Stereochemistry

16

Connections

Building on:

- Drawing organic molecules ch2
- Organic structures ch4
- Nucleophilic addition to the carbonyl group ch9
- Nucleophilic substitution at carbonyl groups ch12

Arriving at:

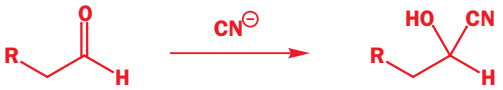
- Three-dimensional shape of molecules
- Molecules with mirror images
- Molecules with symmetry
- How to separate mirror-image molecules
- Diastereoisomers
- Shape and biological activity
- How to draw stereochemistry

Looking forward to:

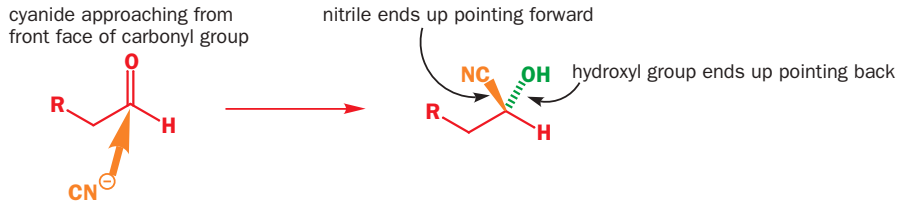
- Diastereoselectivity ch34
- Controlling alkene geometry ch31
- Synthesis in action ch25
- Controlling stereochemistry with cyclic compounds ch33
- Asymmetric synthesis ch45
- Chemistry of life ch49–51

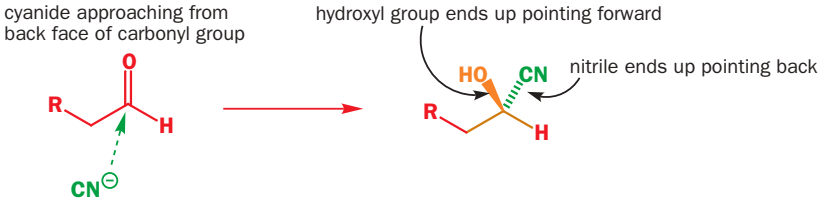
Some compounds can exist as a pair of mirror-image forms

One of the very first reactions you met, back in Chapter 6, was between an aldehyde and cyanide. They give a **cyanohydrin**, a compound containing a nitrile group and a hydroxyl group.

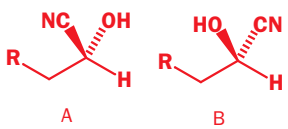


How many products are formed in this reaction? Well, the straightforward answer is one—there's only one aldehyde, only one cyanide ion, and only one reasonable way in which they can react. But this analysis is not *quite* correct. One point that we ignored when we first talked about this reaction, because it was irrelevant at that time, is that the carbonyl group of the aldehyde has two faces. The cyanide ion could attack either from the front face or the back face, giving, in each case, a distinct product.





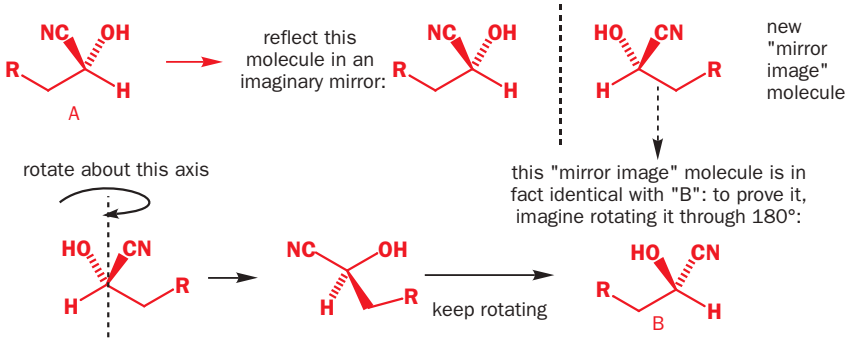
Are these two products different? If we lay them side by side and try to arrange them so that they look identical, we find that we can't—you can verify this by making models of the two structures.



The structures are nonsuperimposable—so they are not identical. In fact, they are **mirror images** of each other: if we reflected one of the structures, A, in a mirror, we would get a structure that *is* identical with B.

■ Remember that the bold wedges represent bonds coming towards you, out of the paper, and the dashed bonds represent bonds going away from you, into the paper.

▶ In reading this chapter, you will have to do a lot of mental manipulation of three-dimensional shapes. Because we can represent these shapes only in two dimensions, we suggest that you make models, using a molecular model kit, of the molecules we talk about. With some practice, you will be able to imagine the molecules you see on the page in three dimensions.

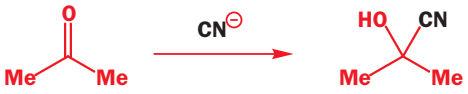


We call two structures that are not identical, but are mirror images of each other (like these two) **enantiomers**. Structures that are not superimposable on their mirror image, and can therefore exist as two enantiomers, are called **chiral**. In this reaction, the cyanide ions are just as likely to attack the 'front' face of the aldehyde as they are the 'back' face, so we get a 50:50 mixture of the two enantiomers.

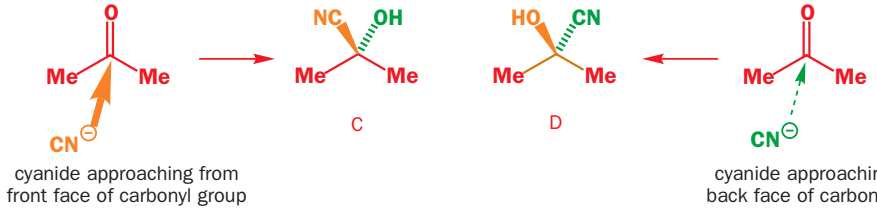
Enantiometers and chirality

- Enantiomers are structures that are not identical, but are *mirror images* of each other
- Structures are *chiral* if they cannot be superimposed upon their mirror image

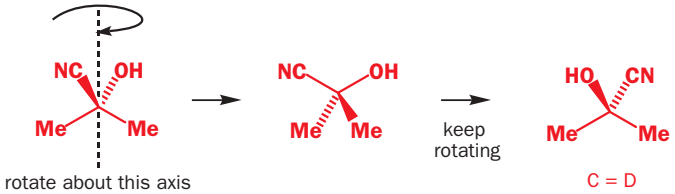
Now consider another similar reaction, which you have also met—the addition of cyanide to acetone.



Again a cyanohydrin is formed. You might imagine that attacking the front or the back face of the acetone molecule could again give two structures, C and D.



However, this time, rotating one to match the other shows that they are superimposable and therefore identical.

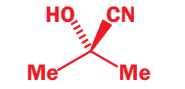


Make sure that you are clear about this: C and D are identical molecules, while A and B are mirror images of each other. Reflection in a mirror makes no difference to C or D; they are superimposable upon their own mirror images, and therefore cannot exist as two enantiomers. Structures that are superimposable on their mirror images are called **achiral**.

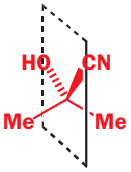
- *Achiral* structures are superimposable on their mirror images

Chiral molecules have no plane of symmetry

What is the essential difference between these two compounds that means one is superimposable on its mirror image and one is not? The answer is symmetry. Acetone cyanohydrin has a plane of symmetry running through the molecule. This plane cuts the central carbon and the OH and CN groups in half and has one methyl group on each side.

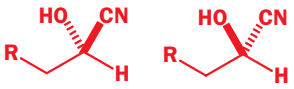


acetone cyanohydrin



plane of symmetry runs through central carbon, OH and CN

On the other hand, the aldehyde cyanohydrin has no plane of symmetry: the plane of the paper has OH on one side and CN on the other while the plane at right angles to the paper has H on one side and RCH_2 on the other. This compound is completely unsymmetrical and has two enantiomers.



■ This statement is, in fact, slightly incomplete, but it outlines such a useful concept that for the time being we shall use it as a valuable guideline.

● Planes of symmetry and chirality

- Any structure that has no plane of symmetry can exist as two mirror-image forms (*enantiomers*)
- Any structure with a plane of symmetry cannot exist as two enantiomers

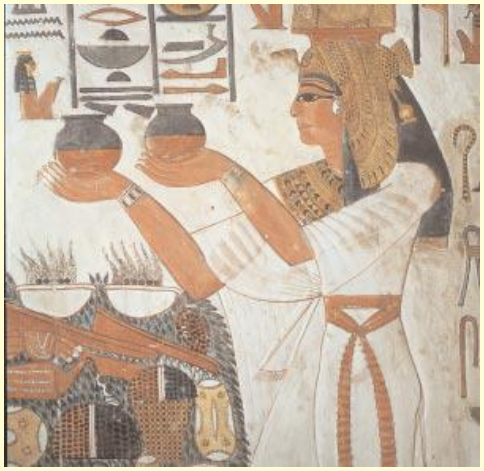
By 'structure', we don't just mean chemical structure: the same rules apply to everyday objects. Some examples from among more familiar objects in the world around us should help make these ideas clear. Look around you and find a chiral object—a car, a pair of scissors, a screw (but not the screwdriver), and anything with writing on it like this page. Look again for achiral objects with planes of symmetry—a plain mug, saucepan, chair, most man-made things without writing on them. The most significant chiral object near you is the hand you write with.

Some examples

Gloves , hands, and socks

Most gloves exist in pairs of nonidentical mirror-image forms: only a left glove fits a left hand and only a right glove fits a right hand. This property of gloves and of the hands inside them gives us the word 'chiral'—*cheir* is Greek for 'hand'. Hands and gloves are chiral; they have no plane of symmetry, and a left glove is not superimposable on its mirror image (a right glove). Feet are chiral too, as are shoes. But socks (usually!) are not. Though we all sometimes have problems finding two socks of a matching colour, once you've found them, you never have to worry about which sock goes on which foot, because socks are achiral. A pair of socks is manufactured as two identical objects, each of which has a mirror plane.

The ancient Egyptians had less care for the chirality of hands and their paintings often show people, even Pharaohs, with two left hands or two right hands—they just didn't seem to notice.



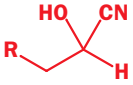
Tennis racquets and golf clubs

If you are left-handed and want to play golf, you either have to play in a right-handed manner, or get hold of a set of left-handed golf clubs. Golf clubs are clearly therefore chiral; they can exist as either of two enantiomers. You can tell this just by looking at a golf club. It has no plane of symmetry, so it must be chiral. But left-handed tennis players have no problem using the same racquets as right-handed tennis players and modern tennis players of either chirality sometimes swap the racquet from hand to hand. Look at a tennis racquet: it has a plane of symmetry, so it's achiral. It can't exist as two mirror-image forms.

To summarize

- A structure *with* a plane of symmetry is *achiral* and *superimposable* on its mirror image and *cannot* exist as two enantiomers
- A structure *without* a plane of symmetry is *chiral* and *not superimposable* on its mirror image and *can* exist as two enantiomers

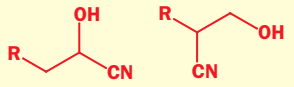
Stereogenic centres



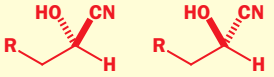
Back to chemistry, and the product from the reaction of an aldehyde with cyanide. We explained above that this compound, being chiral, can exist as two enantiomers. Enantiomers are clearly isomers; they consist of the same parts joined together in a different way. In particular, enantiomers are a type of isomer called **stereoisomers**, because the isomers differ not in the connectivity of the atoms, but only in the overall shape of the molecule.

Stereoisomers and constitutional isomers

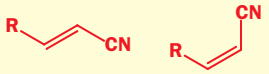
Isomers are compounds that contain the same atoms bonded together in different ways. If the connectivity of the atoms in the two isomers is different, they are **constitutional isomers**. If the connectivity of the atoms in the two isomers is the same, they are **stereoisomers**. Enantiomers are stereoisomers, and so are *E* and *Z* double bonds. We shall meet other types of stereoisomers shortly.



constitutional isomers: the way the atoms are connected up (their *connectivity*) differs



enantiomers



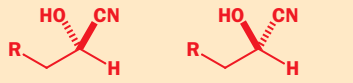
E/*Z* isomers (double bond isomers)

stereoisomers: the atoms have the same connectivity, but are arranged differently

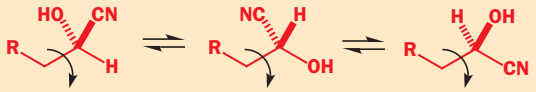
We should also introduce you briefly to another pair of concepts here, which you will meet again in more detail in Chapter 17: *configuration* and *conformation*. Two stereoisomers really are different molecules: they cannot be interconverted without breaking a bond somewhere. We therefore say that they have different **configurations**. But any molecule can exist in a number of **conformations**: two conformations differ only in the temporary way the molecule happens to arrange itself, and can easily be interconverted just by rotating around bonds. Humans all have the same *configuration*: two arms joined to the shoulders. We may have different *conformations*: arms folded, arms raised, pointing, waving, etc.

Configuration and conformation

- Changing the *configuration* of a molecule always means that bonds are broken
- A different configuration is a different molecule
- Changing the *conformation* of a molecule means rotating about bonds, but not breaking them
- Conformations of a molecule are readily interconvertible, and are all the same molecule

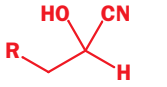


two configurations: going from one enantiomer to the other requires a bond to be broken



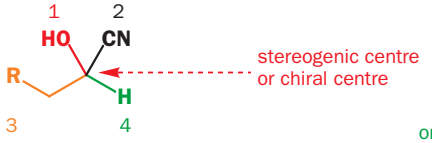
three conformations of the same enantiomer: getting from one to the other just requires rotation about a bond: all three are the same molecule

An aldehyde cyanohydrin is chiral because it does not have a plane of symmetry. In fact, it *cannot* have a plane of symmetry, because it contains a tetrahedral carbon atom carrying four different groups: OH, CN, RCH_2, and H. Such a carbon atom is known as a **stereogenic** or **chiral centre**. The product of cyanide and acetone is not chiral; it has a plane of symmetry, and no chiral centre because two of the groups on the central carbon atom are the same.

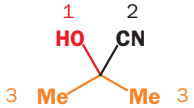


aldehyde cyanohydrin

four different groups



stereogenic centre or chiral centre

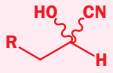


only three different groups

If a molecule contains one carbon atom carrying four different groups it will not have a plane of symmetry and must therefore be chiral. A carbon atom carrying four different groups is a stereogenic or chiral centre.

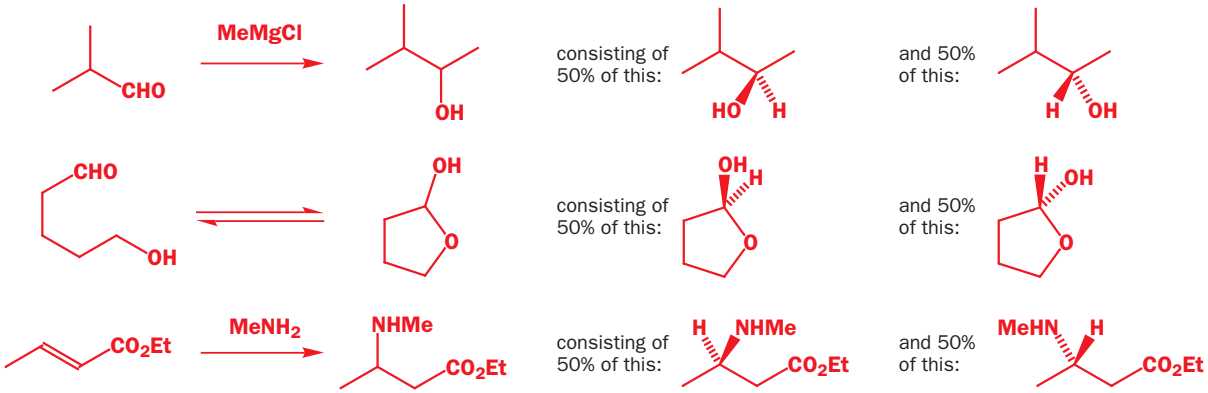
We saw how the two enantiomers of the aldehyde cyanohydrin arose by attack of cyanide on the two faces of the carbonyl group of the aldehyde. We said that there was nothing to favour one face over the other, so the enantiomers must be formed in equal quantities. A mixture of equal quantities of a pair of enantiomers is called a **racemic mixture**.

▶ When we don't show bold and dashed bonds to indicate the three-dimensional structure of the molecule, we mean that we are talking about both enantiomers of the molecule. Another useful way of representing this is with wiggly bonds. Wiggly bonds are in fact slightly ambiguous: chemists use them to mean, as they do here, both stereoisomers, but also to mean just one stereoisomer, but unknown stereochemistry.



● **A racemic mixture is a mixture of two enantiomers in equal proportions. This principle is very important. Never forget that, if the starting materials of a reaction are achiral, and the products are chiral, they will be formed as a racemic mixture of two enantiomers.**

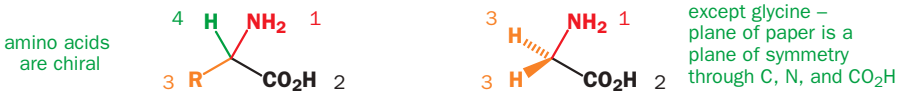
Here are some more reactions you have come across that make chiral products from achiral starting materials. In each case, the principle must hold—equal amounts of the two enantiomers (racemic mixtures) are formed.



Many chiral molecules are present in nature as single enantiomers

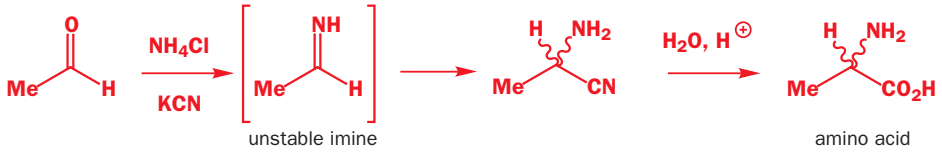
■ Molecules are chiral if they lack a plane of symmetry. You can immediately see that amino acids lack a plane of symmetry because (except glycine) they contain a chiral centre.

Let's turn to some simple, but chiral, molecules—the natural amino acids. All amino acids have a carbon carrying an amino group, a carboxyl group, a hydrogen atom, and the R group, which varies from amino acid to amino acid. So unless R = H (this is the case for glycine), amino acids always contain a chiral centre and lack a plane of symmetry.

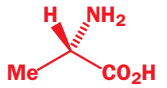


It is possible to make amino acids quite straightforwardly in the lab. The scheme below shows a synthesis of alanine, for example. It is a version of the Strecker synthesis you met in Chapter 12.

laboratory synthesis of racemic alanine from acetaldehyde



Alanine made in this way must be racemic, because the starting materials are achiral. However, if we isolate alanine from a natural source—by hydrolysing vegetable protein, for example—we find that this is not the case. Natural alanine is solely one enantiomer, the one drawn below. Samples of chiral compounds that contain only one enantiomer are called **enantiomerically pure**. We know that 'natural' alanine contains only this enantiomer from X-ray crystal structures.



alanine extracted from plants consists only of this enantiomer

Enantiomeric alanine

In fact, Nature does sometimes (but very rarely) use the other enantiomer of alanine—for example, in the construction of bacterial cell walls. Some antibiotics (such as vancomycin) owe their selectivity to the way they can recognize these 'unnatural' alanine components and destroy the cell wall that contains them.

Before we go further, we should just mention one common point of confusion. Any compound whose molecules do not have a plane of symmetry is chiral. Any sample of a chiral compound that contains molecules all of the same enantiomer is enantiomerically pure. *All* alanine is chiral (the structure has no plane of symmetry) but *lab-produced* alanine is racemic (a 50:50 mixture of enantiomers) whereas *naturally isolated* alanine is enantiomerically pure.

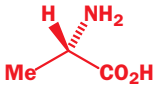
Most of the molecules we find in nature are chiral—a complicated molecule is much more likely not to have a plane of symmetry than to have one. Nearly all of these chiral molecules in living systems are found not as racemic mixtures, but as single enantiomers. This fact has profound implications, for example, in the chemistry of drug design, and we will come back to it later.

R and *S* can be used to describe the configuration of a chiral centre

Before going on to talk about single enantiomers of chiral molecules in more detail, we need to explain how chemists explain which enantiomer they're talking about. We can, of course, just draw a diagram, showing which groups go into the plane of the paper and which groups come out of the plane of the paper. This is best for complicated molecules. Alternatively, we can use the following set of rules to assign a letter, *R* or *S*, to describe the configuration of groups at a chiral centre in the molecule.

▶ Remember—we use the word *configuration* to describe the arrangement of bonds around an atom. Configurations cannot be changed without breaking bonds.

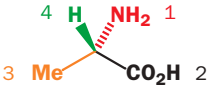
Here again is the enantiomer of alanine you get if you extract alanine from living things.



natural alanine

1 Assign a priority number to each substituent at the chiral centre. Atoms with higher atomic numbers get higher priority.

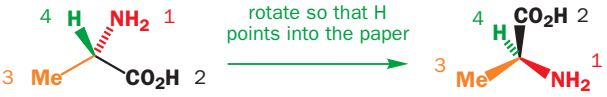
Alanine's chiral centre carries one N atom (atomic number 7), two C atoms (atomic number 6), and one H atom (atomic number 1). So, we assign priority 1 to the NH_2 group, because N has the highest atomic number. Priorities 2 and 3 will be assigned to the CO_2H and the CH_3 groups, and priority 4 to the hydrogen atom; but we need a way of deciding which of CO_2H and CH_3 takes priority over the other. If two (or more) of the atoms attached to the chiral centre are identical, then we assign priorities to these two by assessing the atoms attached to those atoms. In this case, one of the carbon atoms carries oxygen atoms (atomic number 8), and one carries only hydrogen atoms (atomic number 1). So CO_2H is higher priority that CH_3; in other words, CO_2H gets priority 2 and CH_3 priority 3.



▶ These priority rules are the same as those used to assign *E* and *Z* to alkenes, and are sometimes called the Cahn–Ingold–Prelog (CIP) rules, after their devisors.

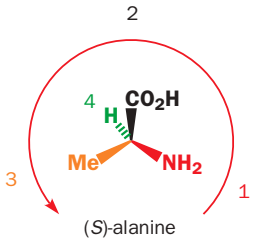
2 Arrange the molecule so that the lowest priority substituent is pointing away from you.

In our example, naturally extracted alanine, H is priority 4, so we need to look at the molecule with the H atom pointing into the paper, like this.



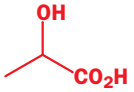
3 Mentally move from substituent priority 1 to 2 to 3. If you are moving in a clockwise manner, assign the label *R* to the chiral centre; if you are moving in an anticlockwise manner, assign the label *S* to the chiral centre.

A good way of visualizing this is to imagine turning a steering wheel in the direction of the numbering. If you are turning your car to the right, you have *R*; if you are turning to the left you have *S*. For our molecule of natural alanine, if we move from NH_2 (1) to CO_2H (2) to CH_3 (3) we're going anticlockwise (turning to the left), so we call this enantiomer (*S*)-alanine.



(*S*)-alanine

You can try working the other way, from the configurational label to the structure. Take lactic acid as an example. Lactic acid is produced by bacterial action on milk; it's also produced in your muscles when they have to work with an insufficient supply of oxygen, such as during bursts of vigorous exercise. Lactic acid produced by fermentation is often racemic, though certain species of bacteria produce solely (*R*)-lactic acid. On the other hand, lactic acid produced by anaerobic respiration in muscles has the *S* configuration.

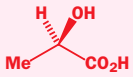


lactic acid

As a brief exercise, try drawing the three-dimensional structure of (*R*)-lactic acid. (You may find this easier if you draw both enantiomers first and then assign a label to each.)

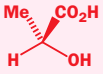
▶ Remember how, in Chapter 3, we showed you how hydrogen atoms at stereogenic centres (we didn't call them that then) could be missed out—we just assume that they take up the fourth vertex of the imagined tetrahedron at the stereogenic centre.

This also brings us to another point about drawing stereogenic centres: always try to have the carbon skeleton lying in the plane of the paper: in other words, try to draw



(*R*)-lactic acid

rather than, say,



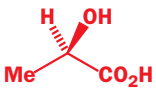
(*R*)-lactic acid

Both are correct but the first will make things a lot easier when we are talking about molecules with several chiral centres!

■ The longer answer is more involved, and we go into it in more detail in Chapter 45.

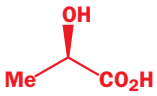
▶ **Plane-polarized light** can be considered as a beam of light in which all of the light waves have their direction of vibration aligned parallel. It is produced by shining light through a polarizing filter.

You should have drawn:



(*R*)-lactic acid

or



(*R*)-lactic acid

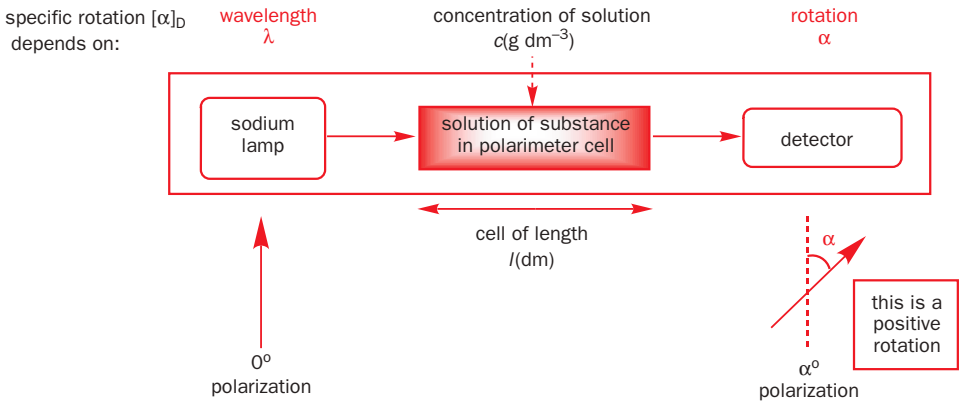
Remember that, if we had made lactic acid in the lab from simple achiral starting materials, we would have got a racemic mixture of (*R*) and (*S*) lactic acid. Reactions in living systems can produce enantiomerically pure compounds because they make use of enzymes, themselves enantiomerically pure compounds of (*S*)-amino acids.

Is there a chemical difference between two enantiomers?

The short answer is *no*. Take (*S*)-alanine (in other words, alanine extracted from plants) and (*R*)-alanine (the enantiomer found in bacterial cell walls) as examples. They both have identical NMR spectra, identical IR spectra, and identical physical properties, with a single important exception. If you shine plane-polarized light through a solution of (*S*)-alanine, you will find that the light is rotated to the right. A solution of (*R*)-alanine rotates plane-polarized light to the left. Racemic alanine, on the other hand, lets the light pass unrotated.

The rotation of plane-polarized light is known as optical activity

Observation of the rotation of plane-polarized light is known as **polarimetry**; it is a straightforward way of finding out if a sample is racemic or if it contains more of one enantiomer than the other. Polarimetric measurements are carried out in a polarimeter, which has a single-wavelength (monochromatic) light source with a plane-polarizing filter, a sample holder, where a cell containing a solution of the substance under examination can be placed, and a detector with a read-out that indicates by how much the light is rotated. Rotation to the right is given a positive value, rotation to the left a negative one.



Specific rotation

The angle through which a sample of a compound (usually a solution) rotates plane-polarized light depends on a number of factors, the most important ones being the path length (how far the light has to pass through the solution), concentration, temperature, solvent, and wavelength. Typically, optical rotations are measured at 20 °C in a solvent such as ethanol or chloroform, and the light used is from a sodium lamp, with a wavelength of 589 nm.

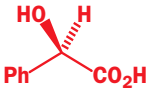
The observed angle through which the light is rotated is given the symbol α. By dividing this value by the path length l (in dm) and the concentration c (in g dm^{-3}) we get a value, [α], which is specific

to the compound in question. The choice of units is eccentric and arbitrary but is universal so we must live with it.

$$[\alpha] = \frac{\alpha}{cl}$$

Most [α] values are quoted as $[\alpha]_D$ (where the D indicates the wavelength of 589 nm, the 'D line' of a sodium lamp) or $[\alpha]_D^{20}$, the 20 indicating 20 °C. These define the remaining variables.

Here is an example. A simple acid, known as mandelic acid, can be obtained from almonds in an enantiomerically pure state.



(*R*)-mandelic acid

28 mg was dissolved in 1 cm^3 of ethanol and the solution placed in a 10 cm long polarimeter cell. An optical rotation α of –4.35° was measured (that is, 4.35° to the left) at 20 °C with light of wavelength 589 nm.

What is the specific rotation of the acid?

First, we need to convert the concentration to grammes per cubic centimetre: 28 mg in 1 cm^3 is the same as 0.028 g cm^{-3}. The path length of 10 cm is 1 dm, so

$$[\alpha]_D^{20} = \frac{\alpha}{cl} = \frac{-4.35}{0.28 \times 1} = -155.4$$

▶ Note that the units of optical rotation are not degrees: by convention, [α] is usually quoted without units.

■ $[\alpha]_D$ values can be used as a guide to the enantiomeric purity of a sample, in other words, to how much of each enantiomer it contains. We will come back to this in Chapter 45.

Enantiomers can be described as (+) or (–)

We can use the fact that two enantiomers rotate plane-polarized light in opposite directions to assign each a label that doesn't depend on knowing its configuration. We call the enantiomer that rotates plane-polarized light to the right (gives a positive rotation) the **(+)-enantiomer** (or the *dextrorotatory* enantiomer) and the enantiomer that rotates plane-polarized light to the left (gives a negative rotation) the **(–)-enantiomer** (or the *laevorotatory* enantiomer). The direction in which light is rotated is not dependent on whether a stereogenic centre is *R* or *S*. An (*R*) compound is equally as likely to be (+) as (–)—of course, if it is (+) then its (*S*) enantiomer must be (–). The enantiomer of mandelic acid we have just discussed, for example, is *R*-(–)-mandelic acid, because its specific rotation is negative, and (*S*)-alanine happens to be *S*-(+)-alanine. The labels (+) and (–) were more useful before the days of X-ray crystallography, when chemists did not know the actual configuration of the molecules they studied, and could distinguish two enantiomers only by the signs of their specific rotations.

Enantiomers can be described as D or L

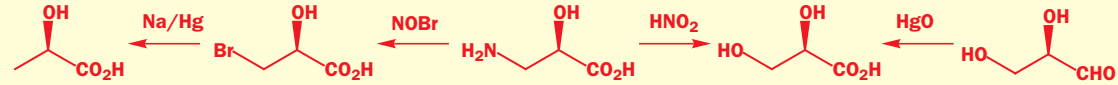
Long before the appearance of X-ray crystallography as an analytical tool, chemists had to discover the detailed structure and stereochemistry of molecules by a complex series of degradations. A molecule was gradually broken down into its constituents, and from the products that were formed the overall structure of the starting molecule was deduced. As far as stereochemistry was concerned, it was possible to measure the specific rotation of a compound, but not to determine its configuration. However, by using series of degradations it was possible to tell whether certain compounds had the same or opposite configurations.

Glyceraldehyde is one of the simplest chiral compounds in nature. Because of this, chemists took it as a standard against which the configurations of other compounds could be compared. The two enantiomers of glyceraldehyde were given the labels D (for dextro—because it was the (+)-enantiomer) and L (for laevo—because it was the (–)-enantiomer). Any enantiomerically pure compound that could be related, by a series of chemical degradations and transformations, to D-(+)-glyceraldehyde was labelled D, and any compound that could be related to L-(–)-glyceraldehyde was labelled L. The processes concerned were slow and laborious (the scheme below shows how (–)-lactic acid was shown to be D-(–)-lactic acid) and are never used today. D and L are now used only for certain well known natural molecules, where their use is established by tradition, for example, the L-amino acids or the D-sugars. These labels, D and L, are in *small capital* letters.

● **Remember that the *R*/*S*, +/–, and D/L nomenclatures all arise from different observations and the fact that a molecule has, say, the *R* configuration gives no clue as to whether it will have + or – optical activity or be labelled D or L. Never try and label a molecule as D/L, or +/–, simply by working it out from the structure. Likewise, never try and predict whether a molecule will have a + or – specific rotation by looking at the structure.**

The correlation between D-(–)-lactic acid and D-(+)-glyceraldehyde

Here, for example, is the way that (–)-lactic acid was shown to have the same configuration as D-(+) glyceraldehyde. We do not expect you to have come across the reactions used here.



D-(–)-lactic acid | (+)-isoserine | (–)-glyceric acid | D-(+)-glyceraldehyde

Diastereoisomers are stereoisomers that are not enantiomers

Two enantiomers are chemically identical because they are mirror images of one another. Other types of stereoisomers may be chemically (and physically) quite different. These two alkenes, for example, are geometrical isomers (or *cis*–*trans* isomers). Their physical chemical properties are different, as you would expect, since they are quite different in shape.

butenedioic acids

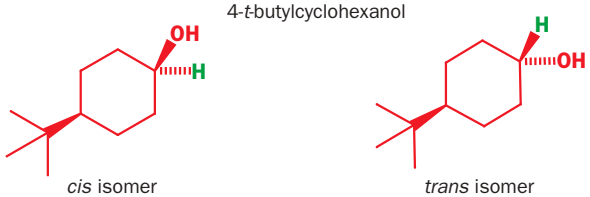
fumaric acid | maleic acid

trans-butenedioic acid (fumaric acid) m.p. 299–300 °C

cis-butenedioic acid (maleic acid) m.p. 140–142 °C

A similar type of stereoisomerism can exist in cyclic compounds. In one of these 4-*t*-butylcyclohexanols the two substituents are on the same side of the ring; in the other, they are on opposite sides of the ring. Again, the two compounds have chemical and physical properties that are quite different.

4-*t*-butylcyclohexanol



cis isomer | *trans* isomer

cis 4-*t*-butylcyclohexanol | *trans* 4-*t*-butylcyclohexanol

mp 82–83 °C | mp 80–81 °C

^{1}H NMR: δ_H of green proton 4.02 | ^{1}H NMR: δ_H of green proton 3.50

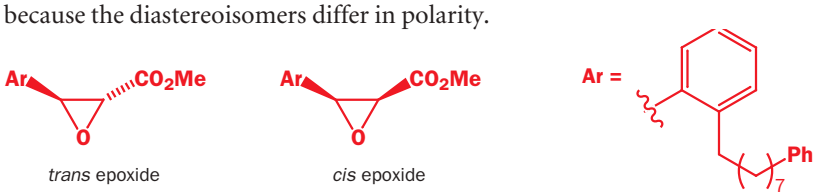
▶ The physical and chemical properties of enantiomers are identical; the physical and chemical properties of diastereoisomers differ. 'Diastereoisomer' is sometimes shortened to 'diastereomer'.

Stereoisomers that are not mirror images of one another are called **diastereoisomers**. Both of these pairs of isomers fall into this category. Notice how the physical and chemical properties of a pair of diastereoisomers differ.

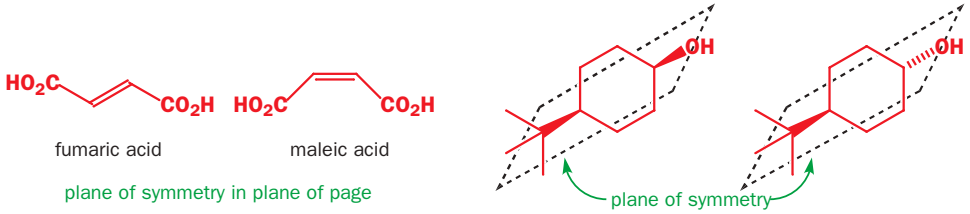
Diastereoisomers can be chiral or achiral

This pair of epoxides was produced by chemists in Pennsylvania in the course of research on drugs intended to alleviate the symptoms of asthma. Clearly, they are again diastereoisomers, and again

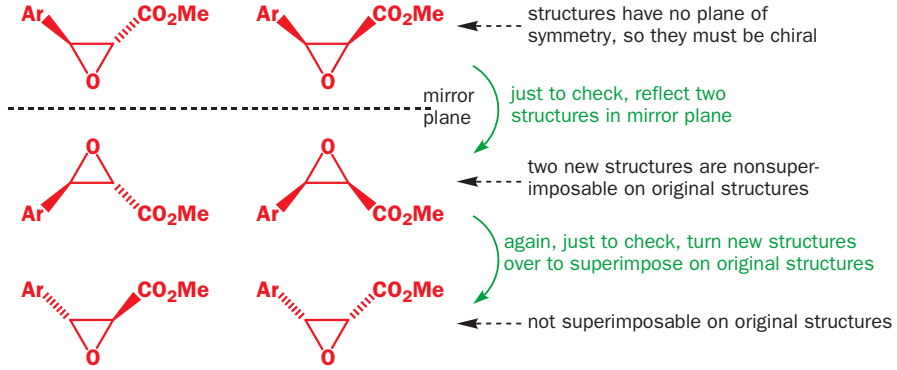
they have different properties. Although the reaction they were using to make these compounds gave some of each diastereoisomer, the chemists working on these compounds only wanted to use the first (*trans*) epoxide. They were able to separate it from its *cis* diastereoisomer by chromatography because the diastereoisomers differ in polarity.



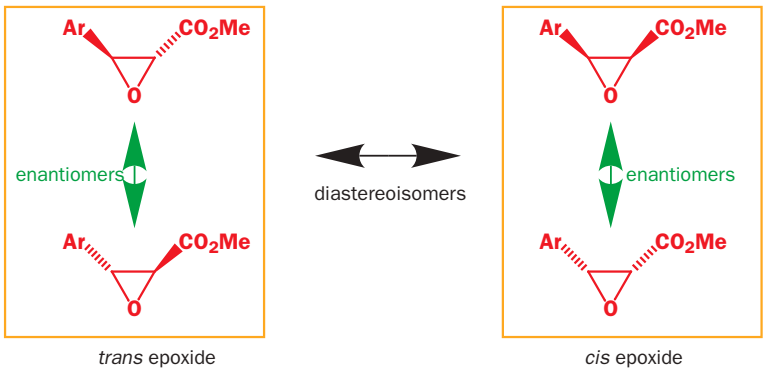
This time, the diastereoisomers are a little more complex than the examples above. The first two pairs of diastereoisomers we looked at were **achiral**—they each had a plane of symmetry through the molecule.



The last pair of diastereoisomers, on the other hand, is chiral. We know this because they do not have a plane of symmetry and we can check that by drawing the mirror image of each one: it is not superimposable on the first structure.



If a compound is chiral, it can exist as two enantiomers. We've just drawn the two enantiomers of each of the diastereoisomers of our epoxide. This set of four structures contains two diastereoisomers (stereoisomers that are not mirror images). These are the two different chemical compounds, the *cis* and *trans* epoxides, that have different properties. Each can exist as two enantiomers (stereoisomers that are mirror images) indistinguishable except for rotation. We have two pairs of diastereoisomers and two pairs of enantiomers. When you are considering the stereochemistry of a compound, always distinguish the diastereoisomers first and then split these into enantiomers if they are chiral.



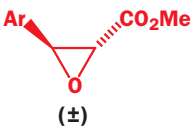
In fact, the chemists working on these compounds wanted only one enantiomer of the *trans* epoxide—the top left stereoisomer. They were able to separate the *trans* epoxide from the *cis* epoxide by chromatography, because they are diastereoisomers. However, because they had made both diastereoisomers in the laboratory from achiral starting materials, both diastereoisomers were racemic mixtures of the two enantiomers. Separating the top enantiomer of the *trans* epoxide from the bottom one was much harder because enantiomers have identical physical and chemical properties. To get just the enantiomer they wanted the chemists had to develop some completely different chemistry, using enantiomerically pure compounds derived from nature.

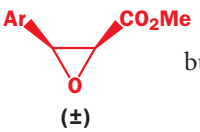
■ We shall discuss how chemists make enantiomerically pure compounds later in this chapter, and in more detail in Chapter 45.

Absolute and relative stereochemistry

When we talk about two chiral diastereoisomers, we have no choice but to draw the structure of one enantiomer of each diastereoisomer, because we need to include the stereochemical information to distinguish them, even if we're talking about a racemic mixture of the two enantiomers. To avoid confusion, it's best to write something definite under the structure, such as '±' (meaning racemic) under a structure if it means 'this diastereoisomer' but not 'this enantiomer of this diastereoisomer'.

So we should say, for example, that the chemists were able to separate these two diastereoisomers





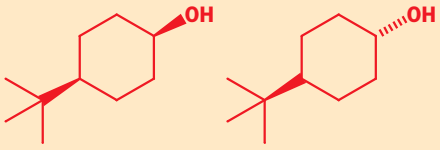
but that they wanted only this enantiomer.

When the stereochemistry drawn on a molecule means 'this diastereoisomer', we say that we are representing **relative stereochemistry**; when it means 'this enantiomer of this diastereoisomer' we say we are representing its **absolute stereochemistry**. Relative stereochemistry tells us only how the stereogenic centres *within a molecule* relate to each other.

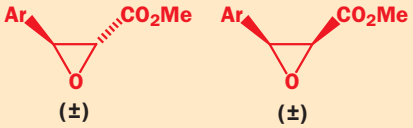
● Enantiometers and diastereoisomers

- **Enantiomers** are stereoisomers that are mirror images. A pair of enantiomers are mirror-image forms of the same compound and have opposite **absolute stereochemistry**
- **Diastereoisomers** are stereoisomers that are not mirror images. Two diastereoisomers are different compounds, and have different **relative stereochemistry**

Diastereoisomers may be achiral (have a plane of symmetry); for example,



Or they may be chiral (have no plane of symmetry); for example,

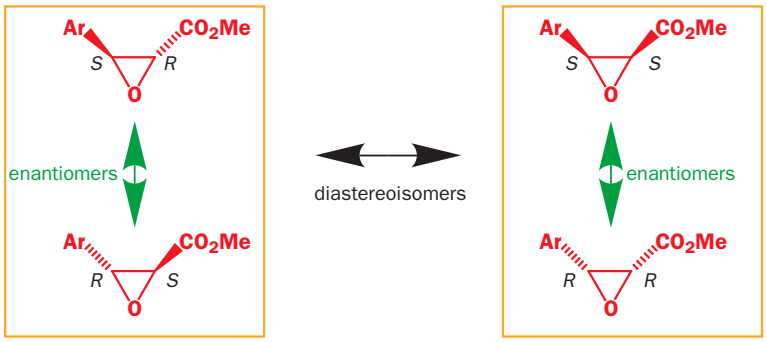


► You need to know, and be able to use, the rules for assigning *R* and *S*; they were explained on p. 000. If you get any of the assignments wrong, make sure you understand why.

Diastereoisomers can arise when structures have more than one stereogenic centre

Let's analyse our set of four stereoisomers a little more closely. You may have already noticed that these structures all contain stereogenic centres—two in each case. Go back to the diagram of the four structures on p. 000 and, without looking at the structures below, assign an *R* or *S* label to each of these stereogenic centres.

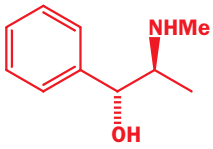
You should have assigned *R*s and *S*s like this.



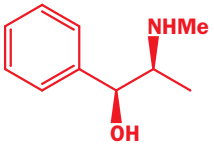
Converting enantiometers and diastereoisomers

- To go from one *enantiomer* to another, *both* stereogenic centres are inverted
- To go from one *diastereoisomer* to another, only *one* of the two is inverted

All the compounds that we have talked about so far have been cyclic, because the diastereoisomers are easy to visualize: two diastereoisomers can be identified because the substituents are either on the same side or on opposite sides of the ring (*cis* or *trans*). But acyclic compounds can exist as diastereoisomers too. Take these two, for example. Both ephedrine and pseudoephedrine are members of the amphetamine class of stimulants, which act by imitating the action of the hormone adrenaline.



ephedrine

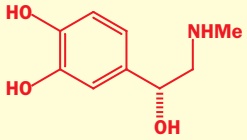


pseudoephedrine

Ephedrine and pseudoephedrine are stereoisomers that are clearly not mirror images of each other—only one of the two stereogenic centres in ephedrine is inverted in pseudoephedrine—so they must be diastereoisomers. Thinking in terms of stereogenic centres is useful, because, just as this compound has two stereogenic centres and can exist as two diastereoisomers, any compound with more than one stereogenic centre can exist in more than one diastereoisomeric form.

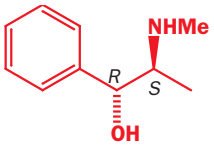
Adrenaline

Adrenaline (also known as epinephrine) has a chiral structure. In nature it is a single enantiomer but it cannot have any diastereoisomers as it has only one stereogenic centre.

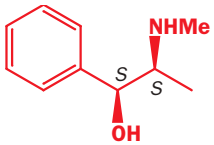


adrenaline

Both compounds are produced in enantiomerically pure form by plants, so, unlike the anti-asthma intermediates above, in this case we are talking about single enantiomers of single diastereoisomers.



(1*R*,2*S*)-(–)-ephedrine



(1*S*,2*S*)-(+)-pseudoephedrine

Ephedrine and pseudoephedrine

Ephedrine is a component of the traditional Chinese remedy 'Ma Huang', extracted from *Ephedra* species. It is also used in nasal sprays as a decongestant. Pseudoephedrine is the active component of the decongestant Sudafed (so should that be Pseudafed?).

The 'natural' enantiomers of the two diastereomers are (–)-ephedrine and (+)-pseudoephedrine, which does not tell you which is which, or (1*R*,2*S*)-(–)-ephedrine and (1*S*,2*S*)-(+)-pseudoephedrine, which does. From that you should be able to deduce the corresponding structures.

▶ If you are asked to explain some stereochemical point in an examination, choose a cyclic example—it makes it much easier.

▶ Remember that (+) and (–) refer to the sign of the specific rotation, while *R* and *S* are derived simply by looking at the structure of the compounds. There is no simple connection between the two!

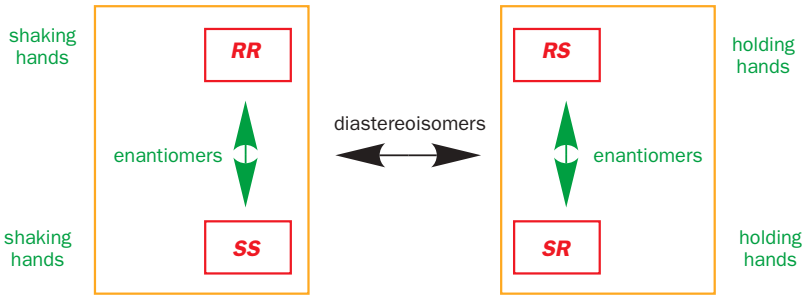
Here are some data on (1*R*,2*S*)-(–)-ephedrine and (1*S*,2*S*)-(+)-pseudoephedrine and their 'unnatural' enantiomers (which have to be made in the laboratory), (1*S*,2*R*)-(+)-ephedrine and (1*R*,2*R*)-(–)-pseudoephedrine.

	(1*R*,2*S*)-(–)-ephedrine	(1*S*,2*R*)-(+)-ephedrine	(1*S*,2*S*)-(+)-pseudoephedrine	(1*R*,2*R*)-(–)-pseudoephedrine
m.p.	40–40.5 °C	40–40.5 °C	117–118 °C	117–118 °C
$[\alpha]_D^{20}$	–6.3	+6.3	+52	–52

Evidently, the diastereoisomers are different compounds with different names and different properties, while the pair of enantiomers are the same compound and differ only in the direction in which they rotate polarized light.

We can illustrate the combination of two stereogenic centres in a compound by considering what happens when you shake hands with someone. Hand-shaking is successful only if you each use the same hand! By convention, this is your right hand, but it's equally possible to shake left hands. The overall pattern of interaction between two right hands and two left hands is the same: a right-hand-shake and a left-handshake are enantiomers of one another; they differ only in being mirror images. If, however, you misguidedly try to shake your right hand with someone else's left hand you end up holding hands. Held hands consist of one left and one right hand; a pair of held hands have totally different interactions from pair of shaking hands; we can say that holding hands is a diastereoisomer of shaking hands.

We can summarize the situation when we have two hands, or two chiral centres, each one *R* or *S*.



What about compounds with more than two stereogenic centres? The family of sugars provides lots of examples. Ribose is a 5-carbon sugar that contains three stereogenic centres. The enantiomer shown here is the one used in the metabolism of all living things and, by convention, is known as D-ribose. The three stereogenic centres of D-ribose have the *R* configuration.

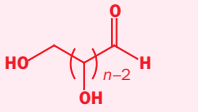
In theory we can work out how many 'stereoisomers' there are of a compound with three stereogenic centres simply by noting that there are 8 ($=2^3$) ways of arranging *R*s and *S*s.

RRR	*RRS*	*RSR*	*RSS*
SSS	*SSR*	*SRS*	*SRR*

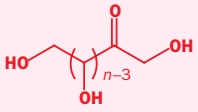
But this method blurs the all-important distinction between diastereoisomers and enantiomers. In each case, the combination in the top row and the combination directly below it are enantiomers (all three centres are inverted); the four columns are diastereoisomers. Three stereogenic centres therefore give four diastereoisomers, each a pair of two enantiomers. Going back to the example of the C_5 aldoses, each of these diastereoisomers is a different sugar. In these diagrams each diasteroisomer is in a frame but the top line shows one enantiomer (D) and the bottom line the other (L).

▶

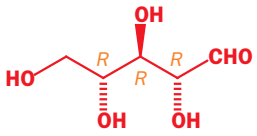
A sugar has the empirical formula $C_nH_{2n}O_n$, and consists of a chain of carbon atoms, one being a carbonyl group and the rest carrying OH groups. If the carbonyl group is at the end of the chain (in other words, it is an aldehyde), the sugar is an aldose. If the carbonyl group is not at the end of the chain, the sugar is a ketose. We come back to all this in detail in Chapter 49. The number of carbon atoms, *n*, can be 3–8: aldoses have *n* – 2 stereogenic centres and ketoses *n* – 3 stereogenic centres. In fact, most sugars exist as an equilibrium mixture of this open-chain structure and a cyclic hemiacetal isomer (Chapter 6).



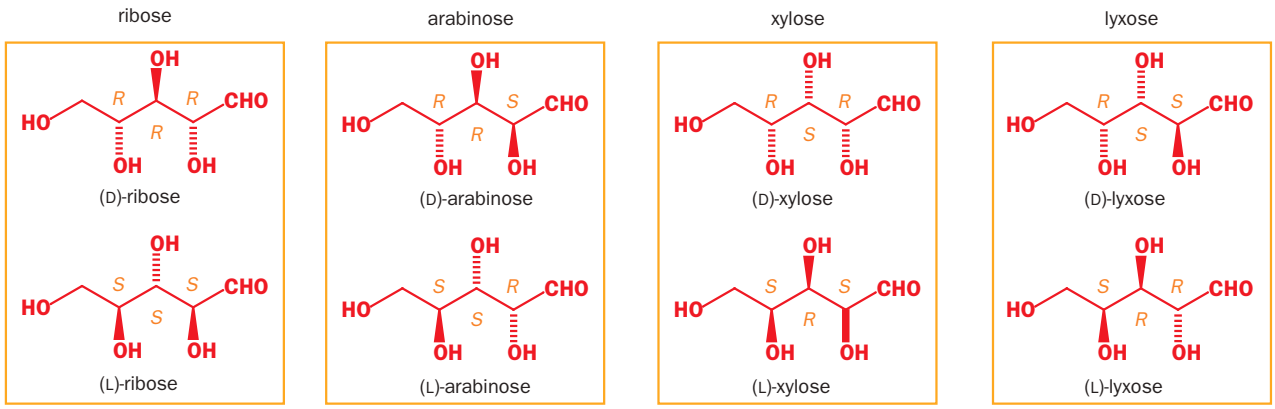
an aldose



a ketose



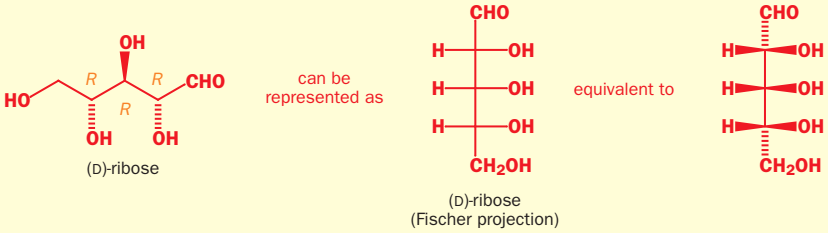
(D)-ribose



Fischer projections

The stereochemistry of sugars used to be represented by Fischer projections. The carbon backbone was laid out in a vertical line and twisted in such a way that all the substituents pointed towards the viewer.

Fischer projections are so unlike real molecules that you should never use them. However, you may see them in older books, and you should have an idea about how to interpret them. Just remember that all the branches down the side of the central trunk are effectively bold wedges (coming towards the viewer), while the central trunk lies in the plane of the paper. By mentally twisting the backbone into a realistic zig-zag shape you should end up with a reasonable representation of the sugar molecule.

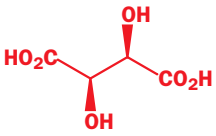


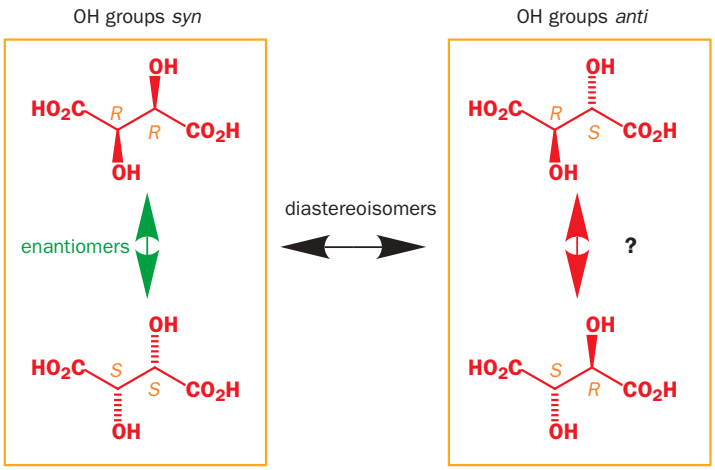
You've probably recognized that there's a simple mathematical relationship between the number of stereogenic centres and the number of stereoisomers a structure can have. Usually, a structure with n stereogenic centres can exist as 2^n stereoisomers. These stereoisomers consist of $2^{(n-1)}$ diastereoisomers, each of which has a pair of enantiomers. This is an oversimplification to be used cautiously because it works only if all diastereoisomers are chiral. We recommend that you find out how many diastereoisomers there are in every new molecule before considering enantiomers.

Why only *usually*?—achiral compounds with more than one stereogenic centre

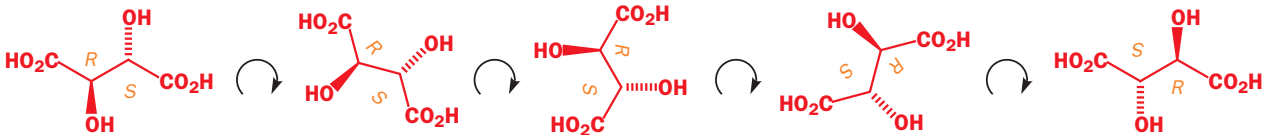
Sometimes, symmetry in a molecule can cause some stereoisomers to be degenerate, or 'cancel out'—there aren't as many stereoisomers as you'd expect. Take tartaric acid, for example.

This stereoisomer of tartaric acid is found in grapes, and its salt, potassium hydrogen tartrate, can precipitate out as crystals at the bottom of bottles of wine. It has two stereogenic centres, so you'd expect $2^2 = 4$ stereoisomers; two diastereoisomers, each a pair of enantiomers.

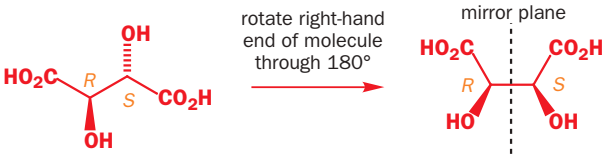




While the pair of structures on the left are certainly enantiomers, if you look carefully at the pair of structures on the right, you'll see that they are, in fact, not enantiomers but identical structures. To prove it, just rotate the top one through 180° in the plane of the paper.



R,S-Tartaric acid and *S,R*-tartaric acid are not enantiomers, but they are identical because, even though they contain stereogenic centres, they are achiral. By drawing *R,S*-tartaric acid after a 180° rotation about the central bond, you can easily see that it has a mirror plane, and so must be achiral.



The formula stating that a compound with n stereogenic centres has 2^{n-1} diastereoisomers has worked but not the formula that states there are 2^n 'stereoisomers'. In general, it's safer not to talk about 'stereoisomers' but to talk first about diastereoisomers and then to assess each one for enantiomers. To say that a compound with two stereogenic centres has four 'stereoisomers' is rather like saying that 'four hands are getting married'. Two people are getting married, each with two hands.

Compounds that contain stereogenic centres but are themselves achiral are called *meso* compounds. This means that there is a plane of symmetry with *R* stereochemistry on one side and *S* stereochemistry on the other.

Meso hand-shaking

We can extend our analogy between hand-shaking and diastereoisomers to *meso* compounds as well. Imagine a pair of identical twins shaking hands. There would be two ways for them to do it: left shakes left or right shakes right: provided you know your left from your right you could tell the two handshakes apart because they are enantiomers. But if the twins hold hands, you will not be able to distinguish left holds right from right holds left, because the twins themselves are indistinguishable—this is the *meso* hand-hold!

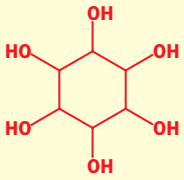
So tartaric acid can exist as two diastereoisomers, one with two enantiomers and the other achiral (a *meso* compound). Since the molecule has symmetry, and *R* is the mirror image of *S*, the *RS* diastereoisomer cannot be chiral.

	Chiral diastereoisomer		Achiral diastereoisomer
	(+)-tartaric acid	(–)-tartaric acid	*meso*-tartaric acid
$[\alpha]_D^{20}$	+12	–12	0
m.p.	168–170 °C	168–170 °C	146–148 °C

Meso diastereoisomers of inositol

Look out for *meso* diastereoisomers in compounds that have a degree of symmetry in their overall structure. Inositol, one of whose diastereomers is an important growth factor, certainly possesses some *meso* diastereoisomers.

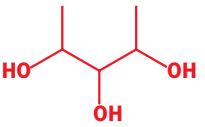
inositol



NMR Spectrum still to come

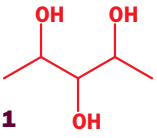
Investigating the stereochemistry of a compound

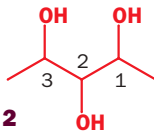
When you want to describe the stereochemistry of a compound our advice is to identify the diastereoisomers and then think about whether they are chiral or not. Here is a simple example, the linear triol 2,3,4-trihydroxypentane or pentan-2,3,4-triol.



This is what you should do.

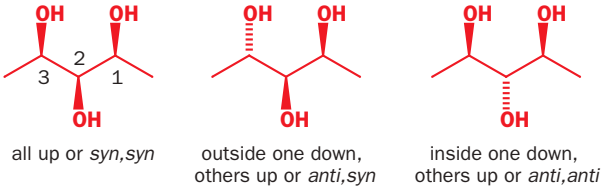
1. Draw the compound with the carbon skeleton in the usual zig-zag fashion running across the page





2. Identify the chiral centres

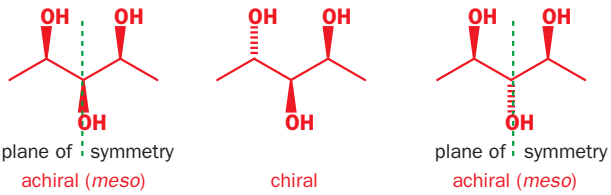
3. Decide how many diastereoisomers there are by putting the substituents at those centres up or down. It often helps to give each diastereoisomer a 'tag' name. In this case there are three diastereoisomers. The three OH groups can be all on the same side or else one of the end OHs or the middle one can be on the opposite side to the rest



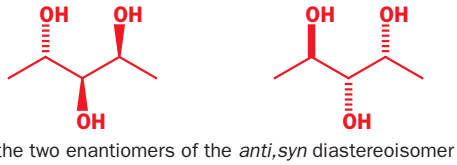
4. By checking on possible planes of symmetry, see which diastereoisomers are chiral. In this case only the plane down the centre can be a plane of symmetry

5. Draw the enantiomers of any chiral diastereoisomer by inverting *all* the stereogenic centres

6. Announce the conclusion

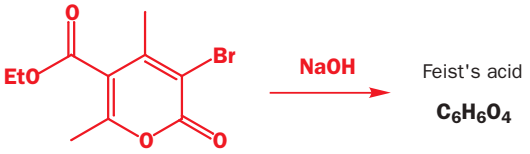


You could have said that there are four 'stereoisomers' but the following statement is much more helpful. There are three diastereoisomers, the *syn,syn*, the *syn,anti*, and the *anti,anti*. The *syn,syn* and the *anti,anti* are achiral (*meso*) compounds but the *syn,anti* is chiral and has two enantiomers.

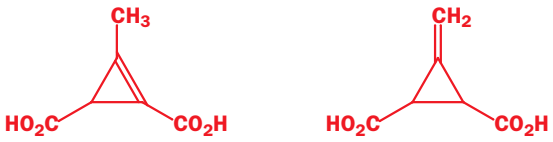


The mystery of Feist's acid

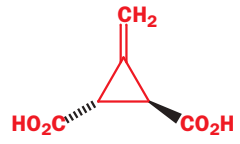
It is hard nowadays to realize how difficult structure-solving was when there were no spectra. A celebrated case was that of 'Feist's acid' discovered by Feist in 1893 from a deceptively simple reaction.



Early work without spectra led to two suggestions, both based on a three-membered ring, and this compound had some fame because unsaturated three-membered rings were rare. The favoured structure was the cyclopropene.

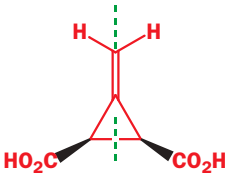


The argument was still going on in the 1950s when the first NMR spectrometers appeared. Though infrared appeared to support the cyclopropene structure, one of the first problems resolved by the primitive 40 MHz instruments available was that of Feist's acid, which had no methyl group signal but did have two protons on a double bond and so had to be the exomethylene isomer after all.



correct structure of Feist's acid

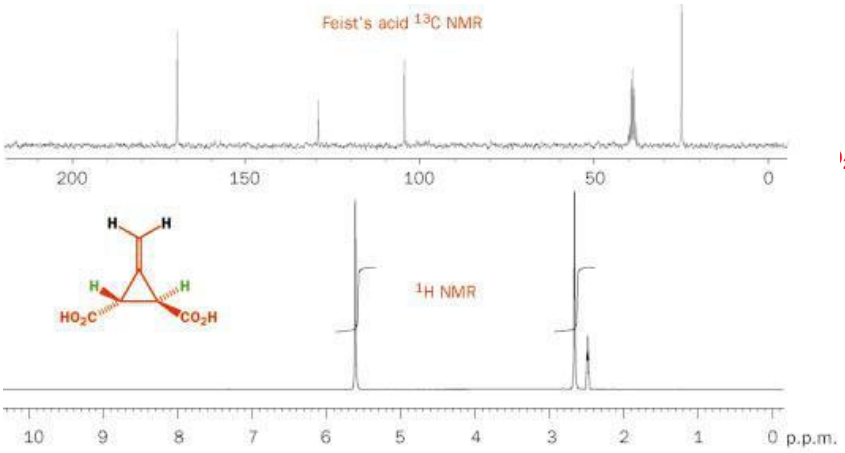
This structure has two chiral centres, so how will we know which diastereoisomer we have? The answer was simple: the stereochemistry has to be *trans* because Feist's acid is chiral: it can be resolved (see later in this chapter) into two enantiomers. Now, the *cis* diacid would have a plane of symmetry, and so would be achiral—it would be a *meso* compound. The *trans* acid on the other hand is chiral—it has only an axis of symmetry. If you do not see this, try superimposing it on its mirror image. You will find that you cannot.

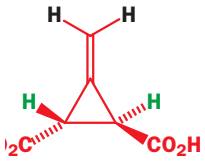


the *cis* diacid has a plane of symmetry

Modern NMR spectra make the structure easy to deduce. There are only two proton signals as the

CO_2H protons exchange in the DMSO solvent needed. The two protons on the double bond are identical (5.60 p.p.m.) and so are the two protons on the three-membered ring which come at the expected high field (2.67 p.p.m.). There are four carbon signals: the C=O at 170 p.p.m., two alkene signals between 100 and 150 p.p.m., and the two identical carbons in the three-membered ring at 25.45 p.p.m.



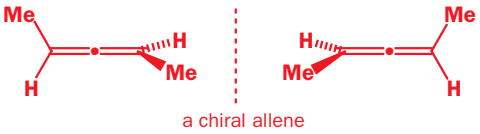


modern ^{1}H NMR of Feist's acid
2.67 (2H, s), 5.60 (2H, s)

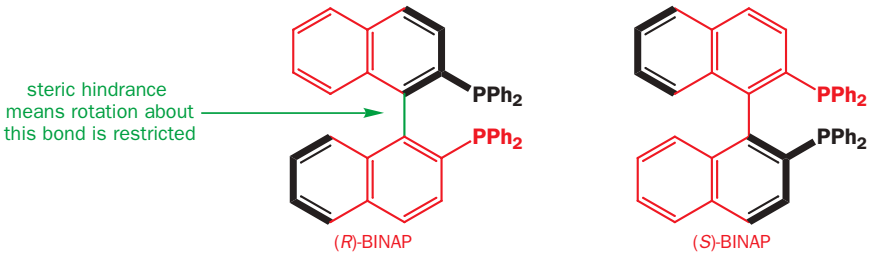
modern ^{13}C NMR of Feist's acid
170.3, 129.8, 105.05, 25.45

Chiral compounds with no stereogenic centres

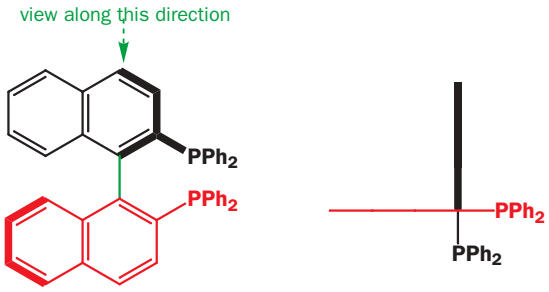
A few compounds are chiral, yet have no stereogenic centres. We will not discuss these in detail, but try making a model of this allene, which has no stereogenic centre.



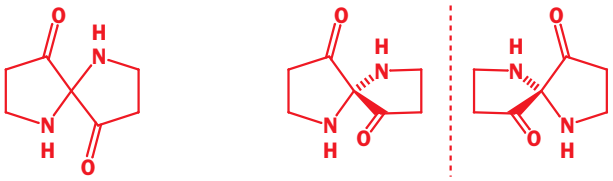
These mirror images (enantiomers) are not superimposable and so the allene is chiral. Similarly, some biaryl compounds such as this important bisphosphine known as BINAP (we come back to BINAP in Chapter 45) exist as two separate enantiomers because rotation about the green bond is restricted.



If you were to look at this molecule straight down along the green bond, you would see that the two flat rings are at right angles to each other and so the molecule has a twist in it rather like the 90° twist in the allene.



These two examples rely on the rigidity of π systems but this simple saturated system is also chiral. These two rings have to be orthogonal because of the tetrahedral nature of the central carbon atom. There can be no plane of symmetry here either but the central carbon is not chiral.

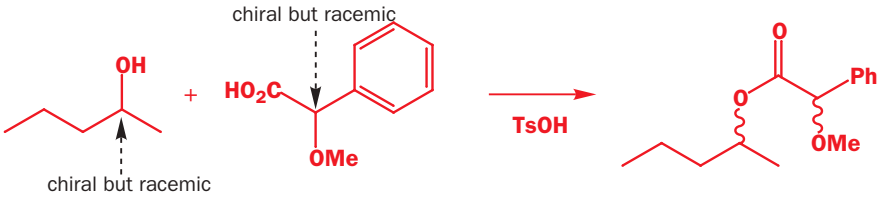


There are other types of chiral molecule but they all share the same feature—there is no plane of symmetry.

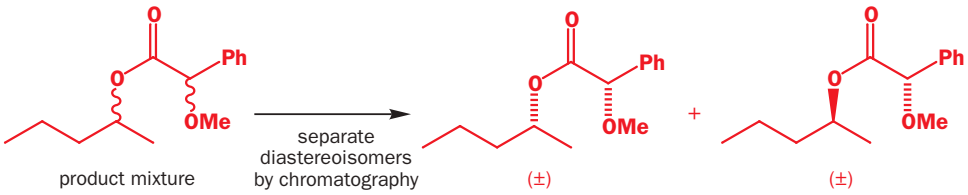
Separating enantiomers is called resolution

Early in this chapter, we said that most of the molecules in nature are chiral, and that Nature usually produces these molecules as single enantiomers. We've talked about the amino acids, the sugars, ephedrine, pseudoephedrine, and tartaric acid—all compounds that can be isolated from natural sources as single enantiomers. On the other hand, in the lab, if we make chiral compounds from achiral starting materials, we are doomed to get racemic mixtures. So how do chemists ever isolate compounds as single enantiomers, other than by extracting them from natural sources? We'll consider this question in much more detail in Chapter 45, but here we will look at the simplest way: using nature's enantiomerically pure compounds to help us separate the components of a racemic mixture into its two enantiomers. This process is called **resolution**.

