient to use Mannich bases instead of the very reactive unsaturated ketones and we will continue with disconnection 'a'.



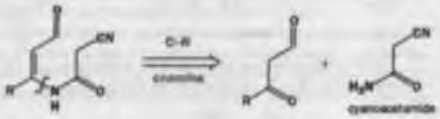
The synthesis is extraordinarily easy. The stable Mannich base is simply heated with the other ketone to give a high yield of the 1,5-diketone. Treatment of that with the HCl salt of NH_2OH in EtOH gives the pyridine directly, also in good yield.



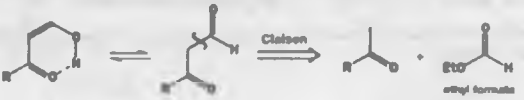


Another direct route leads, as we shall now demonstrate, to pyridones. These useful compounds are the basis for nucleophilic substitutions on the ring (Chapter 43). We choose an example that puts a nitrile in the 3-position. This is significant because the role of nicotinamide in living things (Chapter 50) makes such products interesting to make. Aldol disconnection of a 3-cyano pyridone starts us on the right path.

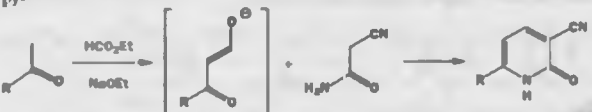
If we now disconnect the C–N bond forming the enamine on the other side of the ring we will expose the true starting materials. This approach is unusual in that the nitrogen atom that is to be the pyridine nitrogen is not added as ammonia but is already present in a molecule of cyanoacetamide.



The keto-aldehyde can be made by a simple Claisen ester condensation (Chapter 28) using the enolate of the methyl ketone with ethyl formate (HCO_2Et) as the electrophile. It actually exists as a stable enol, like so many 1,3-dicarbonyl compounds (Chapter 21).

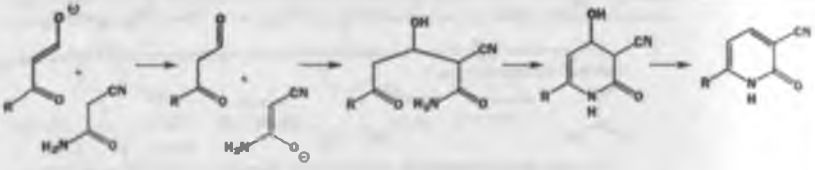


In the synthesis, the product of the Claisen ester condensation is actually the enolate anion of the keto-aldehyde and this can be combined directly without isolation with cyanoacetamide to give the pyridone in the same flask.



What must happen here is that the two compounds must exchange protons (or switch enolates if you prefer) before the aldol reaction occurs. Cyclization probably occurs next through C–N bond formation and, finally, dehydration is forced to give the *Z*-alkene.

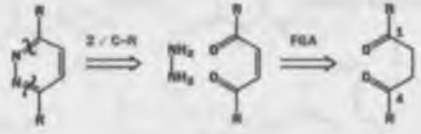
▶ If dehydration occurred first, only the *Z*-alkene could cyclize and the major product, the *E*-alkene, would be wasted



In planning the synthesis of a pyrrole or a pyridine from a dicarbonyl compound, considerable variation in oxidation state is possible. The oxidation state is chosen to make further disconnection of the carbon skeleton as easy as possible. We can now see how these same principles can be applied to pyrazoles and pyridazines.

Pyrazoles and pyridazines from hydrazine and dicarbonyl compounds

Disconnection of pyridazines reveals a molecule of hydrazine and a 1,4-diketone with the proviso that, just as with pyridines, the product will be a dihydropyrazine and oxidation will be needed to give the aromatic compound. As with pyridines, we prefer to avoid the *cis* double bond problem.



As an example we can take the cotton herbicide made by Cyanamid. Direct removal of hydrazine would require a *cis* double bond in the starting material.

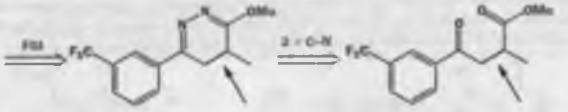
▶ The herbicide kills weeds in cotton crops rather than the cotton plant itself!

Cyanamid cotton herbicide

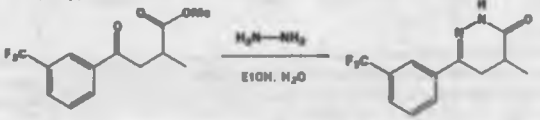
reject *cis* alkene as starting material

If we remove the double bond first, a much simpler compound emerges. Note that this is a keto-ester rather than a diketone.

The alkylation is regioselective because the methylated nitrogen would become like the pyridine-like nitrogen atom and the molecule gains the largest conjugated system involving that nitrogen and the ester.

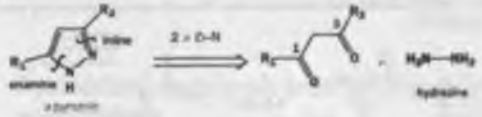


When hydrazine is added to the keto-ester an imine is formed with the ketone but acylation occurs at the ester end to give an amide rather than the imino-ester we had designed. The product is a dihydropyridazolone.

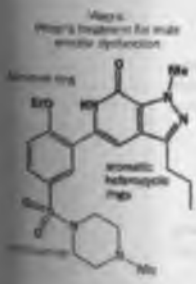


Aromatization with bromine gives the aromatic pyridazolone by bromination and dehydrobromination and now we invoke the nucleophilic substitution reactions introduced in Chapter 43. First we make the chloride with $POCl_3$ and then displace with methanol.

The five-membered ring pyrazoles are even simpler as the starting material is a 1,3-dicarboxyl compound available from the aldol or Claisen ester condensations.

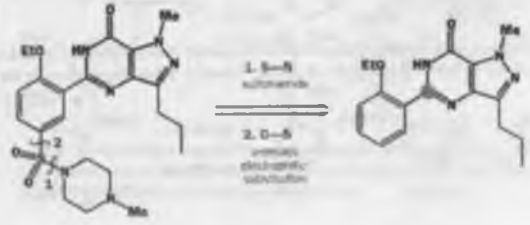


Chemistry hits the headlines—Viagra

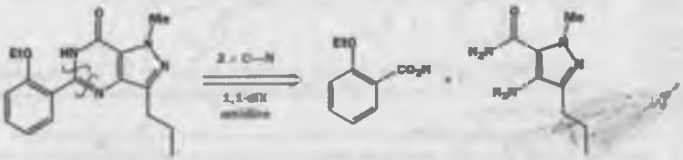


In 1998 chemistry suddenly appeared in the media in an exceptional way. Normally not a favourite of TV or the newspapers, chemistry produced a story with all the right ingredients—sex, romance, human ingenuity—and all because of a pyrazole. In the search for a heart drug, Pfizer uncovered a compound that allowed impotent men to have active sex lives. They called it Viagra.

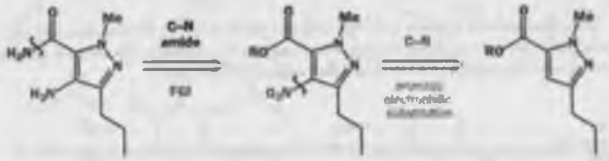
The molecule contains a sulfonamide and a benzene ring as well as the part that interests us most—a bicyclic aromatic heterocyclic system of a pyrazole fused to a pyrimidine. We shall discuss in detail how Pfizer made this part of the molecule and just sketch in the rest. The sulfonamide can be made from the sulfonic acid that can be added to the benzene ring by electrophilic aromatic sulfonation (Chapter 22).



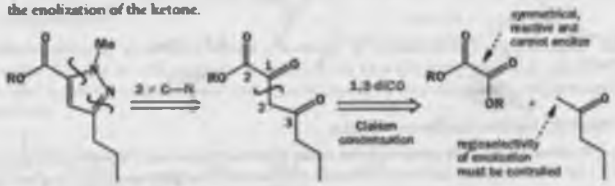
Inspection of what remains reveals that the carbon atom atom in the heterocycles next to the benzene ring (marked with an orange blob) is at the oxidation level of a carboxylic acid. If, therefore, we disconnect both C–N bonds to this atom we will have two much simpler starting materials.



The aromatic acid is available and we need consider only the pyrazole (core pyrazole ring in black in the diagram). The aromatic amino group can be put in by nitration and reduction and the amide can be made from the corresponding ester. This leaves a carbon skeleton, which must be made by ring synthesis.

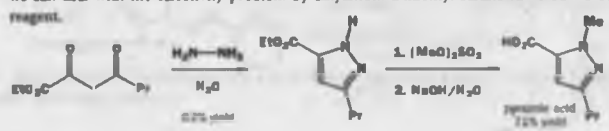


Following the methods we have established so far in this chapter, we can remove the hydrazine portion to reveal a 1,3-dicarbonyl compound. In fact, this is a tricarbonyl compound, a diketo-ester, because of the ester already present and it contains 1,2-, 1,3-, and 1,4-dicarbonyl relationships. The simplest synthesis is by a Claisen ester condensation and we choose the disconnection so that the electrophile is a reactive (oxalate) diester that cannot enolize. The only control needed will then be in the enolization of the ketone.

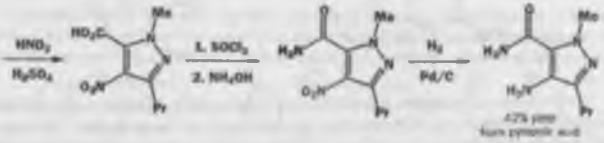


The Claisen ester condensation gives the right product just by treatment with base. The reasons for this are discussed in Chapter 28. We had then planned to react the keto-diester with methylhydrazine but there is a doubt about the regioselectivity of this reaction—the ketones are more electrophilic than the ester all right, but which ketone will be attacked by which nitrogen atom?

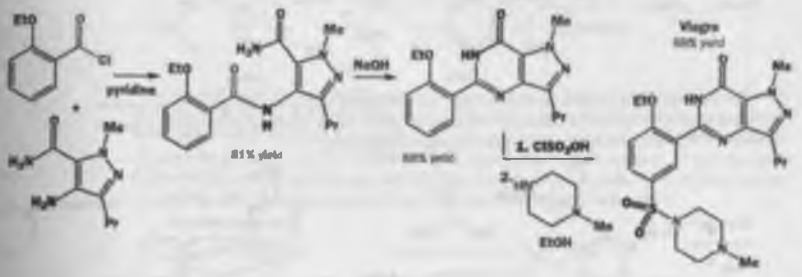
We have already seen the solution to this problem in Chapter 43. If we use symmetrical hydrazine, we can deal with the selectivity problem by alkylation. Dimethyl sulfate turns out to be the best reagent.



The stable pyrazole acid from the hydrolysis of this ester is a key intermediate in Viagra production. Nitration can occur only at the one remaining free position and then amide formation and reduction complete the synthesis of the amino pyrazole amide ready for assembly into Viagra.

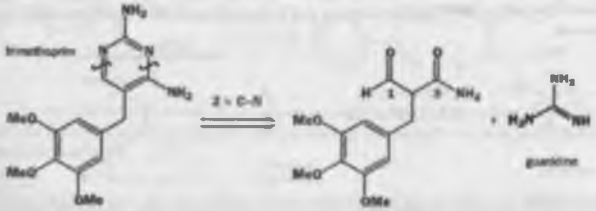


The rest of the synthesis can be summarized very briefly as it mostly concerns material outside the scope of this chapter. You might like to notice how easy the construction of the second heterocyclic ring is—the nucleophilic attack of the nitrogen atom of one amide on to the carbonyl of another would surely not occur unless the product were an aromatic heterocycle.

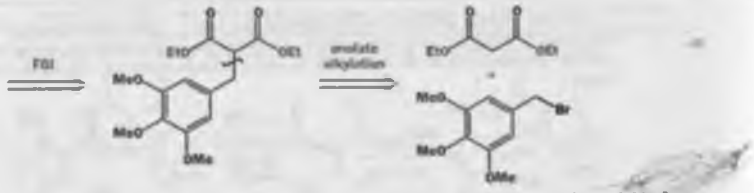


Pyrimidines can be made from 1,3-dicarbonyl compounds and amidines

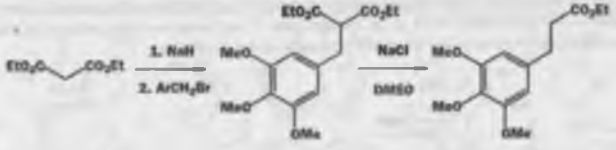
In Chapter 43 we met some compounds that interfere in folic acid metabolism and are used as antibacterial agents. One of them was trimethoprim and it contains a pyrimidine ring (black on the diagram). We are going to look at its synthesis briefly because the strategy used is the opposite of that used with the pyrimidine ring in Viagra. Here we disconnect a molecule of guanidine from a 1,3-dicarbonyl compound.



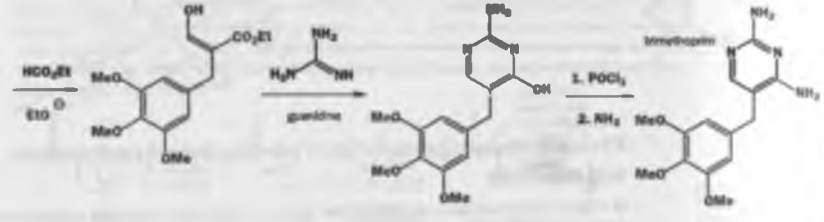
The 1,3-dicarbonyl compound is a combination of an aldehyde and an amide but is very similar to a malonic ester so we might think of making this compound by alkylation of that stable enolate (Chapter 26) with the convenient benzylic bromide.



The alkylation works fine but it turns out to be better to add the aldehyde as an electrophile (*cf.* the pyridone synthesis on p. 000) rather than try to reduce an ester to an aldehyde. The other ester is already at the right oxidation level. Notice the use of the NaCl method of decarboxylation (Chapter 26).

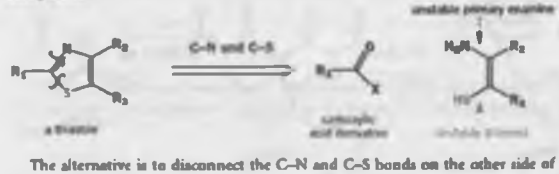


Condensation with ethyl formate (HCO_2Et) and cyclization with guanidine gives the pyrimidine ring system but with an OH instead of the required amino group. Aromatic nucleophilic substitution in the pyrimidone style from Chapter 43 gives trimethoprim.

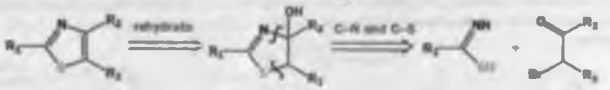


Unsymmetrical nucleophiles lead to selectivity questions

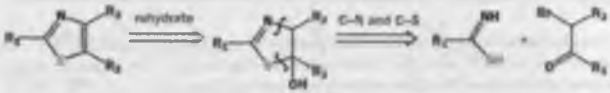
The synthesis of thiazoles is particularly interesting because of a regioselectivity problem. If we try out the two strategies we have just used for pyrimidines, the first requires the reaction of a carboxylic acid derivative with a most peculiar enamine that is also a thioenol. This does not look like a stable compound.



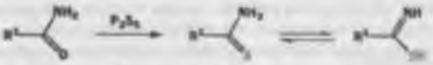
The alternative is to disconnect the C–N and C–S bonds on the other side of the heteroatoms. Here we must be careful what we are about or we will get the oxidation state wrong. We shall do it step by step to make sure. We can rehydrate the double bond in two ways. We can first try putting the OH group next to nitrogen.



Or we can rehydrate it the other way round, putting the OH group next to the sulfur atom, and disconnect in the same way. In both cases we require an electrophilic carbon atom at the alcohol oxidation level and one at the aldehyde or ketone oxidation level. In other words we need an α-haloketone.

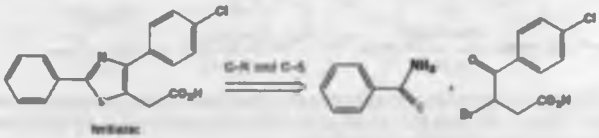


The nucleophile is the same in both cases and it is an odd-looking molecule. That is, until we realize that it is just a tautomer of a thioamide. Far from being odd, thioamides are among the few stable thiocarbonyl derivatives and can be easily made from ordinary amides with P_2S_5 or Lawesson's reagent.



So the only remaining question is: when thioamides combine with α-haloketones, which atom (N or S) attacks the ketone, and which atom (N or S) attacks the alkyl halide? Carbonyl groups are 'hard' electrophiles—their reactions are mainly under charge control and so they react best with basic nucleophiles (Chapter 12). Alkyl halides are 'soft' electrophiles—their reactions are mainly under frontier orbital control and they react best with large uncharged nucleophiles from the lower rows of the periodic table. The ketone reacts with nitrogen and the alkyl halide with sulfur.

Fentiazac, a nonsteroidal anti-inflammatory drug, is a simple example. Disconnection shown that we need thiobenzamide and an easily made α-haloketone (easily made because the ketone can enolize on this side only—see Chapter 21).

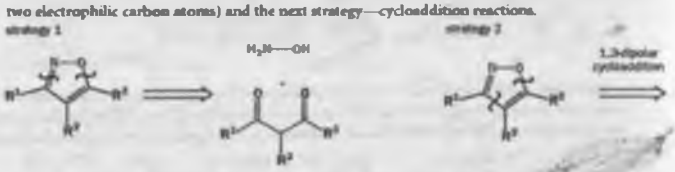


The synthesis involves heating these two compounds together and the correct thiazole forms easily with the double bonds finding their right positions in the product—the only positions for a stable aromatic heterocycle.

Isoxazoles are made from hydroxylamine or by 1,3-dipolar cycloadditions

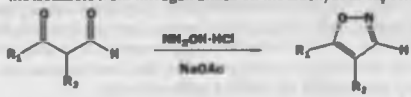
The two main routes for the synthesis of isoxazoles are the attack of hydroxylamine (NH_2OH) on diketones and 1,3-dipolar cycloadditions of nitrile oxides. They thus form a link between the strategy

we have been discussing (cyclization of a nucleophile with two heteroatoms and a compound with two electrophilic carbon atoms) and the next strategy—cycloaddition reactions.

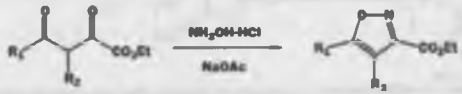


Simple symmetrical isoxazoles are easily made by the hydroxylamine route. If R^1 is R^3, we have a symmetrical and easily prepared 1,3-diketone as starting material. The central R^2 group can be inserted by alkylation of the stable enolate of the diketone (Chapter 26).

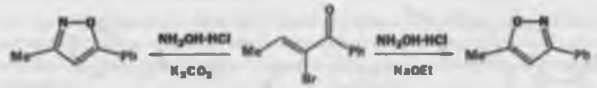
When $R^1 \neq R^3$, we have an unsymmetrical dicarbonyl compound and we must be sure that we know which way round the reaction will proceed. The more nucleophilic end of NH_2OH will attack the more electrophilic carbonyl group. It seems obvious that the more nucleophilic end of NH_2OH will be the nitrogen atom but that depends on the pH of the solution. Normally, hydroxylamine is supplied as the crystalline hydrochloride salt and a base of some kind added to give the nucleophile. The relevant pK_as are shown in the margin. Bases such as pyridine or sodium acetate produce some of the reactive neutral NH_2OH in the presence of the less reactive cation, but bases such as NaOEt produce the anion. Reactions of keto-aldehydes with acetate-buffered hydroxylamine usually give the isoxazole from nitrogen attack on the aldehyde as expected.



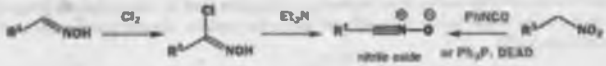
Modification of the electrophile may also be successful. Reaction of hydroxylamine with 1,2,4-diketo-esters usually gives the isoxazole from attack of nitrogen at the more reactive keto group next to the ester.



A clear demonstration of selectivity comes from the reactions of bromoenones. It is not immediately clear which end of the electrophile is more reactive but the reactions tell us the answer.

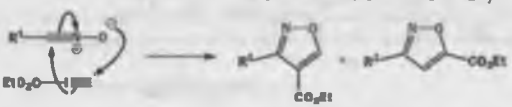


The alternative approach to isoxazoles relies on cycloadditions of nitrile oxides with alkynes. We saw in Chapter 35 that there are two good routes to these reactive compounds, the γ-elimination of chloroximes or the dehydration of nitroalkanes.



A few nitrile oxides are stable enough to be isolated (those with electron-withdrawing or highly conjugating substituents, for example) but most are prepared in the presence of the alkyne by one of these methods because otherwise they dimerize rapidly. Both methods of forming nitrile oxides are compatible with their rapid reactions with alkynes. Reaction with aryl alkynes is usually clean and regioselective.

The alkyne is using its HOMO to attack the LUMO of the nitrile oxide (see Chapter 35 for an explanation). If the alkyne has an electron-withdrawing group, mixtures of isomers are usually formed as the HOMO of the nitrile oxide also attacks the LUMO of the alkyne.

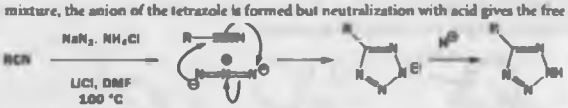


Intramolecular reactions are usually clean regardless of the preferred electronic orientation if the tether is too short to allow any cyclization except one. In this example, even the more favourable orientation looks very bad because of the linear nature of the reacting species, but only one isomer is formed.

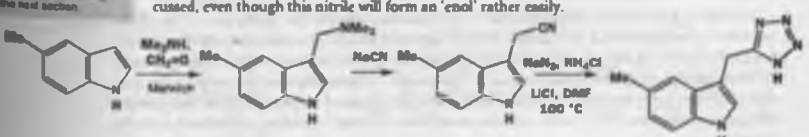
Tetrazoles are also made by 1,3-dipolar cycloadditions

Disconnection of tetrazoles with a 1,3-dipolar cycloaddition in mind is easy to see once we realize that a nitrile (RCN) is going to be one of the components. It can be done in two ways: disconnection of the neutral compound would require hydrazoic acid (HN_3) as the dipole but the anion disconnects directly to azide ion.

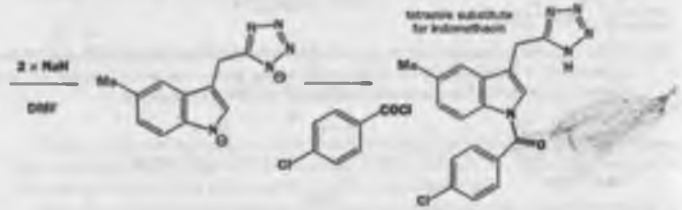
Unpromising though this reaction may look, it actually works well if an ammonium–chloride-buffered mixture of sodium azide and the nitrile is heated in DMF. The reagent is really ammonium azide and the reaction occurs faster with electron-withdrawing substituents in R. In the reaction mixture, the anion of the tetrazole is formed but neutralization with acid gives the free tetrazole.



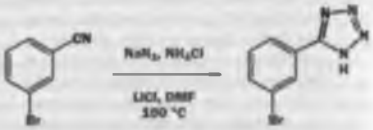
As nitriles are generally readily available this is the main route to simple tetrazoles. More complicated ones are made by alkylation of the product of a cycloaddition. The tetrazole substitute for indomethacin that we mentioned in Chapter 43 is made by this approach. First, the nitrile is prepared from the indole. The 1,3-dipolar cycloaddition works well by the azide route we have just discussed, even though this nitrile will form an 'enol' rather easily.



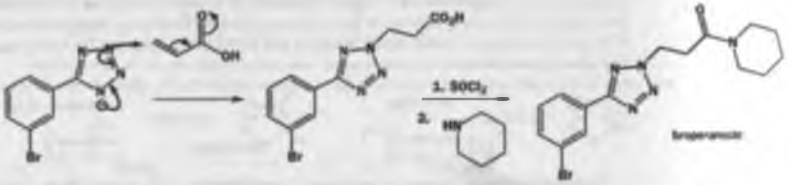
Finally, the indole nitrogen atom must be acylated. The tetrazole is more acidic so it is necessary to form a dianion to get reaction at the right place. The usual rule is followed (see Chapter 24)—the second anion formed is less stable and so it reacts first.



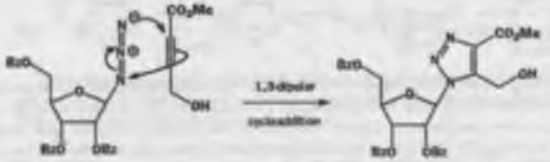
The synthesis of the anti-inflammatory drug broperamole illustrates modification of a tetrazole using its anion. The tetrazole is again constructed from the nitrile—it's an aromatic nitrile with an electron-withdrawing substituent so this will be a good reaction.



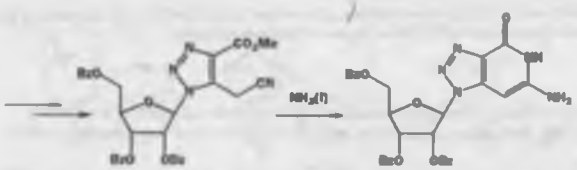
Conjugate addition to acrylic acid (Chapters 10 and 23) occurs to give the other tautomer to the one we have drawn. The anion intermediate is, of course, delocalized and can react at any of the nitrogen atoms. Amide formation completes the synthesis of broperamole.



The difficulty in trying to forecast which way round a 1,3-dipolar cycloaddition will go is well illustrated when a substituted azide adds to an alkyne in the synthesis of 1,2,3-triazoles. Reaction of an alkyl azide with an unsymmetrical alkyne, having an electron-withdrawing group at one end and an alkyl group at the other, gives mostly a single triazole.



It looks as if the more nucleophilic end of the azide has attacked the wrong end of the alkyne but we must remember that (1) it is very difficult to predict which is the more nucleophilic end of a 1,3-dipole and (2) it may be either HOMO (dipole) and LUMO (alkyne) or LUMO (dipole) and HOMO (alkyne) that dominate the reaction. The reason for doing the reaction was to make analogues of natural nucleosides (the natural compounds are discussed in Chapter 49). In this case the OH group was replaced by a cyanide so that a second aromatic ring, a pyridine, can be fused on to the triazole.

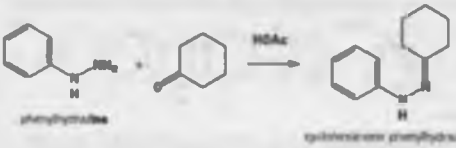


The next section deals with the synthesis of heterocycles where a heterocyclic ring is fused to a benzene ring, the 6/5 system, indole, and the 6/6 systems, quinoline and isoquinoline.

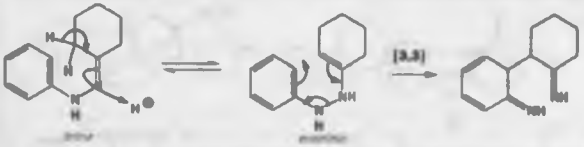
The Fischer indole synthesis

You are about to see one of the great inventions of organic chemistry. It is a remarkable reaction, amazing in its mechanism, and it was discovered in 1883 by one of the greatest organic chemists of all, Emil Fischer. Fischer had earlier discovered phenylhydrazine ($PhNHNH_2$) and, in its simplest form, the Fischer indole synthesis occurs when phenylhydrazine is heated in acidic solution with an aldehyde or ketone.

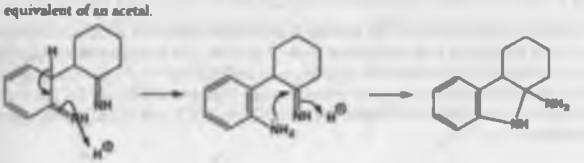
The first step in the mechanism is formation of the phenylhydrazone (the imine) of the ketone. This can be isolated as a stable compound (Chapter 14).



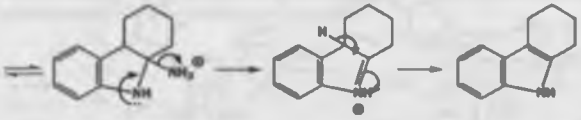
The hydrazone then needs to tautomerize to the enamine, and now comes the key step in the reaction. The enamine can rearrange with formation of a strong C–C bond and cleavage of the weak N–N single bond by moving electrons round a six-membered ring.



Next, re-aromatization of the benzene ring (by proton transfer from carbon to nitrogen) creates an aromatic amine that immediately attacks the other imine. This gives an aminal, the nitrogen equivalent of an acetal.

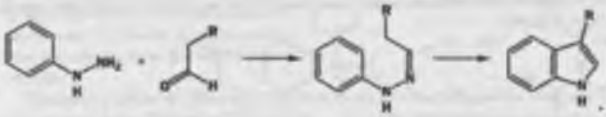


Finally, acid-catalysed decomposition of the aminal in acetal fashion with expulsion of ammonia allows the loss of a proton and the formation of the aromatic indole.

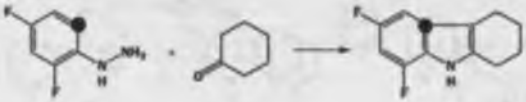


This is admittedly a complicated mechanism but if you remember the central step—the [3,3]-sigmatropic rearrangement—the rest should fall into place. The key point is that the C–C bond is established at the expense of a weak N–N bond. Naturally, Fischer had no idea about [3,3] or any other steps in the mechanism. He was sharp enough to see that something remarkable had happened and skilful enough to find out what it was.

The Fischer method is the main way of making indoles, but it is not suitable for them all. We need now to study its applicability to various substitution patterns. If the carbonyl compound can enolize on one side only, as is the case with an aldehyde, then the obvious product is formed.

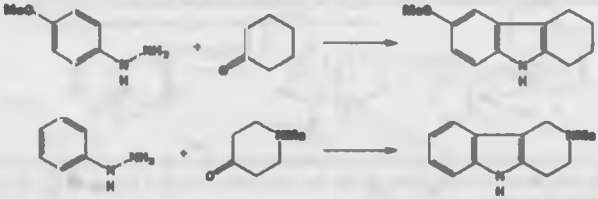


If the benzene ring has only one *ortho* position, then again cyclization must occur to that position. Other substituents on the ring are irrelevant. At this point we shall stop drawing the intermediate phenylhydrazone.

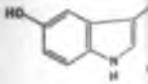


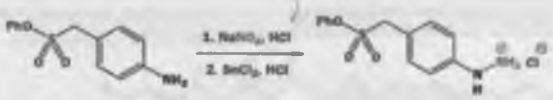
only one free *ortho* position

Another way to secure a single indole as product from the Fischer indole synthesis is to make sure the reagents are symmetrical. These two examples should make plain the types of indole available from symmetrical starting materials.

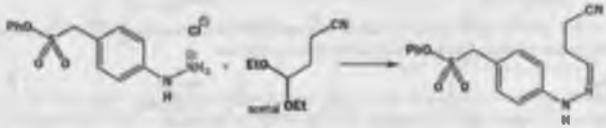


The substitution pattern of the first example is particularly important as the neurotransmitter serotonin is an indole with a hydroxyl group in the 5-position, and many important drugs follow that pattern. Sumatriptan (marketed as Imigran), is an example that we can also use to show that substituted phenylhydrazines are made by reduction of diazonium salts (Chapter 23). The first stage of the synthesis is nitrosation of the aniline and reduction with $SnCl_2$ and HCl to give the salt of the phenylhydrazine.

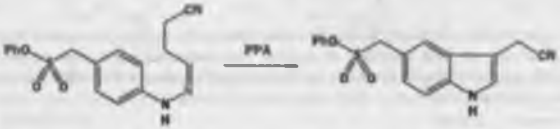




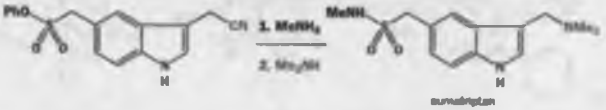
The required aldehyde (3-cyanopropanal) is added as an acetal to prevent self-condensation. The acidic conditions release the aldehyde, which forms the phenylhydrazone ready for the next step.



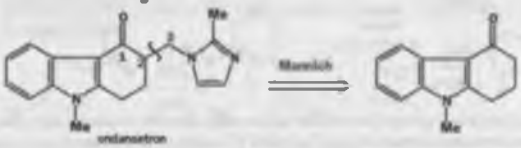
The Fischer indole synthesis itself is catalysed in this case by polyphosphoric acid (PPA), a sticky gum based on phosphoric acid (H_3PO_4) but dehydrated so that it contains some oligomers. It is often used as a catalyst in organic reactions and residues are easily removed in water.



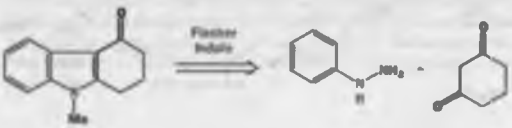
All that remains is to introduce the methyl amino and dimethylamino groups. The sulfonate ester is more reactive than the nitrile so the methyl amino group must go in first.



For some indoles it is necessary to control regioselectivity with unsymmetrical carbonyl compounds. Ondansetron, the anti-nausea compound that is used to help cancer patients take larger doses of antitumour compounds than was previously possible, is an example. It contains an indole and an imidazole ring.



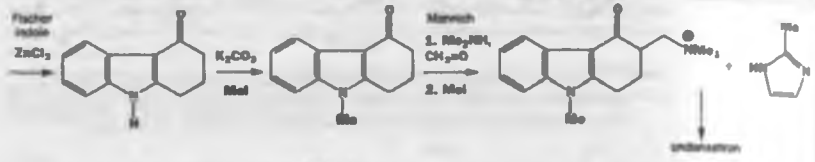
The 1,3 relationship between C–N and C–O suggests a Mannich reaction to add the imidazole ring (Chapter 27), and that disconnection reveals an indole with an unsymmetrical right-hand side, having an extra ketone group. Fischer disconnection will reveal a diketone as partner for phenylhydrazine. We shall leave aside for the moment when to add the methyl group to the indole nitrogen.



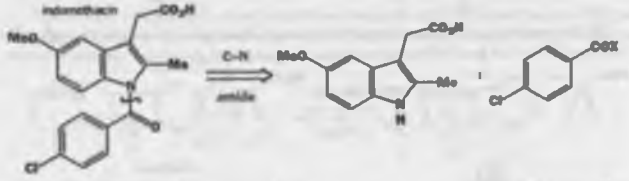
The diketone has two identical carbonyl groups and will enolize (or form an enamine) exclusively towards the other ketone. The phenylhydrazone therefore forms only the enamine we want.

▶ Notice that we have drawn a different geometrical isomer of the imine from the one we have previously drawn and you might even find think that this one cannot cyclize. But the geometry of the phenylhydrazone is unimportant—you might like to think why.

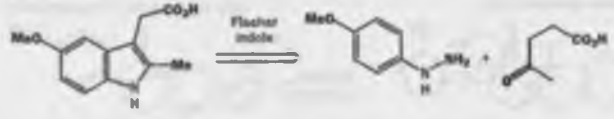
In this case, the Fischer indole reaction was catalysed by a Lewis acid, $ZnCl_2$, and base-catalysed methylation followed. The final stages are summarized below.



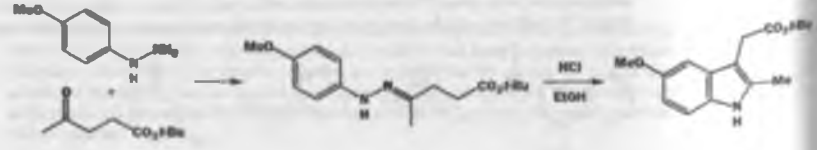
In the worst case, there is no such simple distinction between the two sites for enamine formation and we must rely on other methods of control. The nonsteroidal anti-inflammatory drug indomethacin is a good example. Removing the *N*-acyl group reveals an indole with substituents in both halves of the molecule.



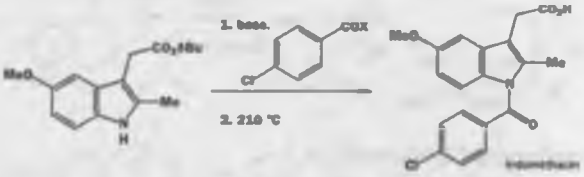
The benzene ring portion is symmetrical and is ideal for the Fischer synthesis but the right-hand half must come from an unsymmetrical open-chain keto-acid. Is it possible to control such a synthesis?



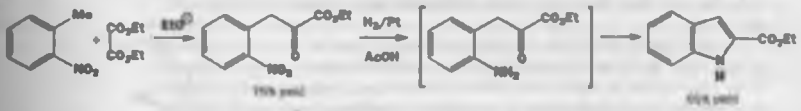
The Fischer indole is acid-catalysed so we must ask: on what side of the ketone is enolization (and therefore enamine formation) expected in acid solution? The answer is away from the methyl group and into the alkyl chain (Chapter 21). This is what we want and the reaction does indeed go this way. In fact, the *t*-butyl ester is used instead of the free acid.



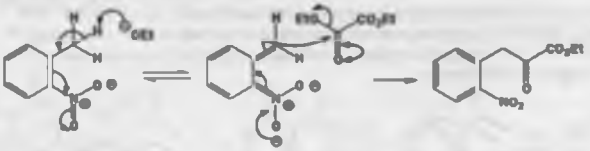
Acylation at the indole nitrogen atom is achieved with acid chloride in base and removal of the *t*-butyl ester gives free indomethacin.



There are many other indole syntheses but we will give a brief mention to only one other and that is because it allows the synthesis of indoles with a different substitution pattern in the benzene ring. If you like names, you may call it the Reissert synthesis, and this is the basic reaction.

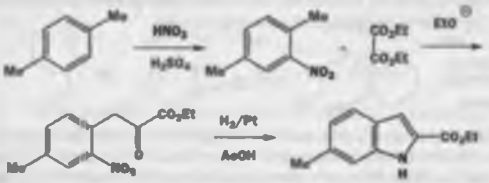


Ethoxide is a strong enough base to remove a proton from the methyl group, delocalizing the negative charge into the nitro group. The anion then attacks the reactive diester (diethyl oxalate) and is acylated by it.

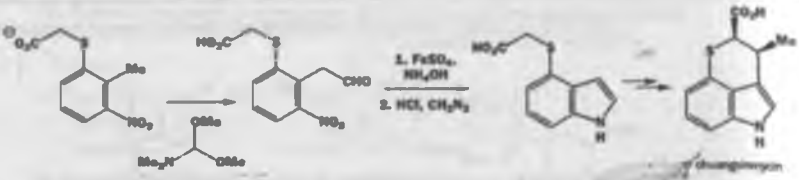


The rest of the synthesis is more straightforward: the nitro group can be reduced to an amine, which immediately forms an enamine by intramolecular attack on the more reactive carbonyl group (the ketone) to give the aromatic indole.

Since the nitro compound is made by nitration of a benzene ring, the preferred symmetry is very different from that needed for the Fischer synthesis. Nitration of *para*-xylene (1,4-dimethylbenzene) is a good example.



The ester products we have been using so far can be hydrolysed and decarboxylated by the mechanism described in the last chapter if a free indole is required. In any case, it is not necessary to use diethyl oxalate as the electrophilic carbonyl compound. The strange antibiotic chuangxinmycin (which you met in Chapter 32) was made by a Reissert synthesis using the acetal of DMF as the electrophile. Here is part of the synthesis.

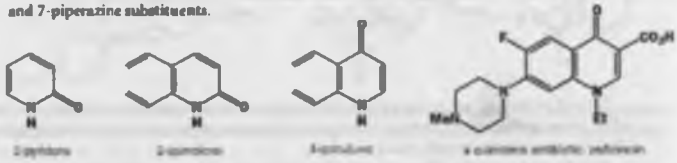


Quinolines and isoquinolines

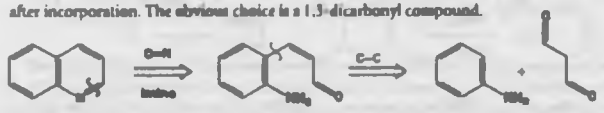
We move from benzo-fused pyrroles to benzo-fused pyridines and meet quinoline and isoquinoline. Isoquinolines will feature as benzylisoquinoline alkaloids in Chapter 51 and their synthesis will mostly be discussed there. In this section we shall concentrate on the quinolines.

Quinoline forms part of the structure of quinine, the malaria remedy found in cinchona bark and known since the time of the Incas. The quinoline in quinine has a 6-MeO substituent and a side chain attached to C4. In discussing the synthesis of quinolines, we will be particularly interested in this pattern. This is because the search for anti-malarial compounds continues and other quinolines with similar structures are among the available anti-malarial drugs.

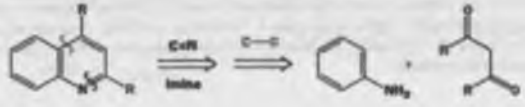
We shall also be very interested in quinolones, analogous to pyridones, with carbonyl groups at positions 2 and 4 as these are useful antibiotics. A simple example is pefloxacin which has a typical 6-F and 7-piperazine substituents.



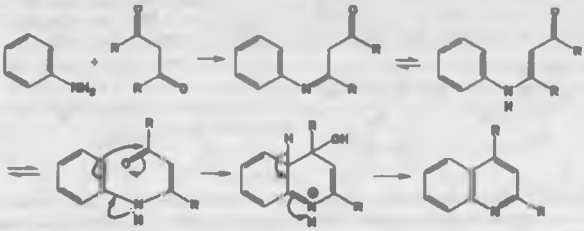
When we consider the synthesis of a quinoline, the obvious disconnections are, first, the C–N bond in the pyridine ring and, then, the C–C bond that joins the side chain to the benzene ring. We will need a three-carbon (C_3) synthon, electrophilic at both ends, which will yield two double bonds after incorporation. The obvious choice is a 1,3-dicarbonyl compound.



The choice of an aromatic amine is a good one as the NH_2 group reacts well with carbonyl compounds and it activates the *ortho* position to electrophilic attack. However, the dialdehyde is malonic dialdehyde, a compound that does not exist, so some alternative must be found. If the quinoline is substituted in the 2- and 4-positions this approach looks better.



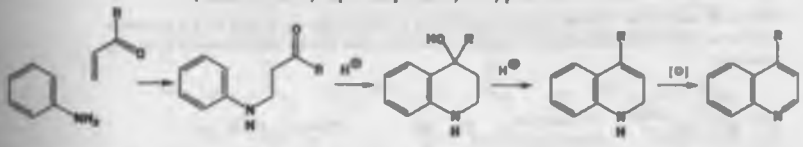
The initially formed imine will tautomerize to a conjugated enamine and cyclization now occurs by electrophilic aromatic substitution



The enamine will normally prefer to adopt the first configuration shown in which cyclization is not possible, and (perhaps for this reason or perhaps because it is difficult to predict which quinoline will be formed from an unsymmetrical 1,3-dicarbonyl compound) this has not proved a very important quinoline synthesis. We shall describe two more important variants on the same theme, one for quinolines and one for quinolones.

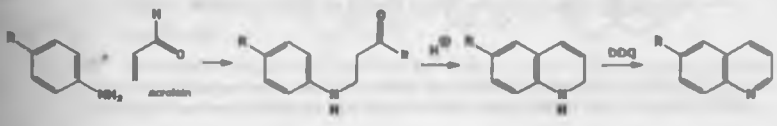
In the synthesis of pyridines it proved advantageous to make a dihydropyridine and oxidize it to a pyridine afterwards. The same idea works well in probably the most famous quinoline synthesis, the Skraup reaction. The diketone is replaced by an unsaturated carbonyl compound so that the quinoline is formed regiospecifically.

The first step is conjugate addition of the amine. Under acid catalysis the ketone now cyclizes in the way we have just described to give a dihydroquinoline after dehydration. Oxidation to the aromatic quinoline is an easy step accomplished by many possible oxidants.

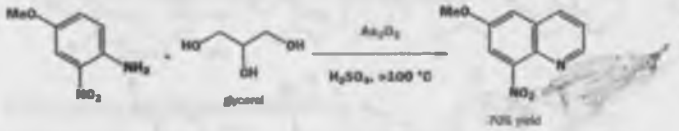


Traditionally, the Skraup reaction was carried out by mixing everything together and letting it rip. A typical mixture to make a quinoline without substituents on the pyridine ring would be the aromatic amine, concentrated sulfuric acid, glycerol, and nitrobenzene all heated up in a large flask at over 100 °C with a wide condenser.

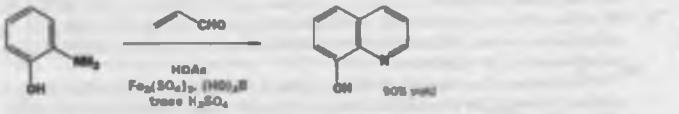
The glycerol was to provide acrolein (CH_2=CH-CHO) by dehydration, the nitrobenzene was to act as oxidant, and the wide condenser...? All too often Skraup reactions did let rip—with destructive results. A safer approach is to prepare the conjugate adduct first, cyclize it in acid solution, and then oxidize it with one of the reagents we described for pyridine synthesis, particularly quinones such as DDQ.



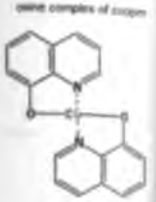
An important use of the traditional Skraup synthesis is to make 6-methoxy-8-nitroquinoline from an aromatic amine with only one free *ortho* position, glycerol, the usual concentrated sulfuric acid, and the oxidant arsenic pentoxide. Though the reported procedure uses 588 grams of As_2O_5, which might disconcert many chemists, it works well and the product can be turned into other quinolines by reduction of the nitro group, diazotization, and nucleophilic substitution (Chapter 23).



The more modern style of Skraup synthesis is used to make 8-quinolinol or 'oxine'. *ortho*-Aminophenol has only one free position *ortho* to the amino group and is very nucleophilic, so acrolein can be used in weak acid with only a trace of strong acid. Iron(III) is the oxidant with a bit of boric acid for luck, and the yield is excellent.

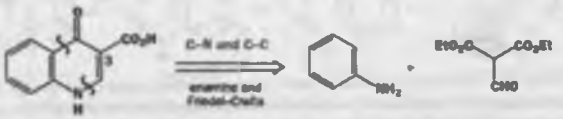


This compound is important because it forms unusually stable metal complexes with metal ions such as Mg(II) or Al(III). It is also used as a corrosion inhibitor on copper because it forms a stable layer of Cu(II) complex that prevents oxidation of the interior.

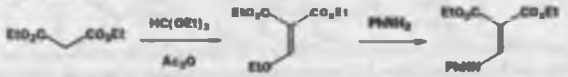


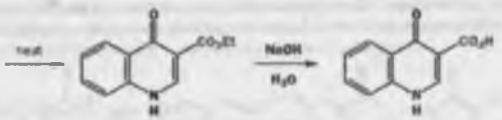
Quinolones also come from anilines by cyclization to an *ortho* position

The usual method for making quinolone antibiotics is possible because they all have a carboxylic acid in the 3-position. Disconnection suggests a rather unstable malonic ester derivative as starting material.

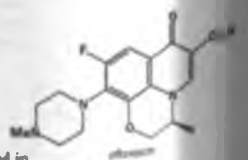


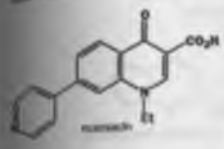
In fact, the enol ether of this compound is easily made from diethyl malonate and ethyl orthoformate [$HC(OEt)_3$]. The aromatic amine reacts with this compound by an addition–elimination sequence giving an enamine that cyclises on heating. This time there is no worry about the geometry of the enamine.





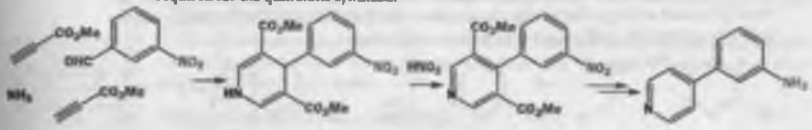
For examples of quinolone antibiotics we can choose ofloxacin, whose synthesis is discussed in detail in Chapter 23, and rosoxacin whose synthesis is discussed overleaf. Both molecules contain the



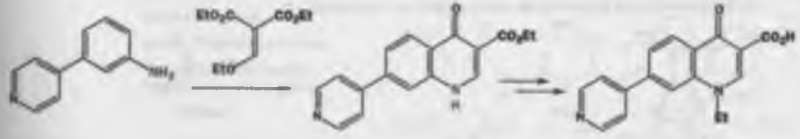


same quinolone carboxylic acid framework, outlined in black, with another heterocyclic system at position 7 and various other substituents here and there.

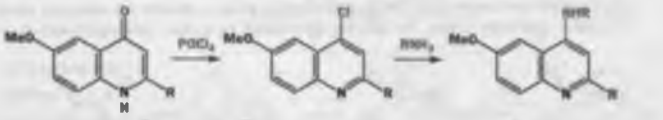
To make rosoxacin two heterocyclic systems must be constructed. Workers at the pharmaceutical company Sterling decided to build the pyridine in an ingenious version of the Hantzsch synthesis using acetylenic esters on 3-nitrobenzaldehyde. The ammonia was added as ammonium acetate. Oxidation with nitric acid made the pyridine, hydrolysis of the esters and decarboxylation removed the acid groups, and reduction with Fe(II) and HCl converted the nitro group into the amino group required for the quinolone synthesis.



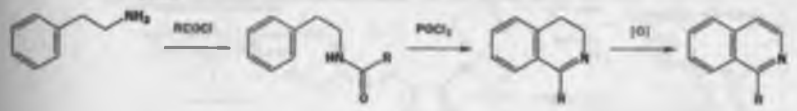
Now the quinolone synthesis can be executed with the same reagents we used before and all that remains is ester hydrolysis and alkylation at nitrogen. Notice that the quinolone cyclization could in theory have occurred in two ways as the two positions *ortho* to the amino group are different. In practice cyclization occurs away from the pyridine ring as the alternative quinolone would be impossibly crowded.



Since quinolones, like pyridones, can be converted into chloro-compounds with $POCl_3$, they can be used in nucleophilic substitution reactions to build up more complex quinolines.



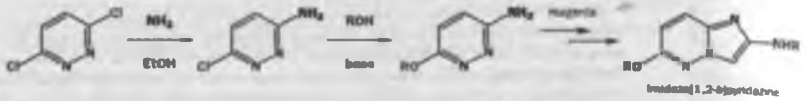
Because isoquinolines are dealt with in more detail in Chapter 51, we will give just one important synthesis here. It is a synthesis of a dihydroisoquinoline by what amounts to an intramolecular Vilsmeier reaction in which the electrophile is made from an amide and $POCl_3$. Since, to make the isoquinoline, two hydrogen atoms must be removed from carbon atoms it makes more sense to use a noble metal such as Pd(0) as the oxidizing agent rather than the reagents we used for pyridine synthesis.



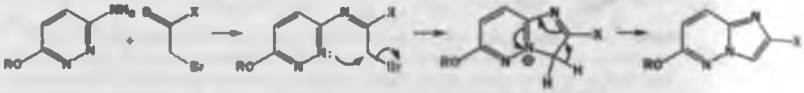
More heteroatoms in fused rings mean more choice in synthesis

The imidazo-pyridazine ring system forms the basis for a number of drugs in human and animal medicine. The synthesis of this system uses chemistry discussed in Chapter 43 to build the pyridazine ring. There we established that it was easy to make dichloropyridazines and to displace the chlorine

atoms one by one with different nucleophiles. Now we will move on from these intermediates to the bicyclic system.

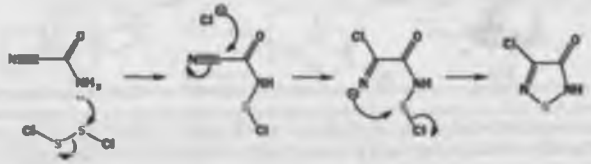


A 2-bromo-acid derivative is the vital reagent. It reacts at the amino nitrogen atom with the carbonyl group and at the pyridazine ring nitrogen atom with the alkyl halide. This is the only way the molecule can organize itself into a ten-electron aromatic system.

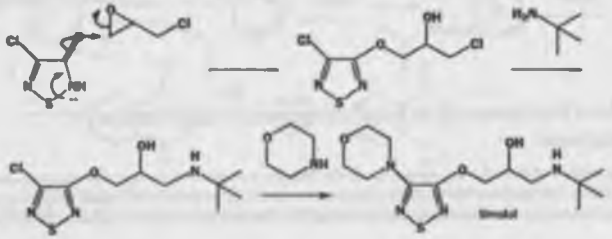


In Chapter 43 we also gave the structure of timolol, a thiadiazole-based β-blocker drug for reduction of high blood pressure. This compound has an aromatic 1,2,5-thiadiazole ring system and a saturated morpholine as well as an aliphatic side chain. Its synthesis relies on ring formation by rather a curious method followed by selective nucleophilic substitution, rather in the style of the last synthesis. The aromatic ring is made by the action of S_2Cl_2 on 'cyanamide'.

This reaction must start by attack of the amide nitrogen on the electrophilic sulfur atom. Cyclization cannot occur while the linear nitrile is in place as chloride ion must first attack CN. Thereafter cyclization is easy. The chloride ion probably comes from disproportionation of ClS^-.



Reaction with epichlorohydrin (the chloroepoxide shown below) followed by amine displacement puts in one of the side chains and nucleophilic substitution with morpholine on the ring completes the synthesis.



Summary: the three major approaches to the synthesis of aromatic heterocycles

We end this chapter with summaries of the three major strategies in the synthesis of heterocycles:

- ring construction by ionic reactions
- ring construction by pericyclic reactions
- modification of existing rings by electrophilic or nucleophilic aromatic substitution or by lithiation and reaction with electrophiles

We will summarize the different applications of these strategies, and also suggest cases for which each strategy is not suitable. This section revises material from Chapter 43 as well since most of the ring modifications appear there.

> This is only a summary. There are more details in the relevant sections of Chapters 43 and 44. There are also many, *many* more ways of making all these heterocycles. These methods are just where we suggest you start.

Ring construction by ionic cyclization

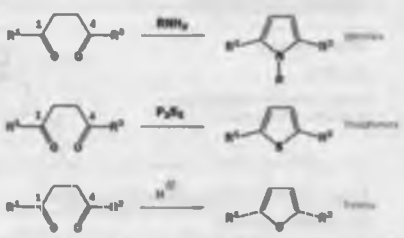
The first strategy you should try out when faced with the synthesis of an aromatic heterocyclic ring is the disconnection of bonds between the heteroatom or atoms and carbon, with the idea of using the heteroatoms as nucleophiles and the carbon fragment as a double electrophile.

Heterocycles with one heteroatom

five-membered rings

pyrroles, thiophenes, and furans

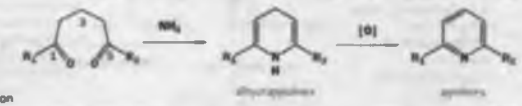
ideally made by this strategy from 1,4-dicarbonyl compounds



six-membered rings

pyridines

made by this strategy from 1,5-dicarbonyl compounds with oxidation

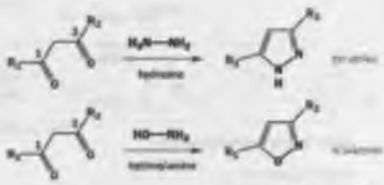


Heterocycles with two adjacent heteroatoms

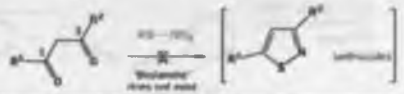
five-membered rings

pyrazoles and isoxazoles

ideally made by this strategy from 1,3-dicarbonyl compounds



Note. This strategy is *not* suitable for isothiazoles as "thial amine" does not exist

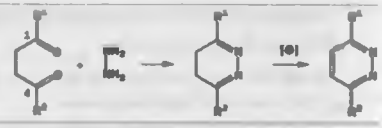


Summary: the three major approaches to the synthesis of aromatic heterocycles

six-membered rings

pyridazines

Ideally made by this strategy from 1,4-dicarbonyl compounds with oxidation

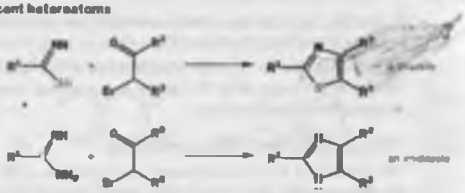


Heterocycles with two non-adjacent heteroatoms

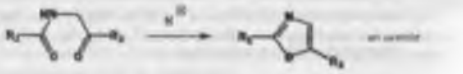
five-membered rings

imidazoles and triazoles

Ideally made by this strategy from a halocarbonyl compound



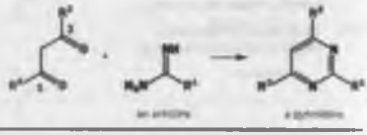
Note. This strategy is not suitable for oxazoles as amides are not usually reactive enough: cyclization of acylated carbonyl compounds is usually preferred



six-membered rings

pyrimidines

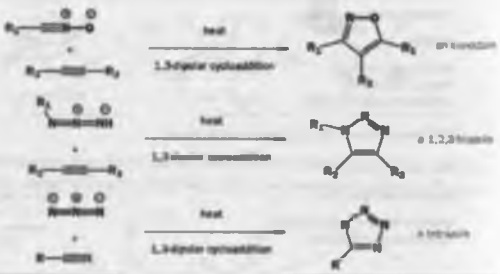
Ideally made by this strategy from 1,3-dicarbonyl compounds



Ring construction by pericyclic reactions

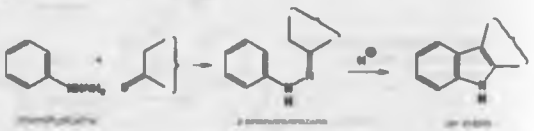
Cycloaddition reactions

1,3-dipolar cycloaddition is ideal for the construction of isoxazoles, 1,2,3-triazoles, and tetrazoles



Sigmatropic rearrangements

a special reaction that is the vital step of the Fischer indole synthesis

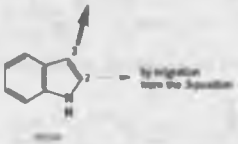


Ring modification

Electrophilic aromatic substitution

works very well on pyrroles, thiophenes and furans where it occurs best in the 2- and 5-positions and nearly as well in the 3- and 4-positions. Often best to block positions where substitution not wanted

works well for indole—occurs only at the 3-position but the electrophile may migrate to the 2-position



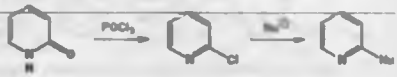
works well for five-membered rings with a sulfur, oxygen, or pyrrole-like nitrogen atom and occurs anywhere that is not blocked (see earlier sections)

Note. Not recommended for pyridine, quinoline, or isoquinoline

Nucleophilic aromatic substitution

works particularly well for pyridine and quinoline where the charge in the intermediate can rest on nitrogen

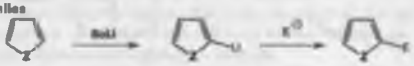
especially important for pyridones and quinolones with conversion to the chloro-compound and displacement of chlorine by nucleophiles and, for quinolines, displacement of fluorine atoms on the benzene ring



works well for the six-membered rings with two nitrogens (pyridazines, pyrimidines, and pyrazines) in all positions

Lithiation and reaction with electrophiles

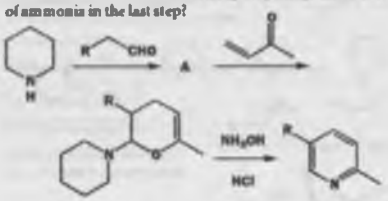
works well for pyrrole (if NH blocked), thiophene, or furan next to the heteroatom. Exchange of Br or I for Li works well for most electrophiles providing any acidic hydrogens (including the NH in the ring) are blocked



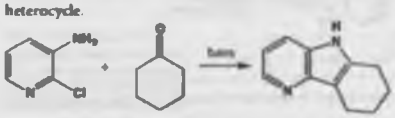
Z = NR, S, or O

Problems

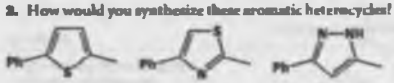
1. In this pyridine synthesis, give a structure for A and mechanisms for the reactions. Why is hydroxylamine used instead of ammonia in the last step?



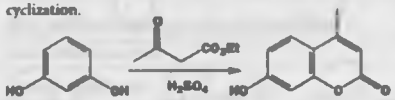
2. Suggest a mechanism for this synthesis of a tricyclic aromatic heterocycle.



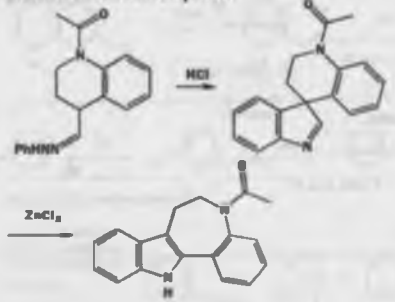
3. How would you synthesize these aromatic heterocycles?



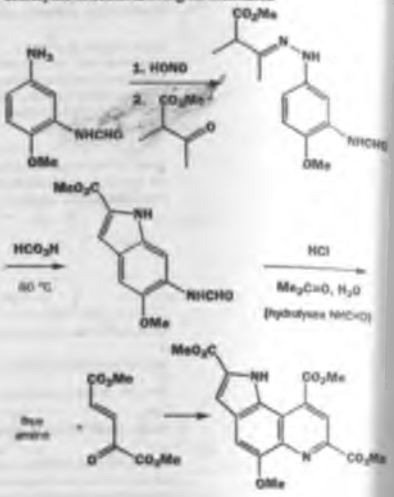
4. Is the heterocyclic ring created in this reaction aromatic? How does the reaction proceed? Comment on the selectivity of the cyclization.



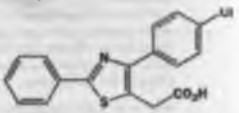
5. Suggest mechanisms for this unusual indole synthesis. How does the second reaction relate to electrophilic substitution at indoles as discussed in Chapter 33?



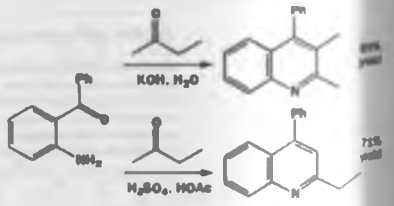
6. Explain the reactions in this partial synthesis of methoxatin, the coenzyme of bacteria living on methanol.



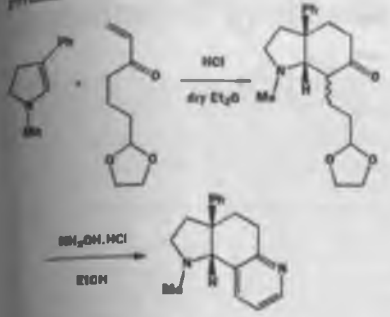
7. Suggest a synthesis of fentiazac, a nonsteroidal anti-inflammatory drug. The analysis is in the chapter but you need to explain why you need these particular starting materials as well as how you would make them.



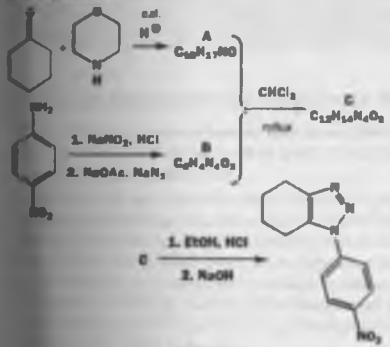
8. Explain why these two quinoline syntheses from the same starting materials give (mainly) different products.



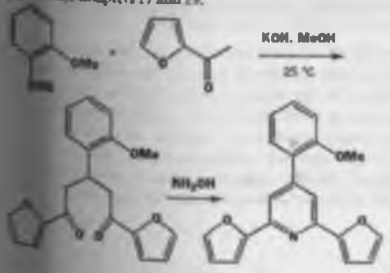
9. Give mechanisms for these reactions used to prepare a fused pyridine. Why is it necessary to use a protecting group?



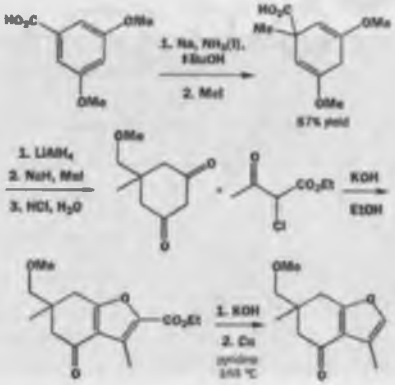
10. Identify the intermediates and give mechanisms for the steps in this synthesis of a triazole.



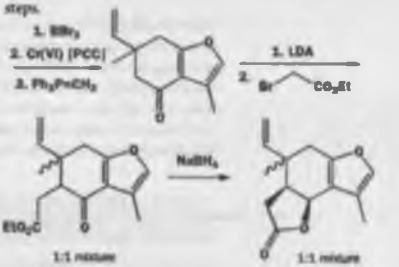
11. Give detailed mechanisms for this pyridine synthesis. The first part reviews Chapters 27 and 29.



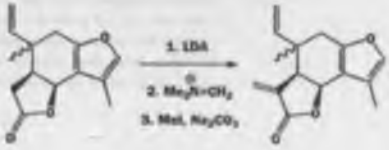
12. This question revises a number of previous chapters, especially 24–26, and 39. Give mechanisms for the reactions in this synthesis of a furan and comment on the choice of reagents for the various steps.



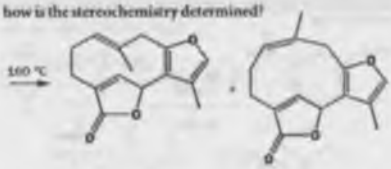
13. This question shows the purpose of making the furan in Problem 12 and revises material from Chapters 33 and 36. The above furan was used in the synthesis of the natural product linderalactone by first alkylation and reduction. Give mechanisms for the reactions and comment on the stereochemistry of these steps.



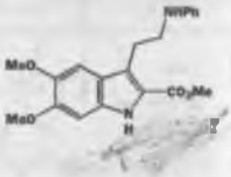
A version of the Mannich reaction on this lactone then gave an unsaturated compound that is still a 1:1 mixture of diastereoisomers. Give mechanisms for these reactions.



Each diastereoisomer of this unsaturated lactone rearranged on heating into a different isomer of a ten-membered cyclic diene. What sort of reaction is this, what kind of isomers are they, and how is the stereochemistry determined?



14. Suggest syntheses for this compound, explaining why you choose this particular approach.



Asymmetric synthesis

45

Connections

Building on:

- Carbonyl group reactions ch6, ch9, ch10, ch12, & ch14
- Controlling stereochemistry ch16, ch33, & ch34
- Electrophilic addition to alkenes ch20
- Aldol reactions ch27
- Diastereoselectivity ch33–ch34
- Cycloadditions ch35

Arriving at:

- Why making pure enantiomers matters
- Chirality derives from nature
- Resolution is the last resort
- The chiral pool provides starting materials
- Chiral auxiliaries are widely used with success
- Chiral reagents and catalysts may be even better
- Industrial asymmetric synthesis
- Two famous methods invented by Sharpless

Looking forward to:

- Main group chemistry ch46–ch47
- Organometallic chemistry ch48

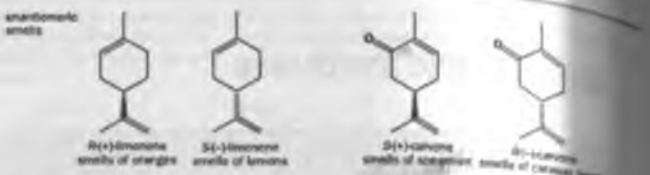
Nature is asymmetrical—nature in the looking-glass

'How would you like to live in Looking-glass House, Kitty! I wonder if they'd give you milk in there? Perhaps looking glass milk isn't good to drink...' Lewis Carroll, *Through the looking-glass and what Alice found there*, Macmillan, 1872.

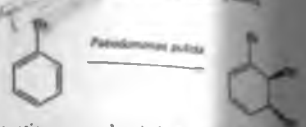
You are chiral, and so are Alice, Kitty, and all living organisms. You may think you look fairly symmetrical in a looking-glass, but as you read this book you are probably turning the pages with your right hand and processing the information with the left side of your brain. Some organisms are rather more obviously chiral: snails, for example, carry shells that could spiral to the left or to the right. Not only is nature chiral, but by and large it exists as just one enantiomer—though some snail shells spiral to the left, the vast majority of marine snail shells spiral to the right; all humans have their stomach on their left and their liver on their right; all honeysuckle climbs by spiralling to the left and all bindweed spirals to the right.

> **'L'univers est dissymétrique', Louis Pasteur, ca. 1860**

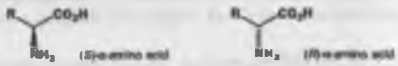
Nature has a left and a right, and it can tell the difference between them. You may think that human beings are sadly lacking in this respect, since as children we all had to learn, rather laboriously, which is which. Yet at an even earlier age, you could no doubt distinguish the smell of oranges from the smell of lemons, even though this is an achievement at least as remarkable as getting the right shoe on the right foot. The smells of orange and lemon differ in being the left- and right-handed versions of the same molecule, limonene. (*R*)-(+)-Limonene smells rounded and orangey; (*S*)-(−)-limonene is sharp and lemony. Similarly, spearmint and caraway seeds smell quite different, though again this pair of aromas differs only in being the enantiomeric forms of the ketone carvone.



Even bacteria know their right from their left: *Pseudomonas putida* is a bacterium that can use aromatic hydrocarbons as a foodstuff, degrading them to diols. The diol produced from bromobenzene is formed as one enantiomer only.

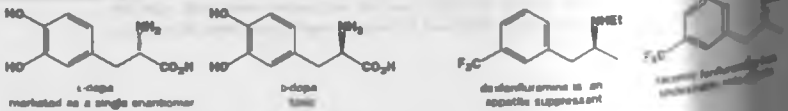


How can this be? We said in Chapter 16 that enantiomers are chemically identical, so how is it that we can distinguish them with our noses and bacteria can produce them selectively? With the answer lies in a proviso to our assumption about the identity of enantiomers: they are identical only *they are placed in a chiral environment*. This concept will underlie all we say in this chapter about ho... to make single enantiomers in the laboratory. We take our lead from Nature; all life is chiral, as all living systems are chiral environments. Nature has chosen to make all its living structures from chiral molecules (amino acids, sugars), and has selected a single enantiomeric form of each. Every amino acid in your body has the *S* and not the *R* configuration, and from this fact, along with the uniform chirality of natural sugars, derives the larger scale chirality of all living structures from the DNA double helix to a blue whale's internal architecture. The answer to Alice's question is most certainly another kitten will be able to degrade the achiral fats in the milk quite easily, but the proteins (which will be made of *S*-amino acids) and L-lactose will be quite indigestible.



For a perfumer or flavour and fragrance manufacturer, the distinction between enantiomers of the same molecule is clearly of great importance. Nonetheless, we could all get by with caraway-flavoured toothpaste. Yet when it comes to drug molecules, making the right enantiomer can be a matter of life and death. Parkinson's disease sufferers are treated with the non-proteinogenic amino acid dopa (3-(3,4-dihydroxyphenyl)alanine; mentioned in Chapter 31). Dopa is chiral, and only (known as L-dopa) is effective in restoring nerve function. (*R*)-dopa is not only ineffective but, in fact, quite toxic, so the drug must be marketed as a single enantiomer. We will look at how it is made industrially later in the chapter.

The amphetamine analogue fenfluramine, whose synthesis you designed while you were revising Chapter 31, used to be marketed as an anorectic (appetite-suppressant)—it stimulates the production of the hormone serotonin and makes the body feel satisfied—until it became clear that some undesirable side-effects could be avoided by administering it solely as the (*S*)-enantiomer. Fenfluramine 'relaunched' as the enantiomerically pure dexfenfluramine, and was reputedly 'a winning point for your overweight patients'—was available in the USA as a component of the 'slimming pill' Redux.



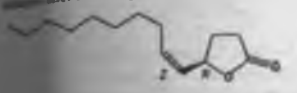
Some bacteria make their cell walls from 'unnatural' *R*-amino acids to make them unassailable by the (*S*-amino-acid-derived) enzymes used by higher organisms to hydrolyse peptides.

You might, of course, retort that, in going through the looking-glass, perhaps Alice's kitten has undergone a universal inversion of configuration so that her proteins are all made of *R*-amino acids. Who can tell?

That is, dopa is not one of the 20 natural amino acids found in proteins; see Chapter 48.

There is no clear relationship between molecular chirality and the chirality of life forms. Right- and left-handed people are made from amino acids and sugars of the same handedness and the rare left-hand-spiralling snails have the same molecular chirality as their more common right-hand-spiralling relatives.

It is not only drugs that have to be manufactured enantiomerically pure. This simple lactone is the pheromone released by Japanese beetles (*Popilia japonica*) as a means of communication. The beetles, whose larvae are serious crop pests, are attracted by the pheromone, and synthetic pheromone is marketed as 'Japonilure' to bait beetle traps. Provided the synthetic pheromone is the correct isomer shown, with the *Z* double bond and the *R* configuration at the stereogenic centre, only 25 μg per trap catches thousands of beetles. You first met this compound in Chapter 32, where we pointed out that double bond stereocontrol was important since the *E*-isomer of the pheromone is virtually useless as a bait (it retains only about 10% of the activity). Even more important is control over the configuration at the chiral centre, because the *S*-enantiomer of the pheromone is not only inactive in attracting the beetles, but acts as a powerful inhibitor of the *R*-enantiomer—even 1% *S*-enantiomer in a sample of pheromone destroys the activity.

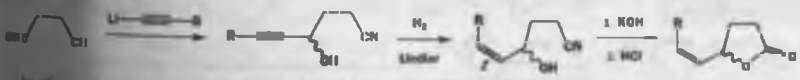


Japanese beetle pheromone

You can see why chemists need to be able to make compounds as single enantiomers. In Chapters 31–34 you looked at relative stereochemistry and how to control it; this chapter is about how to control absolute stereochemistry. In the last 20 years or so, this subject has occupied more organic chemists than probably any other, and we are now at a point where it is not only possible (and in fact essential, because of strict regulatory rules) to make many drug molecules as single enantiomers, but it is also even possible to make some molecules that are indigenous to nature more cheaply in the lab. At least 30% of the world's supply of menthol, for example, is not extracted from plants but is made in Japan using chemical techniques (which you will meet later in this chapter) that produce only a single enantiomer.

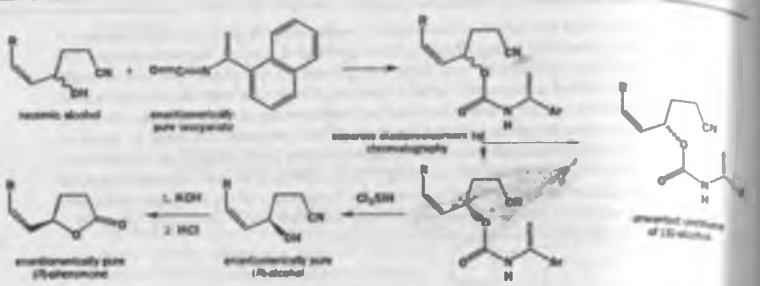
Resolution can be used to separate enantiomers

When we first introduced the concept of enantiomers and chirality in Chapter 16, we stressed that any imbalance in enantiomers always derives ultimately from nature. A laboratory synthesis, unless it involves an enantiomerically pure starting material or reagent, will always give a mixture of enantiomers. Here is just such a synthesis of the Japanese beetle pheromone you have just met. You can see the *Z*-selective Lindlar reduction in use—only one geometrical isomer of the double bond is formed—but, of course, the product is necessarily racemic and therefore useless as beetle bait, because in the original addition of the lithiated alkyne to the aldehyde there can be no control over stereochemistry. If all the starting materials and reagents are achiral, the product must be racemic.



racemic pheromone

In Chapter 16 we introduced you to resolution as a means of separating enantiomers, so if we want just the (*R*) compound, we could try that. Resolving the pheromone itself is not straightforward as there are no convenient functional groups to attach a resolving agent to. But the precursor alcohol can be resolved—William Pirkle did this by reacting the racemic alcohol with an enantiomerically pure amine to make a mixture of the two diastereoisomeric amides which he then separated by chromatography. The resolving agent was removed from one of the diastereoisomers to give a single enantiomer of the alcohol, which could be cyclized to the natural (*R*)-pheromone using base and then acid.



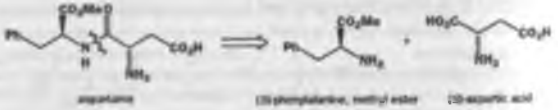
▶ Later in the chapter, you will see an example of resolution of a compound (BINAP) for which there is a demand for both enantiomers as components of chiral catalysts. Resolution is the best option there.

This is not, however, the method used to make Japanese beetle pheromone industrially. Resolution, as you have probably realized, is highly wasteful—if you want just one enantiomer, the other ends up being thrown away. In industrial synthesis, this is not an option unless recycling is possible, since chemical plants cannot afford the expense of disposing of such quantities of high-quality waste. So we need alternative methods of making single enantiomers.

The chiral pool—Nature's 'ready-made' chiral centres

A more economical way of making compounds as single enantiomers is to manufacture them using an enantiomerically pure natural product as a *starting material*, rather than just using one as a resolving agent. This method is known as the **chiral pool strategy**, and relies on finding a suitable enantiomerically pure natural product—a member of the chiral pool—that can easily be transformed into the target molecule. The chiral pool is that collection of cheap, readily available pure natural products, usually amino acids or sugars, from which pieces containing the required chiral centres can be taken and incorporated into the product.

Sometimes the natural products that are needed are immediately obvious from the structure of the target molecule. An apparently trivial example is the artificial sweetener aspartame (marketed as Nutrasweet), which is a dipeptide. Clearly, an asymmetric synthesis of this compound will start with the two members of the chiral pool, the constituent (natural) (*S*)-amino acids, aspartic acid and phenylalanine. In fact, because phenylalanine is relatively expensive for an amino acid, significant quantities of aspartame derive from synthetic (*S*)-phenylalanine made by one of the methods discussed later in the chapter.



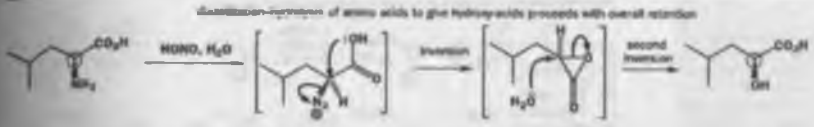
aspartame (S)-phenylalanine, methyl ester (S)-aspartic acid

Most asymmetric syntheses require rather more than one or two steps from chiral pool constituents. Male bark beetles of the genus *Ips* produce a pheromone that is a mixture of several enantiomerically pure compounds. One is a simple diene alcohol (*S*)-(−)-ipsenol. Japanese chemists in the 1970s noted the similarity of part of the structure of ipsenol (in black) to the widely available amino acid (*S*)-leucine and decided to exploit this in a chiral pool synthesis, using the stereogenic centre (green ring) of leucine to provide the stereogenic centre of ipsenol.

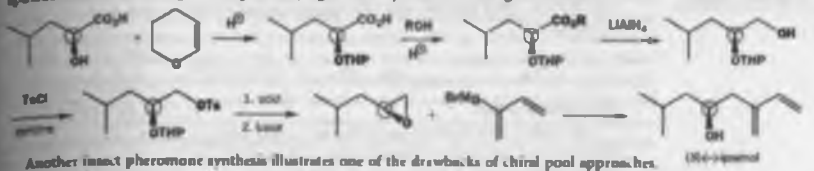
■ Participation was discussed in Chapters 37 and 41. You will see another example of conversion of NH_2 to OH with retention shortly. This is a useful reaction for converting amino acids to many versatile hydroxyacids.

(S)-(−)-ipsenol (S)-leucine

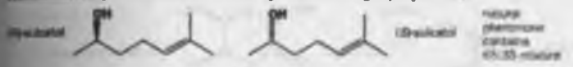
The amino group needs to be converted to a hydroxyl group with retention of configuration. Diazotization followed by hydrolysis does just this because of neighbouring group participation from the carboxylic acid.



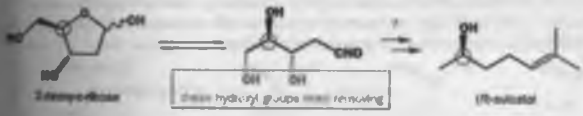
The alcohol was protected as the THP derivative (Chapter 24). Reduction of the acid, via the ester, then allowed introduction of the tosyl leaving group, which was displaced to make an epoxide. The epoxide reacted with a Grignard reagent carrying the diene portion of the target molecule.



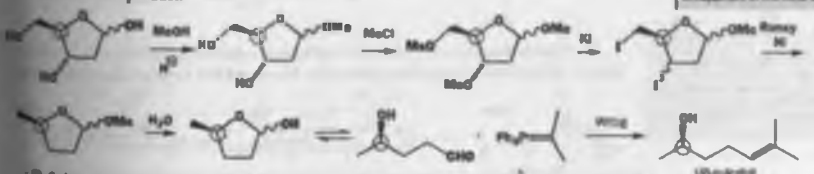
Another insect pheromone synthesis illustrates one of the drawbacks of chiral pool approaches. The ambrosia beetle aggregation pheromone is called sulcatol and is a simple secondary alcohol. This pheromone poses a rather unusual synthetic problem: the beetles produce it as a 65:35 mixture of enantiomers so, in order to mimic the pheromone's effect, the chemist has to synthesize both enantiomers separately and mix them together in the right proportion.



One approach to the (*R*)-enantiomer employs the sugar found in DNA, 2-deoxy-D-ribose, as a source of chirality.

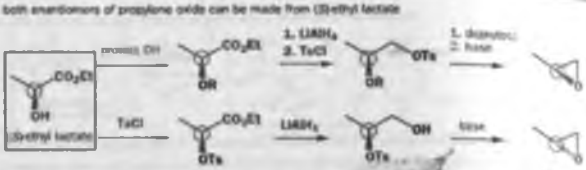


Only one (ringed with green again) of the two defined chiral centres in the sugar appears in the product so, after protecting the hemiacetal, the two free hydroxyl groups were removed by mesylation, substitution by iodide, and reduction. A simple olefination gave (*R*)-sulcatol. Sugars often need simplifying in this way, because only rarely are all their chiral centres (most have more than two!) needed in the final product.

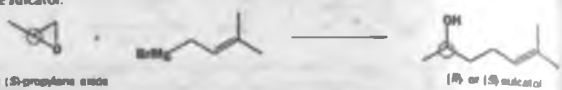


(*R*)-Sulcatol cannot be made by this route, because the L-sugar is unavailable (even D-deoxyribose is quite expensive), so an alternative synthesis was needed that could be adapted to give either enantiomer. The solution is to go back to another hydroxy-acid, ethyl lactate, which is more widely available as its (*S*)-enantiomer, but which can be converted simply to either enantiomer of a key epoxide intermediate. From (*S*)-ethyl lactate, protection of the alcohol, reduction of the ester, and tosylation allows ring closure to one enantiomer of the epoxide; tosylation of the secondary hydroxyl group followed by reduction and ring closure gives the other enantiomer.

both enantiomers of propylene oxide can be made from (S)-ethyl lactate



For this reason, the two enantiomers of propylene oxide are commonly used as "chiral pool" starting materials. These epoxides react with the appropriate Grignard reagent to give either enantiomer of the sulcatol.

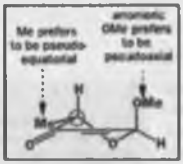


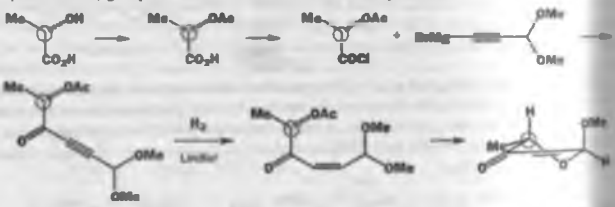
(R) or (S)-propylene oxide (R) or (S)-sulcatol

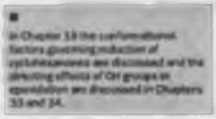
For targets with more than one stereogenic centre, only one need be borrowed from the chiral pool, provided diastereoselective reactions can be used to introduce the others with control over relative stereochemistry. Because the first chiral centre has defined absolute configuration, any diastereoselective reaction that controls the relative stereochemistry of a new chiral centre also defines its absolute configuration. In this synthesis of the rare amino sugar methyl mycaminoside, only one chiral centre comes directly from the chiral pool—the rest are introduced diastereoselectively.

(S)-lactic acid methyl mycaminoside

The ring was built up from acetylated (S)-lactic acid, and a cyclization step introduced the second chiral centre—the methyl group goes pseudoequatorial while the pseudoaxial position is preferred by the methoxy group because of the anomeric effect (Chapter 42).







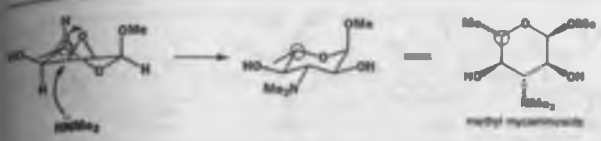
In Chapter 18 the conformational factors governing reduction of cyclohexanones are discussed and the directing effects of OH groups in epoxidation are discussed in Chapters 33 and 34.

The third stereogenic centre was controlled by axial reduction of the ketone to give the equatorial alcohol, which then directed introduction of the fourth and fifth stereogenic centres by epoxidation.

axial attack leads to more stable equatorial alcohol

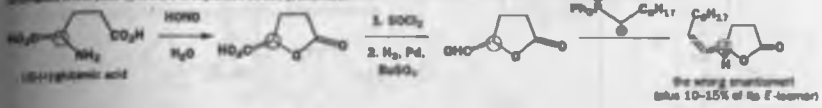
hydroxyl group directs epoxidation to top face by hydrogen bonding

Finally, the simple nucleophilic amine Me_2NH attacks the epoxide with inversion of configuration to give methyl mycaminoside. The conformational drawing shows that all substituents are equatorial except the MeO group, which prefers to be axial because of the anomeric effect.



methyl mycaminoside

The trouble with chiral pool approaches is that the compound you make has to be pretty close in structure to one of the natural products that are readily available or the synthetic route becomes so tortuous that it's even more wasteful than resolution. The second major drawback is the lack of availability of both enantiomers of most natural products, especially useful starting materials like amino acids and sugars—we have just met this problem with the synthesis of micatol from dausgyribose. As a further example, we can return again to our Japanese beetles. Their pheromone can be made from glutamic acid by a short route. Unfortunately, when widely available (*S*)-(+)-glutamic acid is used, the product is the *enantiomer* of the active pheromone, which you will remember is a powerful inhibitor of the natural pheromone. Making the right enantiomer is not economical, because (*R*)-(−)-glutamic acid is about 40 times more expensive than (*S*)-(+)-glutamic acid.

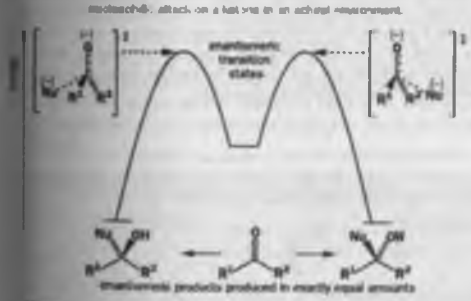


(*S*)-(+)-glutamic acid

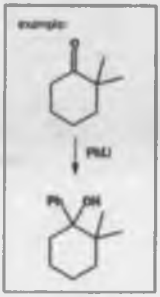
the wrong enantiomer (also 10–15% of its *E*-isomer)

Asymmetric synthesis

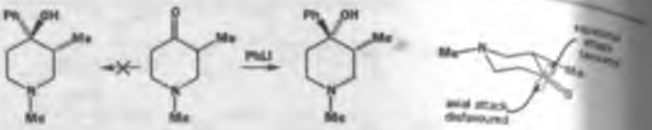
When we create a new stereogenic centre in a previously achiral molecule using achiral reagents (addition of CN^- to aldehydes was the example you met in Chapter 16), we get a racemic mixture because the transition states leading to the two enantiomers are themselves enantiomeric and therefore equal in energy.



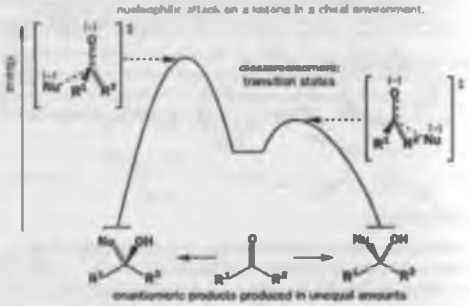
enantiomeric products produced in exactly equal amounts



Diastereoselective synthesis, on the other hand, relies on making the transition states for reactions leading to different diastereoisomers as different in energy as possible and therefore favouring the formation of one diastereoisomer over another. You met this type of stereoselectivity in Chapter 13. Here is a simple example: PhLi adds to this ketone to give one diastereoisomer of the tertiary alcohol and not the other. Attack on one or other face of the ketone leads to diastereomeric transition states: this is perhaps most obvious when you realize that one is axial and one equatorial attack. An energy diagram for this type of reduction appears on the next page.



Now, let's go back to the principle of resolution and see how we can devise a way of improving upon it that doesn't require us to throw away 50% of our product. Resolution works by attaching an enantiomerically pure resolving agent to the racemic substrate distinguishes the substrate's two enantiomers as diastereoisomers (diastereoisomers are chemically different, enantiomers are not). Can we use this same idea to make two enantiomeric (and therefore equal in energy) *transition states* into diastereoisomeric ones (which will therefore be unequal in energy)? If we can, the lower-energy transition state will be favoured and we will get more of one enantiomer than the other.

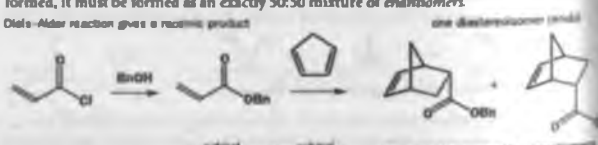


The answer is most definitely yes—what is needed is an enantiomerically pure molecule or part of a molecule that will be present during the reaction and will interact with the transition state of the reaction in such a way that it controls the formation of the new stereogenic centre. This molecule might be a reagent or a catalyst, or it might be covalently attached to the starting material. We will consider all of these possibilities, the last first, and you will see that they really are the most powerful and versatile ways of making enantiomerically pure compounds.

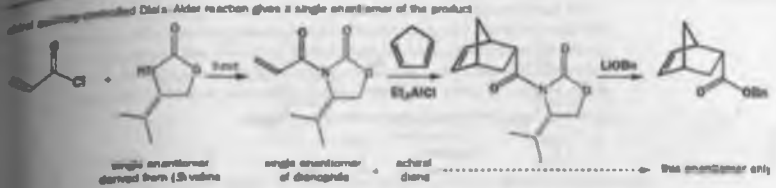
'Auxiliary' has but one 'l'.

Chiral auxiliaries

The product of a Diels–Alder reaction between cyclopentadiene and benzyl acrylate must necessarily be racemic as both reagents are achiral. Though only one *diastereoisomer*—the *endo* product—is formed, it must be formed as an exactly 50:50 mixture of *enantiomers*.

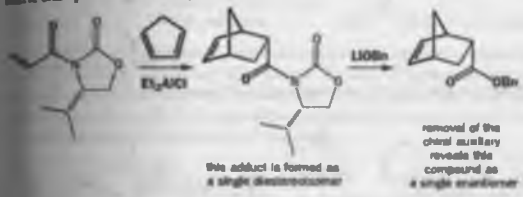


Now see what happens if we replace the achiral benzyl ester group with an amide derived from the natural amino acid valine (Chapter 49). The diastereoselectivity remains the same but the chiral environment created by the single enantiomer covalently bonded to the dienophile has a reconstructive effect: only one enantiomer of the product is formed.



As far as stereoselectivity is concerned, the key step is the Diels–Alder reaction—in each case the diene (cyclopentadiene, shown in black) adds across the dienophile, an acrylic acid derivative. As you would expect from what we said in Chapter 35, both reactions are diastereoselective in that they generate mainly the *endo* product. In the first example, that is all there is to say: the product that is formed is necessarily racemic because all the starting materials in the reaction were achiral.

But, in the second example, a green chiral auxiliary has been attached to one of the starting materials. It contains another stereogenic centre and is enantiomerically pure—it was, in fact, made by a chiral pool strategy from the amino acid (*S*)–valine (*see below*). You can see that it has quite an effect on the reaction—the extra stereogenic centre means that there are now *two* possible diastereoisomeric *endo* products, but only one is formed.



The chiral auxiliary was enantiomerically pure—every molecule had the same configuration at its stereogenic centre. That centre was not involved in the Diels–Alder reaction, so all the products will similarly have the same configuration at the stereogenic centre in the green part of the molecule. So, if one diastereoisomer of the product is formed, all the stereogenic centres in that product must be of a single configuration: in other words the product is diastereoisomerically *and* enantiomerically pure. And when we do the final step of the sequence, to remove the chiral auxiliary, this enantiomeric purity remains, despite the fact that we have removed its source. Overall, by temporary attachment and removal of the auxiliary we have made the same product but as a single enantiomer.

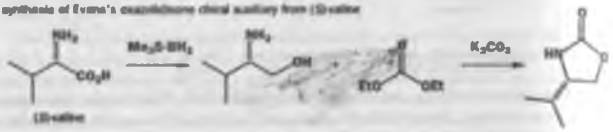
▶ You may note the inclusion of the Et_2AlCl Lewis acid catalyst in the second reaction. As we discussed in Chapter 35, the presence of a Lewis acid increases the rate of Diels–Alder reactions, and in this case is also vital for high stereoselectivity.

This is what we mean by a chiral auxiliary strategy

1. An enantiomerically pure compound (usually derived from a simple natural product like an amino acid), called a chiral auxiliary, is attached to the starting material.
2. A diastereoselective reaction is carried out, which, because of the enantiomeric purity of the chiral auxiliary, gives only one enantiomer of the product.
3. The chiral auxiliary is removed by, for example, hydrolysis, leaving the product of the reaction as a single enantiomer. The best chiral auxiliaries (of which the example above is one) can be recycled, so although stoichiometric quantities are needed, there is no waste.

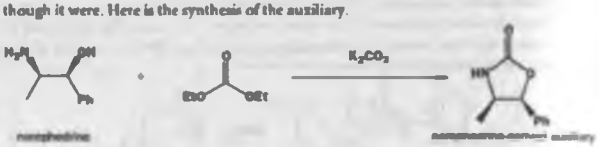
We have introduced you to this chiral auxiliary before any other because it is more commonly used than any other. It is a member of the oxazolidinone (the name of the heterocyclic ring) family of auxiliaries developed by David Evans at Harvard University, and is easily and cheaply made from the amino acid (*S*)-valine. Not only is it cheaply made: it can also be recycled. The last step of the route above, transesterification with benzyl alcohol, regenerates the auxiliary ready for re-use.

synthesis of Evans's oxazolidinone chiral auxiliary from (*S*)-valine



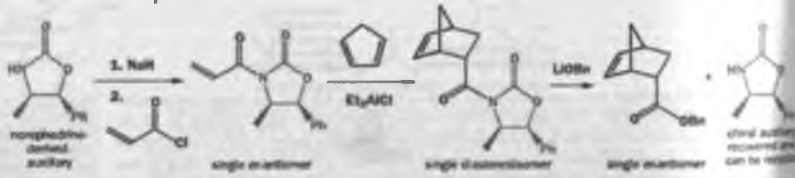
(*S*)-valine

The most versatile chiral auxiliaries should also be available as both enantiomers. Now, for the valine-derived one here, this is not the case—(*R*)-valine is quite expensive since it is not found in nature. However, by starting with the naturally occurring (and cheap) compound norephedrine, we can make an auxiliary that, although not enantiomeric with the one derived from (*S*)-valine, acts as though it were. Here is the synthesis of the auxiliary.



norephedrine

And here it is promoting the same asymmetric Diels–Alder reaction, but giving the enantiomeric product.



norephedrine-derived auxiliary

single enantiomer

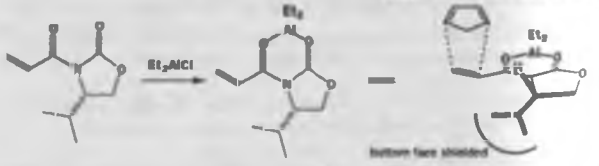
single diastereoisomer

single enantiomer

chiral auxiliary recovered and can be reused

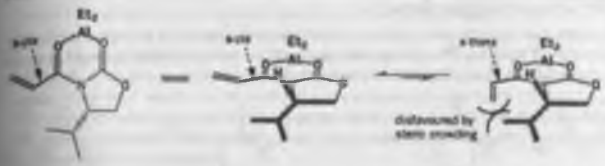
How do these auxiliaries fulfil their role? If we go back to the valine-derived auxiliary and draw the auxiliary-bearing dienophile coordinated with the Lewis acid you can clearly see that the isopropyl group shields the back face of the alkene from attack: when the cyclopentadiene moves in, it must approach from the front face (and remember it will align itself to gain maximum secondary orbital stabilization and therefore give the *endo* product).

cyclopentadiene must attack from top face



bottom face shielded

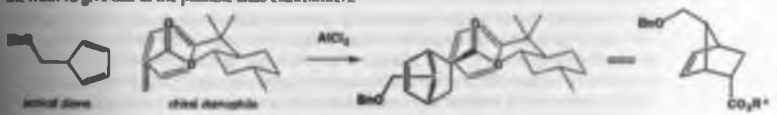
Note that the auxiliary also has the effect of fixing the conformation of the black single bond as *s*-*cis* (we introduced this nomenclature on p. 000). Attack on the top face of the *s*-*trans* conformer would give the enantiomeric product.



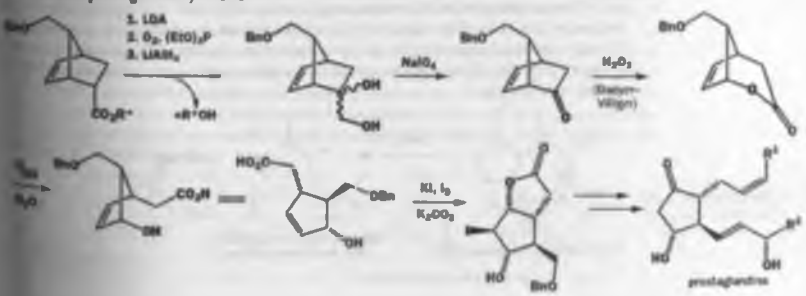
The auxiliary has succeeded in doing what we set out to do (p. 000)—it has made diastereoisomeric the transition states leading to enantiomeric products, the difference in energy arising because of steric crowding of one face of the alkene.

Lest you should imagine that all effective auxiliaries are oxazolidinones, here is a different one—8-phenylmenthol—used by Corey in enantioselective prostaglandin synthesis. 8-Phenylmenthol is made from the natural product pulegone (Chapter 51). Even in the starting material the role of the phenyl group is clearly to crowd one face of the dienophile.

A Lewis acid ($AlCl_3$)-catalysed Diels–Alder reaction with a substituted, but still achiral, cyclopentadiene gives a single enantiomer of the adduct. The sense of asymmetry induced in the reaction is seen more clearly if we redraw the product with 'R*' to represent the chiral auxiliary. The phenyl group on the auxiliary shields the back of the dienophile (as drawn) so that the diene has to add from the front to give one of the possible *endo* enantiomers.

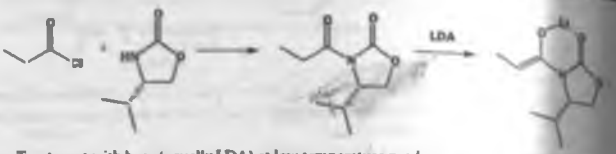


Corey used the four chiral centres created in the reaction to provide the chiral centres around the cyclopentanone ring of the prostaglandins (a family of compounds implicated in inflammation: see Chapter 51). After hydroxylation of the ester's enolate, the auxiliary was removed, this time by reduction. Diol cleavage with periodate (mentioned at the end of Chapter 35) gave a ketone that underwent Baeyer–Villiger oxidation on the more substituted side to give a hydrolysable lactone. Iodolactonization gave a substituted cyclopentanone that Corey used as a starting material for several important prostaglandin syntheses.



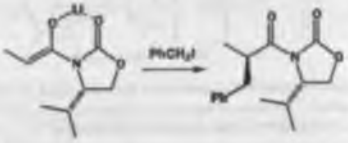
Alkylation of chiral enolates

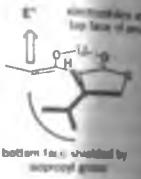
Chiral auxiliaries can be used in plenty of other reactions, and one of the most common types is the alkylation of enolates. Evans's oxazolidinone auxiliaries are particularly appropriate here because they are readily turned into enolizable carboxylic acid derivatives.



Treatment with base (usually LDA) at low temperature produces an enolate, and you can [illegible] see that the auxiliary has been designed to favour attack by electrophiles on only one face of that enolate. Notice too that the bulky auxiliary means that only the *Z*-enolate forms; alkylation of the *E*-enolate on the top face would give the diastereoisomeric product. Coordination of the lithium ion to the other carbonyl oxygen makes the whole structure rigid, fixing the isopropyl group where it can provide maximum hindrance to attack on the 'wrong' face.

Electrophile	Ratio of diastereoisomers
$PhCH_2I$	>99:1
allyl bromide	98:2
EtI	94:6

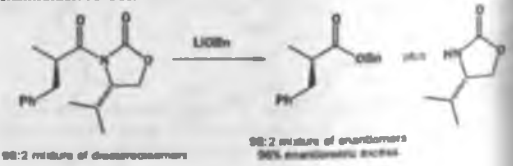




The table in the margin shows the ratio of diastereoisomers produced by this reaction for a few alkylating agents. As you can see, none of these reactions is truly 100% diastereoselective and, indeed, only the best chiral auxiliaries (of which this is certainly one) give >98% of a single diastereoisomer. The problem with less than perfect diastereoselectivity is that, when the chiral auxiliary is removed, the final product is contaminated with some of the other enantiomer. A 98:2 ratio of diastereoisomers will result in a 98:2 ratio of enantiomers.

