Nucleophilic addition to the carbonyl group

6

Connections

Building on:

- Functional groups, including the carbonyl group (C=O) ch2
- Identifying the functional groups in a molecule spectroscopically ch3
- How molecular orbitals explain molecular shapes and functional groups ch4
- How, and why, molecules react together, the involvement of functional groups, and using curly arrows to describe reactions ch5

Arriving at:

- How and why the C=O group reacts with nucleophiles
- Explaining the reactivity of the C=O group using molecular orbitals and curly arrows
- What sorts of molecules can be made by reactions of C=O groups
- How acid or base catalysts improve the reactivity of the C=O group

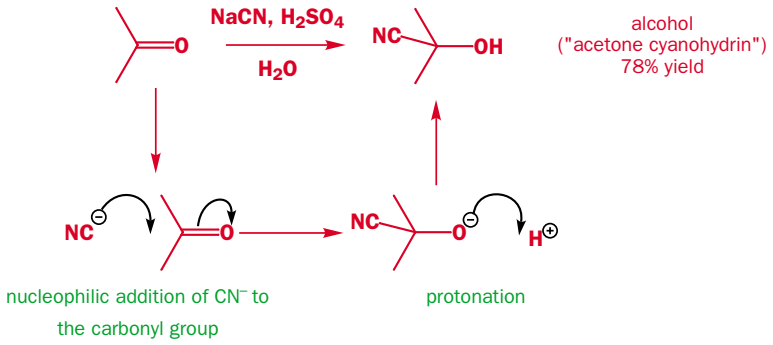
Looking forward to:

- Additions of organometallic reagents ch9
- C=O groups with an adjacent double bond ch10
- How the C=O group in derivatives of carboxylic acids promotes substitution reactions ch12
- Substitution reactions of the C=O group's oxygen atom ch14

Molecular orbitals explain the reactivity of the carbonyl group

We are now going to leave to one side most of the reactions you met in the last chapter—we will come back to them all again later in the book. In this chapter we are going to concentrate on just one of them—probably the simplest of all organic reactions—the addition of a nucleophile to a carbonyl group. The carbonyl group, as found in aldehydes, ketones, and many other compounds, is without doubt the most important functional group in organic chemistry, and that is another reason why we have chosen it as our first topic for more detailed study.

You met nucleophilic addition to a carbonyl group on p. 114 and 119, where we showed you how cyanide reacts with acetone to give an alcohol. As a reminder, here is the reaction again, with its mechanism.



▶ We will frequently use a device like this, showing a reaction scheme with a mechanism for the same reaction looping round underneath. The reagents and conditions next to the arrow across the top will tell you how you might carry out the reaction, and the pathway shown underneath will tell you how it actually works.

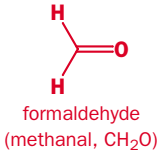
The reaction has two steps: nucleophilic addition of cyanide, followed by protonation of the anion. In fact, this is a general feature of all nucleophilic additions to carbonyl groups.

- **Additions to carbonyl groups generally consist of two mechanistic steps:**
  1. **Nucleophilic attack on the carbonyl group**
  2. **Protonation of the anion that results**

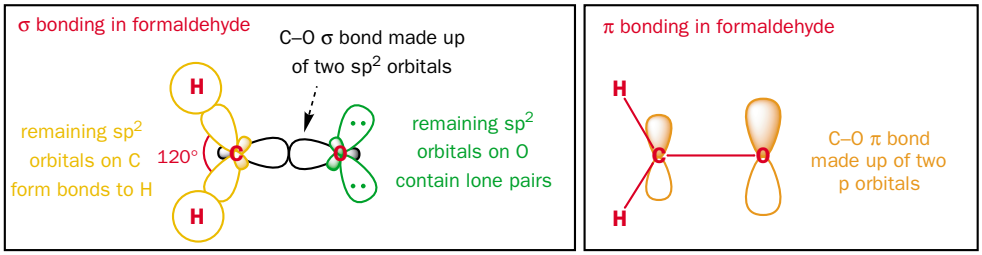
The addition step is more important, and it forms a new C–C σ bond at the expense of the C=O π bond. The protonation step makes the overall reaction addition of HCN across the C=O π bond.

Why does cyanide, in common with many other nucleophiles, attack the carbonyl group? And why does it attack the *carbon* atom of the carbonyl group? To answer these questions we need to look in detail at the structure of carbonyl compounds in general and the orbitals of the C=O group in particular.

The carbonyl double bond, like that found in alkenes (whose bonding we discussed in Chapter 4), consists of two parts: one σ bond and one π bond. The σ bond between the two sp^2 hybridized atoms—carbon and oxygen—is formed from two sp^2 orbitals. The other sp^2 orbitals on carbon form the two σ bonds to the substituents while those on oxygen are filled by the two lone pairs. The sp^2 hybridization means that the carbonyl group has to be planar, and the angle between the substituents is close to 120°. The diagram illustrates all this for the simplest carbonyl compound, formaldehyde (or methanal, CH_2O). The π bond then results from overlap of the remaining p orbitals—again, you can see this for formaldehyde in the diagram.

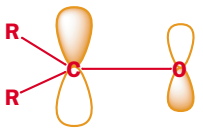


formaldehyde (methanal, CH_2O)

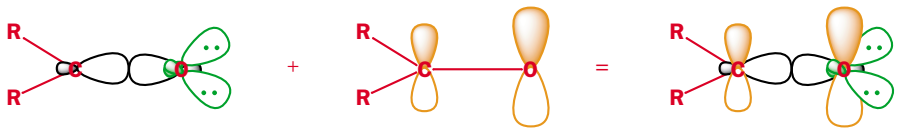


■ You were introduced to the polarization of orbitals in Chapter 4, and we discussed the case of the carbonyl group on p. 103.

Notice that we have drawn the π bond skewed towards oxygen. This is because oxygen is more electronegative than carbon, polarizing the orbital as shown. Conversely, the unfilled π* antibonding orbital is skewed in the opposite direction, with a larger coefficient at the carbon atom. Put all of this together and we get the complete picture of the orbitals of a carbonyl group.



empty, antibonding π* orbital



filled σ sp^2 (lone pair) orbitals

filled π orbital

complete diagram of filled orbitals of C=O bond

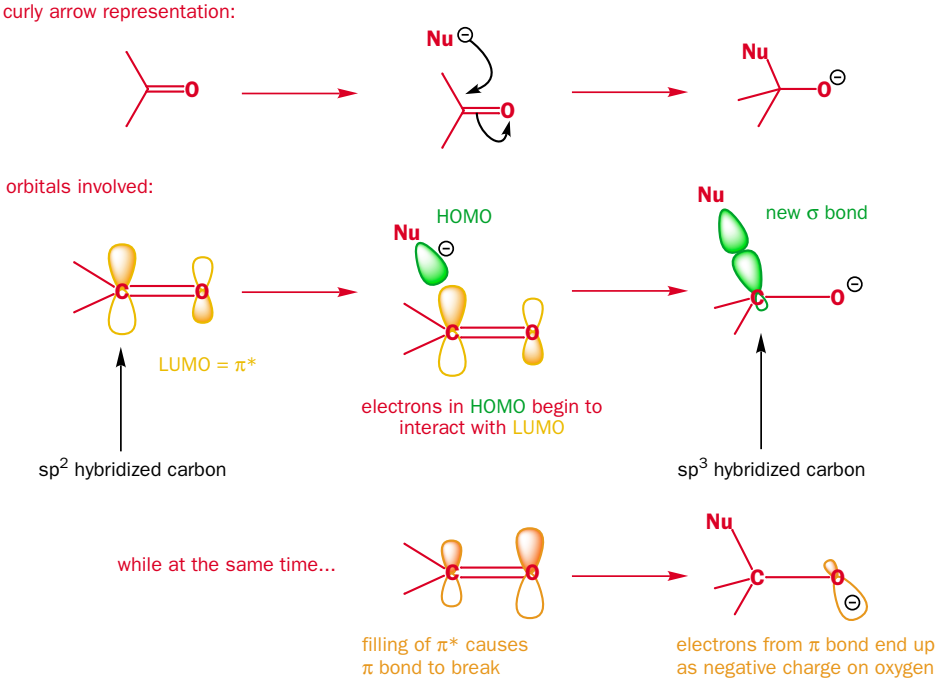
Electronegativities, bond lengths, and bond strengths

Representative bond energies, kJ mol^{-1}				Representative bond lengths, Å				Electronegativity			
C–O	351	C=O	720	C–O	1.43	C=O	1.21	C	2.5	O	3.5

Because there are two types of bonding between C and O, the C=O double bond is rather shorter than a typical C–O single bond, and also over twice as strong—so why is it so reactive? Polarization is the key. The polarized C=O bond gives the carbon atom some degree of positive charge, and this charge attracts negatively charged nucleophiles (like cyanide) and encourages reaction. The polarization of the antibonding π* orbital towards carbon is also important, because, when the carbonyl group reacts with a nucleophile, electrons move from the HOMO of the nucleophile (an sp orbital in this case) into the LUMO of the electrophile—in other words the π* orbital of the C=O bond. The greater coefficient of the π* orbital at carbon means a better HOMO–LUMO interaction, so this is where the nucleophile attacks.

As our nucleophile—which we are representing here as 'Nu$^-$'—approaches the carbon atom, the electron pair in its HOMO starts to interact with the LUMO (antibonding π*) to form a new σ bond.

Filling antibonding orbitals breaks bonds and, as the electrons enter the antibonding π* of the carbonyl group, the π bond is broken, leaving only the C–O σ bond intact. But electrons can't just vanish, and those that were in the π bond move off on to the electronegative oxygen, which ends up with the negative charge that started on the nucleophile. You can see all this happening in the diagram below.

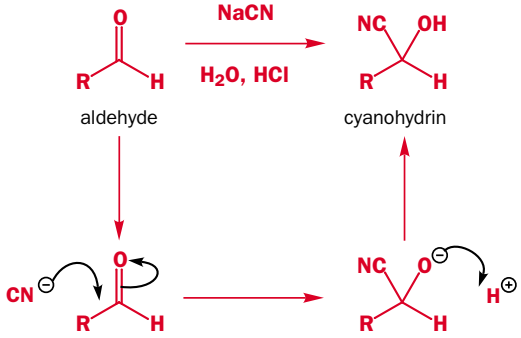


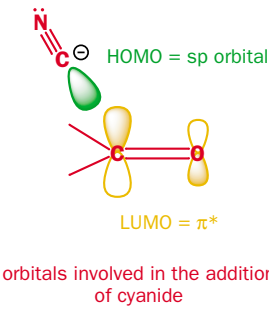
Notice how the trigonal, planar sp^2 hybridized carbon atom of the carbonyl group changes to a tetrahedral, sp^3 hybridized state in the product. For each class of nucleophile you meet in this chapter, we will show you the HOMO–LUMO interaction involved in the addition reaction.

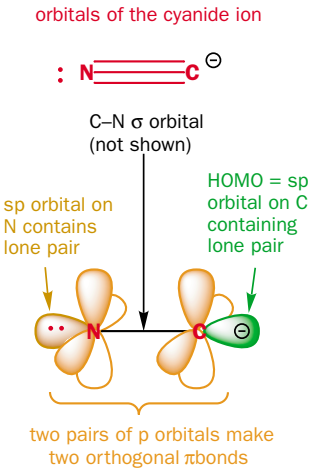
▶ The HOMO of the nucleophile will depend on what the nucleophile is, and we will meet examples in which it is an sp or sp^3 orbital containing a lone pair, or a B–H or metal–carbon σ orbital. We shall shortly discuss cyanide as the nucleophile; cyanide's HOMO is an sp orbital on carbon.

Cyanohydrins from the attack of cyanide on aldehydes and ketones

Now that we've looked at the theory of how a nucleophile attacks a carbonyl group, let's go back to the real reaction with which we started this chapter: cyanohydrin formation from a carbonyl compound and sodium cyanide. Cyanide contains sp hybridized C and N atoms, and its HOMO is an sp orbital on carbon. The reaction is a typical nucleophilic addition reaction to a carbonyl group: the electron pair from the HOMO of the CN^- (an sp orbital on carbon) moves into the C=O π* orbital; the electrons from the C=O π orbital move on to the oxygen atom. The reaction is usually carried out in the presence of acid, which protonates the resulting alkoxide to give the hydroxyl group of the composite functional group known as a cyanohydrin. The reaction works with both ketones and aldehydes, and the mechanism below shows the reaction of a general aldehyde.

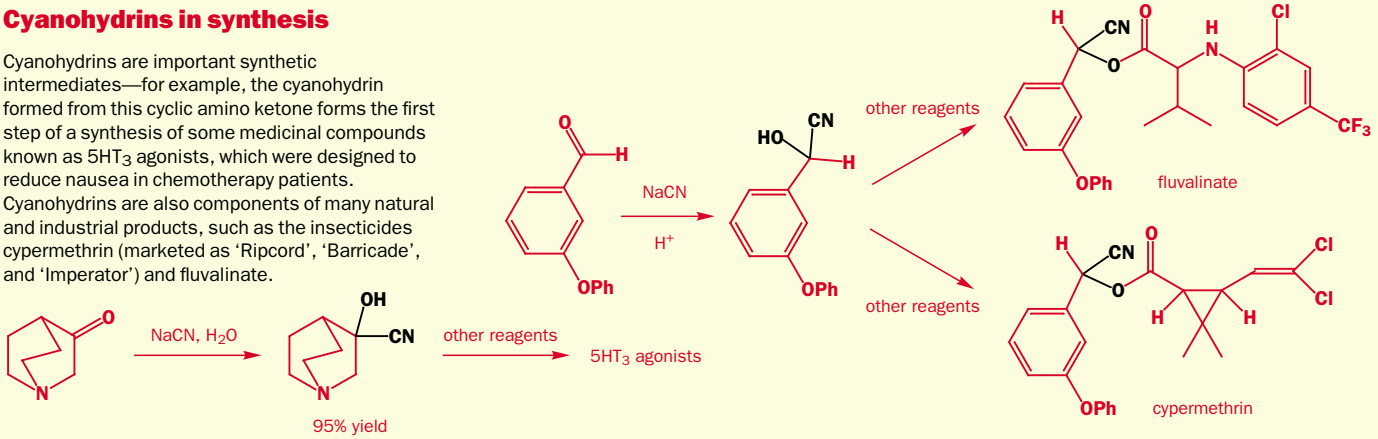






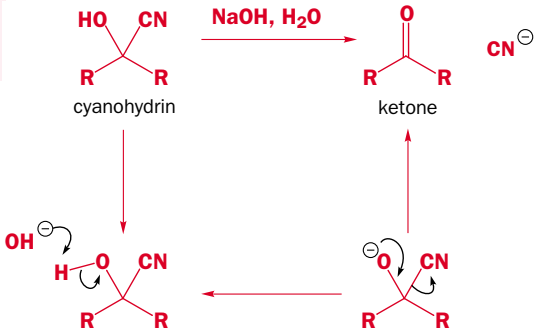
Cyanohydrins in synthesis

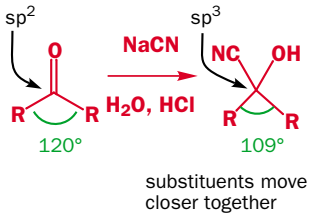
Cyanohydrins are important synthetic intermediates—for example, the cyanohydrin formed from this cyclic amino ketone forms the first step of a synthesis of some medicinal compounds known as $5HT_3$ agonists, which were designed to reduce nausea in chemotherapy patients. Cyanohydrins are also components of many natural and industrial products, such as the insecticides cypermethrin (marketed as 'Ripcord', 'Barricade', and 'Imperator') and fluvalinate.



▶ This is because the cyanide is a good *leaving group*—we'll come back to this type of reaction in much more detail in Chapter 12.

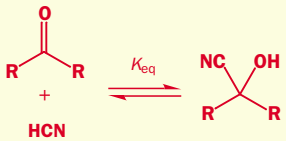
Cyanohydrin formation is reversible: just dissolving a cyanohydrin in water can give back the aldehyde or ketone you started with, and aqueous base usually decomposes cyanohydrins completely.

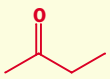




Cyanohydrin formation is therefore an equilibrium between starting materials and products, and we can only get good yields if the equilibrium favours the products. The equilibrium is more favourable for aldehyde cyanohydrins than for ketone cyanohydrins, and the reason is the size of the groups attached

Some equilibrium constants



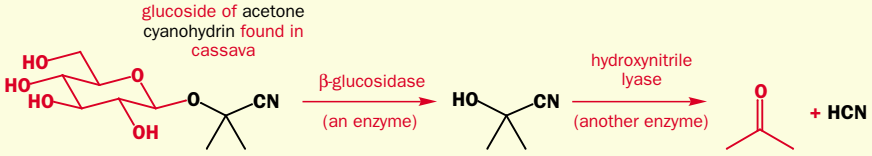
aldehyde or ketone	K_{eq}
PhCHO	212
	28

Cyanohydrins and cassava

The reversibility of cyanohydrin formation is of more than theoretical interest. In parts of Africa the staple food is cassava. This food contains substantial quantities of the glucoside of acetone cyanohydrin (a glucoside is an acetal derived from glucose). We shall discuss the structure of glucose later in this chapter, but for now, just accept that it stabilizes the cyanohydrin.

The glucoside is not poisonous in itself, but enzymes in the human gut break it down and release HCN. Eventually 50 mg HCN per 100 g of cassava can be released and this is enough to kill a human being after a meal of unfermented cassava. If the cassava is crushed with water and allowed to stand ('ferment'), enzymes in the cassava will do the same job and then the HCN can be washed out before the cassava is cooked and eaten.

The cassava is now safe to eat but it still contains some glucoside. Some diseases found in eastern Nigeria can be traced to long-term consumption of HCN. Similar glucosides are found in apple pips and the kernels inside the stones of fruit such as peaches and apricots. Some people like eating these, but it is unwise to eat too many at one sitting!



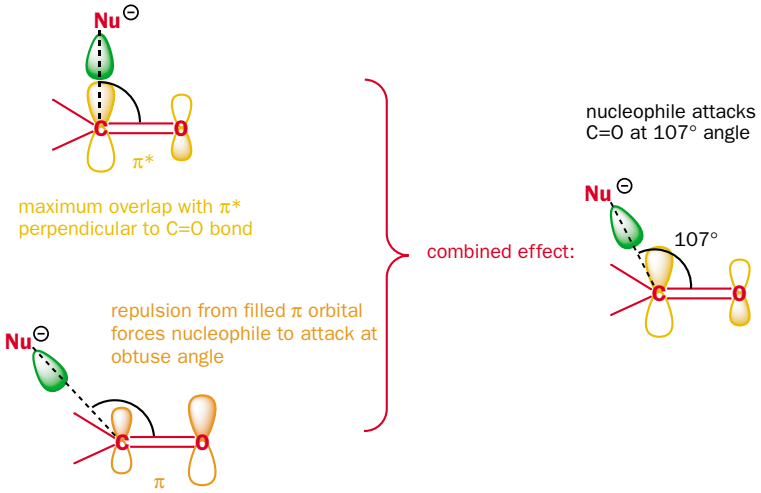
to the carbonyl carbon atom. As the carbonyl carbon atom changes from sp^2 to sp^3, its bond angles change from about 120° to about 109°—in other words, the substituents it carries move closer together. This reduction in bond angle is not a problem for aldehydes, because one of the substituents is just a (very small) hydrogen atom, but for ketones, especially ones that carry larger alkyl groups, this effect can disfavour the addition reaction. Effects that result from the size of substituents and the repulsion between them are called **steric effects**, and we call the repulsive force experienced by large substituents **steric hindrance**.

▶ Steric hindrance (*not* hinderance) is a consequence of repulsion between the electrons in all the filled orbitals of the alkyl substituents.

The angle of nucleophilic attack on aldehydes and ketones

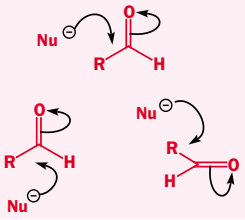
Having introduced you to the sequence of events that makes up a nucleophilic attack at C=O (interaction of HOMO with LUMO, formation of new σ bond, breakage of π bond), we should now tell you a little more about the *direction* from which the nucleophile approaches the carbonyl group. Not only do nucleophiles always attack carbonyl groups at carbon, but they also always approach from a particular angle. You may at first be surprised by this angle, since nucleophiles attack not from a direction perpendicular to the plane of the carbonyl group but at about 107° to the C=O bond. This approach route is known as the **Bürgi–Dunitz trajectory** after the authors of the elegant crystallographic methods that revealed it. You can think of the angle of attack as the result of a compromise between maximum orbital overlap of the HOMO with π* and minimum repulsion of the HOMO by the electron density in the carbonyl π bond.

■The Bürgi–Dunitz angle
Bürgi and Dunitz deduced this trajectory by examining crystal structures of compounds containing both a nucleophilic nitrogen atom and an electrophilic carbonyl group. They found that, when the two got close enough to interact, but were not free to undergo reaction, the nitrogen atom always lay on or near the 107° trajectory decribed here. Theoretical calculations later gave the same 107° value for the optimum angle of attack.



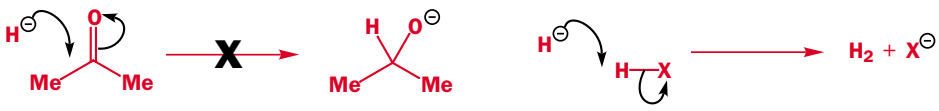
Any other portions of the molecule that get in the way of (or, in other words, that cause *steric hindrance* to) the Bürgi–Dunitz trajectory will greatly reduce the rate of addition and this is another reason why aldehydes are more reactive than ketones. The importance of the Bürgi–Dunitz trajectory will become more evident later—particularly in Chapter 34.

▶ Although we now know precisely from which direction the nucleophile attacks the C=O group, this is not always easy to represent when we draw curly arrows. As long as you bear the Bürgi–Dunitz trajectory in mind, you are quite at liberty to write any of the variants shown here, among others.



Nucleophilic attack by 'hydride' on aldehydes and ketones

Nucleophilic attack by the hydride ion, H^-, is not a known reaction. This species, which is present in the salt sodium hydride, NaH, is so small and has such a high charge density that it only ever reacts as a base. The reason is that its filled 1s orbital is of an ideal size to interact with the hydrogen



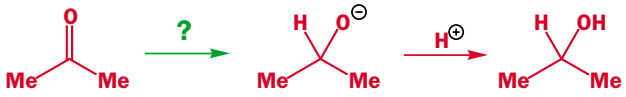
nucleophilic attack by H^- *never happens*

H^- *always* reacts as a base

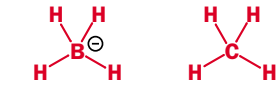
atom's contribution to the σ* orbital of an H–X bond (X can be any atom), but much too small to interact easily with carbon's more diffuse 2p orbital contribution to the LUMO (π*) of the C=O group.

Nevertheless, adding H^- to the carbon atom of a C=O group would be a very useful reaction, as the result would be the formation of an alcohol. This process would involve going down from the aldehyde or ketone oxidation level to the alcohol oxidation level (Chapter 2, pp. 25–36) and would therefore be a reduction. It cannot be done with NaH, but it can be done with some other compounds containing nucleophilic hydrogen atoms.

reduction of a ketone to an alcohol



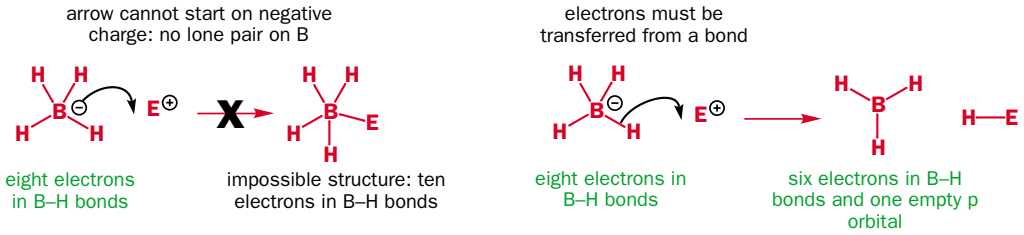
■ In Chapter 4, we looked at isoelectronic BH_3 and CH_3^+. Here, we have effectively just added H^- to both of them.



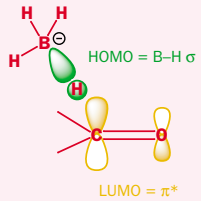
The most important of these compounds is sodium borohydride, $NaBH_4$. This is a water-soluble salt containing the tetrahedral BH_4^- anion, which is isoelectronic with methane but has a negative charge since boron has one less proton in the nucleus than does carbon.

But beware! The boron's negative charge doesn't mean that there is a lone pair on boron—there isn't. You cannot draw an arrow coming out of this charge to form another bond. If you did, you would get a pentacovalent B(V) compound, which would have 10 electrons in its outer shell. Such a thing is impossible with a first row element as there are only four available orbitals (1 × 2s and 3 × 2p). Instead, since all of the electrons (including that represented by the negative charge) are in B–H σ orbitals, it is from a B–H bond that we must start any arrow to indicate reaction of BH_4^- as a nucleophile. By transferring this pair of electrons we make the boron atom neutral—it is now trivalent with just six electrons.

■ Just as we have used Nu^- to indicate any (undefined) nucleophile, here E^+ means any (undefined) electrophile.



▶ The reason that H^- never acts as a nucleophile is that its 1s orbital is too small. The orbitals involved in borohydride reductions are the π* of the C=O group as the LUMO and a B–H σ orbital as the HOMO, so there is a much better orbital match.



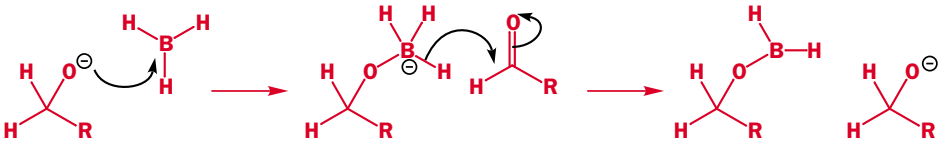
What happens when we carry out this reaction using a carbonyl compound as the electrophile? The hydrogen atom, together with the pair of electrons from the B–H bond, will be transferred to the carbon atom of the C=O group.



Though no hydride ion, H^-, is actually involved in the reaction, the transfer of a hydrogen atom with an attached pair of electrons can be regarded as a 'hydride transfer'. You will often see it described this way in books. But be careful not to confuse BH_4^- with the hydride ion itself. To make it quite clear that it is the hydrogen atom that is forming the new bond to C, this reaction may also be helpfully represented with a curly arrow *passing through* the hydrogen atom.

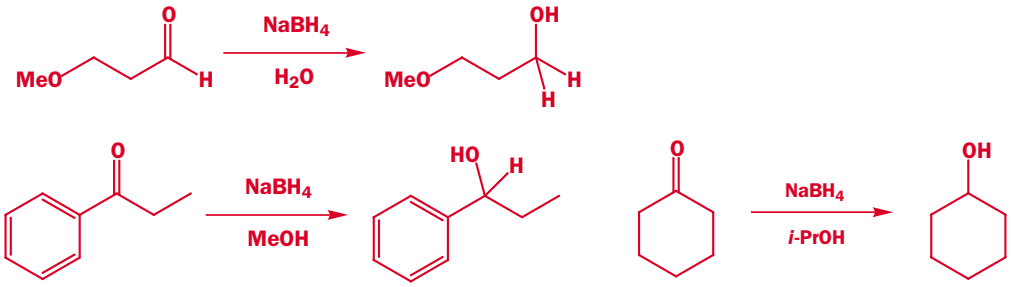


The oxyanion produced in the first step can help stabilize the electron-deficient BH_3 molecule by adding to its empty p orbital. Now we have a tetravalent boron anion again, which could transfer a second hydrogen atom (with its pair of electrons) to another molecule of aldehyde.

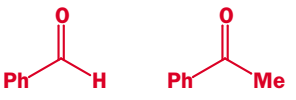


This process can continue so that, in principle, all four hydrogen atoms could be transferred to molecules of aldehyde. In practice the reaction is rarely as efficient as that, but aldehydes and ketones are usually reduced in good yield to the corresponding alcohol by sodium borohydride in water or alcoholic solution. The water or alcohol solvent provides the proton needed to form the alcohol from the alkoxide.

examples of reductions with sodium borohydride

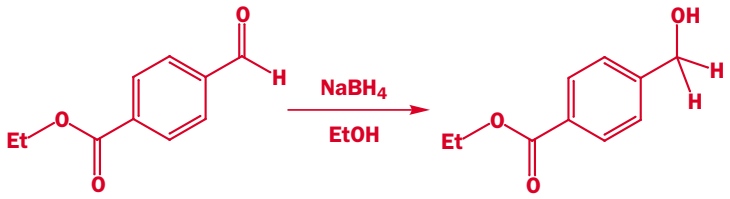


Sodium borohydride is one of the weakest hydride donors available. The fact that it can be used in water is evidence of this as more powerful hydride donors such as lithium aluminium hydride, $LiAlH_4$, react violently with water. Sodium borohydride reacts with both aldehydes and ketones, though the reaction with ketones is slower: for example, benzaldehyde is reduced about 400 times faster than acetophenone in isopropanol.

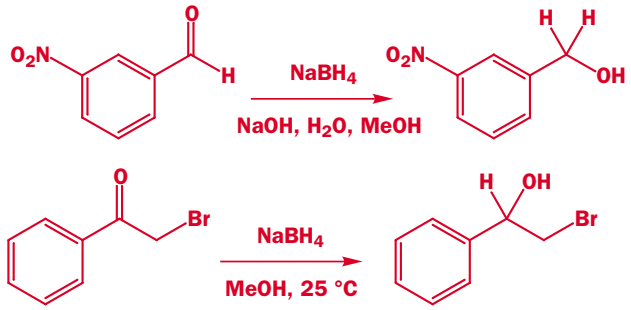


benzaldehyde acetophenone

Sodium borohydride does not react at all with less reactive carbonyl compounds such as esters or amides: if a molecule contains both an aldehyde and an ester, only the aldehyde will be reduced.

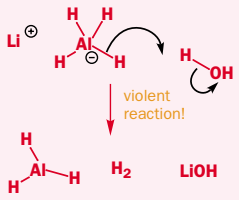


The next two examples illustrate the reduction of aldehydes and ketones in the presence of other reactive functional groups. No reaction occurs at the nitro group in the first case or at the alkyl halide in the second.



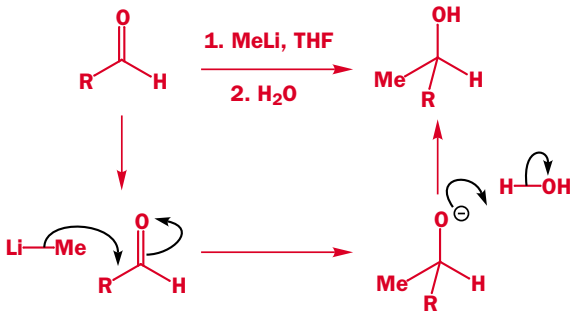
▶

Aluminium is more electropositive (more metallic) than boron and is therefore more ready to give up a hydrogen atom (and the associated negative charge), whether to a carbonyl group or to water. Lithium aluminium hydride reacts violently and dangerously with water in an exothermic reaction that produces highly flammable hydrogen.



Addition of organometallic reagents to aldehydes and ketones

The next type of nucleophile we shall consider is the organometallic reagent. Lithium and magnesium are very electropositive metals, and the Li–C or Mg–C bonds in organolithium or organomagnesium reagents are highly polarized towards carbon. They are therefore very powerful nucleophiles, and attack the carbonyl group to give alcohols, forming a new C–C bond. For our first example, we shall take one of the simplest of organolithiums, methyllithium, which is commercially available as a solution in Et_2O, shown here reacting with an aldehyde. The orbital diagram of the addition step shows how the polarization of the C–Li bond means that it is the carbon atom of the nucleophile that attacks the carbon atom of the electrophile and we get a new C–C bond.



The course of the reaction is much the same as you have seen before, but we need to highlight a few points where this reaction scheme differs from those you have met earlier in the chapter. First of all, notice the legend '1. MeLi, THF; 2. H_2O'. This means that, first, MeLi is added to the aldehyde in a THF solvent. Reaction occurs: MeLi adds to the aldehyde to give an alkoxide. Then (and only then) water is added to protonate the alkoxide. The '2. H_2O' means that water is added in a separate step only when all the MeLi has reacted: it is not present at the start of the reaction as it was in the cyanide reaction and some of the borohydride addition reactions. In fact, water *must not* be present during the addition of MeLi (or of any other organometallic reagent) to a carbonyl group because water destroys organometallics very rapidly by protonating them to give alkanes (organolithiums and organomagnesiums are strong bases as well as powerful nucleophiles). The addition of water, or sometimes dilute acid or ammonium chloride, at the end of the reaction is known as the **work-up**.

Because they are so reactive, organolithiums are usually reacted at low temperature, often –78 °C (the sublimation temperature of solid CO_2), in aprotic solvents such as Et_2O or THF. Organolithiums also react with oxygen, so they have to be handled under a dry, inert atmosphere of nitrogen or argon.

Other common, and commercially available, organolithium reagents include *n*-butyllithium and phenyllithium, and they react with both aldehydes and ketones. Note that addition to an aldehyde gives a secondary alcohol while addition to a ketone gives a tertiary alcohol.



secondary alcohol tertiary alcohol

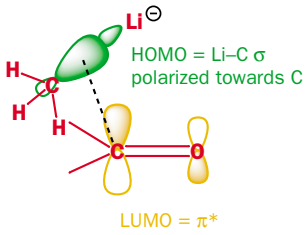
Organomagnesium reagents known as **Grignard reagents** (RMgX) react in a similar way. Some simple Grignard reagents, such as methyl magnesium chloride, MeMgCl, and phenyl magnesium bromide, PhMgBr, are commercially available, and the scheme shows PhMgBr reacting with an aldehyde. The reactions of these two classes of organometallic reagent—organolithiums and Grignard reagents—with carbonyl compounds are among the most important ways of making carbon–carbon bonds, and we will consider them in more detail in Chapter 9.

▶ Organometallic compounds always have a metal–carbon bond.

Electronegativities

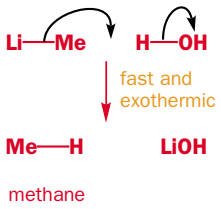
C	Li	Mg
2.5	1.0	1.2

■ We explained on p. 102 the origin of the polarization of bonds to electropositive elements.



orbitals involved in the addition of methyllithium

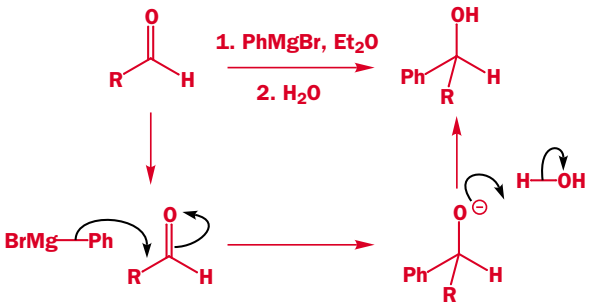
organometallics are destroyed by water



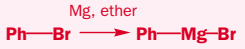
■ **Aprotic solvents** contain no acidic protons, unlike, say, water or alcohols.

■ 'Secondary' and 'tertiary' alcohols are defined on p. 30.

■ Victor Grignard (1871–1935) of the University of Lyon was awarded the Nobel Prize for chemistry in 1912 for his discovery of these reagents.

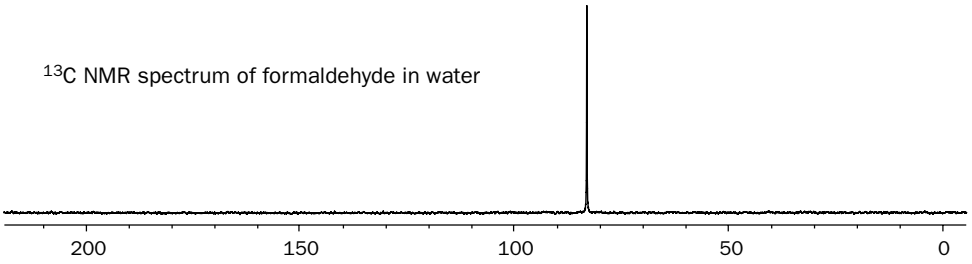


▶ Grignard reagents are made by reacting alkyl or aryl halides with magnesium 'turnings'.

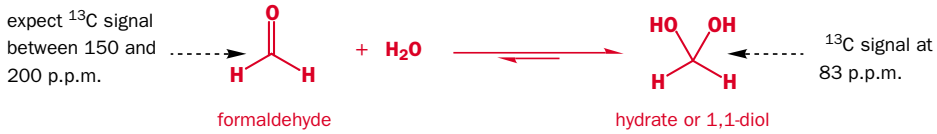


Addition of water to aldehydes and ketones

Nucleophiles don't have to be highly polarized or negatively charged to react with aldehydes and ketones: neutral ones will as well. How do we know? This ^{13}C NMR spectrum was obtained by dissolving formaldehyde, $H_2C{=}O$, in water. You will remember from Chapter 3 that the carbon atoms of carbonyl groups give ^{13}C signals typically in the region of 150–200 p.p.m. So where is formaldehyde's carbonyl peak? Instead we have a signal at 83 p.p.m.—where we would expect tetrahedral carbon atoms singly bonded to oxygen to appear.

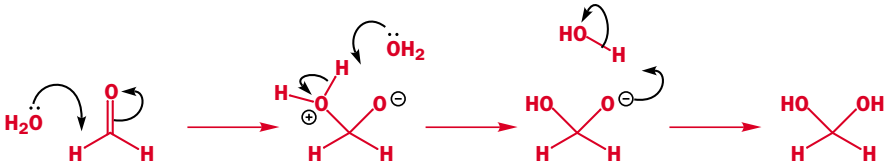


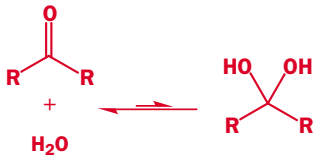
What has happened is that water has added to the carbonyl group to give a compound known as a hydrate or 1,1-diol.