Imagine the reaction between a chiral, but racemic alcohol and a chiral, but racemic carboxylic acid, to give an ester in an ordinary acid-catalysed esterification (Chapter 12).

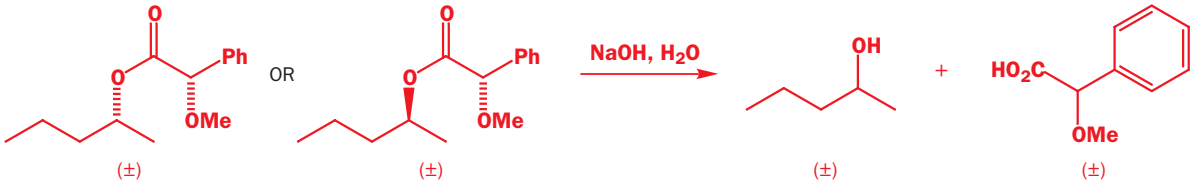


The product contains two chiral centres, so we expect to get two diastereoisomers, each a racemic mixture of two enantiomers. Diastereoisomers have different physical properties, so they should be easy to separate, for example by chromatography.



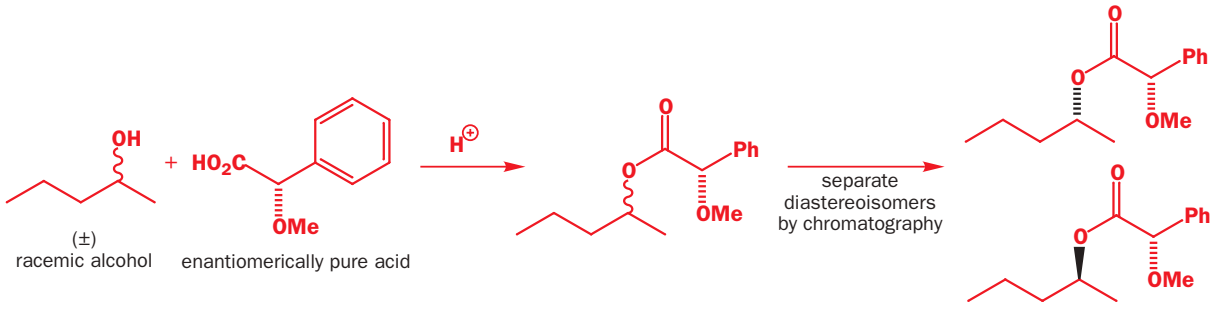
■ Remember that (±) means the compounds are racemic: we're showing only relative, not absolute, stereochemistry.

We could then reverse the esterification step, and hydrolyse either of these diastereoisomers, to regenerate racemic alcohol and racemic acid.



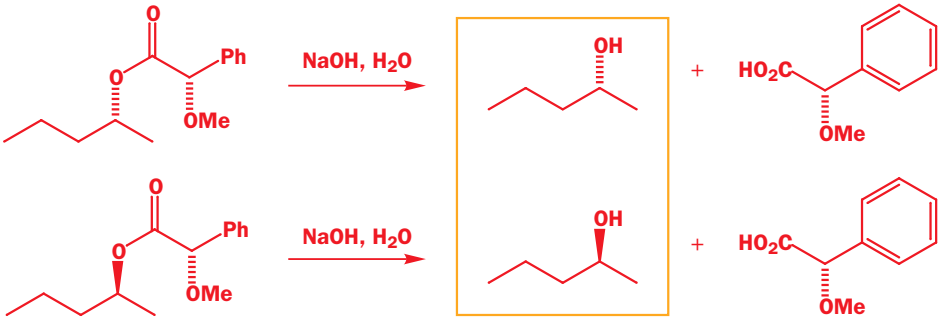
If we repeat this reaction, this time using an enantiomerically pure sample of the acid (available from (*R*)-mandelic acid, the almond extract you met on p. 000), we will again get two diastereoisomeric products, but this time each one will be enantiomerically pure.

■ Note that the stereochemistry shown here *is* absolute stereochemistry.



(±) racemic alcohol — enantiomerically pure acid

If we now hydrolyse each diastereoisomer separately, we have done something rather remarkable: we have managed to separate to two enantiomers of the starting alcohol.

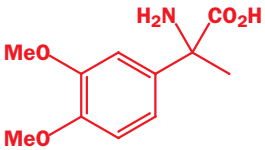


two enantiomers obtained separately: a resolution has been accomplished — acid recovered and can be recycled

A separation of two enantiomers is called a **resolution**. Resolutions can be carried out only if we make use of a component that is already enantiomerically pure: it is very useful that Nature provides us with such compounds; resolutions nearly always make use of compounds derived from nature.

?Heading?

Why Nature uses only one enantiomer of most important biochemicals is an easier question to answer than how this asymmetry came about in the first place, or why L-amino acids and D-sugars were the favoured enantiomers, since, for example, proteins made out of racemic samples of amino acids would be complicated by the possibility of enormous numbers of diastereomers. Some have suggested that life arose on the surface of single chiral quartz crystals, which provided the asymmetric environment needed to make life's molecules enantiomerically pure. Or perhaps the asymmetry present in the spin of electrons released as gamma rays acted as a source of molecular asymmetry. Given that enantiomerically pure living systems should be simpler than racemic ones, maybe it was just chance that the L-amino acids and the D-sugars won out.



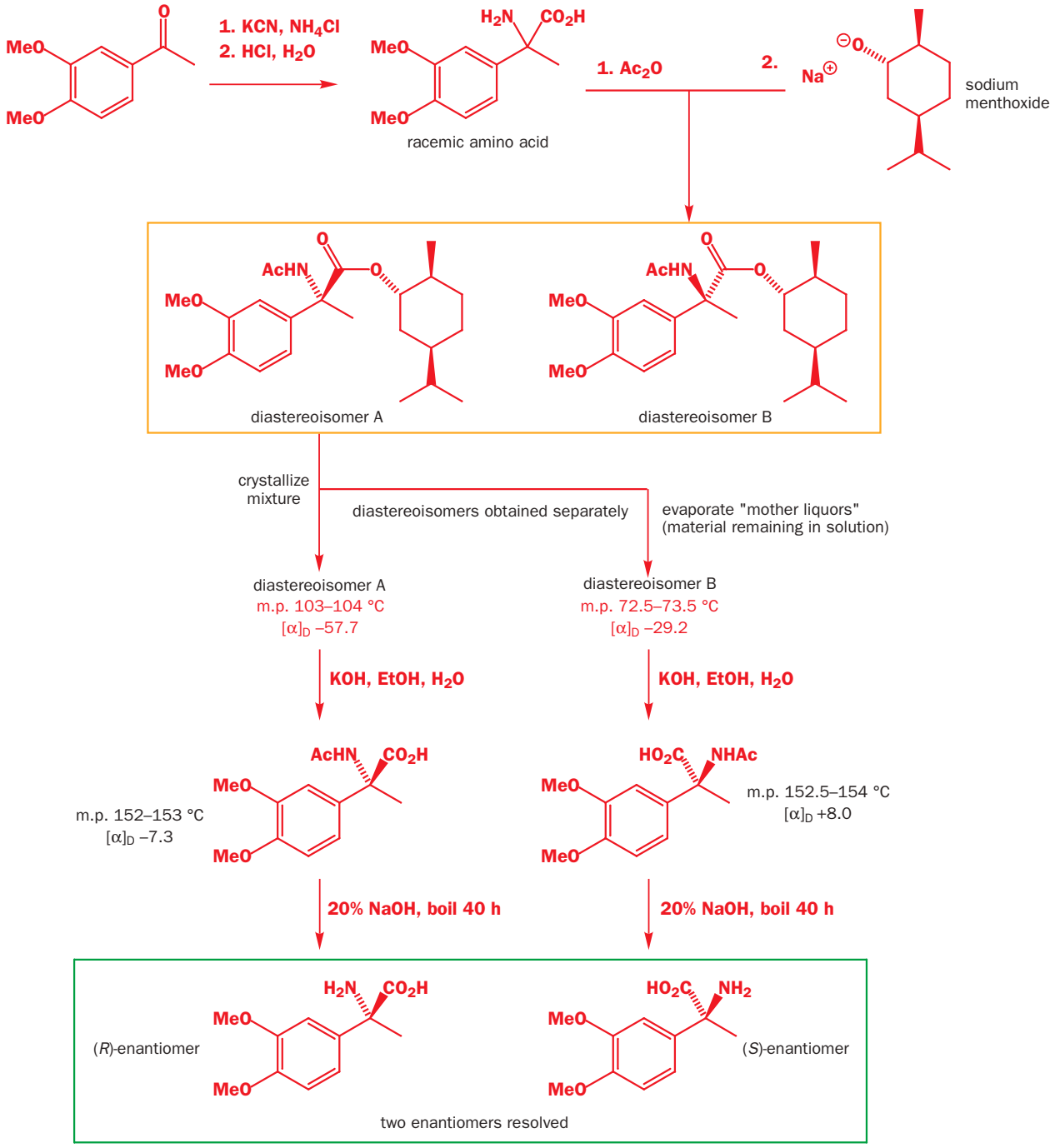
Now for a real example. Chemists studying the role of amino acids in brain function needed to obtain each of the two enantiomers of this compound.

They made a racemic sample using the Strecker synthesis of amino acids that you met in Chapter 12. The racemic amino acid was reacted with acetic anhydride to make the mixed anhydride and then with the sodium salt of naturally derived, enantiomerically pure alcohol menthol to give two diastereoisomers of the ester (see top of facing page).

One of the diastereoisomers turned out to be more crystalline (that is, to have a higher melting point) than the other and, by allowing the mixture to crystallize, the chemists were able to isolate a pure sample of this diastereoisomer. Evaporating the diastereoisomer left in solution (the 'mother liquors') gave them the less crystalline diastereoisomer.

Next the esters were hydrolysed by boiling them in aqueous KOH. The acids obtained were enantiomers, as shown by their (nearly) opposite optical rotations and similar melting points. Finally, a more vigorous hydrolysis of the amides (boiling for 40 hours with 20% NaOH) gave them the amino acids they required for their biological studies (see bottom of facing page).

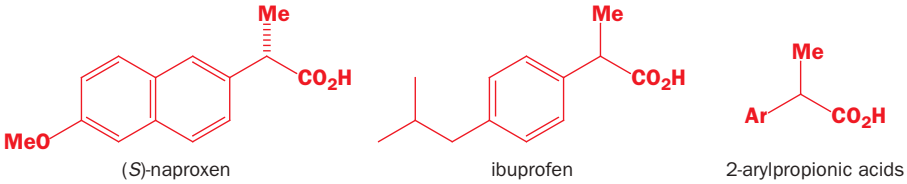
■ Note that the rotations of the pure diastereoisomers were not equal and opposite. These are single enantiomers of different compounds and there is no reason for them to have the same rotation.



Resolutions using diastereoisomeric salts

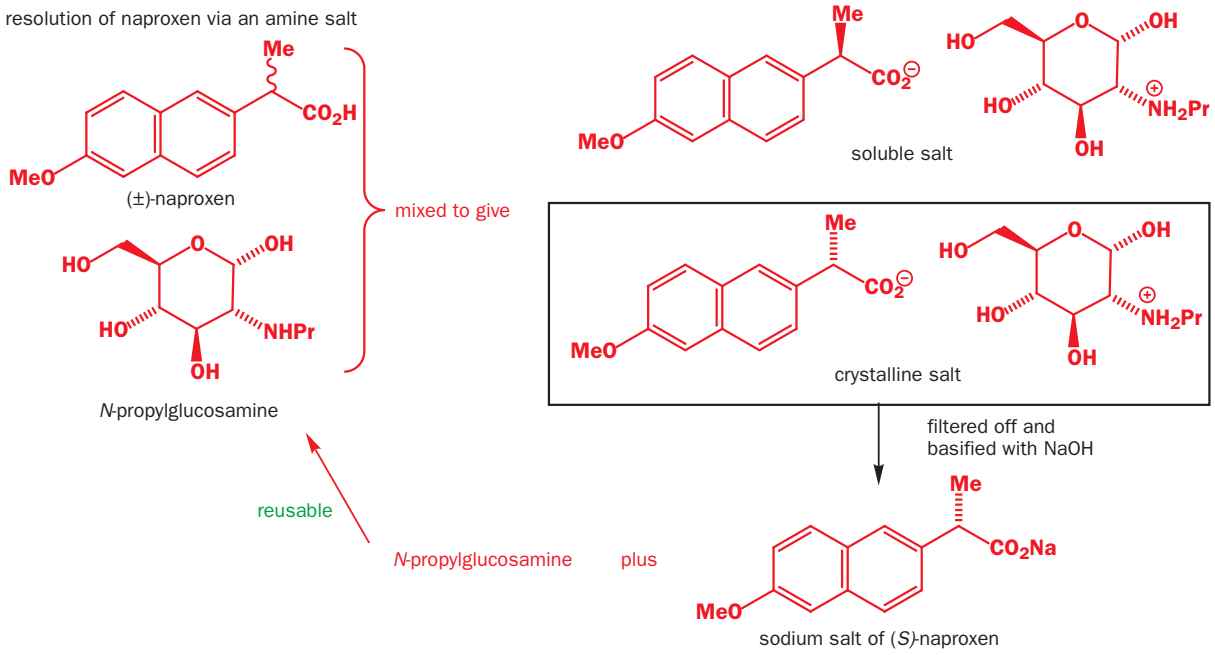
The key point about resolution is that we must bring together two stereogenic centres in such a way that there is a degree of interaction between them: separable diastereoisomers are created from inseparable enantiomers. In the last two examples, the stereogenic centres were brought together in covalent compounds, esters. Ionic compounds will do just as well—in fact, they are often better because it is easier to recover the compound after the resolution.

An important example is the resolution of the enantiomers of naproxen. Naproxen is a member of a family of compounds known as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) which are 2-aryl propionic acids. This class also includes ibuprofen, the painkiller developed by Boots and marketed as Nurofen.



Both naproxen and ibuprofen are chiral but, while both enantiomers of ibuprofen are effective painkillers, and the drug is sold as a racemic mixture (and anyway racemizes in the body) only the (*S*) enantiomer of naproxen has anti-inflammatory activity. When the American pharmaceutical company Syntex first marketed the drug they needed a way of resolving the racemic naproxen they synthesized in the laboratory.

Since naproxen is a carboxylic acid, they chose to make the carboxylate salt of an enantiomerically pure amine, and found that the most effective was this glucose derivative. Crystals were formed, which consisted of the salt of the amine and (*S*)-naproxen, the salt of the amine with (*R*)-naproxen (the diastereoisomer of the crystalline salt) being more soluble and so remaining in solution. These crystals were filtered off and treated with base basic, releasing the amine (which can later be recovered and reused) and allowing the (*S*)-naproxen to crystallize as its sodium salt.



Resolutions can be carried out by chromatography on chiral materials

Interactions even weaker than ionic bonds can be used to separate enantiomers. Chromatographic separation relies on a difference in affinity between a stationary phase (often silica) and a mobile phase (the solvent travelling through the stationary phase, known as the eluent) mediated by, for example, hydrogen bonds or van der Waals interactions. If the stationary phase is made chiral by bonding it with an enantiomerically pure compound (often a derivative of an amino acid), chromatography can be used to separate enantiomers.

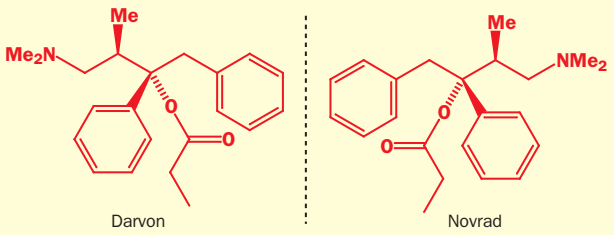
▶ Silica, SiO_2, is a macromolecular array of silicon and oxygen atoms. Its surface is covered with free OH groups, which can be used as an anchor for chiral derivatizing agents.

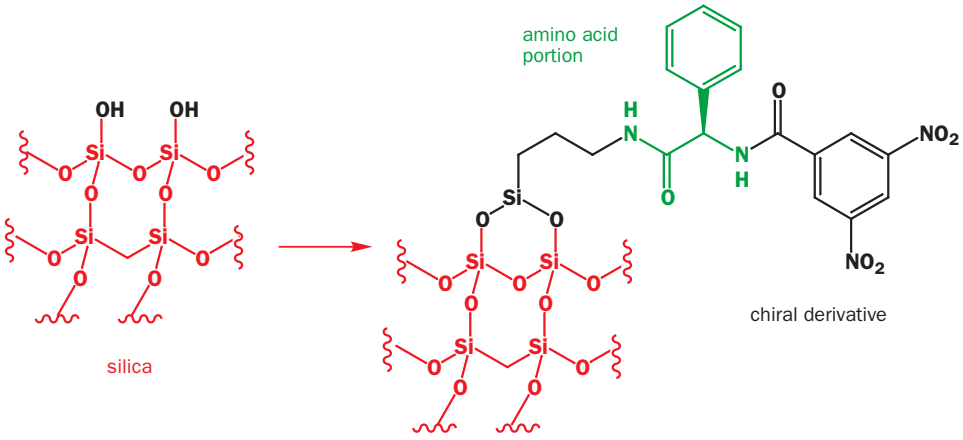
Chiral drugs

You may consider it strange that it was necessary to market naproxen as a single enantiomer, in view of what we have said about enantiomers having identical properties. The two enantiomers of naproxen do indeed have identical properties in the lab, but once they are inside a living system they, and any other chiral molecules, are differentiated by interactions with the enantiomerically pure molecules they find there. An analogy is that of a pair of gloves—the gloves weigh the same, are made of the same material, and have the same colour—in these respects they are identical. But interact them with a chiral environment, such as a hand, and they become differentiable because only one fits.

The way in which drugs interact with receptors mirrors this hand-and-glove analogy quite closely. Drug receptors, into which drug molecules fit like hands in gloves, are nearly always protein molecules, which are enantiomerically pure because they are made up of just L-amino acids. One enantiomer of a drug is likely to interact much better than the other, or perhaps in a different way altogether, so the two enantiomers of chiral drugs often have quite different pharmacological effects. In the case of naproxen, the (*S*)-enantiomer is 28 times as effective as the (*R*). Ibuprofen, on the other hand, is still marketed as a racemate because the two enantiomers have more or less the same painkilling effect.

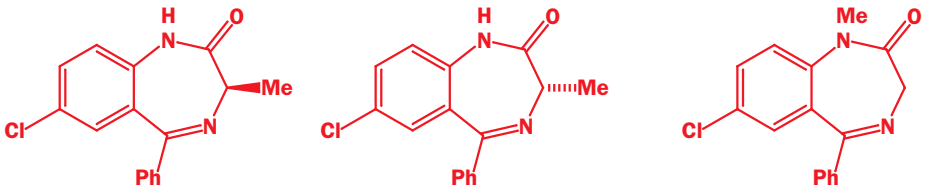
Sometimes, the enantiomers of a drug may have completely different therapeutic properties. One example is Darvon, which is a painkiller. Its enantiomer, known as Novrad, is an anticough agent. Notice how the enantiomeric relationship between these two drugs extends beyond their chemical structures! In Chapter 45 we will talk about other cases where two enantiomers have quite different biological effects.





Chromatography on a chiral stationary phase is especially important when the compounds being resolved have no functional groups suitable for making the derivatives (usually esters or salts) needed for the more classical resolutions described above. For example, the two enantiomers of an analogue of the tranquillizer Valium were found to have quite different biological activities.

an analogue of the tranquillizer Valium

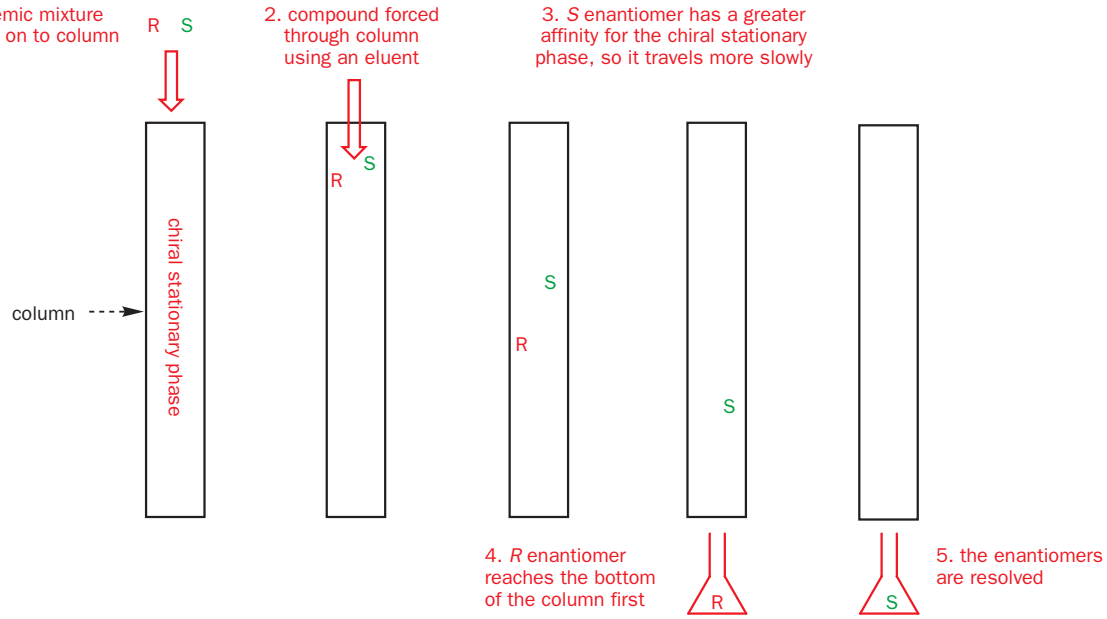


In order to study these compounds further, it was necessary to obtain them enantiomerically pure. This was done by passing a solution of the racemic compound through a column of silica bonded to an amino-acid-derived chiral stationary phase. The (*R*)-(−)-enantiomer showed a lower affinity for the stationary phase, and therefore was eluted from the column first, followed by the (*S*)-(+)-enantiomer.

▶

You can think about chiral chromatography like this. Put yourself in this familiar situation: you want to help out a pensioner friend of yours who sadly lost his left leg in the war. A local shoe shop donates to you all their spare odd shoes, left and right, in his size (which happens to be the same as yours). You set about sorting the lefts from the rights, but are plunged into darkness by a power cut. What should you do? Well, you try every shoe on your right foot. If it fits you keep it; if not it's a left shoe and you throw it out.

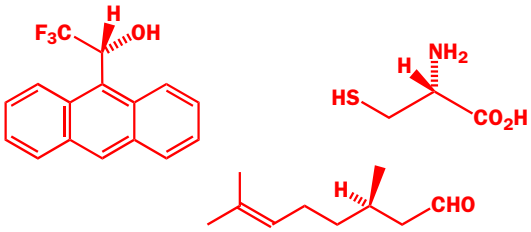
Now this is just what chromatography on a chiral stationary phase is about. The stationary phase has lots of 'right feet' (one enantiomer of an adsorbed chiral molecule) sticking out of it and, as the mixture of enantiomers of 'shoes' flows past, 'right shoes' fit, and stick but 'left shoes' do not and flow on down the column, reaching the bottom first.

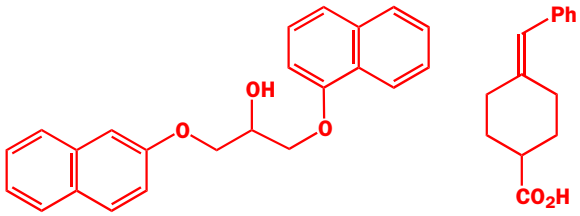


Two enantiomers of one molecule may be the same compound, but they are clearly different, though only in a limited number of situations. They can interact with biological systems differently, for example, and can form salts or compounds with different properties when reacted with a single enantiomer of another compound. In essence, enantiomers behave identically *except* when they are placed in a chiral environment. In Chapter 45, we will see how to use this fact to make single enantiomers of chiral compounds, but next we move on to three classes of reactions in which stereochemistry plays a key role: substitutions, eliminations, and additions.

Problems

1. Assign a configuration, *R* or *S*, to each of these compounds.

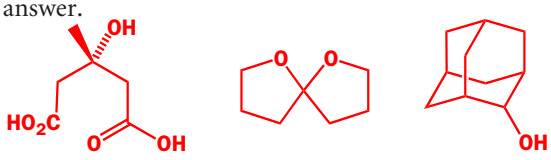




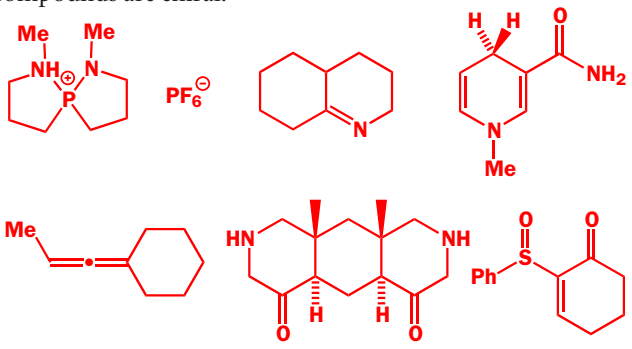
2. If a solution of a compound has a rotation of +12, how could you tell if this was actually +12, or really –348, or +372?

3. Cinderella's glass slipper was undoubtedly a chiral object. But would it have rotated the plane of polarized light?

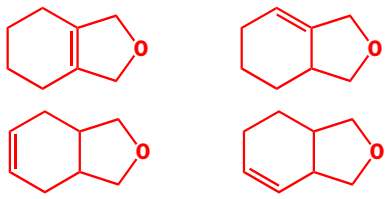
4. Are these compounds chiral? Draw diagrams to justify your answer.



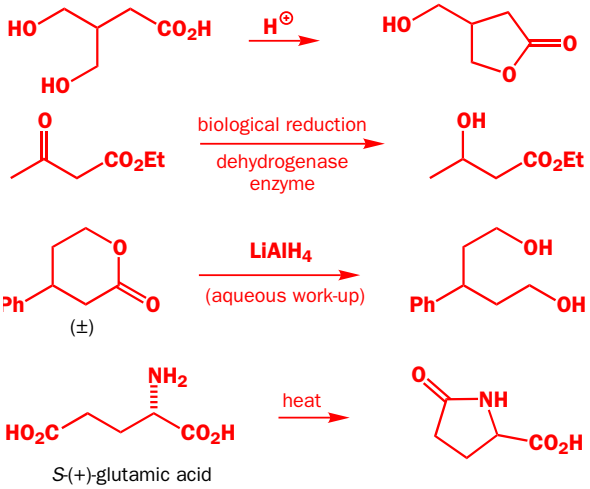
5. What makes molecules chiral? Give three examples of different types of chirality. State with explanations whether the following compounds are chiral.



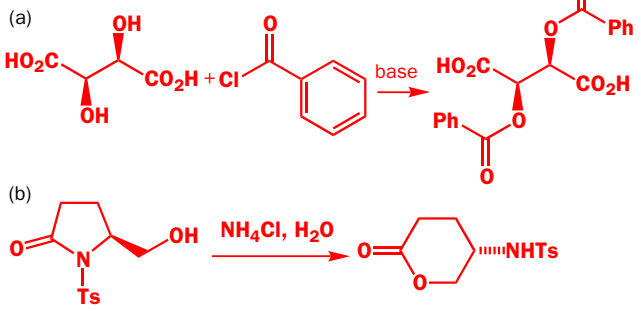
6. Discuss the stereochemistry of these compounds. (*Hint.* This means saying how many diastereoisomers there are, drawing clear diagrams of each, and saying whether they are chiral or not.)



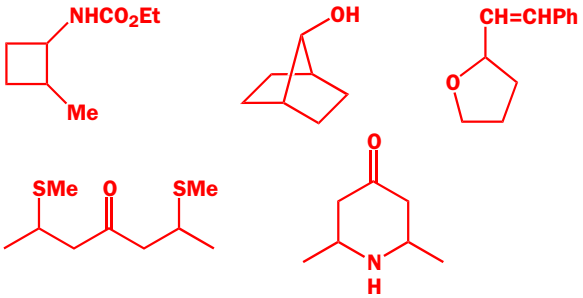
7. In each case state with explanations whether the products of these reactions are chiral and/or optically active.



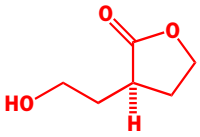
8. Propose mechanisms for these reactions that explain the stereochemistry of the products. All compounds are optically active.



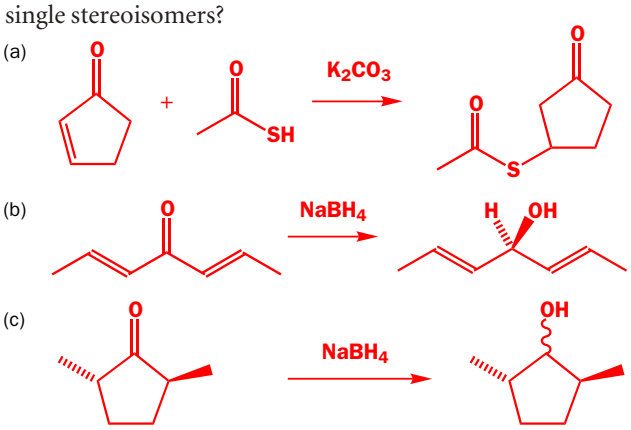
9. Discuss the stereochemistry of these compounds. The diagrams are deliberately poor ones that are ambiguous about the stereochemistry—your answer should use good diagrams that give the stereochemistry clearly.



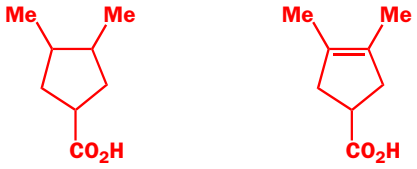
10. This compound racemizes in base. Why is that?



11. Draw mechanisms for these reactions. Will the products be single stereoisomers?

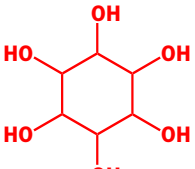


12. How many diastereoisomers of compound **1** are there? State clearly whether each diastereoisomer is chiral or not. If you had made a random mixture of stereosiomers by a chemical reaction, by what types of methods might they be separated? Which isomer(s) would be expected from the hydrogenation of compound 2?



1 2

13. Just for fun, you might like to try and work out just how many diastereoisomers inositol has and how many of them are *meso* compounds.



inositol

Nucleophilic substitution at saturated carbon

17

Connections

Building on:

- Attack of nucleophiles on carbonyl groups ch6, ch9, ch12, & ch14
- Attack of nucleophiles on double bonds conjugated with carbonyl groups ch10
- Substitution at carbonyl groups ch12
- Substitution of the oxygen atom of carbonyl groups ch14
- Stereochemistry ch16
- Transition states, intermediates, and rate expressions ch13

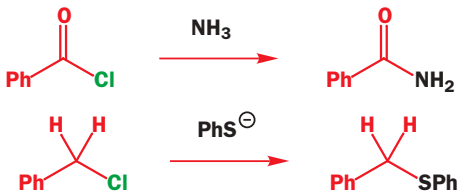
Arriving at:

- Nucleophilic attack on *saturated* carbon atoms, leading to substitution reactions
- How substitution at a saturated carbon atom differs from substitution at C=O
- Two mechanisms of nucleophilic substitution
- Intermediates and transition states in substitution reactions
- How substitution reactions affect stereochemistry
- What sort of nucleophiles can substitute, and what sort of leaving groups can be substituted
- The sorts of molecules that can be made by substitution, and what they can be made from

Looking forward to:

- Elimination reactions ch19
- Substitution reactions with aromatic compounds as nucleophiles ch22
- Substitution reactions with enolates as nucleophiles ch26
- Retrosynthetic analysis ch30

Nucleophilic substitution



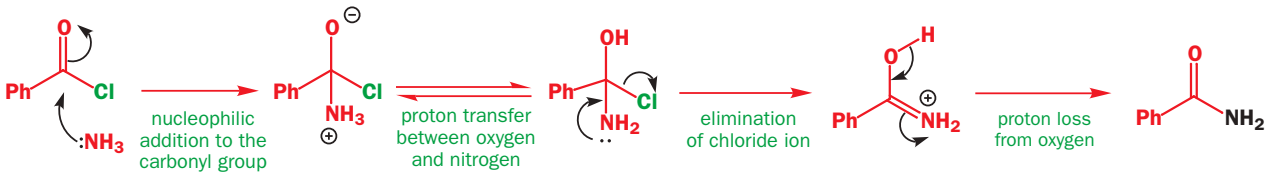
Substitution is the replacement of one group by another. In Chapter 12 we discussed nucleophilic substitution at the carbonyl group, this sort of thing.

The phenyl and carbonyl groups remain in the molecule but the Cl group is replaced by the NH_2 group. We called the molecule of ammonia (NH_3) the **nucleophile** and the chloride was called the **leaving group**. In this chapter we shall be looking at similar reactions at saturated carbon atoms, this sort of thing.

During this reaction, the methyl group remains the same and so does the CH_2 group, but the Cl group is replaced by the PhS group: it is a **substitution reaction**. The reaction happens at the CH_2 group—a *saturated* carbon atom—so the reaction is a **nucleophilic substitution at a saturated carbon atom**. This reaction and the one above may look superficially the same but they are quite different. We also changed the reagent for the substitution at a saturated carbon, because NH_3 would not give a good yield of $MeCH_2NH_2$ in the second type of reaction. The requirements for good reagents are different in substitution at the carbonyl group and at saturated carbon.

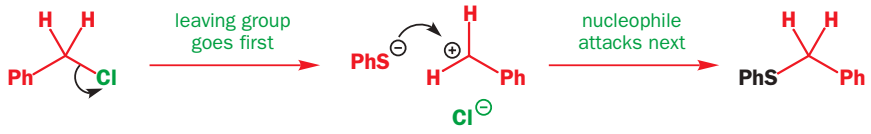
The main change is, of course, the absence of the carbonyl group. Mechanistically this is an enormous difference. The mechanism for the first reaction is:

mechanism of nucleophilic substitution at the carbonyl group

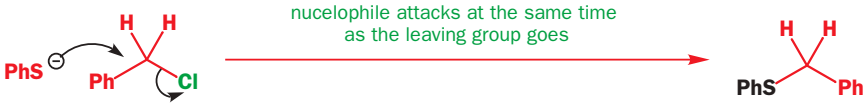


It is immediately obvious that the first step is no longer possible at a saturated carbon atom. The electrons cannot be added to a π bond as the CH_2 group is fully saturated. The nucleophile cannot add first and the leaving group go later because this would give a 5-valent carbon atom. Two new and different mechanisms become possible. Either the leaving group goes first and the nucleophile comes in later, or the two events happen at the same time. The first of these possibilities you will learn to call the **S_N1 mechanism**. The second mechanism, which shows that the only way the carbon atom can accept electrons is if it loses some at the same time, you will learn to call the **S_N2 mechanism**. You will see later that both mechanisms are possible here.

the S_N1 mechanism



the S_N2 mechanism



We shall spend some time looking at the differences between these mechanisms. But first we must establish how we know that there are two mechanisms.

If we look at a commonly used nucleophilic substitution, the replacement of OH by Br, we find that two quite different reaction conditions are used. Tertiary alcohols react rapidly with HBr to give tertiary alkyl bromides. Primary alcohols, on the other hand, react only very slowly with HBr and are usually converted to primary alkyl bromides with PBr_3.

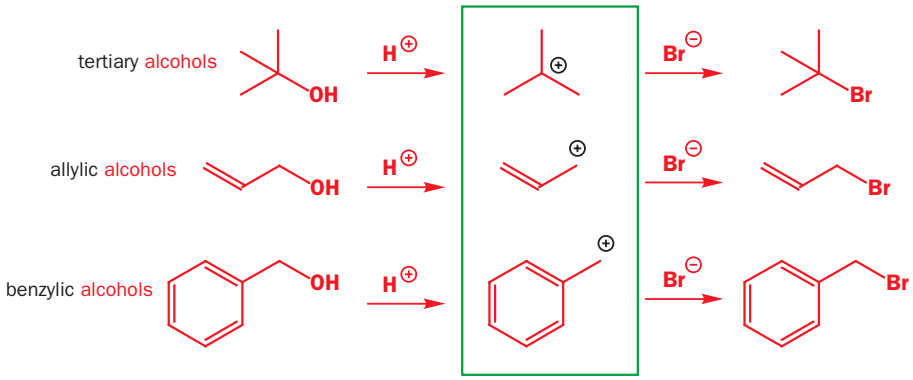
■ The mechanism of the PBr_3 reaction will be discussed when we come to S_N2 reactions later in this chapter.

t-butanol (2-methylpropan-2-ol) → *t*-butyl bromide (2-bromo-2-methylpropane)

n-BuOH (butan-1-ol) → *n*-BuBr (1-bromobutane)

If we collect together those alcohols that react rapidly with HBr to give good yields of alkyl bromides, we find one thing in common: they can all form stable carbocations, that is, cations where the positive charge is on the carbon atom.

alcohols that react rapidly with HBr



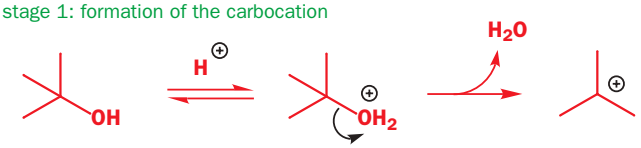
▶ **Carbocation stability**

These carbocations are *relatively* stable as far as carbocations go. But you would not be able to keep even these 'stable' carbocations in a bottle on the shelf. The concept of more and less stable carbocations is important in understanding the S_N1 reaction.

They *can* form carbocations, but *do* they? It is one thing to suggest the existence of a reactive intermediate, another to prove that it is formed. We shall spend some time showing that carbocations do really exist in solution and more time showing that they are indeed intermediates in this mechanism for substitution that you will learn to call the S_N1 mechanism.

the S_N1 mechanism for nucleophilic substitution at saturated carbon

stage 1: formation of the carbocation

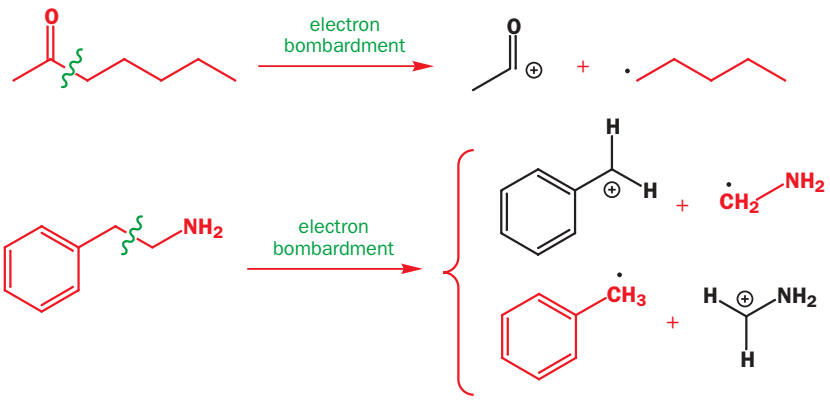


stage 2: capture of the carbocation by the nucleophile

Structure and stability of carbocations

We shall break off this mechanistic discussion to establish the nature of carbocations as ions that can be isolated and as intermediates in substitution reactions. We have seen in Chapter 3 that cations can easily be made in the gas phase by electron bombardment. We met these cations among others.

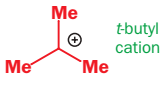
carbocations formed in the mass spectrometer

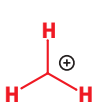


We also met the unusual cation CH_5^+. This cation shares *eight* electrons among five bonds and has a full outer shell like that of the ammonium ion NH_4^+. We call CH_5^+ a **carbonium** ion. The three ions formed in the mass spectrometer have only *three* bonds to the positively charged centre, only *six* electrons in the outer shell, and are electron-deficient. We call these ions **carbenium** ions and we may call both types **carbocations**. Table 17.1 gives a summary of the two types of carbocations.

It is the carbenium ions that interest us in this chapter because they are the intermediates in some nucleophilic substitutions. The simplest possible carbenium ion would be CH_3^+, the methyl cation, and it would be planar with an empty p orbital.

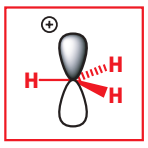
Table 17.1 Carbocations: carbenium ions and carbonium ions

Property	Carbenium ions	Carbonium ions
number of bonds to C^+	3	5
electrons in outer shell	6	8
empty orbital?	yes, a p orbital	no
electron-deficient?	yes	no
example	 *t*-butyl cation	 CH_5^+



methyl cation

planar trigonal sp^2 carbon atom



empty p orbital

two electrons in each C–H bond

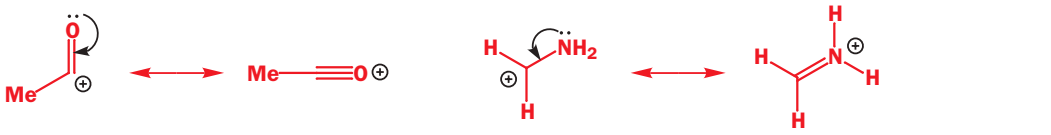
▶ **Carbocation stability**

Avoid any controversy by calling all cations where the charge is on a carbon atom *carbocations*.

an acylium ion

We did not meet this cation when we were discussing mass spectra, but we did meet the three ions on p. 000. The methyl cation is so unstable that it is rarely formed even in the gas phase. Each of these three ions are formed because they have extra stabilization of some sort. The first is an acylium ion which is actually linear with most of the positive charge on the oxygen atom. It is more an oxonium ion than a carbocation. The third ion also has the positive charge carried by a heteroatom—this time it is nitrogen and the cation is more stable. It is much better to have a positive charge on nitrogen than on carbon. Notice that in both of the 'preferred representations' no atom is electron-deficient: all of the C, N, and O atoms have eight electrons.

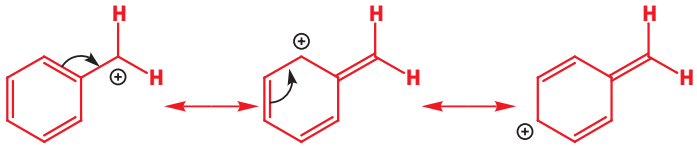
octahedra



this is a better representation because it shows the true linear shape of the cation

this is a better representation because it shows the true trigonal shape of the nitrogen atom

The second ion has no heteroatom but it has a benzene ring and the positive charge is delocalized around the ring, especially into the 2- and the 4- positions.



Thus, none of these three ions is a simple carbenium ion with the charge localized on an electron-deficient carbon atom. Most stable carbocations have extra stabilization of this sort. But even these relatively stable cations cannot be detected in normal solutions by NMR. This is because they are so reactive that they combine with even weak nucleophiles like water or chloride ions. Yet due to Olah's discovery of superacid (also called 'magic acid') in the 1960s we know that carbocations can exist in solution (you can read about this in the box). But are they formed as intermediates in substitution reactions?

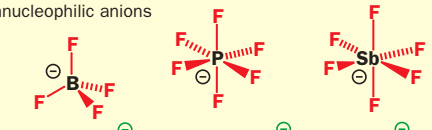
■

George Olah was born in Hungary in 1927 but emigrated to the USA and did most of his work at Case Western Reserve University in Ohio. He got the Nobel prize for his work on cations in 1994. He now works at the University of Southern California.

Stable carbocations in superacid media

Olah's idea was to have a solution containing no nucleophiles. This sounds a bit tricky as any cation must have an anion to balance the charge and surely the anion will be a nucleophile? Well, nearly all anions are nucleophiles but there are some that consist of a negatively charged atom surrounded by tightly held halogen atoms. Examples include BF_4^-, PF_6^-, and SbF_6^-. The first is small and tetrahedral and the others are larger and octahedral.

nonnucleophilic anions

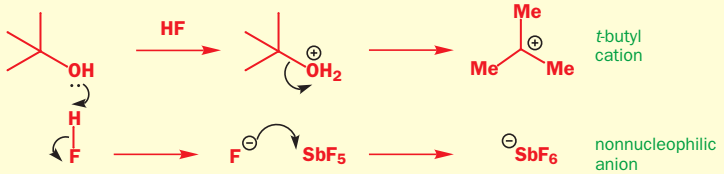


tetrahedral BF_4^- octahedral PF_6^- and SbF_6^-

In these anions, the fluorine atoms are very tightly held around the central atom, which carries the formal negative charge. The negative charge does not correspond to a lone pair of electrons (cf. the role of $NaBH_4$ in carbonyl reductions) and so there is nothing to act as a nucleophile. It was important too to have a nonnucleophilic solvent and low temperatures, and liquid SO_2 at –70 °C proved ideal.

With these conditions, Olah was able to make carbocations from alcohols. He treated *t*-butanol with SbF_5 and HF in liquid SO_2. This is the reaction.

Olah's preparation of the *t*-butyl cation in liquid SO_2

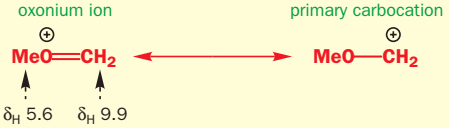


t-butyl cation

nonnucleophilic anion

The proton NMR of this cation showed just one signal for the three methyl groups at 4.15 p.p.m., quite far downfield for C–Me groups. The ^{13}C spectrum also showed downfield Me groups at 47.5 p.p.m., but the key evidence was the shift of the central carbon atom, which came at an amazing 320.6 p.p.m., way downfield from anything we have met before. This carbon is very deshielded—it is positively charged and electron-deficient.

More important data were NMR spectra: both ^1H and ^{13}C NMRs could be run in liquid SO_2 at –70 °C. The proton NMR of the $MeOCH_2$ cation showed a methyl group with a large downfield shift and a CH_2 group that resembled an electron-deficient alkene rather than a saturated carbon atom. The cation is delocalized but the oxonium ion representation is better.



oxonium ion primary carbocation

δ_H 5.6 δ_H 9.9

Carbocations do exist in solution!

Under these conditions acylium ions were also stable and their IR spectra could be run. Even crystals could be prepared so that no doubt remains that these are oxonium ions: both the bond length and the CO stretch are more triple-bond-like than carbon monoxide (see Table 17.2).

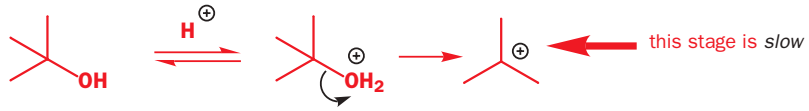
Table 17.2 Does the acylium ion have a triple bond?

	acylium ion Me—C≡O⊕	carbon monoxide ⊖C≡O⊕
ν_{CO}, cm^{-1}	2294	2170
CO bond length, Å	1.108	1.128

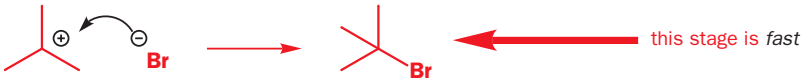
If we mix *t*-BuOH and HBr in an NMR tube and let the reaction run inside the NMR machine, we see no signals belonging to the cation. This proves nothing. We would not expect a reactive intermediate to be present in any significant concentration. There is a simple reason for this. If the cation is unstable, it will react very quickly with any nucleophile around and there will never be any appreciable amount of cation in solution. Its rate of formation will be less, much less, than its rate of reaction. We need only annotate the mechanism you have already seen.

the S_N1 mechanism for nucleophilic substitution at saturated carbon

stage 1: formation of the carbocation



stage 2: capture of the carbocation by the nucleophile



It is comforting that carbocations can be prepared, even under rather artificial conditions, but we shall need other kinds of evidence to convince ourselves that they are intermediates in substitution reactions. It is time to return to the mechanistic discussion.

The S_N1 and S_N2 mechanisms for nucleophilic substitution

The evidence that convinced chemists about these two mechanisms is kinetic: it relates to the rate of the reactions. It was discovered, chiefly by Hughes and Ingold in the 1930s, that some nucleophilic substitutions are first-order, that is, the rate depends only on the concentration of the alkyl halide and *does not depend on the concentration of the nucleophile*, while in other reactions the rate depends on the concentrations of *both* the alkyl halide and the nucleophile. How can we explain this result? In the S_N2 mechanism there is just one step.

■ Edward David Hughes (1906–63) and Sir Christopher Ingold (1893–1970) worked at University College, London in the 1930s. They first thought of many of the mechanistic ideas that we now take for granted.

the S_N2 mechanism: reaction of *n*-BuBr with hydroxide ion

This step must therefore be the **rate-determining step**, sometimes called the slow step. The rate of the overall reaction depends only on the rate of this step. Kinetic theory tells us that the rate of a reaction is proportional to the concentrations of the reacting species such that

$$\text{rate of reaction} = k[n\text{-BuBr}][HO^-]$$

■ There is more about the relationship between reaction rates and mechanisms in Chapter 13.

Quantities in square brackets represent concentrations and the proportionality constant k is called the rate constant. If this mechanism is right, then the rate of the reaction will be simply and linearly proportional to both [*n*-BuBr] and to [HO^-]. And it is. Ingold measured the rates of reactions like these and found that they were second-order (proportional to two concentrations) and he called this mechanism Substitution, Nucleophilic, 2nd Order or S_N2 for short. The rate equation is usually given like this, with k_2 representing the second-order rate constant.

$$\text{rate} = k_2[n\text{-BuBr}][HO^-]$$

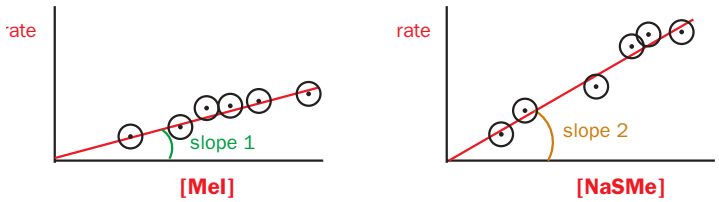
▶ Please note how this symbol is written. The S and the N are both capitals and the N is a subscript.

Usefulness and significance of the rate expression

Now what use is this equation and what does it signify? It is useful because it gives us a test for the S_N2 mechanism. It is usually carried out by varying both the concentration of the nucleophile and the concentration of the carbon electrophile in two separate series of experiments. The results of these experiments would be plotted on two graphs, one for each series. Supposing we wished to see if

the reaction between NaSMe (an ionic solid—the nucleophile will be the anion MeS^-) and MeI were indeed S_N2 as we would expect.

First, we would keep the concentration of NaSMe constant and vary that of MeI and see what happened to the rate. Then we would keep the concentration of MeI constant and vary that of MeSNa and see what happened to the rate. If the reaction is indeed S_N2 we should get a linear relationship in both cases.



▶ Each point on the slope represents a different experiment in which the rate of reaction is measured at a certain concentration of each of the reagents. All the points on the left-hand graph are measured with the concentration of NaSMe the same, but with different concentrations of MeI. On the right-hand graph, the points are measured with the concentration of MeI the same, but with different concentrations of NaSMe.

The first graph tells us that the rate is proportional to [MeI], that is, rate = k_a[MeI] and the second graph that it is proportional to [MeSNa], that is, rate = k_b[MeSNa]. But why are the slopes different? If you look at the rate equation for the reaction, you will see that we have incorporated a constant concentration of one of the reagents into what appears to be the rate constant for the reaction. The true rate equation is

$$\text{rate} = k_2[\text{MeSNa}][\text{MeI}]$$

If [MeSNa] is constant, the equation becomes

$$\text{rate} = k_a[\text{MeI}] \text{ where } k_a = k_2[\text{MeSNa}]$$

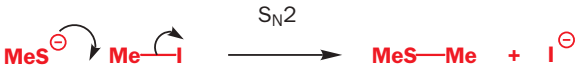
If [MeI] is constant, the equation becomes

$$\text{rate} = k_b[\text{MeSNa}] \text{ where } k_b = k_2[\text{MeI}]$$

If you examine the graphs you will see that the slopes are different because

$$\text{slope 1} = k_a = k_2[\text{MeSNa}], \text{ but slope 2} = k_b = k_2[\text{MeI}]$$

We can easily measure the true rate constant k_2 from these slopes because we know the constant values for [MeSNa] in the first experiment and for [MeI] in the second. The value of k_2 from both experiments should be the same! The mechanism for this reaction is indeed S_N2: the nucleophile MeS^- attacks as the leaving group I^- leaves.



So the usefulness of the rate equation is that it gives us a test for the S_N2 mechanism. But the equation has a meaning beyond that test.

Significance of the S_N2 rate equation

The significance of the equation is that performance of the S_N2 reaction depends both on nucleophile and on the carbon electrophile. We can make a reaction go better by changing either. If we want to displace I^- from MeI by an oxygen nucleophile we might consider using any of those in Table 17.3.

Table 17.3 Oxygen nucleophiles in the S_N2 reaction

Oxygen nucleophile	pK_a of conjugate acid[a]	Rate in S_N2 reaction
HO^-	15.7 (H_2O)	fast
RCO_2^-	about 5 (RCO_2H)	reasonable
H_2O	–1.7 (H_3O^+)	slow
RSO_2O^-	0 (RSO_2OH)	slow

[a] See Chapter 8 for discussion of pK_a values.

The same reasons that made hydroxide ion basic (chiefly that it is unstable as an anion and therefore reactive!) make it a good nucleophile. Basicity is just nucleophilicity towards a proton and nucleophilicity towards carbon must be related. You saw in Chapter 12 that nucleophilicity towards the carbonyl group is directly related to basicity. The same is not quite so true for nucleophilic attack on the saturated carbon atom as we shall see, but there is a relationship nonetheless. So if we want a fast reaction, we should use NaOH rather than, say, Na_2SO_4 to provide the nucleophile.

But that is not our only option. The reactivity and hence the structure of the carbon electrophile matter too. If we want reaction at a methyl group we can't change the carbon skeleton, but we can change the leaving group. Table 17.4 shows what happens if we use the various methyl halides in reaction with NaOH.

Table 17.4 Halide leaving groups in the S_N2 reaction

Halide X in MeX	pK_a of conjugate acid HX	Rate of reaction with NaOH
F	+3	very slow indeed
Cl	–7	moderate
Br	–9	fast
I	–10	very fast

Thus the fastest reaction will be between MeI and NaOH and will give methanol.

We shall discuss nucleophilicity and leaving group ability in more detail later. For the moment, the most important aspect is that the rate of an S_N2 reaction depends on both the nucleophile and the carbon electrophile (and hence the leaving group). Changing the nucleophile or the electrophile changes the value of k_2.

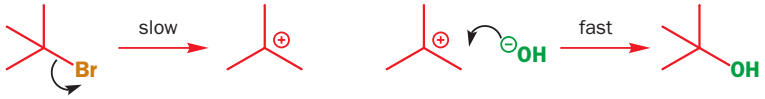
- **The rate of an S_N2 reaction depends upon:**
  - **The nucleophile**
  - **The carbon skeleton**
  - **The leaving group**

It also depends, as do all reactions, on factors like temperature and solvent.

Kinetics for the S_N1 reaction

We shall start with a similar reaction to the S_N2 reaction discussed a few pages back, but we shall replace *n*-butyl bromide with tertiary butyl bromide (*t*-BuBr).

the S_N1 mechanism: reaction of *t*-BuBr with hydroxide ion



stage 1: formation of the carbocation stage 2: reaction of the carbocation

The formation of the cation is the rate-determining step. You can look at this in two ways. Either you could argue that a cation is an unstable species and so it will be formed slowly from a stable neutral organic molecule, or you could argue that the cation is a very reactive species and so all its reactions will be fast, regardless of the nucleophile. Both arguments are correct. In a reaction with an unstable intermediate, the formation of that intermediate is usually the rate-determining step.

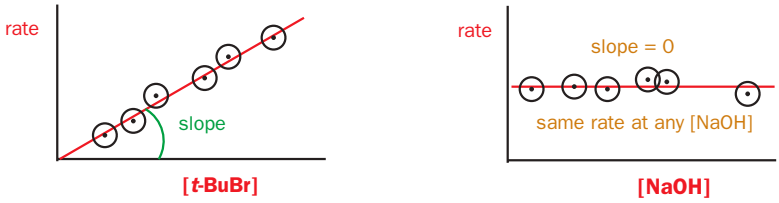
The rate of disappearance of *t*-BuBr is simply the rate of the slow step. This is why the slow step is called the 'rate-determining' step. It is a unimolecular reaction with the simple rate equation

$$\text{rate} = k_1[t\text{-BuBr}]$$

If this is not obvious to you, think of a crowd of people trying to leave a railway station (such as a metro or underground station in a city) through the turnstiles. It doesn't matter how fast they walk away afterwards, it is only the rate of struggling through the turnstiles that determines how fast they leave the station.

Once again, this rate equation is useful because we can determine whether a reaction is S_N1 or S_N2. We can plot the same graphs as we plotted before. If the reaction is S_N2, the graphs look like

those we have just seen. But if it is S_N1, they look like this when we vary [*t*-BuBr] at constant [NaOH] and then vary [NaOH] at constant [*t*-BuBr].



The slope of the first graph is simply the first-order rate constant because

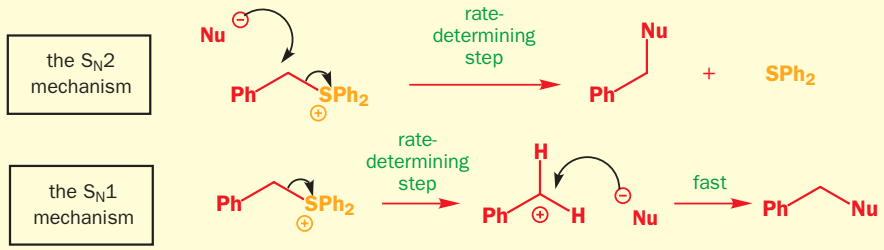
$$\text{rate} = k_1[t\text{-BuBr}]$$

But the slope of the second graph is zero! The rate-determining step does not involve NaOH so adding more of it does not speed up the reaction. The reaction shows first-order kinetics (the rate is proportional to one concentration only) and the mechanism is called S_N1, that is, Substitution, Nucleophilic, 1st order.

This observation is very significant. It is not only the *concentration* of the nucleophile that doesn't matter—its *reactivity* doesn't matter either! We are wasting our time adding NaOH to this reaction—water will do just as well. All the oxygen nucleophiles in Table 17.3 react at the *same* rate with *t*-BuBr though they react at very different rates with MeI.

Stereoisomers and constitutional isomers

We can see the changeover from S_N1 to S_N2 in the reactions of a single compound if we choose one that is good at both mechanisms, such as a benzyl sulfonium salt. Both mechanisms are available for this compound.



Weak nucleophiles react by the S_N1 mechanism while strong ones react by S_N2. We can tell which is which simply by looking at the rates of the reactions (see Table 17.5).

The first three nucleophiles react at the same rate within experimental error while the last two are clearly faster. The first three nucleophiles react at the same rate because they react by the S_N1 mechanism whose rate does not depend on the nucleophile. All the nucleophiles in fact react by S_N1 at the same rate (about 4.0×10^{-5} s^{-1}) but good nucleophiles also react by S_N2. The S_N2 rate for hydroxide is about 70 and for PhS^- about 107. Compare these relative rates with those in Table 17.6 for reactions with MeBr where they all react at different rates by the S_N2 reaction.

Table 17.5 Rate of reaction (10^5k, s^{-1}) of nucleophiles with $PhCH_2S^+Ph_2$

Nucleophile	AcO^-	Cl^-	PhO^-	HO^-	PhS^-
rate	3.9	4.0	3.8	74	107

Table 17.6 Relative rate of reaction (water = 1) of nucleophiles with MeBr

Nucleophile	AcO^-	Cl^-	PhO^-	HO^-	PhS^-
rate	900	1100	2000	1.2×10^4	5×10^7

How can we decide which mechanism (S_N1 or S_N2) will apply to a given organic compound?

The most important factor is the structure of the carbon skeleton. A helpful generalization is that compounds that can form relatively stable cations generally do so and react by the S_N1 mechanism while the others have to react by the S_N2 mechanism.

In fact, the structural factors that make cations unstable also lead to faster S_N2 reactions. Cations are more stable if they are heavily substituted, that is, tertiary, but this is bad for an S_N2 reaction because the nucleophile would have to thread its way into the carbon atom through the alkyl groups. It is better for an S_N2 reaction if there are only small hydrogen atoms on the carbon atom—methyl groups react fastest by the S_N2 mechanism. The effects of the simplest structural variations are summarized in Table 17.7 (where R is a simple alkyl group like methyl or ethyl).

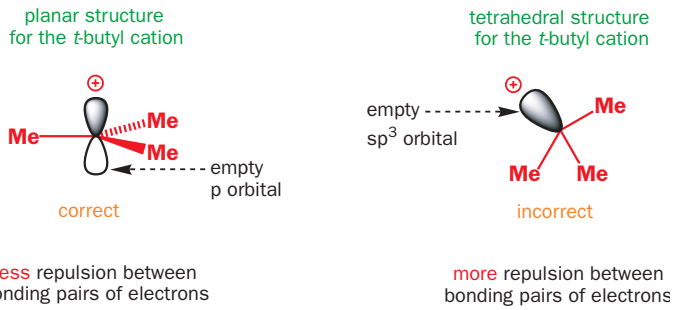
Table 17.7 Simple structures and choice of S_N1 or S_N2 mechanism

structure	Me—X	R, X, H, H	R, X, H, R	R, X, R, R
type	methyl	primary	secondary	tertiary
S_N1 reaction?	no	no	yes	good
S_N2 reaction?	good	good	yes	no

The only doubtful case is the secondary alkyl derivative, which can react by either mechanism, though it is not very good at either. The first question you should ask when faced with a new nucleophilic substitution is: 'Is the carbon electrophile methyl, primary, secondary, or tertiary?' This will start you off on the right foot, which is why we introduced these important structural terms in Chapter 2.

Stability and structure of tertiary carbocations

So why are tertiary cations relatively stable whereas the methyl cation is never formed in solution? Any charged organic intermediate is inherently unstable because of the charge. A carbocation can be formed only if it has some extra stabilization. The *t*-butyl cation that we met earlier in this chapter is planar. Indeed it is a universal characteristic of carbocations that they are planar. The basic instability of the carbocation comes from its electron deficiency—it has an empty orbital. The energy of the unfilled orbital is irrelevant to the overall stability of the cation—it's only the energy of the orbitals with electrons in that matter. For any cation the most stable arrangement of electrons in orbitals results from making filled orbitals as low in energy as possible to give the most stable structure, leaving the highest-energy orbital empty. Thus, of the two structures for the *t*-butyl cation, the planar one has the lower-energy filled orbitals (sp^2) and a higher-energy empty p orbital while the tetrahedral one has higher-energy filled orbitals (sp^3) and a lower-energy empty sp^3 orbital.



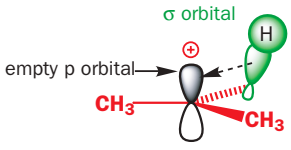
The diagram shows another reason why the planar structure is more stable than the tetrahedral structure for a carbocation. It is better for the filled orbitals to be:

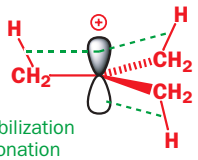
- of the lowest possible energy (so that they contribute most to stability)
- as far from each other as possible (so that they repel each other as little as possible)

Both requirements are fulfilled in the planar structure for the carbocation.

Stabilization of tertiary carbocations by C–H or C–C bonds

Extra stabilization comes to the planar structure from weak donation of σ bond electrons into the empty p orbital of the cation. Three of these donations occur at any one time in the *t*-butyl cation. It

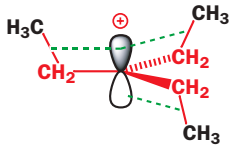




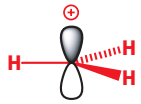
extra stabilization from σ donation into empty p orbital of planar carbocation

doesn't matter if the C–H bonds point up or down; one C–H bond on each methyl group must be parallel to one lobe of the empty p orbital at any one time. The top diagram shows one overlap in orbital terms and the bottom diagram three as dotted lines.

There is nothing special about the C–H bond in donating electrons into an empty orbital. A C–C bond is just as good and some bonds are much better (C–Si). But there must be a bond of some sort—a hydrogen atom by itself has no lone pairs and no σ bonds so it cannot stabilize a cation.



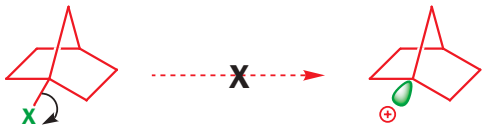
extra stabilization from σ donation into empty p orbital of planar carbocation



no stabilization: no electrons to donate into empty p orbital
note: The C–H bonds are at 90° to the empty p orbital and cannot interact with it

▶ Many textbooks say that alkyl groups are fundamentally electron-donating and thus stabilize cations. This statement does contain some truth but it is important to understand the way in which they really donate electrons—weakly by σ conjugation into empty p orbitals.

If a tertiary cation cannot become planar, it is not formed. A classic case is the cage halide below, which does not react with nucleophiles either by S_N1 or by S_N2. It does not react by S_N1 because the cation cannot become planar nor by S_N2 because the nucleophile cannot approach the carbon atom from the right direction (see below).



carbocation would have to be tetrahedral

In almost all cases, tertiary alkyl halides react rapidly with nucleophiles by the S_N1 mechanism. The nature of the nucleophile is not important: it does not affect the rate and carbocations are reactive enough to combine with even quite weak nucleophiles.

Allylic and benzylic cations

■ We discussed conjugation in allyl cations in Chapter 7.

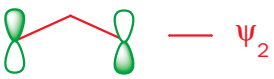
More effective stabilization is provided by genuine conjugation with π or lone-pair electrons. The allyl cation has a filled (bonding) orbital containing two electrons delocalized over all three atoms and an important empty orbital with coefficients on the end atoms only. It's this orbital that is attacked by nucleophiles and so it's the end carbon atoms that are attacked by nucleophiles. The normal curly arrow picture tells us the same thing.

the allyl cation

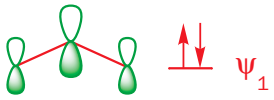
curly arrows

molecular orbitals

empty nonbonding orbital of the allyl cation



filled bonding orbital of the allyl cation



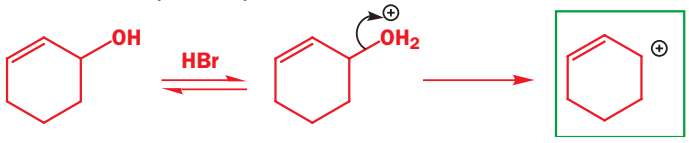
A symmetrical allyl cation can give one product only by the S_N1 reaction. We have already discussed the formation of the cyclohexenyl cation (Chapter 7) and that is a good example. The two delocalized structures are identical and the π bond is shared equally among the three atoms.

the cyclohexenyl cation

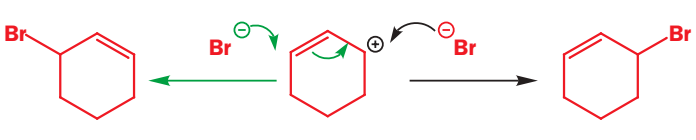
delocalized π bond

Treatment of cyclohexenol with HBr gives the corresponding allylic bromide. Only one compound is formed because attack at either end of the allylic cation gives the same product.

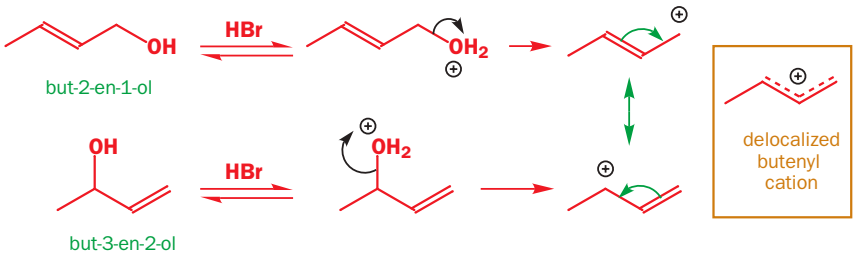
formation of the cyclohexenyl cation



two identical reactions with bromide ion

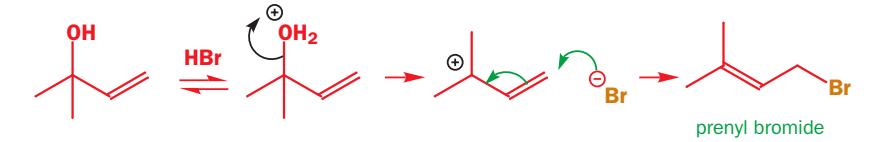


Sometimes when the allylic cation is unsymmetrical this can be a nuisance as a mixture of products may be formed. It doesn't matter which of the two butenols you treat with HBr; you get the same cation.