Enantiomeric excess

When talking about compounds that are neither racemic nor enantiomerically pure (usually called enantiomerically enriched or, occasionally, scalemic) chemists talk not about ratios of enantiomers but about **enantiomeric excess**. Enantiomeric excess (or ee) is defined as the excess of one enantiomer over the other, expressed as a percentage of the whole. So a 98:2 mixture of enantiomers consists of one enantiomer in 96% excess over the other, and we call it an enantiomerically enriched mixture with 96% ee. Why not just say that we have 98% of one enantiomer? Enantiomers are not like other isomers because they are simply mirror images. The 2% of the wrong enantiomer is a racemate of 2% of the right isomer so the mixture contains 4% racemate and 96% of one enantiomer. 96% ee.



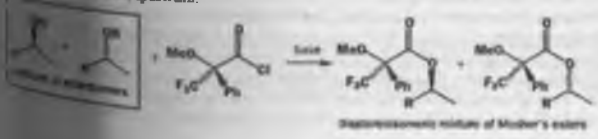
We will see shortly how we can make further use of the chiral auxiliary to increase the ee of the reaction products. But, first, we should consider how to measure ee. One way is simply to measure the angle through which the sample rotates plane-polarized light. The angle of rotation is proportional to the enantiomeric excess of the sample (see the Box). The problem with this method is that to measure an actual value for ee you need to know what rotation a sample of 100% ee gives, and that is not always possible. Also, polarimeter measurements are notoriously unreliable—they depend on temperature, solvent, and concentration, and are subject to massive error due to small amounts of highly optically active impurities.

Optical rotation should be proportional to enantiomeric excess

Imagine you have a sample, A, of an enantiomerically pure compound—a natural product perhaps—and, using a polarimeter, you find that it has an $[\alpha]_D$ of +10.0. Another sample, B, of the same compound, which you know to be enantiomerically pure (perhaps it is a synthetic example), shows an $[\alpha]_D$ of +8.0. What is its enantiomeric excess? Well, you would have got the same value of 8.0 for the $[\alpha]_D$ of B if you had mixed 80% of pure and enantiomerically pure A with 20% of its enantiomer (an achiral compound with no optical rotation). Since you know that sample B is enantiomerically pure, and is the same compound as A, it must therefore consist of 80% enantiomerically pure A mixed with 20% racemic material, or 90% of one enantiomer plus 20% of a 1:1 mixture of the two enantiomers—which is the same as 90% of one enantiomer and 10% of the other, or 80% enantiomeric excess. Optical rotations can give a guide to enantiomeric excess—sometimes (alas) optical purity in this context—but slight impurities of compounds with large rotations can distort the result and there are some examples where the linear relationship between ee and optical rotation fails because of what is known as the Horeau effect. You can read more about this in Eliel and Wilen, *Stereochemistry of organic compounds*, Wiley, 1994.

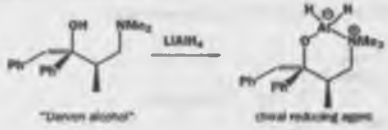
Modern chemists usually use either chromatography or spectroscopy to tell the *difference* between enantiomers. You may protest that we have told you that this is impossible—enantiomers are chemically identical and have identical NMR spectra, so how can chromatography or spectroscopy tell them apart? Well, again, they are identical unless they are in a chiral environment (the principle on which resolution relies). We introduced HPLC on a chiral stationary phase as a way of separating enantiomers preparatively in Chapter 16. The same method can be used analytically—less than a milligram of chiral compound can be passed down a narrow column containing chirally modified silica. The two enantiomers are separated and the quantity of each can be measured (usually by UV absorption or by refractive index changes) and an ee derived. Gas chromatography can be used in the same way—the columns are packed with a chiral stationary phase such as this isoleucine derivative.

Separating enantiomers spectroscopically relies again on putting them into a chiral environment. One way of doing this, if the compound is, say, an alcohol or an amine, is to make a derivative (an ester or an amide) with an enantiomerically pure acyl chloride. The one most commonly used is known as Mosher's acyl chloride, after its inventor Harry Mosher, though there are many others. The two enantiomers of the alcohol or amine now become diastereoisomers, and give different peaks in the NMR spectrum—the integrals can be used to determine ee and, although the ^{1}H NMR of such a mixture of diastereoisomers may become quite cluttered because it is a mixture, the presence of the CF_3 group means that the ratio can alternatively be measured by integrating the two singlets in the ^{19}F NMR spectrum.

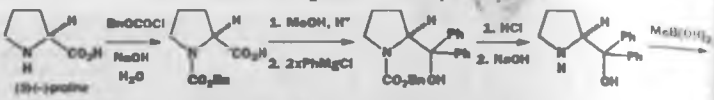


Diastereoisomeric mixture of Mosher's esters

Ratio of diastereoisomers measured by integrating ^{1}H or ^{19}F NMR spectrum



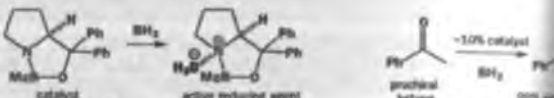
More effective is the chiral borohydride analogue developed by Corey, Bakshi, and Shibata. It is based upon a stable boron heterocycle made from an amino alcohol derived from proline, and is known as the CBS reagent after its developers.



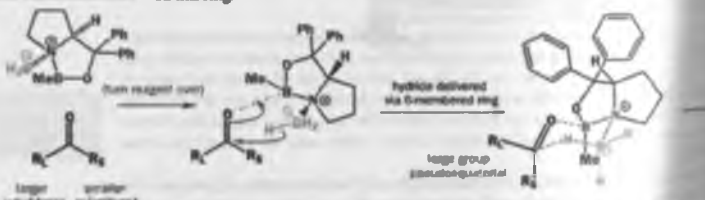
▶ Catalysts not reagents

The fact that the reactions are catalytic in the heterocycle means that relatively little is needed and it can be recovered at the end of the reaction. Later in the chapter you will see catalytic reactions that use 1000 times less catalyst than this one and, indeed, none of the reactions we will mention in the rest of this chapter will use chiral reagents—only chiral catalysts. Note the distinction from chiral auxiliaries here: although auxiliaries are recoverable, they always have to be used in stoichiometric quantities, and recovery is usually a separate step.

The active reducing agent is made by complexing the heterocycle with borane. Only catalytic amounts (usually about 10%) of the boron heterocycle are needed because borane is sufficiently reactive to reduce ketones only when complexed with the nitrogen atom. The rest of the borane can wait until a molecule of catalyst becomes free.



CBS reductions are best when the ketone's two substituents are well differentiated sterically—just as Ph and Me are in the example above. Only when the ketone is complexed with the 'other' boron atom (in the ring) is it electrophilic enough to be reduced by the weak hydride source. The hydride is delivered via a six-membered cyclic transition state, with the enantioselectivity arising from preference of the larger of the ketone's two substituents (R_L) for the pseudoequatorial position on this ring.



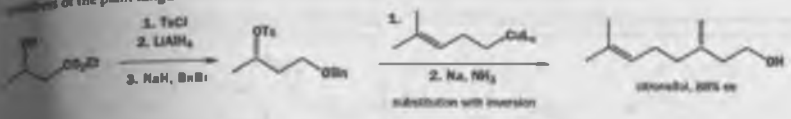
The CBS reagent is one of the best asymmetric reducing agents invented by chemists. Yet [illegible] does asymmetric reductions all the time—and gets 100% ee every time too. Nature uses enzymes as chiral catalysts, and chemists have not been slow to subvert these natural systems to their own ends. The problem with using enzymes is that they are designed to fit into a single biochemical pathway and are often quite substrate-specific, and so are not useful as a general chemical method. However, this can be overcome by using conveniently packaged multienzyme systems, living cells. Yeast is particularly good at reducing ketones, and the best enantioselectivities are obtained when the ketone carries a β-ester group. The reaction is done by stirring the ketone with an aqueous suspension of yeast, which must be fed with plenty of sugar.

■ Reductions with Nature's CBS reagent—ADH—are discussed in Chapter 51.

These reactions are quite messy, and are best done on a large scale! Notice how the selectivity of baker's yeast is the reverse of that of the CBS reagent with respect to the large and small ketone substituents. This is most useful, since (*R*)-proline is expensive, and an enantiomeric yeast cell would be a rarity indeed.

▶ In fact, the enantiomer of the CBS reagent can be made by a resolution strategy.

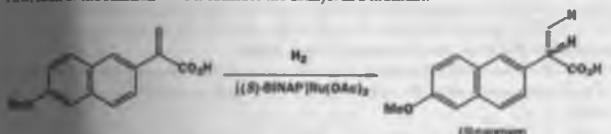
An important application of this baker's yeast reduction is in the synthesis of citronellol. After reduction and protection of the ester, S_N2 substitution of the secondary tosylate group could be achieved with inversion using a copper nucleophile. The 85% ee obtained here is better than that of many natural samples of citronellol: in common with many other terpenes, citronellol extracted from plants varies greatly in enantiomeric purity. It is quite a compliment to the humble yeast that, with a bit of help from Professor Mori's research group, it can outdo most of the more sophisticated creatures of the plant kingdom.



Asymmetric hydrogenation

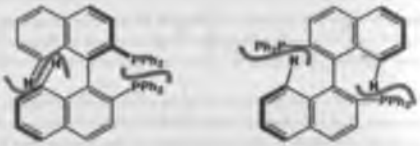
Probably the best-studied way of carrying out enantioselective reduction is to hydrogenate in the presence of a chiral catalyst. You would not normally choose catalytic hydrogenation for reducing a carbonyl group to an alcohol and, indeed, carbonyl reductions using hydrogenation with a chiral catalyst are not usually very enantioselective. Much better are hydrogenations of double bonds, particularly those with nearby heteratoms (OH, NHR) that can coordinate to the metal.

Here is a simple example: it is, in fact, an asymmetric synthesis of the analgesic drug naproxen. First, look at the reaction—we'll consider the catalyst in a moment.



The principle is quite simple—the catalyst selects a single enantiotopic face of the double bond and adds hydrogen across it. Exactly how it does this need not concern you, but we do need to go into more detail about the structure of the catalyst, which consists of a metal atom (Ru) and a ligand, called BINAP.

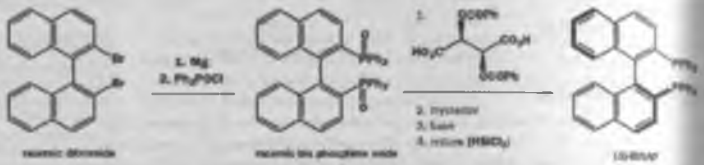
As usual with many other ligands for asymmetric hydrogenation, BINAP is a chelating [illegible] the metal sits between the two phosphorus atoms firmly anchored in a chiral environment. The chirality here is of an unusual sort, since BINAP has no chiral centres. Instead it has axial chirality by virtue of restricted rotation about the bond joining the two naphthalene ring systems. In order for the two enantiomers of BINAP to interconvert, the PPh_2 group would have to force its way either past the other PPh_2 group or round the black hydrogen (see next page). Both pathways are too [illegible] for racemization to occur.



BINAP is not derived from a natural product, and has to be synthesized in the laboratory and resolved.

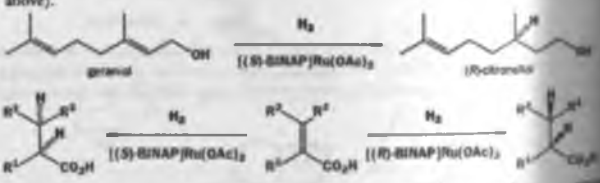
Resolution of BINAP

The scheme shows one method by which BINAP may be made—the resolution step is unusual because it relies on formation of a molecular complex, not a salt. It is the phosphine oxide that is resolved, and then reduced to the phosphine with trichlorosilane.

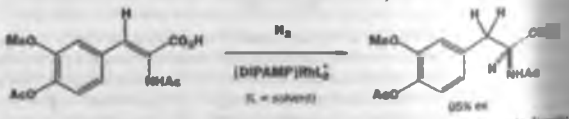


This makes it relatively expensive, but the expense is offset by the economy of catalyst required in such reactions. Whereas about 10 mol% catalyst is needed for CBS reductions, many hydrogenations of this type give high enantiomeric excesses with only 0.0002 mol% BINAP–ruthenium(II) catalyst. Because such minuscule quantities of catalyst are needed, enantioselective hydrogenations are more widely used by industry than any other asymmetric method. The other advantage of the reaction is, of course, that either enantiomer is equally available.

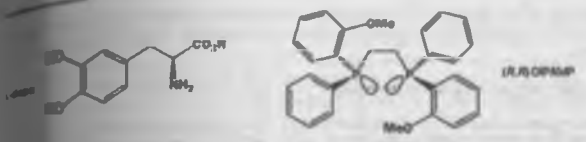
BINAP–ruthenium(II) is particularly good at catalysing the hydrogenation of allylic alcohols and of α,β-unsaturated carboxylic acids to give acids bearing α stereogenic centres (like naproxen above).



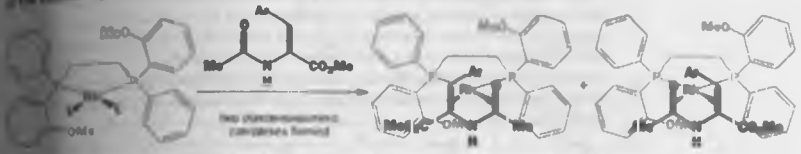
If the double bond also bears an amino group, the products of these reactions are α amino acids and in these cases there is another alternative that works even better, a catalyst based on rhodium. Here is one very important synthesis of an unnatural amino acid using a rhodium catalyst. Again look first at the reaction and then we will discuss the catalyst.



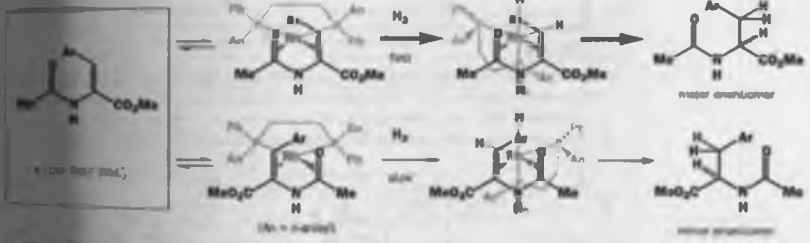
The product can be converted into L-dopa, a drug used to treat Parkinson's disease, and it is this reaction and this catalyst, both developed by Monsanto, that convinced many chemical companies that enantioselective synthesis was possible on a large scale.



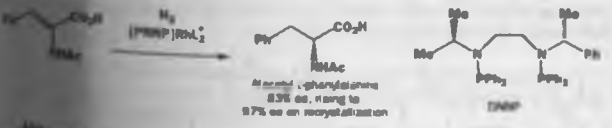
The catalyst is a cationic complex of rhodium with another diphosphine, DIPAMP. DIPAMP's chirality resides in the two stereogenic phosphorus atoms: unlike amines, phosphines are configurationally stable, rather like sulfoxides (which we will discuss in the next chapter). The catalyst imposes chirality on the hydrogenation by coordinating to both the amide group and the double bond of the substrate. Two diastereoisomeric complexes result, since the chiral catalyst can coordinate to either of the enantiotopic faces of the double bond.



It turns out that the enantioselectivity in the reaction arises because one of these diastereoisomeric complexes reacts much more rapidly with hydrogen than the other, ultimately transferring both hydrogen atoms to the same face of the double bond.



Although more limited in scope than the BINAP–Ru(II)-catalysed hydrogenations, rhodium-catalysed hydrogenations are of enormous commercial importance because of the demand for both natural and unnatural amino acids on a vast scale. It is even economical for the more expensive of the natural amino acids to be made synthetically rather than isolated from natural sources—phenylalanine, for example, of industrial importance as a component of the artificial sweetener aspartame, is manufactured by enantioselective hydrogenation.



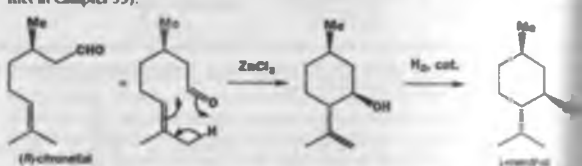
Although DIPAMP is a suitable ligand for this reaction as well, the industrial process uses the diphosphine DNNP. Unfortunately, the product is initially obtained in rather modest enantiomeric excess (83%), but recrystallization improves this to 97%. In the manufacture of aspartame,

coupling with natural (and therefore 100% ee) aspartic acid turns the 1.5% of the minor enantiomer into a diastereoisomeric impurity that can be removed by crystallization (essentially a resolution).

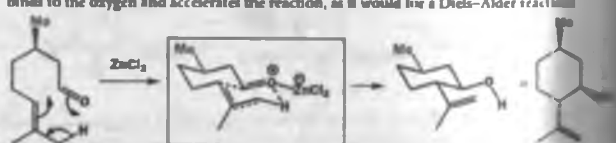
Improving ee by recrystallization

This technique is quite frequently used to improve the ee of almost enantiomerically pure samples, since, in general, crystals are most stable if they consist either of a single enantiomer or of a racemic mixture. Recrystallization of samples with ees greater than about 85% has a good chance of improving the ee of the sample (the minor enantiomer remaining in the mother liquors). Samples with ees much less than this tend to decrease in ee on recrystallization. Much depends on the crystal structure—this is quite a complex science and you can read more about it in Eliel and Wilen, *Stereochemistry of organic compounds*, Wiley, 1994. The difficulty of enriching low ees by recrystallization is one disadvantage of chiral reagent techniques as opposed to chiral auxiliary techniques.

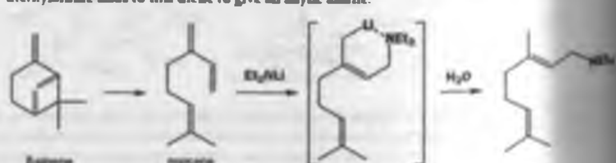
Before leaving asymmetric hydrogenation reactions, we should mention one other related process that has acquired immense importance, again because of its industrial application. You have come across citronellol a couple of times in this chapter already: the corresponding aldehyde citronellal is even more important because it is an intermediate in the a synthesis of L-menthol by the Japanese chemical company Takasago. Takasago manufacture about 30% of the 3500 ton annual worldwide demand for L-menthol from citronellal by using an intramolecular ene reaction (a cyclization you met in Chapter 35).



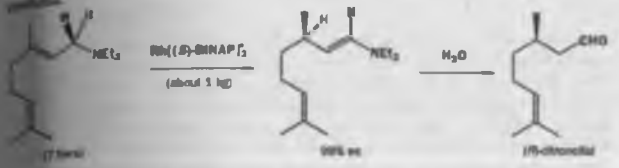
The green methyl group prefers to be equatorial in the transition state and directs the formation of the two new chiral centres. The transition state (in the frame) is like a *trans*-decalin with two fused six-membered chair rings. Both new substituents go equatorial in the product while the Lewis acid binds to the oxygen and accelerates the reaction, as it would for a Diels–Alder reaction.



But it is not this step that makes the synthesis remarkable, but rather Takasago's route to citronellal. Pinene is another terpene that is produced in only low enantiomeric excess by pine trees (and indeed, which is the major enantiomer depends on whether it is a European or a North American pine tree). But in the menthol process none of this matters, and cheap, enantiomerically impure pinene can be used, because the first step is to convert it to an achiral terpene, myrcene. Lithium diethylamide adds to this diene to give an allylic amine.



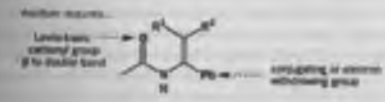
Now for the key step: $[(S)\text{-BINAP}]_2Rh^+$ catalyses the rearrangement of this allylic amine to the enamine, creating a new chiral centre with 98% ee. This reaction is rather like a hydrogenation in which the hydrogen comes from within the same molecule, or you could see it as a [1,3]-prototropic shift (usually disallowed) made possible by participation of the metal's orbitals. However way you look at it, the catalyst selects one of two enantiotopic hydrogen atoms (shown in black and green) and allows only the green one to migrate. This reaction can be run on a quite large scale, needs only 0.01 mol% catalyst, and is a testimony to the power of asymmetric synthesis.



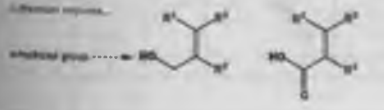
Exactly how this reaction works and exactly what features of $[(S)\text{-BINAP}]_2Rh^+$ make for successful asymmetric induction are not clear. Though we can work out a mechanism for the reaction, we cannot say precisely how the chirality of the ligand directs the formation of the new stereogenic centre. Here, as elsewhere in modern organic chemistry, the experiments get ahead of human understanding.

Rhodium or ruthenium, and which ligands?

The range of diphosphine ligands used in catalytic enantioselective hydrogenation is enormous (though DIPAMP and BINAP are probably the most important), and many of them can be used with Rh or Ru. We can nonetheless give some guidelines to choice of catalyst. In general, Rh demands more of its substrates and less of its diphosphine ligands. Which ligand to choose is a matter of thorough literature searching followed by some experimentation. However, Rh will really give good ees only when hydrogenating electron-poor or conjugated double bonds that carry a β-carbonyl group (necessary for chelation), and the enamides we have been discussing are among the best of these.



Ruthenium forms chiral ligands (BINAP is the one usually used) which hydrogenate both electron-rich and electron-poor double bonds. Ru(BINAP)(OAc)$_2$ works best if the double bond carries an ethoxycarbonyl group—in other words if it is an allylic alcohol or an α,β-unsaturated carboxylic acid. The enantioselective hydrogenation of geraniol (p. 000) is also highly selective, because isolated double bonds are not hydrogenated.



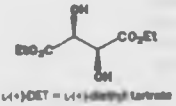
We must leave asymmetric reductions and move on to two asymmetric oxidations, which are probably the two most important asymmetric reactions known. They are both products of the laboratories of Professor Barry Sharpless.

Asymmetric epoxidation

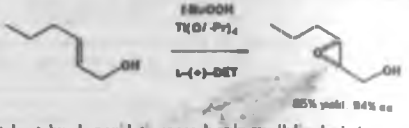
The first of Sharpless's reactions is an oxidation of alkenes by asymmetric epoxidation. You met vanadium as a transition-metal catalyst for epoxidation with *t*-butyl hydroperoxide in Chapter 11.

K.B. Sharpless (1941–) studied at Stanford and was first appointed at MIT but is now at the Scripps Institute in California. His undoubted claim to fame rests on the invention of the three (so far) reactions of enormous significance: AE (asymmetric epoxidation) and AD (asymmetric dihydroxylation) are discussed in this chapter. The third reaction, AA (asymmetric aminohydroxylation), still has to reach the perfection of the first two.

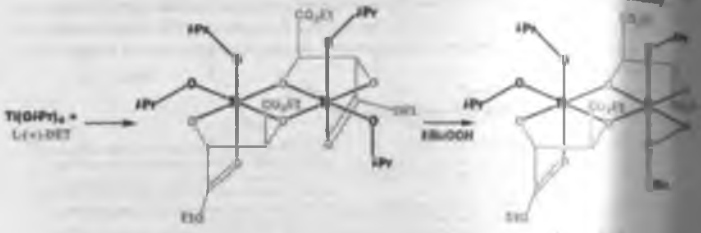
and this new reaction makes use of titanium, as titanium tetraisopropoxide, $Ti(OPr^i)_4$, to do the same thing. Sharpless surmised that, by adding a chiral ligand to the titanium catalyst, he might be able to make the reaction asymmetric. The ligand that works best is diethyl tartrate, and the reaction shown below is just one of many that demonstrate that this is a remarkably good reaction.



L-(+)-DET = L-(+)-diethyl tartrate

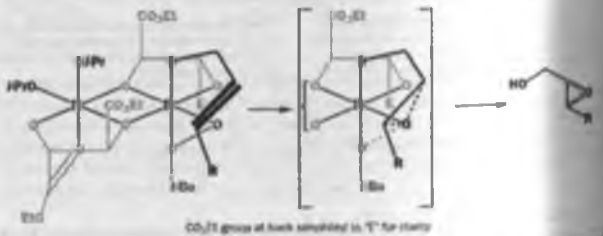


Transition-metal-catalysed epoxidations work only on allylic alcohols, so there is one restriction to the method, but otherwise there are few restrictions on what can be epoxidized enantioselectively. When this reaction was discovered in 1981 it was by far the best asymmetric reaction known. Because of its importance, a lot of work went into discovering exactly how the reaction worked, and the scheme below shows what is believed to be the active complex, formed from two titanium atoms bridged by two tartrate ligands (shown in gold). Each titanium atom retains two of its isopropoxide ligands, and is coordinated to one of the carbonyl groups of the tartrate ligand. The reaction works best if the titanium and tartrate are left to stir for a while so that these dimers can form cleanly.



When the oxidizing agent (*t*-BuOOH, shown in green) is added to the mixture, it displaces one of the remaining isopropoxide ligands and one of the tartrate carbonyl groups.

Now, for this oxidizing complex to react with an allylic alcohol, the alcohol must become coordinated to the titanium too, displacing a further isopropoxide ligand. Because of the shape of the complex the reactive oxygen atom of the bound hydroperoxide has to be delivered to the lower face of the alkene (as drawn), and the epoxide is formed in high enantiomeric excess.

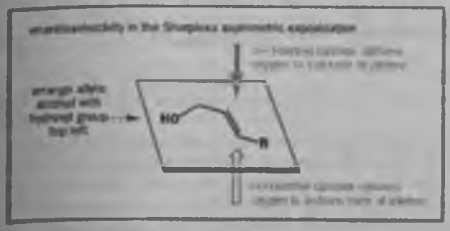


CO_2Et groups at back simplified to 'E' for clarity

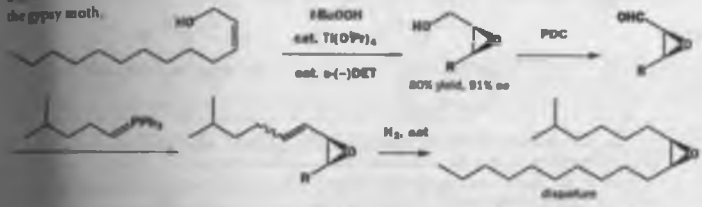
Different allylic alcohols coordinate in the same way to the titanium and reliably present the same enantiotopic face to the bound oxidizing agent, and the preference for oxidation with L-(+)-DET is shown in the schematic diagram below. Tartrate is ideal as a chiral ligand because it is available relatively cheaply as either enantiomer. L-tartrate is extracted from grapes; D-(−)-tartrate is more and more expensive—it is sometimes called unnatural tartrate, but, in fact, it too is natural. By using

(+)-tartrate it is, of course, possible to produce the other enantiomer of the epoxide equally selectively.

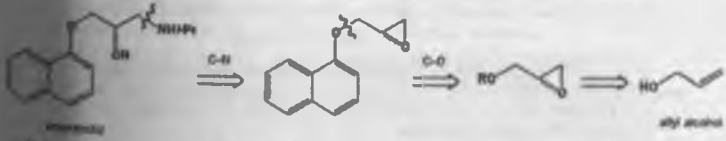
Enantioselectivity in the Sharpless asymmetric epoxidation



Sharpless also found that this reaction works with only a catalytic amount of titanium–tartrate complex, because the reaction products can be displaced from the metal centre by more of the two reagents. The catalytic version of the asymmetric epoxidation is well suited to industrial exploitation, and the American Company J. T. Baker employs it to make synthetic disparlure, the pheromone of the gypsy moth.

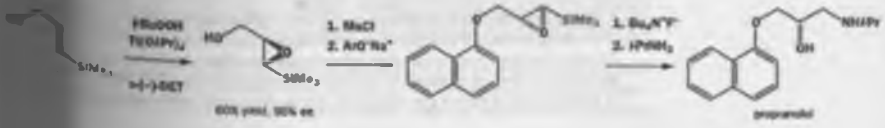


Not many target molecules are themselves epoxides, but the great thing about the epoxide products is that they are highly versatile—they react with many types of nucleophiles to give 1,2-disubstituted products. You met the chiral β-blocker drug propranolol in Chapter 30, and its 1,2,3-substitution pattern makes it a good candidate for synthesis using asymmetric epoxidation.



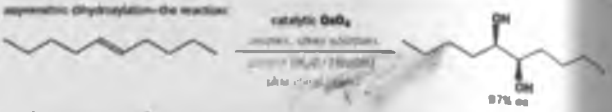
Unfortunately, the obvious starting material, allyl alcohol itself, gives and epoxide which is hard to handle, so Sharpless, who carried out this synthesis of propranolol, used this silicon-substituted allylic alcohol instead.

The hydroxyl group was mesylated and displaced with 1-naphthoxide and, after treatment with fluoride to remove the silicon, the epoxide was opened with isopropylamine.

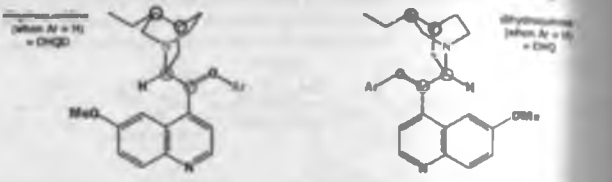


Asymmetric dihydroxylation

The last asymmetric oxidation we will mention really is probably the best asymmetric reaction of all. It is a chiral version of the *syn* dihydroxylation of alkenes by osmium tetroxide. Here is an example. Though the concept is quite simple, the recipe for the reactions is quite complicated as we must approach it step by step.

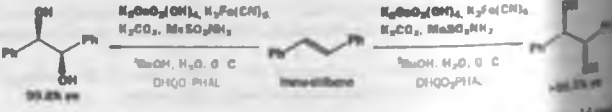


The active reagent is based on osmium(VIII) and is used in just catalytic amounts. There has to be a stoichiometric quantity of another oxidant to reoxidize the osmium after each catalytic cycle—$K_3Fe(CN)_6$ is most commonly used. Because OsO_4 is volatile and toxic, the osmium is usually added as $K_2OsO_2(OH)_4$ which forms OsO_4 in the reaction mixture. The 'other additives' include K_2CO_3 and methanesulfonamide ($MeSO_2NH_2$), which increases the rate of the reaction. How for the chiral ligand. The best ones are based on the alkaloids dihydroquinidine and dihydro... structures are shown below. They coordinate to the osmium through the yellow nitrogen.



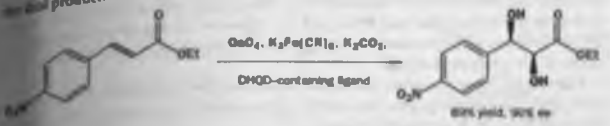
The alkaloids (usually abbreviated to DHQD and DHQ, respectively) must be attached to an aromatic group Ar, the choice of which (like the choice of ligand for enantioselective hydrogenation with Rh) varies according to the substrate. The most generally applicable ligands are these two phthalazines in which each aromatic group Ar carries two alkaloid ligands.

Dihydroquinine and dihydroquinidine are not enantiomeric (although the groups attached to are inverted in dihydroquinidine, the black ones remain the same), but they act on the dihydroxylation as though they were—here, after all that introduction, is a real example, and probably the most remarkable of any in this chapter.

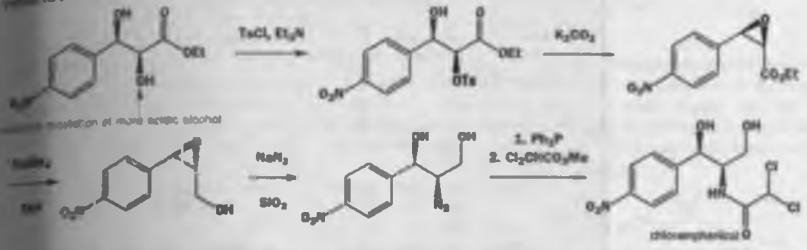


trans-(*E*)-Stilbene dihydroxylates more selectively than any other alkene, and we would probably not be exaggerating if we said that this particular example is the most enantioselective catalytic reaction ever invented. It is also much less fussy about the alkenes it will oxidize than the asymmetric epoxidation. Osmium tetroxide itself is a remarkable reagent, since it oxidizes more or less any kind of alkene, electron-rich or electron-poor, and the same is true of the asymmetric dihydroxylation.

(often abbreviated to AD) reagent. The following example illustrates both this and a synthetic use for the diol product.

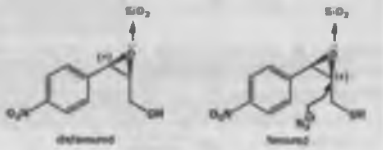


The diol is produced from a double bond that is more electron-poor than most, and can be converted to the antibiotic chloramphenicol in a few more steps.



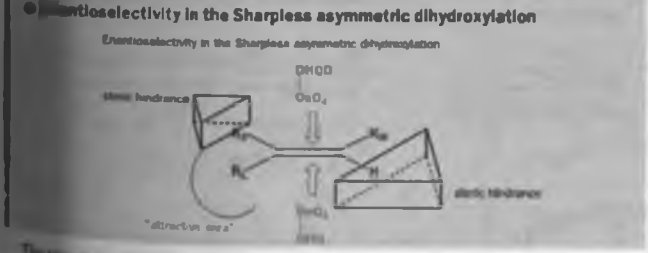
Regioselectivity in this synthesis

This diol cannot be made by the AD reaction. The regioselectivity involved in the formation and reaction of the epoxide need commenting on too. The tosylation is selective because the hydroxyl group near the electron-withdrawing ester is more acidic than the other one—high selectivity here is crucial because tosylation of the other hydroxyl group would lead to the other enantiomer of the epoxide. The regioselectivity of attack of azide on the epoxide must be because of the electron-withdrawing *para* group—acidic silica encourages the reaction to proceed through an S_N1-like (or 'loose S_N2') transition state, with cationic character on the reaction centre. Substitution next to the ring is disfavoured, and the 1,3-diol is formed selectively.



We can sum up the usual selectivity of the AD reaction in another diagram, shown below. With the substrate arranged as shown, with the largest (R_L) and next largest groups (R_M) bottom left and top right, respectively, DHQD-based ligands will direct OsO_4 to dihydroxylate from the top face of the double bond and DHQ-based ligands will direct it to dihydroxylate the bottom.

Enantioselectivity in the Sharpless asymmetric dihydroxylation



The reasons for this must, of course, lie in the way in which the substrate interacts with the osmium–ligand complex. However, even as we write this book, the detailed mechanism of the asymmetric dihydroxylation is still under discussion. What is known is that the ligand forms some sort of

'chiral pocket', like an enzyme active site, with the osmium sitting at the bottom of it. Alkenes can only approach the osmium if they are correctly aligned in the chiral pocket, and steric hindrance forces the alignment shown in the scheme above. The analogy with an enzyme active site goes even further, since it appears that part of the pocket is 'attractive' to aromatic or strongly hydrophobic groups. This part appears to accommodate R_L, part of the reason why the selectivity in the dihydroxylation of *trans*-stilbene is so high.

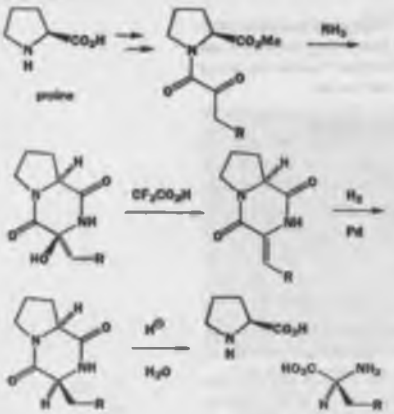
This chapter, more than most, deals with topics under active investigation. New and more powerful methods are appearing all the time and it is quite certain that the decade 2000–10 will see many important advances in asymmetric synthesis.

Summary of methods for asymmetric synthesis

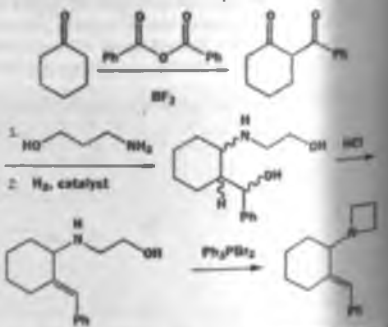
Method	Advantages	Disadvantages	Examples
resolution	both enantiomers available	maximum 50% yield	synthesis of BINAP
chiral pool	100% ee guaranteed	often only 1 enantiomer available	amino acid and sugar-derived synthesis
chiral auxiliary	often excellent ees; can recrystallize to purify to high ee	extra steps to introduce and remove auxiliary	oxazolidinones
chiral reagent	often excellent ees; can recrystallize to purify to high ee	only a few reagents are successful and often for few substrates	enzymes, CBS reducing agent
chiral catalyst	economical; only small amounts of recyclable material used	only a few reactions are really successful; recrystallization can improve only already high ees	asymmetric hydrogenation, epoxidation, dihydroxylation

Problems

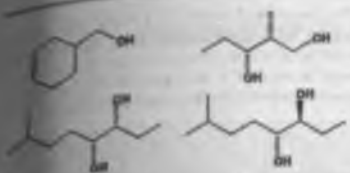
1. Explain how this asymmetric synthesis of amino acids, starting with natural proline, works. Explain the stereoselectivity of each reaction.



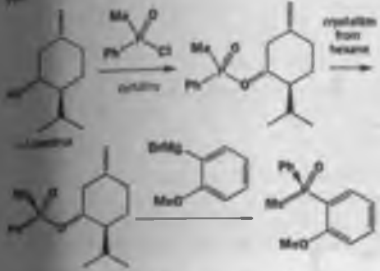
2. This is a synthesis of the racemic drug tazadolene. If the enantiomers of the drug are to be evaluated for biological activity, they must be separated. At which stage would you advocate separating the enantiomers, and how would you do it?



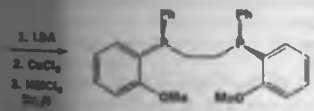
3. How would you make enantiomerically enriched samples of these compounds (either enantiomer)?



4. What is happening in stereochemical terms in this sequence of reactions? What is the other product from the crystallization from hexane? The product is one enantiomer of a phosphine oxide. If you wanted the other enantiomer, what would you do?

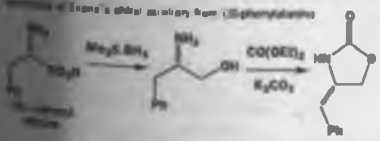


Reveusin. This phosphine oxide is used in the synthesis of DIPAMP, the chiral ligand for asymmetric catalytic hydrogenation mentioned in the chapter. What are the various reagents doing in the conversion into DIPAMP?

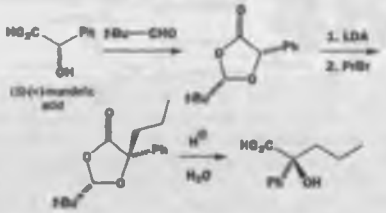


DIPAMP

6. An alternative to the Evans chiral auxiliary described in the chapter is this oxazolidinone, made from natural (S)-(−)-phenylalanine. What strategy is used for this synthesis and why are the conditions and mechanism of the reactions important?



8. In the following reaction sequence, the chirality of mandelic acid is transmitted to a new hydroxy-acid by a sequence of stereochemically controlled reactions. Give mechanisms for the reactions and state whether each is stereospecific or stereoselective. Offer some rationalization for the creation of new stereogenic centres in the first and second reactions.

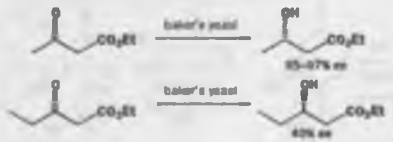


7. This reaction sequence can be used to make enantiomerically enriched amino acids. Which compound is the origin of the chirality and how is it made? Suggest why this particular enantiomer of the amino acid might be made. Suggest reagents for the last stages of the process. Would the enantiomerically enriched starting material be recovered?

8. Submitting this racemic ester to hydrolysis by an enzyme found in pig pancreas leaves enantiomerically enriched ester with the absolute stereochemistry shown. What are the advantages and disadvantages of this method? Why is the ee not 100%?

How could the same enantiomerically enriched compound be formed by chemical means? What are the advantages and disadvantages of this method?

9. The BINAP-catalysed hydrogenations described in the chapter can also be applied to the reduction of ketones—the same ketones indeed as can be reduced by baker's yeast. Compare these results and comment on the differences between them.



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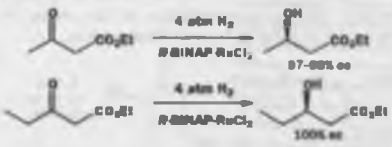
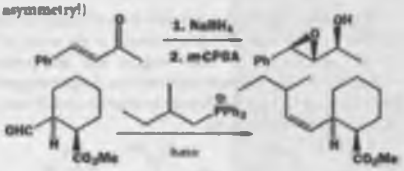
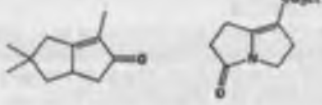


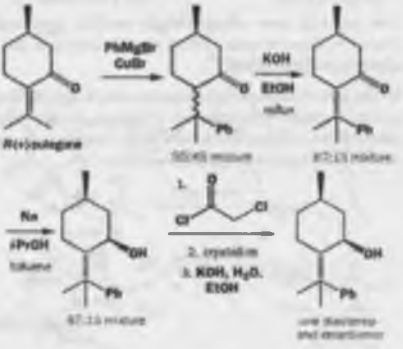
10. Describe the stereochemical happenings in these processes. You should use terms like diastereoselective and diastereotopic where needed. If you wanted to make single enantiomers of the products by these routes, at what stage would you introduce the asymmetry? (You are *not* expected to say *how* you would induce asymmetry!)



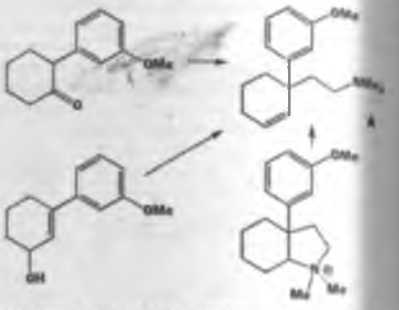
11. Both of these bicyclic compounds readily undergo hydrogenation of the alkene to give the *syn* product. Explain why asymmetric hydrogenation of only one of the compounds would be of much value in synthesis.



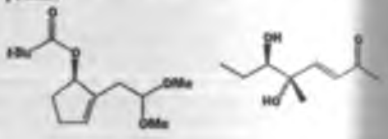
12. Explain the stereochemistry and mechanism in the synthesis of the chiral auxiliary 8-phenylmenthol from (+)-pulegone. After the reduction with Na in *i*-PrOH, what is the minor (13%) component of the mixture?



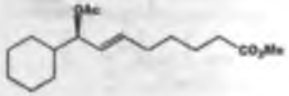
13. The unsaturated amine A, a useful intermediate in the synthesis of the *amaryllidaceae* (daffodil) alkaloids, can be made from the three starting materials shown below. What kind of chemistry is required in each case? Which is best adapted for asymmetric synthesis? Outline your chosen synthesis.



14. Suggest syntheses for single enantiomers of these compounds.



15. Suggest a synthesis of any stereoisomer (for example, *R,Z*) of this compound.



16. Revision. Give mechanisms for the steps in the synthesis of tazadolene in Problem 2.

Organo-main-group chemistry 1: sulfur

46

Connections

Building on:

- Conjugate addition ch10 & ch23
- Nucleophilic substitution at saturated carbon ch17
- Controlling stereochemistry ch16, ch33, & ch34
- Oxidation ch24
- Aldol reactions ch27
- Controlling double bond geometry ch31
- Rearrangements ch36–ch37
- Radicals and carbenes ch39–ch40

Arriving at:

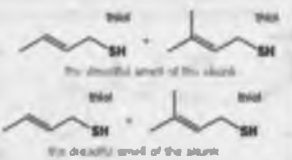
- Sulfur compounds have many oxidation states
- Sulfur is nucleophilic and electrophilic
- Sulfur stabilizes anions and cations
- Sulfur can be removed by reduction or oxidation
- Sulfoxides can be chiral
- Thioacetals provide d^1 reagents
- Allylic sulfides are useful in synthesis
- Epoxides can be made from sulfonium ylids
- Sulfur compounds are good at cationic and [2,3]-sigmatropic rearrangements
- Selenium compounds resemble sulfur compounds

Looking forward to:

- Main group chemistry II: B, Si, and Sn ch47
- Organometallic chemistry ch48
- Biological chemistry ch49–ch51
- Polymerization ch52

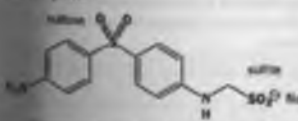
Sulfur: an element of contradictions

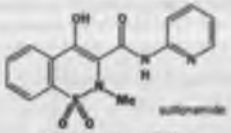
The first organosulfur compounds in this book were the dreadful smell of the skunk and the wonderful smell of the truffle, which pigs can detect through a metre of soil and which is so delightful that truffles cost more than their weight in gold.

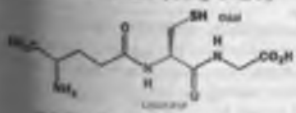


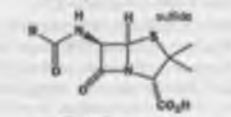
The dreadful smell of the skunk

More useful sulfur compounds have included the leprosy drug dapsone (Chapter 6), the arthritis drug Feldene (Chapter 21), glutathione (Chapter 23), a scavenger of oxidizing agents that protects most living things against oxidation and contains the natural amino acid cysteine (Chapter 49), and, of course, the famous antibiotics, the penicillins, mentioned in several chapters.



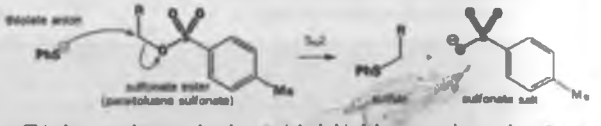




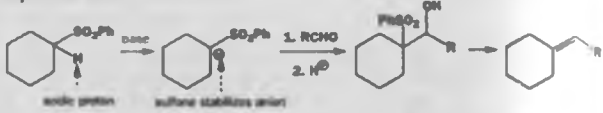


> If you look in the Oxford English dictionary you will see 'sulphur'. This is a peculiarly British spelling—neither the French nor the Americans for example have the 'ph'. It has recently been decided that chemists the world over should use a uniform spelling 'sulfur'.

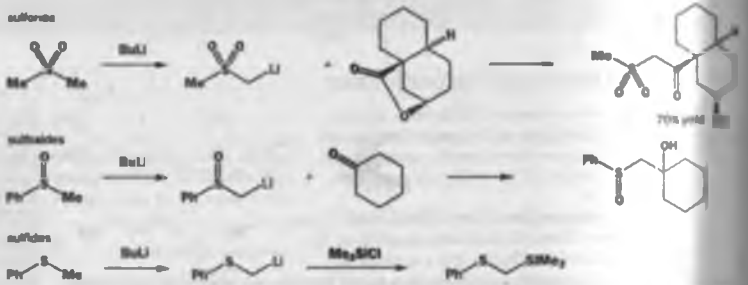
Important reactions have included sulfur as nucleophile and leaving group in the S_N2 reaction (illustrated here; see also Chapter 17), sulfonation of aromatic rings (Chapter 22), formation and reduction of thioacetals (Chapter 24), Lawesson's reagent for converting carbonyl groups to thiocarbonyl groups (Chapter 44).



This chapter gathers together the principles behind these examples together with a discussion of what makes organosulfur chemistry special and also introduces new reactions. We have a lot to explain! In Chapter 31 we introduced you to the Julia olefination, a reaction whose first step is the deprotonation of a sulfone.



Why is this proton easy to remove? This ability to stabilize an adjacent anion is a property shared by all of the most important sulfur-based functional groups. The anions (or better, lithium derivatives) will react with a variety of electrophiles and here is a selection: a sulfone reacting with a ketone, a sulfoxide with a ketone, and a sulfide with a silyl chloride.



You notice immediately the three main oxidation states of sulfur: S(VI), S(IV), and S(II). You might have expected the S(VI) sulfone and perhaps the S(IV) sulfoxide to stabilize an adjacent anion, but the S(II) sulfide? We will discuss this along with many other unusual features of sulfur chemistry. The interesting aspects are what make sulfur different.

The basic facts about sulfur

Sulfur is a p-block element in group VI (or 16 if you prefer) immediately below oxygen and between phosphorus and chlorine. It is natural for us to compare sulfur with oxygen but we will, strangely, compare it with carbon as well.

Sulfur in the periodic table (electronegativity)

C	N	O	F
(2.5)	(3.0)	(3.5)	(4.0)
Si	P	S	Cl
(1.8)	(2.1)	(2.5)	(3.0)

Sulfur is much less electronegative than oxygen; in fact, it has the same electronegativity as carbon, so it is no good trying to use the polarization of the C–S bond to explain anything! It forms reasonably strong bonds to carbon—strong enough for the compounds to be stable but weak enough for

Bond strengths, kJ mol^{-1}

	X = C	X = H	X = F	X = O
C–X	378	418	452	[illegible]
S–X	302	348	284	[illegible]

selective cleavage in the presence of the much stronger C–O bonds. It also forms strong bonds to itself. Elemental crystalline yellow sulfur consists of S_8 molecules—eight-membered rings of sulfur atoms!

crystalline sulfur

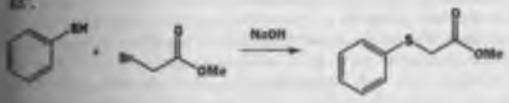
Because sulfur is in the second row of the periodic table it forms many types of compounds not available to oxygen. Compounds with S–S and S–halogen bonds are quite stable and can be isolated, unlike the unstable and often explosive O–halogen and O–O compounds. Sulfur has d orbitals so it can have oxidation states of 2, 4, or 6 and coordination numbers from 0 to 7. Here is a selection of compounds.

Compounds of sulfur

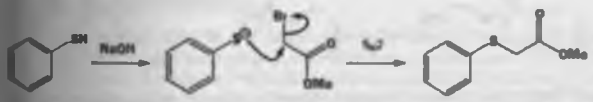
Oxidation state	S(II)			S(IV)		S(VI)		
Coordination number	0	1	2	3	4	4	6	7
Example	S^{2-}	RS^-	R_2S	$R_2S{=}O$	SF_4	R_2SO_2	SF_6	SF_7^-

Sulfur is a very versatile element

As well as this variety of oxidation states, sulfur shows a sometimes surprising versatility in function. Simple S(II) compounds are good nucleophiles as you would expect from the high-energy nonbonding lone pairs ($3sp^3$ rather than the $2sp^3$ of oxygen). A mixture of a thiol (RSH, the sulfur equivalent of an alcohol) and NaOH reacts with an alkyl halide to give the sulfide alone by nucleophilic attack of RS^-.



Thiols (RSH) are more acidic than alcohols so the first step is a rapid proton exchange between the thiol and hydroxide ion. The thiolate anion then carries out a very efficient S_N2 displacement on the alkyl bromide to give the sulfide.

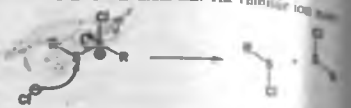


Notice that the thiolate anion does not attack the carbonyl group. Small basic oxyanions have high charge density and low-energy filled orbitals—they are hard nucleophiles that prefer to attack protons and carbonyl groups. Large, less basic thiolate anions have high-energy filled orbitals and are soft nucleophiles. They prefer to attack saturated carbon atoms. Thiols and thiolates are good soft nucleophiles.

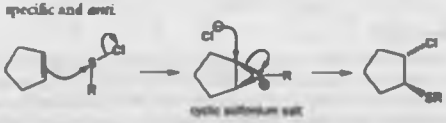
- **Thiols (RSH) are more acidic than alcohols (ROH) but sulfur compounds are better nucleophiles than oxygen compounds towards saturated carbon atoms (S_N2).**

They are also good soft electrophiles. Sulfenyl chlorides (RSCl) are easily made from disulfides (RS–SR) and sulfuryl chloride (SO_2Cl_2). This S(VI) chloride has electrophilic chlorine atoms and is attacked by the nucleophilic disulfide to give two molecules of RSCl and gaseous SO_2. There's a lot of sulfur chemistry here! We start with a nucleophilic attack by one sulfur atom of the disulfide.

The intermediate contains a tricoordinate sulfur cation or sulfonium salt. The chloride ion now attacks the other sulfur atom of this intermediate and two molecules of RSCl result. Each atom of the original disulfide has formed an S–Cl bond. One sulfur atom was a nucleophile towards chlorine and the other an electrophile.

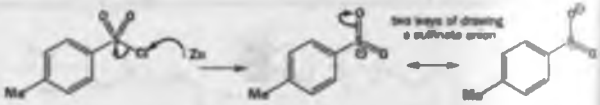


The product of this reaction, the sulfenyl chloride, is also a good soft electrophile towards carbon atoms, particularly towards alkenes. The reaction is very like bromination with a three-membered cyclic sulfonium ion intermediate replacing the bromonium ion of Chapter 20. The reaction is stereospecific and *anti*.

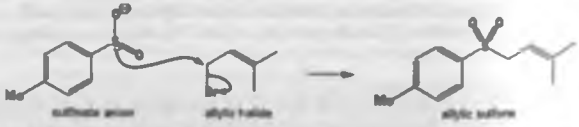


Sulfur at the S(II) oxidation state is both a good nucleophile and a good electrophile. This is also true at higher oxidation states though the compounds become harder electrophiles as the positive charge on sulfur increases. We have already mentioned tosyl (toluene-*para*-sulfonyl) chloride as an electrophile for alkoxide ions in this chapter and in earlier chapters.

At this higher oxidation state it might seem unlikely that sulfur could also be a good nucleophile, but consider the result of reacting TsCl with zinc metal. Zinc provides two electrons and turns the compound into an anion. This anion can also be drawn in two ways.



Surprisingly, this anion is also a good soft nucleophile and attacks saturated carbon atoms through the sulfur atom. In this case attack occurs at the less substituted end of an allylic bromide to give an allylic sulfone, which we will use later on.

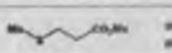
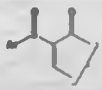


● Sulfur compounds are good nucleophiles and good electrophiles.

As this chapter develops you will see other examples of the versatility of sulfur. You will see how it takes part readily in rearrangements from the simple cationic to the sigmatropic. You will see that it can be removed from organic compounds in either an oxidative or a reductive fashion. You will see that it can stabilise anions or cations on adjacent carbon atoms, and the stabilization of anions is the first main section of the chapter.

Sulfur-based functional groups

We have already met a number of sulfur-containing functional groups and it might be useful to list them for reference.

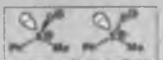
Name	Structure	Importance	Example	Example details
[illegible]	RSH	strong smell, usually bad, but sometimes heavenly		smell and taste of coffee
[illegible]	RS^-	good soft nucleophiles		
[illegible]	RS–SR	cross-links proteins		
[illegible]	RS–Cl	good soft electrophiles		
[illegible]	R–S–R	molecular link		smell and taste of pineapple
[illegible]	R_3S^+	important reagents		old used in epoxidations
[illegible]	$R_2S{=}O$ or $R_2S^+{-}O^-$	many reactions; can be chiral		chiral Michael acceptors
[illegible]	RSO_2R	anion-stabilizing group		
[illegible]	RSO_2OH	strong acids		
[illegible]	RSO_2Cl	turns alcohols into leaving groups		

Sulfur-stabilized anions

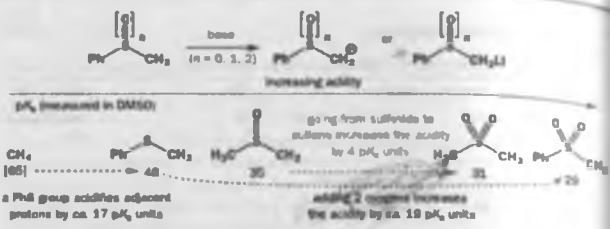
In this chapter we shall discuss some of the rich and varied chemistry of these, and other, organosulfur compounds. The stabilization of anions by sulfur is where we begin, and this theme runs right through the chapter. We will start with sulfides, sulfoxides, and sulfones. Sulfur has six electrons in its outer shell. As a sulfide, therefore, the sulfur atom carries two lone pairs. In a sulfoxide, one of these lone pairs is used in a bond to an oxygen atom—sulfoxides can be represented by at least two valence bond structures. The sulfur atom in a sulfone uses both of its lone pairs in bonding to oxygen, and is usually represented with two S=O double bonds.

Treatment of any of these compounds with strong base produces an anion (or a lithium derivative if BuLi is used) on what was the methyl group. How does the sulfur stabilize the anion? This question has been the subject of many debates and we have not got space to go into the details of all of them. There are at least two factors involved, and the first is evident from this chart of pK_a values for protons next to sulfone, sulfoxide and sulfide functional groups.

▶ Sulfoxides have the potential for chirality—the tetrahedral sulfur atom is surrounded by four different groups (here Ph, Me, O, and the lone pair) and (unlike, say, the tetrahedral nitrogen atom of an amide) has a stable tetrahedral configuration. We will reveal chirality in sulfoxides a little later in the chapter.



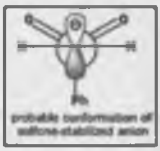
enantiomers of a chiral sulfoxide



■

If you want to read more about the elegant experiments that have been used to probe the structure of sulfonyl anions, see F. Bloch, *The organic chemistry of sulfur*, Academic Press, New York, 1964.

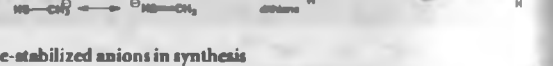
Clearly, the oxygen atoms are important—the best anion-stabilizer is the sulfone, followed by the sulfoxide and then the sulfide. You could compare deprotonation of a sulfone with deprotonation of a ketone to give an enolate (Chapter 21). Enolates have a planar carbon atom and the anion is mainly on the oxygen atom. Sulfone-stabilized carbanions have two oxygen atoms and the anionic centre is probably planar, with the negative charge in a p orbital midway between them. Carbanions next to sulfones are planar, while anions next to sulfoxides and sulfides are believed to be pyramidal (sp^3 hybridized).



Yet the attached oxygen atoms cannot be the sole reason for the stability of anions next to sulfur because the sulfide functional group also acidifies an adjacent proton quite significantly. There is some controversy over exactly why this should be, but the usual explanation is that polarization of the sulfur's 3s and 3p electrons (which are more diffuse, and therefore more polarizable, than the 2s and 2p electrons of oxygen) contributes to the stabilization.

Heading

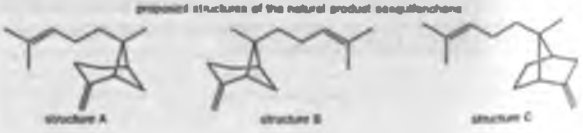
It was long thought that delocalization into sulfur's empty 3d orbitals provided the anion stabilization required, but theoretical work in the last 20 years or so suggests this may not be the case. For example, *ab initio* calculations suggest that the C–S bond in $^-CH_2SH$ is longer than in CH_3SH. The converse would be true if delocalization into the sulfur's d orbitals were important. Delocalization would shorten the bond because it would have partial double bond character. More likely as an addition is found is delocalization into the σ^* orbital of the C–S bond on the other side of the sulfur atom—the equatorial position. dithiane (see p. 000 for more on dithianes) is more acidic than the axial one, and the equatorial anion is more stable because it is delocalized into the C–S bond's σ^* orbital.



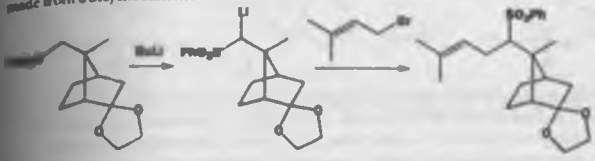
Sulfone-stabilized anions in synthesis

The terpene sesquifenchene is a constituent of Indian valerian root oil. When it was first discovered in 1963, it was assumed to have structure A, related to bergamotene, a constituent of oil of bergamot (the fragrance of Earl Grey tea).

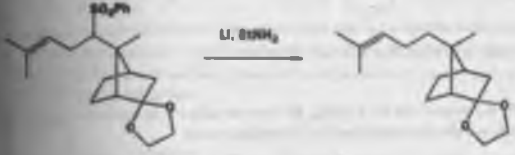
proposed structures of the natural product sesquifenchene



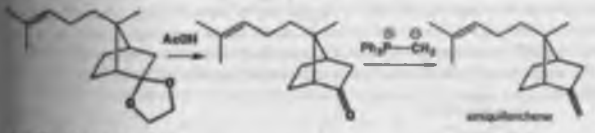
Compound A was synthesized in 1969, but was found not to be identical with sesquifenchene. A new structure was proposed, B, which was synthesized in 1971—but this compound too had different properties from those of natural sesquifenchene! A third structure was proposed, C, and it was made from a bicyclic sulfone.



The bicyclic part of the structure was available in a few steps from norbornadiene. Deprotonation of the sulfone made a nucleophile that could be alkylated with prenyl bromide—a convenient way of joining on the extra five carbon atoms needed in the target structure. Next, the sulfone group had to be got rid of—there are a number of ways of doing this, and these chemists chose a Birch reduction with $EtNH_2$ instead of liquid ammonia. They might equally have tried hydrogenation with Raney nickel (see p. 000) or a sodium–amalgam-type reduction as is used in the Julia olefination (p. 000; you will see aluminium amalgam used in this way on p. 000).



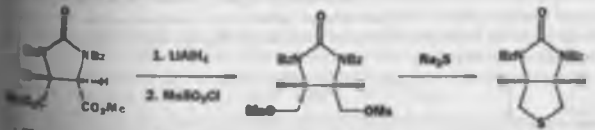
The exocyclic double bond was made by Wittig reaction on the deprotected ketone (aqueous acetic acid removed the dioxolane protecting group). This product had all the characteristics of natural sesquifenchene, confirming its true structure.



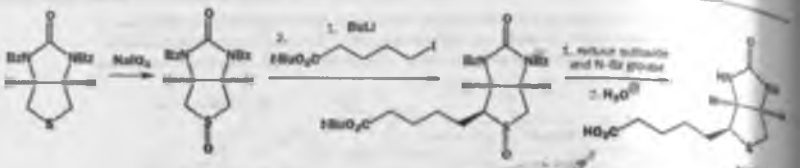
▶ Of course, with today's spectroscopic techniques it is rarely necessary to synthesize a compound to confirm its structure, but misinterpretation still takes place and it is only when the compound is synthesized that the error comes to light.

A sulfoxide-stabilized anion in a synthesis

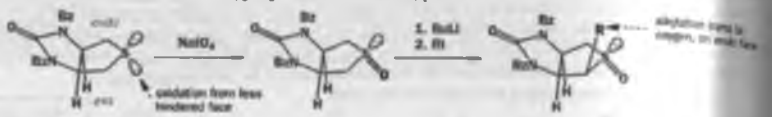
A sulfoxide alkylation formed the key step of a synthesis of the important vitamin biotin. Biotin contains a five-membered heterocyclic sulfide fused to a second five-membered ring, and the bicyclic skeleton was easy to make from a simple symmetrical ester. The vital step is a double S_N2 reaction on primary carbon atoms.



The next step was to introduce the alkyl chain—this was best done by first oxidizing the sulfide to a sulfoxide, using sodium periodate. The sulfoxide was then deprotonated with *n*-BuLi and alkylated with an alkyl iodide containing a carboxylic acid protected as its *t*-butyl ester. Reduction of the sulfoxide and hydrolysis back to the free acid gave biotin.



This synthesis involves some stereochemistry. Biotin carries the alkyl chain next to sulfur on the more hindered *endo* face of the molecule, and any successful synthesis has to address this particular problem. Here, the chemists decided to use the fact that alkylations of cyclic sulfoxides result in stereochemistry between the new alkyl group and the sulfoxide oxygen atom. As expected, oxidation of the sulfide proceeded faster from the *exo* face, giving an 8:1 ratio of *exo*:*endo* sulfoxides. Alkylation *trans* to the *exo* oxygen gave the desired (*endo*) product.

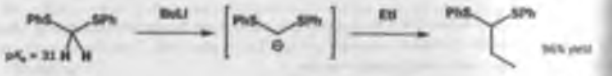


In Chapter 33 we talked about the ways in which cyclic compounds react [illegible] of this sulfide oxidation is what you would expect from the examples we gave there.

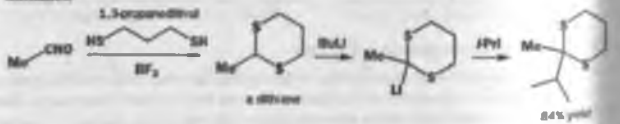
The synthesis is diastereoselective—but not enantioselective since there is no way of distinguishing the left and right sides of the symmetrical sulfoxide.

Thioacetals

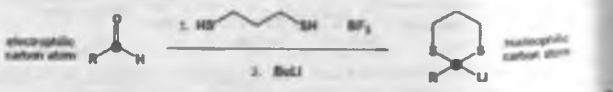
Although sulfide deprotonations are possible, the protons adjacent to *two* sulfide sulfur atoms are rather more acidic and alkylation of thioacetals is straightforward.



In general, thioacetals can be made in a similar way to 'normal' (oxygen-based) acetals by treatment of an aldehyde or a ketone with a thiol and an acid catalyst—though a Lewis acid such as BF_3 is usually needed rather than a protic acid. The most easily made, most stable toward hydrolysis, and most reactive towards alkylation are cyclic thioacetals derived from 1,3-propanedithiol, known as **dithianes**.

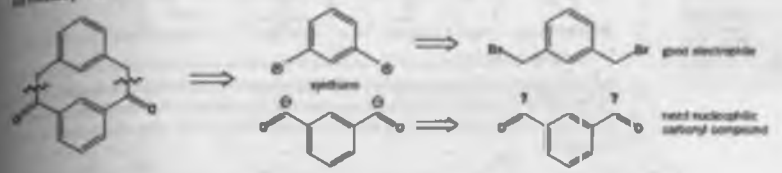


Dithianes are extremely important compounds in organic synthesis because *going from ketone to thioacetal inverts the polarity at the functionalized carbon atom*. Aldehydes, as you are well aware, are electrophiles at the C=O carbon atom, but dithioacetals, through deprotonation to an anion, are nucleophilic at this same atom.

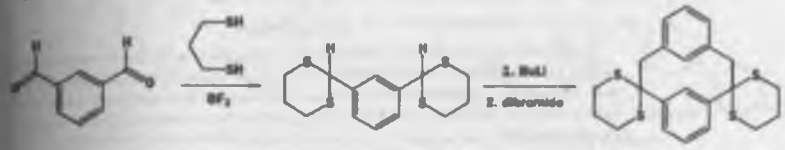


This is a case of umpolung, the concept you met in Chapter 30, and dithianes are among the most important of the umpolung reagents. An example: chemists wanted to make this compound (a

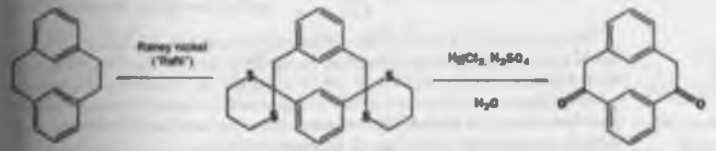
'paracyclophane') because they wanted to study the independent rotation of the two benzene rings, which is hindered in such a small ring. An ideal way would be to join electrophilic benzylic bromides to nucleophilic carbonyl groups, if that were possible.



The dibromide and dialdehyde were both available—what they really wanted was a nucleophilic equivalent of the dialdehyde to react with the dibromide. So they made the dithioacetal.

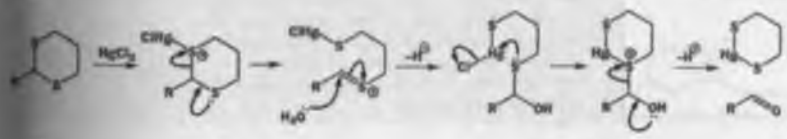


After the dithianes have been alkylated, they can be hydrolysed to give back the carbonyl groups. Alternatively, hydrogenation using Raney nickel replaces the thioacetal with a CH_2 group and gives the unsubstituted cyclophane.



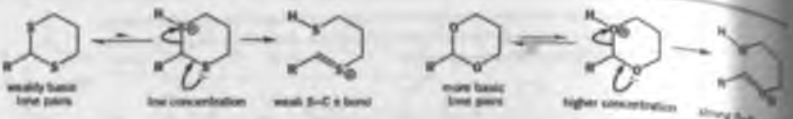
Both of these transformations deserve comment. Dithianes are rather more stable than acetals, and a mercury reagent has to be used to assist their hydrolysis. Mercury(II) and sulfides form strong coordination complexes, and the mercury catalyses the reaction by acting as a sulfur-selective Lewis acid.

Dithianes are also known as umpolung reagents because of their propensity for 'reactivity umpolung'.

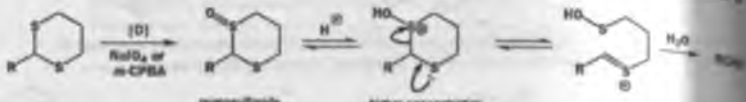


There are two reasons why the normal acid-catalysed hydrolysis of acetals usually fails with thioacetals. Sulfur is less basic than oxygen, so the protonated species is lower in concentration at a given pH, and the sulfur 3p lone pairs are less able to form a stable π bond to carbon than are the oxygen 2p lone pairs.

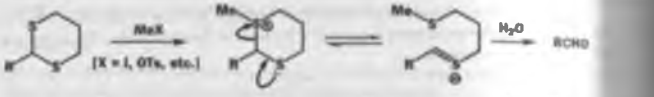
Sulfur compounds are less basic than oxygen compounds and C=S compounds are less stable than C=O compounds.



The most obvious solution to this problem is to provide a better electrophile than the proton for sulfur. Mercury, Hg(II), is one solution. Another is oxidation of one sulfur to the sulfoxide, a process that would be impossible with the oxygen atoms of an ordinary acetal. Protonation can now occur on the more basic oxygen atom of the sulfoxide and the concentration of the vital intermediate is increased.



A third solution is methylation since sulfur is a better nucleophile for saturated carbon than is oxygen. The sulfonium salt can decompose in the same way to give the free aldehyde. There are many more methods for hydrolysing dithioacetals and their multiplicity should make you suspicious that none is very good. The best is probably the Hg(II) method but not everyone likes to use stoichiometric toxic mercury!



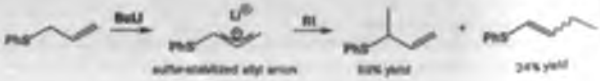
Hydrogenation of C–S bonds in both sulfides and thioacetals is often achieved with Raney nickel. This is a finely divided form of nickel made by dissolving away the aluminium from a powdered nickel–aluminium alloy using alkali. It can be used either as a catalyst for hydrogenation with gaseous hydrogen or as a reagent since it often contains sufficient adsorbed hydrogen (from the reaction of aluminium with alkali) to effect reductions alone. Thioacetalization followed by Raney nickel reduction is a useful way of replacing a C=O group with CH_2.

● Dithianes are d^2 reagents (acyl anion equivalents)

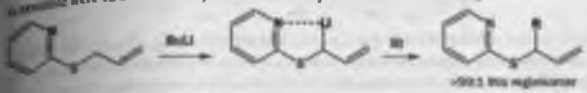
A sequence in which a carbonyl group has been masked as a sulfur derivative, alkylated with an electrophile, and then revealed again is a nucleophilic acylation. These nucleophilic equivalents of carbonyl compounds are known as acyl anion equivalents. In the retrosynthetic terms of Chapter 30 they are d^1 reagents corresponding to the acyl anion synthon.

Allyl sulfides

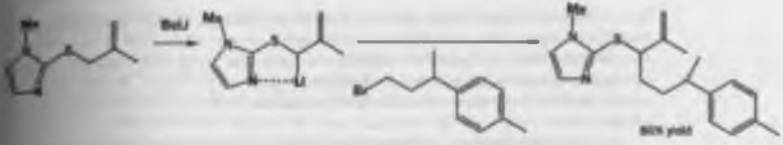
Apart from thioacetals, allyl sulfides are among the easiest sulfides to deprotonate and alkylate because of the conjugating ability of the allyl group. However, the very delocalization that assists anion formation means that the anions often react unregioselectively: lithiated phenyl allyl sulfide, for instance, reacts with hexyl iodide to give a 3:1 ratio of regioisomers.



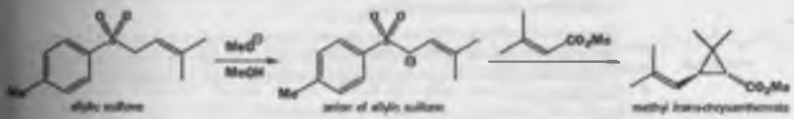
3-Pyridyl allyl sulfide, on the other hand, gives only one regioisomer in its alkylation reactions. It is sensible here to show the 'allyl anion' as a compound with a C–Li bond.



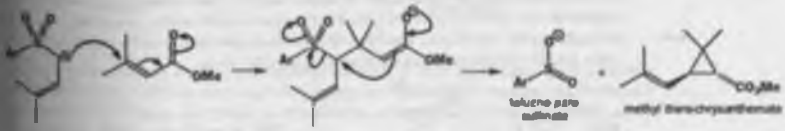
The same is true for a number of other allylic sulfur compounds in which the sulfur carries a lithium-coordinating heteroatom. Coordination encourages reaction next to sulfur (you might say it makes the lithium more at home there) and means that allyl sulfide alkylations can be made quite regioselective. The importance of this is probably not evident to you, but on p. 000 you will meet a synthesis of the natural product nuciferal in which this principle is used—the key step will be the alkylation of this allylic sulfide to give an 86% yield of the product with the alkyl group next to sulfur.



If the sulfur-based anion-stabilizing group is at a higher oxidation level, it is not usually necessary to provide chelating groups to ensure reaction next to sulfur. The allylic sulfone we made earlier in the chapter (p. 000) reacts in this way with an unsaturated ester to give a cyclopropane. Notice how much weaker a base (MeO^-) is needed here, as the anion (and it is an anion if the counterion is Na^+ or K^+) is stabilized by sulfone and alkene.



The first step is conjugate addition of the highly stabilized anion. The intermediate enolate then closes the three-membered ring by favourable nucleophilic attack on the allylic carbon. The leaving group is the sulfinate anion and the stereochemistry comes from the most favourable arrangement in the transition state for this ring closure. The product is the methyl ester of the important chrysanthemic acid found in the natural pyrrethrum insecticides.



We shall see more reactions of this sort in which sulfur has a dual role as anion-stabilizing and leaving group in the next section.

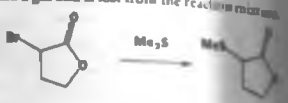
Sulfonium salts

Sulfides are nucleophiles even when not deprotonated—the sulfur atom will attack alkyl halides to form sulfonium salts. This may look strange in comparison with ethers, but it is, of course, a familiar pattern of reactivity for amines, and you have seen phosphonium salts formed in a similar way (Chapters 14 and 31).

This reaction is an equilibrium and it may be necessary in making sulfonium salts from less reactive sulfides (sterically hindered ones for example) to use more powerful alkylating agents with non-nucleophilic counterions, for example, Me_3O^+ BF_4^-, trimethyloxonium fluoroborate (also known as Meerwein's salt). The sulfur atom captures a methyl group from O^+, but the reverse does not happen and the BF_4^- anion is not a nucleophile.

Not only is dimethyl ether a poor nucleophile, it is also a gas and is lost from the reaction mixture.

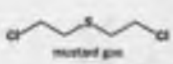
The same principle is used to make sulfides from other sulfides. With that clue, and the position of this reaction in the 'sulfonium salt' section, you should be able to work out the mechanism and say why the reaction works.



The most important chemistry of sulfonium salts is based on one or both of two attributes:

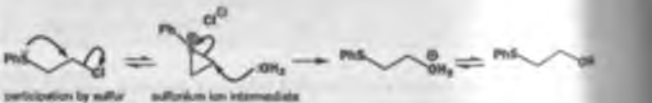
1. Sulfonium salts are electrophiles: nucleophilic substitution displaces a neutral sulfide leaving group
2. Sulfonium salts can be deprotonated to give sulfonium ylids

Sulfonium salts as electrophiles



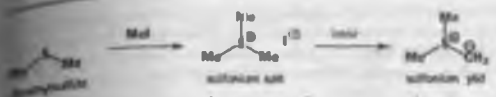
During the First World War, mustard gas was developed as a chemical weapon—it causes the skin to blister and is an intense irritant of the respiratory tract. Its reactivity towards human tissue is related to the following observation and is gruesome testimony to the powerful electrophilic properties of sulfonium ions.

In both cases, intramolecular displacement of the chloride leaving group by the sulfur atom—or, as we should call it, participation by sulfur (see Chapter 37)—gives a three-membered cyclic sulfonium ion intermediate (an episulfonium or thiiranium ion). Nucleophilic attack on this electrophilic sulfonium ion, either by water or by the structural proteins of the skin, is very fast. Of course, mustard gas can react twice in this way. You will see several more examples of reactions in which a sulfonium ion intermediate acts as an electrophile in the next section.

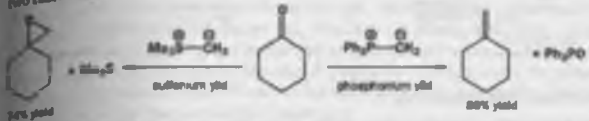


Sulfonium ylids

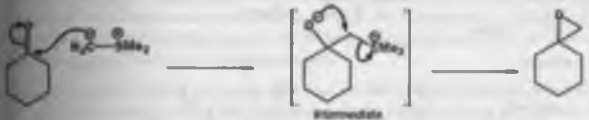
The positive charge carried by the sulfur atom means that the protons next to the sulfur atom in a sulfonium salt are significantly more acidic than those in a sulfide, and sulfonium salts can be deprotonated to give sulfonium ylids.



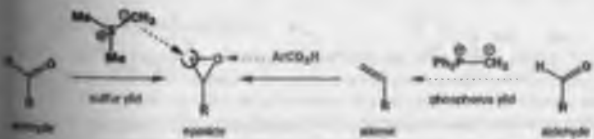
In Chapter 31 we discussed the Wittig reaction of phosphonium ylids with carbonyl compounds. Sulfonium ylids react with carbonyl compounds too, but in quite a different way—compare these two reactions.



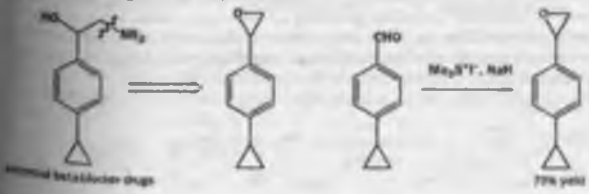
Phosphonium ylids give alkenes while sulfonium ylids give epoxides. Why should this be the case? The driving force in the Wittig reaction is formation of the strong P=O bond—that force is much less in the sulfur analogues (the P=O bond energy in Ph_3PO is 529 kJ mol^{-1}; in Ph_2SO the S=O bond energy is 367 kJ mol^{-1}). The first step is the same in both reactions: the carbanion of the ylid attacks the carbonyl group in a nucleophilic addition reaction. The intermediate in the Wittig reaction cyclises to give a four-membered ring but this does not happen with the sulfur ylids. Instead, the intermediate decomposes by intramolecular nucleophilic substitution of Me_2S by the oxyanion.



We could compare sulfonium ylids with the carbenoids we discussed in Chapter 40—both are nucleophilic carbon atoms carrying a leaving group, and both form three-membered rings by insertion into π bonds. Sulfonium ylids are therefore useful for making epoxides from aldehydes or ketones; other ways you have met of making epoxides (Chapters 20 and 45) started with alkenes that might be made with phosphorus ylids.

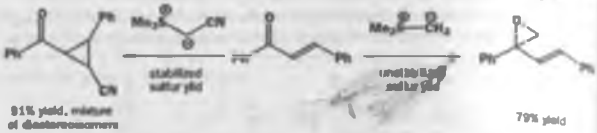


The simplest route to certain potential β-blocker drugs is from an epoxide, and the chemists working on their synthesis decided that, since 4-cyclopropylbenzaldehyde was more readily available than 4-cyclopropyl styrene, they would use the aldehyde as the starting material and make the epoxide in one step using a sulfonium ylid.



■ When we are talking about S ylids or P ylids, 'stabilized' refers to stabilization of the carbanion as explained in Chapter 31.

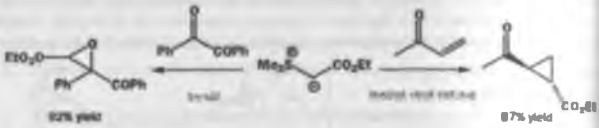
You will recall from Chapter 31 that we divided phosphorus ylids into two categories, 'stabilized' and 'unstabilized', in order to explain the stereochemistry of their alkene-forming reactions. Again, there is a similarity with sulfonium ylids: the same sort of division is needed—this time to explain the different regioselectivities displayed by different sulfonium ylids. Firstly, an example.



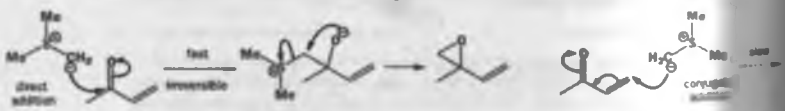
'Stabilized' sulfonium ylids

Changing from the simple sulfonium ylid to one bearing an anion-stabilizing substituent changes the regioselectivity of the reaction. 'Unstabilized' sulfonium ylids give epoxides from α,β-unsaturated carbonyl compounds while 'stabilized' ylids give cyclopropanes. In the absence of the double bond, both types of ylid give epoxides—the ester-stabilized ylid, for example, reacts with benzil to give an epoxide but with methyl vinyl ketone (but-3-en-2-one) to give a cyclopropane.

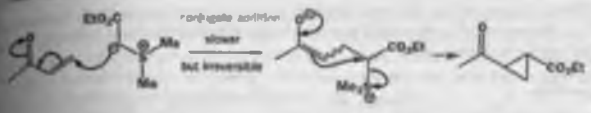
■ Compare this equilibration with the Darzens reaction you met on p. 000.



Why does the stabilized ylid prefer to react with the double bond? In order to understand this, let's consider first the reaction of a simple, unstabilized ylid with an unsaturated ketone. The enone has two electrophilic sites, but from Chapters 10 and 23, in which we discussed the regioselectivity of attack of nucleophiles on Michael acceptors like this, you would expect that direct 1,2-attack on the ketone is the faster reaction. This step is irreversible, and subsequent displacement of the sulfide leaving group by the alkoxide produces an epoxide. It's unimportant whether a cyclopropane product would have been more stable: the epoxide forms faster and is therefore the kinetic product.

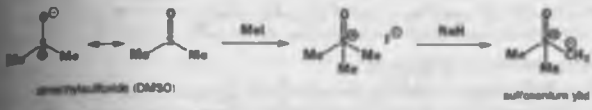


With a stabilized ylid, direct addition to the carbonyl group is, in fact, probably still the faster reaction. But, in this case, the starting materials are sufficiently stable that the reaction is reversible and the sulfonium ylid is re-expelled before the epoxide has a chance to form. Meanwhile, some ylid adds to the ketone in a 1,4 (Michael or conjugate) fashion. 1,4-Addition, although slower, is energetically more favourable because the new C–C bond is gained at the expense of a (relatively) weak C=C π bond rather than a (relatively) strong C=O π bond, and is therefore irreversible. Eventually, all the ylid ends up adding in a 1,4-fashion, generating an enolate as it does so, which cyclizes to give the cyclopropane, which is the thermodynamic product. This is another classic example of kinetic versus thermodynamic control, and you can add it to the mental list of examples you started when you first read Chapter 13.



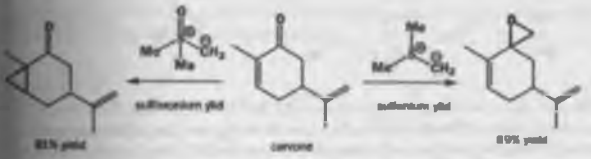
Sulfoxonium ylids

There is another, very important class of stabilized sulfur ylids that owe their stability not to an additional anion-stabilizing substituent but to a more anion-stabilizing sulfur group. These are the sulfoxonium ylids, made from dimethylsulfoxide by S_N2 substitution with an alkyl halide. Note that the sulfur atom is the nucleophile rather than the oxygen atom in spite of the charge distribution. The high-energy sulfur lone pair is better at S_N2 substitution at saturated carbon—a reaction that depends very little on charge attraction (Chapter 17).



dimethylsulfoxide (DMSO) sulfoxonium ylid

Sulfoxonium ylids react with unsaturated carbonyl compounds in the same way as the stabilized ylids that you have met already do—they form cyclopropanes rather than epoxides. The example below shows one consequence of this reactivity pattern—by changing from a sulfonium to a sulfoxonium ylid, high yields of either epoxide or cyclopropane can be formed from an unsaturated carbonyl compound (this one is the terpene carvone).

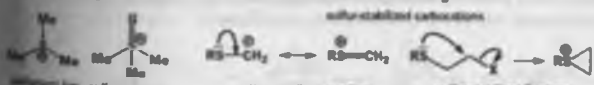


sulfoxonium ylid sulfonium ylid

81% yield carvone 89% yield

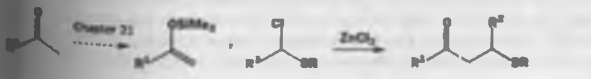
Sulfur-stabilized cations

We have mentioned cations in this chapter several times and now we will gather the various ideas together. Cations are stable on the sulfur atom itself, as you have just seen in sulfonium and sulfoxonium salts. They are stable on adjacent carbon atoms since the sulfur atom contributes a lone pair to form a C–S$^+$ π bond, and they are stable on the next carbon atom along the chain since sulfur contributes a lone pair to form a C–S$^+$ σ bond in a three-membered ring.



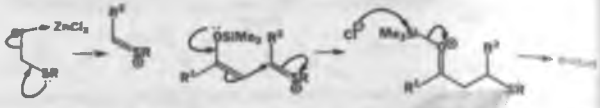
sulfonium ion sulfur-stabilized carbocations sulfur-stabilized α-cation sulfur-stabilized β-cation

You may protest that these last two species are not *carbo*-cations at all but rather sulfonium ions, and you would be right. However, they can be used in place of carbocations as they are electrophilic at carbon so it is useful to think of them as modified carbocations as well as sulfonium ions. Sulfur-stabilized α-cations are easily made from α-chlorosulfides and are useful in alkylation of silyl enol ethers.



Chapter 21

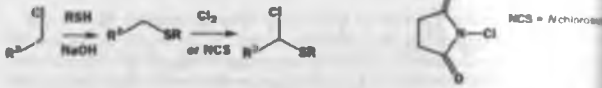
What is the point of this? Silyl enol ethers can be alkylated only by compounds that give carbocations in the presence of Lewis acids. The mechanism for the alkylation therefore involves the formation of a sulfur-stabilized cation.



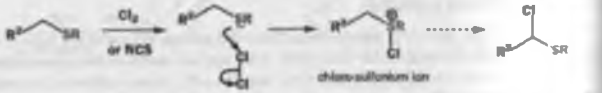
The sulfide (SR) can be removed from the product with Raney nickel to give a simple ketone. This ketone has apparently been made by the alkylation of a silyl enol ether with a primary alkyl group (R^2CH_2). This would be impossible without stabilization of the cation by the sulfur atom.

The Pummerer rearrangement

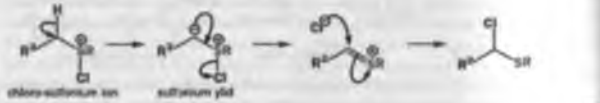
Though the stabilization of the cation by a sulfide is not as good as the stabilization by an ether (the C=S$^+$ bond is weaker than the C=O$^+$ bond), it is still good enough to make the reaction work and, of course, C–O bonds cannot be reduced by any simple reagent. One thing remains—how is the chlorosulfide made in the first place! Remarkably, it is made from the alkyl halide (R^2CH_2) you would use for the (impossible) direct alkylation without sulfur.



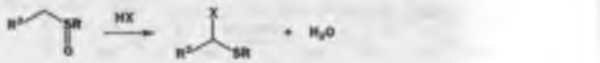
The first step is just the S_N2 displacement of Cl^- by RS^- that you have already seen. The second step actually involves chlorination at sulfur (you have also seen that sulfides are good soft nucleophiles for halogens) to form a sulfonium salt. Now a remarkable thing happens. The chlorine atom is transferred from the sulfur atom to the adjacent carbon atom by the Pummerer rearrangement.



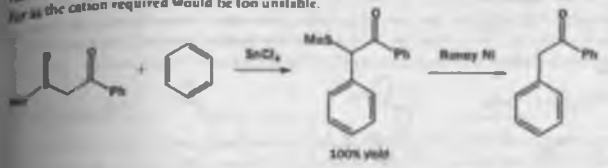
An ylid is first formed by loss of a proton—again, you have seen this—and then chloride is lost to form the same cation that we used in the alkylation reaction. In this step there is no nucleophile available except chloride ion so that adds to the carbon atom.



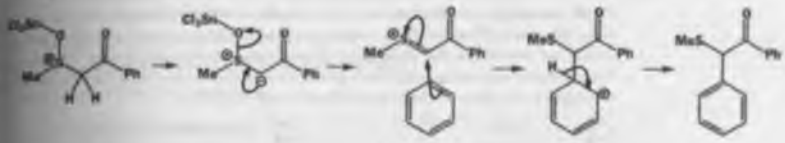
There are many variations on the Pummerer rearrangement but they all involve the same steps: a leaving group is lost from the sulfur atom of a sulfonium ylid to create a cationic intermediate that captures a nucleophile at the α carbon atom. Often the starting material is a sulfoxide.



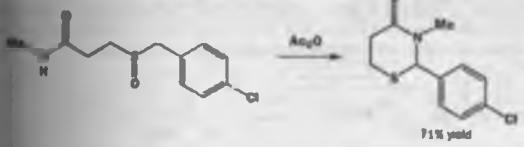
Treatment of a sulfoxide, particularly one with an anion-stabilizing substituent to help ylid formation, produces cations reactive enough to combine with nucleophiles of all sorts, even aromatic rings. The product is the result of electrophilic aromatic substitution (Chapter 22) and, after the sulfur has been removed with Raney nickel, is revealed as a ketone that could not be made without sulfur as the cation required would be too unstable.



A Lewis acid ($SnCl_4$) is used to remove the oxygen from the sulfoxide and the ketone assists ylid formation. The sulfur atom stabilizes the cation enough to counteract the destabilization by the ketone. The Lewis acid is necessary to make sure that no nucleophile competes with benzene.



Most commonly of all, a sulfoxide is treated with acetic anhydride and the cation is captured by an internal nucleophile to form a new ring. Here the nitrogen atom of an amide is the nucleophile. The mechanism is very like that of the last example.



Sulfur-stabilized β-carbocations (three-membered rings)

Three-membered cyclic sulfonium ions, representing β carbocations, are often encountered in participation reactions. We have seen this already in the way mustard gas works, but almost any arrangement of a sulfide with a leaving group on the β carbon atom leads to participation and the formation of a three-membered ring. The product is formed by migration of the PhS group from one carbon atom to another (Chapter 37).

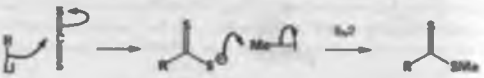
In this case, elimination of a proton from one of the methyl groups leads to an allylic sulfide—you have seen earlier in the chapter how these compounds, and the sulfoxides derived from them, can be used in synthesis. If we make a small change in the structure of the starting material—just joining up the two methyl groups into a cyclopropane—things change quite a bit. It becomes possible to make the starting material by a lithiation reaction because cyclopropyllithiums are significantly stabilized by the three-membered ring (Chapter 8) and the rearrangement goes with carbon rather than sulfur migration.

In the rearrangement, the alcohol is protonated as before but no sulfur participation occurs. Instead, a ring expansion, also assisted by sulfur, produces a four-membered ring and hydrolysis of the α cation (an intermediate you have seen several times) gives a cyclobutanone. The difference between participation through space and C=S$^+$ bond formation is not that great.

Thiocarbonyl compounds

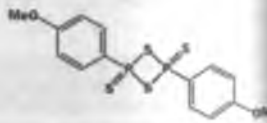
Simple thioaldehydes and thioketones are too unstable to exist and attempts at their preparation lead to appalling smells (Chapter 1). The problem is the poor overlap between the $2sp^2$ orbital on carbon and the $3sp^2$ orbital on sulfur as well as the more or less equal electronegativities of the two elements. Stable thiocarbonyl compounds include dithioesters and thioamides where the extra conjugation of the oxygen or nitrogen atom helps to stabilize the weak C=S bond.

Dithioesters can be made by a method that would seem odd if you thought only of ordinary esters. Organolithium or Grignard reagents combine well with carbon disulfide (CS$_2$—the sulfur analogue of CO_2) to give the anion of a dithioacid. This is a much more nucleophilic species than an ordinary carboxylate anion and combines with alkyl halides to give dithioesters.



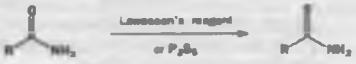
The reaction of dithioesters with Grignard reagents is even more remarkable. Because sulfur and carbon have about the same electronegativity, the Grignard reagent may add to either end of the π bond. If it adds to sulfur, the resulting anion is stabilized by two sulfur atoms, rather like the dithiane anions we have seen earlier in this chapter, and can be used as a d^1 reagent.

Thioamides are usually made by reaction of ordinary amides with P_2S_5 or Lawesson's reagent. Since C=S is so much less stable than C=O, there is a clear case to call in phosphorus to remove the oxygen. The situation is rather like that in the Wittig reaction: C=C is less stable than C=O, so phosphorus is called in to remove the oxygen because of the even greater stability of the P=O bond. Lawesson's reagent has P=S bonds and a slightly surprising structure.



Lawesson's reagent, or, if you prefer, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-phosphetane-2,4-disulfide

We can learn from this compound that sulfur has much less objection to four-membered rings than do oxygen or carbon. We have seen from the structure of sulfur itself (S_8) that it likes eight-membered rings too. Rings of almost any size are acceptable to sulfur as bond angles matter less to second-row elements that are not generally hybridized. Lawesson's reagent converts amides into thioamides and we have seen (Chapter 44) how these are used to make thiazoles.



Sulfoxides

The formation and reactions of sulfoxonium ylids demonstrate how sulfoxides occupy a useful and interesting part of the middle ground between sulfides and sulfones—they are weakly nucleophilic, like sulfides (and can be alkylated with methyl iodide to give sulfoxonium salts as we have just seen), but at the same time they stabilize anions almost as well as sulfones. However, sulfoxides are perhaps the most versatile of the three derivatives because of a good deal of chemistry that is unique to them. There are two reasons why this should be so.

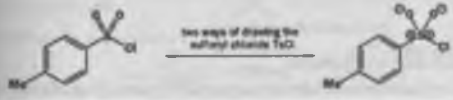
1. Sulfoxides have the potential to be chiral at sulfur
2. Sulfoxides undergo some interesting pericyclic reactions

We shall deal with each of these in turn.

Representing S=O compounds

Sulfoxides are sometimes drawn as S=O and sometimes as S$^+$–O$^-$. The second representation might remind you of the phosphorus ylids used in the Wittig reaction (Chapters 14 and 31), which can be drawn with a P=CH_2 double bond or as P$^+$–CH_2^-. All of these representations are correct—it is a matter of personal choice which you prefer.

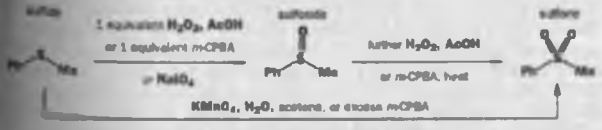
The double bonds are between 2p orbitals of O or C and 3d orbitals of S or P. But when we draw the structure of TsCl we always draw two S=O double bonds. You might think that an alternative structure with two S–O single bonds is not as good and almost nobody draws TsCl that way. Illogical but not unreasonable.



Sulfoxides are chiral

Providing the two groups attached to sulfur are different, a sulfoxide is chiral at the sulfur atom. There are two important ways of making sulfoxides as single enantiomers, both asymmetric versions of reactions otherwise used to make racemic sulfoxides: oxidation and nucleophilic substitution at sulfur.

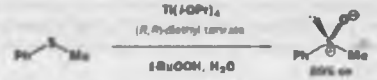
Sulfides are easy to oxidize and, depending on the type and quantity of oxidizing agent used, they can be cleanly oxidized either to sulfoxides or sulfones.



The oxidation of sulfides to sulfoxides can be made asymmetric by using one of the important reactions we introduced in the last chapter—the Sharpless asymmetric epoxidation. The French chemist Henri Kagan discovered in 1984 that, by treating a sulfide with the oxidant *t*-butyl hydroperoxide in the presence of Sharpless's chiral catalyst ($Ti(O^iPr)_4$ plus one enantiomer of diethyl tartrate), the oxygen atom could be directed to one of the sulfide's two enantiotopic lone pairs to give a sulfoxide in quite reasonable enantiomeric excess (ee).

■ For a definition of enantiomeric excess, see Chapter 48.

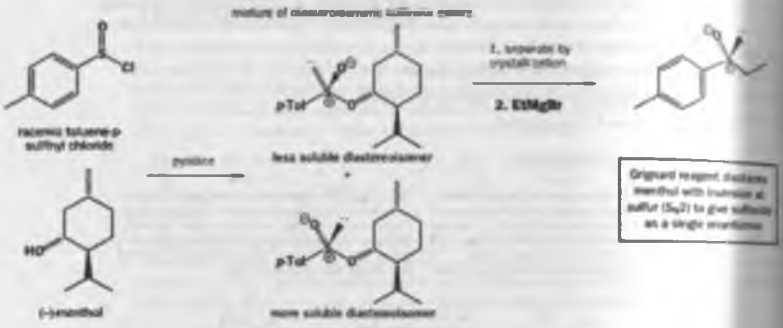
Here is an example where drawing a sulfoxide as S⁺–O⁻ is better.



As yet, this asymmetric oxidation is successful only with simple aryl alkyl sulfoxides like this one and the nucleophilic displacement method is much more widely used since it is more general and gives products of essentially 100% ee.

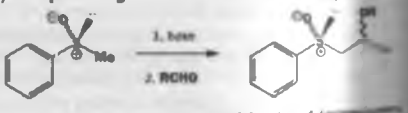
Sulfoxides can alternatively be made by displacement of RO^- from a sulfinate ester with a Grignard reagent.

Sulfinate esters, like sulfoxides, are chiral at sulfur and, if the ester is formed from a chiral alcohol (menthol is best), they can be separated into two diastereoisomers by crystallization—this is really a resolution of the type you first met in Chapter 16. Attack by the Grignard reagent takes place with inversion of configuration at sulfur, giving a single enantiomer of the sulfoxide.

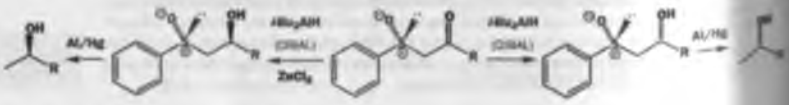


Chiral sulfoxides in synthesis

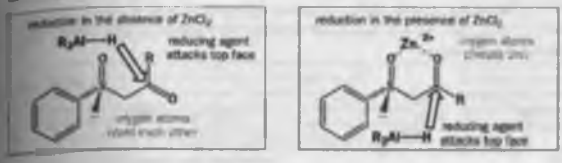
How can the chirality of sulfoxides be made useful? This area of research has received a lot of attention in the last 10–15 years, with many attempts to design reactions in which the chirality at sulfur is transferred to chirality at carbon. Unfortunately, one of the simplest reactions of sulfoxides, the addition of their anions to aldehydes, usually proceeds with no useful stereoselectivity at all.



Some more successful uses of sulfoxides to control new chiral centres at carbon have been developed in Strasbourg by Guy Solladié, and they involve stereoselective reduction of carbonyl groups directed by the sulfoxide's oxygen atom. For example, the synthesis below shows how chirality at sulfur can be transferred to chirality at carbon by using a reduction directed by the S–O bond. If this ketone is treated with the bulky reducing agent DIBAL (i-Bu_2AlH), one alcohol is formed, with less than 5% of the diastereoisomer. Remarkably, if $ZnCl_2$ is added to the mixture, the opposite diastereoisomer is obtained! Reduction of the products with aluminium amalgam removes the sulfoxide (we discussed this process earlier in the chapter) leaving behind enantiomerically enriched samples of the alcohol.



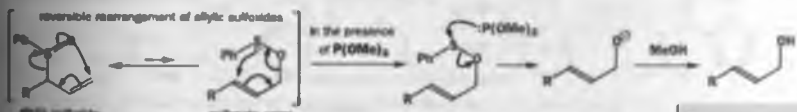
Solladie explained these results by suggesting that, in the absence of $ZnCl_2$, the sulfoxide adopts the conformation that places the two electronegative oxygen atoms as far apart as possible. DIBAL then attacks the less hindered face of the ketone, *syn* to the sulfoxide lone pair. With $ZnCl_2$, on the other hand, the sulfoxide's conformation is fixed by chelation to zinc: attack on the less hindered face of the ketone now gives the other diastereoisomer. Both compounds can be reduced with Al/Hg, which removes the sulfur group, to give opposite enantiomers of a chiral alcohol.



Allylic sulfoxides are not configurationally stable

Most sulfoxides will retain their configuration at sulfur up to temperatures of about 200 °C—indeed, it is estimated that the half-life for racemization of an enantiomerically pure sulfoxide is about 5000 years at room temperature. However, sulfoxides carrying allyl groups are much less stable—they racemize rapidly at about 50–70 °C. A clue to why this should be is provided by the reaction of an allylic sulfoxide with trimethyl phosphite, $P(OMe)_3$.