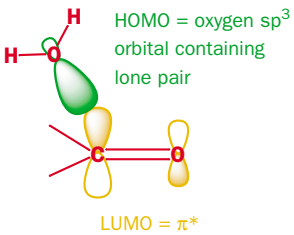
This reaction, like the cyanohydrin formation we discussed at the beginning of the chapter, is an equilibrium, and is quite general for aldehydes and ketones. But, as with the cyanohydrins, the position of the equilibrium depends on the structure of the carbonyl compound. Generally, the same steric factors (pp. 138–139) mean that simple aldehydes are hydrated to some extent while simple ketones are not. However special factors can shift the equilibrium towards the hydrated form even for ketones, particularly if the carbonyl compound is reactive or unstable.

Formaldehyde is an extremely reactive aldehyde as it has no substituents to hinder attack—it is so reactive that it is rather prone to polymerization (Chapter 52). And it is quite happy to move from sp^2 to sp^3 hybridization because there is very little increased steric hindrance between the two hydrogen atoms as the bond angle changes from 120° to 109° (p. 139). This is why our aqueous solution of formaldehyde contains essentially no CH_2O—it is completely hydrated. A mechanism for the hydration reaction is shown below. Notice how a proton has to be transferred from one oxygen atom to the other, mediated by water molecules.





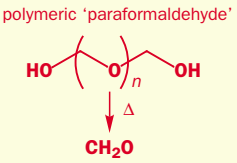
significant concentrations of hydrate are generally formed only from aldehydes



orbitals involved in the addition of water

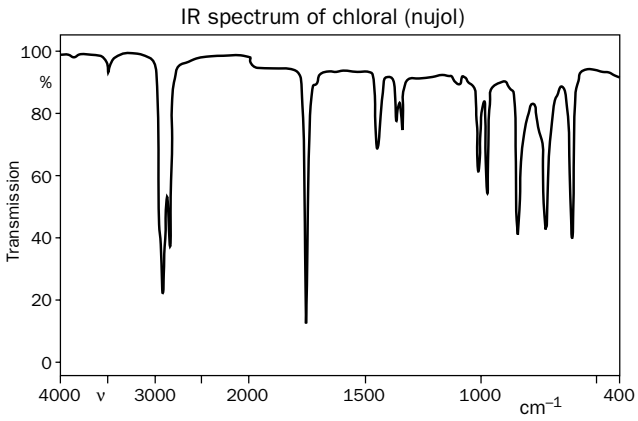
Monomeric formaldehyde

The hydrated nature of formaldehyde poses a problem for chemistry that requires anhydrous conditions such as the organometallic additions we have just been talking about. Fortunately *cracking* (heating to decomposition) the polymeric 'paraformaldehyde' can provide monomeric formaldehyde in anhydrous solution.

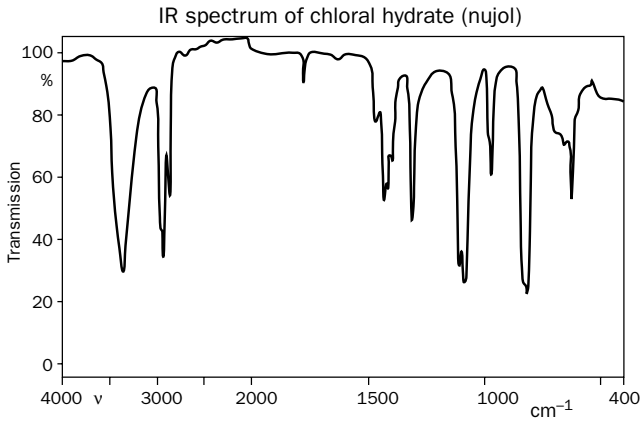


Formaldehyde reacts with water so readily because its substituents are very small: a steric effect. Electronic effects can also favour reaction with nucleophiles—electronegative atoms such as halogens attached to the carbon atoms next to the carbonyl group can increase the extent of hydration according to the number of halogen substituents and their electron-withdrawing power. They increase the polarization of the carbonyl group, which already has a positively polarized carbonyl carbon, and make it even more prone to attack by water. Trichloroacetaldehyde (chloral, Cl_3CHO) is hydrated completely in water, and the product 'chloral hydrate' can be isolated as crystals and is an anaesthetic. You can see this quite clearly in the two IR spectra. The first one is a spectrum of chloral hydrate from a bottle—notice there is no strong absorption between 1700 and 1800 cm^{-1} (where we would expect C=O to appear) and instead we have the tell-tale broad O–H peak at 3400 cm^{-1}. Heating drives off the water, and the second IR spectrum is of the resulting dry chloral: the C=O peak has reappeared at 1770 cm^{-1}, and the O–H peak has gone.

■ Chloral hydrate is the infamous 'knock out drops' of Agatha Christie or the 'Mickey Finn' of Prohibition gangsters.



IR spectrum of chloral (nujol)



IR spectrum of chloral hydrate (nujol)

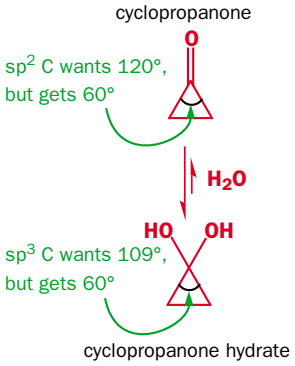
The chart shows the extent of hydration (in water) of a small selection of carbonyl compounds: hexafluoroacetone is probably the most hydrated carbonyl compound possible!



	equilibrium constant K		
acetone	0.001	chloral	2000
acetaldehyde	1.06		
formaldehyde	2280	hexafluoroacetone	1 200 000

Cyclopropanones—three-membered ring ketones—are also hydrated to a significant extent, but for a different reason. You saw earlier how *acyclic* ketones suffer increased steric hindrance when the bond angle changes from 120° to 109° on moving from sp^2 to sp^3 hybridization. Cyclopropanones

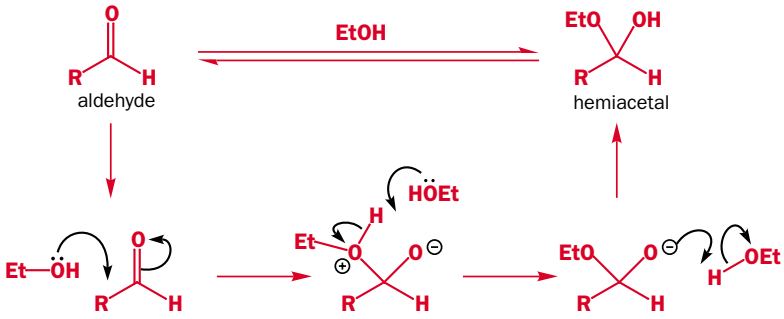
(and other small-ring ketones) conversely prefer the small bond angle because their substituents are already confined within a ring. Look at it this way: a three-membered ring is really very strained, with bond angles forced to be 60°. For the sp^2 hybridized ketone this means bending the bonds 60° away from their 'natural' 120°. But for the sp^3 hybridized hydrate the bonds have to be distorted by only 49° (= 109° – 60°). So addition to the C=O group allows some of the strain inherent in the small ring to be released—hydration is favoured, and indeed cyclopropanone and cyclobutanone are very reactive electrophiles.

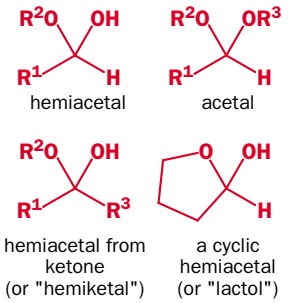


The same structural features that favour or disfavour hydrate formation are important in determining the reactivity of carbonyl compounds with other nucleophiles, whether the reactions are reversible or not. Steric hindrance and more alkyl substituents make carbonyl compounds less reactive towards any nucleophile; electron-withdrawing groups and small rings make them more reactive.

Hemiacetals from reaction of alcohols with aldehydes and ketones

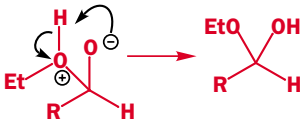
Since water adds to (at least some) carbonyl compounds, it should come as no surprise that alcohols do too. The product of the reaction is known as a **hemiacetal**, because it is halfway to an acetal, a functional group, which you met in Chapter 2 (p. 35) and which will be discussed in detail in Chapter 14. The mechanism follows in the footsteps of hydrate formation: just use ROH instead of HOH.



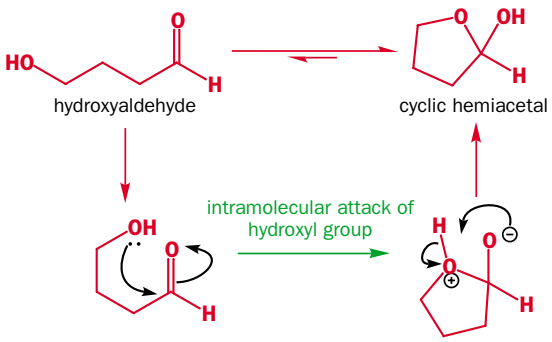


names for functional groups

A proton has to be transferred from one oxygen atom to the other: we have shown ethanol doing this job, with one molecule being protonated and one deprotonated. There is no overall consumption of ethanol in the protonation/deprotonation steps, and the order in which these steps happen is not important. In fact, you could reasonably write them in one step as shown in the margin, without involving the alcohol, and we do this in the next hemiacetal-forming reaction below. As with all these carbonyl group reactions, what is really important is the addition step, not what happens to the protons.



Hemiacetal formation is reversible, and hemiacetals are stabilized by the same special structural features as those of hydrates. However, hemiacetals can also gain stability by being cyclic—when the carbonyl group and the attacking hydroxyl group are part of the same molecule. The reaction is now an **intramolecular** (within the same molecule) addition, as opposed to the **intermolecular** (between two molecules) ones we have considered so far.

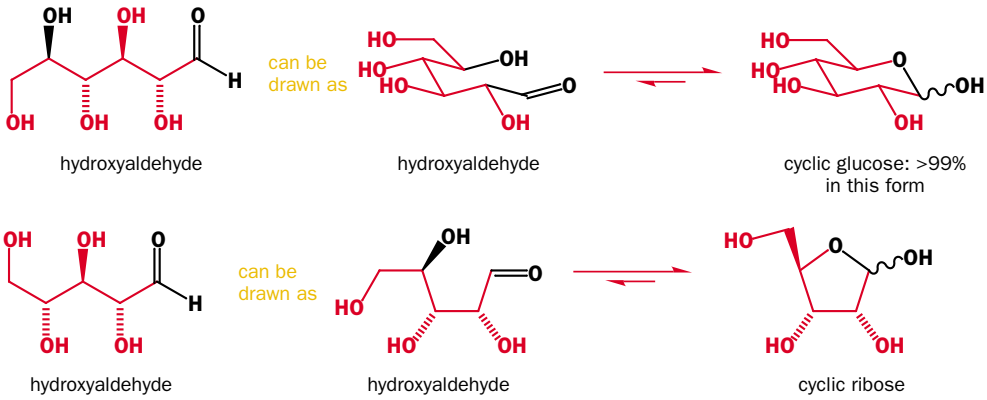


- *Inter*molecular reactions occur between two molecules
- *Intra*molecular reactions occur within the same molecule

We shall discuss the reasons why intramolecular reactions are more favourable, and why cyclic hemiacetals and acetals are more stable, in Chapter 14.

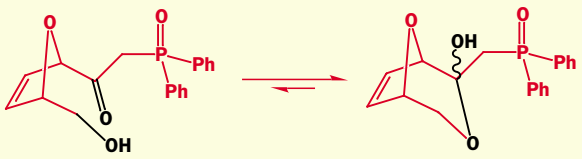
Although the cyclic hemiacetal (also called 'lactol') product is more stable, it is still in equilibrium with some of the open-chain hydroxyaldehyde form. Its stability, and how easily it forms, depend on the size of the ring: five- and six-membered rings are free from strain (their bonds are free to adopt 109° or 120° angles—compare the three-membered rings on p. 145), and five- or six-membered hemiacetals are common. Among the most important examples are many sugars. Glucose, for example, is a hydroxyaldehyde that exists mainly as a six-membered cyclic hemiacetal (>99% of glucose is cyclic in solution), while ribose exists as a five-membered cyclic hemiacetal.

▶ The way we have represented some of these molecules may be unfamiliar to you: we have shown **stereochemistry** (whether bonds come out of the paper or into it—the wiggly lines indicate a mixture of both) and, for the cyclic glucose, **conformation** (the actual shape the molecules adopt). These are very important in the sugars: we devote Chapter 16 to stereochemistry and Chapter 18 to conformation.



Ketones can form hemiacetals

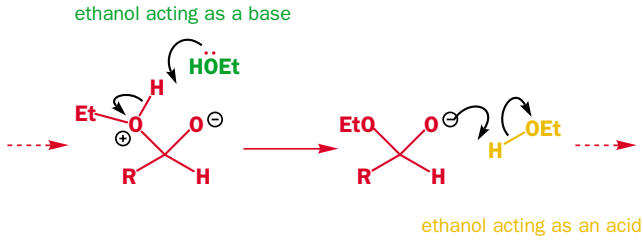
Hydroxyketones also form hemiacetals, but (as you should now expect) they usually do so less readily than hydroxyaldehydes. However, this hydroxyketone must exist solely as the cyclic hemiacetal because it shows no C=O stretch in its IR spectrum. The reason? The starting hydroxyketone is already cyclic, with the hydroxyl group poised to attack the ketone—it can't get away, so cyclization is highly favoured.



Acid and base catalysis of hemiacetal and hydrate formation

▶ A **catalyst** increases the rate of a chemical reaction but emerges from the reaction unchanged.

In Chapter 8 we shall look in detail at acids and bases, but at this point we need to tell you about one of their important roles in chemistry: they act as catalysts for a number of carbonyl addition reactions, among them hemiacetal and hydrate formation. To see why, we need to look back at the mechanisms of hemiacetal formation on p. 145 and hydrate formation on p. 143. Both involve proton-transfer steps like this.

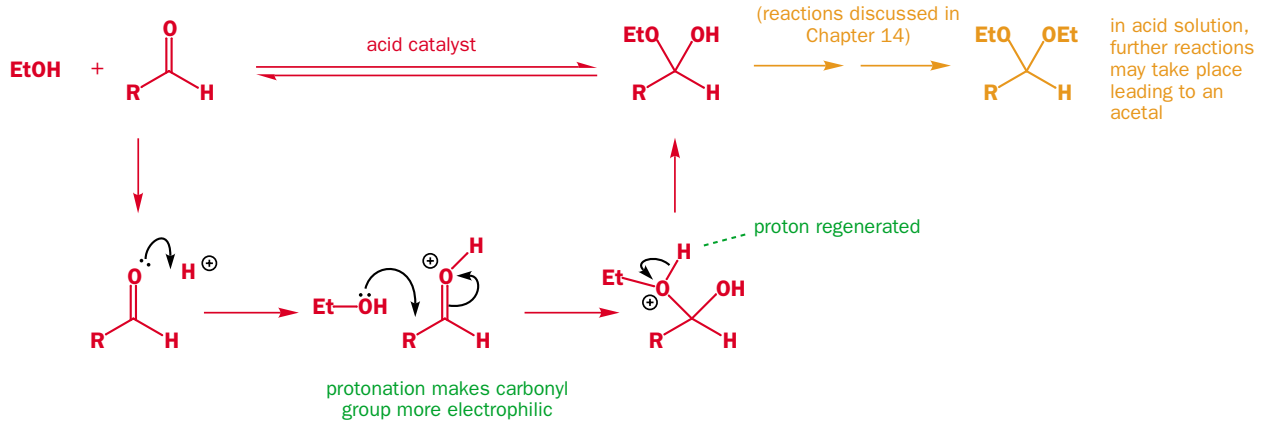


■ We introduced protonation by acid in Chapter 5, pp. 119–121.

In the first proton-transfer step, ethanol acts as a **base**, removing a proton; in the second it acts as an **acid**, donating a proton. Strong acids or strong bases (for example, HCl or NaOH) increase the rate of hemiacetal or hydrate formation because they allow these proton-transfer steps to occur *before* the addition to the carbonyl group.

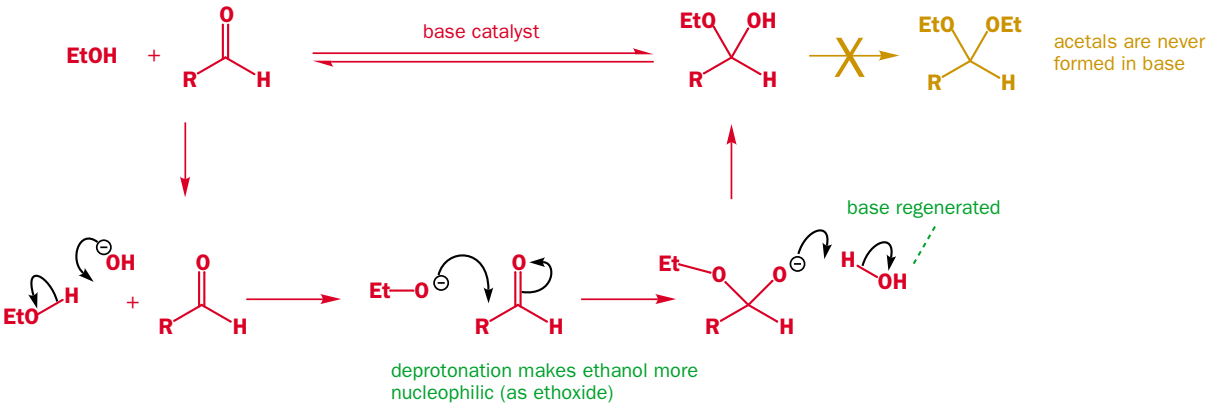
In acid (dilute HCl, say), this is the mechanism. The first step is now protonation of the carbonyl group's lone pair: the positive charge makes it much more electrophilic so the addition reaction is faster. Notice how the proton added at the beginning is lost again at the end—it really is a catalyst. In acid it is also possible for the hemiacetal to react further with the alcohol to form an acetal, but this need not concern you at present.

hemiacetal formation in acid



And this is the mechanism in basic solution. The first step is now deprotonation of the ethanol by hydroxide, which makes the addition reaction faster by making the ethanol more nucleophilic. Again, base (hydroxide) is regenerated in last step, making the overall reaction catalytic in base. The reaction in base always stops with the hemiacetal—acetals never form in base.

hemiacetal formation in base

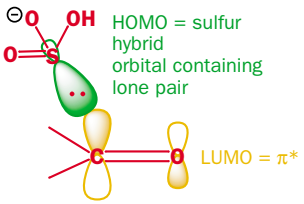


The final step could equally well involve deprotonation of ethanol to give alkoxide—and alkoxide could equally well do the job of catalysing the reaction. In fact, you will often come across mechanisms with the base represented just as 'B⁻' because it doesn't matter what the base is.



These two mechanisms typify acid- and base-catalysed additions to carbonyl groups and we can summarize the effects of the two catalysts.

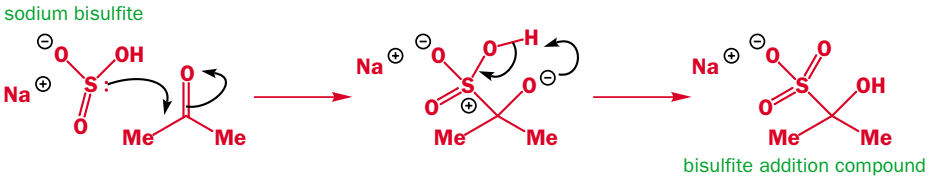
- **For nucleophilic additions to carbonyl groups:**
  - **Acid catalysts work by making the carbonyl group more electrophilic**
  - **Base catalysts work by making the nucleophile more nucleophilic**



orbitals involved in the addition of bisulfite

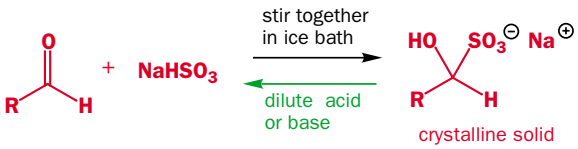
Bisulfite addition compounds

The last nucleophile of this chapter, sodium bisulfite, $NaHSO_3$, adds to aldehydes and some ketones to give what is usually known as a **bisulfite addition compound**. The reaction occurs by nucleophilic attack of a lone pair on the carbonyl group, just like the attack of cyanide. This leaves a positively charged sulfur atom but a simple proton transfer leads to the product.

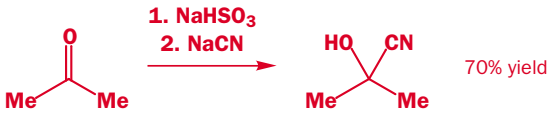


▶ The structure of $NaHSO_3$, sodium bisulfite, is rather curious. It is an oxyanion of a sulfur(IV) compound with a lone pair of electrons—the HOMO—on the sulfur atom, but the charge is formally on the more electronegative oxygen As a 'third row' element (third row of the periodic table, that is) sulfur can have more that just eight electrons—it's all right to have four or six bonds to S or P, unlike, say, B or N.

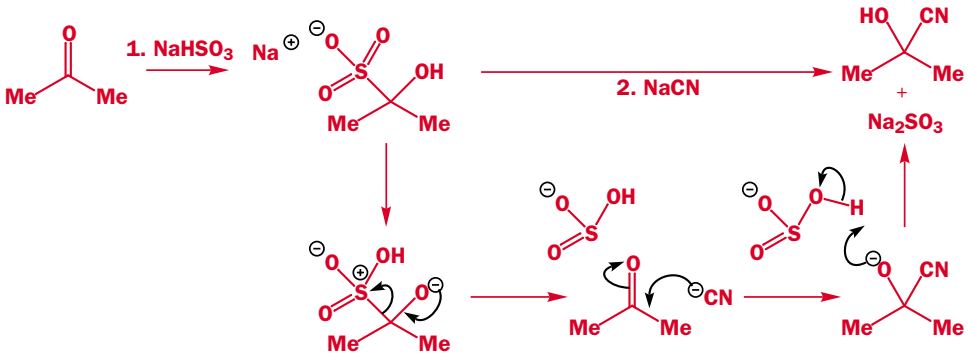
The products are useful for two reasons. They are usually crystalline and so can be used to purify liquid aldehydes by recrystallization. This is of value only because this reaction, like several you have met in this chapter, is reversible. The bisulfite compounds are made by mixing the aldehyde or ketone with saturated aqueous sodium bisulfite in an ice bath, shaking, and crystallizing. After purification the bisulfite addition compound can be hydrolysed back to the aldehyde in dilute aqueous acid or base.



The reversibility of the reaction makes bisulfite compounds useful intermediates in the synthesis of other adducts from aldehydes and ketones. For example, one practical method for making cyanohydrins involves bisulfite compounds. The famous practical book 'Vogel' suggests reacting acetone first with sodium bisulfite and then with sodium cyanide to give a good yield (70%) of the cyanohydrin.



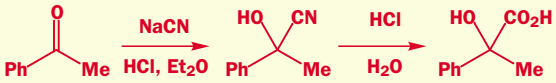
What is happening here? The bisulfite compound forms first, but only as an intermediate on the route to the cyanohydrin. When the cyanide is added, reversing the formation of the bisulfite compound provides the single proton necessary to to give back the hydroxyl group at the end of the reaction. No dangerous HCN is released (always a hazard when cyanide ions and acid are present together).



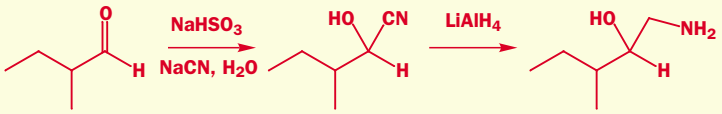
Other compounds from cyanohydrins

Cyanohydrins can be converted by simple reactions into hydroxyacids or amino alcohols. Here is one example of each, but you will have to wait until Chapter 12 for the details and the mechanisms of the reactions. Note that one cyanohydrin was made by the simplest method—just NaCN and acid—while the other came from the bisulfite route we have just discussed.

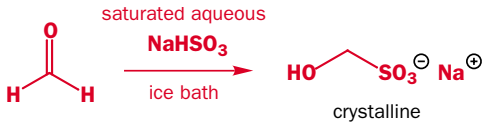
hydroxyacids by hydrolysis of CN in cyanohydrin



amino alcohols by reduction of CN in cyanohydrin



The bisulfite compound of formaldehyde (CH_2O) has special significance. Earlier in this chapter we mentioned the difficulty of working with formaldehyde because it is either an aqueous solution or a dry polymer. One readily available monomeric form is the bisulfite compound. It can be made in water (in which it is soluble) but addition of ethanol (in which it isn't) causes it to crystallize out.



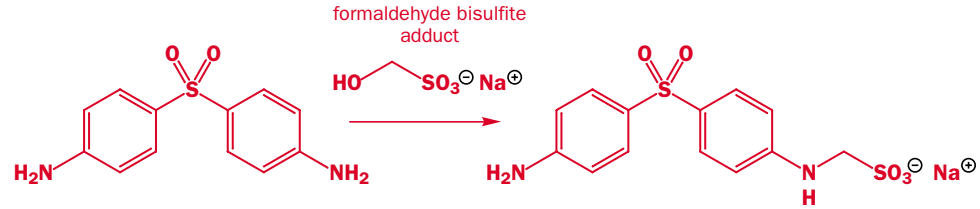
crystalline

The compound is commercially available and, together with the related zinc salt, is widely used in the textile industry as a reducing agent.

The second reason that bisulfite compounds are useful is that they are soluble in water. Some small (that is, low molecular weight) aldehydes and ketones are water-soluble—acetone is an example. But most larger (more than four or so carbon atoms) aldehydes and ketones are not. This does not usually matter to most chemists as we often want to carry out reactions in organic solvents rather than water. But it can matter to medicinal chemists, who make compounds that need to be compatible with biological systems. And in one case, the solubility of bisulfite adduct in water is literally vital.

Dapsone is an antileprosy drug. It is a very effective one too, especially when used in combination with two other drugs in a 'cocktail' that can be simply drunk as an aqueous solution by patients in tropical countries without any special facilities, even in the open air. But there is a problem! Dapsone is insoluble in water.

The solution is to make a bisulfite compound from it. You may ask how this is possible since dapsone has no aldehyde or ketone—just two amino groups and a sulfone. The trick is to use the formaldehyde bisulfite compound and exchange the OH group for one of the amino groups in dapsone.



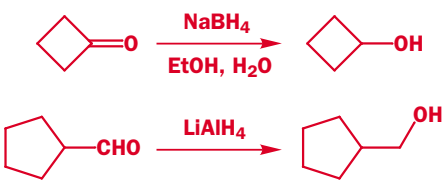
dapsone: antileprosy drug; insoluble in water

water-soluble "pro-drug"

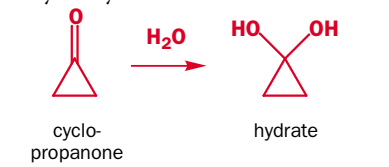
Now the compound will dissolve in water and release dapsone inside the patient. The details of this sort of chemistry will come in Chapter 14 when you will meet imines as intermediates. But at this stage we just want you to appreciate that even the relatively simple chemistry in this chapter is useful in synthesis, in commerce, and in medicine.

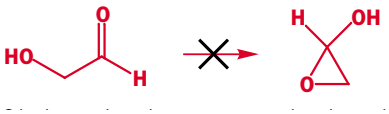
Problems

1. Draw mechanisms for these reactions.



2. Cyclopropanone exists as the hydrate in water but 2-hydroxyethanal does not exist as its hemiacetal. Explain.

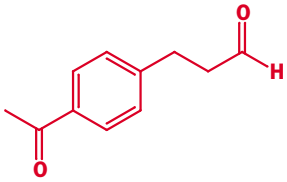




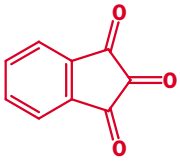
3. One way to make cyanohydrins is illustrated here. Suggest a detailed mechanism for the process.



4. There are three possible products from the reduction of this compound with sodium borohydride. What are their structures? How would you distinguish them spectroscopically, assuming you can isolate pure compounds?



5. The triketone shown here is called 'ninhydrin' and is used for the detection of amino acids. It exists in aqueous solution as a monohydrate. Which of the three ketones is hydrated and why?

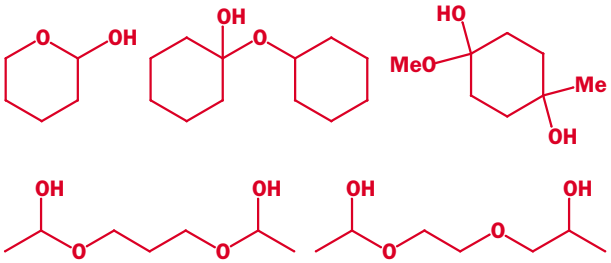


ninhydrin

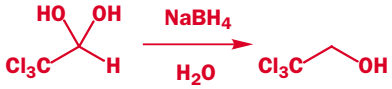
6. This hydroxyketone shows no peaks in its infrared spectrum between 1600 and 1800 cm^{-1} but it does show a broad absorption at 3000 to 3400 cm^{-1}. In the ^{13}C NMR spectrum, there are no peaks above 150 p.p.m. but there is a peak at 110 p.p.m. Suggest an explanation.



7. Each of these compounds is a hemiacetal and therefore formed from an alcohol and a carbonyl compound. In each case give the structure of these original materials.



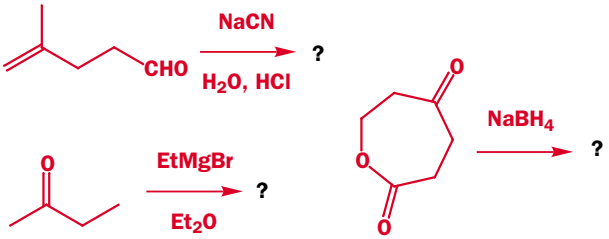
8. Trichloroethanol may be prepared by the direct reduction of chloral hydrate in water with sodium borohydride. Suggest a mechanism for this reaction. (Warning! Sodium borohydride does *not* displace hydroxide from carbon atoms!)



chloral hydrate trichloroethanol

9. It has not been possible to prepare the adducts from simple aldehydes and HCl. What would be the structure of such compounds, if they could be made, and what would be the mechanism of their formation? Why cannot these compounds in fact be made?

10. What would be the products of these reactions? In each case give a mechanism to justify your predictions.



11. The equilibrium constant K_{eq} for formation of the cyanohydrin of cyclopentanone and HCN is 67, while for butan-2-one and HCN it is 28. Explain.

Delocalization and conjugation

7

Connections

Building on:

- Orbitals and bonding ch4
- Representing mechanisms by curly arrows ch5
- Ascertaining molecular structure spectroscopically ch3

Arriving at:

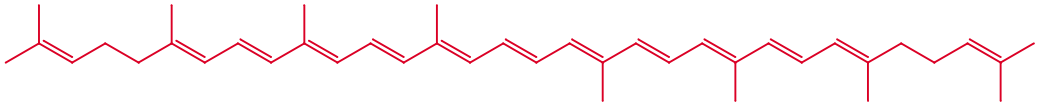
- Interaction between orbitals over many bonds
- Stabilization by the sharing of electrons over molecules
- Where colour comes from
- Molecular shape and structure determine reactivity
- Representing one aspect of structure by curly arrows
- Structure of aromatic compounds

Looking forward to:

- Acidity and basicity ch8
- Conjugate addition and substitution ch10
- Chemistry of aromatic compounds ch22 & ch23
- Enols and enolates ch21, ch25–ch29
- Chemistry of heterocycles ch43 & ch44
- Chemistry of life ch49–ch51

Introduction

As you look around you, you will be aware of many different colours—from the greens and browns outside to the bright blues and reds of the clothes you are wearing. All these colours result from the interaction of light with the pigments in these different things—some frequencies of light are absorbed, others scattered. Inside our eyes, chemical reactions detect these different frequencies and convert them into electrical nerve impulses sent to the brain. All these different pigments have one thing in common—lots of double bonds. For example, the pigment responsible for the red colour in tomatoes, lycopene, is a long-chain polyalkene.



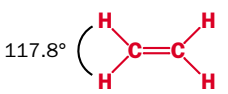
lycopene, the red pigment in tomatoes, rose hips, and other berries

Lycopene contains only carbon and hydrogen while most pigments contain many other elements but nearly all contain double bonds. This chapter is about the properties, such as colour, of molecules that have several double bonds and that depend on the joining up or **conjugation** of the electrons in these double bonds.

In earlier chapters, we talked about basic carbon skeletons made up of σ bonds. In this chapter we shall see how, in some cases, we can also have a large π framework spread over many atoms and how this dominates the chemistry of such compounds. We shall see how this π framework is responsible for the otherwise unexpected stability of certain cyclic polyunsaturated compounds, including benzene and other aromatic compounds. We shall also see how this framework gives rise to the many colours in our world. To understand such molecules properly, we need to start with the simplest of all unsaturated compounds, ethene.

The structure of ethene (ethylene, $CH_2=CH_2$)

The structure of ethene (ethylene) is well known. It has been determined by electron diffraction and is **planar** (*all* atoms are in the same plane) with the bond lengths and angles shown below. The carbon atoms are roughly trigonal and the C–C bond distance is shorter than that of a C–C σ bond.

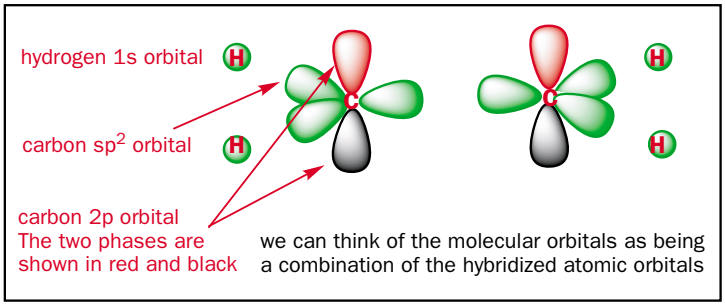


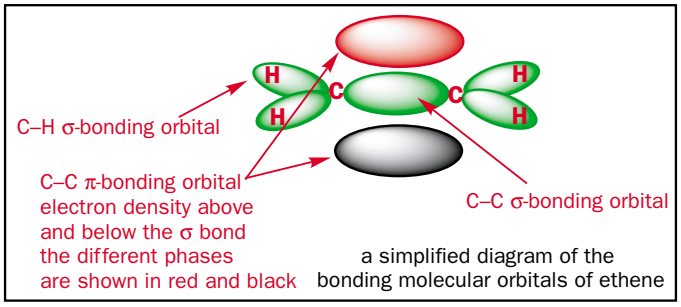
C–H bond length 108 pm
C=C bond length 133 pm

▶

Important point. Ethene is not actually formed by bringing together two carbon atoms and four hydrogen atoms: individual carbon atoms do not hybridize their atomic orbitals and then combine. We are simply trying to rationalize the shapes of molecular orbitals. Hybridization and LCAO are tools to help us accomplish this.

We shall use the approach of Chapter 4 (p. 106) and rationalize the shapes of molecular orbitals by combining the atomic orbitals of the atoms involved using the LCAO (Linear Combination of Atomic Orbitals) approach. Hybridizing the atomic orbitals first makes this simpler. We mix the 2s orbital on each carbon atom with two of the three 2p orbitals to give three sp^2 orbitals leaving the third p orbital unchanged. Two of the sp^2 orbitals overlap with the hydrogen 1s orbitals to form molecular orbitals, which will be the C–H σ bonds. The other sp^2 orbital forms the σ C–C bond by overlapping with the sp^2 orbital on the other carbon. The remaining p orbital can overlap with the p orbital on the other carbon to form a molecular orbital that represents the π bond.



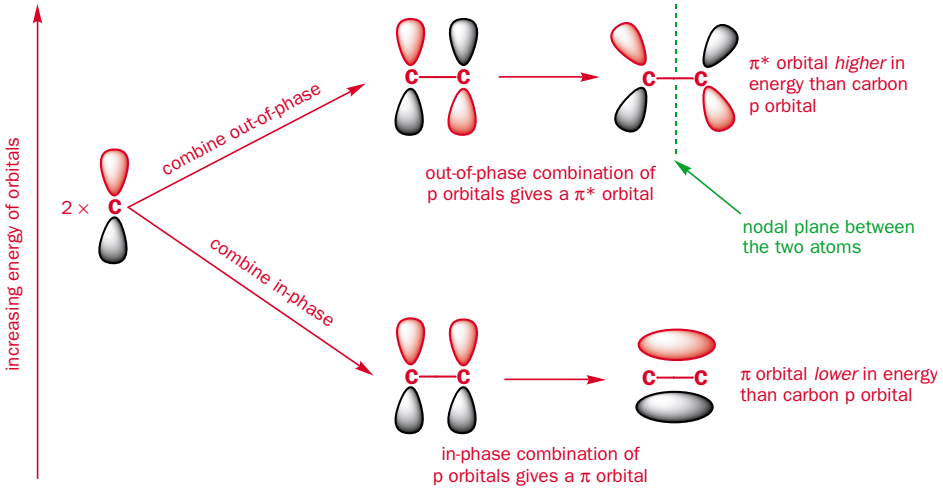


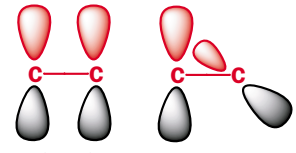
Eth*ene* is chemically more interesting than eth*ane* because of the π bond. In fact, the π bond is the most important feature of ethene. In the words of Chapter 5, the C–C π orbital is the HOMO (Highest Occupied Molecular Orbital) of the alkene, which means that the electrons in it are more available than any others to react with something that wants electrons (an electrophile). Since this orbital is so important, we will look at it more closely.

The π orbital results from combining the two 2p orbitals of the separate carbon atoms. Remember that when we combine *two* atomic orbitals we get *two* molecular orbitals. These result from combining the p orbitals either in-phase or out-of-phase. The in-phase combination accounts for the bonding molecular orbital (π), whilst the out-of-phase combination accounts for the antibonding molecular orbital (π*). As we progress to compounds with more than one alkene, so the number of π orbitals will increase but will remain the same as the number of π* orbitals.