When this cation reacts with Br^-, about 80% goes to one end and 20% to the other, giving a mixture of butenyl bromides. Notice that we have chosen one localized structure for our mechanisms. The choice is meaningless since the other structure would have done as well. It's just rather too difficult to draw mechanisms on the delocalized structure.

Sometimes this ambiguity is useful. The tertiary allylic alcohol 2-methylbut-3-en-2-ol is easy to prepare and reacts well by the S_N1 mechanism because it is both tertiary and allylic. The allylic carbocation intermediate is very unsymmetrical and reacts only at the less substituted end to give 'prenyl bromide'.

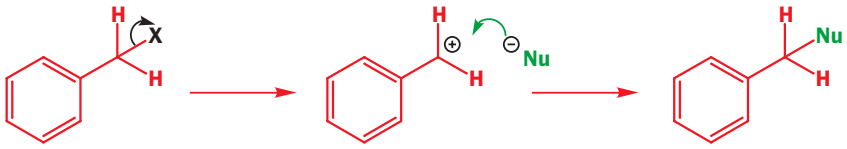


2-methylbut-3-en-2-ol

prenyl bromide
1-bromo-3-methylbut-2-ene

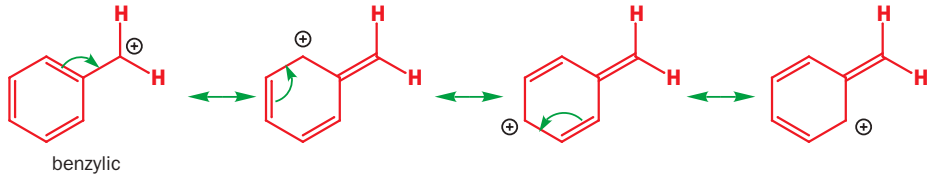
The benzyl cation is about as stable as the allyl cation but lacks its ambiguity of reaction. Though the positive charge is delocalized around the benzene ring, the benzyl cation almost always reacts on the side chain.

formation and reaction of the benzyl cation



If you draw the arrows for the delocalization, you will see that the positive charge is spread right round the ring, to three positions in particular.

delocalization in the benzyl cation



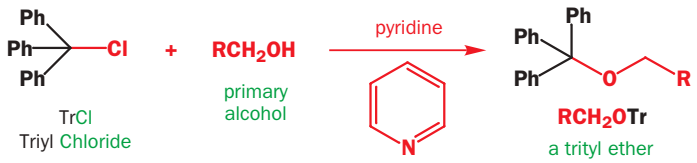
benzylic

An exceptionally stable cation is formed when three benzene rings can help to stabilize the same positive charge. The result is the triphenylmethyl cation or, for short, the trityl cation. The symbol Tr (another of these 'organic elements') refers to the group Ph_3C. Trityl chloride is used to form an ether with a primary alcohol group by an S_N1 reaction. Here is the reaction.

▶ The **regioselectivity** (where the nucleophile attacks) is determined by steric hindrance: attack is faster at the less hindered end of the allylic system.

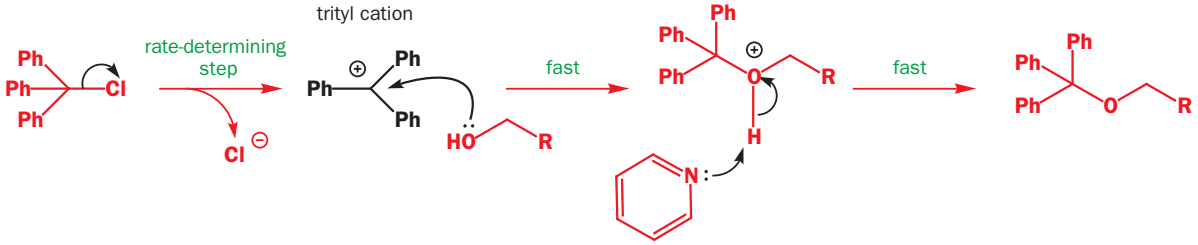
■ Prenyl bromide is a building block for making the class of natural products known as terpenes and discussed in Chapter 49. We come back to reactions of allylic compounds in Chapter 23.

■ This sort of delocalization will be given special importance in Chapter 22



You will notice that pyridine is used as solvent for the reaction. Pyridine (a weak base, pK_a 5.5; see Chapter 8) is not strong enough to remove the proton from the primary alcohol (pK_a about 15), and there would be no point in using a base strong enough to make RCH_2O^- as the neutral alcohol is as good in an S_N1 reaction. Instead the TrCl ionizes first to trityl cation, which now captures the primary alcohol and finally pyridine is able to remove the proton from the oxonium ion. Pyridine does not catalyse the reaction; it just stops it becoming too acidic by removing the HCl formed. Pyridine is also a convenient polar organic solvent for ionic reactions.

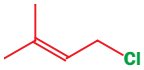
S_N1 formation of trityl ethers:



Rate data for substituted allylic chlorides compared with benzylic chlorides and simple alkyl chlorides on solvolysis in 50% aqueous ethanol give us some idea of the magnitude of stabilization (Table 17.8). These rates are mostly S_N1, but there will be some S_N2 creeping in with the primary compounds. Note the wide range of rates.

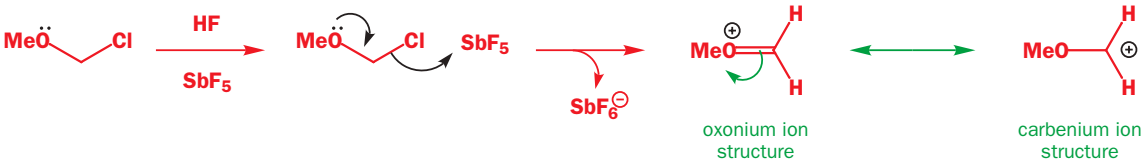
■ A **solvolysis reaction** is a reaction in which the solvent is also the nucleophile.

Table 17.8 Rates of solvolysis of alkyl chlorides in 50% aqueous ethanol at 44.6 °C

Compound	Relative rate	Comments
	0.07	primary chloride: probably all S_N2
	0.12	secondary chloride: can do S_N1 but not very well
	2 100	tertiary chloride: very good at S_N1
	1.0	primary but allylic: S_N1 all right
	91	allylic cation is secondary at one end
	130 000	allylic cation is tertiary at one end: compare with 2100 for simple tertiary
	7 700	primary but allylic and benzylic

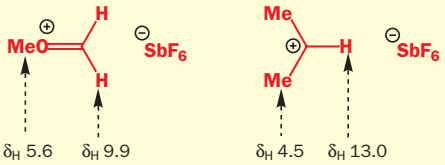
One type of carbocation remains to be discussed, the type with an electron-donating group on the same atom as the leaving group. A classic case is $MeOCH_2Cl$, which loses chloride ion in polar solvents and which can be converted in good yield (89%) to a stable cation using Olah's methods described on p. 000. Even though it is primary (so you might expect S_N2), substitution reactions of

this chloroether, 'methoxymethyl chloride' (or 'MOM chloride') follow the S_N1 mechanism and go via this cation.



The methoxymethyl cation

This cation can be drawn either as an oxonium ion or as a primary carbenium ion. The oxonium ion structure is the more realistic. Primary carbenium ions are not known in solution, let alone as isolable intermediates, and the proton NMR spectrum of the cation compared with that of the isopropyl cation (this is the best comparison we can make) shows that the protons on the CH_2 group resonate at 9.9 p.p.m. instead of at the 13.0 p.p.m. of the true carbenium ion.



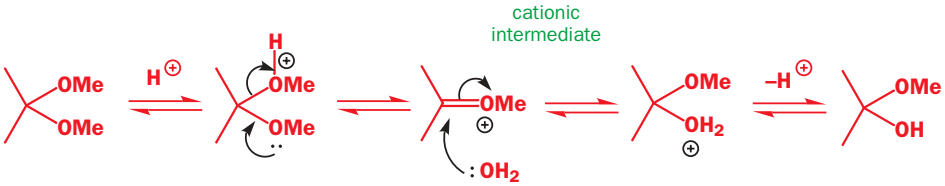
The first step in the hydrolysis of acetals is similar. One alkoxy group is replaced by water to give a hemiacetal.

hydrolysis of acetals – the first step

acetal hemiacetal

We considered the mechanism for this reaction in Chapter 14 but did not then concern ourselves with a label for the first step. It has, in fact, an S_N1 style of rate-determining step: the decomposition of the protonated acetal to give an oxonium ion. If you compare this step with the decomposition of the chloroether we have just described you will see that they are very similar.

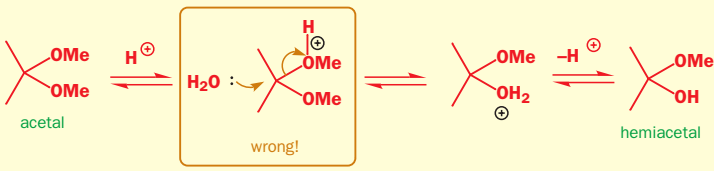
hydrolysis of acetals – S_N1 mechanism for the first step



A common mistake

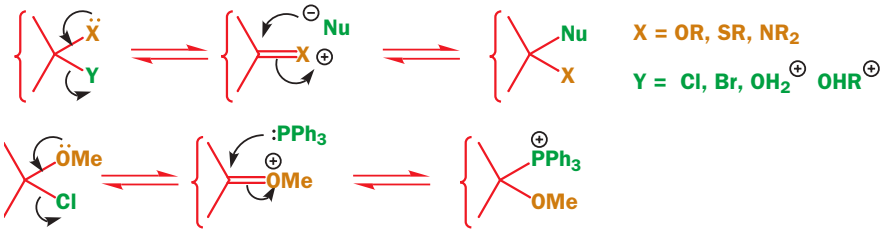
Students of organic chemistry often make a mistake with this mechanism and draw the displacement of the first molecule of methanol by water as an S_N2 reaction.

hydrolysis of acetals – *incorrect* S_N2 mechanism for the first step



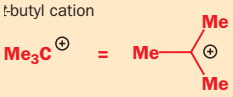
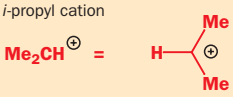
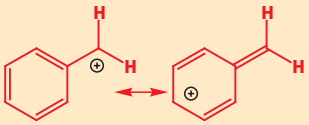
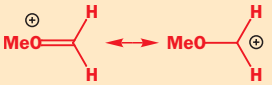
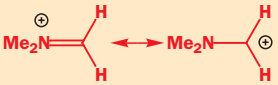
When we discuss the S_N2 reaction shortly you will see that an S_N2 mechanism is unlikely at such a crowded carbon atom. However, the main reason why the S_N2 mechanism is wrong is that the S_N1 mechanism is so very efficient with a neighbouring MeO group. The S_N2 mechanism doesn't get a chance.

This mechanism for the S_N1 replacement of one electronegative group at a carbon atom by a nucleophile where there is another electronegative group at the same carbon atom is very general. You should look for it whenever there are two atoms such as O, N, S, Cl, or Br joined to the same carbon atom. The better leaving groups (such as the halogens) need no acid catalyst but the less good ones (N, O, S) usually need acid. Here is a summary diagram and a specific example.



We now have in Table 17.9 a complete list of the sorts of structures that normally react by the S_N1 mechanism rather than by the S_N2 mechanism.

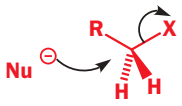
Table 17.9 Stable carbocations as intermediates in S_N1 reactions

Type of cation	Example 1	Example 2
simple alkyl	tertiary (good) *t*-butyl cation 	secondary (not so good) *i*-propyl cation 
conjugated	allylic 	benzylic 
heteroatom-stabilized	oxygen-stabilized(oxonium ions) 	nitrogen-stabilized 

The S_N2 reaction

Small structures that favour the S_N2 reaction

Notice that we said *simple* alkyl groups: of course, primary allylic, benzylic, and RO or R_2N substituted primary derivatives may react by S_N1!



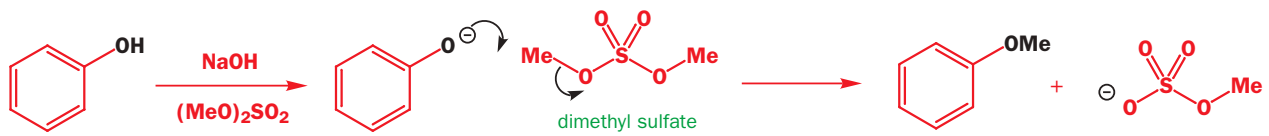
uncluttered approach for nucleophile in S_N2 reactions of methyl compounds (R=H) and primary alkyl compounds (R=alkyl)

Among simple alkyl groups, methyl and primary alkyl groups always react by the S_N2 mechanism and never by S_N1. This is partly because the cations are unstable and partly because the nucleophile can push its way in easily past the hydrogen atoms.

Thus, a common way to make ethers is to treat an alkoxide anion with an alkyl halide. If the alkyl halide is a methyl compound, we can be sure that this will be by the S_N2 mechanism. A strong base, here NaH, will be needed to form the alkoxide ion (Chapter 6) and methyl iodide is a suitable electrophile.

alcohol — alkoxide ion — methyl ether

With phenols, NaOH is a strong enough base and dimethyl sulfate, the dimethyl ester of sulfuric acid, is often used as the electrophile. These variations do not affect the mechanism. As long as we have a good nucleophile (here reactive RO^-), a methyl electrophile, and a good leaving group (here an iodide or a sulfate anion), the S_N2 mechanism will work well.



phenol — dimethyl sulfate — methyl ether — stable sulfate anion is good leaving group

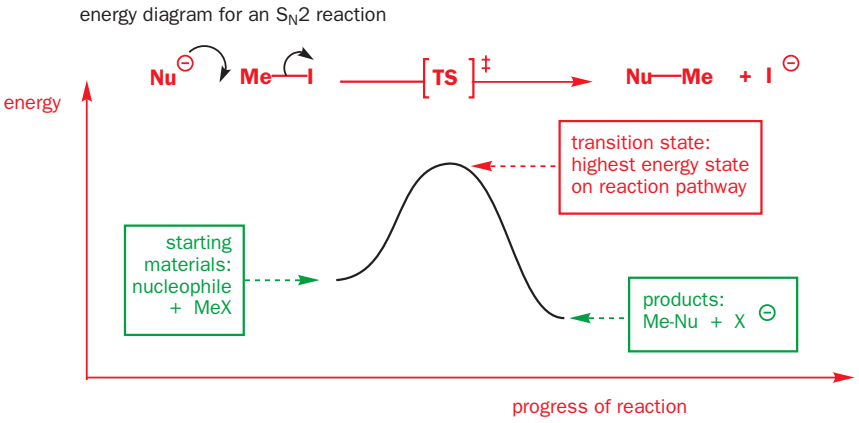
The nature of the nucleophile and the leaving group and the structure of the compound under attack all affect the S_N2 mechanism because its rate expression is

$$\text{rate} = k_2[\text{nucleophile}][\text{MeX}]$$

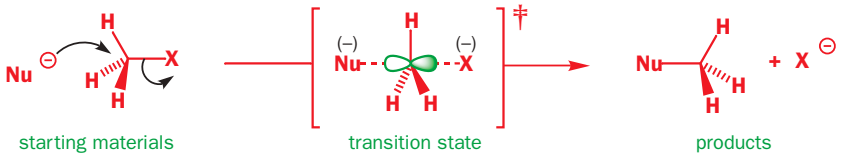
This expression shows that the rate of an S_N2 reaction is proportional both to the concentration of the nucleophile and to the concentration of the alkyl halide (MeX). The alkyl halide combines the carbon skeleton and the leaving group in the same molecule. We must consider all three factors (nucleophile, carbon skeleton, and leaving group) in an S_N2 reaction. So it was worth removing the proton from the alcohol or the phenol in these ether syntheses because we get a better nucleophile that way. We established on p. 000 that this was not worth doing in an S_N1 reaction because the nucleophile is not involved in the rate-determining step.

The transition state for an S_N2 reaction

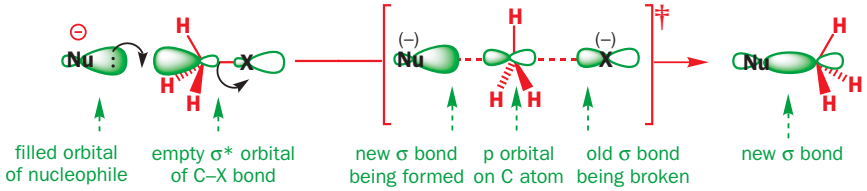
Another way to put this would be to say that the nucleophile, the methyl group, and the leaving group are all present in the transition state for the reaction as explained in Chapter 13. This is the point about halfway through the slow step where the combined reagents reach their highest energy.



A transition state is not an intermediate. It can never be isolated because any change in its structure leads to a lower-energy state. In an S_N2 reaction any molecule at the transition state cannot stay there—it must roll down the slope towards products or back to starting materials. So what does it look like and why are we interested in it? The transition state in an S_N2 reaction is about halfway between the starting materials and the products. The bond to the nucleophile is partly formed and the bond to the leaving group is partly broken. It looks like this.



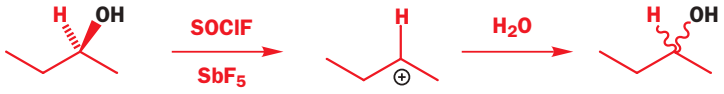
The dashed bonds indicate partial bonds (the C—-Nu bond is partly formed and the C—-X bond partly broken) and the charges in brackets indicate substantial partial charges (about half a minus charge each in this case as they must add up to one!). Transition states are often shown in square brackets and marked with the symbol ‡. Another way to look at this situation is to consider the orbitals. The nucleophile must have lone-pair electrons, which will interact with the σ* orbital of the C–X bond.



In the transition state there is a p orbital at the carbon atom in the middle that shares one pair of electrons between the old and the new bonds. Both these pictures suggest that the transition state for an S_N2 reaction has a more or less planar carbon atom at the centre with the nucleophile and the leaving group arranged at 180° to each other.

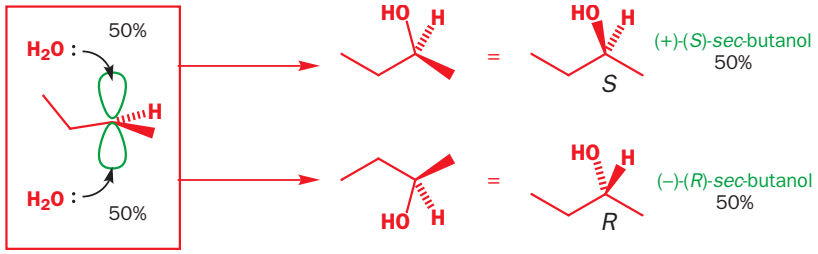
Stereochemistry and substitution

If this is true, it has a very important consequence. The nucleophile attacks the carbon atom on the opposite side from the leaving group and the carbon atom turns inside out as the reaction goes along, just like an umbrella in a high wind. If the carbon atom under attack is a stereogenic centre (Chapter 16), the result will be inversion of configuration. This is easily proved by a simple sequence of reactions. We start by looking at the stereochemistry of an S_N1 reaction.



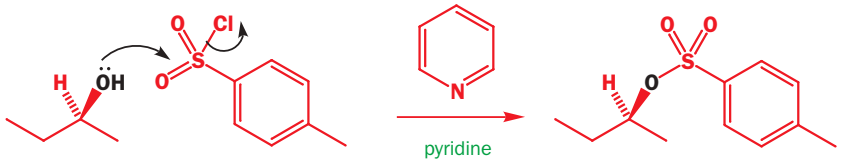
(+)-(*S*)-*sec*-butanol — secondary butyl cation — racemic (±)-*sec*-butanol

Starting with the optically active secondary alcohol *sec*-butanol (or butan-2-ol, but we want to emphasize that it is *secondary*), the secondary cation can be made by the usual method and has a characteristic ^{13}C NMR shift. Quenching this cation with water regenerates the alcohol but without any optical activity. Water has attacked the two faces of the planar cation with exactly equal probability as we described in Chapter 16. The product is an exactly 50:50 mixture of (*S*)-butanol and (*R*)-butanol. It is *racemic*.



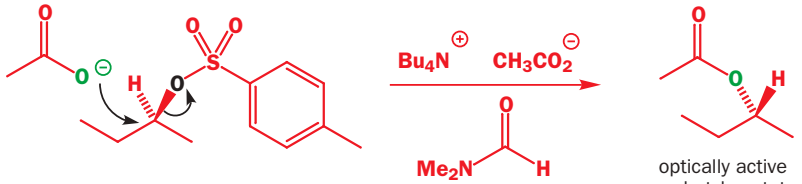
■ TsCl and its synthesis is discussed later in this chapter and in Chapter 22.

If, however, we first make the *para*-toluene sulfonate ('tosylate') by nucleophilic attack of the OH group on the sulfonyl chloride TsCl in pyridine solution, the sulfonate will be formed with retention as no bonds have been formed or broken at the chiral carbon atom. This is a substitution reaction too, but at sulfur rather than at carbon.



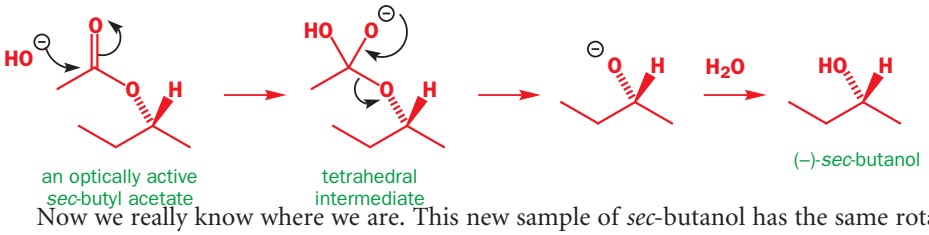
(+)-(*S*)-*sec*-butanol — TsCl *para*-toluene sulfonyl chloride — pyridine — (+)-(*S*)-*sec*-butyl *para*-toluene sulfonate [(+)-(*S*)-*sec*-butyl tosylate]

Now we can carry out an S_N2 reaction on the sulfonate with a carboxylate anion. A *tetra*-alkyl ammonium salt is often used in the polar solvent DMF to get a clean reaction. This is the key step and we don't want any doubt about the outcome.



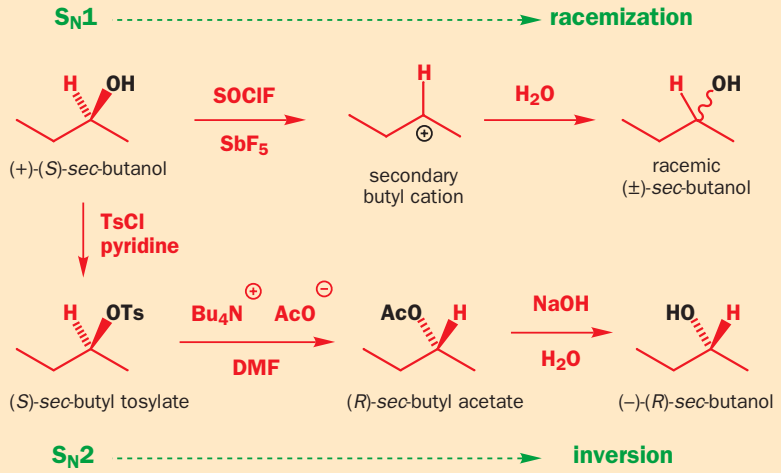
S_N2 reaction — DMF dimethylformamide — optically active *sec*-butyl acetate

The product is optically active and we can measure its rotation. But this tells us nothing. Unless we know the true rotation for pure *sec*-butyl acetate, we don't yet know whether it is optically pure nor even whether it really is inverted. But we can easily find out. All we have to do is to hydrolyse the ester and get the original alcohol back again. We know the true rotation of the alcohol—it was our starting material—and we know the mechanism of ester hydrolysis (Chapter 12)—nucleophilic attack occurs at the carbonyl carbon and retention must be the stereochemical outcome as no reaction occurs at the stereogenic centre.



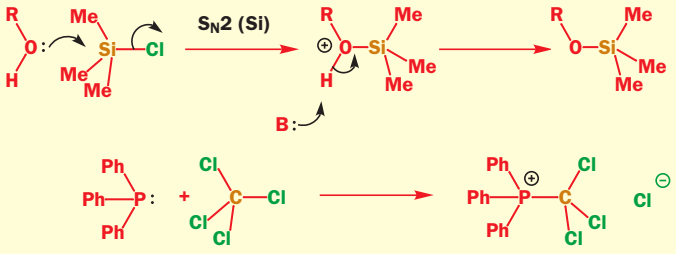
Now we really know where we are. This new sample of *sec*-butanol has the same rotation as the original sample, *but with the opposite sign*. It is (–)-(*R*)-*sec*–butanol. It is optically pure and inverted. Somewhere in this sequence there has been an inversion, and we know it wasn't in the formation of the tosylate or the hydrolysis of the acetate as no bonds are formed or broken at the stereogenic centre in these steps. It must have been in the S_N2 reaction itself.

- **This is a general conclusion.**
  - **The S_N2 reaction goes with inversion of configuration at the carbon atom under attack but the S_N1 reaction generally goes with racemization**



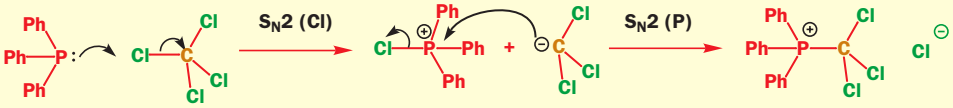
Substitution reactions at other elements

S_N2 reactions can occur at elements other than carbon. Common examples in organic chemistry are silicon, phosphorus, sulfur, and the halogens. The formation of the tosylate above by attack of the alcohol on TsCl is an example of an S_N2 reaction at sulfur. Later in this chapter you will see that alcohols attack phosphorus very easily and that we use the reaction between ROH and PBr_3 to make alkyl bromides. Alcohols also react rapidly with Si–Cl compounds such as Me_3SiCl to give silyl ethers by an S_N2 reaction at silicon. You have already seen several examples of silyl ether formation (p. 000, for example), though up to this point we have not discussed the mechanism. Here it is: B: represents a base such as triethylamine.



For an example of an S_N2 reaction at chlorine we can choose a reaction we will need later in the book. Triphenyl phosphine reacts with CCl_4 to give a phosphonium salt by what looks like an S_N2 reaction at carbon.

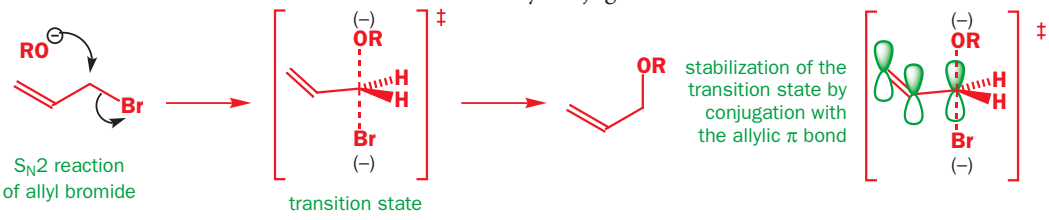
In fact there is no room around the carbon atom of CCl_4 for any nucleophile, let alone such a large one as PPh_3 and the reaction occurs by two separate S_N2 steps: one at chlorine and one at phosphorus.



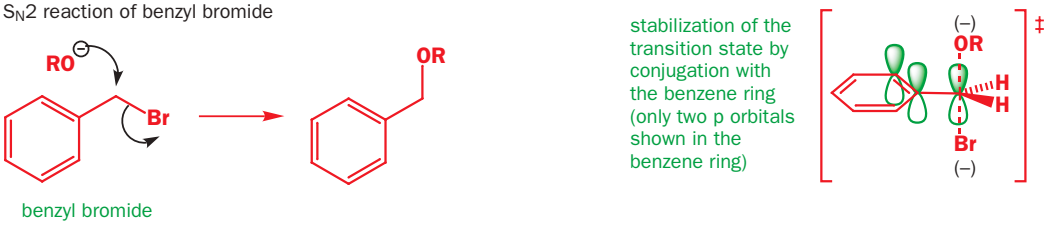
Structural variation and the S_N2 mechanism

We have already established that methyl and primary alkyl compounds react well by the S_N2 mechanism, while secondary alkyl compounds *can* do so. There are other important structural features that also encourage the S_N2 mechanism. Two, allyl and benzyl compounds, also encourage the S_N1 mechanism.

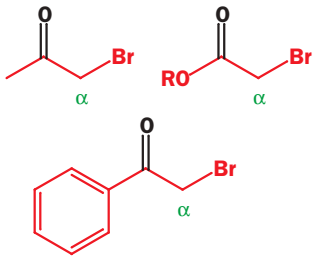
Here you see a typical S_N2 reaction of allyl bromide. We have drawn the transition state for this reaction. This is not because we want to encourage you to do this for all S_N2 reactions but so that we can explain the role of the allyl system. Allyl compounds react rapidly by the S_N2 mechanism because the double bond can stabilize the transition state by conjugation.



The benzyl group acts in much the same way using the π system of the benzene ring for conjugation with the p orbital in the transition state.

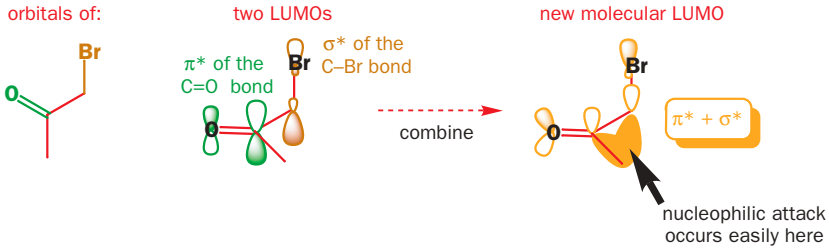


Reactive α-bromo carbonyl compounds



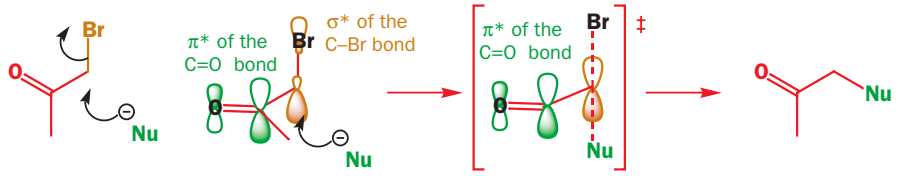
Since the p orbital in question has electrons in it—it shares a pair of electrons with the nucleophile and the leaving group—more effective conjugation is possible with an electron-deficient π bond. The most important example is the carbonyl group: carbon electrophiles like those in the margin give the fastest S_N2 reactions.

With α-bromo carbonyl compounds, substitution leads to two electrophilic groups on neighbouring carbon atoms. Each has a low-energy empty orbital, π* from C=O and σ* from C–Br (this is what makes them electrophilic), and these can combine to form a molecular LUMO (π* + σ*) lower in energy than either. Nucleophilic attack will occur easily where this new orbital has its largest coefficients, shown in orange on the diagram.

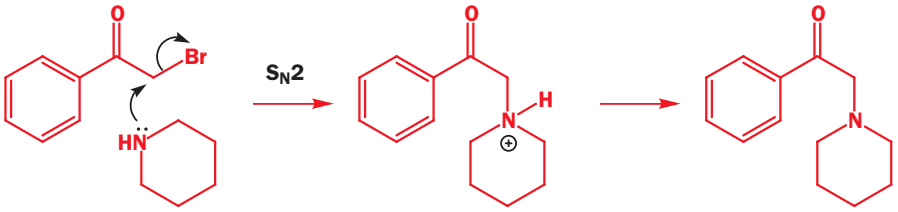


This orange area is on one side of the carbonyl group and in the usual place at the back of the C–Br bond. Each group has become more electrophilic because of the presence of the other—the C=O group makes the C–Br bond more reactive and the Br makes the C=O group more reactive. Another way to put this is that the carbonyl group stabilizes the transition state by overlap of its π* orbital with the full p orbital of the carbon atom under attack. The nucleophile may well attack the carbonyl group but this will be reversible whereas displacement of bromide is irreversible.

transition state for nucleophilic attack on an α-bromo-ketone



There are many examples of this type of reaction. Reactions with amines go well and the amino-ketone products are widely used in the synthesis of drugs.



an amino-ketone

Variation of rate with structure

Some actual data may help at this point. The rates of reaction of the following alkyl chlorides with KI in acetone at 50 °C broadly confirm the patterns we have just analysed. These are relative rates with respect to *n*-BuCl as a 'typical primary halide'. You should not take too much notice of precise figures but rather observe the trends and notice that the vartiations are quite large—the full range from 0.02 to 100 000 is eight powers of ten.

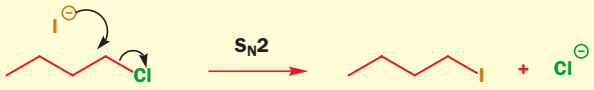
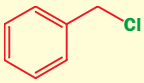
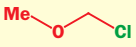
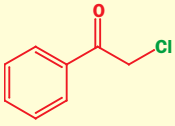


Table 17.10 Relative rates of S_N2 reactions of alkyl chlorides with the iodide ion

Alkyl chloride	Relative rate	Comments
Me—Cl	200	least hindered alkyl chloride
	0.02	secondary alkyl chloride; slow because of steric hindrance
	79	allyl chloride accelerated by π conjugation in transition state
	200	benzyl chloride slightly more reactive than allyl: benzene ring better at π conjugation than isolated double bond
	920	conjugation with oxygen lone pair accelerates reaction
	100 000	conjugation with carbonyl group much more effective than with simple alkene or benzene ring. These α-carbonyl halides are the most reactive of all

Summary of structural variations and nucleophilic substitution

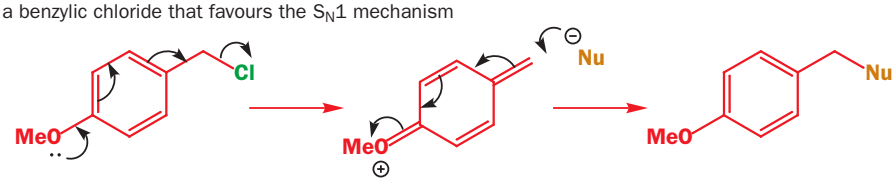
We are now in a position to summarize those effects we have been discussing over the last few pages on both mechanisms. It is simplest to list the structural types and rate each reaction qualitatively.

Table 17.11 Structural variations for the S_N1 and S_N2 reactions

Type of electrophilic carbon atom	S_N1 reaction	S_N2 reaction
methyl (CH_3–X)	no	very bood
primary alkyl (RCH_2–X)	no	good
secondary alkyl (R_2CH–X)	yes	yes
tertiary alkyl (R_3C–X)	very good	no
allylic (CH_2=CH–CH_2–X)	yes	good
benzylic ($ArCH_2$–X)	yes	good
α-carbonyl (RCO·CH_2–X)	no	excellent
α-alkoxy (RO·CH_2–X)	excellent	good
α-amino (R_2N·CH_2–X)	excellent	good

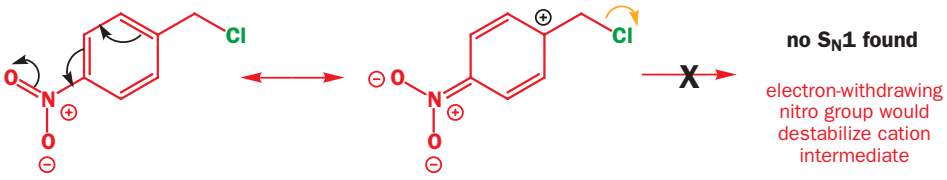
You must not regard this list as fixed and inflexible. The last five types will also be either primary, secondary, or tertiary. If they are primary, as shown, they will favour S_N2 more, but if they are tertiary they will all react by the S_N1 mechanism except the tertiary α-carbonyl (RCO·CR_2–X) compounds, which will still react by the S_N2 mechanism, if rather slowly. If they are secondary they might react by either mechanism. Similarly, a benzylic compound that has a well placed electron-donating group able to make an electronic connection with the leaving group will favour the S_N1 mechanism.

a benzylic chloride that favours the S_N1 mechanism

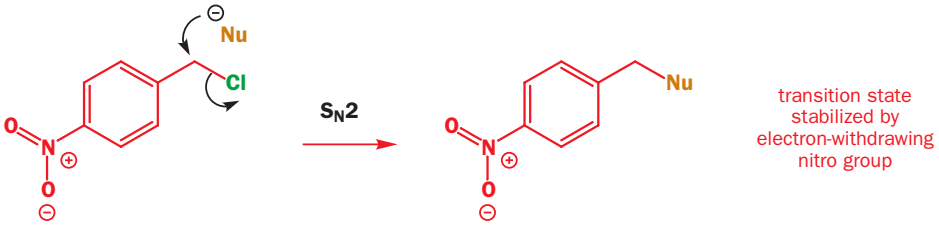


On the other hand, a 4-nitrobenzyl chloride is likely to react by the S_N2 mechanism as the strongly electron-withdrawing nitro group would destabilize the carbocation intermediate of the S_N1 mechanism.

a benzylic chloride that disfavours the S_N1 mechanism



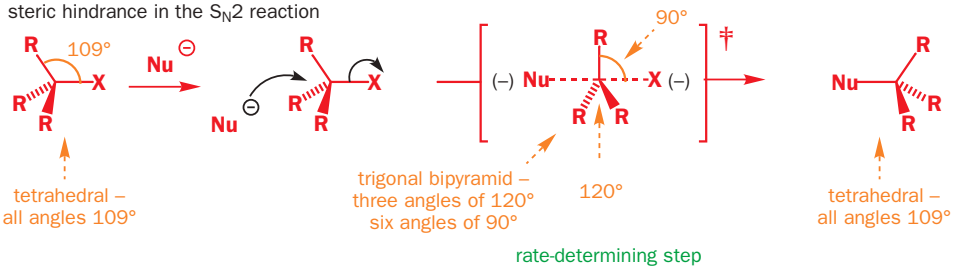
the same benzylic chloride that favours the S_N2 mechanism



▶ Rate measurements for these two compounds are very revealing. We can force them to react by S_N1 by using methanol as the solvent (p. 000). If we set the rate of substitution of the benzyl compound with methanol at 25 °C at 1.0, then the 4-MeO benzyl compound reacts about 2500 times faster and the 4-NO_2 benzyl compound about 3000 times more slowly.

Steric hindrance in nucleophilic substitution

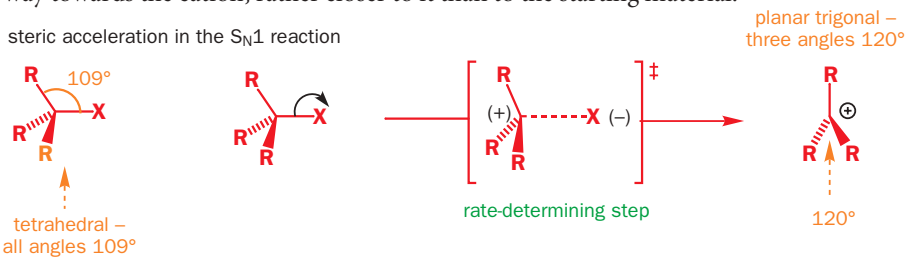
We have already considered the inversion of stereochemistry necessary in an S_N2 mechanism, but there is another steric effect, the rather cruder steric hindrance. In the approach to the S_N2 transition state, the carbon atom under attack gathers in another ligand and becomes (briefly) five-coordinate. The angles between the substituents decrease from tetrahedral to about 90°.



In the starting material there are four angles of about 109°. In the transition state (enclosed in square brackets and marked ‡ as usual) there are three angles of 120° and six angles of 90°, a significant increase in crowding. The larger the substituents R, the more serious this is. We can easily see the effects of steric hindrance if we compare these three structural types:

- methyl: CH_3–X: very fast S_N2 reaction
- primary alkyl: RCH_2–X: fast S_N2 reaction
- secondary alkyl: R_2CH–X: slow S_N2 reaction

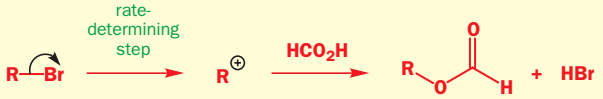
The opposite is true of the S_N1 reaction. The slow step is simply the loss of the leaving group. The starting material is again tetrahedral (four angles of about 109°) and in the intermediate cation there are just three angles of 120°—fewer and less serious interactions. The transition state will be on the way towards the cation, rather closer to it than to the starting material.



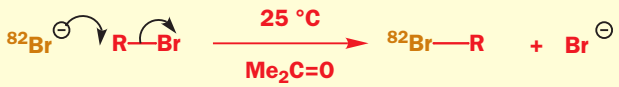
Even in the transition state, the angles are increasing towards 120° and all interactions with the leaving group are diminishing as it moves away. There is steric *acceleration* in the S_N1 reaction rather than steric *hindrance*. This, as well as the stability of *t*-alkyl cations, is why *t*-alkyl compounds react by the S_N1 mechanism.

Rates of S_N1 and S_N2 reactions

Here is a simple illustration of these effects. The green curve in Figure 17.1 (next page) shows the rates (k_1) of an S_N1 reaction: the conversion of alkyl bromides to alkyl formate esters in formic acid at 100 °C. Formic acid is very polar and, though a weak nucleophile, is adequate for an S_N1 reaction.



The red curve in Figure 17.1 shows the rates of displacement of Br^- by radioactive $^{82}Br^-$ in acetone at 25 °C by the S_N2 mechanism, the rates (k_2) being multiplied by 10^5 to bring both curves on to the same graph. The actual values of the rate constants are not important. Table 17.12 gives the relative rates compared with that of the secondary halide, *i*-PrBr, set at 1.0 in each case.



▶ You will often read that *t*-alkyl compounds do not react by the S_N2 mechanism because the steric hindrance would be too great. This is a reasonable assumption given that secondary alkyl compounds are already reacting quite slowly. The truth is that *t*-alkyl compounds react so fast by the S_N1 mechanism that the S_N2 mechanism wouldn't get a chance *even if it went as fast as it goes with methyl compounds*. The nucleophile would have to be about 100 molar in concentration to compensate for the difference in rates and this is impossible! Even pure water is only 55 molar (Chapter 8). You see only the faster of the two possible mechanisms.

- If there are two *steps* in a single mechanism, the *slower* of the two determines the rate of the overall reaction
- If there are two different *mechanisms* available under the reaction conditions, only the *faster* of the two actually occurs.

Rates of S_N1 and S_N2 reactions (contd)

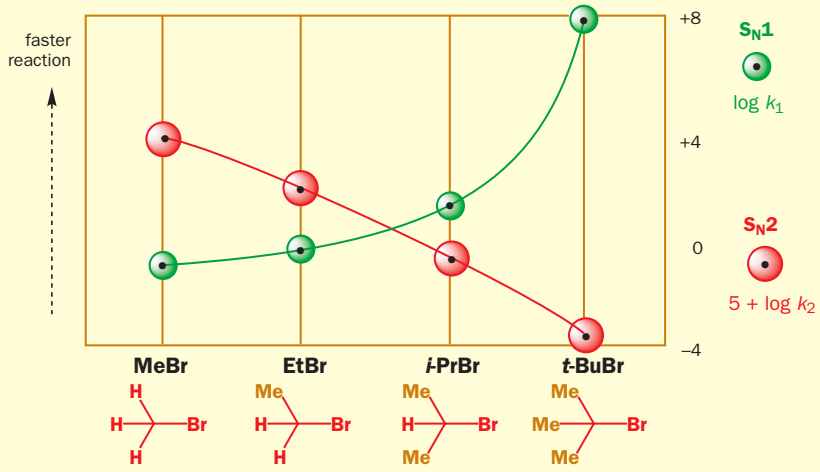
Both curves are plotted on a log scale, the $\log_{10}$ of the actual rate being used on the *y*-axis. The *x*-axis has no real significance; it just shows the four points corresponding to the four basic structures: MeBr, $MeCH_2Br$, Me_2CHBr, and Me_3CBr. The values plotted are given in Table 17.12

Table 17.12 Rates of S_N1 and S_N2 reactions of simple alkyl bromides

alkyl bromide	CH_3Br	CH_3CH_2Br	$(CH_3)_2CHBr$	$(CH_3)_3CBr$
type	methyl	primary	secondary	tertiary
k_1, s^{-1}	0.6	1.0	26	10^8
$10^5 k_2$ ($lm^{-1} s^{-1}$)	13 000	170	6	0.0003
relative k_1	2×10^{-2}	4×10^{-2}	1	4×10^6
relative k_2	6×10^3	30	1	5×10^{-5}

The reactions were chosen to give as much S_N1 reaction as possible in one case and as much S_N2 reaction as possible in the other case. Formic acid is a very polar solvent but a poor nucleophile; this gives the maximum opportunity for a cation to form. Bromide ion is a good nucleophile and acetone is polar enough to dissolve the reagents but not so polar that ionization is encouraged. Of course, you will understand that we cannot prevent the molecules doing the 'wrong' reaction! The values for the 'S_N1' reaction of MeBr and $MeCH_2Br$ are actually the low rates of S_N2 displacement of the bromide ion by the weak nucleophile HCO_2H, while the 'S_N2' rate for *t*-BuBr may be the very small rate of ionization of *t*-BuBr in acetone.

Figure 17.1: S_N1 and S_N2 rates for simple alkyl bromides



The actual values of the rate constants are not important. The graph in Figure 17.1 has been plotted to put the rates of the S_N2 and S_N1 reactions of the secondary alkyl bromide at about the same level to give a graphical illustration of the *relative* speed of the S_N2 reaction with MeBr and the *relative* speed of the S_N1 reaction of *t*-BuBr.

Solvating polar compounds or transition states

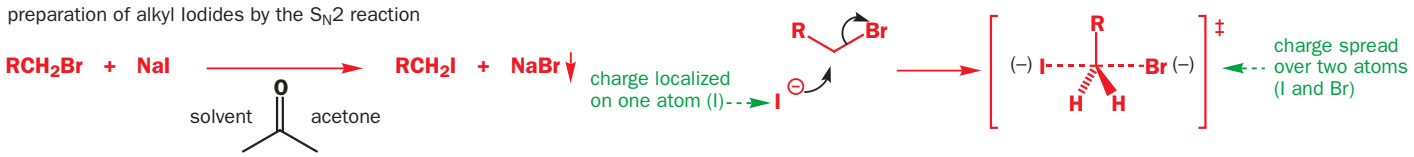
Three things are important:

- Polarity—simply measured by dipole moment. The + end of the dipole stabilizes full or partial anions and the – end of the dipole stabilizes full or partial cations
- Electron donation to cationic centres by lone-pair electrons
- Hydrogen bonding to stabilize full or partial anions

Solvent effects

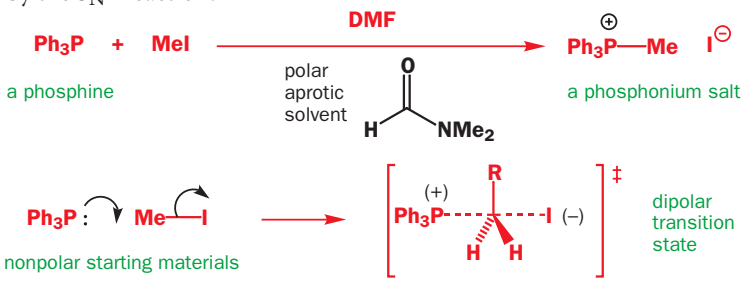
In the box above, you can see acetone used as a solvent for an S_N2 reaction and formic acid (HCO_2H) as solvent for the S_N1 reaction. These are typical choices: a less polar solvent for the S_N2 reaction (just polar enough to dissolve the ionic reagents) and a polar protic solvent for the S_N1 reaction. The S_N1 reaction fairly obviously needs a polar solvent as the rate-determining step usually involves the formation of ions and the rate of this process will be increased by a polar solvent. More precisely, the transition state is more polar than the starting materials and so is stabilized by the polar solvent. Hence solvents like water or carboxylic acids (RCO_2H) are ideal.

It is less obvious why a less polar solvent is better for the S_N2 reaction. The most common S_N2 reactions use an anion as the nucleophile and the transition state is less polar than the localized anion as the charge is spread between two atoms.



A polar solvent solvates the anionic nucleophile and slows the reaction down. A nonpolar solvent destabilizes the starting materials more than it destabilizes the transition state and speeds up the reaction. There is another reason for using acetone for this particular reaction. NaI is very soluble in acetone but NaBr is rather insoluble. The NaBr product precipitates out of solution which helps to drive the reaction over to the right.

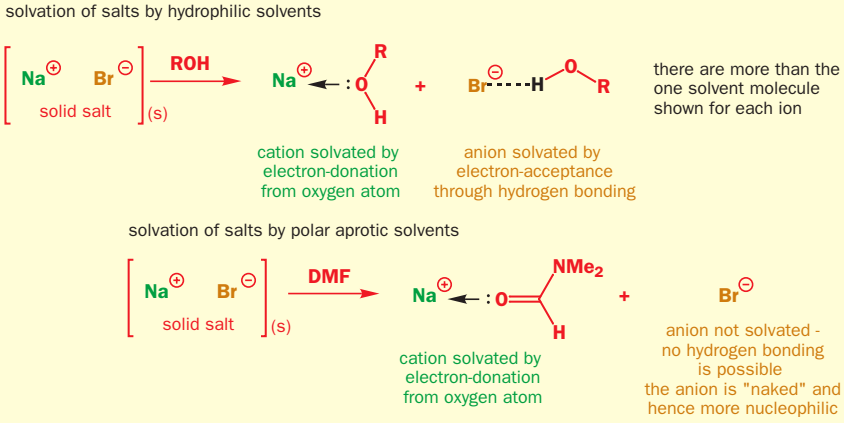
If an S_N2 reaction has neutral starting materials and an ionic product, then a polar solvent is better. A good choice is DMF, a polar aprotic solvent often used for the synthesis of phosphonium salts by the S_N2 reaction.



Polar aprotic solvents

Water, alcohols, and carboxylic acids are polar protic solvents able to form hydrogen bonds (**hydroxylic solvents**). They solvate both cations and anions well. A nucleophilic reagent such as bromide ion must be accompanied by a cation, say, the sodium ion, and hydroxylic solvents dissolve salts such as NaBr by hydrogen bonding to the anion and electron donation to the cation. This is solvation by a polar protic solvent. These solvents do not 'ionize' the salt, which already exists in the solid state as ions; they separate and solvate the ions already present.

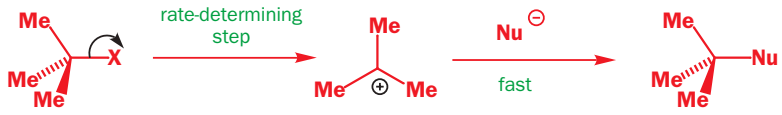
Polar aprotic solvents, on the other hand, have dipole moments and are still able to solvate cations by electron donation from an oxygen atom, but they lack the ability to form hydrogen bonds because any hydrogen atoms they may have are on carbon. Examples include DMF and DMSO (dimethyl sulfoxide).



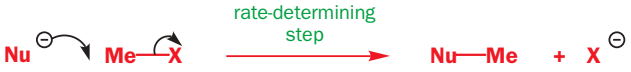
We have considered the important effects of the basic carbon skeleton on the S_N1 and S_N2 reactions and we shall now consider the remaining two possible structural variations: the nucleophile and the leaving group. We shall tackle the leaving group first because it plays an important role in both S_N1 and S_N2 reactions.

The leaving group

We have mostly seen halides and water from protonated alcohols as leaving groups in both S_N1 and S_N2 reactions. Now we need to establish the principles that make for good and bad leaving groups. We might be considering an S_N1 reaction.



Or we might be considering an S_N2 reaction—both have a leaving group, which we are representing as 'X' in these mechanisms. In both cases the C–X bond is breaking in the slow step.



Starting with the halides, two main factors are at work: the strength of the C–halide bond and the stability of the halide ion. The strengths of the C–X bonds have been measured and are listed in Table 17.13. How shall we measure anion stability? One way, which you met in Chapter 8, was to use the pK_a values of the acids HX. We established in Chapter 8 that bond strength can be used to explain pK_a values so these two factors are not independent.

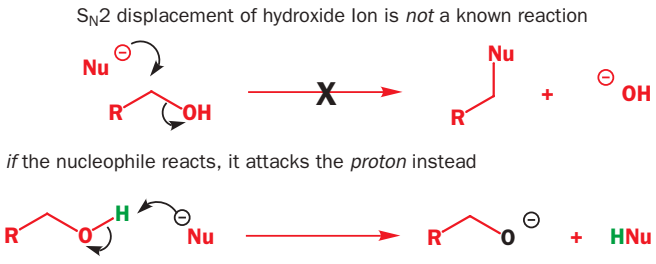
Table 17.13 Halide leaving groups in the S_N1 and S_N2 reactions

Halide (X)	Strength of C–X bond,[1] kJ mol^{-}	pK_a of HX
fluorine	118	+3
chlorine	81	–7
bromine	67	–9
iodine	54	–10

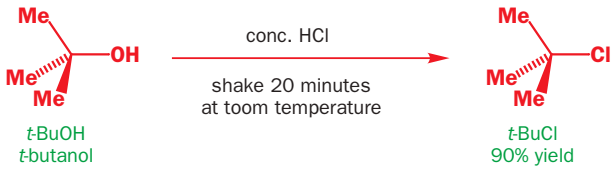
It is clearly easiest to break a C–I bond and most difficult to break a C–F bond. Iodide sounds like the best leaving group. We get the same message from the pK_a values: HI is the strongest acid, so it must ionize easily to H^+ and I^-. This result is quite correct—iodide is an excellent leaving group and fluoride a very bad one with the other halogens in between.

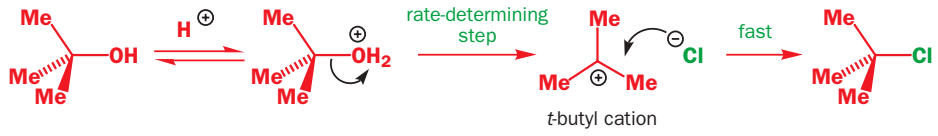
Nucleophilic substitutions on alcohols

Now what about leaving groups joined to the carbon atom by a C–O bond? There are many of these but the most important are OH itself, the carboxylic esters, and the sulfonate esters. First we must make one thing clear. In spite of what you may suppose, alcohols do *not* react with nucleophiles. Why not? Hydroxide ion is very basic, very reactive, and a bad leaving group. If the nucleophile were strong enough to produce hydroxide ion, it would be more than strong enough to remove the proton from the alcohol.



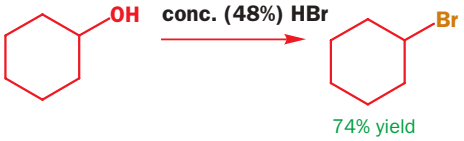
But we want to use alcohols in nucleophilic substitution reactions because they are easily made. The simplest answer is to protonate the OH group with strong acid. This will work only if the nucleophile is compatible with strong acid, but many are. The preparation of *t*-BuCl from *t*-BuOH simply by shaking it with concentrated HCl is a good example. This is obviously an S_N1 reaction with the *t*-butyl cation as intermediate.



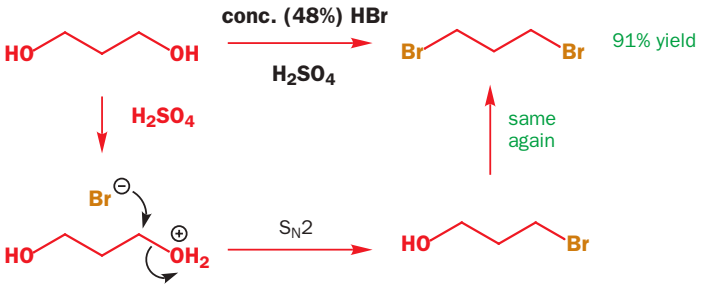


Similar methods can be used to make secondary alkyl bromides with HBr alone and primary alkyl bromides using a mixture of HBr and H_2SO_4. The second is certainly an S_N2 reaction and we show just one stage in a two-step process that is very efficient.

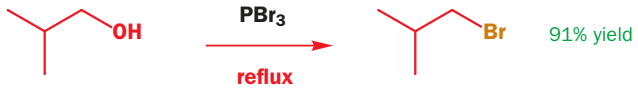
substituting a secondary alcohol in acid



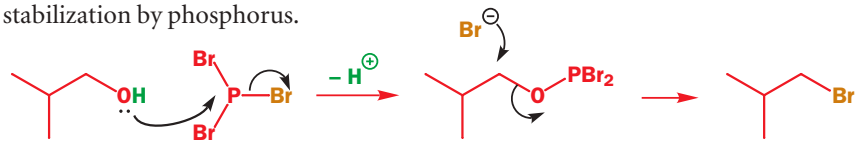
substituting a primary alcohol in acid



Another way is to convert the OH group into a better leaving group by combination with an element that forms very strong bonds to oxygen. The most popular choices are phosphorus and sulfur. Making primary alkyl bromides with PBr_3 usually works well.



The phosphorus reagent is first attacked by the OH group (an S_N2 reaction at phosphorus) and the displacement of an oxyanion bonded to phosphorus is now a good reaction because of the anion stabilization by phosphorus.

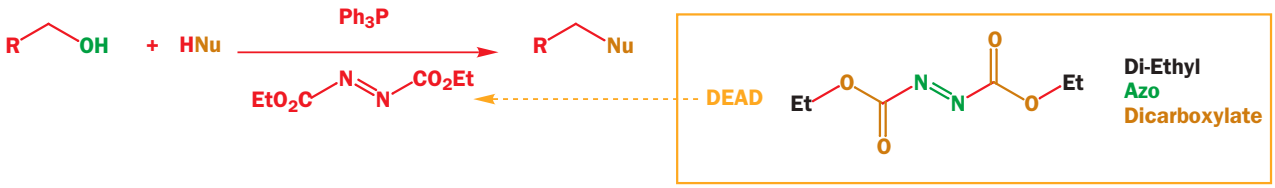


The Mitsunobu reaction is a modern S_N2 reaction using phosphorus chemistry

So far we have seen methods of displacing the OH group by first converting it to something else—a better leaving group like Br, for example. There is one recent invention that allows us to put an alcohol straight into a reaction mixture and get an S_N2 product in one operation. This is the **Mitsunobu reaction**. The alcohol becomes the electrophile, the nucleophile can be whatever you choose, and there are two other reagents.

■ Oyo Mitsunobu was born in 1934 in Japan and works at the Aoyama Gakuin University in Tokyo. He is one of the few modern chemists to have a famous reaction named after him. Please note the spelling of his name: MitsUnObU.

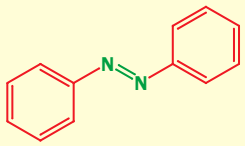
a Mitsunobu reaction



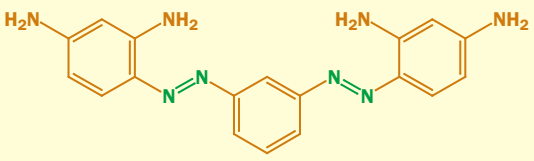
One of these reagents, Ph_3P, triphenylphosphine, is a simple phosphine, rather like an amine but with P instead of N. The other deserves more comment. Its full name is diethyl azodicarboxylate, or DEAD.

Azo compounds

The 'azo' in the name of DEAD refers to two nitrogen atoms joined together by a double bond and compounds such as azobenzene are well known. Many dyestuffs have an azo group in them—Bismarck Brown (mentioned in Chapter 1) is used to dye kippers.



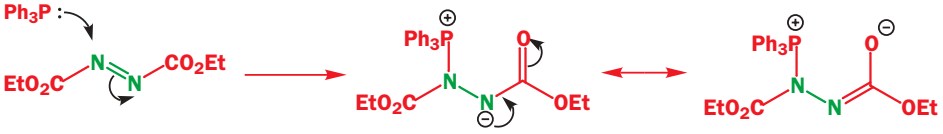
azobenzene



Bismarck Brown Y: an azo dye

So how does the Mitsunobu reaction work? The first step involves neither the alcohol nor the nucleophile. The phosphine adds to the weak N=N π bond to give an anion stabilized by one of the ester groups.

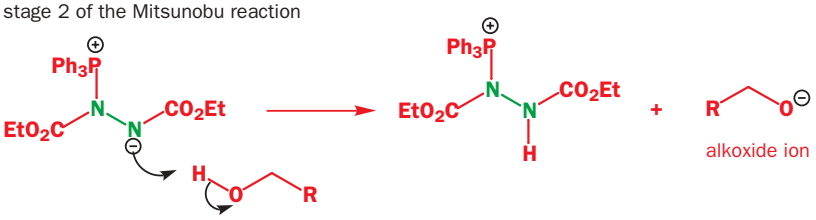
stage 1 of the Mitsunobu reaction



stabilization of the nitrogen anion by the ester group

The anion produced by this first stage is basic enough to remove a proton from the alcohol. This is always what will happen if a strong nucleophile is combined with an alcohol and previously this was a fatal disadvantage when we wanted an S_N2 reaction. But wait and see.

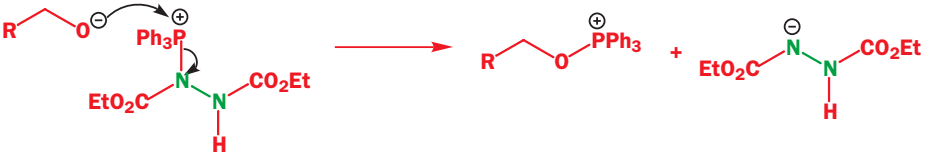
stage 2 of the Mitsunobu reaction



alkoxide ion

Oxygen and phosphorus have a strong affinity as we saw in the conversion of alcohols to bromides with PBr_3 and in the Wittig reaction (Chapter 14, p. 000) and so the new alkoxide ion immediately attacks the positively charged phosphorus atom displacing a second nitrogen anion stabilized in the same way as the first. This is an S_N2 reaction at phosphorus.

stage 3 of the Mitsunobu reaction



The second basic nitrogen anion removes a proton from the nucleophile, which has been patiently waiting in disguised form as HNu while all this is going on. The true nucleophile is now revealed as an anion.

stage 4 of the Mitsunobu reaction

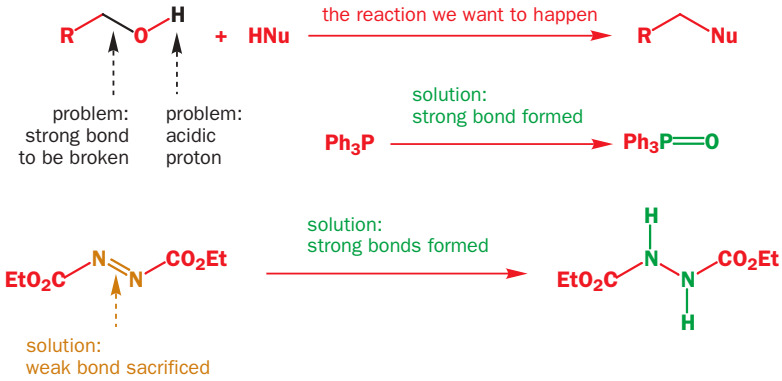
Finally, the anion of the nucleophile attacks the phosphorus derivative of the alcohol in a normal S_N2 reaction at carbon with the phosphine oxide as the leaving group. We have arrived at the products.

stage 5 of the Mitsunobu reaction

S_N2 product phosphine oxide

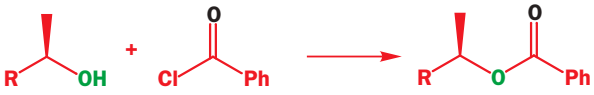
The whole process takes place in one operation. The four reagents are all added to one flask and the products are the phosphine oxide, the reduced azo diester with two NH bonds replacing the N=N double bond, and the product of an S_N2 reaction on the alcohol. Another way to look at this reaction is that a molecule of water must formally be lost: OH must be removed from the alcohol and H from the nucleophile. These atoms end up in very stable molecules—the P=O and N–H bonds are very stable while the N=N bond was weak. This compensates for the sacrifice of the strong C–O bond in the alcohol.

the Mitsunobu reaction – summary



If this is all correct, then the vital S_N2 step should lead to inversion as it always does in S_N2 reactions. This turns out to be one of the great strengths of the Mitsunobu reaction—it is a reliable way to replace OH by a nucleophile with inversion of configuration. The most dramatic example is probably the formation of esters from secondary alcohols with inversion. Normal ester formation leads to retention as the C–O bond of the alcohol is not broken.

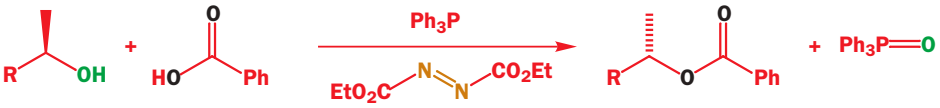
ester formation from a secondary alcohol with retention



The Mitsunobu reaction is used to replace OH by another group with inversion of configuration.

In the Mitsunobu reaction, the C–O bond of the alcohol is broken because the alcohol becomes the electrophile and the acid derivative must be a nucleophile so an acid is better than an acid chloride. The ester is formed with inversion. Note the fate of the oxygen atoms.

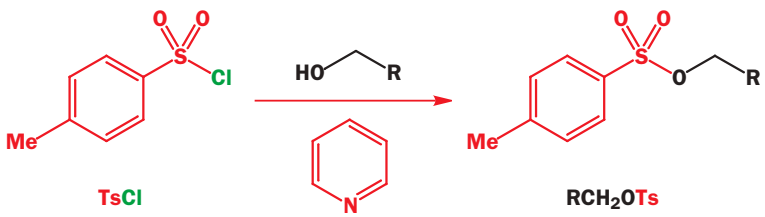
ester formation from a secondary alcohol with inversion by the Mitsunobu reaction



The Mitsunobu reaction is by no means the only way to turn OH groups into leaving groups and a method based on sulfur chemistry is as important.

Tosylate, TsO^-, is an important leaving group made from alcohols

The most important of all these leaving groups are those based on sulfonate esters. The intermediates in the PBr_3 reaction are unstable, but it is usually easy to make stable, usually crystalline toluene-*para*-sulfonates from primary and secondary alcohols. We met these derivatives on p. 000. These isolable but reactive compounds are so popular that they have been given a trivial name ('tosylates') and the functional group has been allocated an 'organic element' symbol Ts. This is what it means.



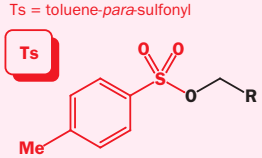
TsCl
toluene-*para*-sulfonyl chloride

RCH_2OTs
alkyl toluene-*para*-sulfonate

■
Sulfonic acids are strong acids (pK_a from Chapter 8) and so any sulfonate is a good leaving group. Another closely related leaving group, methane sulfonate or MsO^- is discussed in Chapter 19 under elimination reactions.

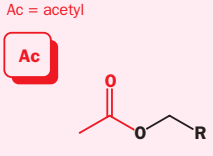
▶ Warning of wrong labelling!

Ts = toluene-*para*-sulfonyl



this compound is RCH_2OTs *not* RCH_2Ts

Ac = acetyl



this compound is RCH_2OAc *not* RCH_2Ac

The leaving groups are toluene-*para*-sulfon**ate**, TsO^-, and acet**ate.** AcO^-, but the substituents are toluene-*para*-sulfon**yl**, Ts–, and acet**yl**, Ac–.

You have already seen the tosyl group used in the inversion sequence on p. 000, where it was displaced by as weak a nucleophile as acetate. This should alert you to the fact that TsO^- can be displaced by almost anything. We choose some examples in which new carbon–carbon bonds are formed. This will be an important topic later in the book when we meet enolate anions (Chapter 21) but our two examples here use sp anions derived from nitriles and acetylenes.

Cyanide ion is a good small nucleophile and displaces tosylate from primary carbon atoms and adds one carbon atom to the chain. As the cyanide (nitrile) group can be converted directly to a carboxylic acid or ester (Chapter 14) this sequence is a useful chain extension.

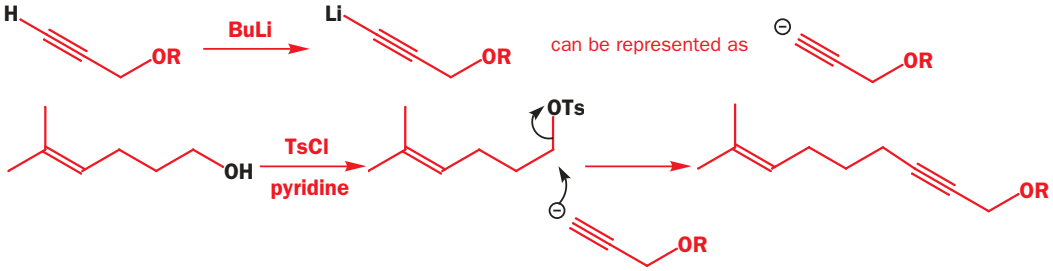
■

Elias J. Corey (1928–), PhD from MIT, works at Harvard University. He invented the disconnection approach to the design of organic synthesis. His group has invented many of the most important modern methods of synthesis, and have made an enormous number of complex compounds. He won the Nobel prize in 1990.