The product obtained is an allylic alcohol with the hydroxyl group at the other end of the allyl system from where the sulfur started—a rearrangement has taken place. We have observed the rearrangement in this case because the $P(OMe)_3$ has trapped the rearrangement product but, even without this reagent, allylic sulfoxides are continually and reversibly rearranging into sulfenate esters by the mechanism shown below.

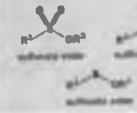


The rearrangement product, which is less stable than the sulfoxide and is therefore never observed directly, is a sulfenate ester. It has no chirality at sulfur so, when it rearranges back to the sulfoxide, it has no 'memory' of the configuration of the starting sulfoxide, and the sulfoxide becomes racemized.

Having read Chapter 36, you should be able to classify the pericyclic rearrangement reaction: it is a [2,3]-sigmatropic rearrangement (make sure you can see why before you read further) and as such is the first of the pericyclic rearrangements of sulfoxides that we shall talk about.

If our proposal that allylic sulfoxides rearrange reversibly to sulfenate esters is correct, then, if we make the sulfenate ester by another route, it too should rearrange to an allylic sulfoxide—and indeed it does. The sulfenate ester arising from reaction of allylic alcohols with PhSCl (phenylsulfenyl chloride) cannot be isolated; instead, the allylic sulfoxide is obtained, usually in very good yield, and this method is often used to make allylic sulfoxides.

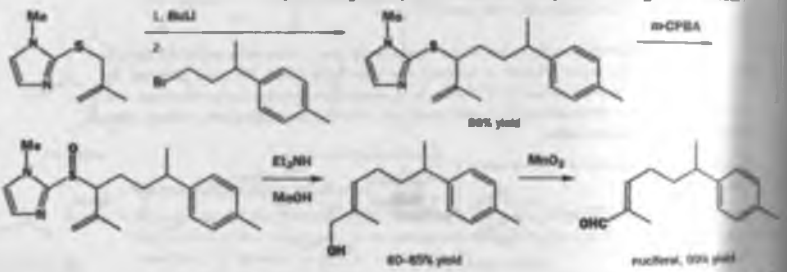
▶ You shouldn't at this stage try to learn all the names for every type of organosulfur compound—what matters is the structures. Here the names are all very similar and easily confused so, just for reference, here are the structures of a sulfonate ester (such as a tosylate or mesylate), a sulfinate ester, and a sulfenate ester.



Uses for [2,3]-sigmatropic rearrangements of sulfoxides

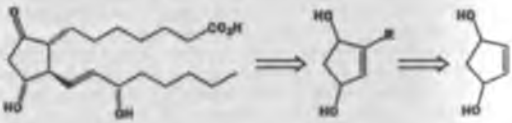
Allylic sulfoxides exist in equilibrium with allyl sulfenate esters. The two interconvert by [2,3]-sigmatropic rearrangement, and the equilibrium lies over to the side of the sulfoxide. Allyl sulfenate esters are therefore impossible to isolate, but they can be trapped by adding a compound known as a thiophile—$P(OMe)_3$ was the example you just saw, but secondary amines like Et_2NH also work—which attacks the sulfur atom to give an allylic alcohol. This can be a very useful way of making certain alcohols, particularly as the starting sulfoxides can be constructed by using sulfur's anion-stabilising ability. What is more, the starting allylic sulfoxides can themselves be made from allylic alcohols using PhSCl—overall then we can use allylic sulfoxide to alkylate allylic alcohols! This scheme should make all this clearer.

We can illustrate the synthesis of allylic alcohols from allylic sulfoxides with this synthesis of the natural product nuciferal. We mentioned this route on p. 000 because it makes use of a heteroatom-allyl sulfide to introduce an alkyl substituent regioselectively. The allyl sulfide is oxidized to the sulfoxide, which is converted to the rearranged allylic alcohol with diethylamine as the thiophile. Nuciferal is obtained by oxidizing the allylic alcohol to an aldehyde with manganese dioxide.



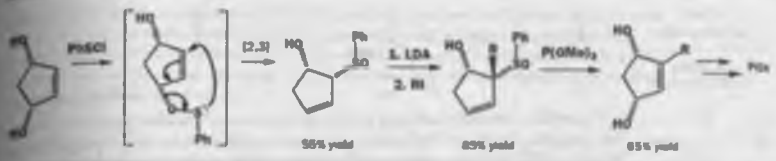
The next example makes more involved use of these [2,3]-sigmatropic allylic sulfoxide–allylic alcohol rearrangements. It comes from the work of Evans (he of the chiral auxiliary) who, in the early 1970s, first demonstrated the synthetic utility of allylic sulfoxides. Here he is using this chemistry to make precursors of the prostaglandins, a family of compounds that modulate hormone activity within the body.

■ Prostaglandins are discussed more thoroughly in Chapter 22.



PGE_1, a prostaglandin

Prostaglandins are trisubstituted cyclopentanones, and the aim was to synthesize them from available cyclopentenediol using allylic sulfoxide chemistry to introduce the long alkyl chain R group. Treating *syn*-cyclopentenediol with PhSCl gave the allylic sulfoxide (either hydroxyl can react but the product is the same). The sulfoxide was deprotonated and reacted with an alkyl halide, and then rearranged back to an allylic alcohol using $P(OMe)_3$ as the thiophile.

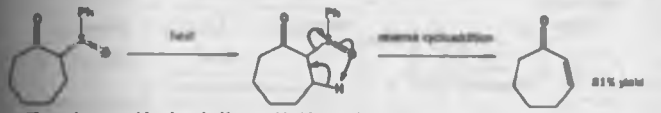


Stereochemistry of sulfoxide reactions

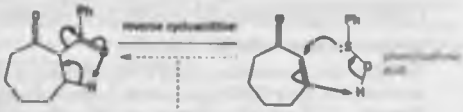
This sequence of reactions contains some interesting stereochemistry. The first rearrangement, from the cyclopentenediol to the allylic sulfenate, is stereospecific—the *syn*-diol gives the *anti*-rearrangement. This is typical of [2,3]-sigmatropic rearrangements—they are suprafacial with respect to the allylic component (see Chapter 35). In the next step, the R group is introduced trans to the hydroxyl group. This is a stereoselective reaction, not a stereospecific one, because the other diastereoisomer of the starting material, with the hydroxyl group and the sulfoxide trans, also gives the product with the R group trans to the hydroxyl group. Finally, there is another stereospecific (suprafacial) [2,3]-sigmatropic reaction to give diol, maintaining the *syn* relative stereochemistry of the hydroxysulfoxide in the stereochemistry of the diol product.

Sulfoxide elimination—oxidation to enones

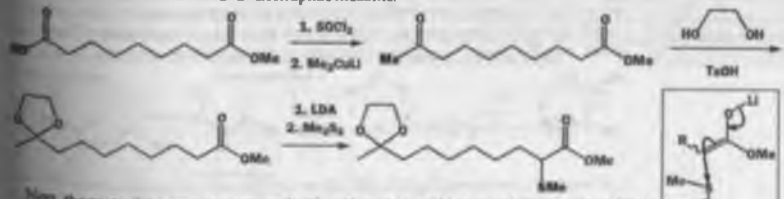
Sulfoxides next to an electron-withdrawing or conjugating group are also unstable on heating, not because they racemize but because they decompose by an elimination process.



The rather unstable phenylsulfenic acid (PhS–OH) is eliminated and the reaction occurs partly because of the creation of conjugation and partly because PhSOH decomposes to volatile products. The elimination is a pericyclic reaction—it may not immediately be obvious what sort, but it is, in fact, a reverse cycloaddition. This is clearest if we draw the mechanism of the reverse reaction.

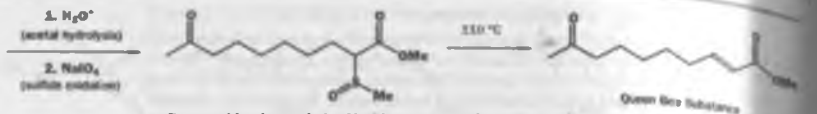


This reaction provides a useful way of introducing a double bond next to a carbonyl group. Here it is in a synthesis by Barry Trost of the Queen Bee Substance (the compound fed by the workers to those bee larvae destined to become queens). The compound is also a pheromone of the termite and is used to trap these destructive pests. Trost started with the monoester of a dicarboxylic acid, which he converted to a methyl ketone by reacting the acyl chloride with a cuprate. The ketone was then protected as a dioxolane derivative to prevent it enolizing, and the sulfur was introduced by reacting the enolate of the ester with the sulfur electrophile MeSSMe.

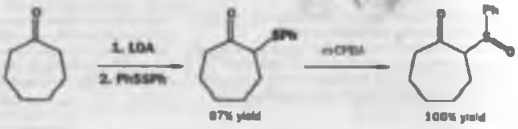


Next, the protecting group was removed with acid, and the sulfide was oxidized to the sulfoxide with sodium periodate ($NaIO_4$) ready for elimination. Heating to 110 °C then gave the Queen Bee Substance in 86% yield.

■ In Chapter 9 we discussed ways of making ketones by nucleophilic attack on carboxylic acid derivatives.

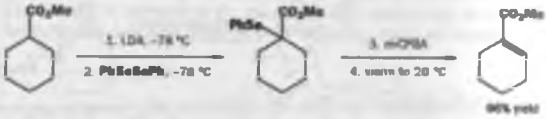


Presumably, the methyl sulfoxide was chosen here because it worked better—it is more usual to use a phenyl sulfoxide, and PhS groups can be introduced in the same way (by reacting enolates with PhSSPh or PhSCl). The cyclohexanone derivative used in our first elimination example was made from cycloheptanone in this way.



▶
Sulfur and selenium have many properties in common, and much sulfur chemistry is mirrored by selenium chemistry. In general, organoselenium compounds tend to be less stable and more reactive than organosulfur ones because the C–Se bond is even weaker than a C–S bond. They also have even fouler odours.

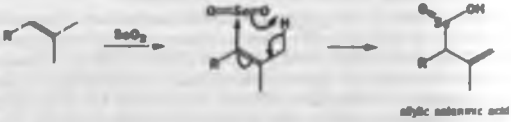
This elimination takes place more easily still when sulfur is replaced by a selenium—PhSe groups can be introduced by the same method, and oxidized to selenoxides with *m*-CPBA at low temperature. The selenoxides are rarely isolated, because the elimination takes place rapidly at room temperature.



Other oxidations with sulfur and selenium

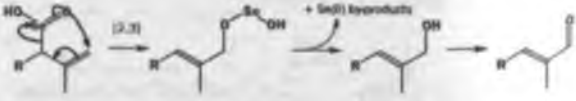
Selenium dioxide and allylic oxidation

Having introduced selenium, we should at this point mention an important reaction that is peculiar to selenium but that is closely related to these pericyclic reactions. Selenium dioxide will react with alkenes in a [4 + 2] cycloaddition reminiscent of the ene reaction.



▶
In a very few special cases, the seleninic acid intermediate has been isolated.

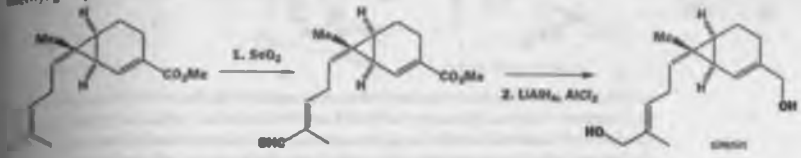
The initial product is an allylic seleninic acid—and just like an allylic sulfoxide (but more so because the C–Se bond is even weaker) it undergoes allylic rearrangement to give an unstable compound that rapidly decomposes to an allylic alcohol. In some cases, particularly this most useful oxidation of methyl groups, the oxidation continues to give an aldehyde or ketone.



Overall, CH_3 has been replaced by CH_2OH or $CH{=}O$ in an allylic position, a transformation similar to the NBS allylic bromination reaction that you met in Chapter 39, but with a very different mechanism. The by-product of the oxidation is a selenium(II) compound, and it can be more practical to carry out the reaction with only a catalytic amount of SeO_2, with a further oxidizing agent,

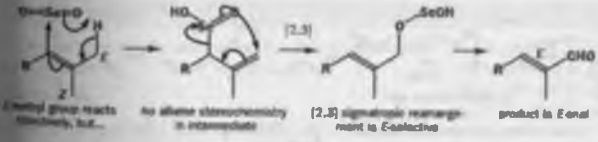
t-butyl hydroperoxide, to reoxidize the Se(II) after each cycle of the reaction. This eliminates the need to get rid of large amounts of selenium-containing products, which are toxic and usually smelly.

In Chapter 40 we left the synthesis of nitrenin at a tantalizing stage. A carbene insertion into a double bond had formed a three-membered ring and the final stage was the oxidation of a terminal methyl group. This is how it was done.



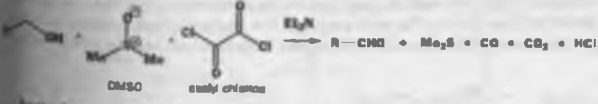
There is some interesting selectivity in this sequence. Only one of the three groups next to the alkene is oxidized and only one (*E*-) isomer of the enal is formed. No position next to the unsaturated ester is oxidized. All these decisions are taken in the initial cycloaddition step. The most nucleophilic double bond uses its more nucleophilic end to attack SeO_2 at selenium. The cycloaddition uses the HOMO (π) of the alkene to attack the LUMO (π* of Se–O). Meanwhile the HOMO (π) of Se–O attacks the LUMO (C–H σ*) of the allylic system.

The stereoselectivity also appears to be determined in this step and it is reasonable to assume that the methyl group *trans* to the main chain will react rather than the other for simple steric reasons. Though this is true, the stereochemistry actually disappears in the intermediate and is finally fixed only in the [2,3]-sigmatropic rearrangement step. Both [2,3]- and [3,3]-sigmatropic rearrangements are usually *E*-selective for reasons discussed in Chapter 36.



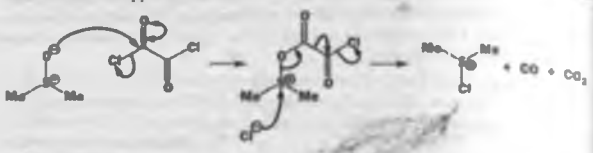
The Swern oxidation

In Chapter 24 we mentioned the Swern oxidation briefly as an excellent method of converting alcohols to aldehydes. We said there that we would discuss this interesting reaction later and now is the time. The mechanism is related to the reactions that we have been discussing and it is relevant that the Swern oxidation is particularly effective at forming enals from allylic alcohols.



In the first step, DMSO reacts with oxalyl chloride to give an electrophilic sulfur compound. You should not be surprised that it is the charged oxygen atom that attacks the carbonyl group rather than the soft sulfur atom. Chloride is released in this acylation and it attacks the positively charge

sulfur atom expelling a remarkable leaving group, which fragments into three pieces: CO_2, CO, and a chloride ion. Entropy favours this reaction.

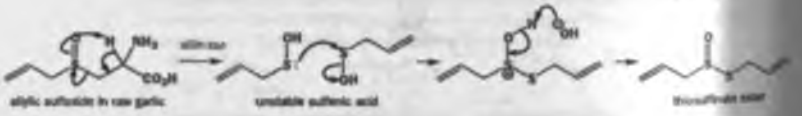


The alcohol has been a spectator of these events so far but the chlorosulfonium ion now formed can react with it to give a new sulfonium salt. This is the sole purpose of all the reactions so far: the new sulfonium salt is stable enough to survive and to be deprotonated by the base (Et_3N). You will recognize the final step both as the redox step and as a close relative to events in the preceding sections.

To conclude: the sulfur chemistry of onions and garlic

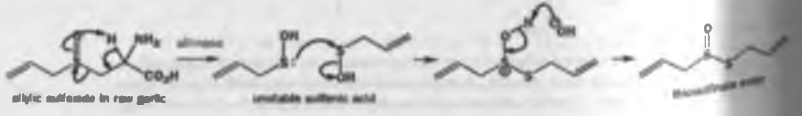
Traditional medicine suggests that onions and garlic are 'good for you' and modern chemistry has revealed some of the reasons. These bulbs of the genus *Allium* exhibit some remarkable sulfur chemistry and we will end this chapter with a few examples. Both onions and garlic are almost odourless when whole but develop powerful smells and, in the case of onions, tear gas properties when they are cut. These all result from the action of alliinase enzymes released by cell damage on unnatural sulfoxides in the bulb.

In garlic, a simple sulfoxide elimination creates an unstable sulfenic acid. When we looked at sulfoxide eliminations before, we ignored the fate of the unstable sulfenic acid, but here it is important. It dimerizes with the formation of an S–S bond and the breaking of a weaker S–O bond.



Another simple elimination reaction on the thiosulfinate ester makes another molecule of the sulfenic acid and a highly unstable unsaturated thioaldehyde, which promptly dimerizes to give a thioacetal found in garlic as a potent platelet aggregation inhibitor.

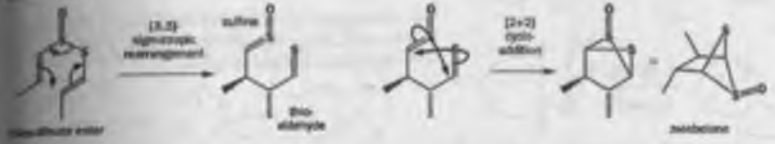
In onions, things start much the same way but the initial amino acid is not quite the same. The skeleton is the same as that of the garlic compound but the double bond is conjugated with the sulfoxide. Elimination and dimerization of the sulfenic acid produce an isomeric thiosulfinate.



Oxidation of the thiosulfinate ester up to the sulfonate level gives the compound responsible for the smell of raw onions, while a hydrogen shift on the conjugated sulfenic acid (not possible with the garlic compound) gives a sulfine, the sulfur analogue of a ketene. The compound has the *Z* configuration expected from the mechanism and is the lachrymator that makes you cry when you cut into a raw onion.

▶ There is still one lone pair on the sulfur atom of a sulfine so the sulfur is trigonal and not linear, rather like the nitrogen in an oxime.

Even more remarkable is the formation of the 'zwiebelanes', other compounds with potential as drugs for heart disease. They are formed in onions from the conjugated thiosulfinate ester by a [3,3]-sigmatropic rearrangement that gives a compound containing a sulfine and a thioaldehyde. We said that sulfines are the sulfur equivalents of ketenes, so you might expect them to do [2 + 2] cycloadditions (Chapter 35) but you might not expect the thioaldehyde to be the other partner. It is, and the result is a target compound with one sulfide and one sulfoxide joined in a four-membered ring.

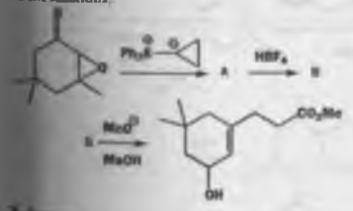


Look at onions with respect! They are not only the cornerstone of tasty cooking but are able to do amazing pericyclic reactions as soon as you cut them open. You can read more about the *Allium* family in Eric Block's review in *Angewandte Chemie* (International Edition in English), 1992, Volume 31, p. 1135.

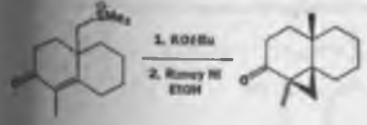
Though you have only seen a couple of examples of the latter, it is clear that organosulfur and organoselenium chemistry are closely related. In the next chapter we will look at the quite different type of chemistry exhibited by organic compounds containing three other heteroatoms—silicon, tin, and boron.

Problems

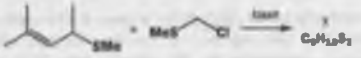
1. Suggest structures for intermediates A and B and mechanisms for the reactions.



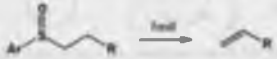
2. Suggest a mechanism for this reaction, commenting on the regiochemistry and the stereochemistry.



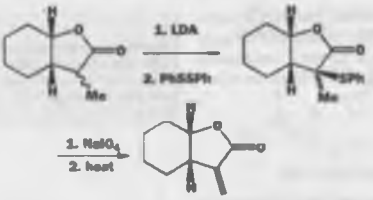
3. The product X of the following reaction has δ_H 1.28 p.p.m. (6H, s), 1.63 p.p.m. (3H, d, *J* 4.5 Hz), 2.45 p.p.m. (6H, s), 4.22 p.p.m. (1H, s), 5.41 p.p.m. (1H, d, *J* 15 Hz), and 5.63 p.p.m. (1H, dq, *J* 15, 4.5 Hz). Suggest a structure for X and a mechanism for its formation.



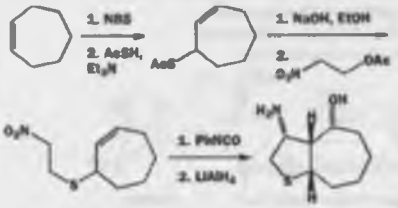
4. The thermal elimination of sulfoxides (example below) is a first-order reaction with almost no rate dependence on substituent at sulfur (Ar) and a modest negative entropy of activation. It is accelerated if R is a carbonyl group (that is, R = COR'). The reaction is (slightly) faster in less polar solvents. Explain.



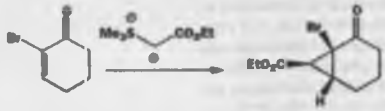
Explain the stereochemistry of the first reaction in the following scheme and the position of the double bond in the final product.



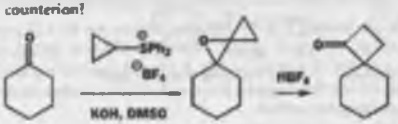
5. Revision content. Explain the reactions and the stereochemistry in these first steps in a synthesis of the B vitamin biotin.



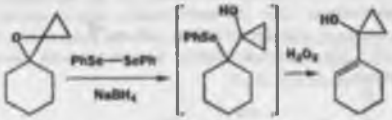
6. Explain the regio- and stereoselectivity of this reaction.



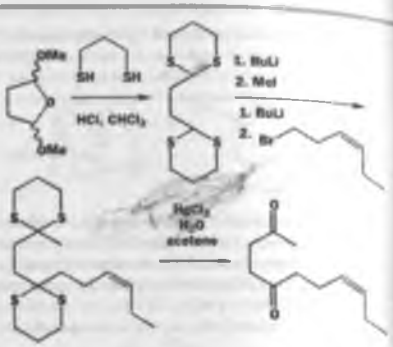
7. Draw mechanisms for these reactions of a sulfonium ylid and the rearrangement of the first product. Why is BF_4^- chosen as the counterion?



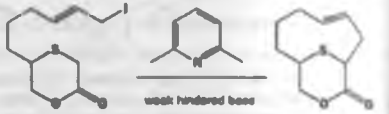
The intermediate may alternatively be reacted with a selenium compound in this sequence of reactions. Explain what is happening, commenting on the regioselectivity. Why is the intermediate in square brackets not usually isolated?



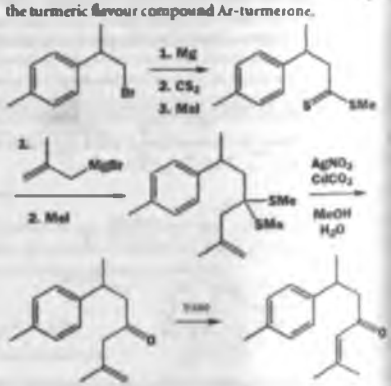
8. Give mechanisms for these reactions, explaining the role of sulfur.



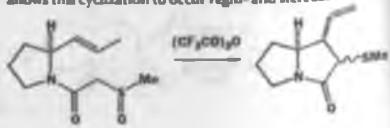
9. Suggest a mechanism for this formation of a nine-membered ring. Warning! The weak hindered base is not strong enough to form an enolate from the lactone.



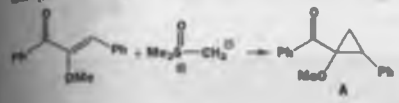
10. Comment on the role of sulfur in the steps in this synthesis of the turmeric flavour compound Ar-turmerone.



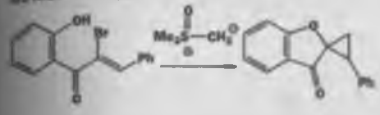
11. Explain how the presence of the sulfur-containing group allows this cyclization to occur regio- and stereoselectively.



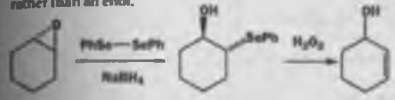
12. Problem 9 in Chapter 32 asked you to interpret the NMR spectrum of a cyclopropane (A). This compound was formed using a sulfur ylid. What is the mechanism of the reaction?



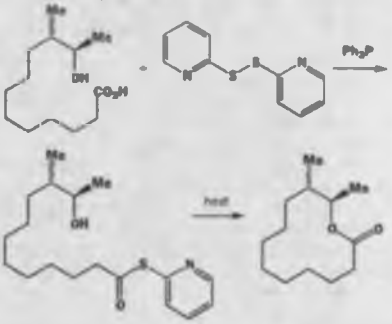
Attempts to repeat this synthesis on the bromo compound below led to a different product. What is different this time?



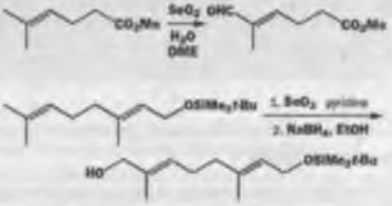
13. Epoxides may be transformed into allylic alcohols by the sequence shown here. Give mechanisms for the reactions and explain why the elimination of the selenium gives an allylic alcohol rather than an enol.



14. In a process resembling the Mitsunobu reaction (Chapter 17), alcohols and acids can be coupled to give esters, even macrocyclic lactones as shown below. In contrast to the Mitsunobu reaction, the reaction leads to retention of stereochemistry at the alcohol. Propose a mechanism that explains the stereochemistry. Why is sulfur necessary here?



15. Suggest mechanisms for these reactions, explaining any selectivity.



Organo-main-group chemistry 2: boron, silicon and tin

47

Connections

Building on:

- Conjugate addition ch10 & ch23
- Nucleophilic substitution at saturated carbon ch17
- Controlling stereochemistry ch18, ch33, & ch34
- Oxidation, reduction, and protection ch24
- Aldol reactions ch27
- Controlling double bond geometry ch31
- Rearrangements ch36–ch37
- Radicals ch38
- Asymmetric synthesis ch45
- Sulfur chemistry ch46

Arriving at:

- Main group elements in organic chemistry
- Boron is electrophilic because of a vacant orbital
- Hydroboration adds boron selectively
- Oxidation removes boron selectively
- Boron chemistry uses rearrangements
- Allyl B, Si, and Sn compounds are useful in synthesis
- Organo-B, -Si, and -Sn compounds can be used in asymmetric synthesis
- Silicon is more electrophilic than carbon
- Silicon stabilizes β carbocations
- Organo-tin compounds are like Si compounds but more reactive
- Tin is easily exchanged for lithium

Looking forward to:

- Organometallic chemistry ch42
- Polymerization ch52

Organic chemists make extensive use of the periodic table

Although typical organic molecules, such as those of which all living things are composed, are constructed from only a few elements (usually C, H, O, N, S, and P and, on occasion, Cl, Br, I, and a few more), there are very many other elements that can be used as the basis for reagents, catalysts, and as components of synthetic intermediates. The metals will be discussed in the next chapter (48) but many main group (p block) elements are also important. These nonmetals bond covalently to carbon and some of their compounds are important in their own right.

More commonly, elements such as Si, P, and S are used in reagents to carry out some transformation but are not required in the final molecule and so must be removed at a later stage in the synthesis. The fact that organic chemists are prepared to tolerate this additional step demonstrates the importance of these reactions. The Julia olefination is an obvious example. The difficult conversion of aldehydes and ketones into alkenes is important enough to make it worthwhile adding a sulfur atom to the starting material and then removing it at the end of the reaction. So many elements are used like this that the list of nonmetals that are *not* used frequently in organic synthesis would be much shorter than the list of those that *are* useful.

In the previous chapter we described the special chemistry of sulfur, and you have previously met that of phosphorus. These two elements may be thought of as analogues of oxygen and nitrogen but many reactions are possible with S and P that are quite impossible with O and N. This chapter will concentrate on the organic chemistry of three other main group elements: boron, which is unusual in this context because it is a first row element, and silicon and tin, which are in the same group as

carbon in the periodic table but in the second and fourth rows. Here they are surrounded by other familiar elements.

Li	Be	B	C	N	O	F	Ne
Na	Mg	Al	Si	P	S	Cl	Ar
			Ge		Se		

Boron

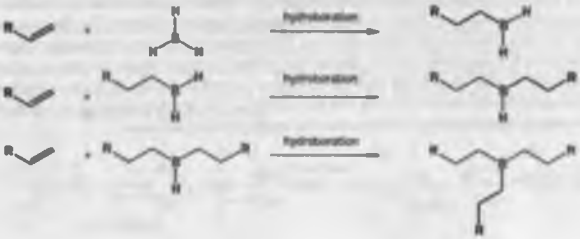
Borane has a vacant p orbital

You have already met boron in useful reagents such as sodium borohydride $NaBH_4$ and borane BH_3 (more correctly, B_2H_6). Both display the crucial feature of boron chemistry, which results directly from its position in group IIIB or 13 of the periodic table. Boron has only three electrons in the 2p shell and so typically forms three conventional two-centre two-electron bonds with other atoms in a planar structure leaving a vacant 2p orbital. Borane exists as a mixture of B_2H_6—a dimer with hydrogen bridges—and the monomer BH_3. Since most reactions occur with BH_3 and the equilibrium is fast we will not refer to this again.

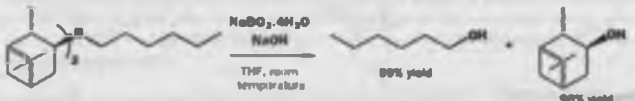
The vacant orbital is able to accept a lone pair of electrons from a Lewis base to give a neutral species or can combine with a nucleophile to form a negatively charged tetrahedral anion. The reducing agent borane–dimethyl sulfide is an example of the Lewis acid behaviour while the borohydride anion would be the result of the imaginary reaction of borane with a nucleophile hydride. The vacant orbital makes borane a target for nucleophiles.

Hydroboration—the addition of boron hydrides to alkenes and alkynes

One of the simplest classes of nucleophiles that attacks borane is that of alkenes. The result, described as **hydroboration**, is an overall addition of borane across the double bond. Unlike most electrophilic additions to alkenes that occur in a stepwise manner via charged intermediates (Chapter 20), this addition is concerted so that both new bonds are formed more or less at the same time. The result is a new borane in which one of the hydrogen atoms has been replaced by an alkene. This monoalkyl borane (RBH_2) is now able to undergo addition with another molecule of the alkene to produce a dialkyl borane (R_2BH) which in turn undergoes further reaction to produce a trialkyl borane (R_3B). All these boranes have a vacant p orbital and are flat so that repeated attack to produce the trialkyl borane is easy and normal if an excess of alkene is present.



If we have a mixed trialkyl borane, you may be concerned about which of the alkyl groups migrates—the usual answer is that they all do! Oxidation proceeds until the borane is fully oxidized to the corresponding borate, which then breaks down to give the alcohols.

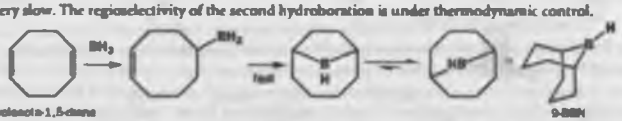


Bulky substituents improve the selectivity of hydroboration

Borane can react one, two, or even three times and this is a disadvantage in many situations so a range of hydroborating reagents has been designed to hydroborate once or twice. Dialkyl boranes R_2BH can hydroborate once only and alkyl boranes RBH_2 twice. In each case the 'dummy' group R must be designed either to migrate badly in the oxidation step or to provide an alcohol that is easily separated from other alcohols. The regioselectivity of hydroboration, good though it is with simple borane, is also improved by very bulky boranes, which explains the choice of dummy groups. Thexyl borane, so-called because the alkyl group is a 'tertiary hexyl' group (t-hexyl), is used when two hydroborations are required and it is easily made by hydroboration with borane since the second hydroboration with the tetrasubstituted alkene is very slow.

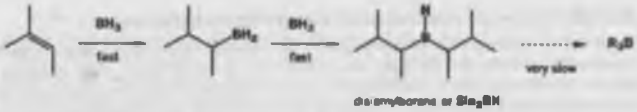
Thexyl borane is often written as $ThBH_2$ and drawn as:

Two dialkyl boranes are in common use. The bicyclic 9-borabicyclo[3.3.1]nonane (9-BBN), introduced in Chapter 34 as a reagent for diastereoselective aldol reactions, is a stable crystalline solid. This is very unusual for an alkyl borane and makes it a popular reagent. It is made by hydroboration of cycloocta-1,5-diene. The second hydroboration is fast because it is intramolecular but the third would be very slow. The regioselectivity of the second hydroboration is under thermodynamic control.



9-BBN is often drawn as:

Disiamylborane (an abbreviation for di-s-isoamyl borane—not a name we should use now, but the abbreviation has stuck) is also easily made by hydroboration of a simple trialkyl alkene with borane. Two hydroborations occur easily, in contrast to the tetrasubstituted alkene above, but the third is very slow. Disiamylborane is exceptionally regioselective because of its very hindered structure. The structures of these reagents are cumbersome to draw in full and they are often abbreviated.



disiamylborane or Sia_2BH

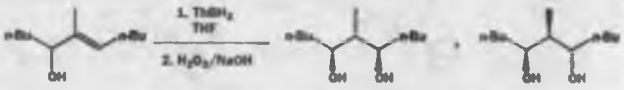
Hydroboration

- Hydroboration is a *syn* addition of a borane to an alkene
- Regioselectivity is high: the boron adds to the carbon less able to support a positive charge

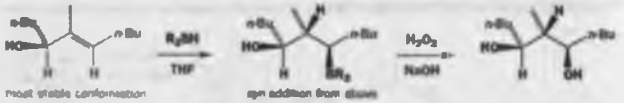
● Hydroboration—contd

- **Oxidation occurs with retention of stereochemistry**
- **The net result of hydroboration–oxidation is addition of water across the double bond**

These bulkier boranes enhance the regioselectivity of hydroboration of trisubstituted alkenes in particular and may also lead to high diastereoselectivity when there is a stereogenic centre next to the alkene. In this next example, an allylic alcohol is hydroborated with thexyl borane. Oxidation reveals complete regioselectivity and a 9:1 stereoselectivity in favour of hydroboration on the same side as the OH group.



The reactive conformation of the alkene is probably the 'Houk' conformation (Chapter 34) with the hydrogen atom on the stereogenic centre eclipsing the alkene. Attack occurs *syn* to the OH group and *anti* to the larger butyl group.



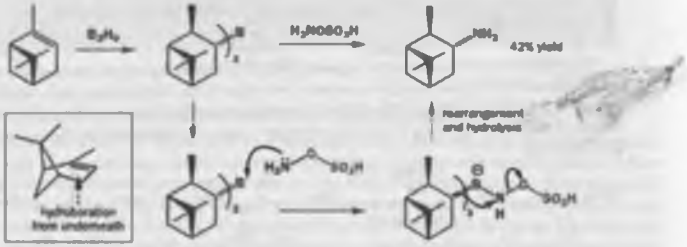
Hydroboration is not restricted to alkenes: alkynes also react well to give vinyl boranes. These may be used directly in synthesis or oxidized to the corresponding enol, which immediately tautomerizes to the aldehyde. An example of this transformation is the conversion of 1-octyne into octanal by hydroboration with disiamylborane and oxidation with sodium perborate under very mild conditions.

Carbon–boron bonds can be transformed stereospecifically into C–O, C–N, or C–C bonds

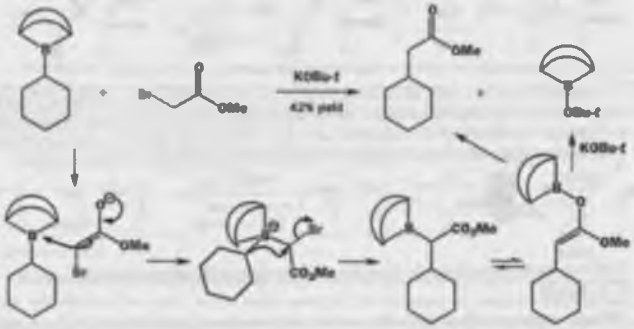
Although oxidation to the alcohol is the most common reaction of organoboranes in organic synthesis, the reaction with $^{-}$O–OH is just one example of a general reaction with a nucleophile of the type $^{-}$X–Y where the nucleophilic atom X can be O, N, or even C, and Y is a leaving group. We will illustrate the formation of carbon–nitrogen and carbon–carbon bonds by this reaction. The underlying principle is to use the vacant orbital on boron to attack the nucleophile and then rely on the loss of the leaving group to initiate a rearrangement of R groups from B to X similar to that observed from B to O in the hydrogen peroxide oxidation. The overall result is insertion of X into the carbon–boron bond with retention.

If X is nitrogen then a direct method of amination results. The required reagent is a chloramine or the rather safer *O*-hydroxylaminesulfonic acid: the leaving group is chloride or sulfonate. The overall

process of hydroboration–amination corresponds to a regioselective *syn* addition of ammonia across the alkene. In the case of pinene the two faces of the alkene are very different—one is shielded by the bridge with the geminal dimethyl group. Addition takes place exclusively from the less hindered side to give one diastereoisomer of one regioisomer of the amine.



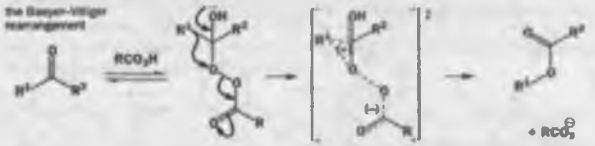
Carbon–carbon bonds can also be made with alkyl boranes. The requirement for a carbon nucleophile that bears a suitable leaving group is met by α-halo carbonyl compounds. The halogen makes enolization of the carbonyl compound easier and then departs in the rearrangement step. The product is a boron enolate with the boron bound to carbon. Under the basic conditions of the reaction, hydrolysis to the corresponding carbonyl compound is rapid.



In this example it is important which group migrates from boron to carbon as that is the group that forms the new C–C bond in the product. We previously compared the oxidation of alkyl boranes with the Baeyer–Villiger reaction (Chapter 37) but the order of migrating groups is the opposite in the two reactions. In the Baeyer–Villiger reaction (migration from carbon to oxygen) the more highly substituted carbon atom migrates best so the order is *t*-alkyl > *s*-alkyl > *n*-alkyl > methyl. In organoborane rearrangements it is the reverse order: *n*-alkyl > *s*-alkyl > *t*-alkyl. Methyl does not feature as you cannot make a B–Me bond by hydroboration.

Why the difference between the Baeyer–Villiger rearrangement and boron chemistry?

The transition state for the Baeyer–Villiger rearrangement has a positive charge in the important area. Anything that can help stabilize the positive charge, such as a tertiary migrating group (R^1), stabilizes the transition state and makes the reaction go better.



In the boron rearrangements, by contrast, the whole transition state has a negative charge. Alkyl groups destabilize rather than stabilize negative charges, but primary alkyl groups destabilize them less than secondary ones do, and so on. This is another reason for choosing tertiary alkyl 'dummy' groups such as *t*-hexyl—they are less likely to migrate.

But what about the case we were considering? The migrating group is secondary and the groups that are left behind on the 9-BBN framework are also secondary. What is the distinction? Again we can use the Baeyer–Villiger reaction to help us. The treatment of bridged bicyclic ketones with peroxy-acids often leads to more migration of the primary alkyl group than of the secondary one.

Bridgehead atoms are bad migrating groups. When the green spot carbon migrates, it drags the whole cage structure with it and distorts the molecule a great deal. When the black spot carbon migrates, it simply slides along the O–O bond and disturbs the cage much less. It is the same with 9-BBN. Migration of the bicyclic group is also unfavourable.

Migration preferences

- For the Baeyer–Villiger reaction, cation-stabilizing groups migrate best: *t*-alkyl > *s*-alkyl > *n*-alkyl > methyl
- For boron rearrangements, cation-stabilizing groups migrate worst: *n*-alkyl > *s*-alkyl > *t*-alkyl
- For both, bridgehead groups migrate badly

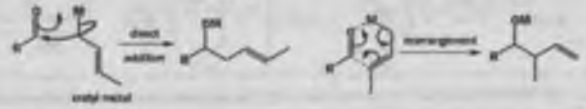
Allyl and crotyl boranes react using the double bond

Allylic boron compounds react with aldehydes in a slightly different way. The first step is, as always, coordination of the basic carbonyl oxygen to the Lewis acid boron. This has two important effects: first, the carbonyl is made more electrophilic and, second, the carbon–boron bond in the allylic fragment is weakened so that migration is easier. The difference is that the reaction that follows is not the now familiar 1,2-rearrangement but one involving the allylic double bond as well, rather like a [3,3]-sigmatropic rearrangement (Chapter 36). The negatively charged boron increases the nucleophilicity of the double bond so that it attacks the carbonyl carbon. The result is a six-membered transition state in which transfer of boron from carbon to oxygen occurs with simultaneous carbon–carbon bond formation. Hydrolytic cleavage of the boron–oxygen bond is often accelerated by hydrogen

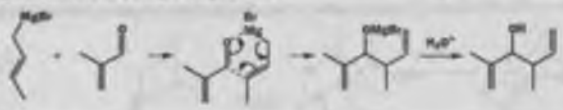
peroxide as in hydroboration. The precise nature of the ligands on boron is not important as this process is successful both for boranes (L = R) and boronates (L = OR).

Other allylic organometallic reagents frequently react with 2,3-rearrangement

It is necessary to have a label of some sort to tell whether an allyl metal has reacted directly or by the mechanism we have just seen, a mechanism common to many metals. An isotopic label such as deuterium or ^{13}C might be used but by far the simplest is a substituent such as a methyl group. The resulting methyl allyl group is known as crotyl. Reaction with an aldehyde can follow two pathways, direct addition leads to one product without rearrangement while addition with rearrangement gives an isomeric product.

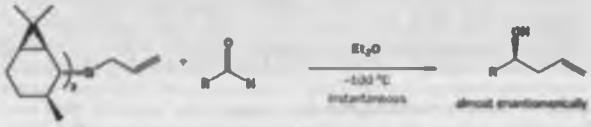


This sort of rearrangement is often known as allylic rearrangement, and even simple Grignard reagents react with aldehydes in this way via a cyclic six-membered transition state (Chapter 9).



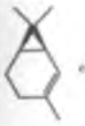
Enantioselective allylation is possible with optically pure ligands on boron

You may not think that allylating an aldehyde is much of an achievement—after all, allyl Grignard reagents would do just the same job. The interest in allyl boranes arises because enantiomerically pure ligands derived from naturally occurring chiral terpenes can easily be incorporated into the allyl borane. H.C. Brown, has investigated a range of terpenes as chiral ligands. The reagent below, B-allyldiis(2-isocaranyl)borane, has two ligands resulting from hydroboration of carene and delivers the allyl group under such exquisite control that the resulting homoallylic alcohol is virtually a single enantiomer. This reaction is one of the fastest in organic chemistry even at the very low temperature of –100 °C and the product is a useful building block. This makes the process more practical as the cooling is required for only a short time.

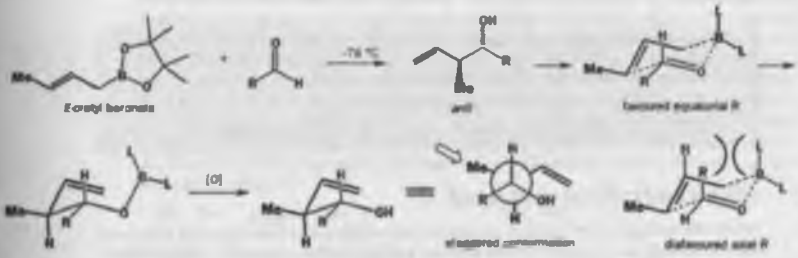


Allyl and crotyl boranes react stereospecifically

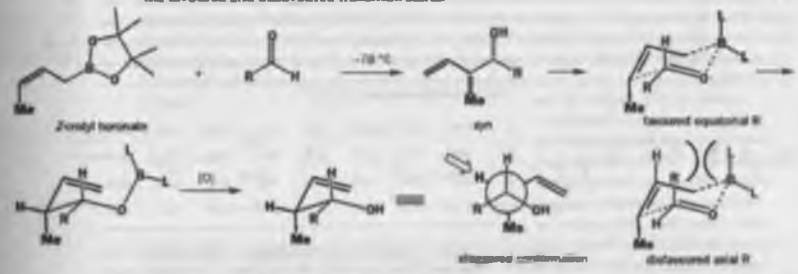
The six-membered transition state for the reaction of an allylic borane or boronate is very reminiscent of the cyclic transition state for the aldol reaction you met in Chapter 34. In this case the only change is to replace the oxygen of the enolate with a carbon to make the allyl nucleophile. The transition state for the aldol reaction was a chair and the reaction was stereospecific so that the geometry of the enolate determined the stereochemistry of the product aldol. The same is true in these reactions. *E*-Crotyl boranes (or boronates) give *anti* homoallylic alcohols and *Z*-crotyl boranes (or boronates)



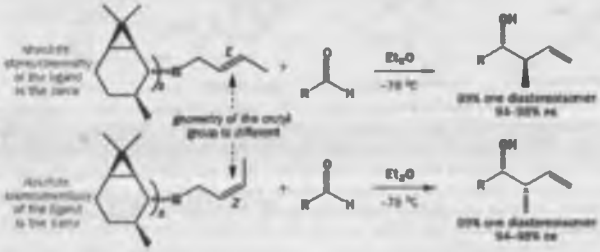
give *syn* alcohols via chair transition states in which the aldehyde R group adopts a pseudoequatorial position to minimize steric repulsion. As with the aldol reaction the short bonds to boron create a very tight transition state, which converts the two-dimensional stereochemistry of the reagent into the three-dimensional structure of the product.



The low temperature is a testament to the reactivity of the crotyl boronates and also helps minimize any isomerization of the reagents while maximizing the effect of the energy differences between the favoured and disfavoured transition states.



The dramatic diastereoselectivity of this process is noteworthy but, of course, the products are racemic—two *anti* isomers from the *E*-crotyl reagent and two *syn* isomers from the *Z* counterpart. This is inevitable as both starting materials are achiral and there is no external source of chirality. You may be wondering if the use of a chiral ligand on boron would allow the production of a single enantiomer of a single diastereoisomer. The simple answer is that it does, very nicely. In fact, there are a number of solutions to this problem using boranes and boronates but the one illustrated uses the same ligand as that used earlier for allylation derived from carene.



Though boron and aluminium form similar reducing agents, such as $NaBH_4$ and $LiAlH_4$, the reactions described so far in this chapter do not occur with aluminium compounds, and compounds with C–Al bonds, other than DIBAL and Me_3Al, are hardly used in organic chemistry. We move on to the other two elements in this chapter, Si and Sn, both members of group IVB (or 14 if you prefer)—the same group as carbon.

Special features of organoboron chemistry

- Boron is electrophilic because of its empty p orbital
- Boron forms strong B–O bonds and weak B–C bonds
- Migration of alkyl groups from boron to O, N, or C is stereospecific

Silicon and carbon compared

Silicon is immediately below carbon in the periodic table and the most obvious similarity is that both elements normally have a valency of four and both form tetrahedral compounds. There are important differences in the chemistry of carbon and silicon—silicon is less important and many books are devoted solely to carbon chemistry but relatively few to silicon chemistry. Carbon forms many stable trigonal and linear compounds containing π bonds; silicon forms few. The most important difference is the strength of the silicon–oxygen σ bond (368 kJ mol^{-1}) and the relative weakness of the silicon–silicon (230 kJ mol^{-1}) bond. Together these values account for the absence, in the oxygen-rich atmosphere of earth, of silicon analogues of the plethora of structures possible with a carbon skeleton.

Average bond energies, kJ mol^{-1}

X	H–X	C–X	O–X	F–X	Cl–X	Br–X	I–X	Si–X
C	416	356	336	485	327	285	213	290
Si	323	290	368	582	391	310	234	230
ratio	1.29	1.23	0.91	0.83	0.84	0.92	0.91	1.26

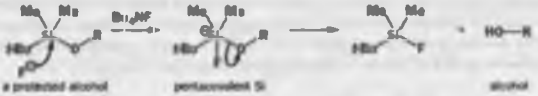
Several of the values in the table are worthy of comment as they give insight into the reactivity differences between carbon and silicon. Bonds to electronegative elements are generally stronger with silicon than with carbon; in particular, the silicon–fluorine bond is one of the strongest single bonds known, while bonds to electropositive elements are weaker. Silicon–hydrogen bonds are much weaker than their carbon counterparts and can be cleaved easily. This section of Chapter 47 is about organic silicon chemistry. We will mostly discuss compounds with four Si–C bonds. Three of these bonds will usually be the same so we will often have a Me_3Si– group attached to an organic molecule. We shall discuss reactions in which something interesting happens to the organic molecule as one of the Si–C bonds reacts to give a new Si–F or Si–O bond. We shall also discuss organosilicon compounds as reagents, such as triethylsilane (Et_3SiH), which is a reducing agent whereas Et_3C–H is not. Here are a few organosilicon compounds.

a useful electrophile — a protected alcohol — an allyl silane — a silyl benzene

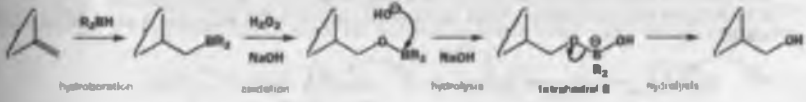
The carbon–silicon bond is strong enough for the trialkyl silyl group to survive synthetic transformations on the rest of the molecule but weak enough for it to be cleaved specifically when we want. In particular, fluoride ion is a poor nucleophile for carbon compounds but attacks silicon very readily. Another important factor is the length of the C–Si bond (1.89 Å)—it is significantly longer than a typical C–C bond (1.54 Å). Silicon has a lower electronegativity (1.8) than carbon (2.5) and therefore C–Si bonds are polarized towards the carbon. This makes the silicon susceptible to attack by nucleophiles.

Silicon has an affinity for electronegative atoms

The most effective nucleophiles for silicon are the electronegative ones that will form strong bonds to silicon, such as those based on oxygen or halide ions with fluoride being pre-eminent. You saw this in the choice of reagent for the selective cleavage of silyl ethers in Chapter 24. Tetrabutylammonium fluoride is often used as this is an organic soluble ionic fluoride and forms a silyl fluoride as the by-product. The mechanism is not a simple S_N2 process and has no direct analogue in carbon chemistry. It looks like a substitution at a hindered tertiary centre, which ought to be virtually impossible. Two characteristics of silicon facilitate the process: first, the long silicon–carbon bonds relieve the steric interactions and, second, the d orbitals of silicon provide a target for the nucleophile that does not have the same geometric constraints as a C–O σ* orbital. Attack of the fluoride on the d orbital leads to a negatively charged pentacoordinate intermediate that breaks down with loss of the alkoxide. There is a discrete intermediate in contrast to the pentacoordinate transition state of a carbon-based S_N2 reaction.



This process is sometimes abbreviated to S_N2 at silicon to save space. The intermediate is a trigonal bipyramid with negatively charged pentacovalent silicon. It is often omitted in drawings because it is formed slowly and decomposes quickly. This mechanism is similar to nucleophilic substitution at boron except that the intermediate is pentacovalent (Si) rather than tetrahedral (B). The hydrolysis of a boron ester at the end of a hydroboration–oxidation sequence would be an example.



The silicon Baeyer–Villiger rearrangement

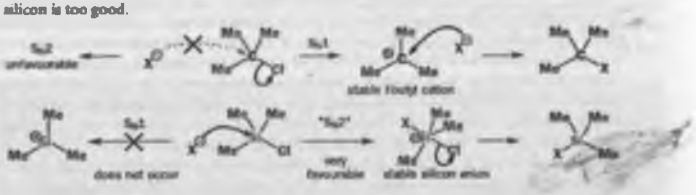
Evidence that the S_N2' reaction at silicon does indeed go through a pentacovalent intermediate comes from the silicon analogue of the migration step in Baeyer–Villiger oxidation. Treatment of reactive organosilanes (that is, those with at least one heteroatom—F, OR, NR_2—attached to silicon to encourage nucleophilic attack of hydroperoxide at silicon) with the same reagent (alkaline hydrogen peroxide) also gives alkyl migration from Si to O with retention of configuration. It would be difficult to draw a mechanism for this reaction without the intermediate. This is a precise copy of the oxidative cleavage of organoboranes that works on silanes.

● Silicon forms strong bonds with oxygen and very strong bonds with fluorine.

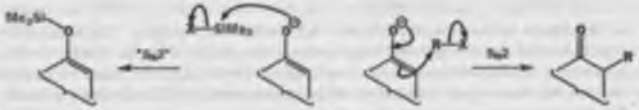
Nucleophilic substitution at silicon

You may wonder why trimethylsilyl chloride does not use the S_N1 mechanism familiar from the analogous carbon compound *t*-butyl chloride. There is, in fact, nothing wrong with the Me_3Si^+

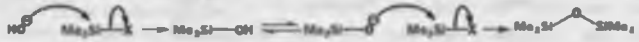
cation—it is often observed in mass spectra, for example. The reason is that the 'S_N2' reaction at silicon is too good.



We should compare the 'S_N2' reaction at silicon with the S_N2 reaction at carbon. There are some important differences. Alkyl halides are soft electrophiles but silyl halides are hard electrophiles. Alkyl halides react only very slowly with fluoride ion but silyl halides react more rapidly with fluoride than with any other nucleophile. The best nucleophiles for saturated carbon are neutral and/or based on elements down the periodic table (S, Se, I). The best nucleophiles for silicon are charged and based on highly electronegative atoms (chiefly F, Cl, and O). A familiar example is the reaction of enolates at carbon with alkyl halides but at oxygen with silyl chlorides (Chapter 21).

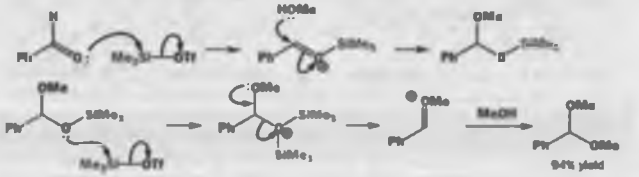


When a Me_3Si group is removed from an organic molecule with hydroxide ion, the product is not the silanol as you might expect but the silyl ether 'hexamethyldisiloxane'. Di-*t*-butyl ether could not be formed under these conditions nor by this mechanism, but only by the S_N1 mechanism in acid solution.

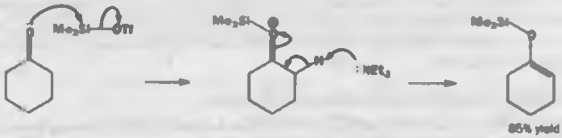


The other side of the coin is that the S_N2 reaction at carbon is *not* much affected by partial positive charge (δ+) on the carbon atom. The 'S_N2' reaction at silicon is affected by the charge on silicon. The most electrophilic silicon compounds are the silyl triflates and it is estimated that they react some 10^8–10^9 times faster with oxygen nucleophiles than do silyl chlorides. Trimethylsilyl triflate is, in fact, an excellent Lewis acid and can be used to form acetals or silyl enol ethers from carbonyl compounds, and to react these two together in aldol-style reactions. In all three reactions the triflate attacks an oxygen atom.

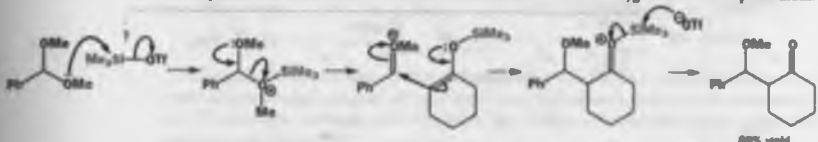
In the acetal formation, silylation occurs twice at the carbonyl oxygen atom and the final leaving group is hexamethyldisiloxane. You should compare this with the normal acid-catalysed mechanism described in Chapter 14 where the carbonyl group is twice protonated and the leaving group is water.



Silyl enol ether formation again results from silylation of carbonyl oxygen but this time no alcohol is added and a weak base, usually a tertiary amine, helps to remove the proton after silylation.

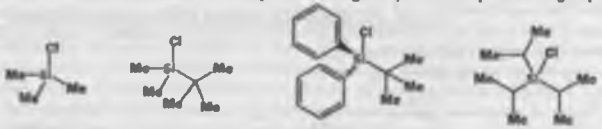


When the acetal and the silyl enol ether are mixed with the same Lewis acid catalyst, Noyori found that an efficient aldol-style condensation takes place with the acetal providing the electrophile. The reaction is successful at low temperatures and only a catalytic amount of the Lewis acid is needed. Under these conditions, with no acid or base, few side-reactions occur. Notice that the final desilylation is carried out by the triflate anion to regenerate the Lewis acid Me_3Si–OTf. Triflate would be a very poor nucleophile for saturated carbon but is reasonable for silicon because oxygen is the nucleophilic atom.



Silyl ethers are versatile protecting groups for alcohols

Silicon-based protecting groups for alcohols are the best because they are the most versatile. They are removed by nucleophilic displacement with fluoride or oxygen nucleophiles and the rate of removal depends mostly on the steric bulk of the silyl group. The simplest is trimethylsilyl (Me_3Si or often just TMS) which is also the most easily removed as it is the least hindered. In fact, it is removed so easily by water with a trace of base or acid that special handling is required to keep this labile group in place.



Replacement of the one of the methyl groups with a much more sterically demanding tertiary butyl group gives the *t*-butyldimethylsilyl (TBDMS) group, which is stable to normal handling and survives aqueous work-up or column chromatography on silica gel. The stability to these isolation and purification conditions has made TBDMS (sometimes over-abbreviated to TBS) a very popular choice for organic synthesis. TBDMS is introduced by a substitution reaction on the corresponding silyl chloride with imidazole in DMF. Yields are usually virtually quantitative and the conditions are mild. Primary alcohols are protected in the presence of secondary alcohols. Removal relies on the strong affinity of fluoride for silicon and is usually very efficient and selective.

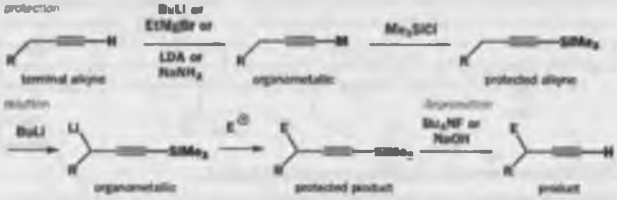
However, a protecting group is useful only if it can be introduced and removed in high yield without affecting the rest of the molecule and if it can survive a wide range of conditions in the course of the synthesis. The extreme steric bulk of the *t*-butyldiphenylsilyl (TBDPS) group makes it useful for selective protection of unhindered primary alcohols in the presence of secondary alcohols.

TBDPSCl diol imidazole TBDPS ether

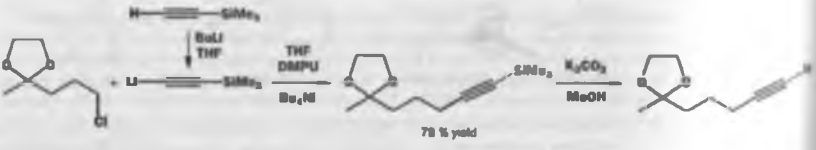
The most stable common silyl protecting group (triisopropylsilyl or TIPS) has three branched alkyl substituents to protect the central silicon from attack by nucleophiles which would lead to cleavage. All three hindered silyl groups (TBDMS, TBDPS, and TIPS) have excellent stability but can still be removed with fluoride.

Alkynyl silanes are used for protection and activation

Terminal alkynes have an acidic proton (pK_a ca. 25) that can be removed by very strong bases such as organometallic reagents (Grignards, RLi, etc.). While this is often what is intended, in other circumstances it may be an unwanted side-reaction that would consume an organometallic reagent or interfere with the chosen reaction. Exchange of the terminal proton of an alkyne for a trimethylsilyl group exploits the relative acidity of the proton and provides a neat solution to these problems. The $SiMe_3$ group protects the terminus of the alkyne during the reaction but can then be removed with fluoride or sodium hydroxide. A classic case is the removal of a proton next door to a terminal alkyne.



Additionally, acetylene itself is a useful two-carbon building block but is not very convenient to handle as it is an explosive gas. Trimethylsilylacetylene is a distillable liquid that is a convenient substitute for acetylene in reactions involving the lithium derivative as it has only one acidic proton. The synthesis of this alkynyl ketone is an example. Deprotonation with butyl lithium provides the alkynyl lithium that reacted with the alkyl chloride in the presence of iodide as nucleophilic catalyst (see Chapter 17). Removal of the trimethylsilyl group with potassium carbonate in methanol allowed further reaction on the other end of the alkyne.

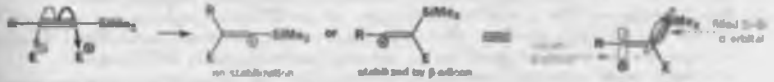


Silicon stabilizes a positive charge on the β carbon

In common with ordinary alkynes, silylated alkynes are nucleophilic towards electrophiles. The presence of the silicon has a dramatic effect on the regioselectivity of this reaction: attack occurs only at the atom directly bonded to the silicon. This must be because the intermediate cation is stabilized.

The familiar hierarchy of carbocation stability—tertiary > secondary > primary—is due to the stabilization of the positive charge by donation of electron density from adjacent C–H or C–C bonds (their filled σ orbitals to be precise) that are aligned correctly with the vacant orbital (Chapter 17). The electropositive nature of silicon makes C–Si bonds even more effective donors so that a β-silyl

group stabilizes a positive charge so effectively that the course of a reaction involving cationic intermediates is often completely controlled. This is stabilization by σ donation.

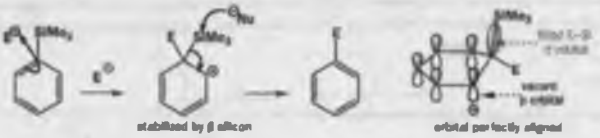


The stabilization of the cation weakens the C–Si bond by the delocalization of electron density so that the bond is more easily broken. Attack of a nucleophile, particularly a halogen or oxygen nucleophile, on silicon removes it from the organic fragment and the net result is electrophilic substitution in which the silicon has been replaced by the electrophile.

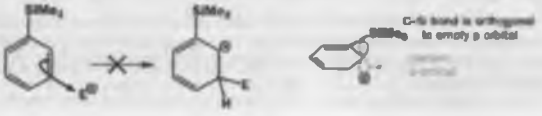
This is useful for the synthesis of alkynyl ketones, which are difficult to make directly with conventional organometallic reagents such as alkynyl–Li or –MgBr because they add to the ketone product. Alkynyl silanes react with acid chlorides in the presence of Lewis acids, such as aluminium chloride, to give the ketones.

Aryl silanes undergo *ipso* substitution with electrophiles

Exactly the same sort of mechanism accounts for the reactions of aryl silanes with electrophiles under Friedel–Crafts conditions. Instead of the usual rules governing *ortho*, *meta*, and *para* substitution using the directing effects of the substituents, there is just one rule: the silyl group is replaced by the electrophile at the same atom on the ring—this is known as *ipso* substitution. Actually, this selectivity comes from the same principles as those used for ordinary aromatic substitution (Chapter 22): the electrophile reacts to produce the most stable cation—in this case β to silicon. Cleavage of the weakened C–Si bond by any nucleophile leads directly to the *ipso* product.

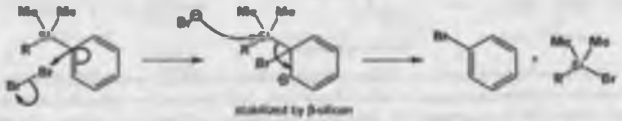


There is an alternative site of attack that would lead to a cation β to silicon, that is, *meta* to silicon. This cation is not particularly stable because the vacant p orbital is orthogonal to the C–Si bond and so cannot interact with it. This illustrates that it is more important to understand the origin of the effect based on molecular orbitals rather than simply to remember the result.

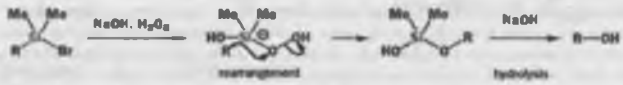


This reactivity of aryl silanes is used to convert the stable phenyl dimethylsilyl group into a more reactive form for conversion into an alcohol by the 'silyl Baeyer–Villiger' reaction described above. Overall this makes the phenyl dimethylsilyl group a bulky masked equivalent for a hydroxyl group. This is useful because the silane will survive reaction conditions that the alcohol might not and the steric bulk allows stereoselective reactions. Ian Fleming at Cambridge has made extensive use of this group and the conversion into an alcohol by several reagents all of which depend on the *ipso* substitution of the phenyl silane. The reaction with bromine is typical. Bromobenzene is produced together with a silyl bromide that is activated towards subsequent oxidation.

The mechanism of electrophilic desilylation is the same as that for electrophilic aromatic substitution except that the proton is replaced by trimethylsilyl. The important difference is that the silicon stabilizes the intermediate cation, and hence the transition state leading to it, to a dramatic extent so that the rate is much faster. This is the first step with bromine.



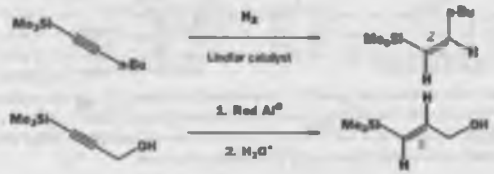
The rest of the reaction sequence involves displacement of Br– by HOO–, addition of hydroxide, rearrangement, and hydrolysis. All these steps involve the silicon atom and the details are given a few pages back.



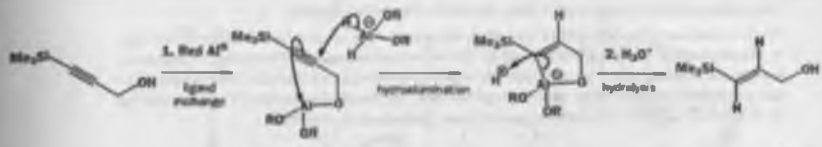
● Trimethylsilyl and other silyl groups stabilize a positive charge on a β carbon and are lost very easily. They can be thought of as very reactive protons or 'super protons'.

Vinyl silanes can be prepared stereospecifically

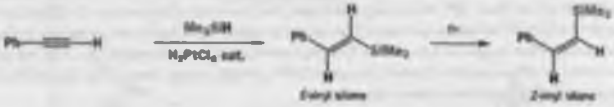
Controlled reduction of alkynyl silanes produces the corresponding vinyl silanes and the method of reduction dictates the stereochemistry. Lindlar hydrogenation adds a molecule of hydrogen across the alkyne in a *cis* fashion to produce the *Z*-vinyl silane. Red Al reduction of a propargylic alcohol leads instead to the *E*-isomer.



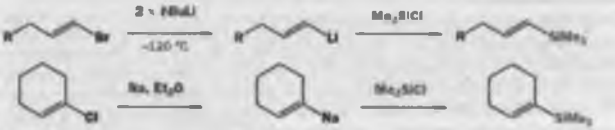
The mechanism of the second reaction is a *trans* hydroalumination helped by coordination of the alane to the triple bond and external nucleophilic attack. The regioselectivity of the hydroalumination is again determined by silicon: the electrophilic alane attacks the alkyne on the carbon bearing the silyl group (the *ipso* carbon).



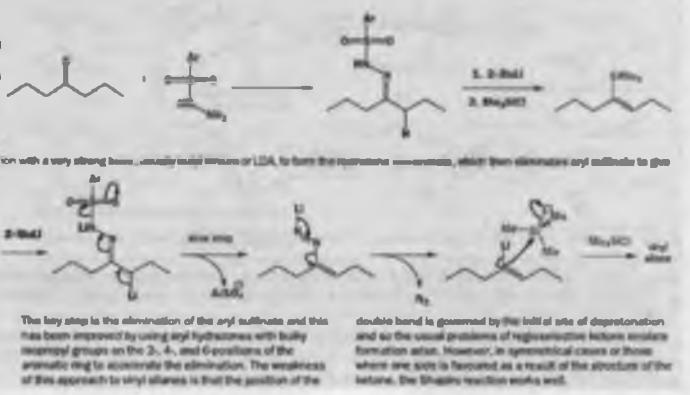
Instead of adding two hydrogen atoms to an alkynyl silane we could add H and $SiMe_3$ to a simple alkyne by hydrosilylation (addition of hydrogen and silicon). This is a *cis* addition process catalysed by transition metals and leads to a *trans* (*E*-) vinyl silane. One of the best catalysts is chloroplatinic acid (H_2PtCl_6) as in this formation of the *E*-vinyl silane from phenylacetylene. In this case photochemical isomerization to the *Z*-isomer makes both available. Other than the need for catalysis, this reaction should remind you of the hydroboration reactions earlier in the chapter. The silicon atom is the electrophilic end of the Si–H bond and is transferred to the less substituted end of the alkyne.

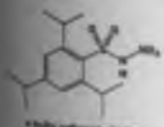


Vinyl silanes can also be prepared from vinyl halides by metal–halogen exchange to form the corresponding vinylic organometallic and coupling with a silyl chloride. Notice that both of these reactions happen with retention of configuration. This route is successful for acyclic and cyclic compounds and even vinyl chlorides, which are much less reactive, can be used with the lithium containing some of the more powerfully reducing sodium as the metal.



Vinyl silanes can be prepared directly from ketones using the Shapiro reaction

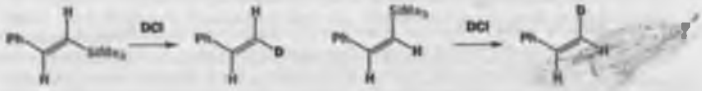




The key step is the elimination of the aryl sulfinate and this has been improved by using aryl hydrazones with bulky isopropyl groups on the 2-, 4-, and 6-positions of the aromatic ring to accelerate the elimination. The weakness of this approach to vinyl silanes is that the position of the double bond is governed by the initial site of deprotonation and so the usual problems of regioselective ketone enolate formation arise. However, in symmetrical cases or those where one side is favoured as a result of the structure of the ketone, the Shapiro reaction works well.

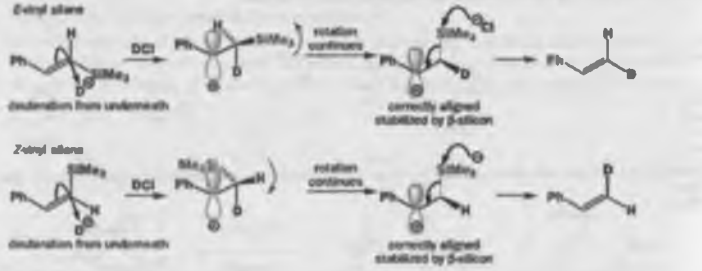
Vinyl silanes offer a regio- and stereoselective route to alkenes

Vinyl silanes react with electrophiles in a highly regioselective process in which the silicon is replaced by the electrophile at the *ipso* carbon atom. The stereochemistry of the vinyl silane is important because this exchange usually occurs with retention of geometry as well. Consider the reaction of the two vinyl silanes derived from phenyl acetylene with the simple electrophile D^+. Deuterons are chemically very similar to protons but are, of course, distinguishable by NMR.

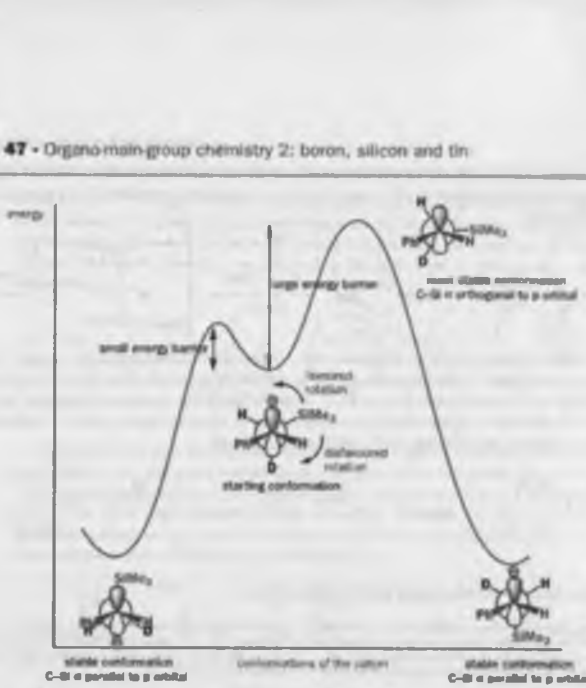


In principle, the alkenes could be protonated at either end but protonation next to silicon leads to the more stable cation β to silicon. In the vinyl silane the C–Si bond is orthogonal to the p orbitals of the π bond, but as the electrophile (D^+ here) attacks the π bond, say from underneath, the Me_3Si group starts to move upwards. As it rotates, the angle between the C–Si bond and the remaining p orbital decreases from 90°. As the angle decreases, the interaction between the C–Si bond and the empty p orbital of the cation increases. There is every reason for the rotation to continue in the same direction and no reason for it to reverse. The diagram shows that, in the resulting cation, the deuterium atom is in the position formerly occupied by the Me_3Si group, *trans* to Ph. Loss of the Me_3Si group now gives retention of stereochemistry.

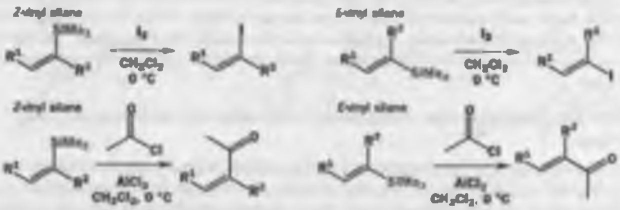
The intermediate cation has only a single bond and so rotation might be expected to lead to a mixture of geometrical isomers of the product but this is not observed. The bonding interaction between the C–Si bond and the empty p orbital means that rotation is restricted. This stabilization weakens the C–Si bond and the silyl group is quickly removed before any further rotation can occur. The stabilization is effective only if the C–Si bond is correctly aligned with the vacant orbital, which means it must be in the same plane—rather like a π bond. Here is the result for both *E*- and *Z*-isomers of the vinyl silane.



We can illustrate the two alternative rotations with an energy diagram: one rotation leads directly to a stable conformation with the C–Si bonding orbital parallel to the vacant p orbital, while the other passes through a very-high-energy conformation that has the two orbitals orthogonal and so derives no stabilization from the presence of silicon. It is this energy barrier that effectively prevents rotation and leads to electrophilic substitution with retention of double bond geometry. The favoured rotation simply continues the rotation from starting material to cation.



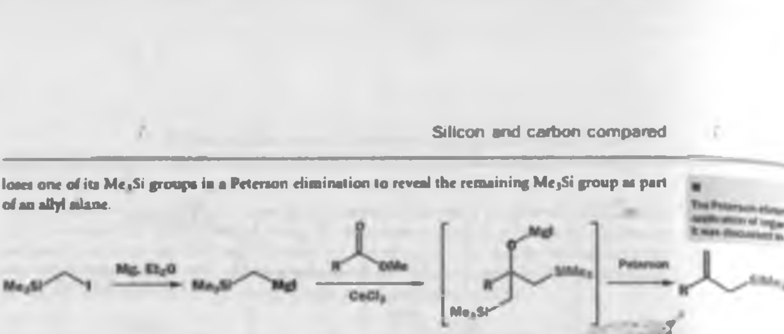
It is unusual for silicon to be required in the final product of a synthetic sequence and the stereospecific removal of silicon from vinyl silanes makes them useful reagents that can be regarded as rather stable vinylic organometallic reagents that will react with powerful electrophiles preserving the double bond location and geometry. **Protodesilylation**, as the process of replacing silicon with a proton is known, is one such important reaction. The halogens are also useful electrophiles while organic halides, particularly acid chlorides, in the presence of Lewis acids, form vinyl halides and unsaturated ketones of defined geometry.



Allyl silanes are readily available

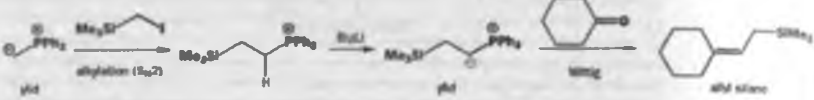
If the silyl group is moved along the carbon chain by just one atom, an allyl silane results. Allyl silanes can be produced from allyl organometallic reagents but there is often a problem over which regioisomer is produced and mixtures often result. Better methods control the position of the double bond using one of the methods introduced in Chapter 31. Two useful examples take advantage of the Wittig reaction and the Peterson olefination to construct the alkene linkage. The reagents are prepared from trimethylsilyl halides either by formation of the corresponding Grignard reagent or alkylation with a methylene Wittig reagent and deprotonation to form a new ylid. The Grignard reagent, with added cerium trichloride, adds twice to esters to give the corresponding tertiary alcohol which

loses one of its Me_3Si groups in a Peterson elimination to reveal the remaining Me_3Si group as part of an allyl silane.



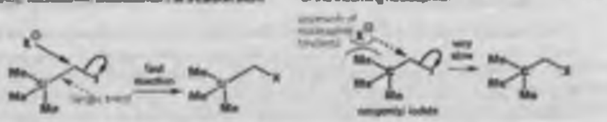
The Peterson elimination is ... It was discussed in detail in Chapter ...

The Wittig reagent is made by alkylation of the simplest ylid with the same silicon reagent. Notice that the leaving group (iodide) is on the carbon next to silicon, not on the silicon itself. Anion formation occurs next to phosphorus, because Ph_3P^+ is much more anion-stabilizing than Me_3Si. The ylid reacts with carbonyl compounds such as cyclohexanone in the usual way to produce the allyl silane with no ambiguity over which end of the allyl system is silylated.



Silicon exerts a surprisingly small steric effect

The Me_3Si group is, of course, large. But the C–Si bond is long and the Me_3Si group has a smaller steric effect than the Me_3C(t-butyl) group. For evidence, look at the fast [illegible] at a carbon atom next to an Me_3Si group occurs normally whereas the infamous 'neopentyl' equivalent (see Chapter 17) reacts very slowly if at all. The Me_3Si group can get out of the way of the incoming nucleophile.



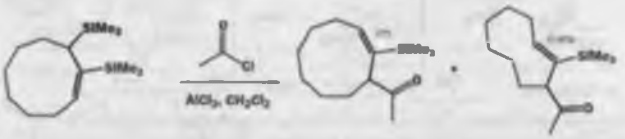
The carbon–silicon bond has two important effects on the adjacent alkene. The presence of a high-energy filled σ orbital of the correct symmetry to interact with the π system produces an alkene that is more reactive with electrophiles, due to the higher-energy HOMO, and the same σ orbital stabilizes the carbocation if attack occurs at the remote end of the alkene. This lowers the transition state for electrophilic addition and makes allyl silanes much more reactive than isolated alkenes.

Allyl silanes are more reactive than vinyl silanes but also react through β-silyl cations

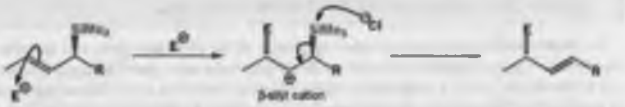
Vinyl silanes have C–Si bonds orthogonal to the p orbitals of the alkene—the C–Si bond is in the nodal plane of the π bond—so there can be no interaction between the C–Si bond and the π bond. Allyl silanes, by contrast, have C–Si bonds that can be, and normally are, parallel to the p orbitals of the π bond so that interaction is possible.

The evidence that such interaction does occur is that allyl silanes are more reactive than vinyl silanes as a result of the increased energy of the HOMO due to the interaction of the π bond with the C–Si bond. Conversely, vinyl silanes are thermodynamically more stable than the allyl isomers by

about 8 kJ mol^{-1}. This is evident from the acetylation of a compound having both vinyl silane and allyl silane functional groups. It reacts exclusively as an allyl silane, shown in black, with double bond migration to produce two double bond isomers (*cis* and *trans* cyclononenes) of the vinyl silane product. The vinylic silicon is not involved as the C–Si bond is orthogonal to the π system throughout.



Allyl silanes react with electrophiles with even greater regioselectivity than that of vinyl silanes. The cation β to the silyl group is again formed but there are two important differences. Most obviously, the electrophile attacks at the other end of the allylic system and there is no rotation necessary as the C–Si bond is already in a position to overlap efficiently with the intermediate cation. Electrophilic attack occurs on the face of the alkene *anti* to the silyl group. The process is terminated by loss of silicon in the usual way to regenerate an alkene.

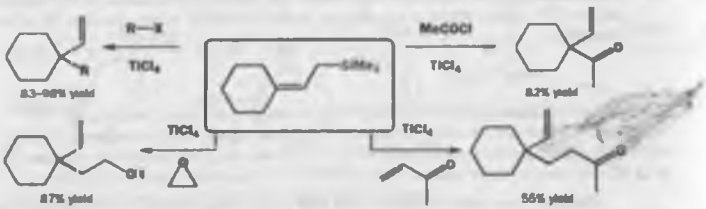


Molecular orbitals demonstrate the smooth transition from the allyl silane, which has a π bond and a C–Si σ bond, to the allylic product with a new π bond and a new σ bond to the electrophile. The intermediate cation is mainly stabilized by σ donation from the C–Si bond into the vacant p orbital but it has other σ-donating groups (C–H, C–C, and C–E) that also help. The overall process is electrophilic substitution with allylic rearrangement. Both the site of attachment of the electrophile and the position of the new double bond are dictated by the silicon.

Allyl silanes react with a wide variety of electrophiles, rather like the ones that react with silyl enol ethers, provided they are activated, usually by a Lewis acid. Titanium tetrachloride is widely used but other successful Lewis acids include boron trifluoride, aluminium chloride, and trimethylsilyl triflate. Electrophiles include the humble proton generated from acetic acid. The regiocontrol is complete. No reaction is observed at the other end of the allylic system. All our examples are on the allyl silane we prepared earlier in the chapter.

The first reaction is the general reaction with electrophiles and the second shows that even reaction with a proton occurs at the other end of the allyl system with movement of the double bond.

Other electrophiles include acylium ions produced from acid chlorides, carbocations from tertiary halides or secondary benzylic halides, activated enones, and epoxides all in the presence of Lewis acid. In each case the new bond is highlighted in black.



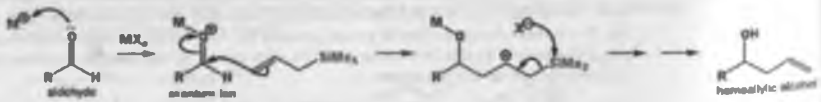
● Heading

Vinyl and aryl silanes react with electrophiles at the same (*ipso* or α) atom occupied by silicon. Allyl silanes react at the end of the alkene furthest from silicon (γ). In both cases a β-silyl cation is an intermediate.

In enantiomerically pure systems one enantiomer of the allyl silane gives one enantiomer of the product. The stereogenic centre next to silicon disappears and a new one appears at the other end of the alkene. This is a consequence of the molecule reacting in a well defined conformation by a well defined mechanism. The conformation is controlled by allylic strain (Chapter 34) which compels the proton on the silyl-bearing stereogenic centre to eclipse the alkene in the reactive conformation and the electrophile attacks *anti* to silicon for both steric and stereoelectronic reasons. In these examples of Lewis-acid-promoted alkylation with a *t*-butyl group, *E*- and *Z*-isomers both react highly stereoselectively to give enantiomeric products. The reactions are completely stereospecific.

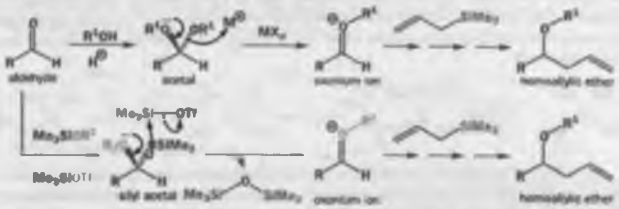
Lewis acids promote couplings via oxonium ions

Allyl silanes will also attack carbonyl compounds when they are activated by coordination of the carbonyl oxygen atom to a Lewis acid. The Lewis acid, usually a metal halide such as $TiCl_4$ or $ZnCl_2$, activates the carbonyl compound by forming an oxonium ion with a metal–oxygen bond. The allyl silane attacks in the usual way and the β-silyl cation is desilylated with the halide ion. Hydrolysis of the metal alkoxide gives a homoallylic alcohol.

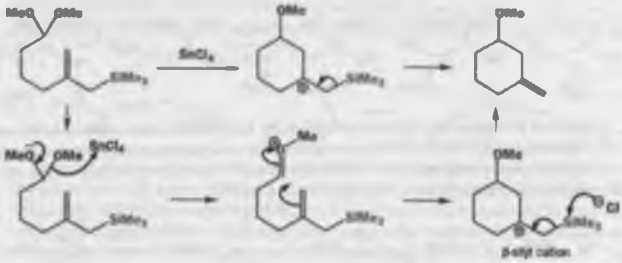


A closely related reactive oxonium ion can be prepared by Lewis-acid-catalysed breakdown of the corresponding acetal. Alternatively, especially if the acetal is at least partly a silyl acetal, the same oxonium ion can be produced *in situ* using yet more silicon in the form of TMSOTf as the Lewis acid catalyst. All these intermediate oxonium ions act as powerful electrophiles towards allyl silanes producing homoallylic alcohols or ethers.

▶ Note how the Me_3Si group mimics the behaviour of a proton over to the extent of producing $(Me_3Si)_2O$—the silicon analogue of water.

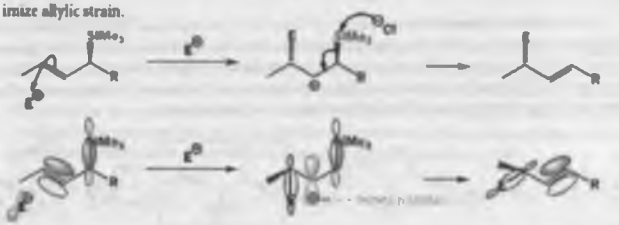


The regiocontrol that results from using an allyl silane to direct the final elimination is illustrated by this example of an intramolecular reaction on to an acetal promoted by tin tetrachloride. The same reaction can be run in the absence of silicon but the intermediate cation can then lose a range of protons to produce five different products!



Crotyl silanes are powerful reagents in stereoselective synthesis

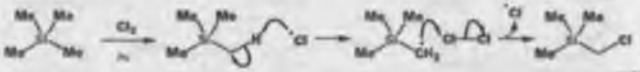
Crotyl silanes offer the possibility of diastereoselectivity in reactions with aldehydes in the same way as the corresponding boranes. The mechanism is completely different because crotyl trialkylsilanes react via an open transition state as the silicon is not Lewis acidic enough to bind the carbonyl oxygen of the electrophile. Instead, the aldehyde has to be activated by an additional Lewis acid or by conversion into a reactive oxonium ion by one of the methods described above. The stereoelectronic demands of the allylic silane system contribute to the success of this transformation. Addition takes place in an S_E2' sense so that the electrophile is attached to the remote carbon on the opposite side of the π system to that originally occupied by silicon and the newly formed double bond is *trans* to minimize allylic strain.



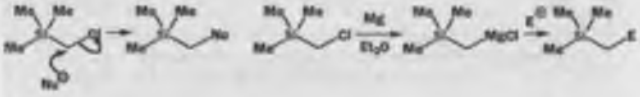
Radicals, anions, and S_N2 transition states stabilized by silicon

In Chapter 31 we discussed the Peterson reaction, which uses carbanions next to silicon, and the reagent Me_3SiCH_2Cl was used to make a Grignard reagent for this reaction. In fact, the chloride can

be made directly from Me_4Si (tetramethylsilane used as a zero point in NMR spectra) by photochemical chlorination. A chlorine atom removes a hydrogen atom from one of the methyl groups to leave a primary radical next to silicon, which reacts in turn with a chlorine molecule, and the radical chain continues.

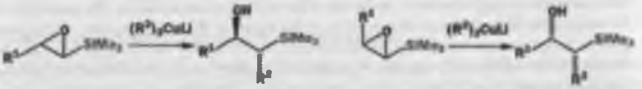


We might suspect that silicon stabilizes the intermediate carbon-centred radical as primary radicals are not usually stable, but we can prove nothing as there is no alternative. This chloride is a very useful reagent. It readily reacts by the S_N2 mechanism, in spite of the large Me_3Si group, which makes us suspect that silicon encourages the S_N2 reaction at neighbouring carbon. It also readily forms organometallic reagents such as Grignard reagents and lithium derivatives and these were used in the Peterson reaction. This makes us suspect that the Me_3Si group stabilizes anions. Can all this really be true?

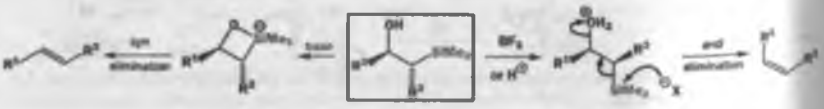


It is all true. Evidence that a silyl group stabilizes the S_N2 transition state comes from the reactions of the epoxides of vinyl silanes. These compounds can be made stereospecifically with one equivalent of a buffered peroxy-acid such as *m*-CPBA. Epoxidation is as easy as the epoxidation of simple alkenes. You will see in a moment why acid must be avoided.

These epoxides react stereospecifically with nucleophiles to give single diastereoisomers of adducts. If a carbon nucleophile is used (cuprates are best), it is obvious from the structure of the products that nucleophilic attack has occurred at the end of the epoxide next to silicon. This is obviously an S_N2 reaction because it is stereospecific: in any case an S_N1 reaction would have occurred at the other end of the epoxide through the β-silyl cation.

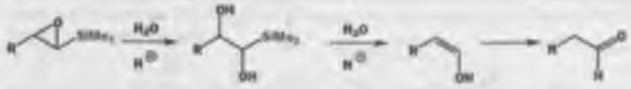


When we discussed the Peterson reaction in Chapter 31, we explained that each diastereoisomer of a β-silyl alcohol can eliminate, depending on the reaction conditions, to give either geometrical isomer of the alkene but we did not explain how these diastereoisomers could be made. This is how they are made. Elimination in base is a Wittig-style *syn* process but an *anti* elimination occurs in acid. Here are the reactions on one of the diastereoisomers we have just made.



If the nucleophile is water—as it might be in the work-up of the original epoxidation in acid solution—the product is a diol, which eliminates by the *anti* mechanism in acid solution to give initially an enol and then, under the same conditions, a carbonyl compound. All these steps are often carried

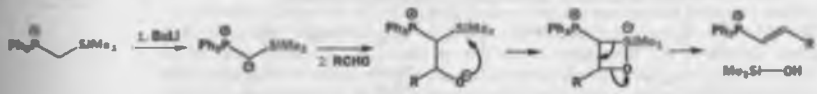
out in the one reaction to convert the epoxide to the carbonyl compound in one operation. Stereochemistry does not matter in this reaction.



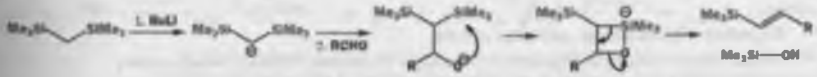
Silicon-stabilized carbanions

We are going to concentrate on the most important of these properties: silyl groups stabilize carbanions. We can show that this is true rather easily. Here are two reactions of carbanions with aldehydes.

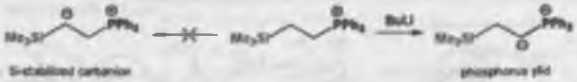
The first reagent has a choice: it can do either the Wittig or the Peterson reaction; it prefers the Peterson reaction. This merely tells us that nucleophilic attack at silicon is faster than nucleophilic attack at phosphorus. The carbanion part of the ylid is next to silicon but it could be nowhere else.



There is, however, a choice in the second reaction. There are six methyl groups on the two Me_3Si groups and one CH_2 between them. That makes eighteen methyl hydrogens and only two on the CH_2 group. Yet the base removes one of the two. It is better to have an anion stabilized by two silicon atoms. Silicon does stabilize a carbanion. There is, of course, no choice in the elimination step—O^- must attack one of the Me_3Si groups and the Peterson reaction must occur.



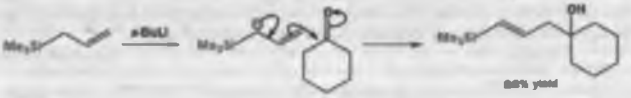
These reactions are also useful syntheses of vinyl phosphine oxides and of vinyl silanes. The stabilization of anions is weak—weaker than from phosphorus or sulfur—but still useful. The Wittig reagent used to make allyl silanes earlier in this chapter illustrates this point.



Si-stabilized carbanion

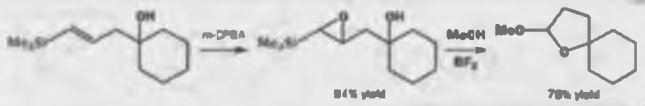
phosphorus ylid

If you want to make an 'anion' stabilized by one Me_3Si group it is better to use an organolithium or organomagnesium compound made from a halide, the most important being the simplest as we have seen. But given just a little extra help—even an alkene—anions can be made with bases. So an allyl silane can give a lithium derivative (using *s*-BuLi as the very strong base) that reacts with electrophiles in the same position as do the allyl silanes themselves—the γ-position relative to the Me_3Si group. In this example the electrophile is a ketone and no Lewis acid is needed.

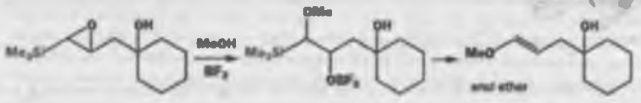


The product is a vinyl silane as the Me_3Si group is retained in this reaction of the anion. The reaction is stereoselective in favour of the *E*-alkene as might be expected. The alkene can be epoxidized

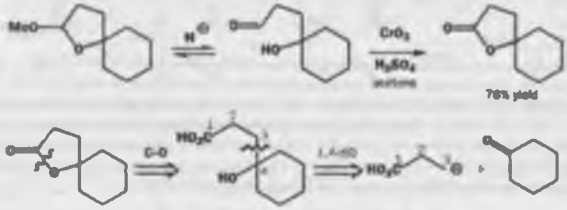
and the epoxide opened in the reaction we discussed earlier in the chapter. If methanol is used as the nucleophile with BF_3 as the Lewis acid, cyclic acetals are formed.



Nucleophilic attack occurs next to silicon and Peterson elimination gives an enol ether that cyclizes to the acetal under the acidic conditions.

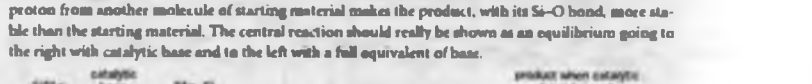


The cyclic acetal is a protected form of the hydroxy-aldehyde and oxidation under acidic conditions (CrO_3 in H_2SO_4) gives a good yield of the spirocyclic lactone. In the whole process from allyl silane to lactone, the allyl silane is behaving as a d^3 synthon or **homoenolate**.



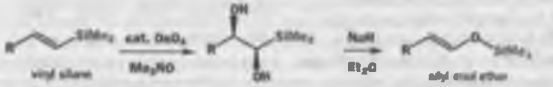
Migration of silicon from carbon to oxygen

Much of silicon chemistry is dominated by the strong Si–O bond and this leads to some surprising reactions. When compounds with an OH and a silyl group on the same carbon atom are treated with a catalytic amount of base, the silyl group migrates from carbon to oxygen. That all sounds reasonable until you realize that it must go through a three-membered ring. It is, in effect, a nucleophilic substitution at silicon. The reaction is known as the **Brook rearrangement**.

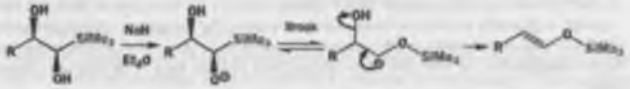


No such reaction could occur at a carbon centre (it would be impossible by Baldwin's rules; see Chapter 42), and the difference is that nucleophilic substitution at silicon goes through a pentacovalent intermediate so that a linear arrangement of nucleophile and leaving group is not required. The product anion is less stable than the oxyanion formed at the start of the reaction but removal of a proton from another molecule of starting material makes the product, with its Si–O bond, more stable than the starting material. The central reaction should really be shown as an equilibrium going to the right with catalytic base and to the left with a full equivalent of base.

By itself, the Brook rearrangement is not very useful but, if the carbanion can do something else other than just get protonated, something useful may happen. We have seen what happens to the epoxides of vinyl silanes. Dihydroxylation of the same alkenes also gives interesting chemistry when the diols are treated with base.

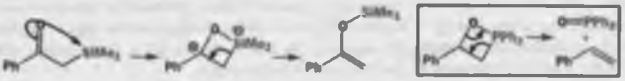


The overall reaction is the insertion of an oxygen atom between the silicon and the alkene and the product is a useful silyl enol ether (Chapter 21). The Brook rearrangement takes place first but the carbanion has a leaving group (OH) on the neighbouring carbon atom so an E1cB reaction (Chapter 19) occurs next.



It is remarkable that the other OH group does not lose a proton because a Peterson reaction could then follow. Perhaps the three-membered cyclic intermediate is formed more easily than the four-membered ring. This would be the case if carbon were the electrophilic atom. Rearrangements from carbon to oxygen through four-membered rings do occur: examples are the 'sila-Pummerer' rearrangement and the rather annoying tendency of α-silyl carbonyl compounds to rearrange to silyl enol ethers. The sila-Pummerer rearrangement is like the normal Pummerer rearrangement (discussed in Chapter 46) except that a silyl group rather than a proton migrates to oxygen.

We could no doubt find uses for α-silyl carbonyl compounds if they did not rearrange with C to O silyl migration simply on heating. The mechanism is similar to that of the sila-Pummerer rearrangement except that the nucleophile that attacks the silicon atom via a four-membered ring intermediate is carbonyl oxygen rather than sulfoxide oxygen. The intermediate might remind you of the intermediate in the Wittig reaction: a C–Si or C–P bond is sacrificed in both cases in favour of an Si–O or a P–O bond.



These last examples show that there is some similarity between silicon and sulfur or phosphorus. Now we shall see similarities with an element further down group IV—tin.

Organotin compounds

Tin is quite correctly regarded as a metal but in the +4 oxidation state it forms perfectly stable organic compounds, known as stannanes, many of which are available commercially. The tin atom is rather large, which means that it forms long covalent bonds that are easily polarized. The table of important bond lengths of the group IV (14) elements C, Si, and Sn shows that all bonds to carbon are shorter than the corresponding ones to silicon, which are in turn shorter and, as a result, stronger than those to tin.

Organotin chemistry exploits the weakness of C–Sn bonds to deliver whatever is attached to the tin to another reagent. You have already seen (Chapter 39) tributyltin hydride used as a radical reducing agent because of the ease with which the Sn–H bond can be broken. Carbon substituents can be transferred by a radical mechanism too but organotins transfer the organic group intact by polar mechanisms as well. This reactivity is closest to that of a conventional organometallic reagent but the organotins are stable distillable liquids that can be stored unlike Grignard reagents. You may be concerned about the fact that there are four substituents on the central tin atom and, in principle, all of them could be transferred. In practice, alkyl groups transfer only very slowly indeed so that the tributylstannyl group (Bu_3Sn–), the most popular tin-based functional group, is generally transferred intact during reactions. The exception to this is tetramethyltin which has only methyl groups and therefore must transfer one of them. Methyl ketones may be made from tetramethyltin and acid chlorides. Contrast this with the inert NMR reference tetramethylsilane!

Bonds to carbon, silicon, and tin compared

	Bond length, nm					
X	C–X	N–X	Si–X	O–X	S–X	Sn–X
C	0.153	0.100	0.178	0.141	0.180	0.22
Si	0.188	0.148	0.205	0.163	0.214	
Sn	0.22	0.17	0.24	0.21	0.24	0.28

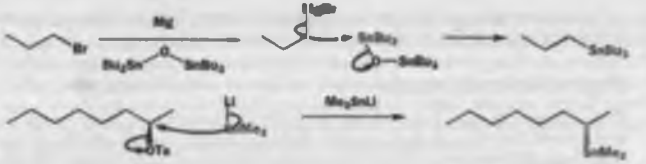
Tin compounds are often volatile and are usually toxic, so beware! They were very effective as "antifouling" paints for boats but they killed too many marine creatures and are now banned.

Organotin compounds are like reactive organosilicons

Organotin chemistry is useful because the familiar patterns of organosilicon chemistry are followed but the reactions proceed more easily because the bonds to tin are weaker and tin is more electropositive than silicon. Thus vinyl, allyl, and aryl stannanes react with electrophiles in exactly the same manner as their silicon counterparts but at a faster rate.

- Organostannanes are more reactive than organosilanes and use the same mechanisms.

The preparation of organostannanes is also similar to that of organosilanes. Organometallic reagents react with organotin electrophiles such as the trialkyl halides or bis(tributyltin) oxide. This is one method for the preparation of alkyl tributyltin using allyl Grignard and bis(tributyltin) oxide. Alternatively, the polarity can be reversed and a stannyl lithium, generated by deprotonation of the hydride or reductive cleavage of Me_3Sn–$SnMe_3$ with lithium metal, will add to organic electrophiles such as alkyl halides and conjugate acceptors. The first reaction is S_N2 at tin (probably with a 5-valent tin anion as intermediate) and the second is S_N2 at carbon.

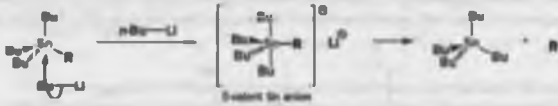


Direct hydrostannylation of an alkyne with a tin hydride can be radical-initiated in the way we saw in Chapter 39. The product of kinetic control is the *Z*-isomer but, if there is excess tin hydride or enough radicals are present, isomerization into the more stable *E*-isomer occurs. The regiocontrol of this process is good with terminal alkynes.