α β notation

Theoretical chemists would label the energy of an electron in the p orbital as 'α' and that of an electron in the molecular orbital resulting from the combination of two p orbitals as 'α + β'. (Both α and β are, in fact, negative, which means that α + β is lower in energy than α.) The corresponding energy of an electron in the antibonding orbital is 'α – β'. Whilst α represents the energy an electron would have in an *atomic* orbital, β represents the change in energy when the electron is delocalized over the two carbon atoms. Since the π bond contains two electrons, both in the lowest-energy molecular orbital, the π orbital, the total energy of the electrons is 2α + 2β. If, instead, the two electrons remained in the atomic orbitals, their energy would be just 2α. Therefore the system is 2β lower in energy if the electrons are in the π molecular orbital rather than the atomic orbitals.





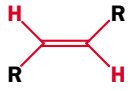
the two p orbitals can only overlap if they are parallel

The π bond contains two electrons and, since we fill up the energy level diagram from the lowest-energy orbital upwards, both these electrons go into the bonding molecular orbital. In order to have a strong π bond, the two atomic p orbitals must be able to overlap effectively. This means they must be parallel.

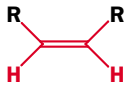
There are two isomers (*cis* and *trans* or *E* and *Z*) of many alkenes

The π bond has electron density both above and below the σ bond as the parallel p orbitals overlap locking the bond rigid. Hence no rotation is possible about a double bond—the π bond must be broken before rotation can occur. One consequence of this locking effect of the double bond is that there are two isomers of a disubstituted alkene. One is called a *cis* or *Z* alkene, the other a *trans* or *E* alkene.

▶ By contrast, a C–C σ bond has electron density along the line joining the two nuclei and allows free rotation.



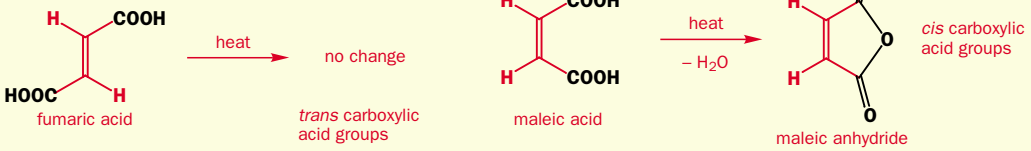
a *trans* or *E* alkene



a *cis* or *Z* alkene

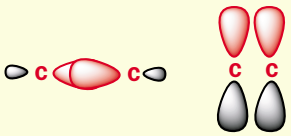
Alkenes resist rotation

Maleic and fumaric acids were known in the nineteenth century to have the same chemical composition and the same functional groups and yet they were different compounds—why remained a mystery. That is, until 1874 when van't Hoff proposed that free rotation about double bonds was restricted. This meant that, whenever each carbon atom of a double bond had two different substituents, isomers would be possible. He proposed the terms *cis* (Latin meaning 'on this side') and *trans* (Latin meaning 'across or on the other side') for the two isomers. The problem was: which isomer was which? On heating, maleic acid readily loses water to become maleic anhydride so this isomer must have both acid groups on the same side of the double bond.

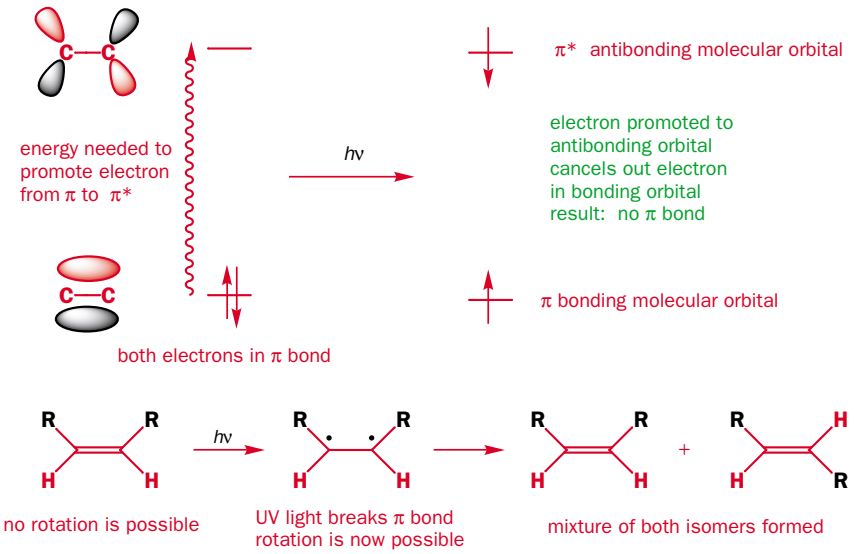


It is possible to interconvert *cis* and *trans* alkenes, but the π bond must be broken first. This requires a considerable amount of energy—around 260 kJ mol^{-1}. One way to break the π bond would be to promote an electron from the π orbital to the π* orbital (from HOMO to LUMO). If this were to happen, there would be one electron in the bonding π orbital and one in the antibonding π* orbital and hence no overall bonding. Electromagnetic radiation of the correct energy could promote the electron from HOMO to LUMO. The correct energy actually corresponds to light in the ultraviolet (UV) region of the spectrum. Thus, shining UV light on an alkene would promote an electron from its bonding π molecular orbital to its antibonding π* molecular orbital, thereby breaking the π bond (but not the σ bond) and allowing rotation to occur.

Notice that it takes less energy to break a C–C π bond than a C–C σ bond (about 260 kJ mol^{-1} compared to about 350 kJ mol^{-1}). This is because the sideways overlap of the p orbitals to form a π bond is not as effective as the head-on overlap of the orbitals to form a σ bond. Enough energy is available to break the π bond if the alkene is heated to about 500 °C.



overlap of orbitals is more efficient in a σ bond than in a π bond

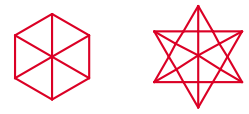


Molecules with more than one C–C double bond

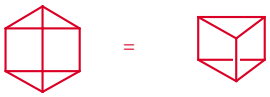
Benzene has three strongly interacting double bonds

The rest of this chapter concerns molecules with more than one C–C double bond and what happens to the π orbitals when they interact. To start, we shall take a bit of a jump and look at the structure of benzene. Benzene has been the subject of considerable controversy since its discovery in 1825. It was

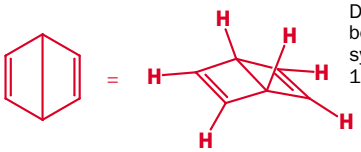
soon worked out that the formula was C_6H_6, but how were these atoms arranged? Some strange structures were suggested until Kekulé proposed the correct structure in 1865.



these diagrams represent old structures for benzene. They do not represent compounds that could ever be made

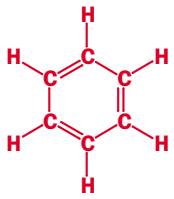


prismane synthesized 1973



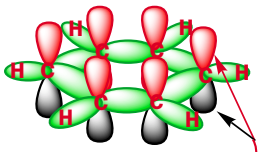
Dewar benzene synthesized 1963

these early suggestions for the structure of benzene have now been made. they are certainly not benzene, but entirely different compounds



Kekulé's structure for benzene

σ bonds shown in green

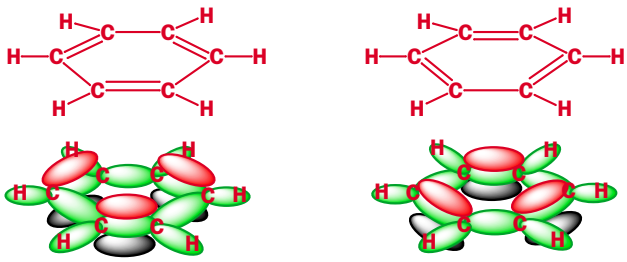


a single p orbital different phases shown in red and black

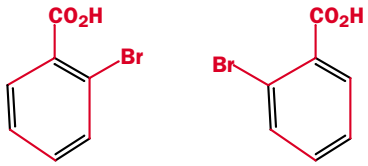
Let's look at the molecular orbitals for Kekulé's structure. As in simple alkenes, each of the carbon atoms is sp^2 hybridized leaving the remaining p orbital free.

The σ framework of the benzene ring is like the framework of an alkene. The problem comes with the p orbitals—which pairs do we combine to form the π bonds? There seem to be two possibilities.

combining different pairs of p orbitals puts the double bonds in different postions



With benzene itself, these two forms are equivalent but, if we had a 1,2- or a 1,3-disubstituted benzene compound, these two forms would be different. A synthesis was designed for these two compounds but it was found that both compounds were identical. This posed a bit of a problem to Kekulé—his structure didn't seem to work after all. His solution was that benzene rapidly equilibrates, or 'resonates' between the two forms to give an averaged structure in between the two.



2-bromobenzoic acid '6'-bromobenzoic acid

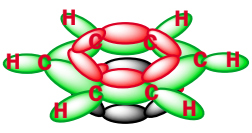
if the double bonds were localized then these two compound would be chemically different. (the double bonds are drawn shorter than the single bonds to emphasize the difference)

■

Combining these six atomic p orbitals actually produces *six* molecular orbitals. We shall consider the form of all these orbitals later in the chapter when we discuss benzene and aromaticity more fully.

The molecular orbital answer to this problem, as you may well know, is that all six p orbitals can combine to form (six) new molecular orbitals, one of which (the one lowest in energy) consists of a ring of electron density above and below the plane of the molecule. Benzene *does not resonate* between the two Kekulé structures—the electrons are in molecular orbitals spread equally over all the carbon atoms. However the term 'resonance' is still sometimes used (but not in this book) to describe this mixing of molecular orbitals.

We shall describe the π electrons in benzene as **delocalized**, that is, no longer localized in specific double bonds between two particular carbon atoms but spread out, or delocalized, over all six atoms in the ring. An alternative drawing for benzene shows the π system as a ring and does not put in the double bonds.





the circle represents the delocalized system

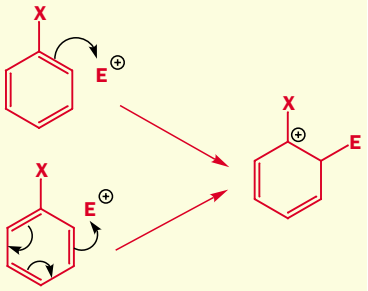
The Kekulé structure is used for mechanisms

This representation does present a slight problem to modern organic chemists, however: it is not possible to draw mechanisms using the delocalized representation of benzene. The curly arrows we use represent two electrons. This means that in order to write sensible mechanisms we still draw benzene as though the double bonds were localized. Keep in mind though that these double bonds are not really localized and it does not matter which way round we draw them.



this representation cannot be used for mechanisms

it does not matter which way round you draw the benzene ring – both drawings give the same result but one uses more arrows to get there



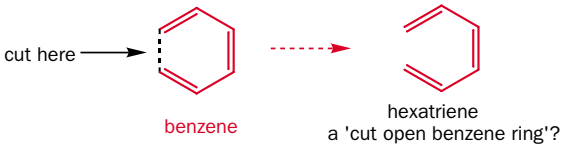
We are saying that *the π electrons are not localized* in alternating double bonds but are actually *spread out over the whole system* in a molecular orbital shaped like a ring (we will look at the shapes of the others later). The electrons are therefore said to be **delocalized**. Theoretical calculations confirm this model, as do experimental observations. Electron diffraction studies show benzene to be a regular, planar hexagon with all the carbon–carbon bond lengths identical (139.5 pm). This bond length is in between that of a carbon–carbon single bond (154.1 pm) and a full carbon–carbon double bond (133.7 pm). A further strong piece of evidence for this ring of electrons is revealed by proton NMR and is discussed on on p. 251.

Delocalization terminology

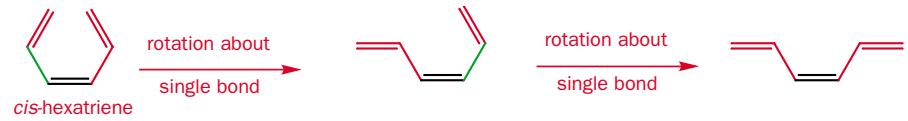
What words should be used to describe delocalization is a vexed question. Terms such as resonance, mesomerism, conjugation, and delocalization are only a few of the ones you will find in books. You will already have noticed that we don't like 'resonance' because it suggests that the structure vibrates rapidly between localized structures. We shall use conjugation and delocalization: conjugation focuses on the sequence of alternating double and single bonds while delocalization focuses on the molecular orbitals covering the whole system. Electrons are *delocalized* over the whole of a *conjugated* system.

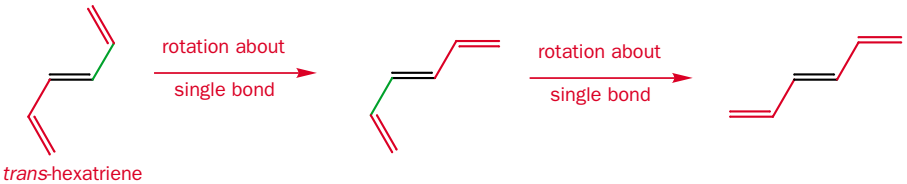
Noncyclic polyenes

What would the structure be like if the three C–C double bonds were not in a ring as they are in benzene but were instead in a chain. What is the structure of hexatriene? Are the bond lengths still all the same?



There are two isomers of hexatriene: a *cis* form and a *trans* form. The name refers to the geometry about the central double bond. The two isomers have different chemical and physical properties. Rotation is still possible about the single bonds (although slightly more difficult than around a normal single bond) and there are three different planar conformations possible for each isomer. Keeping the central black double bond the same, we can rotate about each of the green σ bonds in turn. Each row simply shows different ways to draw the same compound.

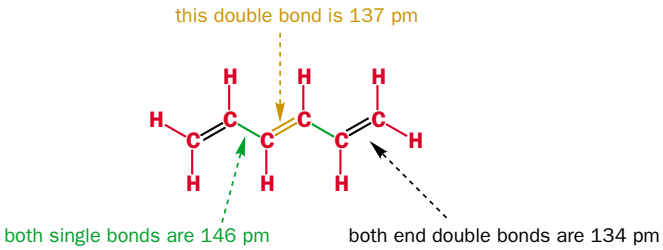




The structures of both *cis*- and *trans*-hexatriene have been determined by electron diffraction and two important features emerge.

- Both structures are essentially planar (the *cis* form is not quite for steric reasons)
- There are double and single bonds but the central double bond in each case is slightly longer than the end double bonds and the single bonds are slightly shorter than a 'standard' single bond

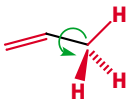
The most stable structure of *trans*-hexatriene is shown here.



standard values: single bond: 154 pm
double bond: 134 pm

Why is this structure planar and why are the bond lengths different from their 'standard' values? This sounds like the situation with benzene and again the answers lie in the molecular orbitals that can arise from the combination of the six p orbitals. Just as in benzene, these orbitals can all combine to give one big molecular orbital over the whole molecule. However, the p orbitals can overlap and combine only if the molecule isplanar.

■ This aspect of structure is called **conformation** and is the subject of Chapter 18.

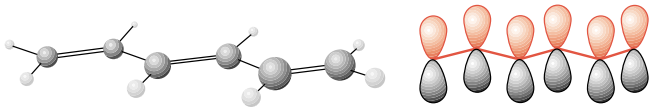


rotation about this bond requires only about 3 kJ mol^{-1}

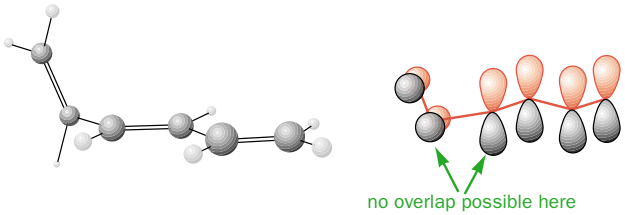


because of the overlap of the p orbitals on carbons 2 and 3, rotation is now harder and requires more than **30** kJ mol^{-1}

Since the p orbitals on carbons 2 and 3 overlap, there is some partial double bond character in the central σ bond, helping to keep the structure planar. This overlap means that it is slightly harder to rotate this 'formal single bond' than might be expected—it requires about 30 kJ mol^{-1} to rotate it whereas the barrier in propene is only around 3 kJ mol^{-1}.



when all the atoms are planar all six p orbitals can overlap



if we rotate about a single bond, one pair of p orbitals can no longer overlap with the others

This explains why the compound adopts a planar structure but, in order to understand why the bond lengths are slightly different from their expected values or even why they are not all the same as in benzene, we must look at the *all* the molecular orbitals for hexatriene. Before we can do this, we must first study some simpler systems and address the important question of conjugation seriously.

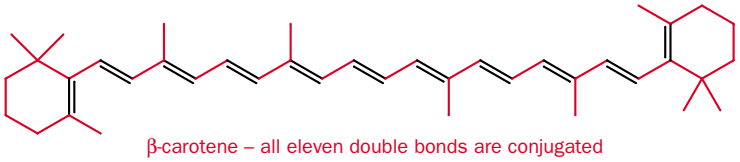
Conjugation

In benzene and hexatriene every carbon atom is sp^2 hybridized with the remaining p orbital available to overlap with its neighbours. The uninterrupted chain of p orbitals is a consequence of having alternate double and single bonds. When two double bonds are separated by just one single bond, the two double bonds are said to be **conjugated**. Conjugated double bonds have different properties from isolated double bonds, both physically (they are often longer as we have already seen) and chemically (Chapters 10, 23, and 35).

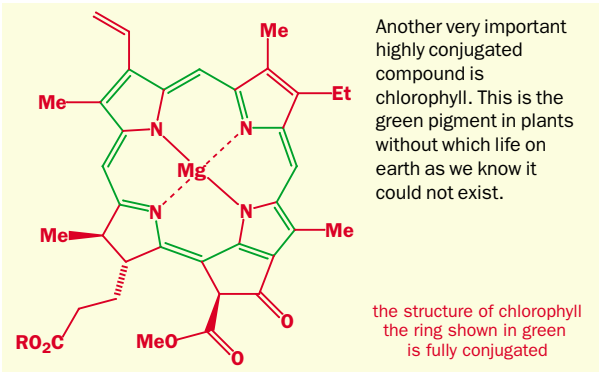
Conjugated systems

In the dictionary, 'conjugated' is defined, among other ways, as 'joined together, especially in pairs' and 'acting or operating as if joined'. This does indeed fit very well with the behaviour of such conjugated double bonds since the properties of a conjugated system are often different from those of the component parts. We are using *conjugation* to describe bonds and *delocalization* to describe electrons.

You have already met several conjugated systems: remember lycopene at the start of this chapter and β-carotene in Chapter 3? All eleven double bonds in β-carotene are separated by only one single bond. We again have a long chain in which all the p orbitals can overlap to form molecular orbitals.



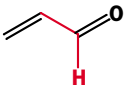
β-carotene – all eleven double bonds are conjugated



Another very important highly conjugated compound is chlorophyll. This is the green pigment in plants without which life on earth as we know it could not exist.

the structure of chlorophyll
the ring shown in green
is fully conjugated

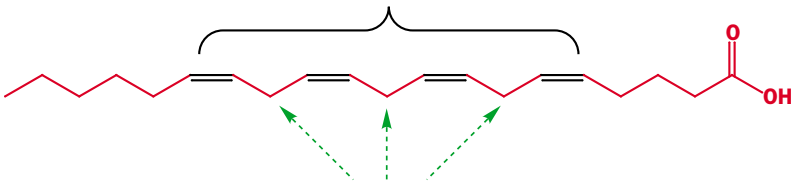
It is not necessary to have two carbon–carbon double bonds in order to have a conjugated system—the C–C and C–O double bonds of propenal (acrolein) are also conjugated. The chemistry of such conjugated carbonyl compounds is significantly different from the chemistry of their component parts (Chapter 10).



propenal (acrolein):
here the C-C double bond is
conjugated with an aldehyde group

What is important though is that the double bonds are separated by *one and only one* single bond. Remember the unsaturated fatty acid, linoleic acid, that you met in Chapter 3? Another fatty acid with even more unsaturation is arachidonic acid. None of the four double bonds in this structure are conjugated since in between any two double bonds there is an sp^3 carbon. This means there is no p orbital available to overlap with the ones from the double bonds. The saturated carbon atoms insulate the double bonds from each other.

these four double bonds are not conjugated
– they are all separated by two single bonds



these tetrahedral sp^3 carbons prevent any possible
overlap of the p orbitals in the double bonds

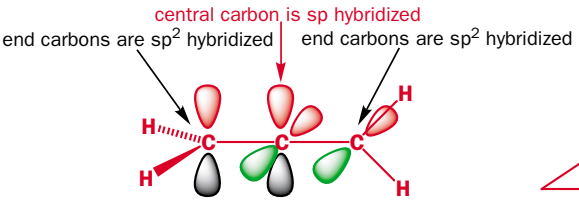
If an atom has two double bonds directly attached to it, that is, there are no single bonds separating them, again no conjugation is possible. The simplest compound with such an arrangement is allene.



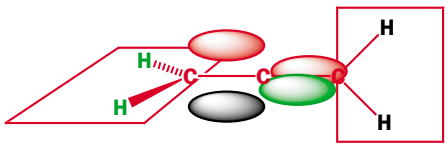
allene

If we look at the arrangement of the p orbitals in this system, it is easy to see why no delocalization is possible—the two π bonds are perpendicular to each other.

central carbon is sp hybridized
end carbons are sp^2 hybridized
end carbons are sp^2 hybridized



the π bonds formed as a result
of the overlap of the p orbitals
must be at right angles to each other



not only are the two π bonds perpendicular,
but the two methylene groups are too

Requirements for conjugation

- Conjugation requires double bonds separated by one single bond
- Separation by two single bonds or no single bonds will not do

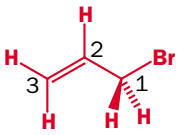
The allyl system

The allyl cation

We would not say that two p orbitals are conjugated—they just make up a double bond—so just how many p orbitals do we need before something can be described as conjugated? It should be clear that in butadiene the double bonds are conjugated—here we have four p orbitals.





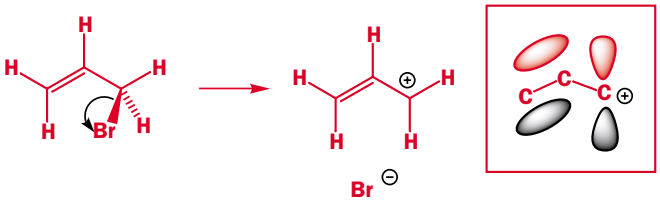


allyl bromide

Is it possible to have three p orbitals interacting? How can we get an isolated p orbital–after all, we can't have half a double bond. Let us look for a moment at allyl bromide (prop-2-enyl bromide or 1-bromoprop-2-ene). Carbon 1 in this compound has got four atoms attached to it (a carbon, two hydrogens, and a bromine atom) so it is tetrahedral (or sp^3 hybridized).

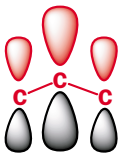
Bromine is more electronegative than carbon and so the C–Br bond is polarized towards the bromine. If this bond were to break completely, the bromine would keep both electrons from the C–Br bond to become bromide ion, Br^-, leaving behind an organic cation. The end carbon would now only have three groups attached and so it becomes trigonal (sp^2 hybridized). This leaves a vacant p orbital that we can combine with the π bond to give a new molecular orbital for the allyl system.

the p orbital has the correct symmetry to combine with the π bond to form a new molecular orbital for the allyl system



▶ As more orbitals combine it becomes more difficult to represent the molecular orbitals convincingly. We shall often, from now on, simply use the atomic orbitals to represent the molecular orbitals.

Rather than trying to combine the p orbital with the π bond, it is easier for us to consider how three p orbitals combine; after all, we thought of the π bond as a combination of two p orbitals. Since we are combining three atomic orbitals (the three 2p orbitals on carbon) we shall get three molecular orbitals. The lowest-energy orbital will have them all combining in-phase. This is a bonding orbital since all the interactions are bonding.

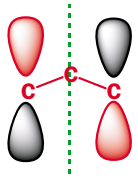


the bonding molecular orbital of the allyl system, Ψ_1

▶ Remember:

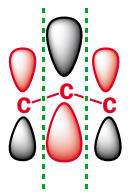
1. We are simply combining atomic *orbitals* here—whether or not any of the orbitals contain any electrons is irrelevant. We can simply fill up the resultant molecular orbitals later, starting with the orbitals lowest in energy and working upwards until we have used up any electrons we may have.
2. This method allows us to work out, without too much difficulty, the shapes and energies of the molecular orbitals. The *compound* does not split its molecular orbitals into atomic orbitals and then recombine them into new molecular orbitals; we do.

The next orbital requires one node, just as higher-energy atomic orbitals have extra nodes (Chapter 4). The only way to include a node and maintain the symmetry of the system is to put the node through the central atom. This means that when this orbital is occupied there will be no electron density on this central atom. Since there are no interactions between adjacent atomic orbitals (either bonding or antibonding), this is a nonbonding orbital.



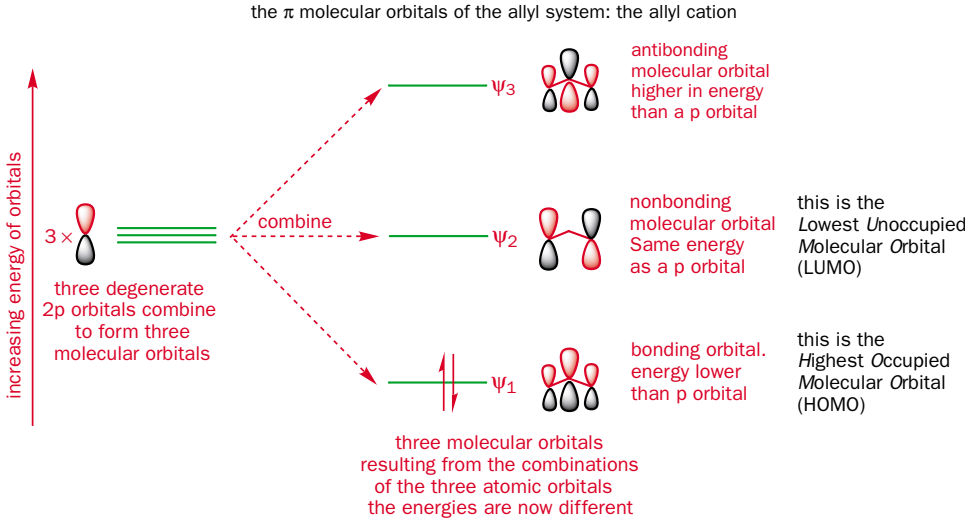
nodal plane through the middle atom nonbonding Ψ_2

The final molecular orbital must have two nodal planes. All the interactions of the atomic orbitals are out-of-phase so the resulting molecular orbital is an antibonding orbital.

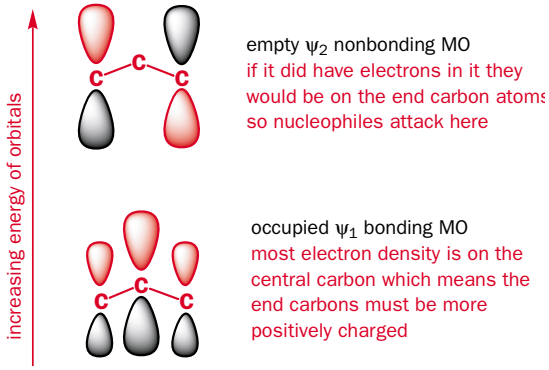


two nodal planes antibonding Ψ_3

We can summarize all this information in a molecular orbital energy level diagram.



The two electrons that were in the π bond now occupy the orbital lowest in energy, the bonding molecular orbital Ψ_1, and now spread over three carbon atoms. The electrons highest in energy and so most reactive are those in the HOMO. However, in this case, since the allyl cation has an overall positive charge, we wouldn't really expect it to act as a nucleophile. Of far more importance is the vacant nonbonding molecular orbital—the LUMO, the nonbonding Ψ_2. It is this orbital that must be attacked if the allyl cation reacts with a nucleophile. From the shape of the orbital, we can see that the incoming electrons will attack the end carbon atoms not the middle one since, if this orbital were full, all electron density in it would be on the end carbon atoms, not the middle one. A different way of looking at this is to see which carbon atoms in the system are most lacking in electron density. The only orbital in this case with any electrons in it is the bonding molecular orbital Ψ_1. From the relative sizes of the coefficients on each atom we can see that the middle carbon has more electron density on it than the end ones; therefore the end carbons must be more positive than the middle one and so a nucleophile would attack the end carbons.



▶ There are also all the molecular orbitals from the σ framework but we do not need to consider these: the occupied σ-bonding molecular orbitals are considerably lower in energy than the molecular orbitals for the π system and the vacant antibonding molecular orbitals for the σ bonds are much higher in energy than the π antibonding molecular orbital.

▶ The term **coefficient** describes the contribution of an individual atomic orbital to a molecular orbital. It is represented by the size of the lobes on each atom.

Representations of the allyl cation

How can we represent all this information with curly arrows? The simple answer is that we can't. Curly arrows show the *movement* of a pair of electrons. The electrons are not really moving around in this system—they are simply spread over all three carbon atoms with most electron density on the middle carbon. Curly arrows can give us an indication of the equivalence of the two end carbons, showing that the positive charge is shared over these two atoms.



curly arrows show the positive charge is shared over both the end atoms

The curly arrows we used in this representation are slightly different from the curly arrows we used (Chapter 5) to represent mechanisms by the forming and breaking of bonds. We still arrive at the second structure by supposing that the curly arrows mean the movement of two electrons so that the right-hand structure results from the 'reaction' shown on the left-hand structure, but these 'reactions' would be the movement of electrons *and nothing more*. In particular, no atoms have moved and no σ bonds have been formed or broken. These two structures are just two different ways of

drawing the same species. The arrows are **delocalization arrows** and we use them to remind us that our simple fixed-bond structures do not tell the whole truth. To remind us that these are delocalization arrows, we use a different reaction arrow, a single line with arrowheads on each end (↔).

The problem with these structures is that they seem to imply that the positive charge (and the double bond for that matter) is jumping from one end of the molecule to the other. This, as we have seen, is just not so. Another and perhaps better picture uses dotted lines and partial charges. However, as in the representation of benzene with a circle in the middle, we cannot draw mechanisms on this structure. Each of the representations has its value and we shall use both.

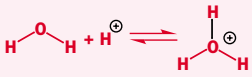


a structure to emphasize the equivalence of both bonds and the sharing of the charge at both ends

▶ Do not confuse this delocalization arrow with the equilibrium sign. A diagram like this would be wrong:



The equilibrium arrows may be used only if atoms have moved and the species differ by at least a σ bond. Maybe the simplest reaction that could be shown this way would be the protonation of water where a proton moves and an O–H σ bond, shown in black, is formed or broken.

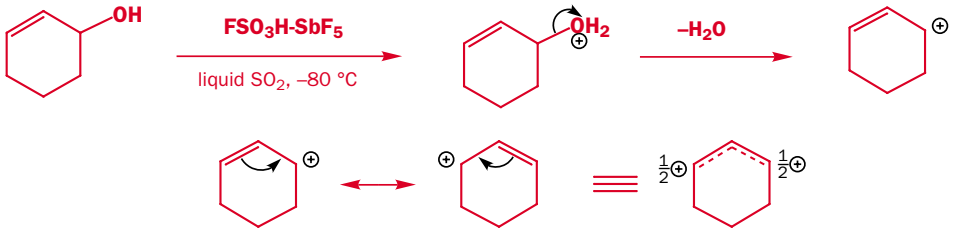


A summary of the allyl cation system

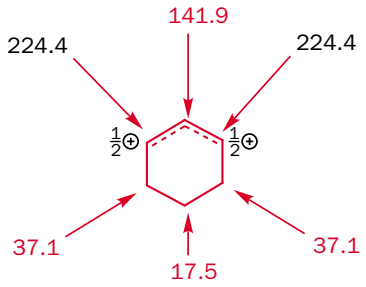
- The two electrons in the π system are spread out over all three carbon atoms with most electron density on the central carbon
- There are no localized double and single bonds—both C–C bonds are identical and in between a double and single bond
- Both end carbons are equivalent
- The positive charge is shared equally over the two end carbons. The LUMO of the molecule shows us that this is the site for attack by a nucleophile

The delocalized allyl cation can be compared to localized carbocations by NMR

In the reaction below, a very strong acid (called 'superacid'—see Chapter 17) protonates the OH group of 3-cyclohexenol, which can then leave as water. The resulting cation is, not surprisingly, unstable and would normally react rapidly with a nucleophile. However, at low temperatures and if there are no nucleophiles present, the cation is relatively stable and it is even possible to record a carbon NMR spectrum (at –80 °C).



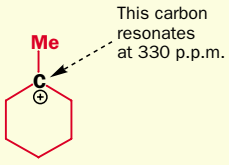
The NMR spectrum of this allylic cation reveals a plane of symmetry, which confirms that the positive charge is spread over two carbons. The large shift of 224 p.p.m. for these carbons indicates very strong deshielding (that is, lack of electrons) but is nowhere near as large as a localized cation. The middle carbon's shift of 142 p.p.m. is almost typical of a normal double bond indicating that it is neither significantly more nor less electron-rich than normal.



the ^{13}C NMR shifts in p.p.m.
notice the plane of symmetry down the middle

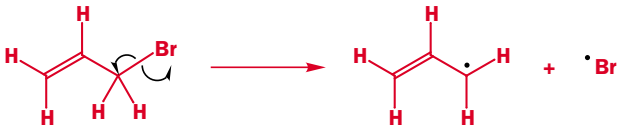
Carbocation ^{13}C shift

This localized carbocation shows an enormous shift of 330 p.p.m. indicating very little shielding of the positively charged carbon atom. Again, due to the instability of this species, the ^{13}C spectrum was recorded at low temperature.



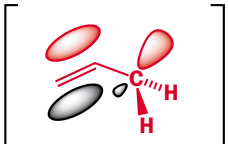
The allyl radical

When we made the allyl cation from allyl bromide, the bromine atom left as bromide ion taking both the electrons from the C–Br bond with it—the C–Br bond broke **heterolytically**. What if the bond broke **homolytically**—that is, carbon and bromine each had one electron? A bromine atom and an allyl radical (remember a radical has an unpaired electron) would be formed. This reaction can be shown using the single-headed fish hook curly arrows from Chapter 5: normal double-headed arrows show the movement of two electrons; single-headed arrows show the movement of one.

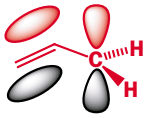


homolytic cleavage of the C–Br bond forms a bromine atom and the allyl radical

Now the end carbon has a single unpaired electron. What do we do with it? Before the bond broke, the end carbon was tetrahedral (sp^3 hybridized). We might think that the single electron would still be in an sp^3 orbital. However, since an sp^3 orbital cannot overlap efficiently with a π bond, the single electron would then have to be localized on the end carbon atom. If the end carbon atom becomes trigonal (sp^2 hybridized), the single electron could be in a p orbital and this could overlap and combine with the π bond. This would mean that the radical could be spread over the molecule in the same orbital that contained the cation.

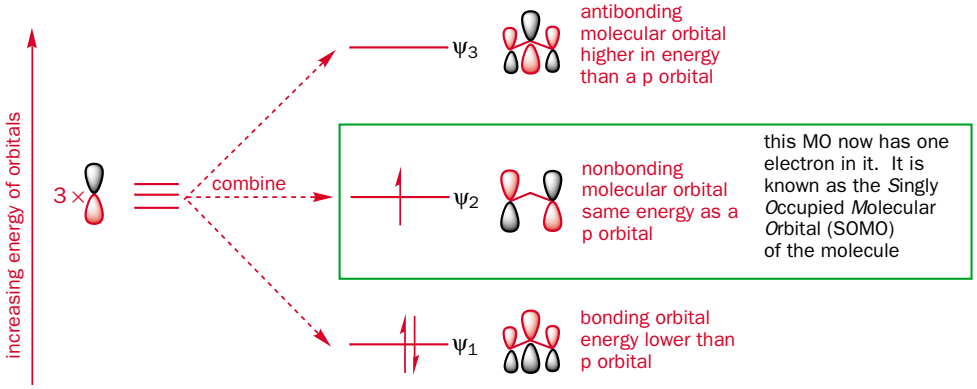


inefficient overlap of sp^3 orbital and π bond



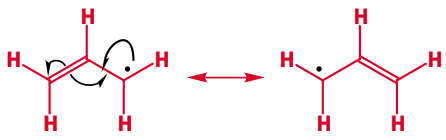
efficient overlap of p orbital and π bond

So once again we have three p orbitals to combine. This is the same situation as before. We have the same atoms, the same orbitals, and so the same energy levels. In fact, the molecular orbital energy level diagram for this compound is *almost the same* as the one for the allyl cation: the only difference is the number of electrons in the π system. Whereas in the allyl cation π system we only had two electrons, here we have three (two from the π bond plus the single one). Where does this extra electron go? Answer: in the next lowest molecular orbital—the nonbonding molecular orbital.



the π molecular orbitals of the allyl system: the allyl radical

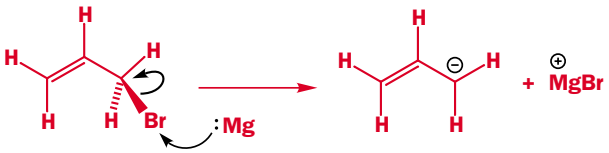
The extra electron is in an orbital all by itself. This orbital must be the HOMO of the molecule but is also the LUMO since it still has room for one more electron. It is actually called the **Singly Occupied Molecular Orbital** (**SOMO**), for obvious reasons. The shape of this orbital tells us that the single electron is located on the end carbon atoms. This can also be shown using delocalization arrows (again single-headed arrows to show movement of one electron).