Corey's synthesis of leukotrienes, human metabolites that control many important natural defence reactions like inflammation, involves the lithium derivative of an alkyne prepared by deprotonation with the very strong base butyllithium. The tosyl derivative of a primary alcohol reacts with this lithium derivative and a perfectly normal S_N2 reaction follows. The alkyne provides the carbanion (Chapter 8) for the displacement of the tosylate.

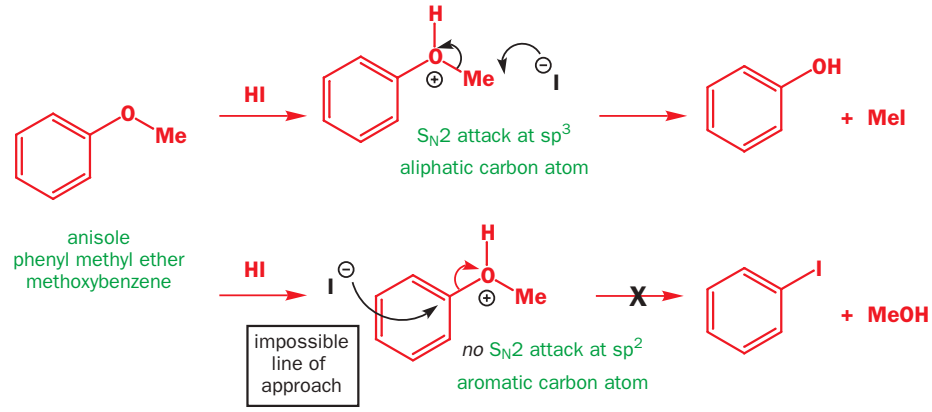
■

Leukotrienes will be discussed in detail in Chapter 51. They are C_{20} chain compounds, normally with three double bonds as their name suggests.

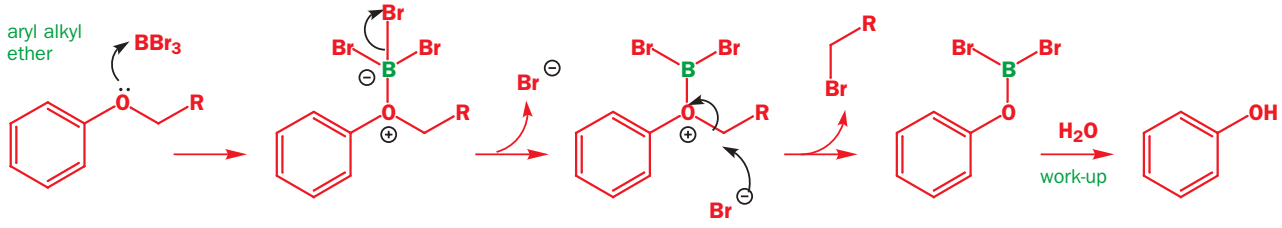


Ethers as electrophiles

Ethers are stable molecules, which do not react with nucleophiles: they must be stable because THF and Et_2O are used as solvents. But we can make them react by using an acid with a nucleophilic counterion (HBr or HI, for example) and then nucleophilic attack will occur preferentially at the more susceptible carbon atom. Aryl alkyl ethers cleave only on the alkyl side. We shall explain in Chapter 23 why nucleophilic attack does not occur on a benzene ring.



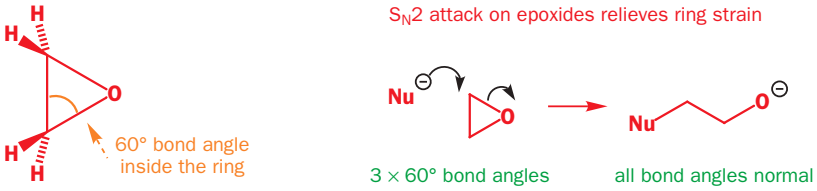
So far we have used only protic acids to help oxygen atoms to leave. Lewis acids work well too, and the cleavage of aryl alkyl ethers with BBr_3 is a good example. Trivalent boron compounds have an empty p orbital so they are very electrophilic and prefer to attack oxygen. The resulting oxonium ion can be attacked by Br^- in an S_N2 reaction.



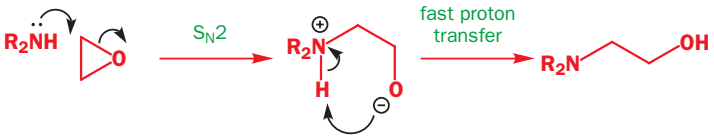
Epoxides

One type of ether reacts in nucleophilic substitution without acids or Lewis acids. The leaving group is genuinely an alkoxide anion RO^-. Obviously, some extra special feature must be present in these ethers making them unstable and this feature is ring strain. They are the three-membered cyclic ethers called **epoxides** (or oxiranes). You will see how to make these compounds in Chapter 20. The ring strain comes from the angle between the bonds in the three-membered ring which has to be 60° instead of the ideal tetrahedral angle of 109°. You could subtract these numbers and say that there is '49° of strain' at each carbon atom, making about 150° of strain in the molecule. This is a lot. The idea of strain is that the molecule wants to break open and restore the ideal tetrahedral angle at all atoms. This can be done by one nucleophilic attack.

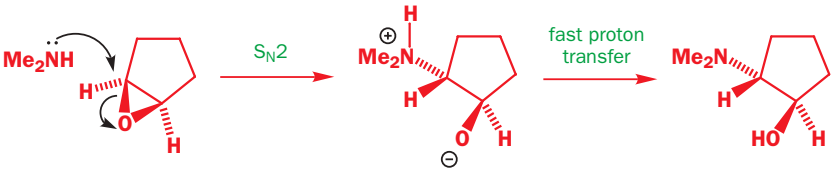
We first discussed the idea of ring strain in Chapter 6, p. 000. The true origin of strain is the poor overlap between the orbitals forming the σ bonds inside the three-membered ring. This is discussed in Chapter 15 where another piece of evidence for ring strain is the peculiar chemical shifts in the proton NMR spectra of epoxides and other three-membered rings.



Epoxides react cleanly with amines to give amino-alcohols. We have not so far featured amines as nucleophiles because their reactions with alkyl halides are often bedevilled by overreaction (see the next section), but with epoxides they give good results.



It is easy to see that inversion occurs in these S_N2 reactions if we put the epoxide on the side of another ring. With a five-membered ring only *cis*-fusion of the epoxide is possible and nucleophilic attack with inversion gives the *trans* product. As the epoxide is *up*, attack has to come from underneath. Notice that the new C–N bond is *down* and that the H atom at the site of attack was *down* in the epoxide but is *up* in the product. Inversion has occurred.



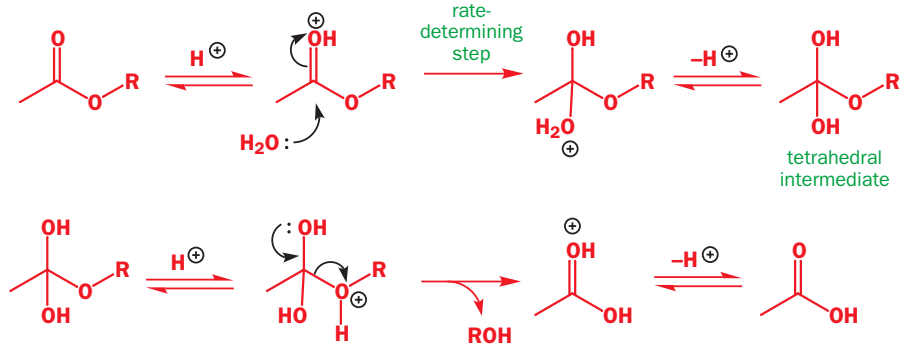
The product of this reaction is used in the manufacture of the antidepressant drug eclanamine by the Upjohn Company. Because the starting material must be a single diastereoisomer (the *cis* or *syn* isomer) and inversion has occurred at one carbon atom, the product must be the *trans* or *anti* diastereoisomer. The starting material cannot be a single enantiomer as it is not chiral (it has a plane of symmetry). Though the product *is* chiral, it cannot be optically active as no optically active reagents have gone into the reaction (Chapter 15). The biological activity in the drug requires this diastereoisomer.

Esters

Nucleophilic attack on esters in acidic or basic solution normally occurs at the carbonyl group (Chapter 12). We are going to concentrate here on what happens to the hydrolysis of simple esters in acid solution as the alkyl group varies in size.

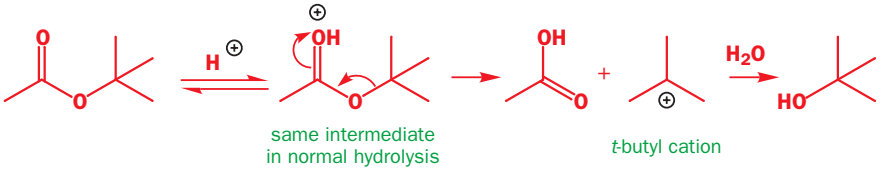
The slow step is the addition of water, which increases the crowding at the central carbon atom. As the alkyl group R is made larger, the reaction gets slower and slower. Then a dramatic thing happens. If the alkyl group R is made *tertiary*, the reaction suddenly becomes very fast indeed—faster than when R was methyl under the same conditions. Clearly, the mechanism has changed. It is no

normal ester hydrolysis in acid solution



longer the normal ester hydrolysis but has become an S_N1 reaction at the alkyl group. It is still a substitution reaction but at the saturated carbon atom rather than at the carbonyl group. The first step is the same, but the protonated ester is a good leaving group and so the intermediate decomposes to the *t*-alkyl cation without needing water at all.

the S_N1 mechanism for *t*-alkyl ester hydrolysis in acid solution



▶ **t-Butyl esters**

If you have several ester groups in a molecule and want to remove one without disturbing the others, then a *t*-butyl ester is the answer as it can be 'hydrolysed' in acid solution under very mild conditions. *t*-Butyl esters are used in protecting groups because they are so easily hydrolysed and this aspect of their chemistry is discussed in Chapter 24.

Nucleophiles

We have established that the nucleophile is not important in the *rate* of an S_N1 reaction. We need now to discuss two ways in which it is important. Both concern the nature of the product. A better nucleophile will not accelerate the S_N1 reaction but it may determine which product is formed. In the reactions of tertiary alcohols with concentrated HCl or HBr there is always more water than halide ion present and yet the *t*-alkyl halide is formed in good yield.

reaction of tertiary alcohols with hydrogen halides

This is partly because the halide ion is a better nucleophile than water for a carbocation as both are charged and partly because, if water does act as a nucleophile, it merely regenerates the starting material, which may react again.

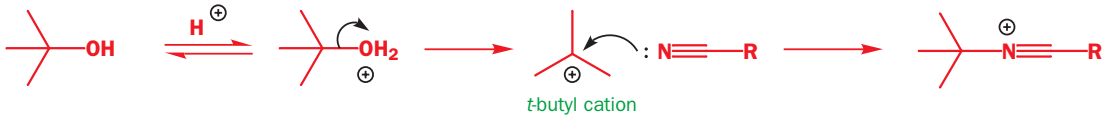
A more interesting result of the unimportance of the nucleophile in the rate is that very poor nucleophiles indeed may react in the absence of anything better. In Chapter 8 we established that nitriles are only weakly basic because the lone pair of electrons on the nitrogen atom is in a low-energy sp orbital. They are not good nucleophiles either.

nitriles

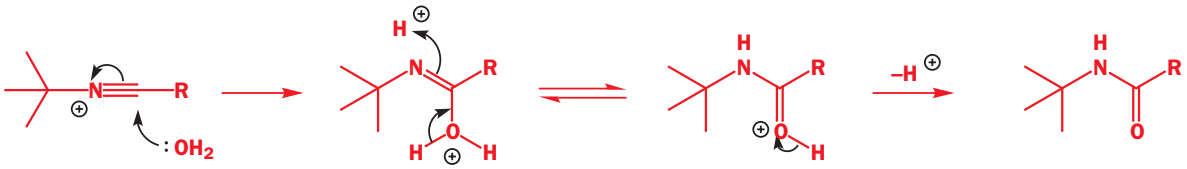
lone pair in sp orbital

nitriles are only weakly basic

If we dissolve *t*-butanol in a nitrile as solvent and add strong acid, a reaction does take place. The acid does not protonate the nitrile, but does protonate the alcohol to produce the *t*-butyl cation in the usual way. This cation is reactive enough to combine with even such a weak nucleophile as the nitrile.



The resulting cation is captured by the water molecule released in the first step and an exchange of protons leads to an amide.



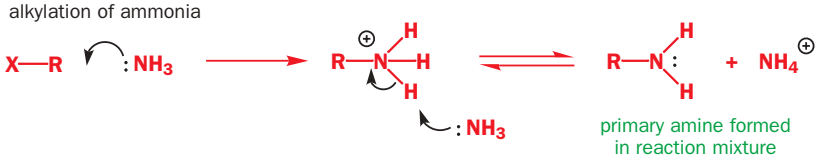
The overall process is called the **Ritter reaction** and is one of the few reliable ways to make a C–N bond to a tertiary centre.

Nucleophiles in the S_N2 reaction

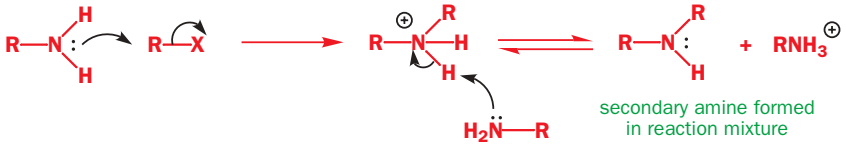
Nitrogen nucleophiles

Reactions between ammonia and alkyl halides rarely lead to single products. The problem is that the primary amine product is at least as nucleophilic as the starting material and is formed in the reaction mixture so that it in turn reacts with the alkyl halide.

alkylation of ammonia

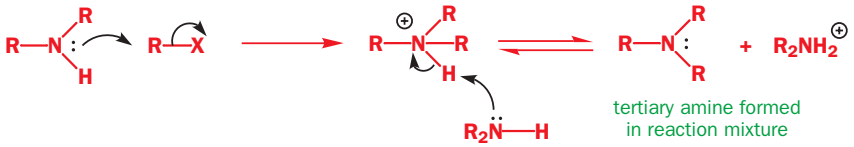


alkylation of the primary amine

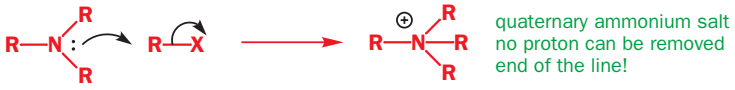


Even this is not all! If the alkylation were to continue, the secondary and the tertiary amines would be produced all together in the reaction mixture. The reaction comes to an end only when the *tetra*-alkylammonium salt R_4N^+ is formed. This salt could be the product if a large excess of alkyl halide RI is used, but other more controlled methods are needed for the synthesis of primary, secondary, and tertiary amines.

alkylation of the secondary amine



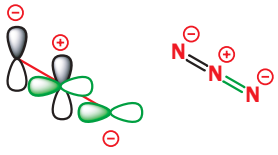
alkylation of the tertiary amine



One solution for primary amines is to replace ammonia with azide ion N_3^-. This is a linear triatomic species, nucleophilic at both ends—a little rod of electrons able to insert itself into almost any electrophilic site. It is available as the water-soluble sodium salt NaN_3.

Azide reacts only once with alkyl halides because the product, an alkyl azide, is no longer nucleophilic.

structure of azide ion N_3^-



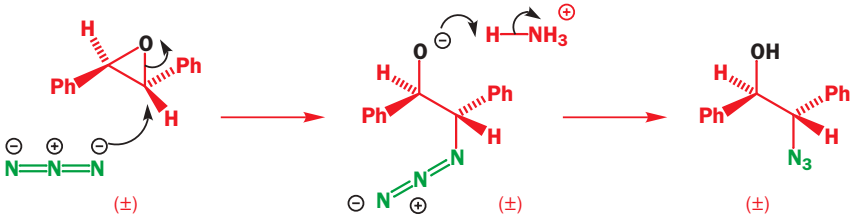
■ You should compare the structure of azide with those of ketene (p.000) and allene (p.000).

A warning about azides

Azides can be converted by heat—or even sometimes just by a sharp blow—suddenly into nitrogen gas. In other words they are potentially explosive, particularly inorganic (that is, ionic) azides and small covalent organic azides.

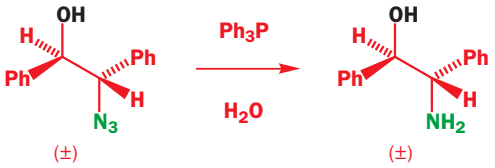
The alkyl azide produced can be reduced to the primary amine by a number of methods such as catalytic hydrogenation (Chapter 24) or $LiAlH_4$ (Chapter 12). This method has a similar philosophy to the reductive amination discussed in Chapter 14.

Azide reacts cleanly with epoxides too: here is an example with some stereochemistry in an open-chain epoxide.

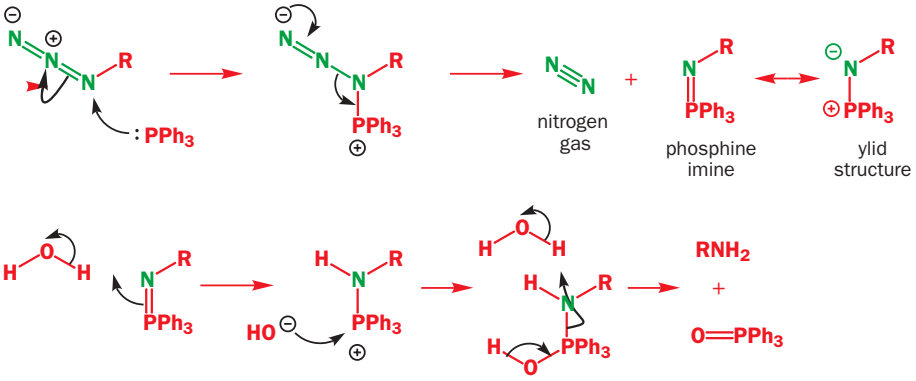


The epoxide is one diastereoisomer (*trans*) but racemic and the symbol (±) under each structure reminds you of this (Chapter 15). Azide attacks at either end of the three-membered ring (the two ends are the same) to give the hydroxy-azide. The reaction is carried out in a mixture of water and an organic solvent with ammonium chloride as buffer to provide a proton for the intermediate.

Next, triphenylphosphine in water was used for reduction to the primary amine. This process might remind you of the Mitsunobu reaction earlier in this chapter.



One possible mechanism follows. What is certainly true is that a molecule of nitrogen is lost and a molecule of water is 'dismembered' and shared between the reagents. The phosphorus atom gets the oxygen and the nitrogen atom gets the two hydrogens. These (P=O and N–H rather than N–O and P–H) are the stronger bonds.



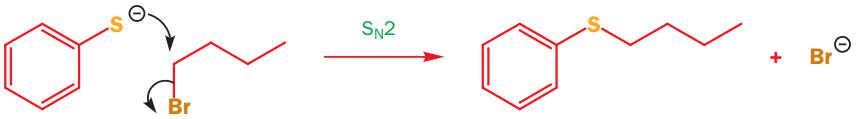
Sulfur nucleophiles are better than oxygen nucleophiles in S_N2 reactions

Thiolate anions make excellent nucleophiles in S_N2 reactions on alkyl halides. It is enough to combine the thiol, sodium hydroxide, and the alkyl halide to get a good yield of the sulfide.

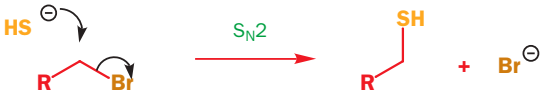
There is no competition between hydroxide and thiol because thiols are more acidic than water (pK_a of RSH is typically 9–10, pK_a of PhSH is 6.4, pK_a of H_2O is 15.7; Chapter 8) and there is a rapid proton transfer from sulfur to oxygen.

The thiolate anion produced then acts as a nucleophile in the S_N2 reaction.

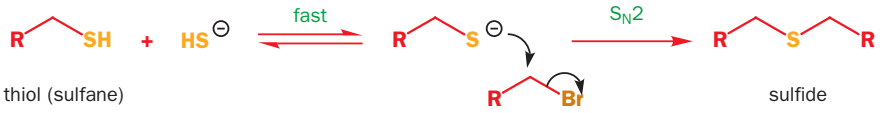
the S_N2 reaction with a thiolate anion as nucleophile



But how do you make a thiol in the first place? The obvious way to make aliphatic thiols would be by an S_N2 reaction using NaSH on the alkyl halide.

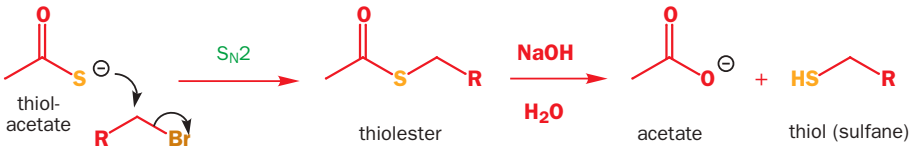


This works well but, unfortunately, the product easily exchanges a proton and the reaction normally produces the symmetrical sulfide—this should remind you of what happened with amines!



The solution is to use the anion of thiolacetic acid, usually the potassium salt. This reacts cleanly through the more nucleophilic sulfur atom and the resulting ester can be hydrolysed in base to liberate the thiol.

the S_N2 reaction with a thiolacetate anion as nucleophile



Effectiveness of different nucleophiles in the S_N2 reaction

■ This was discussed in Chapter 12.

Just to remind you of what we said before: basicity is nucleophilicity towards protons and nucleophilicity towards the carbonyl group parallels basicity almost exactly.

During this chapter you have had various hints that nucleophilicity towards saturated carbon is not so straightforward. Now we must look at this question seriously and try to give you helpful guidelines.

1 If the atom that is forming the new bond to carbon is the same over a range of nucleophiles—it might be oxygen, for example, and the nucleophiles might be HO^-, PhO^-, AcO^-, and TsO^-—then nucleophilicity does parallel basicity. The anions of the weakest acids are the best nucleophiles. The order for the nucleophiles we have just mentioned will be: $HO^- > PhO^- > AcO^- > TsO^-$. The actual values for the rates of attack of the various nucleophiles on MeBr in EtOH relative to the rate of reaction with water (=1) are given in Table 17.14

Table 17.14 Relative rates (water = 1) of reaction with MeBr in EtOH

Nucleophile X	pK_a of HX	Relative rate
HO^-	15.7	1.2×10^4
PhO^-	10.0	2.0×10^3
AcO^-	4.8	9×10^2
H_2O	–1.7	1.0
ClO_4^-	–10	0

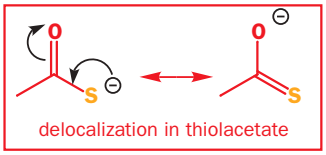
2 If the atoms that are forming the new bond to carbon are *not* the same over the range of

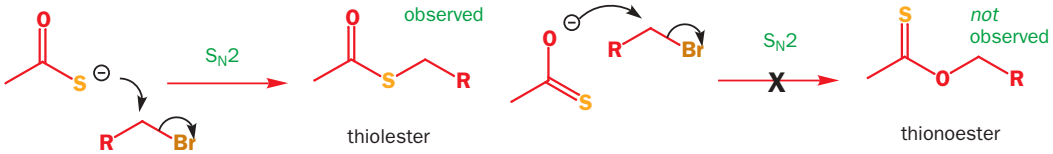
nucleophiles we are considering, then another factor is important. In the very last examples we have been discussing we have emphasized that RS^- is an excellent nucleophile for saturated carbon. Let us put that another way. RS^- is a better nucleophile for saturated carbon than is RO^-, even though RO^- is more basic than RS^- (Table 17.15).

Table 17.15 Relative rates (water = 1) of reaction with MeBr in EtOH

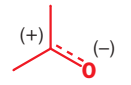
Nucleophile X	pK_a of HX	Relative rate
PhS^-	6.4	5.0×10^7
PhO^-	10.0	2.0×10^3

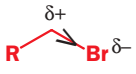
You might have noticed that the thiolacetate ion could have reacted with an alkyl halide through sulfur or through oxygen:





▶ We had a similar discussion in Chapter 10 when we were considering nucleophiles attacking conjugated C=C–C=O systems. Attack at C=O in these systems tends to be electrostatically controlled, while nucleophilic attack at C=C is under orbital (HOMO–LUMO) control.





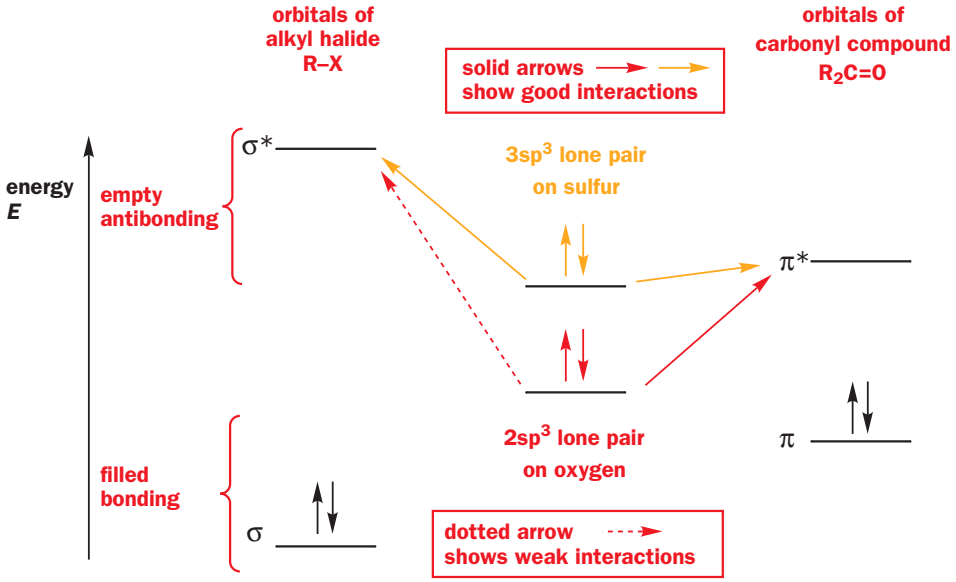
It is clear then that sulfur is a better nucleophile than is oxygen for saturated carbon. Why should this be? There are two main factors controlling bimolecular reactions: electrostatic attraction (simple attraction of opposite charges) and productive interactions between the HOMO of the nucleophile and the LUMO of the electrophile.

Reactions of nucleophiles with protons and with carbonyl groups are heavily influenced by electrostatic attraction (as well as by HOMO–LUMO interactions). The proton is, of course, positively charged. The carbonyl group too has a substantial positive charge on the carbon atom, which comes from the uneven distribution of electrons in the C=O π bond (Chapter 4).

There is, of course, also some polarity in the bond between a saturated carbon atom and a leaving group, say, a bromine atom, but this is a much smaller effect leading only to very small charge separation represented as δ+. In alkyl iodides, one of the best electrophiles in S_N2 reactions, there is in fact almost no dipole at all—the electronegativity of C is 2.55 and that of I is 2.66. Electrostatic attraction is unimportant in S_N2 reactions.

So what does matter? Only HOMO–LUMO interactions matter. In nucleophilic attack on the carbonyl group, the nucleophile added in to the low-energy π* orbital. In attack on a saturated carbon atom, the nucleophile must donate its electrons to the σ* orbital of the C–X bond as we discussed in Chapter 10.

typical arrangement of molecular energy levels



The higher-energy ($3sp^3$) lone-pair electrons on sulfur overlap better with the high-energy σ* orbital of the C–X bond than do the lower-energy ($2sp^3$) lone-pair electrons on oxygen because the higher energy of the sulfur electrons brings them closer in energy to the C–X σ* orbital. Notice that both elements overlap well with the lower-energy π* orbital. The conclusion is that nucleophiles from lower down the periodic table are more effective in S_N2 reactions than those from the top few rows. Typically, nucleophilic power towards saturated carbon goes like this.

$I^- > Br^- > Cl^- > F^-$

$RSe^- > RS^- > RO^-$

$R_3P: > R_3N:$

Nucleophiles in substitution reactions

Some rates (relative to that of water = 1) of various nucleophiles towards methyl bromide in ethanol are shown in Table 17.16.

Table 17.16 Relative rates (water = 1) of reaction of nucleophiles with MeBr in EtOH

nucleophile	F^-	H_2O	Et_3N	Br^-	PhO^-	EtO^-	I^-	PhS^-
relative rate	0.0	1.0	1400	5000	2.0×10^3	6×10^4	1.2×10^5	5.0×10^7

You have met a similar sequence before in Chapter 10, and it would be useful to review the terms we used then. Nucleophiles like R_3P: and RS^-, the ones that react well with saturated carbon, are referred to as **soft** nucleophiles and those that are more basic and react well with carbonyl groups referred to as **hard** nucleophiles. These are useful and evocative terms because the soft nucleophiles are rather large and flabby with diffuse high-energy electrons while the hard nucleophiles are small with closely held electrons and high charge density. When we say 'hard' (nucleophile or electrophile) we refer to species whose reactions are dominated by electrostatic attraction and when we say 'soft' (nucleophile or electrophile) we refer to species whose reactions are dominated by HOMO–LUMO interactions.

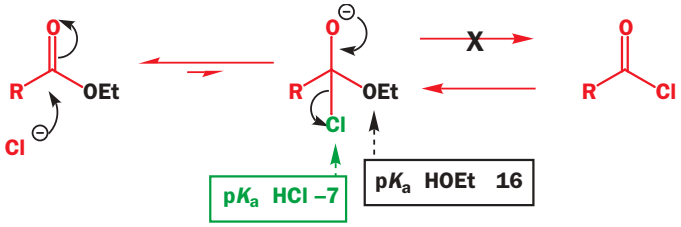
▶ Just to remind you: reactions dominated by electrostatic attraction also need to pass electrons from HOMO to LUMO, but reactions that are dominated by HOMO–LUMO interactions need have *no* contribution from electrostatic attraction.

● It is worth summarizing the characteristics of the two types of nucleophile.

Hard nucleophiles X	Soft nucleophiles Y
small	large
charged	neutral
basic (HX weak acid)	not basic (HY strong acid)
low-energy HOMO	high-energy HOMO
like to attack C=O	like to attack saturated carbon
such as RO^-, NH_2^-, MeLi	such as RS^-, I^-, R_3P

Nucleophiles and leaving groups compared

In nucleophilic attack on the carbonyl group, a good nucleophile is a bad leaving group and vice versa because the intermediate chooses to expel the best leaving group. If that is the nucleophile, it just goes straight back out again.



Chloride ion will always be the best leaving group from the intermediate, however it is formed, and the attempt to make an acid chloride from an ester with NaCl is doomed. Chloride is a good leaving group from C=O and a bad nucleophile towards C=O while EtO^- is a bad leaving group from C=O and a good nucleophile towards C=O.

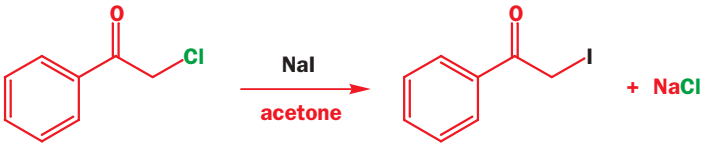
The S_N2 reaction is different because it does not have an intermediate. Therefore anything that lowers the energy of the transition state will speed up both the forward and the back reactions. We need to consider two results of this: the rate of the reaction and which way it will go.

Table 17.17 Relative rates (water = 1) of reaction with MeBr in EtOH

Nucleophile X	pK_a of HX	Relative rate
I^-	–10	1.2×10^5
Br^-	–9	5.0×10^3
Cl^-	–7	1.1×10^3
F^-	+3	0

Iodide ion is one of the best nucleophiles towards saturated carbon because it is at the bottom of its group in the periodic table and its lone-pair electrons are very high in energy. This is in spite of the very low basicity of iodide (Table 17.17). It reacts rapidly with a variety of alkyl derivatives and alkyl iodides can be made by displacement of chloride or tosylate by iodide.

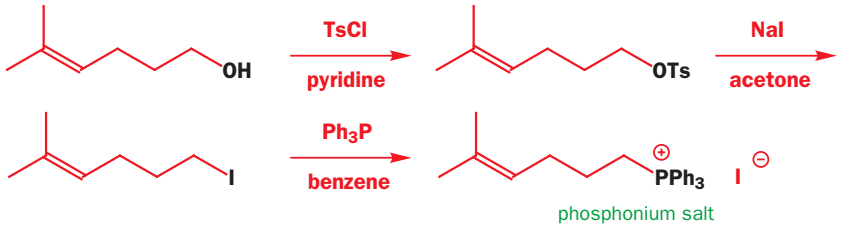
▶ The first of these reactions is assisted by precipitation of NaCl from acetone, which drives the reaction along.



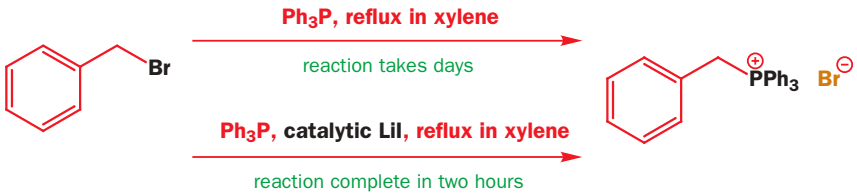
ROTs + NaI ⟶ RI + NaOTs

But why are these alkyl iodides made? They are needed for reactions with other nucleophiles in which iodide is again displaced. As well as being one of the best nucleophiles for saturated carbon, iodide ion is one of the best leaving groups from saturated carbon (see p. 000). Yields are often higher if the alkyl iodide is prepared than if the eventual nucleophile is reacted directly with the alkyl tosylate or chloride.

An example is the synthesis of the phosphonium salt used by Corey in a synthesis of terpenes (Chapter 51). An unsaturated primary alcohol was first made into its tosylate, the tosylate was converted into the iodide, and the iodide into the phosphonium salt.

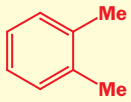


However, iodine is expensive and a way round that problem is to use a catalytic amount of iodide. The next phosphonium salt is formed slowly from benzyl bromide but the addition of a small amount of LiI speeds up the reaction considerably.

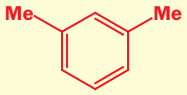


Xylenes

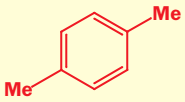
The solvent 'xylene' needs some explanation. Xylene is the trivial name for dimethyl benzene and there are three isomers. Mixed xylenes are isolated cheaply from oil and often used as a relatively high boiling solvent (b.p. about 140 °C) for reactions at high temperature. In this case, the starting materials are soluble in xylene but the product is a salt and conveniently precipitates out during the reaction.



ortho-xylene
1,2-dimethyl benzene

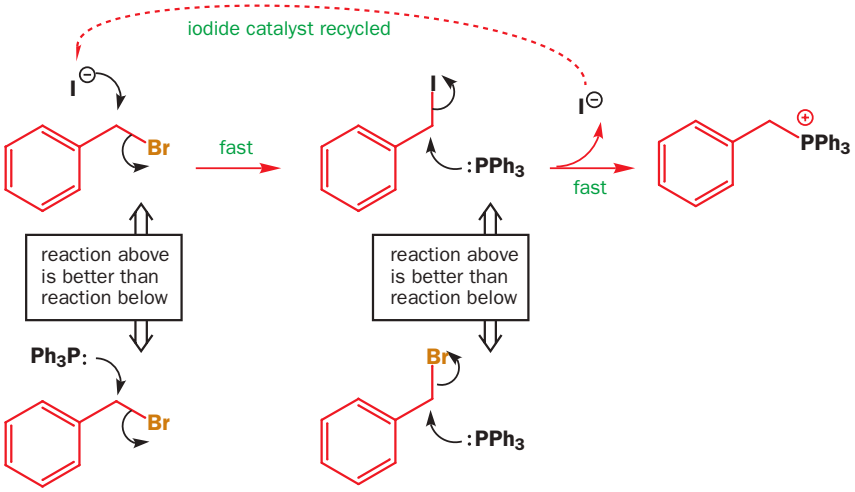


meta-xylene
1,3-dimethyl benzene



para-xylene
1,4-dimethyl benzene

The iodide reacts as a better nucleophile than Ph_3P and then as a better leaving group than Br^-. Each iodide ion goes round and round many times as a **nucleophilic catalyst**.



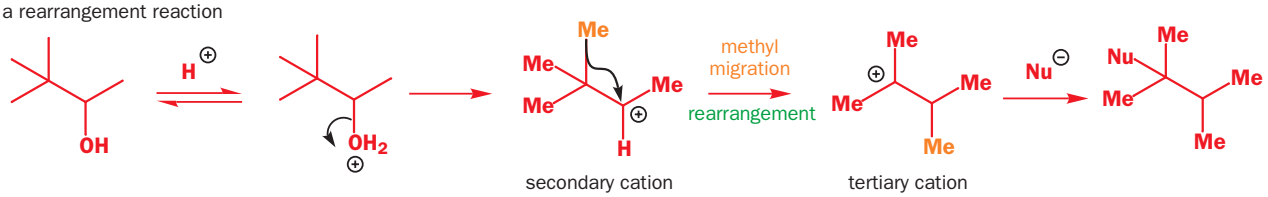
Looking forward: elimination and rearrangement reactions

Simple nucleophilic substitutions at saturated carbon atoms are fundamental reactions found wherever organic chemistry is practised. They are used in industry on an enormous scale to make 'heavy chemicals' and in pharmaceutical laboratories to make important drugs. They are worth studying for their importance and relevance.

There is another side to this simple picture. These were among the first reactions whose mechanisms were thoroughly investigated by Ingold in the 1930s and since then they have probably been studied more than any other reactions. All our understanding of organic mechanisms begins with S_N1 and S_N2 reactions and you need to understand these basic mechanisms properly. Some of the more sophisticated investigations into nucleophilic substitutions have clouded the main issues by looking at minute details and we shall not discuss these.

We shall, however, be returning to this sort of chemistry in several further chapters. The carbocations you met in this chapter are reactive species. One of the most convincing pieces of evidence for their formation is that they undergo reactions other than simple addition to nucleophiles. The carbon skeleton of the cation may rearrange.

a rearrangement reaction

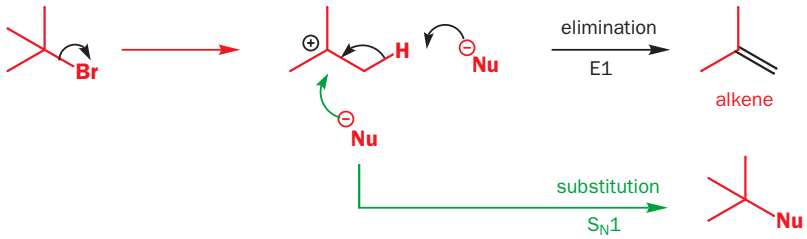


secondary cation

tertiary cation

You will meet rearrangements in several chapters later in the book especially Chapter 37. Another common fate of cations, and something that may also happen instead of an intended S_N1 or S_N2 reaction, is an elimination reaction where an alkene is formed by the nucleophile acting as a base to remove HX instead of adding to the molecule.

an elimination reaction (E1)

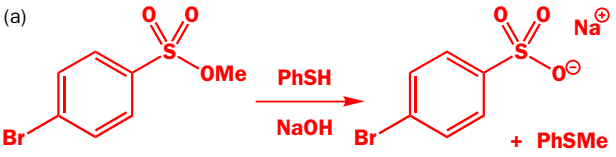


You will meet elimination reactions in the next chapter but one (19) after some further exploration of stereochemistry.

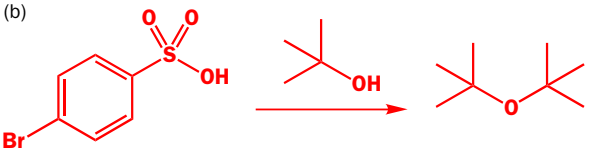
Problems

1. Suggest mechanisms for the following reactions, commenting on your choice of S_N1 or S_N2.

(a)

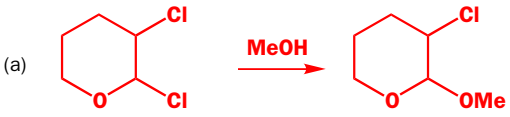


(b)



2. Draw mechanisms for the following reactions. Why were acidic conditions chosen for the first reaction and basic conditions for the second?

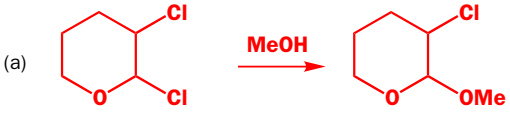
(a)



(b)

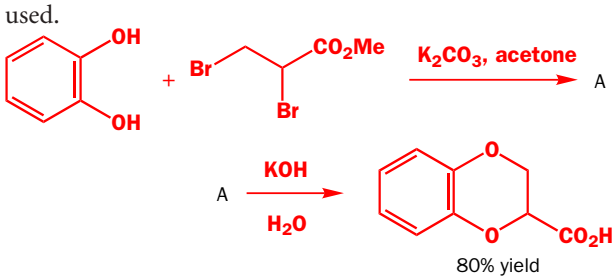
3. Draw mechanisms for these reactions, explaining why these particular products are formed.

(a)

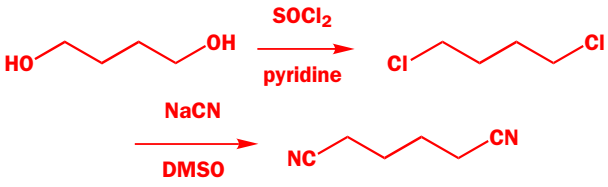


(b)

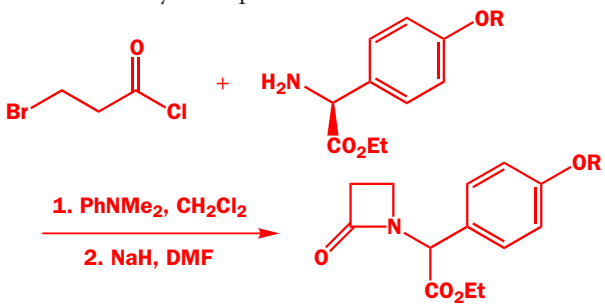
4. The chemistry shown here is the first step in the manufacture of Pfizer's doxasolin (Cardura), a drug for hypertension. Draw mechanisms for the reactions involved and comment on the bases used.



5. Suggest mechanisms for these reactions, commenting on the choice of reagents and solvents. How would you convert the final product into diethyl hexanedioate [diethyl adipate, $EtO_2C(CH_2)_4CO_2Et$]?



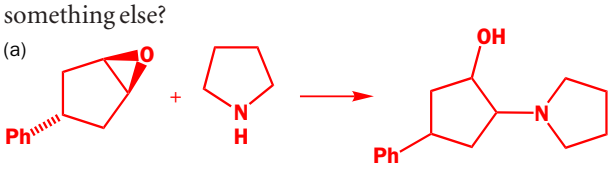
6. Draw mechanisms for these reactions and describe the stereochemistry of the product.



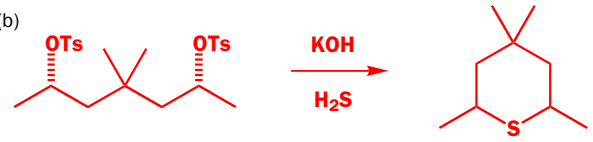
7. Suggest a mechanism for this reaction. You will find it helpful first of all to draw good diagrams of reagents and products.

8. Predict the stereochemistry of these products. Are they single diastereoisomers, enantiomerically pure, or racemic, or something else?

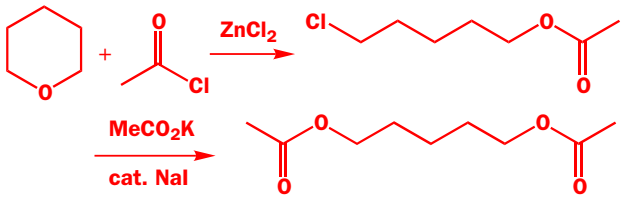
(a)



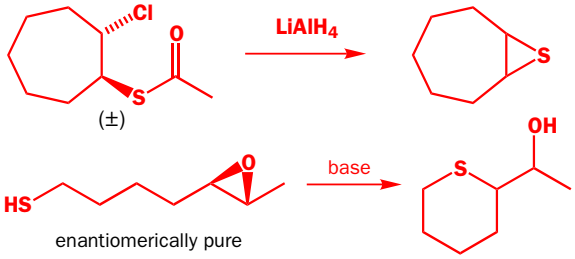
(b)



9. What are the mechanisms of these reactions, and what is the role of the $ZnCl_2$ in the first step and the NaI in the second?

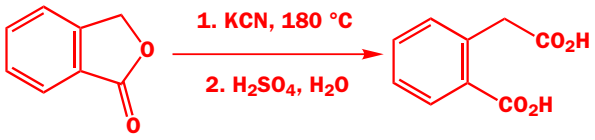


10. Describe the stereochemistry of the products of these reactions.



11. Identify the intermediates in these syntheses and give mechanisms for the reactions.

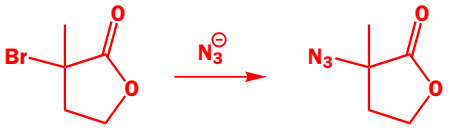
(a)



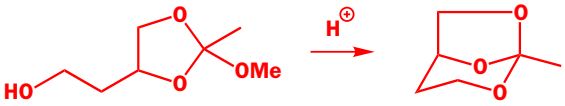
(b)

12. State with reasons whether these reactions will be either S_N1 or S_N2.

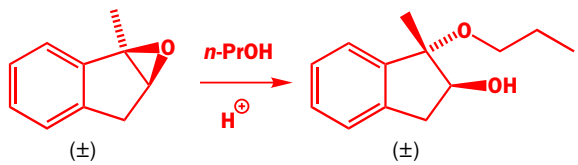
(a)



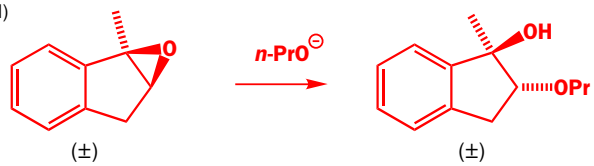
(b)



(c)



(d)



Conformational analysis

18

Connections

Building on:

- How to determine a molecule's structure ch3, ch11, & ch15
- How some molecules can exist as stereoisomers ch16

Arriving at:

- If I could see a molecule, what would its three-dimensional shape (conformation) be?
- What effect does a molecule's shape have on its reactions?
- How single bonds are free to rotate, but spend most of their time in just two or three well-defined arrangements
- How rings of atoms are usually not planar, but 'puckered'
- How 'puckered' six-membered rings have the most well-defined arrangements of atoms
- How to draw six-membered rings accurately
- How to use the known arrangements of the atoms in a six-membered ring to predict and explain their reactions

Looking forward to:

- How conformation, and the alignment of atoms, can affect elimination reactions ch19
- How NMR spectroscopy backs up what we have said in this chapter ch32
- How the conformation of molecules dictates how they react—e.g. from which direction they will be attacked by reagents ch33 & ch45
- How the alignment of bonds can allow groups in molecules to move around (rearrangement reactions) or allow C–C bonds to break (fragmentation reactions) ch37 & ch38
- How the alignment of orbitals controls reactivity (stereoelectronics) ch42
- The accurate drawing of rings as transition states is necessary ch35 & ch36

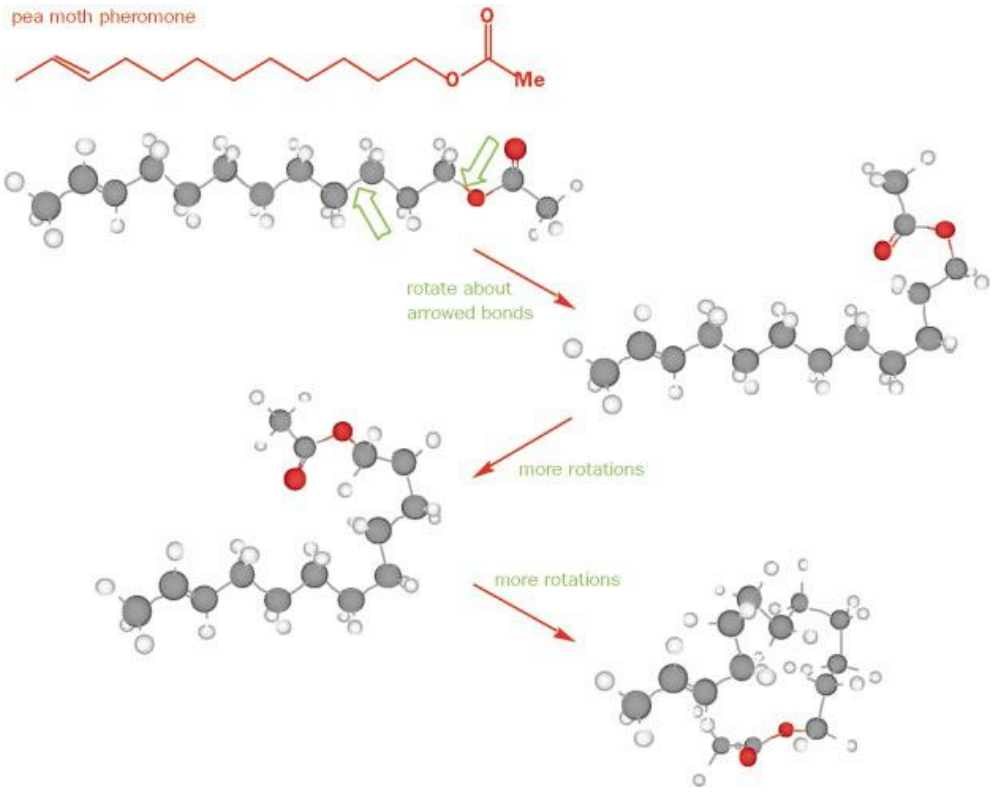
Bond rotation allows chains of atoms to adopt a number of conformations

Several chapters of this book have considered how to find out the structure of molecules. We have seen X-ray crystallography pictures, which reveal exactly where the atoms are in crystals; we have looked at IR spectroscopy, which gives us information about the bonds in the molecule, and at NMR spectroscopy, which gives us information about the atoms themselves. Up to now, we have mainly been interested in determining which atoms are bonded to which other atoms and also the shapes of small localized groups of atoms. For example, a methyl group has three hydrogen atoms bonded to one carbon atom and the atoms around this carbon are located at the corners of a tetrahedron; a ketone consists of a carbon atom bonded to two other carbon atoms and doubly bonded to an oxygen atom with all these atoms in the same plane.

But, on a slightly larger scale, shape is not usually so well defined. Rotation is possible about single bonds and this rotation means that, while the localized arrangement of atoms stays the same (every saturated carbon atom is still always tetrahedral), the molecule as a whole can adopt a number of different shapes. Shown on the next page are several snapshot views of one molecule—it happens to be a pheromone used by pea moths to attract a mate. Although the structures look dissimilar, they differ from one another only by rotation about one or more single bonds. Whilst the overall shapes differ, the localized structure is still the same: tetrahedral sp^3 carbons; trigonal planar sp^2 carbons. Notice another point too, which we will pick up on later: the arrangement about the double bond always remains the same because double bonds can't rotate.

At room temperature in solution, all the single bonds in the molecule are constantly rotating—the chances that two molecules would have exactly the same shape at any one time are quite small.

Yet, even though no two molecules have exactly the same shape at any one time, they are still all the same chemical compound—they have all the same atoms attached in the same way. We call the different shapes of molecules of the same compound different **conformations**.



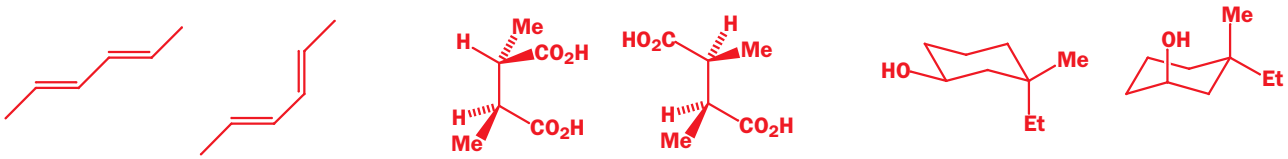
▶ **Make models**

If you find this hard to see, get a set of molecular models and build the first one of each pair. You should be able to rotate it straightforwardly into the second without breaking your model. Our advice throughout this chapter, certainly with things that you find difficult to understand from the two-dimensional drawings to which we are limited, is to *make models*.

Conformation and configuration

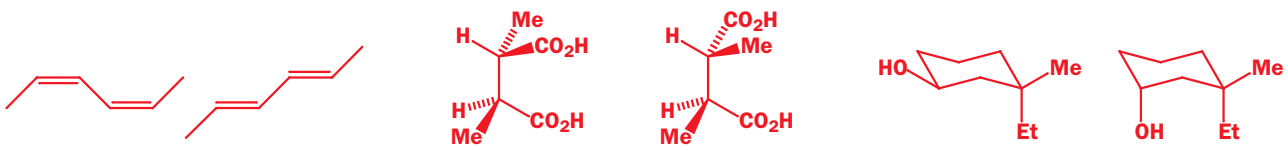
To get from one conformation to another, we can rotate about as many single bonds as we like. The one thing we can't do though is to break any bonds. This is why we can't rotate about a double bond—to do so we would need to break the π bond. Below are some pairs of structures that can be interconverted by rotating about single bonds: they are all different conformations of the same molecule.

three compounds, each shown in two conformations



The next block of molecules is something quite different: these pairs can only be interconverted by breaking a bond. This means that they have different **configurations**—configurations can be interconverted only by breaking bonds. Compounds with different configurations are called **stereoisomers** and we dealt with them in Chapter 16.

three pairs of stereoisomers: each member of a pair has a different configuration

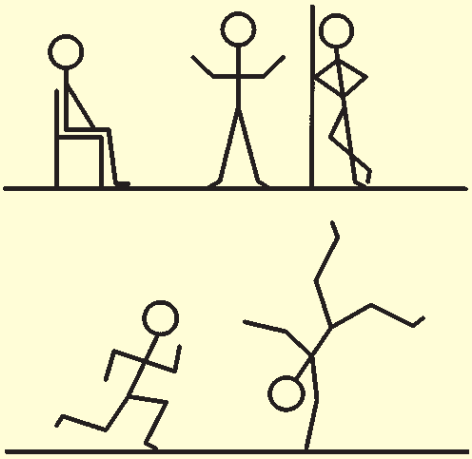


Rotation or bond breaking?

- Structures that can be interconverted simply by rotation about single bonds are **conformations** of the same molecule
- Structures that can be interconverted only by breaking one or more bonds have different **configurations**, and are stereoisomers

Conformation and configuration

Some conformations are more stable than others...

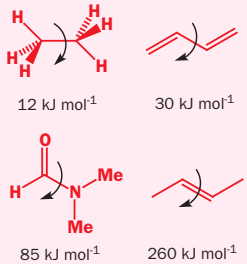


And now for a different **configuration** altogether...

Barriers to rotation

We saw in Chapter 7 that rotation about the C–N bond in an amide is relatively slow at room temperature—the NMR spectrum of DMF clearly shows two methyl signals (p. 000). In Chapter 13 you learned that the rate of a chemical process is associated with an energy barrier (this holds both for reactions and simple bond rotations): the lower the rate, the higher the barrier. The energy barrier to the rotation about the C–N bond in an amide is usually about 80 kJ mol^{-1}, translating into a rate of about 0.1 s^{-1} at 20 °C. Rotation about single bonds is much faster than this at room temperature, but there is nonetheless a barrier to rotation in ethane, for example, of about 12 kJ mol^{-1}.

barriers to rotation about different types of bond



Rates and barriers

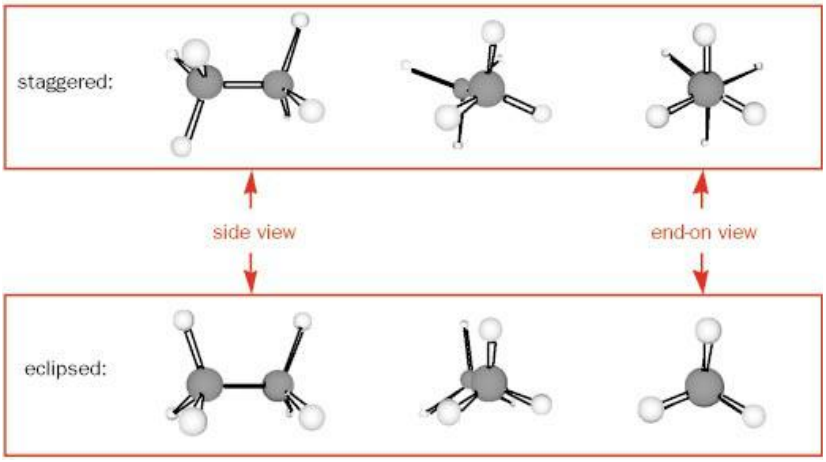
It can be useful to remember some simple guidelines to the way in which energy barriers relate to rates of rotation. For example:

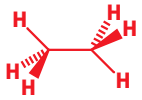
- A barrier of 73 kJ mol^{-1} allows one rotation every second at 25 °C (that is, the rate is 1 s^{-1})
- Every 6 kJ mol^{-1} changes the rate at 25 °C by about a factor of 10
- To see signals in an NMR spectrum for two different conformations, they must interconvert no faster than (very roughly) 1000 s^{-1}—a barrier of about 55 kJ mol^{-1} at 25 °C. This is why NMR shows two methyl signals for DMF, but only one set of signals for butadiene. See p. 000 for more on this
- For conformations to interconvert slowly enough for them to exist as different compounds, the barrier must be over 100 kJ mol^{-1}. The barrier to rotation about a C=C double bond is 260 kJ mol^{-1}—which is why we can separate *E* and *Z* isomers

Conformations of ethane

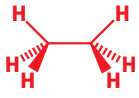
Why should there be an energy barrier in the rotation about a single bond? In order to answer this question, we should start with the simplest C–C bond possible—the one in ethane. Ethane has two extreme conformations called the **staggered** and **eclipsed conformations**. Three different views of these are shown below.

the two extreme conformations of ethane, staggered and eclipsed, each shown from three different viewpoints





the staggered conformation of ethane



the eclipsed conformation of ethane

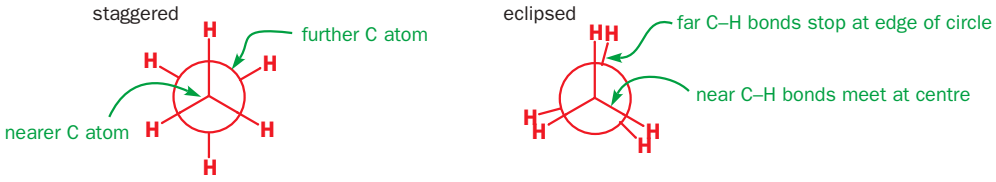
You can see why the conformations have these names by looking at the end-on views in the diagram. In the eclipsed case the near C–H bonds completely block the view of the far bonds, just as in a solar eclipse the moon blocks the sun as seen from the Earth. In the staggered conformation, the far C–H bonds appear in the gaps between the near C–H bonds—the bonds are staggered.

Chemists often want to draw these two conformations quickly and two different methods are commonly used, each with its own merits. In the first method, we simply draw the side view of the molecule and use wedged and hashed lines to show bonds not in the plane of the paper (as you saw in Chapter 16). Particular attention must be paid to which of the bonds are in the plane and which go into and out of the plane.

In the second method we draw the end-on view, looking along the C–C bond. This view is known as a **Newman projection**, and Newman projections are subject to a few conventions:

- The carbon atom nearer the viewer is at the junction of the front three bonds
- The carbon further away (which can't in fact be seen in the end-on view) is represented by a large circle. This makes the perspective inaccurate—but this doesn't matter
- Bonds attached to this further carbon join the *edge* of the circle and do not meet in the centre
- Eclipsed bonds are drawn slightly displaced for clarity—as though the bond were rotated by a tiny fraction

Newman projections for the staggered and eclipsed conformations of ethane are shown below.

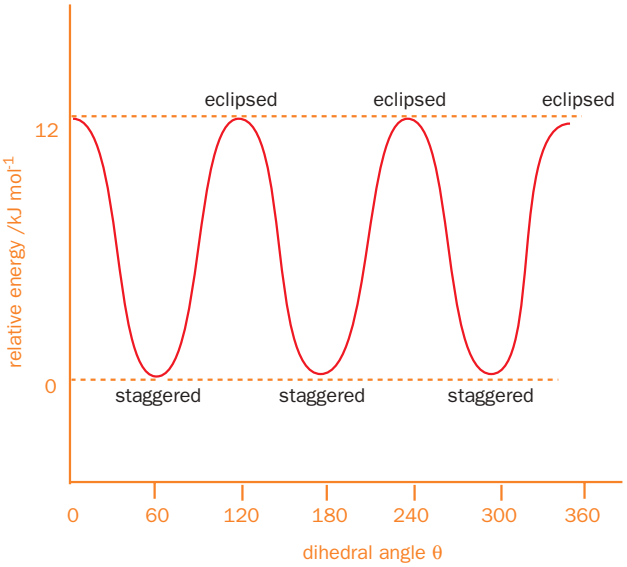


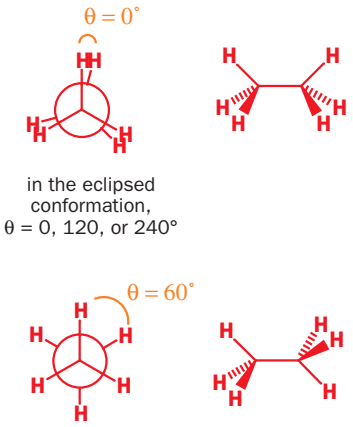
The staggered and eclipsed conformations of ethane are not identical in energy: the staggered conformation is lower in energy than the eclipsed by 12 kJ mol^{-1}, the value of the rotational barrier. Of course, there are other possible conformations too with energies in between these extremes, and we can plot a graph to show the change in energy of the system as the C–C bond rotates. We define the **dihedral angle**, θ (sometimes called the torsion angle), to be the angle between a C–H bond at the nearer carbon and a C–H bond at the far carbon. In the staggered conformation, θ = 60° whilst in the eclipsed conformation, θ = 0°.

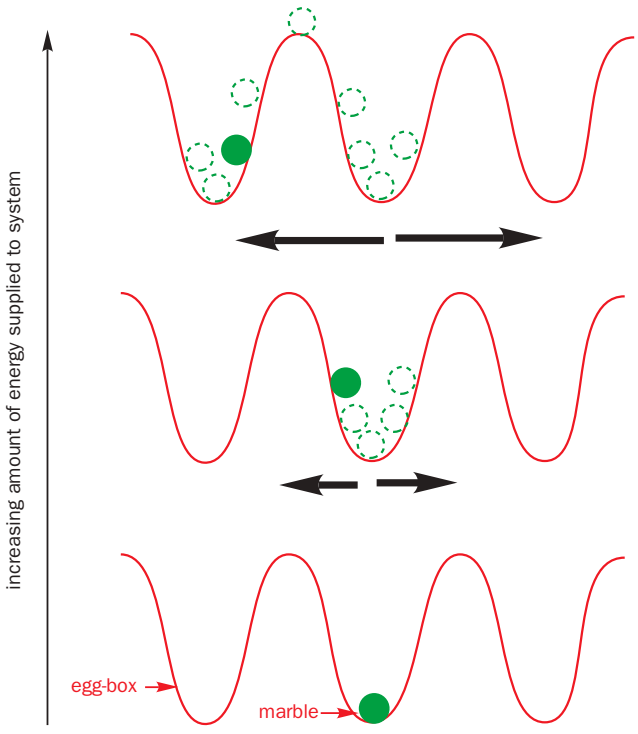
The energy level diagram shows the staggered conformation as a potential energy minimum whilst the eclipsed conformation represents an energy maximum. This means that the eclipsed conformation is not a stable conformation since any slight rotation will lead to a conformation lower in energy. The molecule will actually spend the vast majority of its time in a staggered or nearly staggered conformation and only briefly pass through the eclipsed conformation *en route* to another staggered conformation. It might help to compare the situation here with that of a marble in an egg-box. The marble will sit at the bottom of one of the wells. Rock the egg-box about gently, and the marble will stay in the well but it will roll around a bit, perhaps making its way a centimetre or so up the side. Shake the egg-box more vigorously and eventually the marble will go all the way over the side and down into a new well. One thing is certain: it won't sit on top of the ridge, and the amount of time it will spend there is insignificant.

But *why* is the eclipsed conformation higher in energy than the staggered conformation? At first glance it might seem reasonable to suggest that there is some steric interaction between the hydrogen atoms in the eclipsed conformation that is reduced in the staggered conformation. However, this is not the case, as is shown by these space-filling models. The hydrogen atoms are just too small to get in each other's way. It has been estimated that steric factors make up less than 10% of the rotational barrier in ethane.

▶ Picturing dihedral angles is sometimes hard—one way to do it is to imagine the two C–H bonds drawn on to two facing pages of a book. The dihedral angle is then the angle between the pages, measured perpendicular to the spine.



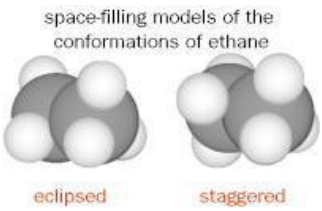




given enough energy the marble will go over the energy maximum and into a different well. You would be very surprised if the marble stuck on the ridge!

when we supply energy by rocking the box, the marble moves but still stays within the well.

with no shaking (no energy), the marble remains in the lowest energy state at the bottom of the well.

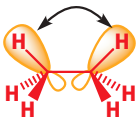


■ Space-filling models represent atoms as spheres with dimensions determined by the van der Waals radius of the atom.

There are two more important reasons why the staggered conformation of ethane is lower in energy than the eclipsed conformation. The first is that the electrons in the bonds repel each other and this repulsion is at a maximum in the eclipsed conformation. The second is that there may be some stabilizing interaction between the C–H σ bonding orbital on one carbon and the C–H σ* antibonding orbital on the other carbon, which is greatest when the two orbitals are exactly parallel: this only happens in the staggered conformation.

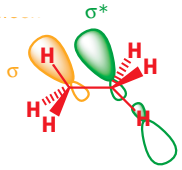
eclipsed:

filled orbitals repel



staggered:

stabilizing interaction between filled C–H σ bond...

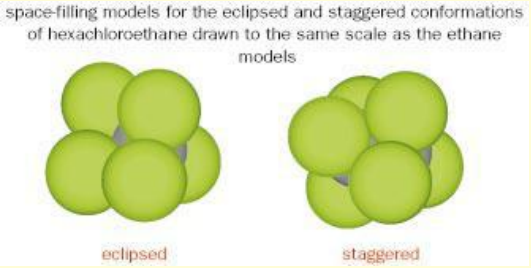


and empty C–H σ* antibonding orbital

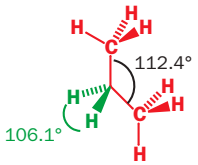
Of course, the real picture is probably a mixture of all three effects, each contributing more or less depending on the compound under consideration.

Hexachloroethane

Compare ethane with hexachloroethane, C_6Cl_6. The chlorine atoms are much larger than hydrogen atoms (van der Waals radius: H, about 130 pm; Cl, about 180 pm) and now they do physically get in the way of each other. This is reflected in the increase in the rotational barrier from 12 kJ mol^{-1} in C_2H_6 to 45 kJ mol^{-1} in C_2Cl_6 (although other factors also contribute).



Conformations of propane



there is greater repulsion between two C–C bonds than between two C–H bonds

Propane is the next simplest hydrocarbon. Before we consider what conformations are possible for propane we should first look at its geometry. The C–C–C bond angle is not 109.5° (the tetrahedral angle—see Chapters 2 and 4) as we might expect but 112.4°. Consequently, the H–C–H bond angle on the central carbon is smaller than the ideal angle of 109.5°, only 106.1°. Once more, this does not necessarily mean that the two methyl groups on the central carbon clash in some way, but instead that two C–C bonds repel each other more than two C–H bonds do.