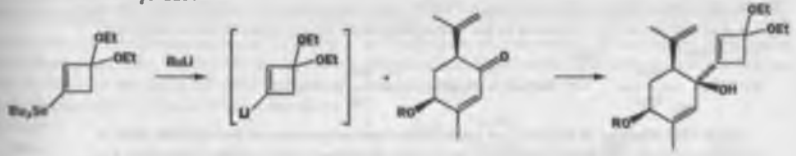
Addition of a tributyltin radical to the alkyne gives the more substituted linear (sp) vinyl radical (see Chapter 39). Addition of a hydrogen atom from another molecule of Bu_3SnH occurs preferentially from the less hindered side (the Bu_3Sn group already in the molecule is in the plane of the p orbital containing the unpaired electron) to give the *Z*-vinyl stannane. If there is more Bu_3SnH around, reversible addition of $Bu_3Sn^{\bullet}$ radicals to either end of the vinyl stannane equilibrates it to the more stable *E*-isomer.

Tin–lithium exchange is rapid

Organotin compounds are usually simply not reactive enough to be useful nucleophiles. Conversion into the corresponding organolithiums provides a much more reactive reagent. This is achieved in the same way as lithium–halogen exchange described in Chapter 9 and has essentially the same mechanism. The principle is simple. A very reactive nucleophile such as butyl lithium reacts at the tin and expels an organolithium species. The process is thermodynamically controlled, so the more stable the organolithium, the more likely it is to form. By having three of the groups on tin as butyl and adding another butyl from the organolithium, the choice is between the re-formation of butyl lithium or creation of an organolithium from the fourth substituent. If this is a vinyl, allyl, aryl, or alkynyl group this emerges as the most stable organolithium and is produced without any lithium halide present. The by-product is tetrabutyltin which is nonpolar and unreactive and can usually be separated by chromatography from the product of the reaction.

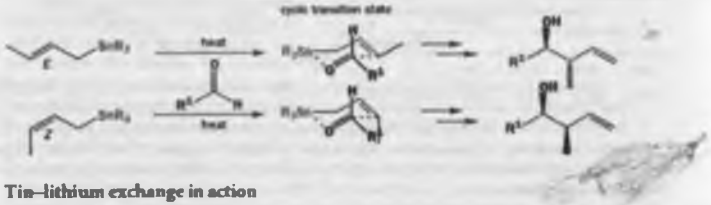


Such a tin–lithium exchange was the key to the preparation of a functionalized vinyl organolithium that was coupled to an enone in a synthesis of a natural product. Direct addition of the cyclobutenyllithium to the less hindered face of the carbonyl group gave one diastereoisomer of the product.



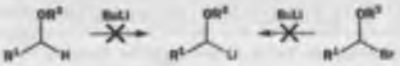
Crotyl stannanes react with good stereochemical control

Crotyl stannanes are important reagents in organic synthesis because they can be prepared with control over the double bond geometry and will tolerate the presence of additional functional groups. This allows stereoselective synthesis of functionalized acyclic molecules. The control arises from the well-defined transition states for the crotylation reaction. Tin is more electropositive than silicon and can accept a lone pair of electrons in a purely thermal reaction with no added Lewis acid. The carbonyl group of the aldehyde can coordinate to the tin and lead, through a cyclic transition state, to give *anti* products from *E*-crotyl tin reagents and *syn* products from the *Z*-crotyl isomer.



Tin–lithium exchange in action

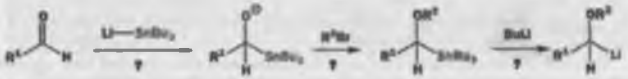
Many organolithium compounds are useful reagents and no doubt many more would be if only they could be made. Tin chemistry allows us to make organolithium compounds that cannot be made by direct lithiation. An excellent example is a lithium derivative with an oxygen atom on the same carbon. The hydrogen atom is not particularly acidic and cannot be removed by BuLi, while the bromide is unstable and will not survive treatment with BuLi.



Heading

- **Tin/lithium exchange occurs rapidly and stereospecifically with BuLi**
- **Other elements that can be replaced by Li: RX + BuLi gives RLi when X = SnR_3, Br, I, SeR**

However, the problem should be easily solved with tin chemistry. The idea is to add a tributyltin lithium reagent to the aldehyde, mask the alkoxide formed, and then exchange the tributyl tin group for lithium.

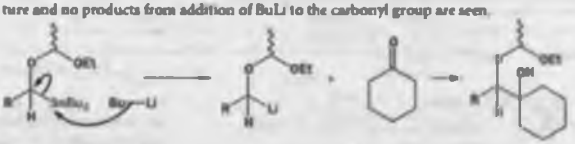


First, the Bu_3Sn–Li reagent has to be made. This can be done in two ways. Treatment of any tin compound with BuLi results in nucleophilic attack at tin but LDA is much less nucleophilic and can be used to remove a proton from tributyltin hydride. Otherwise, we can accept that BuLi will always attack tin and provide two tin atoms so that nucleophilic attack on one expels the other as the lithium derivative.

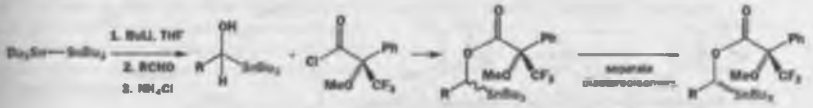
These THF solutions of Bu_3Sn–Li are stable only at low temperatures so the aldehyde must be added immediately. The lithium alkoxide adduct can be neutralized and the alcohol isolated but it is also unstable and must be quenched immediately with an alkyl halide. The preferred one is ethoxyethyl chloride, which reacts with base catalysis.

These protected hydroxystannanes are stable compounds and can even be distilled. Treatment with BuLi and an electrophile such as an aldehyde or ketone gives the product from addition of the

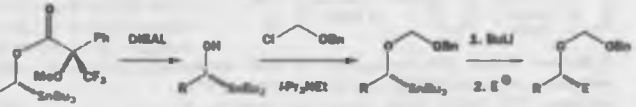
organolithium derivative to the carbonyl group. Tin–lithium exchange is rapid even at low temperature and no products from addition of BuLi to the carbonyl group are seen.



The most surprising thing about these reagents, invented and exploited by W. Clark Still at Columbia University, is that they can be prepared in stable enantiomerically pure forms and that the stereochemistry is preserved through exchange with lithium and reaction with electrophiles. It is very unusual for organolithium compounds to be configurationally stable. Still first quenched the Bu_3SnLi adducts with one enantiomer of an acid chloride and resolved by separating the diastereoisomers.



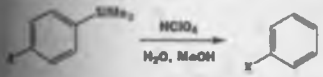
The ester was cleaved by reduction with DIBAL (i-Bu_2AlH) and an achiral version of the normal protecting group put in place. It would obviously be silly to create unnecessary diastereomeric mixtures in these reactions. Then the tin could be exchanged first with lithium and then with an electrophile, even an alkyl halide, with retention of configuration and without loss of enantiomeric purity. The intermediate organolithium compound must have had a stable configuration.



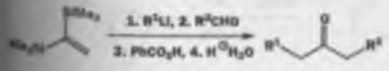
The exchange of tin for lithium or other metals is probably the most valuable job it does. Reagents such as BuLi attack tin or boron directly rather than removing a proton. Silicon is not usually attacked in this way and proton removal is more common. In the next chapter we shall see how transition metals open up a treasure chest of more exotic reactions for which the reactions in this chapter are a preparation.

Problems

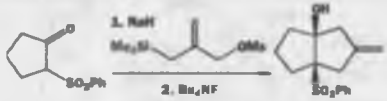
1. The Hammett ρ value for the following reaction is −4.8. Explain this in terms of a mechanism. If the reaction were carried out in deuterated solvent, would the rate change and would there be any deuterium incorporation into the product? What is the silicon-containing product?



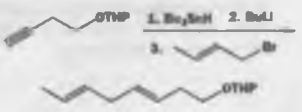
2. Identify the intermediates in this reaction sequence and draw mechanisms for the reactions, explaining the special role of the Me_3Si group.



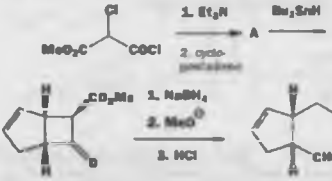
3. The synthesis of a compound used in a problem in Chapter 38 (fragmentation) is given below. Give mechanisms for the reactions explaining the role of silicon.



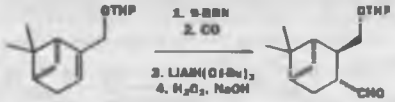
4. Give mechanisms for the following reactions, drawing structures for all the intermediates including stereochemistry. How would the reaction with Bu_3SnH have to be done?



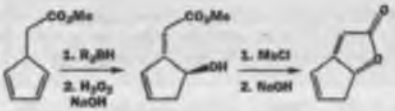
6. Explain the following reactions. In particular, explain the role of tin and why it is necessary and discuss the stereochemistry.



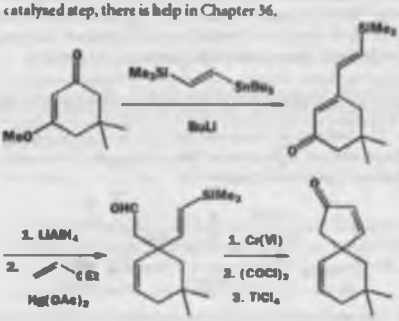
6. Explain the stereochemistry and mechanism of this hydroboration–carbonylation sequence.



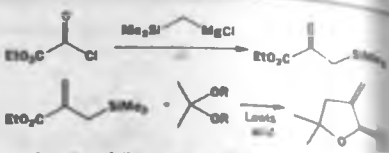
7. Give mechanisms for these reactions explaining: (a) the regio- and stereoselectivity of the hydroboration; (b) why such an odd method was used to close the lactone ring.



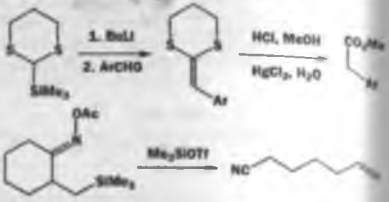
8. Revision content. Give mechanisms for these reactions, commenting on the role of silicon and the stereochemistry of the cyclization. The $LiAlH_4$ simply reduces the ketone to the corresponding alcohol. If you have trouble with the Hg(II)-catalysed step, there is help in Chapter 36.



9. Give mechanisms for these reactions, explaining the role of silicon. Why is this type of lactone difficult to make by ordinary acid- or base-catalysed reactions?



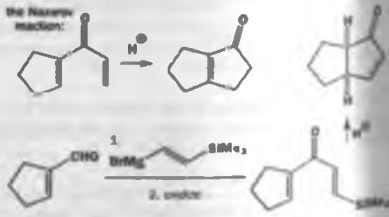
10. Revision of Chapters 38 and 46. How would you prepare the starting material for these reactions? Give mechanisms for the various steps. Why are these sequences useful?



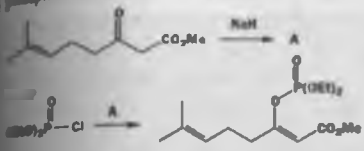
11. How would you carry out the first step in this sequence? Give a mechanism for the second step and suggest an explanation for the stereochemistry. You may find that a Newman projection (Chapters 32 and 33) helps.

12. Revision of Chapter 36. Give a mechanism for this reaction and explain why it goes in this direction.

13. The Nazarov cyclization (Chapter 36) normally gives a cyclopentenone with the alkene in the more substituted position. This can be altered by the following sequence. Give a mechanism for the reaction and explain why the silicon makes all the difference.

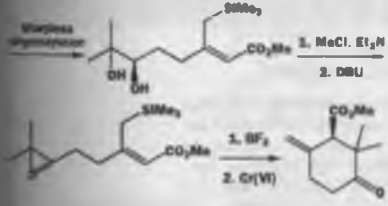


14. This is rather a long problem but it gives you the chance to see an advanced piece of chemistry involving several elements—P, Si, Sn, Mg, B, Ni, Cr, Os, and Li—and it revises material from Chapters 23, 33, and 45 at least. It starts with the synthesis of this phosphorus compound: what is the mechanism and selectivity?



Next, reaction with a silicon-substituted Grignard reagent in the presence of Ni(II) gives an allyl silane. What kind of reaction is this, what was the role of phosphorus, and why was a metal other than sodium added? (You know nothing specific about Ni as yet but you should see the comparison with another metal. Consult Chapter 23 if you need help.)

Asymmetric dihydroxylation (Chapter 45) is straightforward though you might like to comment on the chemoselectivity. The diol is converted into the epoxide and you should explain the regio- and chemoselectivity of this step. The next step is perhaps the most interesting: what is the mechanism of the cyclization, what is the role of silicon, and how is the stereochemistry controlled?



Reaction of this ketone with a stannyl-lithium reagent gives one diastereoisomer of a bridged lactone. Again, give a mechanism for this step and explain the stereochemistry. Make a good conformational drawing of the lactone.

Treatment of the tin compound with MeLi and a complex aldehyde represented as RCHO gave an adduct that was used in the synthesis of some compounds related to Taxol. What is the mechanism of the reaction, and why is tin necessary?

Organometallic chemistry

48

Connections

Building on:

- Conjugate addition ch10 & ch22
- Nucleophilic substitution at saturated carbon ch17
- Controlling stereochemistry ch16, ch33, & ch34
- S_N2 and S_N2' ch23
- Oxidation and reduction ch24
- Cycloadditions ch35
- Rearrangements ch36–ch37
- Radicals and carbenes ch39–ch40
- Aromatic heterocycles ch42–ch44
- Asymmetric synthesis ch45
- Chemistry of B, Si, and Sn ch47

Arriving at:

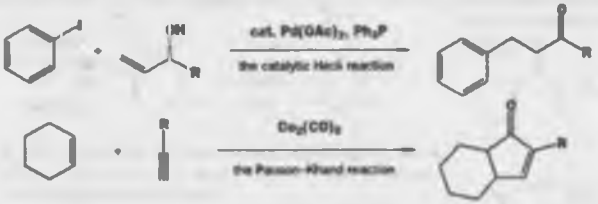
- Transition metals form organic compounds
- There are σ- and π-complexes given 'η' numbers
- The bonding is described with the usual orbitals
- Most stable complexes have 18 valency electrons
- Metals catalyse 'impossible' reactions
- Oxidative insertion, reductive elimination, and ligand migration from metal to carbon are key steps
- Carbon monoxide inserts into metal–carbon bonds
- Palladium is the most important metal
- C–C, C–O, and C–N bonds can be made with Pd catalysis
- Cross-coupling of two ligands is common
- Allyl cation complexes are useful electrophiles

Looking forward to:

- The chemistry of life, especially nucleic acids ch49
- Steroids ch51
- Polymerization ch52

Transition metals extend the range of organic reactions

Some of the most exciting reactions in organic chemistry are based on transition metals. How about these two for example? The first is the **Heck reaction**, which allows nucleophilic addition to an unactivated alkene. Catalytic palladium (Pd) is needed to make the reaction go. The second, the **Pauson–Khand reaction**, is a special method of making five-membered rings from three components: an alkene, an alkyne, and carbon monoxide (CO). It requires cobalt (Co). Neither of these reactions is possible without the metal.



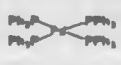
Reagents and complexes containing transition metals are important in modern organic synthesis because they allow apparently impossible reactions to occur easily. This chemistry com-

plements traditional functional-group-based chemistry and significantly broadens the scope of organic chemistry. This chapter introduces the concepts of metal–ligand interaction, describes the most important reactions that can occur while ligands are bound to the metal, and demonstrates the power of organometallic chemistry in synthesis. Many industries now use transition-metal-catalysed reactions routinely so it is important that you have a basic grounding in what they do.

There is a contradiction in what is required of a metal complex for useful synthetic behaviour. Initially, it is useful to have a stable complex that will have a significant lifetime enabling study and, ideally, storage but, once in the reaction vessel, stability is actually a disadvantage as it implies slow reactivity. An ideal catalyst is a complex that is stable in the resting state, for storage, but quickly becomes activated in solution, perhaps by loss of a ligand, allowing interaction with the substrate. Fortunately, there is a simple guide to the stability of transition metal complexes. If a complex satisfies the 18-electron rule for a stable metal complex it means that the metal at the centre of the complex has the noble gas configuration of 18 electrons in the valence shells. The total of 18 is achieved by combining the electrons that the metal already possesses with those donated by the coordinating ligands. The requirement for 18 electrons comes from the need to fill one 's' orbital, five 'd' orbitals, and three 'p' orbitals with two electrons in each. This table gives you the number of valence electrons each metal starts with before it has acquired any ligands. Notice that the 'new' group numbers 1–18 give you the answer without any calculation. The most important are highlighted.

Group Number of valence electrons	IVB (4)	VB (5)	VIB (6)	VIIB (7)	VIIIB (8, 9, and 10)			IA (11)
	4	5	6	7	8	9	10	11
3d	Ti	V	Cr	Mn	Fe	Co	Ni	Cu
4d	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag
5d	Hf	Ta	W	Re	Os	Ir	Pt	Au

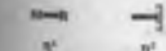
Metals to the left-hand side of this list obviously need many more electrons to make up the magic 18. Chromium, for example, forms stable complexes with a benzene ring, giving it six electrons, and three molecules of carbon monoxide, giving it two each: 6 + 6 + 2 + 2 + 2 = 18. Palladium is happy with just four triphenylphosphines (Ph_3P:) giving it two each: 10 + 2 + 2 + 2 + 2 = 18.



You may already know from your inorganic studies that there are exceptions to the 18-electron rule including complexes of Ti, Zr, Ni, Pd, and Pt, which all form stable 16-electron complexes. An important 16-electron Pd(II) complex with two chlorides and two acetonitriles (MeCN) as ligands appears in the margin. The so-called platinum metals Ni, Pd, and Pt are extremely important in catalytic processes, as you will see later on. The stable 16-electron configuration results from a high-energy vacant orbital caused by the complex adopting a square planar geometry. The benefit of this vacant orbital is that it is a site for other ligands in catalytic reactions.

Ligands can be attached in many different ways

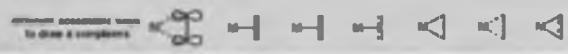
Transition metals can have a number of ligands attached to them and each ligand can be attached in more than one place. This affects the reactivity of the ligand and the metal because each additional point of attachment means the donation of more electrons. We usually show the number of atoms involved in bonding to the metal by the hapto number η. A simple Grignard reagent is η^1 (pronounced 'eta-one') as the magnesium is attached only to one carbon atom. A metal–alkene complex is η^2 because both carbon atoms of the alkene are equally involved in bonding to the metal. In these cases the η designation is not very useful as there are no alternatives and it is usually omitted.



Representing bonds in transition metal complexes

It is difficult to know exactly how to draw the bonding in metal complexes and there are often several different, acceptable representations. There is no problem when the metal forms a σ bond to atoms such as Cl or C as the simple line we normally use for covalent bonds means exactly what it says. The problems arise with ligands that form σ bonds by donating both their electrons and with π complexes. Everyone writes phosphine–boron compounds with two charges but we normally draw the same sort of bond between a phosphine and, say, Pd as a simple line with no charges.

You will sometimes see π complexes drawn with simpler dotted lines going to the middle of the π bond, sometimes with dotted σ bonds, and sometimes with bonds (simple or dotted) going to the ends of the old π bond. These are all acceptable as the bonding is complex as you will see. We might almost say that the ambiguity is helpful: we often don't know either the exact nature of the bonding or the number of other ligands in the complex. In the diagrams in this section we have shown the main bond from metal to ligand as a heavy line in the simplest representation but we also offer alternatives with simple and dotted bonds. Don't worry about this—things should become clearer as the chapter develops. When you have to draw the structure of a complex but you don't know the exact bonding, just draw a line from metal to ligand.

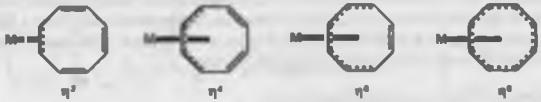


The bonding in these two complexes is very different. In the first there is a simple σ bond between the metal and the alkyl group as in a Grignard reagent R–MgBr and this type of complex is called a σ complex. In the alkene complex, bonding is to the p orbitals only. There are no σ bonds to the metal, which sits in the middle of the π bond in between the two p orbitals. This type of complex is called a π complex.

These labels are useful where there is a choice of type of bonding as with allylic ligands. The metal can either form a σ bond to a single carbon (hence η^1), or form a π complex with the p orbitals of all three carbons of the allyl system and this would be η^3. If the π complex is made from an allyl cation, the ligand has two electrons, but it has four if it is made from an allyl anion.

Similarly, cyclopentadienyl anion can act as a σ ligand (η^1), an allyl ligand (η^3), or, most usually, as a cyclopentadienyl ligand (η^5). The distinction is very important for electron counting as these three different situations contribute 2, 4, or 6 electrons, respectively, to the complex.

Neutral ligands can also bond in a variety of ways. Cyclooctatetraene can act as an alkene (η^2), a diene (η^4), a triene (η^6), or a tetraene (η^8), and the reactivity of the ligand changes accordingly. These are all π complexes with the metal above or below the black portion of the ring and with the thick bond to the metal at right angles to the alkene plane.

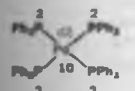


To determine the number of electrons around the transition metal in a complex the valence electrons from the metal ion are added to those contributed by all the ligands. The numbers of electrons donated by various classes of ligands are summarized in the table. Anions such as halides, cyanide, alkoxide, hydride, and alkyl donate two electrons, as do neutral ligands with a lone pair such as phosphines, amines, ethers, sulfides, carbon monoxide, nitriles, and isonitriles. Unsaturated ligands can contribute as many as eight electrons and can be neutral or negatively charged. If the overall total is eighteen, then the complex is likely to be stable.

Ligand characteristics

	Formal charge	Electrons donated
anionic ligands		
$Cl^{\ominus}$ $Br^{\ominus}$ $I^{\ominus}$ $R_{2N}^{\ominus}$ $R_{2P}^{\ominus}$ $R_{S}^{\ominus}$ $R_{alkyl}^{\ominus}$	−1	2
neutral σ-donor ligands		
	0	2

	Hapto number	Formal charge	Electrons donated
Unsaturated σ- or π-donor ligands			
allyl, π-allyl	η^1	−1	2
alkene	η^2	0	2
π-allyl cation	η^3	+1	2
π-allyl anion	η^3	−1	4
diene—conjugated	η^4	0	4
dienyl, cyclopentadienyl (anions)	η^5	−1	6
arenes, trienes	η^6	0	6
trienyl, cycloheptatrienyl (anions)	η^7	−1	8
cyclooctatetraene	η^8	0	8
carbene, nitrene, oxo	η^1	0	2



total: 4 × 2e + 10e = 18e

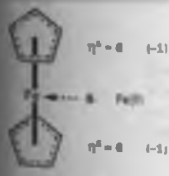
Note

Note that $(Ph_3P)_4Pd$ is a stable complex and is not a useful catalyst until at least one of the ligands is lost.

Electron counting helps to explain the stability of metal complexes

Counting electrons in most complexes is simple if you use the table of ligand characteristics above and the table on p. 000. Tetrakistriphenylphosphine palladium(0) is an important catalyst as you will see later in the chapter. Each neutral phosphine donates two electrons making a total of eight and palladium still has its full complement of ten valence electrons as it is in the zero oxidation state. Overall, the complex has a total of eighteen electrons and is a stable complex. In the diagrams that follow, the formal charges are highlighted in green and the numbers of electrons contributed shown in black.

All of the different classes of ligands listed in the table can be treated in this way. The cyclopentadienyl ligands contribute six electrons each and have a formal negative charge, shown in green, which means that the iron in ferrocene is in the +II oxidation state and will have six valence electrons left. The total for the complex is again eighteen and ferrocene is an extremely stable complex.



total: 3 × 6e = 18e

The oxidation state of metals in complexes

As well as the problem of bond drawing, there is a potential problem over oxidation states too. You can either say that ferrocene is a complex of Fe(II), having two fewer electrons than the normal eight, with two cyclopentadienyl anions contributing six electrons each, or you can say that it is a complex of Fe(0), having eight electrons, with two cyclopentadienyl ligands each contributing five electrons. The simplest approach is to say that a metal is in the (0) oxidation state unless it has σ bonds to ligands such as Cl, AcO, or Me that form bonds with shared electrons. You do not count neutral ligands such as Ph_3P that provide two of their own electrons. Grignard reagents RMgBr have two ligands that share electrons (R and Br) and a number of others, probably two others, that donate both their electrons. Magnesium is in the +2 oxidation state.

a Pd(II) complex

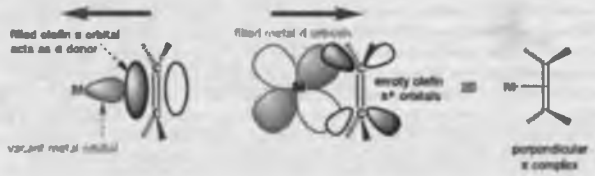
The useful complex $(MeCN)_2PdCl_2$ has palladium in the +2 oxidation state because of its two chlorine atoms and the number of electrons is 8 for the Pd(II) oxidation state and another two each from the four ligands making 16 in all. This complex does not fulfil the 18-electron rule and is reactive. You would have got the same answer if you had counted ten for the palladium, two each for the nitriles, and one each for the chlorines, but this is not so realistic.

Transition metal complexes exhibit special bonding

The majority of ligands have a lone pair of electrons in a filled sp^n type orbital that can overlap with a vacant metal 'dsp' orbital, derived from the vacant d, p, and s orbitals of the metal, to form a conventional two-electron two-centre σ bond. Ligands of this type increase the electron density on the central metal atom. This is the sort of bond that used to be called 'dative covalent' and represented by an arrow. Nowadays it is more common to represent all bonding to metals of whatever kind by simple lines.

A bonding interaction is also possible between any filled d orbitals on the metal and vacant ligand orbitals of appropriate symmetry such as π* orbitals. This leads to a reduction of electron density on the metal and is known as back-bonding. An example would be a complex with carbon monoxide. Many metals form these complexes and they are known as **metal carbonyls**. The ligand (CO) donates the lone pair on carbon into an empty orbital on the metal while the metal donates electrons into the low-energy π* orbital of CO. Direct evidence for this back-bonding is an increase in the C–O bond length and a lowering of the infrared stretching frequency from the population of the π* orbital of the carbonyl.

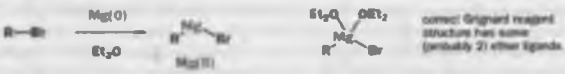
When an unsaturated ligand such as an alkene approaches the metal sideways to form a π complex, similar interactions lead to bonding. The filled π orbitals of the ligand bond to empty d orbitals of the metal, while filled d orbitals on the metal bond to the empty π* orbitals of the ligand. The result is a π complex with the metal–alkene bond perpendicular to the plane of the alkene. The bond has both σ and π character.



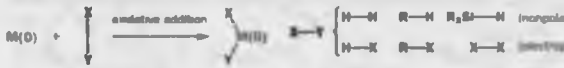
Coordination to a metal by any of these bonding methods changes the reactivity of the ligands dramatically and this is exploited in the organometallic chemistry we will be discussing in the rest of the chapter. You do not need to understand all the bonding properties of metal complexes but you need to be able to count electrons, to recognize both σ and π complexes, and to realize that complexes show a balance between electron donation and electron withdrawal by the metal.

Oxidative addition inserts metal atoms into single bonds

Potential ligands that do not have a lone pair or filled π type orbital are still able to interact with transition metal complexes but only by breaking a σ bond. This is the first step in a wide variety of processes and is described as **oxidative addition** because the formal oxidation state of the transition metal is raised by two, for example, M(0) to M(II), in the process. This is the result of having two extra ligands bearing a formal negative charge. You have seen this process in the formation of Grignard reagents (Chapter 9)

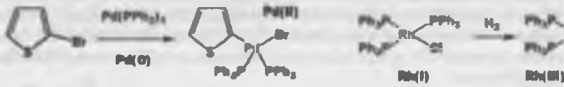


The number of coordinated ligands also increases by two so the starting complex is usually in low oxidation state (0 or 1; the diagram shows 0) and coordinatively unsaturated, that is, it has an empty site for a ligand and, say, only 16 electrons, like $(MeCN)_2PdCl_2$, whereas the product is usually coordinatively saturated, that is, it cannot accept another ligand unless it loses one first.



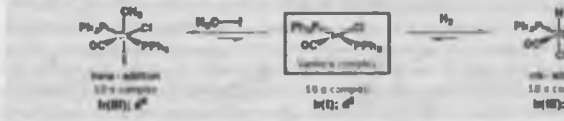
Introduces a new organic ligands on to metal

Oxidative addition occurs for a number of useful neutral species including hydrogen, carbon–hydrogen bonds, and silanes as well as polarized bonds containing at least one electronegative atom. The resulting species with metal–ligand bonds allow useful chemical transformations to occur. Important examples include the oxidative addition of Pd(0) to aryl iodides and the activation of Wilkinson's catalyst for hydrogenation in solution by oxidative addition to a hydrogen molecule.



Vaska's complex

There are a number of possible mechanisms for oxidative addition and the process one followed depends on the nature of the reacting partners. Vaska's complex $(trans\text{-}IrCl(CO)(PPh_3)_2)$ has been extensively studied and it reacts differently with hydrogen and methyl iodide. Hydrogen is added in a *cis* fashion, consistent with concerted formation of the two new iridium–hydrogen bonds. The 18e⁻ d^8, Ir(I) complex becomes a new 18e⁻, d^6, Ir(III) species. With methyl iodide the kinetic product is that of *trans* addition, which is geometrically impossible from a concerted process. Instead, an S_N2-like mechanism is followed involving nucleophilic displacement of iodide followed by ionic recombination.

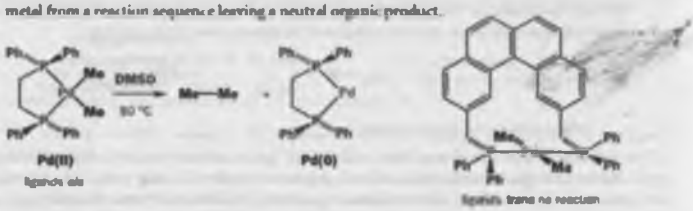


Reductive elimination removes metal atoms and forms new single bonds

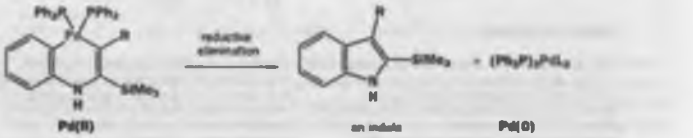
If we want to use organometallic chemistry to make organic compounds other than those containing metals, we must be able to remove the ligands from the coordination sphere of the metal at the end of the reaction. Neutral organic species such as alkenes, phosphines, and carbon monoxide can simply dissociate in the presence of other suitable ligands but those that are bound to the metal with shared electrons require a more active process. Fortunately, most reactions that occur around a transition metal are reversible and so the reverse of oxidative addition, known as reductive elimination, provides a simple route for the release of neutral organic products from a complex. Our general reaction shows M(II) going to M(0) releasing X–Y. These two ligands were separate in the complex but are bound together in the product. A new X–Y σ bond has been formed.

removes organic ligands from metal producing new organic product

The ligands to be eliminated must be *cis* to one another for reductive elimination to occur. This is because the process is concerted. Two examples from palladium chemistry make this point clear. Warming in DMSO causes ethane production from the first palladium complex because the two methyl groups are *cis* in the square planar complex. The more elaborate second bisphosphine forces the two methyl groups to be *trans* and reductive elimination does not occur under the same conditions. Reductive elimination is one of the most important methods for the removal of a transition metal from a reaction sequence leaving a neutral organic product.

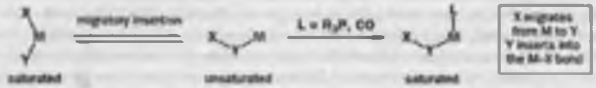


In fact, no one wants to make ethane that way (if at all) but many other pairs of ligands can be coupled by reductive elimination. We will see many examples as the chapter develops but here is an indole synthesis that depends on a reductive elimination at palladium as a last step. In the starting material, palladium has two normal σ bonds and is Pd(II). The two substituents bond together to form the indole ring and a Pd(0) species is eliminated. Notice the use of 'L' to mean an undefined ligand of the phosphine sort.

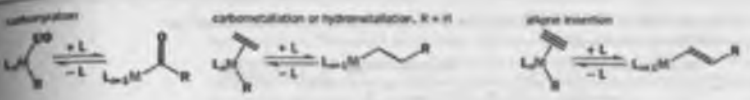


Migratory insertion builds ligand structure

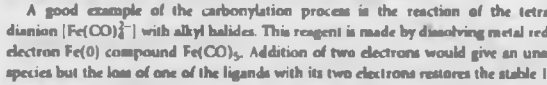
Two ligands can also react together to produce a new complex that still has the composite ligand attached to the metal ready for further modification. This process involves migration of one of the ligands from the metal to the other ligand and insertion of one of the ligands into the other metal–ligand bond and is known as migratory insertion. The insertion process is reversible and, as the metal effectively loses a ligand in the process, the overall insertion may be driven by the addition of extra external ligands (L) to produce a coordinatively saturated complex. As with reductive elimination, a *cis* arrangement of the ligands is required and the migrating group (X) retains its stereochemistry (if any) during the migration.



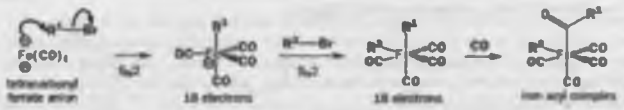
Migratory insertion is the principal way of building up the chain of a ligand before elimination. The group to be inserted must be unsaturated in order to accommodate the additional bonds and common examples include carbon monoxide, alkenes, and alkynes producing metal–acyl, metal–alkyl, and metal–alkenyl complexes, respectively. In each case the insertion is driven by additional external ligands, which may be an increased pressure of carbon monoxide in the case of carbonylation or simply excess phosphine for alkene and alkyne insertions. In principle, the chain extension process can be repeated indefinitely to produce polymers by Ziegler–Natta polymerization, which is described in Chapter 52.



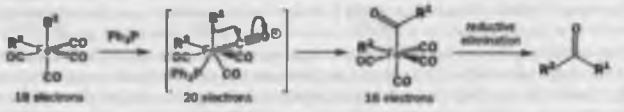
A good example of the carbonylation process is the reaction of the tetracarbonyl ferrate dianion $[Fe(CO)_4]^{2-}$ with alkyl halides. This reagent is made by dissolving metal reduction of the 18-electron Fe(0) compound $Fe(CO)_5$. Addition of two electrons would give an unstable 20-electron species but the loss of one of the ligands with its two electrons restores the stable 18-electron structure.



This iron anion is a good soft nucleophile for alkyl halides and can be used twice over to produce first a monoanion with one alkyl group and then a neutral complex with two alkyl groups and four CO ligands. Each of these complexes has 18 electrons as the electrons represented by the negative charges are retained by the iron to form the new Fe–C bonds. If extra CO is added by increasing the pressure, CO inserts into one Fe–C bond to form an iron acyl complex. Finally, reductive elimination couples the acyl group to the other alkyl group in a conceptually simple ketone synthesis. It does not matter which Fe–C bond accepts the CO molecule: the same unsymmetrical ketone is produced at the end.

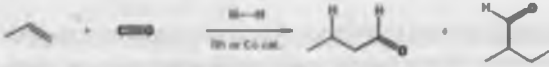


Any good two-electron ligand will cause the CO insertion: Ph_3P is often used instead of an increased CO pressure. The phosphine adds to the iron and pushes out the poorest ligand (one of the alkyl groups) on to a CO ligand in a process of **ligand migration**. In simple form it looks like this though the phosphine addition and alkyl migration may be concerted to avoid the formation of a 20-electron complex as intermediate.



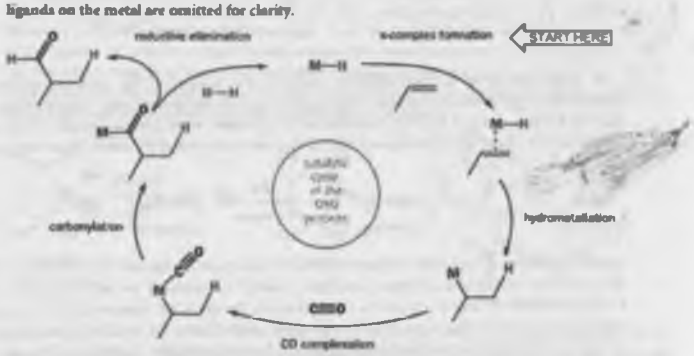
Carbon monoxide incorporation extends the carbon chain

Carbonylation (the addition of carbon monoxide to organic molecules) is an important industrial process as carbon monoxide is a convenient one-carbon feedstock and the resulting metal–acyl complexes can be converted into aldehydes, acids, and their derivatives. The **OXO process** is the hydroformylation of alkenes such as propene and uses two migratory insertions to make higher value aldehydes. Though a mixture is formed this is acceptable from very cheap starting materials.

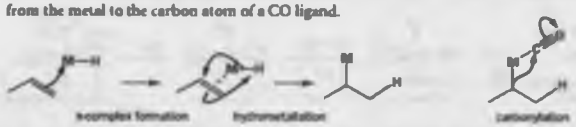


A catalytic cycle (going clockwise from the top) shows the various stages of alkene coordination, hydrometallation to produce an alkyl metal species, coordination of carbon monoxide followed by insertion, and finally reductive cleavage with hydrogen to produce the metal–hydride intermediate.

which is then ready for another cycle. The steps leading to the other regioisomeric aldehyde and the ligands on the metal are omitted for clarity.

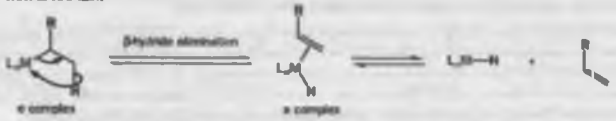


The mechanisms of the two key steps are worth discussion. **Hydrometallation** occurs by initial π-complex formation followed by addition of the metal to one end of the alkene and hydrogen to the other. Both of these regioisomers are formed. The **carbonyl insertion reaction** is another migration from the metal to the carbon atom of a CO ligand.



Insertion reactions are reversible

The reverse process, **decarbonylation**, is also fast but can be arrested by maintaining a pressure of carbon monoxide above the reaction mixture. The reverse of hydrometallation involves the elimination of a hydride from the adjacent carbon of a metal alkyl to form an alkene complex. This process is known as **β-hydride elimination** or simply **β elimination**. It requires a vacant site on the metal as the number of ligands increases in the process and so is favoured by a shortage of ligands as in 16-electron complexes. The metal and the hydride must be *syn* to each other on the carbon chain for the elimination to be possible. The product is an alkene complex that can lose the neutral alkene simply by ligand exchange. So β elimination is an important final step in a number of transition-metal-catalysed processes but can be a nuisance because, say, Pd–Et complexes cannot be used as β elimination is too fast.



Palladium(0) is most widely used in homogeneous catalysis

These elementary steps form the basis for organo-transition-metal chemistry and are the same regardless of which metal is present and the detailed structure of the ligands. This is an enormous and rapidly expanding field that could not be discussed here without doubling the size of the book! Instead, we will concentrate on the chemistry of the most important transition metal, palladium,

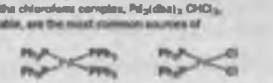
▶ Hydrogenation with homogeneous catalysis involves a soluble catalyst rather than the more common heterogeneous catalysis with, say, Pd metal dispersed on an insoluble charcoal support as in Chapter 24. In general terms homogeneous catalysts are those that are soluble in the reaction mixture.

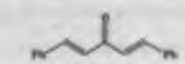
which is the most widely used both in industrial and academic laboratories on both a minute and very large scale. The variety of reactions that can be catalysed together with the range of functional groups tolerated, and usually excellent chemo- and regioselectivity, has meant that an ever increasing amount of research has gone into this area of chemistry. Most syntheses of big organic molecules now involve palladium chemistry in one or more key steps.

Choice of palladium complex

▶ It is supposed that dba complexes the palladium atom through its alkenes.

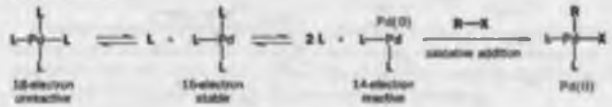
There are many available complexes of palladium(0) and palladium(II). Tetrakis(triphenylphosphine)palladium(0), $Pd(PPh_3)_4$, and tris(dibenzylidene acetone)dipalladium(0), $Pd_2(dba)_3$, or the chloroform complex, $Pd_2(dba)_3.CHCl_3$, which is air-stable, are the most common sources of palladium(0). The detailed structures of some palladium complexes, particularly the dimers, are beyond the scope of this book but we will discuss the reactions in detail.





Palladium(II) complexes are generally more stable than their palladium(0) counterparts. The dichloride $PdCl_2$ exists as a polymer and is relatively insoluble in most organic solvents. However, $(PhCN)_2PdCl_2$ and $(MeCN)_2PdCl_2$ (both easily prepared from $PdCl_2$) are soluble forms of $PdCl_2$, as the nitrile ligands are readily displaced in solution. Bis(triphenylphosphine)palladium(II) chloride complexes are air stable and readily prepared from $PdCl_2$. Palladium is, of course, an expensive metal—these complexes cost about £50–100 per gram—but very little is needed for a catalytic reaction.

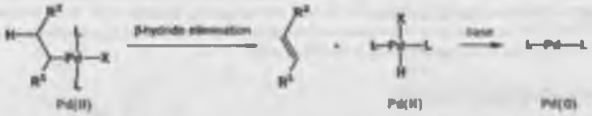
We should review the basic chemistry of palladium, as you will be seeing many more examples of these steps in specialized situations. Palladium chemistry is dominated by two oxidation states. The lower, palladium(0), present in tetrakis(triphenylphosphine)palladium, for example, is nominally electron-rich, and will undergo oxidative addition with suitable substrates such as halides and triflates (TfO⁻ = $CF_3SO_2O^-$), resulting in a palladium(II) complex. Oxidative addition is thought to occur on the coordinatively unsaturated 14-electron species, formed by ligand dissociation in solution.



The resulting σ alkyl bond in such complexes is very reactive, especially towards carbon–carbon π bonds. Thus an alkene in the reacting system will lead to coordination followed by migratory insertion into the palladium–carbon σ bond. This process is like hydrometallation and is called **carbopalladation** as carbon and palladium are attached to the ends of the alkene system. There is no change in oxidation state during this process, although the ligands (often phosphines) must dissociate to allow coordination of the alkene and associate to provide a stable final 16-electron product.

Theoretically, it is possible for the process of olefin coordination and insertion to continue as in Ziegler–Natta polymerization (Chapter 52) but with palladium the metal is expelled from the molecule by a β-hydride elimination reaction and the product is an alkene. For the whole process to be catalytic, a palladium(0) complex must be regenerated from the palladium(II) product of β-hydride elimination. This occurs in the presence of base which removes HX from the palladium(II) species.

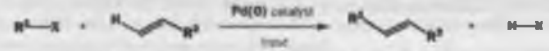
This is another example of reductive elimination: one that forms a hydrogen halide rather than a carbon–carbon or carbon–hydrogen bond as described earlier.



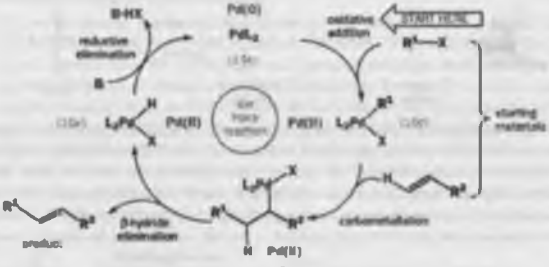
The speed of the intramolecular β-hydride elimination means that the original substrate for the oxidative addition reaction must be chosen with care—the presence of hydrogen at an sp^3 carbon in the β position must be avoided. Thus, substrates for oxidative addition reactions in palladium chemistry are frequently vinylic, allylic, or aromatic and never ethyl or *n*-propyl.

The Heck reaction couples together a halide or triflate and an alkene

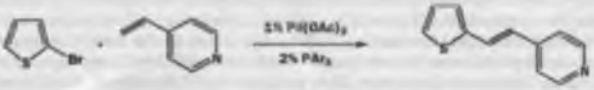
All the individual steps outlined above combine to make up the catalytic pathway in the Heck reaction, which couples an alkene with a halide or triflate to form a new alkene. The R^1 group in R^1X can be aryl, vinyl, or any alkyl group without β Hs on an sp^3 carbon atom. The group X can be halide (Br or I) or triflate (OSO_2CF_3). The alkene can be mono- or disubstituted and can be electron-rich, -poor, or -neutral. The base need not be at all strong and can be Et_3N, NaOAc, or aqueous Na_2CO_3. The reaction is very accommodating.



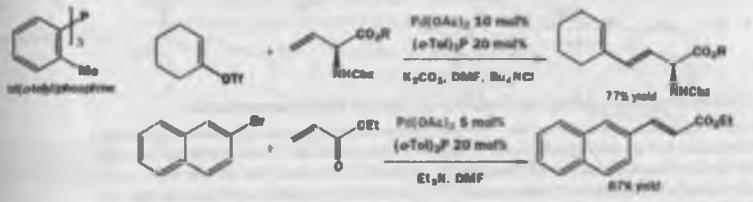
The palladium-catalysed addition of aryl, vinyl, or substituted vinyl groups to organic halides or triflates, the Heck reaction, is one of the most synthetically useful palladium-catalysed reactions. The method is very efficient, and carries out a transformation that is difficult by more traditional techniques. The mechanism involves the oxidative addition of the halide, insertion of the olefin, and elimination of the product by a β-hydride elimination process. A base then regenerates the palladium(0) catalyst. The whole process is a catalytic cycle.



The choice of substrates is limited to aryl, heteroaryl, vinylic, and benzylic halides and triflates, as the presence of an sp^3 carbon in the β position carrying a hydrogen rapidly results in β-hydride elimination. The reaction tolerates a variety of functional groups, and works well with both electron-withdrawing and electron-donating groups on either substrate. Here is an example using a heterocyclic compound we featured earlier reacting with another heterocycle.

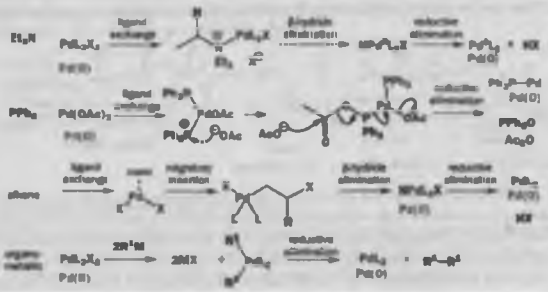


Protected amino acids can be made without any racemization and electron-withdrawing groups such as esters promote excellent regioselectivity in favour of terminal attack. These three examples rely on *in situ* reduction of the palladium(II) acetate by tri(*o*-tolyl)phosphine, a popular more sterically demanding aromatic phosphine.

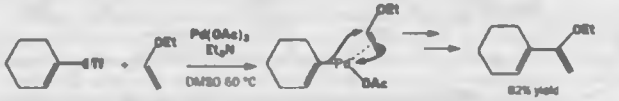


In situ formation of palladium(0) by reduction of Pd(II)

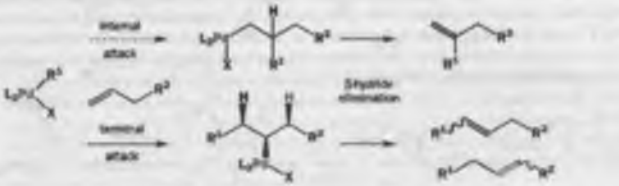
In reactions requiring palladium(0), formation of the active complex may be achieved more conveniently by reduction of a palladium(II) complex, for example, $Pd(OAc)_2$. Any phosphine may then be used in the reaction, without the need to synthesize and isolate the corresponding palladium(0)–phosphine complex. Only 2–3 equivalents of phosphine may be needed, making the palladium(0) complex coordinatively unsaturated and therefore very reactive. The reduction of palladium(II) to palladium(0) can be achieved with amines, phosphines, alkenes, and organometallics such as DIBAL-H, butyl lithium, or trialkyl aluminium. The mechanisms are worth giving as they illustrate the basic steps of organometallic chemistry.



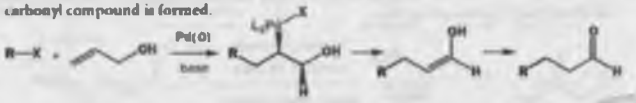
In contrast, electron-donating groups such as ethers lead to attack at the end of the alkene substituted by oxygen to produce in this case the 1,1-disubstituted product. These reactions must be dominated by the interaction of the filled p orbital of the alkene with an empty d orbital on Pd. This is an example of a Heck reaction working in the absence of a phosphine ligand.



In the β-hydride elimination step, the palladium and hydride must be coplanar for reaction to take place, as this is a *syn* elimination process. For steric reasons, the R group will tend to eclipse the smallest group on the adjacent carbon as elimination occurs, leading predominantly to a *trans* double bond in the product.

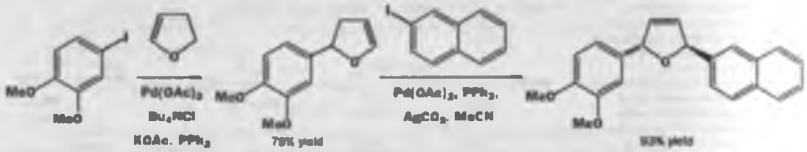


Where there is a choice as to which hydride can be lost to form the alkene, the stability of the possible product alkenes often governs the outcome as the β-hydride elimination is reversible. The reaction of allylic alcohols is particularly important as the more stable of the two alkenes is the enol and a carbonyl compound is formed.

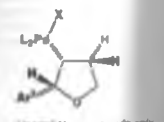


Hydropalladation–dehydropalladation can lead to alkene isomerization

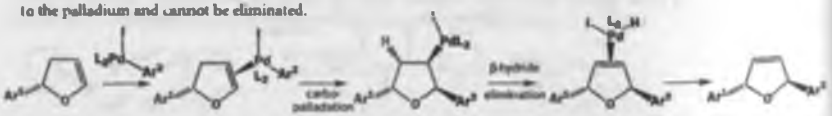
As β-hydride elimination is reversible, hydropalladation with the opposite regiochemistry provides a mechanism for forming regioisomers of the alkene. This allows the most stable alkene that is accessible by the hydropalladation–dehydropalladation sequence to dominate. The only restriction is that all of these processes are *syn*. The migration can be prevented by the addition of bases like silver carbonate, which effectively removes the hydrogen halide from the palladium complex as soon as it is formed. This synthesis of a complex *trans* dihydrofuran involves the Heck reaction followed by alkene isomerization and then a Heck reaction without migration to preserve the stereochemistry.

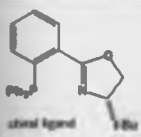


Oxidative addition of the aryl iodide (Ar^1 = 3,4-dimethoxyphenyl) to a palladium(0) complex, formed from $Pd(OAc)_2$ by reduction (with the phosphine?) gives the active palladium(II) complex $ArPdOAcL_2$. Carbopalladation occurs as expected on an electron-rich alkene to give the product of aryl addition to the oxygen end of the alkene in a *syn* fashion. β-Hydride elimination must occur away from the aryl group to give a new alkene complex as there is no *syn* H on the other side. The alkene has moved one position round the ring. Hydropalladation in the reverse sense gives a new σ complex, which could eliminate either the black or the green hydrogens. Elimination of the green H gives the enol ether, which is the most stable alkene possible due to conjugation.



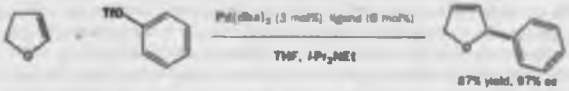
The second Heck reaction involves a naphthyl iodide (Ar^2 = 2-naphthyl) but the initial mechanism is much the same. However, the enol ether has two diastereotopic faces: *syn* or *anti* to the aromatic substituent (Ar^1) introduced in the first step. Palladium is very sensitive to steric effects and generally forms less hindered complexes where possible. Thus coordination of the palladium(II) intermediate occurs on the face of the enol ether *anti* to Ar^1. This in turn controls all the subsequent steps, which must be *syn*, leading to the *trans* product. The requirement for *syn* β-hydride elimination also explains the regiochemical preference of the elimination. In this cyclic structure there is only one hydrogen (green) that is *syn*, the one on the carbon bearing the naphthyl substituent is *anti* to the palladium and cannot be eliminated.



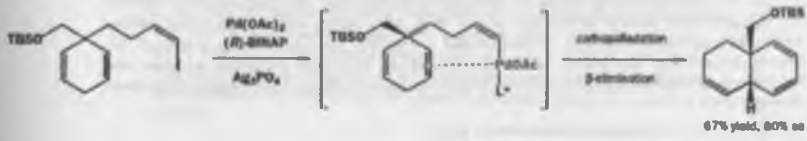


Heck reactions can be enantioselective

With chiral ligands the Heck reaction can be enantioselective. The amino-acid-derived phosphine ligand in the margin controls the Heck reaction of phenyl triflate with dihydrofuran. The ligand selects one enantiotopic face of the alkene (see Chapter 45 if you have forgotten this term) and the usual double bond migration and β elimination complete the reaction.

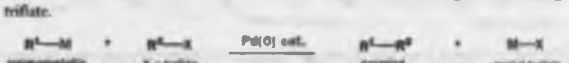


The famous ligand BINAP controls an intramolecular Heck reaction to give decalin derivatives with good enantiomeric excess. BINAP is the optically pure phosphine built into the palladium catalyst. The presence of silver ions accelerates the reaction as well as preventing double bond isomerization in the original substrate. This time the chiral ligand selects which double bond is to take part in the reaction. The vinyl palladium species is tethered to the alkene and can reach only the same face. The faces of the alkenes are diastereotopic but the two alkenes are enantiotopic and you must know your right from your left to choose one rather than the other.

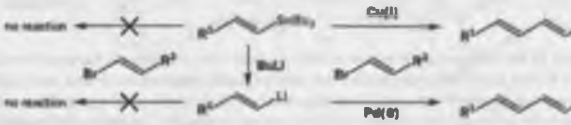


Cross-coupling of organometallics and halides

Other than β-hydride elimination, another important pathway by which palladium(II) intermediates can lead to neutral organic fragments is reductive elimination. This forms the basis of the mechanism for cross-coupling reactions between an organometallic reagent and an organic halide or triflate.

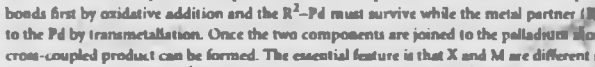


This is a reaction that seems very attractive for synthesis but, in the absence of a transition metal catalyst, the yields are very low. We showed in the last chapter how vinyl silanes can be made with control over stereochemistry and converted into lithium derivatives with retention. Neither of these vinyl metals couple with vinyl halides alone. But in the presence of a transition metal—Cu(I) for Li and Pd(0) for Sn—coupling occurs stereospecifically and in good yield.



The mechanism involves oxidative addition of the halide or triflate to the initial palladium(0) phosphine complex to form a palladium(II) species. The key slow step is a **transmetallation**, so called because the nucleophile (R^1) is transferred from the metal in the organometallic reagent to the palladium and the counterion (X = halide or triflate) moves in the opposite direction. The new palladium(II) complex with two organic ligands undergoes reductive elimination to give the coupled product and the palladium(0) catalyst ready for another cycle.

The reaction is important because it allows the coupling of two different components (R^1 and R^2). If this is to happen, the substituents, M (metal) on R^1 and X (halide or triflate) on R^2, must be different electronically. Both components form σ complexes with Pd but the halide partner (R^2X) bonds first by oxidative addition and the R^2–Pd must survive while the metal partner (R^1M) bonds to the Pd by transmetallation. Once the two components are joined to the palladium atom, only the cross-coupled product can be formed. The essential feature is that X and M are different so that R^2X combines with Pd(0) and R^1M with Pd(II). There can then be no confusion.



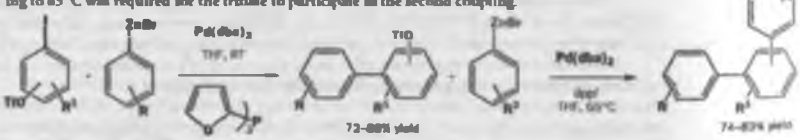
The halide partner (R^2X) must be chosen with care, as β-hydride elimination would decompose the first intermediate during the slow transmetallation step. The choice for R^2 is restricted to substituents without β-hydrogen atoms: vinyl, allyl, benzyl, and polyfluoroalkyl halides, triflates, and phosphates have all been coupled successfully. The organometallic reagent (R^1M) can be based on magnesium, zinc, copper, tin, silicon, zirconium, aluminium, or boron and the organic fragment can have a wide variety of structures as coupling is faster than β-hydride elimination.

R^1—M R^1 = almost anything including examples with β H

M = MgX, ZnX, Cu, SnR_3, SiR_3/TASF, $ZrCp_2Cl$, $AlMe_2$, $B(OR)_2$

R^2—X R^2 must not have β Hs that can eliminate X = I, Br, (Cl), OTf, $OPO(OR)_2$

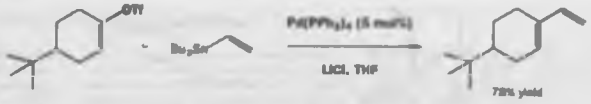
The difference in relative reactivity of aromatic iodides and triflates was exploited in this sequential synthesis of substituted terphenyls by repeated coupling with organozinc reagents. The more reactive iodide coupled at room temperature with palladium(0) and *tris*-furylphosphine but warming to 65 °C was required for the triflate to participate in the second coupling.



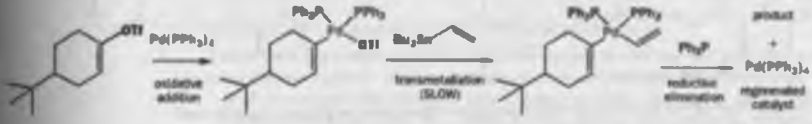
In spite of the wide range of organometallic reagents that can be used there are two classes that have proved particularly popular because they are stable intermediates in their own right and can be prepared separately before the coupling reaction. These cross-couplings are known by the names of the two chemists whose work made the reactions so valuable. The Stille coupling employs a stannane as the organometallic component (R^1M) while the Suzuki coupling relies on a boronic acid.

The Stille coupling uses stannanes as the organometallic component

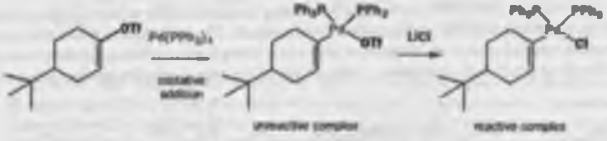
Since the first reported use in the late 1970s, the Stille coupling has been widely used for the coupling of both aromatic and vinylic systems.



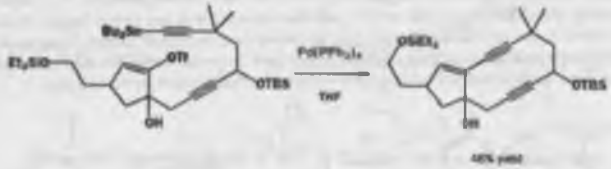
The mechanism involves the oxidative addition of the vinyl or aromatic triflate or halide to give a palladium intermediate. This then undergoes a transmetallation reaction with the organostannane, giving an organopalladium intermediate in which both components are σ-bound. This complex then undergoes a reductive elimination step, releasing the product and thereby regenerating the palladium(0) catalyst.



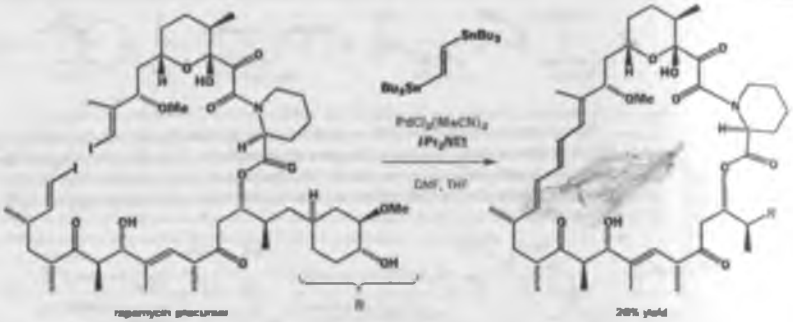
The reaction will also occur if the vinyl or aryl halide is used in place of the triflate. However, the triflates have been more widely used as they are readily prepared from phenols or enolizable aldehydes or ketones. In these reactions, the presence of a source of halide (typically LiCl) is generally required. This may be because the triflate is a counterion and is not bound to the metal as a ligand. If transmetallation is to occur some other ligand must be added to give the necessary square coplanar geometry.



The Stille reaction, which represents over half of all current cross-coupling reactions, has been used in total synthesis with excellent results. The reaction may also be carried out intramolecularly and with alkynyl stannanes instead of the more usual aryl or vinyl stannanes, even to form medium-sized rings. This example forms a ten-membered ring containing two alkynes.

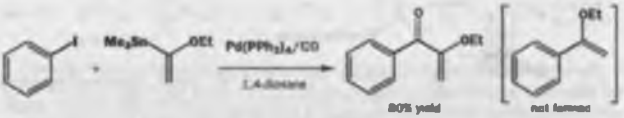


Nicolaou's synthesis of rapamycin uses the reaction twice in the macrocyclization (cyclization reaction to form a large ring) step. This illustrates an important feature of palladium-catalysed cross-couplings—the geometry of both double bonds involved in the coupling is preserved in the product. This seems a very complex example and the molecule is complex. But just inspect the black region and you will see two simple Stille couplings. These reactions work with complex molecules having many functional groups, even if the yield isn't great (26%!).

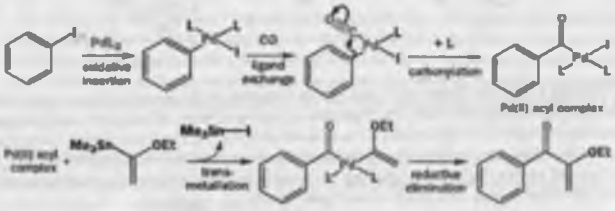


The Stille coupling may be combined with carbonylation in two ways. Acid chlorides may be used as substrates for the reaction with vinyl or aryl stannanes. However, an atmosphere of carbon monoxide is frequently required to prevent decarbonylation after the oxidative addition step.

More recently, it has been shown that performing the normal Stille reaction in the presence of carbon monoxide may also lead to carbonylated products. These reactions can take place in a CO saturated solution, under one atmosphere of pressure. Using these conditions, excellent yields of the carbonylated product can be obtained, without any of the normal coupling product being present.

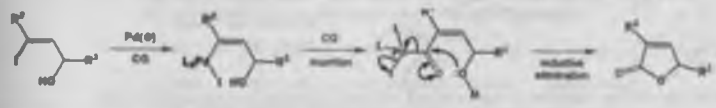


The mechanism is like that of a normal Stille coupling except that the carbon monoxide first exchanges for one of the phosphine ligands and then very rapidly inserts to produce an acyl palladium(II) complex. This then undergoes transmetallation with the vinyl stannane in the usual way forming trimethylstannyl iodide and the palladium complex with two carbon ligands. Reductive elimination gives the masked diketone and regenerates the palladium(0) catalyst. Transmetallation is the slow step in these coupling reactions so that there is time for the carbon monoxide insertion first. The final step—reductive elimination—releases the Pd(0) catalyst for the next cycle.



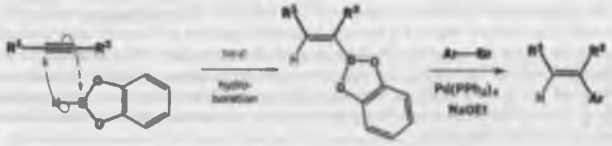
Acyl palladium species react like activated acid derivatives

Carbonylation of a halide or triflate provides a direct route to a range of chain-extended acyl derivatives. A carbonyl group substituted with Pd(II) – halide or triflate – is a reactive acylating agent, rather like an acid anhydride, as Pd(II) is a good leaving group. Reaction with alcohols and amines gives esters and amides, while reduction with tributyltin hydride gives the aldehyde. Intramolecular attack by alcohols leads to lactones as demonstrated in the conversion of a vinyl iodide into a 2H-furanone (butenolide). We will see more of these reactions later.

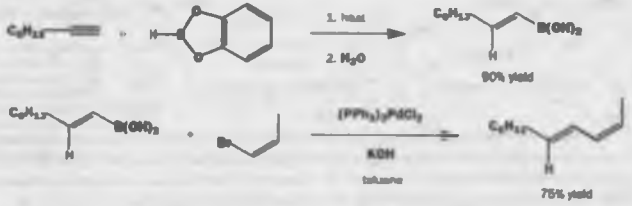


The Suzuki coupling couples boronic acids to halides

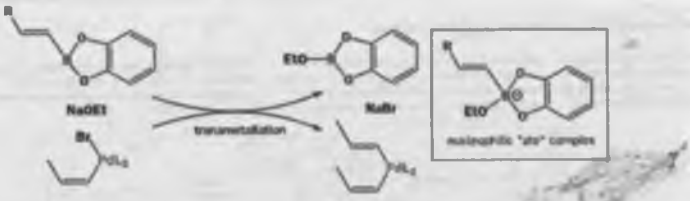
Since first being published in 1979, the Suzuki coupling of a boronic acid with a halide or triflate has developed into one of the most important cross-coupling reactions, totalling about a quarter of all current palladium-catalysed cross-coupling reactions. The original version consisted of hydroboration of an alkyne with catecholborane, followed by palladium(0)-catalysed coupling of the resulting vinyl boronate with an aromatic iodide or bromide. The hydroboration is generally regioselective for the less hindered position and addition of boron and hydrogen occurs cis stereospecifically.



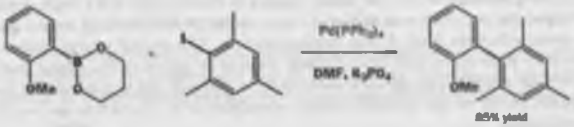
As in the Stille coupling, the geometry of both unsaturated components is preserved during the coupling so this is an excellent method for stereospecific diene synthesis. Hydroboration of octyne followed by hydrolysis of the boronate gave exclusively the *E*-vinyl boronic acid. Coupling with the *Z*-vinyl bromide in toluene with palladium(0) catalysis with potassium hydroxide as the base gave the *E,Z*-diene in good yield. These dienes are very useful in the Diels–Alder reaction (Chapter 35).



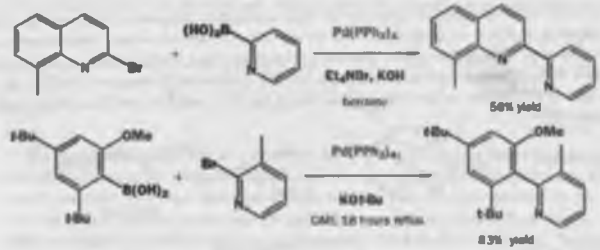
The mechanism is very similar to that of the Stille coupling. Oxidative addition of the vinylic or aromatic halide to the palladium(0) complex generates a palladium(II) intermediate. This then undergoes a transmetallation with the alkenyl boronate, from which the product is expelled by reductive elimination, regenerating the palladium(0) catalyst. The important difference is the transmetallation step, which explains the need for an additional base, usually sodium or potassium ethoxide or hydroxide, in the Suzuki coupling. The base accelerates the transmetallation step leading to the borate directly presumably via a more nucleophilic 'ate' complex.



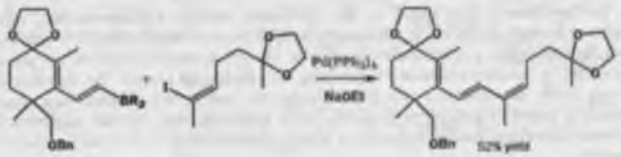
Sterically demanding substrates are tolerated well and Suzuki coupling has been used in a wide range of aryl–aryl cross-couplings. This example has three *ortho* substituents around the newly formed bond (marked in black) and still goes in excellent yield. It also shows that borate esters can be used instead of boronic acids.



Coupling of aromatic heterocycles goes well. The 2-position of a pyridine is very electrophilic and not at all nucleophilic (Chapter 43) but couplings at this position are fine with either the halide or the boronic acid in that position. Clearly, it is a mistake to see either of these substituents as contributing a 'nucleophilic carbon'. It is better to see the reaction as a coupling of two equal partners and the two substituents (halide and boronic acid) as a control element to ensure cross-coupling and prevent dimerization. In the second example potassium *tert*-butoxide was crucial as weaker and less hindered bases gave poor yields.

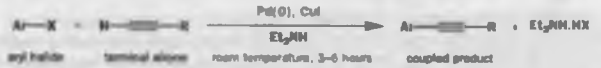


Due to the excellent stereoselectivity of the Suzuki coupling, the reaction has been used in the synthesis of the unsaturated units of a range of natural products including trisporol B. The key step is the stereocontrolled synthesis of an *E,Z*-diene. The geometry of both double bonds comes stereospecifically with retention of configuration from single geometrical isomers of the starting materials.



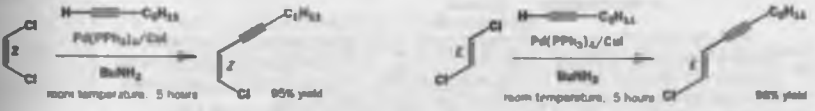
The Sonogashira coupling uses alkynes directly

The coupling of terminal alkynes with aryl or vinyl halides under palladium catalysis is known as the Sonogashira reaction. This catalytic process requires the use of a palladium(0) complex, is performed in the presence of base, and generally uses copper iodide as a co-catalyst. One partner, the aryl or vinyl halide, is the same as in the Stille and Suzuki couplings but the other has hydrogen instead of tin or boron as the 'metal' to be exchanged for palladium.



The mild conditions usually employed, frequently room temperature, mean that the reaction can be used with thermally sensitive substrates. The mechanism of the reaction is similar to that of the Stille and Suzuki couplings. Oxidative addition of the organic halide gives a palladium(II) intermediate that undergoes transmetallation with the alkynyl copper (generated from the terminal alkyne, base, and copper iodide). Reductive elimination with coupling of the two organic ligands gives the product and regenerates the palladium(0) catalyst.

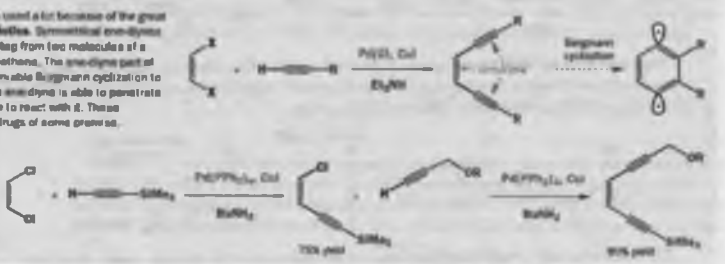
It is often more convenient, as in the Heck reaction, to use a stable and soluble Pd(II) derivative such as bis(triphenylphosphine)palladium(II) chloride instead of Pd(0). This is rapidly reduced *in situ* to give a coordinatively unsaturated, catalytically active, palladium(0) species. The geometry of the alkene is generally preserved so that *cis* (*Z*) and *trans* (*E*) dichloroethylene give the two different geometrical isomers of the enyne below in >99% stereochemical purity as well as excellent yield.



Ene-diynes and the Bergmann cyclization

The Sonogashira reaction is used a lot because of the great potential of ene-diyne antibiotics. Symmetrical ene-diynes may be synthesized in one step from two molecules of a terminal alkyne and 1,2-dihaloethene. The ene-diyne part of the molecule does the rearrangement cyclization to give a benzene diradical. The ene-diyne is able to penetrate DNA and the diradical is able to react with it. These compounds are anticancer drugs of some promise.

To make useful biologically active components, however, the reaction is performed sequentially, viewing different functionality on each of the alkyne units.

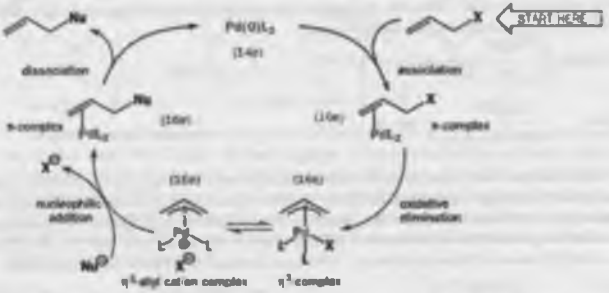


Allylic electrophiles are specifically activated by palladium(0)

Allylic compounds with good leaving groups, such as bromide and iodide, are excellent allylating agents but they suffer from loss of regiochemistry due to competition between the direct S_N2 and

S_N2' reaction. This problem together with the associated stereochemical ambiguity was described in Chapter 23. In contrast, π-allyl cation complexes of palladium allow both the stereochemistry and regiochemistry of nucleophilic displacement reactions to be controlled.

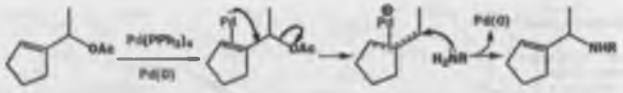
In addition, leaving groups (X) that are usually regarded as rather unreactive can be used, which means that the electrophilic partner is more stable in the absence of palladium making handling easier. Acetate (X = OAc) is the most commonly used leaving group, but a wide range of other functional groups (X = OCO_2R, $OPO(OR)_2$, Cl, Br, OPh) will perform a similar role. The full catalytic cycle is shown with the intermediate π-allyl complex in equilibrium between the neutral version, which has the leaving group coordinated to palladium, and the cationic π-allyl, in which one of the phosphine ligands has displaced the anion.



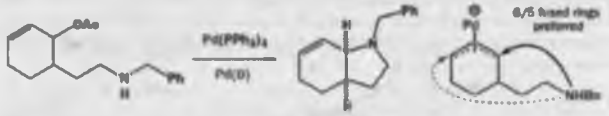
▶ The Pd π-allyl cation complex

You can represent the palladium π-allyl cation complex in two ways. Either you draw a neutral allyl group complexed to Pd^0 or you draw an allyl cation complexed to neutral Pd. Though the counting is different (Pd^+ has only 9 electrons, the neutral one has 11 but the allyl cation only 7), both come out as η^3 16-electron species, which is just as well as they are different views of the same thing.

Soft nucleophiles (Nu) generally give the best results so, for carbon–carbon bond formation, stabilized enolates such as malonates are best, but for C–X (X = O, N, S) bond formation the reaction is successful with alkoxides, amines, cyanide, and thioalkoxides. This example shows an amine attacking outside the ring probably because the alkene prefers to be inside the ring.



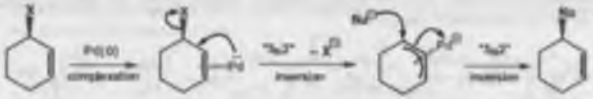
The intramolecular reaction works well to give heterocyclic rings—the regioselectivity is usually determined by the length of the chain and how far it can reach. Here a 6/5 fused product is preferred to a bridged product containing two seven-membered rings.



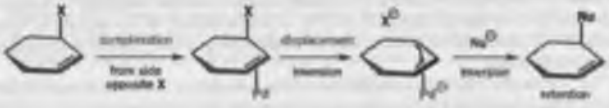
The reaction usually proceeds with *retention* of configuration at the reacting centre. As in S_N2 reactions going with retention (Chapter 37), this can mean only a double inversion. Coordination of Pd to the double bond of the allylic acetate occurs on the less hindered face opposite the leaving group and the nucleophile adds to the face of the π-allyl Pd cation complex opposite the Pd. The net result is displacement of the leaving group by the nucleophile with retention. Thereafter, the

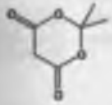
▶ The ligands around palladium are omitted for the sake of clarity.

nucleophile attacks from the less hindered face of the resulting π-allyl complex (that is, away from the metal) leading to overall retention of configuration.



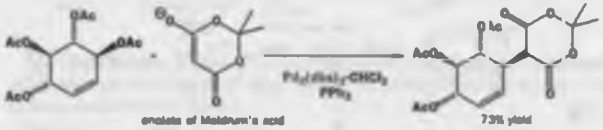
The rather vague arrows on the middle two diagrams are the best we can do to show how Pd(0) uses its electrons to get rid of the leaving group and how it accepts them back again when the nucleophile adds. They are not perfect but it is often difficult to draw precise arrows for organometallic mechanisms. The double inversion process is perhaps more apparent in a perspective view.





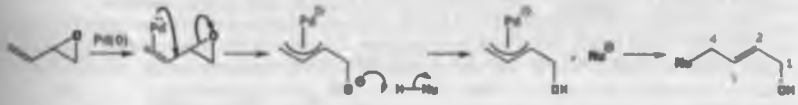
Meldrum's acid

The reaction of this allylic acetate with the sodium salt of Meldrum's acid (structure in margin) demonstrates the retention of configuration in the palladium(0)-catalyzed process. The tetraacetate and the intermediate π-allyl complex are symmetrical, thus removing any ambiguity in the formation or reaction of the π-allyl complex and hence in the regiochemistry of the overall reaction.



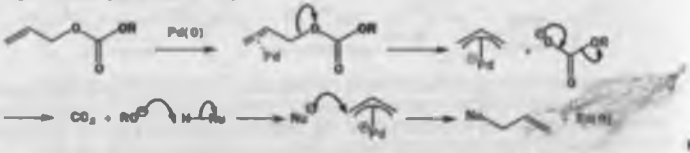
Vinyl epoxides provide their own alkoxide base

Vinyl epoxides and allylic carbonates are especially useful electrophiles because under the influence of palladium(0) they produce a catalytic amount of base since X^- is an alkoxide anion. This is sufficiently basic to deprotonate most nucleophiles that participate in allylic alkylations and thus no added base is required with these substrates. The overall reaction proceeds under almost neutral conditions, which is ideal for complex substrates. The relief of strain in the three-membered ring is responsible for the epoxide reacting with the palladium(0) to produce the zwitterionic intermediate. Attack of the negatively charged nucleophile at the less hindered end of the π-allyl palladium intermediate preferentially leads to overall 1,4-addition of the neutral nucleophile to vinyl epoxides.



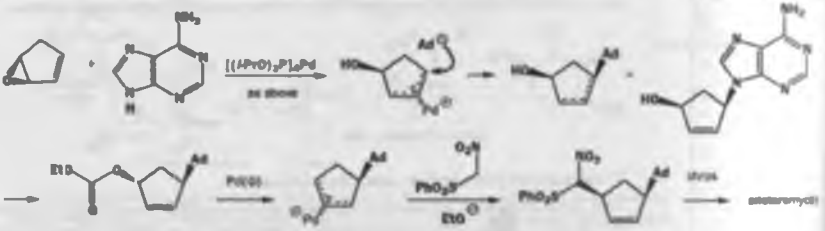
Retention of stereochemistry is demonstrated by the reaction of a substituted malonate with epoxycyclopentadiene. Palladium adds to the *side* opposite the epoxide so the nucleophile is forced to add from the same side as the OH group. This, no doubt, helps 1,4-regioselectivity. The required palladium(0) phosphine complex was formed from a palladium(II) complex as in the Heck reaction.

Allylic carbonates produce the required alkoxide by decarboxylation of the carbonate anion that is displaced in the formation of the π-allyl palladium intermediate. Deprotonation creates the active nucleophile, which rapidly traps the π-allyl palladium complex to give the allylated product and regenerates the palladium(0) catalyst.



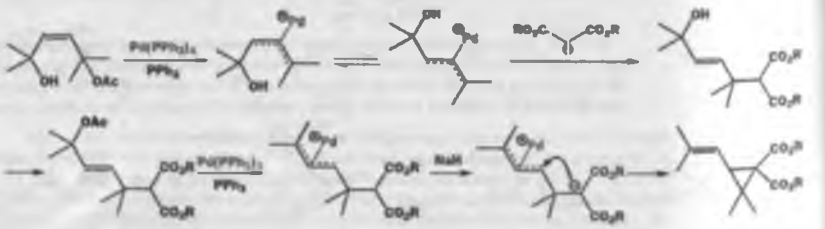
Trost and his group have used both of these palladium-catalysed alkylations in a synthesis of aristeromycin from epoxycyclopentadiene. The *cis* stereochemistry of this carbocyclic nucleotide analogue is of paramount importance and was completely controlled by retention of configuration in both substitutions.

The first reaction is between epoxycyclopentadiene and adenine, one of the heterocyclic building blocks of nucleic acids, and follows the course we have just described to give a *cis*-1,4-disubstituted cyclopentene. The alcohol is then activated by conversion into the carbonate, which reacts with phenylsulfonylnitromethane, which could later be converted into an alcohol. Once again, retention of stereochemistry during the palladium-catalysed substitution gives the *cis* product.

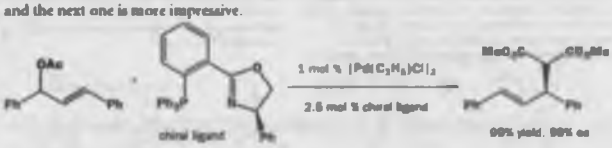


Intramolecular alkylations lead to ring synthesis

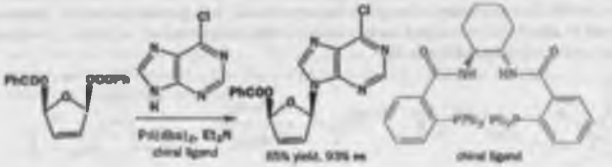
π-Allyl intermediates may also be used in cyclization reactions including the synthesis of small and medium-sized rings using an intramolecular nucleophilic displacement. Three-membered rings form surprisingly easily taking advantage of the fact that the leaving group can be remote from the nucleophile. The precursors can also be prepared by allylic alkylation. The sodium salts of malonate esters react with the monoacetate under palladium catalysis to give the allylic alcohol. Acetylation activates the second alcohol to displacement so that the combination of sodium hydride as base and palladium(0) catalyst leads to cyclization to the cyclopropane. The regioselectivity of the cyclization is presumably governed by steric hindrance as is usual for allylic alkylations with palladium(0).



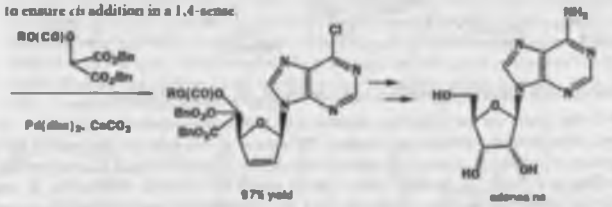
Optically pure ligands on Pd in allylic alkylation can give good enantiomeric excess. You have already seen the first chiral amino-phosphine as the ligand in a chiral Heck reaction and it also gives excellent results in this example. It has to be said, however, that this is a very well behaved example and the next one is more impressive.



A C_2 symmetric bis(amidophosphine) ligand was used by Trost to prepare the natural nucleoside adenosine (see Chapter 49 for nucleosides) in similar fashion to the carbocyclic analogue described above. The key enantioselective step was the first allylic alkylation that selected between two enantiotopic benzoates in the *meso* dihydrofuran derivative to give one enantiomer the expected *cis* product.



The second benzoate is displaced by a malonate anion, which allows the CH_2OH group to be added at the other side of the dihydrofuran. No enantioselectivity is needed in this step—it is enough to ensure *cis* addition in a 1,4-sense.

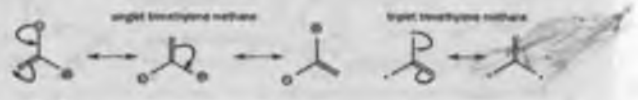


Palladium can catalyse cycloaddition reactions

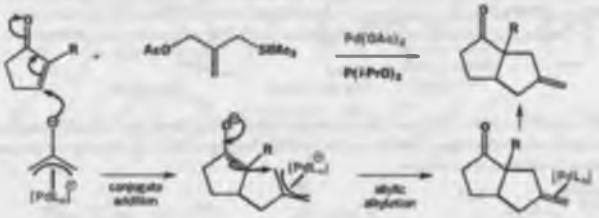
The presence of five-membered rings such as cyclopentanes, cyclopentenes, and dihydrofurans in a wide range of target molecules has led to a variety of methods for their preparation. One of the most successful of these is the use of trimethylenemethane [3 + 2] cycloaddition, catalysed by palladium(0) complexes. The trimethylenemethane unit in these reactions is derived from 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate which is at the same time an allyl silane and an allylic acetate. This makes it a weak nucleophile and an electrophile in the presence of palladium(0). Formation of the palladium π-allyl complex is followed by removal of the trimethylsilyl group by nucleophilic attack of the resulting acetate ion, thus producing a zwitterionic palladium complex that can undergo cycloaddition reactions.

Trimethylene methane

The symmetrical molecule with three CH_2 groups arranged trigonally about a carbon atom is interesting theoretically. It could have a singlet structure with two charges, both of which can be delocalized, but no neutral form can be drawn. Alternatively, it could be a triplet with the two unpaired electrons evenly distributed over the three CH_2 groups. This form is probably preferred and the singlet form is definitely known only as the palladium complex we are now describing. You might compare the singlet and triplet structures of trimethylene methane with those of carbenes in Chapter 40.

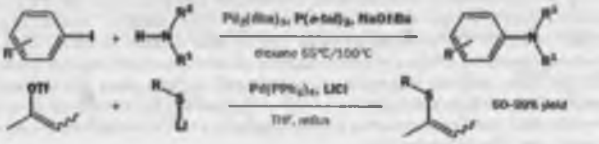


The normal course of the reaction is to react with an alkene with electron-withdrawing substituents present, which make the substrate prone to Michael-type conjugate addition. The resulting cyclization product has an *exo* methylene group. Cyclopentenones illustrate this overall 'cycloaddition' nicely. The mechanism is thought to be stepwise with conjugate addition of the carbanion followed by attack of the resulting enolate on the π-allyl palladium unit to form a five-membered ring—not a real cycloaddition at all.

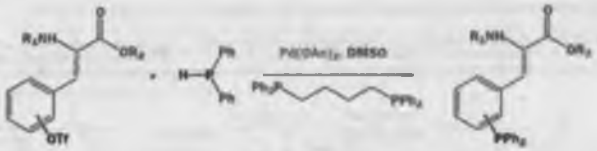


Heteroatom couplings produce aryl– or vinyl– N, –S, or –P bonds

While the major use for palladium catalysis is to make carbon–carbon bonds, which are difficult to make using conventional reactions, the success of this approach has recently led to its application to forming carbon–heteroatom bonds as well. The overall result is a nucleophilic substitution at a vinylic or aromatic centre, which would not normally be possible. A range of aromatic amines can be prepared directly from the corresponding bromides, iodides, or triflates and the required amine in the presence of palladium(0) and a strong alkoxide base. Similarly, lithium thiolates couple with vinylic triflates to give vinyl sulfides provided lithium chloride is present.



The mechanisms and choice of catalyst, usually a palladium(0) phosphine complex, are the same as those of coupling reactions involving oxidative addition, transmetallation, and reductive elimination. Phosphines do not require additional base for the coupling with aromatic triflates and the reaction has no difficulty in distinguishing the two phosphines present.

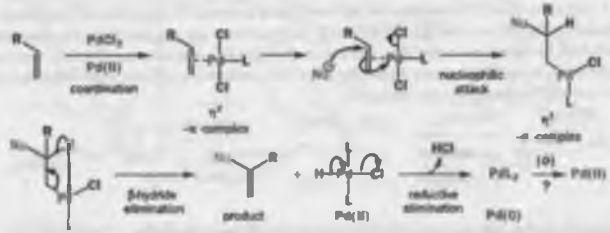


Alkenes are attacked by nucleophiles when coordinated to palladium(II)

The importance of transition-metal-catalysed reactions lies in their ability to facilitate reactions that would not occur under normal conditions. One such reaction is nucleophilic attack on an isolated double bond. While the presence of a conjugating group promotes the attack of nucleophiles, in its absence no such reaction occurs. Coordination of an alkene to a transition metal ion such as palladium(II) changes its reactivity dramatically as electron density is drawn towards the metal and away from the π orbitals of the alkene. This leads to activation towards attack by nucleophiles just as for conjugate addition and unusual chemistry follows. Unusual, that is, for the alkene; the palladium centre behaves exactly as expected.

Many nucleophiles, such as water, alcohols, and carboxylates, are compatible with the Pd(II) complex and can attack the complexed alkene from the side opposite the palladium. The attack of the nucleophile is regioselective for the more substituted position. This parallels attack on bromonium ions but is probably governed by the need for the bulky palladium to be in the less hindered position. The resulting Pd(II) σ-alkyl species decomposes by β-hydride elimination to reveal the substituted alkene. Reductive elimination of a proton and the leaving group, usually chloride, leads to palladium(0). The weakness of this reaction is that the catalytic cycle is not complete: Pd(II) not Pd(0) is needed to complex the next alkene.

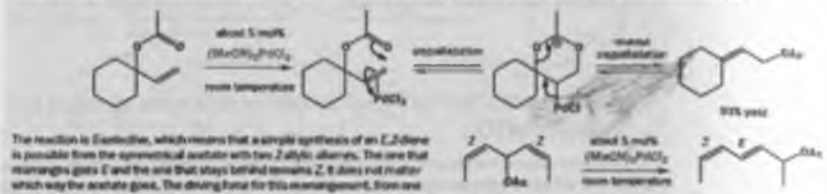
Unfortunately, this regioselectivity is not the same as in the Heck reaction where attack mostly occurs at the end of the alkene. Internal nucleophiles transferred from the palladium to the alkene usually prefer the end of the alkene but external nucleophiles usually prefer the other end.



A Pd(II) salt such as $Pd(OAc)_2$ adds to an alkene to give, via the π complex, a product with Pd at one end of the alkene and OAc at the other. This is oxypalladation but this product is not usually isolated as it decomposes to the substituted alkene. This reaction is occasionally used with various nucleophiles but it needs a lot of palladium.

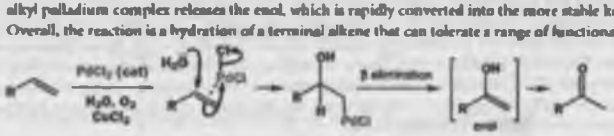
Please note again that our representations for organometallic steps such as oxypalladation are intended to help organic chemists' understanding and may well be disputed by experts.

Allylic rearrangement by reversible oxypalladation

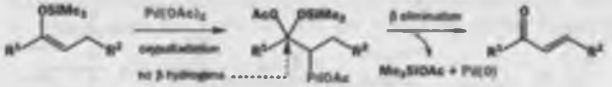


There are two solutions to this problem. We could use stoichiometric Pd(II) but this is acceptable only if the product is very valuable or the reaction is performed on a small scale. It is better to use an external oxidant to return the palladium to the Pd(II) oxidation state so that the cycle can continue. Air alone does not react fast enough (even though Pd(0) must be protected from air to avoid oxidation) but, in combination with Cu(I) chloride, oxygen completes the catalytic cycle. The Cu(II) chloride oxidizes Pd(0) to Pd(II) and is itself oxidized back to Cu(II) by oxygen, ready to oxidize more palladium.

This combination of reagents has been used to oxidize terminal vinyl groups to methyl ketones and is known as the **Wacker oxidation**. The nucleophile is simply water, which attacks the activated alkene at the more substituted end in an oxypalladation step. β-Hydride elimination from the resulting σ-alkyl palladium complex releases the enol, which is rapidly converted into the more stable keto form. Overall, the reaction is a hydration of a terminal alkene that can tolerate a range of functional groups.

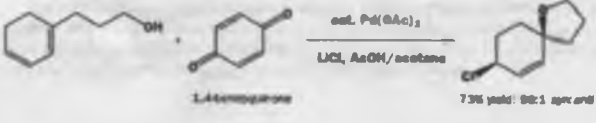


A related reaction is the oxidation of allyl enol ethers to enones. This requires stoichiometric palladium(II), though reoxidation of Pd(0) with benzoquinone can cut that down to about half an equivalent, but does ensure that the alkene is on the right side of the ketone. The first step is again oxypalladation and β elimination puts the alkene in conjugation with the ketone chiefly because there are no β hydrogens on the other side.

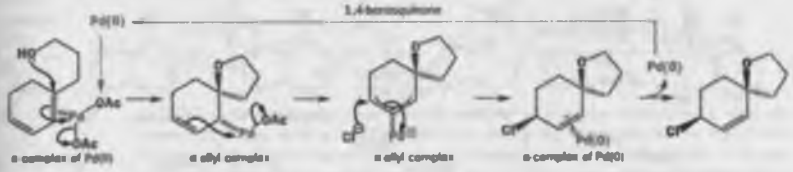


Alcohols and amines are excellent intramolecular nucleophiles

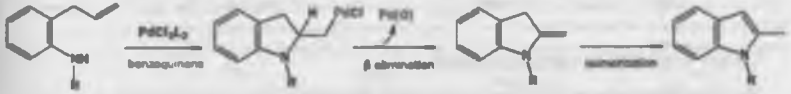
Cyclic ethers and amines can be formed if the nucleophile is an intramolecular alcohol or amine. Stoichiometric palladium can be avoided by using benzoquinone as the stoichiometric oxidant with a catalytic amount of palladium. In this example intramolecular oxypalladation of a diene is followed by attack of an external nucleophile on a π-allyl complex.



Palladium coordinates to one face of the diene promoting intramolecular attack by the alcohol on the opposite face. The resulting σ-alkyl palladium can form a π-allyl complex with the palladium on the lower face simply by sliding along to interact with the double bond. Nucleophilic attack of chloride from the lithium salt then proceeds in the usual way on the face opposite palladium. The overall addition to the diene is therefore *cis*.

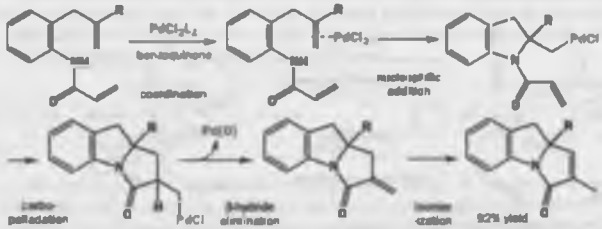


Nitrogen nucleophiles also attack alkenes activated by Pd(II) and benzoquinone can again act as a reoxidant allowing the use of catalytic quantities of palladium. The mechanism follows the same pattern as for oxygen nucleophiles including the final isomerization to produce the most stable regioisomer of product. In this example the product is an aromatic indole (Chapter 43) so the double bond migrates into the five-membered ring.



(R = H, Ac, Ts)

If the substrate lacks a hydrogen suitable for β elimination and there is another alkene present in the molecule, the σ-alkyl palladium intermediate can follow a Heck pathway to form a bicyclic structure in a tandem reaction sequence. Once again, the final step is a palladium-hydride-mediated isomerization to give the endocyclic alkene.

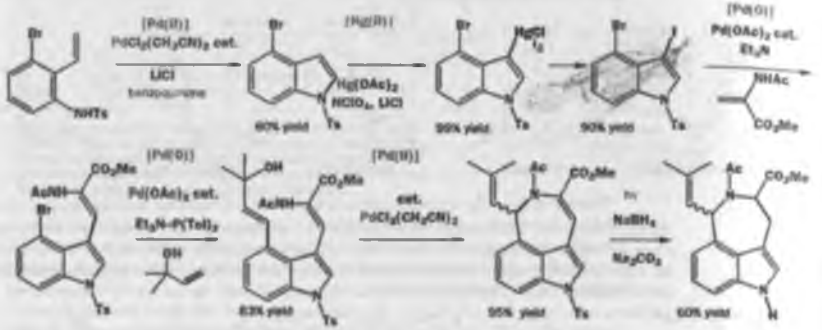


Palladium catalysis in the total synthesis of a natural alkaloid

We end this chapter with a synthesis of *N*-acetyl clavicipitic acid methyl ester, an ergot alkaloid, by Hegedus. The power of organo-transition-metal chemistry is illustrated in five steps of this seven-step process. Each of the organometallic steps catalysed by Pd(0) or Pd(II) has been described in this chapter. The overall yield is 18%, a good result for a molecule of such complexity.

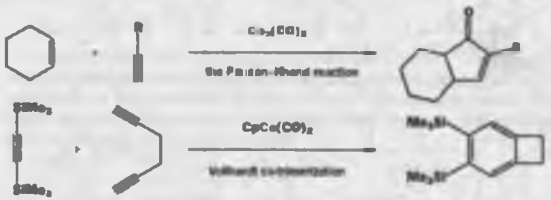
The first step is to make an indole by Pd(II)-catalysed cyclization in the presence of benzoquinone as reoxidant. The nucleophilic nature of the 3-position of the indole (Chapter 43) was exploited to introduce the required iodine functionality. Rather than direct iodination, a high yielding two-step procedure involving mercuration followed by iodination was employed. The more reactive iodide was then involved in a Heck coupling with an unsaturated side chain in the absence of phosphine

ligands. The remaining aromatic bromide then underwent a second Heck reaction with an allylic alcohol to introduce the second side chain. Cyclization of the amide on to the allylic alcohol was achieved with palladium catalysis, not as might have been expected with palladium(0) but instead with palladium(II), to produce the seven-membered ring. Finally, the conjugated double bond was reduced and the sulfonamide removed with sodium borohydride with photolysis.



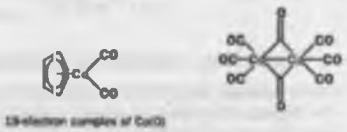
Other transition metals: cobalt

We have concentrated on palladium because it is the most important of the transition metals but we must not leave you with the idea that it is the only one. We shall end with two reactions unique to cobalt—the Pauson–Khand reaction that we mentioned right at the start of the chapter and the Vollhardt co-trimerization. You will see at once that cobalt has a special affinity with alkynes and with carbon monoxide.



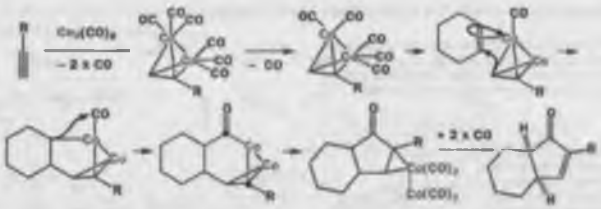
▶ Take care to distinguish between Co and CO in these reactions.

The structure of the cobalt reagents is worth a mention. Cobalt has nine electrons so the second reagent is easy: nine from Co, five from the cyclopentadienyl, and two each from the two COs giving 18 in all. But why is the first reagent a dimer? The monomer $Co(CO)_4$ would have 9 + 8 = 17 electrons.



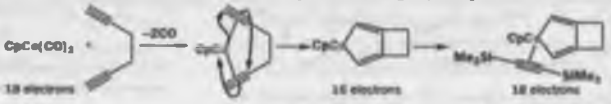
The Pauson–Khand reaction starts with the replacement of two CO molecules, one from each Co atom, with the alkyne to form a double σ complex with two C–Co σ bonds, again one to each Co atom. One CO molecule is then replaced by the alkene and this π complex in its turn gives a σ complex with one C–Co σ bond and one new C–C σ bond, and a C–Co bond is sacrificed in a ligand coupling reaction. Then a carbonyl insertion follows and reductive elimination gives the product, initially as a cobalt complex.

▶ In the middle few structures, showing the vital steps, we omit all the molecules except the one that reacts.

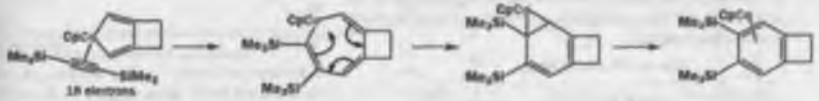


This is an extraordinary reaction because so much seems to happen with no control except the presence of the two cobalt atoms. The alkene reacts so that the more substituted end bonds to the carbonyl group. This is because the ligand coupling occurs to the less substituted end, as in other coupling reactions. The stereochemistry of the alkene is preserved because the coupling step puts the C–C and C–Co bonds in at the same time in a *syn* fashion and the migration to the CO ligand is stereospecific with retention. This is one of the most complicated mechanisms you are likely to meet and few organic chemists can draw it out without looking it up.

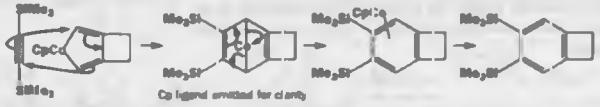
The Vollhardt co-trimerization is so-called because it uses cobalt to bring three alkynes into a ring and it is one of the rare ways of making a benzene ring in one step. First, the dialkyne completes with the cobalt—each alkyne replaces one CO molecule. Then the double π complex rearranges to a double σ complex by a cycloaddition forming a new C–C σ bond. This new five-membered ring cobalt heterocycle has only 16 electrons so it can accept the remaining alkyne to give an 18-electron complex.



There are now two possible routes to the final product. Reductive elimination would insert the new alkyne into one of the old C–Co bonds and form a seven-membered ring heterocycle. This could close in an electrocyclic reaction to give the new six-membered ring with the cobalt fused on one side and hence the cobalt complex of the new benzene.



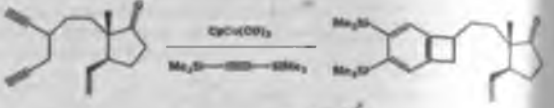
Alternatively, the new alkyne could do a Diels–Alder reaction on the five-membered cobalt heterocycle to give a bridged six-membered ring that could extrude cobalt to give the same benzene complex. The CpCo group can form a stable complex with only four of the benzene electrons and these can be profitably exchanged for two molecules of carbon monoxide to re-form the original catalyst.



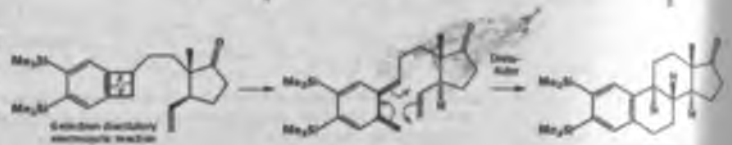
We have selected a few reactions of Co, Fe, and Cu with honourable mentions for Pt, Ir, and Cr. We could have focused on other elements—Ni, W, Ti, Zr, Mn, Ru, and Rh all have special reactions. Transition metal chemistry, particularly involving palladium catalysis, occupies a central role in modern organic synthesis because complex structures can be assembled in few steps with impressive regio- and stereochemical control. There are many books devoted entirely to this subject if you wish to take it further.