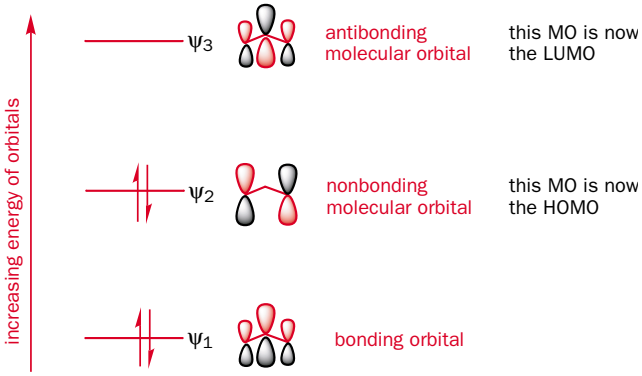
the single electron can be on either of the end carbon atoms

The allyl anion

What would have happened if both electrons from the C–Br bond in allyl bromide had stayed behind on the carbon? If we had removed the bromine atom with a metal, magnesium for example (Chapter 9), both electrons would remain leaving an overall negative charge on the allyl system.



reaction of allyl bromide with a metal gives the allyl anion



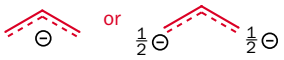
the π molecular orbitals of the allyl system: the allyl anion

Again, this system is much more stable if the negative charge can be spread out rather than localized on one end carbon. This can be accomplished only if the negative charge is in a p orbital rather than an sp^3 orbital. The molecular orbital energy level diagram is, of course, unchanged: all we have to do is put the extra electron in the nonbonding orbital. Altogether we now have four electrons in the π system—two from the π bond and two from the negative charge. Both the bonding and the nonbonding orbitals are now fully occupied.

Where is the electron density in the allyl anion π system? The answer is slightly more complicated than that for the allyl cation because now we have two full molecular orbitals and the electron density comes from a sum of both orbitals. This means there is electron density on all three carbon atoms. However, the HOMO for the anion is now the nonbonding molecular orbital. It is this orbital that contains the electrons highest in energy and so most reactive. In this orbital there is no electron density on the middle carbon; it is all on the end carbons. Hence it will be the end carbons that will react with electrophiles. This is conveniently represented by curly arrows.



the curly arrows give a good representation of the HOMO and they show the negative charge concentrated on the end carbon atoms. But the structures suggest localized bonds and charges



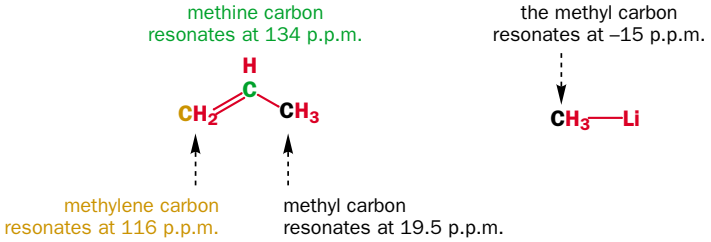
these two structures emphasize the equivalence of the bonds and that the charge is spread out

A summary of the allyl anion system

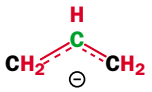
- There are no localized double and single bonds—both C–C bonds are the same and in between a double and single bond
- Both end carbons are the same
- The four electrons in the π system are spread out over all three carbon atoms. In the bonding orbital most electron density is on the central carbon but, in the nonbonding orbital, there is electron density only on the end carbons
- The electrons highest in energy and so most reactive (those in the HOMO) are to be found on the end carbons. Electrophiles will therefore react with the end carbons

Such predictions from a consideration of the molecular orbitals are confirmed both by the reactions of the allyl anion and by its NMR spectrum. It is possible to record a carbon NMR spectrum of the allyl anion directly (for example, as its lithium derivative). The spectrum shows only two signals: the middle carbon at 147 p.p.m. and the two end carbons both at 51 p.p.m.

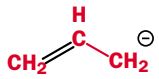
The central carbon's shift of 147 p.p.m. is almost typical of a normal double bond carbon whilst the end carbons' shift is in between that of a double bond and a saturated carbon bearing a negative charge. Notice also that the central carbon in the allyl cation and the anion have almost identical chemical shifts—142 and 147 p.p.m., respectively. If anything, the *anion* central carbon is more deshielded. Compare this with the spectra for methyllithium and propene itself. Methyllithium shows a single peak at –15 p.p.m. and propene shows three ^{13}C signals as indicated below.



the central carbon
resonates at 147 p.p.m.



both end carbons
resonate at 51 p.p.m.



a localized structure like this would have a very different spectrum

Other allyl-like systems

The carboxylate anion

You may already be familiar with one anion very much like the allyl anion—the carboxylate ion formed on deprotonating a carboxylic acid with a base. In this structure we again have a double bond adjacent to a single bond but here oxygen atoms replace two of the carbon atoms.



a carboxylic acid — a carboxylate anion

X-ray crystallography shows both carbon–oxygen bond lengths in this anion to be the same (136 pm), in between that of a normal carbon–oxygen double bond (123 pm) and single bond (143 pm). The negative charge is spread out equally over the two oxygen atoms.



the electrons are delocalized over the π system

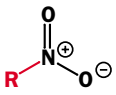
these structures emphasize the equivalence of the two C–O bonds and that the negative charge is spread over both oxygen atoms

The molecular orbital energy diagram for the carboxylate anion is the very similar to that of the allyl system. There are just two main differences.

1. The coefficients of the atomic orbitals making up the molecular orbitals will change because oxygen is more electronegative than carbon and so has a greater share of electrons
2. The absolute values of the energy levels will be different from those in the allyl system, again because of the difference in the electronegativities. Compare with the differences between the molecular orbitals for ethene and a carbonyl, p. 103

The nitro group

The nitro group consists of a nitrogen bonded to two oxygen atoms and a carbon (for example, an alkyl group). There are two ways of representing the structure: one using formal charges, the other using a dative bond. Notice in each case that one oxygen is depicted as being doubly bonded, the other singly bonded. Drawing both oxygen atoms doubly bonded is incorrect—*nitrogen cannot have five bonds* since this would represent ten electrons around it and there are not enough orbitals to put them in.



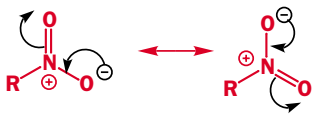
two ways of representing the nitro group the stucture on the left has formal charges on the nitrogen and one oxygen, the other has a dative bond from the nitrogen



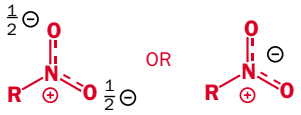
incorrect drawing of the nitro group *nitrogen cannot have five bonds*

▶ Notice that the delocalization over the nitro group is similar to that over the carboxylate group. In fact, the nitro group is isoelectronic with the carboxylate group, that is, both systems have the same number of electrons.

The problem with the two correct drawings is that they do not show the equivalence of the two N–O bonds. However, we do have an N–O double bond next to an N–O single bond which means that the negative charge is delocalized over both of the oxygen atoms. This can be shown by curly arrows.



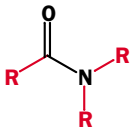
the electrons are delocalized over the π system



these structures emphasize the equivalence of the two N–O bonds and that the negative charge is spread over both oxygen atoms

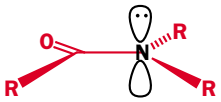
Just to reiterate, the same molecular orbital energy diagram can be used for the allyl systems and the carboxylate and nitro groups. Only the absolute energies of the molecular orbitals are different since different elements with different electronegativities are used in each.

The amide group



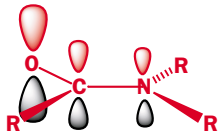
an amide

The amide is a very important group in nature since it is the link by which amino acids join together to form peptides, which make up the proteins in our bodies. The structure of this deceptively simple group has an unexpected feature, which is responsible for much of the stability of proteins.



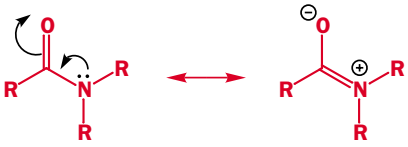
nitrogen is trigonal with its lone pair in a p orbital

In the allyl anion, carboxylate, and nitro systems we had four electrons in the π system spread out over three atoms. The nitrogen in the amide group also has a pair of electrons that could conjugate with the π bond of the carbonyl group. Again, for effective overlap with the π bond, the lone pair of electrons must be in a p orbital. This in turn means that the nitrogen must be sp^2 hybridized.

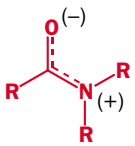


the lowest π orbital of the amide the same arrangement of p orbitals as in the allyl systen

In the carboxylate ion, a negative charge was shared (equally) between two oxygen atoms. In an amide there is no charge as such—the lone pair on nitrogen is shared between the nitrogen and the oxygen. However, since oxygen is more electronegative than nitrogen, it has more than its fair share of the electrons in this π system. (This is why the p orbital on the oxygen atom in the lowest bonding orbital shown above is slightly larger than the p orbital on the nitrogen.) The delocalization can be shown using curly arrows.



This representation suffers from the usual problems. Curly arrows show the movement of a pair of electrons. The structure on the left, therefore, suggests that electrons are flowing from the nitrogen to the oxygen. *This is not true*: the molecular orbital picture tells us that the electrons are unevenly distributed over the three atoms in the π system with a greater electron density on the oxygen. The curly arrows show us how to draw an alternative diagram. The structure on the right implies that the nitrogen's lone pair electrons have moved completely on to the oxygen. Again this is not true; there is simply more electron density on the oxygen than on the nitrogen. The arrows are useful in that they help us to depict how the electrons are unevenly shared in the π system.



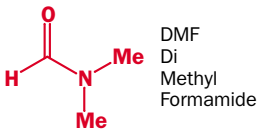
A better representation might be this structure. The charges in brackets indicate substantial, though not complete, charges, maybe about a half plus or minus charge. However, we cannot draw mechanisms on this structure and all these representations have their uses.

- **Let us summarize these points.**
  - **The amide group is planar—this includes the first carbon atoms of the R groups attached to the carbonyl group and to the nitrogen atom**
  - **The lone pair electrons on nitrogen are delocalized into the carbonyl group**
  - **The C–N bond is strengthened by this interaction—it takes on partial double bond character. This also means that we no longer have free rotation about the C–N bond which we would expect if it were only a single bond**
  - **The oxygen is more electron-rich than the nitrogen. Hence we might expect the oxygen rather than the nitrogen to be the site of electrophilic attack**
  - **The amide group as a whole is made more stable as a result of the delocalization**

The amide is a functional group of exceptional importance so we shall look at these points in more detail.

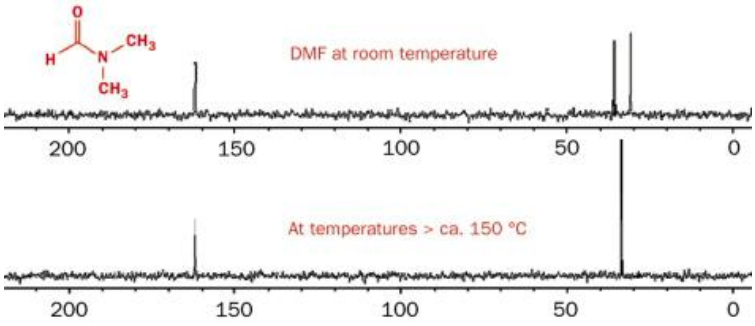
The structure of the amide group

How do we know the amide group is planar? X-ray crystal structures are the simplest answer. Other techniques such as electron diffraction also show that simple (noncrystalline) amides have planar structures. *N*,*N*-dimethylformamide (DMF) is an example.

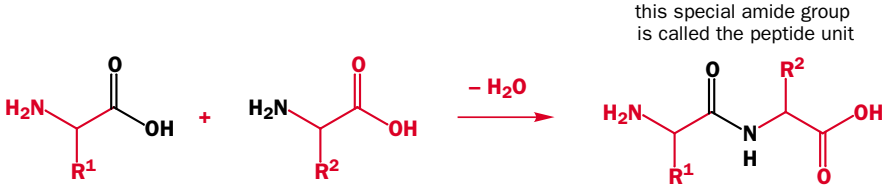


DMF
Di
Methyl
Formamide

The C–N bond length to the carbonyl group is closer to that of a standard C–N double bond (127 pm) than to that of a single bond (149 pm). This partial double bond character is responsible for the restricted rotation about this C–N bond. We must supply 88 kJ mol^{-1} if we want to rotate the C–N bond in DMF (remember a full C–C double bond takes about 260 kJ mol^{-1}). This amount of energy is not available at room temperature and so, for all intents and purposes, the amide C–N bond is locked at room temperature as if it were a double bond. This is shown in the carbon NMR spectrum of DMF. How many carbon signals would you expect to see? There are three carbon atoms altogether and three signals appear—the two methyl groups on the nitrogen are different. If free rotation were possible about the C–N bond, we would expect to see only two signals. In fact, if we record the spectrum at higher temperatures, we do indeed only see two signals since now there is sufficient energy available to overcome the rotational barrier and allow the two methyl groups to interchange.

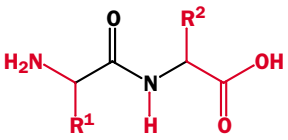


Proteins are composed of many amino acids joined together with amide bonds. The amino group of one can combine with the carboxylic acid group of another to give an amide. This special amide, which results from the combining of two amino acids, is known as a **peptide**—two amino acids join to form a dipeptide; many join to give a polypeptide.



amino acid 1 amino acid 2 two amino acids, joined together by a peptide bond, form a dipeptide

The peptide unit so formed is a planar, rigid structure since there is restricted rotation about the C–N bond. This means that two isomers should be possible—a *cis* and a *trans*.



C=O and N–H are *trans*



C=O and N–H are *cis*

It is found that nearly all the peptide units found in nature are *trans*. This is not surprising since the *cis* form is more crowded (a *trans* disubstituted double bond is lower in energy than a *cis* for the same reason).

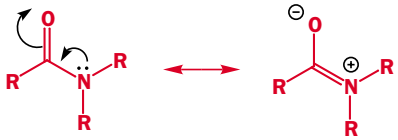
Protein shape and activity

This planar, *trans* peptide unit poses serious limitations on the shapes proteins can adopt. Understanding the shapes of proteins is very important—enzymes, for example, are proteins with catalytic properties. Their catalytic function depends on the shape adopted: alter the shape in some way and the enzyme will no longer work.

▶ In Chapter 3 we saw that IR spectroscopy shows carbonyl groups in the region 1600–1800 cm^{-1}. At the higher end of that region the C=O stretches of very reactive acid chlorides and acid anhydrides show that they have full C=O double bonds. At the lower end of that region the C=O stretching frequency of amides comes at about 1660 cm^{-1} showing that they are halfway to being single bonds. These relationships will be explored further in Chapter 15. The conjugation of the nitrogen's lone pair with the carbonyl bond *strengthens* the C–N bond but *weakens* the carbonyl bond. The weaker the bond, the less energy it takes to stretch it and so the lower the IR absorption frequency. Overall the molecule is more stable, as is reflected in the reactivity (or lack of it) of the amide group, Chapter 12.

Reactivity of the amide group

Just as delocalization stabilizes the allyl cation, anion, and radical, so too is the amide group stabilized by the conjugation of the nitrogen's lone pair with the carbonyl group. This, together with the fact that the amine part is such a poor leaving group, makes the amide one of the least reactive carbonyl groups (we shall discuss this in Chapter 12).



the oxygen atom's withdrawal of electrons *weakens* the carbonyl bond

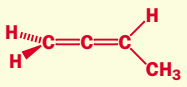
Furthermore, the amine part of the amide group is unlike any normal amine group. Most amines are easily protonated. However, since the lone pair on the amide's nitrogen is tied up in the π system, it is less available for protonation or, indeed, reaction with any electrophile. As a result, an amide is preferentially protonated on the oxygen atom but it is difficult to protonate even there (see next chapter, p. 201). Conjugation affects reactivity.

The conjugation of two π bonds

The simplest compound that can have two conjugated π bonds is butadiene. As we would now expect, this is a planar compound that can adopt two different conformations by rotating about the single bond. Rotation is somewhat restricted (around 30 kJ mol^{-1}) but nowhere near as much as in an amide (typically 60–90 kJ mol^{-1}). What do the molecular orbitals for the butadiene π system look like? The lowest-energy molecular orbital will have all the p orbitals combining in-phase. The next lowest will have one node, and then two, and the highest-energy molecular orbital will have three nodes (that is, all the p orbitals will be out-of-phase).

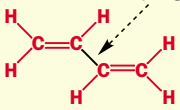
Isomers of butadiene

Butadiene normally refers to 1,3-butadiene. It is also possible to have 1,2-butadiene which is another example of an allene (p. 157).



1,2-butadiene
an allene

rotation about this single bond is only slightly restricted

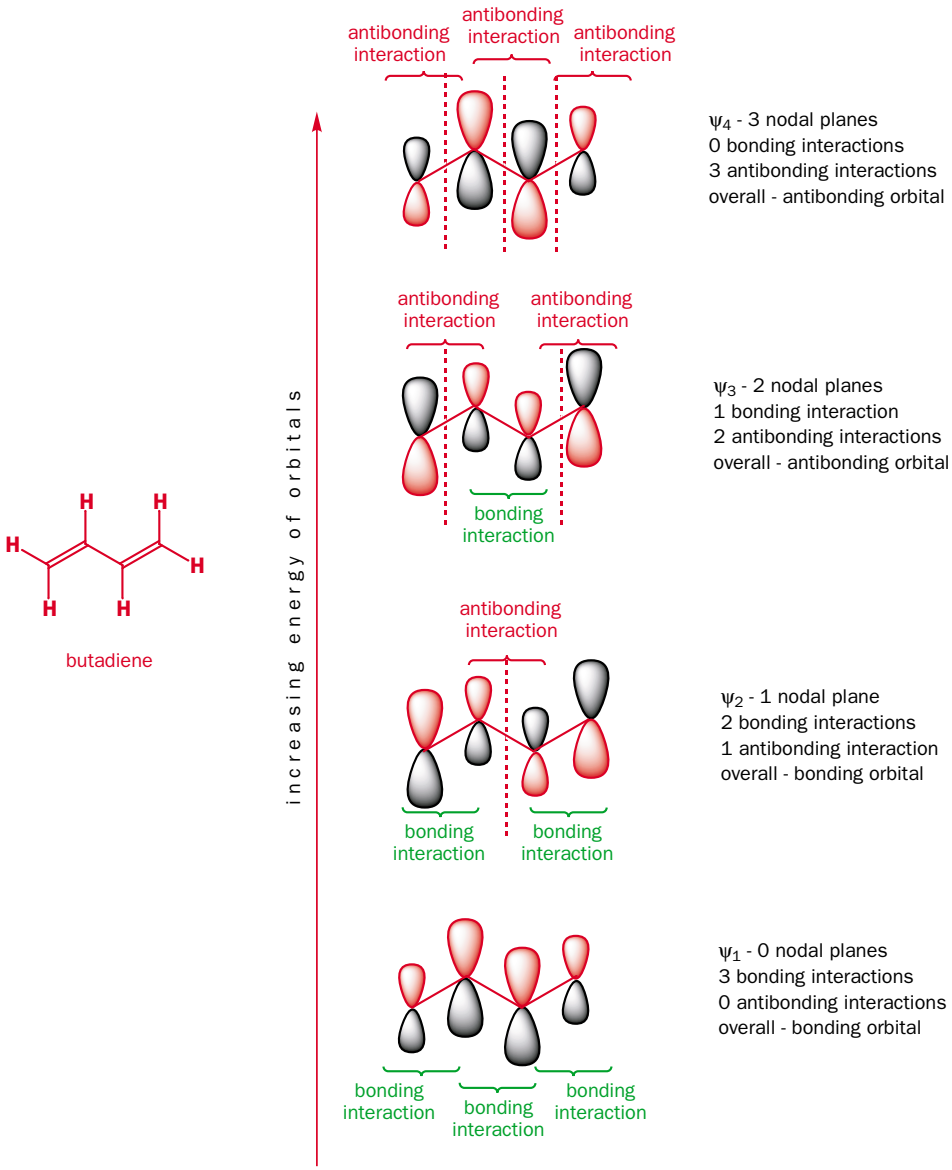


1,3-butadiene
a conjugated diene

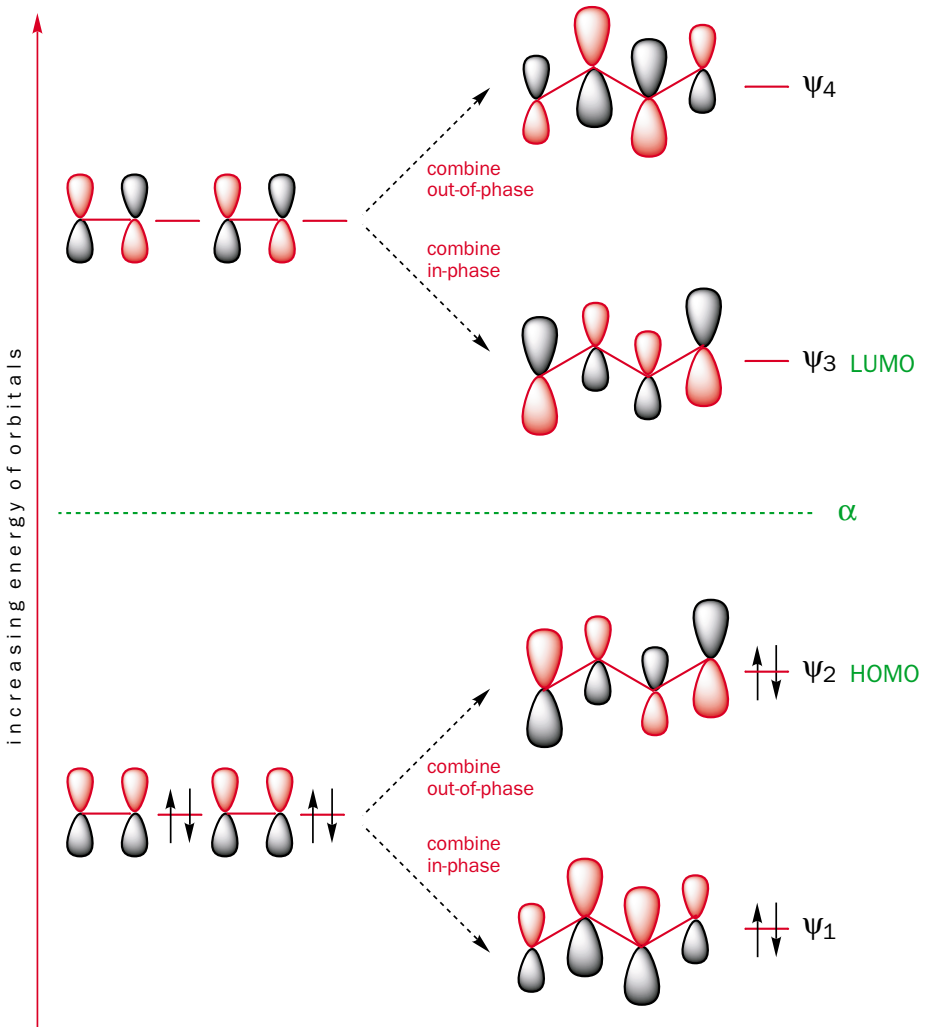
The molecular orbitals of butadiene

Butadiene has two π bonds and so four electrons in the π system. Which molecular orbitals are these electrons in? Since each molecular orbital can hold two electrons, only the two molecular orbitals lowest in energy are filled. Let's have a closer look at these orbitals. In Ψ_1, the lowest-energy bonding orbital, the electrons are spread out over all four carbon atoms (above and below the plane) in one continuous orbital. There is bonding between all the atoms. The other two electrons are in Ψ_2. This orbital has bonding interactions between carbon atoms 1 and 2, and also between 3 and 4 but an *antibonding* interaction between carbons 2 and 3. Overall, in both the occupied π orbitals there are

electrons between carbons 1 and 2 and between 3 and 4, but the antibonding interaction between carbons 2 and 3 in Ψ_2 partially cancels out the bonding interaction in Ψ_1. This explains why all the bonds in butadiene are not the same and why the middle bond is more like a single bond while the end bonds are double bonds. If we look closely at the coefficients on each atom in orbitals Ψ_1 and Ψ_2, it can be seen that the bonding interaction between the central carbon atoms in Ψ_1 is greater than the antibonding one in Ψ_2. Thus butadiene does have some double bond character between carbons 2 and 3, which explains why there is the slight barrier to rotation about this bond.



In our glimpse of hexatriene earlier in this chapter we saw a similar effect, which we could now interpret if we looked at all the molecular orbitals for hexatriene. We have three double bonds and two single bonds with slightly restricted rotation. Both butadiene and hexatriene have double bonds and single bond: neither compound has all its C–C bond lengths the same, yet both compounds are conjugated. What is the real evidence for conjugation? How does the conjugation show itself in the properties and reactions of these compounds? To answer these questions, we need to look again at the energy level diagram for butadiene and compare it with that of ethene. A simple way to do this is to make the orbitals of butadiene by combining the orbitals of ethene.



We have drawn the molecular orbital diagram for the π molecular orbitals of butadiene as a result of combining the π molecular orbitals of two ethene molecules. There are some important points to notice here.

- The overall energy of the two bonding butadiene molecular orbitals is lower than that of the two molecular orbitals for ethene. This means that butadiene is more thermodynamically stable than we might expect if its structure were just two isolated double bonds
- The HOMO for butadiene is *higher* in energy relative to the HOMO for ethene. This means butadiene should be *more* reactive than ethene towards nucleophiles
- The LUMO for butadiene is *lower* in energy than the LUMO for ethene. Consequently, butadiene would be expected to be *more* reactive towards nucleophiles than ethene
- So whilst butadiene is more stable than two isolated double bonds, *it is also more reactive* (Chapter 20)

■

Recall that on p. 153 we saw how it was possible to promote an electron from HOMO to LUMO in an isolated double bond using UV light and that this allowed rotation about this bond. In butadiene, however, promoting an electron from the HOMO to the LUMO actually *increases* the electron density between the two central atoms and so stops rotation.

Butadiene model

A simple theoretical model of the butadiene system predicts the energy of the bonding Ψ_1 orbital to be [α + 1.62β] and that of bonding orbital Ψ_2 to be [α + 0.62β]. With both of these orbitals fully occupied, the total energy of the electrons is [4α + 4.48β]. Remember that the energy of the bonding π molecular orbital for ethene was [α + β] (p. 152) so, if we were to have two localized π bonds (each with two electrons), the total energy would be [4α + 4β]. This theory predicts that butadiene with both double bonds conjugated is lower in energy than it would be with two localized double bonds by 0.48β. Both α and β are negative; hence [4α + 4.48β] is *lower* in energy than [4α + 4β] by 0.48β.

UV and visible spectra

In Chapter 2 we saw how, if given the right amount of energy, electrons can be promoted from a low-energy atomic orbital to a higher-energy one and how this gives rise to an atomic absorption spectrum. Exactly the same process can occur with molecular orbitals. In fact, we have already seen (p. 153) that UV light can promote an electron from the HOMO to the LUMO in a double bond.

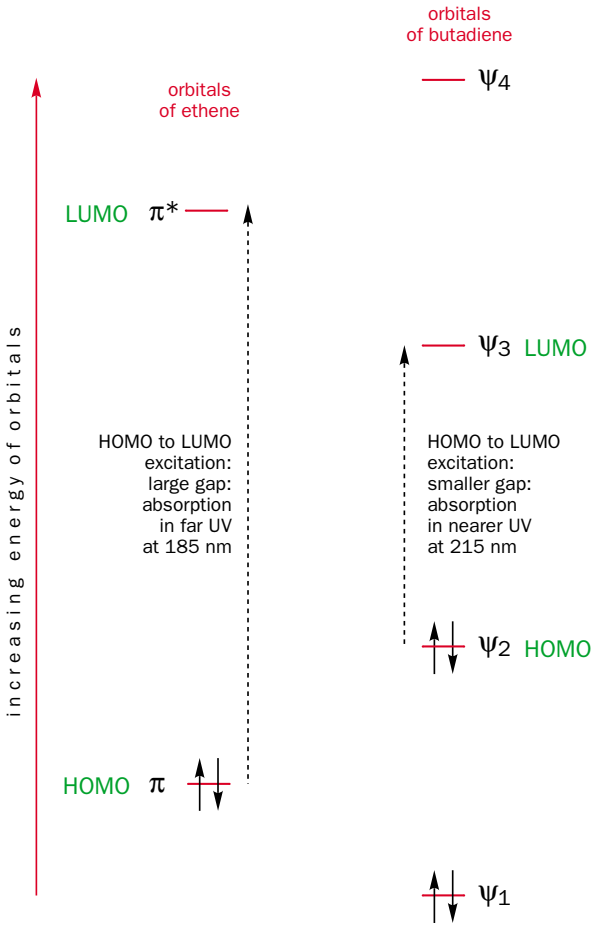
HOMO–LUMO gap

Electrons can be promoted from any filled orbital to any empty orbital. The smallest energy difference between a full and empty molecular orbital is between the HOMO and the LUMO. The smaller this difference, the less energy will be needed to promote an electron from the HOMO to the LUMO: the smaller the amount of energy needed, the longer the wavelength of light needed since $\Delta E = h\nu$. Therefore, an important measurement is the wavelength at which a compound shows maximum absorbance, λ_{max}. A difference of more than about 4 eV (about 7×10^{-19} J) between HOMO and LUMO means that λ_{max} will be in the ultraviolet region (wavelength, λ, < 300 nm). If the energy difference is between about 3 eV (about 4×10^{-19} J) and 1.5 eV (about 3×10^{-19} J) then λ_{max} will be in the visible part of the spectrum.

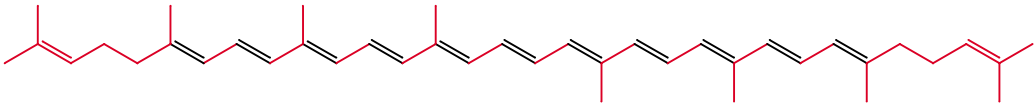
■ We can get a good estimate of the absolute energies of molecular orbitals from photoelectron spectroscopy and electron transmission spectroscopy (see Chapter 2). Such experiments suggest energies for the HOMO and LUMO of butadiene to be –9.03 and +0.62 eV, respectively, whilst for ethene they are –10.51 and +1.78 eV, respectively.

We have seen above that the energy difference between the HOMO and LUMO for butadiene is less than that for ethene. Therefore we would expect butadiene to absorb light of longer wavelength than ethene (the longer the wavelength the lower the energy, $\Delta E = hc/\lambda$). This is found to be the case: butadiene absorbs at 215 nm compared to 185 nm for ethene. The conjugation in butadiene means it absorbs light of a longer wavelength than ethene. In fact, this is true generally.

● **The more conjugated a compound is, the smaller the energy transition between its HOMO and LUMO and hence the longer the wavelength of light it can absorb. Hence UV–visible spectroscopy can tell us about the conjugation present in a molecule.**



Both ethene and butadiene absorb in the far-UV region of the electromagnetic spectrum (215 nm is just creeping into the UV region) but, if we extend the conjugation further, the gap between HOMO and LUMO will eventually be sufficiently decreased to allow the compound to absorb visible light and hence be coloured. A good example is the red pigment in tomatoes we introduced at the start of the chapter. It has eleven conjugated double bonds (plus two unconjugated) and absorbs light at about 470 nm.



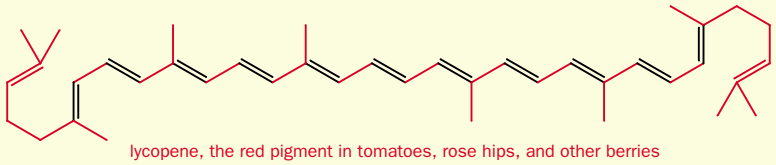
lycopene, the red pigment in tomatoes, rose hips, and other berries

The colour of pigments depends on conjugation

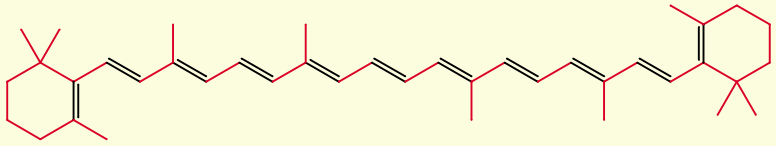
You can see now that it is no coincidence that this compound and the two other highly conjugated compounds we met earlier, chlorophyll and β-carotene, are all highly coloured natural pigments. In fact, all dyes and pigments are highly conjugated compounds.

Natural pigments

The similarities between lycopene and β-carotene are easier to see if the structure of lycopene is twisted. Lycopene is a precursor of carotene so, when a cell makes carotene, it makes lycopene *en route*.



lycopene, the red pigment in tomatoes, rose hips, and other berries



β-carotene, the red pigment in carrots and other vegetables

If a compound absorbs one colour, it is the complementary colour that is transmitted—the red glass of a red light bulb *doesn't* absorb red light; it absorbs everything else letting only red light through. Here is a table of approximate wavelengths for the various colours. The last column gives the approximate length a conjugated chain must be in order to show the colour in question. The number *n* refers to the number of double bonds in conjugation.

Approximate wavelengths for different colours

Absorbed frequency, nm	Colour absorbed	Colour transmitted	$R(CH{=}CH)_nR$, n =
200–400	ultraviolet	—	< 8
400	violet	yellow-green	8
425	indigo-blue	yellow	9
450	blue	orange	10
490	blue-green	red	11
510	green	purple	
530	yellow-green	violet	
550	yellow	indigo-blue	
590	orange	blue	
640	red	blue-green	
730	purple	green	

Every extra conjugated double bond in a system increases the wavelength of light that is absorbed. If there are fewer than about eight conjugated double bonds, the compound absorbs in

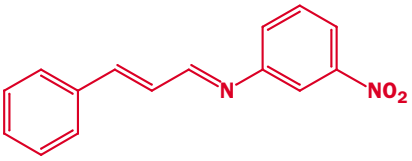
the ultraviolet and we don't notice the difference. With more than eight conjugated double bonds, the absorption creeps into the visible and, by the time it reaches 11, the compound is red. If we wanted a blue or green compound, we should need a very large number of conjugated double bonds and such pigments do not usually rely on π bonds alone.

Transitions from bonding to antibonding π orbitals are called π → π* transitions. A much smaller energy gap is available if we use electrons in a nonbonding orbital as the electrons start off much higher in energy and can be promoted to low-lying antibonding π orbitals. We call these transitions n → π*, where the 'n' stands for nonbonding. It is easy to find coloured compounds throughout the whole range of wavelengths by this means. The colour of blue jeans comes from the pigment indigo. The two nitrogen atoms provide the lone pairs that can be excited into the π* orbitals of the rest of the molecule. These are low in energy because of the two carbonyl groups. Yellow light is absorbed by this pigment and indigo-blue light transmitted.



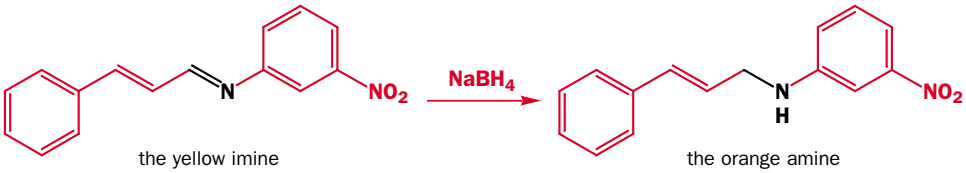
colourless precursor to indigo — indigo: the pigment of blue jeans

Jeans are dyed by immersion in a vat of reduced indigo, which is colourless since the conjugation is interrupted by the central single bond. When the cloth is hung up to dry, the oxygen in the air oxidizes the 'pigment' to indigo and the jeans turn blue. Conjugation is the key to colour.



Many conjugated compounds are yellow because, although they have their λ_{max} in the UV, the broad absorption tails into the visible and the compound weakly absorbs violet light making it pale yellow. An example is this imine with a long conjugated system joining the two aromatic rings together.

The imine is yellow but when it is reduced to the amine, breaking the conjugation in the middle so that the two benzene rings are no longer linked together, the result is a dark orange compound. This is rather surprising because you would normally expect the compound with the longer conjugated system to absorb at longer wavelengths. Check with the table above to see that an orange compound definitely absorbs at longer wavelengths than a yellow compound.



the yellow imine — the orange amine

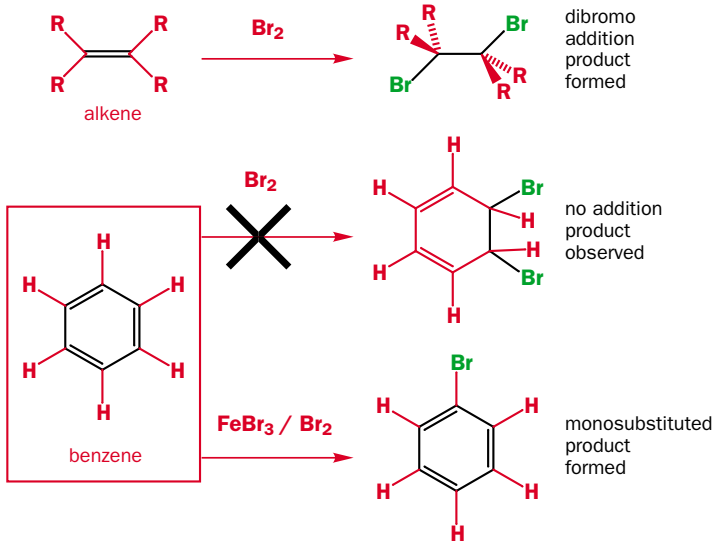
The answer to this paradox lies in the change of hybridization of the nitrogen atom. In the imine, the nitrogen is trigonal and the lone pair is in an sp^2 orbital in the plane of the conjugated system. No delocalization of the lone pair is possible and the UV absorption comes from a simple π → π* transition. When the imine is reduced, the C–N bond can rotate and the amine can be trigonal too, but with the N–H bond in the plane and the lone pair in a p orbital conjugated with the right-hand benzene ring. The absorption giving the orange colour is an n → π* transition not a π → π* transition. Even delocalization of a lone pair into one benzene ring with a nitro group can give a longer wavelength absorption than a conjugated system of bonding electrons.

Aromaticity

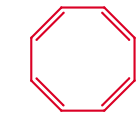
Let us now return to the structure of benzene. Benzene is unusually stable for an alkene and is not normally described as an alkene at all. For example, whereas normal alkenes readily react with

■ This chemistry is discussed in Chapter 22.

bromine to give dibromoalkane *addition* products, benzene reacts with bromine only with difficulty—it needs a Lewis acid catalyst and then the product is a mono*substituted* benzene and not an addition compound.