As in the case of ethane, two extreme conformations of propane are possible—in one the C–H and C–C bonds are staggered; in the other they are eclipsed.

the staggered conformation of propane

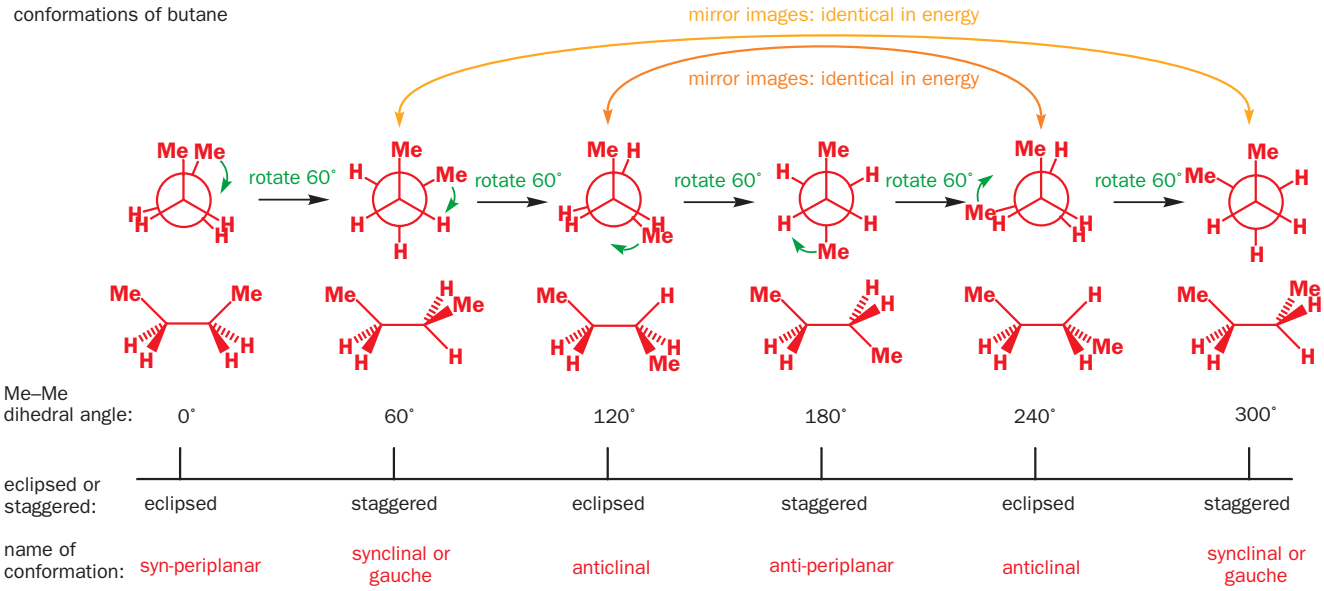
the eclipsed conformation of propane

▶ Notice that when we draw the eclipsed conformation we have to offset the front and back bonds slightly to see the substituents clearly. In reality, one is right behind the other.

The rotational barrier is now slightly higher than for ethane: 14 kJ mol^{-1} as compared to 12 kJ mol^{-1}. This again reflects the greater repulsion of electrons in the coplanar bonds in the eclipsed conformation rather than any steric interactions. The energy graph for bond rotation in propane would look exactly the same as that for ethane except that the barrier is now 14 kJ mol^{-1}.

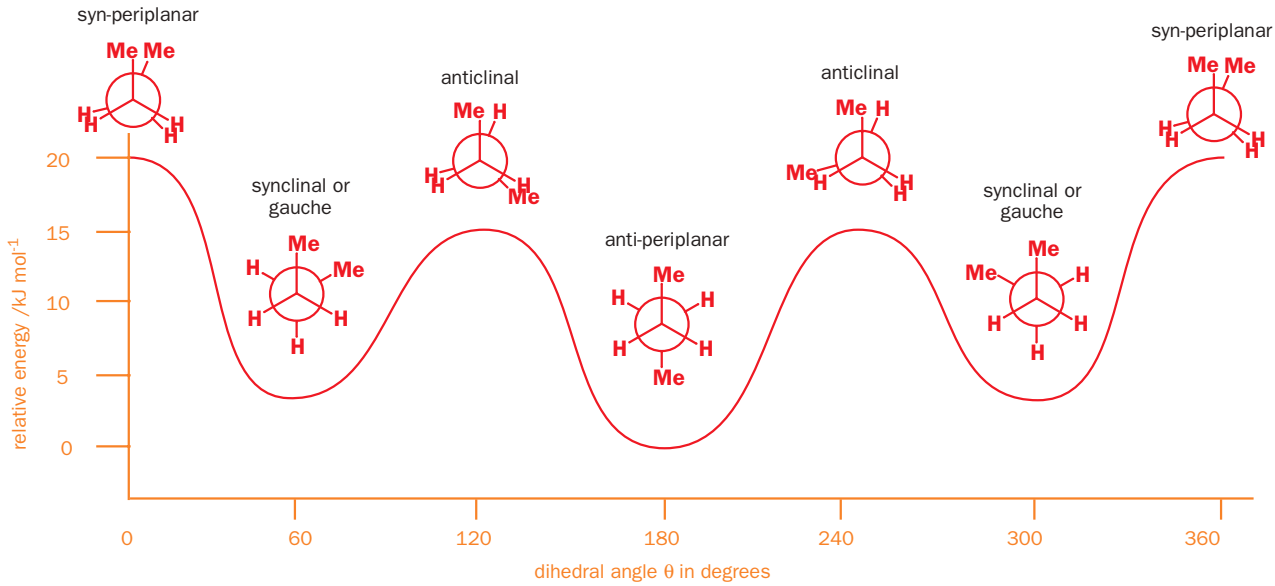
Conformations of butane

With butane things start to get slightly more complicated. Now we have effectively replaced two hydrogen atoms in ethane by larger methyl groups. These *are* large enough to get in the way of each other, that is, steric factors become a significant contribution to the rotational energy barriers. However, the main complication is that, as we rotate about the central C–C bond, not all the staggered conformations are the same, and neither are all the eclipsed conformations. The six conformations that butane can adopt as the central C–C bond is rotated in 60° intervals are shown below.



Look closely at these different conformations. The conformations with dihedral angles 60° and 300° are actually mirror images of each other, as are the conformations with angles 120° and 240°. This means that we really only have four different maxima or minima in energy as we rotate about the central C–C bond: two types of eclipsed conformations, which will represent maxima in the energy-rotation graph, and two types of staggered conformations, which will represent minima. These four different conformations have names, shown in the bottom row of the diagram. In the **syn-periplanar** and **anti-periplanar** conformations the two C–Me bonds lie in the same plane; in the **synclinal** (or gauche) and **anticlinal** conformations they slope towards (*syn*) or away from (*anti*) one another.

Before we draw the energy-rotation graph, let's just stop and think what it might look like. Each of the eclipsed conformations will be energy maxima but the syn-periplanar conformation ($\theta = 0°$) will be higher in energy than the two anticlinal conformations ($\theta = 120°$ and 240°): in the syn-periplanar-conformation two methyl groups are eclipsing each other whereas in the anticlinal conformations each methyl group is eclipsing only a hydrogen atom. The staggered conformations will be energy minima but the two methyl groups are furthest from each other in the anti-periplanar conformation so this will be a slightly lower minimum than the two synclinal (gauche) conformations.



As in ethane, the eclipsed conformations are not stable since any rotation leads to a more stable conformation. The staggered conformations are stable since they each lie in a potential energy well. The anti-periplanar conformation, with the two methyl groups opposite each other, is the most stable of all. We can therefore think of a butane molecule as rapidly interconverting between synclinal and anti-periplanar conformations, passing quickly through the eclipsed conformations on the way. The eclipsed conformations are energy maxima, and therefore represent the transition states for interconversion between conformers.

If we managed to slow down the rapid interconversions in butane (by cooling to very low temperature, for example), we would be able to isolate the three stable conformations—the anti-periplanar and the two synclinal conformations. These different stable conformations of butane are some sort of isomers. They are called *confor*mational iso*mers* or **conformers** for short.

▶ The rotation is very rapid indeed: the barrier of 20 kJ mol^{-1} corresponds to a rate at room temperature of 2×10^9 s^{-1}. This is far too fast for the different conformers to be detected by NMR (see p. 000): the NMR spectrum of butane shows only one set of signals representing an average of the two conformations.

Conformations and conformers

Butane can exist in an infinite number of *conformations* (we have chosen to show only the six most significant) but has only three *conformers* (potential energy minima)—the two synclinal (gauche) conformations and the anti-periplanar conformation.

▶ You now have a more thorough explanation of the zig-zag arrangement of carbon chains, first introduced in Chapter 2 when we showed you how to draw molecules realistically. This is the shape you get if you allow all the C–C bonds to take up the anti-periplanar conformation, and will be the most stable conformation for any linear alkane.

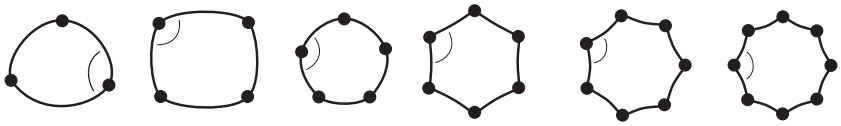
You will see why such detailed conformational analysis of acyclic compounds is so important in Chapter 19 on eliminations where the products of the reactions can be explained only by considering the conformations of the reactants and the transition states. But first we want to use these ideas to explain another branch of organic chemistry—the conformation of ring structures.

Ring strain

Up to now, we haven't given an entirely accurate impression of rings. We have been drawing them all as if they were planar—though this is actually not the case. In this section you will learn how to draw rings more accurately and to understand the properties of the different conformations adopted.

If we assume that in fully saturated carbocyclic rings each carbon is sp^3 hybridized, then each bond angle would ideally be 109.5°. However, in a planar ring, the carbon atoms don't have the luxury of choosing their bond angles: internal angle depends only on the number of atoms in the ring. If this angle differs from the ideal 109.5°, there will be some sort of strain in the molecule. This is best seen in the picture below where the atoms are forced planar. The more strained the molecules are, the more the bonds curve—in a strain-free molecule, the bonds are straight.

■ We have used ring strain a number of times to explain the reactivity and spectra of cyclic molecules.



all internal angles 109.5°

Number of atoms in ring	Internal angle in planar ring	109.5°—internal angle[a]
3	60°	49.5°
4	90°	19.5°
5	108°	1.5°
6	120°	–10.5°
7	128.5°	–19°
8	135°	–25.5°

[a] A measure of strain per carbon atom.

Notice how in the smaller rings the bonds curve outwards, whilst in the larger rings the bonds curve inwards. The table gives values for the internal angles for regular planar polygons and an indication of the strain per carbon atom due to the deviation of this angle from the ideal tetrahedral angle of 109.5°.

This data is best presented as a graph and the ring strains per carbon atom in planar rings for ring sizes up to seventeen are shown on p. 000. Whether the bonds are strained inwards or outwards is not important so only the magnitude of the strain is shown.

From these figures (represented in the graph on p. 000), note:

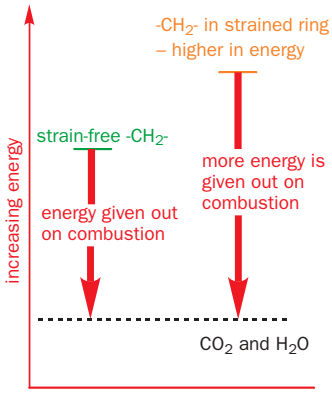
- The ring strain is largest for three-membered rings but rapidly decreases through a four-membered ring and reaches a minimum for a five-membered ring
- A planar five-membered ring is predicted to have the minimum level of ring strain
- The ring strain keeps on increasing (although less rapidly) as the rings get larger after the minimum at 5

But what we really need is a measure of the strain in actual compounds, not just a theoretical prediction in planar rings, so that we can compare this with the theoretical angle strain. A good measure of the strain in real rings is obtained using heats of combustion. Look at the following heats of combustion for some straight-chain alkanes. What is striking is that the difference between any two in the series is very nearly constant at around –660 kJ mol^{-1}.

■ A similar measurement was used in Chapter 7 to demonstrate the stabilization of benzene due to its aromaticity.

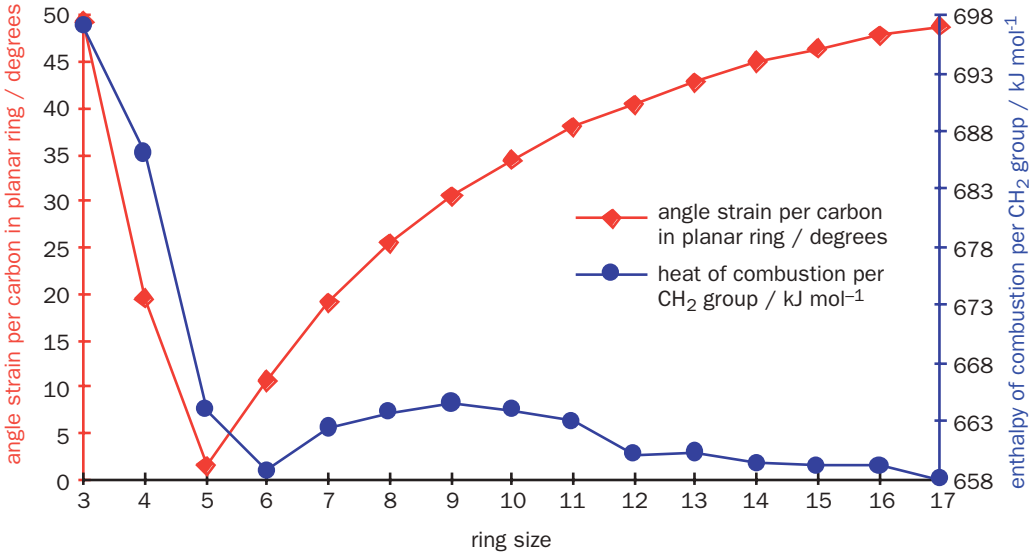
Heats of combustion for some straight-chain alkanes

Straight-chain alkane	$CH_3(CH_2)_nCH_3$: n =	$-\Delta H_{combustion}$, kJ mol^{-1}	Difference, kJ mol^{-1}
ethane	0	1560	
propane	1	2220	660
butane	2	2877	657
pentane	3	3536	659
hexane	4	4194	658
heptane	5	4853	659
octane	6	5511	658
nonane	7	6171	660
decane	8	6829	658
undecane	9	7487	658
dodecane	10	8148	661



If we assume (as is reasonable) that there is no strain in the straight-chain alkanes, then each extra methylene group, –CH_2–, contributes on average an extra 658.7 kJ mol^{-1} to the heat of combustion for the alkane. A cycloalkane $(CH_2)_n$ is simply a number of methylene groups joined together. If the cycloalkane is strain-free, then its heat of combustion should be $n \times 658.7$ kJ mol^{-1}. If, however, there is some strain in the ring that makes the ring less stable (that is, raises its energy) then more energy is given out on combustion.

Now, let's put all this together in a graph showing, for each ring size: (a) angle strain per CH_2 group; and (b) heat of combustion per CH_2 group.



Points to notice in the green-coloured graph:

- The greatest strain by far is in the three-membered ring, cyclopropane ($n = 3$)

▶ Chemists class rings as small, normal, medium, and large depending on their size.
- small, $n = 3$ or 4
- normal, $n = 5$, 6, or 7
- medium, $n = 8$–about 14
- large, $n >$ about 14

This is because these different classes all have different properties and synthetic routes to making them. The groupings are evident in the graph.

- The strain decreases rapidly with ring size but reaches a minimum for cyclohexane *not* cyclopentane as you might have predicted from the angle calculations
- The strain then increases but not nearly as quickly as the angle calculation suggested: it reaches a maximum at around $n = 9$ and then decreases once more
- The strain does not go on increasing as ring size increases but instead remains roughly constant after about $n = 14$
- Cyclohexane ($n = 6$) and the larger cycloalkanes ($n \geq 14$) all have heats of combustion per $-CH_2-$ group of around 658 kJ mol^{-1}, the same value as that of a $-CH_2-$ group in a straight-chain alkane, that is, *they are essentially strain-free*

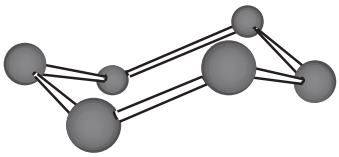
Why are there discrepancies between the two graphs? Specifically:
- Why are six-membered rings and large rings are virtually strain-free?
- Why there is still some strain in five-membered rings even though the bond angles in a planar structure are almost 109.5°?

The answer to the first point, as you may already have guessed, is that the assumption that the rings are planar is simply not correct. It is easy to see how large rings can fold up into many different conformations as easily as acyclic compounds do. It is less clear to predict what happens in six-membered rings.

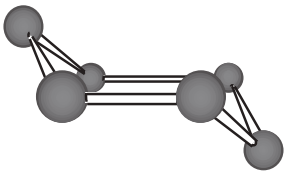
Six-membered rings

▶ By far the easiest way to get to grips with these different shapes is by building models. We strongly recommend you do this!

If you were to join six tetrahedral carbon atoms together, you would probably find that you ended up with a shape like this.



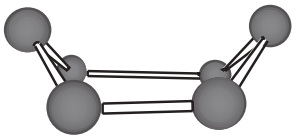
the carbon skeleton for cyclohexane



cyclohexane as a "chair"

All the carbon atoms are certainly not in the same plane, and there is no strain because all the bond angles are 109.5°. If you squash the model against the desk, forcing the atoms to lie in the same plane, it springs back into this shape as soon as you let go. If you view the model from one side (the second picture above) you will notice that four carbon atoms lie in the same plane with the fifth above the plane and the sixth below it (though it's important to realize that all six are identical—you can check this by rotating your model). The slightly overly imaginative name for this conformation—the **chair conformation**—derives from this view.

There is another conformation of cyclohexane that you might have made that looks like this.

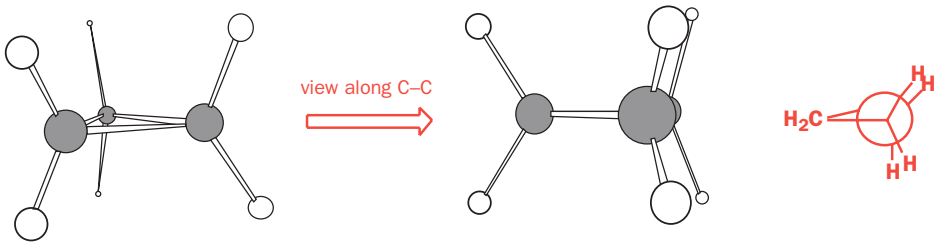


the boat conformation of cyclohexane

This conformation is know as the **boat conformation**. In this conformation there are still four carbon atoms in one plane, but the other two are both above this plane. Now all the carbon atoms are not the same—the four in the plane are different from the ones above. However, this is not a stable conformation of cyclohexane, even though there is no bond angle strain (all the angles are 109.5°). In order to understand why not, we must go back a few steps and answer our other question: why is cyclopentane strained even though a planar conformation has virtually no angle strain?

Smaller rings (thee, four, and five members)

The three carbon atoms in cyclopropane must lie in a plane since it is always possible to draw a plane through any three points. All the C–C bond lengths are the same which means that the three carbon atoms are at the corners of an equilateral triangle. From the large heat of combustion per methylene group (p. 000) we know that there is considerable strain in this molecule. Most of this is due to the bond angles deviating so greatly from the ideal tetrahedral value of 109.5°. Most but not all. If we view along one of the C–C bonds we can see a further cause of strain—all the C–H bonds are eclipsed.

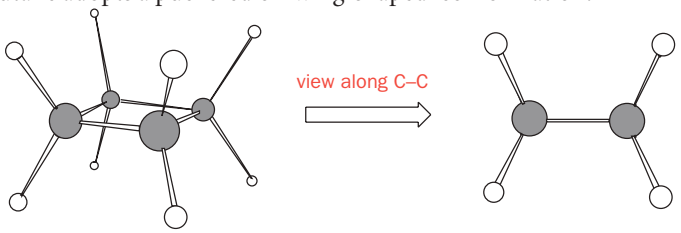


a side-on view of cyclopropane

viewing cyclopropane (almost) along a C–C bond shows that all the C–H bonds are eclipsed

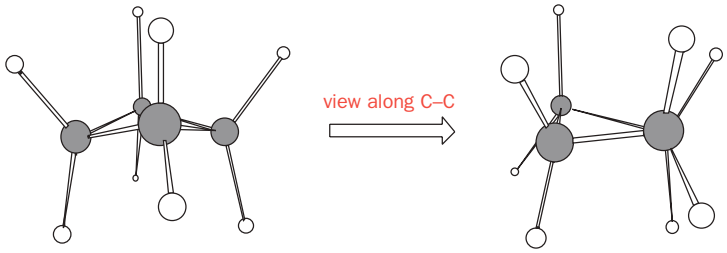
The eclipsed conformation of ethane is an energy maximum and any rotation leads to a more stable conformation. In cyclopropane it is not possible to rotate any of the C–C bonds and so all the C–H bonds are forced to eclipse their neighbours.

In fact, in any planar conformation all the C–H bonds will be eclipsed with their neighbours. In cyclobutane, the ring distorts from a planar conformation in order to reduce the eclipsing interactions, even though this reduces the bond angles further and so increases the bond angle strain. Cyclobutane adopts a puckered or 'wing-shaped' conformation.



planar cyclobutane (not the real conformation)

side-on view of planar cyclobutane shows eclipsing C–H bonds



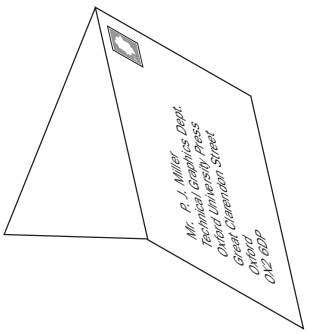
the puckered 'wing' conformation of cyclobutane

C–H bonds no longer fully eclipsed

This explains why cyclopentane is not entirely strain-free even though in a planar conformation the C–C–C bond angles are close to 109.5°. The heat of combustion data give us an indication of the total strain in the molecule, not just the contribution of angle strain. There is strain in planar cyclopentane caused by the eclipsing of adjacent C–H bonds. As in cyclobutane, the ring distorts to reduce the eclipsing interactions but this increases the angle strain. Whatever happens, there is always going to be some strain in the system. The minimum energy conformation adopted is a balance of the two opposing effects. Cyclopentane adopts a shape approximating to an 'open envelope', with four atoms in a plane and one above or below it. The atoms in the ring rapidly take turns not to be in the plane, and cyclopentanes have much less well-defined conformational properties than cyclohexanes, to which we shall now return.

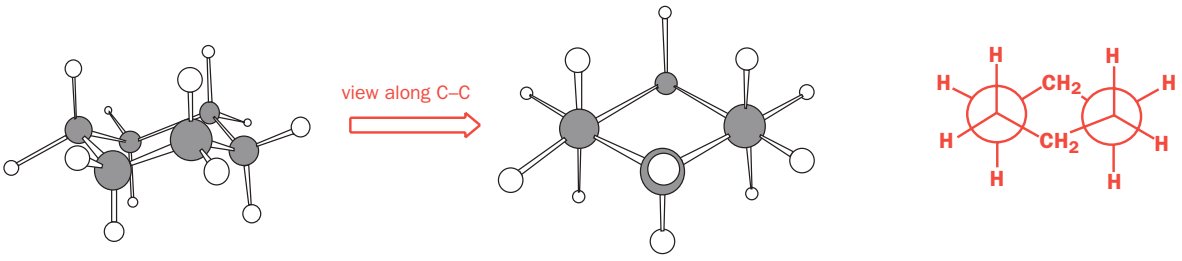
■ We shall consider the conformations, and reactions, of cyclopentanes in Chapter 33.

"open envelope" conformation of cyclopentane



A closer look at cyclohexane

The heats of combustion data show that cyclohexane is virtually strain-free. This must include strain from eclipsing interaction as well as angle strain. A model of the chair conformation of cyclohexane including all the hydrogen atoms looks like this.



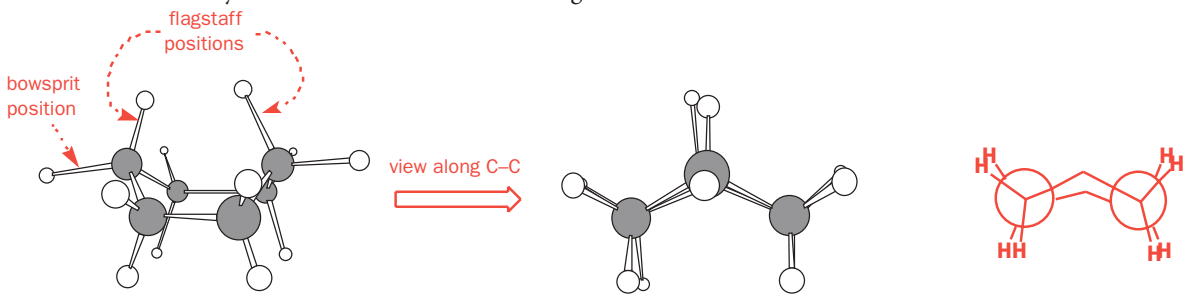
A side-on view of the chair conformation of cyclohexane

A view of cyclohexane looking along two of the C–C bonds.

A Newman projection of the same view

The view along two of the C–C bonds clearly shows that there are no eclipsing C–H bonds in the chair conformation of cyclohexane—in fact, all the bonds are fully staggered, giving the lowest energy possible. This is why cyclohexane is strain-free.

Contrast this with the boat conformation. Now all the C–H bonds are eclipsed, and there is a particularly bad interaction between the 'flagstaff' C–H bonds.

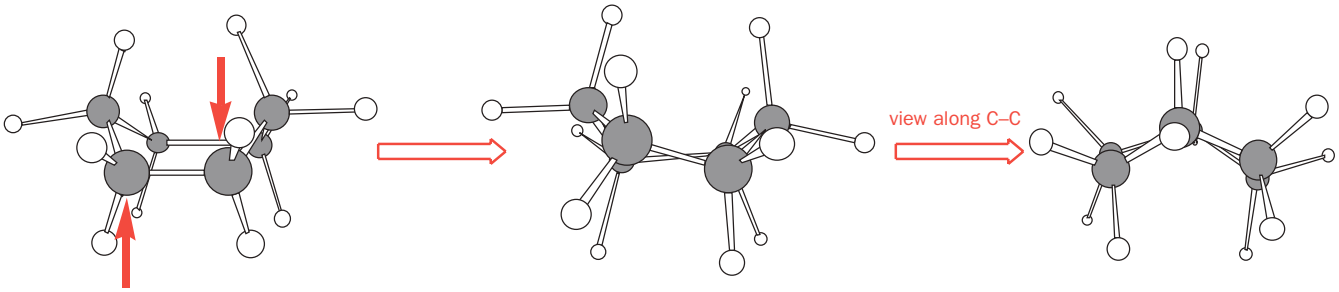


a side-on view of the boat conformation of cyclohexane

a view of the boat conformation looking along two of the C–C bonds

Newman projection of the same view

This explains why the boat conformation is much less important than the chair conformation. Even though both are free from angle strain, the eclipsing interactions in the boat conformation make it approximately 25 kJ mol^{-1} higher in energy than the chair conformation. In fact, as we shall see later, the boat conformation represents an energy maximum in cyclohexane whilst the chair conformation is an energy minimum. Earlier we saw how the eclipsing interactions in planar cyclobutane and cyclopentane could be reduced by distortion of the ring. The same is true for the boat conformation of cyclohexane. The eclipsing interactions can be relieved slightly if the two 'side' C–C bonds twist relative to each other.



pushing these two carbon atoms in the direction shown....

...gives a slightly different conformation in which the eclipsing interactions have been reduced: the "twist-boat:" conformation

an end-on view of the twist-boat conformation shows how the eclipsing interactions have been reduced

▶

A **local energy minimum** is the bottom of the potential energy well, but not necessarily the deepest possible well, which is the **global energy minimum**. Small changes in conformation will increase the energy, although a large change may be able to decrease the energy further. As an example, the synclinal (gauche) conformation of butane is a local energy minimum; the anti-periplanar conformation is the global energy minimum.

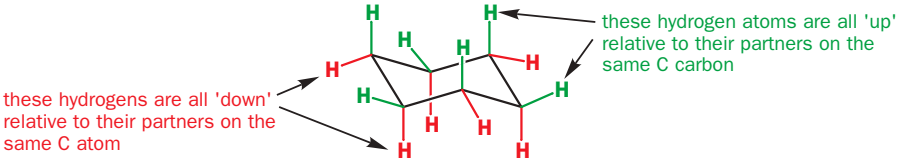
This twisting gives rise to a slightly different conformation of cyclohexane called the **twist-boat conformation**, which, although not as low in energy as the chair form, is lower in energy (by 4 kJ mol^{-1})

than the boat form and is a local energy minimum as we shall see later. Cyclohexane has two stable conformers, the chair and the twist boat. The chair form is approximately 21 kJ mol^{-1} lower in energy than the twist-boat form.

Drawing cyclohexane

Take another look at the chair conformation on p. 000. All six carbon atoms are identical, but there are two types of protons—one type stick either vertically up or down and are called **axial** hydrogen atoms; the other sort stick out sideways and are called **equatorial** hydrogen atoms.

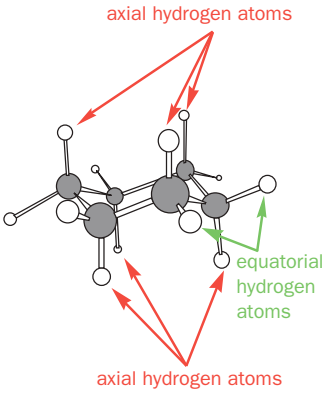
As you go round the ring, notice that each of the CH_2 groups has one hydrogen sticking up and one sticking down. However, all the 'up' ones alternate between axial and equatorial, as do all the 'down' ones.



Before going any further, it's important that you learn how to draw cyclohexane properly. Without cluttering the structure with Cs and Hs, a chemist would draw cyclohexane as one of these three structures.

Up to now, we have simply used the hexagon A to represent cyclohexane. We shall see that, whilst this is not strictly accurate, it is nonetheless still useful. The more correct structures B and C (which are actually just different views of the same molecule) take some practice to draw properly. A recommended way of drawing cyclohexane is shown in the box.

■ Compare the equator and axis of the earth: equatorial bonds are around the equator of the molecule. Note the spelling.



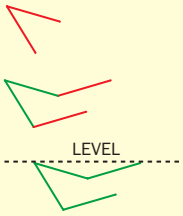
Guidelines for drawing cyclohexane

The carbon skeleton

Trying to draw the chair conformation of cyclohexane in one continuous line can lead to some dreadful diagrams. The easiest way to draw a chair conformation is by starting off with one end.

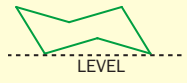
Next draw in two parallel lines of equal length.

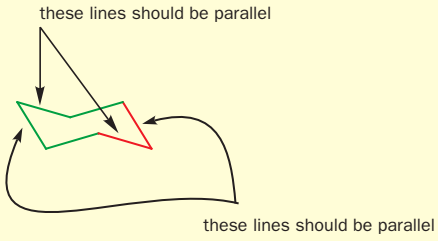
At this stage, the top of the new line should be level with the top of the original pair.



Finally, the last two lines should be added. These lines should be parallel to the first pair of lines as shown

and the lowest points should also be level.

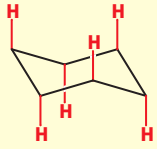




Adding the hydrogen atoms

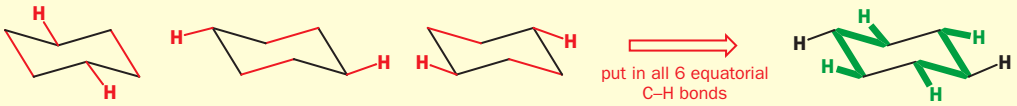
This is often the trickiest part. Just remember that you are trying to make each of the carbon atoms look tetrahedral. (Note that we don't normally use wedged and hashed bonds; otherwise things get really messy.)

The axial bonds are relatively easy to draw in. They should all be vertically aligned and alternate up and down all round the ring.



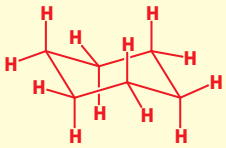
Guidelines for drawing cyclohexane (contd)

The equatorial bonds require a little more care to draw. The thing to remember is that each equatorial bond must be parallel to two C–C bonds.



in each diagram, all the red bonds are parallel

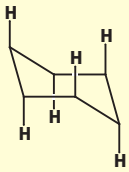
The complete diagram with all the hydrogen atoms should look like this.



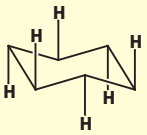
Common mistakes

If you follow all the guidelines above, you will soon be drawing good conformational diagrams. However, a few common mistakes have been included to show you what not to do!

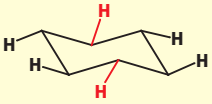
how *not* to draw cyclohexanes...



the chair has been drawn with the middle bonds horizantal, so the upper points of the chair are not level. This means the axial hydrogens can no longer be drawn vertical

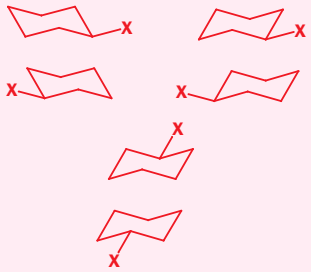


the axial hydrogens have been drawn alternating up and down on the wrong carbons. This structure is impossible because none of the carbons can be tetrahedral



the red hydrogens have been drawn at the wrong angles – look for the parallel lines and the 'W' and 'M'

▶ There is only one type of equatorial conformer, and one type of axial conformer. Convince yourself that these drawings are exactly the same conformation just viewed from different vantage points.



substituent equatorial

substituent axial

▶ Make a model of cyclohexane and try the ring inversion for yourself.

The ring inversion (flipping) of cyclohexane

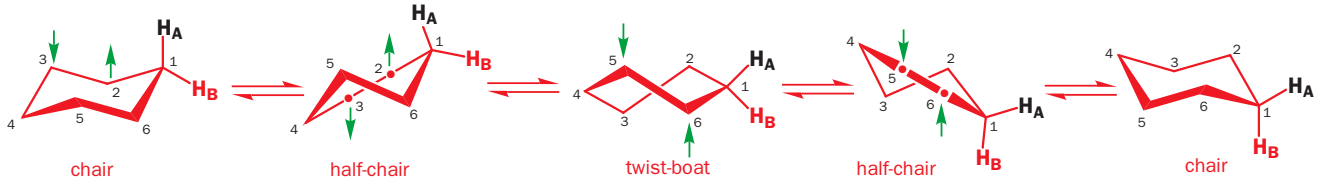
Given that this chair conformer is the preferred conformation for cyclohexane, what would you expect its ^{13}C NMR spectrum to look like? All six carbon atoms are the same so there should only be one signal (and indeed there is, at 25.2 p.p.m.). But what about the ^{1}H NMR spectrum? The two different sorts of protons (axial and equatorial) ought to resonate at different frequencies, so two signals should be seen (each with coupling to neighbouring protons). In fact, there is only *one* resonance in the proton spectrum, at 1.40 p.p.m.

In a monosubstituted cyclohexane, there should be two isomers detectable—one with the substituent axial, the other with the substituent equatorial. But again at room temperature only one set of signals is seen.

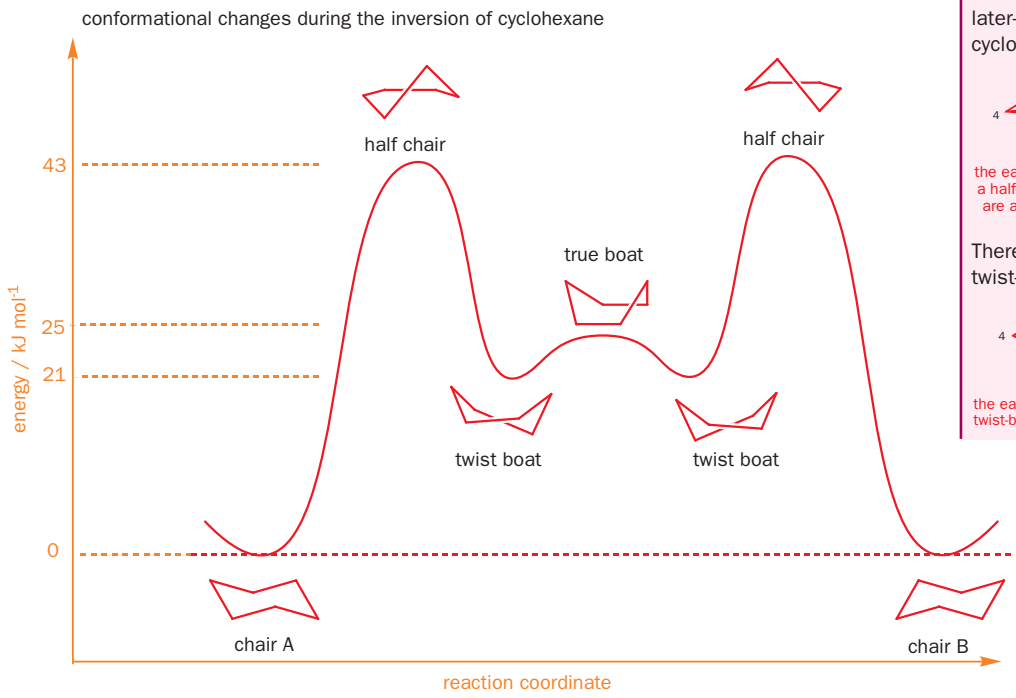
This changes when the NMR spectrum is run at low temperature. Now two isomers are visible, and this gives us a clue as to what is happening: the two isomers are conformers that interconvert—rapidly at room temperature, but more slowly when the temperature is lowered. Recall that NMR does not distinguish between the three different stable conformers of butane (two synclinal and one anti-periplanar) because they are all rapidly interconverting so fast that only an average is seen. The same happens with cyclohexane—just by rotating bonds (that is, without breaking any!) cyclohexane can **ring invert** or 'flip'. After ring inversion has taken place, all the bonds that were axial are now equatorial and vice versa.

ring inversion of a monosubstituted cyclohexane
notice that the hydrogen atom shown changes from axial to equatorial

The whole inversion process can be broken down into the conformations shown below. The green arrows show the direction in which the individual carbon atoms should move in order to get to the next conformation.

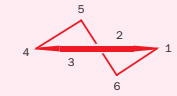


The energy profile for this ring inversion shows that the half-chair conformation is the energy maximum on going from a chair to a twist boat. The true boat conformation is the energy maximum on interchanging between two mirror-image twist-boat conformers, the second of which is converted to the other chair conformation through another half-chair.



It's clear from the diagram that the barrier to ring inversion of cyclohexane is 43 kJ mol^{-1}, or a rate at 25 °C of about 2×10^5 s^{-1}. Ring inversion also interconverts the axial and equatorial protons, so these are also exchanging at a rate of 2×10^5 s^{-1} at 25 °C—too fast for them to be detected individually by NMR, which is why they appear as an averaged signal.

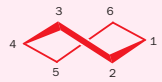
In the **half-chair** conformation of cyclohexane, four *adjacent* carbon atoms are in one plane with the fifth above this plane and the sixth below it. You will this conformation again later—it represents the energy minimum for cyclohexene, for example.



the easiest way of drawing a half-chair. Carbons 1–4 are all in the same plane

an alternative perspective of a half-chair conformation

There are also a number of ways of drawing a twist-boat conformer.



the easiest way to draw a twist-boat conformation. . .

. . . although it's easier to see why it's called a twist boat from this viewpoint

This would be a good point to remind you again of Chapter 13. This energy profile shows the conversion of one chair to another via two twist-boat *intermediates* (local energy minima). In between the energy minima are energy maxima, which are the *transition states* for the process. The progress of the ring-flipping 'reaction' is shown along an arbitrary 'reaction coordinate'.

Rates and spectroscopy

NMR spectrometers behave like cameras with a shutter speed of *about* 1/1000 s. Anything happening faster than that, and we get a blurred picture; things happening more slowly give a sharp picture. In fact, a more exact number for the 'shutter speed' of an NMR machine (not a real shutter speed—just figuratively speaking!) is given by the equation

$$k = \pi \Delta\nu / \sqrt{2} = 2.22 \times \Delta\nu$$

where k is the fastest exchange rate that still gives individual signals and $\Delta\nu$ is the separation of those signals in the NMR spectrum measured in hertz. For example, on a 200 MHz spectrometer, two signals separated by 0.5 p.p.m. are 100 Hz apart, so any process exchanging with a rate slower than 222 s^{-1} will still allow the NMR machine to show two separate signals; if they exchange with a rate faster than 222 s^{-1} only an averaged signal will be seen.

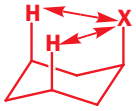
The equation above holds for any spectroscopic method, provided we think in terms of differences between signals or peaks measured in hertz. So, for example, a difference between two IR absorptions of 100 cm^{-1} can be represented as a wavelength of 0.01 cm (1×10^{-4} m) or a frequency of 3×10^{12} s^{-1}. IR can detect changes happening a lot faster than NMR can—its 'shutter speed' is of the order of one-trillionth of a second.

Substituted cyclohexanes

In a monosubstituted cyclohexane, there can exist two different chair conformers: one with the substituent axial, the other with it equatorial. The two chair conformers will be in rapid equilibrium (by the process we have just described) but they will not have the same energy. In almost all cases, *the conformer with the substituent axial is higher in energy*, which means there will be less of this form present at equilibrium.

this conformation is lower in energy

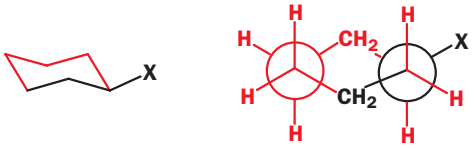
For example, in methylcylcohexane (X = CH_3), the conformer with the methyl group axial is 7.3 kJ mol^{-1} higher in energy than the conformer with the methyl group equatorial. This energy difference corresponds to a 20:1 ratio of equatorial:axial conformers at 25 °C.



There are two reasons why the axial conformer is higher in energy than the equatorial conformer. The first is that the axial conformer is destabilized by the repulsion between the axial group X and the two axial hydrogen atoms on the same side of the ring. This interaction is known as the **1,3-diaxial interaction**. As the group X gets larger, this interaction becomes more severe and there is less of the conformer with the group axial.

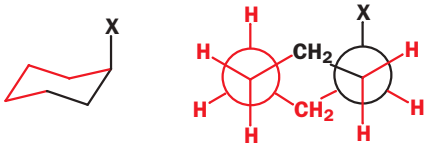
The second reason is that in the equatorial conformer the C–X bond is anti-periplanar to two C–C bonds, while, for the axial conformer, the C–X bond is synclinal (gauche) to two C–C bonds.

equatorially substituted cyclohexane:



the black bonds are anti-periplanar (only one pair shown for clarity)

axially substituted cyclohexane:



the black bonds are synclinal (gauche) (only one pair shown for clarity)

The table shows the preference of a number of substituted cyclohexanes for the equatorially substituted conformer over the axially substituted conformer.

$$K = \frac{\text{concentration of equatorial conformer}}{\text{concentration of axial conformer}}$$

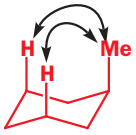
X	Equilibrium constant, *K*	Energy difference between axial and equatorial conformers, kJ mol^{-1}	% with substituent equatorial
H	1	0	50
Me	19	7.3	95
Et	20	7.5	95
i-Pr	42	9.3	98
t-Bu	>3000	>20	>99.9
OMe	2.7	2.5	73
Ph	110	11.7	99

Note the following points.

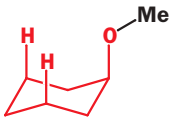
- The three columns in the table are three different ways of expressing the same information. However, just looking at the percentages column, it is not immediately obvious to see how much more of the equatorial conformer there is—after all, the percentages of equatorial conformer for methyl, ethyl, isopropyl, *t*-butyl, and phenyl-cyclohexanes are all 95% or more. Looking at the equilibrium constants gives a much clearer picture

- The amount of equatorial conformer present does increase in the order Me < Et < *i*-Pr < *t*-Bu, but perhaps not quite as expected. The ethyl group *must* be physically larger than a methyl group but there is hardly any difference in the equilibrium constants. The increase in the proportion of equatorial conformer on going from Et to *i*-Pr is only a factor of two but for *t*-butylcyclohexane, it is estimated that there is about 3000 times more of the equatorial conformer than the axial conformer
- The same anomaly occurs with the methoxy group—there is a much greater proportion of the conformer with a methoxy group axial than with a methyl group axial. This is despite the fact that the methoxy group is physically larger than a methyl group

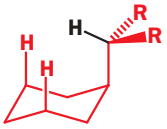
The equilibrium constant does not depend on the actual size of the substituent, but rather its interaction with the neighbouring axial hydrogens. In the case of the methoxy group, the oxygen acts as link and removes the methyl group away from the ring, lessening the interaction. The groups Me, Et, *i*-Pr, and *t*-Bu all need to point some atom towards the other axial hydrogens, and for Me, Et, and *i*-Pr this can be H. Only for *t*-Bu must a methyl group be pointing straight at the axial hydrogens, so *t*-Bu has a much larger preference for the equatorial position than the other alkyl groups. In fact, the interactions between an axial *t*-butyl group and the axial hydrogen atoms are so severe that the group virtually always stays in the equatorial position. As we shall see later, this can be very useful.



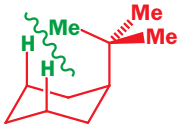
in the axial conformer of methylcyclohexane, there is a direct interaction between the methyl group and the axial hydrogen atoms



in methoxycyclohexane, the methyl group is removed somewhat from the ring



when a methyl, ethyl or *i*-propyl group is axial, only a hydrogen atom need lie directly over the ring



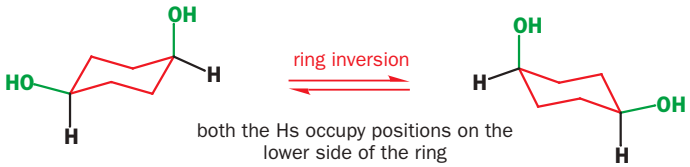
the steric requirements for putting a *t*-butyl group axial are enormous since now there is a severe interaction between a methyl group and the axial protons

What happens with more than one substituent on the ring?

When there are two or more substituents on the ring, stereoisomerism is possible. For example, there are two isomers of 1,4-cyclohexanediol—in one (the *cis* isomer) both the substituents are either above or below the cyclohexane ring; in the other (the *trans* isomer) one hydroxyl group is above the ring whilst the second is below. For a *cis*-1,4-disubstituted cyclohexane with both the substituents the same, ring inversion leads to a second identical conformation, while for the *trans* configuration there is one conformation with both groups axial and one with both groups equatorial.

cis-1,4-cyclohexanediol

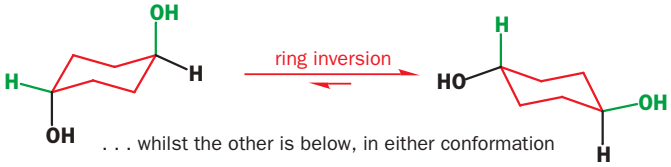
both the OH groups occupy positions on the upper side of the cyclohexane ring



both the Hs occupy positions on the lower side of the ring

in *trans*-1,4-cyclohexanediol, one OH group is above the plane of the ring in either conformation. .

trans-1,4-cyclohexanediol



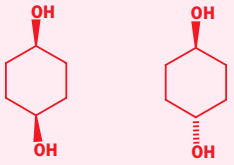
. . . whilst the other is below, in either conformation

conformer with both OHs axial

the more stable conformer with both OHs equatorial

▶ Ring inversion interconverts all of the axial and equatorial substituents, but it does not change which face of the ring a substituent is on. If an equatorial substituent starts off above the ring (that is, 'up' relative to its partner on the same C atom) it will end up above the ring, but now axial. Axial and equatorial are *conformational* terms; which side of the ring a substituent is on depends on the compound's *configuration*.

▶ The *cis* and *trans* compounds are different diastereoisomers. Consequently, they have different chemical and physical properties and cannot interconvert simply by rotating bonds.



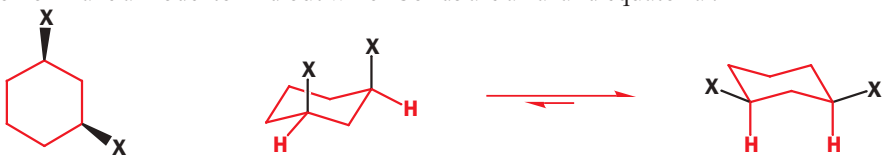
m.p. 113–114 °C m.p. 143–144 °C

This contrasts with the two *conformers* of *trans*-1,4-dimethoxycyclohexane (diaxial or diequatorial), which rapidly interconvert at room temperature without breaking any bonds.

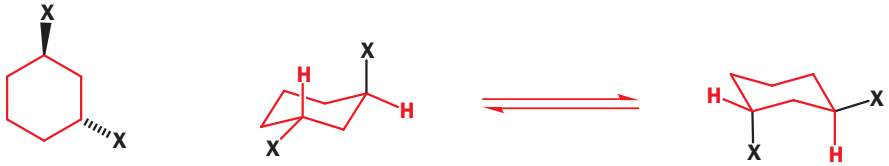
▶ It is not always easy to decide if an equatorial substituent is 'up' or 'down'. The key is to compare it with its axial partner on the same C atom—axial substituents very clearly point 'up' or 'down'. If the axial partner is 'up', the equatorial substituent must be 'down' and vice versa.

The chair-structure diagrams contain much more information than the simple 'hexagon' diagrams that we have used up to now. The former show both configuration and conformation—they show which stereoisomer (*cis* or *trans*) we are talking about and also (for the *trans* compound) the conformation adopted (diaxial or the more stable diequatorial). In contrast, the simpler hexagon diagrams carry no information about the conformation—only information about which isomer we are dealing with. This can be useful, because it enables us to talk about one configuration of a compound without specifying the conformation. When you are solving a problem requiring conformational diagrams to predict the configuration of a product, always start and finish with a configurational (hexagon) drawing.

The chair conformer of *cis*-1,4-disubstituted cyclohexane has one substituent equatorial, the other axial. This will not necessarily be this case for other substitution patterns; for example, the chair conformer of a *cis*-1,3-disubstituted cyclohexane has either both substituents axial or both equatorial. Remeber, the '*cis*' and '*trans*' prefixes merely indicate that both groups are on the same 'side' of the cyclohexane ring. Whether the substituents are both axial/equatorial or one axial and the other equatorial depends on the substitution pattern. Each time you meet a molecule, draw the conformation or make a model to find out which bonds are axial and equatorial.

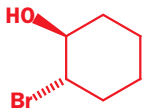


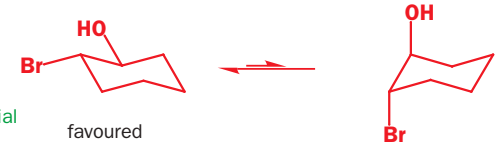
cis-1,3-disubstituted cyclohexane — in both conformers, both substituents are 'up'



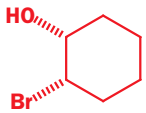
trans-1,3-disubstituted cyclohexane — in both conformers one substituent is 'up', the other 'down'

What if the two substituents on the ring are different? For the *cis* 1,3-disubstituted example above, there is no problem, because the favoured conformation will still be the one that places these two different substituents equatorial. But when one substituent is axial and the other equatorial (as they happen to be in the *trans* diastereoisomer above) the preferred conformation will depend on what those substituents are. In general, the favoured conformation will place the maximum number of substituents equatorial. If both conformations have the same number of equatorial substituents, the one with the larger substituent equatorial will win out, and the smaller group will be forced to be axial. Various possibilities are included in the examples below.

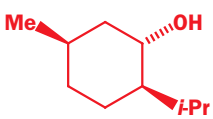




two substituents equatorial none axial — favoured — no substituents equatorial two axial

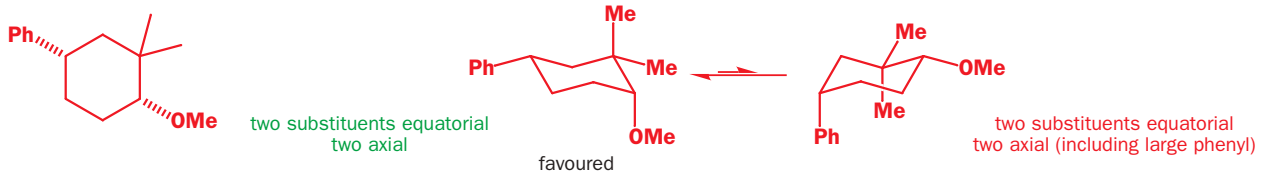


one substituents equatorial one axial (smaller OH) — favoured — one substituents equatorial one axial (large Br)



isomenthol

two substituents equatorial one axial — favoured — one substituent equatorial two axial



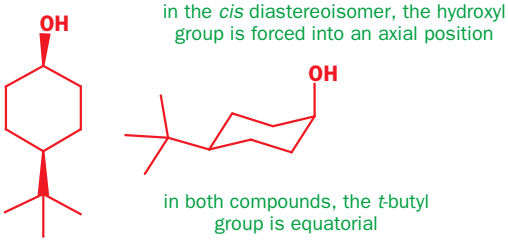
This is only a guideline, and in many cases it is not easy to be sure. Instead of concerning ourselves with these uncertainties, we shall move on to some differentially substituted cyclohexanes for which it is absolutely certain which conformer is preferred.

Locking groups—*t*-butyl groups, decalins, and steroids

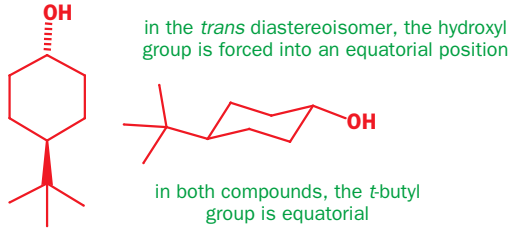
t-Butyl groups

We have already seen how a *t*-butyl group always prefers an equatorial position in a ring. This makes it very easy to decide which conformation the two different compounds below will adopt.

cis-4-*t*-butylcyclohexanol

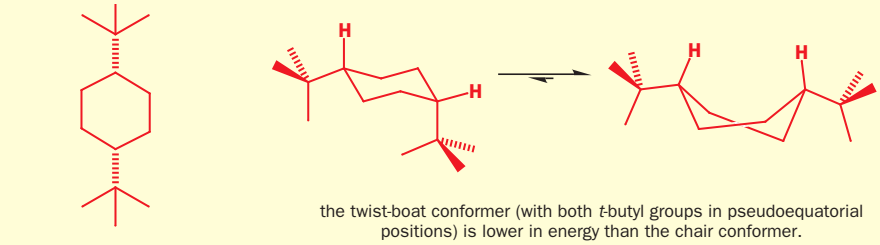


trans-4-*t*-butylcyclohexanol



Cis-1,4-di-*t*-butylcyclohexane

An axial *t*-butyl group really is very unfavourable. In *cis*-1,4-di-*t*-butylcyclohexane, one *t*-butyl group would be forced axial if the compound existed in a chair conformation. To avoid this, the compound prefers to pucker into a twist boat so that the two large groups can both be in equatorial positions (or 'pseudoequatorial', since this is not a chair).

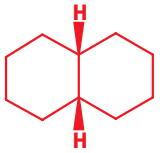


cis-1,4-di-*t*-butylcyclohexane

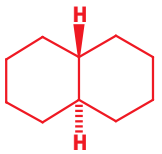
the twist-boat conformer (with both *t*-butyl groups in pseudoequatorial positions) is lower in energy than the chair conformer.

Decalins

It is also possible to lock the conformation of a cyclohexane ring by joining another ring to it. **Decalin** is two cyclohexane rings fused at a common C–C bond. Two diastereoisomers are possible, depending on whether the hydrogen atoms at the ring junction are *cis* or *trans*. For *cis*-decalin, the second ring has to join the first so that it is axial at one point of attachment and equatorial at the other; for *trans*-decalin, the second ring can be joined to the first in the equatorial position at both attachment points.

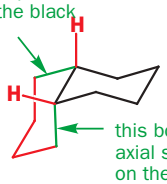


cis-decalin

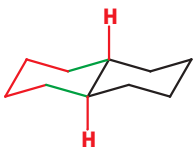


trans-decalin

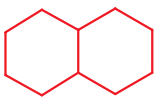
this bond is an equatorial substituent on the black ring



this bond is an axial substituent on the black ring



both green bonds are equatorial substituents on the black ring

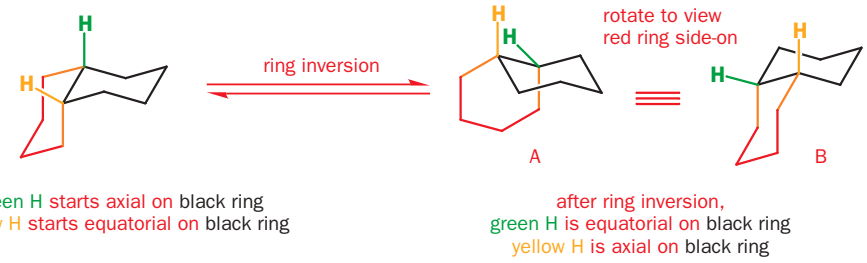


decalin

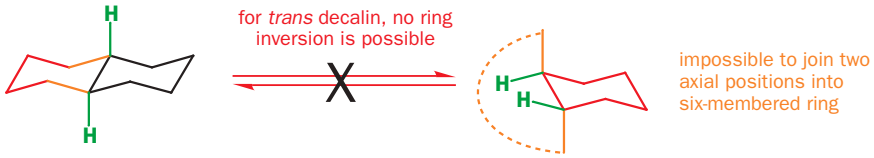
▶ If you find it hard to visualize the ring inversion of *cis*-decalin, you are not alone! The best way to think about it is to ignore the second ring till the very end: just concentrate on what happens to one ring (black in this diagram), the hydrogens at the ring junction, and the (orange) bonds next to these hydrogens that form the 'stumps' of the second ring. Flip the black ring, and the 'stumps', and the hydrogens swap from axial to equatorial and vice versa. Draw the result, but don't fill in the second ring yet or it will usually just come out looking like a flat hexagon (as in diagram A). Instead, rotate the complete (black) ring 60° about a vertical axis so that both of the orange 'stumps' can form part of a chair, which can now be filled in (diagram B). To make a chair (and not a hexagon) they must be pointing in a convergent direction, as the orange bonds are in B but not A.

When a cyclohexane ring inverts, the substituents that were equatorial become axial and vice versa. This is fine for *cis*-decalin, which has an axial–equatorial junction, but it means that ring inversion is not possible for *trans*-decalin. For *trans*-decalin to invert, the junction would have to become axial–axial, and it's not possible to link the axial positions to form a six-membered ring. *Cis*-decalin, on the other hand, ring inverts just as fast as cyclohexane.

ring inversion of *cis*-decalin

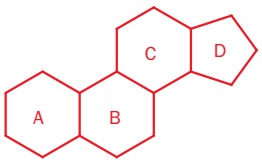


no ring inversion in *trans*-decalin



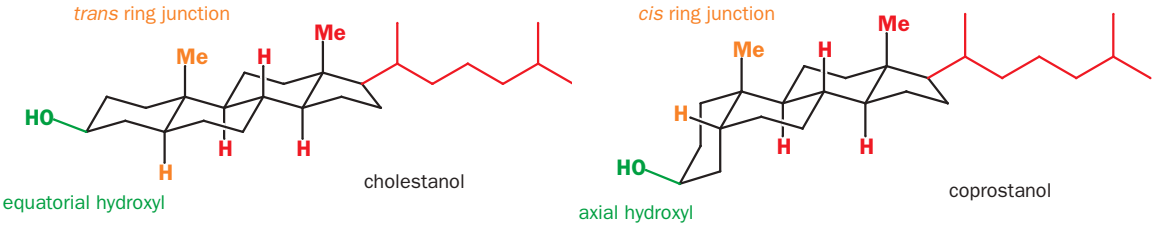
Steroids

Steroids are an important class of compounds occurring in all animals and plants and have many important functions from regulating growth (anabolic steroids) and sex drive (all sex hormones are steroids) to acting as a self-defence mechanism in plants, frogs, and even sea cucumbers. A steroid is defined by its structure: all steroids contain a basic carbon framework consisting of four fused rings—three cyclohexane rings and one cyclopentane ring—labelled and joined together as shown in the margin.



the steroid skeleton

Just as in the decalin system, each ring junction could be *cis* or *trans*, but it turns out that all steroids have all *trans*-junctions except where rings A and B join which is sometimes *cis*. Examples are cholestanol (all *trans*) and coprostanol (A and B fused *cis*).



■ It was a desire to explain the reactions of steroids that led Sir Derek Barton (1918–98) to discover, in the 1940s and 1950s, the principles of conformational analysis described in this chapter. It was for this work that he shared the Nobel prize in 1969. We will come back to steroids in more detail in Chapter 51.

Because steroids (even those with a *cis* A–B ring junction) are essentially substituted *trans*-decalins they can't ring flip. This means, for example, that the hydroxyl group in cholestanol is held equatorial on ring A while the hydroxyl group in coprostanol is held axial on ring A. The steroid skeleton really is remarkably stable—samples of sediment 1.5×10^9 years old have been found to contain steroids still with the same ring-junction stereochemistry.

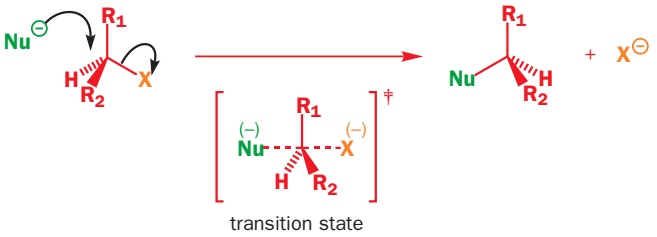
Axially and equatorially substituted rings react differently

We shall be using ring structures throughout the rest of the book, and you will learn how the conformation affects chemistry extensively. Here we shall give a few examples in which the outcome of a reaction may depend on whether a functional group is axial or equatorial. In many of the examples, the functional group will be held in its axial or equatorial position by 'locking' the ring using a *t*-butyl group or a fused ring system such as *trans*-decalin.

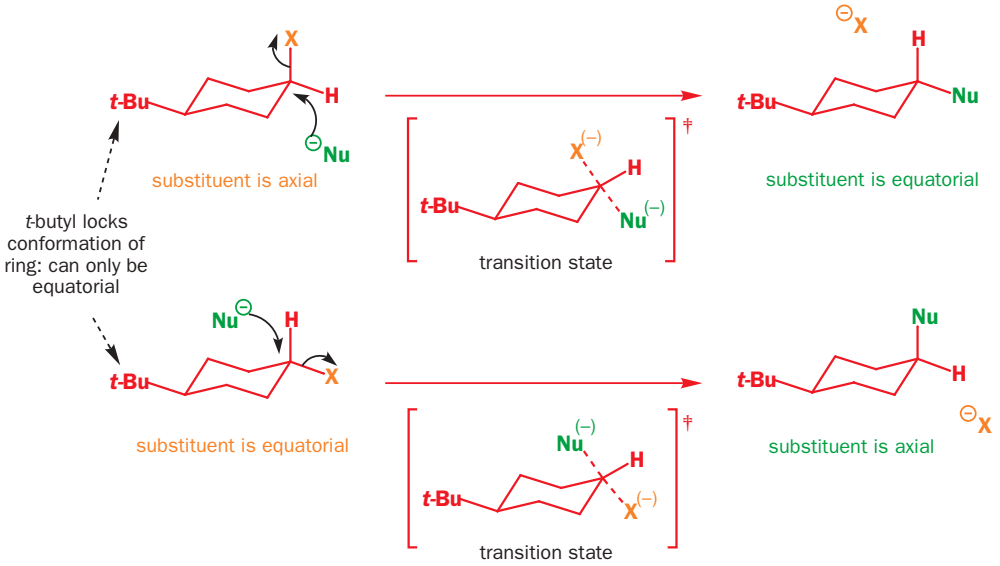
Nucleophilic substitution

In the last chapter we looked at two mechanisms for nucleophilic substitution: S_N1 and S_N2. We saw that the S_N2 reaction involved an inversion at the carbon centre. Recall that the incoming nucleophile had to attack the σ* orbital of the C–X bond. This meant that it had to approach the leaving group directly from behind, leading to inversion of configuration.

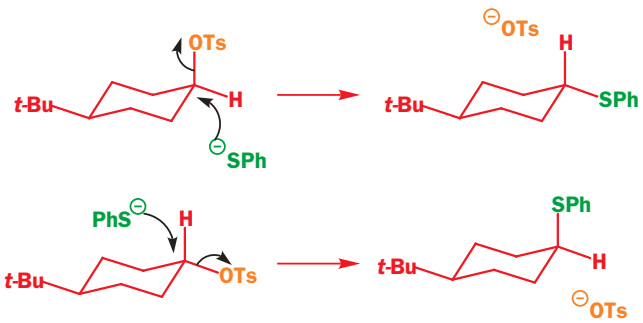
inversion during nucleophilic substitution at saturated carbon



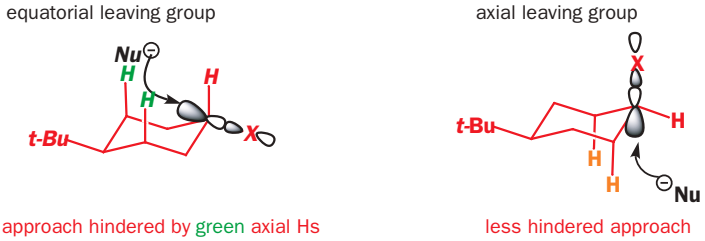
What do you think would happen if a cyclohexane derivative underwent an S_N2 reaction? If the conformation of the molecule is fixed by a locking group, the inversion mechanism of the S_N2 reaction, means that, if the leaving group is axial, then the incoming nucleophile will end up equatorial and vice versa.



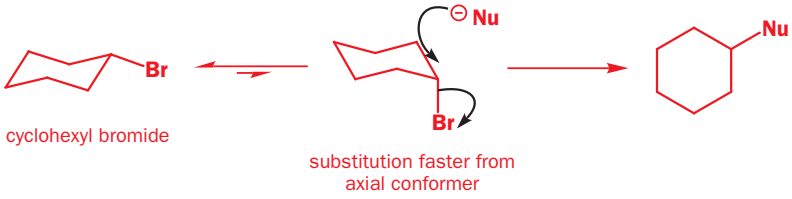
Substitution reactions are not very common for substituted cyclohexane. The substituted carbon in a cyclohexane ring is a secondary centre—in the last chapter, we saw that secondary centres do not react well via either S_N1 or S_N2 mechanisms (p. 000). To encourage an S_N2 mechanism, we need a good attacking nucleophile and a good leaving group. One such example is shown—the substitution of a tosylate by PhS^-.



It is found that the substitution of an axial substituent proceeds faster than the substitution of an equatorial substituent. There are several contributing factors making up this rate difference, but probably the most important is the direction of approach of the nucleophile. The nucleophile must attack the σ* of the leaving group, that is, directly behind the C–X bond. In the case of an equatorially substituted compound, this line of attack is hindered by the (green) axial hydrogens—it passes directly through the region of space they occupy. For an axial leaving group, the direction of attack is parallel with the (orange) axial hydrogens anti-periplanar to the leaving group, and approach is much less hindered.

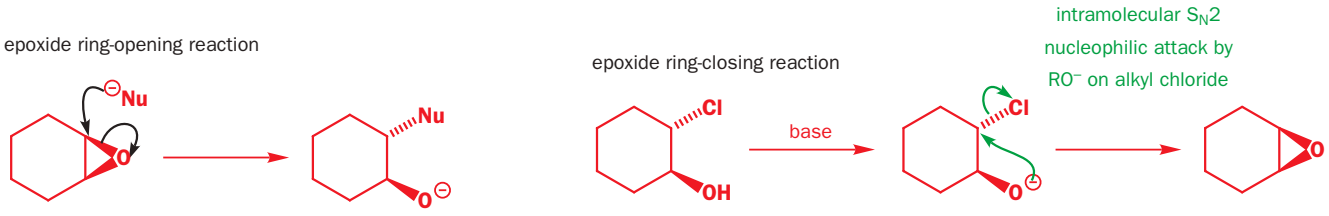


We must assume that this holds even for simple unsubstituted cyclohexanes, and that substitution reactions of cyclohexyl bromide, for example, occur mainly on the minor, axial conformer. This slows down the reaction because, before it can react, the prevalent equatorial conformer must first flip axial.