Steroid synthesis by the Vollhardt co-trimerization

This product is interesting for two further reactions that revise chemistry from Chapters 36 and 47. If the original acetylene has a special substituent this emerges from the co-trimerization on the five-membered ring.



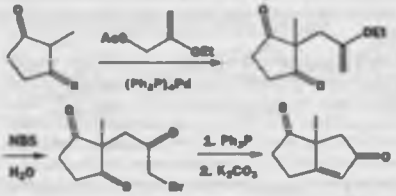
Heating the benzocyclobutene causes an electrocyclic opening (Chapter 36) of the four-membered ring to give a diene that does an intramolecular Diels–Alder rearrangement on the alkene attached to the five-membered ring. The product has the skeleton of the steroids (Chapter 51).



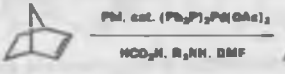
This compound is not a steroid because steroids do not have Me_3Si groups, but these can be removed (Chapter 47) by protodesilylation and this sequence is a very short synthesis of an important compound.

Problems

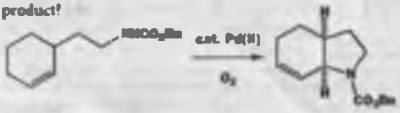
1. Suggest mechanisms for these reactions, explaining the role of palladium in the first step.



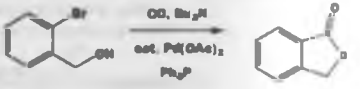
2. This Heck style reaction does not lead to regeneration of the alkene. Why not? What is the purpose of the formic acid (HCO_2H) in the reaction mixture?



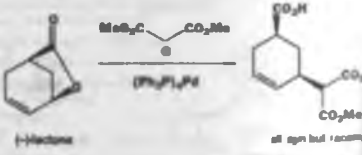
3. Cyclization of this unsaturated amine with catalytic Pd(II) under an atmosphere of oxygen gives a cyclic unsaturated amine in 95% yield. How does the reaction work? Why is the atmosphere of oxygen necessary? Explain the stereo- and regiochemistry of the reaction. How would you remove the CO_2Bn group from the product?



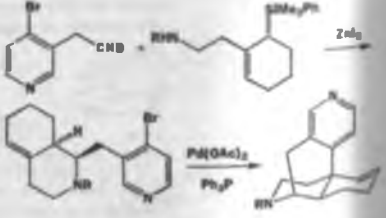
4. Suggest a mechanism for this lactone synthesis.



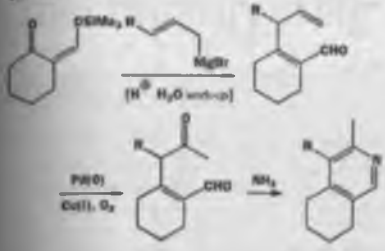
5. Explain why enantiomerically pure lactone gives all syn but racemic product in this palladium-catalysed reaction.



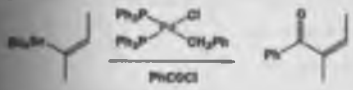
6. Revision of Chapter 47. The synthesis of a bridged tricyclic amine shown below starts with an enantiomerically pure alkyl silane. Give mechanisms for the reactions, explaining how the stereochemistry is controlled in each step.



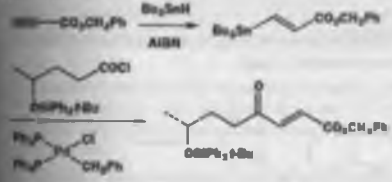
7. Revision of Chapter 44. Explain the reactions in this sequence commenting on the regioselectivity of the organometallic steps.



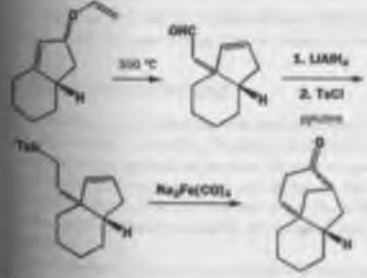
8. Give a mechanism for this carbonylation reaction. Comment on the stereochemistry and explain why the yield is higher if the reaction is carried out under a carbon monoxide atmosphere.



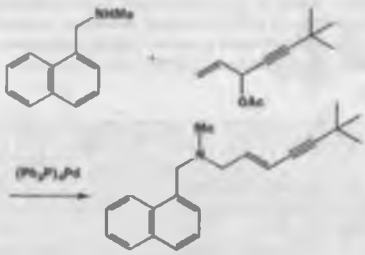
Hence explain this synthesis of part of the antifungal compound pyrenophorin.



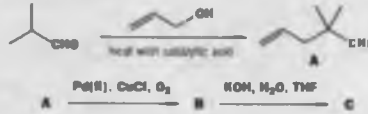
9. Explain the mechanism and stereochemistry of these reactions. The first is revision and the second is rather easy!



10. The synthesis of an antifungal drug was completed by this [illegible]-catalysed reaction. Give a mechanism and explain the [illegible] and stereoselectivity.



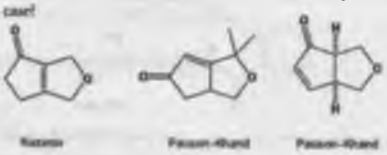
11. Some revision content. Work out the structures of the compounds in this sequence and suggest mechanisms for the reactions, explaining any selectivity.



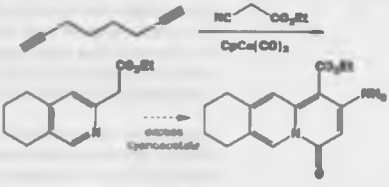
B has IR: 1730, 1710 cm^{-1}; δ_H 9.4 p.p.m. (1H, s), 2.6 p.p.m. (2H, s), 2.0 p.p.m. (3H, s), and 1.0 p.p.m. (6H, s).

C has IR: 1710 cm^{-1}; δ_H 7.3 p.p.m. (1H, d, J 5.5 Hz), 6.8 p.p.m. (1H, d, J 5.5 Hz), 2.1 p.p.m. (2H, s), and 1.15 p.p.m. (6H, s).

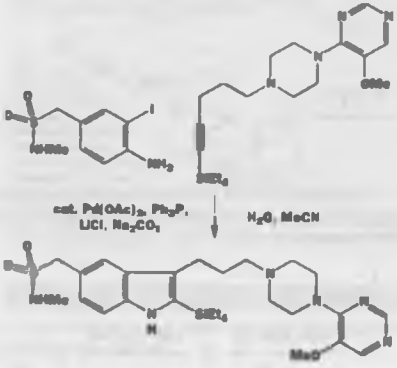
12. Revision of Chapter 36. What would be the starting materials for the synthesis of these cyclopentenones by the Nazarov reaction and by the Pauson–Khand reaction? Which do you prefer in each case?



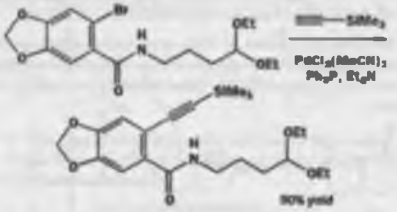
13. A variation on the Vollhardt co-trimerization allows the synthesis of substituted pyridines. Draw the structures of the intermediates in this sequence. In the presence of an excess of the cyanoacetate a second product is formed. Account for this too.



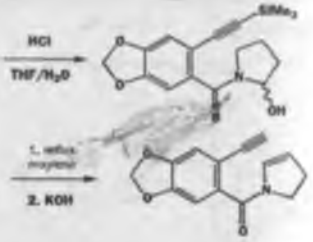
14. The synthesis of the Bristol–Myers Squibb anti-migraine drug Avitriptan (a 5-HT1D receptor antagonist) involves this palladium-catalyzed indole synthesis. Suggest a mechanism and comment on the regioselectivity of the alkyne attachment.



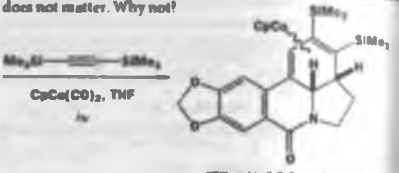
15. A synthesis of the natural product γ-lycorane starts with a palladium-catalyzed reaction. What sort of a reaction is this, and how does it work?



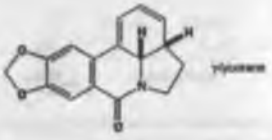
The next two steps are a bit of revision: draw mechanisms for these and comment on the survival of the Me_3Si group.



Now the key step—and you should recognize this easily. What is happening here? Though the product is a mixture of isomers, this does not matter. Why not?



Finally, this mixture must be converted into γ-lycorane. Suggest how this might be done.



The chemistry of life

49

Connections

Building on:

- Acidity and basicity ch8
- Carbonyl chemistry ch12 & ch14
- Stereochemistry ch16
- Conformational analysis ch18
- Enolate chemistry and synthesis ch24 -ch30
- Heterocycles ch42–ch44
- Asymmetric synthesis ch45
- Sulfur chemistry ch46

Arriving at:

- Nucleic acids store information for the synthesis of proteins
- Modified nucleosides can be used as antiviral drugs
- Nucleotides have a role in energy storage
- Proteins catalyse reactions and provide structure
- Other amino acid derivatives act as methylating and reducing agents
- Sugars store energy, enable recognition, and protect sensitive functional groups
- How to make and manipulate sugars and their derivatives
- Lipids form the basis of membrane structures

Looking forward to:

- Mechanisms in biological chemistry ch50
- Natural products ch51
- Polymers ch52

Life runs on chemistry, and the chemical side of biology is fascinating for that reason alone. But from the point of view of a textbook, biological chemistry's combination of structures, mechanisms, new reactions, and synthesis is also an ideal revision aid. We shall treat this chemistry of living things in three chapters

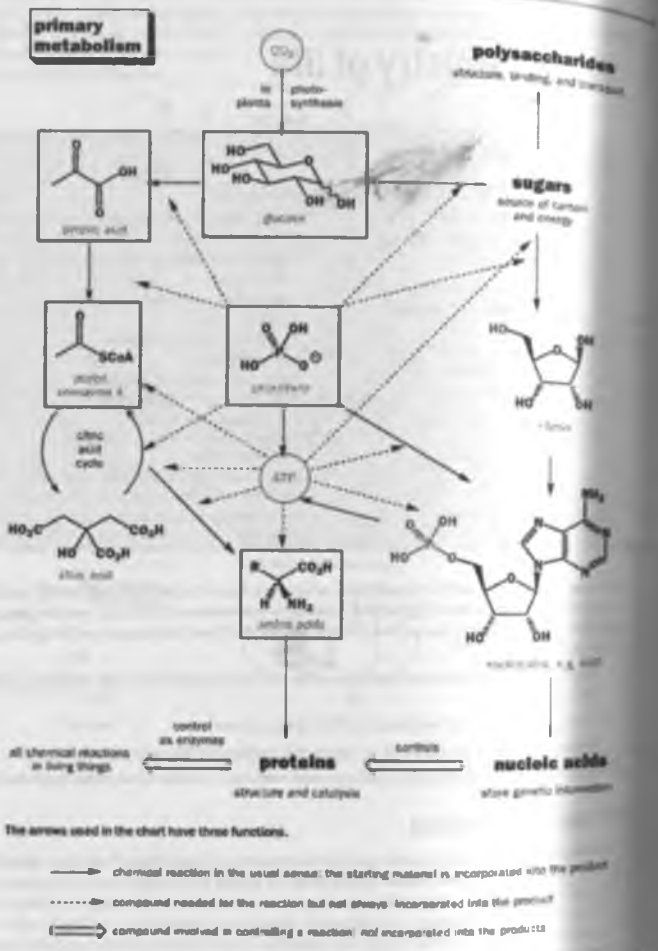
- Chapter 49 introduces the basic molecules of life and explains their roles along with some of their chemistry
- Chapter 50 discusses the mechanisms of biological reactions
- Chapter 51 develops the chemistry of compounds produced by life: natural products

We start with the most fundamental molecules and reactions in what is called primary metabolism.

Primary metabolism

It is humbling to realize that the same molecules are present in all living things from the simplest single-cell creatures to ourselves. Nucleic acids contain the genetic information of every organism, and they control the synthesis of proteins. Proteins are partly structural—as in connective tissue—and partly functional—as in enzymes, the catalysts for biological reactions. Sugars and lipids used to be the poor relations of the other two but we now realize that, as well as having a structural role in membranes, they are closely associated with proteins and have a vital part to play in recognition and transport.

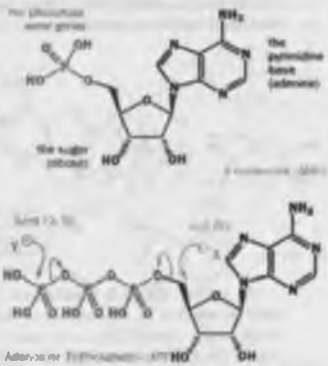
The chart overleaf shows the molecules of primary metabolism and the connections between them, and needs some explanation. It shows a simplified relationship between the key structures (emphasized in large black type). It shows their origins—from CO_2 in the first instance—and picks out some important intermediates. Glucose, pyruvic acid, citric acid, acetyl coenzyme A (Acetyl CoA), and ribose are players on the centre stage of our metabolism and are built into many important molecules.



We hope that this chart will allow you to keep track of the relationships between the molecules of metabolism as you develop a more detailed understanding of them. We will now look briefly at each type of molecule.

Life begins with nucleic acids

Nucleic acids are unquestionably top level molecules because they store our genetic information. They are polymers whose building blocks (monomers) are the nucleotides, themselves made of three parts—a heterocyclic base, a sugar, and a phosphate ester. A nucleoside lacks the phosphate. In the example alongside, adenine is the base (black), adenosine is the nucleoside (base and sugar), and the nucleotide is the whole molecule (base + sugar + phosphate).



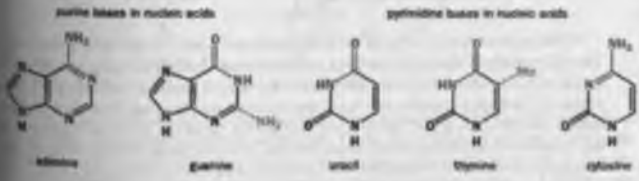
This nucleotide is called AMP—Adenosine MonoPhosphate. Phosphates are key compounds in nature because they form useful stable linkages between molecules and can also be built up into reactive molecules by simply multiplying the number of phosphate residues. The most important of these nucleotides is also one of the most important molecules in nature—Adenosine TriPhosphate or ATP.

ATP is a highly reactive molecule because phosphates are stable anions and good leaving groups. It can be attacked by hard nucleophiles at a phosphate group (usually the end one) or by soft nucleophiles at the CH_2 group on the sugar. We shall see examples of both reactions soon. When a new reaction is initiated in nature, very often the first step is a reaction with ATP to make the compound more reactive. This is rather like our use of TsCl to make alcohols more reactive or converting acids to acid chlorides to make them more reactive.

There are five heterocyclic bases in DNA and RNA

In nucleic acids there are only five bases, two sugars, and one phosphate group possible. The bases are monocyclic pyrimidines or bicyclic purines and are all aromatic.

- There are only two purine bases found in nucleic acids, adenine (A), which we have already met, and guanine (G)
- The three pyrimidine bases are the simpler and they are uracil (U), thymine (T), and cytosine (C). Cytosine is found in DNA and RNA, uracil in RNA only, and thymine in DNA only.

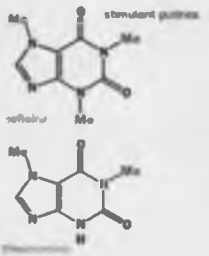


■
You met pyrimidines on p. 000 and learned how to make them on p. 000. But the purine ring system may be new to you. It isn't always easy to find the ten or ten electrons in these compounds. Check for yourself that you can do this. You may need to draw delocalized structures essentially for U, T, and G.

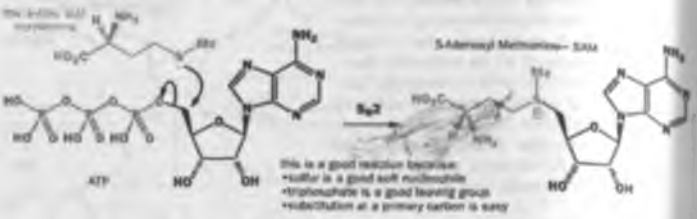
The stimulants in tea and coffee are methylated nucleic acid purines

An important natural product for most of us is a fully methylated purine present in tea and coffee—caffeine. Theobromine, the partly methylated version, is present in chocolate, and both caffeine and theobromine act as stimulants. Caffeine is a crystalline substance easily extracted from coffee or tea with organic solvents. It is extracted industrially with liquid CO_2 (or if you prefer 'Nature's natural effervescence') to make decaffeinated tea and coffee.

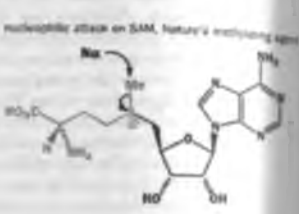
If we, as chemists, were to add those methyl groups we should use something like MeI, but Nature uses a much more complicated reagent. There is a great deal of methylating going on in living



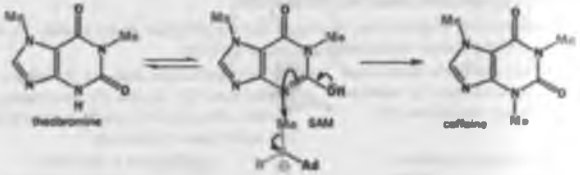
things—and the methyl groups are usually added by *S*-adenosyl methionine (or SAM), formed by reaction of methionine with ATP.



The product (SAM) is a sulfonium salt and could be attacked by nucleophiles at three different carbon atoms. Two are primary centres —good for S_N2 reactions—but the third is the methyl group, which is even better. Many nucleophiles attack SAM in this way.



In the coffee plant, theobromine is converted into caffeine with a molecule of SAM. The methylation occurs on nitrogen partly because this preserves both the aromatic ring and the amide functionality and also because the enzyme involved brings the two molecules together in the right orientation for *N*-methylation.



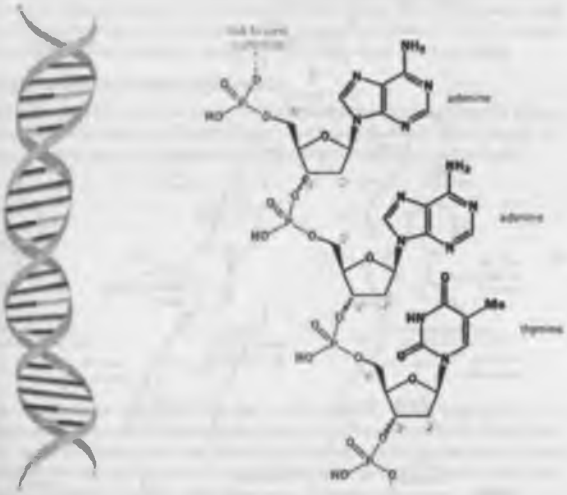
At this point we should just point out something that it's easy to forget: there is *only one chemistry*. There is no magic in biological chemistry, and Nature uses the same chemical principles as we do in the chemical laboratory. All the mechanisms that you have studied so far will help you to draw mechanisms for biological reactions and most reactions that you have met have their counterparts in nature. The difference is that Nature is very very good at chemistry, and all of us are only just learning. We still do much more sophisticated reactions *inside* our bodies without thinking about them than we can do *outside* our bodies with all the most powerful ideas available to us at the beginning of the twenty-first century.

Nucleic acids exist in a double helix

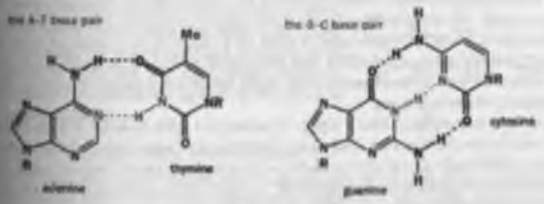
One of the most important discoveries of modern science was the elucidation of the structures of DNA and RNA as the famous double helix by Watson and Crick in 1953. They realized that the basic structure of base–sugar–phosphate was ideal for a three-dimensional coil. The structure of a small part of DNA is shown opposite.

Notice that the 2′ (pronounced 'two prime') position on the ribose ring is vacant. There is no OH group there and that is why it is called *Deoxy*ribo-Nucleic Acid (DNA). The nucleotides link the two

remaining OH groups on the ribose ring and these are called the 5'- and 5'-positions. This piece of DNA has three nucleotides (adenine, adenine, and thymine) and so would be called –AAT– for short.



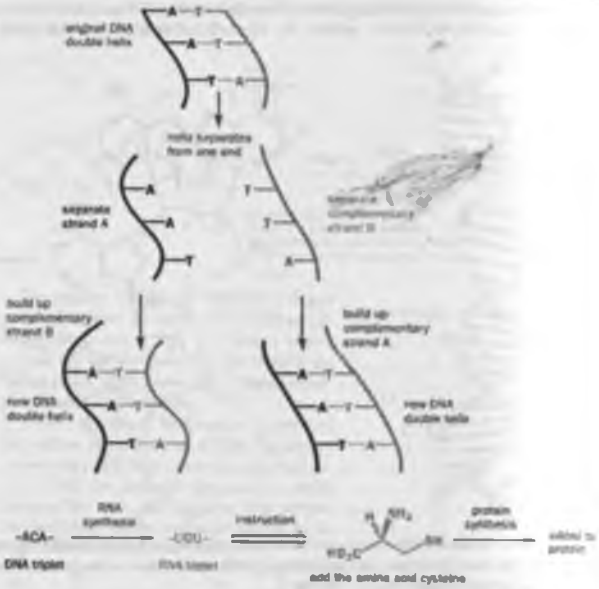
Each polymeric strand of DNA coils up into a helix and is bonded to another strand by hydrogen bonds between the bases. Each base pairs up specifically with another base —adenine with thymine (A–T) and guanine with cytosine (G–C)—like this.



There is quite a lot to notice about these structures. Each purine (A or G) is bonded specifically to one pyrimidine (T or C) by two or by three hydrogen bonds. The hydrogen bonds are of two kinds: one links an amine to a carbonyl group (black in the diagram) and one links an amine to an imine (green in the diagram). In this way, each nucleotide reliably recognizes another and reliably pairs with its partner. The short strand of DNA above (–ATT–) would pair reliably with –TTA–.

How the genetic information in DNA is passed to proteins

In the normal structure of DNA each strand is paired with another strand called the complementary strand because it has each base paired with its complementary base. When DNA replicates, the strands separate and a new strand with complementary structure grows alongside each. In this way the original double helix now becomes two identical double helices and so on.



This is a crude simplification of a beautiful process and you should turn to a biochemistry textbook for more details. The actual building up of a strand of DNA obviously involves a complex series of chemical reactions. The DNA is then used to build up a complementary strand of RNA, which does have the 2' hydroxyl group, and the RNA then instructs the cell on protein synthesis using three-nucleotide codes to indicate different amino acids. Again, the details of this process are beyond the scope of this book, but the code is not.

Each set of three nucleotides (called a triplet or codon) in a DNA molecule tells the cell to do something. Some triplets tell it to start work or stop work but most represent a specific amino acid. The code UGU in RNA tells the cell 'add a molecule of cysteine to the protein you are building'. The code UGA tells the cell 'stop the protein at this point'. So a bit of RNA reading UGUUGA would produce a protein with a molecule of cysteine at the end.

There are four bases available for DNA and so there are $4^3 = 64$ different triplet codons using three bases in each codon. There are only 20 amino acids used in proteins so that gives plenty of spare codons. In fact 61 of the 64 are used as codons for amino acids and the remaining three are 'stop' signals. Thus the code ATT in DNA would produce the complementary UAA and this is another 'stop' signal.

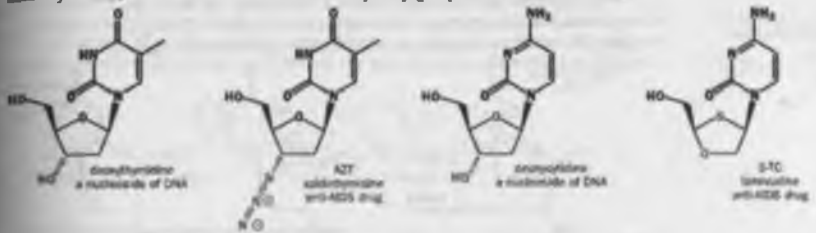
Base	Complementary base in DNA	Complementary base in RNA
A	T	U
C	G	G
G	C	C
U	*	*
T	A	*

* T occurs in DNA only and is replaced by U in RNA.

But that doesn't leave a 'start' signal! This signal is the same (TAC in DNA = AUG in RNA) as that for the amino acid methionine, which you met as a component of SAM, the biological methylating agent. In other words, all proteins start with methionine. At least, they are all made that way, though the methionine is sometimes removed by enzymes before the protein is released. These code letters are the same for all living things except for some minor variations in some microorganisms.

AIDS is being treated with modified nucleosides

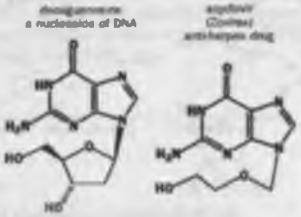
Modified nucleosides have proved to be among the best antiviral compounds. The most famous anti-AIDS drug, AZT (zidovudine from GlaxoWellcome), is a slightly modified DNA nucleoside (3'-azidothymidine). It has an azide at C3' instead of the hydroxyl group in the natural nucleoside.



Doctors are having some spectacular success at the moment (1998) against HIV and AIDS by using a combination of AZT and a much more modified nucleoside 3-TC (lamivudine) which is active against AZT-resistant viruses. This drug is based on cytosine but the sugar has been replaced by a different heterocycle though it is recognizably similar especially in the stereochemistry.

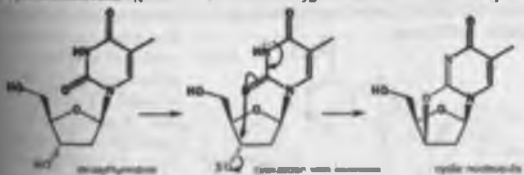
The last drug to mention is acyclovir (Zovirax), the cold sore (herpes) treatment. Here is a modified guanosine in which only a ghost of the sugar remains. There is no ring at all and no stereochemistry.

The bottom edge of the sugar ring has been done away with so that a simple alkyl chain remains. This compound has proved amazingly successful as an antiviral agent and it is highly likely that more modified nucleosides will appear in the future as important drugs.

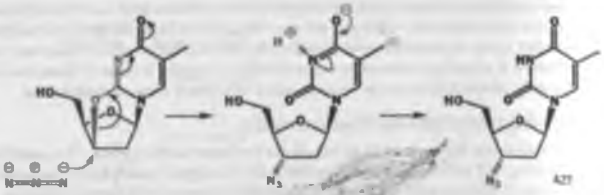


Cyclic nucleosides and stereochemistry

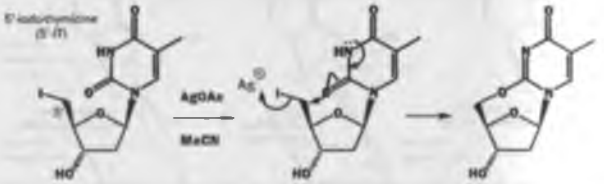
We know the relative stereochemistry around the ribose ring of the nucleosides in DNA and RNA because the bases can be persuaded to cyclize on to the ring in certain reactions. Treatment of deoxythymidine with reagents that make oxygen atoms into leaving groups leads to cyclization by intramolecular S_N2 reaction. The amide oxygen of the base attacks the 3'-position in the sugar ring.



This S_N2 reaction has to happen with inversion, proving that the base and the 3'-OH group are on opposite sides of the ribose ring. The cyclized product is useful too. If it is reacted with azide ion the ring reopens with inversion in another S_N2 reaction and AZT is formed.

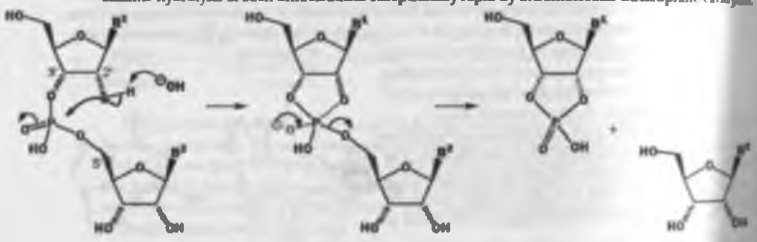


We can show that the primary alcohol is on the same side of the ring as the base by another cyclization reaction. Treatment of the related iodide with a silver(I) salt gives a new seven-membered ring. This reaction can happen only with this stereochemistry of starting material.



In ribonucleic acids, the fact that the 2′- and 3′-OH groups are on the same side of the ring makes alkaline hydrolysis of such dinucleotides exceptionally rapid by intramolecular nucleophilic catalysis.

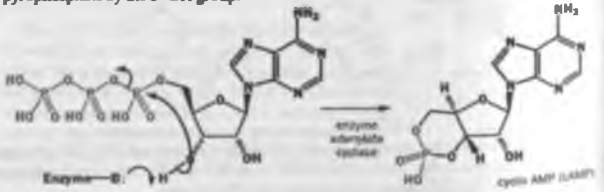
■ The substituents B^1 and B^2 represent any purine or pyrimidine base.



The alkali removes a proton from the 2′-OH group, which cyclizes on to the phosphate link—possible only if the ring fusion is *cis*. The next reaction involves breakdown of the pentacovalent phosphorus intermediate to give a cyclic phosphate. One nucleoside is released by this reaction and the second follows when the cyclic phosphate is itself cleaved by alkali.

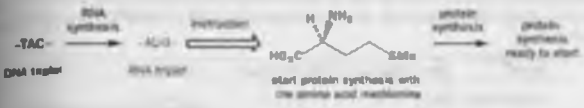
The simplest cyclic phosphate that can be formed from a nucleotide is also important biologically as it is a messenger that helps to control such processes as blood clotting and acid secretion in the stomach. It is cyclic AMP (cAMP), formed enzymatically from ATP by nucleophilic displacement of pyrophosphate by the 3′-OH group.

▶ Note that cAMP has a trans 6,5-fused ring junction.



Proteins are made of amino acids

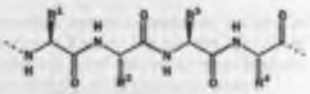
The molecule of methionine, which we met as a component of SAM, is a typical amino acid of the kind present in proteins. It is the starter unit in all proteins and is joined to the next amino acid by an amide bond. In general, we could write:



Now we can add the next amino acid using its correct codon, but we want to show the process in general so we shall use the general structure in the margin. All amino acids have the same basic structure and differ only in the group 'R'. Both structures are the same and have the same (*S*) stereochemistry.

two views of the general amino acid structure

The process then continues with more amino acids added in turn to the right-hand end of the growing molecule. A section of the final protein drawn in a more realistic conformation might look like this.



The basic skeleton of the protein zig-zags up and down in the usual way; the amide bonds (shown in black) are rigid because of the amide conjugation and are held in the shape shown. Each amino acid may have a different substituent (R^1, R^2, R^3, etc.) or some may be the same.

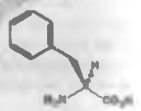
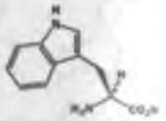
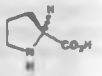
A catalogue of the amino acids

So what groups are available when proteins are being made? The simplest amino acid, glycine, has no substituents except hydrogen and is the only amino acid that is not chiral. Four other amino acids have alkyl groups without further functionality. The next table gives their structures together with two abbreviations widely used for them. The three-letter code (which has nothing to do with the codon in DNA!) is almost self-explanatory as are the one-letter codes in this group, but some of the one-letter codes for the other amino acids are not so obvious.

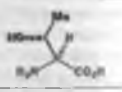
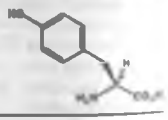
Name	Three-letter code	One-letter code	Structure
glycine	Gly	G	
alanine	Ala	A	
valine	Val	V	
leucine	Leu	L	
isoleucine	Ile	I	

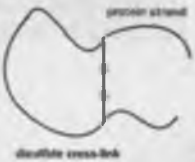
▶ Many of the compounds we discuss in this chapter will be salts under biological conditions. Most carboxylic acids will exist as anions, as will the phosphates you have just seen, and most amines as cations as they would be protonated at pH 7. Amino acids exist in biological systems as zwitterions. For simplicity, we will usually draw functional groups in the simplest and most familiar way, leaving the question of protonation to be addressed separately if required.

These amino acids form hydrophobic (water-repelling) nonpolar regions in proteins. There are three more of this kind with special roles. Phenylalanine and tryptophan have aromatic rings and, though they are still hydrophobic, they can form attractive π-stacking interactions with other aromatic molecules. Enzyme-catalysed hydrolysis of proteins often happens next to one of these residues. Proline is very special. It has its amino group inside a ring and has a different shape from all the other amino acids. It appears in proteins where a bend or a twist in the structure is needed.

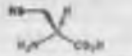
Name	Three-letter code	One-letter code	Structure
phenylalanine	Phe	F	
tryptophan	Trp	W	
proline	Pro	P	

The rest of the amino acids have functional groups of various kinds and we shall deal with them by function. The simplest have hydroxyl groups and there are three of them—two alcohols and a phenol. Serine in particular is important as a reactive group in enzymatic reactions. It is a good nucleophile for carbonyl groups.

Name	Three-letter code	One-letter code	Structure
serine	Ser	S	
threonine	Thr	T	
tyrosine	Tyr	Y	



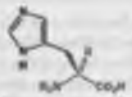
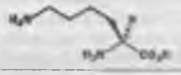
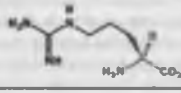
Next come the two compounds we have already met, the sulfur-containing cysteine and methionine. Cysteine has a thiol group and methionine a sulfide. These are very important in protein structure—methionine starts off the synthesis of every new protein as its N-terminal amino acid, while cysteine forms S–S bridges linking two parts of a protein together. These disulfide links may be important in holding the three-dimensional shape of the molecule.

Name	Three-letter code	One-letter code	Structure
cysteine	Cys	C	
methionine	Met	M	

Cysteine and hairdressing

Thiols (RSH) are easily oxidized, by air, for example, to disulfides (RS–SR). This chemistry of cysteine is used by hairdressers to give 'perms' or permanent waves. The hair proteins are first reduced so that any disulfide (cystine to systeine) cross-links within each strand are reduced to thiols. Then the hair is styled and the final stage is the 'set' when the hair is oxidized so that disulfide cross-links are established to hold its shape for a good long time. The disulfide resulting from cross-links between the thiol groups of cysteine is known as cystine – beware of confusing the names!

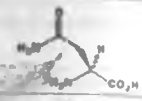
The amino acids with a second amino group are important because of their basicity and they are vital to the catalytic activity of many enzymes. Histidine has a pK_aH very close to neutrality (6.5) and can function as an acid or a base. Lysine and arginine are much more basic, but are normally protonated in living things. An extra column in this table gives the pK_aH of the extra amino groups.

Name	Three-letter code	One-letter code	pK_{aH}	Structure
histidine	His	H	6.5	
lysine	Lys	K	10.0	
arginine	Arg	R	12.0	

Essential amino acids

If you saw 'Jurassic Park' you may recall that the brilliant device was the 'lysine option'. The dinosaurs were genetically modified so as to need lysine in their diet. The idea was that they would die unless lysine was provided by their keepers. Lysine was a good choice as it is one of the 'essential' amino acids for humans. If we are not given it in our diet, we die. Of course, any normal diet, including the human beings eaten by the escaped dinosaurs, would also contain plenty of lysine. The other essential amino acids (for humans) are His, Ile, Leu, Met, Phe, Thr, Trp, and Val.

Finally, we come to the acidic amino acids—those with an extra carboxylic acid group. We are going to include their amides too as they also occur in proteins. This group is again very much involved in the catalytic activity of enzymes. The two acids have pK_as for the extra CO_2H group of about 4.5.

Name	Three-letter code	One-letter code	Structure
aspartic acid	Asp	D	
asparagine	Asn	N	
glutamic acid	Glu	E	
glutamine	Gln	Q	

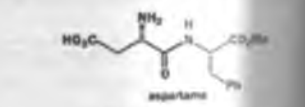
Sometimes it is not known whether the acids or their amides are present and sometimes they are present interchangeably. Aspartic acid or asparagine has the codes Asx and B while glutamic acid or glutamine is Glx or Z.

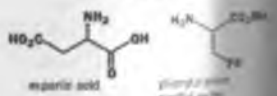
Now perhaps you can see that a protein is an assembly of many different kinds of group attached to a polyamide backbone. Some of the groups are purely structural, some control the shape of the protein, some help to bind other molecules, and some are active in chemical reactions.

Most amino acids are readily available to chemists. If proteins are hydrolysed with, say, concentrated HCl, they are broken down into their amino acids. This mixture is tricky to separate, but the acidic ones are easy to extract with base while the aromatic ones crystallize out easily.

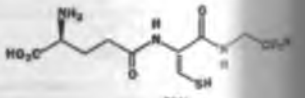
Amino acids combine to form peptides and proteins

In nature, the amino acids are combined to give proteins with hundreds or even thousands of amino acids in each one. Small assemblies of amino acids are known as **peptides** and the amide bond that links them is called a **peptide bond**. One important dipeptide is the sweetening agent aspartame, whose synthesis was discussed in Chapter 25. It is composed (and made) of the amino acid aspartic acid (Asp) and the methyl ester of phenylalanine. Only this enantiomer has a sweet taste and it is very sweet indeed—about 180 times as sweet as sucrose. Only a tiny amount is needed to sweeten drinks and so it is much less fattening than sucrose and is 'safe' because it is degraded in the body to Asp and Phe, which are there in larger amounts anyway.

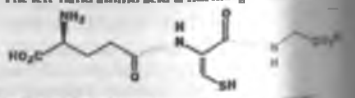

aspartame


aspartic acid

An important tripeptide is **glutathione**. So important is this compound that it is present in almost all tissues of most living things. It is the 'universal thiol' that removes dangerous oxidizing agents by allowing itself to be oxidized to a disulfide.

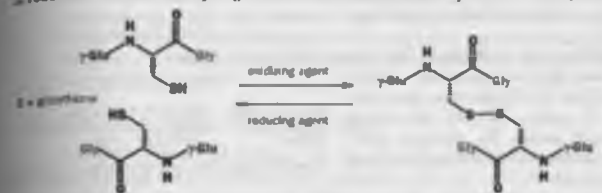

glutathione = RSH

Glutathione is not quite a simple tripeptide. The left-hand amino acid is normal glutamic acid but it is joined to the next amino acid through its γ-CO_2H group instead of the more normal α-CO_2H group. The middle amino acid is the vital one for the function—cysteine with a free SH group. The *C*-terminal acid is glycine.

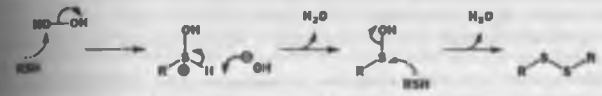

γ-Glu (glutamic acid joined through its γ-CO_2H group)

cysteine

Thiols are easily oxidized to disulfides, as we have already seen in our discussion on hairdressing (though the redox chemistry of glutathione is a matter of life or death and not merely a bad hair day), and glutathione sacrifices itself if it meets an oxidizing agent. Later, the oxidized form of glutathione is reduced back to the thiol by reagents we shall meet in the next chapter (NADH, etc.).



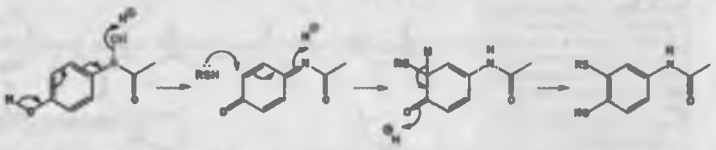
If we imagine that the stray oxidizing agent is a peroxide, say, H_2O_2, we can draw a mechanism to show how this can be reduced to water as glutathione (represented as RSH) is oxidized to a disulfide.



Paracetamol overdoses

Paracetamol is a popular and safe analgesic if used properly but an overdose is insidiously dangerous. The patient often seems to recover only to die later from liver failure. The problem is that paracetamol is metabolized into an oxidizing compound that destroys glutathione.

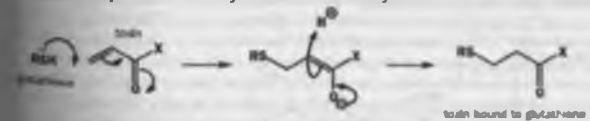

paracetamol



Glutathione intercepts this oxidizing agent by a most unusual mechanism. The glutathione rearrangement loses water to give a quinone imine which is attacked by glutathione on the aromatic ring. The product is stable and safe but, for every molecule of glutathione is consumed.

There is no problem if a normal dose is taken—there is plenty of glutathione to deal with that. But if an overdose is taken, all the glutathione may be used up and irreversible liver damage occurs.

Glutathione also detoxifies some of the compounds we have earlier described as very dangerous carcinogens such as Michael acceptors and 2,4-dinitrohalobenzenes. In both cases the thiol acts as a nucleophile for these electrophiles. Most of the time there is enough glutathione present in our cells to attack these poisons before they attack DNA or an enzyme.



The toxin is now covalently bound to glutathione and so is no longer electrophilic. It is harmless and can be excreted. More glutathione will be synthesized from glutamic acid, cysteine, and glycine to replace that which is lost.

Proteins are Nature's chemical laboratories

Longer peptides are called proteins, though where exactly the boundary occurs is difficult to say.

The structure of the hormone insulin (many diabetics lack this hormone and must inject themselves with it daily) was deduced in the 1950s by Sanger. It has two peptide chains, one of 21 amino acids and one of 30, linked by three disulfide bridges—just like the links in oxidized glutathione. This is a very small protein.

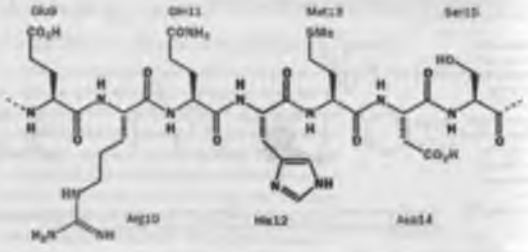
Enzymes are usually bigger. One of the smaller enzymes—ribonuclease (which hydrolyses RNA) from cows—has a chain of 124 amino acids with four internal disulfide bridges. The abundance of the various amino acids in this enzyme is given in this table.

Type	Amino acid (number)*	Total
structural	A (12), F (3), M (4), L (2), P (4), V (9), G (3), I (3)	40
cross-linking	C (8)	8
basic	K (10), R (4), H (4)	18
acids and amides	E (5), Q (7), D (5), N (10)	27
hydroxyl	T (10), S (15), Y (6)	31

* See notes earlier in this section for one-letter codes of amino acids.

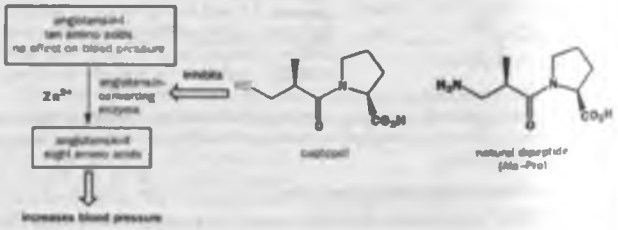
There are 48 structural and cross-linking amino acids concerned with the shape of the protein but over half of the amino acids have functional groups sticking out of the chain—amino, hydroxy, acid groups, and the like. In fact, the enzyme uses only a few of these functional groups in the reaction it catalyses (the hydrolysis of RNA)—probably only two histidines and one lysine—but it is typical of enzymes that they have a vast array of functional groups available for chemical reactions.

Below is part of the structure of ribonuclease surrounding one of the catalytic amino acids (His12). There are seven amino acids in this sequence. Every one is different and every one has a functionalized side chain. This is part of a run of ten amino acids between Phe8 and Ala19. This strip of peptide has six different functional groups (two acids, one each of amide, guanidine, imidazole, sulfide, and alcohol) available for chemical reactions. Only the histidine is actually used.

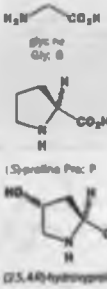


▶ Proteins are conventionally drawn and described with the amino (N) terminus to the left and the carboxyl (C) terminus to the right. This section of ribonuclease would be called 'glutamyl arginyl glutaminyl histidyl methionyl aspartyl seryl…' or, more briefly, –Glu–Arg–Gln–His–Met–Asp–Ser– or, more briefly still, –ERQHMDS–. The numbers on the diagram such as 'Glu9' tell us that this glutamic acid residue is number 9 from the N-terminus.

One reason for disease is that enzymes may become overactive and it may be necessary to design specific inhibitors for them to treat the disease. Angiotensin-Converting Enzyme (ACE) is a zinc-dependent enzyme that cleaves two amino acids off the end of angiotensin I to give angiotensin II, a protein that causes blood pressure to rise.



It is necessary in some situations for our blood pressure to rise (when we stand up for instance!) but too much too often is a very bad thing leading to heart attacks and strokes. Captopril is a treatment for high blood pressure called an 'ACE inhibitor' because it works by inhibiting the enzyme. It is a dipeptide mimic, having one natural amino acid and something else. The 'something else' is an SH group replacing the NH_2 group in the natural dipeptide. Captopril binds to the enzyme because it is *like* a natural dipeptide but it inhibits the enzyme because it is *not* a natural dipeptide. In particular, the SH group is a good ligand for Zn(II). Many people are alive today because of this simple deception practised on an enzyme.



Structural proteins must be tough and flexible

In contrast with the functional enzymes, there are purely structural proteins such as collagen. Collagen is the tough protein of tendons and is present in skin, bone, and teeth. It contains large amounts of glycine (every third amino acid is glycine), proline, and hydroxyproline (again about a third of the amino acids are either Pro or Hyp).

In the enzyme above there were only three glycines and four prolines and no hydroxyproline at all. Hydroxyproline is a specialized amino acid that appears almost nowhere else and, along with proline, it establishes a very strong triply coiled structure for collagen. The glycine is necessary as there is no room in the inside of the triple coil for any larger amino acid. Functionalized amino acids are rare in collagen.

Hydroxyproline and scurvy

Hydroxyproline is a very unusual amino acid. There is no genetic codon for the insertion of Hyp into a growing polypeptide: human collagen is not made that way. The collagen molecule is first assembled with Pro where Hyp ends up. Then some proline residues are oxidized to hydroxyproline. This oxidation requires vitamin C, and without it collagen cannot be formed. This is why vitamin C deficiency causes scurvy – the symptoms of scurvy (teeth falling out, sores, blisters) are caused by the inability to make collagen.

Proteins are enormously diverse in structure and function and we will be looking at a few of their reactions in the next chapter.

Sugars—just energy sources?

Sugars are the building blocks of carbohydrates. They used to be thought of as essential but rather dull molecules whose *only* functions were the admittedly useful provision of energy and cell wall construction. We have already noted that ribose plays an intimate role in DNA and RNA structure and function. More recently, biochemists have realized that carbohydrates are much more exciting. They are often found in intimate association with proteins and are involved in recognition of one protein by another and in adhesion processes.

That may not sound very exciting, but take two examples. How does a sperm recognize the egg and penetrate its wall? The sperm actually binds to a carbohydrate on the wall of the egg in what was the first event in all of our lives. Then how does a virus get inside a cell? If it fails to do so, it has no life. Viruses depend on host cells to reproduce. Here again, the recognition process involves specific carbohydrates. One of the ways in which AIDS is being tackled with some success is by a combination of the antiviral drugs we met earlier in this chapter with HIV protease inhibitor drugs, which also to prevent recognition and penetration of cells by HIV.

We now know that many vital activities as diverse as healing, blood clotting, infection, prevention of infection, and fertilization all involve carbohydrates. Mysterious compounds such as 'sialyl Lewis-X', unknown a few years ago, are now known to be vital to our health and happiness. Far from being dull, carbohydrates are exciting molecules and our future depends on them. It is well worthwhile to spend some time exploring their structure and chemistry.

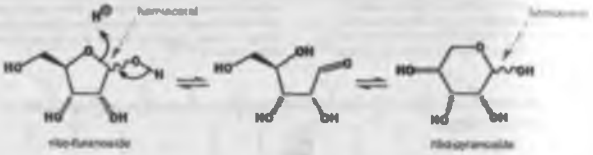
Sugars normally exist in cyclic forms with much stereochemistry

The most important sugar is glucose. It has a saturated six-membered ring containing oxygen and it is best drawn in a chair conformation with nearly all the substituents equatorial. It can also be drawn reasonably as a flat configurational diagram.

We have already met one sugar in this chapter, ribose, because it was part of the structure of nucleic acids. This sugar is a five-membered saturated oxygen heterocycle with many OH groups. Indeed, you can define a sugar as an oxygen heterocycle with every carbon atom bearing an oxygen-based functional group—usually OH, but alternatively C=O.

Both our drawings of glucose and ribose show a number of stereogenic centres and one centre undefined—the OH group is marked with a wavy line. This is because one centre in both sugars is a hemiacetal and therefore the molecule is in equilibrium with an open-chain hydroxy-aldehyde. For glucose, the open-chain form is this.

When the ring closes again, any of the OH groups could cyclize on to the aldehyde but there is no real competition—the six-membered ring is more stable than any of the alternatives (which could have three-, four-, five-, or seven-membered rings—check for yourself). However, with ribose there is a reasonable alternative.

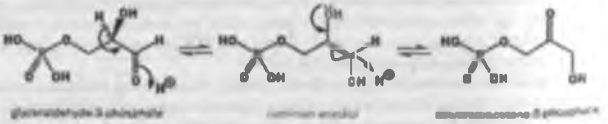


The most important sugars may exist in an open-chain form, as a five-membered oxygen heterocycle (called a furanoside after the aromatic furan) or a six-membered oxygen heterocycle (called a pyranoside after the compound pyran).

From triose to glucose requires doubling the number of carbon atoms

We will return to that in a moment, but let us start from the beginning. The simplest possible sugar is glyceraldehyde, a three-carbon sugar that cannot form a cyclic hemiacetal.

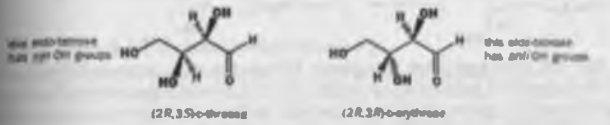
Glyceraldehyde is present in cells as its phosphate which is in equilibrium with dihydroxyacetone phosphate. This looks like a complicated rearrangement but it is actually very simple—the two compounds have a common enol through which they interconvert.



Glyceraldehyde is an aldehyde sugar or aldose and dihydroxyacetone is a keto-sugar or ketose. That ending '-ose' just refers to a sugar. These two molecules combine to form the six-carbon sugar

fructose. In living things and this reaction is a key step in the synthesis of organic compounds from CO_2 in plants.

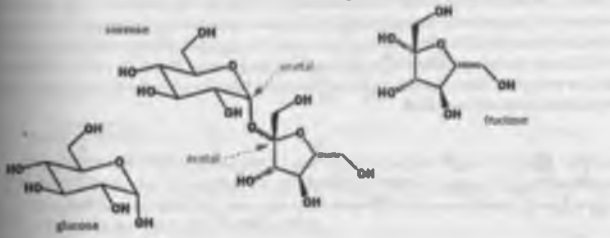
When we come to the four-carbon sugars, or tetroses, two are important. They are diastereoisomers called erythrose and threose. You can see from this series that each aldose has $n - 2$ stereogenic centres in its carbon chain where n is the total number of carbon atoms in that chain.



(2*R*,3*S*)-D-threose (2*R*,3*R*)-D-erythrose

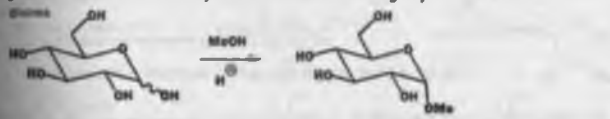
■ These sugars first have given their names to a stereochemical designation—'erythro' and 'threo'—are used to describe diastereoisomers that resemble these two sugars. We do not use these rather ambiguous terms in this book, preferring more precise or vivid terms such as *R,R* or *anti* as appropriate.

We shall take a longer look at the stereochemistry and reactions of glucose and the important keto-hexose, fructose. These two are often found together in cells and are combined in the same molecule as sucrose—ordinary sugar. In this molecule, glucose appears as a pyranose (six-membered ring) and fructose as a furanose (five-membered ring). They are joined through an acetal at what were hemiacetal positions, and sucrose is a single diastereoisomer.



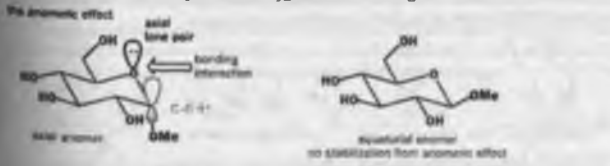
Sugars can be fixed in one shape by acetal formation

This is the simplest way to fix glucose in the pyranose form—any alcohol, methanol, for example, gives an acetal and, remarkably, the acetal has an *axial* OR group.



Acetal formation is under thermodynamic control (Chapter 14) so the axial compound must be the more stable. This is because of the anomeric effect—so called because this C atom is called the anomeric position and the acetal diastereoisomers are called anomers. The effect is a bonding interaction between the axial lone pair on the oxygen atom in the ring and the σ* orbital of the OMe group.

■ The anomers often have anomers in Chapter 42, and you should check that you can still write down the mechanism of acetal formation you learned in Chapter 14.

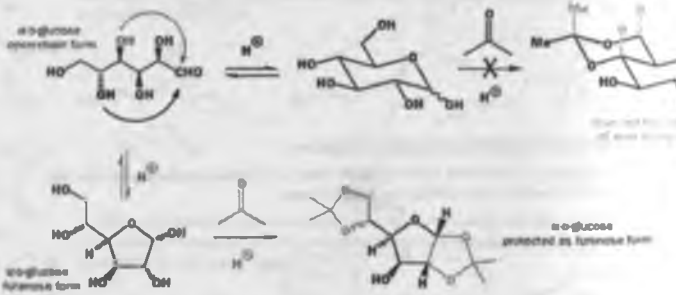


The formation of acetals allows a remarkable degree of control over the chemistry of sugars. Apart from the simple glucoside acetal we have just seen, there are three important acetals worth understanding because of the way in which they illustrate stereoelectronic effects—the interplay of

stereochemistry and mechanism. If we make an acetal from methyl glucoside, we get a single compound as a single stereoisomer.

The new acetal could have been formed between any of the adjacent OH groups in the starting material but it chose the only pair (the black OH groups) to give a six-membered ring. The stereochemistry of glucose is such that the new six-membered ring is *trans*-fused on the old so that a beautifully stable all-chair bicyclic structure results, with the phenyl group in an equatorial position in the new chair acetal ring. It does not matter which OH group adds to benzaldehyde first because acetal formation is under thermodynamic control and this product is the most stable possible acetal.

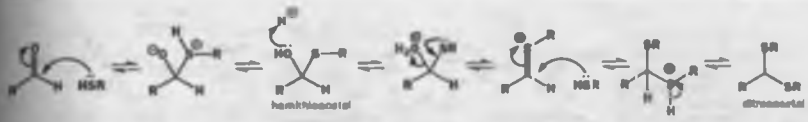
Acetals formed from sugars and acetone have a quite different selectivity. For a start, cyclic acetals of acetone prefer to be five- rather than six-membered rings. In a six-membered ring, one of the acetone's methyl groups would have to be axial, so the five-membered ring is preferred. A 5/5 or 5/6 ring fusion is more stable if it is *cis*, and so acetone acetals ('acetonides') form preferentially from *cis* 1,2-diols. Glucose has no neighbouring *cis* hydroxyls in the pyranose form, but in the furanose form it can have two pairs. Formation of an acetal with acetone fixes glucose in the furanose form. This is all summarized in the scheme below.



The open-chain form of glucose is in equilibrium with both pyranose and furanose forms by hemiacetal formation with the black and green OH groups, respectively. Normally, the pyranose form is preferred, but the furanose form can form a double acetal with acetone, one acetal having *cis*-fused 5/5 rings and the other being on the side chain. This is the product.

If we want to fix glucose in the open-chain form, we must make an 'acetal' of quite a different kind using a thiol (RSH) instead of an alcohol, an aldehyde, or a ketone.

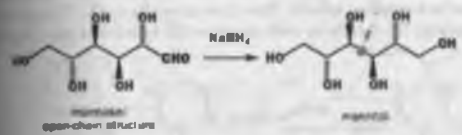
The thiol combines with the aldehyde group of the open-chain form to give a stable dithioacetal. The dithioacetal is evidently more stable than the alternative hemiacetals or monothioacetals that could be formed from the pyranose or furanose forms.

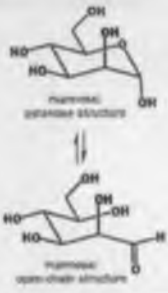


Sugar alcohols are important in food chemistry

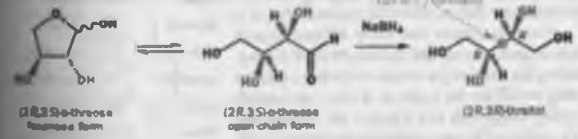
Another reaction of the open-chain form of sugars is reduction of the aldehyde group. This leads to a series of polyols having an OH group on each carbon atom. We will use mannose as an example. Mannose is a diastereoisomer of glucose having one axial OH group (marked in black) and, like glucose, is in equilibrium with the open-chain form.

If we redraw the open-chain form in a more realistic way, and then reduce it with $NaBH_4$, the product is mannitol whose symmetry is interesting. It has C_2 symmetry with the C_2 axis at right angles to the chain and marked with the orange dot.

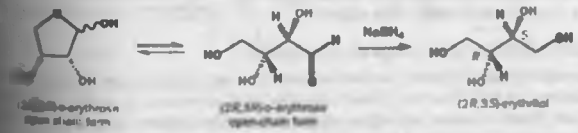




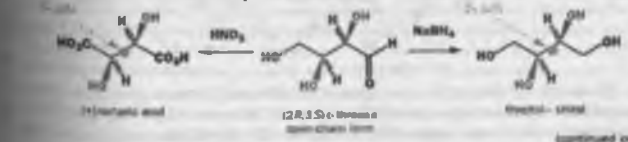
The simplification of stereochemistry results because the two ends of the sugar both now have CH_2OH groups so that the possibility of C_2 and planar symmetry arises. If we look at the two four-carbon sugars we can establish some important stereochemical correlations. Threose is reduced to threitol which has a C_2 axis like that of mannitol.



Erythrose on the other hand reduces to erythritol, which is not chiral.

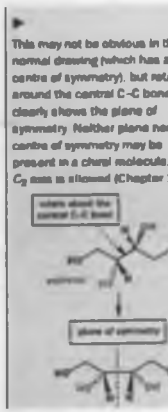


The important correlation is that threose is reduced or oxidized to chiral compounds—the oxidation product is tartaric acid—while erythrose is reduced or oxidized to *meso* compounds. This may help you to remember the labels erythro- and threo- should you need to.

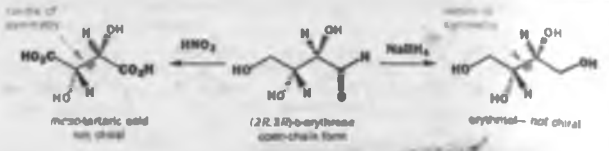


(continued overleaf)

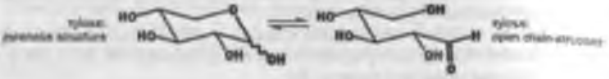
C_2 means that the axis of symmetry is twofold; rotating 180° gives the same structure.



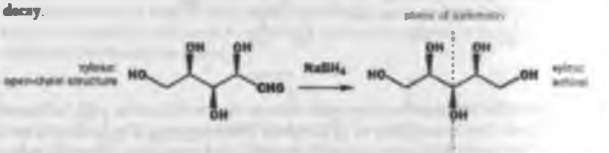
This may not be obvious in the normal drawing (which has a centre of symmetry), but rotation around the central C–C bond clearly shows the plane of symmetry. Neither plane nor centre of symmetry may be present in a chiral molecule, but a C_2 axis is allowed (Chapter 16).



In the pentoses and hexoses there are again sugars that are reduced to *meso* alcohols and some that are reduced to C_2 symmetric alcohols. The C_5 sugar xylose has the same stereochemistry as glucose from C2 to C4 but lacks the CH_2OH group at C6.



Xylose is reduced to the *meso* alcohol xylitol. This alcohol is more or less as sweet as sugar and, as xylose (which is not sweet) can be extracted in large quantities from waste products such as sawdust or corncobs, xylitol is used as a sweetener in foods. There is an advantage in this. Though we can digest xylitol (so it is fattening), the bacteria on teeth cannot so that xylitol does not cause tooth decay.



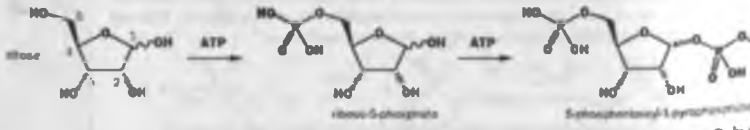
By careful manipulation of protecting groups such as acetals and reactions such as reduction and oxidation, it is possible to transform sugars into many different organic compounds retaining the natural optical activity of the sugars themselves. As some sugars are also very cheap, they are ideal starting points for the synthesis of other compounds and are widely used in this way (Chapter 45). Sucrose and glucose are very cheap indeed—probably the cheapest optically active compounds available. Here are the relative (to glucose = 1) prices of some other cheap sugars.

Sugar	Price[a]	Sugar	Price[a]
glucose	1	sorbitol	2
rhamnose	75	mannitol	4
galactose	8	dulcitol[b]	70
xylose	20	xylitol	15
ribose	100	sucrose	1

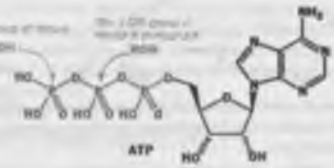
[a] Prices relative to glucose = 1.
[b] Dulcitol is the reduction product of galactose.

Chemistry of ribose—from sugars to nucleotides

We have said little about selective reactions of pentoses so we shall turn now to the synthesis of nucleotides such as AMP. In nature, ribose is phosphorylated on the primary alcohol to give ribose-5-phosphate. This is, of course, an enzyme-catalysed reaction but it shows straightforward chemoselectivity such as we should expect from a chemical reaction.

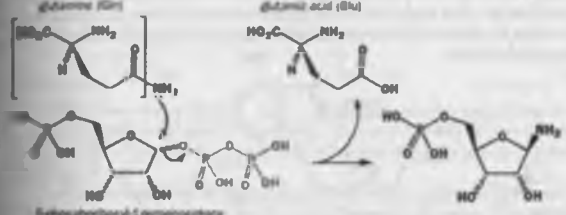


The second step is a pyrophosphorylation at the anomeric position to give PRPP. Only one diastereomer is produced as presumably the two anomers interconvert rapidly and only the one isomer reacts under control by the enzyme. This selectivity would be very difficult to achieve chemically.

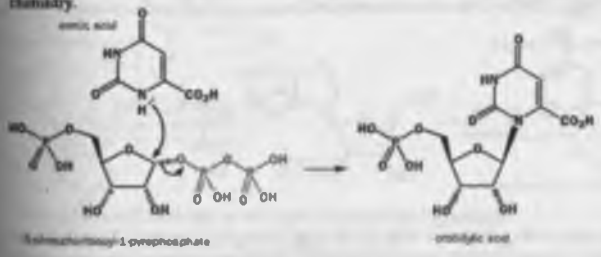


▶
You will notice that these two reactions illustrate the flexibility with which ATP can activate biological molecules. In the first reaction, the nucleophilic OH group of ribose attacks the terminal phosphate group, but in the second the OH group must attack the middle phosphate residue. This would be impossible to control chemically.

Now the stage is set for an S_N2 reaction. The nucleophile is actually the amide group of glutamine but the amide is hydrolysed by the same enzyme in the same reaction and the result is as if a molecule of ammonia had done an S_N2 reaction displacing the pyrophosphate from the anomeric position. An NH_2 group is introduced, which is then built into the purine ring-system in a series of reactions involving simple amino acids. These reactions are too complex to describe here.



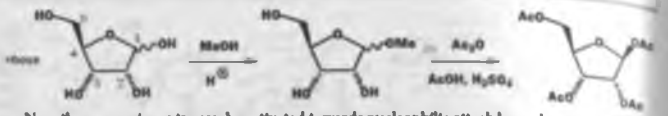
By contrast, if a pyrimidine is to be made, Nature assembles a general pyrimidine structure first and adds it in one step to the PRPP molecule, again in an S_N2 reaction using a nitrogen nucleophile. This general nucleotide, orotidylic acid, can be converted into the other pyrimidine nucleotides by simple chemistry.



The chemical version—protection all the way

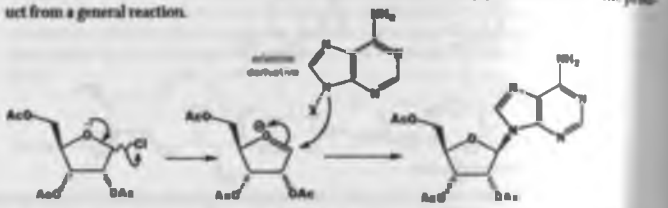
In a chemical synthesis (work that led to Alexander (Lord) Todd's Nobel prize) there are rather different problems. We cannot achieve the remarkable selectivity between the different OH groups achieved in Nature so we have to protect any OH group that is not supposed to react. We also prefer to add pre-formed purines and pyrimidines to a general electrophile derived from ribose. The first step is to form acetate esters from all the OH groups. Since ribose is rather unstable to acetylation conditions, the methyl glycoside (which is formed under very mild conditions) is used. This fixes the sugar in the furanose form. Now the tetraacetate can be made using acetic anhydride in acidic solution. All of the OH groups react by nucleophilic attack on the carbonyl group of the anhydride with retention of configuration except for the anomeric OH, which esterifies by an S_N1 mechanism. This, of course, epimerizes the anomeric centre but the crystalline diastereoisomer shown can be isolated easily.

■
Alexander Todd (1907–97), better known as Lord Todd, was a Scot who pioneered the modern interaction between chemistry and biochemistry in his work at Frankfurt, Oxford, Edinburgh, London, CalTech, Manchester, and Cambridge. He won the Nobel prize in 1957 for his work on the synthesis of the most important coenzymes and nucleotides. This was a remarkable achievement because he had to find out how to do phosphate, ribose, and purine chemistry — none of which was known when he started, and none of which was easy as this brief excursion should show.

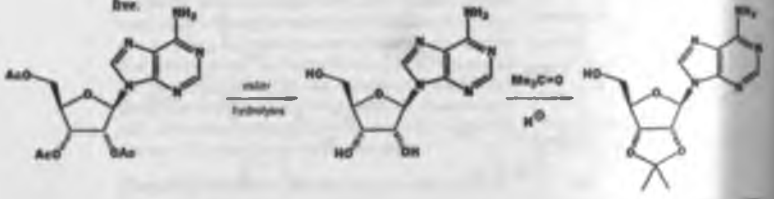


Now the anomeric centre can be activated towards nucleophilic attack by replacement of acetate by chloride. This is again an S_N1 reaction and produces a mixture of chlorides. The other esters are stable to these conditions.

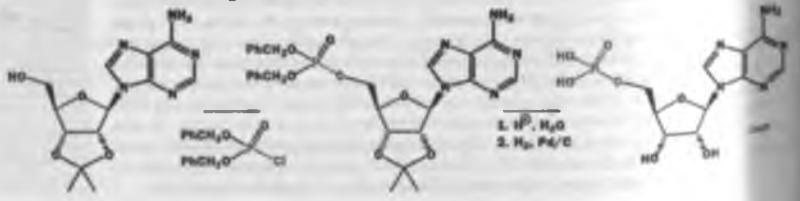
Replacement of the chlorine by the purine or pyrimidine base is sometimes quite tricky and silver or silyl derivatives are often used. Lewis acid catalysis is necessary to help the chloride ion leave in this S_N1 reaction. We shall avoid detailed technical discussion and simply draw the adenosine product from a general reaction.



Now we need to remove the acetates and put a phosphate specifically on the 5-position. The acetates can be removed with retention by ester hydrolysis and we already know how to protect the 2-OH and 3-OH groups. They are cis to each other so they will form an acetal with acetone leaving the 5-OH group free.



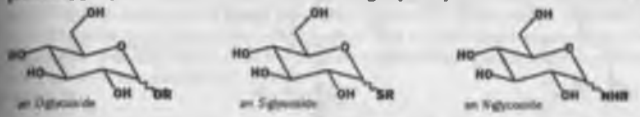
Putting on the phosphate is tricky too and more protection is necessary. This phosphorus compound with one chloride as leaving group and two benzyl esters as protecting groups proved ideal. The benzyl esters can be removed by hydrogenation (Chapter 24) and the acetal by treatment with dilute acid to give AMP.



The chemical synthesis involves a lot more selective manipulation of functional groups, particularly by protection, than is necessary in the biological synthesis. However, this synthesis paved the way to the simple syntheses of nucleotides and polynucleotides carried out routinely nowadays. The usual method is to build short runs of nucleotides and then let the enzymes copy them—a real partnership between biology and chemistry.

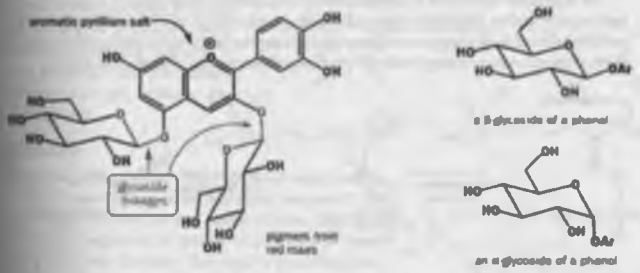
Glycosides are everywhere in nature

Many alcohols, thiols, and amines occur in nature as glycosides, that is as *O*-, *S*-, or *N*-acetals at the anomeric position of glucose. The purpose of attaching these compounds to glucose is often to improve solubility or transport across membranes—to expel a toxin from the cell, for example. Sometimes glucose is attached in order to stabilize the compound so that glucose appears as Nature's protecting group, rather as a chemist would use a TIP group (Chapter 24).



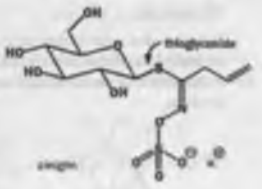
O-Glycosides occur in immense variety with glucose and other sugars being joined to the OH groups of alcohols and phenols to form acetals. The stereochemistry of these compounds is usually described by the Greek letters α and β. If the OR bond is down, we have an α-glycoside; if up, a β-glycoside.

An attractive example is the pigment of red roses, which is an interesting aromatic oxygen heterocycle (an anthocyanidin). Two of the phenolic OH groups are present as β-glycosides.

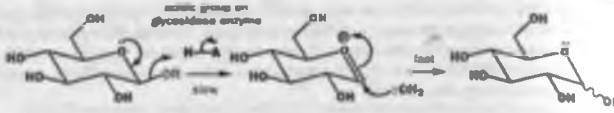


Protect yourself from cancer with green vegetables: *S*-glycosides

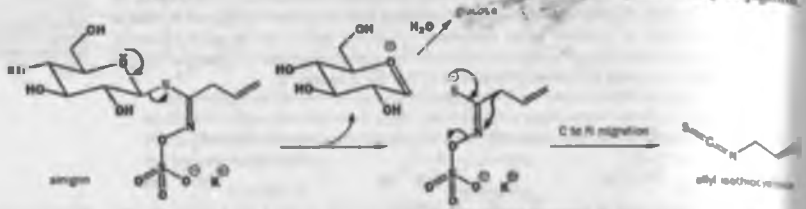
We will take an important series of *S*-glycosides for further chemical discussion in this chapter. It is clear that there are special benefits to health in eating broccoli and brussels sprouts because of their potent sulfur-containing anti-cancer compounds. These compounds are unstable isothiocyanates and are not, in fact, present in the plant but are released on damage by, for example, cutting or cooking when a glycosidase (an enzyme which hydrolyses glycosides) releases the sulfur compound from its glucose protection. A simple example is sinigrin.



When a glycosidase enzyme cleaves an *O*-glycoside, we should expect a simple general acid catalysed first step followed by fast addition of water to the intermediate oxonium ion, essentially the same mechanism as is shown by the chemical reaction (Chapter 13).

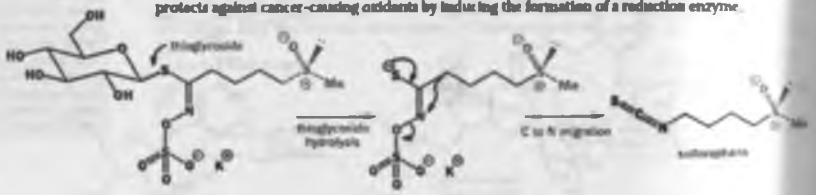


The *S*-glycosides of the sinigrin group start to hydrolyse in the same way. The sulfur atom is the better leaving group when it leaves as an anion (though worse than oxygen when the hydrolysis occurs in acidic conditions—see p. 008) and these anions are additionally stabilized by conjugation.



The next step is very surprising. A rearrangement occurs, rather similar to the Beckmann rearrangement (Chapter 37), in which the alkyl group migrates from carbon to nitrogen and an isothiocyanate (R–N=C=S) is formed. Sinigrin occurs in mustard and horseradish and it is the release of the allyl isothiocyanate that gives them their 'hot' taste. When mustard powder is mixed with water, the hot taste develops over some minutes as sinigrin is hydrolysed to the isothiocyanate.

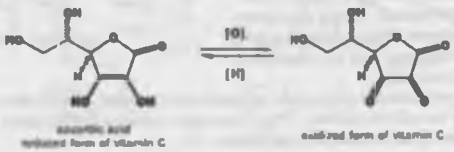
The *S*-glycoside in broccoli and brussels sprouts that protects from cancer is somewhat similar but has one more carbon atom in the chain and contains a sulfoxide group as well. Hydrolysis of the *S*-glycoside is followed by the same rearrangement, producing a molecule called sulforaphane. Sulforaphane protects against cancer-causing oxidants by inducing the formation of a reduction enzyme.



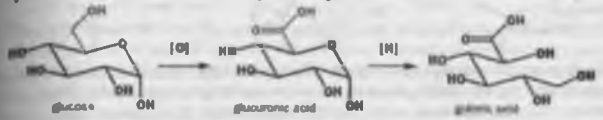
Compounds derived from sugars

Vitamin C

Nature makes some important compounds from simple sugars. Vitamin C—ascorbic acid—is one of these. Like glutathione, it protects us from stray oxidants as well as being involved in primary redox pathways (we mentioned earlier its role in collagen synthesis). Its reduced and oxidized forms are these.

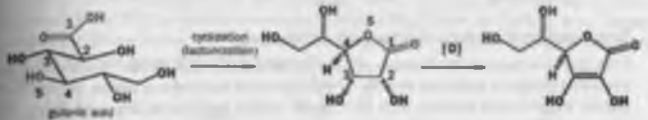


Vitamin C looks very like a sugar as it has six carbon atoms, each having an oxygen atom as substituent as well as an oxygen heterocycle, and it is no surprise that it is made in nature from glucose. We shall give just an outline of the process, which appropriately involves a lot of oxidation and reduction. The first step takes the primary alcohol of glucose to a carboxylic acid known as glucuronic acid. Next comes a reduction of the masked aldehyde to give 'gulonic acid'. Both reactions are quite reasonable in terms of laboratory chemistry.

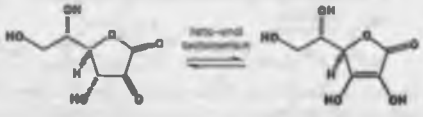


▶ We have given names for these relatively well known sugar derivatives, but you do not need to learn them.

It is pretty obvious what will happen to this compound as it is an open-chain carboxylic acid with five OH groups. One of the OH groups will cyclize on to the acid to form a lactone. Kinetically, the most favourable cyclization will give a five-membered ring, and that is what happens. Now we are getting quite close to ascorbic acid and it is clear that oxidation must be the next step so that the double bound can be inserted between C2 and C3.

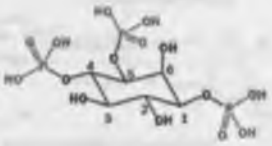


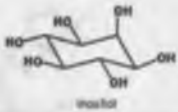
This looks a strange reaction but it is really quite logical. One of the secondary OH groups must be oxidized to a ketone. This is the 2-OH group and then the resulting ketone can simply enolize to give ascorbic acid.



Inositols

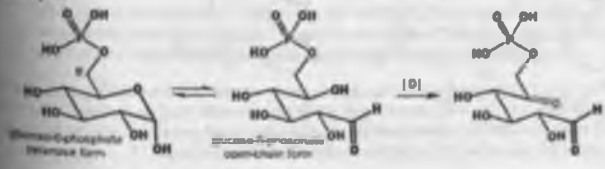
We have already discussed the widespread sugar alcohols such as mannitol but more important compounds are cyclic sugar alcohols having a carbocyclic ring (cyclitols). The most important is inositol which controls many aspects of our chemistry that require communication between the inside and the outside of a cell. Inositol-1,4,5-triphosphate (IP_3) can open calcium channels in cell membranes to allow calcium ions to escape from the cell.



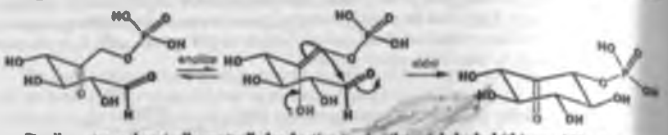


■ This inositol is known as 'myo-inositol' and is just one of many possible stereoisomers. Inositol was mentioned in Chapter 15.

Inositol is made in nature from glucose-6-phosphate by an aldol reaction that requires preliminary ring opening and selective oxidation (this would be tricky in the lab without protecting groups!).



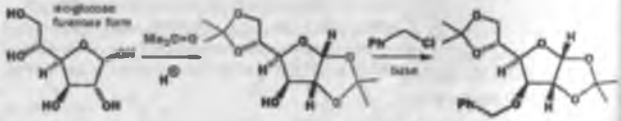
The resulting ketone can be enolized on the phosphate side and added to the free aldehyde group to form the cyclohexane ring. We can draw the mechanism for the aldol reaction easily if we first change the conformation.



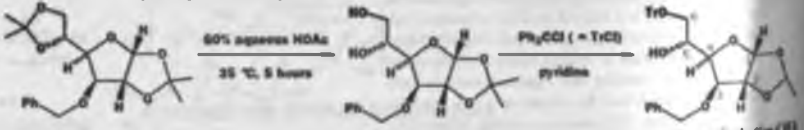
Finally, a stereochemically controlled reduction to give the axial alcohol (this would be the stereoselectivity expected with $NaBH_4$ for example; see Chapter 18) gives *myo*-inositol. The number and position of the phosphate esters can be controlled biochemically. This control is vital in the biological activity and would be difficult in the laboratory.

Learning from Nature—the synthesis of inositols

If we wish to devise a chemical version of the biosynthesis of inositols, we need to use cleverly devised protecting groups to make sure that the right OH group is oxidized to a ketone. We can start with glucose trapped in its furanose form by a double acetone acetal as we discussed above. The one remaining OH group is first blocked as a benzyl ether.

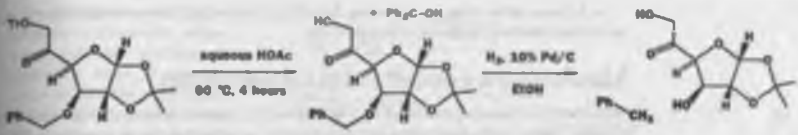


Next, one of the acetals is hydrolysed under very mild conditions, and the primary alcohol is protected as a trityl ether. This is an S_N1 reaction with an enormous electrophile—no big that it goes on primary alcohols only.

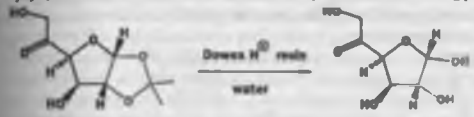


Notice that each oxygen atom in this molecule of protected glucose is now different. Only the OH at C5 is free, and its time has come: it can now be oxidized using a Swern procedure with dimethylsulfoxide as the oxidant (Chapter 46).

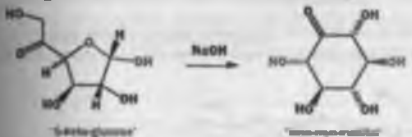
Now we can strip away the protecting groups one by one and it is instructive to see how selective these methods are. The trityl group comes off in aqueous acetic acid by another S_N1 reaction in which water captures the triphenylmethyl cation, and the benzyl group is removed by hydrogenolysis—hydrogen gas over a 10% palladium on charcoal catalyst in ethanol.



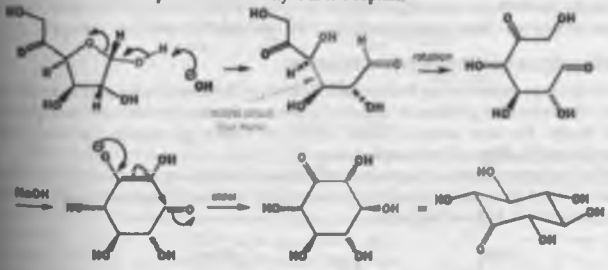
Finally, the acetone acetal is removed by acid hydrolysis. Because free sugars are difficult to isolate it is convenient to use an acidic resin known as 'Dowex'. The resin (whose polymeric structure is discussed in Chapter 52) can simply be filtered off at the end of the reaction and the solid product isolated by lyophilization—evaporation of water at low pressure below freezing point. The yield is quantitative.



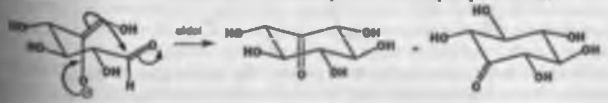
All of the hydroxyl groups are now free except the one tied up in the hemiacetal and that, of course, is in equilibrium with the open-chain hydroxy-aldehyde as we have already seen. Treatment of this free 'glucose ketone' with aqueous NaOH gives the ketone of *myo*-inositol as the major product together with some of the other diastereoisomers.



The simplest explanation of this result is that the chemical reaction has followed essentially the same course as the biological one. First, the hemiacetal is opened by the base to give the open-chain keto-aldehyde. Rotation about a C–C bond allows a simple aldol condensation between the enolate of the ketone as nucleophile and the aldehyde as electrophile.



The enolate must prefer to attack the aldehyde in the same way as in the biological reaction to give the all-equatorial product as the conformational drawing shows. The arrangement of the enolate in the aldol reaction itself will be the same as in the cyclization of the phosphate above.



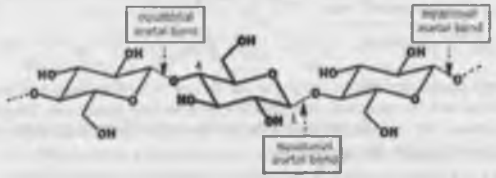
As in many other cases, by improving the rate and perfecting the stereoselectivity, the enzyme makes much better a reaction that already works.

Most sugars are embedded in carbohydrates

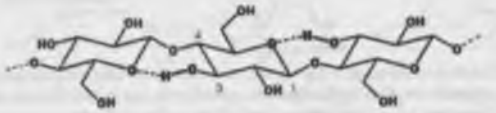
Before we leave the sugars we should say a little about the compounds formed when sugars combine together. These are the saccharides and they have the same relationship to sugars as peptides and proteins have to amino acids. We have met one simple disaccharide, sucrose, but we need to meet some more important molecules.

▶ This is literally an astronomical amount: it's about the mass of one of the moons of Mars, Deimos. Our moon weighs 10^{22} kg.

One of the most abundant compounds in nature is cellulose, the structural material of plants. It is a glucose polymer and is produced in simply enormous quantities (about 10^{15} kg per year). Each glucose molecule is joined to the next through the anomeric bond (C1) and the other end of the molecule (C4). Here is that basic arrangement.



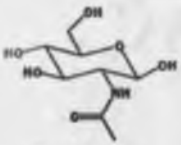
Notice that the anomeric bonds are all equatorial. This means that the cellulose molecule is linear in general outline. It is made rigid by extra hydrogen bonds between the 2-OH groups and the ring oxygen atoms—like this.



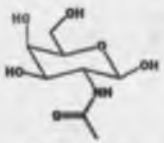
The polymer is also coiled to increase stability still further. All this makes cellulose very difficult to hydrolyse, and humans cannot digest cellulose as we do not have the necessary enzymes. Only ruminants, such as cows, whose many stomachs harbour some helpful bacteria, can manage it.

Amino sugars add versatility to saccharides

To go further in understanding the structural chemistry of life we need to know about amino sugars. These molecules allow proteins and sugars to combine and produce structures of remarkable variety and beauty. The most common amino sugars are *N*-acetyl-glucosamine and *N*-acetyl-galactosamine, which differ only in stereochemistry.

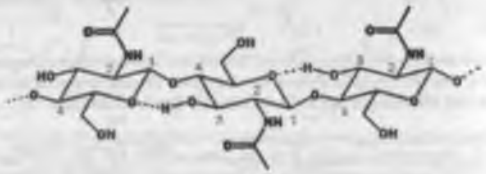


N-acetyl-glucosamine



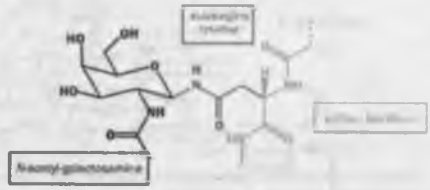
N-acetyl-galactosamine

The hard outer skeleton of insects and shellfish contains chitin, a polymer very like cellulose but made of acetyl glucosamine instead of glucose itself. It coils up in a similar way and provides the toughness of crab shells and beetle cases.



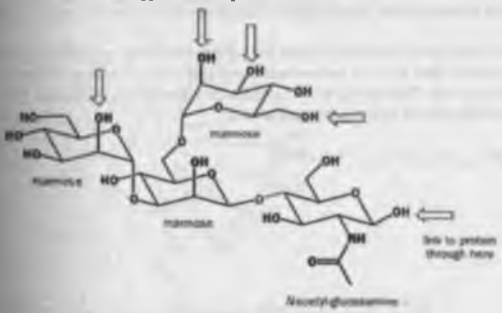
Ordinary cell membranes must not be so tough as they need to allow the passage of water and complex molecules through channels that can be opened by molecules such as inositol phosphates.

These membranes contain glycoproteins—proteins with amino-sugar residues attached to asparagine, serine, or threonine in the protein. The attachment is at the anomeric position so that these compounds are *O*- or *N*-glycosides of the amino sugars. Here is *N*-acetyl-galactosamine attached to an asparagine residue as an *N*-glycoside.

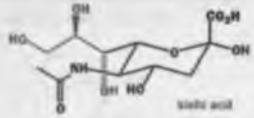


The cell membrane normally contains less than 10% of sugars but these are vital to life. Because the sugars (*N*-acetyl-glucosamine and *N*-acetyl-galactosamine) are covered with very polar groups (OH and amide) they prefer to sit outside the membrane in the aqueous extracellular fluid rather than within the nonpolar membrane itself. When two cells meet, the sugars are the first things they see. We cannot go into the details of the biological processes here, but even the structures of these saccharides dangling from the cell are very interesting. They contain amino sugars, again particularly *N*-acetyl-glucosamine and *N*-acetyl-galactosamine, and they are rich in mannose.

In addition, they are usually branched at one of the mannose residues that is joined to two other mannoses on one side and to one glucosamine on the other. The glucosamine leads back eventually to the protein through a link to asparagine like the one we have just seen. The two mannoses are linked to more sugars at positions marked by the green arrows and provide the recognition site. The structure below is a typical branchpoint.



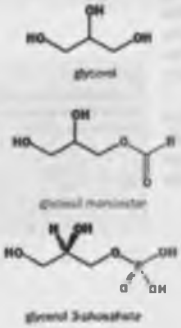
You should begin to see from structures like these just how versatile sugar molecules can be. From just four sugars we have constructed a complex molecule with up to 13 possible link sites. With more sugars added, the possibilities become enormous. It is too early to say what medical discoveries will emerge from these molecules, but one that is likely to be important is sialyl Lewis X. This tetrasaccharide is also branched but it contains a different type of molecule—a C_9 sugar with a CO_2H group, called sialic acid.



Sialic acid has the CO_2H group at the anomeric position, a typical *N*-acetyl group, and a unique side chain (in green) with three more OH groups. Sialyl Lewis X has sialic acid at the end of a branched sugar chain. The branchpoint is the familiar *N*-acetyl-glucosamine through which the molecule is eventually linked to the glycoprotein. The remaining sugars are galactose, a diastereoisomer of glucose, and a sugar we have not seen before, fucose. Fucose often appears in saccharides of this kind and is a six-carbon sugar without a primary OH group. It is like galactose with Me instead of CH_2OH.

sialyl Lewis X

Stalyl Lewis X can also form a stable complex with calcium ions as the diagram shows and this may be vital to its activity. It is certainly involved in leukocyte adhesion to cells and is therefore vital in the prevention of infection.



glycerol

glyceryl monoester

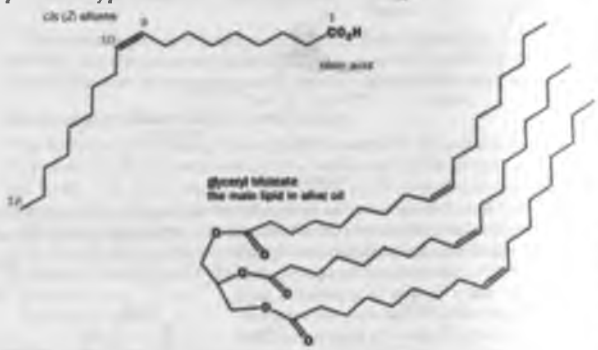
glycerol 3-phosphate

Lipids

Lipids (fats) are the other important components of cell membranes. Along with cholesterol, also a component of the cell membrane, they have acquired a bad name, but they are nonetheless essential to the function of membranes as selective barriers to the movement of molecules.

The most common types of lipids are esters of glycerol. Glycerol is just propane-1,2,3-triol but it has interesting stereochemistry. It is not chiral as it has a plane of symmetry, but the two primary OH groups are enantiotopic (Chapter 10). If one of them is changed—by esterification, for example—the molecule becomes chiral. Natural glycerol phosphate is such an ester and it is optically active.

A typical lipid in foodstuffs is the triester formed from glycerol and oleic acid, which is the most abundant lipid in olive oil. Oleic acid is a 'mono-unsaturated fatty acid'—it has one *Z* double bond in the middle of the C_{18} chain. This bond gives the molecule a marked kink in the middle. The compound actually present in olive oil is the triester, also kinked.



cis (Z) alkene

oleic acid

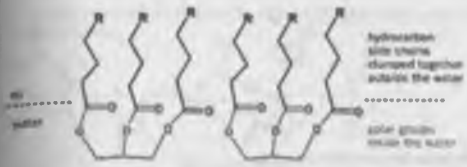
glyceryl trioleate
the main lipid in olive oil

Oil and water do not mix

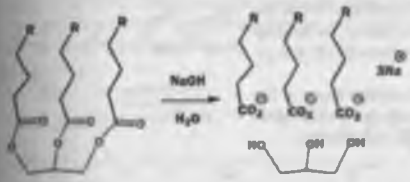
The lipid has, more or less, the conformation shown in the diagram with all the polar ester groups at one end and the hydrocarbon chains bunched together in a nonpolar region. Oil and water do not mix. It is said, but triglyceride lipids associate with water in a special way. A drop of oil spreads out on water in a very thin layer. It does so because the ester groups sit inside the water and the hydrocarbon side chains stick out of the water and associate with each other.

■

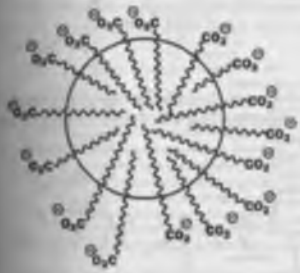
You may have done the 'Langmuir trough' experiment in a physical chemistry practical class. This involves measuring the size of a molecule by placing an oil to spread on the surface of water in a rectangular trough



When triglycerides are boiled up with alkali, the esters are hydrolysed and a mixture of carboxylate salts and glycerol is formed. This was how soap was made—hard soap was the sodium salt and soft soap the potassium salt.

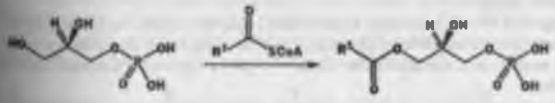


When a soap is suspended in water, the carboxylate groups have a strong affinity for the water and so oily globules or micelles are formed with the hydrocarbon side chain inside. It is these globules that remove greasy dirt from you or your clothes.

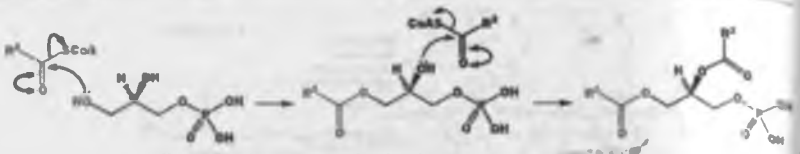


Nature uses thiol esters to make lipids

The repulsion between molecules having oily or aqueous properties is the basis for membrane construction. The lipids found in membranes are mostly based on glyceryl phosphate and normally contain three different side chains—one saturated, one unsaturated, and one very polar.

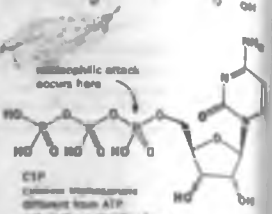


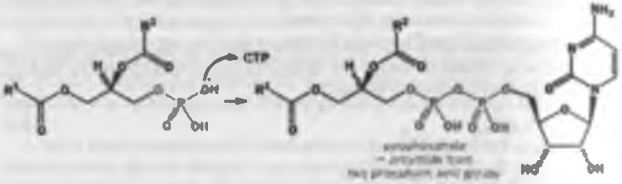
The saturated chain is added first, at C1 of glyceryl phosphate. The reagent is a thiol ester called acyl coenzyme A, whose full structure you will see in the next chapter. This reaction occurs by simple nucleophilic attack on the carbonyl group of the thiol ester followed by loss of the better leaving group, the thiolate anion. Then the process is repeated at the second OH group where an unsaturated fatty acid, perhaps oleic acid, is added by the same mechanism.



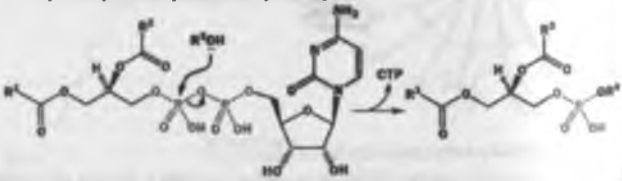
The third acylation requires the phosphate to act as the acylating agent and a polar alcohol to be introduced to form a phosphate ester. This reaction actually occurs by the activation of the phosphate as a pyrophosphate. Pyrophosphates are really acid anhydrides so it is not surprising that they act as acylating agents. The first step is a reaction with cytidine triphosphate (CTP) doing a job we might expect from ATP.

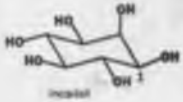
Nucleophilic attack by the phosphate group of the phosphoglyceride at the point indicated on CTP gives the pyrophosphate required for the acylation step.



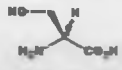


The anhydride is now attacked by an alcohol acting as a nucleophile. The attack occurs only at the electrophilic phosphorus centre further from the nucleotide. This is an impressive piece of regioselectivity and is presumably controlled by the enzyme.





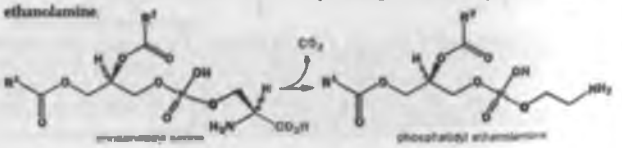
inositol



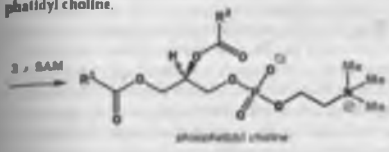
the amino acid serine (Ser)

This third chain is rather different from the other two—it's a phosphate diester, and the alcohol portion can be inositol joined through the OH group at C1 or it can be the amino acid serine, joined through its OH group.

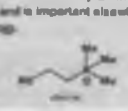
The compound formed from serine is particularly important as it can be transformed into the most dramatically concentrated of these phospholipids. A decarboxylation using a coenzyme (we shall look at the mechanism of this reaction in Chapter 51) gives a very simple molecule, phosphatidyl ethanolamine.



Finally, three methylations on the nitrogen atom by SAM (see p. 000) gives the zwitterion phosphatidyl choline.

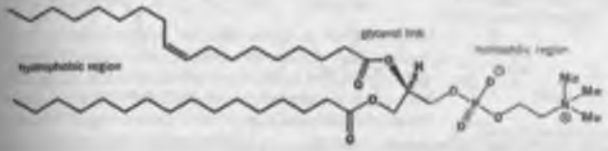


Choline is a tetraalkyl ammonium salt and is important elsewhere in biology.

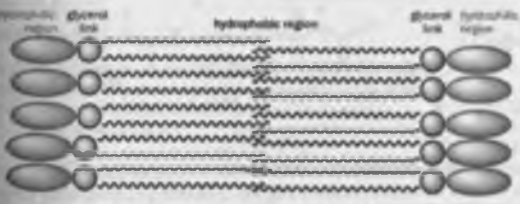


Phospholipids form membranes spontaneously

The choline terminus of the molecule is very polar indeed. Phosphatidyl choline adopts a shape with the nonpolar chains (R^1 and R^2) close together, and it should be clear that this is an ideal molecule for the construction of membranes.



We have already seen how oils such as glyceryl trioleate form thin layers on water while soaps from the alkaline hydrolysis of glycerides form micelles. Phosphatidyl choline forms yet another structure—it spontaneously forms a membrane in water. The hydrophobic hydrocarbon chains line up together on the inside of the membrane with the hydrophilic choline residues on the outside.

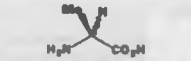


This is just a small piece of a cross-section of the membrane. These membranes are called lipid bilayers because two rows of molecules line up to form two layers back-to-back. The charged, hydrophilic region on the outside is solvated by the water and the hydrocarbon tails are repelled by the water and attracted to each other by weak forces such as van der Waals attractions.

Full structural analysis of a real cell membrane reveals a chemically diverse thin sheet composed of phospholipid bilayers penetrated by glycoproteins containing the amino sugars we discussed earlier. The amount of each component varies but there is usually about 50:50 phospholipid:protein, with the protein containing about 10% sugar residues. The phospholipids' main role is as a barrier while the glycoproteins have the roles of recognition and transport.

Bacteria and people have slightly different chemistry

We have many times emphasized that all life has very similar chemistry. Indeed, in terms of biochemistry there is little need for the classifications of mammals, plants, and so on. There is only one important division—into prokaryotes and eukaryotes. Prokaryotes, which include bacteria, evolved first and have simple cells with no nucleus. Eukaryotes, which include plants, mammals, and all



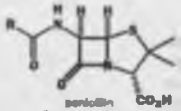
(S)-Ala from normal proteins

(R)-Ala from bacterial cell walls

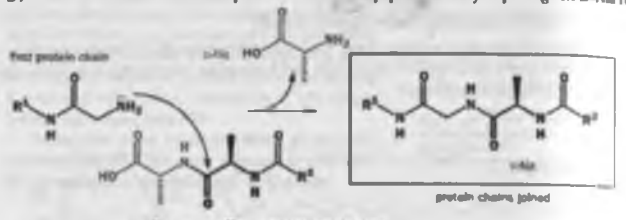
other multicellular creatures, evolved later and have more complex cells including nuclei. Even so, much of the biochemistry on both sides of the divide is the same.

When medicinal chemists are looking for ways to attack bacteria, one approach is to interfere with chemistry carried out by prokaryotes but not by us. The most famous of these attacks is aimed at the construction of the cell walls of some bacteria that contain 'unnatural' (*R*)- (or D-) amino acids. Bacterial cell walls are made from glycopeptides of an unusual kind. Polysaccharide chains are cross-linked with short peptides containing (*R*)-alanine (D-Ala). Before they are linked up, one chain ends with a glycine molecule and the other with D-Ala–D-Ala. In the final step in the cell wall synthesis, the glycine attacks the D-Ala–D-Ala sequence to form a new peptide bond by displacing one D-Ala residue.

▶ The reason bacteria use these 'unnatural' D-amino acids in their cell walls is to protect them against the enzymes in animals and plants, which cannot digest proteins containing D amino acids.

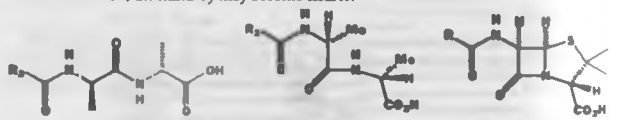


penicillin
β-lactam in black



protein chains joined

The famous molecule that interferes with this step is penicillin, though this was not even suspected when penicillin was discovered. We now know how penicillin works. It inhibits the enzyme that catalyses the D-Ala transfer in a very specific way. It first binds specifically to the enzyme, so it must be a mimic of the natural substrate, and it then reacts with the enzyme and inactivates it by blocking a vital OH group at the active site. If we emphasize the peptide nature of penicillin and compare it with D-Ala–D-Ala, the mimicry may become clearer.