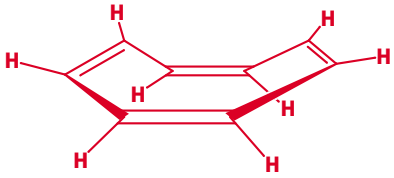


Bromine reacts with benzene in a substitution reaction (a bromine atom replaces a hydrogen atom), *keeping the benzene structure intact*. This ability to retain its ring structure through all sorts of chemical reactions is one of the important differences of benzene compared to alkenes and one that originally helped to define the class of aromatic compounds to which benzene belongs.


cyclooctatetraene

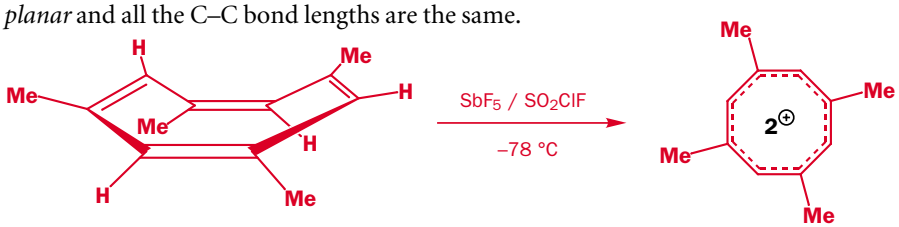
Cyclooctatetraene has four double bonds in a ring. What do you think its structure will be?

You will probably be surprised to find cyclooctatetraene (COT for short), unlike benzene, is *not* planar. Also *none* of the double bonds are conjugated—there are indeed alternate double and single bonds in the structure but conjugation is possible only if the p orbitals of the double bonds can overlap; here they do not. Since there is no conjugation, there are two C–C bond lengths in cyclooctatetraene—146.2 and 133.4 pm—which are typical for single and double C–C bonds. If possible, make a model of cyclooctatetraene for yourself—you will find the compound naturally adopts the shape below. This shape is often called a 'tub'.



Chemically, cyclooctatetraene behaves like an alkene not like benzene. Bromine, for example, does not form a substitution product but an addition product. There is something strange going on here—why is benzene so different from other alkenes and why is cyclooctatetraene so different from benzene? The mystery deepens when we look at what happens when we treat cyclooctatetraene with powerful oxidizing or reducing agents.

If 1,3,5,7-tetramethylcyclooctatetraene is treated at low temperature (–78 °C) with SbF_5/SO_2ClF (strongly oxidizing conditions) a dication is formed. This cation, unlike the neutral compound, is *planar* and all the C–C bond lengths are the same.

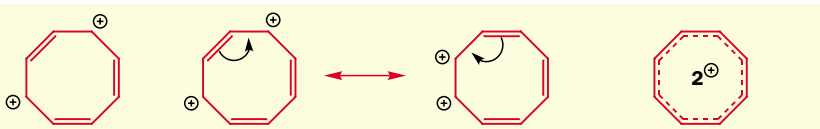


neutral compound is tub-shaped

dication is planar

Drawing the dication

The dication still has the same number of atoms as the neutral species only fewer electrons. Where have the electrons been taken from? The π system now has two electrons less. We could draw a structure showing two localized positive charges but this would not be ideal since the charge is spread over the whole ring system.



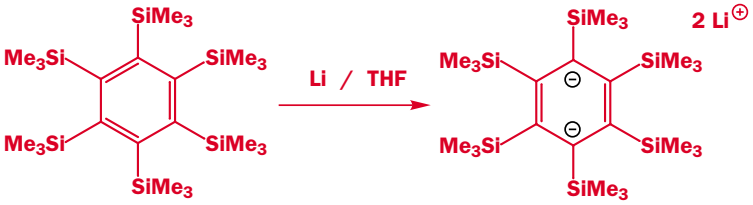
one structure with localized charges

the charges can be delocalized all round the ring

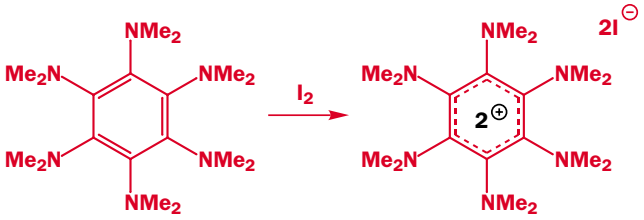
structure to show equivalence of all the carbon atoms

It is also possible to *add* electrons to cyclooctatetraene by treating it with alkali metals and a di*anion* results. X-ray structures reveal this dianion to be planar, again with all C–C bond lengths the same (140.7 pm). The difference between the anion and cation of cyclooctatetraene on the one hand and cyclooctatetraene on the other is the number of electrons in the π system. The cation has six π electrons, the anion has ten, but neutral cyclooctatetraene has eight.

Substituted benzene compounds, such as the one below with six silicon atoms around the edge, can also react with lithium to give a dianion. This dianion, with eight π electrons, is now no longer planar.



Treatment of benzene itself with the strongly oxidizing SbF_5/SO_2ClF reagent has no effect but it is possible to oxidize substituted derivatives. Hexakis(dimethylamino)-benzene, for example, can be oxidized with iodine. Again, the resulting dication is nonplanar and all the C–C bond lengths are not the same.



Do you see a pattern forming? The important point is not the number of conjugated atoms but the *number of electrons in the π system*. When they have 4 or 8 π electrons, both benzene and cyclooctatetraene adopt nonplanar structures; when they have 6 or 10 π electrons, a planar structure is preferred.

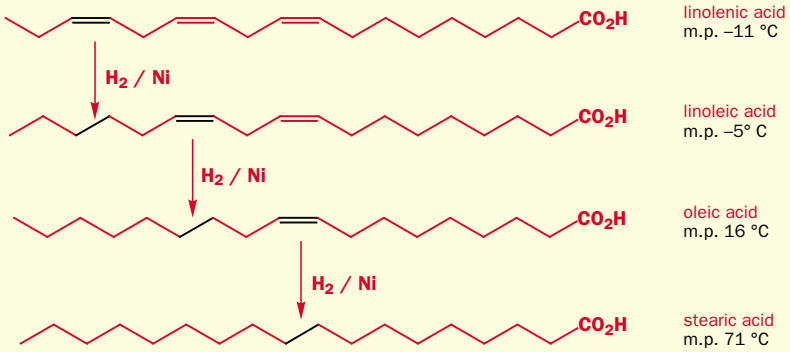
If you made a model of cyclooctatetraene, you might have tried to force it to be flat. If you managed this you probably found that it didn't stay like this for long and that it popped back into the tub shape. The strain in planar COT can be overcome by the molecule adopting the tub conformation. The strain is due to the numbers of atoms and double bonds in the ring—it has nothing to do with the number of electrons. The planar dication and dianion of COT still have this strain. The fact that these ions do adopt planar structures must mean there is some other form of stabilization that outweighs the strain of being planar. This extra stabilization is called **aromaticity**.

Heats of hydrogenation of benzene and cyclooctatetraene

It is possible to reduce unsaturated C=C double bonds using hydrogen gas and a catalyst (usually nickel or palladium) to produce fully saturated alkanes. This process is called hydrogenation and it is exothermic (that is, energy is released) since a thermodynamically more stable product, an alkane, is produced.

Margarine manufacture

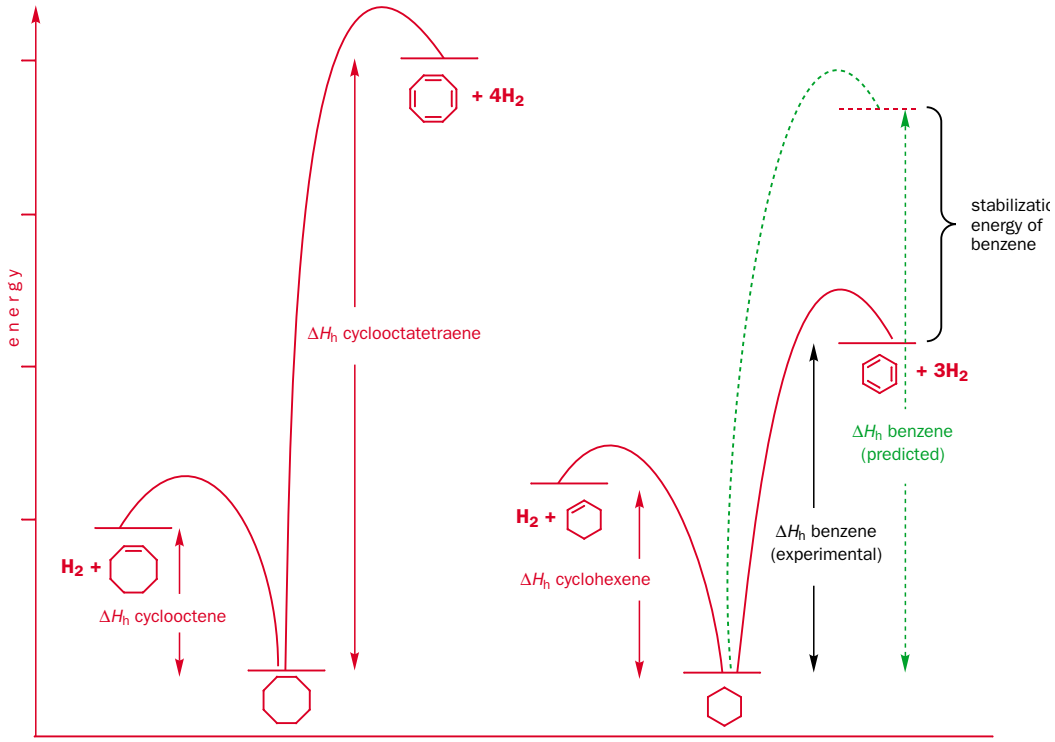
This reaction is put to good use in the manufacture of margarines. One of the ingredients in many margarines is hydrogenated vegetable oil. When polyunsaturated fats are hydrogenated they become more solid. This means that, rather than having to pour our margarine on to our toast in the morning, we can spread it. We saw the second acid in this series, linoleic acid, at the start of Chapter 2.



melting points (m.p.s) of some common fatty acids

When *cis*-cyclooctene is hydrogenated, 96 kJ mol^{-1} of energy is released. Cyclooctatetraene releases 410 kJ mol^{-1} on hydrogenation. This value is approximately four times one double

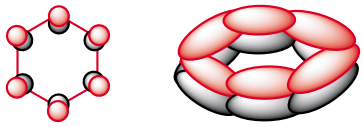
bond's worth, as we might expect. However, whereas the heat of hydrogenation for cyclohexene is 120 kJ mol^{-1}, on hydrogenating benzene, only 208 kJ mol^{-1} is given out, which is much less than the 360 kJ mol^{-1} that we would have predicted. This is shown in the energy level diagram below.



Benzene has six π molecular orbitals

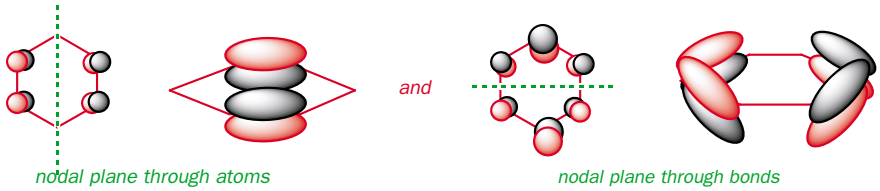
The difference between the amount of energy we expect to get out on hydrogenation (360 kJ mol^{-1}) and what is observed (208 kJ mol^{-1}) is about 150 kJ mol^{-1}. This represents a crude measure of just how extra stable benzene really is relative to what it would be like with three localized double bonds.

In order to understand the origin of this stabilization, we must look at the molecular orbitals. We can think of the π molecular orbitals of benzene as resulting from the combination of the six p orbitals. We have already encountered the molecular orbital lowest in energy with all the orbitals combining in-phase.



the lowest energy MO for benzene has all the p orbitals combining in-phase

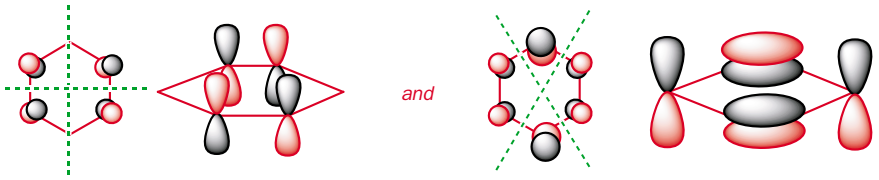
The next lowest molecular orbital will have one nodal plane. How can we divide up the six atoms symmetrically with one nodal plane? There are two ways depending on whether or not the nodal plane passes through a bond or an atom.



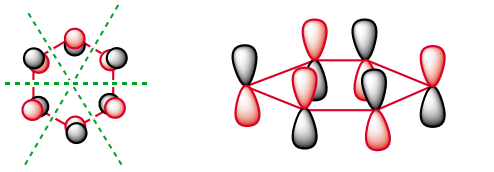
there are two ways of symmetrically dividing the six carbon atom one has a node through two atoms, the other through two C–C bonds

It turns out that these two different molecular orbitals both have exactly the same energy, that is, they are **degenerate**. This isn't obvious from looking at them but, nevertheless, it is so.

The next molecular orbital will have two nodal planes and again there are two ways of arranging these, which lead to two degenerate molecular orbitals.



with two nodal planes, there are again two possible molecular orbitals



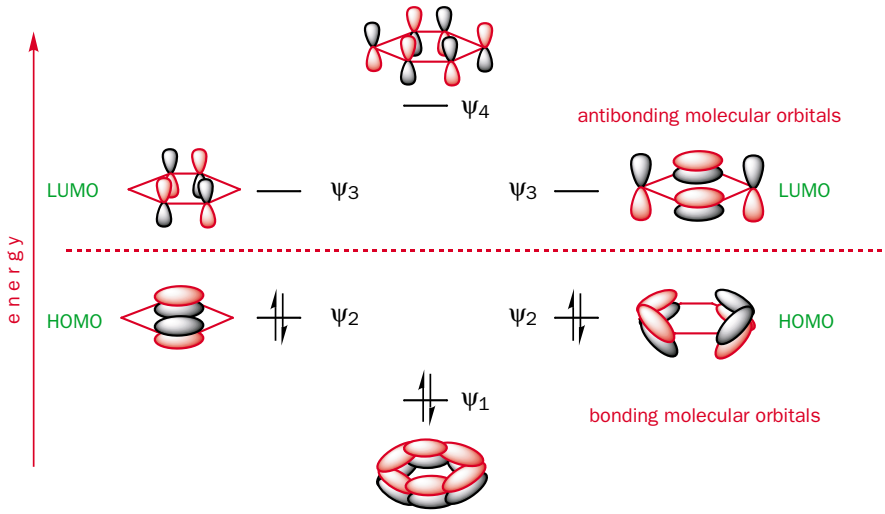
the MO highest in energy has all p orbitals combining out-of-phase

The final molecular orbital will have three nodal planes, which must mean all the p orbitals combining out-of-phase.

These then are the six π molecular orbitals for benzene. We can draw an energy level diagram to represent them.

Benzene model

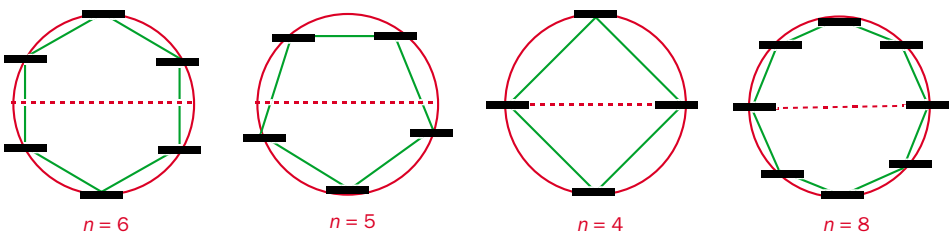
Whilst the HOMOs for benzene are the degenerate π molecular orbitals (Ψ_2), the next molecular orbital down in energy is not actually the π molecular orbital (Ψ_1). This all-bonding π molecular orbital (Ψ_1) is so stable that *four* σ bonding molecular orbitals actually come in between the π molecular Ψ_1 and Ψ_2 orbitals but are not shown in this molecular orbital energy level diagram. The greatest contribution to stability comes from this lowest-energy π bonding molecular orbital (Ψ_1). This allows bonding interactions between all adjacent atoms. Theory tells us that the energy of this orbital is $\alpha + 2\beta$ whilst that of the degenerate bonding molecular orbitals is $\alpha + \beta$. When all these bonding molecular orbitals are fully occupied, the total energy of the electrons is $6\alpha + 8\beta$, which is 2β lower in energy than we would predict for three localized double bonds. Butadiene had a theoretical stabilization energy of just 0.48β relative to two isolated double bonds so 2β is really quite significant.



the π molecular orbitals for benzene. The dashed line represents the energy of an isolated p orbital
all orbitals below this line are bonding, all above it are antibonding.
Benzene has six electrons in its π system so all the bonding MOs are fully occupied

The π molecular orbitals of conjugated cyclic hydrocarbons can be easily predicted

Notice that the layout of the energy levels is a regular hexagon with its apex pointing downwards. It turns out that the energy level diagram for the molecular orbitals resulting from the combination of *any* regular cyclic arrangement of p orbitals can be deduced from the appropriately sided polygon. If we take a regular polygon with one corner pointing downwards and draw a circle round it so that all the corners touch the circle, the energies of the molecular orbitals will be where the corners touch the circle. The circles should be of the same size and the polygons fitted inside the circle. The horizontal diameter represents the energy of a carbon p orbital and so, if any energy levels are on this line, they must be nonbonding. All those below are bonding; all those above antibonding.



— = energy level of MO relative to energy of p orbital indicated by dashed line

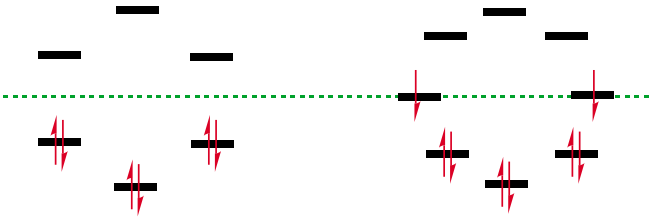
n = number of carbon atoms in ring

Notes on these energy level diagrams:

- This method predicts the energy levels for the molecular orbitals of planar, monocyclic, arrangements of identical atoms (usually all C) only
- The dashed line represents an energy level α and in each case the circle radius is 2β
- There is always one single molecular orbital lower in energy than all the others (at energy $\alpha + 2\beta$). This is because there is always one molecular orbital where all the p orbitals combine in-phase
- If there are an even number of atoms, there is also a single molecular orbital highest in energy; otherwise there will be a pair of degenerate molecular orbitals highest in energy
- All the molecular orbitals come in degenerate pairs except the one lowest in energy and, for even-numbered systems, the one highest in energy

Now we can begin to put all the pieces together and make sense of what we know so far. Let us compare the energy level diagrams for benzene and planar cyclooctatetraene. We are not concerned with the actual shapes of the molecular orbitals involved, just the energies of them.

▶ Of course, this isn't the molecular orbital energy level diagram for real cyclooctatetraene since COT is not planar but tub-shaped.



MO level diagram for benzene

MO level diagram for *planar* cyclooctatetraene

Benzene has six π electrons, which means that all its bonding molecular orbitals are fully occupied giving a closed shell structure. COT, on the other hand, has eight electrons. Six of these fill up the bonding molecular orbitals but there are two electrons left. These must go into the degenerate pair of nonbonding orbitals. Hund's rule (Chapter 4) would suggest one in each. Therefore this planar structure for COT would not have the closed shell structure that benzene has—it must either lose or gain two electrons in order to have a closed shell structure with all the electrons in bonding orbitals. This is exactly what we have already seen—both the dianion and dication are planar, allowing delocalization all over the ring, whereas neutral COT adopts a nonplanar tub shape with localized bonds.

Hückel's rule tells us if compounds are aromatic

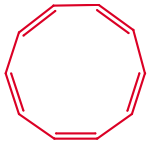
Using this simple method to work out the energy level diagrams for other rings, we find that there is always a single low-energy bonding orbital (composed of all p orbitals combining in-phase) and then pairs of degenerate orbitals. Since the single orbital will hold two electrons when full and the degenerate pairs four, we shall have a closed shell of electrons in these π orbitals only when they contain $2 + 4n$ electrons (n is an integer 0, 1, 2, etc.). This is the basis of Hückel's rule.

■ This is not a strict definition of aromaticity. It is actually very difficult to give a concise definition. Hückel's rule is certainly a good guide but also important is the extra stability of the compound (shown, for example, in resistance to changes to its π system) and low reactivity towards electrophiles. Perhaps the best indication as to whether or not a compound is aromatic is the proton NMR spectrum. The protons attached to an aromatic ring are further downfield than would otherwise be expected (Chapter 11).

● Hückel's rule

Planar, fully conjugated, monocyclic systems with $(4n + 2)$ π electrons have a closed shell of electrons all in bonding orbitals and are exceptionally stable. Such systems are said to be aromatic.

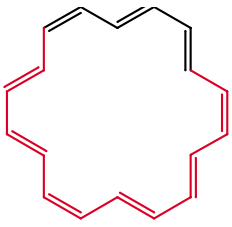
Analogous systems with $4n$ π electrons are described as anti-aromatic



all-*cis*-[10]annulene

That the π system is fully conjugated and planar are important conditions for aromaticity. The next $(4n + 2)$ number after six is ten so we might expect this cyclic alkene to be aromatic.

If this annulene with five *cis* double bonds were planar, each internal angle would be 144°. Since a normal double bond has bond angles of 120°, this would be far from ideal. This compound can be made but it does *not* adopt a planar conformation and therefore is not aromatic even though it has ten π electrons. By contrast, [18]annulene, which is also a $(4n + 2)$ π electron system ($n = 4$), does adopt a planar conformation and *is* aromatic (as shown by proton



[18]-annulene

▶ **Annulenes** (meaning ring alkenes) are compounds with alternating double and single bonds. The number in brackets tells us how many carbon atoms there are in the ring. Using this nomenclature, you could call benzene [6]annulene and cyclooctatetraene [8]annulene—but don't.

NMR). Note the *trans–trans–cis* double bonds: all bond angles can be 120°. [20]annulene presumably could become planar (it isn't quite) but since it is a 4n p electron system rather than a 4n + 2 system, it is not aromatic and the structure shows localized single and double bonds.

The importance of the system being monocyclic is less clear. The problem that often arises is 'exactly how do we count the π electrons?'. Taking a simple example, should we consider naphthalene as two benzene rings joined together or as a ten π electron system?



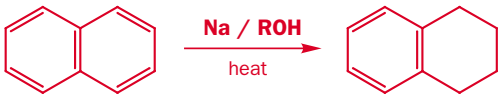
should we count naphthalene as two benzene rings or one large ring with 10 π electrons?

1,6-Methano[10]annulene is rather like naphthalene but with the middle bond replaced by a methylene bridging group. This compound is almost flat (carbons 1 and 6 are raised slightly out of the plane) and shows aromatic character.

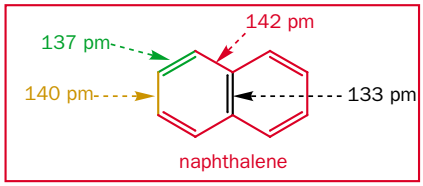


1,6-methano[10]annulene

From its chemistry, it is very clear that naphthalene is aromatic but perhaps a little less so than benzene itself. For example, naphthalene can easily be reduced to tetralin (1,2,3,4-tetrahydronaphthalene) which still contains a benzene ring. Also, in contrast to benzene, all the bond lengths in naphthalene are not the same.



naphthalene tetralin

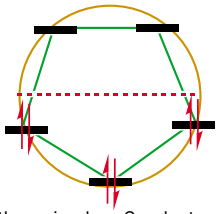


naphthalene

Hückel's rule is very useful and it helps us to predict and understand the aromatic stability of numerous other systems. Cyclopentadiene, for example, has two double bonds that are conjugated but the whole ring is not conjugated since there is a methylene group in the ring. However, this compound is relatively easy to deprotonate (see next chapter, p. 000) to give a very stable anion in which all the bond lengths are the same. How many electrons does this system have? Each of the double bonds contributes two electrons and the negative charge (which must be in a p orbital to complete the conjugation) contributes a further two making six altogether. The energy level diagram shows us that six π electrons completely fill the bonding molecular orbitals thereby giving a stable structure.



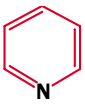
deprotonation of cyclopentadiene gives the stable cyclopentadienyl anion



the anion has 6π electrons completely filling the bonding MOs

Aromatic heterocyclic compounds

So far all the aromatic compounds you have seen have been hydrocarbons. However, most aromatic systems are **heterocyclic**—that is, involving atoms other than carbon and hydrogen. A simple example is pyridine.

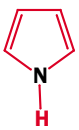


pyridine

In this structure a nitrogen replaces one of the CH groups in benzene. The ring still has three double bonds and thus six π electrons. Consider the structure shown below, pyrrole. This is also aromatic but how can we count six π electrons?

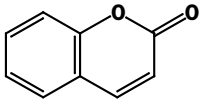
In the cyclopentadiene ring above, there were also two double bonds and on deprotonation one carbon could formally contribute the other two electrons needed for aromaticity. In pyrrole the nitrogen's lone pair can make up the six π electrons needed for the system to be aromatic.

We are really just beginning to scratch the surface of aromatic chemistry. You will meet many aromatic compounds in this book: in Chapter 22 we shall look at the chemistry of benzene and in Chapters 43 and 44 we shall discuss heterocyclic aromatic compounds. We shall finish off this chapter with a few more examples of some common aromatic compounds. In each case the aromatic part of the molecule—which may be one ring or several rings—is outlined in black.



pyrrole

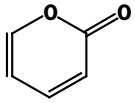
First, a compound released by many cut plants, especially grasses, with a fresh delightful smell usually called 'new mown hay'. Coumarin is also present in some herbs such as lavender. It contains a benzene ring and an α-pyrone fused together.



coumarin – the smell of 'new mown hay' also found in lavender

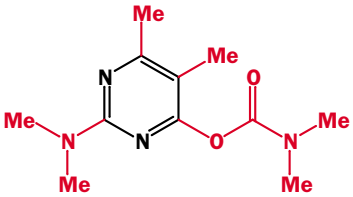


benzene

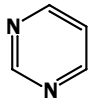


α-pyrone

Next, pirimicarb, a selective insecticide that kills sap-sucking aphid pests but does not affect the useful predators such as ladybirds (ladybugs) that eat them. It contains a pyrimidine ring—a benzene ring with two nitrogen atoms.

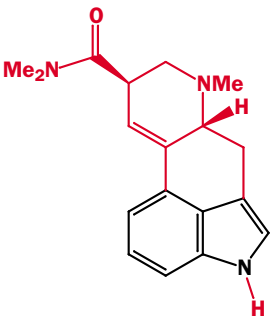


pirimicarb – a selective insecticide which kills aphids but not ladybirds



pyrimidine

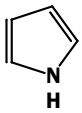
LSD stands for LySergic acid Diethylamide. It is the hallucinogenic drug 'acid'. When people walk off a building claiming that they can fly, they are probably on acid. It contains an indole ring made up of a benzene ring and a pyrrole ring fused together.



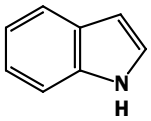
LSD, lysergic acid diethylamide, the infamous 'acid' giving hallucinations and unfounded confidence in flying



benzene

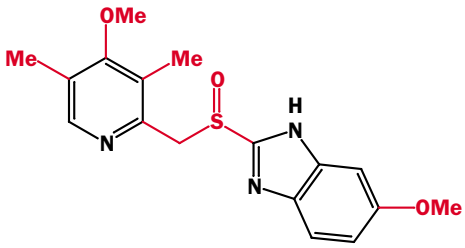


pyrrole

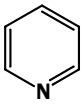


indole

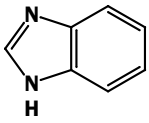
The world's best selling medicine in 1998 was Omeprazole, an antiulcer drug from Astra. It prevents excess acid in the stomach and allows the body to heal ulcers. It contains a pyridine ring and a benzimidazole ring, two aromatic heterocycles.



Omeprazole
Astra's best selling antiulcer drug

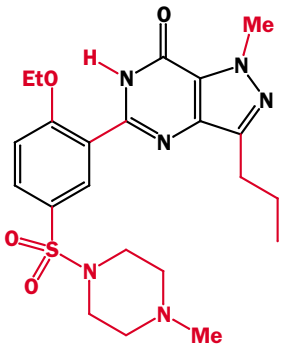


pyridine

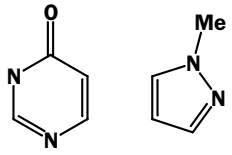


benzimidazole

The drug in the news in 1999 was Viagra, Pfizer's cure for male impotence. In the first three months after its release in 1998, 2.9 million prescriptions were issued for Viagra. It contains a simple benzene ring and a more complex heterocyclic system, which can be divided into two aromatic heterocyclic rings.



Viagra
Pfizer's treatment
for male impotence
(male erectile dysfunction)

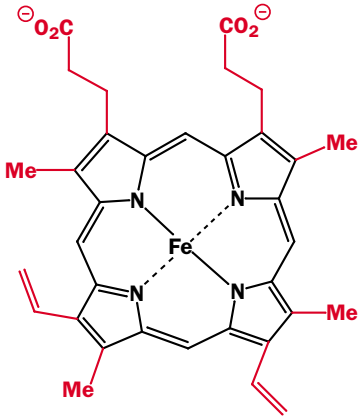


pyrimidone pyrazole

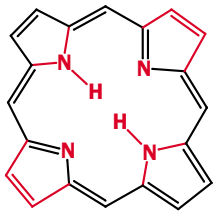


benzene

Finally, the iron compound haem, part of the haemoglobin molecule we use to carry oxygen around in our bloodstream. It contains the aromatic porphyrin ring system with its eighteen electrons arranged in annulene style. Chlorophyll, mentioned earlier in this chapter, has a similar aromatic ring system.



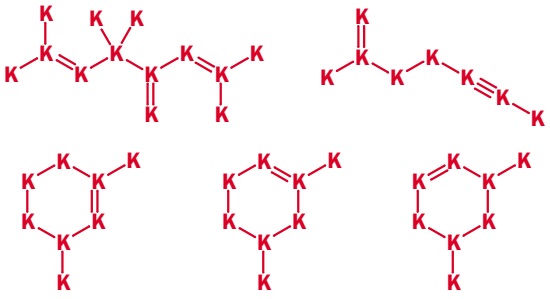
haem – part of the haemoglobin that
transports oxygen in the blood



porphyrin or porphin
one 18 π electron ring is shown in black.
Others are possible

Problems

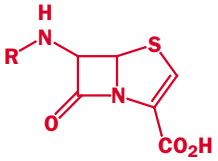
1. Are these molecules conjugated? Explain your answer in any reasonable way.



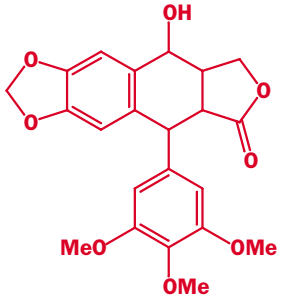
2. Draw a full orbital diagram for all the bonding and antibonding π orbitals in the three-membered cyclic cation shown here. The molecule is obviously very strained. Might it survive by also being aromatic?



3. How extensive are the conjugated systems in these molecules?



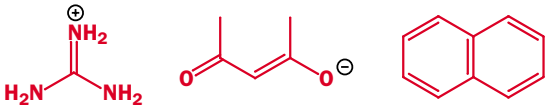
a β-lactam antibiotic



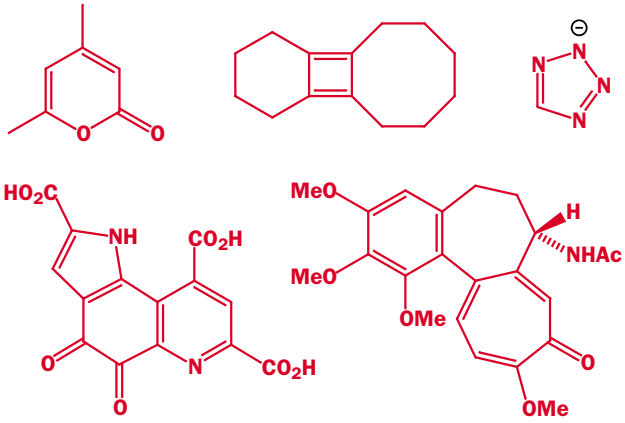
the anti-cancer compound
podophyllotoxin

4. Draw diagrams to illustrate the conjugation present in these molecules. You should draw three types of diagram: (**a**) conjugation arrows to give at least two different ways of representing the molecule joined by the correct 'reaction' arrow; (**b**) a diagram with dotted lines and partial charges (if any) to show the double bond and charge distribution (if any); and (**c**) a diagram of the

atomic orbitals that make up the lowest-energy bonding molecular orbital.

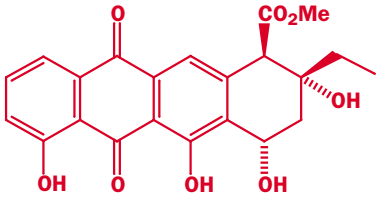


5. Which of these compounds are aromatic? Justify your answer with some electron counting. You are welcome to treat each ring separately or two or more rings together, whichever you prefer.

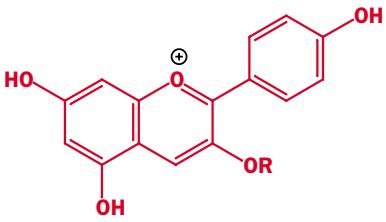


methoxatin: co-enzyme from bacteria living on methane

colchicine: compound from Autumn crocus used to treat gout

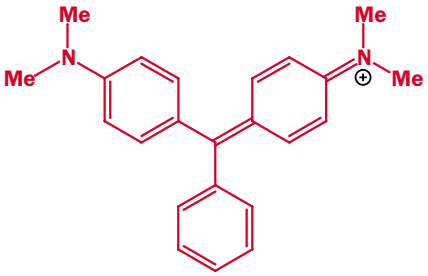


aklavinone: a tetracycline antibiotic

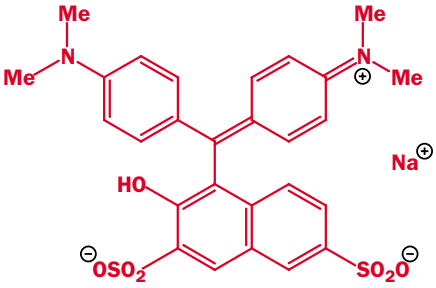


callistephin: natural red flower pigment

6. A number of water-soluble pigments in the green/blue/violet ranges used as food dyes are based on cations of the type shown here. Explain why the general structure shows such long wavelength absorption and suggest why the extra functionality (OH group and sulfonate anions) is put into 'CI food green 4' a compound approved by the EU for use in food under E142.



general structure for water soluble food dye in the green/blue/violet range



green food dye 'CI food green 4' [E142]

7. Turn to Chapter 1 and look at the structures of the dyes in the shaving foam described on p. 000. Comment on the structures in comparison with those in Problem 6 and suggest where they get their colour from and why they too have extra functional groups. Then turn to the beginning of Chapter 1 (p. 000) and look at the structures of the compounds in the 'spectrum of molecules'. Can you see what kind of absorption leads to each colour? You will want to think about the conjugation in each molecule but you should not expect to correlate structures with wavelengths in any even roughly quantitative way.

8. Go through the list of aromatic compounds at the end of the chapter and see how many electrons there are in the rings taken separately or taken together (if they are fused). Are all the numbers of the $(4n + 2)$ kind?

Acidity, basicity, and pK_a

8

Connections

Building on:

- Conjugation and molecular stability ch7
- Curly arrows represent delocalization and mechanisms ch5
- How orbitals overlap to form conjugated systems ch4

Arriving at:

- Why some molecules are acidic and others basic
- Why some acids are strong and others weak
- Why some bases are strong and others weak
- Estimating acidity and basicity using pH and pK_a
- Structure and equilibria in proton-transfer reactions
- Which protons in more complex molecules are more acidic
- Which lone pairs in more complex molecules are more basic
- Quantitative acid/base ideas affecting reactions and solubility
- Effects of quantitative acid/base ideas on medicine design

Looking forward to:

- Acid and base catalysis in carbonyl reactions ch12 & ch14
- The role of catalysts in organic mechanisms ch13
- Making reactions selective using acids and bases ch24

Note from the authors to all readers

This chapter contains physical data and mathematical material that some readers may find daunting. Organic chemistry students come from many different backgrounds since organic chemistry occupies a middle ground between the physical and the biological sciences. We hope that those from a more physical background will enjoy the material as it is. If you are one of those, you should work your way through the entire chapter. If you come from a more biological background, especially if you have done little maths at school, you may lose the essence of the chapter in a struggle to understand the equations. We have therefore picked out the more mathematical parts in boxes and you should abandon these parts if you find them too alien. We consider the general principles behind the chapter so important that we are not prepared to omit this essential material but you should try to grasp the principles without worrying too much about the equations. The ideas of acidity, basicity, and pK_a values together with an approximate quantitative feel for the strength and weakness of acids and bases are at least as central for biochemistry as they are for organic chemistry. Please do not be discouraged but enjoy the challenge.

Introduction

This chapter is all about acidity, basicity, and pK_a. Acids and bases are obviously important because many organic and biological reactions are catalysed by acids or bases, but what is pK_a and what use is it? pK_a tells us how acidic (or not) a given hydrogen atom in a compound is. This is useful because, if the first step in a reaction is the protonation or deprotonation of one of the reactants, it is obviously necessary to know where the compound would be protonated or deprotonated and what strength acid or base would be needed. It would be futile to use too weak a base to deprotonate a compound but, equally, using a very strong base where a weak one would do would be like trying to

crack open a walnut using a sledge hammer—you would succeed but your nut would be totally destroyed in the process.

The aim of this chapter is to help you to understand *why* a given compound has the pK_a that it does. Once you understand the trends involved, you should have a good feel for the pK_a values of commonly encountered compounds and also be able to predict the values for unfamiliar compounds.