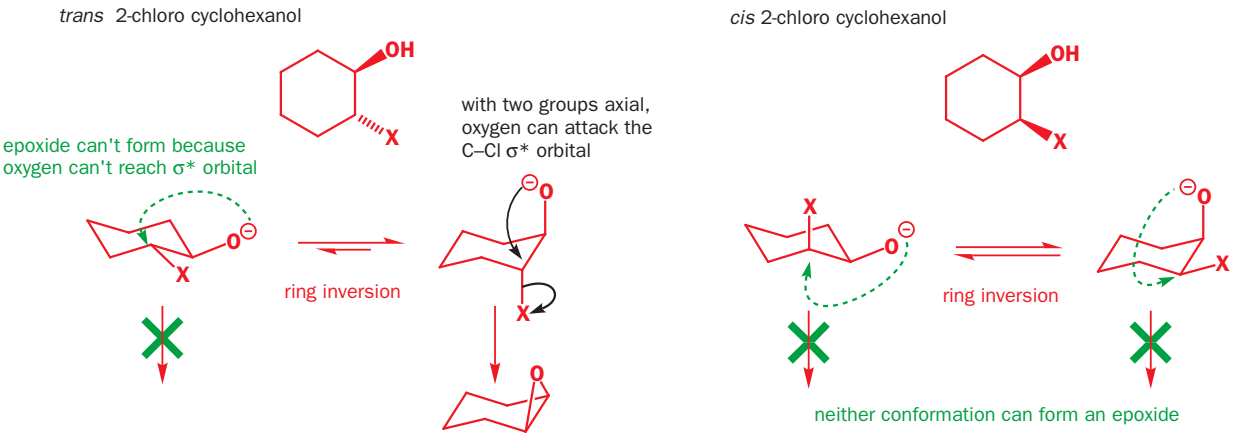
Epoxides

In the last chapter you met epoxides as electrophiles reacting with nucleophiles such as amines and azide, and we shall look at this sort of reaction again in a few pages time. Epoxides can be formed from compounds containing an adjacent hydroxyl group and a leaving group by treatment with base. The reaction is essentially the reverse of their ring-opening reaction with nucleophiles.

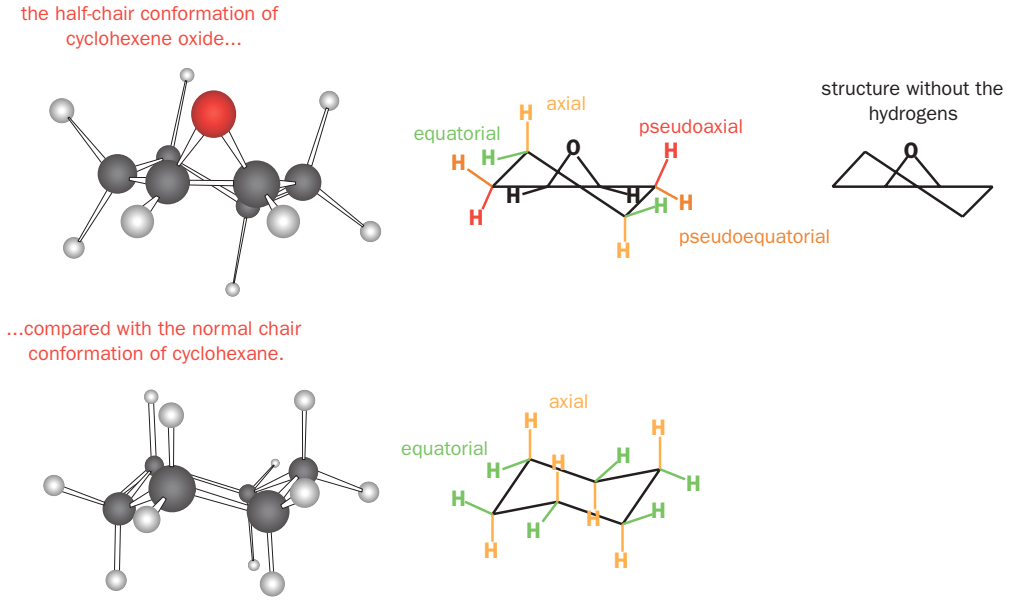


As for intermolecular substitutions, the incoming nucleophile must still attack into the σ* orbital of the leaving group. In the formation of an epoxide, such an attack can take place only if both groups are axially substituted. As a consequence, only a *trans* 2-chloro cyclohexanol can form an epoxide, and then only when in the less energetically favourable conformation with both groups axial. Of course, as the diaxial conformer reacts, rapid ring inversion of the major equatorial isomer ensures that it is replaced.

■ In Chapter 37 you will meet the alternative **rearrangement reactions** that occur if you try and force *cis*-substituted compounds like these to react.

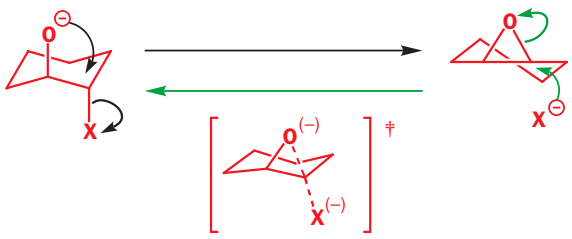


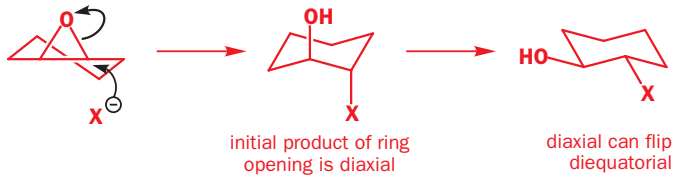
It is impossible for the CO bonds of the product epoxide ring to adopt perfectly axial and equatorial positions. If you make a model of cyclohexene oxide you will see that the ring is a slightly deformed chair—it is more of a half-chair conformation in which four of the carbon atoms are in the same plane (you met this on p. 000).



The usual way of drawing cyclohexene oxide is shown: notice that the distortion due to the three-membered ring changes the orientation of the axial and equatorial hydrogens next to the ring—they are **pseudoaxial** and **pseudoequatorial**. The hydrogens on the back of the ring (this part of the ring remains about the same as in the chair conformation) can be still considered as 'normal' axial and equatorial hydrogens.

We said that the epoxide-forming reaction is essentially the reverse of the epoxide-opening reaction. If we took a snapshot of the transition state for either reaction, we would not be able to tell whether it was the RO^- that was attacking the C–X σ* to form the epoxide or the X^- attacking the C–O σ* of the epoxide to form a ring-opened alcohol. In other words, the transition state is the same for both reactions.

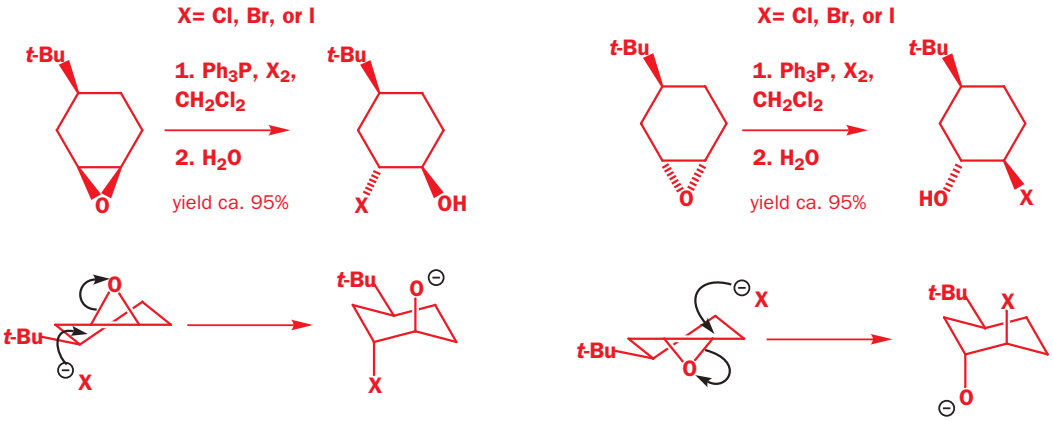




Since ring closure is only possible when the starting material is diaxially substituted, this has to mean that ring opening is similarly only possible if the *product* is diaxial. This is a general principle: *ring opening of cyclohexene oxides always leads directly to diaxial products.* The diaxially substituted product may then subsequently flip to the diequatorial one.

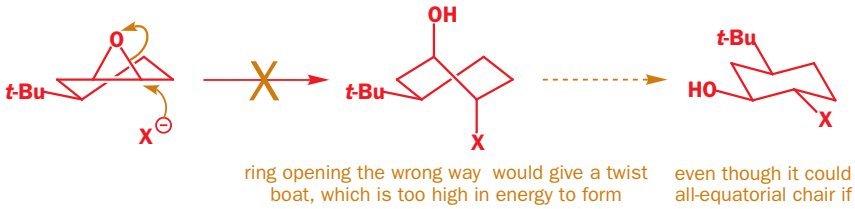
How do we know this to be true? If the ring bears a *t*-butyl substituent, ring flipping is impossible, and the diaxial product has to stay diaxial. An example is nucleophilic attack of halide on the two epoxides shown below.

▶ Ph_3P/X_2 is a way of making reactive, unsolvated X^- in nonpolar solvent, favouring S_N2.



Points to note:

- The *t*-butyl group locks the conformation of the epoxide. Whereas cyclohexene oxide can flip (see above), enabling the nucleophile to attack either of the epoxide carbon atoms, here the ring is conformationally rigid
- The nucleophile must attack from the opposite side of the epoxide into the C–O σ*. This means that the nucleophile and hydroxyl group end up *trans* in the product
- In each case the epoxide opens only at the end that gives the diaxially substituted chair. Ring opening at the other end would still give a diaxially substituted product, but it is a diaxially substituted high-energy twist-boat conformation. The twist boat can, in fact, flip to give an all-equatorial product, but this is a kinetically controlled process, and it is the barrier to reaction that matters, not the stability of the final product

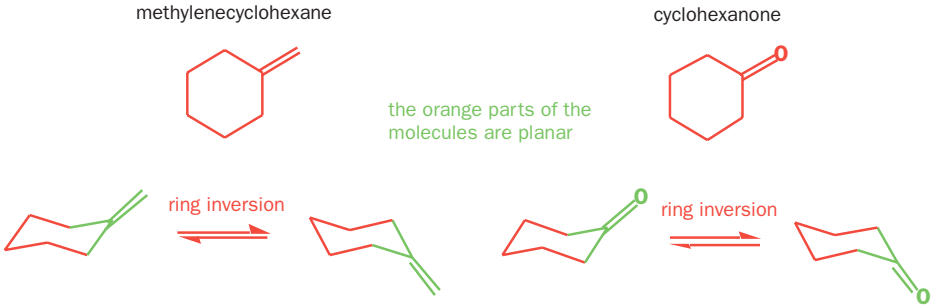


Axial attack on half-chairs

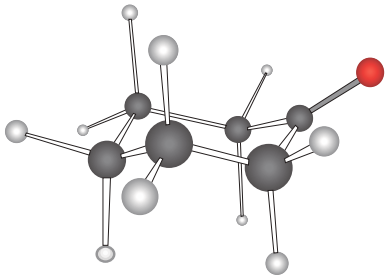
Epoxide openings are not alone in always giving diaxial products. We can give the general guideline that, for any reaction on a six-membered ring that is not already in the chair conformation, axial attack is preferred. You will see in later chapters that this is true for cyclohexenes, which also have the half-chair conformation described in the next section. Cyclohexanones, on the other hand, already have a chair conformation, and so can be attacked axially or equatorially.

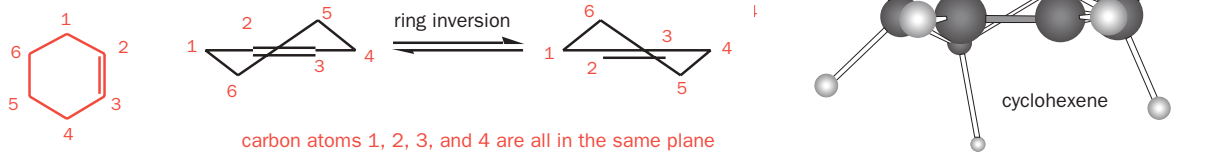
Rings containing sp^2 hybridized carbon atoms: cyclohexanone and cyclohexene

Every ring you've seen in this chapter has been fully saturated. You've seen the distortion to a half-chair resulting from fusion of a six-membered ring with an epoxide—what happens if some of the tetrahedral carbons are replaced with trigonal (sp^2) hybridized ones? Well, for one sp^2 carbon atom the simple answer is nothing—the conformation is not significantly altered by the presence of just one sp^2 centre in a ring. The conformations of methylenecyclohexene and cyclohexanone—along with a model of cyclohexanone—are shown below.



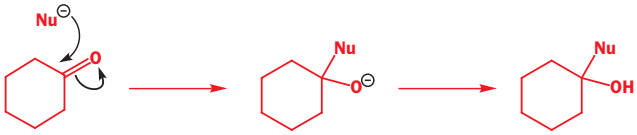
Six-membered rings with *more than one* sp^2 C atom do lose their chair conformation—they become flattened to some degree when there are one or more double bonds included in the ring. Cyclohexene, with just one double bond in the ring, has a half-chair conformation similar to that of its related epoxide, cyclohexene oxide. The usual conformational diagram of cyclohexene is shown below. The barrier for ring inversion of cyclohexene is around 22 kJ mol^{-1} (about half that for cyclohexane).


cyclohexanone

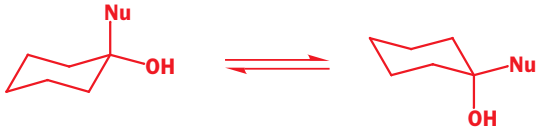


cyclohexene

We will look more closely at the reactions of cyclohexene along with other alkenes in later chapters. For now, we return to the chemistry of cyclohexanones. Before you had read this chapter you might simply have drawn the mechanism for nucleophilic attack on cyclohexanone as shown.

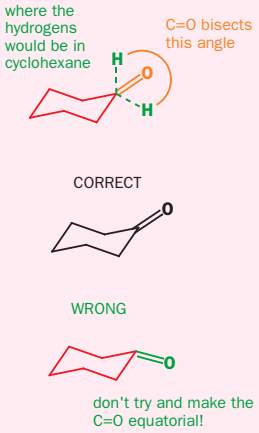


The product contains the two functional groups Nu and OH, which you now know can be arranged in two conformations: one in which the alcohol is axial and one in which it is equatorial. But we can't predict which conformation is more favourable without knowing what the group Nu is: if Nu is smaller than OH (H, say) then the conformation with the hydroxyl



▶ Drawing cyclohexanones

Make sure you point the ketone in the right direction! It should bisect the angle there would be between the axial and equatorial substituents, if the carbon atom were tetrahedral. It's always best to put the carbonly group at one of the 'end' carbons of the ring: it's much harder to get it right if you join it to one of the middle ones.

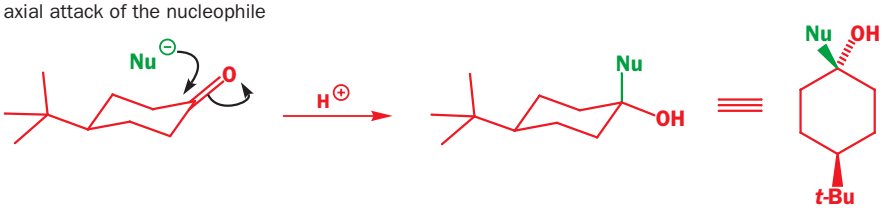


group equatorial will be lower in energy; if Nu is large then the most stable conformation will have the alcohol group axial and Nu equatorial.

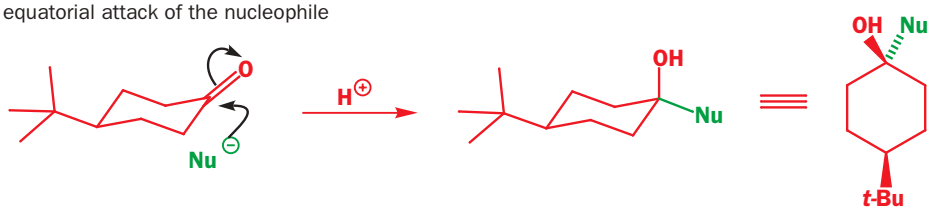
Now think of a nucleophile attacking 4-*t*-butylcyclohexanone. Since the *t*-butyl group locks the ring, whether Nu is axial or equatorial will depend only on which face of the C=O group it attacked. Attack on the same face as the *t*-butyl group leaves the nucleophile axial and the hydroxyl group equatorial; attack on the opposite face leaves the nucleophile equatorial and the hydroxyl group axial. The nucleophile is said to attack either in an axial or equatorial manner, depending on where it ends up. It's easier to see this in a diagram.

■ Remember the guideline in the summary box on p. 000: unlike cyclohexene oxides, cyclohexanones are already chairs, so they can be attacked from the axial *or* the equatorial direction.

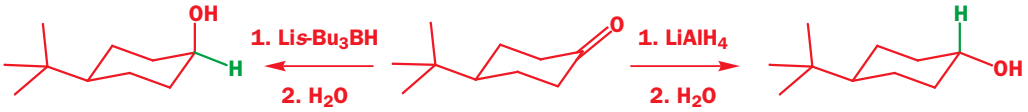
axial attack of the nucleophile



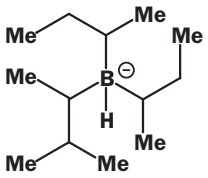
equatorial attack of the nucleophile

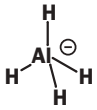


Now for the observation—we'll try and explain it later. In general, large nucleophiles attack equatorially and small nucleophiles attack axially. For example, reduction of 4-*t*-butylcyclohexanone with lithium aluminium hydride in Et_2O gives 90% of the *trans* alcohol: 90% of the hydride has added axially. AlH_4^- is quite small as nucleophiles go: to make more of the *cis* alcohol we need a larger nucleophile—lithium tri-*sec*-butylborohydride, for example, sold under the name of L-selectride®. This is so large that it only attacks equatorially, yielding typically 95% of the *cis* alcohol.



large nucleophile: 96% equatorial attack small nucleophile: 90% axial attack





Carbon-centred nucleophiles follow the same trend—the table shows that, as size increases from the slender ethynyl anion through primary and secondary organometallics to *t*-BuMgBr, the axial selectivity drops off correspondingly.

■ The diagrams on p. 000 make this clear.

Now the difficult part—why? This is a question that is very difficult to answer because the answer really is not known for certain. It's certainly true that the direction of approach for axial attack is more hindered than for equatorial attack, and this is certainly the reason large nuclophiles prefer to attack equatorially.

▶ Ph is flat and can slip through.

	% of product resulting from	
Nucleophile	**Axial attack**	**Equatorial attack**
HC≡CNa	88	12
MeLi	35	65
PhLi	42	58
MeMgBr	41	59
EtMgBr	29	71
i-PrMgBr	18	82
t-BuMgBr	0	100

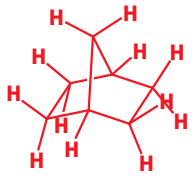
But if this is the case, why do small ones actually *prefer* to attack axially? There must be another factor that favours axial attack for those nucleophiles small enough to avoid the bad interactions with the other axial hydrogens. At the transition state, the forming $-O^-$ oxygen substituent is moving in either an axial or an equatorial direction. Just as the axial substituent is less favourable than an equatorial one, so is the transition state leading there, and the route leading to the equatorial hydroxyl group is favoured.

Multiple rings

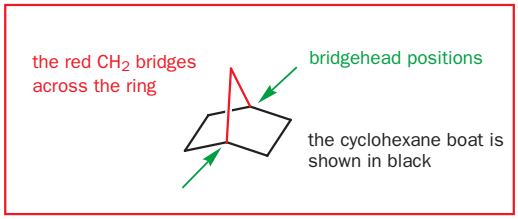
Cyclohexane sometimes adopts a twist-boat conformation, but never a true boat structure, which represents an energy maximum. But boat structures are important in some bicyclic compounds where the compound simply doesn't have any choice in the conformation it adopts. The simplest compound locked into a boat structure is norbornane. The CH_2 bridge *has* to be diaxial (otherwise it can't reach), which means that the cyclohexane ring part of the structure has no choice but to be a boat.

norbornane

without the hydrogens



with hydrogens included

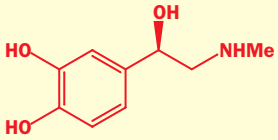


Nor-

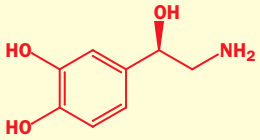
The *nor-* prefix has a number of meanings in 'trivial' organic nomenclature. Here it tells us that this structure is like that of the parent compound but less one or more alkyl groups—that is, *no R* groups. This isn't the derivation of the word though—historically it comes from the German *Nitrogen ohne Radikal* ('nitrogen without R-groups')—it was used first for amines such noradrenaline (also known as norephinephrine)and norephedrine. You met ephedrine in Chapter 16.

camphor
(bornane skeleton in red)

norbornane



adrenaline



noradrenaline

Look closely at the structure of norbornane with its full quota of hydrogen atoms, and you will see that all of the hydrogen atoms on the six-membered ring (except those on the bridgehead carbons) eclipse hydrogens on neighbouring carbon atoms. There is some evidence that the next member in this series of bicyclic alkanes, [2.2.2]-bicyclooctane, flexes slightly to avoid the eclipsing interactions.

[2.2.2]bicyclooctane

[2.2.2]-bicyclooctane

It is worth briefly explaining this systematic name. *Octane* is obvious—it's C_8. And *bicyclo* is the minimum two rings required to define the structure. [2.2.2] means that each linking chain from one bridgehead to the other is two carbon atoms long. This system of nomenclature allows norbornane to be given the systematic (and less memorable) name [2.2.1]-bicycloheptane. In Chapter 8 you met the bases DBU (1,8-diazabicyclo[5.4.0]undecene-7) and DBN (1,5-diazabicyclo[3.4.0]nonene-5) named in the same way—and you will meet them again in the very next chapter, as they are particularly good bases for the promotion of elimination reactions.

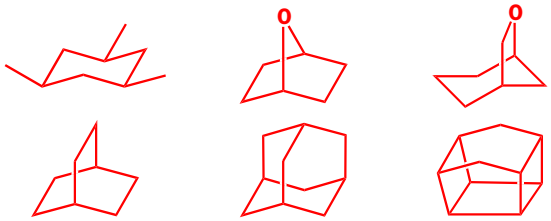
To conclude...

You may wonder why we have spent most of this chapter looking at six-membered rings, ignoring other ring sizes almost totally. Apart from the fact that six is the most widespread ring size in organic chemistry, the reactions of six-membered rings are also the easiest to explain and to understand. The

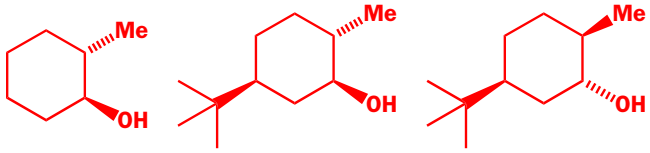
conformational principles we have outlined for six-membered rings (relief of ring strain, staggered favoured over eclipsed, equatorial favoured over axial, direction of attack) hold, in modified form, for other ring sizes as well. These other rings are less well-behaved than six-membered rings because they lack the well-defined strain-free conformations that cyclohexane is blessed with. We shall now leave sterochemistry in rings for some time, but we come back to these more difficult rings—and how to tame them—in a whole chapter on controlling stereochemistry with cyclic compounds, Chapter 33.

Problems

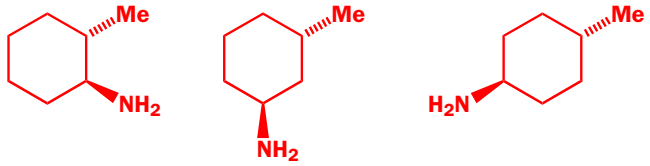
1. Identify the chair or boat six-membered rings in the following structures and say why that particular shape is adopted.



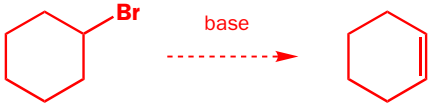
2. Draw clear conformational drawings for these molecules, labelling each substituent as axial or equatorial.



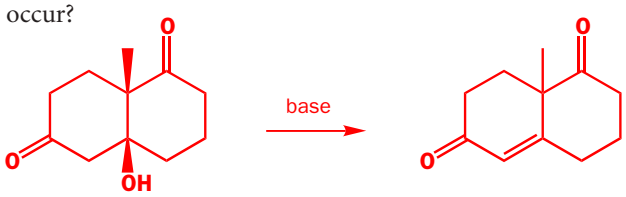
3. Would the substituents in these molecules be axial or equatorial or a mixture of the two?



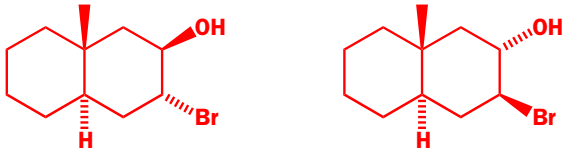
4. Why is it difficult for cyclohexyl bromide to undergo an E2 reaction? When it is treated with base, it does undergo an E2 reaction to give cyclohexene. What conformational changes must occur during this reaction?



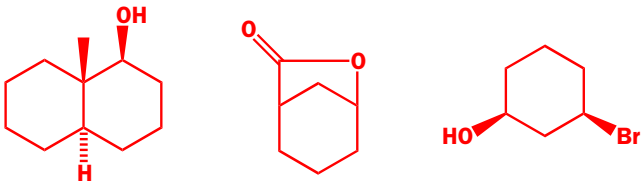
5. Treatment of this diketoalcohol with base causes an elimination reaction. What is the mechanism, and which conformation must the molecule adopt for the elimination to occur?



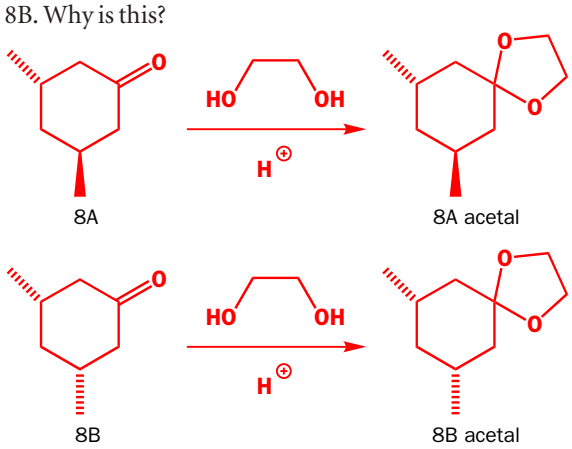
6. Which of these two compounds would form an epoxide on treatment with base?



7. Draw conformational diagrams for these compounds. State in each case why the substituents have the positions you state. To what extent could you confirm your predictions experimentally?



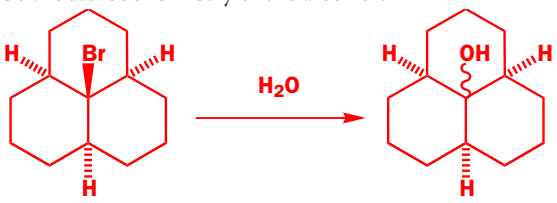
8. It is more difficult to form an acetal of compound 8A than of 8B. Why is this?



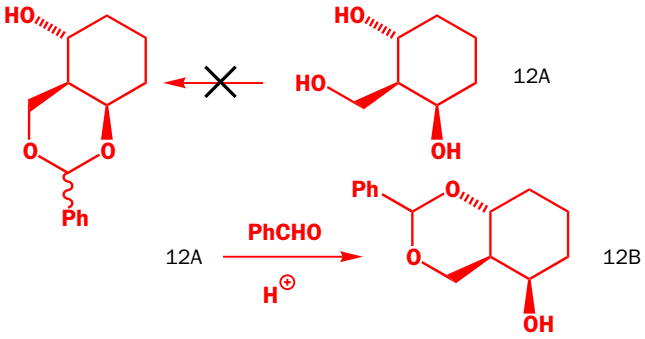
9. Predict which products would be formed on opening these epoxides with nucleophiles, say, cyanide ion.

10. These two sugar analogues are part of the structure of two compounds used to treat poultry diseases. Which conformations would they prefer?

11. Hydrolysis of the tricyclic bromide shown here in water gives an alcohol. What is the conformation of the bromide and what will be the stereochemistry of the alcohol?



12. Treatment of the triol 12A with benzaldehyde in acid solution produces one diastereoisomer of the acetal 12B and none of the alternative acetal. Why is this acetal preferred? (*Hint.* What controls acetal formation?) What is the stereochemistry of the undefined centre in 12B?



Elimination reactions

19

Connections

Building on:

- Mechanisms of nucleophilic substitution at saturated carbon ch17
- Conformation ch18

Arriving at:

- Elimination reactions
- What factors favour elimination over substitution
- The three important mechanisms of elimination reactions
- The importance of conformation in elimination reactions
- How to use eliminations to make alkenes (and alkynes)

Looking forward to:

- Electrophilic additions to alkenes (the reverse of the reactions in this chapter) ch20
- How to control double-bond geometry ch31

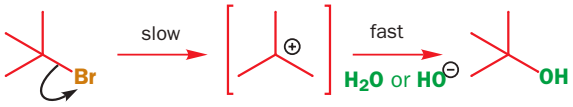
Substitution and elimination

Substitution reactions of *t*-butyl halides, you will recall from Chapter 17, invariably follow the S_N1 mechanism. In other words, the rate-determining step of their substitution reactions is unimolecular—it involves only the alkyl halide. And this means that, no matter what the nucleophile is, the reaction goes at the same rate. You can't speed this S_N1 reaction up, for example, by using hydroxide instead of water, or even by increasing the concentration of hydroxide. 'You'd be wasting your time,' we said (p. 000).

■ Remember the turnstiles at the railway station (p. 000).

nucleophilic substitution reactions of *t*-BuBr

rate = k[*t*-BuBr]



t-butyl bromide — *t*-butanol

reaction goes at the same rate whatever the nucleophile

You'd also be wasting your alkyl halide. This is what actually happens if you try the substitution reaction with a *concentrated* solution of sodium hydroxide.

reaction of *t*-BuBr with concentrated solution of NaOH

rate = k[*t*-BuBr][HO^-]

t-butyl bromide — isobutene (2-methylpropene)

elimination reaction forms alkene

The reaction stops being a substitution and an alkene is formed instead. Overall, HCl has been lost from the alkyl halide, and the reaction is called an **elimination**.

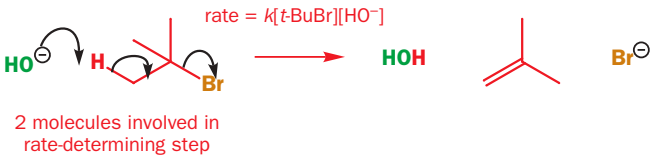
In this chapter we will talk about the mechanisms of elimination reactions—as in the case of substitutions, there is more than one mechanism for eliminations. We will compare eliminations with substitutions—either reaction can happen from almost identical starting materials, and you will learn how to predict which is the more likely. Much of the mechanistic discussion relates very closely to Chapter 17, and we suggest that you should make sure you understand all of the points in that chapter before tackling this one. This chapter will also tell you about uses for elimination reactions. Apart from a brief look at the Wittig reaction in Chapter 14, this is the first time you have met a way of making alkenes.

Elimination happens when the nucleophile attacks hydrogen instead of carbon

The elimination reaction of *t*-butyl bromide happens because the nucleophile is *basic*. You will recall from Chapter 12 that there is *some* correlation between basicity and nucleophilicity: strong bases are usually good nucleophiles. But being a good nucleophile doesn't get hydroxide anywhere in the substitution reaction, because it doen't appear in the first-order rate equation. But being a good base does get it somewhere in the elimination reaction, because hydroxide is involved in the rate-determining step of the elimination, and so it appears in the rate equation. This is the mechanism.

▶ The correlation is best for attack at C=O. In Chapter 17, you met examples of nucleophiles that are good at substitution at saturated carbon (such as I^-, Br^-, PhS^-) but that are not strong bases.

E2 elimination



The hydroxide is behaving as a base because it is attacking the hydrogen atom, instead of the carbon atom it would attack in a substitution reaction. The hydrogen atom is acidic, but proton removal can occur because bromide is a good leaving group. As the hydroxide attacks, the bromide is forced to leave, taking with it the negative charge. Two molecules—*t*-butyl bromide and hydroxide—are involved in the rate-determining step of the reaction. This means that the concentrations of both appear in the rate equation, which is therefore second-order

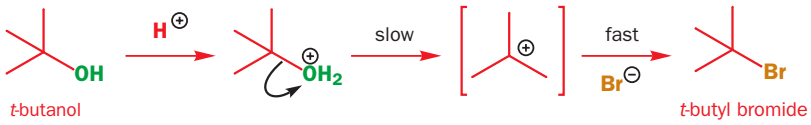
$$\text{rate} = k_2[t\text{-BuBr}][HO^-]$$

■ *Note*. No subscripts or superscripts, just plain E2.

and this mechanism for elimination is termed **E2**, for *elimination, bimolecular*.

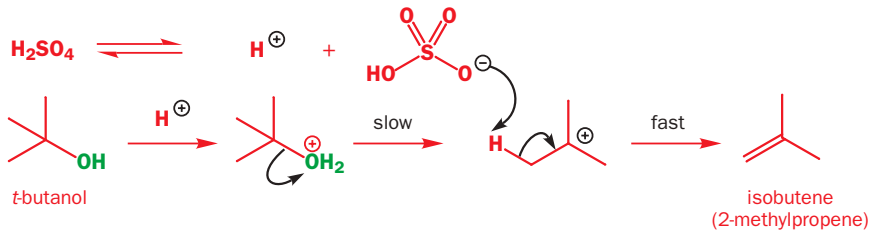
Now let's look at another sort of elimination. We can approach it again by thinking about an S_N1 substitution reaction. It is another one you met early in Chapter 17, and it is the reverse of the one at the beginning of this chapter.

nucleophilic substitution of *t*-BuOH with HBr



Bromide, the nucleophile, is not involved in the rate-determining step, so we know that the rate of the reaction will be independent of the concentration of Br^-. But what happens if we use an acid whose counterion is such a weak nucleophile that it doesn't even attack the carbon of the carbocation? Here is an example—*t*-butanol in sulfuric acid doesn't undergo substitution, but undergoes elimination instead.

E1 elimination of *t*-BuOH in H_2SO_4



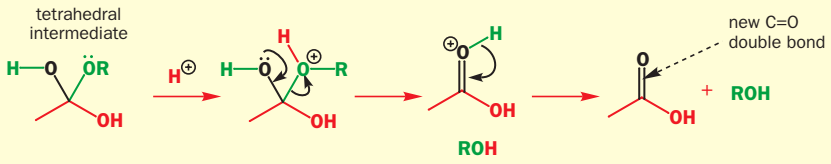
Now, the HSO_4^- is not involved in the rate-determining step—HSO_4^- is not at all basic and only behaves as a base (that is, it removes a proton) because it is even more feeble as a nucleophile. The rate equation will not involve the concentration of HSO_4^-, and the rate-determining step is the same as that in the S_N1 reaction—unimolecular loss of water from the protonated *t*-BuOH. This elimination mechanism is therefore called **E1**.

We will shortly come back to these two mechanisms for elimination, plus a third, but first we need to answer the question: when does a nucleophile start behaving as a base?

Elimination in carbonyl chemistry

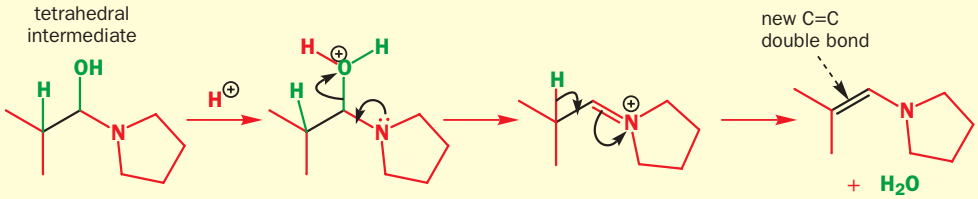
We have left detailed discussion of the formation of alkenes till this chapter, but we used the term elimination in Chapters 12 and 14 to describe the loss of a leaving group from a tetrahedral intermediate. For example, the final steps of the acid-catalysed ester hydrolysis shown below involve E1 elimination of ROH to leave a double bond: C=O rather than C=C.

E1 elimination of ROH during ester hydrolysis



In Chapter 14, you even saw an E1 elimination giving an alkene. That alkene was an enamine—here is the reaction.

E1 elimination of H_2O during enamine formation

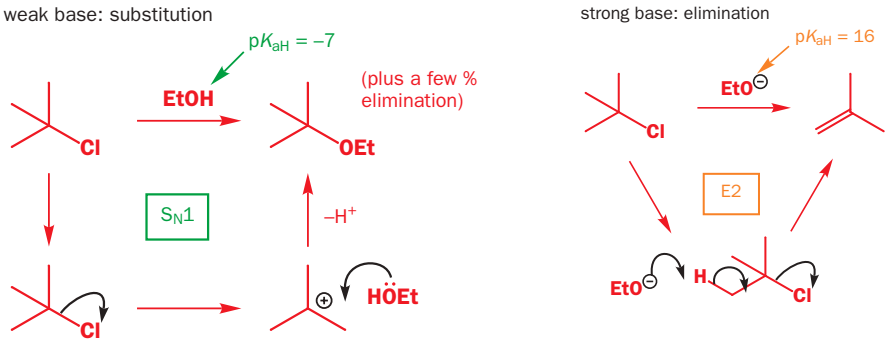


How the nucleophile affects elimination versus substitution

Basicity

You have just seen molecules bearing leaving groups being attacked at two distinct electrophilic sites: the carbon to which the leaving group is attached, and the hydrogen atoms on the carbon adjacent to the leaving group. Attack at carbon leads to substitution; attack at hydrogen leads to elimination. Since strong bases attack protons, it is generally true that, the more basic the nucleophile, the more likely that elimination is going to replace substitution as the main reaction of an alkyl halide.

Here is an example of this idea at work.



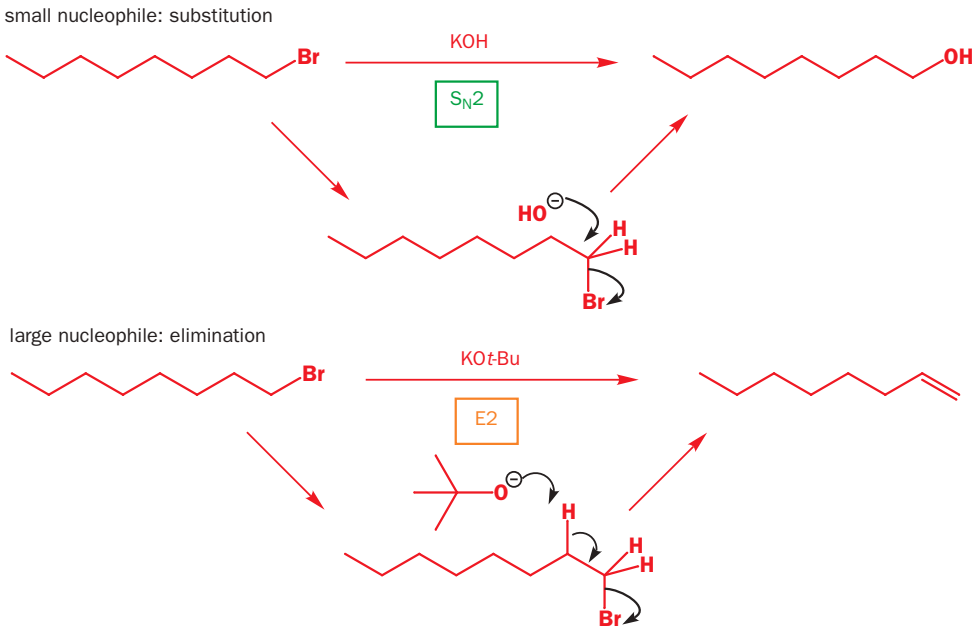
Elimination, substitution, and hardness

We can also rationalize selectivity for elimination versus substitution, or attack of H versus attack on C in terms of hard and soft electrophiles (p. 000). In an S_N2 substitution, the carbon centre is a soft electrophile—it is essentially uncharged, and with leaving groups such as halide the C–X σ* is a relatively low-energy LUMO. Substitution is therefore favoured by nucleophiles whose HOMOs are best able to interact with this LUMO—in other words soft nucleophiles. In contrast, the C–H σ* is higher in energy because the atoms are less electronegative. This, coupled with the hydrogen's small size, makes the C–H bond a hard electrophilic site, and as a result hard nucleophiles favour elimination.

Size

For a nucleophile, attacking a carbon atom means squeezing past its substituents—and even for unhindered primary alkyl halides there is still one alkyl group attached. This is one of the reasons

that S_N2 is so slow on hindered alkyl halides—the nucleophile has difficulty getting to the reactive centre. Getting at a more exposed hydrogen atom in an elimination reaction is much easier, and this means that, as soon as we start using hard, basic nucleophiles that are also bulky, elimination becomes preferred over substitution, even for primary alkyl halides. One of the best bases for promoting elimination and avoiding substiutution is potassium *t*-butoxide. The large alkyl substituent makes it hard for the negatively charged oxygen to attack carbon in a substitution reaction, but it has no problem attacking hydrogen.



Temperature

Temperature has an important role to play in deciding whether a reaction is an elimination or a substitution. In an elimination, two molecules become three. In a substitution, two molecules form two new molecules. The two reactions differ therefore in the change in entropy during the reaction: ΔS is greater for elimination than for substitution. In Chapter 13, we discussed the equation

$$\Delta G = \Delta H - T\Delta S$$

This equation says that a reaction in which ΔS is positive is more exothermic at higher temperature. Eliminations should therefore be favoured at high temperature, and this is indeed the case: most eliminations you will see are conducted at room temperature or above.

■ This explanation is simplified, because what matters is the rate of the reaction, not the stability of the products. A detailed discussion is beyond the scope of the book, but the general argument still holds.

To summarize these three effects:

- **Nucleophiles that are strong bases favour elimination over substitution**
- **Nucleophiles (or bases) that are bulky favour elimination over substitution**
- **High temperatures favour elimination over substitution**

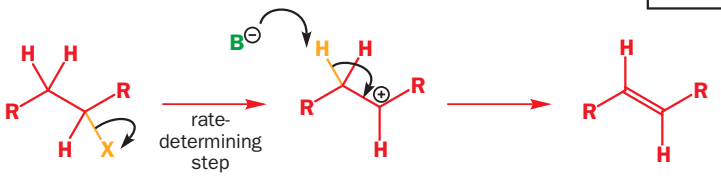
E1 and E2 mechanisms

Now that you have seen a few examples of elimination reactions, it is time to return to our discussion of the two mechanisms for elimination. To summarize what we have said so far:

- E1 describes an elimination reaction (E) in which the rate-determining step is unimolecular (1) and does not involve the base. The leaving group leaves in this step, and the proton is removed in a separate second step

general mechanism for E1 elimination

rate = k[alkyl halide]



- E2 describes an elimination (E) that has a bimolecular (2) rate-determining step that must involve the base. Loss of the leaving group is simultaneous with removal of the proton by the base

▶ The loss of the leaving group and removal of the proton are **concerted.**

general mechanism for E2 elimination

rate = k[B^-][alkyl halide]

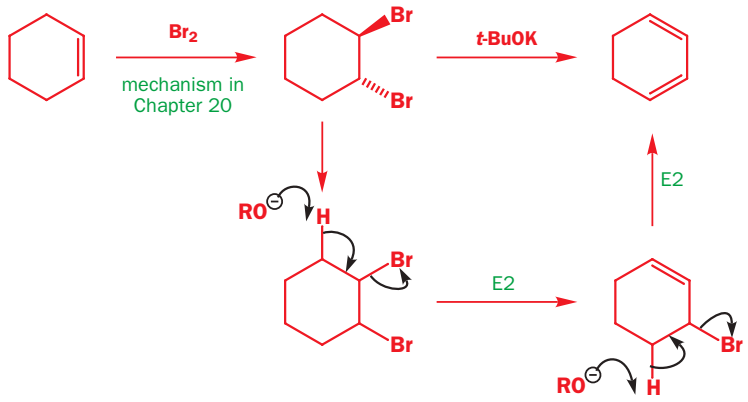
There are a number of factors that affect whether an elimination goes by an E1 or E2 mechanism. One is immediately obvious from the rate equations: only the E2 is affected by the concentration of base, so at high base concentration E2 is favoured. The rate of an E1 reaction is not even affected by what base is present—so E1 is just as likely with weak as with strong bases, while E2 goes faster with strong bases than weak ones: strong bases at whatever concentration will favour E2 over E1. If you see a strong base being used for an elimination, it is certainly an E2 reaction. Take the first elimination in this chapter as an example.

reaction of *t*-butyl bromide with concentrated hydroxide

With less hindered alkyl halides hydroxide would not be a good choice as a base for an elimination because it is rather small and still very good at S_N2 substitutions (and even with tertiary alkyl halides, substitution outpaces elimination at low concentrations of hydroxide). So what are good alternatives?

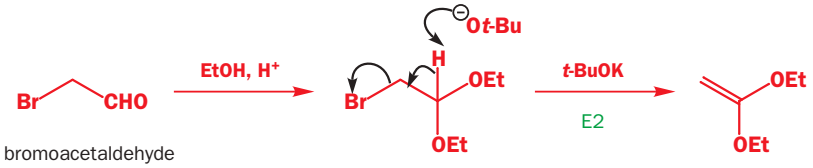
We have already mentioned the bulky *t*-butoxide—ideal for promoting E2 as it's both bulky and a strong base (pK_{aH} = 18). Here it is at work converting a dibromide to a diene with two successive E2 eliminations. Since dibromides can be made from alkenes (you will see how in the next chapter), this is a useful two-step conversion of an alkene to a diene.

synthesis of a diene by a double E2 elimination

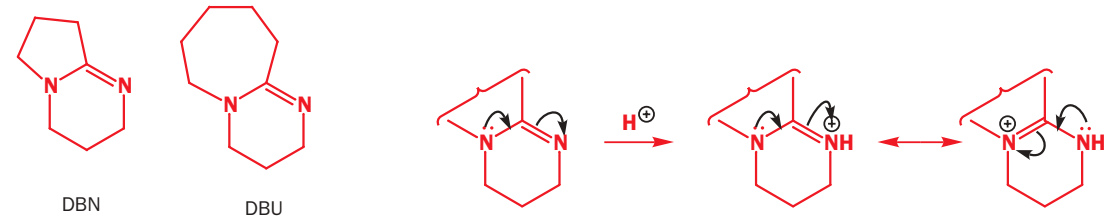


The product of the next reaction is a 'ketene acetal'—you met ketene, CH_2=C=O, in Chapter 15. Unlike most acetals, this one can't be formed directly from ketene (ketene is too unstable), so

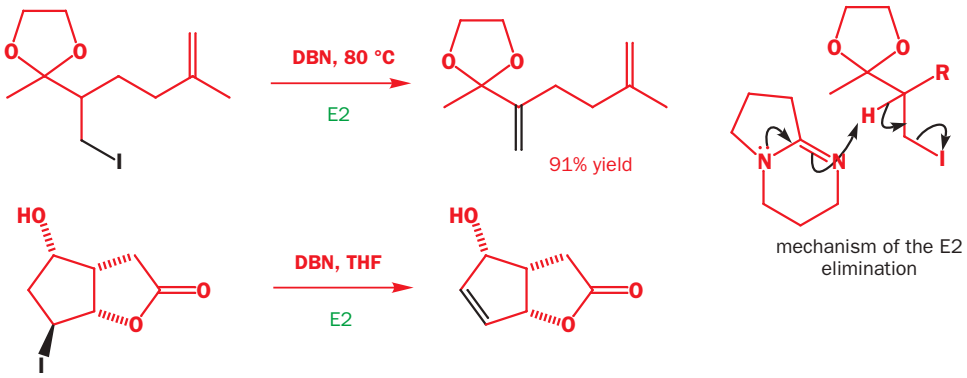
instead, the acetal is made by the usual method from bromoacetaldehyde, and then HBr is eliminated using *t*-BuOK.



Among the most commonly used bases for converting alkyl halides to alkenes are two that you met in Chapter 8 and that received a mention at the end of Chapter 18: DBU and DBN. These two bases are amidines—delocalization of one nitrogen's lone pair on to the other, and the resulting stabilization of the protonated amidinium ion, makes them particularly basic, with pK_{aH}s of about 12.5. There is not much chance of getting those voluminous fused rings into tight corners—so they pick off the easy-to-reach protons rather than attacking carbon atoms in substitution reactions.

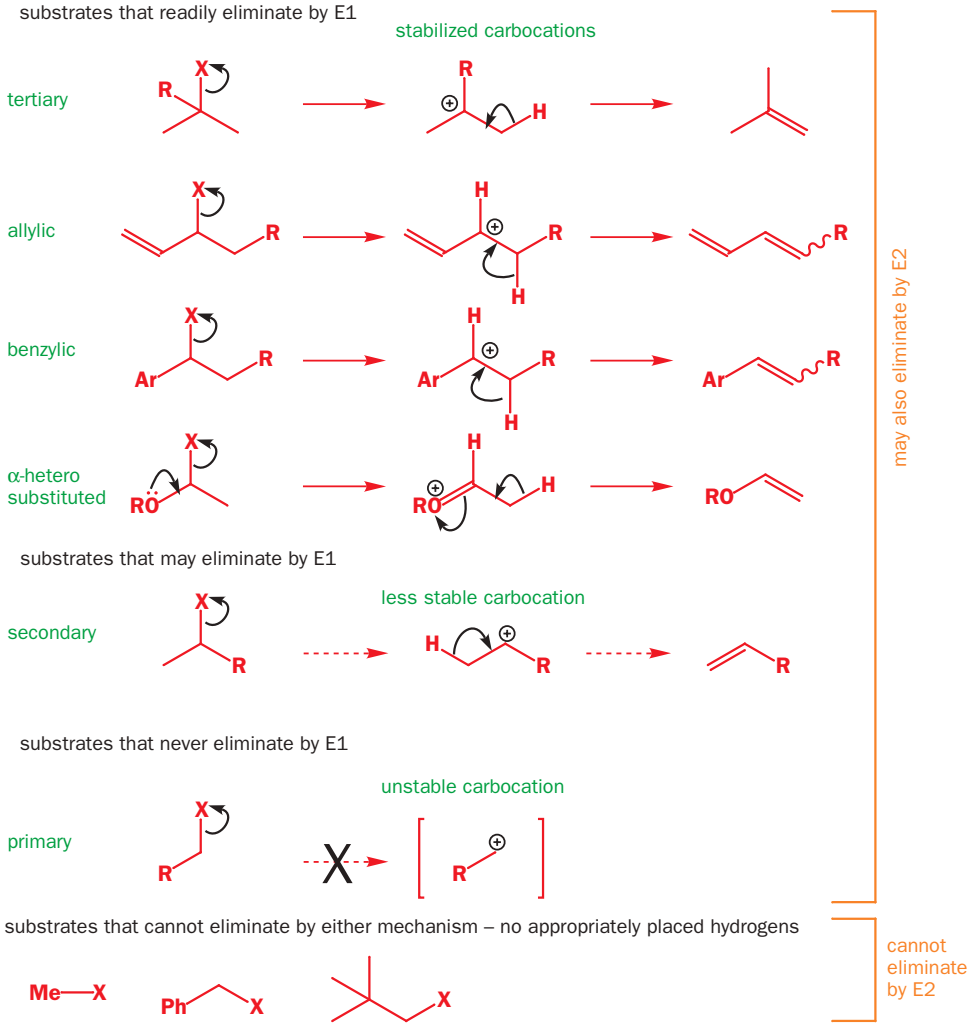


DBU or DBN will generally eliminate HX from alkyl halides to give alkenes. In these two examples, the products were intermediates in the synthesis of natural products.

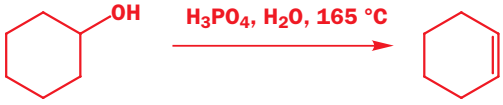


Substrate structure may allow E1

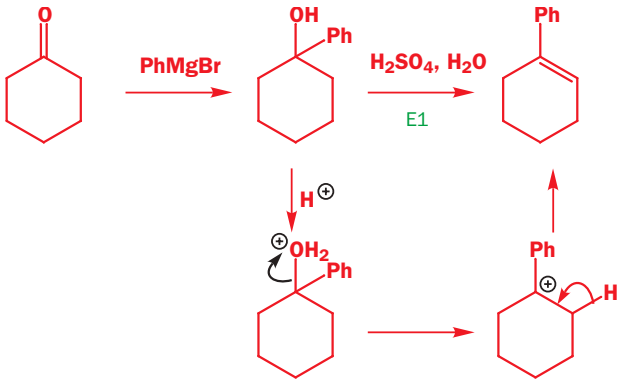
The first elimination of the chapter (*t*-BuBr plus hydroxide) illustrates something very important: the starting material is a tertiary alkyl halide (and would therefore *substitute* only by S_N1) it can *eliminate* by either E2 (with strong bases) or E1 (with weak bases). The steric factors that disfavour S_N1 at hindered centres don't exist for eliminations. Nonetheless, E1 can occur *only* with substrates that can ionize to give relatively stable carbocations—tertiary, allylic or benzylic alkyl halides, for example. Secondary alkyl halides may eliminate by E1, while primary alkyl halides only ever eliminate by E2 because the primary carbocation required for E1 would be too unstable. The chart on the facing page summarizes the types of substrate that can undergo E2—but remember that any of these substrates, under the appropriate conditions (in the presence of strong bases, for example), may also undergo E2. For completeness, we have also included in this chart three alkyl halides that cannot eliminate by either mechanism simply because they do not have any hydrogens to lose from carbon atoms adjacent to the leaving group.



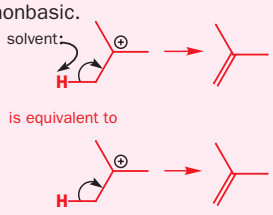
Polar solvents also favour E1 reactions because they stabilize the intermediate carbocation. E1 eliminations from alcohols in aqueous or alcohol solution are particularly common, and very useful. An acid catalyst is used to promote loss of water, and in dilute H_2SO_4 or HCl the absence of good nucleophiles ensures that substitution does not compete. Under these conditions, the secondary alcohol cyclohexanol gives cyclohexene.



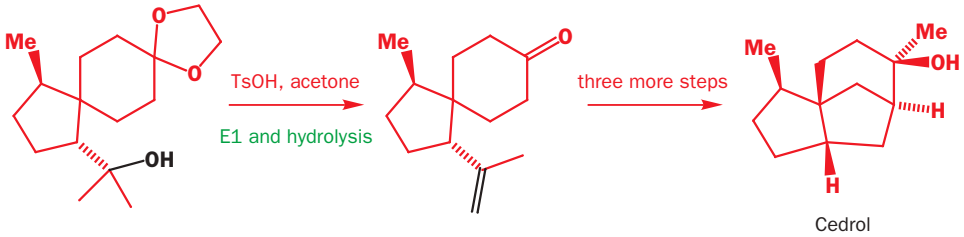
But the best E1 eliminations of all are with tertiary alcohols. The alcohols can be made using the methods of Chapter 9: nucleophilic attack by an organometallic on a carbonyl compound. Nucleophilic addition, followed by E1 elimination, is the best way of making this substituted cyclohexene, for example. Note that the the proton required in the first step is recovered in the last—the reaction requires only catalytic amounts of acid.



▶ In E1 mechanisms, once the leaving group has departed almost anything will serve as a base to remove a proton from the intermediate carbocation. Weakly basic solvent molecules (water or alcohols), for example, are quite sufficient, and you will often see the proton just 'falling off' in reaction mechanisms. We showed the loss of a proton like this in the last example, and in the chart on p. 000. The superacid solutions we described in Chapter 17 were designed with this in mind—the counterions BF_4^- and SbF_6^- are not only nonnucleophilic but also nonbasic.



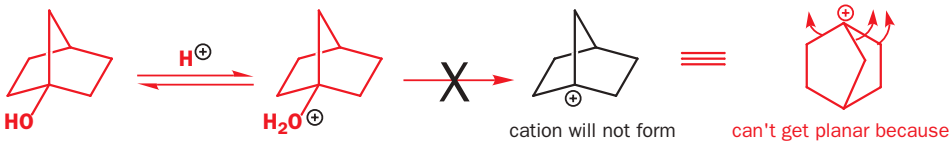
Cedrol is important in the perfumery industry—it has a cedar wood fragrance. Corey's synthesis includes this step—the acid (toluenesulfonic acid) catalyses both the E1 elimination and the hydrolysis of the acetal.



Cedrol

At the end of the last chapter you met some bicyclic structures. These sometimes pose problems for elimination reactions. For example, this compound will not undergo elimination by either an E1 or an E2 mechanism. We shall see shortly what the problem with E2 is, but for E1 the hurdle to be overcome is the formation of a planar carbocation. The bicyclic structure prevents the bridgehead carbon becoming planar so, although the cation would be tertiary, it is very high in energy and does not form. You could say that the nonplanar structure forces the cation to be an empty sp^3 orbital instead of an empty p orbital, and we saw in Chapter 4 that it is always best to leave the orbitals with the highest possible energy empty.

■ 'Bridgehead' was defined on p. 000.



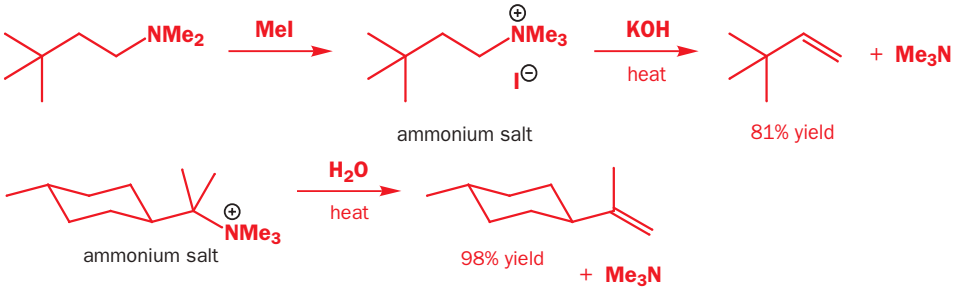
Bredt's rule

The impossibility of planar bridgehead carbons means that double bonds can never be formed to bridgehead carbons in bicyclic systems. This principle is known as 'Bredt's rule', but, as with all rules, it is much more important to know the reason than to know the name, and Bredt's rule is simply a consequence of the strain induced by a planar bridgehead carbon.

The role of the leaving group

We haven't yet been very adventurous with our choice of leaving groups for eliminations: all you have seen so far are E2 from alkyl halides and E1 from protonated alcohols. This is deliberate: the vast majority of the two classes of eliminations use one of these two types of starting materials. Since the leaving group is involved in the rate-determining step of both E1 and E2, in general, any good leaving group will lead to a fast elimination. You may, for example, see amines acting as leaving groups in eliminations of quaternary ammonium salts.

eliminations from quaternary ammonium salts



Both E1 and E2 are possible, and from what you have read so far you should be able to spot that there is one of each here: in the first example, a stabilized cation cannot be formed (so E1 is

impossible), but a strong base is used, allowing E2. In the second, a stabilized tertiary cation could be formed (so *either* E1 or E2 might occur), but no strong base is present, so the mechanism must be E1.

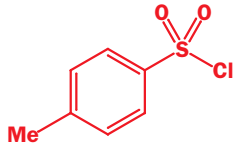
E2 elimination

E1 elimination

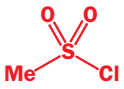
You have just seen that hydroxyl groups can be turned into good leaving groups in acid, but this is only useful for substrates that can react by E1 elimination. The hydroxyl group is *never* a leaving group in E2 eliminations, since they have to be done in base.

● **OH^- is never a leaving group in an E2 reaction.**

For primary and secondary alcohols, the hydroxyl is best made into a leaving group for elimination reactions by sulfonylation with toluene-*para*-sulfonyl chloride (tosyl chloride, TsCl) or methanesulfonyl (mesyl chloride, $MeSO_2Cl$ or MsCl).



toluene-*para*-sulfonyl chloride
(tosyl chloride, TsCl)



methanesulfonyl chloride
(mesyl chloride, MsCl)

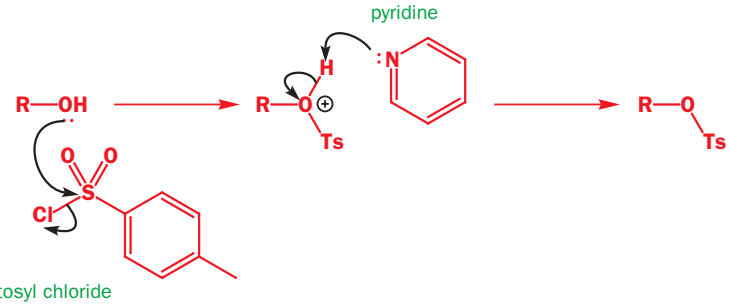
▶ There is a new 'organic element' here: –Ms = $–SO_2Me$.

Toluenesulfonate esters (tosylates) can be made from alcohols (with TsCl, pyridine). You have already met tosylates in Chapter 17 because they are good electrophiles for substitution reactions with *nonbasic* nucleophiles. With strong bases such as *t*-BuOK, NaOEt, DBU, or DBN they undergo very efficient elimination reactions. Here are two examples.

E2 eliminations of tosylates

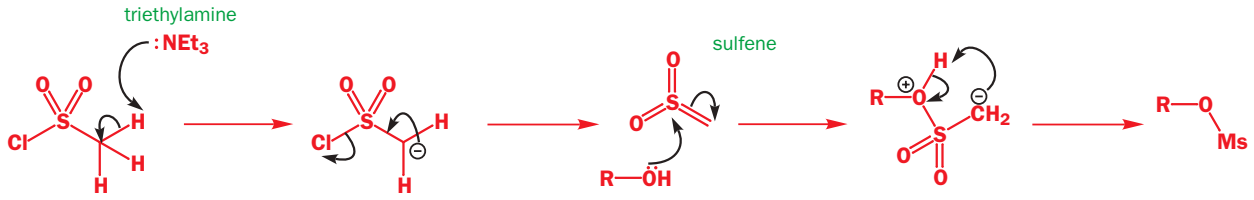
Methanesulfonyl chloride may be a new reagent to you. In the presence of a base (usually triethylamine, Et_3N) it reacts with alcohols to give methanesulfonate esters, but the mechanism differs from the mechanism with TsCl. The first step is an elimination of HCl from the sulfonyl chloride (this can't happen with TsCl, because there are no available protons) to give a **sulfene**. The sulfene is highly electrophilic at sulfur, and will react with any alcohol (including tertiary alcohols, which react very slowly with TsCl). Here are the two mechanisms compared.

formation of toluenesulfonates (tosylates): reagents ROH + TsCl + pyridine



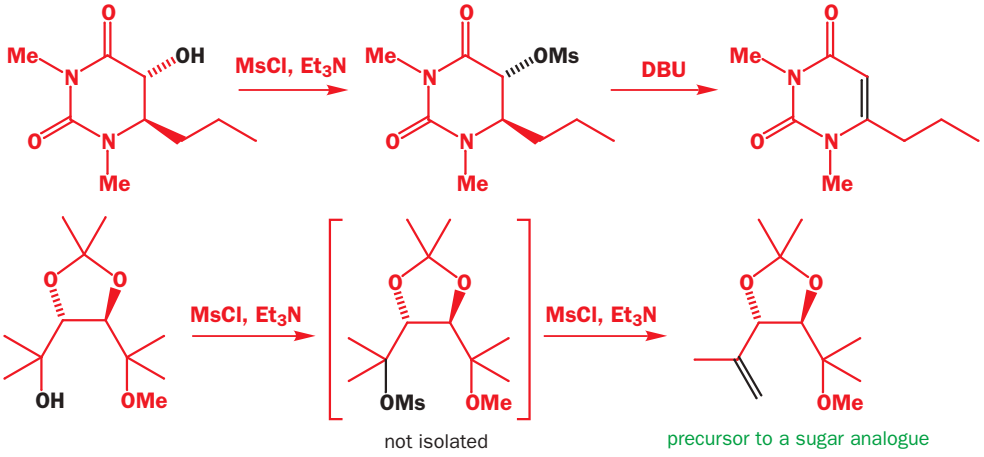
tosyl chloride

formation of methanesulfonates (mesylates): reagents ROH + MsCl + triethylamine



Methanesulfonyl esters (or **mesylates**) can be eliminated using DBU or DBN, but a good way of using MsCl to convert alcohols to alkenes is to do the mesylation and elimination steps in one go, using the same base (Et_3N) for both. Here are two examples making biologically important molecules. In the first, the mesylate is isolated and then eliminated with DBU to give a synthetic analogue of uracil, one of the nucleotide bases present in RNA. In the second, the mesylate is formed and eliminated in the same step using Et_3N, to give a precursor to a sugar analogue.

■ More about RNA bases and sugars in Chapter 49.



The second example here involves (overall) the elimination of a tertiary alcohol—so why couldn't an acid-catalysed E1 reaction have been used? The problem here, nicely solved by the use of the mesylate, is that the molecule contains an acid-sensitive acetal functional group. An acid-catalysed reaction would also have risked eliminating methanol from the other tertiary centre.

How to distinguish E1 from E2: kinetic isotope effects

We have told you what sorts of starting materials and conditions favour E1 or E2 reactions, but we haven't told you how we know this. E1 and E2 differ in the order of their rate equations with respect to the base, so one way of finding out if a reaction is E1 or E2 is to plot a graph of the variation of rate with base concentration. But this can be difficult with E1 reactions because the base (which need be only very weak) is usually the solvent. More detailed evidence for the differences between reaction mechanisms comes from studying the rates of elimination in substrates that differ only in that one or more of the protons have been replaced by deuterium atoms. These differences are known as **kinetic isotope effects**.

Up to now you have probably (and rightly) been told that isotopes of an element (that is, atoms that differ only in the number of neutrons their nuclei contain) are chemically identical. It may come as a surprise to find that this is not quite true: isotopes do differ chemically, but this difference is only significant for hydrogen—no other element has one isotope twice as massive as another! Kinetic isotope effects are the changes in rate observed when a (^{1}H) hydrogen atom is replaced by a (^{2}H) deuterium atom in the same reaction. For any reaction, the kinetic isotope effect is defined as

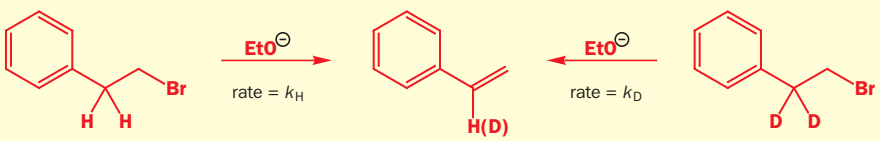
$$\text{KIE} = \frac{k_H}{k_D}$$

k_H: rate with substrate containing ^{1}H

k_D: rate with substrate containing ^{2}H

Changing H for D can affect the rate of the reaction only if that H (or D) is involved in the rate-determining step. The theoretical maximum is about 7 for reactions at room temperature in which a bond to H or D is being broken. For example, the rates of these two eliminations can be compared, and k_H/k_D turns out to be 7.1 at 25 °C.

■ The calculations that give this result are beyond the scope of this book, but you can find them in textbooks on physical organic chemistry.

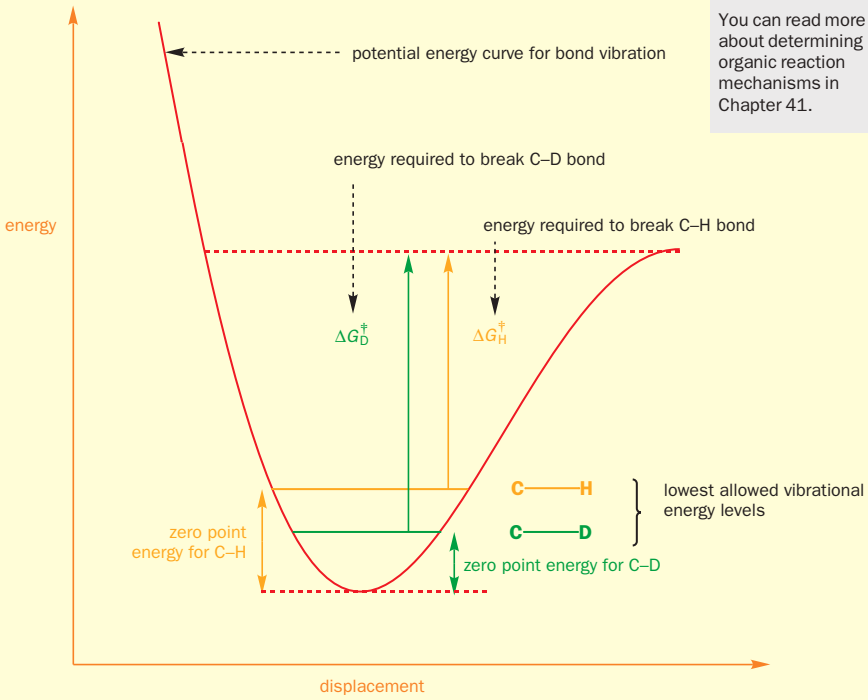


The kinetic isotope effect tells us that the C–H (or C–D) bond is being broken during the rate-determining step, and so the reaction must be an E2 elimination. It's evidence like this that allows us to piece together the mechanisms of organic reactions.

How do kinetic isotope effects come about? Even in its lowest energy state a covalent bond never stops vibrating. If it did it would violate a fundamental physical principle, Heisenberg's uncertainty principle, which states that position and momentum cannot be known exactly at the same time: a nonvibrating pair of atoms have precisely zero momentum and precisely fixed locations. The minimum vibrational energy a bond can have is called the zero point energy (E_0) – given by the expression $E_0 = \frac{1}{2}h\nu$.