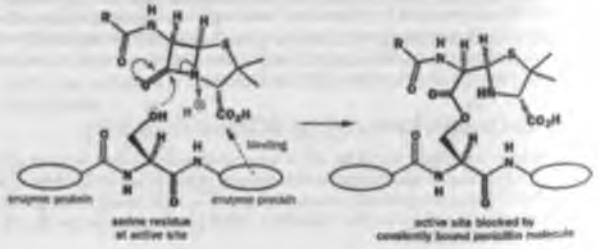
acyl-D-Ala–D-Ala rearrangement back to front and upside down

acyl-D-Ala–D-Ala rearrangement in the penicillin shape

the peptide part of penicillin

Penicillin imitates D-Ala and binds to the active site of the enzyme, encouraging the OH group of a serine residue to attack the reactive, strained β-lactam. This same OH group of the same serine residue would normally be the catalyst for the D-Ala–D-Ala cleavage used in the building of the bacterial cell wall. The reaction with penicillin 'protects' the serine and irreversibly inhibits the enzyme. The bacterial cell walls cannot be completed, and the bacterial cells literally burst under the pressure of their contents. Penicillin does not kill bacteria whose cell walls are already complete but it does prevent new bacteria being formed.

▶ Our current last line of defence against bacteria resistant to penicillin, and other antibiotics, is vancomycin. Vancomycin works by binding to the D-Ala–D-Ala sequences of the bacterial cell wall.



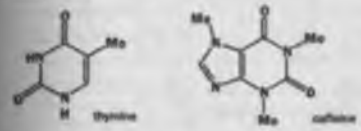
enzyme protein — serine residue at active site — enzyme protein — binding

active site blocked by covalently bound penicillin molecule

You have seen many instances in this chapter of the importance of a good understanding of both the chemistry and the biochemistry of living things if medicine is to advance; it is at the frontier of chemistry and biology that many of the most important medical advances are being made.

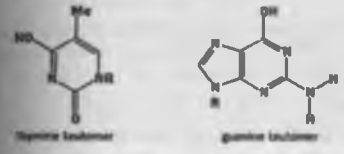
Problems

1. Do you consider that thymine and caffeine are aromatic compounds? Explain.



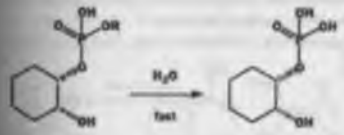
thymine — caffeine

2. It is important that we draw certain of the purine and pyrimidine bases in their preferred tautomeric forms. The correct pairings are given early in the chapter. What alternative pairings would be possible with these (minor) tautomers of thymine and guanine? Suggest reasons (referring to Chapter 43 if necessary) why the major tautomers are preferred.



thymine tautomer — guanine tautomer

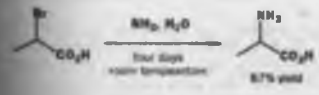
3. Dialkyl phosphates are generally hydrolysed quite slowly at near-neutral pHs but this example hydrolyses much more rapidly. What is the mechanism and what relevance has it to RNA chemistry?



fast

Revision of Chapter 41. This reaction is subject to general base catalysis. Explain.

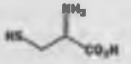
4. Primary amines are not usually made by displacement reactions on halides with ammonia. Why not? The natural amino acids can be made by this means in quite good yield. Here is an example.



87% yield

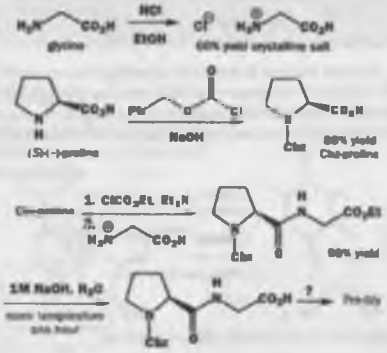
Why does this example work? Comment on the state of the reagents and products under the reaction conditions. What is the product and how does it differ from the natural amino acid?

5. Human hair is a good source of cystine, the disulfide dimer of cysteine. The hair is boiled with aqueous HCl and HCO_2H for a day, the solution concentrated, and a large amount of sodium acetate added. About 5% of the hair by weight crystallizes out as pure cystine $[\alpha]_D$ −216. How does the process work? Why is such a high proportion of hair cystine? Why is no cysteine isolated by this process? What is the stereochemistry of cystine? Make a good drawing of cystine to show its symmetry. How would you convert the cystine to cysteine?



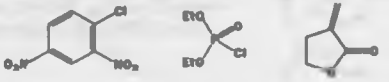
(S)-cysteine

6. A simple preparation of a dipeptide is given below. Explain the reactions, drawing mechanisms for the interesting steps. Which steps are protection, activation, coupling, and deprotection? Explain the reasons for protection and the nature of the activation. Why is the glycine added to the coupling step as its hydrochloride? What reagent(s) would you use for the final deprotection step?

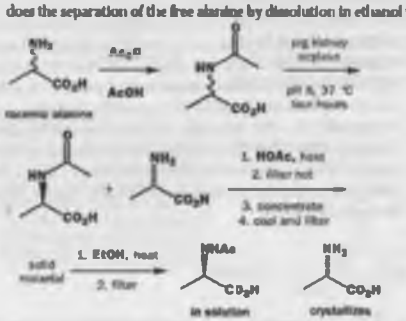


glycine — 60% yield crystalline salt — (S)-proline — 80% yield Cbz-proline — 90% yield

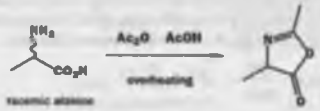
7. Suggest how glutathione might detoxify these dangerous chemicals in living things. Why are they still toxic in spite of this protection?



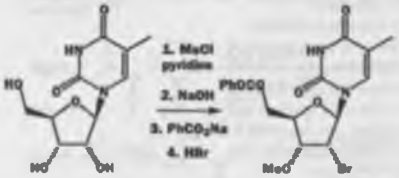
8. Alanine can be resolved by the following method, using a pig kidney acylase. Draw a mechanism for the acylation step. Which isomer of alanine acylates faster? In the enzyme-catalysed reaction, which isomer of the amide hydrolyses faster? In the separation, why is the mixture heated in acid solution, and what is filtered off? How does the separation of the free alanine by dissolution in ethanol work?



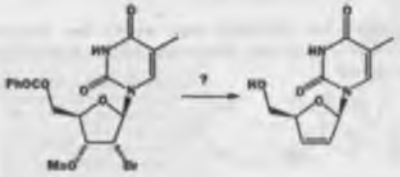
If the acylation is carried out carelessly, particularly if the heating is too long or too strong, a by-product may form that is not hydrolysed by the enzyme. How does this happen?



9. A patent discloses this method of making the anti-AIDS drug d4T. The first few stages involve differentiating the three hydroxyl groups of 5-methyluridine as shown below. Explain the reactions, especially the stereochemistry at the position of the bromine atom.

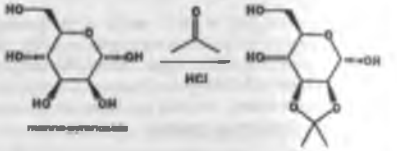


Suggest how the synthesis might be completed.

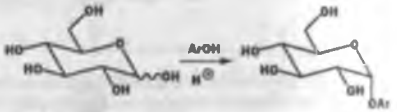


10. Mannose usually exists as the pyranoside shown below. This is in equilibrium with the furanoside. What is the conformation of the pyranoside and what is the stereochemistry of the furanoside? What other stereochemical change will occur more quickly than this isomerization?

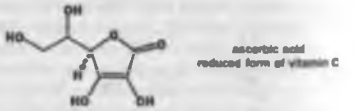
Treatment of mannose with acetone and HCl gives the acetal shown. Explain the selectivity.



11. How are glycosides formed from phenols (in Nature or in the laboratory)? Why is the stereochemistry of the glycoside not related to that of the original sugar?



12. Draw all the keto and enol forms of ascorbic acid (vitamin C). Why is the one shown the most stable?



13. 'Caustic soda' (NaOH) was used to clean ovens and clear blocked drains. Many commercial products for these jobs with fancy names still contain NaOH. Even concentrated sodium carbonate (Na_2CO_3) does quite a good job. How do these cleansers work? Why is NaOH so dangerous to humans, particularly if it gets in the eye?

14. Bacterial cell walls contain the unnatural amino acid D-alanine. If you wanted to prepare a sample of D-ala, how would you go about it? (*Hint.* There is not enough in bacteria to make that a worthwhile source, but have you done Problem 8 yet?)

Mechanisms in biological chemistry 50

Connections

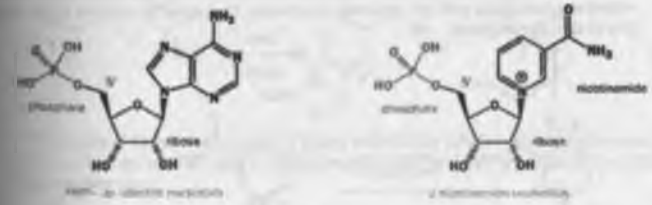
Building on:
- Acidity and basicity ch2
- Carbonyl chemistry ch12 & ch14
- Stereochemistry ch16
- Conformational analysis and elimination ch18–ch19
- Enolate chemistry and synthesis ch24–ch30
- Pericyclic reactions ch35–ch36
- Determining mechanisms ch13 & ch41
- Heterocycles ch42–ch44
- Asymmetric synthesis ch45
- Sulfur chemistry ch46
- Chemistry of life ch49

Arriving at:
- How Nature makes small molecules using ordinary organic mechanisms
- Enzymes are Nature's catalysts, speeding up reactions by factors of 10^6 or more
- Coenzymes and vitamins are Nature's versions of common organic reagents
- Reductions with NADH
- Reductive amination, deamination, and decarboxylation with pyridoxal
- Enol chemistry with lysine enamines, with coenzyme A, and with phosphoenolpyruvate
- Umpolung chemistry with thiamine as a d^1 reagent
- Carboxylation with biotin
- Oxidations with FAD
- How Nature makes aromatic amino acids

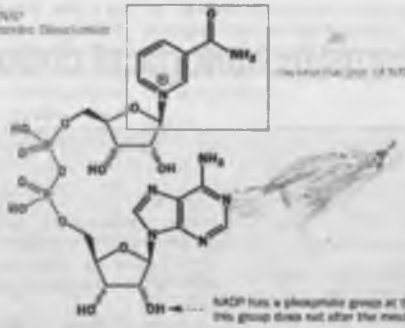
Looking forward to:
- Natural products ch51

Nature's $NaBH_4$ is a nucleotide: NADH or NADPH

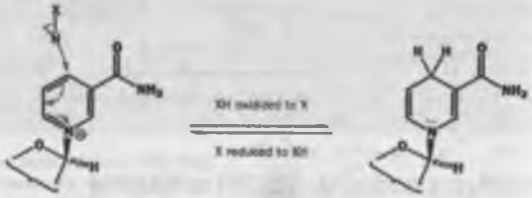
In Chapter 49 we spent some time discussing the structure of nucleotides and their role as codons in protein synthesis. Now we shall see how Nature uses different nucleotides as reagents. Here is the structure of AMP, just to remind you, side by side with a new pyridine nucleotide.



These two nucleotides can combine together as a pyrophosphate to give a dinucleotide. Notice that the link is not at all the same as in the nucleic acids. The latter are joined by one phosphate that links the 3'–5' positions. Here we have a *pyrophosphate* link between the two 5'-positions.



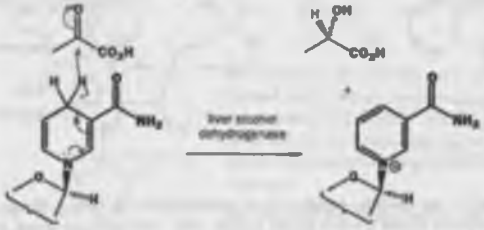
Notice also the positive charge on the nitrogen atom of the pyridine ring. This part of the molecule does all the work and from now on we will draw only the reactive part for clarity. This is NAD$^+$, nicotine adenine dinucleotide, and it is one of Nature's most important oxidizing agents. Some reactions use NADP instead but this differs only in having an extra phosphate group on the adenosine portion so the same part structure will do for both. NAD$^+$ and NADP both work by accepting a hydrogen atom and a pair of electrons from another compound. The reduced compounds are called NADH and NADPH.



NAD$^+$ — Nature's oxidizing agent NADH — Nature's reducing agent

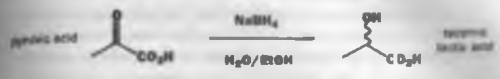
The reduction of NAD$^+$ (and NADP) is reversible, and NADH is itself a reducing agent. We will first look at one of its reactions: a typical reduction of a ketone. The ketone is pyruvic acid and the reduction product lactic acid, two important metabolites. The reaction is catalyzed by the enzyme liver alcohol dehydrogenase.

▶ The names of enzymes are usually chosen to tell us where they come from and what job they do and the name ends '-ase'. A dehydrogenase is clearly a redox enzyme as it removes (or adds) hydrogen.

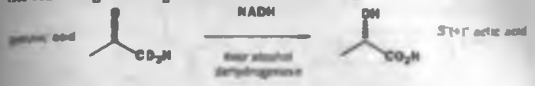


NADH — Nature's reducing agent NAD$^+$ — Nature's oxidizing agent

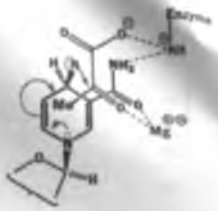
This is a reaction that would also work in the laboratory with $NaBH_4$ as the reducing agent, but there is a big difference. The product from the $NaBH_4$ reaction *must* be racemic—no optical activity has been put in from compound, reagent, or solvent.



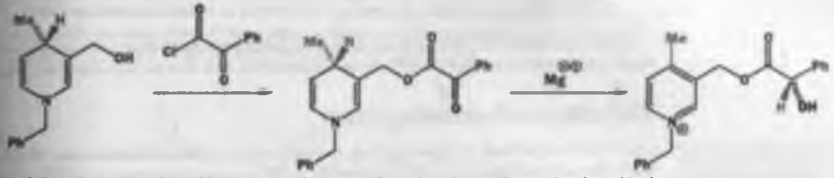
But the product from the enzymatic reaction is optically active. The two faces of pyruvic acid's carbonyl group are enantiotopic and, by controlling the addition so that it occurs from one face only, the reaction gives a single enantiomer of lactic acid.



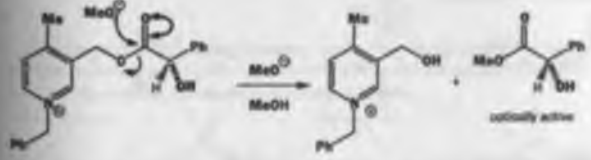
Both the enzyme and the reagent NADH are single enantiomers and they cooperate by binding. The enzyme binds both the substrate (pyruvic acid) and the reagent (NADH) in a specific way so that the hydride is delivered to one enantiotopic face of the ketone. Pyruvic acid under physiological conditions will be the anion, pyruvate, so it is held close to the positively charged amino group of a lysine residue on the enzyme that also binds the amino group of NADH. A magnesium(II) cation, also held by the enzyme, binds the carbonyl group of the amide of NADH and the ketone in pyruvate. If this model is correct, only the top H atom (as drawn) of the diastereotopic CH_2 group in NADH should be transferred to pyruvate. This has been proved by deuterium labelling.



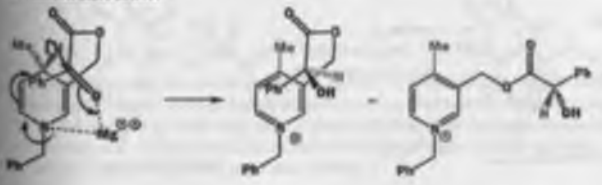
Supporting evidence comes from a model system using a much simpler reducing agent. A dihydropyridine with a primary alcohol replacing the amide group in NADH and a simple benzyl group replacing the nucleotide forms stable esters with keto-acids. As soon as the ester is treated with magnesium(II) ions, intramolecular and stereospecific reduction occurs. The hydride ion is transferred from a stereogenic centre, which replaces the diastereotopic CH_2 group in NADH.



When the ester is cleaved by transesterification with methoxide ion, the newly released hydroxyester is optically active.

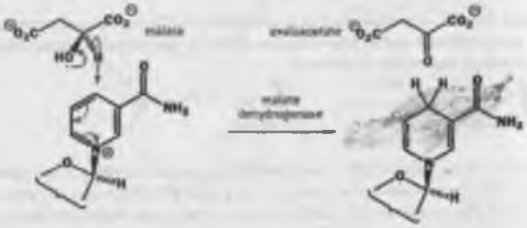


The details of the reaction are probably a good model for the NADH reaction even down to the activation by magnesium(II) ions. A possible transition state would be very similar to the NADH transition state above.



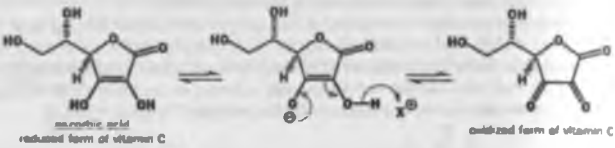
▶ The other two reactions are of a more complex type that we will meet soon when we show how acetyl coenzyme A is a key reagent in the building of carbon–carbon chains.

Many other reactions use NADH as a reducing agent or NAD^+ as oxidizing agent. These molecules of NAD^+ are used in the citric acid cycle (see the chart on p. 000). One of these oxidations is the simple transformation of a secondary alcohol (malate) to a ketone (oxaloacetate).



▶ Ascorbic acid is usually described as an antioxidant rather than a reducing agent though mechanistically they are the same.

Other redox reagents include dinucleotides such as FAD (flavine adenine dinucleotide), lipoic acid, which we will meet when we discuss the chemistry of thiamine, and ascorbic acid (vitamin C), which you met in Chapter 49. Ascorbic acid can form a stable enolate anion that can transfer a hydride ion to a suitable oxidant.

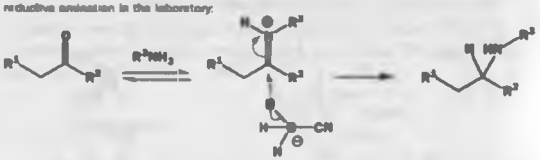


In this mechanism 'X^{n+}' represents an oxidant—a dangerously reactive peroxide perhaps, or even Fe(III) which must be reduced to Fe(II) as part of the reaction cycle of many iron-dependent enzymes.

Reductive amination in nature

■ For more on reductive amination, see Chapter 14.

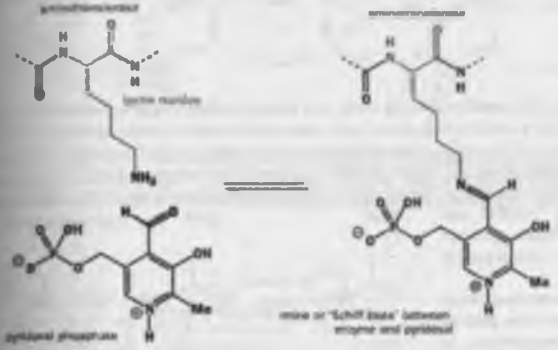
One of the best methods of amine synthesis in the laboratory is **reductive amination**, in which an imine (formed from a carbonyl compound and an amine) is reduced to a saturated amine. Common reducing agents include $NaCNBH_3$ and hydrogen with a catalyst.



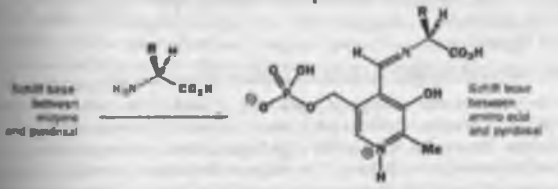
This reaction, of course, produces racemic amines. But Nature transforms this simple reaction into a stereospecific and reversible one that is beautiful in its simplicity and cleverness. The reagents are a pair of substituted pyridines called **pyridoxamine** and **pyridoxal**.

You might imagine that pyridoxamine is a product of reductive amination of pyridoxal with ammonia. In practice it doesn't work like that. Nature uses an amine transfer rather than a simple reductive amination, and the family of enzymes that catalyse the process is the family of aminotransferases.

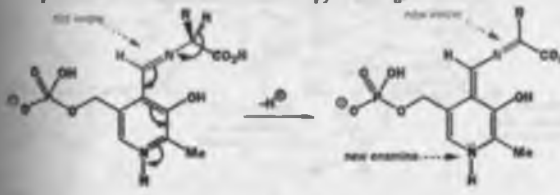
Pyridoxal is a coenzyme and it is carried around on the side chain of a lysine residue of the enzyme. Lysine has a long flexible side chain of four CH_2 groups ending with a primary amine (NH_2). This group forms an imine (what biochemists call a 'Schiff base') with pyridoxal. An imine is a good functional group for this purpose as imine formation is easily reversible.



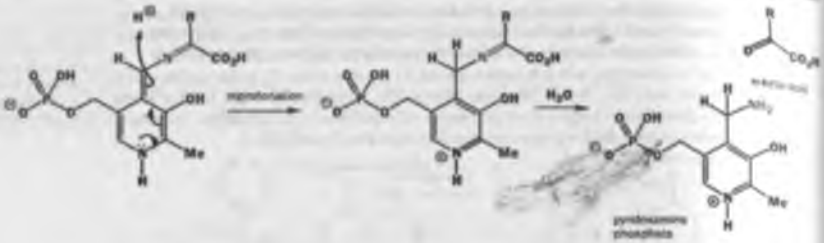
When reductive amination or its reverse is required, the pyridoxal is transferred from the lysine imine to the carbonyl group of the substrate to form a new imine of the same sort. The most important substrates are the amino acids and their equivalent α-keto-acids.



Now the simple but amazing chemistry begins. By using the protonated nitrogen atom of the pyridine as an electron sink, the α proton of the amino acid can be removed to form a new imine at the top of the molecule and an enamine in the pyridine ring.

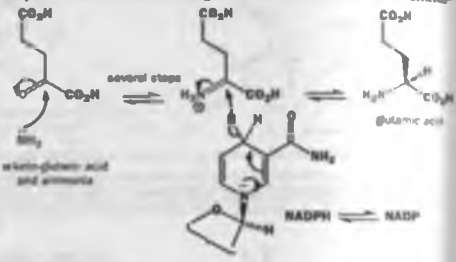


Now the electrons can return through the pyridine ring and pick up a proton at the top of the molecule. The proton can be picked up where it came from, but more fruitfully it can be picked up at the carbon atom on the other side of the nitrogen. Hydrolysis of this imine releases pyridoxamine and the keto-acid. All the natural amino acids are in equilibrium with their equivalent α-keto-acids by this mechanism, catalysed by an aminotransferase.



Reversing this reaction makes an amino acid stereospecifically out of an α-keto-acid. In fact, a complete cycle is usually set up whereby one amino acid is converted to the equivalent α-keto-acid while another α-keto-acid is converted into its equivalent amino acid. This is true transamination.

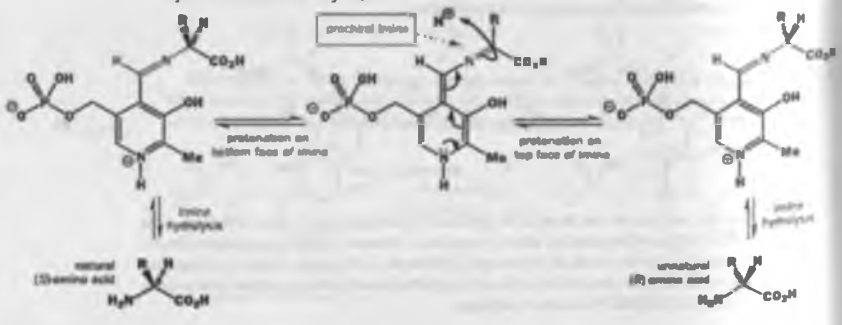
Amino acids get used up (making proteins, for example) so, to keep life going, ammonia must be brought in from somewhere. The key amino acid in this link is glutamic acid. A true reductive amination using NADPH and ammonia builds glutamic acid from α-keto-glutaric acid.



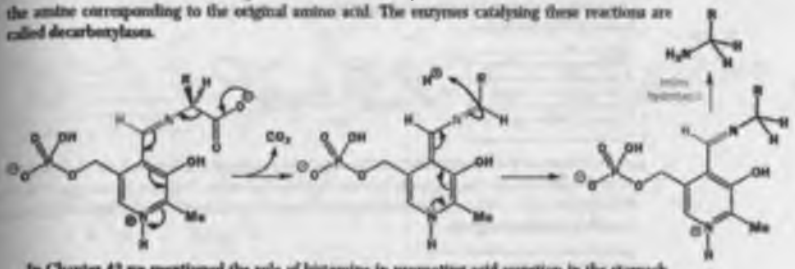
The other amino acids can now be made from glutamic acid by transamination. At the end of their useful life they are transaminated back to glutamic acid which, in mammals at least, gives its nitrogen to urea for excretion.

Pyridoxal is a versatile reagent in the biochemistry of amino acids

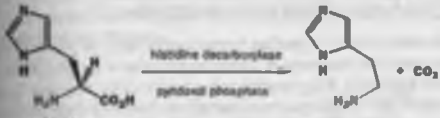
Pyridoxal is the reagent in other reactions of amino acids, all involving the imine as intermediate. The simplest is the racemization of amino acids by loss of a proton and its replacement on the other face of the enamine. The enamine, in the middle of the diagram below, can be reprotonated on either face of the prochiral imine (shown in green). Protonation on the bottom face would take us back to the natural amino acid from which the enamine was made in the first place. Protonation on the top face leads to the unnatural amino acid after 'hydrolysis' of the imine (really transfer of pyridoxal to a lysine residue of the enzyme).



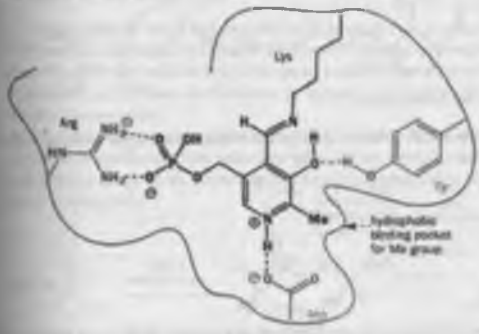
A very similar reaction is decarboxylation. Starting from the same imine we could lose carbon dioxide instead of a proton by a very similar mechanism. Reprotonation and imine transfer releases the amine corresponding to the original amino acid. The enzymes catalysing these reactions are called decarboxylases.



In Chapter 43 we mentioned the role of histamine in promoting acid secretion in the stomach, and its role in causing gastric ulcers. The drug cimetidine was designed to counteract the effect of histamine. Histamine is produced in the body by decarboxylation of histidine using the mechanism you have just seen.



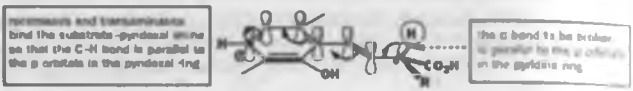
How is it possible for the same reagent operating on the same substrate (an amino acid) to do at will one of two quite different things—removal and/or exchange of a proton and decarboxylation? The answer, of course, lies in the enzymes. These hold pyridoxal exceptionally tightly by using all the available handles: the hydroxy and phosphate groups, the positively charged nitrogen atom, and even the methyl group. The diagram shows the proposed binding of the lysine imine of pyridoxal by an aminotransferase.

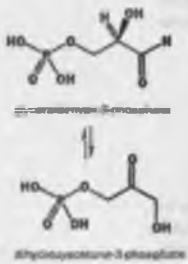


The green line shows an imaginary shape of the enzyme chain into which fit acidic groups and basic groups forming hydrogen bonds to groups on the coenzyme. Around the methyl group are alkyl-substituted amino acids, which form a hydrophobic region. Even when the lysine attachment is exchanged for the substrate, all these interactions remain in place. The substrate is bound by similar interactions with other groups on the enzyme.

Control over the choice of reaction arises because the different enzymes bind the substrate–pyridoxal imine in different ways. Decarboxylases bind so that the C–C bond to be broken is held orthogonal to the pyridine ring and parallel to the p orbitals in the ring. Then the bond can be broken and CO_2 can be lost.

Racemases and transaminases bind the substrate–pyridoxal imine so that the C–H bond is parallel to the p orbitals in the ring so that proton removal can occur. Enzymes do not speed reactions up indiscriminately—they can selectively accelerate some reactions at the expense of others, even those involving the same reagents.

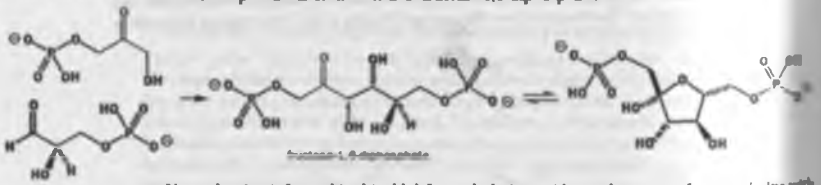




Nature's enols—lysine enamines and coenzyme A

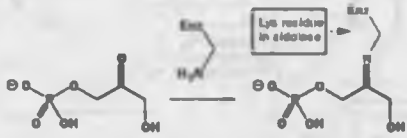
The glycolysis pathway breaks down glucose to produce energy, and in doing so produces smaller molecules for use in the citric acid cycle. In reverse, it allows the synthesis of the six-carbon sugar fructose from two three-carbon fragments. A key reaction is the step in which these two C_3 units combine. They are glyceraldehyde and dihydroxyacetone and we met them and their interconversion in the last chapter.

The reaction is effectively an aldol condensation between the enol of the keto-sugar phosphate and the electrophilic aldehyde of glyceraldehyde phosphate and the enzyme is named appropriately **aldolase**. The product is the keto-hexose fructose-1,6-diphosphate.

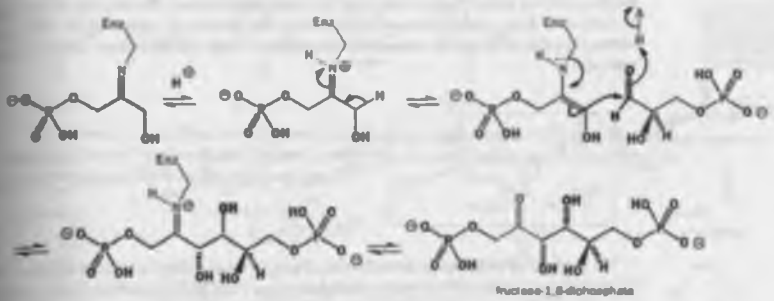


■ The rest of the aldolase molecule is represented by 'Enz'.

No enolate ion is formed in this aldol. Instead a lysine residue in the enzyme forms an imine with the keto-triose.



Proton transfers allow this imine to be converted into an enamine, which acts as the nucleophile in the aldol reaction. Stereochemical control (it's a *syn* aldol) comes from the way in which the two molecules are held by the enzyme as they combine. The product is the imine, which is hydrolysed to the open-chain form of fructose-1,6-diphosphate.

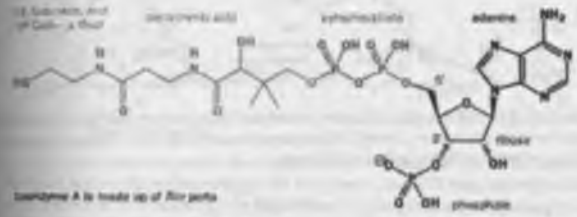


fructose-1,6-diphosphate

Many other reactions in nature use enamines, mostly those of lysine. However, a more common enol equivalent is based on thiol esters derived from coenzyme A.

Coenzyme A and thiol esters

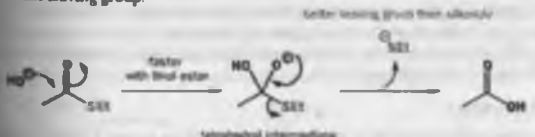
Coenzyme A is an adenine nucleotide at one end, linked by a 5'-pyrophosphate to pantothenic acid, a compound that looks rather like a tripeptide, and then to an amino thiol. Here is the structure broken down into its parts.



Coenzyme A is made up of five parts

By now you will realize that most of this molecule is there to allow interaction with the various enzymes that catalyse the reactions of coenzyme A. We will abbreviate it from now on as CoASH where the SH is the vital thiol functional group, and all the reactions we will be interested in are those of esters of CoASH. These are thiol esters, as opposed to normal 'alcohol esters', and the difference is worth a few comments.

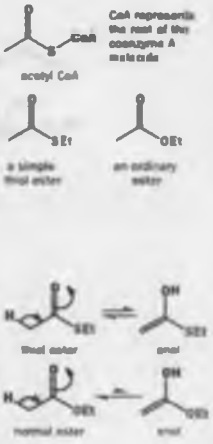
Thiol esters are less conjugated than ordinary esters (see Chapter 28, p. 800), and ester hydrolysis occurs more rapidly with thiol esters than with ordinary esters because in the rate-determining step (nucleophilic attack on the carbonyl group) there is less conjugation to destroy. The thiolate is also a better leaving group.



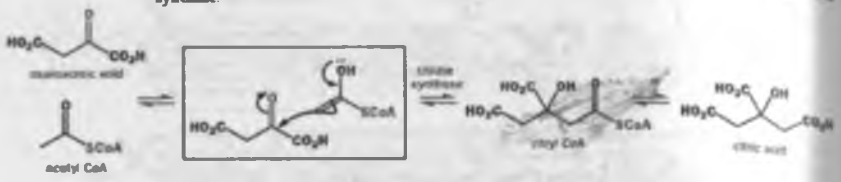
tetrahedral intermediate

Another reaction that goes better with thiol esters than with ordinary esters is enolization. This is an equilibrium reaction and the enol has lost the conjugation present in the ester. The thiol ester has less to lose so is more enolized. This is the reaction of acetyl CoA that we are now going to discuss. We have mentioned the citric acid cycle several times and it has appeared in two

▶ Compare this structure with that of NAD— the adenine nucleotide is the same, as is the 5'-pyrophosphate link. The difference is at the other end of that link where we find this new tripeptide-like molecule and not another nucleotide. There is also a 3'-phosphate on the ribose ring not present in NAD.

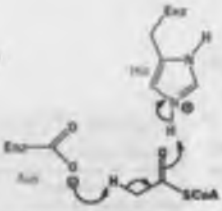


diagrams but we have not so far discussed the chemistry involved. The key step is the synthesis of citric acid from oxaloacetate and acetyl CoA. The reaction is essentially an aldol reaction between the enol of an acetate ester and an electrophilic ketone and the enzyme is known as citrate synthase.

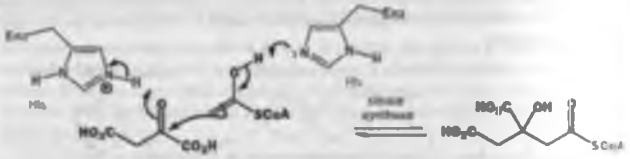


The mechanism in the frame shows the enol of acetyl CoA attacking the reactive ketone. In nature the enolization is catalysed by a basic carboxylate group (Asp) and an acidic histidine, both part of the enzyme, so that even this easy reaction goes faster.

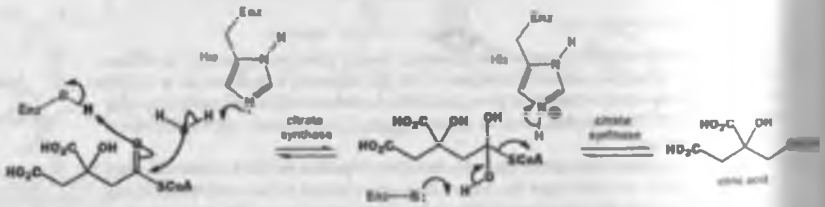
In the C–C bond-forming step, the same histidine is still there to remove the enol proton again and another histidine, in its protonated form, is placed to donate a proton to the oxygen atom of the ketone. You should see now why histidine, with a pK_{aH} of about 7, is so useful to enzymes: it can act either as an acid or as a base.



▶ This is general acid catalysis, as described in Chapter 41.



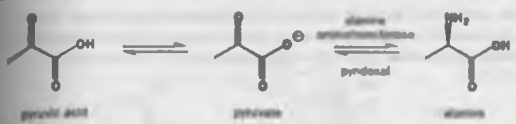
Even the hydrolysis of the reactive thiol ester is catalysed by the enzyme and the original histidine again functions as a proton donor. Acetyl CoA has played its part in all steps. The enolization and the hydrolysis in particular are better with the thiol ester.



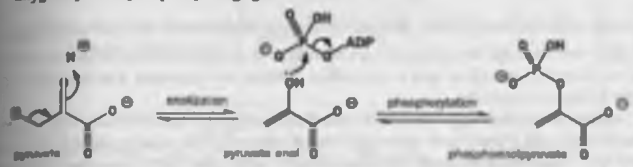
CoA thiol esters are widely used in nature. Mostly they are acetyl CoA, but other thiol esters are also used to make enols. We will see more of this chemistry in the next chapter. The two enol equivalents that we have met so far are quite general: lysine enamines can be used for any aldehyde or ketone and CoA thiol esters for any ester. Another class of enol equivalent—the enol ester—has just one representative but it is a most important one.

Phosphoenolpyruvate

Pyruvic acid is an important metabolite in its own right as we shall see shortly. It is the simplest α-keto-acid (2-oxopropanoic acid). Having the two carbonyl groups adjacent makes them more reactive: the ketone is more electrophilic and enolizes more readily and the acid is stronger. Pyruvate is in equilibrium with the amino acid alanine by an aminotransferase reaction catalysed by pyridoxal (above).

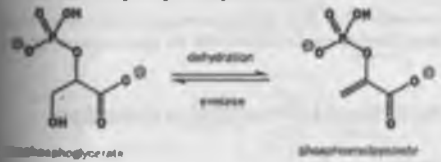


Nature uses the enol phosphate of pyruvic acid (phosphoenolpyruvate or PEP) as an important reagent. We might imagine making this compound by first forming the enol and then esterifying an oxygen by some phosphorylating agent such as ATP.

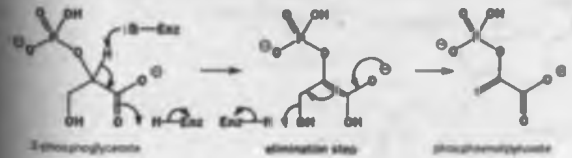


Now, in fact, this reaction does occur in nature as part of the glycolysis pathway, but it occurs almost entirely in reverse. PEP is used as a way to make ATP from ADP during the oxidation of energy-storing sugars. An enol is a better leaving group than an ordinary alcohol especially if it can be protonated at carbon. The reverse reaction might look like this.

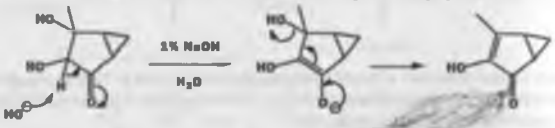
PEP is also used as an enol in the making of carbon–carbon bonds when the electrophile is a sugar molecule and we will see this reaction in the next chapter. So, if PEP is not made by enolization of pyruvate, how is it made? The answer is by dehydration. The phosphate is already in place when the dehydration occurs, catalysed by the enzyme enolase.



You saw in Chapter 19 how simple OH groups could be lost in dehydration reactions. Either the OH group was protonated by strong acid (this is not an option in living things) or an enol or enolate pushed the OH group out in an E1cB-like mechanism. This must be the case here as the better leaving group (phosphate) is ignored and the worse leaving group (OH) expelled.



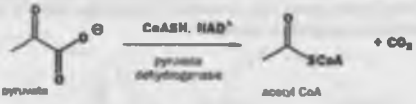
This would be an unusual way to make an enol in the laboratory but it can be used, usually to make stable enols. An example that takes place under mildly basic conditions is the dehydration of the bicyclic keto-diol in dilute sodium hydroxide—presumably by an E1cB mechanism.



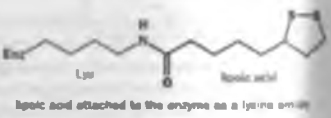
Pyruvic acid and acetyl CoA: the link between glycolysis and the citric acid cycle

We have now examined the mechanism of several steps in glycolysis and one in the citric acid cycle and we have seen enough to look at the outline of these two important processes and the link between them (see opposite).

You have already seen that citric acid is made from acetyl CoA. The acetyl CoA comes in its turn from pyruvic acid. Pyruvic acid comes from many sources but the most important is glycolysis. acetyl CoA is the link between glycolysis and the citric acid cycle. The key reaction involves both CoASH and pyruvate and carbon dioxide is lost. This is an oxidation as well and the oxidant is NAD^+. The overall reaction is easily summarized.



This looks like a simple reaction based on very small molecules. But look again. It is a very strange reaction indeed. The molecule of CO_2 clearly comes from the carboxyl group of pyruvate, but how is the C–C bond cleaved, and how does acetyl CoA join on? If you try to draw a mechanism you will see that there must be more to this reaction than meets the eye. The extra features are two new cofactors, thiamine pyrophosphate and lipoic acid, and the reaction takes place in several stages with some interesting chemistry involved.



lipoic acid attached to the enzyme as a lysine amide

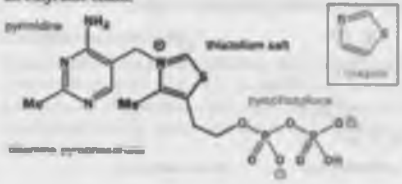
Lipoic acid is quite a simple molecule with a cyclic disulfide as its main feature. It is attached to the enzyme as an amide with lysine. Our first concern will be with the much more complex coenzyme thiamine pyrophosphate.

Nature's acyl anion equivalent (d^1 reagent) is thiamine pyrophosphate

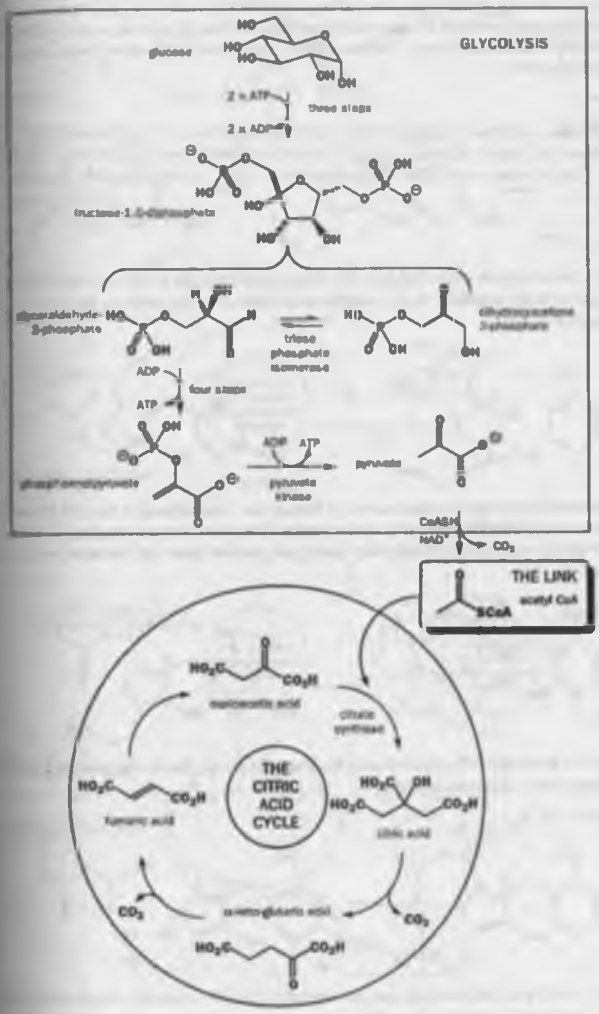
▶ We will abbreviate pyrophosphate to 'OPP' in structures.

▶ Do not confuse thiamine with thymine, one of the pyrimidine bases on DNA. The DNA base thymine is just a pyrimidine; thymidine is the corresponding nucleoside. The coenzyme thiamine is a more complicated molecule, that contains a different pyrimidine.

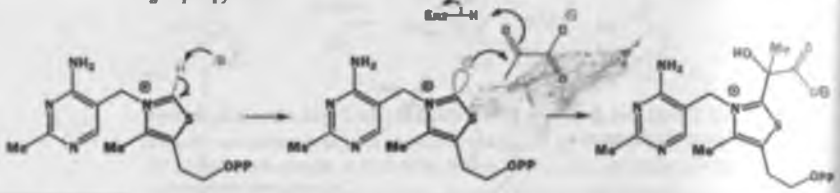
Thiamine pyrophosphate looks quite like a nucleotide. It has two heterocyclic rings, a pyrimidine similar to those found in DNA and a thiazolium salt. This ring has been alkylated on nitrogen by the pyrimidine part of the molecule. Finally, there is a pyrophosphate attached to the thiazolium salt by an ethyl side chain.



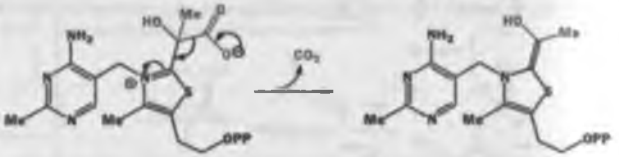
the link between glycolysis and the citric acid cycle



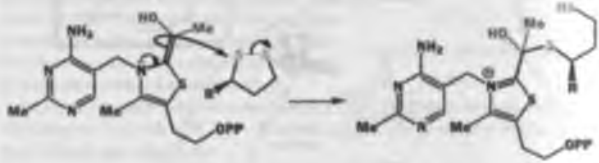
The key part of the molecule for reactivity is the thiazolium salt in the middle. The proton between the N and S atoms can be removed by quite weak bases to form an ylid. You saw sulfonium ylids in Chapter 46, and there is some resemblance here, but this ylid is an ammonium ylid with extra stabilization from the sulfur atom. The anion is in an sp^2 orbital, and it adds to the reactive carbonyl group of pyruvate.



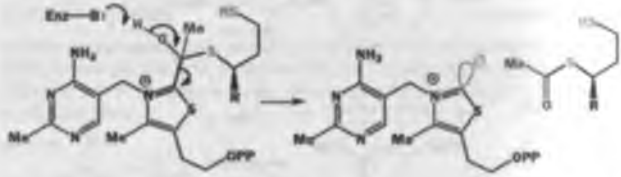
Now the carboxylate can be lost from the former pyruvate as the positively charged imine in the thiamine molecule provides a perfect electron sink to take away the electrons from the C–C bond that must be broken.



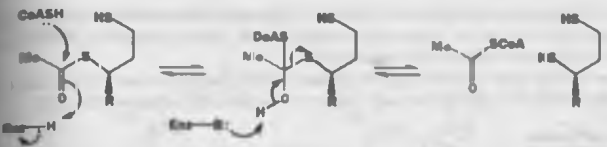
This new intermediate contains a new and strange C=C double bond. It has OH, N, and S substituents making it very electron-rich. As the nitrogen is the most electron-donating you can view it as an enamine, and it attacks the disulfide functional group of lipoic acid, the other cofactor in the reaction.



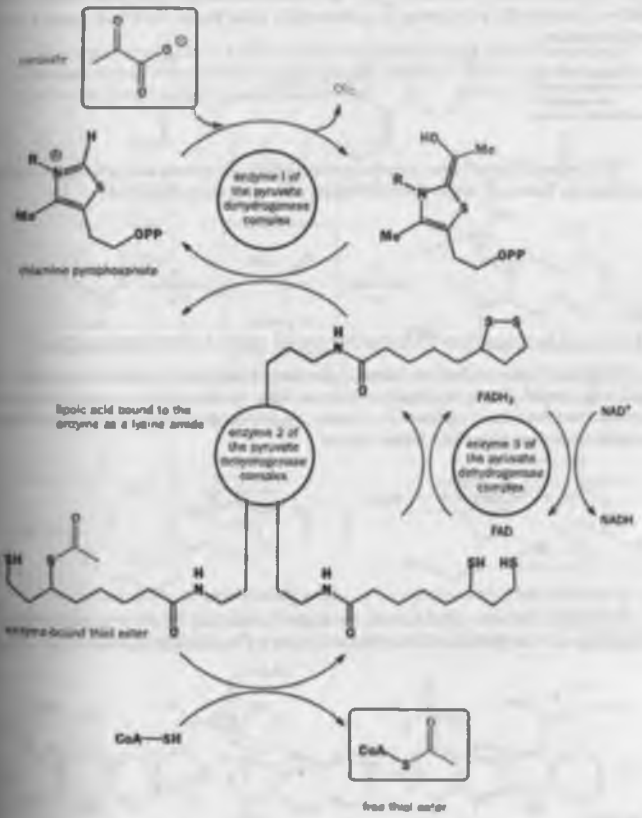
Now the thiamine can be expelled using the green OH group. The leaving group is again the ylid of thiamine, which functions as a catalyst.



The product is a thiol ester and so can exchange with CoASH in a simple ester exchange reaction. This is a nucleophilic attack on the carbonyl group and will release the reduced form of lipoic acid. All that is necessary to complete the cycle is the oxidation of the dithiol back to the disulfide. This is such an easy reaction to do that it would occur in air anyway but it is carried out in nature by FAD, a close relative of NAD^+.



This is one of the most complicated sequences of reactions that we have discussed so far. It is critical to living things because it links glycolysis and the citric acid cycle. Nature has provided not one enzyme but three enzymes to catalyse this process. In the cell they are massed together as a single protein complex.



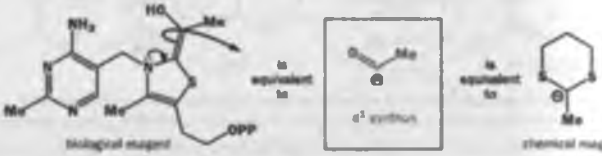
At the centre is 'enzyme 2' which binds the acetyl group through a lipoic acid–lysine amide. On the one side this acetyl group is delivered from pyruvate by the ministrations of thiamine pyrophosphate and 'enzyme 1' and on the other it is delivered to CoA as the free thiol ester. Enzyme 3 recycles

the reduced lipoic acid using FAD and then NAD^+. This remarkable assembly of proteins maintains stocks of acetyl CoA for use in the citric acid cycle and for building complex organic molecules by enol chemistry, as we will see in the next chapter.

One reaction in this sequence is worth detailed analysis. The enzyme-bound lipoic thiol ester is a perfectly normal thiol ester and we would expect it to be formed by acylation of the thiol.

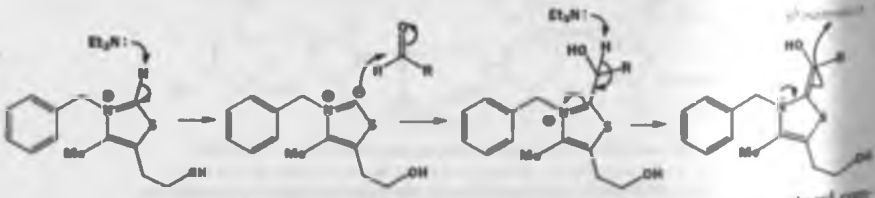
But this thiol ester is not formed by the expected mechanism in the enzymatic reaction. Thiamine delivers a nucleophilic acetyl group to an *electrophilic* sulfur atom—the reverse polarity to normal ester formation.

The compound formed from thiamine pyrophosphate and pyruvic acid is Nature's nucleophilic acetyl group. This is a d^1 reagent like the dithiane anion you met in Chapter 46.



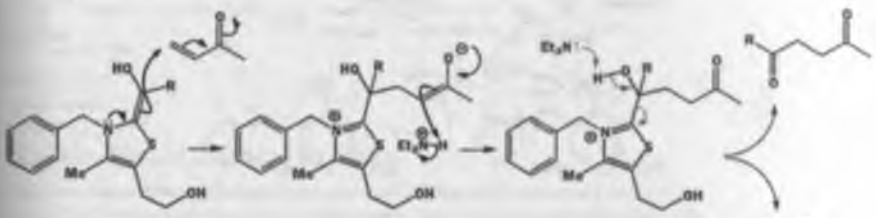
If this is really true and not just a theoretical analogy, it ought to be possible to learn from Nature and design useful d^1 reagents based on thiamine. This was done by Stetter using simplified thiamines. The pyrimidine is replaced by a benzene ring and the pyrophosphate is removed. This leaves a simple thiazolium salt called a Stetter reagent.

By analogy with the biological reaction, we need only a weak base (Et_3N) to make the ylid from the thiazolium salt. The ylid adds to aldehydes and creates a d^1 nucleophile equivalent to an acyl anion.

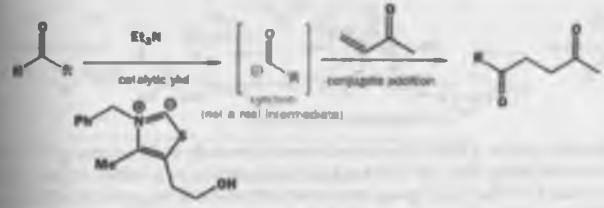


A useful application of these reagents is in conjugate addition to unsaturated carbonyl compounds. Few d^1 reagents will do this as most are very basic and prefer to add directly to the carbonyl

group. Notice that a tertiary amine, pK_{aH} about 10, is strong enough to remove both protons in this sequence.

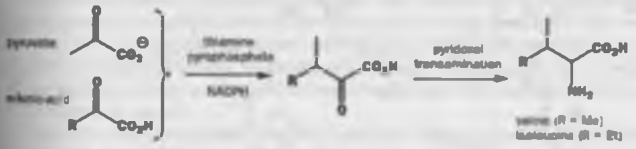


The organic product is a 1,4-diketone and the thiazolium ylid is released to continue with another cycle of the reaction. Like thiamine, the thiazolium ylid is catalyst. Processes like this, which copy nature, are called biomimetic.

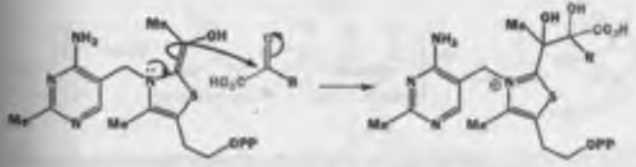


Rearrangements in the biosynthesis of valine and isoleucine

In nature, thiamine pyrophosphate also catalyses reactions of α-keto-acids other than pyruvic acid. One such sequence leads through some remarkable chemistry to the biosynthesis of the branched-chain amino acids valine and isoleucine.

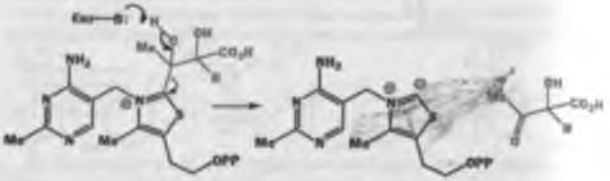


The remarkable aspect of this chemistry is that it involves 1,2-alkyl shifts in pinacol-like rearrangements (Chapter 37). The sequence starts as before and we will pick it up after the addition and decarboxylation of pyruvate and as the resulting d^1 reagent adds to the new α-keto-acid.

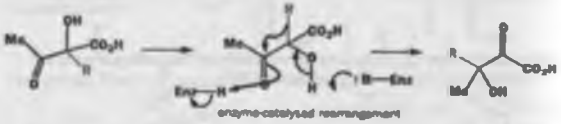


Decomposition of this product with the release of the thiazolium ylid also releases the product of coupling between the two keto-acids: a 1-hydroxy-2-keto-acid (in green). The original keto group of

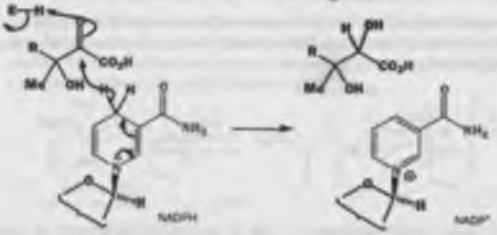
the pyruvate reappears—it's clear that an acetyl anion equivalent (the d^1 reagent) has added to the keto group of the new keto-acid. The thiazolium ylid is free to catalyse the next round of the reaction.



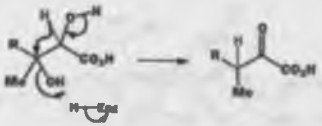
The green hydroxy-keto-acid is now primed for rearrangement. The migration of the group R is pushed by the removal of a proton from the OH group and pulled by the electron-accepting power of the keto group. Notice that the group R (Me or Et) migrates in preference to CO_2H. Usually in rearrangements the group better able to bear a positive charge migrates (Chapter 37).



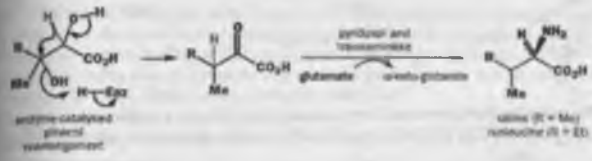
Control in this reaction is likely to be exerted stereoelectronically by the enzyme as it was in the pyridoxal reactions above. Since the C–R bond is held parallel to the p orbitals of the ketone, R migration occurs, but if the CO_2H group were to be held parallel to the p orbitals of the ketone, decarboxylation would occur. Next, a simple reduction with NADPH converts the ketone into an alcohol and prepares the way for a second rearrangement.



The second rearrangement is even more like a pinacol rearrangement because the starting material is a 1,2-diol. The tertiary alcohol is protonated and leaves, and again the CO_2H group does not migrate even though the alternative is merely hydride.

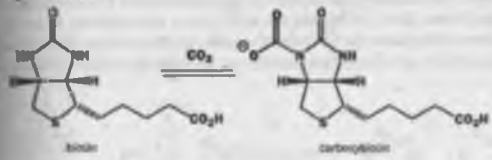


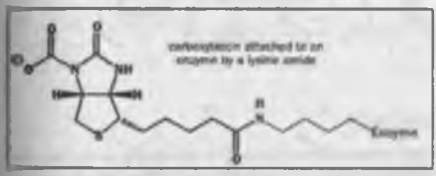
Finally, a pyridoxal transamination converts the two keto-acids stereospecifically to the corresponding amino acids, valine (R = Me) and isoleucine (R = Et). The donor amino acid is probably glutamate—it usually is in amino acid synthesis.



Carbon dioxide is carried by biotin

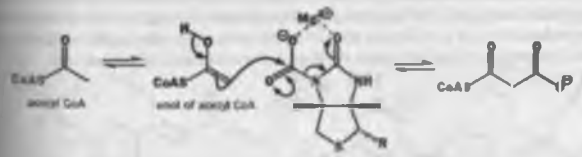
We have added and removed carbon dioxide on several occasions in this chapter and the last but we have not until now said anything about how this happens. You would not expect gaseous CO_2 to be available inside a cell: instead CO_2 is carried around as a covalent compound with another coenzyme—**biotin**.





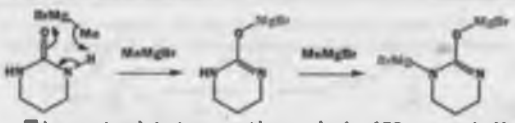
Biotin has two fused five-membered heterocyclic rings. The lower is a cyclic sulfide and has a long side chain ending in a carboxylic acid for attachment—yes, you've guessed it—to a lysine residue of a protein. The upper ring is a urea—it has a carbonyl group flanked by two nitrogen atoms. It is this ring that reversibly captures CO_2, on the nitrogen atom opposite the long side chain. The attachment to the enzyme as a lysine amide gives it an exceptionally long flexible chain and allows it to deliver CO_2 wherever it's needed.

One of the important points at which CO_2 enters as a reagent carried by biotin is in fatty acid biosynthesis where CO_2 is transferred to the enol of acetyl CoA. A magnesium(II) ion is also required and we may imagine the reaction as a nucleophilic attack of the enol on the magnesium salt of carboxybiotin. Most of the CO_2 transfers we have met take place by mechanisms of this sort: nucleophilic attack on a bound molecule of CO_2, usually involving a metal ion.

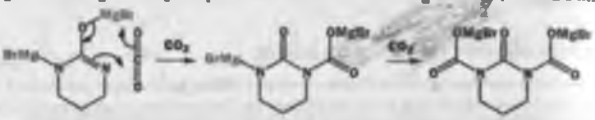


Very similar reactions can be carried out in the laboratory. This simple cyclic urea reacts twice with the Grignard reagent MeMgBr to give a dimagnesium derivative, probably having the structure shown with one O–Mg and one N–Mg bond.

■ We will see in the next chapter how acetoacetyl CoA is used in the biosynthesis of fatty acids and polyketides.

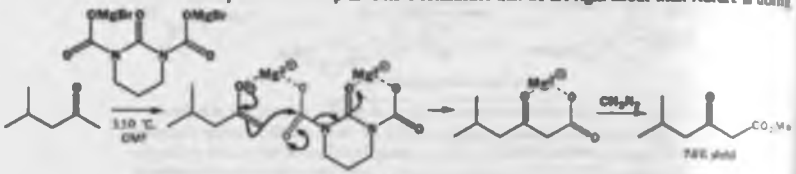


This magnesium derivative reacts with two molecules of CO_2 to give a double adduct with both nitrogens combining with CO_2. The product is stable as the double magnesium salt, which is a white powder.

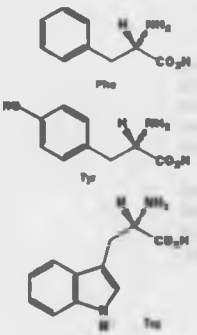


Diazomethane esterification appeared in Chapter 40, p. 000

Simply heating this white powder with a ketone leads to efficient carboxylation and the unstable keto-acid may be trapped with diazomethane to form the stable methyl ester. The mechanism is presumably very like that drawn above for the transfer of CO_2 from carboxybiotin to acetyl CoA. Reactions like this *prove* nothing about the biochemical reaction but they at least show us that such reactions are possible and help us to have confidence that we are right about what Nature is doing.

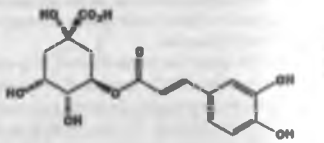


The shikimic acid pathway

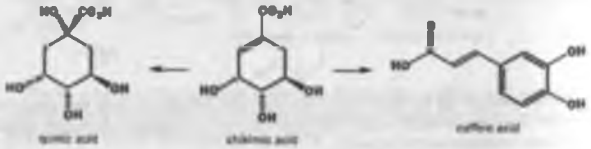


We have described reactions from various different pathways in this chapter so far, but now we are going to look at one complete pathway in detail. It is responsible for the biosynthesis of a large number of compounds, particularly in plants. Most important for us is the biosynthesis of the aromatic amino acids Phe (phenylalanine), Tyr (tyrosine), and Trp (tryptophan). These are 'essential' amino acids for humans—we have to have them in our diet as we cannot make them ourselves. We get them from plants and microorganisms.

So how do plants make aromatic rings? A clue to the chemistry involved comes from the structure of caffeyl quinic acid, a compound that is present in instant coffee in some quantity. It is usually about 15% of the soluble solids from coffee beans.



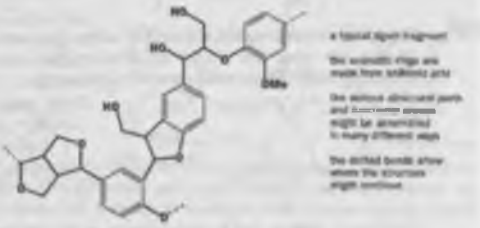
This ester has two six-membered rings—one aromatic and one rather like the sugar alcohols we were discussing in the last chapter. You might imagine making an aromatic ring by the dehydration (losing three molecules of water) of a cyclohexane triol and the saturated ring in caffeyl quinic acid looks a good candidate. It is now known that both rings come from the same intermediate, shikimic acid.

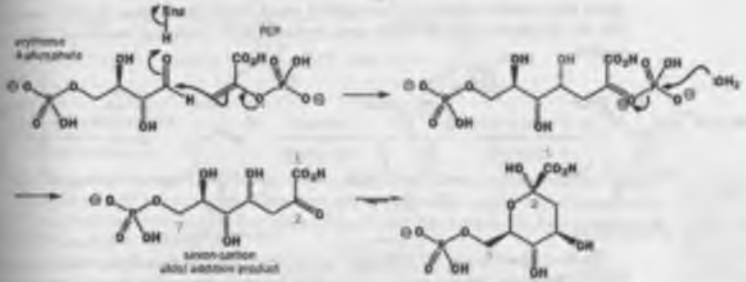


This key intermediate has given its name to Nature's general route to aromatic compounds and many other related six-membered ring compounds: the **shikimic acid pathway**. This pathway contains some of the most interesting reactions (from a chemist's point of view) in biology. It starts with an aldol reaction between phosphoenol pyruvate as the nucleophilic enol component and the C_4 sugar erythrose 4-phosphate as the electrophilic aldehyde.

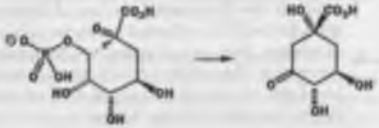
Wood

Even the structural material of plants, lignin, comes from the shikimic acid pathway. Lignin— from which wood is made— has a variable structure according to the plant and the position in the plant. A typical polymer is shown here.

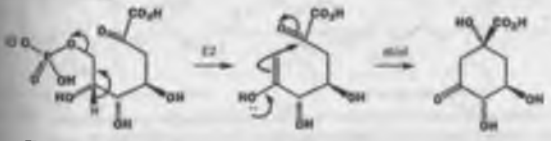




Hydrolysis of the phosphate releases the aldol product, a C_7 α-keto-acid with one new stereogenic centre, which is in equilibrium with a hemiacetal, just like a sugar. This intermediate has the right number of carbon atoms for shikimic acid and the next stage is a cyclization. If we redraw the C_7 α-keto-acid in the right shape for cyclization we can see what is needed. The green arrow shows only which bond needs to be formed.

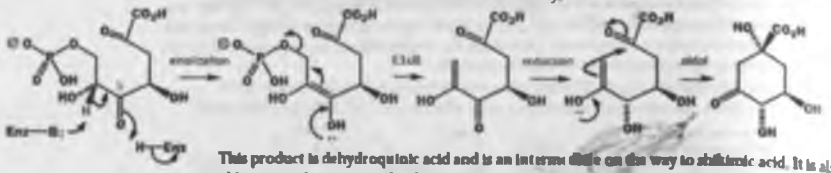


This reaction looks like an aldol reaction too and there is an obvious route to the required enol by elimination of phosphate. This would require the removal of a proton (green in the diagram) that is not at all acidic.

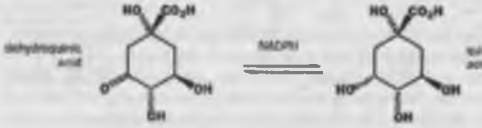


The problem can be avoided if the hydroxyl group at C5 is first oxidized to a ketone (NAD$^+$ is the oxidant). Then the green proton is much more acidic, and the elimination becomes an E1cB

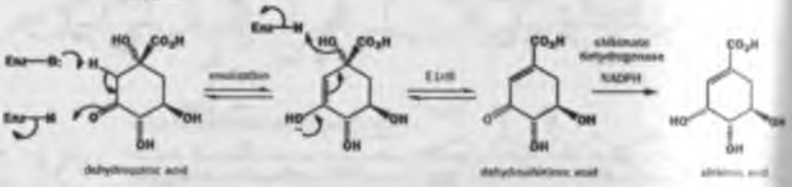
reaction, similar to the one in the synthesis of PEP. True, the ketone must be reduced back to the alcohol afterwards but Nature can deal with that easily.



This product is dehydroquinic acid and is an intermediate on the way to shikimic acid. It is also in equilibrium with quinic acid, which is not an intermediate on the pathway but which appears in some natural products like the coffee ester caffeyl quinic acid.

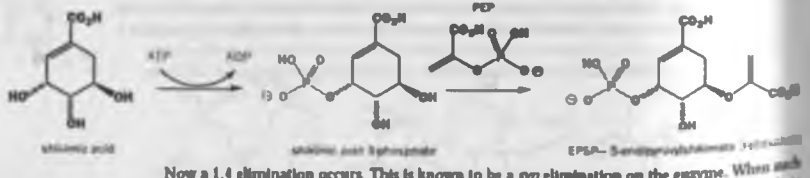


The route to shikimic acid in plants involves, as the final steps, the dehydration of dehydroquinic acid and then reduction of the carbonyl group. Doing the reactions this way round means that the dehydration can be E1cB—much preferred under biological conditions. This is what happens.

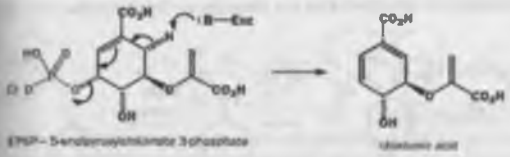


The final reduction uses NADPH as the reagent and is, of course, totally stereoselective with the hydride coming in from the top face of the green ketone as drawn. At last we have arrived at the halfway stage and the key intermediate, shikimic acid.

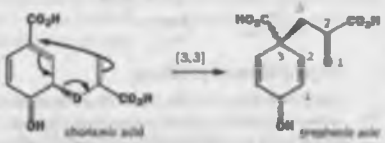
The most interesting chemistry comes in the second half of the pathway. The first step is a chemoselective phosphorylation of one of the three OH groups by ATP—as it happens, the OH group that has just been formed by reduction of a ketone. This step prepares that OH group for later elimination. Next, a second molecule of PEP appears and adds to the OH group at the other side of the molecule. This is PEP in its enol other role, forming an acetal under acid catalysis. The reaction occurs with retention of stereochemistry so we know that the OH group acts as a nucleophile and that the ring–OH bond is not broken.



Now a 1,4 elimination occurs. This is known to be a *syn* elimination on the enzyme. When such reactions occur in the laboratory, they can be *syn* or *anti*. The leaving group is the green phosphate added two steps before.

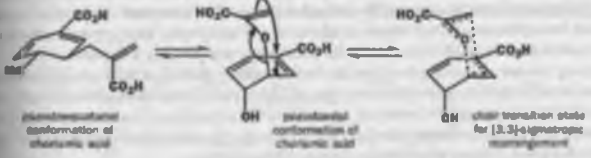


The product is chorismic acid and this undergoes the most interesting step of all—a [3,3]-sigmatropic rearrangement. Notice that the new (black) σ bond forms on the same face of the ring as the old (green) σ bond: this is, as you should expect, a suprafacial rearrangement.



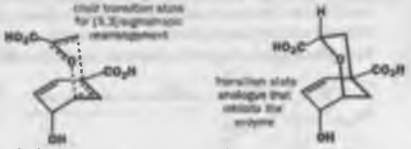
■ For more on sigmatropic rearrangements, see Chapter 35.

The most favourable conformation for chorismic acid has the substituents pseudoequatorial but the [3,3]-sigmatropic rearrangement cannot take place in that conformation. First, the diaxial conformation must be formed and the chair transition state achieved. Then the required orbitals will be correctly aligned.

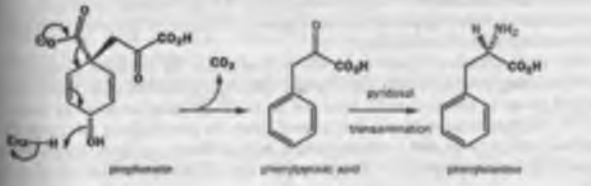


These reactions occur well without the enzyme (Chapter 36) but the enzyme accelerates this reaction by about a 10^6 increase in rate. There is no acid or base catalysis and we may suppose that the enzyme binds the transition state better than it binds the starting materials. We know this to be the case, because close structural analogues of the six-membered ring transition *state* also bind to the enzyme and stop it working. An example is shown alongside—a compound that resembles the transition state but can't react.

▶ By binding the transition state (not the starting materials) strongly, the enzyme lowers the activation energy for the reaction

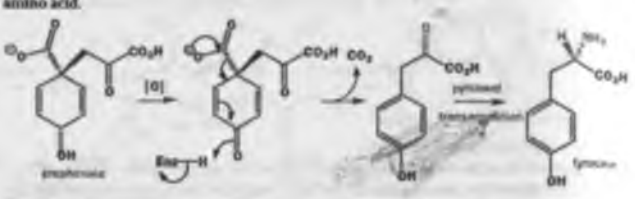


We have arrived at prephenic acid, which as its name suggests is the last compound before aromatic compounds are formed, and we may call this the end of the shikimic acid pathway. The final stages of the formation of phenylalanine and tyrosine start with aromatization. Prephenic acid is unstable and loses water and CO_2 to form phenylpyruvic acid. This α-keto-acid can be converted into the amino acid by the usual transamination with pyridoxal.



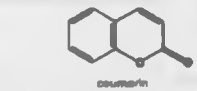
The route to tyrosine requires a preliminary oxidation and then a decarboxylation with the

electrons of the breaking C–C bond ending up in a ketone group. Transamination again gives the amino acid.

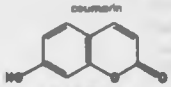


Other shikimate products

Many natural products are formed from the shikimate pathway. Most can be recognized by the aromatic ring joined to a three-carbon atom side chain. Two simple examples are coumarin, responsible for the smell of mown grass and hay, and umbelliferone, which occurs in many plants and is used in suntan oils as it absorbs UV light strongly. These compounds have the same aryl-C_3 structure as Phe and Tyr, but they have an extra oxygen atom attached to the benzene ring and an alkene in the C_3 side chain.

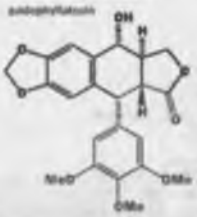


coumarin



umbelliferone

An important shikimate metabolite is podophyllotoxin, an antitumour compound—some podophyllotoxin derivatives are used to combat lung cancer. The compound can be split up notionally into two shikimate-derived fragments (shown in red and green). Both are quite different and there is obviously a lot of chemistry to do after the shikimic acid pathway is finished.

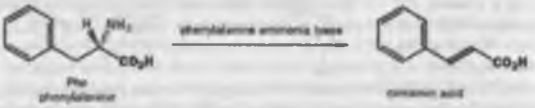


podophyllotoxin

Among the more interesting reactions involved in making all three of these natural products are the loss of ammonia from phenylalanine to give an alkene and the introduction of extra OH groups around the benzene rings. We know how a *para* OH of Tyr is introduced directly by the oxidation of prephenic acid before decarboxylation and it is notable that the extra oxygen functionalities appear next to that point. This is a clue to the mechanism of the oxidation.

Alkenes by elimination of ammonia—phenyl ammonia lyase

Many amino acids can lose ammonia to give an unsaturated acid. The enzymes that catalyse these reactions are known as amino acid ammonia lyases. The one that concerns us at the end of the shikimic acid pathway is phenylalanine ammonia lyase, which catalyses the elimination of ammonia from phenylalanine to give the common metabolite cinnamic acid.

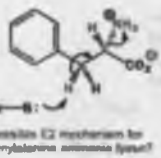


Phe

phenylalanine

phenylalanine ammonia lyase

cinnamic acid



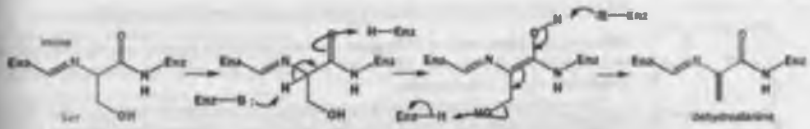
possible E2 mechanism for phenylalanine ammonia lyase?

This reaction gives only *E* cinnamic acid and the proton *anti* to the amino group is lost. This might make us think that we have an E2 reaction with a base on the enzyme removing the required proton. But a closer look at this mechanism makes it very unconvincing. The proton that is removed has no acidity and ammonia is not a good leaving group. It is very unusual for Nature to use an enzyme to make a reaction happen that doesn't happen at all otherwise. It is much more common for Nature to make a good reaction better.

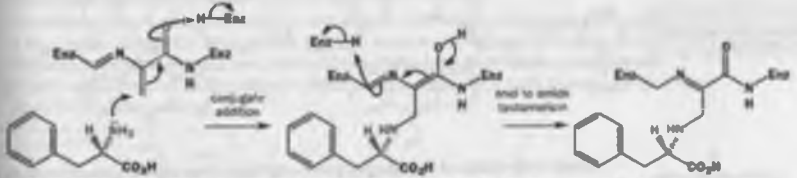
So how does an ammonia lyase work? The enzyme makes the ammonia molecule into a much better leaving group by using a serine residue. This serine is attached to the protein through its carbonyl group by the usual amide bond but its amino group is bound as an imine. This allows it to eliminate water to form a double bond before the phenylalanine gets involved. The elimination converts serine into a dehydroalanine residue. This is an E1cB elimination using only general acid and base catalysis as the proton to be lost is acidic and an enol can be an intermediate.

▶ *A lyase* is an enzyme that catalyses *lysis*: it breaks something down.

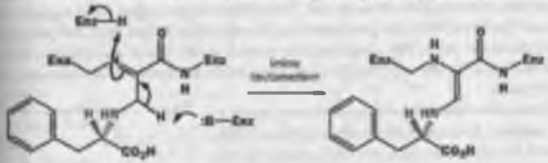
▶ Eliminations of ammonium salts (Chapter 19, p. 000) require very strong bases—much stronger than those available to enzymes—and fully alkylated amines. You can't protonate an amine in the presence of strong base.



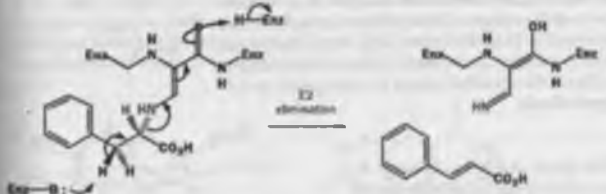
The alkene of the dehydroenzyme is conjugated with a carbonyl group—it's electrophilic and the amino group of Phe can add to it in conjugate fashion. When the enol tautomerizes back to a carbonyl compound, it can be protonated on the imine carbon because the imine is conjugated to the enol. This might remind you of pyridoxal's chemistry (p. 000).



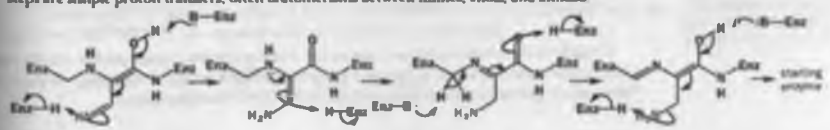
A second tautomerism makes an enamine—again very like the pyridoxal mechanisms you saw earlier.



Now at last the secret is revealed. We can break the C–N bond and use the carbonyl group as an electron sink. The acidity of the proton that must be lost is no greater but the nitrogen atom has become a very much better leaving group.



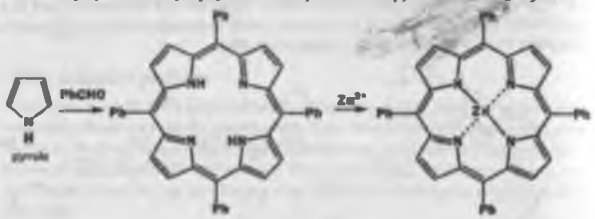
The difficult elimination is accomplished by making it an ammonia transfer reaction rather than an elimination of ammonia. Recycling the enzyme does eventually require elimination of ammonia but in an easy E1cB rather than a difficult E2 reaction. Overall, a difficult reaction—elimination of ammonia—is accomplished in steps that involve no strong acids or strong bases, and most of the steps are simple proton transfers, often tautomerisms between imines, enols, and amides.



Haemoglobin carries oxygen as an iron(II) complex

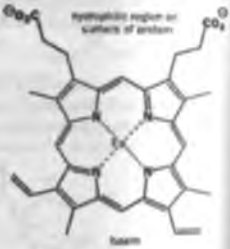
Biological oxidations are very widespread. Human metabolism depends on oxidation, and on getting oxygen, which makes up 20% of the atmosphere, into cells. The oxygen transporter, from atmosphere to cell, is haemoglobin.

The reactive part of haemoglobin is a porphyrin. These are aromatic molecules with 18 electrons around a conjugated ring formed from four molecules of a five-membered nitrogen heterocycle. Chemically, symmetrical porphyrins are easily made from pyrrole and an aldehyde.



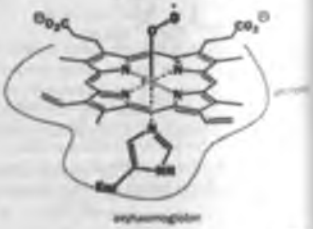
The hole in the middle of a porphyrin is just the right size to take a divalent transition metal in the first transition series, and zinc porphyrins, for example, are stable compounds. Once the metal is inside a porphyrin, it is very difficult to get out. Two of the nitrogen atoms form normal covalent bonds (the ones that were NH in the porphyrin) and the other two donate their lone pairs to make four ligands around the metal. The complexed zinc atom is square planar and still has two vacant sites—above and below the (more or less) flat ring. These can be filled with water molecules, ammonia, or other ligands.

The porphyrin part of haemoglobin is called haem, and it is an iron(II) complex. It is unsymmetrically substituted with carboxylic acid chains on one side and vinyl groups on the other.



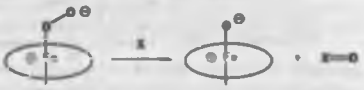
Haem is bound to protein to make haemoglobin (in blood) and myoglobin (in muscle). The hydrophilic carboxylate groups stick out into the surrounding medium, while the majority of the molecule is embedded in a hydrophobic cleft in the protein, lined with amino acids such as leucine and valine. The octahedral coordination sphere of the iron(II) is completed with a histidine residue from the protein and an oxygen molecule.

The oxygen complex can be drawn like this or, alternatively, as an Fe(III) complex of an oxyanion (below).



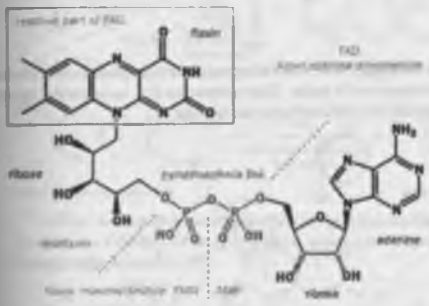
It is difficult to draw detailed mechanisms for oxidations by iron complexes but it is the oxygen atom further from Fe that reacts. You can see in principle how breakage of the weak O–O bond could deliver an oxygen atom to a substrate and leave an Fe(III)–O^- complex behind.

Oxygen molecules are transferred from haemoglobin to other haems, such as the enzyme P450, and to a wide range of oxidizing agents. Almost any molecule we ingest that isn't a nutrient—a drug molecule, for example—is destroyed by oxidation. The details of the mechanisms of these oxidations have proved very difficult to elucidate, but the hydroxylation of benzene is an exception. We do know how it happens, and it's another case of Nature using enzymes to do some really remarkable chemistry.



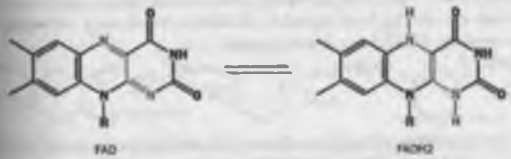
Aromatic rings are hydroxylated via an epoxide intermediate

The oxidizing agents here are related to FAD. We said little about $FADH_2$ as a reducing agent earlier in this chapter because it is rather similar to NADH which we have discussed in detail. FAD is another dinucleotide and it contains an AMP unit linked through the 5' position by a pyrophosphate group to another nucleotide. The difference is that the other nucleotide is flavin mononucleotide. Here is the complete structure.



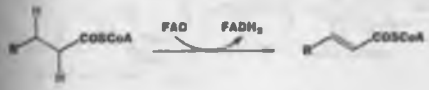
The whole thing is FAD. Cutting FAD in half down the middle of the pyrophosphate link would give us two nucleotides, AMP and FMN (flavin mononucleotide). The sugar in each case is ribose (in its furanose form in AMP but in open-chain form in FMN) so the flavin nucleoside is riboflavin. We can abbreviate this complex structure to the reactive part, which is the flavin. The rest we shall just call 'R'.

▶ Riboflavin is also known as vitamin B_2 as you may see on the side of your cornflakes packet.

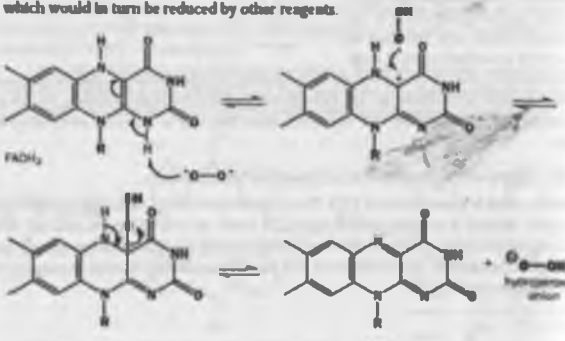


Redox reactions with FAD involve the transfer of two hydrogen atoms to the part of the molecule shown in green. Typical reactions of FAD involve dehydrogenations—as in double bond formation from single bonds. Of course, one of the H atoms can be transferred to FAD as a proton—only one need be a hydride ion H^-, though both could be transferred as radicals ($H^\cdot$).

▶ You should contrast this with the redox reactions of NAD where only one hydrogen atom is transferred.

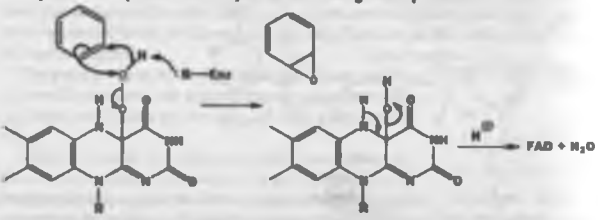


After FAD has been used as an oxidant in this fashion, the $FADH_2$ reacts with molecular oxygen to give a hydroperoxide, which decomposes back to FAD and gives an anion of hydrogen peroxide, which would in turn be reduced by other reagents.

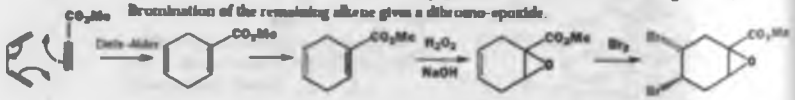


▶ Note the radical steps in this sequence. The reactions of oxygen, whose ground state is a triplet diradical (see Chapter 4), are typically radical processes.

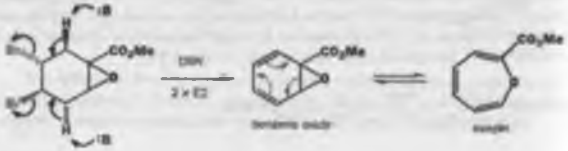
In the reactions we are now concerned with, the hydroperoxide intermediate itself is the important reagent, before it loses hydroperoxide anion. This intermediates is an oxidizing agent—for example, it reacts quite dramatically with benzene to give an epoxide.



This benzene oxide may look very dubious and unstable, but benzene oxides can be made in the laboratory by ordinary chemical reactions (though not usually by the direct oxidation of benzene). We can instead start with a Diels–Alder reaction between butadiene and an alkyne. Epoxidation with a nucleophilic reagent ($HO–O^-$ from H_2O_2 and NaOH) occurs chemoselectively on the more electrophilic double bond—the one that is conjugated to the electron-withdrawing carbonyl group. Bromination of the remaining alkene gives a dibromo-epoxide.

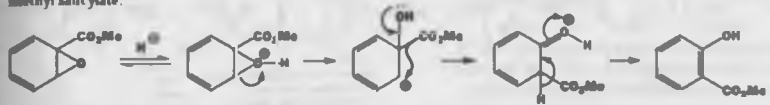


This is an ordinary electrophilic addition to an alkene so the two bromine atoms are *anti* in the product. Elimination under basic conditions with DBN gives the benzene oxide.

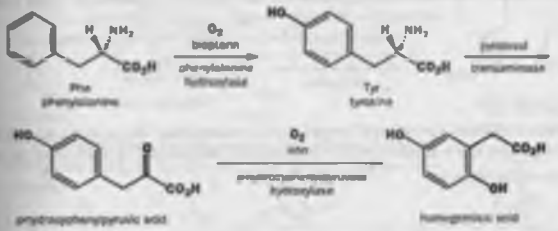


At least, it ought to have given the benzene oxide! The compound turned out to have a fluxional structure—it was a mixture of compounds that equilibrate by a reversible disrotatory electrocyclic reaction.

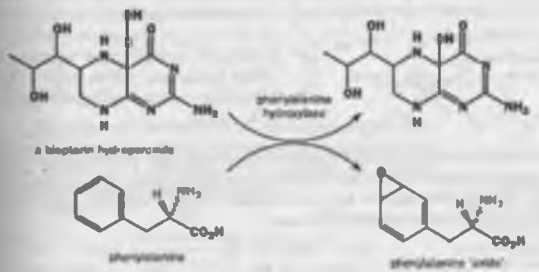
Treatment with acid turns the benzene oxide/oxepin into an aromatic ring by a very interesting mechanism. The epoxide opens to give the cation, which is *not* conjugated with the electron-withdrawing CO_2Me group, and then a migration of that CO_2Me group occurs. This has been proved by isotope labelling experiments. The final product is the *ortho*-hydroxy-ester, known as methyl salicylate.



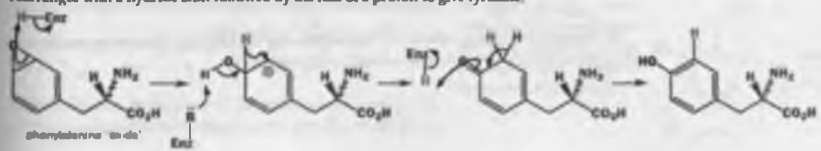
This chemistry seems rather exotic, but in the degradation of phenylalanine two benzene oxide intermediates and two such rearrangements occur one after the other. This is the initial sequence.



The first reaction involves a hydroperoxide related to the FAD hydroperoxide you have just seen but based on a simpler heterocyclic system, a biopterin. The reaction is essentially the same and a benzene oxide is formed.

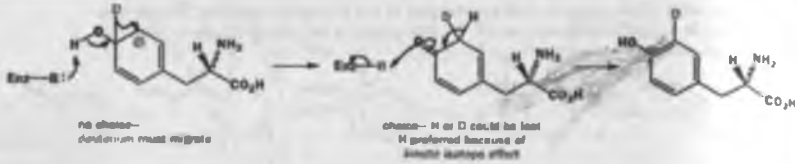


The biopterin product is recycled by elimination of water, reduction using NADPH as the reagent, and reaction with molecular oxygen. The other product, the phenylalanine oxide, rearranges with a hydride shift followed by the loss of a proton to give tyrosine.

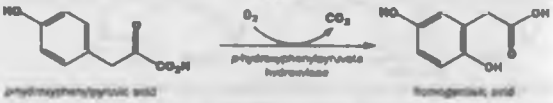


▶ This rearrangement is known as the 'NIH shift', after its discovery at the National Institutes of Health at Bethesda, Maryland.

We know that this is the mechanism because we can make the green H a deuterium atom. We then find that deuterium is present in the tyrosine product *ortho* to the phenolic hydroxyl group. When the migration occurs, the deuterium atom must go as there is no alternative, but in the next step there is a choice and H loss will be preferred to D loss because of the kinetic isotope effect (Chapter 19). Most of the D remains in the product.

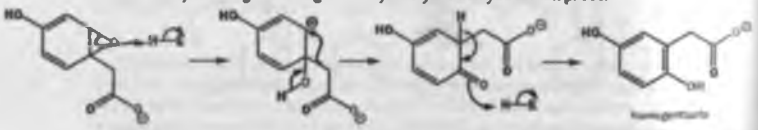


A shift of a larger group comes two steps later in the synthesis of homogentisic acid. Another labelling experiment, this time with $^{18}O_2$, shows that both atoms of oxygen end up in the product.

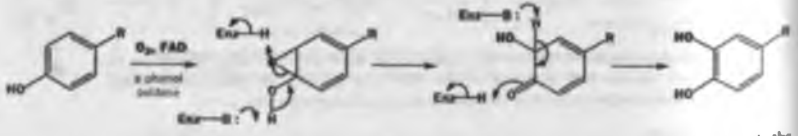


The key intermediate is a peroxy acid formed after decarboxylation. The peroxy acid is perfectly placed for an intramolecular epoxidation of a double bond in the benzene ring next to the side chain.

The epoxide can now rearrange with the whole side chain migrating in a reaction very similar to the laboratory rearrangement to give methyl salicylate that you saw on p. 800.



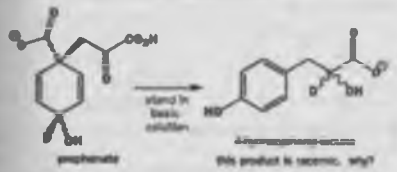
When hydroxylation occurs next to an OH group that is already there, no NIH shift occurs. This is because the epoxide is opened by the push of electrons from the OH group and there is only one H atom to be lost anyway. The cofactor for these enzymes is slightly different, being again the hydroperoxide from FAD, but the principle is the same.



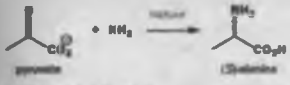
In the next chapter you will see how hydroxylation of benzene rings plays an important part in the biosynthesis of alkaloids and other aromatic natural products.

Problems

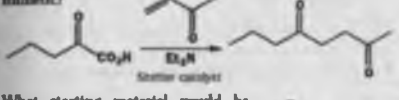
1. On standing in alkali in the laboratory, prephenic acid rearranges to 4-hydroxyphenyl-lactic acid with specific incorporation of deuterium label as shown. Suggest a mechanism, being careful to draw realistic conformations.



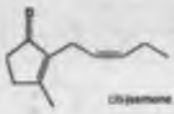
2. Write a full reaction scheme for the conversion of ammonia and pyruvate to alanine in living things. You will need to refer to the section of the chapter on pyridoxal to be able to give a complete answer.



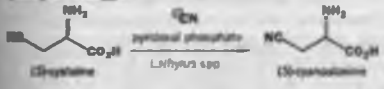
3. Give a mechanism for this reaction. You will find the Stetter catalyst described in the chapter. How is this sequence biomimetic?



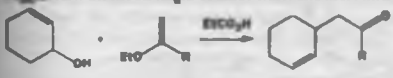
What starting material would be required for formation of the natural product *cis*-jasmone by an intramolecular aldol reaction (Chapter 27). How would you make this compound using a Stetter reaction?



4. The amino acid cyanoalanine is found in leguminous plants (*Lathyrus*) but not in proteins. It is made in the plant from cysteine and cyanide by a two-step process catalysed by pyridoxal phosphate. Suggest a detailed mechanism.

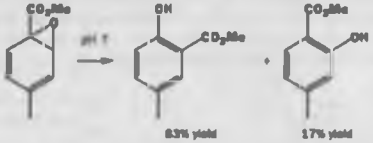


5. This chemical reaction might be said to be similar to a reaction in the shikimic acid pathway. Compare the two mechanisms and suggest how the model might be made closer and more interesting.



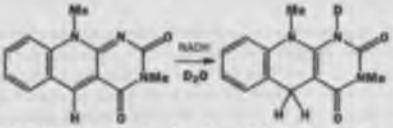
6. Stereospecific deuteration of the substrate for enolase, the enzyme that makes phosphoenol pyruvate, gives the results shown below. What does this tell us definitely about the reaction and what might it suggest about the mechanism?

7. This rearrangement was studied as a biomimetic version of the NIH shift. Write a mechanism for the reaction. Do you consider it a good model reaction? If not, how might it be made better?



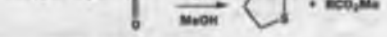
8. The following experiments relate to the chemical and biological behaviour of NADH. Explain what they tell us.

(a) This FAD analogue can be reduced *in vitro* with NADH in D_2O with deuterium incorporation in the product as shown.

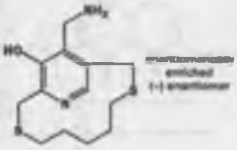


(b) NADH does not reduce benzaldehyde *in vitro* but it does reduce this compound.

9. Oxidation of this simple thiol ester gives a five-membered cyclic disulfide. The reaction is proposed as a model for the behaviour of lipoic acid in living things. Draw a mechanism for the reaction and make the comparison.

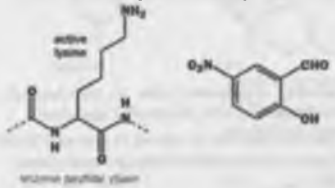


10. This curious compound is chiral—indeed it has been prepared as the (–) enantiomer. Explain the nature of the chirality.

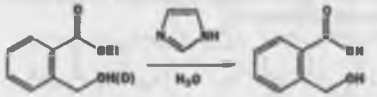


This compound has been used as a chemical model for pyridoxamine. For example, it transaminates phenylpyruvate under the conditions shown here. Comment on the analogy and the role of Zn(II). In what ways is the model compound worse and in what ways better than pyridoxamine itself?

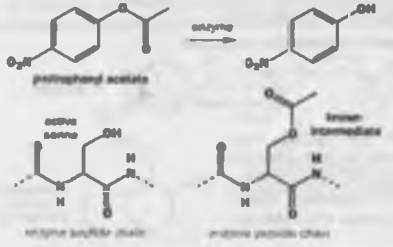
11. Enzymes such as aldolase, thought to operate by the formation of an imine and/or an enamine with a lysine in the enzyme, can be studied by adding $NaBH_4$ to a mixture of enzyme and substrate. For example, treatment of the enzyme with the aldehyde shown below and $NaBH_4$ gives a permanently inhibited enzyme that on hydrolysis reveals a modified amino acid in place of one of the lysines. What is the structure of the modified amino acid, and why is this particular aldehyde chosen?



12. This question is about the hydrolysis of esters by 'serine' enzymes. First, interpret these results: The hydrolysis of this ester is very much faster than that of ethyl benzoate itself. It is catalysed by imidazole and there is a primary isotope effect (Chapter 41) $k_{(OH)}/k_{(OD)} = 3.5$. What is the mechanism? What is the role of the histidine?



The serine enzymes have a serine residue vital for catalysis. The serine OH group is known to act as a nucleophilic catalyst. Draw out the mechanism for the hydrolysis of *p*-nitrophenyl acetate.

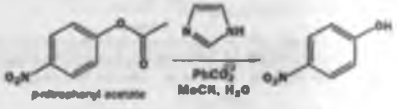


The enzyme also has a histidine residue vital for catalysis. Use your mechanism from the first part of the question to say how the histidine residue might help. The histidine residue is known to help both the formation and the hydrolysis of the intermediate. The enzyme hydrolyses both *p*-nitrophenyl acetate and *p*-nitrophenyl thiolacetate at the same rate. Which is the rate-determining step?

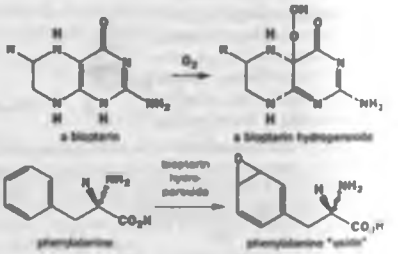
Finally, an aspartic acid residue is necessary for full catalysis and this residue is thought to use its CO_2^- group as a general base. A chemical model shows that the hydrolysis of *p*-nitrophenyl acetate in aqueous acetonitrile containing sodium benzoate and imidazole follows the rate law:

rate = k[*p*-nitrophenyl acetate][benzoate][imidazole].

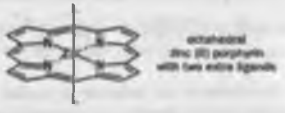
Suggest a mechanism for the chemical reaction.



13. Give mechanisms for the biological formation of biopterin hydroperoxide and its reaction with phenylalanine. The reactions were discussed in the chapter but no details were given.



14. Revision of Chapter 48. How many electrons are there on the iron atom in the oxyhaemoglobin structure shown in the chapter? Does it matter if you consider the complex to be of Fe(II) or Fe(III)? Why do zinc porphyrins need two extra ligands and what type of ligands should they be?



Natural products

51

Connections

Building on:

- Stereochemistry ch16
- Conformational analysis ch18
- Enolate chemistry and synthesis ch24–ch30
- Pericyclic reactions ch35–ch36
- Rearrangement and fragmentation ch37–ch38
- Radicals ch39
- Chemistry of life ch49
- Mechanisms in biological chemistry ch50

Arriving at:

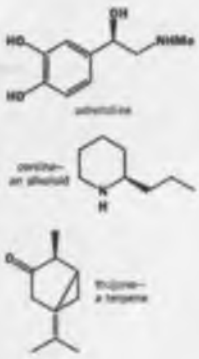
- Natural products are made by secondary metabolism
- Natural products come in enormous variety, but fall mainly into four types: alkaloids, polyketides, terpenes, and steroids
- Alkaloids are amines made from amino acids
- Pyrrolidine alkaloids from ornithine; benzylisoquinoline alkaloids from tyrosine
- Morphine alkaloids are made by radical cyclizations
- Fatty acids are built up from acetyl CoA and malonyl CoA subunits
- Polyketides are unreduced variants of fatty acids
- Terpenes are made from mevalonic acid
- Steroids are tetracyclic terpene derivatives
- Biomimetic synthesis: learning from Nature

Looking forward to:

- Organic synthesis ch53

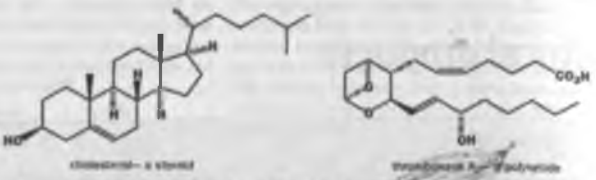
Introduction

By natural products, we mean the molecules of nature. Of course, all life is made of molecules, and we will not be discussing in great detail the major biological molecules, such as proteins and nucleic acids, which we looked at in Chapters 49 and 50. In this chapter we shall talk much more about molecules such as adrenaline (epinephrine). Adrenaline is a human hormone. It is produced in moments of stress and increases our blood pressure and heart rate ready for 'fight or flight'. You've got to sit an exam tomorrow—surge of adrenaline. To an organic chemist adrenaline is intensely interesting because of its remarkable biological activity—but it is also a molecule whose chemical reactions can be studied, whose NMR spectrum can be analysed, which can be synthesized, and which can be imitated in the search for new medicines.