Originally, a substance was identified as an acid if it exhibited the properties shown by other acids: a sour taste (the word acid is derived from the Latin *acidus* meaning 'sour') and the abilities to turn blue vegetable dyes red, to dissolve chalk with the evolution of gas, and to react with certain 'bases' to form salts. It seemed that all acids must therefore contain something in common and at the end of the eighteenth century, the French chemist Lavoisier erroneously proclaimed this common agent to be oxygen (indeed, he named oxygen from the Greek *oxus* 'acid' and *gennao* 'I produce'). Later it was realized that some acids, for example, hydrochloric acid, did not contain oxygen and soon hydrogen was identified as the key species. However, not all hydrogen-containing compounds are acidic, and at the end of the nineteenth century it was understood that such compounds are acidic only if they produce hydrogen ions H^+ in aqueous solution—the more acidic the compound, the more hydrogen ions it produces. This was refined once more in 1923 by J.N. Brønsted who proposed simple definitions for acids and bases.

■ Other definitions of acids and bases are useful, the most notable being those of Lewis, also proposed in 1923. However, for this chapter, the Brønsted definition is entirely adequate.

Brønsted definitions of acids and bases

- An acid is a species having a tendency to lose a proton
- A base is a species having a tendency to accept a proton

Acidity

An isolated proton is incredibly reactive—formation of H_3O^+ in water

Hydrochloric acid is a strong acid: the free energy $\Delta G°$ for its ionization equilibrium in water is –40 kJ mol^{-1}.

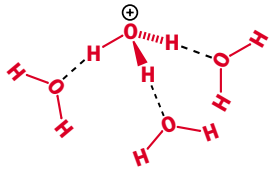
$$HCl\,(aq) \rightleftharpoons H^+\,(aq) + Cl^-\,(aq) \qquad \Delta G°_{298K} = -40\ kJ\ mol^{-1}$$

Such a large negative $\Delta G°$ value means that the equilibrium lies well over to the right. In the gas phase, however, things are drastically different and $\Delta G°$ for the ionization is +1347 kJ mol^{-1}.

$$HCl\,(g) \rightleftharpoons H^+\,(g) + Cl^-(g) \qquad \Delta G°_{298K} = +1347\ kJ\ mol\text{-}1$$

This $\Delta G°$ value corresponds to 1 molecule of HCl in 10^{240} being dissociated! This means that HCl does not spontaneously ionize in the gas phase—it does not lose protons at all. Why then is HCl such a strong acid in water? The key to this problem is, of course, the water. In the gas phase we would have to form an isolated proton (H^+, hydrogen ion) and chloride ion and this is energetically very unfavourable. In contrast, in aqueous solution the proton is strongly attached to a water molecule to give the very stable **hydronium ion**, H_3O^+, and the ions are no longer isolated but solvated. Even in the gas phase, adding an extra proton to neutral water is highly exothermic.

$$H_2O\,(g) + H^+\,(g) \longrightarrow H_3O^+\,(g) \qquad \Delta H° = -686\ kJ\ mol^{-1}$$



a structure for a solvated hydronium ion in water the dashed bonds represent hydrogen bonds

In fact, an isolated proton is so reactive that it will even add on to a molecule of methane in the gas phase to give CH_5^+ in a strongly exothermic reaction (you have already encountered this species in mass spectrometry on p. 52). We are therefore extremely unlikely to have a naked proton in the gas phase and certainly *never* in solution. In aqueous solution a proton will be attached to a water molecule to give a hydronium ion, H_3O^+ (sometimes called a hydroxonium ion). This will be solvated just as any other cation (or anion) would be and hydrogen bonding gives rise to such exotic species as $H_9O_4^+$ ($H_3O^+{\cdot}3H_2O$) shown here.

Every acid has a conjugate base

In water, hydrogen chloride donates a proton to a water molecule to give a hydronium ion and chloride ion, both of which are strongly solvated.

$$HCl\ (aq) + H_2O\ (l) \rightleftharpoons H_3O^+\ (aq) + Cl^-(aq)$$

In this reaction water is acting as a base, according to our definition above, by accepting a proton from HCl which in turn is acting as an acid by donating a proton. If we consider the reverse reaction (which is admittedly insignificant in this case since the equilibrium lies well over to the right), the chloride ion accepts a proton from the hydronium ion. Now the chloride is acting as a base and the hydronium ion as an acid. The chloride ion is called the **conjugate base** of hydrochloric acid and the hydronium ion, H_3O^+, is the **conjugate acid** of water.

● **For any acid and any base**

$$AH + B \rightleftharpoons BH^+ + A^-$$

where AH is an acid and A^- is its conjugate base and B is a base and BH^+ is its conjugate acid, that is, ***every acid has a conjugate base associated with it and every base has a conjugate acid associated with it.***

For example, with ammonia and acetic acid

$$CH_3COOH + NH_3 \rightleftharpoons NH_4^+ + CH_3COO^-$$

the ammonium ion, NH_4^+, is the conjugate acid of the base ammonia, NH_3, and the acetate ion, CH_3COO^-, is the conjugate base of acetic acid, CH_3COOH.

Water can behave as an acid or as a base

If a strong acid is added to water, the water acts as a base and is protonated by the acid to become H_3O^+. If we added a strong base to water, the base would deprotonate the water to give hydroxide ion, OH^-, and here the water would be acting as an acid. Such compounds that can act as either an acid or a base are called **amphoteric**.

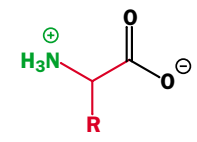
With a strong enough acid, we can protonate almost anything and, likewise, with a strong enough base we can deprotonate almost anything. This means that, to a certain degree, all compounds are amphoteric. For example, hydrochloric acid will protonate acetic acid.



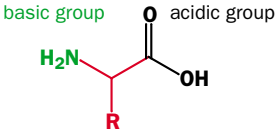
In this example acetic acid is acting as a base! Other compounds need acids even stronger than HCl to protonate them. Remember that, in chemical ionization mass spectrometry (p. 52), protonated methane, CH_5^+, was used to protonate whatever sample we put in to the machine in order to give us a cation; CH_5^+ is an incredibly strong acid.

The amino acids you encountered in Chapter 2 are amphoteric. Unlike water, however, these compounds have separate acidic and basic groups built into the same molecule.

When amino acids are dissolved in water, the acidic end protonates the basic end to give a species with both a positive and a negative charge on it. A neutral species that contains both a positive and a negative charge is called a **zwitterion**.



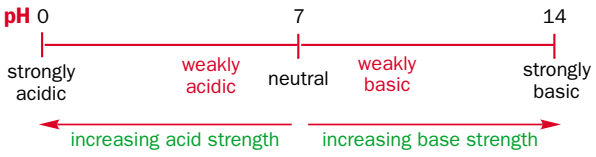
an amino acid zwitterion



How the pH of a solution depends on the concentration of the acid

You are probably already familiar with the pH scale: acidic solutions all have a pH of less than 7—the lower the pH the more acidic the solution; alkaline solutions all have pHs greater than 7—the higher the pH, the more basic the solution. Finally, pH 7 is neither acidic nor alkaline but neutral.

The pH of a solution is only a measure of the acidity of the solution; it



tells us nothing about how strong one acid might be relative to another. The pH of a solution of a given acid varies with its concentration: as we dilute the solution, the acidity falls and the pH increases. For example, as we decrease the concentration of HCl in an aqueous solution from 1 to 0.1 to 0.01 to 0.001 mol dm^{-3}, the pH changes from 0 to 1 to 2 to 3.

What a pH meter actually measures is the concentration of hydronium ions in the solution. The scale is a logarithmic one and is defined as

$$pH = -\log[H_3O^+]$$

Our solutions of HCl above therefore have hydronium ion concentrations of $[H_3O^+] = 10^0$, 10^{-1}, 10^{-2}, and 10^{-3} mol dm^{-3} respectively. Since the scale is logarithmic, a pH difference of 1 corresponds to a factor of 10 in hydronium ion concentration, a pH difference of 2 corresponds to a factor of 100, and so on.

The ionization of water

Pure water at 25 °C has a pH of 7.00. This means that the concentration of hydronium ions in water must be 10^{-7} mol dm^{-3} (of course, it is actually the other way round: the hydronium ion concentration in pure water is 10^{-7} mol dm^{-3}; hence its pH is 7.00). Hydronium ions in pure water can arise only from the self-dissociation or autoprotolysis of water.

$$H_2O + H_2O \rightleftharpoons H_3O^+(aq) + OH^-(aq)$$

■ Don't worry—water is still safe to drink despite all this acid and hydroxide in it! This is, of course, because the concentrations of hydronium and hydroxide ions are *very* small (10^{-7} mol dm^{-3} corresponds to about 2 parts per billion). This very low concentration means that there are not enough free hydronium (or hydroxide) ions in water either to do us any harm when we drink it, *or to catalyse chemical reactions*.

In this reaction, one molecule of water is acting as a base, receiving a proton from the other, which in turn is acting as an acid by donating a proton. From the equation we see that, for every hydronium ion formed, we must also form a hydroxide ion and so in pure water the concentrations of hydroxide and hydronium ions are equal.

$$[H_3O^+] = [OH^-] = 10^{-7} \text{ mol dm}^{-3}$$

The product of these two concentrations is known as the ionization constant of water, K_W (or as the ionic product of water, or maybe sometimes as the autoprotolysis constant, K_{AP})

$$K_W = [H_3O^+][OH^-] = 10^{-14} \text{ mol}^2 \text{ dm}^{-6} \text{ at } 25\,^\circ\text{C}$$

This is a constant in aqueous solutions, albeit a very, very small one. This means that, if we know the hydronium ion concentration, we also know the hydroxide concentration and vice versa since the product of the two concentrations always equals 10^{-14}.

For example

It is easy to work out the pH of a 0.1 M solution of sodium hydroxide,

$[NaOH] = 0.1$ M

and, since the sodium hydroxide is fully ionized, $[OH^-] = 0.1$ M but $[OH^-] \times [H_3O^+] = 10^{-14}$.

So

$$[H_3O^+] = \frac{10^{-14}}{0.1} = 10^{-13} \text{mol dm}^{-3}$$

$$pH = -\log[H_3O^+] = -\log(10^{-13}) = 13$$

How the pH of a solution also depends on the acid in question

If we measured the pH of an aqueous solution of an organic acid and compared it to an equally concentrated solution of HCl, we would probably find the pHs different. For example, whilst 0.1M HCl has a pH of 1, the same concentration of acetic acid has a pH of 3.7 and is much less acidic. This can only mean that a 0.1M solution of acetic acid contains fewer hydronium ions than a 0.1M solution of HCl.

● **Aqueous hydrochloric acid (or any strong acid) has a lower pH than an equal concentration of aqueous acetic acid (or any weak acid) because it is more fully dissociated and thereby produces more hydronium ions.**

For hydrochloric acid, the equilibrium lies well over to the right: in effect, HCl is completely dissociated.

$$HCl(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + Cl^-(aq)$$

Acetic acid is not fully dissociated—the solution contains both acetic acid and acetate ions.

$$CH_3COOH\ (aq) + H_2O\ (l) \rightleftharpoons H_3O^+\ (aq) + CH_3COO^-\ (aq)$$

Acids as preservatives

Acetic acid is used as a preservative in many foods, for example, pickles, mayonnaise, bread, and fish products, because it prevents bacteria and fungi growing. However, its fungicidal nature is not due to any lowering of the pH of the foodstuff. In fact, it is the *undissociated* acid that acts as a bactericide and a fungicide in concentrations as low as 0.1–0.3%. Besides, such a low concentration has little effect on the pH of the foodstuff anyway.

Although acetic acid can be added directly to a foodstuff (disguised as E260), it is more common to add vinegar which contains between 10 and 15% acetic acid. This makes the product more 'natural' since it avoids the nasty 'E numbers'. Actually, vinegar has also replaced other acids used as preservatives, such as propionic (propanoic) acid (E280) and its salts (E281, E282, and E283).

The definition of pK_a

Now we need to be clearer about 'strong' and 'weak' acids. In order to measure the strength of an acid relative to water and find out how effective a proton donor it is, we must look at the equilibrium constant for the reaction

$$AH\ (aq) + H_2O\ (l) \rightleftharpoons H_3O^+\ (aq) + A^-\ (aq)$$

The position of equilibrium is measured by the equilibrium constant for this reaction K_{eq}.

$$K_{eq} = \frac{[H_3O^+][A^-]}{[AH][H_2O]}$$

The concentration of water remains essentially constant (at 55.56 mol dm^{-3}) with dilute solutions of acids wherever the equilibrium may be and a new equilibrium constant, K_a, is defined and called the **acidity constant**.

$$K_a = \frac{[H_3O^+][A^-]}{[AH]}$$

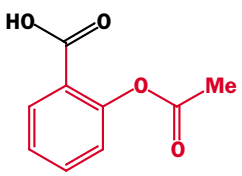
Like pH, this is also expressed in a logarithmic form, pK_a.

● pK_a = – log K_a

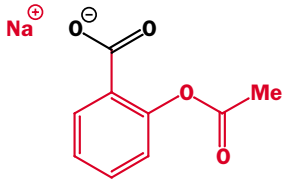
Because of the minus sign in this definition, the lower the pK_a, the larger the equilibrium constant, K_a, is and hence the stronger the acid. *The pK_a of the acid is the pH where it is exactly half dissociated.* At pHs above the pK_a, the acid HA exists as A$^-$ in water; at pHs below the pK_a, it exists as undissociated HA.

At pHs above the pK_a of the acid, it will also be more soluble in water. Hydrocarbons are insoluble in water—oil floats on water, for example. Unless a compound has some hydrophilic groups in it that can hydrogen bond to the water, it too will be insoluble. Ionic groups considerably increase a compound's solubility and so the ion A$^-$ is much more soluble in water than the undissociated acid HA. In fact water can solvate both cations and anions, unlike some of the solvents you will meet later. This means that we can increase the solubility of a neutral acid in water by increasing the proportion of its conjugate base present. All we need to do is raise the pH.

A simple example is aspirin: whilst the acid itself is not very soluble in water, the sodium salt is much more soluble (soluble aspirin is actually the sodium or calcium salt of 'normal' aspirin).



aspirin
not very soluble in water



the sodium (or calcium) salt of aspirin is more soluble in water

Conversely, if the pH of a solution is lowered, the amount of the acidic form present increases, and the solubility decreases. In the acidic environment of the stomach (around pH 1–2), soluble aspirin will be converted back to the normal acidic form and precipitate out of solution.

▶ How concentrated is water ? Very concentrated you may say—but the concentration is limited. We know that one mole of pure water has a mass of 18 g and occupies 18 cm^3. So, in one dm^3, there are 1000/18 = 55.56 mol. *You cannot get more concentrated water than this* (unless you did something drastic like taking it into a black hole!).

▶ This is how we can work out that the pK_a of the acid is the pH at which it is exactly half dissociated: we can rearrange the equation for K_a to give

$$[H_3O^+] = K_a \times \frac{[AH]}{[A^-]}$$

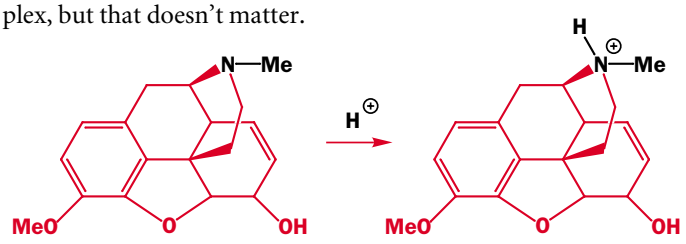
Taking minus the log of both sides gives us

$$pH = pK_a + \log\left(\frac{[A^-]}{[AH]}\right)$$

If the concentrations of acid AH and its conjugate base A$^-$ are equal, the term in brackets equals 1 and log (1) = 0 and so the pH simply equals the pK_a of the acid.

This means that, if we took a 0.1 M aqueous solution of acetic acid and raised its pH from 3.7 (its natural pH) to 4.76 (the pK_a of acetic acid) using dilute sodium hydroxide solution, the resultant solution would contain equal concentrations of acetic acid and acetate ion.

In the same way, organic bases such as amines can be dissolved by *lowering* the pH. Codeine (7,8-didehydro-4,5-epoxy-3-methoxy-17-methylmorphinan-6-ol) is a commonly used painkiller. Codeine itself is not very soluble in water but it does contain a basic nitrogen atom that can be protonated to give a more soluble salt. It is usually encountered as a phosphate salt. The structure is complex, but that doesn't matter.



neutral codeine
sparingly soluble in water

the conjugate acid is much more soluble in water

Charged compounds can be separated by acid–base extraction

Adjusting the pH of a solution often provides an easy way to separate compounds. Since weak acids form soluble anions at pHs above their pK_a values, this presents us with an easy method for extracting organic acids from mixtures of other compounds. For example, if we dissolve the mixture of compounds in dichloromethane (which is **immiscible** with water, that is, it will not mix with water but instead forms a separate layer) and 'wash' this solution with aqueous sodium hydroxide, any organic acids present will be converted to their water-soluble salts and dissolve into the water layer. We have extracted the organic acids into the aqueous layer. If we then separate and acidify the aqueous layer, the acid form, being less soluble in water, will precipitate out. If the acid form has a charge and the conjugate base is neutral as with amines, for example, now the cationic acid form will be more soluble in water than the conjugate base.

● Acid–base extraction

For a neutral weak organic acid HA

$$HA(aq) + H_2O \rightleftharpoons H_3O^{\oplus}(aq) + A^{\ominus}(aq)$$

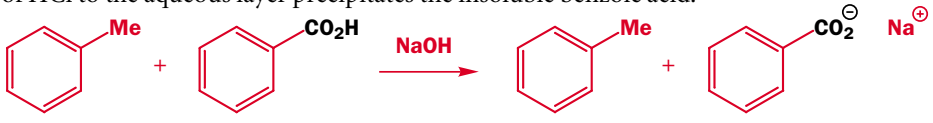
- **Anionic A^- is more soluble *in water* than the neutral acid HA**
- **Neutral acid HA is more soluble *in organic solvents* than anionic A^-**

For a neutral weak organic base B

$$HB^{\oplus}(aq) + H_2O \rightleftharpoons H_3O^{\oplus}(aq) + B(aq)$$

- **The cationic acid HB^+ is more soluble *in water* than the neutral conjugate base B**
- **The neutral conjugate base, B is more soluble *in organic solvents* than the cationic acid HB^+**

Separating a mixture of benzoic acid ($PhCO_2H$) and toluene (PhMe) is easy: dissolve the mixture in CH_2Cl_2, add aqueous NaOH, shake the mixture of solutions, and separate the layers. The CH_2Cl_2 layer contains all the toluene. The aqueous layer contains the sodium salt of benzoic acid. Addition of HCl to the aqueous layer precipitates the insoluble benzoic acid.



insoluble in water | insoluble in water | insoluble in water | soluble in water

In the same way, any basic compounds dissolved in an organic layer could be extracted by washing the layer with dilute aqueous acid and recovered by raising the pH, which will precipitate out the less soluble neutral compound.

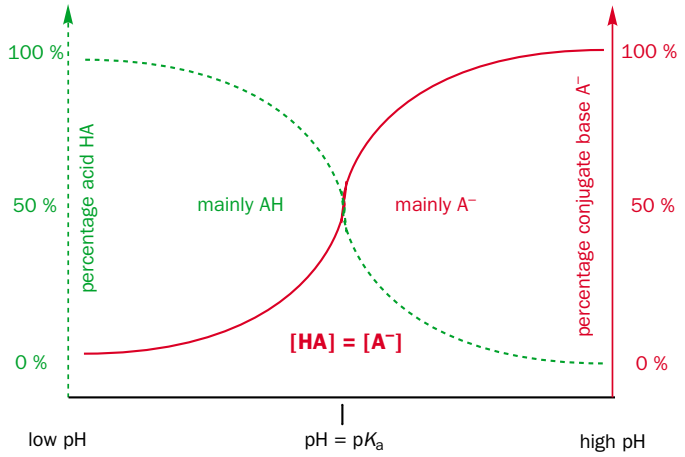
Whenever you do any extractions or washes in practical experiments, just stop and ask yourself: 'What is happening here? In which layer is my compound and why?' That way you will be less likely to throw the wrong layer (and your precious compound) away!

Benzoic acid preserves soft drinks

Benzoic acid is used as a preservative in foods and soft drinks (E210). Like acetic acid, it is only the acid form that is effective as a bactericide. Consequently, benzoic acid can be used as a preservative only in foodstuffs with a relatively low pH, ideally less than its pK_a of 4.2. This isn't usually a problem: soft drinks, for example, typically have a pH of 2–3. Benzoic acid is often added as the sodium salt (E211), perhaps because this can be added to the recipe as a concentrated solution in water. At the low pH in the final drink, most of the salt will be protonated to give benzoic acid proper, which presumably remains in solution because it is so dilute.

A graphical description of the pK_a of acids and bases

For both cases, adjusting the pH alters the proportions of the acid form and of the conjugate base. The graph plots the concentration of the free acid AH (green curve) and the ionized conjugate base A^- (red curve) as percentages of the total concentration as the pH is varied.



At low pH the compound exists entirely as AH and at high pH entirely as A^-. At the pK_a the concentration of each species, AH and A^-, is the same. At pHs near the pK_a the compound exists as a mixture of the two forms.

An acid's pK_a depends on the stability of its conjugate base

HCl is a much stronger acid than acetic acid: the pK_a of HCl is around –7 compared to 4.76 for acetic acid. This tells us that in solution K_a for hydrogen chloride is 10^7 mol dm^{-3} whilst for acetic acid it is only $10^{-4.76} = 1.74 \times 10^{-5}$ mol dm^{-3}. Why are the equilibria so different? Why does hydrogen chloride fully dissociate but acetic acid do so only partially?

$$HCl\ (aq) + H_2O\ (l) \rightleftharpoons H_3O^+\ (aq) + Cl^-\ (aq) \qquad K_a = 10^7$$

$$CH_3COOH\ (aq) + H_2O\ (l) \rightleftharpoons H_3O^+\ (aq) + CH_3COO^-\ (aq) \qquad K_a = 1.74 \times 10^{-5}$$

The answer must have something to do with the conjugate base A^- of each acid HA, since this is the only thing that varies from one acid to another. In both the equilibria above, water acts as a base by accepting a proton from the acid. For the hydrochloric acid equilibrium in the reverse direction, the chloride ion is not a strong enough base to deprotonate the hydronium ion. Acetate, on the other hand, is easily protonated by H_3O^+ to give neutral acetic acid, which means that acetate must be a stronger base than chloride ion.

Acid and conjugate base strength

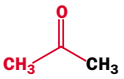
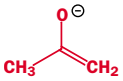
- The stronger the acid HA, the weaker its conjugate base, A^-
- The stronger the base A^-, the weaker its conjugate acid AH

For example, hydrogen iodide has a very low pK_a of –10. This means that HI is a strong enough acid to protonate most things. Its conjugate base, iodide ion, is therefore not very basic at all—in fact, we very rarely think of it as a base—it will not deprotonate anything. A very powerful base is methyllithium, MeLi. Here we effectively have CH_3^- (but see Chapter 9), which can accept a proton to become neutral methane, CH_4. Methane is therefore the conjugate acid in this case. Clearly, methane isn't at all acidic—its pK_a is about 48.

Table 8.1 gives a list of compounds and their approximate pK_a values.

Over the next few pages we shall be considering the reasons for these differences in acid strength but we are first going to consider the simple consequences of mixing acids or bases of different strength.

Table 8.1 The pK_a value of some compounds

Acid	pK_a	Conjugate base
HI	ca. –10	I^-
HCl	ca. –7	Cl^-
H_2SO_4	ca. –3	HSO_4^-
HSO_4^-	2.0	SO_4^{2-}
CH_3COOH	4.8	CH_3COO^-
H_2S	7.0	HS^-
NH_4^+	9.2	NH_3
C_6H_5OH	10.0	$C_6H_5O^-$
CH_3OH	15.5	CH_3O^-
	20.0	
	25	
NH_3	33	NH_2^-
C_6H_6	ca. 43	$C_6H_5^-$
CH_4	ca. 48	CH_3^-

The difference in pK_a values tells us the equilibrium constant between two acids or bases

If we have a mixture of two bases in a pot and we throw in a few protons, where will the protons end up? Clearly, this depends on the relative strengths of the bases—if they are equally strong, then the protons will be shared between them equally. If one base is stronger than the other, then this base will get more than its fair share of protons. If we put into our pot not two bases but one base and an acid, then it's exactly the same as putting in two bases and then adding some protons—the protons end up on the strongest base. Exactly how the protons are shared depends on the difference in strengths of the two bases, which is related to the difference in the pK_as of their conjugate acids.

▶ An alternative way of looking at this is that chloride ion is much happier being a chloride ion than acetate is being an acetate ion: *the chloride ion is fundamentally more stable than is the acetate ion.*

▶ Have a close look at Table 8.1 for there are some interesting points to notice.

- Look at the acids themselves—we have neutral, cationic, and even anionic acids
- Notice the range of different elements carrying the negative charge of the conjugate bases—we have iodine, chlorine, oxygen, sulfur, nitrogen, and carbon and many more are possible
- Most importantly, notice the vast range of pK_a values: from around –10 to 50. This corresponds to a difference of 10^{60} in the equilibrium constants and these are by no means the limits. Other compounds or intermediates can have pK_a values even greater or less than these.

In a mixture of two acids or two bases

- **The ratio of K_a values gives us an indication of the equilibrium constant for the reaction between a base and an acid**
- **The difference in pK_as gives us the log of the equilibrium constant.**

■ That the difference in pK_as gives the log of the equilibrium constant can easily be shown by considering, as an example, the equilibrium for the reaction between hydrogen sulfate and acetate.

$$HSO_4^- + CH_3OO^-(aq) \rightleftharpoons CH_3COOH(aq) + SO_4^{2-}$$

$$K_{eq} = \frac{[SO_4^{2-}][CH_3COOH]}{[HSO_4^-][CH_3COO^-]}$$

The equilibrium constant for this reaction is simply the K_a for the hydrogen sulfate equilibrium divided by the K_a for the acetic acid equilibrium.

$$K_{eq} = \frac{[SO_4^{2-}][CH_3COOH]}{[HSO_4^-][CH_3COO^-]} = \frac{[H_3O^+][SO_4^{2-}]}{[HSO_4^-]} \times \frac{[CH_3COOH]}{[H_3O^+][CH_3COO^-]}$$

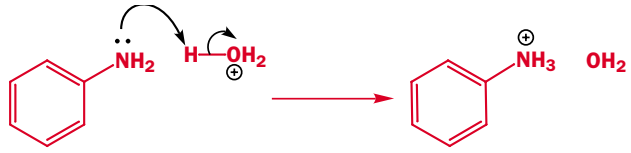
$$K_{eq} = K_a(HSO_4^-) \times \frac{1}{K_a(CH_3COOH)} = \frac{10^{-2}}{10^{-4.8}} = 10^{2.8} \approx 600$$

This tells us in our case that, if we mixed sodium hydrogen sulfate and sodium acetate in water, we would end up with mainly sodium sulfate and acetic acid, the equilibrium constant for the reaction above being approximately 600.

As an example, let us look at a method for acetylating aromatic amines in aqueous solution. This reaction has a special name—the Lumière–Barbier method. We shall consider the acetylation of aniline $PhNH_2$ (a basic aromatic amine) using acetic anhydride. The procedure for this reaction is as follows.

1 Dissolve one equivalent of aniline in water to which one equivalent of hydrochloric acid has been added.

Aniline is not soluble in water to any significant degree. This isn't surprising as aniline is just a hydrophobic hydrocarbon with an amine group. The HCl (pK_a –7) protonates the aniline (pK_a of the conjugate acid of aniline is 4.6) to give the hydrochloride. Now we have a salt that is very soluble in water.

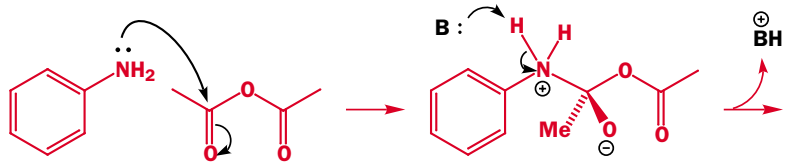


aniline
insoluble in water

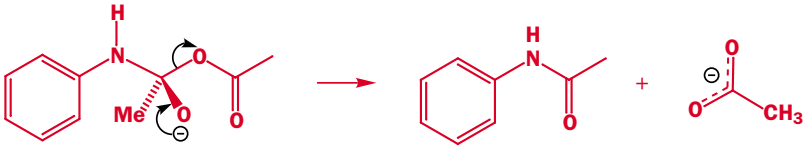
anilinium ion
soluble in water

2 Warm to 50°C and add 1.2 equivalents of acetic anhydride followed by 1.2 equivalents of aqueous sodium acetate solution.

The acetic anhydride could be attacked by either the water, the acetate, or by aniline itself. Aniline is much more nucleophilic than the other two nucleophiles but only aniline itself can attack the anhydride: *protonated aniline has no lone pair and is not nucleophilic.* This, then, is the role of the sodium acetate—to act as a base and deprotonate the aniline hydrochloride. The pK_as of the aniline hydrochloride and acetic acid are about the same, around 4.7. An equilibrium will be set up to give some neutral aniline which will then attack the acetic anhydride and form the amide.



aniline attacks π* of acetic anhydride — deprotonation of ammonium ion



acetate is a good leaving group — the product - an amide

3 Cool in ice and filter off crystals of product, acetanilide.

The product is insoluble in water and, because it is an amide, is much less basic than aniline (pK_a of conjugate acid < 0) and so is not protonated to give a water-soluble salt.

More from pK_as: Calculating the pK_a values for water acting as a base and as an acid

The material in this box is quite mathematical and may be skipped if you find it too alien.

How easy is it to protonate or deprotonate water?

All our reactions so far have been in water and it is easy to forget that water itself also competes for protons. If, for example, we have both sulfuric acid H_2SO_4 and hydrochloric acid HCl in aqueous solution, hydrochloric acid with its lower pK_a (–7) will not protonate the conjugate base of sulfuric acid (pK_a –3), hydrogen sulfate HSO_4^-: both acids will protonate water instead. So water is a stronger base than either chloride or hydrogen sulfate ions. In fact, we can work out the pK_a for the protonation of water.

We want to answer the questions: 'How easy is it to protonate water? What strength of acid do we need?'

Look at this simple reaction:

$$H_3O^+(aq) + H_2O(l) \rightleftharpoons H_2O(l) + H_3O^+(aq)$$

Obviously, the equilibrium constant for the equation above will be 1 since both sides of the equation are the same. But we don't use normal equilibrium constants—we use the acidity constant, K_a, which is slightly different. Remember that this is actually the normal equilibrium constant for the reaction multiplied by $[H_2O] = 55.56$, the 'concentration' of water. This is normally useful in that it cancels out the $[H_2O]$ term in the denominator but not in this case.

Here we have

$$K_a = K_{eq} \times [H_2O] = \frac{[H_2O][H_3O^+]}{[H_2O][H_3O^+]} \times [H_2O] = [H_2O] = 55.56$$

so the pK_a for the protonation of water is: $pK_a(H_3O^+) = -\log(55.56) = -1.74$.

The pK_a also equals the pH when we have equal concentrations of acid and conjugate base. A solution would be quite acidic if exactly half of the number of water molecules present were hydronium ions—its pH would be –1.74.

So with water acting as a base

$$AH(aq) + H_2O(l) \rightleftharpoons H_3O^+(aq) + A^-(aq)$$

It is clear that for any acid with a lower pK_a than –1.74, the equilibrium will lie over to the right.

- **Acids with a lower pKa than –1.74 will *protonate* water completely**

We can also work out the pK_a for water acting as an acid. Now the equilibrium is

$$H_2O(l) + H_2O(l) \rightleftharpoons H_3O^+(aq) + OH^-(aq)$$

Going through the same calculations as before, we find

$$K_a = K_{eq} \times [H_2O] = \frac{[H_3O^+][OH^-]}{[H_2O][H_2O]} \times [H_2O]$$

$$= \frac{K_{AP}}{[H_2O]} = \frac{10^{-14}}{55.56} = 1.80 \times 10^{-16}$$

so the pK_a for the *deprotonation* of water is: $pK_a(H_2O) = -\log(1.80 \times 10^{-16}) = 15.74$.

This means that, if we put in water a base whose conjugate acid's pK_a is greater than 15.74, it will simply be protonated by the water and give an equivalent amount of hydroxide ions.

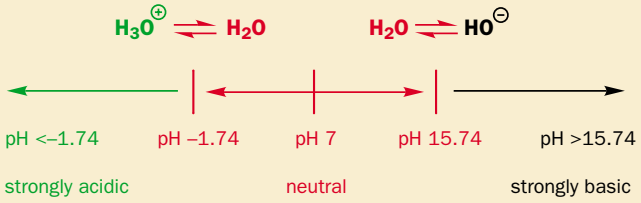
- **Bases B whose conjugate acid HB has a higher pK_a than 15.74 will *deprotonate* water completely**

■

Any sharp-eyed readers may notice an inconsistency in the statement that the pK_a equals the pH when we have equal concentrations of acid and conjugate base. If, when $[A^-] = [AH]$, the pK_a = pH, then the pK_a for water equals the pH when $[H_2O] = [H_3O^+]$. We *assume* that $[H_2O]$ is constant at 55.56 mol dm^{-3} and so $[H_3O^+]$ must also equal 55.56 mol dm^{-3} and hence pH = pK_a = –log(55.56). This assumption cannot be valid here: rather $[H_2O] + [H_3O^+]$ should equal approximately 55.56 mol dm^{-3}.

- **The strongest base in aqueous solution is OH^- and the strongest acid in aqueous solution is H_3O^+. Remember that:**
  - **Addition of stronger bases than OH^- just gives more OH^- by the deprotonation of water**
  - **Addition of stronger acids than H_3O^+ just gives more H_3O^+ by protonation of water**

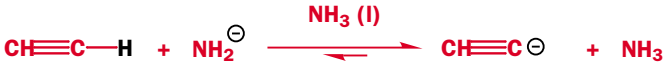
  Also remember that:
  - **The pH of pure water at 25°C is 7.00 (not the pK_a)**
  - **The pK_a of H_2O is 15.74**
  - **The pK_a of H_3O+ is –1.74**



The choice of solvent limits the pK_a range we can use

In water, our effective pK_a range is only –1.74 to 15.74, that is, it is determined by the solvent. This is known as the **levelling effect** of the solvent. This is an important point. It means that, if we want to remove the proton from something with a high pK_a, say 25–30, it would be impossible to do this in water since the strongest base we can use is hydroxide. If we do need a stronger base than OH^-, we must use a different solvent system.

For example, if we wanted to deprotonate ethyne (acetylene, pK_a 25), then hydroxide (the strongest base we could have in aqueous solution, pK_a 15.7) would establish an equilibrium where only 1 in $10^{9.3}$ ($10^{15.7}/10^{25}$) ethyne molecules were deprotonated. This means about 1 in 2 billion of our ethyne molecules will be deprotonated at any one time. Since, no matter what base we dissolve in water, we will only at best get hydroxide ions, this is the best we could do in water. So, in order to deprotonate ethyne to any appreciable extent, we must use a different solvent that does not have a pK_a less than 25. Conditions often used to do this reaction are sodium amide ($NaNH_2$) in liquid ammonia.



Using the pK_as of NH_3 (ca. 33) and ethyne (25) we would predict an equilibrium constant for this reaction of 10^8 ($10^{-25}/10^{-33}$)—well over to the right. Amide ions can be used to deprotonate alkynes.

▶ Because the pK_a values for very strong acids and bases are so hard to determine, you will find that they often differ in different texts—sometimes the values are no better than good guesses! However, while the absolute values may differ, the relative values (which is the important thing because we need only a rough guide) are usually consistent.

Since we have an upper and a lower limit on the strength of an acid or base that we can use in water, this poses a bit of a problem: How do we know that the pK_a for HCl is greater than that of H_2SO_4 if both completely protonate the water? How do we know that the pK_a of methane is greater than that of ethyne since both the conjugate bases fully deprotonate water? The answer is that we can't simply measure the equilibrium for the reaction in water—we can do this only for pK_as that fall between the pK_a values of water itself. Outside this range, pK_a values are determined in other solvents and the results are extrapolated to give a value for what the pK_a in water might be.

Constructing a pK_a scale

We now want to look at ways to rationalize the different pK_a values for different compounds—we wouldn't want to have to memorize all the values. You will need to get a feel for the pK_a values of

different compounds and, if you know what factors affect them, it will make it much easier to predict an approximate pK_a value, or at least understand why a given compound has the pK_a value that it does.

A number of factors affect the strength of an acid, AH.

$$AH\ (solvent) \rightleftharpoons A^-\ (solvent) + H^+\ (solvent)$$

These include:

1. Intrinsic stability of the conjugate base, anion A^-. Stability can arise, for example, by having the negative charge on an electronegative atom or by spreading the charge over other groups. Either way, the more 'stable' the conjugate base, the less basic it will be and so the stronger the acid
2. Bond strength A–H. Clearly, the easier it is to break this bond, the stronger the acid
3. The solvent. The better the solvent is at stabilizing the ions formed, the easier it is for the reaction to occur

Acid strength

- **The most important factor in the strength of an acid is the stability of the conjugate base—the more stable the conjugate base, the stronger the acid**
- **An important factor in the stability of the conjugate base is which element the negative charge is on—the more electronegative the element, the more stable the conjugate base**

The negative charge on an electronegative element stabilizes the conjugate base

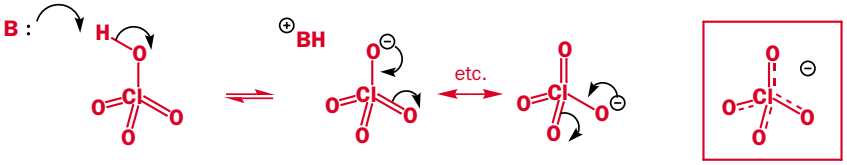
The pK_a values for second row hydrides CH_4, NH_3, H_2O, and HF are about 48, 33, 16, and 3, respectively. This trend is due to the increasing electronegativities across the period: F^- is much more stable than CH_3^-, because fluorine is much more electronegative than carbon.

Weak A–H bonds make stronger acids

However, on descending group VII (group 17), the pK_a values for HF, HCl, HBr, and HI decrease in the order 3, –7, –9, and –10. Since the electronegativities decrease on descending the group we might expect an increase in pK_as. The decrease observed is actually due to the weakening bond strengths on descending the group and to some extent the way in which the charge can be spread over the increasingly large anions.