In order to break a covalent bond, a certain amount of energy is required to separate the nuclei from their starting position. This energy has to raise the vibration state of the bond from the zero point energy to the point where it breaks. Because the zero point energy of a C–H bond is higher than that for a C–D bond, the C–H bond has a head start in energy terms. The energy required to break a C–H bond is less than that required to break a C–D bond, so reactions breaking C–H bonds go faster than those breaking C–D bonds, provided bond breaking is occurring in the rate-determining step. This is only the case in E2 reactions, not E1 reactions, so the general rule is that, if changing C–H for C–D changes the rate of the elimination, the reaction must be E2 and not E1.

zero point energy and kinetic isotope effects

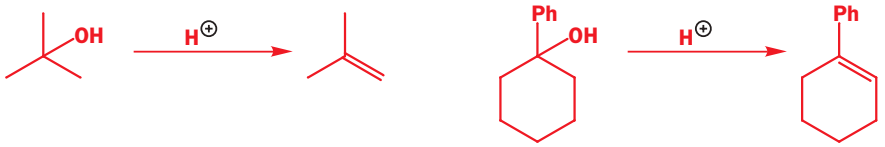


■ You can read more about determining organic reaction mechanisms in Chapter 41.

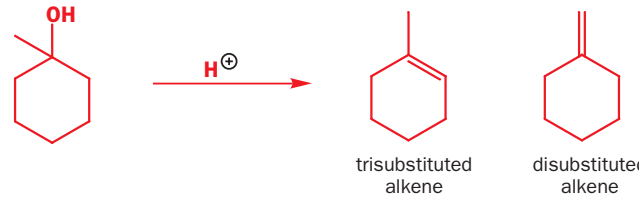
E1 reactions can be stereoselective

For some eliminations only one product is possible. For others, there may be a choice of two (or more) alkene products that differ either in the location or stereochemistry of the double bond. We shall now move on to discuss the factors that control the stereochemistry (geometry) and regiochemistry (that is, where the double bond is) of the alkenes, starting with E1 reactions.

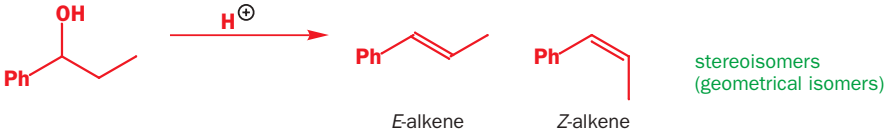
only one alkene possible



two regioisomeric alkenes possible



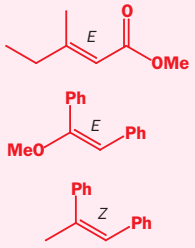
two stereoisomeric alkenes possible



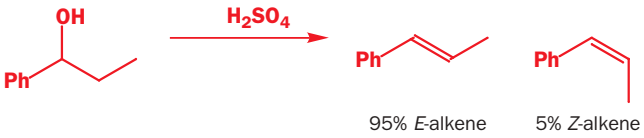
For steric reasons, *E*-alkenes (and transition states leading to *E*-alkenes) are usually lower in energy than *Z*-alkenes (and the transition states leading to them) because the substituents can get

▶ *E* and *Z* alkenes

The *E*/*Z* nomenclature was introduced in Chapter 7, and now that you have read Chapter 16 we can be more precise with our definition. For disubstituted alkenes, *E* corresponds to *trans* and *Z* corresponds to *cis*. To assign *E* or *Z* to tri- or tetrasubstituted alkenes, the groups at either end of the alkene are given an order of priority according to the same rules as those outlined for *R* and *S* in Chapter 16. If the two higher priority groups are *cis*, the alkene is *Z*; if they are *trans* the alkene is *E*. Of course, molecules don't know these rules, and sometimes (as in the second example here) the *E* alkene is less stable than the *Z*.

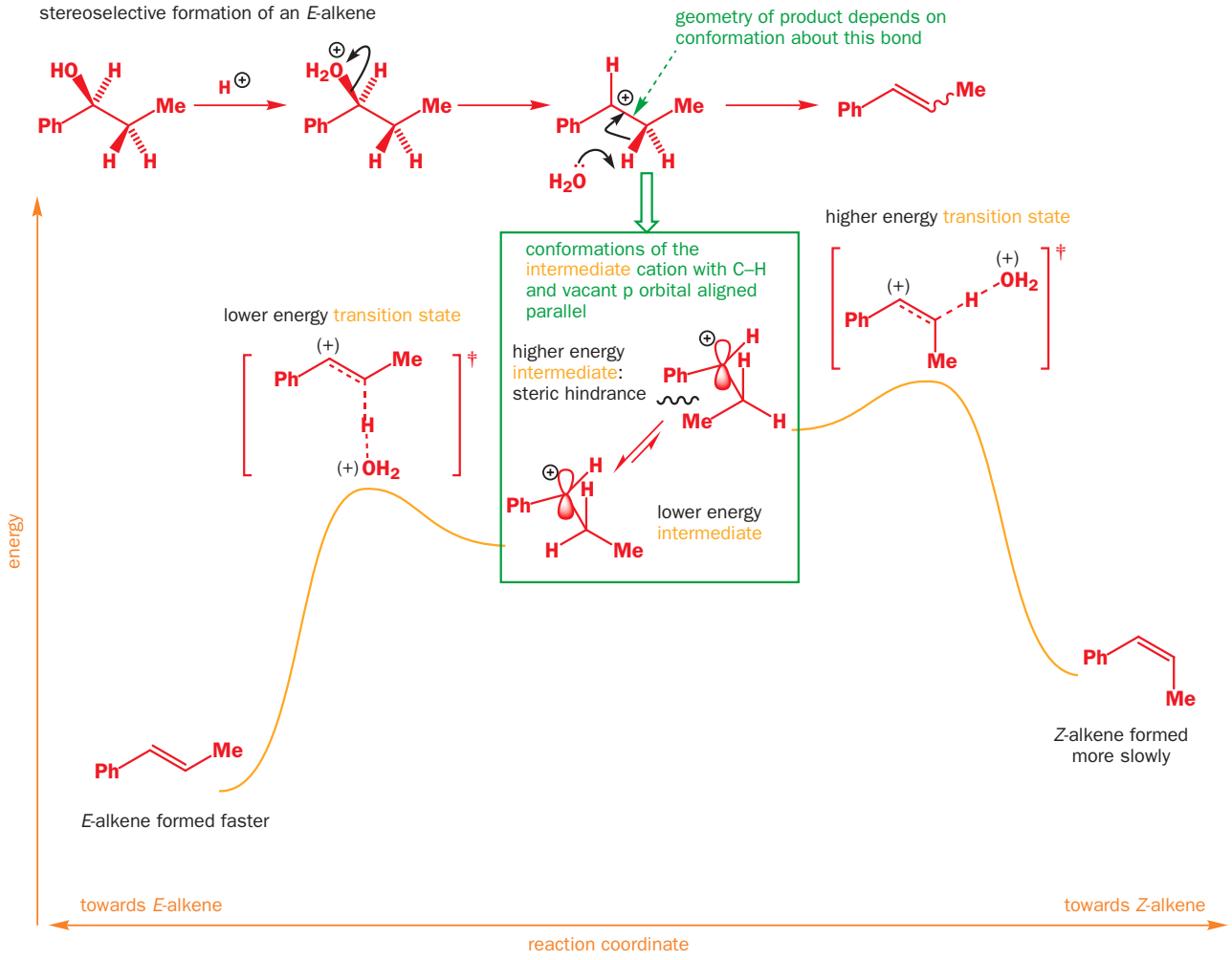


farther apart from one another. A reaction that can choose which it forms is therefore likely to favour the formation of *E*-alkenes. For alkenes formed by E1 elimination, this is exactly what happens: the less hindered *E*-alkene is favoured. Here is an example.

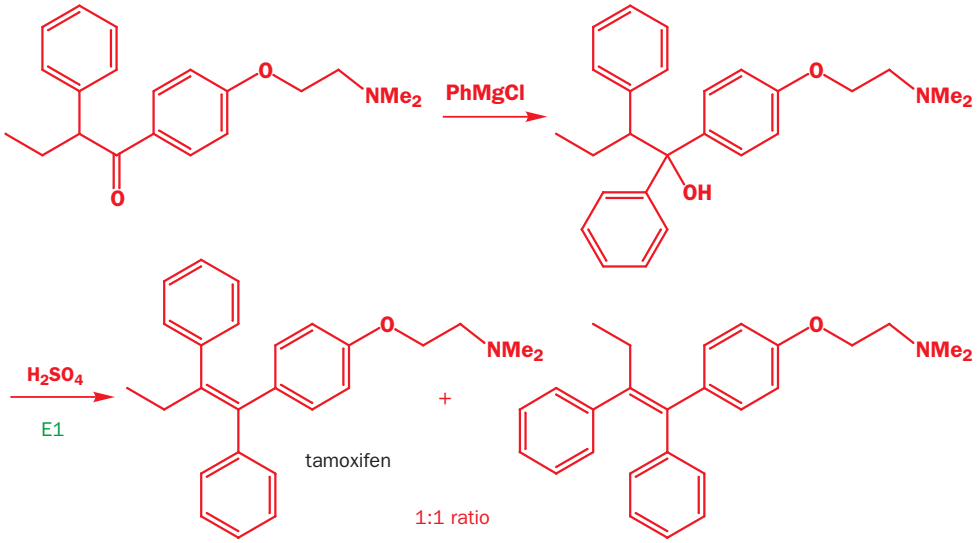


■
In Chapter 41, we shall discuss why the transition states for decomposition of high-energy intermediates like carbocations are very similar in structure to the carbocations themselves.

The geometry of the product is determined at the moment that the proton is lost from the intermediate carbocation. The new π bond can only form if the vacant p orbital of the carbocation and the breaking C–H bond are aligned parallel. In the example shown there are two possible conformations of the carbocation with parallel orientations, but one is more stable than the other because it suffers less steric hindrance. The same is true of the transition states on the route to the alkenes—the one leading to the *E*-alkene is lower in energy and more *E*-alkene than *Z*-alkene is formed. The process is steroselective, because the reaction chooses to form predominantly one of two possible stereoisomeric products.

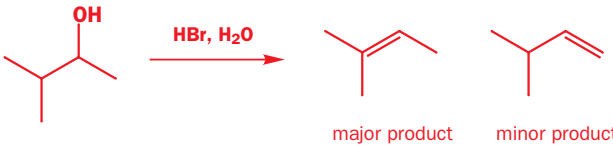


Tamoxifen is an important drug in the fight against breast cancer, one of the most common forms of cancer. It works by blocking the action of the female sex hormone oestrogen. The tetrasubstituted double bond can be introduced by an E1 elimination: there is no ambiguity about where the double bond goes, though the two stereoisomers form in about equal amounts.



E1 reactions can be regioselective

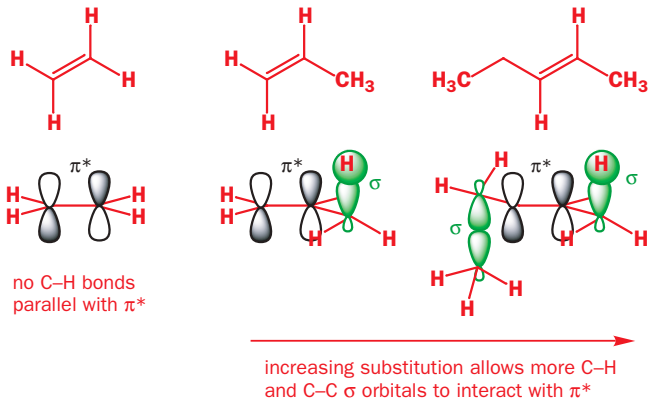
We can use the same ideas when we think about E1 eliminations that can give more than one regioisomeric alkene. Here is an example.



The major product is the alkene that has the more substituents, because this alkene is the more stable of the two possible products.

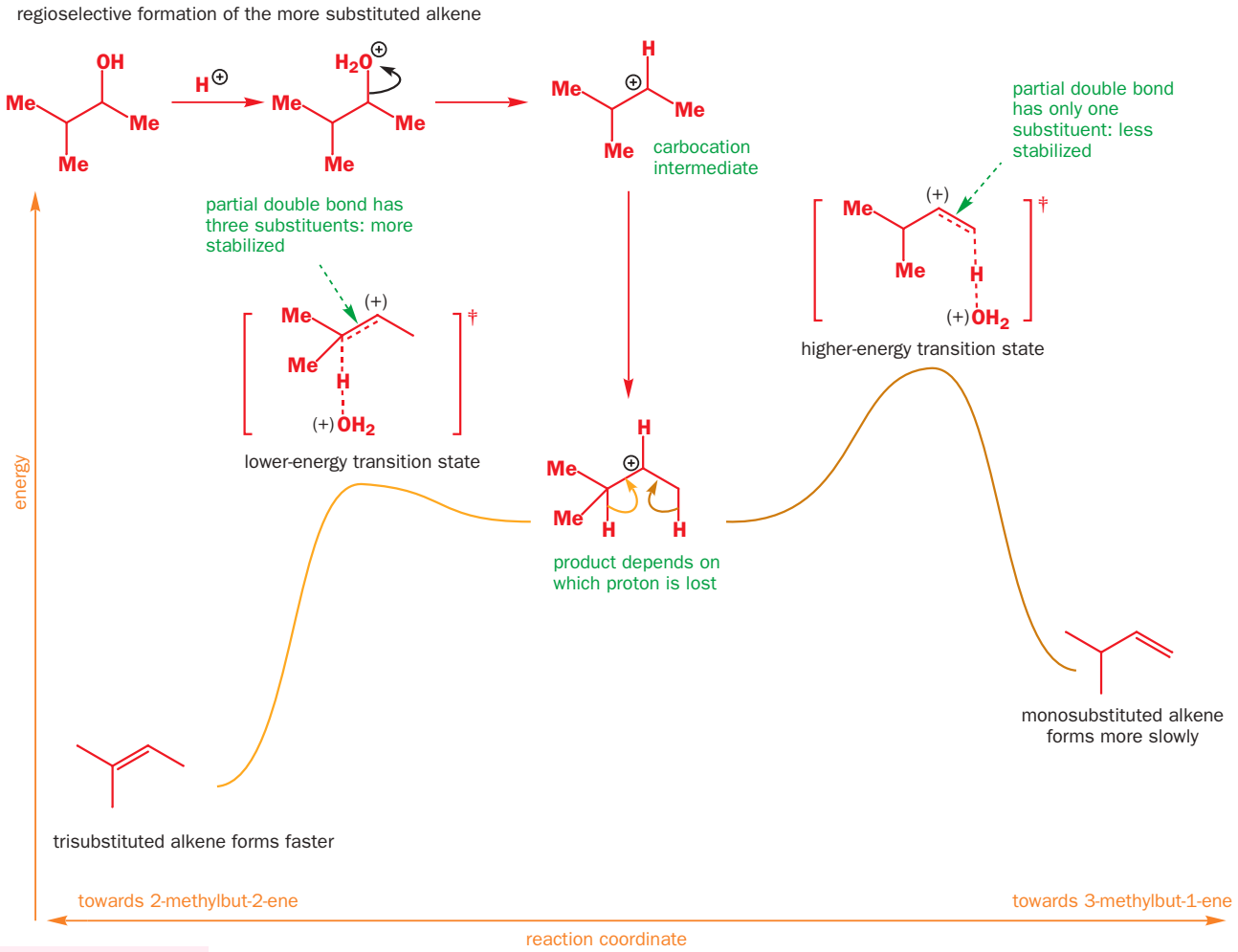
● More substituted alkenes are more stable.

This is quite a general principle, and you have already seen several examples of it in action (p. 000). But why should it be true? The reason for this is related to the reason why more substituted carbocations are more stable. In Chapter 17 we said that the carbocation is stabilized when its empty p orbital can interact with the filled orbitals of parallel C–H and C–C bonds. The same is true of the π system of the double bond—it is stabilized when the empty π* antibonding orbital can interact with the filled orbitals of parallel C–H and C–C bonds. The more C–C or C–H bonds there are, the more stable the alkene.



The more substituted alkene is more stable, but this does not necessarily explain why it is the one that forms faster. To do that, we should look at the transition states leading to the two alkenes. Both form from the same carbocation, but which one we get depends on which proton is lost. Removal of the proton on the right (brown arrow) leads to a transition state in which there is a monosubstituted double bond partly formed. Removal of the proton on the left (orange arrow) leads

to a partial double bond that is trisubstituted. This is more stable—the transition state is lower in energy, and the more substituted alkene forms faster.

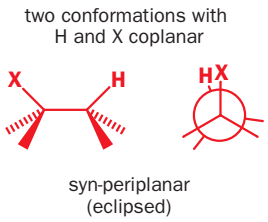


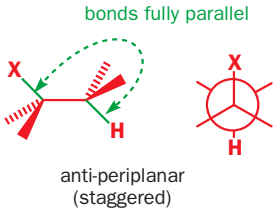
▶ This explanation of both stereo- and regioselectivity in E1 reactions is based on *kinetic* arguments—which alkene forms faster. But it is also true that some E1 eliminations are reversible: the alkenes may be protonated in acid to re-form carbocations, as you will see in the next chapter. This re-protonation allows the more stable product to form preferentially under *thermodynamic* control. In any individual case, it may not be clear which is operating. However, with E2 reactions, which follow, only kinetic control applies: E2 reactions are never reversible.

Although E1 reactions show some stereo- and regioselectivity, the level of selectivity in E2 reactions can be much higher because of the more stringent demands on the transition state for E2 elimination. We will come back to the most useful ways of controlling the geometry of double bonds in Chapter 31.

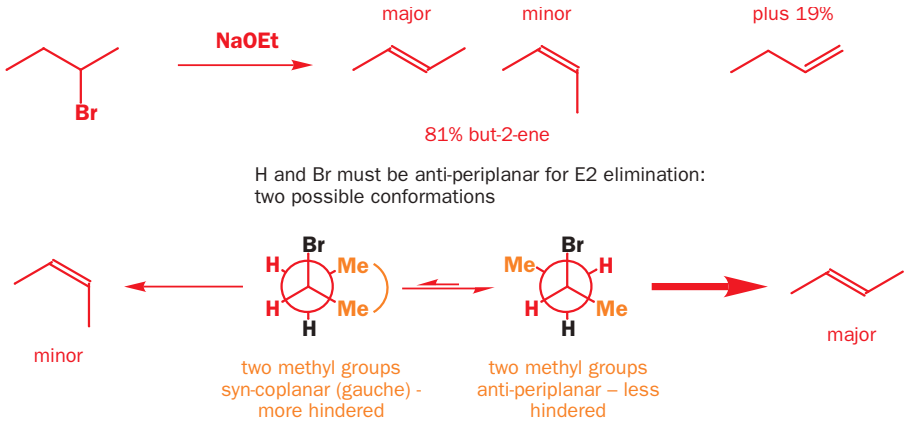
E2 eliminations have anti-periplanar transition states

In an E2 elimination, the new π bond is formed by overlap of the C–H σ bond with the C–X σ* anti-bonding orbital. The two orbitals have to lie in the same plane for best overlap, and now there are two conformations that allow this. One has H and X syn-periplanar, the other anti-periplanar. The anti-periplanar conformation is more stable because it is staggered (the syn-periplanar conformation is eclipsed) but, more importantly, only in the anti-periplanar conformation are the bonds (and therefore the orbitals) truly parallel.





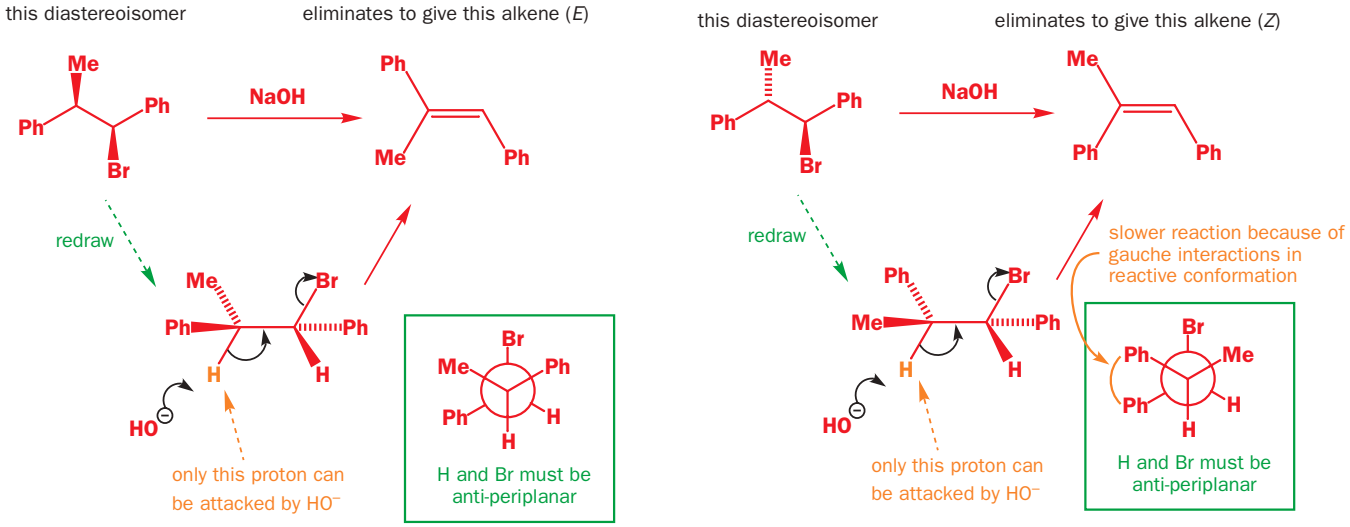
E2 eliminations therefore take place from the anti-periplanar conformation. We shall see shortly how we know this to be the case, but first we consider an E2 elimination that gives mainly one of two possible stereoisomers. 2-Bromobutane has two conformations with H and Br anti-periplanar, but the one that is less hindered leads to more of the product, and the *E*-alkene predominates.



There is a choice of protons to be eliminated—the stereochemistry of the product results from which proton is anti-periplanar to the leaving group when the reaction takes place, and the reaction is stereoselective as a result.

E2 eliminations can be stereospecific

In the next example, there is only one proton that can take part in the elimination. Now there is no choice of anti-periplanar transition states. Whether the product is *E* or *Z*, the E2 reaction has only one course to follow. And the outcome depends on which diastereoisomer of the starting material is used. When the first diastereoisomer is drawn with the proton and bromine anti-periplanar, as required, and in the plane of the page, the two phenyl groups have to lie one in front and one behind the plane of the paper. As the hydroxide attacks the C–H bond and eliminates Br^-, this arrangement is preserved and the two phenyl groups end up *trans* (the alkene is *E*). This is perhaps easier to see in the Newman projection of the same conformation.



The second diastereoisomer forms the *Z*-alkene for the same reasons: the two phenyl groups are now on the same side of the H–C–C–Br plane in the reactive anti-periplanar conformation (again, this is clear in the Newman projection) and so they end up *cis* in the product. Each diastereoisomer gives a different alkene geometry, and they do so at different rates. The first reaction

is about ten times as fast as the second because, although this anti-periplanar conformation is the only reactive one, it is not necessarily the most stable. The Newman projection for the second reaction shows clearly that the two phenyl groups have to lie synclinal (gauche) to one another: the steric interaction between these large groups will mean that, at any time, a relatively small proportion of molecules will adopt the right conformation for elimination, slowing the process down.

Reactions in which the stereochemistry of the product is determined by the stereochemistry of the starting material are called **stereospecific**.

■ A stereospecific reaction is not simply a reaction that is very stereoselective! The two terms have different mechanistic meanings, and are not just different degrees of the same thing.

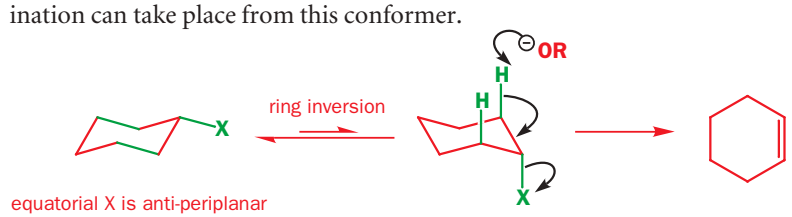
● Stereoselective or stereospecific?

- **Stereoselective reactions give one predominant product because the reaction pathway has a choice. Either the pathway of lower activation energy is preferred (kinetic control) or the more stable product (thermodynamic control)**
- **Stereospecific reactions lead to the production of a single isomer as a direct result of the mechanism of the reaction and the stereochemistry of the starting material. There is no choice. The reaction gives a different diastereoisomer of the product from each stereoisomer of the starting material**

E2 eliminations from cyclohexanes

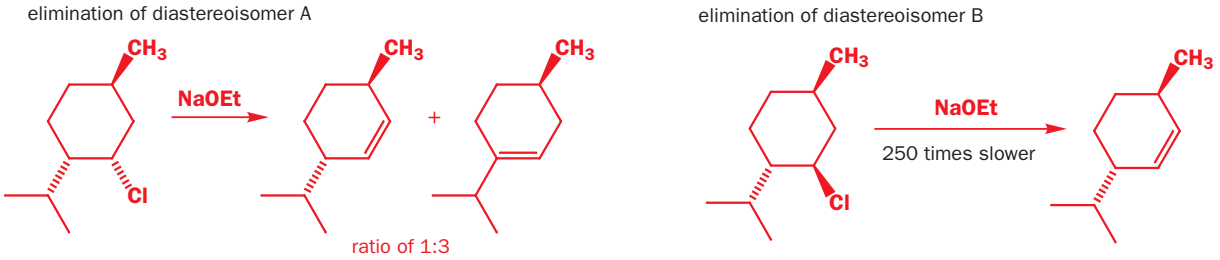
The stereospecificity of the reactions you have just met is very good evidence that E2 reactions proceed through an anti-periplanar transition state. We know with which diastereoisomer we started, and we know which alkene we get, so there is no question over the course of the reaction.

More evidence comes from the reactions of substituted cyclohexanes. You saw in Chapter 18 that substituents on cyclohexanes can be parallel with one another only if they are both axial. An equatorial C–X bond is anti-periplanar only to C–C bonds and cannot take part in an elimination. For unsubstituted cyclohexyl halides treated with base, this is not a problem because, although the axial conformer is less stable, there is still a significant amount present (see the table on p. 000), and elimination can take place from this conformer.



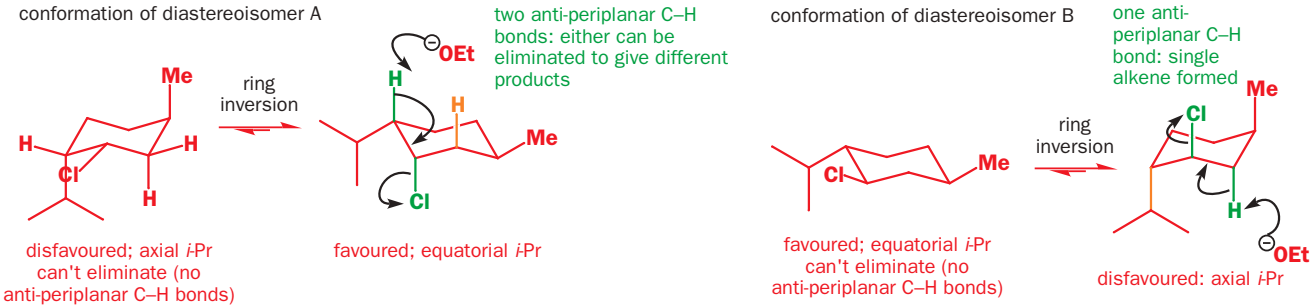
● For E2 elimination in cyclohexanes, both C–H and C–X must be axial.

These two diastereoisomeric cyclohexyl chlorides derived from menthol react very differently under the same conditions with sodium ethoxide as base. Both eliminate HCl but diastereoisomer A reacts rapidly to give a mixture of products, while diastereoisomer B (which differs only in the configuration of the carbon atom bearing chlorine) gives a single alkene product but very much more slowly. We can safely exclude E1 as a mechanism because the same cation would be formed from both diastereoisomers, and this would mean the ratio of products (though not necssarily the rate) would be the same for both.



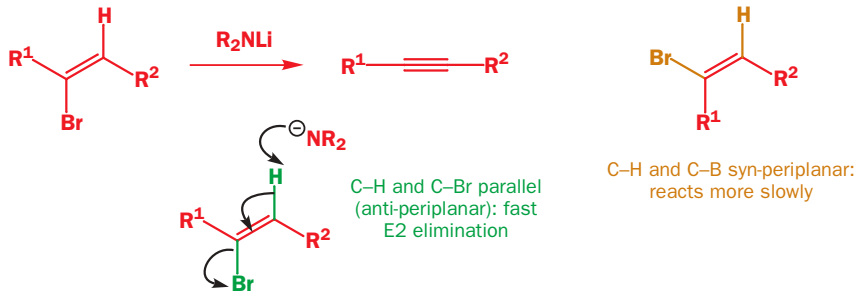
The key to explaining reactions like this is to draw the conformation of the molecules. Both will adopt a chair conformation, and generally the chair having the largest substituent equatorial (or the largest *number* of substituents equatorial) is the more stable. In these examples the isopropyl group is most influential—it is branched and will have very severe 1,3-diaxial interactions if it occupies an axial position. In both diastereoisomers, an equatorial *i*-Pr also means an equatorial Me: the only difference is the orientation of the chlorine. For diastereoisomer A, the chlorine is forced axial in the major conformer: there is no choice, because the relative configuration is fixed in the starting material. It's less stable than equatorial Cl, but is ideal for E2 elimination and there are two protons that are anti-periplanar available for removal by the base. The two alkenes are formed as a result of each of the possible protons with a 3:1 preference for the more substituted alkene (see below).

For diastereoisomer B, the chlorine is equatorial in the lowest-energy conformation. Once again there is no choice. But equatorial leaving groups cannot be eliminated by E2: in this conformation there is no anti-periplanar proton. This accounts for the difference in rate between the two diastereoisomers. A has the chlorine axial virtually all the time ready for E2, while B has an axial leaving group only in the minute proportion of the molecules that happen not to be in the lowest-energy conformation, but that have all three substituents axial. The all-axial conformer is much higher in energy, but only in this conformer can Cl^- be eliminated. The concentration of reactive molecules is low, so the rate is also low. There is only one proton anti-periplanar and so elimination gives a single alkene.



E2 elimination from vinyl halides: how to make alkynes

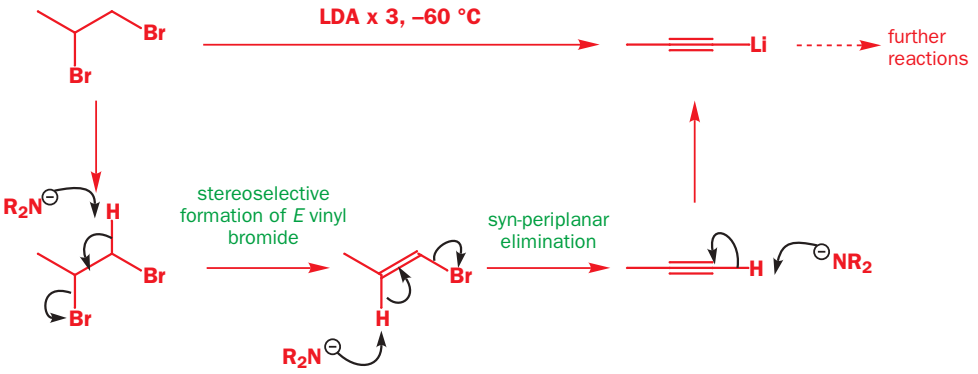
An anti-periplanar arrangement of C–Br and C–H is attainable with a vinylic bromide too, provided the Br and H are *trans* to one another. E2 elimination from the *Z* isomer of a vinyl bromide gives an alkyne rather faster than elimination from the *E* isomer, because in the *E* isomer the C–H and C–Br bonds are syn-periplanar.



▶ The base used here is LDA (lithium diisopropylamide) made by deprotonating *i*-Pr_2NH with BuLi. LDA is very basic (pK_a about 35) but too hindered to be nucleophilic—ideal for promoting E2 elimination.

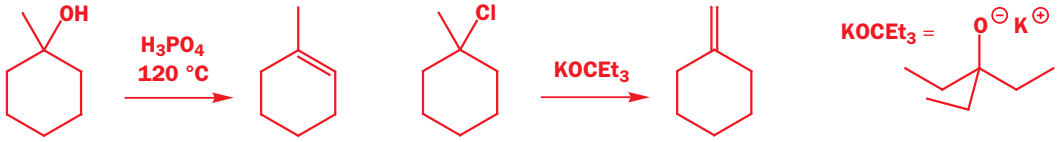
Vinyl bromides can themselves be made by elimination reactions of 1,2-dibromoalkanes. Watch what happens when 1,2-dibromopropane is treated with three equivalents of LDA: first, elimination to the vinyl halide; then, elimination of the vinyl halide to the alkyne. The terminal alkyne is amply acidic enough to be deprotonated by LDA, and this is the role of the third equivalent. Overall, the reaction makes a lithiated alkyne (ready for further reactions) from a fully saturated starting material. This may well be the first reaction you have met that makes an alkyne from a starting material that doesn't already contain a triple bond.

making an alkyne from 1,2-dibromopropane



The regioselectivity of E2 eliminations

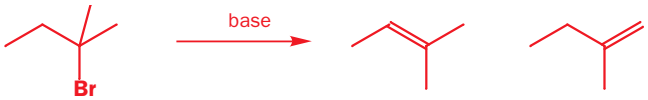
Here are two deceptively similar elimination reactions. The leaving group changes and the reaction conditions are very different but the overall process is elimination of HX to produce one of two alkenes.



In the first example acid-catalysed elimination of water from a tertiary alcohol produces a trisubstituted alkene. Elimination of HCl from the corresponding tertiary alkyl chloride promoted by a very hindered alkoxide base (more hindered than *t*-BuOK because all the ethyl groups have to point away from one another) gives exclusively the less stable disubstituted alkene.

The reason for the two different regioselectivities is a change in mechanism. As we have already discussed, acid-catalysed elimination of water from tertiary alcohols is usually E1, and you already know the reason why the more substituted alkene forms faster in E1 reactions (p. 000). It should come to you as no surprise now that the second elimination, with a strong, hindered base, is an E2 reaction. But why does E2 give the less substituted product? This time, there is no problem getting C–H bonds anti-periplanar to the leaving group: in the conformation with the Cl axial there are two equivalent ring hydrogens available for elimination, and removal of either of these would lead to the trisubstituted alkene. Additionally, any of the three equivalent methyl hydrogens are in a position to undergo E2 elimination to form the disubstituted alkene whether the Cl is axial or equatorial—and yet it is these and only these that are removed by the hindered base. The diagram summarizes two of the possibilities.

The base attacks the methyl hydrogens because they are less hindered—they are attached to a primary carbon atom, well away from the other axial hydrogens. E2 eliminations with hindered bases typically give the less substituted double bond, because the fastest E2 reaction involves deprotonation at the least substituted site. The hydrogens attached to a less substituted carbon atom are also more acidic. Think of the conjugate bases: a *t*-butyl anion is more basic (because the anion is destabilized by the three alkyl groups) than a methyl anion, so the corresponding alkane must be less acidic. Steric factors are evident in the following E2 reactions, where changing the base from ethoxide to *t*-butoxide alters the major product from the more to the less substituted alkene.



NaOEt	69%	31%
t-BuOK	28%	73%

Elimination regioselectivity

- E1 reactions give the more substituted alkene
- E2 reactions may give the more substituted alkene, but become more regioselective for the less substituted alkene with more hindered bases

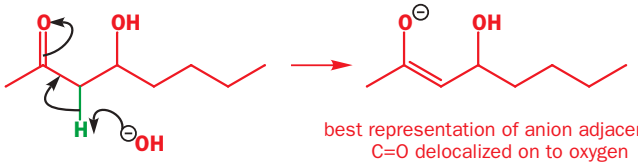
Hofmann and Saytsev

Traditionally, these two opposite preferences—for the more or the less substituted alkenes—have been called 'Saytsev's rule' and 'Hofmann's rule', respectively. You will see these names used (along with a number of alternative spellings—acceptable for Saytsev, whose name is transliterated from Russian, but not for Hofmann: this Hofmann had one f and two n's), but there is little point remembering which is which (or how to spell them)—it is far more important to understand the reasons that favour formation of each of the two alkenes.

Anion-stabilizing groups allow another mechanism—E1cB

To finish this chapter, we consider a reaction that at first sight seems to go against what we have told you so far. It's an elimination catalysed by a strong base (KOH), so it looks like E2. But the leaving group is hydroxide, which we categorically stated cannot be a leaving group in E2 eliminations.

The key to what is going on is the carbonyl group. In Chapter 8 you met the idea that negative charges are stabilized by conjugation with carbonyl groups, and the table on p. 000 demonstrated how acidic a proton adjacent to a carbonyl group is. The proton that is removed in this elimination reaction is adjacent to the carbonyl group, and is therefore also rather acidic (pK_a about 20). This means that the base can remove it without the leaving group departing at the same time—the anion that results is stable enough to exist because it can be delocalized on to the carbonyl group.



green proton acidified (p*K*a ca. 20) by adjacent carbonyl group

best representation of anion adjacent to C=O delocalized on to oxygen

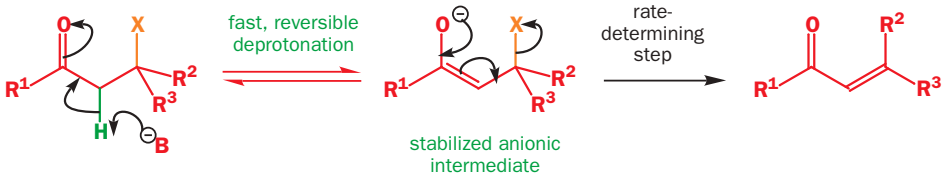
▶ This delocalized anion is called an **enolate**, and we will discuss enolates in more detail in Chapter 21 and beyond.

Although the anion is stabilized by the carbonyl group, it still prefers to lose a leaving group and become an alkene. This is the next step.

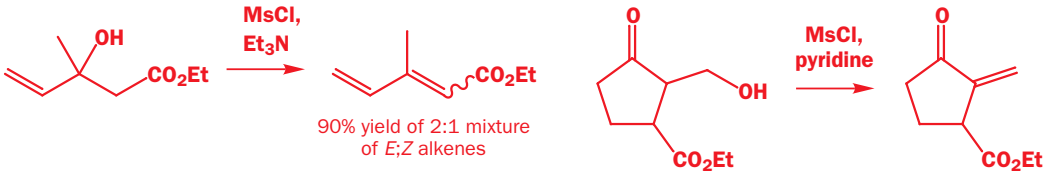
■ *Note.* E1cB has no super- or subscripts, a lower-case c, and an upper-case B.

This step is also the rate-determining step of the elimination—the elimination is unimolecular, and so is some kind of E1 reaction. But the leaving group is not lost from the starting molecule, but from the *conjugate base* of the starting molecule, so this sort of elimination, which starts with a deprotonation, is called **E1cB** (cB for conjugate Base). Here is the full mechanism, generalized for other carbonyl compounds.

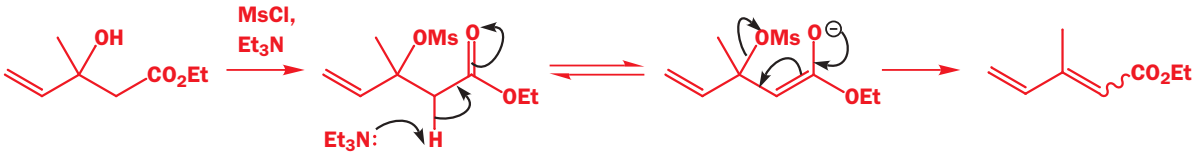
the E1cB mechanism

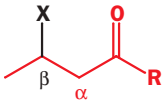


It's important to note that, while HO^- is never a leaving group in E2 reactions, it can be a leaving group in E1cB reactions. The anion it is lost from is already an alkoxide—the oxyanion does not need to be created. The establishment of conjugation also assists loss of HO^-. As the scheme above implies, other leaving groups are possible too. Here are two examples with methanesulfonate leaving groups.



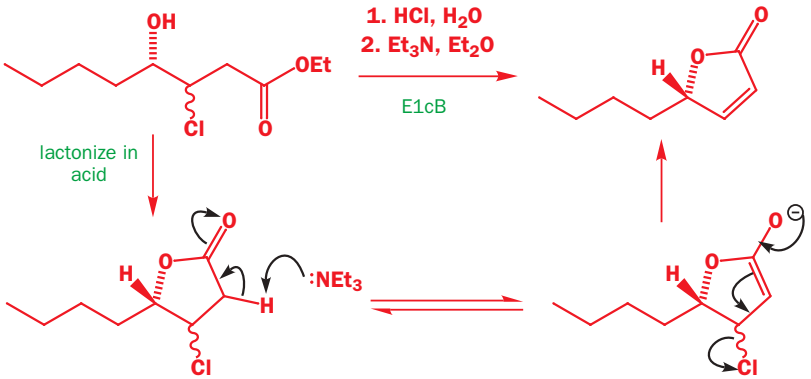
The first looks E1 (stabilized cation); the second E2—but in fact both are E1cB reactions. The most reliable way to spot a likely E1cB elimination is to see whether the product is a conjugated carbonyl group. If it is, the mechanism is probably E1cB.





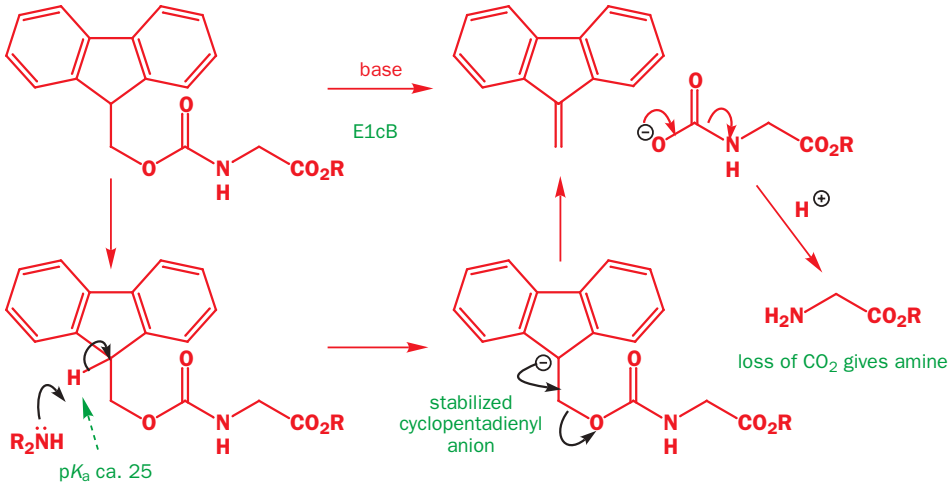
a β-halocarbonyl compound

β-Halocarbonyl compounds can be rather unstable: the combination of a good leaving group and an acidic proton means that E1cB elimination is extremely easy. This mixture of diastereoisomers is first of all lactonized in acid (Chapter 12), and then undergoes E1cB elimination with triethylamine to give a product known as **butenolide**. Butenolides are widespead structures in naturally occurring compounds.

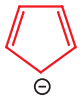


You will have noticed that we have shown the deprotonation step in the last few mechanisms as an equilibrium. Both equilibria lie rather over to the left-hand side, because neither triethylamine (pK_{aH} about 10) nor hydroxide (pK_{aH} = 15.7) is basic enough to remove completely a proton next

to a carbonyl group ($pK_a \geq 20$). But, because the loss of the leaving group is essentially irreversible, only a small amount of deprotonated carbonyl compound is necessary to keep the reaction going. The important point about substrates that undergo E1cB is that there is some form of anion-stabilizing group next to the proton to be removed—it doesn't have to stabilize the anion very well but, as long as it makes the proton more acidic, an E1cB mechanism has a chance. Here is an important example with two phenyl rings helping to stabilize the anion, and a carbamate anion ($R2N—CO_2^-$) as the leaving group.



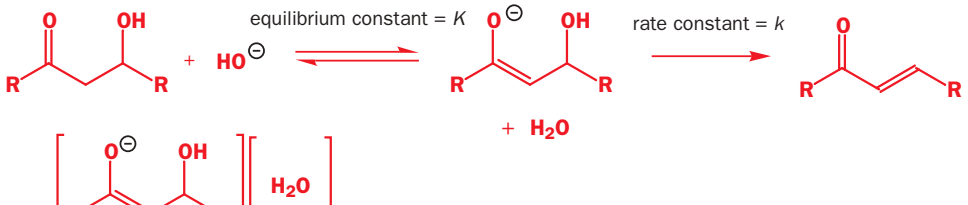
The proton to be removed has a pK_a of about 25 because its conjugate base is an aromatic cyclopentadienyl anion (we discussed this in Chapter 8). The E1cB elimination takes place with a secondary or tertiary amine as the base. Spontaneous loss of CO_2 from the eliminated product gives an amine, and you will meet this class of compounds again shortly in Chapter 25 where we discuss the Fmoc protecting group.



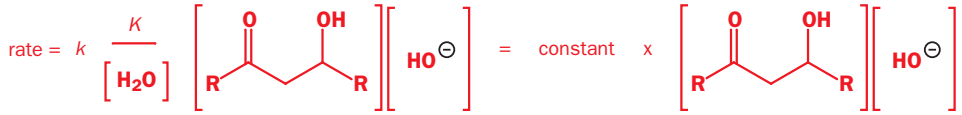
6 π electrons aromatic cyclopentadienyl anion

The E1cB rate equation

The rate-determining elimination step in an E1cB reaction is unimolecular, so you might imagine it would have a first-order rate equation. But, in fact, the rate is also dependent on the concentration of base. This is because the unimolecular elimination involves a species—the anion—whose concentration is itself determined by the concentration of base by the equilibrium we have just been discussing. Using the following general E1cB reaction, the concentration of the anion can be expressed as shown.



The rate is proportional to the concentration of the anion, and we now have an expression for that concentration. We can simplify it further because the concentration of water is constant.

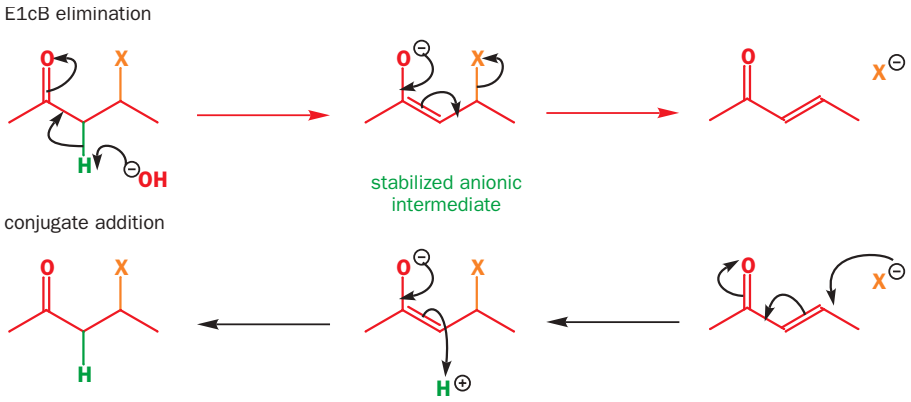


Just because the base (hydroxide) appears in this rate equation doesn't mean to say it is involved in the rate-determining step. Increasing the concentration of base makes the reaction go faster by increasing the amount of anion available to eliminate.

> **For reactions with several steps in which the rate-determining step is not the first, the concentrations of species involved in those earlier steps will appear in the rate equation, even though they take no part in the rate-determining step itself.**

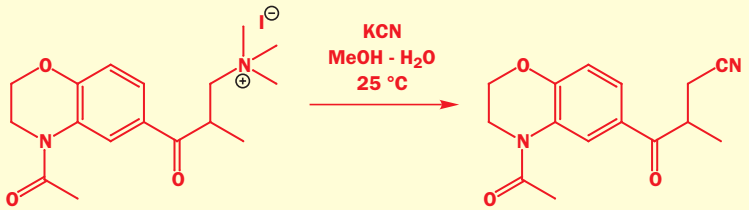
E1cB eliminations in context

It is worthwhile comparing the E1cB reaction with some others with which you are familiar: for a start, you may have noticed that it is the reverse of the conjugate addition reactions we introduced in Chapter 10. In Chapter 10, conjugated carbonyl compounds were the starting materials; now they are the products—but both reactions go through a stabilized anion intermediate. E1cB reactions are so general that they are by far the most common way of making the enone starting materials for conjugate additions.

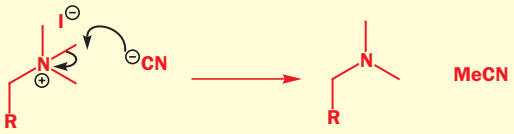


A deceptive S_N2 substitution

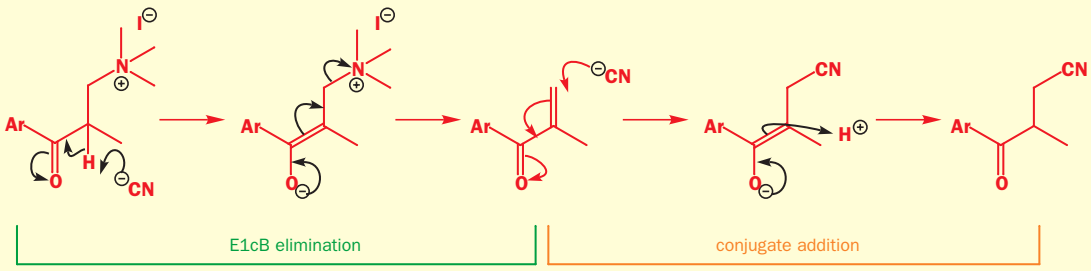
In some rare cases, you may see E1cB elimination and conjugate addition taking place in a single reaction. Look at this 'substitution' reaction, for example. Apparently, the ammonium salt has been substituted by the cyanide in what looks to be an S_N2 reaction.



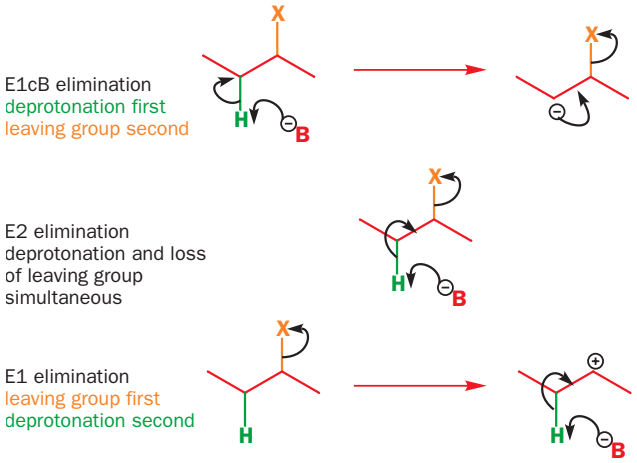
A little consideration will tell you that it can't be S_N2 though, because, if it were, it would go like this.



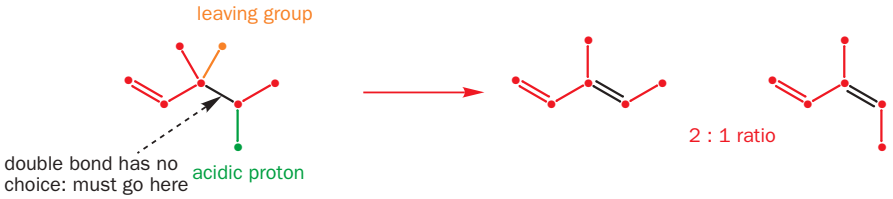
Instead, the mechanism is first an E1cB elimination, followed by conjugate addition.



We can also compare it with the other elimination reactions you have met by thinking of the relative timing of proton removal and leaving group departure. E1 is at one end of the scale: the leaving group goes first, and proton removal follows in a second step. In E2 reactions, the two events happen at the same time: the proton is removed as the leaving group leaves. In E1cB the proton removal moves in front of leaving group departure.

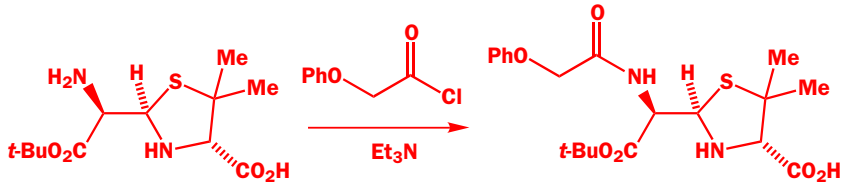


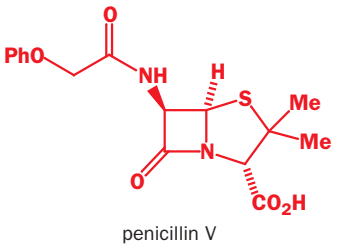
We talked about regio- and stereoselectivity in connection with E1 and E2 reactions. With E1cB, the regioselectivity is straightforward: the location of the double bond is defined by the position of: (a) the acidic proton and (b) the leaving group.



E1cB reactions may be stereoselective—this one, for example, gives mainly the *E*-alkene product (2:1 with *Z*). The intermediate anion is planar, so the sterochemistry of the starting materials is irrelevant, the less sterically hindered (usually *E*) product is preferred. This double E1cB elimination, for example, gives only the *E,E*-product.

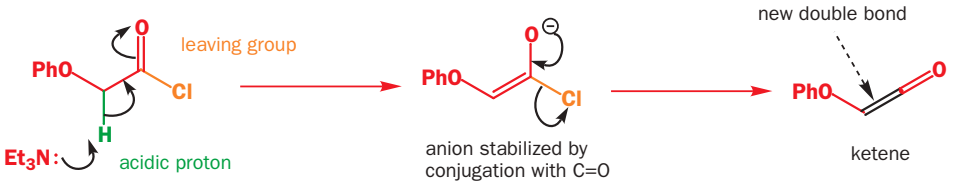
To finish this chapter we need to tell you about two E1cB eliminations that you may meet in unexpected places. We have saved them till now because they are unusual in that the leaving group is actually part of the anion-stabilizing group itself. First of all, try spotting the E1cB elimination in this step from the first total synthesis of penicillin V in 1957.



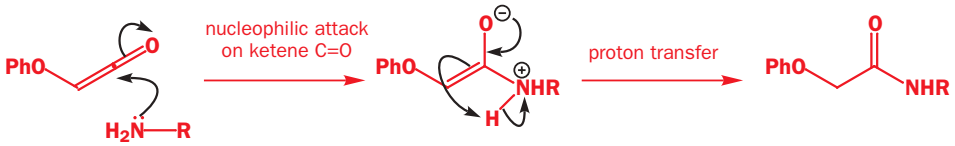


penicillin V

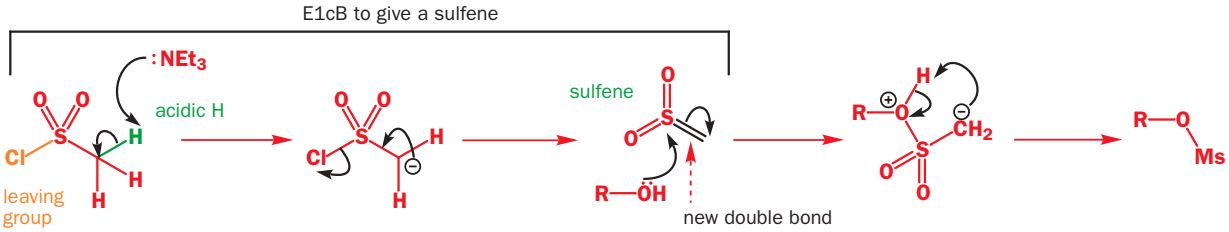
The reaction is deceptively simple—formation of an amide in the presence of base—and you would expect the mechanism to follow what we told you in Chapter 12. But the acyl chloride is, in fact, set up for an E1cB elimination—and you should expect this whenever you see an acyl chloride *with acidic protons next to the carbonyl group* used in the presence of triethylamine.



The product of the elimination is a substituted ketene—a highly reactive species whose parent (CH_2=C=O) we talked about in Chapter 15. It is the ketene that reacts with the amine to form the amide.

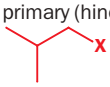
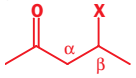


The second 'concealed' E1cB elimination is in the elimination of HCl from MsCl, which we showed you on p. 000 of this chapter. You can now see the similarity with the acyl chloride mechanism above.



To conclude...

The table summarizes the general pattern of reactivity expected from various structural classes of alkyl halides (or tosylates, mesylates) in reactions with a representative range of nucleophiles (which may behave as bases).

	Poor nucleophile (e.g. H_2O, ROH)[a]	**Weakly basic nucleophile (e.g. I^-, RS^-)**	**Strongly basic, unhindered nucleophile (e.g. RO^-)**	**Strongly basic, hindered nucleophile (e.g. DBU, DBN, *t*-BuO^-)**
methyl 	no reaction	S_N2	S_N2	S_N2
primary (unhindered) 	no reaction	S_N2	S_N2	E2
primary (hindered) 	no reaction	S_N2	E2	E2
secondary 	S_N1, E1 (slow)	S_N2	E2	E2
tertiary 	E1 or S_N1	S_N1, E1	E2	E2
β to anion-stabilizing group 	E1cB	E1cB	E1cB	E1cB

[a] Acid conditions.

Some points about the table:

- Methyl halides cannot eliminate as there are no appropriately placed protons
- Increasing branching favours elimination over substitution and strongly basic hindered nucleophiles always eliminate unless there is no option
- Good nucleophiles undergo substitution by S_N2 unless the substrate is tertiary and then the intermediate cation can eliminate by E1 as well as substitute by S_N1
- High temperatures favour elimination by gearing up the importance of entropy in the free energy of reaction ($\Delta G = \Delta H - T\Delta S$). This is a good way of ensuring E1 in ambiguous cases

Electrophilic addition to alkenes

20

Connections

Building on:

- Elimination reactions that form alkenes ch19
- Stability of carbocations, and their reactions during the S_N1 reaction ch17
- *Nucleophilic* addition to conjugated alkenes ch10

Arriving at:

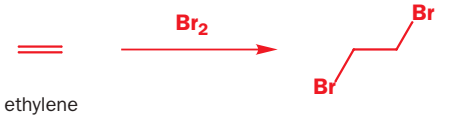
- Reactions of simple, unconjugated alkenes with *electrophiles*
- Converting C=C double bonds to other functional groups by electrophilic addition
- How to predict which end of an unsymmetrical alkene reacts with the electrophile
- Stereoselective and stereospecific reactions of alkenes
- How to make alkyl halides, epoxides, alcohols, and ethers through electrophilic addition

Looking forward to:

- Electrophilic addition to alkenes carrying oxygen substituents (enols and enolates) ch21
- Electrophilic addition to aromatic rings ch22
- Reactions of alkenes by pericyclic reactions ch35
- Reactions of alkenes with boranes ch47

Alkenes react with bromine

Bromine (Br_2) is brown, and one of the classic tests for alkenes is that they turn a brown aqueous solution of bromine colourless. Alkenes decolourize bromine water: alkenes react with bromine. The product of the reaction is a dibromoalkane, and the reaction below shows what happens with the simplest alkene, ethylene (ethene).



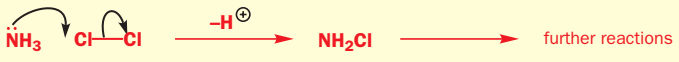
ethylene (ethene)

1,2-dibromoethylene

In order to understand this reaction, and the other similar ones you will meet in this chapter, you need to think back to Chapter 5, where we started talking about reactivity in terms of nucleophiles and electrophiles. As soon as you see a new reaction, you should immediately think to yourself, 'Which reagent is the nucleophile; which reagent is the electrophile?' Evidently, neither the alkene nor bromine is charged, but Br_2 has a low-energy empty orbital (the Br–Br σ*), and is therefore an electrophile. The Br–Br bond is exceptionally weak, and bromine reacts with nucleophiles like this.

Chloramines

Have you ever wondered why conventional wisdom (and manufacturers' labels) warns against mixing different types of cleaning agent? The danger arises from nucleophilic attack on another halogen, chlorine. Some cleaning solutions contain chlorine (bleach, to kill moulds and bacteria, usually for the bathroom) while others contain ammonia (to dissolve fatty deposits, usually for the kitchen). Ammonia is nucleophilic, chlorine electrophilic, and the products of their reaction are the highly toxic and explosive chloramines NH_2Cl, $NHCl_2$, and NCl_3.



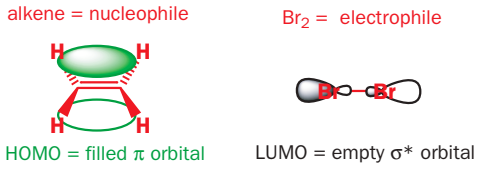
chloramine

The alkene must be the nucleophile, and its HOMO is the C=C π bond. This is a very important point, because in the first reactions of alkenes you met, in Chapter 10, the conjugated alkene was an *electrophile*. We told you about conjugated alkenes first, because their chemistry is very similar to the

chemistry of the carbonyl group. But normal, simple, unconjugated alkenes are electron-rich—they have no nearby carbonyl group to accept electrons—and they typically act as *nucleophiles* and attack *electrophiles*.

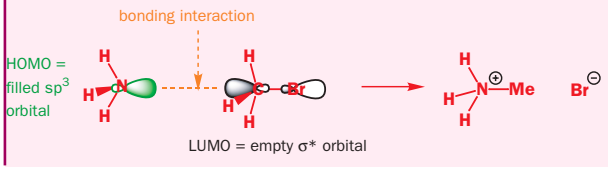
● Simple, unconjugated alkenes are nucleophilic and react with electrophiles.

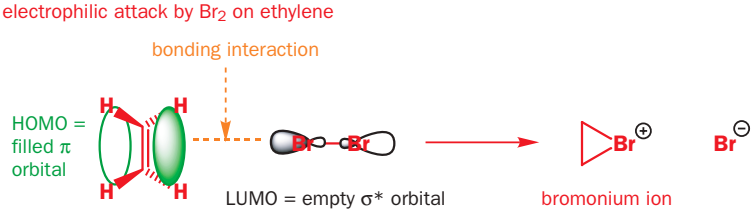
When it reacts with Br_2, the alkene's filled π orbital (the HOMO) will interact with the bromine's empty σ* orbital to give a product. But what will that product be? Look at the orbitals involved.



The highest electron density in the π orbital is right in the middle, between the two carbon atoms, so this is where we expect the bromine to attack. The only way the π HOMO can interact in a bonding manner with the σ* LUMO is if the Br_2 approaches end-on—and this is how the product forms. The symmetrical three-membered ring product is called a **bromonium ion**.

▶ In Chapter 17, you saw many examples of S_N2 reactions at carbon, and some at Si, P, and S. This reaction is also a nucleophilic substitution (from the point of view of the bromine) at Br. Just replace the alkene with another nucleophile, and Br–Br with Me–Br, and you are on familiar ground again.





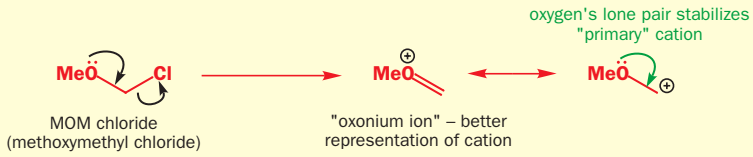
How shall we draw curly arrows for the formation of the bromonium ion? We have a choice. The simplest is just to show the middle of the π bond attacking Br–Br, mirroring what we know happens with the orbitals.

But there is a problem with this representation: because only one pair of electrons is moving, we can't form two new C–Br bonds. We should really then represent the C–Br bonds as partial bonds. Yet the bromonium ion is a real intermediate with two proper C–Br bonds (read the box in the margin on p. 000 for evidence of this). So an alternative way of drawing the arrows is to involve a lone pair on bromine.

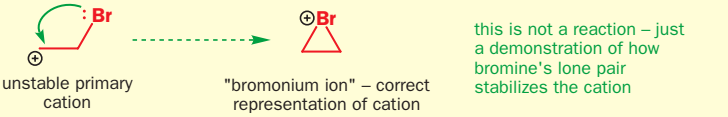
We think the first way represents more accurately the key orbital interaction involved, and we shall use that one, but the second is acceptable too.

Another way of thinking about bromonium ions

You can think of the bromonium ion as a carbocation that has been stabilized by interaction with a nearby bromine atom. You have seen a similar effect with oxygen—this 'oxonium ion' was an intermediate, for example, in the S_N1 substitution of MOM chloride on p. 000 of Chapter 17.



The bromine is one atom further away but, with bromine being lower in the periodic table and having more diffuse lone pairs, it can have a similar stabilizing effect, despite the angle strain in a three-membered ring.

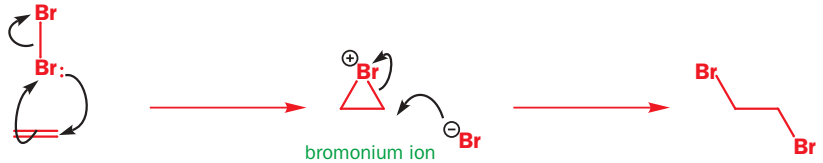


The two stypes of stabilization are not equivalent: the cation and the bromonium ion are different molecules with different shapes, while the two representations of the oxonium ion are just that—they aren't different molecules. This stabilization of an adjacent cationic centre by a heteroatom with at least one lone pair to form a three-membered ring intermediate is not restricted to bromine or the other halogens but is also an important aspect of the chemistry of compounds containing oxygen, sulfur, or selenium, as you will see in Chapter 46.

Of course, the *final* product of the reaction isn't the bromonium ion. The second step of the reaction follows on at once: the bromonium ion is an electrophile, and it reacts with the bromide ion lost from the bromine in the addition step. We can now draw the correct mechanism for the whole reaction, which is termed **electrophilic addition** to the double bond, because bromine is an electrophile. Overall, the molecule of bromine *adds across* the double bond of the alkene.

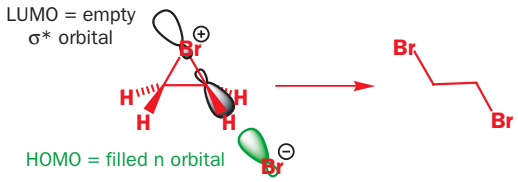
■ Compare the second step with the way nucleophiles attack epoxides, Chapter 17, p. 000.

electrophilic addition of bromine to ethylene



Attack of Br^- on a bromonium ion is a normal S_N2 substitution—the key orbitals involved are the HOMO of the bromide and the σ* of one of the two carbon–bromine bonds in the strained three-membered ring. As with all S_N2 reactions, the nucleophile maintains maximal overlap with the σ* by approaching in line with the leaving group but from the opposite side, resulting in inversion at the carbon that is attacked. The stereochemical outcome of more complicated reactions (discussed below) is important evidence for this overall reaction mechanism.

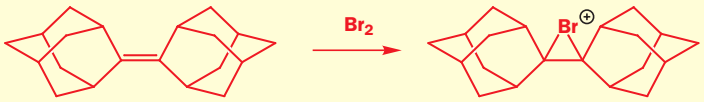
orbitals involved in the opening of the bromonium ion



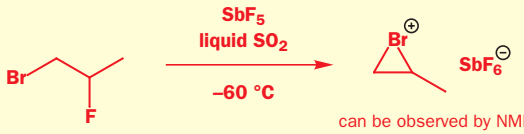
Why doesn't the bromine simply attack the positive charge and re-form the bromine molecule? Well, in fact, it does and the first step is reversible.

How do we know bromonium ions exist?

Very hindered alkenes form bromonium ions that are resistant to nucleophilic attack. In one very hindered case, the bromine ion just can't get at the bromonium ion to attack it, and the bromonium ion is sufficiently stable to be characterized by X-ray crystallography. In another case, the use of superacid systems (Chapter 17) has allowed direct NMR observation of the bromonium ion intermediate to the bromination of propene.



crystalline solid



can be observed by NMR

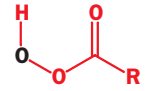
Oxidation of alkenes to form epoxides

The electrophilic addition of bromine to alkenes is an oxidation. The starting alkene is at the alcohol oxidation level, but the product has two carbons at the alcohol oxidation level—the elimination reactions of dibromides to give alkynes that you met in the last chapter (p. 000) should convince you of this. There are a number of other oxidants containing electrophilic oxygen atoms that react with nucleophilic alkenes to produce epoxides (oxiranes). You can view epoxides as the oxygen analogues of bromonium ions, but unlike bromonium ions they are quite stable.