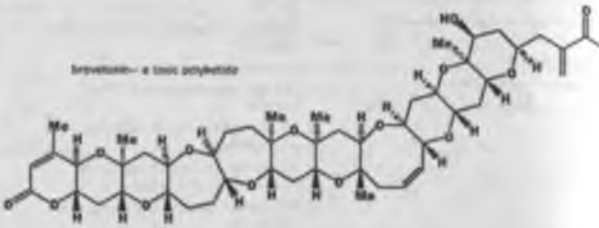
By the end of this chapter we hope you will be able to recognize some basic classes of natural products and know a bit about their chemistry. We will meet alkaloids such as coniine, the molecule in hemlock that killed Socrates, and terpenes such as thujone, which was probably the toxin in absinthe that killed the nineteenth-century artists in Paris.

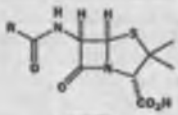
Then there are the ambiguous natural products such as the steroid cholesterol, which may cause innumerable deaths through heart disease but which is a vital component of cell walls, and the polyketide thromboxane, one drop of which would instantaneously clot all the blood in your body but without which you would bleed to death if you cut yourself.



▶
Before moving on, just pause to admire brevetoxin, a wonderful and deadly molecule. Look at the alternating oxygen atoms on the top and bottom faces of alternate rings. Look at the rings themselves—six-, seven-, and eight-membered but each with one and no more than one oxygen atom. Trace the continuous carbon chain running from the lactone carbonyl group in the bottom left-hand corner to the aldehyde carbonyl in the top right. There is no break in this chain and, other than the methyl groups, no branch. With 22 stereogenic centres, this is a beautiful piece of molecular architecture. If you want to read more about brevetoxin, read the last chapter in Nicolaou and Sorensen's *Classics in total*

We will look at the structural variety within these four important classes and beyond, from perhaps the smallest natural product, nitric oxide, NO (which controls penile erections in men), to something approaching the largest—the polyketide brevetoxin, the algal product in 'red tides', which appear in coastal waters from time to time and kill fish and those who eat the fish.





penicillin
e.g. penicillin G, R = $PhCH_2$

Many natural products are the source of important life-saving drugs—consider the millions of lives saved by penicillin, a family of amino acid metabolites.

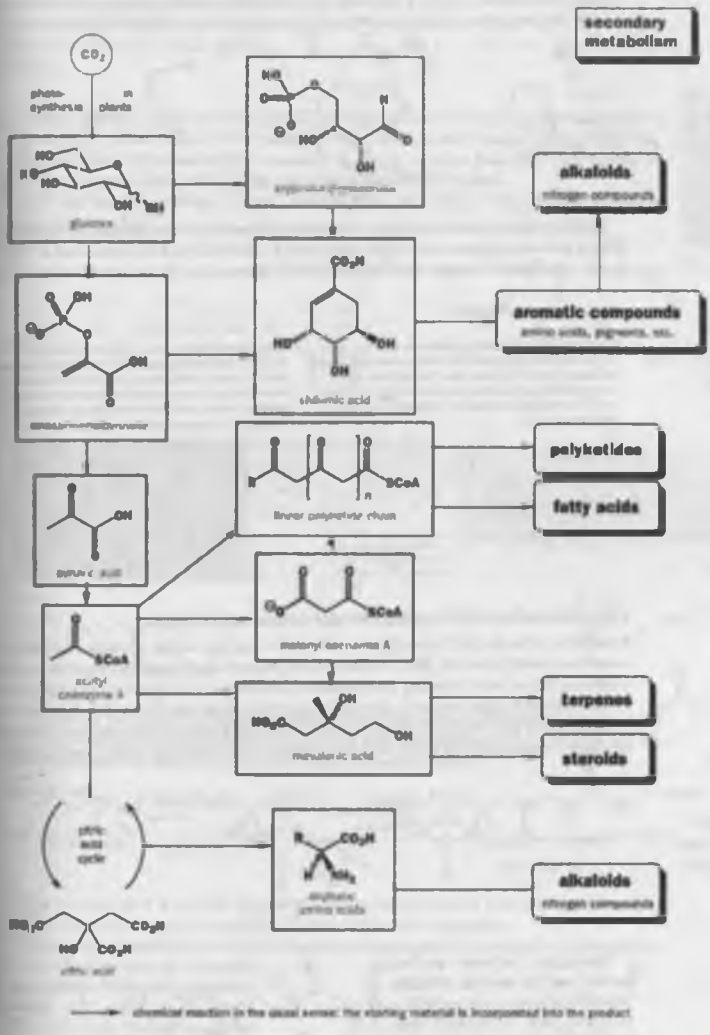
Natural products come from secondary metabolism

The chemical reactions common to all living things involve the primary metabolism of the 'big four' we met in Chapter 49—nucleic acids, proteins, carbohydrates, and lipids. Now we must look at chemical reactions that are more restricted. They occur perhaps in just one species, though more commonly in several. They are obviously, then, not essential for life, though they usually help survival. These are the products of **secondary metabolism**.

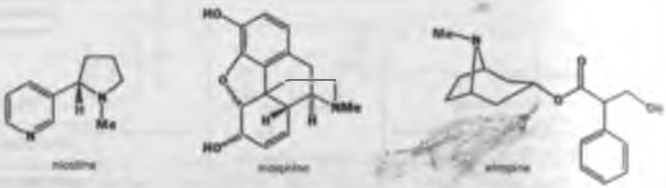
The exploration of the compounds produced by the secondary metabolism of plants, microorganisms, fungi, insects, mammals, and every other type of living thing has hardly begun. Even so, the variety and richness of the structures are overwhelming. Without some kind of classification the task of description would be hopeless. We are going to use a biosynthetic classification, grouping substances not by species but by methods of biological synthesis. Though every species is different, the basic chemical reactions are shared by all. The chart on p. 000 relates closely to the chart of primary metabolism in the previous chapter.

Alkaloids are basic compounds from amino acid metabolism

Alkaloids were known in ancient times because they are easy to extract from plants and some of them have powerful and deadly effects. Any plant contains millions of chemical compounds, but some plants, like the deadly nightshade, can be mashed up and extracted with aqueous acid to give a few compounds soluble in that medium, which precipitate on neutralization. These compounds were seen to be 'like alkali' and Meissner, the apothecary from Halle, in 1819 named them 'alkaloids'. Lucrezia Borgia already knew all about this and put the deadly nightshade extract atropine in her eyes (to make her look beautiful: atropine dilates the pupils) and in the drinks of her


secondary metabolism
CO_2
photosynthesis in plants
glucose
alkaloids
nitrogen compounds
shikimic acid
aromatic compounds
amino acids, pigments, etc.
polyketides
fatty acids
SCoA
acetyl coenzyme A
terpenes
steroids
mevalonic acid
citric acid cycle
aliphatic amino acids
alkaloids
nitrogen compounds
chemical reaction in the usual sense: the starting material is incorporated into the product

political adversaries to avoid any trouble in the future. Now, we would simply say that they are basic because they are amines. Here is a selection with the basic amino groups marked in black.

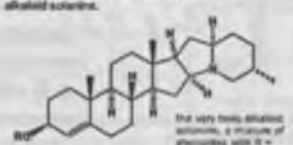


nicotine morphine atropine

Natural products are often named by a combination of the name of the organism from which they are isolated and a chemical part name. These compounds are all amines so all their names end in '-ine'. They appear very diverse in structure but all are made in nature from amino acid, and we will look at three types.

Solanaceous alkaloids

The Solanaceae family includes not only deadly nightshade (*Atropa belladonna*—hence atropine) plants but also potatoes and tomatoes. Parts of these plants also contain toxic alkaloids: for example, you should not eat green potatoes because they contain the toxic alkaloid solanine.

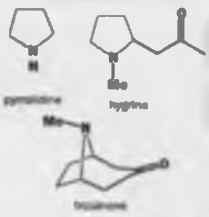


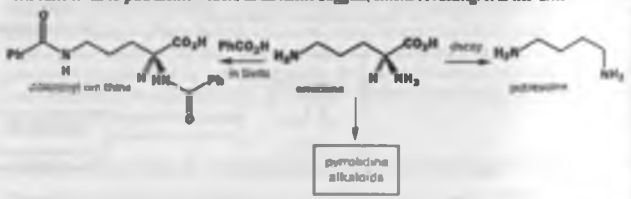
The very toxic alkaloid solanine, a mixture of glycosides with R = glucose, rhamnose, etc.

Atropine is a racemic compound but the (*S*)-enantiomer occurs in henbane (*Hyoscyamus niger*) and was given a different name, hyoscyamine, before the structures were known. In fact, hyoscyamine racemizes very easily just on heating in water or on treatment with weak base. This is probably what happens in the deadly nightshade plant.

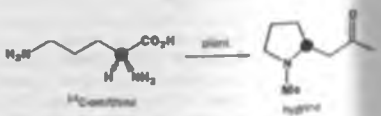
Pyrrolidine alkaloids are made from the amino acid ornithine

Pyrrolidine is the simple five-membered cyclic amine and pyrrolidine alkaloids contain this ring somewhere in their structure. Both nicotine and atropine contain a pyrrolidine ring as do hygrine and tropinone. All are made in nature from ornithine. Ornithine is an amino acid not usually found in proteins but most organisms use it, often in the excretion of toxic substances. If birds are fed benzoic acid ($PhCO_2H$) they excrete dibenzoyl ornithine. When dead animals decay, the decarboxylation of ornithine leads to putrescine which, as its name suggest, smells revolting. It is the 'smell of death'.





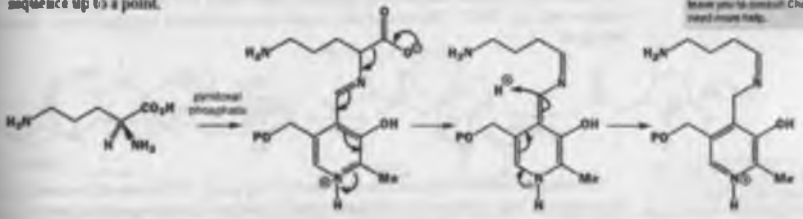
Biosynthetic pathways are usually worked out by isotopic labelling of potential precursors and we shall mark the label with a coloured blob. If ornithine is labelled with ^{14}C and fed to the plant, labelled hygrine is isolated.



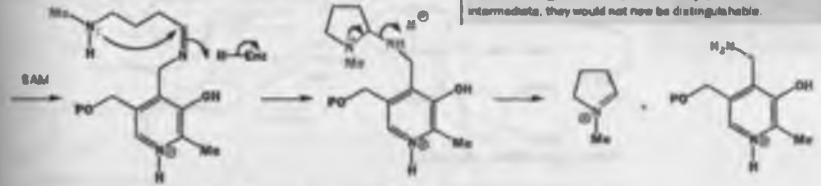
If each amino group in ornithine is labelled in turn with ^{15}N, the α amino group is lost but the γ amino group is retained.

Further labelling experiments along these lines showed that the CO_2H group as well as the α amino group was lost from ornithine and that the rest of the molecule makes the pyrrolidine ring. The three-carbon side-chain in hygrine comes from acetate, or rather from acetyl CoA, and the *N*-methyl group comes from SAM. We can now work through the biosynthesis.

The first step is a pyridoxal-catalysed decarboxylation of ornithine, which follows the normal sequence up to a point.



Now the terminal amino group is methylated by SAM and the secondary amine cyclises on to the pyridoxal imine to give an aminal. Decomposition of the aminal the other way round expels pyridoxamine and releases the salt of an electrophilic imine.

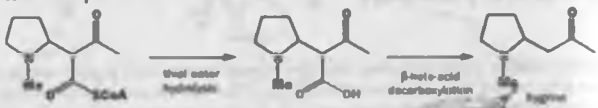


The rest of the biosynthesis does not need pyridoxal, but it does need two molecules of acetyl CoA. In Chapter 50 we noted that this thiol ester is a good electrophile and also enolizes easily. We need both reactivities now in a Claisen ester condensation of acetyl CoA.

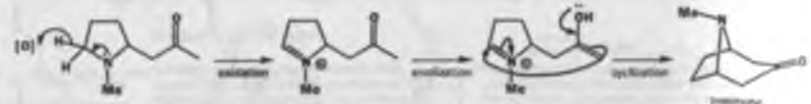
The new keto-ester is very like the acetoacetates we used in Chapter 27 to make stable enolates and the CoA thiol ester will exist mainly as its enol, stabilized by conjugation.

This enol reacts with the imine salt we have previously made and it will be easier to see this reaction if we redraw the enol in a different tautomeric form. The imine salt does not have to wait around for acetonacetyl CoA to be made. The cell has a good stock of acetyl CoA and its condensation product.

All that remains to form hygrine is the hydrolysis of the CoA thiol ester and decarboxylation of the keto-acid. This is standard chemistry, but you should ensure that you can draw the mechanisms for these steps.

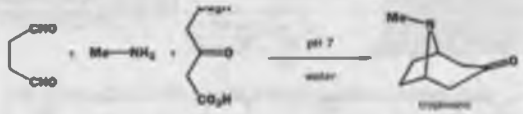


Tropinone is made from hygrine and it is clear what is needed. The methyl ketone must enolize and it must attack another imine salt resembling the first but on the other side of the ring. Such salts can be made chemically by oxidation with Hg(II) and biologically with an oxidizing enzyme and, say, NAD^+. The symbol [O] represents an undefined oxidizing agent, chemical or biological.



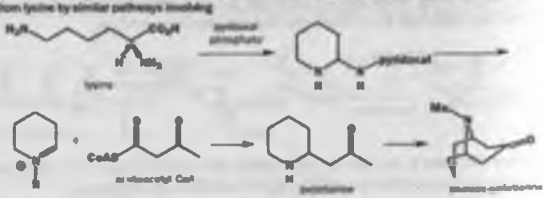
▶ The cyclization step looks dreadful when drawn on a flat molecule, but it looks much better in the conformation of tropinone shown below.

This complex route to tropinone was imitated as long ago as 1917 in one of the most celebrated reactions of all time, Robinson's tropinone synthesis. Robinson argued on purely chemical grounds that the sequence of imine salts and enols, which later (1970) turned out to be Nature's route, could be produced under 'natural' conditions (aqueous solution at pH 7) from a C_4 dialdehyde, $MeNH_2$ and acetone dicarboxylic acid. It worked and the intermediates must be very similar to those in the biosynthesis.



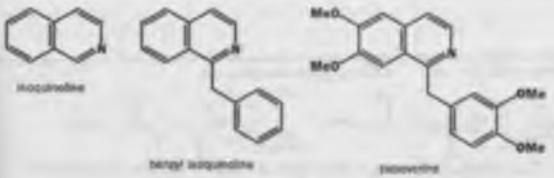
Other pyrrolidine alkaloids

There are many pyrrolidine alkaloids derived from ornithine and another large family of piperidine alkaloids derived from lysine by similar pathways involving decarboxylation and cyclization initiated by pyridoxal. We will not discuss these compounds in detail.

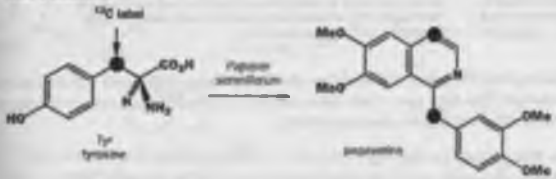


Benzyl isoquinoline alkaloids are made from tyrosine

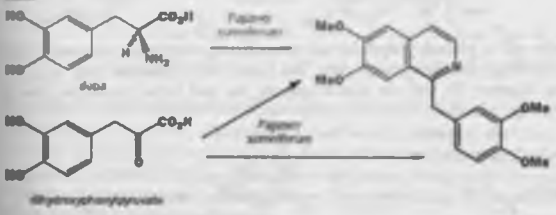
We switch to a completely different kind of alkaloid made from a different kind of amino acid. The benzyl isoquinoline alkaloids have a benzyl group attached to position 2 of an isoquinoline ring. Usually the alkaloids are oxygenated on the benzene ring and many are found in opium poppies (*Papaver somniferum*). For all these reasons papaverine is an ideal example.



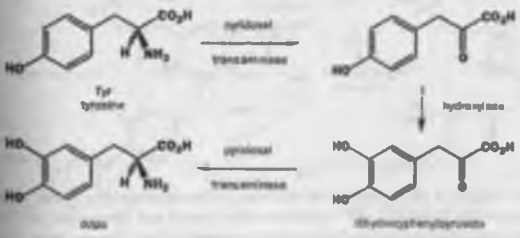
Labelling shows that these alkaloids come from two molecules of tyrosine. One must lose CO_2 and the other NH_3. We can easily see how to divide the molecule in half, but the details will have to wait a moment.



The question of when the extra OH groups are added was also solved by labelling and it was found that dihydroxyphenyl pyruvate was incorporated into both halves but the dihydroxyphenyl alanine (an important metabolite usually called 'dopa') was incorporated only into the isoquinoline half.

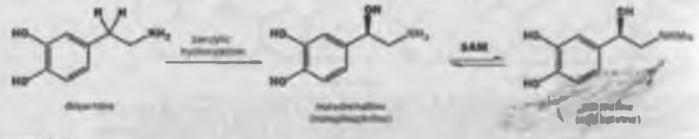


The amino acid and the keto-acid are, of course, related by a pyridoxal-mediated transaminase and the hydroxylation must occur right at the start. Both of these reactions are discussed in Chapter 50.



Catecholamines

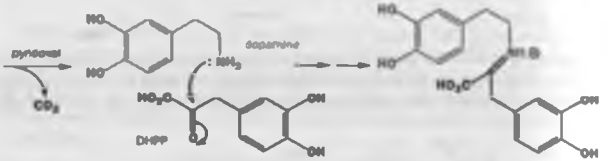
Dopa and dopamine are important compounds because they are the precursors to adrenaline in humans. Decarboxylation of dopa gives dopamine, which an



oxidase (Chapter 50) hydroxylates enzymatically at the benzylic position to give noradrenaline (norepinephrine).

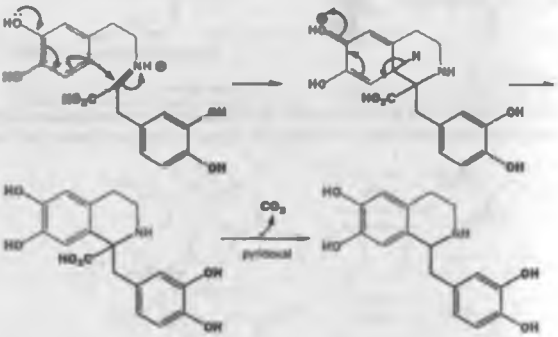
The family of hormones that includes adrenaline and noradrenaline is often called the catecholamines (catechol is 1,2-dihydroxybenzene). The hormones are produced in the adrenal gland around the kidneys and regulate several important aspects of metabolism. They help to control the breakdown of stored sugars to release glucose and they have a direct effect on blood pressure, heart rate, and breathing. The relative proportion of noradrenaline and its N-methylated analogue, adrenaline, controls these things.

Pyridoxal-mediated decarboxylation of dopa gives dopamine and this reacts with the keto-acid to form an imine salt. This is an open-chain imine salt unlike the cyclic ones we saw in the pyrrolidine alkaloids, but it will prove to have similar reactivity.

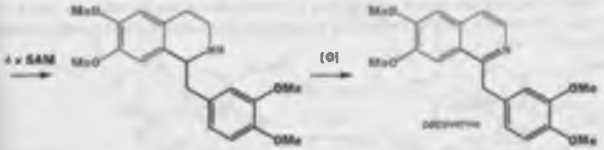


The imine salt is perfectly placed for an intramolecular electrophilic aromatic substitution by the electron-rich dihydroxyphenyl ring. This closes the isoquinoline ring in a Mannich-like process (Chapter 27) with the phenol replacing the enol in the pyrrolidine alkaloid biosynthesis.

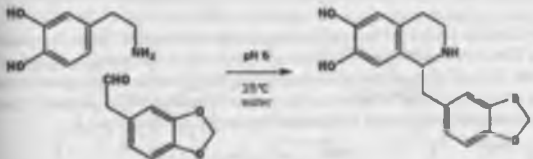
■ Even in biological electrophilic aromatic substitutions, it is still important to remember to write in the hydrogen atom at the place of substitution (Chapter 22)!



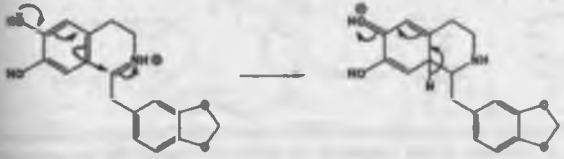
The cyclization product is still an amino acid and it can be decarboxylated by pyridoxal. Now we have something quite like papaverine but it lacks the methyl groups and the aromatic heterocyclic ring. Methylation needs SAM and is done in two stages for a reason we will discover soon. The final oxidation should again remind you of the closing stages of the tropinone route.



The reaction to make the isoquinoline ring can be carried out chemically under very mild conditions providing that we use an aldehyde as the carbonyl component. Then it works very well with rather similar compounds.

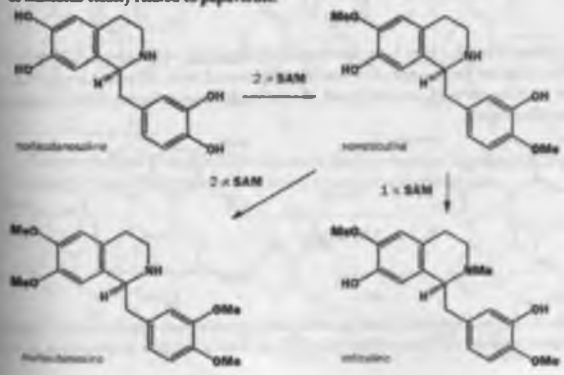


The mechanism is straightforward—the imine is formed and will be protonated at pH 6, ready for the C–C bond formation, which is both a Mannich reaction and an electrophilic aromatic substitution.



Complex benzyl isoquinoline alkaloids are formed by radical coupling

A more interesting series of alkaloids arises when benzyl isoquinoline alkaloids cyclize by radical reactions. Phenols easily form radicals when treated with oxidizing agents such as Fe(III), and benzyl isoquinoline alkaloids with free phenolic hydroxyl groups undergo radical reactions in an intramolecular fashion through a similar mechanism. Here are the details of some methylations of a class of alkaloids closely related to papaverine.



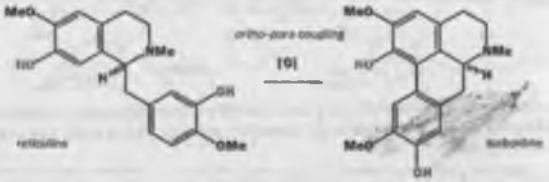
▶ The reaction also works with an aryl pyruvic acid, but the decarboxylation is more difficult to organize without pyridoxal.

▶ Notice that it was not necessary to protect the OH groups—the acetal on the lower ring is not for protection, and this group (methylenedioxy or dioxolan) is present in many benzyl isoquinoline alkaloids. It is formed in nature by oxidation of an MeO group *ortho* to an OH group on a benzene ring.

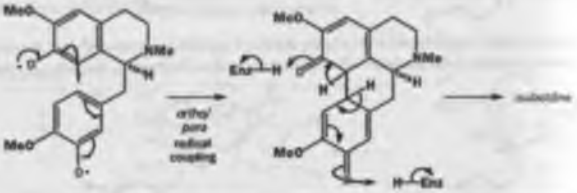
■ See Chapter 35.

▶ The names of the alkaloids should not, of course, be learned, but they are a convenient handle for quick reference. The prefix 'nor' means without a methyl group, in this case the N-Me group, as you can see with norreticuline and reticuline (see p. 000).

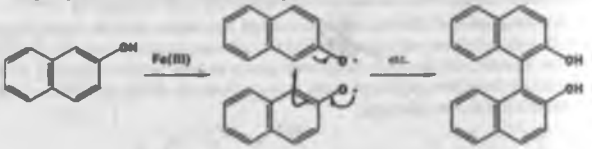
Methylating only one phenol on each ring of norreticuline leaves the other one free for radical coupling. Reticuline is oxidized in the plant to isoboldine by a radical cyclization with the formation of a new C–C bond.



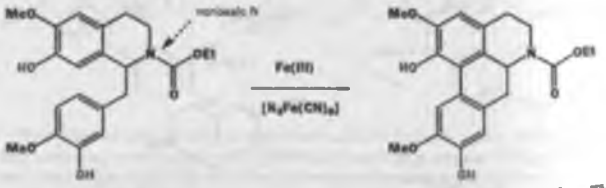
The new C–C bond is marked in black and the free phenolic OH is in green. Notice the relationship between them. The new bond is between a carbon atom *ortho* to one OH group and a carbon atom *para* to the other. We shall see in all these phenolic couplings that the *ortho* and *para* positions are the only activated ones (*ortho*/*ortho*, *ortho*/*para*, and *para*/*para* couplings are all possible). Oxidation occurs at the phenolic hydroxyl groups, and the resulting oxygen radicals couple.



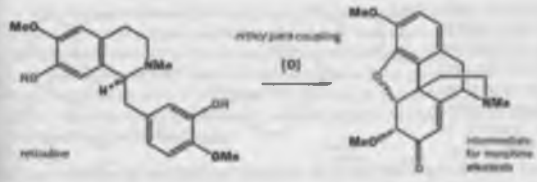
Phenol coupling occurs chemically under oxidation with Fe(III). The most famous example is the coupling of 2-naphthol to give binaphthol—an *ortho*/*ortho* coupling. The stereochemistry of binaphthyls like this was discussed in Chapter 45.



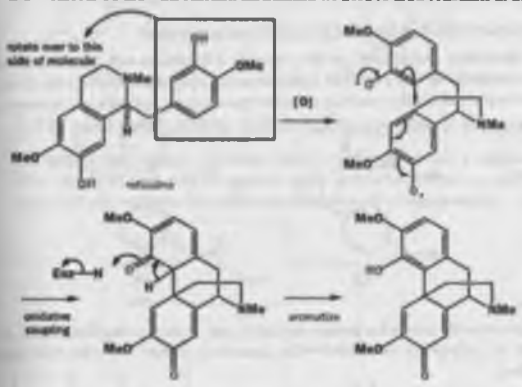
Similar phenol couplings have been attempted in the laboratory with compounds in the benzyl isoquinoline series but the nitrogen atom interferes if it is at all basic. When it has a carbonyl substituent the reactions do work reasonably well, but the yields are poor. Nature is still much better at this reaction than we are.



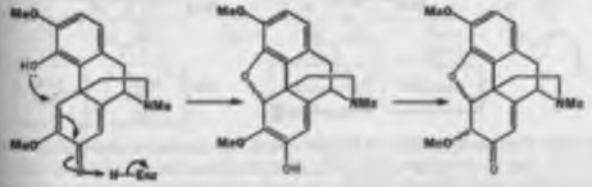
Reticuline is also the source of the morphine alkaloids by *ortho*/*para* radical coupling. The roles of the two rings are reversed this time and it is quite difficult to see at first how the structures are related.



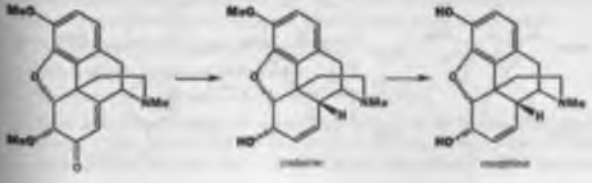
A great deal has happened in this reaction, but the new C–C bond (black) is *ortho* to the green oxygen atom in the top ring and *para* to the green oxygen atom in the bottom ring, so *ortho*/*para* coupling has occurred. To draw the reaction mechanism we need to draw reticuline in the right conformation.



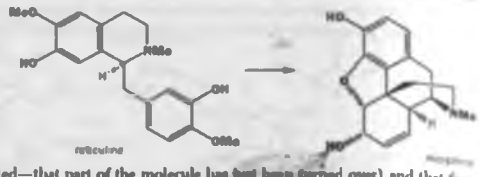
One of the two rings can re-aromatize but the other has a quaternary carbon atom so no proton can be lost from this site. Instead, the OH group in the top ring adds in conjugate fashion to the enone in the bottom ring.



This intermediate gives rise to the important alkaloids codeine and morphine, which differ only by a methyl group. Nature can remove methyl groups as well as add them.

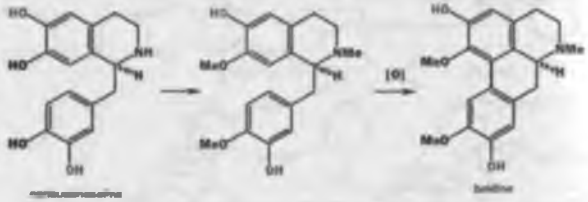


These alkaloids have plenty of stereochemistry. Indeed, if we compare the structures of reticuline and morphine, we can see that the one stereogenic centre in reticuline (marked in green) is still there in morphine (it hasn't been inverted—that part of the molecule has just been turned over) and that four new stereogenic centres marked in black have been added. These centres all result from the original twisting of reticuline to allow phenol coupling except for the one bearing an OH group, which comes from a stereoselective reduction.

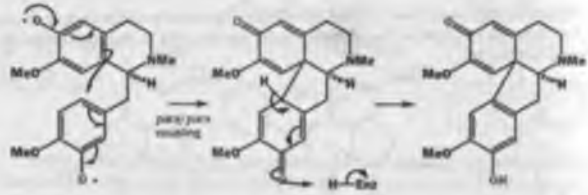


Boldine, an isomer of isoboldine, is formed by rearrangement

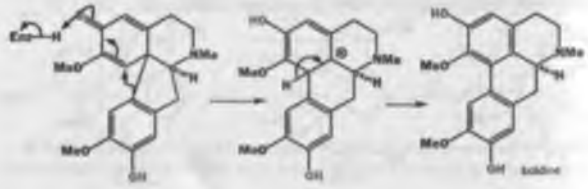
We mentioned isoboldine a while back, so there must be a boldine as well. This alkaloid is also formed from norlaudanosoline by a different methylation sequence and oxidative radical coupling. Looking at the structure of boldine you may see what appears to be a mistake on someone's part.



The coupling is correctly *para* in the bottom ring but is *meta* in the top ring. But there is no mistake (neither by the authors nor by Nature!)—this structure is correct and it has been made by *para*/*para* coupling.

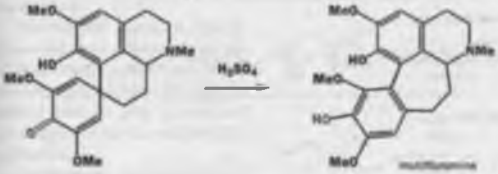


One of the rings has aromatized, but the other cannot—this should remind you of the morphine biosynthesis. However, there is no nucleophilic OH group here capable of conjugate addition to the enone so a rearrangement occurs instead. The new bond to the lower ring migrates across the top ring. You might even say that the lower ring does an intramolecular conjugate addition on the upper ring.



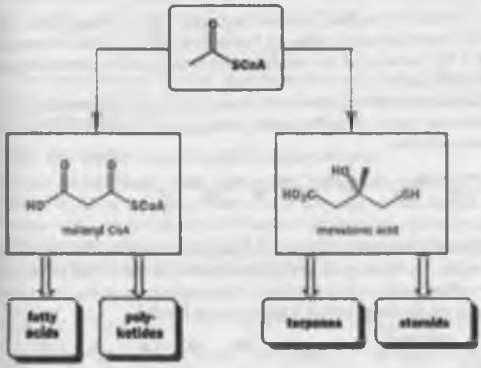
After the rearrangement there is a proton available to be lost and the cation can aromatize. The *para* relationship in the original coupling product has become a *meta* relationship by rearrangement. You should be able to recognize this rearrangement from Chapter 37: it is a dienone–phenol rearrangement.

In rearrangements like these with cationic intermediates, the group that can best support a positive charge usually prefers to migrate. The reasons for this are discussed in Chapter 37. Here is a purely chemical example of the same reaction, giving 82% yield in acidic solution. The bond that migrates is marked in black.



Fatty acids and other polyketides are made from acetyl CoA

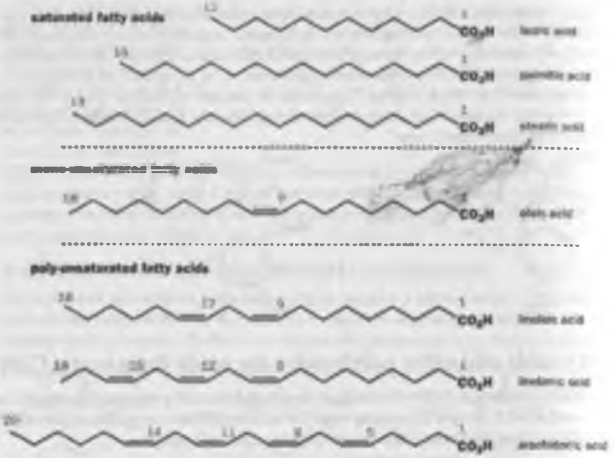
The sections that remain in this chapter show how Nature can take a very simple molecule—acetyl CoA—and build it up into an amazing variety of structures. There are two main pathways from acetyl CoA and each gives rise to two important series of natural products.



We shall discuss these four types of compounds in the order shown so that we start with the simplest, the fatty acids. You met these compounds in Chapter 49 as their glyceryl esters, but you now need to learn about the acids in more detail and outline their biosynthesis. Compare the structures of the typical fatty acids in the chart overleaf.

These are just a few of the fatty acids that exist, but all are present in our diet and you'll find many referred to on the labels of processed foods. You should notice a number of features.

- They have straight chains with no branching
- They have even numbers of carbon atoms
- They may be saturated with no double bonds in the chain, or
- They may have one or more C=C double bonds in the chain, in which case they are usually *cis* (*Z*) alkenes. If there is more than one C=C double bond, they are not conjugated (either with the CO_2H group or with each other)—there is normally one saturated carbon atom between them.

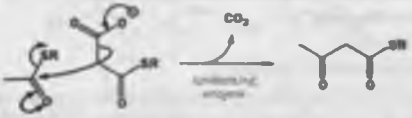


Palmitic acid (C_{16} saturated) is the most common fatty acid in living things. Oleic acid (C_{18} mono-unsaturated) is the major fatty acid in olive oil. Arachidonic acid (C_{20} tetra-unsaturated) is a rare fatty acid, which is the precursor of the very important prostaglandins, thromboxanes, and leukotrienes, of which more later.

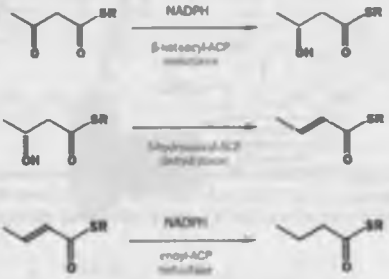
The prevalence of fatty acids with even numbers of carbon atoms suggests a two-carbon building block, the most obvious being acetate. If labelled acetate is fed to plants, the fatty acids emerge with labels on alternate carbons like this.

The green blob might represent deuterium (as a CD_3 group) and the black blob ^{13}C. In fact, the reactions are more complex than this suggests as CO_2 is also needed as well as CoA and it turns out that only the first two-carbon unit is put in as acetyl CoA. The remainder are added as malonyl CoA. If labelled malonyl CoA is fed, the starter unit, as it is called, is not labelled.

Malonyl CoA is made from acetyl CoA and CO_2 carried, as usual, on a molecule of biotin (Chapter 50). The first stage in the fatty acid biosynthesis proper is a condensation between acetyl CoA (the starter unit) and malonyl CoA with the loss of CO_2. This reaction could be drawn like this.



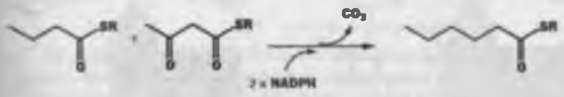
Notice that CO_2 is lost as the new C–C bond is formed. When chemists use malonates, we like to make the stable enol using both carbonyl groups, condense, and only afterwards release CO_2 (Chapter 28). Nature does this in making acetoacetyl CoA during alkaloid biosynthesis, but here she works differently.



The next step is reduction of the ketone group.

This NADPH reaction is typically stereo- and chemoselective, though the stereochemistry is rather wasted here as the next step is a dehydration, typical of what is now an aldol product, and occurring by an enzyme-catalysed E1cB mechanism.

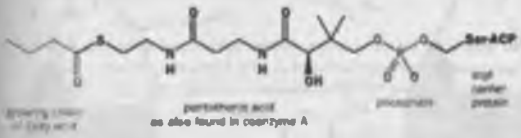
The elimination is known to be a *cis* removal of H and OH and the double bond is exclusively *trans* (*E*). Only later in the nonconjugated unsaturated fatty acids do we get *Z*-alkenes. Finally, in this cycle, the double bond is reduced using another molecule of NADPH to give the saturated side chain.



Now the whole cycle can start again using this newly made C_4 fatty acid as the starter unit and building a C_6 fatty acid and so on. Each time the cycle turns, two carbon atoms are added to the acyl end of the growing chain.

Fatty acid synthesis uses a multienzyme complex

We have not told you the whole truth so far. Did you notice that 'SCoA' in the structures had been replaced by 'SR' and that a mysterious 'ACP' had crept into the enzyme names? That was because these reactions actually happen while the growing molecule is attached as a thiol ester to a long side-chain on an acyl carrier protein (ACP). The long side-chain is closely related to CoA and is attached through a phosphate to a serine residue of the ACP.



All of the enzymes needed for one cycle are clumped together to form two large proteins (ACP, the acyl carrier protein, and CE, the condensing enzyme) which associate in a stable dimer. The long side-chain passes the substrate from enzyme to enzyme so that synthesis can be continuous until the chain is finished and only then is the thiol ester hydrolysed. The chart on p. 000 illustrates this.

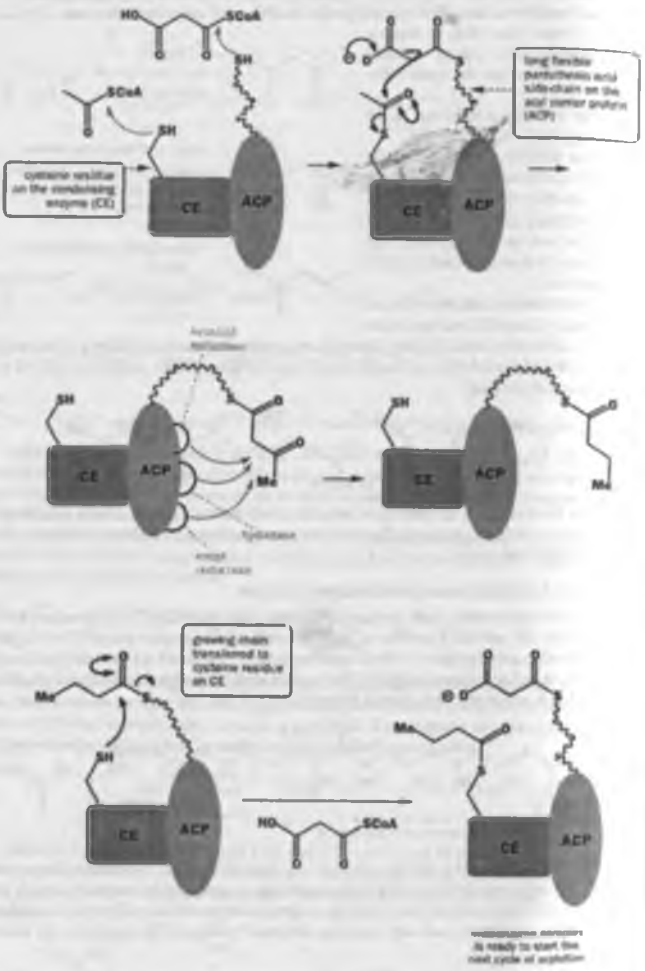
■

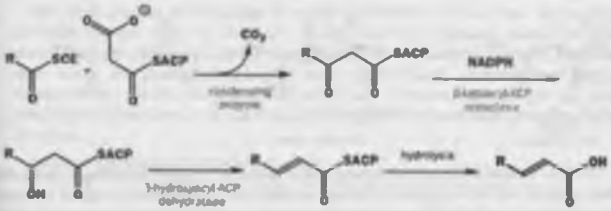
You saw a smaller multienzyme complex in Chapter 30 (p. 000), but this one is much more complex. More are being discovered all the time—Nature invented the production line well before Henry Ford.

There are three ways of making unsaturated fatty acids

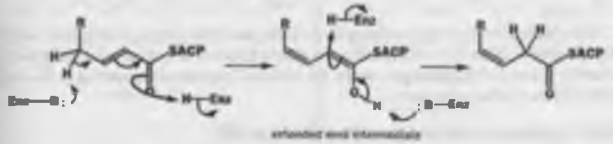
Conjugated unsaturated fatty acids are made simply by stopping the acylation cycle at that stage and hydrolysing the thiol ester linkage between the unsaturated acyl chain and ACP. They always have the *E* (*trans*) configuration and are the starting points for other biosynthetic pathways.

fatty acid biosynthesis: schematic diagram of the multienzyme dimer

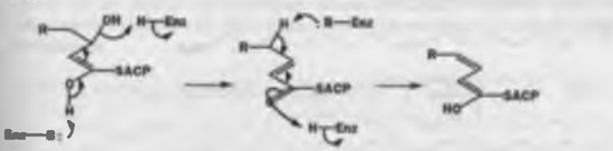




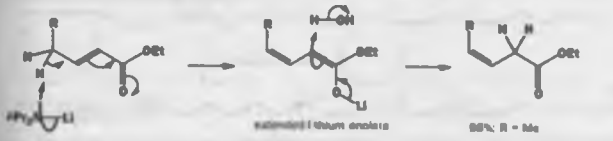
The second method makes *Z*-3,4-unsaturated acids by deconjugation from the *E*-2,3-unsaturated acids catalysed by an isomerase while the acyl chain is still attached to ACP. This is an anaerobic route as no oxidation is required (the double bond is already there—it just has to be moved) and is used by prokaryotes such as bacteria.



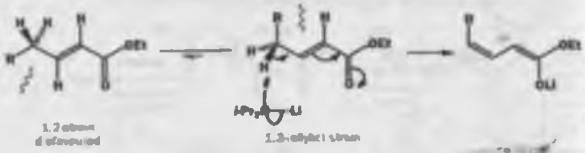
Removal of a proton from C4 forms an extended enol, which can be protonated at C2 or C4. Protonation at C4 is thermodynamically favoured as it leads to the conjugated alkene. But protonation at C2 is kinetically favoured, and this leads to the nonconjugated alkene. The geometry of the new alkene depends on the conformation of the chain when the first (deprotonation) step occurs. It is thought that this is the best conformation for the previous reaction, the dehydration step, and that no rotation of the chain occurs before the isomerase gets to work.



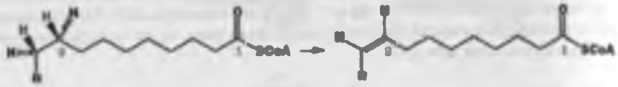
You may think this a rather unlikely reaction, but the same thing can be done in the laboratory. If a simple unsaturated ester is converted into its lithium enolate and then reprotonated with water, the major product is the ester of the *Z*-3,4-enoic acid. Yields and stereoselectivities are excellent.



One explanation suggests that control is exercised by a favourable conformation in which 1,3-allylic strain is preferred to 1,2-strain. It looks as though Nature has again seized on a natural chemical preference and made it even better.



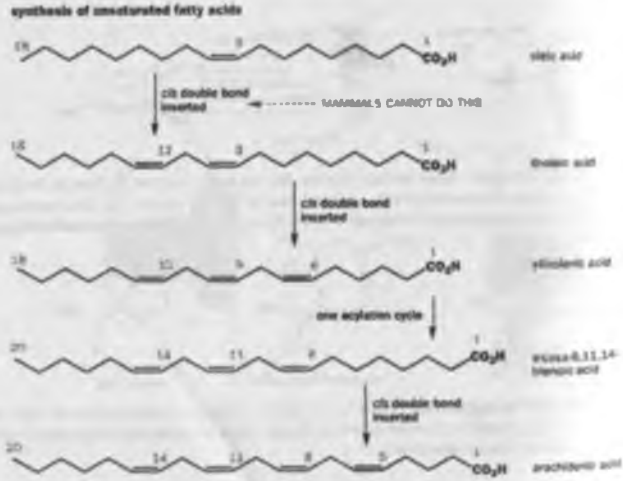
The third method is a concerted stereospecific removal of two adjacent hydrogen atoms from the chain of a fatty acid after synthesis. This is an aerobic route as oxidation is required and is used by mammals such as ourselves. The stereochemistry of the reaction is known from labelling studies to be *cis* elimination.



This oxidation involves a chain of reagents including molecular oxygen, Fe(III), FAD, and NAD^+. A hydroxylation followed by a dehydration or a sulfur-promoted dehydrogenation has been suggested for the removal of the hydrogen atoms. The chemical reaction corresponding to the biological reaction has not yet been discovered.

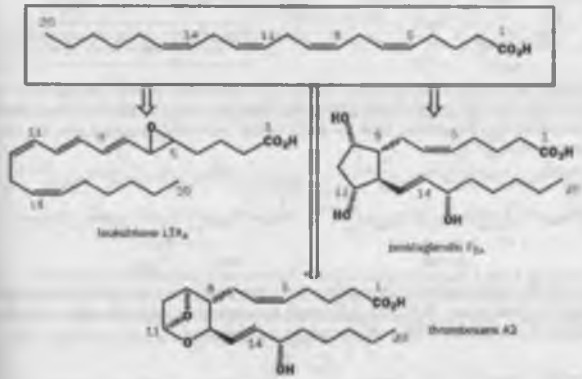
What is so important about unsaturated fatty acids?

Mammals can insert a *cis*-alkene into the chain, providing that it is no further away from the carbonyl group than C9. We cannot synthesize linoleic or linolenic acids (see chart a few pages back) directly as they have alkenes at C12 and C15. These acids must be present in our diet. And why are we so keen to have them? They are needed for the synthesis of arachidonic acid, a C_{20} tetraenoic acid that is the precursor for some very interesting and important compounds. Here is the biosynthesis of arachidonic acid.

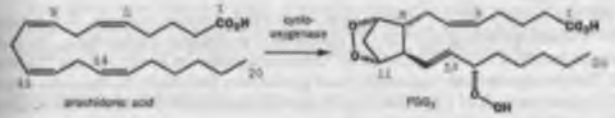


The final product of this chain of events—arachidonic acid—is one of the eicosanoids, so called because *eicosa* is Greek for 'twenty', and the systematic names for these compounds contain 'eicosanoic acid' in some form. The leukotrienes resemble arachidonic acid most closely, the prostaglandins have a closed chain forming a five-membered ring, and the thromboxanes resemble the prostaglandins but have a broken chain. All are C_{20} compounds with the sites of the alkenes (C5, C8, C11, and C14) marked by functionality or some other structural feature.

compounds synthesized from arachidonic acid

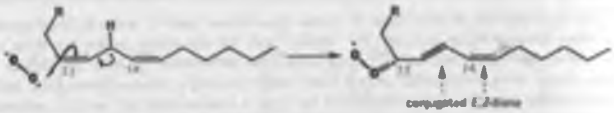


These compounds are all unstable and all are involved in transient events such as inflammation, blood clotting, fertilization, and immune responses. They are produced locally and decay quickly and are implicated in autoimmune diseases like asthma and arthritis. They are made by oxidation of arachidonic acid—you can see this best if you redraw the molecule in a different conformation.



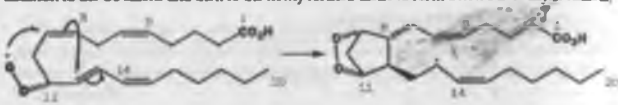
The first step is a radical abstraction of a hydrogen atom from an allylic position by oxygen (perhaps carried on an iron atom in a haem). The atom removed is between two alkenes so that the resulting radical is doubly allylic.

This allylic radical captures a molecule of oxygen at C11 to form a new oxyradical. The reaction occurs at one end of the delocalized radical so that the product is a conjugated diene and the new alkene is *trans* (*E*).

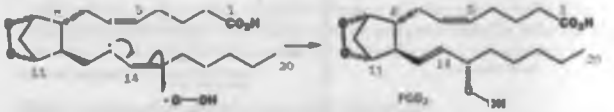


conjugated E,Z-diene

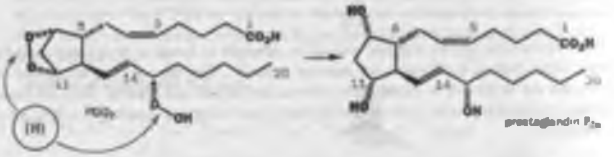
Now we need to resume the full structure of the intermediate because the oxyradical does an elaborate addition to the C8 alkene and then to the newly formed diene to form a new stable allylic radical.



Three new stereogenic centres are created in this cyclization, at C8, C9, and C12, and all are under full control both from the centre already present and from the way in which the molecule folds up under the guidance of the enzyme. Now the allylic radical reacts with oxygen to give the unstable hydroperoxide PGG_2.



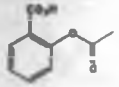
This unstable prostaglandin has been isolated from sheep but, as it has a half-life of only 5 minutes, this is no trivial matter. Both weak O–O bonds are now reduced enzymatically to give the first reasonably stable compound, $PGF_{2\alpha}$ (PG just means prostaglandin).



The best evidence for this pathway comes from labelled oxygen molecules. If a mixture of ^{16}O–^{16}O (ordinary oxygen) and ^{18}O–^{18}O is supplied to an organism making $PGF_{2\alpha}$, the product has either both black OH is as ^{16}O or both as ^{18}O but no molecules are formed with one ^{16}O and one ^{18}O. These isotopes are easily measured by mass spectrometry. Both black OHs then come from one and the same molecule of oxygen—not an obvious conclusion when you inspect the molecule of $PGF_{2\alpha}$, and thus good evidence for this pathway.

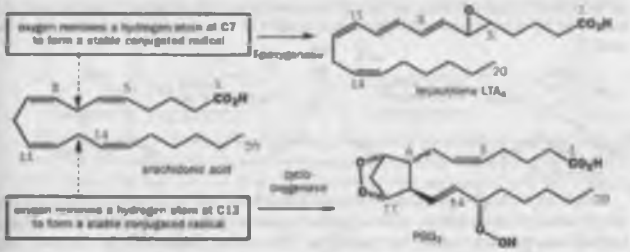
How aspirin works

The enzyme that catalyses these rearrangement reactions, cyclooxygenase, is an important target for medicinal chemists. Inhibiting PG synthesis can bring about a reduction of inflammation and pain. In fact, this is how aspirin works. It was not, of course, designed to work that way and its mode of action was discovered decades after its use began. There is a price to pay for such a useful drug. PGs also control acid secretion in the stomach and aspirin inhibits their synthesis there too as a stomach ulceration can result.

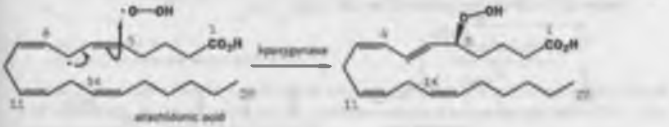


aspirin

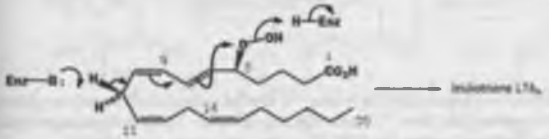
Each of the other families of eicosanoids—thromboxanes and leukotrienes—has interesting biosynthetic pathways too, but we will mention only one small detail. A completely different oxidation enzyme, lipoxygenase, initiates a separate pathway leading to the leukotrienes, but the first steps are very similar. They just occur elsewhere in the arachidonic acid molecule.



The initially formed radical is stabilized by two double bonds in the same way as that we have just seen and reacts with oxygen in the same way again to give a *trans*-alkene and a new hydroperoxide.



The next step is something quite new. No new C–C bond is formed: instead, the diene attacks the hydroperoxide to give an epoxide and a fully conjugated triene. The new double bond is *cis* this time, which is what we should expect from the conformation we have been using. This is LTA_4 and all the other leukotrienes are made from this compound.

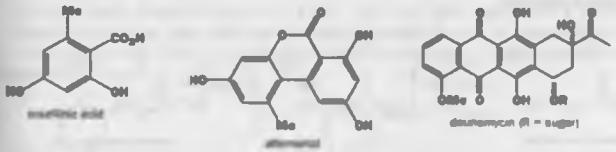


The relatively recent discovery of these unstable molecules of incredibly powerful biological activity means that we by no means know all about them yet. They are very important to our well-being and important medical advances are bound to follow from a better understanding.

■ Prostaglandins and leukotrienes have appeared several times before in this book, and you can read about aspects of their laboratory synthesis on pp. 000 and 000.

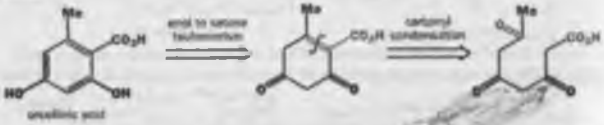
Aromatic polyketides come in great variety

The fatty acid pathway or, as we should call it now, the acyl polymalonate pathway, also gives rise to an inexhaustible variety of aromatic and other compounds belonging to the family of the polyketides. You saw in Chapter 50 how the shikimic acid pathway makes aromatic compounds but the compounds below are from the polyketide route.

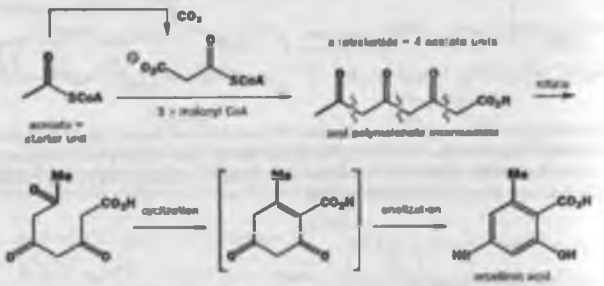


You might immediately be struck by the extent of oxygenation in these compounds. The shikimic acid route produced Ar–C_3 compounds with at most one OH group in the *para* position and others

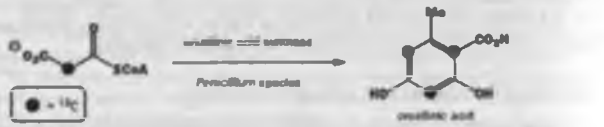
added *ortho* to that first OH group. Here we have multiple oxygenation with a predominant 1,3 pattern. If we try to arrange an acyl polymalonate product to make orsellinic acid, this is what we shall need.



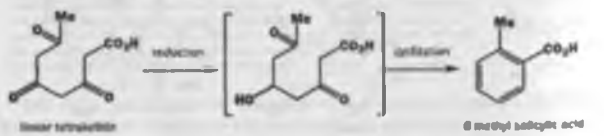
Merely by writing ketones instead of phenols and doing one dehydration corresponding to a simple carbonyl condensation, we have reached a possible starting material which is a typical acyl polymalonate product without any reductions. This is what polyketides are. The fatty acids are assembled with full reduction at each stage. Polyketides are assembled from the same process but without full reduction; indeed, as the name polyketide suggests, many are made without any reduction at all. This is the biosynthesis of orsellinic acid.



This route has been demonstrated by feeding ^{13}C-labelled malonyl CoA to a microorganism. The orsellinic acid produced has three ^{13}C atoms only, seen by an $M + 3$ peak in the mass spectrum. The location of the labels can be proved by NMR. The starter unit, acetate, is not labelled.

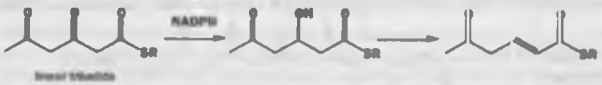


As the polyketide chain is built up, any of the reductions or eliminations from fatty acid biosynthesis can occur at any stage. The simple metabolite 6-methyl salicylic acid (6-MSA) is made in the microorganism *Penicillium patulum*, and it could come from the same intermediate as orsellinic acid with one reduction.

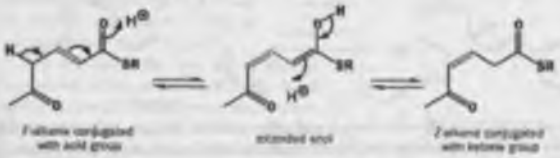


Reduction to the alcohol or to the unsaturated acid or ketone would give the right oxidation level and could occur as the chain is built, after it is completed, or after cyclization. In fact, reduction to

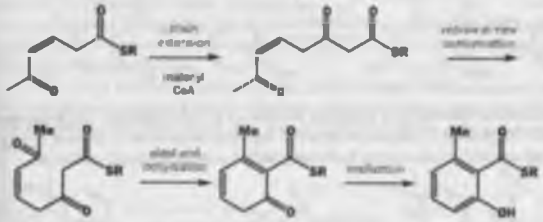
the conjugated unsaturated triketide occurs as the third acetate unit is added, just as the fatty acid route would lead us to expect.



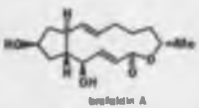
This intermediate cannot cyclize as it has a *trans* double bond and the ends cannot reach each other. First, the double bond is moved out of conjugation with the COSR group, again as in the fatty acids, except that here the new *Z* double bond moves into conjugation with the remaining keto group.



Now the last chain extension occurs and the completed *Z*-tetraketide cyclizes to 6-methyl salicylic acid. Chemically, we would prefer not to carry the unstable *Z*-enone through several steps, but Nature controls these reactions very precisely.



This precise sequence was discovered only through very careful double labelling experiments and after the discovery of specific inhibitors for the enzyme. Since polyketides can be made from the acyl polymalonate pathway with or without reduction and elimination at any step, the number of possible structures is vast. With more reduction, no aromatic ring can be formed: macrolide antibiotics such as brefeldin A come from this route.

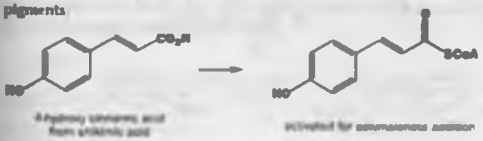


brefeldin A

If you examine this structure, you should be able to find a continuous carbon chain made from an acetate starter unit and seven malonyl CoA units with full or partial reduction occurring after many acylation steps.

Other starter units

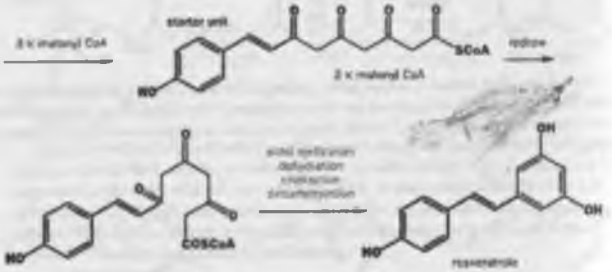
So far we have started the chain with acetate, but many other starter units are used. Some important groups of compounds use shikimic acid metabolites such as cinnamic acid (Chapter 50) as starter units. They include the widespread plant flavones and the anthocyanidin flower pigments.



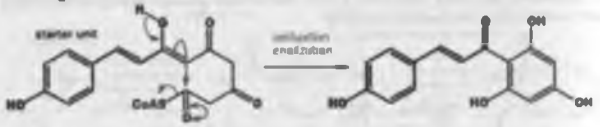
A hydroxy cinnamic acid from shikimic acid

activated for nucleophilic addition

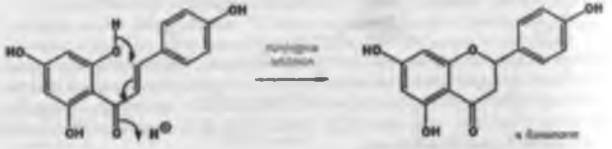
The most common sequence uses three malonyl CoA acylations followed by cyclization to a new aromatic ring. The simplest type is exemplified by resveratrole, the compound in red wine that helps to prevent heart disease. Each step in this sequence is a simple reaction that you have met before.



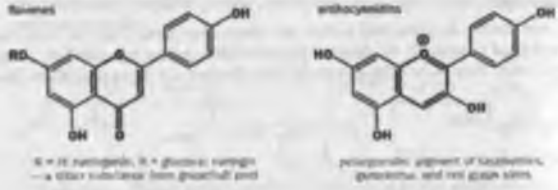
A different cyclization leads to the flavones and anthocyanidins. Reaction of the stable enol from a 1,3-diketone with the thiol ester as electrophile results in acylation at carbon in the manner of the Claisen ester condensation (Chapter 28) with loss of CoASH and the formation of a trihydroxybenzene ring.



This cyclization is followed by a conjugate addition of an *ortho* phenolic OH group on to the enone system. The product is a flavanone structure, which is always drawn a different way up to the molecules we have just been discussing. Redrawing the last product shows the cyclization.

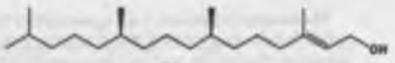


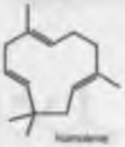
Aromatization of the central oxygen heterocycle by oxidation leads to the flavones, which are yellow or orange depending on their substituents. Dehydration leads to the red or blue anthocyanidins, pigments of flowers and fruit. This important group of molecules also includes plant growth hormones and defence compounds.



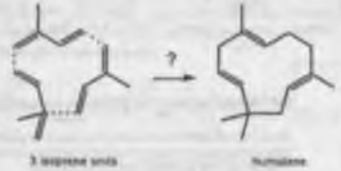
Terpenes are volatile constituents of plant resins and essential oils

Terpenes were originally named after turpentine, the volatile oil from pine trees used in oil painting, whose major constituent is α-pinene. The term was rather vaguely used for all the volatile oily compounds, insoluble in water and usually with resiny smells from plants. The oils distilled from plants, which often contain perfumery or flavouring materials, are called essential oils and these too contain terpenes. Examples include camphor from the camphor tree, used to preserve clothes from moths, humulene from hops, which helps to give beer its flavour, and phytol, found in many plants.

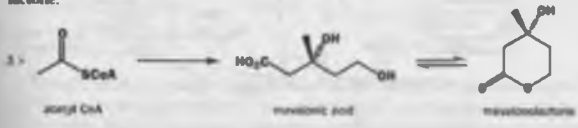




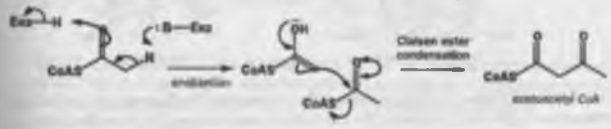
You will notice that they are all aliphatic compounds with a scattering of double bonds and rings, few functional groups, and an abundance of methyl groups. A better definition (that is, a biosynthetically based definition) arose when it was noticed that all these compounds have 5*n* carbon atoms. Pinene and camphor are C_{10} compounds, humulene is C_{15}, and phytol is C_{20}. It seemed obvious that terpenes were made from a C_5 precursor and the favourite candidate was isoprene (2-methylbuta-1,3-diene) as all these structures can be drawn by joining together 2-, 3-, or 4-isoprene skeletons end to end. Humulene illustrates this idea.



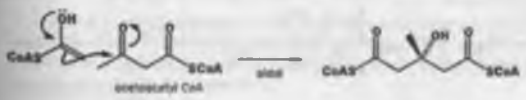
In fact, this is not correct. Isoprene is not an intermediate, and the discovery of the true pathway started when acetate was, rather surprisingly, found to be the original precursor for all terpenes. The key intermediate is mevalonic acid, formed from three acetate units and usually isolated as its lactone.



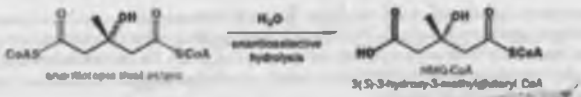
The first step is the Claisen ester condensation of two molecules of acetyl CoA, one acting as an enol and the other as an electrophilic acylating agent to give acetoacetyl CoA. We saw the same reaction in the biosynthesis of the pyrrolidine alkaloids earlier in this chapter.



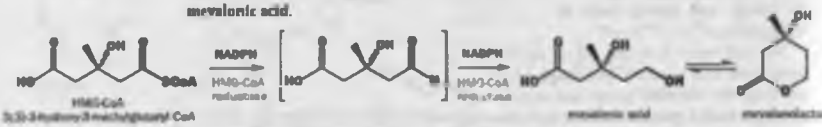
The third molecule of acetyl CoA also functions as a nucleophilic enol and attacks the keto group of acetoacetyl CoA. This is not a Claisen ester condensation—it is an aldol reaction between the enol of a thiol ester and an electrophilic ketone.



We have drawn the product with stereochemistry even though it is not chiral. This is because one of the two enantiotopic thiol esters is hydrolysed while this intermediate is still bound to the enzyme, so a single enantiomer of the half-acid/half-thiol ester results.

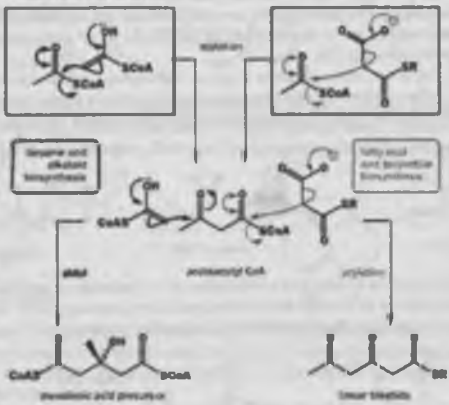


The remaining thiol ester is more electrophilic than the acid and can be reduced by the nucleophilic hydride from NADPH. Just as in $LiBH_4$ reductions of esters (Chapter 24), the reaction does not stop at the aldehyde level, and two molecules of NADPH are used to make the alcohol. This is mevalonic acid.



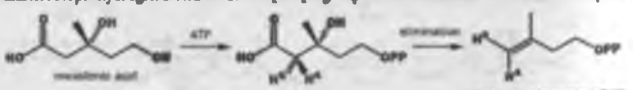
Different pathways; different reactivity

Acetyl CoA (as an enol) and malonyl CoA are both acylated by acetyl CoA as an electrophile, but the behaviour of the two nucleophiles is different when they react with acetoacetyl CoA. Malonyl CoA is decarboxylated by loss of CO2 and then does the aldol reaction. This could be enzymatic control.

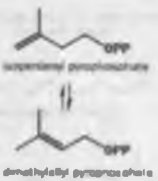


Mevalonic acid is indeed the true precursor of the terpenes but it is a C_6 compound and so it must lose a carbon atom to give the C_5 precursor. The spare carbon atom becomes CO_2 by an elimination reaction. First, the primary alcohol is pyrophosphorylated with ATP (Chapter 40), then the CO_2H group and the tertiary alcohol are lost in a concerted elimination. We know it is concerted because labelling the diastereotopic hydrogen atoms on the CH_2CO_2H group reveals that the elimination is stereospecific.

▶ 'PP' indicates the pyrophosphate group transferred from ATP.

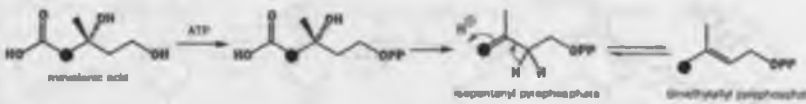


So is isopentenyl pyrophosphate the C_5 intermediate at last? Well, yes and no. There are actually two closely related C_5 intermediates, each of which has a specific and appropriate role in terpene biosynthesis. Isopentenyl pyrophosphate is in equilibrium with dimethylallyl pyrophosphate by a simple allylic proton transfer.

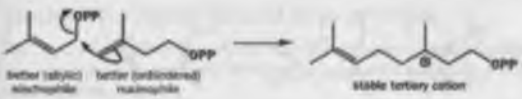


This is again a concerted reaction and again we know that by proton labelling. One of the two enantiotopic protons (H^S in the diagram) is lost from the bottom face of the allylic CH_2 group while the new proton is added to the top face of the alkene. This is an *anti* rearrangement overall.

The stereochemical details are interesting in establishing the mechanism but not important to remember. What is important is that the origin of the two methyl groups in dimethylallyl pyrophosphate is quite distinct and can easily be traced if you always draw the intermediates in the way we have drawn them. We will now switch to ^{13}C labelling to make the point.

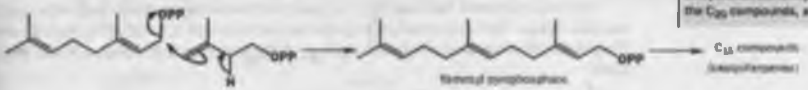


The two C_5 intermediates now react with each other. The dimethylallyl pyrophosphate is the better electrophile because it is allylic, and allylic compounds are good at both S_N1 and S_N2 reactions (Chapter 17). Isopentenyl pyrophosphate is the better nucleophile because it can react through an unhindered primary carbon atom to produce a tertiary cation. This is what we have in mind.



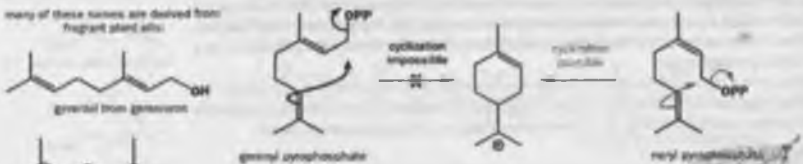
Though this idea reveals the thinking behind the reaction, in fact it does not go quite like this. The product is one particular positional and geometrical isomer of an alkene and the cation is not an intermediate. Indeed, the reaction is also stereospecific (discovered again by proton labelling, but we will not give the rather complex details) and this too suggests a concerted process.

Geranyl pyrophosphate is the starting point for all the monoterpenes. It is still an allylic pyrophosphate and repeating the alkylation with another molecule of isopentenyl pyrophosphate gives farnesyl pyrophosphate, the starting point for the sesquiterpenes, and so on.

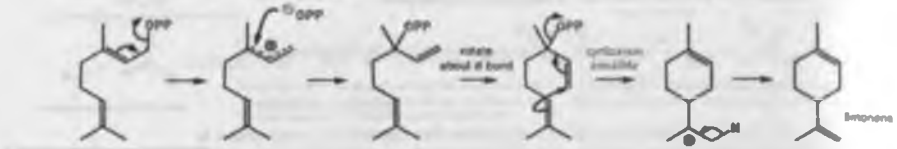


As soon as we start to make typical cyclic monoterpenes from geranyl pyrophosphate we run into a snag. We cannot cyclize geranyl pyrophosphate because it has a *trans* double bond! We could cyclize the *cis* compound (neryl pyrophosphate), and it used to be thought that this was formed from the *trans* compound as an intermediate.

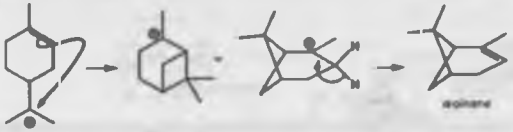
▶ Though terpenes are made from C_5 units, they are classified in C_{10} units. The monoterpenes are the C_{10} compounds, the sesquiterpenes (sesqui is Latin for one-and-a-half) are the C_{15} compounds, the diterpenes are the C_{20} compounds, and so on.



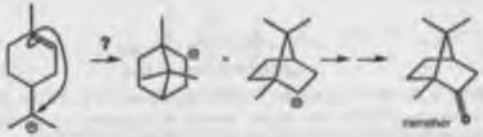
It is now known that Nature gets round this problem without making neryl pyrophosphate. An allylic rearrangement occurs to move the pyrophosphate group to the tertiary centre. This is an unfavourable rearrangement thermodynamically and probably occurs via the allyl cation and catalysed by Mg(II). There is no longer any geometry about the alkene. The molecule can now rotate freely about a single bond and cyclization can occur. Even if only a small amount of the rearranged allylic pyrophosphate is present, that can rearrange and more can isomerize.



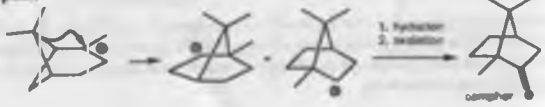
More interesting compounds come from the cyclization of the first formed cation. The remaining alkene can attack the cation to form what looks at first to be a very unstable compound but which is actually a tertiary carbocation with the pinene skeleton.



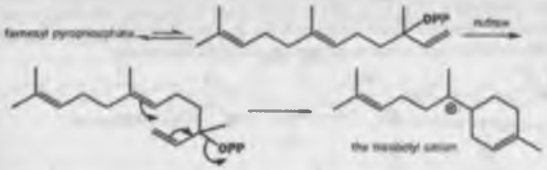
The camphor skeleton looks as though it might be formed by cyclization of the wrong end of the alkene on to the cation. This would certainly give the right skeleton but the intermediate secondary cation is rather unlikely.



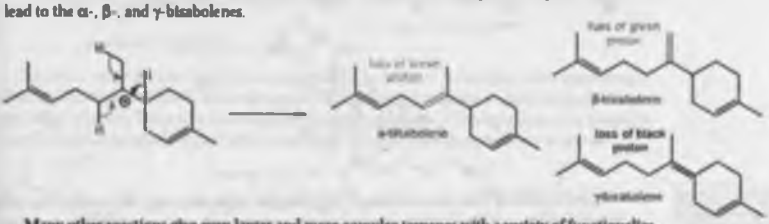
There is a better route. The more likely cation formed on the way to pinene could rearrange to the camphor cation. This is a known chemical reaction and is a simple 1,2-shift of the kind discussed in Chapter 37. However the new cation is formed, addition of water and oxidation would give camphor.



In the sesquiterpene series, similar cyclizations lead to an amazing variety of products. After the initial unfavourable allylic rearrangement of the pyrophosphate group, farnesyl pyrophosphate can give a six-membered ring cation known as the bisabolyl cation.



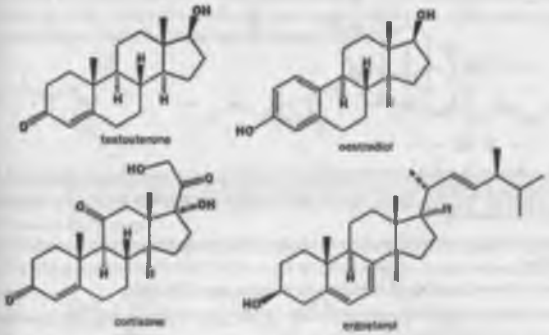
This cation does many things but it takes its name from the three fairly random proton losses that lead to the α-, β-, and γ-bisabolenes.



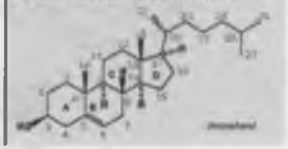
Many other reactions give even larger and more complex terpenes with a variety of functionalization but we will treat only one group in detail. These compounds are so important to us that they are given a different name.

Steroids are metabolites of terpene origin

Two types of human hormone are steroidal—the sex hormones such as oestradiol and testosterone and the adrenal hormones such as cortisone. Cholesterol is a steroid too, as is vitamin D, derived from ergosterol.

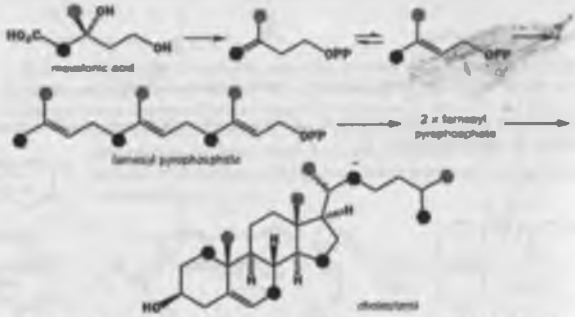


▶ For reference, here is the numbering of the steroid nucleus, not because we want you to learn it, but because it is often used without explanation in books and it is not obvious.

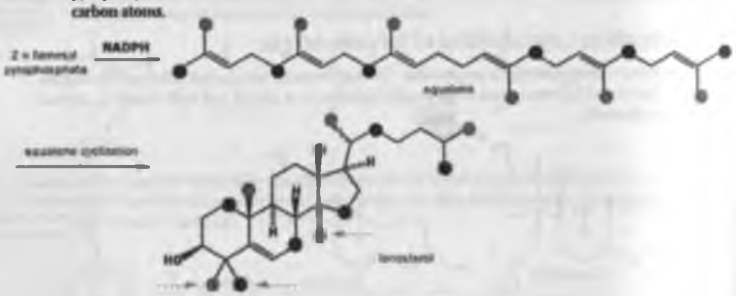


All share the skeleton of four fused rings, three six-membered and one five-membered and conventionally lettered A–D. Beyond the ring stereochemistry and some common oxygenation patterns they share little else. Some (such as the female sex hormones) have an aromatic A ring; some have side-chains on the five-membered ring.

At first glance, it is not at all clear that steroids are terpenoid in origin. The 5n numbers are absent—cholesterol is a C_{27} compound while the others variously have 20, 21, or 23 carbon atoms. Studies with labelled mevalonic acid showed that cholesterol is terpenoid, and that it is formed from two molecules of farnesyl pyrophosphate ($2 \times C_{15} = C_{30}$ so three carbon atoms must be lost). Labelling of one or other of the methyl groups (two experiments combined in one diagram!) showed that two of the green carbon atoms and one of the black carbon atoms were lost during the biosynthesis.



It is not obvious how the two farnesyl pyrophosphate molecules could be combined to make the steroid skeleton, and the chemistry involved is extraordinary and very interesting. The first clues came from the discovery of the intermediates squalene and lanosterol. Squalene is obviously the farnesyl pyrophosphate dimer we have been looking for while lanosterol looks like cholesterol but still has all 30 carbon atoms.



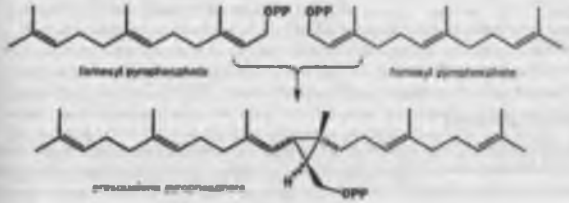
The three carbon atoms that are lost from lanosterol (C_{30}) in its conversion to cholesterol (C_{27}) are marked with brown arrows. Now at least we know which carbon atoms are lost. But many questions remain to be answered.

- How does farnesyl pyrophosphate dimerize so that two electrophilic carbon atoms (CH_2OPP) join together?
- Why does the formation of squalene require the reducing agent NADPH?
- How does squalene cyclize to lanosterol so that the very odd labelling pattern can be achieved?
- Where do the three lost carbon atoms go?
- How is the stereochemistry controlled?

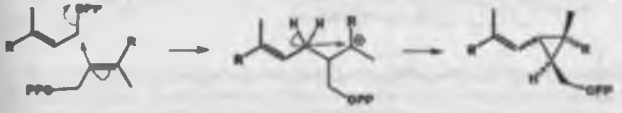
Before we tell you the answers, be warned: prepare for some surprises, and be ready to hold back outright disbelief!

The formation of squalene from farnesyl pyrophosphate

If the reducing agent NADPH is omitted from the cell preparation, squalene is not formed. Instead, another farnesyl pyrophosphate dimer accumulates—presqualene pyrophosphate—which has a three-membered ring and in which we can see that the two molecules of farnesyl pyrophosphate are joined in a slightly more rational way.



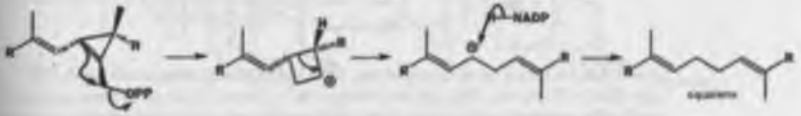
Maybe it's not so obvious that this is more rational! The first C–C bond formation is quite straightforward. The alkene in the red molecule attacks the allylic pyrophosphate in the black molecule in a simple S_N2' reaction. The product is a stable carbocation. Only one C–C bond remains to be formed to close the three-membered ring and this occurs by the loss of a proton from the black molecule.



R
We will abbreviate the long terpene side-chain to 'R' from now on.

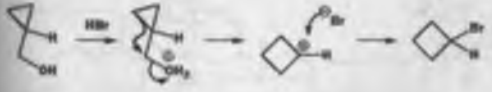
This is a very remarkable reaction. Such reactions do not occur chemically: this biological one occurs only because the molecule is held in the right shape by the enzyme and because the new ring is three-membered. Three-membered rings are very easily formed but also very easily opened—and that is what happens to this ring. In the presence of NADPH, a series of rearrangements gives a series of carbocations, the last of which is trapped by reduction.

The first step is the migration of one of the bonds (shown in green) of the three-membered ring to displace the pyrophosphate leaving group, expand the ring to four-membered, and release some strain. Now the cyclobutyl cation breaks down to give an open-chain allylic cation stabilized by one of the alkenes. This is the cation that is reduced by NADPH.



If you follow this sequence backwards, you will see that the originally formed 'rational' bond (shown in green) is the one that migrated and is retained in squalene, while the second bond is cleaved in the last step.

This may all seem far-fetched, but it happens in laboratory reactions too! Treatment of the simplest cyclopropyl alcohol with HBr gives cyclobutyl bromide by a similar rearrangement.

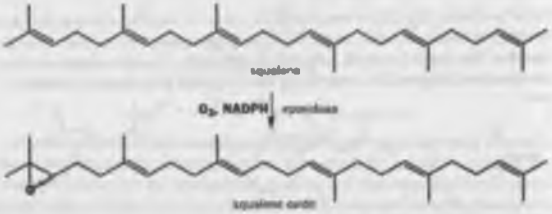


In fact, cyclopropylmethyl compounds, cyclobutyl compounds, and homoallyl compounds are all in equilibrium in acid solution and mixtures of products are often formed. The delocalized cation

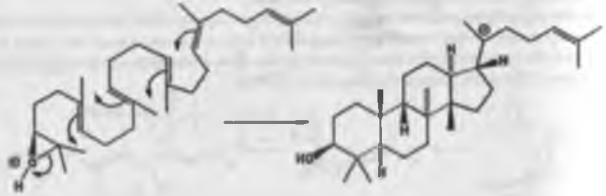
shown has been suggested as an intermediate. Make sure that you can draw mechanisms for each starting material to give the intermediate cation and from the cation to each product.

Squalene to lanosterol

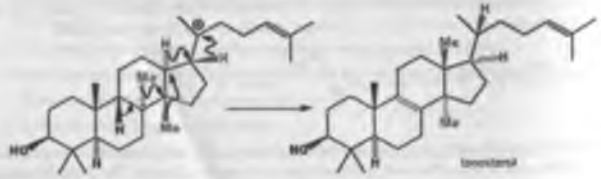
The next step is simple—the epoxidation of one of the terminal double bonds—but it leads to two of the most remarkable reactions in all of biological chemistry. Squalene is not chiral, but enzymatic epoxidation of one of the enantiotopic alkenes gives a single enantiomer of the epoxide with just one stereogenic centre.



We will start now to draw squalene in a coiled up way as the next step is the polycyclization of the epoxide. The basic reaction is best seen first in the flat, though we will draw the stereochemistry immediately. The first alkene cyclizes on to the epoxide and then each remaining alkene cyclizes on to the next to give a stable tertiary cation.

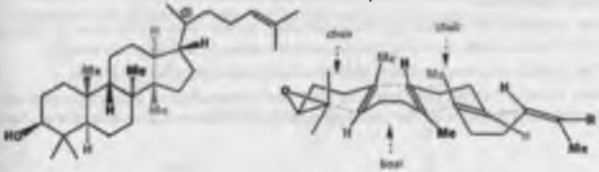


By analogy with what has gone before, you might now expect a tame hydration or reduction of this cation. Nothing of the sort! A rearrangement occurs in which *five* consecutive 1,2-shifts are followed by an elimination. Since this reaction organizes the backbone of the steroids, it is often called the **steroid backbone rearrangement**.



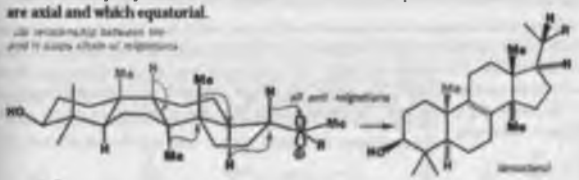
Finally, we have reached lanosterol. Now we will go back over these two steps and discuss them a bit more. Consider first the regiochemistry of the cyclization. The epoxide opens in the way we would expect to give positive charge at the more substituted carbon atom and then all the alkenes attack through their less substituted end (again as we would expect to give positive charge at the more substituted carbon atom)—all except one. The third alkene cyclizes the 'wrong' way—this is presumably a result of the way the molecule is folded.

We learn much more about the folding by examining the stereochemistry of the product cation. First, all of the stereochemistry of each alkene is faithfully reproduced in the product: the cyclization is stereospecific. This is emphasized to colour in the diagram. The green stereochemistry arises because the green Me and H were *trans* in the first alkene of squalene, the black Me and H *trans* in the second, and the brown *trans* in the third. But what about the relationship between the green methyl and the black H? Or between the black and brown methyls? These were determined by the folding and the key observation is that all the relationships are *trans* except that between the green Me and the black H. Now we can draw a conformation for the cyclization.



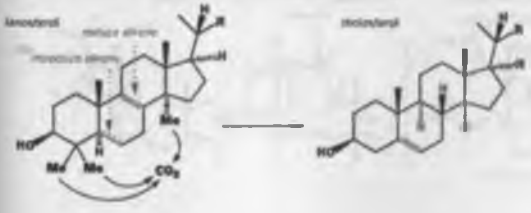
When the transition state for a ring closure forms a chair then a *trans* relationship results. This is the case for the black Me and brown Me. When a boat is formed a *cis* relationship results. This is the case for the green Me and black H. Squalene folds up in a chair–boat–chair conformation and that leads to the observed stereochemistry.

Next, we need to look at the stereochemistry of the rearrangement step. If we draw the product cation as nearly as possible in the conformation of folded squalene, we will see which substitutents are axial and which equatorial.



Each group that migrates (black) is axial and is anti-periplanar to the one before so that each migrating group does an S_N2 reaction on the migration terminus with inversion. The chain stops because of the *cis* relationship between the green Me and H in ring B and an elimination of the green H is all that can happen.

The remainder of the biosynthesis of cholesterol requires various redox reactions and is a bit of an anticlimax: the details are summarized in the scheme below.



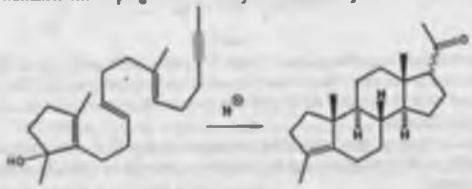
Biomimetic synthesis: learning from Nature

When new and academic-looking reactions are discovered in the laboratory, it often seems only a short time before they are found in nature as well. However, the development of polyolefin cyclization reactions in synthesis occurred by the reverse philosophy—it was inspiration from Nature that led W. S. Johnson to use the reactions in synthesis, including steroid synthesis. This is biomimetic synthesis, a strategy that is bound to work provided we can just master the practical details.

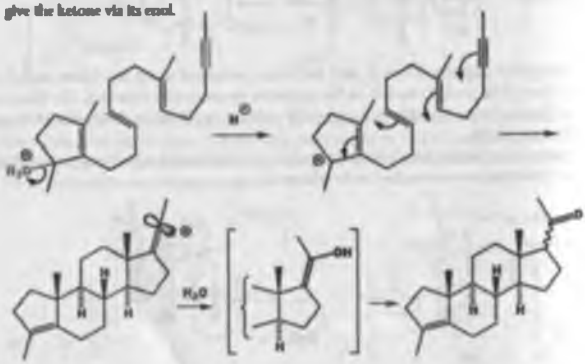
There are quite a lot of differences between the chemical and the biochemical versions so far—the chemical ones are less complex and less sophisticated but more versatile. The reactions are just cyclizations without the backbone rearrangements. The most important points of difference are:

- The cyclization is usually begun with a cation from treatment of a cyclic tertiary alcohol rather than an epoxide
- The cyclization sequence is terminated with an alkyne or an allyl silane rather than with simple alkene
- The substituents are placed in the correct positions in the starting material as no rearrangement follows cyclizations
- The cyclizations are all stereospecific as in nature but the rings coil up in an all-chair fashion rather than in a chair–boat–chair fashion as there is no enzyme to shape the molecule
- The product cation is quenched by addition of water rather than loss of a proton

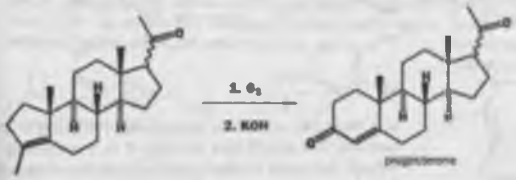
Here is one of Johnson's best examples which leads eventually to a biomimetic synthesis of the human hormone progesterone. The cyclization occurs just on treatment of the tertiary alcohol with acid.



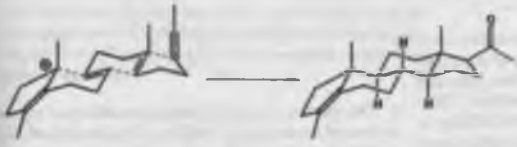
The first step is the formation of a symmetrical allyl cation, which then initiates the cyclization. The next double bond is disubstituted so that it has no built-in regioselectivity but prefers to form a six-membered rather than a five-membered ring B. The next double bond is trisubstituted and directs the formation of a six-membered ring C. The alkyne, being linear, can react only through its inner end and so a five-membered ring D is formed. The resulting linear vinyl cation picks up a molecule of water to give the ketone via its enol.



The five-membered ring A is there to ensure efficient initiation of the cyclization by the symmetrical allylic cation. It can easily be opened with ozone and the product cyclized to progesterone.



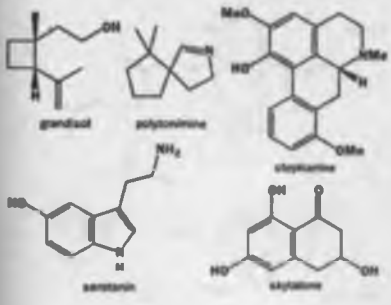
The conformation of the molecule in the moment of cyclization can be seen easily by working backwards from the product. The green dashed lines show new bonds that are being formed. All the six-membered rings in the transition state are chairs and all the ring junctions *trans*. This is an impressive result as there is no enzyme to help the molecule fold up in this way.

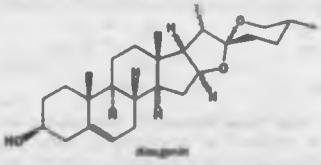


By studying the chemistry that Nature uses in living things we can learn new reactions as well as new ways in which to carry out known reactions. Many of the reactions in this chapter would be laughed at by worldly wise chemists if they appeared in a research proposal, but they have been evolved over millions of years to do precise jobs under mild conditions. Humans have been doing complex organic chemistry for only about a hundred years so that learning from Nature is one of the most important ways in which organic chemistry is advancing at the beginning of the twenty-first century.

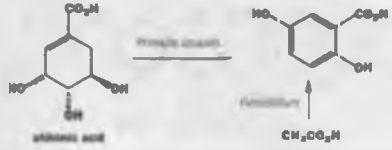
Problems

1. Assign each of these natural products to a general class (such as amino acid metabolite, terpene, polyketide) explaining what makes you choose that class. Then assign them to a more specific part of the general class (for example, tetraketide, sesquiterpene).

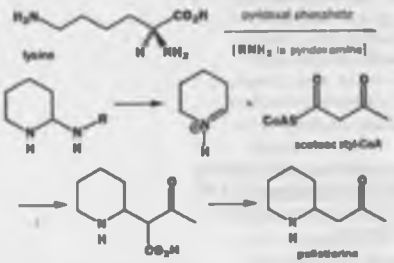




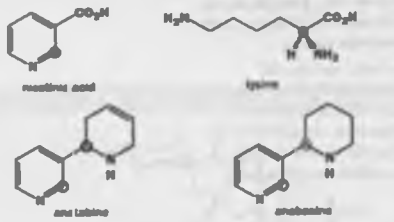
2. Some compounds can arise from different sources in different organisms. 2,5-Dihydroxybenzoic acid comes from shikimic acid (Chapter 50) in *Primula acaulis* but from acetate in *Penicillium* species. Outline details.



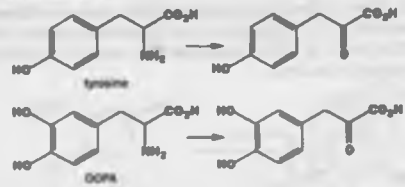
3. The piperidine alkaloid pelletierine was mentioned in the chapter but full details of its biosynthesis were not given. There follows an outline of the intermediates and reagents used. Fill in the details. Pyridoxal chemistry is discussed in Chapter 50.

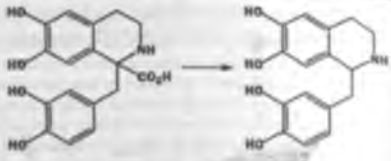


4. The rather similar alkaloids anabasine and anatabine come from different biosynthetic pathways. Labelling experiments outlined below show the origin of one carbon atom from lysine and others from nicotinic acid. Suggest detailed pathways. (*Hint.* Nicotinic acid and the intermediate you have been using in Problem 3 in the biosynthesis of the piperidine alkaloid are both electrophilic at position 2. You also need an intermediate derived from nicotinic acid which is nucleophilic at position 3. The biosynthesis involves reduction.)

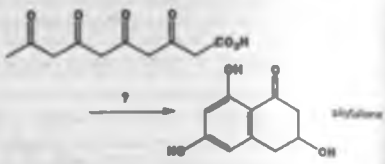


5. The three steps in the biosynthesis of papaverine set out below involve pyridoxal (or pyridoxamine). Write detailed mechanisms.

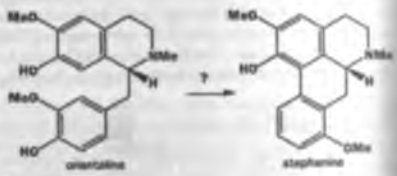




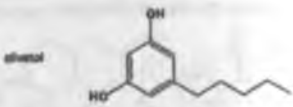
6. Concentrate now on the biosynthesis of akytalone in the first problem. You should have identified it as a pentaketide. Now consider how many different ways the pentaketide chain might be folded to give akytalone.



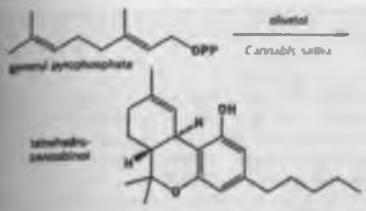
7. This question concerns the biosynthesis of stephanine, another compound mentioned in Problem 1. You should have deduced that it is a benzylisoquinoline alkaloid. Now suggest a biosynthesis from orientaline.



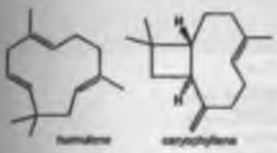
8. Suggest a biosynthesis of olivetol.



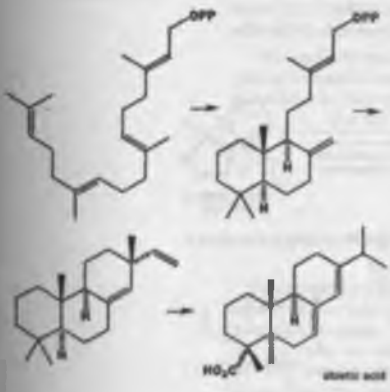
9. Tetrahydrocannabinol, the major psychoactive compound in marijuana, is derived in the *Cannabis* plant from olivetol and geranyl pyrophosphate. Details of the pathway are unknown. Make some suggestions and outline a labelling experiment to establish whether your suggestions are correct.



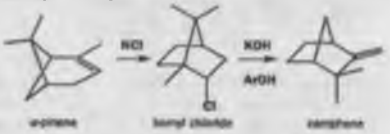
10. Both humulene, mentioned in the chapter, and caryophyllene are made in nature from farnesyl pyrophosphate in different plants. Suggest detailed pathways. How do the enzymes control which product is formed?



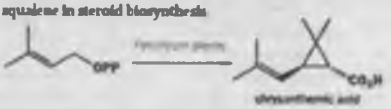
11. Abietic acid is formed in nature from mevalonate via the intermediates shown. Give some more details of the cyclization and rearrangement steps and compare this route with the biosynthesis of the steroids.



12. Borneol, camphene, and α-pinene are made in nature from geranyl pyrophosphate. The biosynthesis of α-pinene and the related camphor is described in the chapter. In the laboratory bornyl chloride and camphene can be made from α-pinene by the reactions described below. Give mechanisms for these reactions and say whether you consider them to be biomimetic.

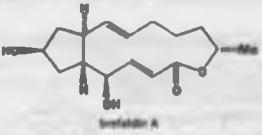


13. Suggest a biosynthetic route to the monoterpene chrysanthemic acid that uses a reaction similar to the formation of squalene in steroid biosynthesis.

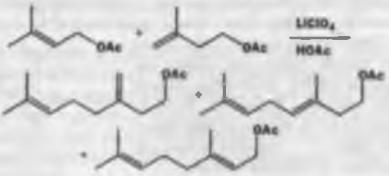


How could the same route also lead to the natural products yomogi alcohol and artemisia ketone?

14. In the chapter we suggested that you could detect an acetate starter unit and seven malonate additional units in the skeleton of brefeldin. Give the mechanism of the addition of the first malonyl CoA unit to acetate. Draw out the structure of the complete acyl polymalonate chain and state clearly what must happen to each section of it (reduction, elimination, etc.) to get brefeldin A.



15. This chemical experiment aims to imitate the biosynthesis of terpenes. A mixture of products results. Draw a mechanism for the reaction. To what extent is it biomimetic, and what can the natural system do better?



Polymerization

52

Connections

Building on:

- Carbonyl chemistry ch12 & ch14
- Substitution reactions ch17
- Radical reactions ch28
- Protecting groups and synthesis ch24–ch26
- The aldol reaction ch27
- Making double bonds ch31
- Cycloadditions ch35
- Heterocycles ch43–ch44
- Organometallics ch45
- The chemistry of life ch49
- Natural products ch51

Arriving at:

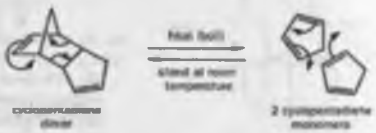
- Some molecules react together to form oligomers
- Some molecules spontaneously polymerize
- Polyamides, polyesters, and polycarbonates are formed by substitution reactions at carbonyl groups
- Polyurethane foams are formed by nucleophilic attack on isocyanates
- Epoxy adhesives work by polymerization via substitution reactions at saturated carbon
- The most important polymers are derived from alkene monomers
- Alkenes can be polymerized by radical, cationic, anionic, or organometallic methods
- Cross-linking or co-polymerization changes the physical properties of polymers
- Reactions on polymers are involved in paint drying, rubber strengthening, and the chemical synthesis of peptides

Most of the things you can see about you at this moment are made of organic polymers. Skin, clothes, paper, hair, wood, plastic, and paint are among them. Teeth, muscle, glue, cling film, starch, crab shells, and marmalade are all polymer-based too. In this chapter we will explore the world of polymers. We will ask questions like these:

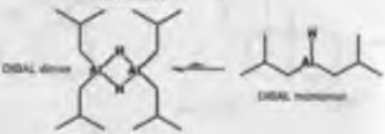
- What makes a molecule prefer to react with others of its kind to form a polymer?
- What mechanisms are available for polymerization reactions?
- How can polymerization reactions be controlled?
- How are the properties of polymers related to their molecular structure?

Monomers, dimers, and oligomers

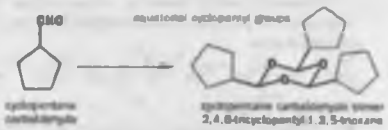
Cyclopentadiene featured in Chapter 35 as an important diene in the Diels–Alder reaction. If you try to buy 'cyclopentadiene' you will find that the catalogues list only 'dicyclopentadiene' or 'cyclopentadiene dimer'. The dimerization of cyclopentadiene is reversible: the monomer dimerizes by a Diels–Alder reaction at room temperature to give the dimer and the reaction is reversed on heating. So the dimer is a good source of the monomer.



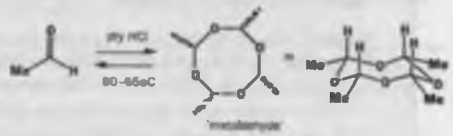
Other familiar cases of stable dimers are neutral boron and aluminium hydrides. DIBAL, for example, exists as two molecules linked by Al–H–Al bonds in a four-membered ring. Again, the dimer is a practical source of monomer for chemical reactions.



Simple aldehydes easily form trimers. When cyclopentanecarbaldehyde is prepared, it is a colourless liquid. On standing, particularly with traces of acid, it forms the crystalline trimer. The trimer is a stable six-membered heterocycle with all substituents equatorial.

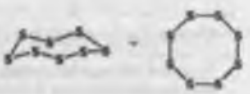


Acetaldehyde (ethanal) forms a liquid trimer called 'paraldehyde', which reverts to the monomer on distillation with catalytic acid. More interesting is 'metaldehyde', the common slug poison, which is an all-*cis* tetramer (2,4,6,8-tetramethyl-1,3,5,7-tetroxocane) formed from acetaldehyde with dry HCl at below 0 °C. Metaldehyde is a white crystalline solid that has all the methyl groups pseudoequatorial, and it reverts to acetaldehyde on heating.

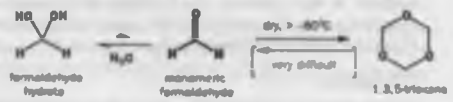


Another tetramer is methyl lithium. MeLi is a very reactive compound in the monomeric state, and it crystallizes as a tetramer: a tetrahedron of lithium atoms with a methyl group 'plugged in' to the centre of each face.

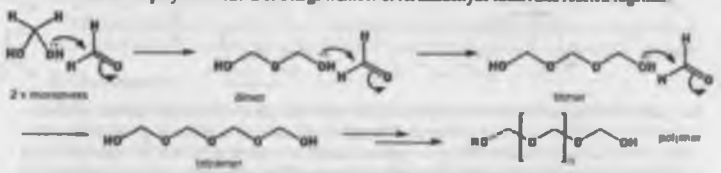
Whereas oxygen gas consists of diatomic molecules O_2, crystalline sulfur is S_8, a cyclic octomer. Such multiples are usually called oligomers (oligo = a few). The monomer in this case would be the sulfur atom. The shape of the S_8 ring is very similar to that of the eight-membered ring of metaldehyde.