Delocalization of the negative charge stabilizes the conjugate base

The acids HClO, $HClO_2$, $HClO_3$, and $HClO_4$ have pK_a values 7.5, 2, –1, and about –10, respectively. In each case the acidic proton is on an oxygen attached to chlorine, that is, *we are removing a proton from the same environment in each case*. Why then is perchloric acid, $HClO_4$, some 17 orders of magnitude stronger in acidity than hypochlorous acid, HClO? Once the proton is removed, we end up with a negative charge on oxygen. For hypochlorous acid, this is localized on the one oxygen. With each successive oxygen, the charge can be more delocalized, and this makes the anion more stable. For example, with perchloric acid, the negative charge can be delocalized over all four oxygen atoms.

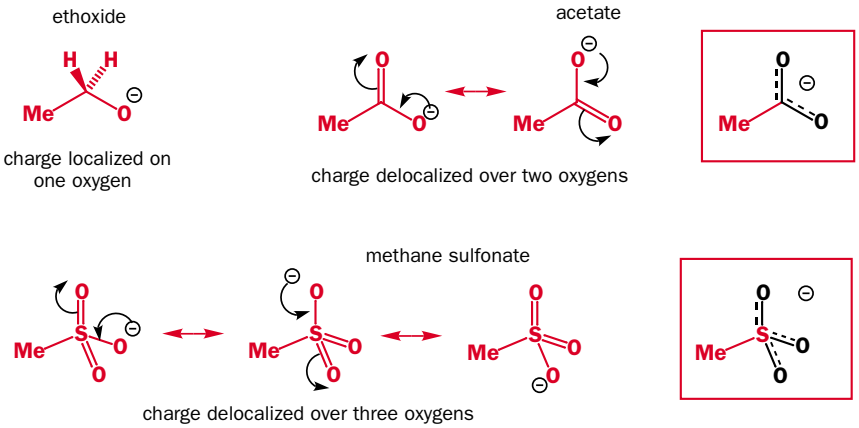


the negative charge on the perchlorate anion can be delocalized equally over all four oxygens

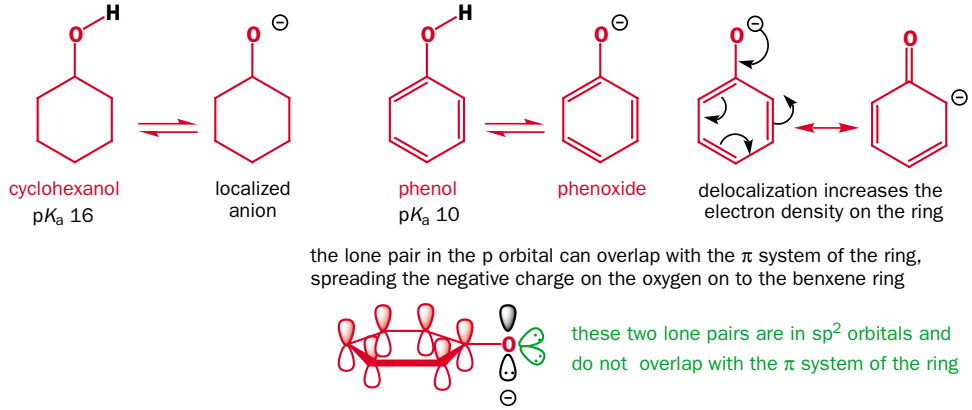
That the charge is spread out over all the oxygen atoms equally is shown by electron diffraction studies: whereas perchloric acid has two types of Cl–O bond, one 163.5 pm and the other three 140.8 pm long, in the perchlorate anion all Cl–O bond lengths are the same, 144 pm, and all O–Cl–O bond angles are 109.5°.

■ *Just to remind you*: these delocalization arrows do not indicate that the charge is actually moving from atom to atom. These structures simply show that the charge is spread out in the molecular orbitals and mainly concentrated on the oxygen atoms.

Similar arguments explain the pK_as for other oxygen acids, for example, ethanol (pK_a, 15.9), acetic acid (4.8), and methane sulfonic acid (–1.9). In ethoxide, the negative charge is localized on one oxygen atom, whilst in acetate the charge is delocalized over two oxygens and in methane sulfonate it is spread over three oxygens.



In phenol, PhOH, the OH group is directly attached to a benzene ring. On deprotonation, the negative charge can again be delocalized, not on to other oxygens but this time on to the aromatic ring itself.



The effect of this is to stabilize the phenoxide anion relative to the conjugate base of cyclohexanol where no delocalization is possible and this is reflected in the pK_as of the two compounds: 10 for phenol but 16 for cyclohexanol.

● Get a feel for pK_as!

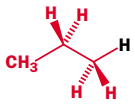
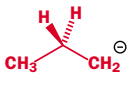
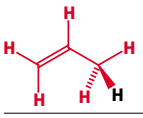
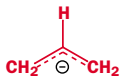
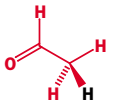
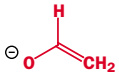
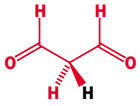
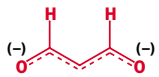
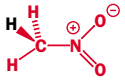
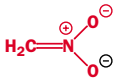
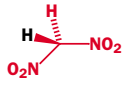
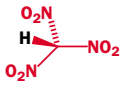
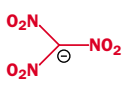
Notice that these oxygen acids have pK_as that conveniently fall in units of 5 (approximately).

Acid	RSO_2OH	RCO_2H	ArOH	ROH
Approx. pK_a	0	5	10	15

The same delocalization of charge can stabilize anions derived from deprotonating carbon acids. These are acids where the proton is removed from carbon rather than oxygen and, in general, they are weaker than oxygen acids because carbon is less electronegative. If the negative charge can be delocalized on to more electronegative atoms such as oxygen or nitrogen, the conjugate base will be stabilized and hence the acid will be stronger.

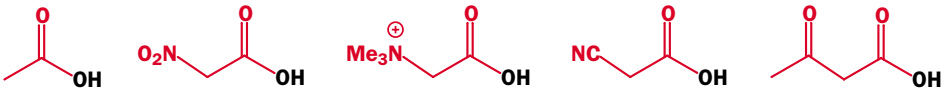
Table 8.2 shows a selection of carbon acids with their conjugate bases and pK_as. In each case the proton removed is shown in black.

Table 8.2 The conjugate bases and pK_as of some carbon acids

Acid	Conjugate base	pK_a	Comments
		~50	charge is localized on one carbon—difficult since carbon is not very electronegative
		~43	charge is delocalized over π system—better but still not really good
		13.5	charge is delocalized over π system but is mainly on the electronegative oxygen—much better
		5	charge delocalized over π system but mainly over two oxygens—better still
		~48	charge is localized on one carbon—again very unsatisfactory
		10	charge is delocalized but mainly on oxygens of nitro group
		4	charge can be delocalized over two nitro groups—more stable anion
		0	charge can be delocalized over three nitro groups—very stable anion

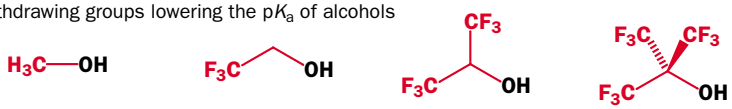
It isn't necessary for a group to be conjugated in order to spread the negative charge: any group that withdraws electrons will help to stabilize the conjugate base and therefore increase the strength of the acid. Some examples are shown below for both oxygen and carbon acids.

electron-withdrawing groups lowering the pK_a of carboxylic acids



pK_a 4.76 pK_a 1.7 pK_a 1.8 pK_a 2.4 pK_a 3.6

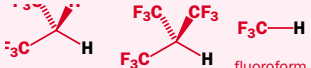
electron-withdrawing groups lowering the pK_a of alcohols



pK_a 15.5 pK_a 12.4 pK_a 9.3 pK_a 5.4

- Notice how very electron-withdrawing the nitro group is—it lowers the pK_a of acetic acid even more than a quaternary ammonium salt!
- Notice also that the fourth alcohol with three CF_3 groups is almost as acidic as acetic acid.

electron-withdrawing groups lowering the pK_as of carbon acids

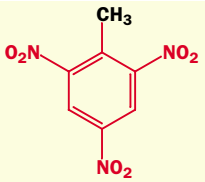


pK_a ca. 22 pK_a ca. 10 fluoroform pK_a 26

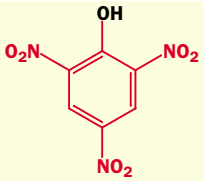
Picric acid is a very acidic phenol

Electron-withdrawing effects on aromatic rings will be covered in more detail in Chapter 22 but for the time being note that electron-withdrawing groups can considerably lower the pK_as of substituted phenols and carboxylic acids, as illustrated by picric acid.

2, 4, 6-Trinitrophenol's more common name, picric acid, reflects the strong acidity of this compound (pK_a 0.7 compared to phenol's 10.0). Picric acid used to be used in the dyeing industry but is little used now because it is also a powerful explosive (compare its structure with that of TNT!).



trinitrotoluene, TNT

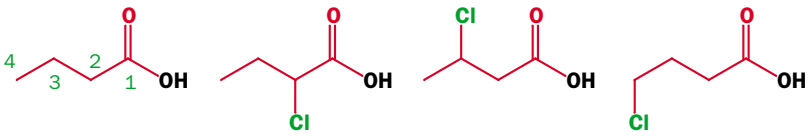


picric acid

▶ Study carefully the pK_as for the haloform series, CHX_3—they may not do what you think they should! Chloroform is much more acidic than fluoroform even though fluorine is more electronegative (likewise with bromoform and chloroform). The anion CF_3^- must be slightly destabilized because of some backdonation of electrons. The anion from chloroform and bromoform may also be stabilized by some interaction with the d orbitals (there aren't any on fluorine). The conjugate base anion of bromoform is relatively stable—you will meet this again in the bromoform/iodoform reaction (Chapter 21).

Electron withdrawal in these molecules is the result of σ bond polarization from an inductive effect (Chapter 5). The electrons in a σ bond between carbon and a more electronegative element such as N, O, or F will be unevenly distributed with a greater electron density towards the more electronegative atom. This polarization is passed on more and more weakly throughout the carbon skeleton. The three fluorine atoms in CF_3H reduce the pK_a to 26 from the 48 of methane, while the nine fluorines in $(CF_3)_3CH$ reduce the pK_a still further to 10.

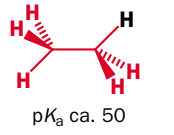
Such inductive effects become less significant as the electron-withdrawing group gets further away from the negative charge as is shown by the pK_as for these chlorobutanoic acids: 2-chloro acid is significantly stronger than butanoic acid but by the time the chlorine atom is on C4, there is almost no effect.



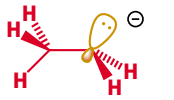
pK_a 4.8 pK_a 2.8 pK_a 4.1 pK_a 4.5

Hybridization can also affect the pK_a

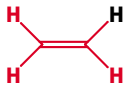
The hybridization of the orbital from which the proton is removed also affects the pK_a. Since s orbitals are held closer to the nucleus than are p orbitals, the electrons in them are lower in energy, that is, more stable. Consequently, the more s character an orbital has, the more tightly held are the electrons in it. This means that electrons in an sp orbital (50% s character) are lower in energy than those in an sp^2 orbital (33% s character), which are, in turn, lower in energy than those in an sp^3 orbital (25% s character). Hence the anions derived from ethane, ethene, and ethyne increase in stability in this order and this is reflected in their pK_as. Cyanide ion, ^-CN, with an electronegative element as well as an sp hybridized anion, is even more stable and HCN has a pK_a of about 10.



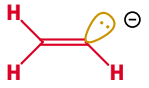
pK_a ca. 50



lone pair of $CH_3CH_2^-$ in sp^3 orbital



pK_a ca. 44



lone pair of $CH_2{=}CH^-$ in sp^2 orbital



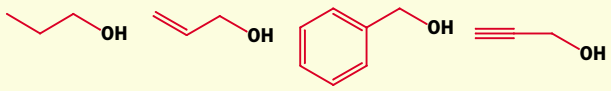
pK_a ca. 26



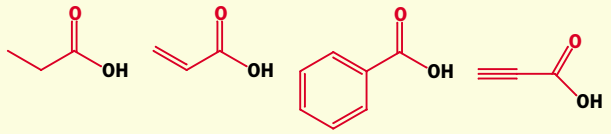
lone pair of $HC{\equiv}C^-$ in sp orbital

More remote hybridization is also important

The more s character an orbital has, the more it holds on to the electrons in it. This makes an sp hybridized carbon less electron-donating than an sp^2 one, which in turn is less electron-donating than an sp^3 carbon. This is reflected in the pK_as of the compounds shown here.



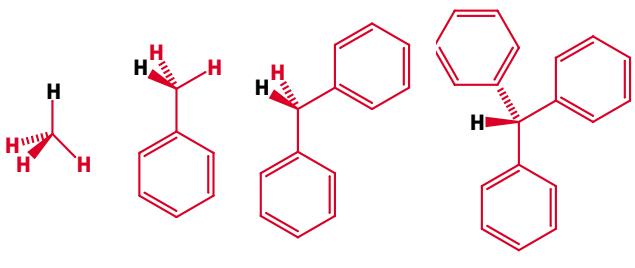
pK_a 16.1 pK_a 15.5 pK_a 15.4 pK_a 13.5



pK_a 4.9 pK_a 4.2 pK_a 4.2 pK_a 1.9

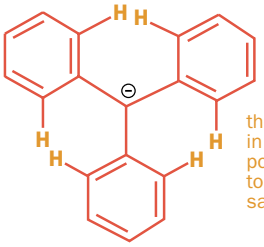
Highly conjugated carbon acids

If we can delocalize the negative charge of a conjugate anion on to oxygen, the anion is more stable and consequently the acid is stronger. Even delocalization on to carbon alone is good if there is enough of it, which is why some highly delocalized hydrocarbons have remarkably low pK_as for hydrocarbons. Look at this series .

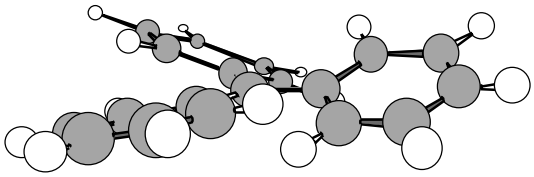


pK_a ca. 48 pK_a ca. 40 pK_a ca. 33 pK_a ca. 32

Increasing the number of phenyl groups decreases the pK_a—this is what we expect, since we can delocalize the charge over all the rings. Notice, however, that each successive phenyl ring has less effect on the pK_a: the first ring lowers the pK_a by 8 units, the second by 7, and the third by only 1 unit. In order to have effective delocalization, the system must be planar (Chapter 7). Three phenyl rings cannot arrange themselves in a plane around one carbon atom because the *ortho*-hydrogens clash with each other (they want to occupy the same space) and the compound actually adopts a propeller shape where each phenyl ring is slightly twisted relative to the next.

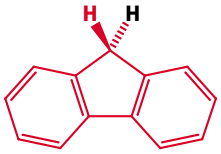


the hydrogens in the *ortho* positions try to occupy the same space

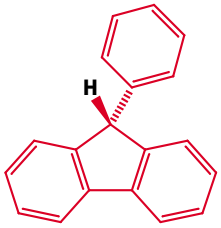


each phenyl ring is staggered relative to the next

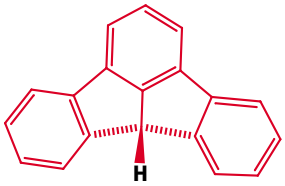
Even though complete delocalization is not possible, each phenyl ring does lower the pK_a because the sp^2 carbon on the ring is electron-withdrawing. If we force the system to be planar, as in the compounds below, the pK_a is lowered considerably.



fluorene, pK_a 22.8
in the anion, the whole system is planar



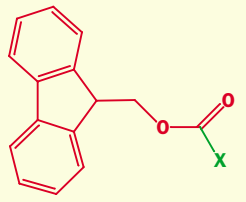
9-phenylfluorene, pK_a 18.5
in the anion, only the two fused fings can be planar



fluoradene pK_a 11
in the anion, the whole system is planar

The 'Fmoc' protecting group

Sometimes in organic chemistry, when we are trying to do a reaction on one particular functional group, another group in the molecule may also react with the reagents, often in a way that we do not want. If a compound contains such a vulnerable group, we can 'protect' it by first converting it into a different less reactive group that can easily be converted back to the group that we want later. An example of such a 'protecting group' is the Fmoc group used (for example, as the chloride, X = Cl) to protect amines or alcohols.

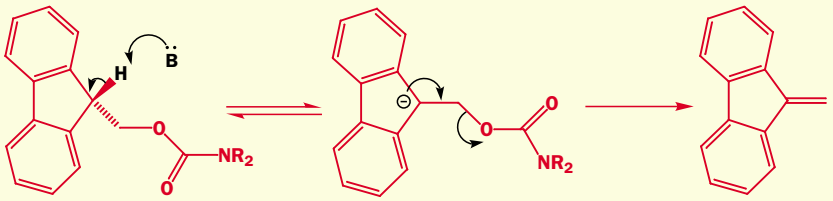


Fmoc-X

Fmoc = 9-**F**luorenyl**m**ethyl**o**xy**c**arbonyl

Fmoc-Cl + NHR_2 ⟶ **Fmoc-NR_2 + HCl**

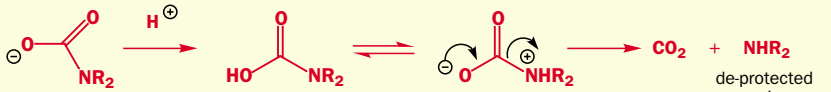
The protecting group is removed using a base. This works because of the acidity of the proton in position 9 on the fluorene ring. Removal of that proton causes a breakup of the molecule with the release of the amine at the end.



protected amine

anion is stabilized by conjugation but can undergo elimination

9-methylenefluorene

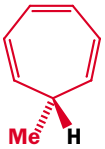


de-protected amine

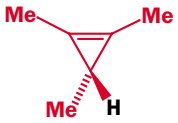
We saw in Chapter 7 how some compounds can become aromatic by gaining or losing electrons. Cyclopentadiene is one such compound, which becomes aromatic on deprotonation. The stability gained in becoming aromatic is reflected in the compound's pK_a.



cyclopentadiene
pK_a 15.5



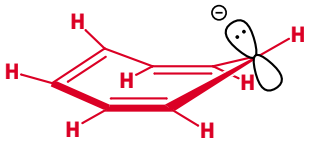
cycloheptatriene
pK_a ca. 36



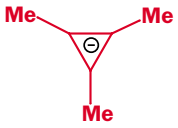
trimethylcyclopropene
pK_a ca. 62



anion is planar
6π electrons
make it aromatic



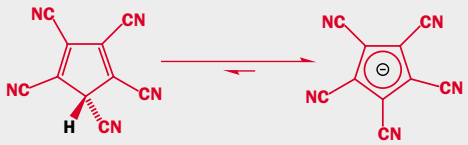
anion not planar
neither aromatic or anti-aromatic



anion is planar
4π electrons
make it anti-aromatic

■

This is by no means as far as we can go. The five cyanide groups stabilize this anion so much that the pK_a for this compound is about –11 and it is considerably more acidic than cyclopentadiene (pK_a 15.5).



Compare the pK_a of cyclopentadiene with that of cycloheptatriene. Whilst the anion of the former has 6 π electrons (which makes it isoelectronic with benzene), the anion of the latter has 8 π electrons. Remember that on p. 176 we saw how $4n$ π electrons made a compound anti-aromatic? The cycloheptatrienyl anion does have $4n$ π electrons but it is not anti-aromatic because it isn't planar. However, it certainly isn't aromatic either and its pK_a of around 36 is about the same as that of propene. This contrasts with the cyclopropenyl anion, which must be planar since any three points define a plane. Now the compound is anti-aromatic and this is reflected in the very high pK_a (about 62). Other compounds may become aromatic on losing a proton. We looked at fluorene a few pages back: now you will see that fluorene is acidic because its anion is aromatic (14 π electrons).

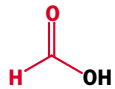
- **The more stabilized the conjugate base, A^-, the stronger is the acid, HA. Ways to stabilize A^- include:**
  - **Having the charge on an electronegative element**
  - **Delocalizing the negative charge over other carbon atoms, or even better, over more electronegative atoms**
  - **Spreading out the charge over electron-withdrawing groups by the polarization of σ bonds (inductive)**
  - **Having the negative charge in an orbital with more s character**
  - **Becoming aromatic**

Electron-donating groups decrease acidity

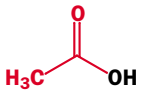
▶

The anions are also stabilized by solvation. Solvation is reduced by increasing the steric hindrance around the alkoxide.

All of the substituents in the examples above have been electron-withdrawing and have helped to stabilize the negative charge of the conjugate base, thereby making the acid stronger. What effect would electron-donating groups have? As you would expect, these destabilize the conjugate base because, instead of helping to spread out the negative charge, they actually put more in. The most common electron-donating groups encountered in organic chemistry are the alkyl groups. These are weakly electron-releasing (p. 416).



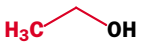
formic (methanoic) acid
pK_a 3.7



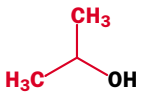
acetic (ethanoic) acid
pK_a 4.8



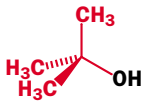
methanol
pK_a 15.5



ethanol
pK_a 16.0

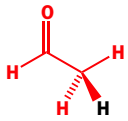


isopropyl alcohol
pK_a 17.1

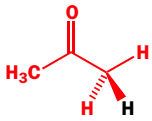


tert-butyl alcohol
pK_a 19.2

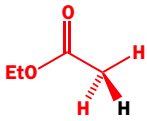
Although to a lesser extent than amides (p. 165), the ester group is also stabilized by conjugation. In this case, the 'ethoxide part' of the ester is electron-releasing. This explains the pK_as shown below.



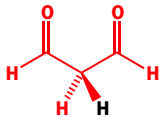
acetaldehyde
(ethanal)
pK_a 13.5



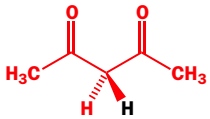
acetone
(propanone)
pK_a 20



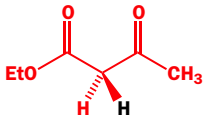
ethyl acetate
(ethyl ethanoate)
pK_a 25



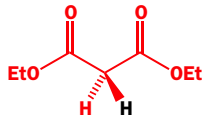
propandial
pK_a ca. 5



acetylacetone
(2,4-pentanedione)
pK_a 8.9



ethyl acetoacetate
(ethyl 3-oxobutanoate)
pK_a 10.6



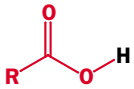
diethyl malonate
(diethyl propanedioate)
pK_a 12.9

Nitrogen acids

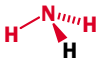
Oxygen acids and carbon acids are by far the most important examples you will encounter and by now you should have a good understanding of why their pK_a values are what they are. Before we move on to bases, it would be worthwhile to remind you how different nitrogen acids are from oxygen acids, since the conjugate bases of amines are so important. The pK_a of ammonia is much greater than the pK_a of water (about 33 compared with 15.74). This is because oxygen is more electronegative than nitrogen and so can stabilize the negative charge better. A similar trend is reflected in the pK_as of other nitrogen compounds, for example, in the amide group. Whilst the oxygen equivalent of an amide (a carboxylic acid) has a low pK_a, a strong base is needed to deprotonate an amide. Nevertheless, the carbonyl group of an amide does lower the pK_a from that of an amine (about 30) to around 17. It's not surprising, therefore, that the two carbonyl groups in an imide lower the pK_a still further, as in the case of phthalimide. Amines are not acidic, amides are weakly acidic (about the same as alcohols), and imides are definitely acidic (about the same as phenols).



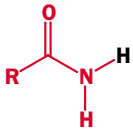
water
pK_a 15.74



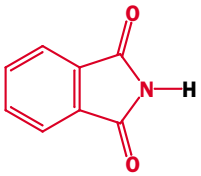
carboxylic acid
pK_a ca. 5



ammonia
pK_a ca. 33



amide
pK_a ca. 17



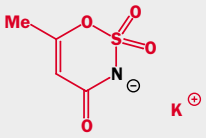
phthalimide
pK_a 8.3

Basicity

A **base** is a substance that can accept a proton by donating a pair of electrons. We have already encountered some—for example, ammonia, water, the acetate anion, and the methyl anion. The question we must now ask is: how can we measure a base's strength? To what extent does a base attract a proton? We hope you will realize that we have already addressed this problem by asking the same question from a different viewpoint: to what extent does a protonated base want to keep its proton? For example if we want to know which is the stronger base—formate anion or acetylide anion—we look up the pK_as for their conjugate acids. We find that the pK_a for formic acid (HCO_2H) is 3.7, whilst the pK_a for ethyne (acetylene) is around 25. This means that ethyne is much more reluctant to part with its proton, that is, acetylide is much more basic than formate. This is all very well for anions—we simply look up the pK_a value for the neutral conjugate acid, but what if we want to know the basicity of ammonia? If we look up the pK_a for ammonia we find a value around 33 but this is the value for deprotonating neutral ammonia to give the amide ion, NH_2^-.

■

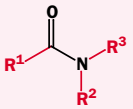
The potassium salt of 6-methyl-1,2,3-oxathiazin-4-one 2,2-dioxide known as acesulfame-K is used as an artificial sweetener (trade name Sunett). Here the negative charge is delocalized over both the carbonyl and the sulfone groups.



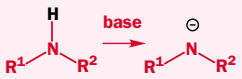
acesulfame-K

▶Amides

Do not get confused with the two uses of the word 'amide' in chemistry. Both the carbonyl compound and the 'ionic' base formed by deprotonating an amine are known as amides. From the context it should be clear which is meant—most of the time chemists (at least organic chemists!) mean the carbonyl compound.



the amide group



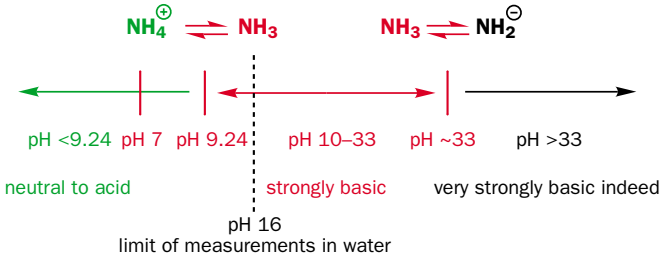
an amine

an amide base
e.g. sodium amide
$NaNH_2$

▶Get a feel for pK_as!

Remember that the pK_a also represents the pH when we have equal concentrations of acid and conjugate base, that is, NH_3 and NH_4^+ in this case. You know that ammonia is a weak base and that an aqueous solution is alkaline so it should come as no surprise that its pK_a is on the basic side of 7. To be exact, at pH 9.24 an aqueous solution of ammonia contains equal concentrations of ammonium ions and ammonia.

If we want to know the *basicity* of ammonia, we must look up the pK_a of its conjugate acid, the ammonium cation, NH_4^+, protonated ammonia. Its pK_a is 9.24 which means that ammonia is a weaker base than hydroxide—the pK_a for water (the conjugate acid of hydroxide) is 15.74 (p. 190). Now we can summarize the states of ammonia at different pH values.



Scales for basicity—pK_B and pK_{aH}

The material in this box is quite mathematical and may be skipped if you find it too alien.

It is often convenient to be able to refer to the basicity of a substance directly. In some texts a different scale is used, pK_B. This is derived from considering how much hydroxide ion a base forms in water rather than how much hydronium ion the conjugate acid forms.

For the pK_B scale:

$$B(aq) + H_2O \rightleftharpoons OH^-(aq) + BH^+(aq)$$

$$K_B = \frac{[OH^-][BH^+]}{[B]}$$

Hence

$$pK_B = -\log(K_B)$$

For the pK_a scale:

$$BH^+(aq) + H_2O \rightleftharpoons H_3O^+(aq) + B(aq)$$

$$K_A = \frac{[H_3O^+][B]}{[BH^+]}$$

Hence

$$pK_A = -\log(K_A)$$

Just as in the acid pK_a scale, the lower the pK_a the stronger the acid, in the basic pK_B scale, the lower the pK_B, the stronger the base. The two scales are related: the product of the equilibrium constants simply equals the ionic product of water.

$$K_B \times K_A = \frac{[OH^-][BH^+]}{[B]} \times \frac{[H_3O^+][B]}{[BH^+]}$$

$$= [OH^-][H_3O^+] = K_W = 10^{-14}$$

that is,

$$pK_A + pK_B = pK_W = 14$$

There is a separate scale for bases, but it seems silly to have two different scales, the basic pK_B and the familiar pK_a, when one will do and so we will stick to pK_a. However, to avoid any misunderstandings that can arise from amphoteric compounds like ammonia, whose pK_a is around 33, we will either say:

- The pK_a of ammonia's conjugate acid is 9.24

or, more concisely,

- The pK_{aH} of ammonia is 9.24 (where pK_{aH} simply means the pK_a of the conjugate acid)

What factors affect how basic a compound is?

This really is the same as the question we were asking about the strength of an acid—the more 'stable' the base, the weaker it is. The more accessible the electrons are, the stronger the base is. Therefore a negatively charged base is more likely to pick up a proton than a neutral one; a compound in which the negative charge is delocalized is going to be less basic than one with a more concentrated, localized charge, and so on. We have seen that carboxylic acids are stronger acids than simple alcohols because the negative charge formed once we have lost a proton is delocalized over two oxygens in the carboxylate but localized on just one oxygen for the alkoxide. In other words, the alkoxide is a stronger base because its electrons are more available to be protonated. Since we have already considered anionic bases, we will now look in more detail at neutral bases.

▶

The most important factor in the strength of a base is which element the lone pair (or negative charge) is on. The more electronegative the element, the tighter it keeps hold of its electrons, and so the less available they are to accept a proton, and the weaker is the base.



There are two main factors that determine the strength of a neutral base: how accessible is the lone pair and to what extent can the resultant positive charge formed be stabilized either by delocalization or by the solvent. The accessibility of the lone pair depends on its energy—it is usually the HOMO of the molecule and so, the higher its energy, the more reactive it is and hence the stronger the base. The lone pair is lowered in energy if it is on a very electronegative element or if it can be delocalized in some manner.

This explains why ammonia is 10^{10} times more basic than water: since oxygen is more electronegative than nitrogen, its lone pair is lower in energy. In other words, the oxygen atom in water wants to keep hold of its electrons more than the nitrogen in ammonia does and is therefore less likely to donate them to a proton. The pK_{aH} for ammonia (that is, the pK_a for ammonium ion) is 9.24 whilst the pK_{aH} for water (the pK_a for hydronium ion) is –1.74. Nitrogen bases are the strongest neutral bases commonly encountered by the organic chemist and so we will pay most attention to these in the discussion that follows.

▶ pK_{aH}!
We use pK_{aH} to mean the pK_a of the conjugate acid.

Neutral nitrogen bases

Ammonia is the simplest nitrogen base and has a pK_{aH} of 9.24. Any substituent that increases the electron density on the nitrogen therefore raises the energy of the lone pair thus making it more available for protonation and increasing the basicity of the amine (larger pK_{aH}). Conversely, any substituent that withdraws electron density from the nitrogen makes it less basic (smaller pK_{aH}).

Effects that increase the electron density on nitrogen

We can increase the electron density on nitrogen either by attaching an electron-releasing group or by conjugating the nitrogen with an electron-donating group. The simplest example of an electron-releasing group is an alkyl group (p. 416). If we successively substitute each hydrogen in ammonia by an electron-releasing alkyl group, we should increase the amine's basicity. The pK_{aH} values for various mono-, di-, and trisubstituted amines are shown in Table 8.4.

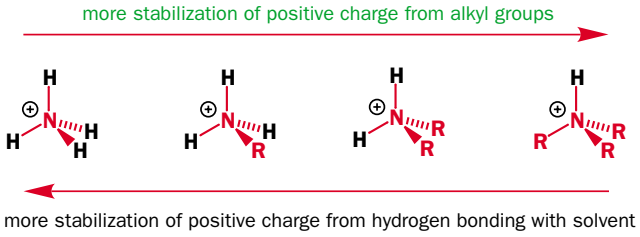
Table 8.4 pK_{aH} values for primary, secondary, and tertiary amines

R	pK_{aH} RNH_2	pK_{aH} R_2NH	pK_{aH} R_3N
Me	10.6	10.8	9.8
Et	10.7	11.0	10.8
n-Pr	10.7	11.0	10.3
n-Bu	10.7	11.3	9.9

Points to notice in Table 8.4:

- All the amines have pK_{aH}s greater than that of ammonia (9.24)
- All the primary amines have approximately the same pK_{aH} (about 10.7)
- All the secondary amines have pK_{aH}s that are slightly higher
- Most of the tertiary amines have pK_{aH}s lower than those of the primary amines

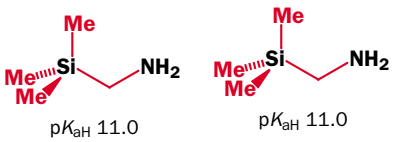
The first point indicates that our prediction that replacing the hydrogens by electron-releasing alkyl groups would increase basicity was correct. A strange feature though is that, whilst substituting one hydrogen of ammonia increases the basicity by more than a factor of ten (one pK_a unit), substituting two has less effect and in the trisubstituted amine the pK_{aH} is actually *lower*. So far we have only considered one cause of basicity, namely, the availability of the lone pair but the other factor, the stabilization of the resultant positive charge formed on protonation, is also important. Each successive alkyl group does help stabilize the positive charge because it is electron-releasing but there is another stabilizing effect—the solvent. Every hydrogen attached directly to nitrogen will be hydrogen bonded with solvent water and this also helps to stabilize the charge: the more hydrogen bonding, the more stabilization. The observed basicity therefore results from a combination of effects: (1) the increased availability of the lone pair and the stabilization of the resultant positive charge, which increases with successive replacement of hydrogen atoms by alkyl groups; and (2) the stabilization due to solvation, an important part of which is due to hydrogen bonding and this effect decreases with increasing numbers of alkyl groups.



Gas phase acidity
If we look at the pK_{aH} values in the gas phase, we can eliminate the hydrogen bonding contribution and we find the basicity increases in the order we expect, that is, tertiary > secondary > primary.

Introducing alkyl groups is the simplest way to increase the electron density on nitrogen but there are other ways. Conjugation with an electron-donating group produces even stronger bases (p. 202) but we could also increase the electron density by using elements such as silicon. Silicon is more

■ Remember that Me_4Si, tetramethyl silane, in carbon NMR resonates at 0.0 p.p.m.? This is another consequence of silicon being more electropositive than carbon—the methyl carbons of TMS are more shielded and so resonate at a smaller chemical shift than other saturated carbons.



pK_{aH} 11.0 pK_{aH} 11.0

electropositive than carbon, that is, it pushes more electron density on to carbon. This extra donation of electrons also means that the silicon compound has a higher pK_{aH} value than its carbon analogue since the nitrogen's lone pair is higher in energy.

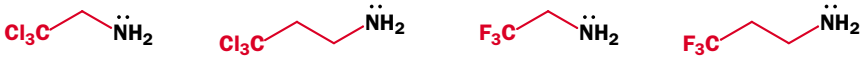
Effects that decrease the electron density on nitrogen

The lone pair on nitrogen will be *less* available for protonation, and the amine *less* basic, if:

- **The nitrogen atom is attached to an electron-withdrawing group**
- **The lone pair is in an sp or sp^2 hybridized orbital**
- **The lone pair is conjugated with an electron-withdrawing group**
- **The lone pair is involved in maintaining the aromaticity of the molecule**

■ Compare this summary with the one for the stabilization of the conjugate base A^- on p. 196. In both cases, we are considering the same factors.

The pK_{aH}s of some amines in which the nitrogen is attached either directly or indirectly to an electron-withdrawing group are shown below. We should compare these values with typical values of about 11 for simple primary and secondary amines.



pK_{aH} 5.5 pK_{aH} 9.65 pK_{aH} 5.7 pK_{aH} 8.7

The strongly electron-withdrawing CF_3 and CCl_3 groups have a large effect when they are on the same carbon atom as the NH_2 group but the effect gets much smaller when they are even one atom further away. Inductive effects fall off rapidly with distance.

Hybridization is important

As explained on p. 194, the more s character an orbital has, the more tightly it holds on to its electrons and so the more electron-withdrawing it is. This is nicely illustrated by the series in Table 8.5.

- These effects are purely inductive electron withdrawal. Satisfy yourself there is no conjugation possible
- The last compound's pK_{aH} is very low. This is even less basic than a carboxylate ion.

Table 8.5 pK_{aH}s of unsaturated primary, secondary, and tertiary amines

R	RNH_2	R_2NH	R_3N
$H_3C—CH_2—CH_2—$	10.7	11.0	10.3
$H_2C=CH—CH_2—$	9.5	9.3	8.3
$HC\equiv C—CH_2—$	8.2	6.1	3.1

If the lone pair itself is in an sp^2 or an sp orbital, it is more tightly held (the orbital is lower in energy) and therefore much harder to protonate. This explains why the lone pair of the nitrile group is not at all basic and needs a strong acid to protonate it.



lone pair in sp^3 orbital pK_{aH} 10.7

lone pair in sp^2 orbital pK_{aH} 9.2

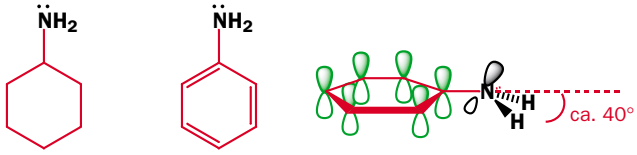
lone pair in sp^3 orbital pK_{aH} 10.8

lone pair in sp orbital pK_{aH} ca. –10

■ Of course, electron-withdrawing groups on the benzene ring will affect the availability of the lone pair. For example, the pK_{aH} of *p*-nitro aniline is only 1.11. This explains why certain aromatic amines (for example, nitroanilines and dibromoanilines) can't be acetylated using the Lumière–Barbier method (p. 188).