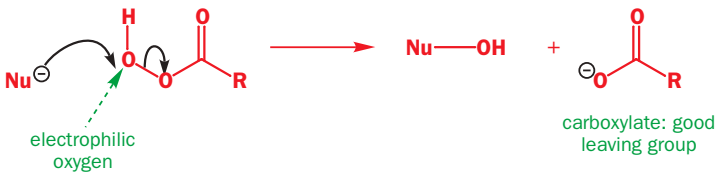
The simplest epoxide, ethylene oxide (or oxirane itself), can be produced on the tonne scale by the direct oxidation of ethene by oxygen at high temperature over a silver catalyst. These conditions are hardly suitable for general lab use, and the most commonly used epoxidizing agents are peroxy-carboxylic acids. **Peroxy-acids** (or **peracids**) have an extra oxygen atom between the carbonyl group and their acidic hydrogen—they are half-esters of hydrogen peroxide (H_2O_2). They are rather less acidic than carboxylic acids because their conjugate base is no longer stabilized by delocalization into the carbonyl group reagent. But they are electrophilic at oxygen, because attack there by a nucleophile displaces carboxylate, a good leaving group. The LUMO of a peroxy-carboxylic acid is the σ* orbital of the weak O–O bond.

■ You have met epoxides being formed by intramolecular substitution reactions, but the oxidation of alkenes is a much more important way of making them. Their alternative name derives from a systematic way of naming rings: 'ox' for the O atom, 'ir' for the three-membered ring, and 'ane' for full saturation. You may meet oxetane (remember the oxaphosphetane in the Wittig reaction, Chapter 14, p. 000) and, while THF is never called oxolane, dioxolane is another name for five-membered cyclic acetals.

oxirane oxetane dioxolane

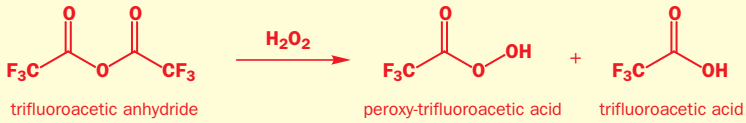


peroxy-carboxylic acid

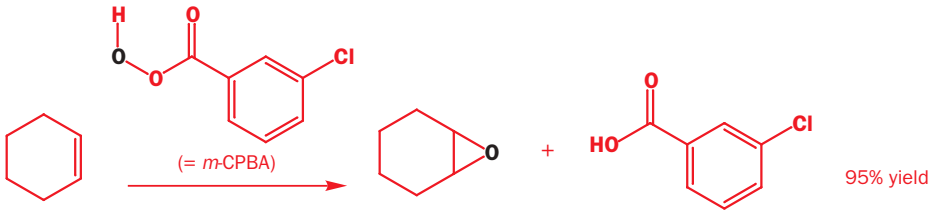


Making peroxy-acids

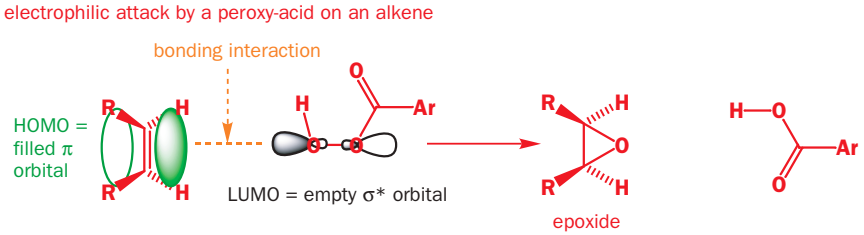
Peroxy-acids are prepared from the corresponding acid anhydride and high-strength hydrogen peroxide. In general, the stronger the parent acid, the more powerful the oxidant (because the carboxylate is a better leaving group): one of the most powerfully oxidizing peroxy-acids is peroxy-trifluoroacetic acid. Hydrogen peroxide, at very high concentrations (> 80%), is explosive and difficult to transport.

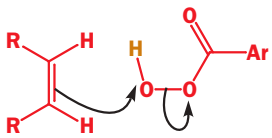


The most commonly used peroxy-acid is known as *m*-CPBA, or *meta*-ChloroPeroxyBenzoic Acid. *m*-CPBA is a safely crystalline solid. Here it is, reacting with cyclohexene, to give the epoxide in 95% yield.

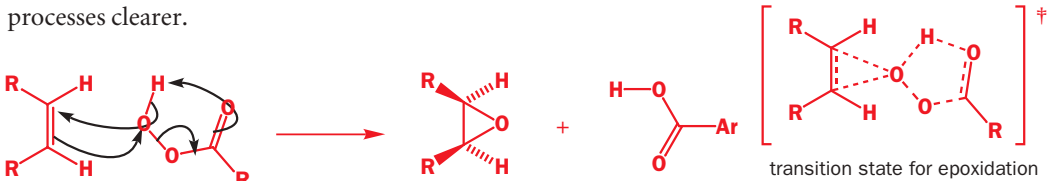


As you will expect, the alkene attacks the peroxy-acid from the centre of the HOMO, its π orbital. First, here is the orbital involved.



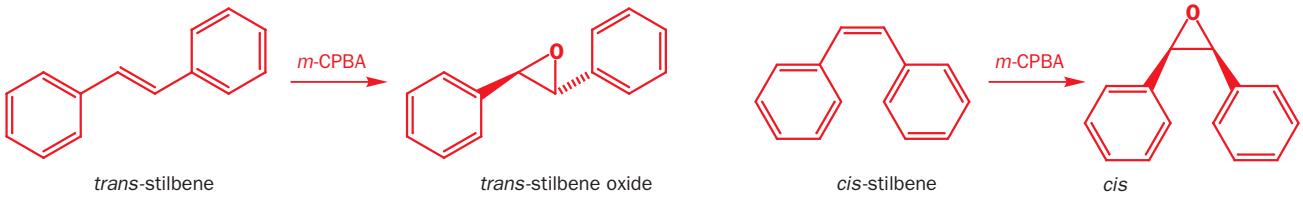


And now the curly arrow mechanism. The essence of the mechanism is electrophilic attack by the weak, polarized O–O bond on the π orbital of the alkene, which we can represent most simply as shown in the margin. But, in the real reaction, a proton (shown in brown in this mechanism) has transferred from the epoxide oxygen to the carboxylic acid by-product. You can represent this all in one step if you draw the arrows carefully. Start with the nucleophilic π bond: send the electrons on to oxygen, breaking O–O and forming a new carbonyl bond. Use those electrons to pick up the proton, and use the old O–H bond's electrons to make the second new C–O bond. Dont' be put off by the spaghetti effect—each arrow is quite logical when you think the mechanism through. The transition state for the reaction makes the bond-forming and -breaking processes clearer.



Epoxidation is stereospecific

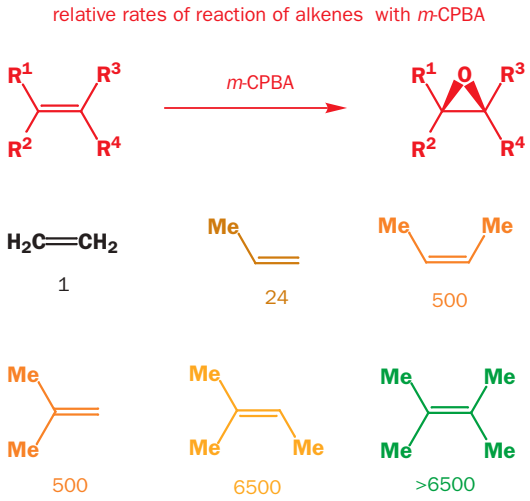
Because both new C–O bonds are formed on the same face of the alkene's π bond, the geometry of the alkene is reflected in the stereochemistry of the epoxide. The reaction is therefore stereospecific. Here are two examples demonstrating this: *cis*-alkene gives *cis*-epoxide and *trans*-alkene gives *trans*-epoxide.



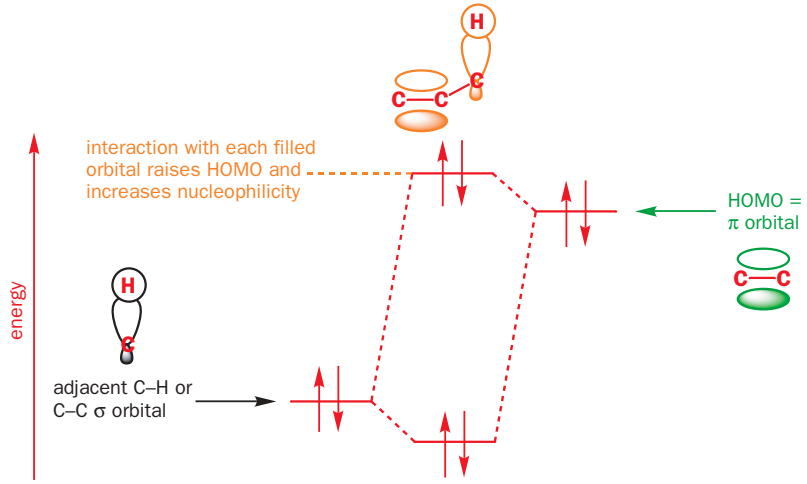
trans-stilbene *trans*-stilbene oxide *cis*-stilbene *cis*

More substituted alkenes epoxidize faster

Peracids give epoxides from alkenes with any substitution pattern (except ones conjugated with electron-withdrawing groups, for which a different reagent is required: see Chapter 23) but the chart alongside shows how the rate varies according to the number of substituents on the double bond.

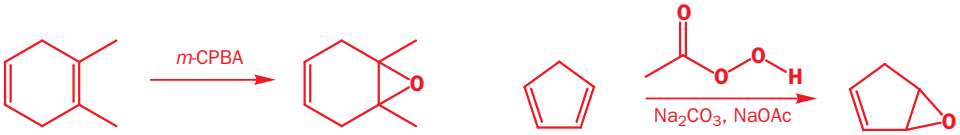


Not only are more substituted double bonds more stable (as you saw in Chapter 19), but they are more nucleophilic. We showed you in Chapter 17 that alkyl groups are electron-donating because they stabilize carbocations. This same electron-donating effect raises the energy of the HOMO of a double bond, and makes it more nucleophilic. You can think of it this way: every C–C or C–H bond that can allow its σ orbital to interact with the π orbital of the alkene will raise the HOMO of the alkene slightly, as shown by the energy level diagram. The more substituents the alkene has, the more the energy is raised.

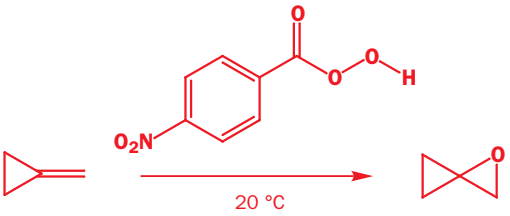


The differences in reactivity between alkenes of different substitution patterns can be exploited to produce the epoxide only of the more reactive alkene of a pair, provided the supply of oxidant is limited. In the first example below, a tetrasubstituted alkene reacts in preference to a *cis* disubstituted one. Even when two alkenes are equally substituted, the effect of epoxidizing one of them is to reduce the nucleophilicity of the second (the new oxygen atom is electron-withdrawing, and dienes are in

general more nucleophilic than alkenes: see below). The monoepoxide of cyclopentadiene is a useful intermediate and can be prepared by direct epoxidation of the diene under buffered conditions.



p-Nitroperoxybenzoic acid is dangerously explosive, but it is sufficiently reactive to produce this remarkable and highly strained *spiro* epoxide (oxaspiropentane), which was made in order to study its reactions with nucleophiles.

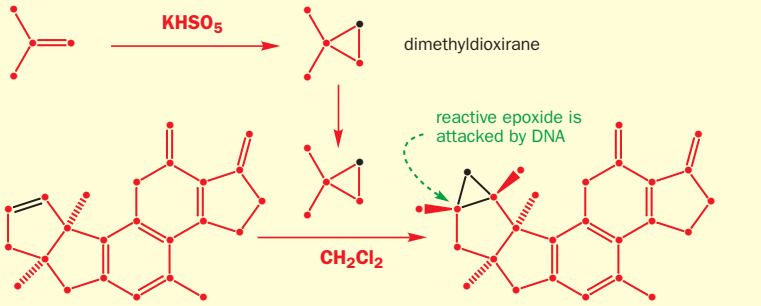


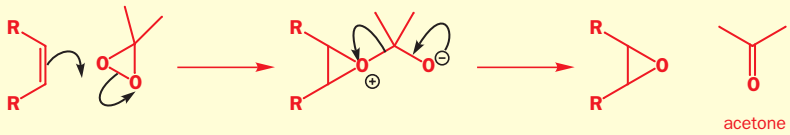
▶ You may notice additives in peroxy-acid epoxidations, such as sodium carbonate/sodium acetate here. These are buffers, added to prevent the reaction mixture becoming too acidic—remember, the carboxylic acid is a by-product of the epoxidation. Some epoxides are unstable in acid, as we shall see shortly.

▶ ***Spiro*** compounds have two rings joined at a single atom. Compare **fused** rings (joined at two adjacent atoms) and **bridged** rings (joined two nonadjacent atoms).

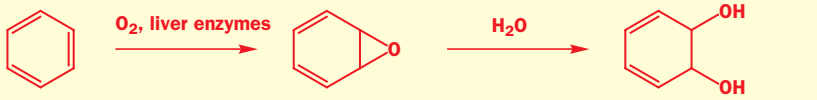
Dimethyldioxirane and carcinogenic epoxides

Certain fungi, especially the mould *Aspergillus sp.* (which grows on damp grain), produce a group of the most carcinogenic substances known to man, the aflatoxins. One of the toxins (which are, of course, entirely natural) is metabolized in the human body to the epoxide shown below. Some American chemists decided to synthesize this epoxide to investigate its reaction with DNA, hoping to discover exactly how it causes cancer. The epoxide is far too reactive to be made using a peroxy-acid (because of the acid by-product), and instead these chemists used a relatively new reagent called dimethyldioxirane. Dimethyldioxirane is made by oxidizing acetone with $KHSO_5$, but is too reactive to be stored for more than a short period in solution. After it has transferred an oxygen atom in the epoxidation step, only innocuous acetone is left, as shown by the mechanism below.





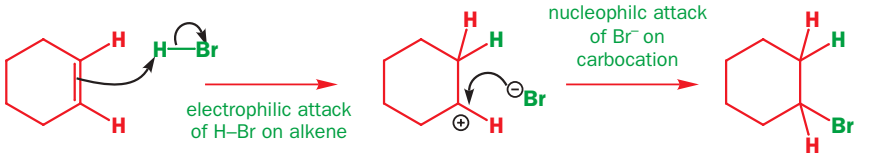
The liver is home to a wide variety of enzymes that carry out oxidation—the aim is to make unwanted water-insoluble molecules more polar and therefore soluble by peppering them with hydroxyl groups. Unfortunately, some of the intermediates in the oxidation processes are highly reactive epoxides that damage DNA. This is the means by which benzene and other aromatic hydrocarbons cause cancer, for example. Note that it is very hard to epoxidize benzene by chemical (rather than biological) methods.



Electrophilic addition to unsymmetrical alkenes is regioselective

In epoxidation reactions, and in electrophilic additions of bromine, each end of the alkene is joined to the same sort of atom (Br or O). But in the addition reactions of other electrophiles, H–Br for example, there is a choice: which carbon gets the H and which gets the Br? You will need to be able to predict, and to explain, reactions of unsymmetrical alkenes with HBr, but we should start by looking at the reaction with a symmetrical alkene—cyclohexene. This is what happens. When H–Br reacts as an electrophile, it is attacked at H, losing Br^-. Unlike a bromine atom, a hydrogen atom can't form a three-membered ring cation—it has no lone pairs to use. So electrophilic addition of a proton (which is what this is) to an alkene gives a product best represented as a carbocation. This carbocation rapidly reacts with the bromide ion just formed. Overall, H–Br adds across the alkene. This is a useful way of making simple alkyl bromides.

electrophilic addition of HBr to cyclohexene



cyclohexene

cyclohexyl bromide

Here are two more syntheses of alkyl bromides, but this time we need to ask our question about which end of the alkene is attacked, because the alkenes are unsymmetrical (they have different substituents at each end). First, the results.

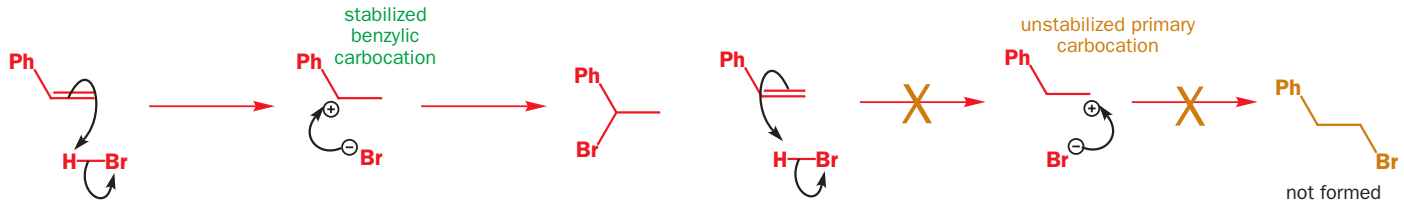
styrene

1-bromo-1-phenylethane

isobutene

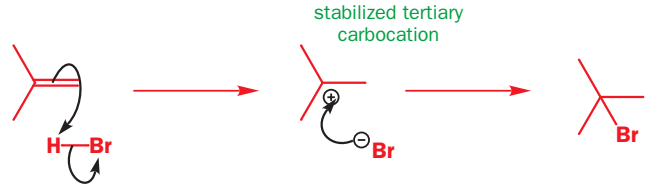
t-butyl bromide

In each case, the bromine atom ends up on the more substituted carbon, and the mechanism explains why. There are the two possible outcomes for protonation of styrene by HBr, but you should immediately be able to spot which is preferred, even if you don't know the outcome of the reaction. Protonation at one end gives a stabilized, benzylic cation, while protonation at the other would give a highly unstable primary cation, and therefore does not take place. The benzylic cation gives the benzylic alkyl bromide.



not formed

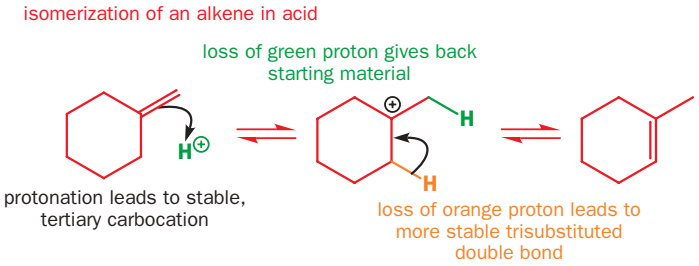
You get the same result with isobutene: the more stable, tertiary cation leads to the product; the alternative primary cation is not formed.



Markovnikov's rule

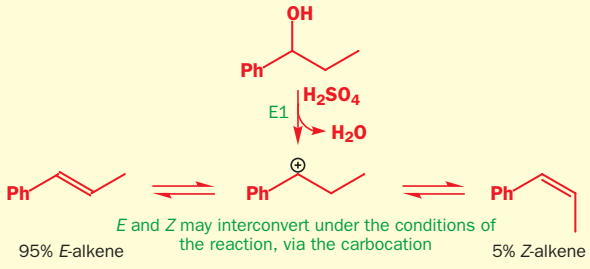
There is a traditional mnemonic called 'Markovnikov's rule' for electrophilic additions of H–X to alkenes, which can be stated as 'The hydrogen ends up attached to the carbon of the double bond that had more hydrogens to start with.' We don't suggest you learn this rule, though you may hear it referred to. As with all 'rules' it is much more important to understand the reason behind it. For example, *you* can now predict the product of the reaction below. Markovnikov couldn't.

The protonation of alkenes to give carbocations is quite general. The carbocations may trap a nucleophile, as you have just seen, or they may simply lose a proton to give back an alkene. This is just the same as saying the protonation is reversible, but it needn't be the same proton that is lost. A more stable alkene may be formed by losing a different proton, which means that acid can catalyse the isomerization of alkenes—both between *Z* and *E* geometrical isomers and between regioisomers.

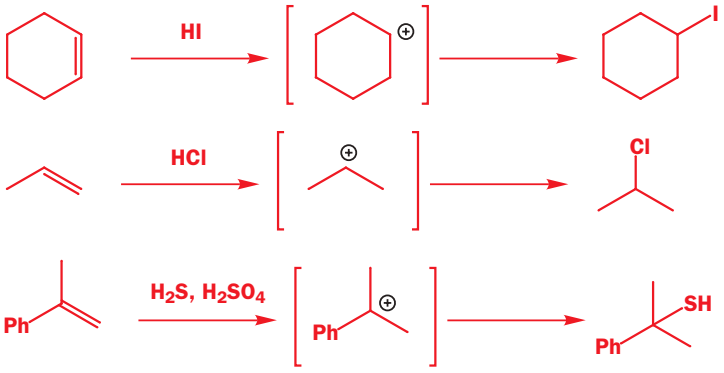


E1 and isomerization

The isomerization of alkenes in acid is probably a good part of the reason why E1 eliminations in acid generally give *E*-alkenes. In Chapter 19, we explained how *kinetic* control could lead to *E*-alkenes: interconversion of *E*- and *Z*-alkenes under the conditions of the reaction allows the *thermodynamic* product to prevail.



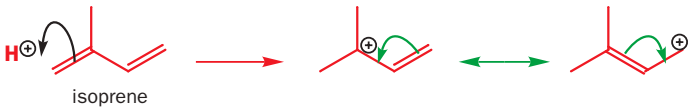
Other nucleophiles may also intercept the cation: for example, alkenes can be treated with HCl to form alkyl chlorides, with HI to form alkyl iodides, and with H_2S to form thiols.



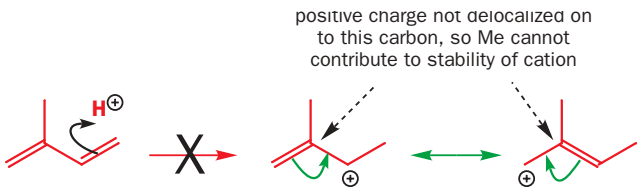
Electrophilic addition to dienes

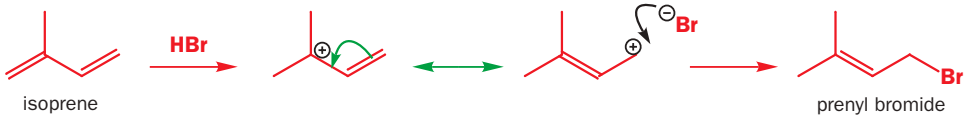
Earlier in the chapter you saw the epoxidation of a diene to give a monoepoxide: only one of the double bonds reacted. This is quite a usual observation: dienes are more nucleophilic than isolated alkenes. This is easy to explain by looking at the relative energy of the HOMO of an alkene and a diene—this discussion is on p. 000 of Chapter 7. Dienes are therefore very susceptible to protonation

by acid to give a cation. This is what happens when 2-methylbuta-1,3-diene (isoprene) is treated with acid. Protonation gives a stable delocalized allylic cation.



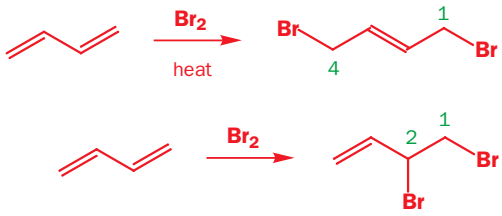
Why protonate this double bond and not the other one? The cation you get by protonating the other double bond is also allylic, but it cannot benefit from the additional stabilization from the methyl group because the positive charge is not delocalized on to the carbon carrying the methyl.





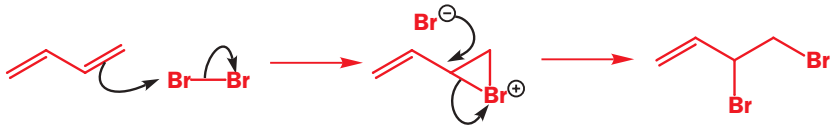
If the acid is HBr, then nucleophilic attack by Br^- on the cation follows. The cation is attacked at the less hindered end to give the important compound prenyl bromide. This is very much the sort of reaction you met in Chapter 17—it is the second half of an S_N1 substitution reaction on an allylic compound.

Overall, the atoms H and Br are added to the ends of the diene system. The same appears to be the case when dienes are brominated with Br_2.

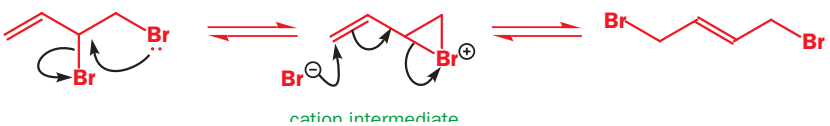


Changing the conditions slightly gives a different outcome. If the reaction is done at lower temperatures, the bromine just adds across one of the double bonds to give a 1,2-dibromide.

This compound turns out to be the kinetic product of the bromination reaction. The 1,4-dibromide is formed only when the reaction is heated, and is the thermodynamic product. The mechanism is electrophilic attack on the diene to give a bromonium ion, which bromide opens to give the dibromide. We have shown the bromide attacking the more substituted end of the bromide—though we can't know this for sure (attack at either end gives the same product), you are about to see (in the next section) evidence that this is the usual course of reactions of unsymmetrical bromonium ions.



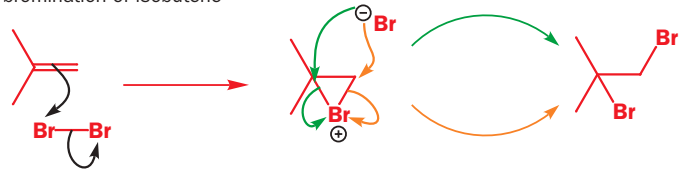
This 1,2-dibromide can still react further, because it can undergo nucleophilic substitution. Bromide is a good nucleophile and a good leaving group and, with an allylic system like this, S_N1 can take place in which both the nucleophile and the electrophile are bromine. The intermediate is a cation, but here the carbocation is disguised as the bromonium ion because bromine's lone pair can help stabilize the positive charge. Bromide can attack where it left, returning to starting material, but it can also attack the far end of the allylic system, giving the 1,4-dibromide. The steps are all reversible at higher temperatures, so the fact that the 1,4-dibromide is formed under these conditions must mean it is more stable than the 1,2-dibromide. It is not hard to see why: it has a more substituted double bond and the two large bromine atoms are further apart.



Unsymmetrical bromonium ions open regioselectively

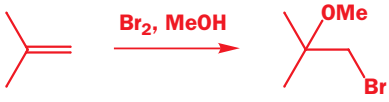
We ignored the issue of symmetry in the alkene when we discussed the bromination of alkenes, because even unsymmetrical alkenes give the same 1,2-dibromides whichever way the bromide attacks the bromonium ion.

bromination of isobutene



same product whichever end is attacked

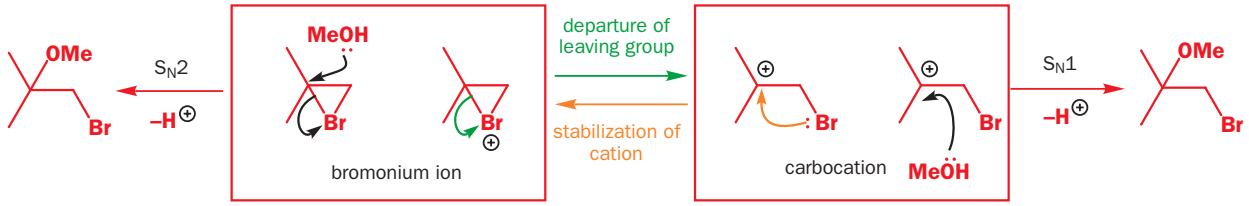
But when a bromination is done in a nucleophilic solvent—water or methanol, for example—solvent molecules compete with the bromide to open the bromonium ion. As you know, alcohols are much worse nucleophiles than bromide but, because the concentration of solvent is so high (remember—the concentration of water in water is 55M), the solvent gets there first most of the time. This is what happens when isobutene is treated with bromine in methanol. An ether is formed by attack of methanol only at the *more substituted* end of the bromonium ion.



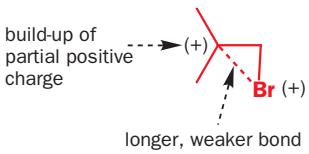
methanol attacks at the more substituted end of the bromonium ion

Methanol is attacking the bromonium ion where it is most hindered, so there must be some effect at work more powerful than steric hindrance. One way of looking at this is to reconsider our assumption that bromonium ion opening is an S_N2 process. Here, it hardly looks S_N2. We have a tertiary centre, so naturally you expect S_N1, via the cation below. But we have already said that cations like this can be stabilized by formation of the three-membered bromonium ion and, if we let this happen, we have to attack the bromonium ion which gets us back to where we started: an S_N2 mechanism!

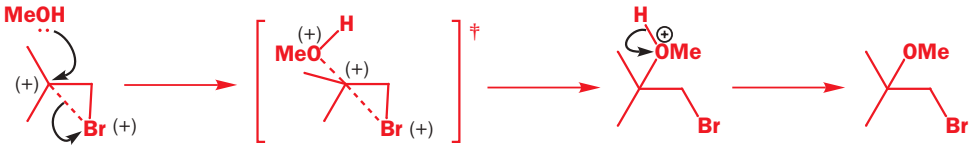
two limiting mechanisms for substitution on bromonium ion



The answer to the conundrum is that substitution reactions don't always go by pure S_N1 or pure S_N2 mechanisms: sometimes the mechanism is somewhere in between. Perhaps the leaving group starts to leave, creating a partial positive charge on carbon which is intercepted by the nucleophile. This provides a good explanation of what is going on here. The bromine begins to leave, and a partial positive charge builds up at carbon. The departure of bromine can get to a more advanced state at the tertiary end than at the primary end, because the substituents stabilize the build-up of positive charge. The bromonium ion can be more accurately represented as shown in the margin, with one C–Br bond longer than the other, and more polarized than the other.

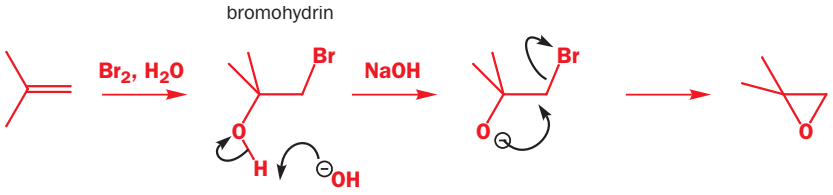


The nucleophile now has a choice: does it attack the more accessible, primary end of the bromonium ion, or does it attack the more charged end with the weaker C–Br bond? Here, the latter is clearly the faster reaction. The transition state has considerable positive charge on carbon, and is known as a **loose S_N2 transition state**.



loose S_N2 transition state

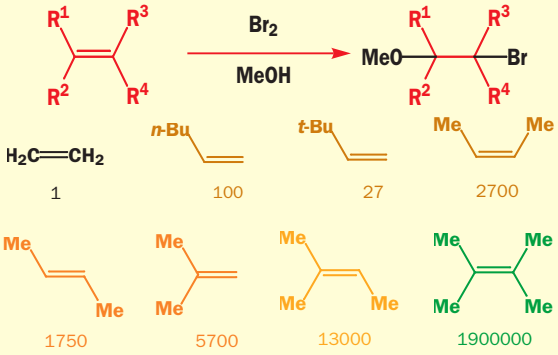
The products of bromination in water are called **bromohydrins**. They can be treated with base, which deprotonates the alcohol. A rapid intramolecular S_N2 reaction follows: bromide is expelled as a leaving group and an epoxide is formed. This can be a useful alternative synthesis of epoxides avoiding peroxy-acids.



Rates of bromination of alkenes

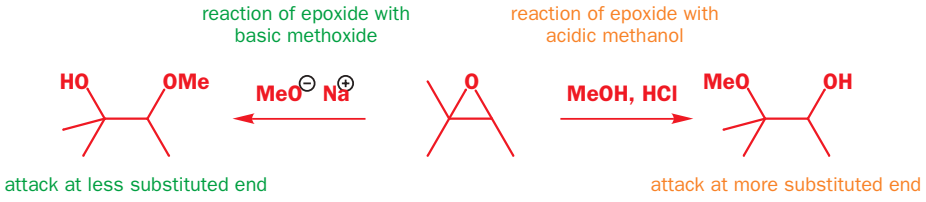
The pattern you saw for epoxidation with peroxy-acids (more substituted alkenes react faster) is followed by bromination reactions too. The bromonium ion is a reactive intermediate, so the rate-determining step of the brominations is the bromination reaction itself. The chart shows the effect on the rate of reaction with bromine in methanol of increasing the number of alkyl substituents from none (ethylene) to four. Each additional alkene substituent produces an enormous increase in rate. The degree of branching (Me versus *n*-Bu versus *t*-Bu) within the substituents has a much smaller, negative effect (probably of steric origin) as does the geometry (*E* versus *Z*) and substitution pattern (1,1-disubstituted versus 1,2-disubstituted) of the alkene.

relative rates of reaction of alkenes with bromine in methanol solvent.

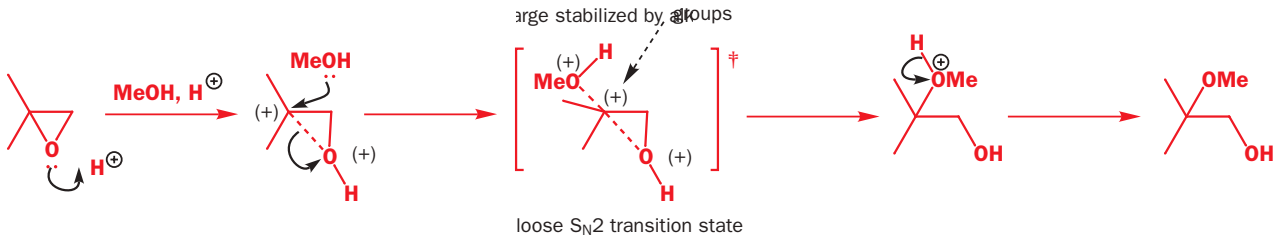


The regioselectivity of epoxide opening can depend on the conditions

Although epoxides, like bromonium ions, contain strained three-membered rings, they require either acid catalysis or a powerful nucleophile to react well. Compare these two reactions of a 1,1,2-trisubstituted epoxide. They are nucleophilic substitutions related to those we introduced in Chapter 17 (p. 000) but in that chapter we carefully avoided discussing epoxides of the unsymmetrical variety. In this example, the regiochemistry reverses with the reaction conditions. Why?

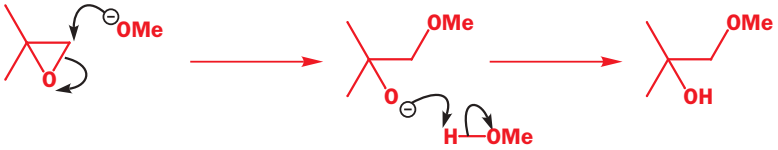


We'll start with the acid-catalysed reaction, because it is more similar to the examples we have just been discussing—opening happens at the more substituted end. Protonation by acid produces a positively charged intermediate that bears some resemblance to the corresponding bromonium ion. The two alkyl groups make possible a build-up of charge on the carbon at the tertiary end of the protonated epoxide, and methanol attacks here, just as it does in the bromonium ion.

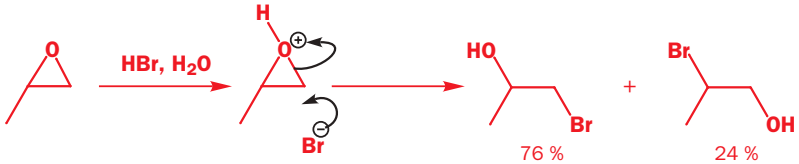


■ Remember, S_N1 can be fast only with good leaving groups.

In base, there can be no protonation of the epoxide, and no build-up of positive charge. Without protonation, the epoxide oxygen is a poor leaving group, and leaves only if pushed by a strong nucleophile: the reaction becomes pure S_N2. Steric hindrance becomes the controlling factor, and methoxide attacks only the primary end of the epoxide.



This example makes the matter look deceptively clear-cut. But with epoxides, regioselectivity is not as simple as this because, even with acid catalysts, S_N2 substitution at a primary centre is very fast. For example, Br^- in acid attacks this epoxide mainly at the less substituted end, and only 24% of the product is produced by the 'cation-stabilized' pathway. It is very difficult to override the preference of epoxides unsubstituted at one end to react at that end.

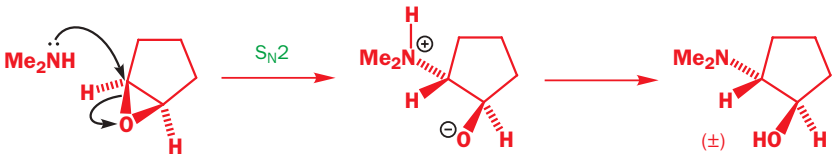


major pathway is S_N2 on less substituted end

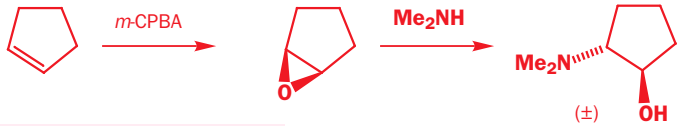
For most substitution reactions of epoxides, then, regioselectivity is much higher if you give in to the epoxide's desire to open at the less substituted end, and enhance it with a strong nucleophile under basic conditions.

Electrophilic additions to alkenes can be stereoselective

Although they really belong in Chapter 17 with other nucleophilic substitution reactions, we included the last few examples of epoxide-opening reactions here because they have many things in common with the reactions of bromonium ions. Now we are going to make the analogy work the other way when we look at the stereochemistry of the reactions of bromonium ions, and hence at the stereoselectivity of electrophilic additions to alkenes. We shall first remind you of an epoxide reaction from Chapter 17, where you saw this.



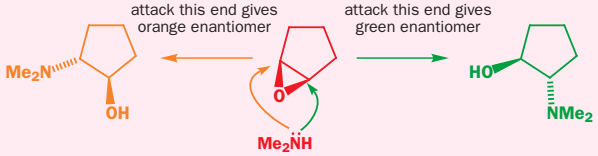
The epoxide ring opening is stereospecific: it is an S_N2 reaction, and it goes with inversion. The epoxide starts on the top face of the ring, and the amino group therefore ends up on the bottom face. In other words, the two groups end up *anti* or *trans* across the ring. You now know how to make this epoxide—you would use cyclopentene and *m*-CPBA, and in two steps you could 'add' an OH group and a Me_2N group *anti* across the double bond.



Now we can move on to look at the stereochemistry of electrophilic addition to alkenes.

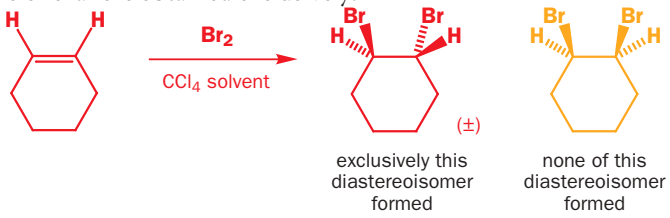
▶ The reaction is stereospecific because it's the stereochemistry of the epoxide that determines the outcome of the reaction. The S_N2 reaction has no choice but to go with inversion. We discussed the terms stereospecific and stereoselective on p. 000.

▶ Notice the all important (±) symbol below the products in the diagram. They are single diastereoisomers, but they are *necessarily* formed as racemic mixtures, as we discussed in Chapter 16. You can look at it this way: the Me_2NH will attack the two identical ends of the epoxide with precisely equal probability. Both give the same *anti* diastereoisomer, but each gives an opposite enantiomer. The two enantiomers will be formed in precisely equal amounts.



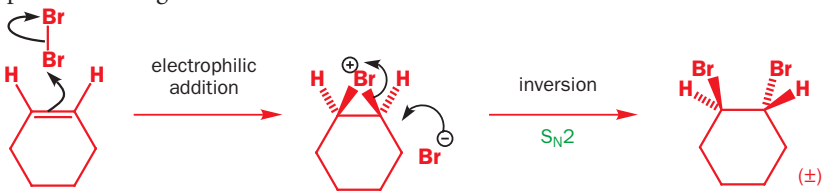
Electrophilic addition to alkenes can produce stereoisomers

When cyclohexene is treated with bromine in carbon tetrachloride, the racemic *anti*-1,2-dibromocyclohexane is obtained exclusively.



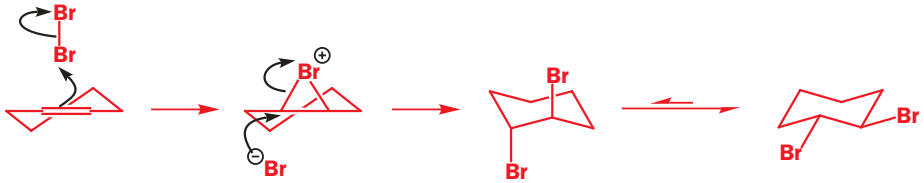
▶ We don't need to write (±) next to the isomer that isn't formed, because it is an achiral structure—it has a plane of symmetry and is a *meso* compound. See p. 000.

The result is no surprise if we think first of the formation of the bromonium ion that is opened with inversion in an S_N2 reaction. Here is the mechanism drawn 'flat', which is all we need to explain the stereochemistry of the product. The fact that this reaction (like other similar ones) gives a single diastereoisomer is one of the best pieces of evidence that electrophilic additions of Br_2 to alkenes proceed through a bromonium ion.



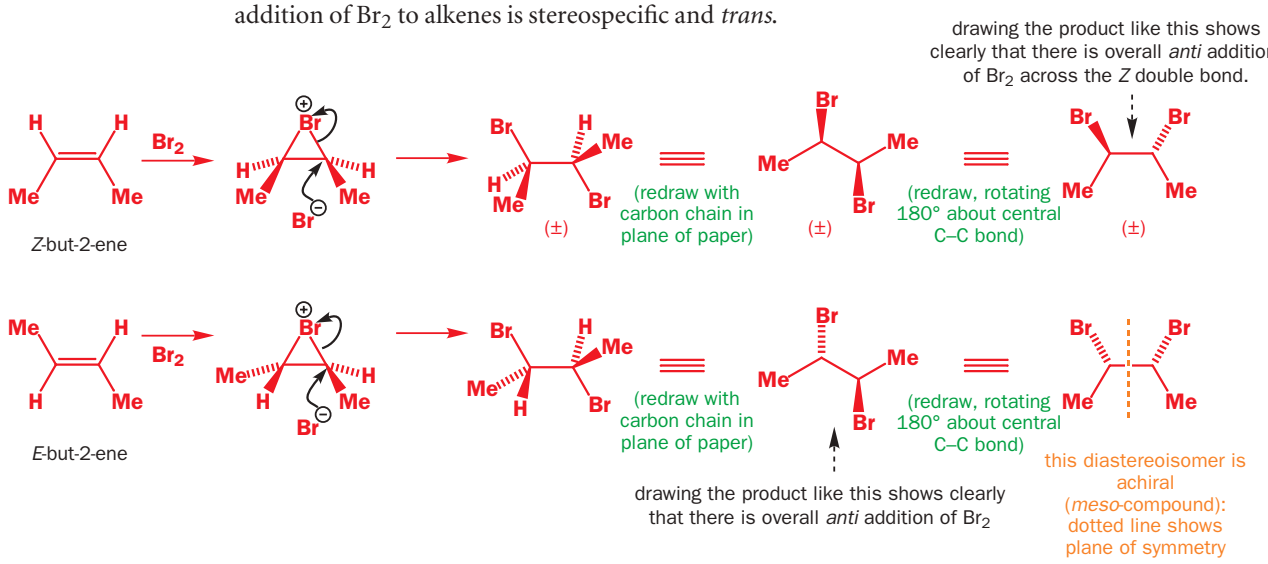
But these compounds are six-membered rings, so we will get a more accurate picture of what is going on if we draw them in their correct conformation. Cyclohexene is a flattened chair, as you saw in Chapter 18, and the bromonium ion can be drawn as a flattened chair too, like an epoxide (p. 000). Bromonium opening mirrors epoxide opening closely and, for the same reason, it will open only to give the diaxial product. In the absence of a locking group, the diaxial 1,2-dibromocyclohexane rapidly flips to the diequatorial conformation. This, of course, has no effect on the relative configuration, which will always be *anti*.

■ This part of the discussion is a revision of the material in Chapter 18. When dealing with six-membered rings, you should always aim to draw their conformation, though in this case you can explain the result adequately without conformational diagrams.



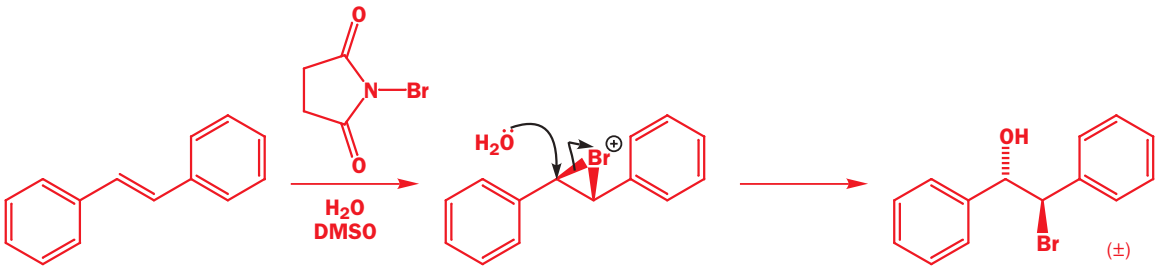
Bromination of alkenes is stereospecific, because the geometry of the starting alkene determines which product diastereoisomer is obtained. We couldn't demonstrate this with cyclohexene, because only a *Z* double bond is possible in a six-membered ring. But bromination or chlorination of *Z*- and *E*-2-butene in acetic acid produces a single diastereoisomer in each case, and they are different from each other. *Anti* addition occurs in both cases—more evidence that a bromonium ion is the intermediate. In the scheme below, the product of each reaction is shown in three different ways. Firstly, the two new C–Br bonds are shown in the plane of the paper to highlight the inversion of configuration during the bromonium opening step. Secondly, this diagram has been rotated to place the carbon chain in the plane of the paper and highlight the fact that these are indeed two different diastereoisomeric products. In this conformation you can clearly see that there has been an *anti*-addition across the *E* double bond. Thirdly, the middle bond has been rotated 180° to give an (unrealistically) eclipsed conformation. We show this conformation for two reasons: it makes it clear that the addition across the *Z*-butene is stereospecific and *anti* too, and it also makes it quite clear that the product of the *E*-butene bromination is achiral: you can see the plane of symmetry in this conformation, and this is why we haven't placed (±) signs next to the products from the *E*-alkene. Note that in all

three different views of each product the same stereoisomer is represented. There is no change of configuration, only changes of conformation to help you understand what is going on. If you cannot follow any of the 'redrawing' steps, make a model. With practice, you will soon learn to manipulate mental models in your head, and to see what happens to substituents when bonds are rotated. Most importantly, don't let all of this more subtle stereochemical discussion cloud the simple message: addition of Br_2 to alkenes is stereospecific and *trans*.



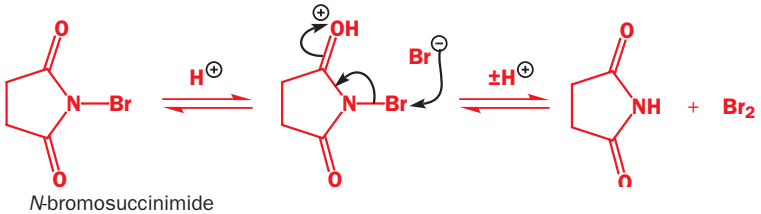
Bromonium ions as intermediates in stereoselective synthesis

You will not be surprised to learn that the other nucleophiles (water and alcohols) you saw intercepting bromonium ions earlier in the chapter also do so stereospecifically. The following reaction can be done on a large scale, and produces a single diastereoisomer of the product (racemic, of course) because water opens the bromonium ion with inversion.

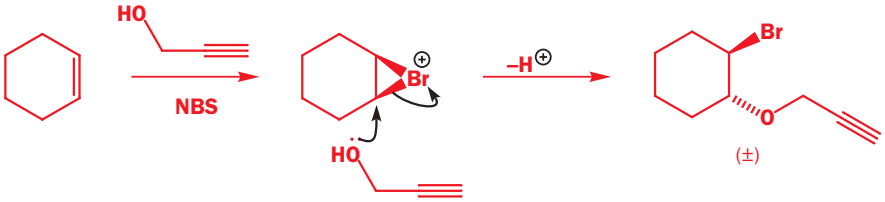


The reagent used to form the bromonium ion here is not bromine, and may be new to you. It is called *N*-bromosuccinimide, or NBS for short. Unlike the noxious brown liquid bromine, NBS is an easily handled crystalline solid, and is perfect for electrophilic addition of bromine to alkenes when the bromonium ion is not intended to be opened by Br^-. It works by providing a very small concentration of Br_2 in solution: a small amount of HBr is enough to get the reaction going, and thereafter every addition reaction produces another molecules of HBr which liberates more Br_2 from NBS. In a sense, NBS is a source of 'Br^+'.

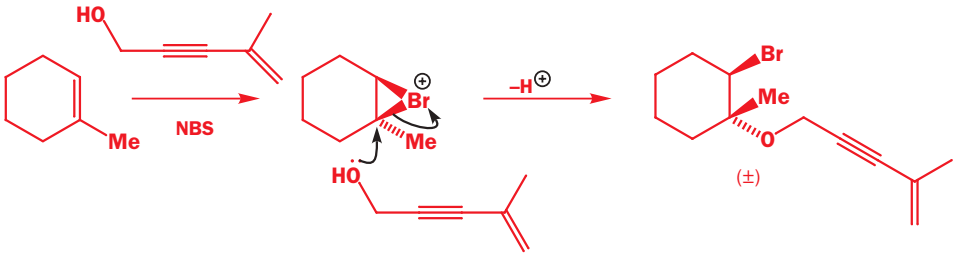
▶ NBS is known to act as a source of Br_2 because the results of reactions of NBS and of Br_2 in low concentration are identical.



With NBS, the concentration of Br^- is always low, so alcohols compete with Br^- to open the epoxide even if they are not the solvent. In the next example, the alcohol is 'propargyl alcohol', prop-2-yn-1-ol. It gives the expected *anti*-disubstituted product with cyclohexene and NBS.



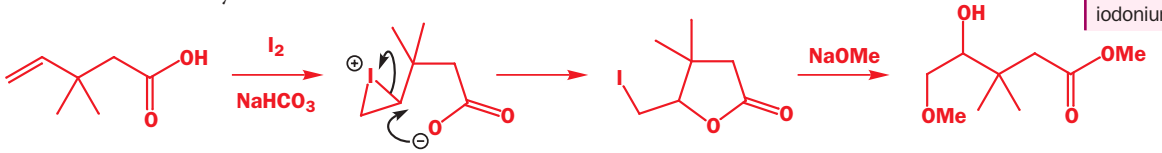
When 1-methylcyclohexene is used as the starting material, there is additionally a question of regioselectivity. The alcohol attacks the more hindered end of the bromonium ion—the end where there can be greatest stabilization of the partial positive charge in the 'loose S_N2' transition state. This reaction really does illustrate the way in which a mechanism can lie in between S_N1 and S_N2. We see a configurational inversion, indicative of an S_N2 reaction, happening at a tertiary centre where you would usually expect S_N1.



Iodolactonization and bromolactonization make new rings

To finish our discussion of bromonium ions, you need to know about one more important class of reactions, those in which the nucleophile is located within the same molecule as the bromonium ion. Here is an example: the nucleophile is a carboxylate, and the product is a lactone (a cyclic ester). This type of reaction—the cyclization of an unsaturated acid—is known as a bromolactonization. Intermolecular attack on the bromonium ion by bromide ion does not compete with the intramolecular cyclization step.

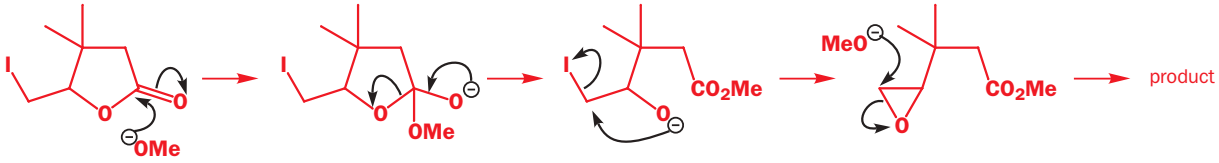
Every example of electrophilic addition of a halogen to an alkene that we have shown you so far has been with bromine. This is quite representative: bromine is the most widely used halogen for electrophilic addition, since its reactivity is second only to iodine, yet the products are more stable. However, in these lactonization reactions, iodine is the more commonly used reagent, and the products of iodolactonizations are important intermediates (you will meet them again in Chapter 33). In the next example, the iodolactonization product is treated with sodium methoxide, which appears (a) to hydrolyse the lactone, and (b) to substitute the iodide for OMe. In fact, there is a little more to this than meets the eye.



The first step is now familiar to you: electrophilic attack of iodine to form an iodonium ion, which cyclizes to the iodolactone; the key step of the mechanism is shown above.

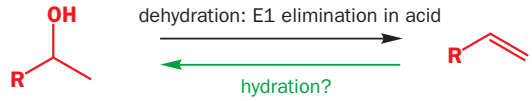
▶ It should be mentioned at this point that five-membered ring formation is the norm in iodolactonizations—you will need to wait until Chapter 42 to hear the full details why—but here this preference is reinforced by the preference for opening at the more substituted end of an iodonium or bromonium ion.

Methoxide must attack the carbonyl group, liberating an alkoxide that immediately cyclizes, with the iodide as a leaving group, to form an epoxide. Finally, methoxide attacks the epoxide at the less hindered end. Contrast the regioselectivities for attack on the iodonium ion with attack on the epoxide.

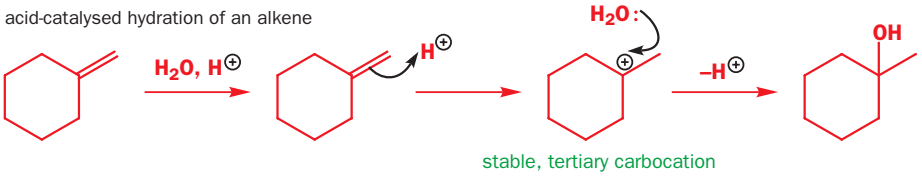


How to add water across a double bond

In the last chapter, you saw alkenes being made from alcohols by E1 elimination—dehydration—under acid catalysis. The question we are going to answer in this section is: how can you make this elimination run backwards—in other words, how can you hydrate a double bond?

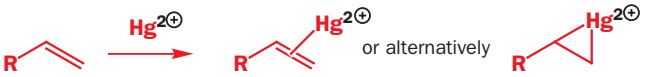


It is possible on occasion simply to use aqueous acid to do this. The reaction works only if protonation of the alkene can give a stable, tertiary cation. The cation is then trapped by the aqueous solvent.

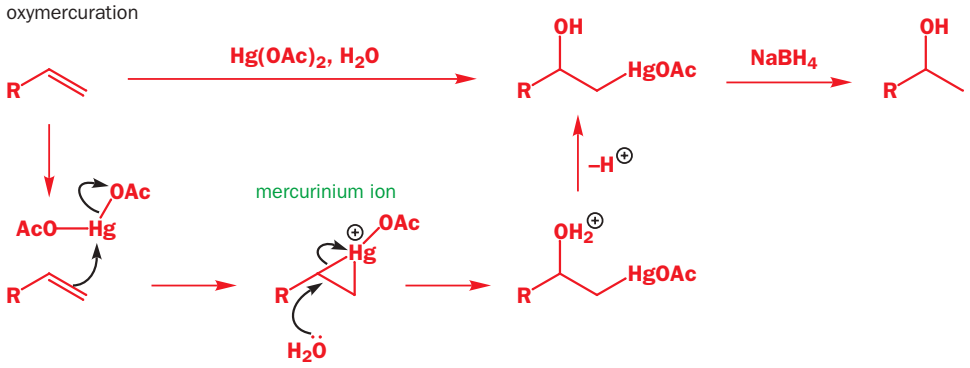


In general, though, it is very difficult to predict whether aqueous acid will hydrate the alkene or dehydrate the alcohol. The method we are about to introduce is much more reliable. The key is to use a transition metal to help you out. Alkenes are soft nucleophiles (p. 000) and interact well with soft electrophiles such as transition metal cations. Here, for example, is the complex formed between an alkene and mercury(II) cation. Don't be too concerned about the weird bond growing from the middle of the alkene: this is a shorthand way of expressing the rather complex bonding interaction between the alkene and mercury. An alternative, and more useful, representation is the three-membered ring on the right.

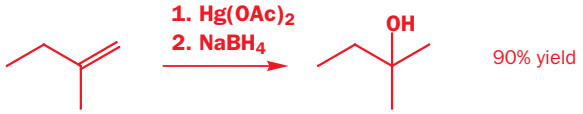
■ There is more detail on organometallic chemistry in Chapter 48.



The complex should remind you of a bromonium ion, and rightly so, because its reactions are really rather similar. Even relatively feeble nucleophiles such as water and alcohols, when used as the solvent, open the 'mercurinium' ion and give alcohols and ethers. In the next scheme, the mercury(II) is supplied as mercury(II) acetate, $Hg(OAc)_2$, which we shall represent with two covalent Hg–O bonds (simply because it helps with the arrows and with electron-accounting to do so). Unsurprisingly, water attacks at the more substituted end of the mercuronium ion.



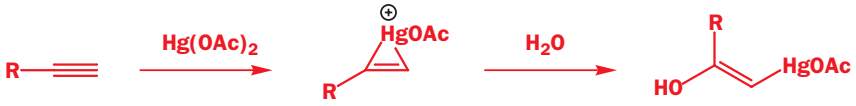
We've added OH and Hg(II) across the alkene, and the reaction is termed an **oxymercuration**. But a problem remains: how to get rid of the metal. The C–Hg bond is very weak and the simplest way to replace Hg with H is to cleave with a reducing agent. $NaBH_4$ works fine. Here is an example of oxymercuration–demercuration at work—the intermediate organomercury is not isolated.



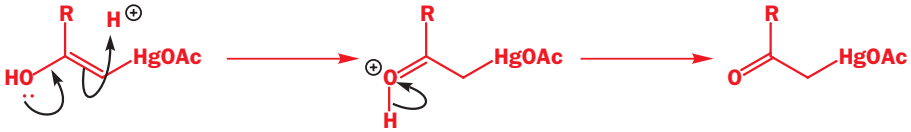
■ This reaction is discussed in more detail in Chapter 39.

Hydration of alkynes

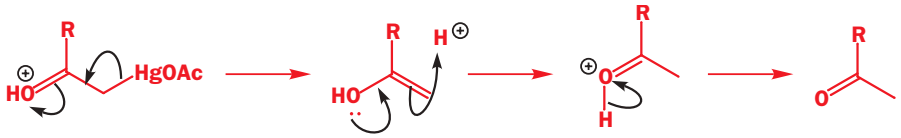
Oxymercuration works particularly well with alkynes. Here are the conditions, and the product, following the analogy of alkene hydration, should be the compound shown at the right-hand end of the scheme below.



But the product isolated from an alkyne oxymercuration is in fact a ketone. You can see why if you just allow a proton on this initial product to shift from oxygen to carbon—first protonate at C then deprotonate at O. C=O bonds are stronger than C=C bonds, and this simple reaction is very fast.



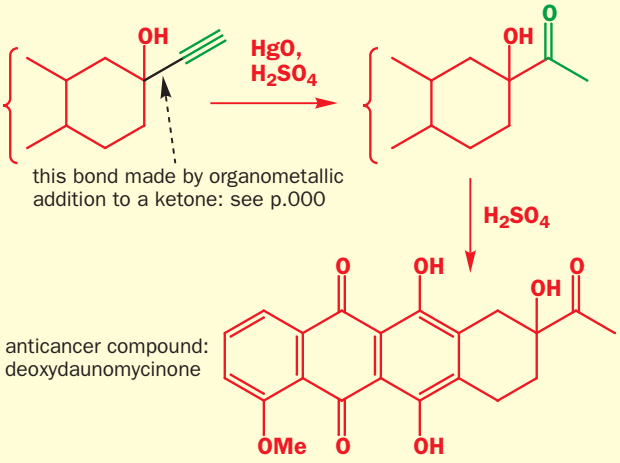
We now have a ketone, but we also still have the mercury. That is no problem when there is a carbonyl group adjacent, because any weak nucleophile can remove mercury in the presence of acid as shown below. Finally, another proton transfer (from O to C again) gives the real product of the reaction: a ketone.

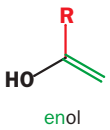


This is truly a very useful way of making methyl ketones, because terminal alkynes can be made using the methods of Chapter 9 (addition of metallated alkynes to electrophiles).

Anticancer compounds

The anthracyclinone class of anticancer compounds (which includes daunomycin and adriamycin) can be made using a mercury(II)-promoted alkyne hydration. You saw the synthesis of alkynes in this class on p. 000 where we discussed additions of metallated alkynes to ketones. Here is the final step in a synthesis of the anticancer compound deoxydaunomycinone: the alkyne is hydrated using Hg^{2+} in dilute sulfuric acid; the sulfuric acid also catalyses the hydrolysis of the phenolic acetate to give the final product.



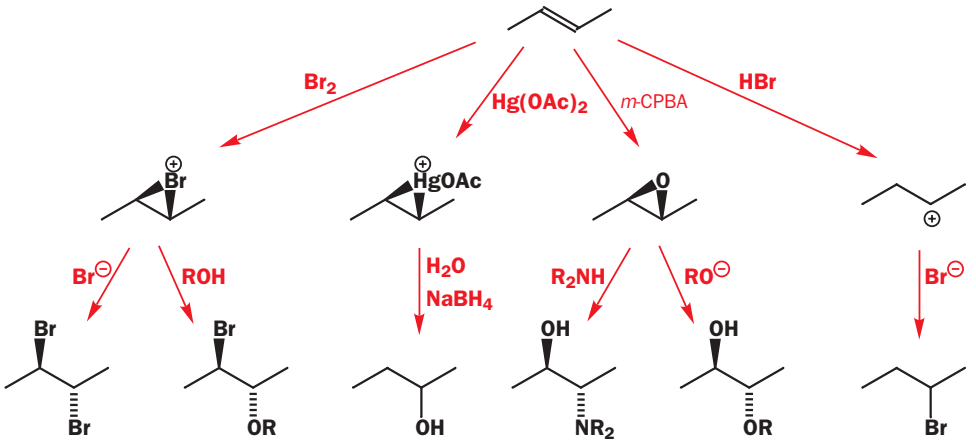


enol

Those alkenes carrying hydroxyl groups are called **enols** (ene + ol), and they are among the most important intermediates in chemistry. They happen to be involved in this reaction, and this was a good way to introduce you to them but, as you will see in the next chapter and beyond, enols (and their deprotonated sisters, enolates) have far reaching significance in chemistry.

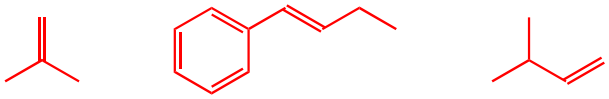
To conclude...

Electrophilic addition to double bonds gives three-membered ring intermediates with Br_2, with Hg^{2+}, and with peroxy-acids (in which case the three-membered rings are stable and are called epoxides). All three classes of three-membered rings react with nucleophiles to give 1,2-difunctionalized products with control over (1) regioselectivity and (2) stereoselectivity. Protonation of a double bond gives a cation, which also traps nucleophiles, and this reaction can be used to make alkyl halides. Some of the sorts of compounds you can make by the methods of this chapter are shown below.

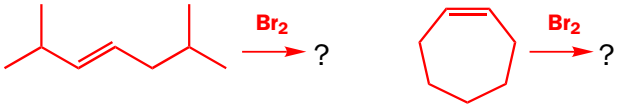


Problems

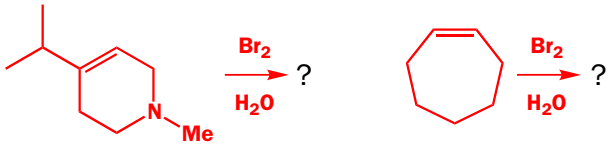
1. Predict the orientation in HCl addition to these alkenes.



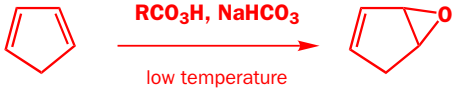
2. Suggest mechanisms and products for these reactions.



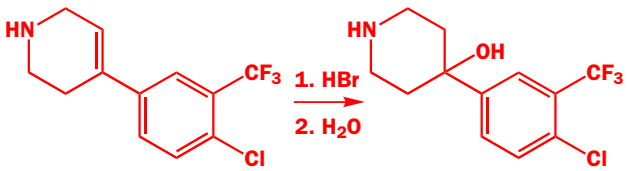
3. What will be the products of addition of bromine water to these alkenes?



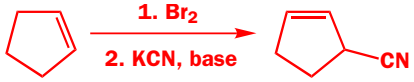
4. By working at low temperature with one equivalent of a buffered solution of a peroxy-acid, it is possible to prepare the monoepoxide of cyclopentadiene. Why are the precautions necessary and why does the epoxidation not occur again?



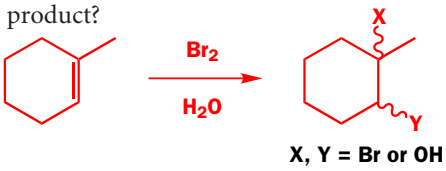
5. The synthesis of a tranquillizer uses this step. Give mechanisms for the reactions.



6. Explain this result.

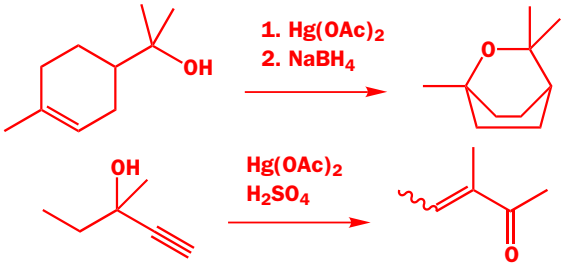


7. Bromination of this alkene in water gives a single product in good yield. What is the structure and stereochemistry of this product?

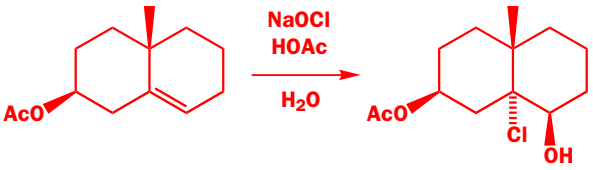


X, Y = Br or OH

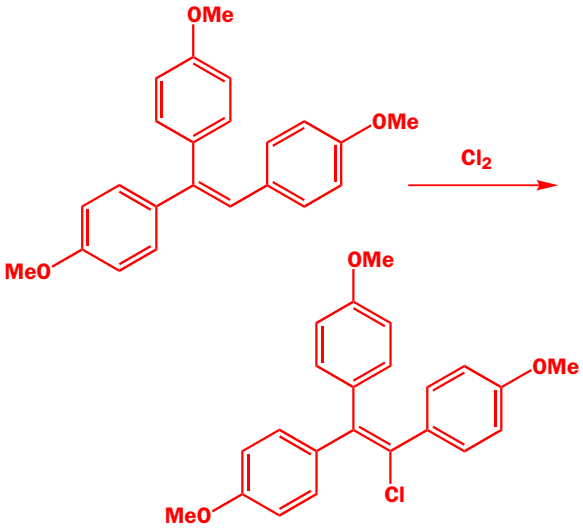
8. Suggest mechanisms for these reactions.



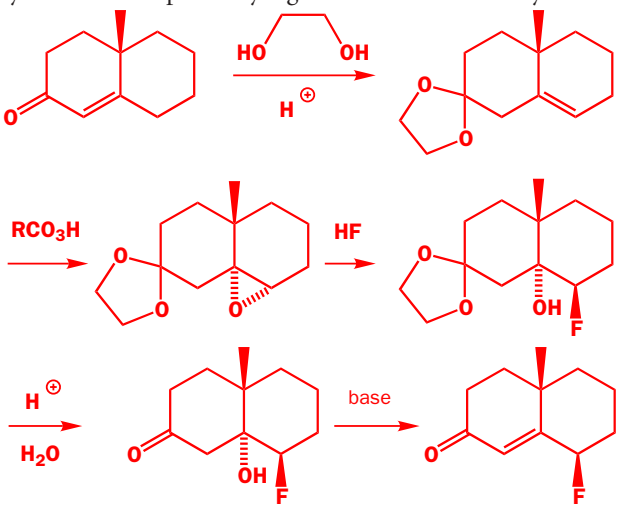
9. Comment on the formation of a single diastereoisomer in this reaction.



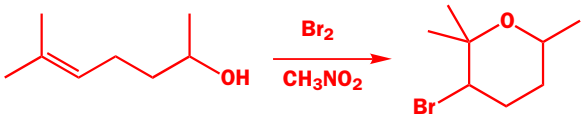
10. Chlorination of this triarylethylene leads to a chloro-alkene rather than a dichloroalkane. Suggest a mechanism and an explanation.



11. Revision problem. Give mechanisms for each step in this synthesis and explain any regio- and stereochemistry.



12. Suggest a mechanism for the following reaction. What is the stereochemistry and conformation of the product?



12A

13. Give a mechanism for this reaction and show clearly the stereochemistry of the product.