If you buy formaldehyde (methanal), which is in fact a gas, b.p. –19 °C, you have four choices. You can buy a 37% aqueous solution 'formalin' which is mostly hydrate in equilibrium with a small amount of formaldehyde, or the crystalline trimer (1,3,5-trioxane), or a white solid called (misleadingly) 'paraformaldehyde', or another white solid called polyoxymethylene.

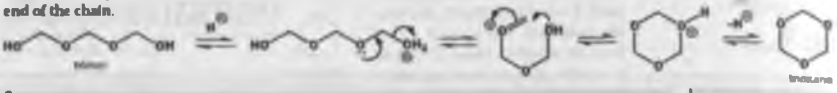


Trioxane is not a good source of formaldehyde as it is very stable but the two other solids are good sources. Both paraformaldehyde and, more obviously, polyoxymethylene are polymers. Each molecule of either polymer consists of a large number of formaldehyde molecules reacted together.



Paraformaldehyde is made by evaporation of aqueous formaldehyde to dryness and is a water-soluble polymer. Polyoxymethylene is made by heating formaldehyde with catalytic sulfuric acid and is *not* soluble in water. They are both linear polymers of formaldehyde, so how can they be so different? The answer is in the polymer chain length—the *n* in the diagram. Paraformaldehyde is water-soluble because it has short chain lengths, about $n = 8$ on average, and so it has many hydrophilic OH groups. Polyoxymethylene has much longer chain lengths, $n > 100$ on average, and so has very few OH groups per monomer of formaldehyde.

Trioxane is formed when the trimer cyclizes instead of continuing to polymerize. All the oligomers and polymers of formaldehyde have this potential as there is a hemiacetal group at each end of the chain.



● Summary of what we know so far

Not much, you might think. Actually we have mentioned some important things about polymerization, which we will discuss further in the pages that follow.

- **Polymerization tends to occur at low temperature**
- **Depolymerization tends to occur at high temperature**
- **Polymerization competes with cyclic oligomer formation**
- **Different polymers of the same monomer can have different chain lengths**
- **The chain length varies about a mean value in a given polymer**
- **The properties of polymers depend on chain length (among other things!)**

Check back over these last few pages to make sure you see which pieces of evidence establish each of these points.

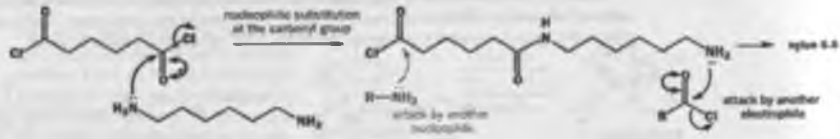
▶ There is no strict limit to the terms oligomer and polymer. You have just seen us refer to paraformaldehyde— on average an octomer— as a polymer. The terms monomer, dimer, trimer, tetramer, etc. do have exact meanings. Oligomer usually means > 3 and < 25 but different authors will use the term in different ways.

Polymerization by carbonyl substitution reactions

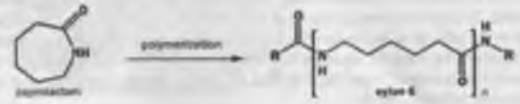
In general, carbonyl compounds do not polymerize by themselves. It is only the exceptional reactivity of formaldehyde as an electrophile that allows repeated nucleophilic addition of hemiacetal intermediates. A more common way to polymerize carbonyl compounds is to use two different functional groups that react together by carbonyl substitution to form a stable functional group such as an amide or an ester. Nylon is just such a polymer.

Polyamides

You may have carried out the nylon rope trick in a practical class. The diacid chloride of adipic acid is dissolved in a layer of a heavy organic solvent such as CCl_4 and a layer of aqueous hexane-1,6-diamine is carefully placed on top. With a pair of tweezers you can pick up the film of polymer that forms at the interface and draw it out to form a fibre. The reaction is a simple amide formation.

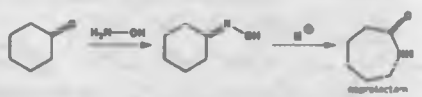


After the first amide is formed, one end of the new molecule is nucleophilic and the other electrophilic so that it can grow at both ends. The polymer is made up of alternating $-NH(CH_2)_6NH-$ and $-(CH_2)_4CO-$ units, each having six carbon atoms, and is called 'nylon 6,6'. Another and much simpler way to make nylon is to polymerize caprolactam. This monomer is a cyclic amide and the polymer does not have alternating units—instead, each unit is the same.

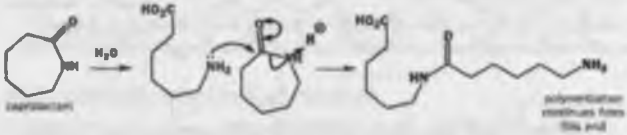


Caprolactam

Caprolactam can be made by the Beckmann rearrangement of the oxime of cyclohexanone. (Check that you can draw the mechanisms of both these reactions and look at Chapters 14 and 17 if you find you can't.) Cyclohexanone used to be made by the oxidation of cyclohexane with molecular oxygen until the explosion at Flixborough in Lincolnshire on 1 June 1974 that killed 28 people. Now cyclohexanone is made from phenol.



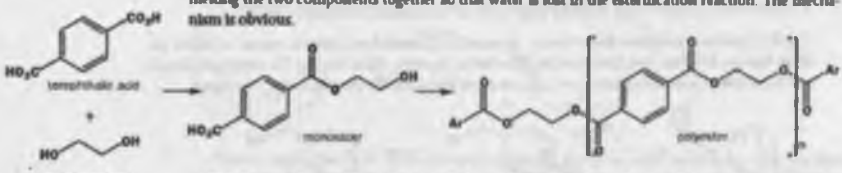
So how is this polymerization initiated? A small amount of water is added to hydrolyse some of the caprolactam to 6-aminohexanoic acid. The amino group can then attack another molecule of caprolactam and so on. The amount of water added influences the average chain length of the polymer.



These synthetic polyamides are made up of the same repeating unit but will inevitably have a range of molecular weights as the polymer length will vary. This is a different story from that of the natural polyamides—peptides and proteins—that you met in Chapter 49. Those polymers were made of twenty or so different monomers (the amino acids) combined in a precise order with a precise stereochemistry and all molecules of the same protein have the same length. Nonetheless, some of their uses are almost identical: both nylon and wool are polyamides, for example.

Polyesters

Much the same act can be carried out with dicarboxylic acids and diols. The most famous example is the polymer of ethylene glycol (ethane-1,2-diol) and terephthalic acid, which can be made simply by melting the two components together so that water is lost in the esterification reaction. The mechanism is obvious.

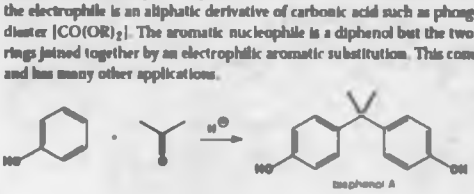


This linear polymer, like nylon, is well shaped for making long fibres and is now so important for making clothes that it is usually just called 'polyester' rather than by the older names such as 'Terylene'.

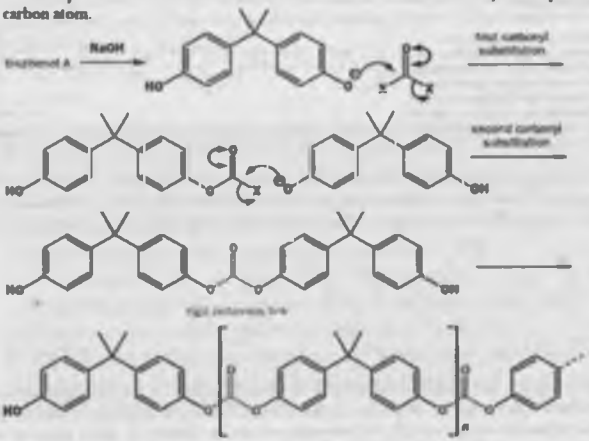
Polycarbonates

These too are made by carbonyl substitution reactions, but this time the nucleophile is aromatic and the electrophile is an aliphatic derivative of carbonic acid such as phosgene ($COCl_2$) or a carbonate diester [$CO(OR)_2$]. The aromatic nucleophile is a diphenol but the two OH groups are on separate rings joined together by an electrophilic aromatic substitution. This compound is called bisphenol A and has many other applications.

a
Make sure that you can draw the mechanism for this reaction—this electrophilic aromatic substitution is known (Chapter 22). If you need a hint, look at the synthesis of Sulcatol on the next page.



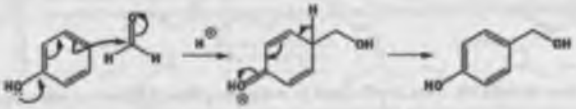
The diphenol reacts with the carbonic acid derivative, which is doubly electrophilic at the same carbon atom.



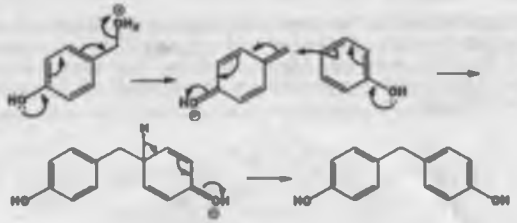
After two carbonyl substitutions the rigid carbonate ester group is formed. This polymer is neither as flexible nor as linear as the previous examples. The carbonate portion is conjugated to the benzene rings and held rigidly in the conformation shown by the anomeric effect (Chapter 42). The only flexibility is where the CMe_2 group links the two benzene rings. This is a polymer that combines transparency, lightness, and strength with just enough flexibility not to be brittle. Your safety glasses are probably made of polycarbonate.

Polymerization by electrophilic aromatic substitution

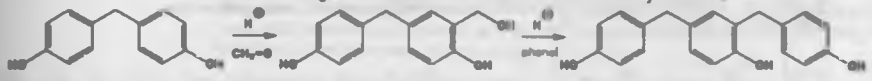
The first synthetic polymers to be of any use were the 'phenol formaldehyde resins' of which the most famous, Bakelite, was discovered by Bakeland at the turn of the century. He combined phenol and formaldehyde in acid solution and got a reaction that starts like the bisphenol A synthesis.



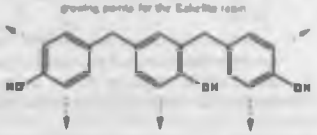
A second acid-catalysed electrophilic aromatic substitution now occurs to link a second phenol to the first. The rather stable benzylic cation makes a good intermediate.



Formaldehyde is reactive enough to continue and put another substituent ortho to the OH group in one of the rings. The mechanisms are the same as those we have just written.



The carbon chains are *meta* related on the central ring so for the first time we have a branched polymer. Complexity can rapidly increase as more phenols linked through more formaldehydes can be joined on to this core structure at several points. Each benzene ring could, in theory, form three new C–C bonds.



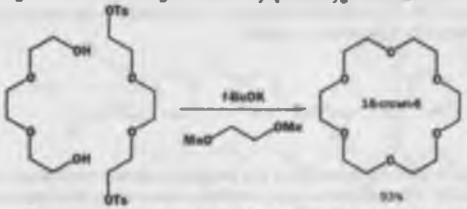
These polymers have the useful property of being thermosetting—they are made from liquid mixtures that polymerize on heating to form a solid polymer, and can therefore be moulded easily.

Polymerization by the S_N2 reaction

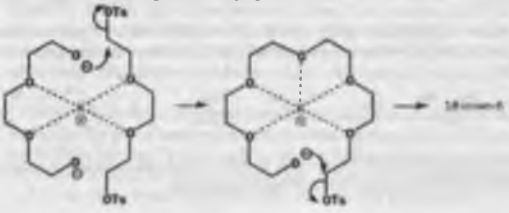
In principle, co-polymerization of a 1,2-diol and a 1,2-dihalide might lead to a polyether.

This route is not used because of the large amounts of base needed. One molecule of base is consumed for each new C–O bond made, and these reactions terminate quickly before long chains are made. It is more useful for making the cyclic oligomers called 'crown ethers'. 18-Crown-6 has an eighteen-membered ring with six evenly spaced oxygen atoms.

the discovered the use of crown ethers
on p. 000.

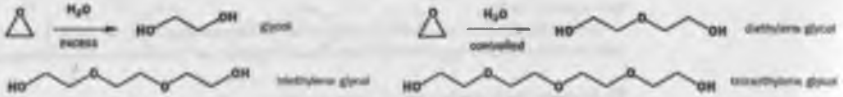


These crown ethers have cavities ideal for complex formation with metal ions. They can even carry metal ions into solution in organic solvents. This one, 18-crown-6, is the right size for potassium ions, and a solution of $KMnO_4$ and 18-crown-6 in benzene, so-called 'purple benzene', is a useful oxidizing agent. The high-yielding oligomerization is a template reaction with a potassium ion holding the two reagents together. If a base such as $Bu_4N^+OH^-$ (which cannot form complexes) is used with the same reagents, linear polymers result.

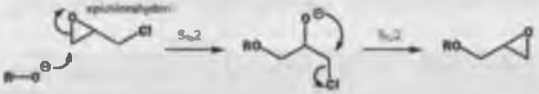


A more practical way to make linear polyethers is by polymerization of epoxides. Each time an epoxide is opened by a nucleophile, it releases a nucleophilic oxyanion that can attack another epoxide, and so on. The whole process can be initiated by just a catalytic amount of a nucleophile such as an alkoxide or an amine.

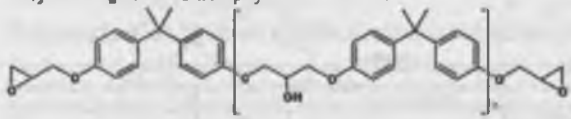
This reaction cannot be controlled—once it is initiated, it runs to completion. Treatment of ethylene oxide with controlled amounts of water does lead to the important coolant ethylene glycol (excess water) and the oligomers di-, tri-, and tetraethylene glycol. These are important solvents for polar compounds. Triethylene glycol is also the starting material for the synthesis of 18-crown-6 above.



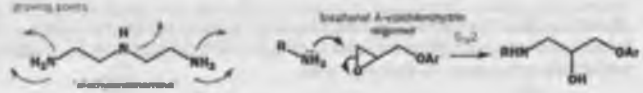
A subtle method of controlling the reaction so that it can be made to run at will is to use bisphenol A as the diol and epichlorohydrin as the epoxide. Epichlorohydrin reacts with nucleophiles at the epoxide end, but the released alkoxide ion immediately closes down at the other end to give a new epoxide.



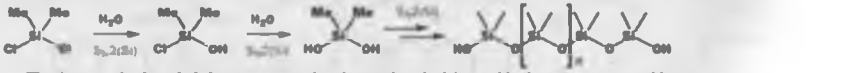
With bisphenol A in alkaline solution, this reaction happens twice and a bis adduct is formed. Further reaction with more bisphenol A creates oligomers with about 8–10 bisphenol A molecules and an epoxide at each end. This is a reasonably stable neutral compound with two terminal epoxides, just waiting for initiation for polymerization to start.



In the CIBA–Geigy glue Araldite, strong enough to glue aeroplane wings on to the fuselage, a solution of this oligomer is mixed with a solution of a polyfunctional amine such as diethylenetriamine. Since each NH_2 group can react twice and the NH group once with epoxides, the final polymer has a densely cross-linked structure and is very strong. The reaction is again a simple S_N2 process.



A totally different kind of polymer is a poly-silylether. Dimethylsilyl dichloride polymerizes easily on treatment with hydroxide. Silicon is more susceptible to the S_N2 reaction than is carbon and long chains grow quickly.

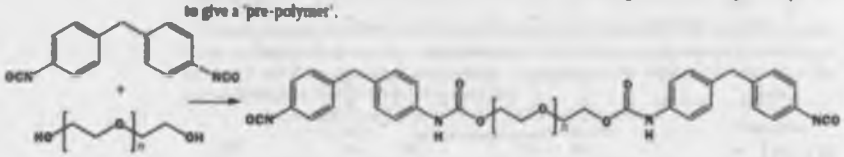


This linear poly(dimethylsiloxane) is an oil and is used in the lab in oil baths as it is more stable and less smelly than conventional paraffin baths at high temperatures.

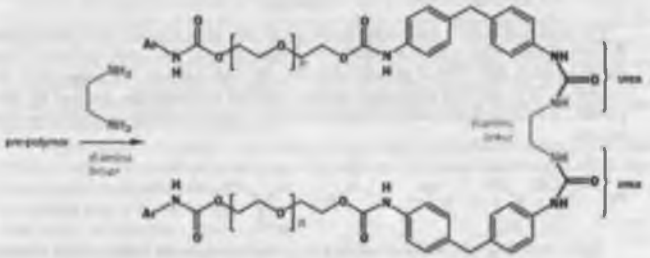
Polymerization by nucleophilic attack on isocyanates

Isocyanates react with alcohol nucleophiles to give urethanes—hybrids between carbonates and ureas—half-esters and half-amides of carbonic acid. Nucleophilic attack occurs at the very reactive linear (sp) carbon in the centre of the isocyanate.

To make a polymer it is necessary to react aryl diisocyanates with diols. Some important polymers of the type, called elastanes, are made by using long-chain aliphatic diols from partly polymerized epoxides, rather like those discussed in the last section, and reacting them with diaryl diisocyanates to give a 'pre-polymer'.



The next stage is to initiate an exothermic linking of the residual terminal isocyanates with simple diamines. The reaction is again nucleophilic attack on the isocyanate, but the new functional group is now a urea rather than a urethane. Showing just one end of the growing polymer:



These polymers have short rigid portions (the aromatic rings and the ureas) joined by short flexible 'hinges' (the diamine linker and the CH_2 group between the aromatic ring) and long very flexible portions (the polyether) whose length can be adjusted. The polymer is easily stretched and regains its shape on relaxation—it is an elastomer.

Why should it matter that the second polymerization is exothermic? If the diamine linker is added as a solution in a volatile hydrocarbon such as heptane, the heat of the polymerization causes the heptane to boil and the polymer becomes a foam. What is more, the length of the polyether chain determines what kind of foam results. Shorter (~500 $-OCH_2CH_2O-$ units) chains give rigid foams but longer chains (>1000 $-OCH_2CH_2O-$ units) give soft foams. This is only a bare outline of one of the many skills polymer chemists now have in the design of materials. The results are all around us.

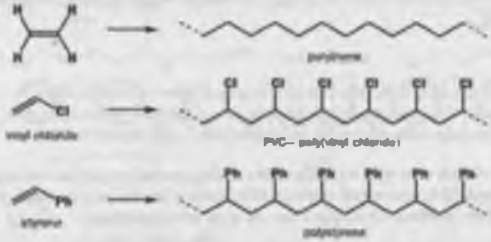
So far we have discussed polymerization that has been essentially of one kind—bifunctional molecules have combined in normal ionic reactions familiar from the rest of organic chemistry where a nucleophilic functional group attacks an electrophilic functional group. The new bonds have generally been C–O or C–N. We need now to look at the polymerization of alkenes. In these reactions, C–C bonds will be formed and many of the reactions may be new to you.

Polymerization of alkenes

Formaldehyde polymerizes because the two resulting C–O σ bonds are very slightly more stable than its C=O π bond, but the balance is quite fine. Alkenes are different: two C–C σ bonds are always considerably more stable than an alkene, so thermodynamics is very much on the side of alkene polymerization. However, there is a kinetic problem. Formaldehyde polymerizes without our intervention, but alkenes do not. We will discuss four quite distinct mechanisms by which alkene polymerization can be initiated—two ionic, one organometallic, and one radical.

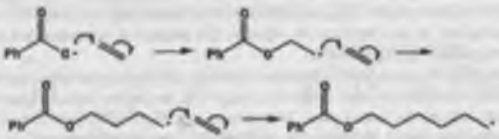
Radical polymerization of alkenes: the most important polymerization of all

We will start with the radical mechanism simply because it is the most important. A bigger tonnage of polymers is made by this method than by any other, including the three most familiar ones—polythene (polyethylene), PVC (poly(vinyl chloride)), and polystyrene.

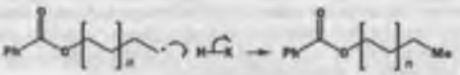


Polythene is difficult to make and was discovered only when chemists at ICI were attempting to react ethylene with other compounds under high pressure. Even with the correct reagents, radical initiators like AIBN or peroxides (Chapter 30), high pressures and temperatures are still needed. At 75 °C and 1700 atmospheres pressure ethylene polymerization, initiated by dibenzoyl peroxide, is a radical chain reaction. The peroxide is first cleaved homolytically to give two benzoate radicals.

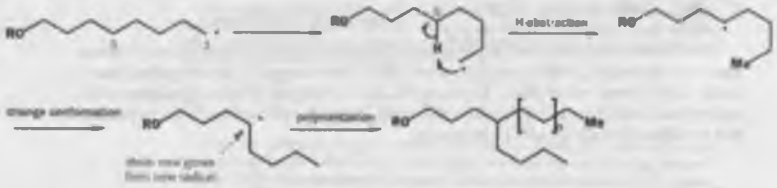
These oxyradicals add to the alkene to give an unstable primary carbon radical that adds to another molecule of alkene, and so on.



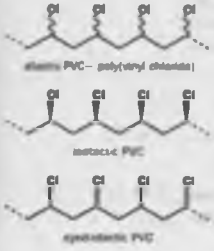
Eventually, the chain is terminated by combination with another radical (unlikely) or by hydrogen abstraction from another polymer molecule. This approach to polythene synthesis, using ethylene liquefied by pressure and small amounts (<0.005% by weight) of peroxide, produces relatively low molecular weight polymer as a white solid.



Radical polymerization can lead to branched polymers by intramolecular hydrogen atom transfer, a process sometimes called **backbiting**. Removal of H through a six-membered transition state moves the growing radical atom five atoms back down the chain, and leads to butyl side-chains. A more stable secondary radical is produced and chain growth then occurs from that point.

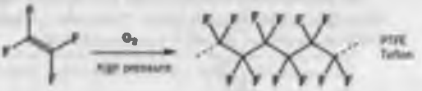


Radical polymerization of vinyl chloride and styrene is much easier than that of ethylene because the intermediate radicals are more stable. You saw in Chapter 30 that any substituent stabilizes a radical, but Cl and Ph are particularly good because of conjugation of the unpaired electron with a lone pair on chlorine or the π bonds in the benzene ring.



Neither PVC nor polystyrene is very crystalline and polystyrene often has poor mechanical strength. Both of these may be results of the stereorandom nature of the polymerization process. The substituents (Cl or Ph) are randomly to one side or other of the polymer chain and so the polymer is a mixture of many diastereoisomers as well as having a range of chain lengths. Such polymers are called **atactic**. In some polymerizations, it is possible to control stereochemistry, giving (instead of atactic polymers) **isotactic** (where all substituents are on the same side of the zig-zag chain) or **syndiotactic** (where they alternate) polymers.

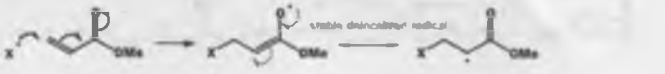
A unique polymer is formed by the radical polymerization of tetrafluoroethylene and is called PTFE or Teflon. The outside of the polymer consists of a layer of fluorine atoms which repel all other molecules. It is used as the coating in nonstick pans and as a bearing that needs no lubrication. Two pieces of Teflon slide across one another almost without friction.



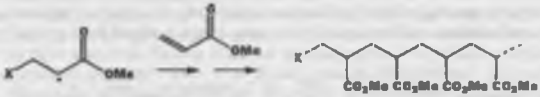
Something else is special about this polymerization—it is done in solution. Normally, no solvent is used because it would be difficult to separate from the polymer product. However, PTFE interacts with no other molecules. It precipitates from all known solvents and can be isolated easily by filtration.

Acrylics—easily made polymers of acrylate esters

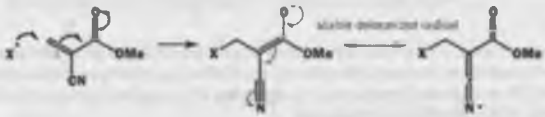
Alkenes conjugated with carbonyl groups, such as acrylates (derivatives of acrylic acid), are easily polymerized by a variety of mechanisms. Indeed, these compounds are often difficult to store because they polymerize spontaneously when traces of weak nucleophiles (even water) or radicals (even oxygen) are present. Radical polymerization occurs very easily because the intermediate carbon radical is stabilized by conjugation with the carbonyl group.



Polymerization follows the mechanism that we have seen several times already, and each radical has the same additional stabilization from the carbonyl group.



With two stabilizing groups on the carbon radical, polymerization becomes even easier. A famous example is 'SuperGlue', which is methyl 2-cyanoacrylate. The monomer in the tube polymerizes on to any surface (wood, metal, plastic, fingers, eyelids, lips, ...) catalysed by traces of moisture or air, and the bonds, once formed, are very difficult to break. The intermediate radical in this polymerization is stabilized by both CN and CO_2Me groups.

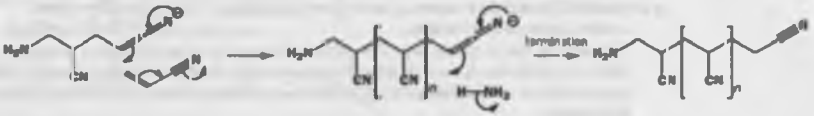


Though there are many other polymers made by radical pathways, we need now to look at the two main ionic routes—anionic and cationic polymerization.

Anionic polymerization is multiple conjugate addition

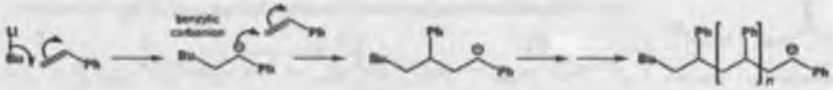
We have seen in Chapter 23 how alkenes conjugated with electron-withdrawing groups undergo conjugate addition to give an enolate anion as an intermediate. This enolate anion is itself nucleophilic and could attack another molecule of the conjugate alkene. Acrylonitrile is polymerized in liquid ammonia at low temperature by this method. Small amounts of alkali metal are added to generate NH_2^-, initiating polymerization.

The chain grows by repetition of the last step: each new C–C bond-forming step produces a new anion stabilized by the nitrile group. Termination probably occurs most frequently by proton capture from the solvent. The result is poly(acrylonitrile).



'Living polymers' by the anionic polymerization of styrene

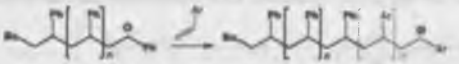
Nucleophilic addition to styrene is possible only because the intermediate carbanion is stabilized by conjugation into the benzene ring. It needs a more reactive carbanion than the benzyl anion to initiate the polymerization, and an unstabilized nonconjugated organolithium compound like butyl lithium is the answer.



It is clear enough how the chain is propagated, but how is it terminated? You might expect protonation to bring things to a close, but there cannot be any acid (even a weak one) present—if there were, it would have already been destroyed by the butyl lithium. To terminate the polymerization, a weak acid must be added in a *separate step*—water will do.

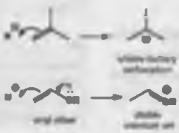
When this polystyrene sample is analyzed, it is found to consist of a remarkably narrow range of chain lengths—almost all the chains are the same. Such polymers are known as monodisperse. This result must mean that all the BuLi molecules must add immediately to a styrene molecule and that chain growth then occurs at the same rate for each chain until the styrene is used up.

There is a useful expansion of this idea. Under the conditions of the polymerization (before the water is added), these almost identical chain lengths all end with a carbanion. If, instead of adding water, we add another monomer (say, 4-chlorostyrene) it too will add to the end of the chain and polymerize until it is used up, producing new chains again of about the same length. This will be the situation after the second polymerization.



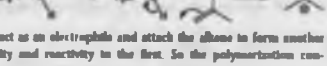
And still the polymer is active towards further polymerization. Indeed, these polymers are called 'living polymers' because they can go on growing when a new monomer is added. The final result, after as many monomers have been added as is required and the living polymer has been quenched, is a polymer with blocks of one monomer followed by blocks of another. These polymers are called **block co-polymers** for obvious reasons.

Cationic polymerization requires stabilized carbocations

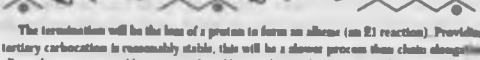


Cationic polymerization is used only for alkenes that can give a tertiary carbocation on protonation or for vinyl ethers that can give an oxonium ion. In other words, the cation intermediate must be quite stable. If it isn't, the chain is terminated too quickly by loss of a proton.

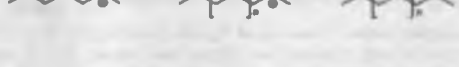
The initiator for isobutene (2-methylpropene) polymerization is usually a Lewis acid with a proton source. We shall illustrate isobutene polymerization with BF_3 as the Lewis acid and water as the proton source.



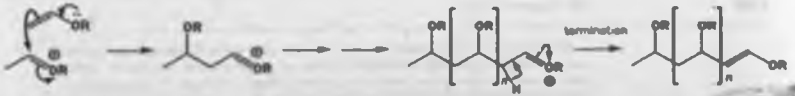
The tertiary carbocation can now act as an electrophile and attack the alkene to form another tertiary carbocation of similar stability and reactivity to the first. So the polymerization continues.



The termination will be the loss of a proton to form an alkene (an E1 reaction). Providing that the tertiary carbocation is reasonably stable, this will be a slower process than chain elongation, especially as there are no good bases around, and long polymer chains may result.



The polymerization of vinyl ethers follows much the same mechanism, using the oxonium ion as an intermediate instead of the tertiary carbocation. Termination might again be by loss of a proton or by picking up a nucleophile at the oxonium ion centre.

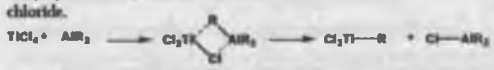


One of the best polymers for building strong rigid heat-resistant objects is polypropylene but this can be made by none of the methods we have examined so far. We need now to look at the polymerization of alkenes in the coordination sphere of a transition metal.

Ziegler–Natta polymerization gives isotactic polypropylene

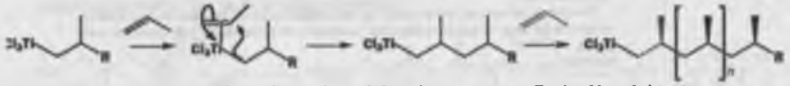
Propylene can be polymerized by a titanium/aluminium catalyst developed by Ziegler and Natta. The mere fact that polymerization is possible is remarkable, but this polymer also has stereoregularity and can be isotactic. The overall process is shown on the right.

The mixed metal compounds react to form a titanium σ complex that is the true catalyst for the polymerization. An alkyl group is transferred from aluminium to titanium in exchange for a chloride.

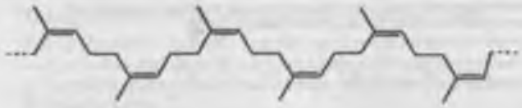


The alkyl-Ti σ complex can form a π complex with the first molecule of propene and then carry out a carbo-titanation of the π bond. This establishes the first C–C bond.

Insertion of the next propene by a repeat of the previous step now starts the polymerization. Each new C-C bond is formed on the coordination sphere of the Ti atom by transformation of a π complex into a σ complex. Repetition of this process leads to polymerization. We have shown the polymer with isotactic stereochemistry, and this control over the stereochemistry reflects the close proximity of the new propene molecule and the growing polymer.



One important elastane polymer that can be made by polymerization in a Ziegler–Natta fashion is rubber. Natural rubber is a polymeric terpene (Chapter 51) made from mevalonic acid and has a branched structure with regular trisubstituted alkenes, which are all in the *Z*-configuration.

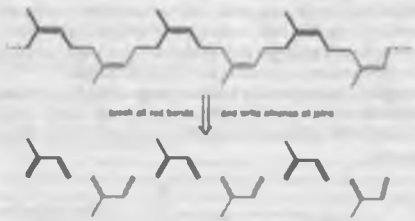


Looked at as a polymer, rubber is made up of C_5 units joined together by C–C bonds. We should naturally expect to make a hydrocarbon polymer from alkenes, so if we separate these C_5 units we find that they are dienes rather than simple alkenes. If you have read Chapter 51, they might be familiar to you as the isoprene units from which terpenes were originally supposed to be made.

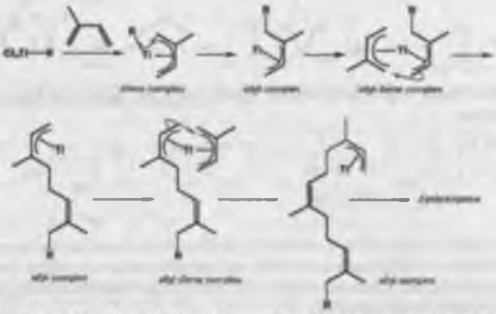
■ The organometallic principles relating to this section can be found in Chapter 46.

▶ This is a simplification as the catalyst is a solid and the active Ti atom almost certainly Ti(III) rather than Ti(IV) as we have shown here. The third Cl ligand is in fact shared with other Ti atoms in the crystal. Coordination of the active Ti(III) atom must be such that each σ complex is a 16-electron species while the π complexes are 18-electron species.

▶ In fact, the reaction can lead either to isotactic or syndiotactic polymer depending on the detailed structure of the catalyst.



The all-*cis* structure of natural rubber is vital to its elasticity. The all-*trans* compound is known and it is hard and brittle. Though dienes such as isoprene can easily be polymerized by cationic methods, the resulting 'rubber' is not all-*cis* and has poor elasticity and durability. However, polymerization of isoprene in the Ziegler–Natta way gives an all-*cis* (98–99% at least) polyisoprene very similar to natural rubber.



One possible explanation is that each isoprene unit adds to the titanium (and we will drop the pretence at this point that we have any idea which other ligands are on the Ti atom) to form an η^4 diene complex. This must necessarily have the *s-cis* conformation. Addition of R to one end of this complex gives an η^2 allyl complex still maintaining the *cis* configuration. The next diene then adds to form a new η^4 diene complex, coupled to the allyl complex, and so on. As the chain grows, each diene is added as an η^4 complex and an all-*cis* polymer results.

Co-polymerization

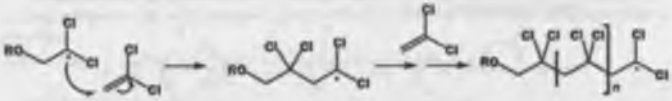
If two or more monomers polymerize to give a single polymer containing different subunits, the product is a co-polymer and the process is called co-polymerization. Protein synthesis is an example from nature; amino acids are polymerized stepwise to give proteins of precise sequence and precise length. We can do the same thing chemically providing that we do it in a stepwise fashion—we shall discuss this later. In most cases, chemical co-polymerization cannot be precisely ordered, but still gives useful results.

It may have surprised you, when you read the fine print on packaging, that some quite different materials are made out of the same polymer. PVC, for example, is widely used in clothing, 'vinyl' floor and seat coverings, pipework, taps, and lab stopcocks. Some of these applications require strength and rigidity; others flexibility. How is this possible with the same polymer? Some variation can be achieved by the addition of **plasticizers**—additives that are blended into the polymer mixture but are not chemically bonded to it. Another approach is to use a co-polymer with a smaller amount of a different (but often similar) monomer built randomly into the growing polymer chain. This is quite different from the alternating co-polymers that we saw under carbonyl substitution polymerization, such as nylon 6.6 or the block co-polymers we met a page or two back.

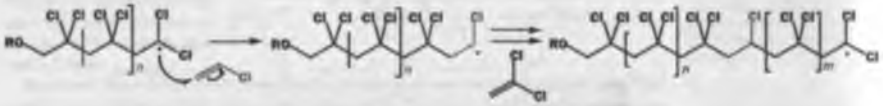
▶ A polymer is a chemical compound while a plastic is a mixture of a polymer and other substances (plasticizers, pigments, fibres, etc.), which allow it to be used in a certain way.

We will choose the example of elastane films for food wrapping—'ClingFilm'. These can be made from poly(vinylidene dichloride) (this is poly(1,1-dichloroethene)) into which a small amount of vinyl chloride is co-polymerized. The method is radical polymerization and the initiator usually a peroxide in aqueous suspension.

Polymerization continues adding vinyl chloride or vinylidene dichloride more or less at random. At first, several dichloroalkene molecules will add, simply because there are more of them.



Every now and then a vinyl chloride adds in, followed again by a number of dichloroalkenes to give the co-polymer.



Eventually, polymerization will be terminated by the usual methods and the final co-polymer will have a random mixture of dichloroalkene (mostly) and monochloroalkene, roughly in proportion to their availabilities in the polymerization mixture. The precise properties of the resulting polymer will depend on the ratio of the two monomers.

Synthetic rubbers can be made by co-polymerization of alkenes and dienes

Radical co-polymerization of styrene and butadiene produces a material that is very like natural rubber. The initiator is a one-electron oxidizing agent, and a thiol (RSH) is used to start the polymerization process. The mixture is about 3:1 butadiene:styrene so there are no long runs of one monomer in the product. We will use butadiene as the starter unit.

The first radical is an allylic radical, stabilized by conjugation with the remaining alkene in the old butadiene molecule. Addition could now occur to another butadiene or to styrene.

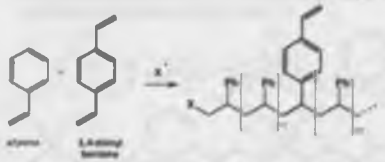
The product is the stabilized benzylic radical with the more stable *trans* double bond. Stabilization of radicals by allylic and benzylic groups is about the same, so the two monomers will react roughly in proportion to their concentration. The final product will be a random co-polymer of about 3:1 buta-

chains in styrene with mainly *E*-alkenes. It is an elastomer used for tyres and other applications where a tough and flexible 'rubber' is needed.

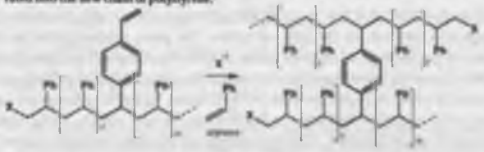
Cross-linked polymers

Many linear polymers are too flexible to be of use in making everyday objects because they lack the strength, the rigidity, or the elasticity for the job. Linear polymers can be stiffened and strengthened by bonds between the chains. This process is known as cross-linking and we will look now at some ways in which this can be achieved.

All that is really needed is a co-polymer with a small amount of a compound similar to the main monomer but with at least one more functional group than is strictly necessary to form a linear polymer. For example, a small amount of 1,4-divinylbenzene co-polymerized with styrene leads to a linear polymer in which some of the phenyl rings carry a 4-vinyl group.

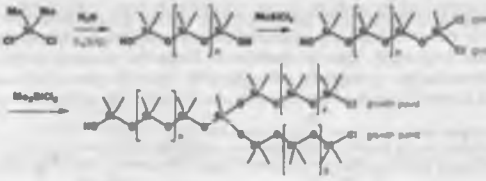


When another chain polymerizes nearby, the spare vinyl group in the first chain may be incorporated into the new chain of polystyrene.

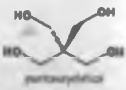


Not all of the spare vinyl groups will be caught up in a new chain of polymerizing styrene, but that need not matter if there are enough of them. It is simply a question of adding enough 1,4-divinyl benzene to get the required degree of cross-linking. These cross-linked styrenes are often made into small beads for polymer-supported reagents, as described below.

Divinyl benzene has two identical 'arms', which become growing points in polymerization. In the polymerization of Me_2SiCl_2 we had two growing points (the two chlorine atoms) on each monomer. To get cross-linking we need a third, provided by (a small amount of) $MeSiCl_3$.

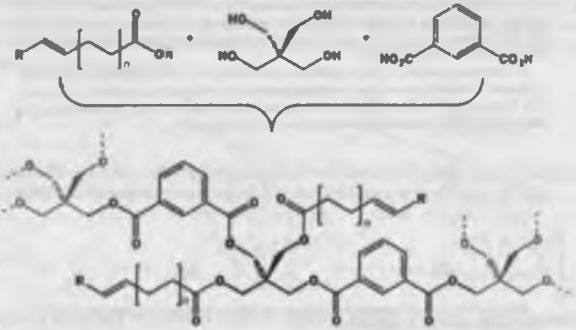


The four-armed cross-linking agent known as pentaerythritol is made from acetaldehyde and formaldehyde in aqueous base. The four arms are arranged in a tetrahedron around a quaternary carbon atom.



pentaerythritol

Co-polymerization of pentaerythritol and two other monomers—an unsaturated acid and benzene 1,3-dicarboxylic acid—gives a network of polymer chains branching out from the quaternary carbon atom at the centre of pentaerythritol. The reaction is simply ester formation by a carbonyl substitution reaction at high temperature (> 200 °C). Ester formation between acids and alcohols is an equilibrium reaction but at high temperatures water is lost as steam and the equilibrium is driven over to the right.



The black pentaerythritol at the centre of the polymer is shown with two each of the ester side chains, though this need not be the case, of course. The green pentaerythritol molecules are the growing points of the network of polymer chains. It is obvious why the benzene dicarboxylic acid is helpful in linking growing points together, but what is the point of the long-chain unsaturated acid? These are naturally occurring acids as described in Chapter 51 and the alkenes are used for further cross-linking under oxidative conditions as described in the next section. Such polymers are called 'alkyd resins' and are used in paints. They form emulsions in water ('emulsion paints') and the ester groups do not hydrolyse under these conditions as water cannot penetrate the polymer network. As the paint 'dries' it is cross-linked by oxygen in the air.

It is not necessary to have quite such a highly branched cross-linking agent to make a network of polymer chains. A triply branched compound is the basis for one of the strongest polymers known—one that we take for granted every time we use the kitchen. It is made by a very simple reaction.

Melamine

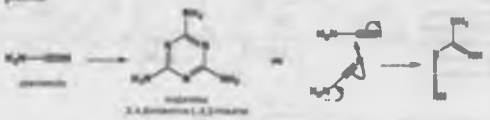
You saw a carbonyl addition reaction forming a polymer right at the beginning of the chapter—the polymerization of formaldehyde. If an amine is added to formaldehyde, condensation to form imines and imine salts occurs readily. These intermediates are themselves electrophilic so we have the basis for ionic polymerization—electrophilic and nucleophilic molecules present in the same mixture. Reaction with a second molecule of amine gives an aminal, the nitrogen equivalent of an acetal.

imine salt aminal

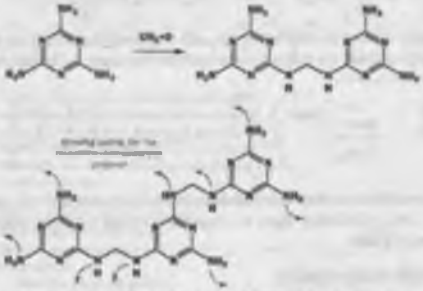
There are now two nucleophilic atoms in the molecule. Each can react with formaldehyde to form more C–N bonds and so on, making two growth points for the polymer.

We do better if we have two or even three nucleophilic amino groups present in the same molecule. With three amino groups we will produce a branching polymer of great strength

and the most important of the triazines is melamine. This compound is itself produced by the trimerization of a simple compound, cyanamide $H_2N–CN$, and has given its name to a group of plastics.



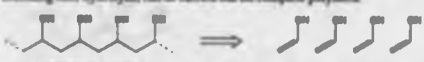
When the triazine reacts with formaldehyde, branched polymerization can occur by the same mechanism as the one we drew above for simple amines. Further condensations with formaldehyde allow amines to be attached in many places, and each new amine unit adds many new growing points. An exceptionally strong polymer results.



These resins are used to make 'unbreakable' plastic plates and for the famous kitchen surface Formica®. Partly polymerized melamine–formaldehyde mixtures are layered with other polymers such as cellulose (Chapter 48) and phenol–formaldehyde resins and the polymerization is completed under pressure with heat. The result is the familiar, tough, heat-resistant surface.

Reactions of polymers

We have so far given the impression that all polymers are formed fully armed, as it were, from monomers already having the correct functionality. This is, indeed, often the case because it can be very difficult to persuade polymers to carry out any reactions—reagents cannot penetrate their interiors. Polyester fabrics can be washed without any of the ester linkages being hydrolysed in the washing machine because the water cannot penetrate the fibres. However, some useful reactions, including ester hydrolysis, can be carried out on complete polymers.



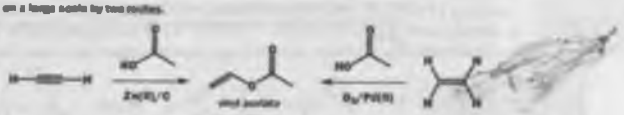
Poly(vinyl alcohol) is an important example. Inspection of the structure reveals that this is a typical alkene polymer but the monomer would have to be vinyl alcohol—the unstable enol of acetaldehyde. The way to make the polymer is to start with something else and only later

convert the polymer product into poly(vinyl alcohol). The most common method of doing this is to use radical polymerization of vinyl acetate, the enol ester of acetaldehyde, and hydrolyze the ester afterwards.

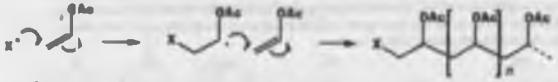
Vinyl acetate

Vinyl acetate is manufactured on a large scale by two routes.

Satisfy yourself that you can at least see what is happening here – if you are stuck on the Pd(II)-catalysed reaction, refer to Chapter 48 and look at oxypalladation and the Wacker reaction for clues.



The polymerization of the enol acetate goes in the usual way.

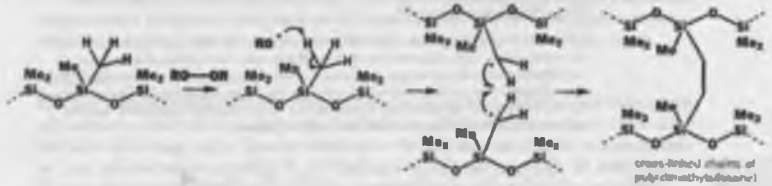


The complete polymer may now be attacked by reagents that cleave the ester groups. Water is a possibility, but methanol penetrates the polymer better and ester exchange in alkaline solution gives poly(vinyl alcohol).

Poly(vinyl alcohol) is soluble in water, unlike almost all other polymers, and that gives it many uses in glues and even as a solubilizing agent in chemical reactions to make other polymers. Poly(vinyl acetate) is used in paints.

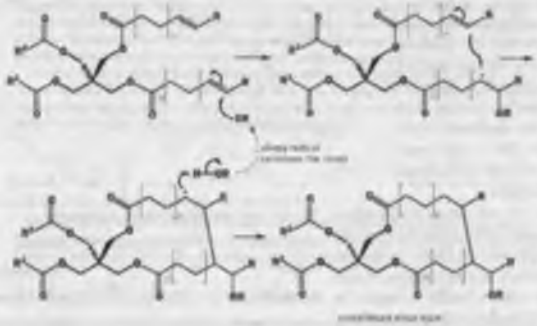
Cross-linking of pre-formed polymers

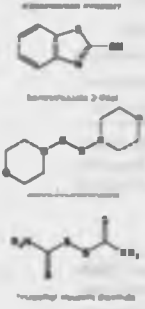
We have already discussed cross-linking during polymerization but cross-linking is often carried out after the initial polymer is made. You saw earlier how poly(dimethylsiloxane) can be cross-linked by co-polymerization with $MeSiCl_3$. An alternative way of cross-linking the linear polymer uses radical reactions to convert silicone oil into silicone putty. Peroxides are used in this process.



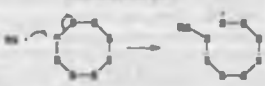
A similar sort of reaction occurs during the cross-linking of alkyd resins for paint manufacture. You may recall that the alkenes are incorporated in these resins for a reason not yet made clear. Now those alkene units come into their own. Oxygen is the reagent and it works by radical dimerization of the chains (see overleaf).

The most important of all of these types of reactions is the vulcanization of rubber. Originally, the raw rubber was just heated with sulfur (S_8) and cross-linking of the polyisoprene chains with short chains of sulfur atoms gave it extra strength without destroying the elasticity. Nowadays, a vulcanizing initiator, usually a thiol or a simple disulfide, is added as well. Some examples are





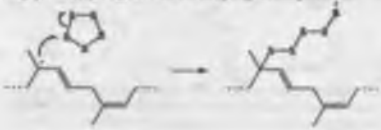
shown in the margin. The thiols give sulfur radicals with oxygen and the disulfides cleave easily as the S–S bond is weak (about 160 kJ mol^{-1} in S_8). We will write all these as RS$^{\bullet}$. The initiators either attack the rubber directly or attack sulfur to open the S_8 ring.



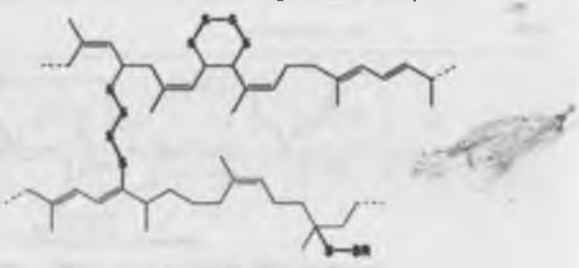
The newly released sulfur radical can bite back on to the sulfur chain and close a ring of 5–7 sulfur atoms, releasing a short chain of sulfur atoms attached to the initiator and terminating in a sulfur radical.

Now the attack on rubber can start. We know that vulcanized rubber has many *E* alkenes, whereas unvulcanized rubber is all *Z*-alkenes. This suggests that the sulfur radicals do not add to the alkenes but rather abstract allylic hydrogen atoms. Writing only a small section of rubber, we have:

The new allylic radical can do many things, but it might, for example, capture one of the sulfur rings present (S_1 to S_8). We will use the S_8 ring we have just made.



This sulfur radical can attack another chain to give a cross-link or bite back to give a link within the same chain. Many different sulfur links are formed and the next diagram summarizes a part of the vulcanized rubber structure. There is some license here: in reality the links would not be as dense as this, and more than two chains would be involved. Notice the two chains joined by one cross-link, the internal cross-link in the black chain, the attachment of the initiator (RS) to the green chain, and the (*E,E*)-dienes in both chains.



We have not given compositions of complete plastics in general, but you might like to know the typical composition of a motor tyre. Notice that the ratio of sulfur to rubber is about 1:40—that gives an idea of how many cross-links there are. Notice also that the rubber contains a great deal of carbon to improve the wear of the rubber. The roles of the other materials are explained in the table.

Typical composition of rubber motor tyre

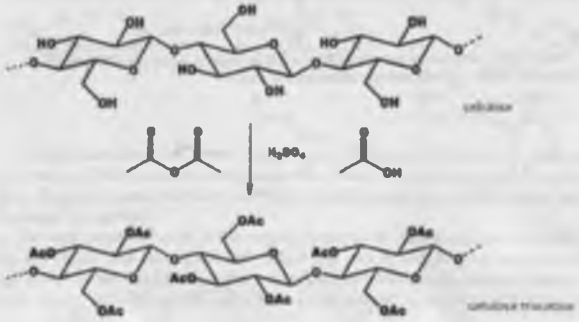
Component	Parts by weight, %	Function
rubber	61	basic structure
carbon black	27	reinforcement
oils and waxes	4.9	processing aid
sulfur	1.5	vulcanizing agent
organic disulfide	0.4	accelerates vulcanization
zinc oxide (ZnO)	3	activates vulcanization
stearic acid	0.6	activates vulcanization

This makes only 98.4% in total and there are small amounts of other materials such as antioxidants to prolong the life of the rubber.

Though synthetic diene polymers have now replaced natural rubber in many applications, they too need to be cross-linked by vulcanization using essentially the same reactions, though the details vary from product to product and from company to company.

Chemical reactions of cellulose

We met cellulose, the bulk polysaccharide of woody plants, in Chapter 49. It is a strong and flexible polymer but no use for making fabrics or films as it cannot be processed. One solution to this problem is to carry out chemical reactions that transform its properties. Acid-catalysed acetylation with acetic anhydride gives a triacetate with most of the free OH groups converted into esters.



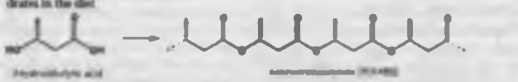
The starting material for this process is wood pulp, cloth, or paper waste and the acetic acid is added first to 'swell' the material and allow it to take up the reagents better. Organic solvents often do this to polymers. The anhydride now carries out the acid-catalyzed acetylation and the cellulose triacetate, unlike the cellulose, dissolves in the reaction mixture. The new polymer is often known simply as 'acetate'.

Another cellulose product is rayon. This is really cellulose itself, temporarily modified so that it can be dissolved and processed to give films or fibres. The starting material (from wood, cloth, or paper) is impregnated with concentrated NaOH solution. Addition of CS_2 allows some of the OH groups to react to give a 'xanthate' salt that is soluble in water.

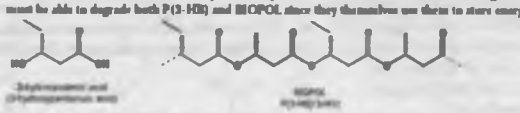
Injection of the viscous solution of cellulose xanthate into an acidic (H_2SO_4) bath regenerates the cellulose by the reverse of this reaction, as a film or a fibre depending on the process. The result is known as 'cellophane' if it is a film or 'viscose rayon' if it is a fibre.

Biodegradable polymers and plastics

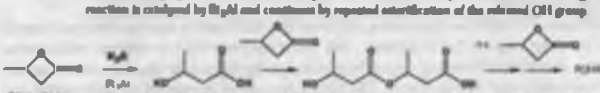
It is necessary to take only a short walk in most cities to see that plastics are not very easily degraded biologically, and it is becoming more important to design plastics, for packaging at least, that have built-in susceptibility to bacteria or fungi. Natural polymers based on proteins and polysaccharides do have that advantage, and one approach is to use a near-natural polymer, poly(hydroxybutyrate) or P(3-HB). This compound is found in some microorganisms as massive (by microorganism standards!) wholly granules occupying substantial parts of the cell—up to 80% of the dry weight of the cell. It seems that it is used as a storage compound (like starch or fat in our case) for excess carbohydrates in the diet.



A co-polymer of P(3-HB) and poly(hydroxyvalerate) P(3-HV) is also found in microorganisms and performs the same function. This polyester forms the basis for a good strong but flexible plastic for containers such as toiletries, and is produced by ICI under the name 'BIOPOL'. Microorganisms must be able to degrade both P(3-HB) and BIOPOL since they themselves use them to store energy.



BIOPOL and the two simple polymers P(3-HB) and P(3-HV) are manufactured by fermentation. They can also be produced chemically by the polymerization of a four-membered lactone (β-butyrolactone). The polymerization is initiated by a water molecule that opens the first lactone ring. The reaction is catalysed by Et_3Al and continues by repeated esterification of the released OH group.



Biological degradation requires that fungi or microorganisms can attack the polymer with their enzymes. This happens efficiently with very few polymers (because these enzymes do not exist) and is, of course, the reason that they are used: people tolerate ugly plastic window frames because they don't rot.

One way in which most polymers do decay is by the action of oxygen in the air and of light. You will be familiar with the way that some polymers go yellow after a time and some become brittle. Coloured plastics, in particular, absorb light and oxygen-induced radical reactions follow. The polymer becomes too cross-linked and loses flexibility. One ingenious application of this natural process helps to degrade the polythene rings that hold cans of beer in packs. These are often discarded and decay quite quickly because some carbon monoxide has been incorporated into the polyethylene to make it more sensitive to photolysis.

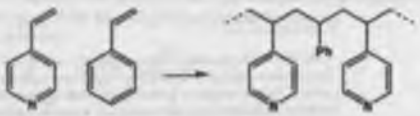
Chemical reagents can be bonded to polymers

We have left this subject to the end of the chapter because it uses all of the principles we have established earlier on. It requires an understanding of radical polymerization, co-polymerization, cross-linking, functionalization of polymers after they have been made, and so on. This is a rapidly growing subject and we can only outline the basics.

If you are already wondering why anyone would bother to attach reagents to polymers, just think of the problems you have had in the lab in separating the product you want from the other products of the reaction, often the spent reagent and inorganic by-products. If the reagent is attached to a polymer, the work-up becomes easier as the spent reagent will still be attached and can just be filtered off. Polymer-supported reagents can often be reused and their reactions can even be automated.

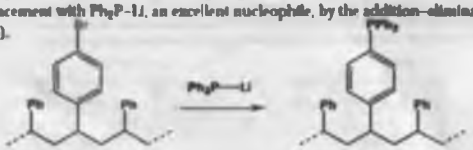
You may already be familiar with ion-exchange resins and we will start with them. They are commonly based on the co-polymer of styrene and 1,4-divinyl benzene we discussed earlier. The polymerization is carried out in an emulsion in water so that the organic molecules are in tiny droplets. The resulting polymer forms as more or less spherical beads of less than a millimetre in diameter. They can be put through a series of sieves to ensure even sizes if required. The surface of each bead bristles with benzene rings (attached to the polymer backbone) that can be sulfonated in the *para* position just like toluene.

A good proportion of the rings become sulfonated, and the outside of each bead is now coated with strongly acidic sulfonic acid groups. The polymer is an acidic reagent that is not soluble in any normal solvent. It can be packed into a column or simply used as a heterogeneous reagent. In any case, whatever reaction we are doing, there is no difficulty in separating the organic product from the acid.



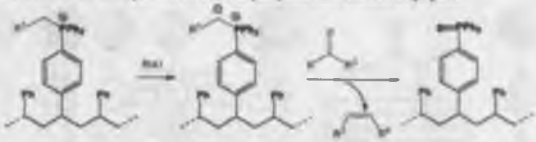
A useful basic polymer is made by co-polymerization of 4-vinyl pyridine and styrene.

These polymers are reagents in themselves, but a new style of chemistry is being developed around the idea of attaching reagents to the polymer. Poly 4-bromostyrene (or a co-polymer with styrene itself) allows a number of different groups to be attached in the place of the bromine atom. One example is a polymer-bound Wittig reagent. The phosphine can be introduced by nucleophilic displacement with $Ph_2P^-Li^+$, an excellent nucleophile, by the addition–elimination mechanism (Chapter 23).



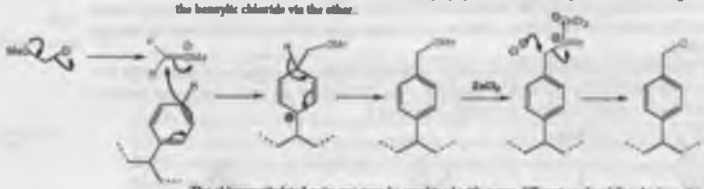
Though we have shown only one bromine atom and hence only one Ph_2P group on the polymer, almost all of the benzene rings in polystyrene can be functionalized if the bromopolymer is made by bromination of polystyrene in the presence of a Lewis acid. Now the phosphine can be alkylated with an alkyl halide of your choice to form a phosphonium salt, still on the polymer.

Treatment of the polymer with BuLi and then the aldehyde gives a Wittig reaction (Chapter 31) that releases the alkene product but leaves the phosphine oxide bound to the polymer.

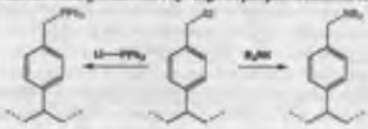


The phosphine oxide can be reduced back to the phosphine (for example, with Cl_3SiH) while still bound to the polymer and the polymer-bound reagent can be used again. Separation of $Ph_3P{=}O$ from alkene products after a Wittig reaction can be quite a nuisance so the ease of work-up alone makes this an attractive procedure.

It is not necessary to attach the functional group directly to the benzene ring. There are some advantages in separating the reaction from the polymer by a 'spacer', normally a chain of aliphatic carbon atoms. It may allow reagents to approach more easily and it may allow a higher 'loading' of functional groups per bead. Even a spacer of one CH_2 group makes S_N2 reactions not only possible but favourable at the benzylic position and the most important of these spacers is introduced by chloromethylation. Reaction of the cross-linked polystyrene with $MeOCH_2Cl$ and a Lewis acid gives the benzylic chloride via the ether.



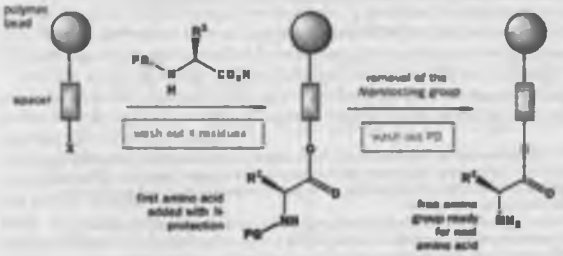
The chloromethylated resin can now be considered with many different nucleophiles. Amines give basic ion-exchange resins while $Ph_2P{-}Li$ gives a phosphine suitable for complexation to transition metals.



Automated peptide synthesis uses polymer-bound reagents

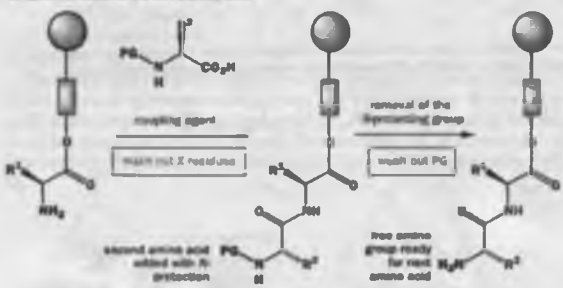
Automated polymer-based synthesis comes into its own when a stepwise polymerization is required with precise control over the addition of particular monomers in a specific sequence. This is almost a definition of peptide synthesis. Nature attaches each amino acid to a different "polymer" (transfer RNA) and uses a "computer program" (the genetic code) to assemble the polymers in the right order so that the amino acids can be joined together while bound to another polymer (a ribosome). No protection of any functional groups is necessary in this process.

Chemical synthesis of peptides uses a similar approach but our more primitive chemistry has not yet escaped from the need for full protection of all functional groups not involved in the coupling step. The idea is that the first amino acid is attached to a polymer bead through its carboxyl group (and a spacer) and then each *N*-protected amino acid is added in turn. After each addition, the *N*-protection must be removed before the next amino acid is added. The growing peptide chain is attached to the polymer so that all waste products, removed protecting groups, excess reagents, and inorganic rubbish can be washed out after each operation.



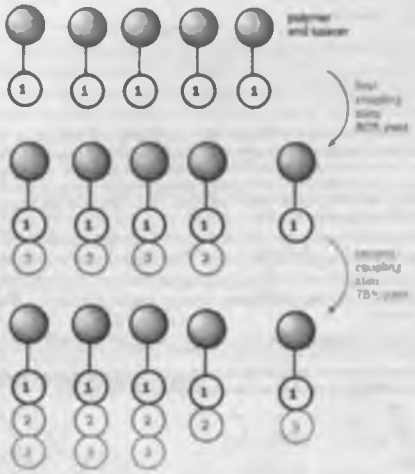
Stage 1 involves two chemical reactions—linking the first amino acid to the polymer and removing the *N*-protecting group—and two washing operations. These four steps would take time if everything were in solution but, with the compounds attached to polystyrene beads, they can be carried out simply by packing the beads into a column chromatography-style and passing reagents and solvents through.

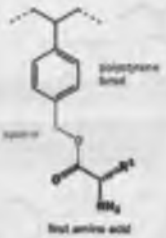
Stage 2 involves the addition of the second *N*-protected amino acid with a reagent to couple it to the free amino group of the amino acid already in place. Removal of the protecting group from the new amino acid is needed, followed by washes, as in stage 1.



This process must now be repeated until all of the amino acids have been added. Finally, all the side-chain protecting groups must be removed and the bond joining the peptide chain to the polymer must be broken to give the free peptide. That is the process in outline, but we need now to look at some of the chemistry involved.

It is obviously important that all reactions are very efficient. Suppose that the coupling step joining the second amino acid on to the first goes in 80% yield. This may not seem bad for a chemical reaction, but it would mean that 20% of the chains consisted of only the first amino acid while 80% contained correctly both first and second. Now what happens when the third amino acid is added?

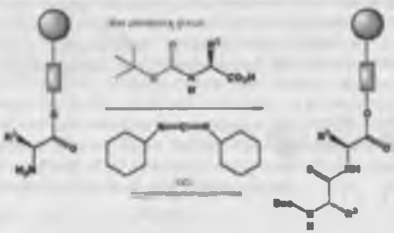




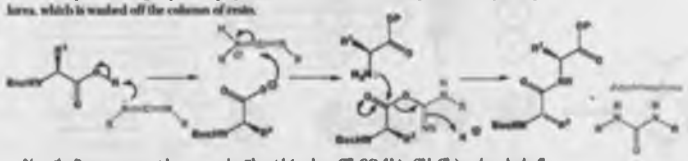
The diagram shows that four out of five growing chains will be right (1–2) after the first coupling step, but after the second (we have put this one at 75% yield for convenience) only three of the five are correct (1–2–3). One of the others has the sequence 1–2 and the other 1–3. This situation will rapidly deteriorate and the final peptide will be a mixture of thousands of different peptides. So, for a start, each reaction must occur in essentially 100% yield. This can be achieved with efficient reactions and an excess of reagents (which are not a problem in polymer-supported reactions as the excess is washed away).

Now some detail—and we will discuss the Merrifield version of peptide synthesis. Spherical cross-linked polystyrene beads of about 50 μm in diameter are used and attached to various spacers of which the simplest is just a CH_2 group from the chloromethylated polystyrene we have just discussed. The caesium (Cs) salt of the amino acid is used to displace the chloride as it is a better nucleophile than the Na or K salts. A better alternative is 'Pam' (shown in the margin). It can be used as the nucleophile to displace the chloride first. The amino acid is then added after purification. No chloromethyl groups can remain on the polymer with this spacer.

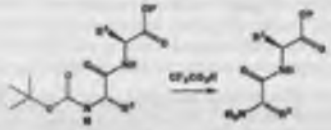
The next stage is to link the carboxyl group of the second amino acid on to the amino group of the first. The Boc group (Chapter 24) is usually used for amino group protection in the Merrifield method and DCC (dicyclohexylcarbodiimide) is used to activate the new amino acid. Here is a summary of this step, using symbols again for polymer and spacer.



The details of the reaction mechanism with DCC were given in Chapter 41, p. 000, and can be shown more easily if we mark the polymer and spacer as 'P' and the cyclohexyl groups as 'R'. The DCC is protonated by the free carboxylic acid and is then attacked by the carboxylate anion. The intermediate is rather like an anhydride with a C=NR group replacing one of the carbonyl groups. It is attacked by the amino group of the polymer-bound amino acid. The by-product is dicyclohexylurea, which is washed off the column of resin.



Now the Boc group must be removed with acid (such as CF_3CO_2H in CH_2Cl_2) and washed off the column leaving the free NH_2 group of amino acid number two ready for the next step.



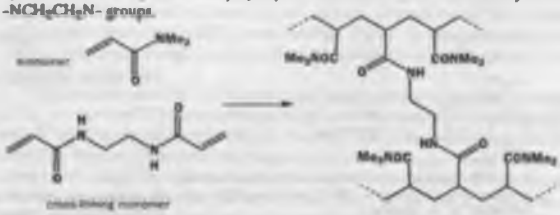
The synthesis continues with repetition of these two steps until the peptide chain is complete. The peptide is cleaved from the resin, usually with HF in pyridine or CF_3SO_3OH in CF_3CO_2H and given a final purification from small amounts of peptides of the wrong sequence by chromatography, usually HPLC.

This process is routinely automated in commercially available machines. Solutions of all of the protected amino acids required are stored in separate containers and a preprogrammed sequence of coupling and deprotection leads rapidly to the complete peptide in days rather than the years needed for solution chemistry. The most dramatic illustration of this came with the publication of a heroic traditional synthesis of bovine pancreatic ribonuclease A (an enzyme with 124 amino acids) by Hirschmann, side-by-side with one by Merrifield using functionalised polystyrene as we have described. The traditional method required 22 co-workers, while the Merrifield method needed only one.

Peptide synthesis on polyacrylamide gel

Another method of polymer-supported peptide synthesis has been developed by Sheppard. Most things are different in this approach, which is better adapted for polar solvents and automated

operation. The polymer is a polyacrylamide cross-linked with bis-acrylamides joined by $-NCH_2CH_2N-$ groups.

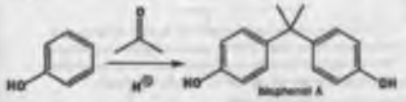


Polar solvents such as water or DMF penetrate the beads, making them swell much more than do the polystyrene resins. This exposes more reactive groups and increases the loading of peptide chains on each bead. The first amino acid is attached through its carboxyl group to an amino group on the polymer, added during or after polymerization by incorporating more 1,2-diaminoethane. The favoured amino protecting group is now Fmoc (see Chapter 24), which has the advantage that it can be removed under basic conditions (piperidine) which do not affect acid-labile side-chain protecting groups.

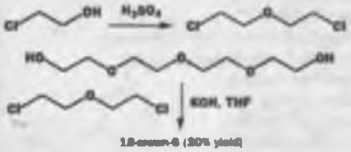
Methods like these have made polymer-supported synthesis so valuable a method that it is now being developed for many reactions old and new. A recent (1998) issue of the journal *Perkin Transactions 1* reported two syntheses of natural products in which every step was carried out using a polymer-supported reagent. Polymers are vital to us in everyday life in a multitude of ways and new polymers are being invented all the time. We have done no more than scratch the surface of this subject and you should turn to more specialized books if you want to go further.

Problems

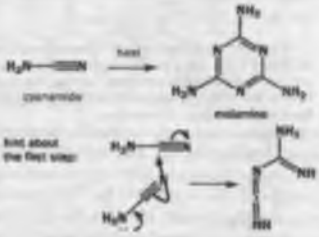
1. The monomer bisphenol A is made by the following reaction. Suggest a detailed mechanism.



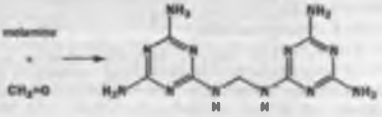
2. An alternative synthesis of 18-crown-6 to the one given in the chapter is outlined below. How would you describe the product in polymer terms? What is the monomer? How would you make 15-crown-5?



3. Melamine is formed by the trimerization of cyanamide and a hint was given in the chapter as to the mechanism of this process. Expand that hint into a full mechanism.



Melamine is polymerized with formaldehyde to make formica. Draw a mechanism for the first step in this process.

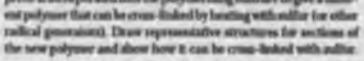


4. An acidic resin can be made by the polymerization of 4-vinylpyridine initiated by AIBN and heat followed by treatment of the polymer with bromoacetate. Explain what is happening and give a representative part structure of the acidic resin.

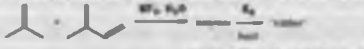
6. An artificial rubber may be made by cationic polymerization of isobutylene using acid initiation with BF_3 and water. What is the mechanism of the polymerization, and what is the structure of the polymer?

This rubber is too weak to be used commercially and 5–10% isoprene is incorporated into the polymerizing mixture to give a different polymer that can be cross-linked by heating with sulfur (or other radical generators). Draw representative structures for sections of the new polymer and show how it can be cross-linked with sulfur.

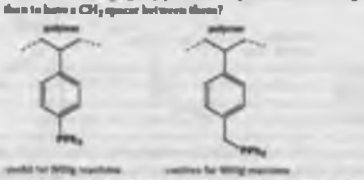
8. When sodium metal is dissolved in a solution of naphthalene in THF, a green solution of a radical anion is produced. What is its structure?



This green solution initiates the polymerization of butadiene to give a 'living polymer'. What is the structure of this polymer and why is it called 'living'?



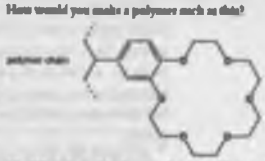
7. We introduced the idea of a spacer between a benzene ring (in a polystyrene resin) and a functional group in the chapter. If a polymer is being designed to do Wittig reactions, why would it be better to have a Ph_3P group joined directly to the benzene ring than to have a CH_2 spacer between them?



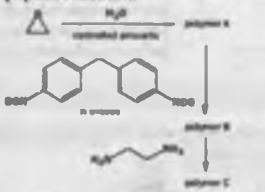
If you need a hint, draw out the reagents that you would add to the polymer to do a Wittig reaction and work out what you would get in each case.

9. A useful reagent for the oxidation of alcohol is 'PCC' (pyridinium chlorochromate). Design a polymeric (or at least polymer-bound) reagent that should show similar reactivity. What would be the advantage of the polymer-bound reagent over normal PCC?

9. A polymer that might bind specifically to metal ions and be able to extract them from solution would be based on a crown ether. How would you make a polymer such as this?

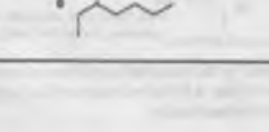


10. What is a 'block co-polymer'? What polymer would be produced by this sequence of reactions? What special physical properties would it have?



11. Why does polymerization occur only at relatively low temperatures often below 200 °C? What occurs at higher temperatures? Formaldehyde polymerizes only below about 100 °C but ethylene still polymerizes up to about 300 °C. Why the difference?

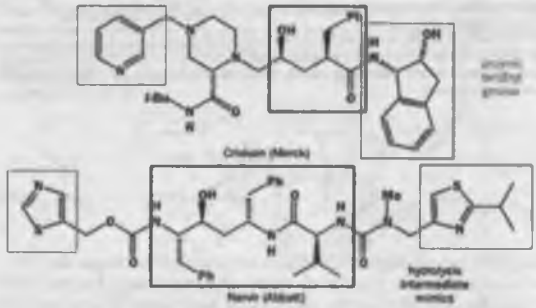
12. Polyvinyl chloride) (PVC) is used for rigid structures like window frames and gutters with only small amounts of additives such as pigments. If PVC is used for flexible things like plastic bags, about 20–30% of dialkyl phthalates such as the compound below are incorporated during polymerization. Why is this?

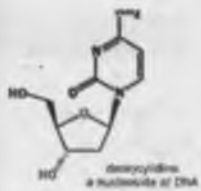


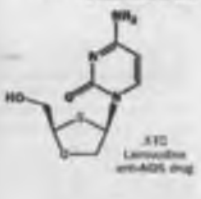
On the left is a section of normal protein with glycine and phenylalanine residues (Chapter 49). In the middle is the intermediate formed when a molecule of water attacks the amide carbonyl group. On the right is a piece of the HIV protease inhibitor. The amide nitrogen atom has been replaced by a CH_2 group (ringed in black) so that no 'hydrolysis' of the C–C bond can occur. The inhibitor may bind but it cannot react.

Enzymes ideally bind their substrates strongly and the product of the reaction much more weakly. If they are to accelerate the reaction they need to lower the energy of the transition state (Chapters 13 and 41) and they can do this by binding the transition state of the reaction strongest of all. We cannot literally synthesize a transition state analogue because transition states are by definition unstable, but intermediate analogues can be synthesized. The inhibitor above has one OH group instead of the two in the genuine intermediate but this turns out to be the vital one. This knowledge was acquired from an X-ray crystal structure showing how the enzyme binds the substrate. The inhibitor binds well to the enzyme but cannot react so it blocks the active site.

These compounds are a good deal more sophisticated than this simple analysis suggests. For example, HIV protease is a dimeric enzyme and experience with this class of protease suggested correctly that more or less symmetrically placed heterocyclic rings (Chapters 42–44) would greatly improve binding. Here are two of the inhibitors with the active site binding portion framed in black and the heterocyclic binding portions framed in green.





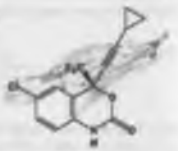


These developments looked so promising that Merck even set up a completely new research station at West Point, Pennsylvania, dedicated to this work. The biochemist in charge, Dr Irving Segal, was one of the victims of the Lockerbie bombing in 1988 but his work lives on as Crixivan (indinavir) is now one of the cocktail of three drugs (AZT and 3TC, shown with the nucleoside it imitates, are the others) that has revolutionized the treatment of HIV. Before this treatment most HIV victims were dead within 2 years. Now no one knows how long they will survive as the combination of the three drugs reduces the amount of virus below detectable levels.

Crixivan was not the first compound that Merck discovered. Many others fell by the wayside because they were not active enough, were too toxic, didn't last long enough in the body, or for other reasons. Crixivan was developed from cooperation between biochemists, virologists, X-ray crystallographers, and molecular modellers as well as organic chemists. When the choice of Crixivan from the various drug candidates had been made and the chemists were trying to make enough of it for trials and use, there was an exceptionally urgent task. They knew that a kilo of compound was needed to keep each patient alive and well for a year. Merck built a dedicated plant for the manufacture of Crixivan at Elkton, Virginia, in 1995. Within 1 year, production was running at full blast and there are thousands of people alive today as a result.

The AIDS crisis led to cooperation between the pharmaceutical companies unparalleled since the development of penicillin during the Second World War. Fifteen companies set up an AIDS drug development collaboration programme and government agencies and universities have all joined in.

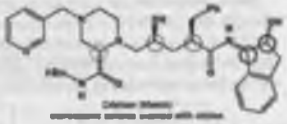
The battle is not yet won, of course, but the HIV protease inhibitors are being followed by a new generation of nonnucleoside reverse transcriptase inhibitors, which promise to be less toxic to humans. An example is the DuPont–Merck compound DMP 266, made as a single enantiomer and now under clinical trials. This compound, though it contains a most unusual cyclotrimeric amide linkage, is nevertheless a much simpler compound than Crixivan. We shall devote most of this final chapter to the synthesis of the established and chemically more interesting drug Crixivan.



DMP 266

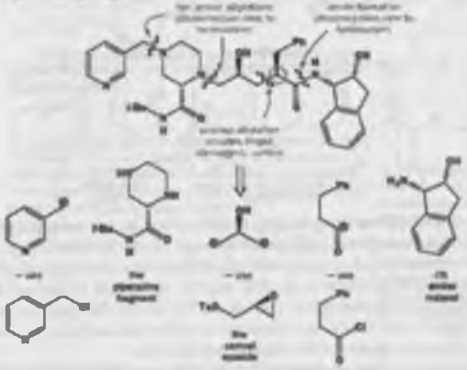
The synthesis of Crixivan

Crixivan is a formidable synthetic target. It is probably the most complex compound ever made in quantity by organic synthesis and very large amounts must be made because one kilo is needed per patient per year. The complexity largely arises from the stereochemistry. There are five stereogenic centres, marked with coloured circles on this diagram, and their disposition means that three separate pieces of asymmetric synthesis must be devised. There are, of course, also many functional groups and four different rings.



Crixivan (Merck), [illegible] marked with circles

The two black centres are 1,2-related and we have already discussed them in part at the end of Chapter 41. The green centre are 1,3-related and we saw in Chapter 41 that this type of control is possible though difficult. The orange centre is 1,4-related to the nearer green centre and must be considered separately.

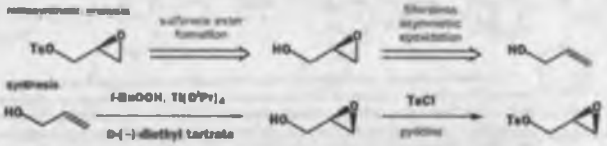


The challenge with Crixivan, as with any drug, is to make it efficiently—high yields, few steps. It has five stereogenic centres, so the chemists developing the synthesis needed to address the issue of diastereoselectivity. And it is a single enantiomer, so an asymmetric synthesis was required. We can start by looking at some likely disconnections, summarized in the scheme above. They are all disconnections of the sorts you met in Chapter 20, and they all correspond to reliable reactions.

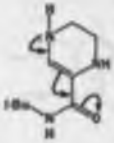
These disconnections split the molecule into five manageable chunks (synthons), three of which contain stereogenic centres and will have to be made as single enantiomers. The final stereogenic

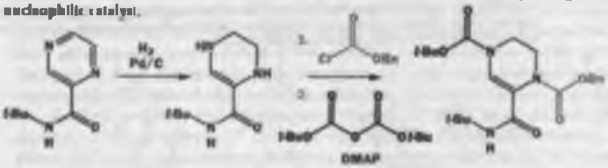
centre (ringed in the disconnection diagram) would have to be made in the enolate alkylation step, so this step will have to be done diastereoselectively.

Let's take these three chiral synthons in turn. First, the simplest one: the central epoxide. The reagent we need here will carry a leaving group, such as a tosylate, and it can easily be made from the epoxy-alcohol. This gives a very good way of making this compound as a single enantiomer—a Sharpless asymmetric epoxidation of allyl alcohol.



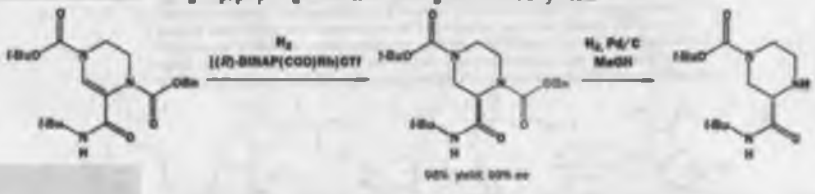
Next, the piperazine fragment. This has two nucleophilic nitrogen atoms and they will both need protecting with different protecting groups to allow them to be revealed one at a time. It will also need to be made as a single enantiomer. In an early route to Crixivan, this was done by resolution, but enantioselective hydrogenation provides a better alternative. Starting from a pyridine derivative, a normal hydrogenation over palladium on charcoal could be stopped at the tetrahydropyrazine stage. The two nitrogens in this compound are quite different because one is conjugated with the amide while one is not (the curly arrows in the margin show this). The more nucleophilic nitrogen—the one *not* conjugated with the amide—was protected with benzyl chloroformate to give the Cbz derivative. Now the less reactive nitrogen can be protected with a Boc group, using DMAP as a nucleophilic catalyst.





You met asymmetric hydrogenation using BINAP–metal complexes in Chapter 45 as a method for the synthesis of amino acids. The substrate and catalyst are slightly different here, but the principle is the same: the chiral ligand, BINAP, directs addition of hydrogen across the double bond with almost perfect enantioselectivity and in very high yield. In Chapter 45 we described this as addition to one enantiotopic face of the alkene. A further hydrogenation step allowed selective removal of the Cbz group, preparing one of the two nitrogen atoms for alkylation.

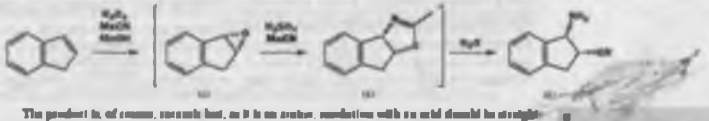
■ COD = cyclooctadiene.



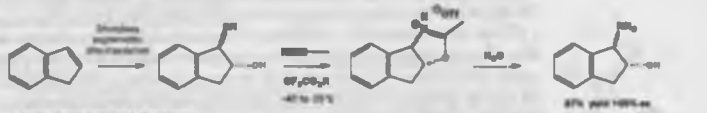
▶ H_2O_2 and MeCN react to give a "peroxyimidic acid"—the C=N analogue of a peroxy-acid—as the true epoxidising agent.

The remaining chiral fragment is a compound whose synthesis was discussed in Chapter 41, and you should turn to p. 000 for more details of the mechanisms in the reaction sequence. It can be made on a reasonably large scale (600 kg) in one reaction vessel, starting from indene. First, the double bond is epoxidized, not with a peroxy-acid but with the cheaper hydrogen peroxide in an acetonitrile–methanol mixture. Acid-catalysed opening of the epoxide leads to a cation, which takes part in a reversible Ritter reaction with the acetonitrile solvent, leading to a single diastereoisomer of a heterocyclic intermediate which is hydrolysed to the amino-alcohol.

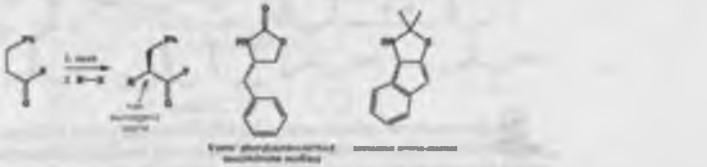
■



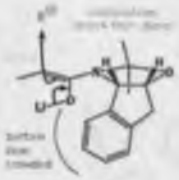
The product is, of course, racemic but, as it is an amine, resolution with an acid should be straightforward. Crystallization of its tartrate salt, for example, leads to the required single enantiomer in 98.5% ee. With such cheap starting materials, resolution is just about acceptable, even though it wastes half the material. It would be better to oxidize the indene enantioselectively, and retain the enantiomeric purity through the sequence: it is indeed possible to carry out a very selective Sharpless asymmetric dihydroxylation (Chapter 45) of indene, and the diol serves as an equally good starting material for the Ritter reaction. The stereogenic centre carrying the green hydroxyl group remains firmly in place throughout the route, and controls the absolute configuration of the final product.



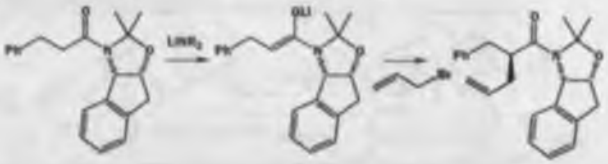
Both resolution and Sharpless asymmetric dihydroxylation were successful in the synthesis of Crinivan but the best method is one we shall keep till later. Only one stereogenic centre remains, and its stereoselective formation turns out to be the most remarkable reaction of the whole synthesis. The centre is the one created in the planned enolate alkylation step.



The obvious way to make this centre is to make V a chiral auxiliary; the required acyl chloride could be used to acylate the auxiliary, which would direct a diastereoselective alkylation, before being removed and replaced with the amino-alcohol portion. But the amino-alcohol itself, certainly once protected, has a remarkable similarity to Evans' oxazolidinone auxiliaries (Chapter 43), and it turns out that this amino-alcohol will function very successfully as a chiral auxiliary, which does not need to be removed, avoiding waste and saving steps! The amino-alcohol was acylated with the acyl chloride, and the amide was protected as the nitrogen analogue of an acetonide by treating with 2-methoxypropene (the methyl enol ether of acetone) and an acid catalyst. The enolate of this amide reacts highly diastereoselectively with alkylating agents, including, for example, allyl bromide.



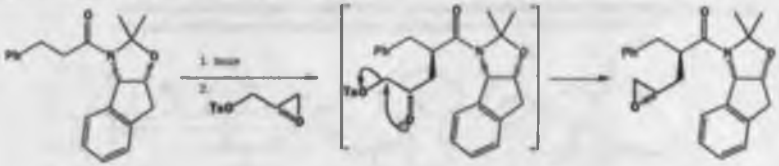
The reason for the stereoselectivity is not altogether clear, but we would expect the bulky nitrogen substituents to favour formation of the *cis* enolate. With the amino-alcohol portion arranged as shown, the top face is more open to attack by electrophiles.



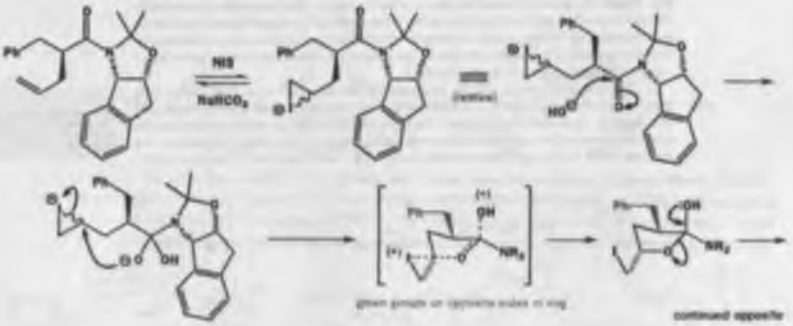
■

How do we know that this happens, and that the reaction does not go simply via direct displacement of tosylate?

The enolate also reacted diastereoselectively with the epoxy-tosylate prepared earlier. The epoxide, being more electrophilic than the tosylate, is opened first, giving an alkoxide, which closes again to give a new epoxide.



The absolute configuration at the stereogenic centre in the epoxide was, of course, already fixed (by the earlier *enantioselective* Sharpless epoxidation). However, it also turned out to be possible to make this compound by a different route involving a *diastereoselective* reaction of the alkylation product from allyl bromide, again directed by the amino-alcohol-derived auxiliary. The reagents make the reaction look like an iodolactonization—and, indeed, there are many similarities with the diastereoselective iodolactonizations of Chapter 33. NIS (*N*-iodosuccinimide, the iodine analogue of NBS) provides an 'I^+' source, reacting reversibly and non-stereoselectively with the alkene. Of the two diastereoisomeric iodonium ions, one may cyclize rapidly by intramolecular attack of the amide carbonyl group. Cyclization of the other diastereoisomer is prevented by steric hindrance between the parts of the molecule coloured green. Opening of the five-membered ring gives a single diastereoisomer of the iodoalcohol, which was closed to the epoxide by treatment with base.



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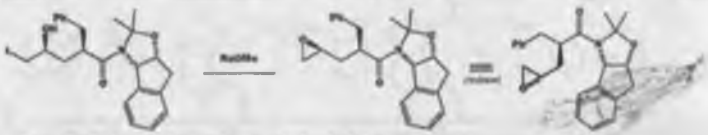
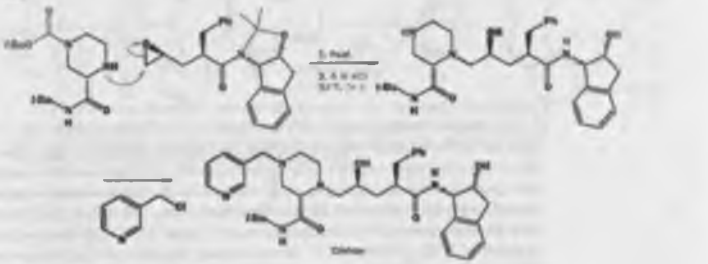


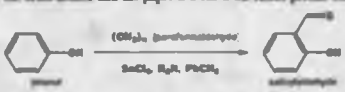
Three of the five fragments have now been assembled, and only the two amine components remain. The first alkylation makes use of the epoxide to introduce the required 1,2-amino-alcohol functionality. The protected enantiomerically pure piperazine reacted with the epoxide, and the product was treated with acid to deprotect both the second piperazine nitrogen and the 'acetonide' group left over from the earlier chiral auxiliary step. The newly liberated secondary amine was alkylated with the reactive aha-bromide 3-chloromethyl pyridine, and the final product was crystallized as its sulfate salt.



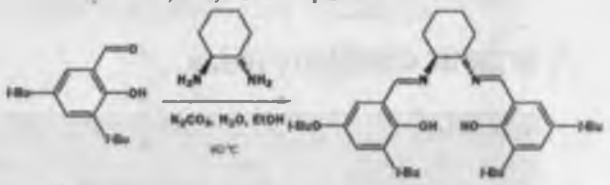
The future of organic chemistry

Not all organic chemists can be involved in such exciting projects as the launching of a new anti-AIDS drug. But the chemistry used in this project was invented by chemists in other institutions who had no idea that it would eventually be used to make Crixivan. The Sharpless asymmetric epoxidation, the catalytic asymmetric reduction, the stereoselective enolate alkylations, and the various methods tried out for the enantiomerically pure amine (salen (resolution, enzymatic kinetic resolution) were developed by organic chemists in research laboratories. Some of these famous chemists like Sharpless invented new methods, some made new compounds, some studied new types of molecules, but all built on the work of other chemists.

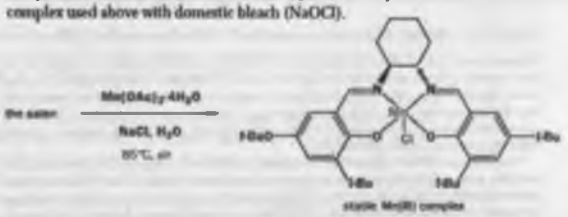
In 1988 Giovanni Casiraghi, a rather less famous chemist from the University of Parma, published a paper in the *Journal of the Chemical Society* about selective reactions between phenols and formaldehyde. He and his colleagues made the modest discovery that controlled reactions to give salicylaldehydes could be achieved in toluene with $SnCl_4$ as catalyst. The reaction is regioselective for the *ortho* isomer and the paper described the rather precise conditions needed to get a good yield.



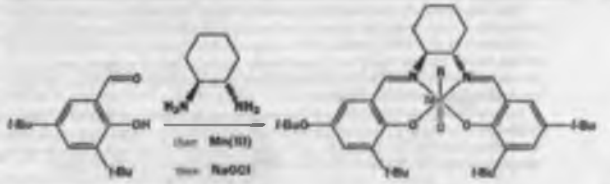
The reaction was also successful for substituted salicylaldehydes. When Jacobsen came to develop his asymmetric epoxidation, which, unlike the Sharpless asymmetric epoxidation, works for simple alkenes and not just for allylic alcohols, he chose 'salens' as his catalysts, partly because they could be made so easily from salicylaldehydes. For example:



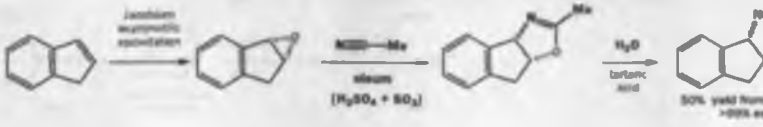
This 'salen' is the ligand for manganese in the asymmetric epoxidation. The stable brown Mn(III) complex can be made from it with $Mn(OAc)_3$ in excellent yield and this can be oxidized to the active complex used above with domestic bleach (NaOCl).



Jacobsen epoxidation turned out to be the best large-scale method for preparing the *cis*-amino-indanol for the synthesis of Crixivan. This process is very much the cornerstone of the whole synthesis. During the development of the first laboratory route into a route usable on a very large scale, many methods were tried and the final choice fell on this relatively new type of asymmetric epoxidation. The Sharpless asymmetric epoxidation works only for allylic alcohols (Chapter 45) and so is no good here. The Sharpless asymmetric dihydroxylation works best on *cis*-alkenes than on *trans*-alkenes. The Jacobsen epoxidation works best on *cis*-alkenes. The catalyst is the Mn(III) complex easily made from a chiral diamine and an aromatic salicylaldehyde (a 2-hydroxybenzaldehyde).



The chirality comes from the diamine and the oxidation from ordinary domestic bleach (NaOCl), which continually recreates the Mn=O bond as it is used in the epoxidation. Only 0.7% catalyst is needed to keep the cycle going efficiently. The epoxide is as good as the diol in the Ritter reaction and the whole process gives a 50% yield of enantiomerically pure *cis*-amino-indanol on a very large scale.



Organic chemistry today

53

Connections

Building on:

- The rest of the book (Ch1–Ch52)

Arriving at:

- How organic chemistry produced an AIDS treatment in collaboration with biologists

Looking forward to:

- Life on a chemist

Modern science is based on interaction between disciplines

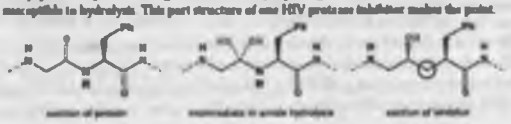
Organic chemistry has transformed the materials of everyday life, as we have seen in Chapter 52, but this is merely a glimpse of the future of organic materials where light-emitting polymers, polymers that conduct electricity, self-reproducing organic compounds, molecules that work (nano engineering), and even molecules that think may transform our world in ways not yet imagined. These developments are the result of cooperation between organic chemists and physicists, engineers, material scientists, computer experts, and many others.

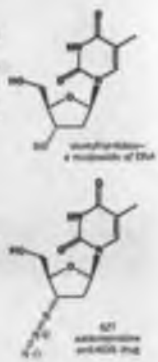
The most dramatic developments at the beginning of the twenty-first century are new methods in medicine from collaborations between organic chemists and biologists. (The biochemical background is sketched out in Chapters 49–51.) The media's favourite 'a cure for cancer' is already not just 'a cure' but hundreds of successful cures for the hundreds of diseases collectively called 'cancer'. A newspaper headline in 1980 revealed that there was some chance of survival for all known types of childhood cancer. We are going to discuss just one equally dramatic medical development, the treatment of AIDS. Like the treatment of cancer, this is a story that is only just starting, but enough is known to make it a gripping story full of hope.

When AIDS (Acquired Immune Deficiency Syndrome) first came into the news in the 1980s it was a horror story of mysterious deaths from normally harmless diseases after the patient's immune system had been weakened and eventually destroyed. The cause was identified by biologists as a new virus: HIV (Human Immunodeficiency Virus) and antiviral drugs, notably AZT (Chapter 48), were used with some success. These drugs imitate natural nucleotides (AZT imitates deoxythymidine) and inhibit the virus from copying its RNA into DNA inside human cells by inhibiting the enzyme 'reverse transcriptase'.

These drugs also inhibit our own enzymes and are very toxic. Biologists then discovered an alternative point of attack. An enzyme unique to the virus cuts up long proteins into small pieces essential for the formation of new HIV particles. If this enzyme could be inhibited, no new viruses would be formed, and the inhibitor should not damage human chemistry. Several companies invented HIV protease inhibitors, which looked more like small pieces of proteins with the weak link of the amide bond replaced by a more stable C–C bond.

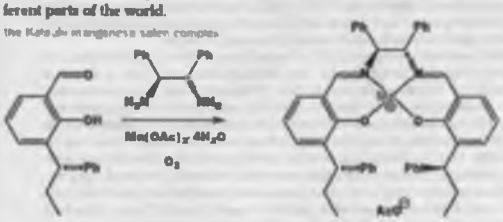
Real peptides are usually poor drugs because we have our own peptidases which quickly cut up ingested proteins into their constituent amino acids by hydrolysis of the amide link. Drugs that imitate peptides may avoid this ignominious fate by replacing the amide bond with another bond less susceptible to hydrolysis. This part structure of one HIV protease inhibitor makes the point.





In the same year (1980) that Jacobsen reported his asymmetric epoxidation, a group led by Tsutomu Katsuki at the University of Kyushu in Japan reported a closely related asymmetric epoxidation. The chiral catalyst is also a salen and the metal manganese. The oxidant is iodosobenzene (PhI=O) but this method works best for *E* alkenes. It is no coincidence that Katsuki and Jacobsen both worked for Sharpless. It is not unusual for similar discoveries to be made independently in different parts of the world.

the Katsuki manganese salen complex



It did not enter Castraghi's wildest dreams that his work might some day be useful in a matter of life and death. Nor did his four co-workers nor Jacobsen's more numerous co-workers see clearly the future applications of their work. By its very nature it is impossible to predict the outcome or the applications of research. But be quite sure of one thing. Good research and exciting discoveries come from a thorough understanding of the fundamentals of organic chemistry and require chemists to work as a team. The Italian work is a model of careful experimentation and a thorough study of reaction conditions together with sensible explanations of their discoveries using the same curly arrows we have been using. The Harvard team probably had a clearer idea that they were into something significant and worked with equal care and precision. Jacobsen's name is famous but both teams at Parma and Harvard Universities were needed to make the work available to Merck.

Hexamethylenetetramine

Hexamethylenetetramine is a [illegible] such as those we met in Chapter 52) of formaldehyde and ammonia containing six formaldehyde and four ammonia molecules. It has a beautifully symmetrical cage structure belonging to the adamantane series.

Hexamethylenetetramine is a crystalline compound used as a convenient source of formaldehyde for, among other things, polymerization reactions. It has a tetrahedral symmetry, as does adamantane, which might be regarded as the basic structural unit (not the same as the monomer!) of diamonds. Diamond is of course a polymer of carbon atoms.

When Jacobsen's epoxidation was fully described in 1990–91, the Castraghi method was abandoned in favour of an even older method discovered in the 1930s by Duff. The remarkable Duff reaction uses hexamethylenetetramine, the oligomer of formaldehyde and ammonia, to provide the extra carbon atom. The otherwise unknown Duff worked at Birmingham Technical College. Later in 1972, a William E. Smith, working in the GEC chemical laboratories at Schenectady, New York, found how to make the Duff reaction more general and better yielding by using CF_3CO_2H as catalyst. Even so, this method gives a lower yield than the Castraghi method but it uses no dangerous reagents (particularly no stoichiometric tin) and is more suitable for large-scale work. When Duff was inventing his reaction or Smith was modifying the conditions, asymmetric synthesis was not even a gleam in anyone's eyes. It is impossible even for the inventor to predict whether a discovery is important or not.

the Duff reaction

The Sharpless asymmetric dihydroxylation works best for *trans* disubstituted alkenes, while the Jacobsen epoxidation works best for *cis* disubstituted alkenes. Even in this small area, there is a need for better and more general methods. Organic chemistry has a long way to go.

If you continue your studies in organic chemistry beyond the scope of this book, you will want to read of modern work in more specialized areas. Your university library should have a selection of books on topics such as: orbitals and chemical reactions; NMR spectroscopy; enzyme mechanisms; organometallic chemistry; biosynthesis; asymmetric synthesis; combinatorial chemistry; and molecular modelling. This book should equip you with enough fundamental organic chemistry to explore these topics with understanding and enjoyment and, perhaps, to discover what you want to do for the rest of your life. All of the chemists mentioned in this chapter and throughout the book began their careers as students of chemistry at universities somewhere in the world. You have the good fortune to study chemistry at a time when more is understood about the subject than ever before, when information is easier to retrieve than ever before, and when organic chemistry is more interrelated with other disciplines than ever before. Duff, Smith, and Cantwright felt themselves part of an international community of organic chemists in industry and universities but never has that community been so well founded as it is nowadays. Travel to laboratories in other countries is commonplace for students of organic chemistry now and even at home you can travel on the internet to other countries and see what is going on in chemistry there. You might try the web pages of our institutions for a start: Cambridge is http://www.ch.cam.ac.uk/; Liverpool is http://www.liv.ac.uk/Chemistry/; and Manchester is http://www.ch.man.ac.uk/. There is a general index to chemistry all over the world on http://www.ch.cam.ac.uk/ChemSiteIndex.html.

■

If you want to read more about these discoveries we suggest: 'Practical asymmetric synthesis', R. W. Dodson and P. J. Parsons, *Chemistry and Industry (London)*, 1988, 413–16. The references for the Pfizer work is: G. Cainelli, G. Cardillo, G. Puglia, and S. Tavernini, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1052–55. These journals will be in your department or university library.