The low pK_{aH} of aniline ($PhNH_2$), 4.6, is partly due to the nitrogen being attached to an sp^2 carbon but also because the lone pair can be delocalized into the benzene ring. In order for the lone pair to be fully conjugated with the benzene ring, the nitrogen would have to be sp^2 hybridized with the lone pair in the p orbital. This would mean that both hydrogens of the NH_2 group would be in the same plane as the benzene ring but this is not found to be the case. Instead, the plane of the NH_2 group is about 40° away from the plane of the ring. That the lone pair is partially conjugated into the ring is shown indirectly by NMR shifts and by the chemical reactions that aniline undergoes. Notice

that, when protonated, the positive charge cannot be delocalized over the benzene ring and any stabilization derived from the lone pair in unprotonated aniline being delocalized into the ring is lost.



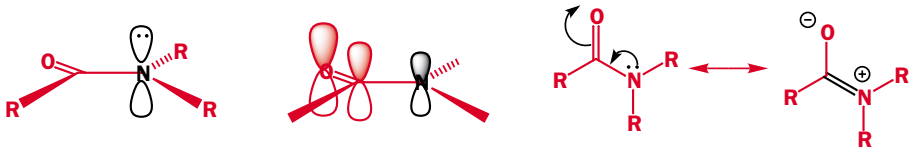
cyclohexylamine
pK_{aH} 10.7

aniline
pK_{aH} 4.6

the NH_2 group is about 40° away from being in the plane of the ring

Amides are weak bases protonated on oxygen

In contrast to aromatic amines, the amide group is completely planar (p. 165) with the nitrogen sp^2 hybridized and its lone pair in the p orbital, thereby enabling it to overlap effectively with the carbonyl group.

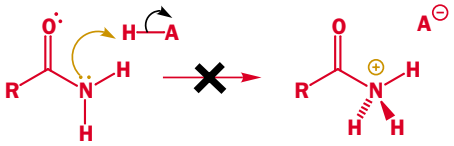


nitrogen is sp^2 hybridized with its lone pair in a p orbital

good overlap with the carbonyl group

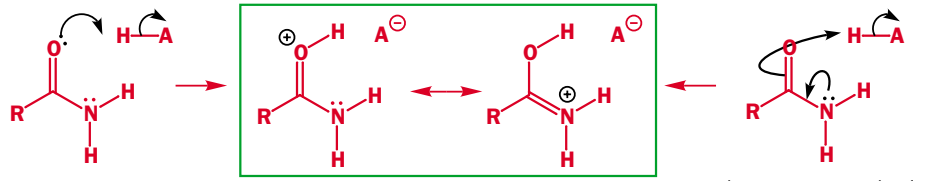
delocalization of nitrogen's lone pair into π system

This delocalization 'ties up' the lone pair and makes it much less basic: the pK_{aH} for an amide is typically between 0 and –1. Because of the delocalization amides are not protonated on nitrogen.



no protonation occurs on the nitrogen atom

Protonation at nitrogen would result in a positive charge on the nitrogen atom. Since this is adjacent to the carbonyl, whose carbon is also electron-deficient, this is energetically unfavourable. Protonation occurs instead on the carbonyl oxygen atom. We can draw the mechanism for this using either a lone pair on oxygen or on nitrogen.

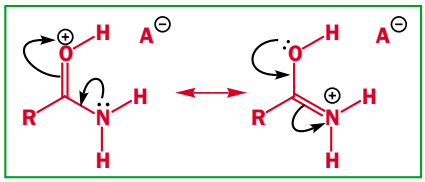


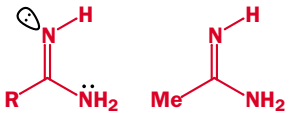
protonation occurs on the oxygen atom

these structures are just two different ways to draw the same delocalized cation

these arrows emphasise the contribution of the nitrogen's lone pair.

Furthermore, if the amide were protonated at nitrogen, the positive charge could not be delocalized on to the oxygen but would have to stay localized on the nitrogen. In contrast, when the amide is protonated on the oxygen atom, the charge can be delocalized on to the nitrogen atom making the cation much more stable. We can see this if we draw delocalization arrows on the structures in the green box.



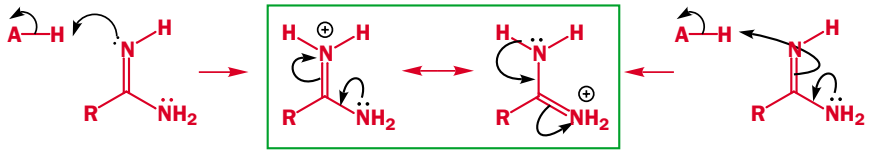


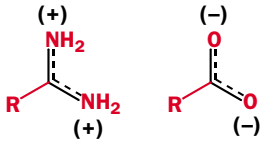
an amidine pK_{aH} 12.4

Amidines are stronger bases than amides or amines

An amidine is the nitrogen equivalent of an amide—a C=NH group replaces the carbonyl. Amidines are much more basic than amides, the pK_{aH}s of amidines are larger than those of amides by about 13 so there is an enormous factor of 10^{13} in favour of amidines. In fact, they are among the strongest neutral bases.

An amidine has two nitrogen atoms that could be protonated—one is sp^3 hybridized, the other sp^2 hybridized. We might expect the sp^3 nitrogen to be more basic but protonation occurs at the sp^2 nitrogen atom. This happens because we have the same situation as with an amide: only if we protonate on the sp^2 nitrogen can the positive charge be delocalized over both nitrogens. We are using *both* lone pairs when we protonate on the sp^2 nitrogen.





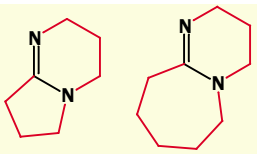
amidinium cation carboxylate anion

The electron density on the sp^2 nitrogen in an amidine is increased through conjugation with the sp^3 nitrogen. The delocalized amidinium cation has identical C–N bond lengths and a positive charge shared equally between the two nitrogen atoms. It is like a positively charged analogue of the carboxylate ion.

Amidine bases

Two frequently used amidine bases are DBN (1,5-*diazabicyclo*[3.4.0]*non*ene-5) and DBU (1,8-*diazabicyclo*[5.4.0]*un*decene-7).

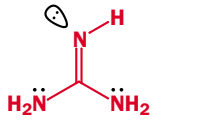
They are easier to make, more stable, and less volatile than simpler amidines.



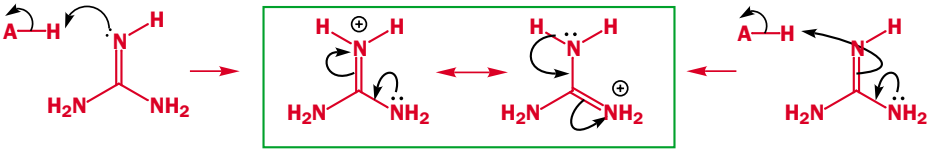
DBN DBU

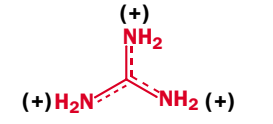
Guanidines are very strong bases

Even more basic is guanidine, pK_{aH} 13.6, nearly as strong a base as NaOH! On protonation, the positive charge can be delocalized over three nitrogen atoms to give a very stable cation. All three nitrogen lone pairs cooperate to donate electrons but protonation occurs, as before, on the sp^2 nitrogen atom.



guanidine: pK_a 13.6

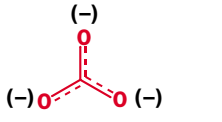




very stable guanidinium cation each (+) is a third of a positive charge

This time the resulting guanidinium ion can be compared to the very stable carbonate dianion. All three C–N bonds are the same length in the guanidinium ion and each nitrogen atom has the same charge (about one-third positive). In the carbonate dianion, all three C–O bonds are the same length and each oxygen atom has the same charge (about *two*-thirds negative as it is a dianion).

Imidazoline is a simple cyclic amidine and its pK_{aH} value is just what we expect, around 11. Imidazole, on the other hand, is less basic (pK_{aH} 7.1) because both nitrogens are attached to an electron-withdrawing sp^2 carbon. However, imidazole, with its two nitrogen atoms, is more basic than pyridine (pK_{aH} 5.2) because pyridine only has one nitrogen on which to stabilize the positive charge.

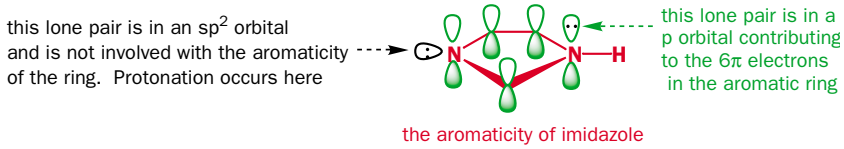


very stable carbonate dianion each (–) is two-thirds of a negative charge



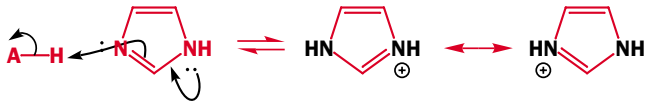
imidazoline pK_{aH} 11 imidazole pK_{aH} 7.1 imidazolium cation pyridine pK_{aH} 5.2 pyridinium cation

Both imidazole and pyridine are aromatic—they are flat, cyclic molecules with 6 π electrons in the conjugated system (p. 177). Imidazole has one lone pair that is and one that is not involved in the aromaticity (Chapter 43).



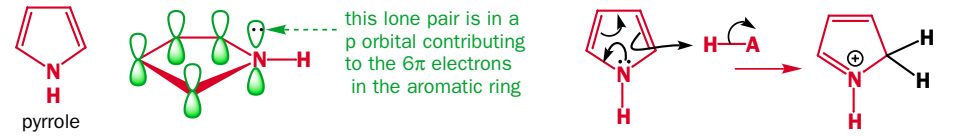
the aromaticity of imidazole

Protonation occurs on the nitrogen atom having the sp^2 lone pair because both lone pairs contribute and the resulting delocalized cation is still aromatic. Pyridine is also protonated on its sp^2 lone pair (it is the only one it has!) and the pyridinium ion is also obviously aromatic—it still has three conjugated π bonds in the ring.



aromatic imidazole aromatic imidazoium ion

This contrasts to pyrrole in which the lone pair on the only nitrogen atom is needed to complete the six aromatic π electrons and is therefore delocalized around the ring. Protonation, if it occurs at all, occurs on carbon rather than on nitrogen since the cation is then delocalized. But the cation is no longer aromatic (there is a saturated CH_2 group interrupting the conjugation) and so pyrrole is not at all basic (pK_{aH} about –4).



pyrrole
pK_{aH} ca. –4

the aromaticity of pyrrole

aromatic pyrrole nonaromatic cation

Neutral oxygen bases

We have already seen that water is a much weaker base than ammonia because oxygen is more electronegative and wants to keep hold of its electrons (p. 199). Oxygen bases in general are so much weaker than their nitrogen analogues that we don't regard them as bases at all. It is still important to know the pK_{aH}s of oxygen compounds because the first step in many acid-catalysed reactions is protonation at an oxygen atom. Table 8.6 gives a selection of pK_{aH}s of oxygen compounds.

Table 8.6 pK_{aH}s of oxygen compounds

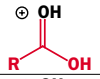
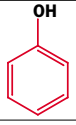
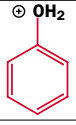
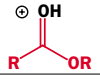
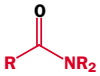
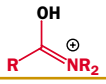
Oxygen compound	Oxygen compound (conjugate base A)	Approximate pK_{aH} of oxygen compound (pK_a of acid HA)	Conjugate acid HA of oxygen compound
ketone		–7	
carboxylic acid		–7	
phenol		–7	
carboxylic ester		–5	

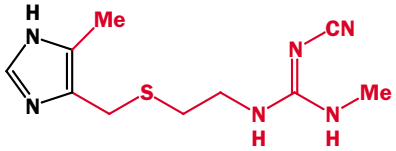
Table 8.6 (continued)

Oxygen compound	Oxygen compound (conjugate base A)	Approximate pK_{aH} of oxygen compound (pK_a of acid HA)	Conjugate acid HA of oxygen compound
alcohol		–4	
ether		–4	
water		–1.74	
amide		–0.5	

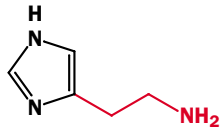
All the same factors of electron donation and withdrawal apply to oxygen compounds as well as to nitrogen compounds, but the effects are generally much less pronounced because oxygen is so electronegative. In fact, most oxygen compounds have pK_{aH}s around –7, the notable exception being the amide, which, because of the electron donation from the nitrogen atom, has a pK_{aH} around –0.5 (p. 201). They are all effectively nonbasic and strong acids are needed to protonate them.

pK_a in action—the development of the drug cimetidine

The development of the anti-peptic ulcer drug cimetidine gives a fascinating insight into the important role of pK_a in chemistry. Peptic ulcers are a localized erosion of the mucous membrane, resulting from overproduction of gastric acid in the stomach. One of the compounds that controls the production of the acid is histamine. (Histamine is also responsible for the symptoms of hay fever and allergies.)



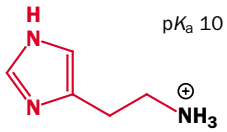
cimetidine



histamine

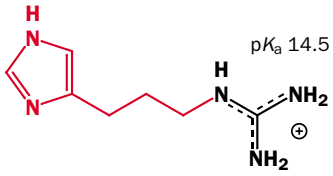
Histamine works by binding into a receptor in the stomach lining and stimulating the production of acid. What the developers of cimetidine at SmithKline Beecham wanted was a drug that would bind to these receptors without activating them and thereby prevent histamine from binding but not stimulate acid secretion itself. Unfortunately, the antihistamine drugs successfully used in the treatment of hay fever did not work—a different histamine receptor was involved. Notice that cimetidine and histamine both have an imidazole ring in their structure. This is not coincidence—cimetidine's design was centred around the structure of histamine.

In the body, most histamine exists as a salt, being protonated on the primary amine and the early compounds modelled this. The guanidine analogue was synthesized and tested to see if it had any antagonistic effect (that is, if it could bind in the histamine receptors and prevent histamine binding). It did bind but unfortunately it acted as an *agonist* rather than an *antagonist* and stimulated acid secretion rather than blocking it. Since the guanidine analogue has a pK_{aH} even greater than histamine (about 14.5 compared to about 10), it is effectively all protonated at physiological pH.



pK_a 10

the major form of histamine at physiological pH (7.4)



pK_a 14.5

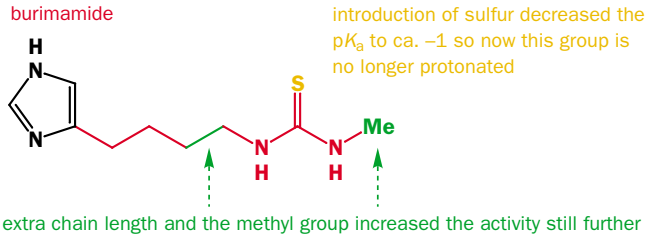
the guanidine analogue
the extra carbon in the chain was found to increase the efficacy of the drug

▶

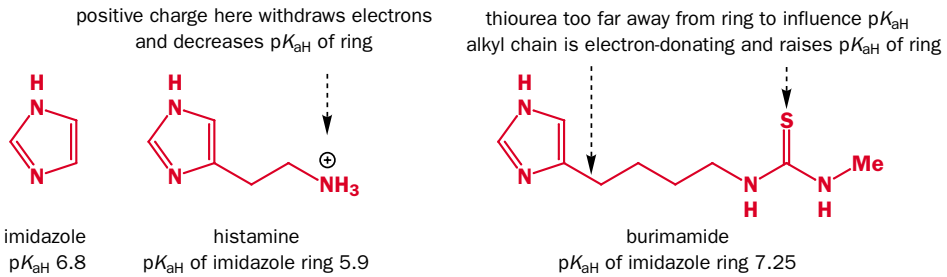
Histamine in this example is an **agonist** in the production of gastric acid. It binds to specific sites in the stomach cells (receptor sites) and triggers the production of gastric acid (mainly HCl).

An **antagonist** works by binding to the same receptors but not stimulating acid secretion itself. This prevents the agonist from binding and stimulating acid production.

The agonistic behaviour of the drug clearly had to be suppressed. The thought occurred to the SmithKline Beecham chemists that perhaps the positive charge made the compound agonistic, and so a polar but much less basic compound was sought. Eventually, they came up with burimamide. The most important change is the replacement of the C=NH in the guanidine compound by C=S. Now instead of a guanidine we have a thiourea which is much less basic. (Remember that amidines, p. 202, are very basic but that amides aren't? The thiourea is like the amide in that the sulfur withdraws electrons from the nitrogens.) The other minor adjustments, increasing the chain length and adding the methyl group on the thiourea, further increased the efficacy.



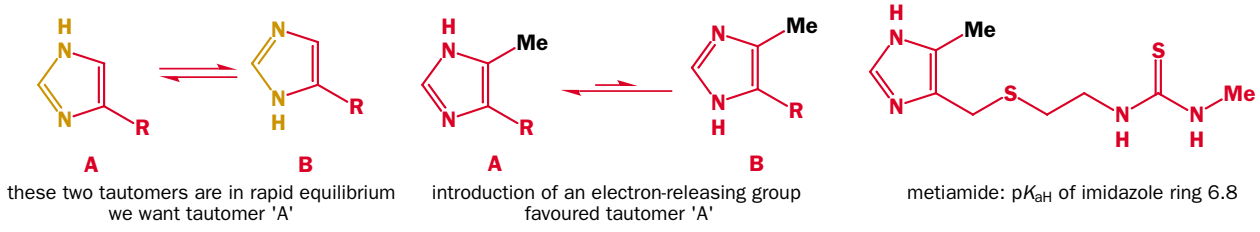
The new compound was a fairly good antagonist (that is, bound in the receptors and blocked histamine) but more importantly shown no agonistic behaviour at all. The compound was such a breakthrough that it was given a name, 'burimamide', and even tested in man. Burimamide was good, but unfortunately not good enough—it couldn't be given orally. A rethink was needed and this time attention was focused on the imidazole ring.



The pK_{aH} of the imidazole ring in burimamide is significantly greater than that in histamine: the longer alkyl group in burimamide is electron-donating and raises the pK_{aH} of the ring. In histamine, on the other hand, the positive charge of the protonated amine withdraws electrons and decreases the pK_{aH}. This means, of course, that there will be a greater proportion of protonated imidazole (imidazolium cation) in burimamide and this might hinder effective binding in the histamine receptor site. So the team set out to lower the pK_{aH} of the imidazole ring. It was known that a sulfur occupies just about the same space as a methylene group, $-CH_2-$, but is more electron-withdrawing. Hence 'thiaburimamide' was synthesized.



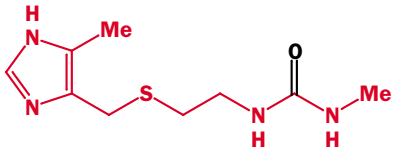
In turns out that one tautomer of the imidazole ring binds better than the other (and much better than the protonated form). The introduction of a methyl group on the ring was found to increase the proportion of this tautomer and did indeed improve binding to the histamine receptor, even though the pK_{aH} of the ring was raised because of the electron-donating character of the methyl group.



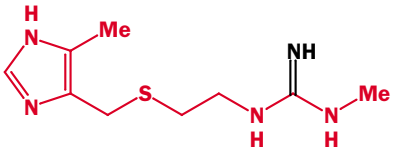
▶ When the drug was invented, the company was called Smith, Kline, and French (SKF) but after a merger with Beechams the company is now called SmithKline Beecham or SB. Things may have changed further by the time you read this book.

■ **Tautomers** are isomers differing only in the positions of hydrogen atoms and electrons. Otherwise the carbon skeleton is the same. They will be explained in Chapter 21.

The new drug, metiamide, was ten times more effective than burimamide when tested in man. However, there was an unfortunate side-effect: in some patients, the drug caused a decrease in the number of white blood cells, leaving the patient open to infection. This was eventually traced back to the thiourea group. The sulfur had again to be replaced by oxygen, to give a normal urea and, just to see what would happen, by nitrogen to give another guanidine.



urea analogue of metiamide



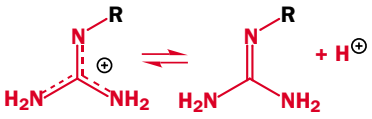
guanidine analogue of metiamide

Neither was as effective as metiamide but the important discovery was that the new guanidine no longer showed the agonistic effects of the earlier guanidine. Of course, the guanidine would also be protonated so we had the same problem we had earlier—how to decrease the pK_{aH} of the guanidine.

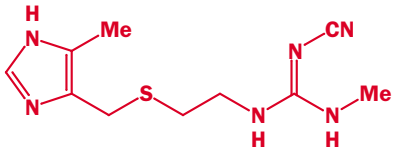
A section of this chapter considered the effect of electron-withdrawing groups on pK_{aH} and showed that they reduce the pK_{aH} and make a base less basic. This was the approach now adopted—the introduction of electron-withdrawing groups on to the guanidine to lower its pK_{aH}. Table 8.7 shows the pK_{aH}s of various substituted guanidines.

Table 8.7 pK_{aH}s of substituted guanidines

R	H	Ph	CH_3CO	NH_2CO	MeO	CN	NO_2
pK_{aH}	14.5	10.8	8.33	7.9	7.5	–0.4	–0.9



Clearly, the cyano- and nitro-substituted guanidines would not be protonated at all. These were synthesized and found to be just as effective as metiamide but without the nasty side-effects. Of the two, the cyanoguanidine compound was slightly more effective and this was developed and named 'cimetidine'.

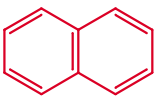


the end result, cimetidine

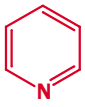
The development of cimetidine by Smith, Kline, and French from the very start of the project up to its launch on the market took thirteen years. This enormous effort was well rewarded—Tagamet (the trade name of the drug cimetidine) became the best-selling drug in the world and the first to gross more than one billion dollars per annum. Thousands of ulcer patients worldwide no longer had to suffer pain, surgery, or even death. The development of cimetidine followed a rational approach based on physiological and chemical principles and it was for this that one of the scientists involved, Sir James Black, received a share of the 1988 Nobel Prize for Physiology or Medicine. None of this would have been possible without an understanding of pK_as.

Problems

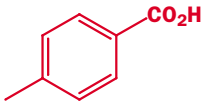
1. If you wanted to separate a mixture of naphthalene, pyridine, and *p*-toluic acid, how would you go about it? All three compounds are insoluble in water.



naphthalene



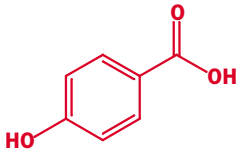
pyridine



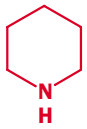
para-toluic acid

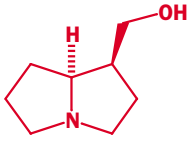
2. In the separation of benzoic acid from toluene we suggested using NaOH solution. How concentrated a solution would be necessary to ensure that the pH was above the pK_a of benzoic acid (pK_a 4.2)? How would you estimate how much solution to use?

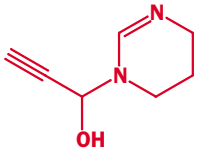
3. What species would be present if you were to dissolve this hydroxy-acid in: (a) water at pH 7; (b) aqueous alkali at pH 12; or (c) a concentrated solution of a mineral acid?



4. What would you expect to be the site of (**a**) protonation and (**b**) deprotonation if the compounds below were treated with an appropriate acid or base. In each case suggest a suitable acid or base for both purposes.

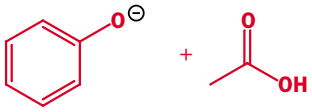






5. Suggest what species would be formed by each of these combinations of reagents. You are advised to use pK_a values to help you and to beware of some cases where 'no change' might be the answer.

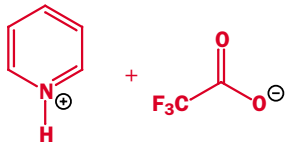
(a)



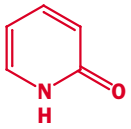
(b)

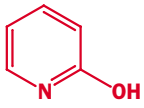


(b)



6. What is the relationship between these two molecules? Discuss the structure of the anion that would be formed by the deprotonation of each compound.

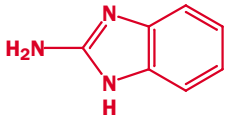


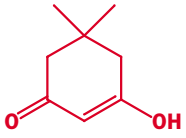


7. What species would be formed by treating this compound with: (**a**) one equivalent; (**b**) two equivalents of $NaNH_2$ in liquid ammonia?



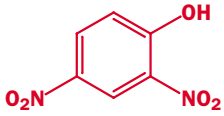
8. The carbon NMR spectra of these compounds could be run in D_2O under the conditions shown. Why were these conditions necessary and what spectrum would you expect to observe?

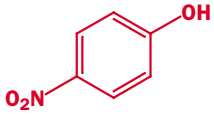


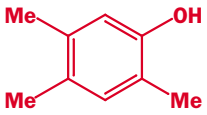


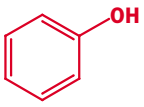
^{13}C spectrum run in DCl/D_2O ^{13}C spectrum run in NaOD/D_2O

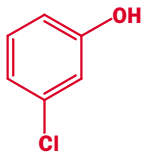
9. The phenols shown here have approximate pK_a values of 4, 7, 9, 10, and 11. Suggest with explanations which pK_a value belongs to which phenol.





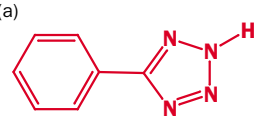




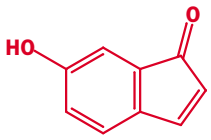


10. Discuss the stabilization of the anions formed by the deprotonation of (**a**) and (**b**) and the cation formed by the protonation of (**c**). Consider delocalization in general and the possibility of aromaticity in particular.

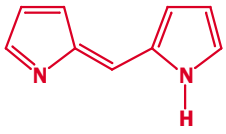
(a)



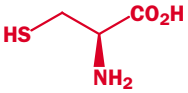
(b)



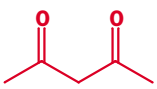
(c)

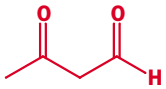


11. The pK_a values for the amino acid cysteine are 1.8, 8.3, and 10.8. Assign these pK_a values to the functional groups in cysteine and draw the structure of the molecule in aqueous solution at the following pHs: 1, 5, 9, and 12.

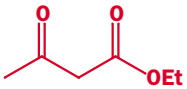


12. Explain the variations in the pK_a values for these carbon acids.

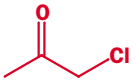

pK_a 9



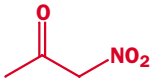
pK_a 5.9



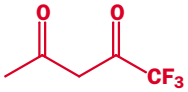
pK_a 10.7



pK_a 16.5



pK_a 5.1



pK_a 4.7

13. Explain the various pK_a values for these derivatives of the naturally occurring amino acid glutamic acid. Say which pK_a belongs to which functional group and explain why they vary in the different derivatives.



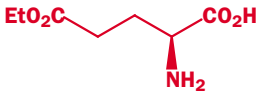
glutamic acid; pK_as 2.19, 4.25, and 9.67



glutamine; pK_as 2.17 and 9.13



diethyl ester; pK_a 7.04

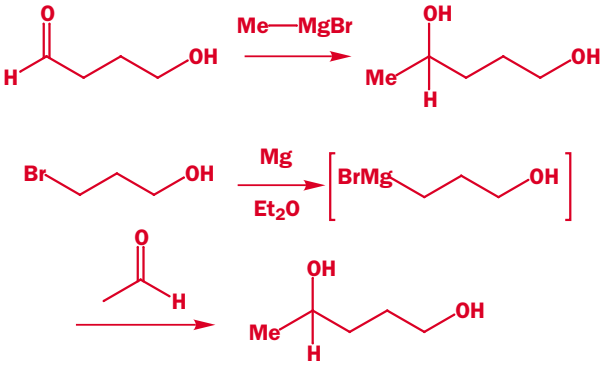


monoethyl ester;
pK_as 2.15 and 9.19



monoethyl ester;
pK_as 3.85 and 7.84

14. Neither of these methods of making pentan-1,4-diol will work. Explain why not—what will happen instead?



Using organometallic reagents to make C–C bonds

9

Connections

Building on:

- Electronegativity and the polarization of bonds ch4
- Grignard reagents and organolithiums attack carbonyl groups ch6
- C–H deprotonated by very strong bases ch8

Arriving at:

- Organometallics: nucleophilic and often strongly basic
- Making organometallics from halo-compounds
- Making organometallics by deprotonating carbon atoms
- Using organometallics to make new C–C bonds from C=O groups

Looking forward to:

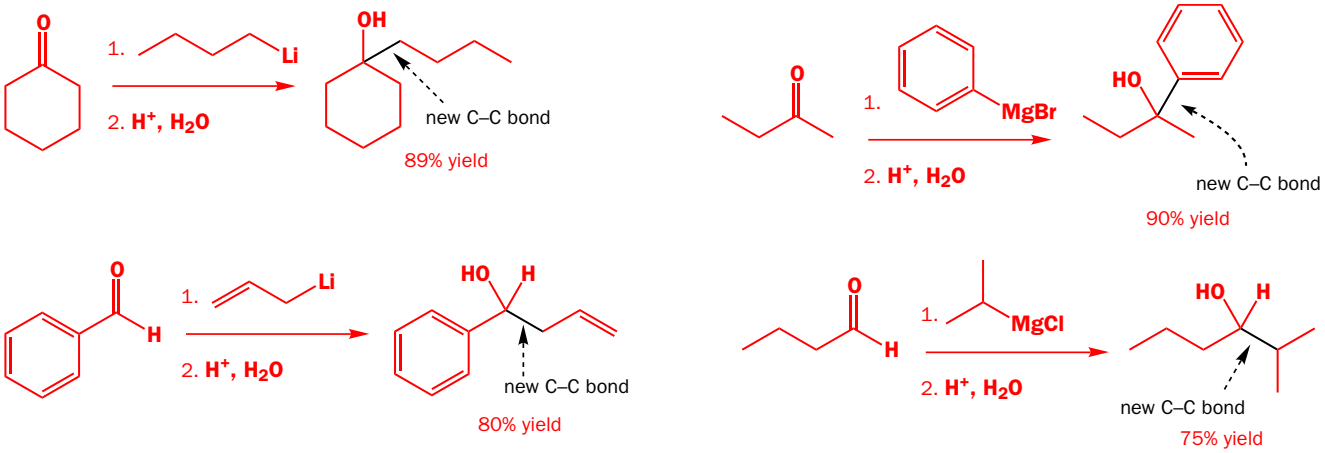
- More about organometallics ch10 & ch48
- More ways to make C–C bonds from C=O groups ch26–ch29
- Synthesis of molecules ch 25 & ch30

Introduction

In Chapters 2–8 we covered basic chemical concepts, which mostly fall under the headings 'structure' (Chapters 2–4 and 7) and 'reactivity' (Chapters 5, 6, and 8). These concepts are the bare bones supporting all of organic chemistry, and now we shall start to put flesh on these bare bones. In Chapters 9–23 we will tell you about the most important classes of organic reaction in more detail.

One of the things organic chemists do, for all sorts of reasons, is to make molecules. And making organic molecules means making C–C bonds. In this chapter we are going to look at one of the most important ways of making C–C bonds: using organometallics, such as organolithiums and Grignard reagents, and carbonyl compounds. We will consider reactions such as these.

■ You met these types of reactions in Chapter 6: in this chapter we will be adding more detail with regard to the nature of the organometallic reagents and what sort of molecules can be made using the reactions.



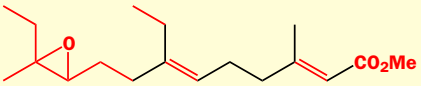
The organometallic reagents act as nucleophiles towards the electrophilic carbonyl group, and this is the first thing we need to discuss: why are organometallics nucleophilic? We then move on to, firstly, how to make organometallics, then to the sort of electrophiles they will react with, and then finally to the sort of molecules we can make with them.

Organometallic compounds contain a carbon–metal bond

The polarity of a covalent bond between two different elements is determined by electronegativity. The more electronegative an element is, the more it attracts the electron density in the bond. So the

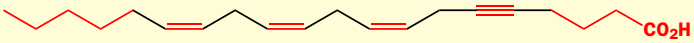
How important are organometallics for making C–C bonds?

As an example, let's take a molecule known as 'juvenile hormone'. It is a compound that prevents several species of insects from maturing and can be used as a means of controlling insect pests. Only very small amounts of the naturally occurring compound can be isolated, but it can instead be made in the lab from simple starting materials. At this stage you need not worry about how, but we can tell you that, of the sixteen C–C bonds in the final product, seven were made by reactions of organometallics, many of them the sort of reactions we will describe in this chapter. This is not an isolated example. As further proof, take this important enzyme inhibitor, closely related to arachidonic acid which you met in Chapter 7. It has been made by a succession of C–C bond-forming reactions using organometallics: eight of the twenty C–C bonds in the product were formed using organometallic reactions.



Cecropia juvenile hormone

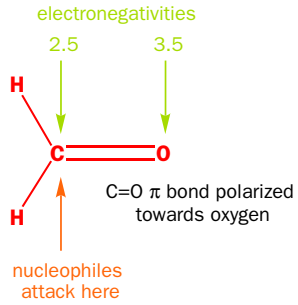
black bonds made by organometallic reactions

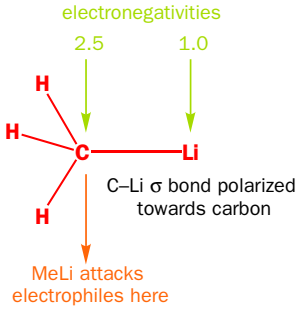


an enzyme inhibitor

greater the *difference* between the electronegativities, the greater the difference between the attraction for the bonding electrons, and the more polarized the bond becomes. In the extreme case of complete polarization, the covalent bond ceases to exist and is replaced by electrostatic attraction between ions of opposite charge. We discussed this in Chapter 4 (p. 000), where we considered the extreme cases of bonding in NaF.

When we discussed (in Chapter 6) the electrophilic nature of carbonyl groups we saw that their reactivity is a direct consequence of the polarization of the carbon–oxygen bond towards the more electronegative oxygen, making the carbon a site for nucleophilic attack. In organolithium compounds and Grignard reagents the key bond bond is polarized in the opposite direction—*towards* carbon—making carbon a nucleophilic centre. This is true for most organometallics because, as you can see from this edited version of the periodic table, metals (such as Li, Mg, Na, K, Ca, and Al) all have lower electronegativity than carbon.

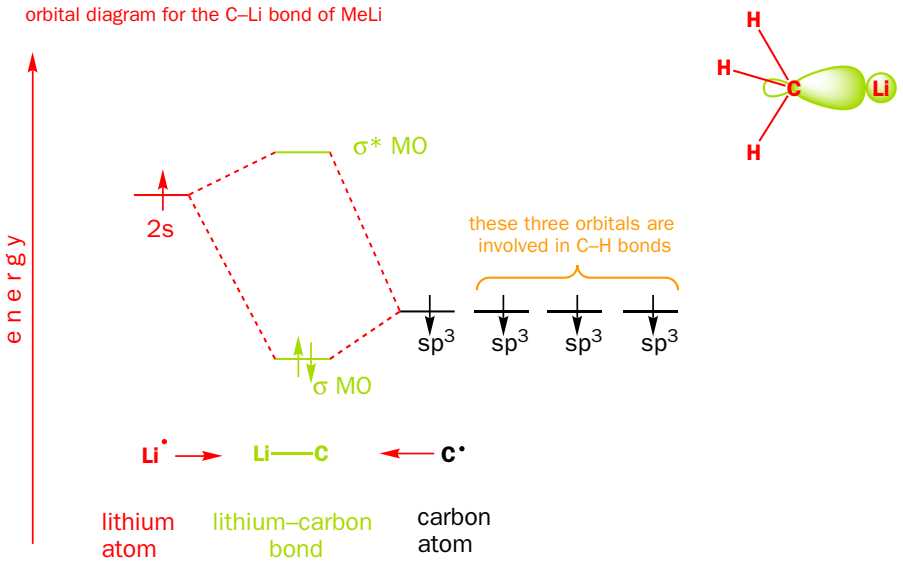




Pauling electronegativities of selected elements

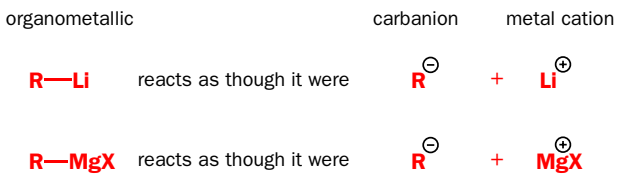
								H 2.2								
Li 1.0	Be 1.6											B 2.0	C 2.5	N 3.04	O 3.5	F 4.0	
Na 0.9	Mg 1.3											Al 1.6	Si 1.9	P 2.2	S 2.6	Cl 3.2	
K 0.8	Ca 1.0									Cu 1.9	Zn 1.7				Se 2.6	Br 3.0	

The orbital diagram—the kind you met in Chapter 4—represents the C–Li bond in methyllithium in terms of a sum of the atomic orbitals of carbon and lithium. Remember that, the more



electronegative an atom is, the lower in energy its atomic orbitals are (p. 000). The filled C–Li σ orbital that arises is closer in energy to the carbon's sp^3 orbital than to the lithium's 2s orbital, so we can say that the carbon's sp^3 orbital makes a greater contribution to the C–Li σ bond and that the C–Li bond has a larger coefficient on carbon. Reactions involving the filled σ orbital will therefore take place at C rather than Li. The same arguments hold for the C–Mg bond of Grignard reagents.

We can also say that, because the carbon's sp^3 orbital makes a greater contribution to the C–Li σ bond, the σ bond resembles a filled C sp^3 orbital—in other words it *resembles* a lone pair on carbon. This is a useful idea because it allows us to think about the way in which methyllithium reacts—as though it were an ionic compound Me^-Li^+—and you may sometimes see MeLi or MeMgCl represented in mechanisms as Me^-.



▶ You have already met cyanide (p. 000), a carbon nucleophile that really does have a lone pair on carbon. Cyanide's lone pair is stabilized by being in a lower-energy sp orbital (rather than sp^3) and by having the electronegative nitrogen atom triply bonded to the carbon.

▶ Carbon atoms that carry a negative charge, for example Me^-, are known as **carbanions**.

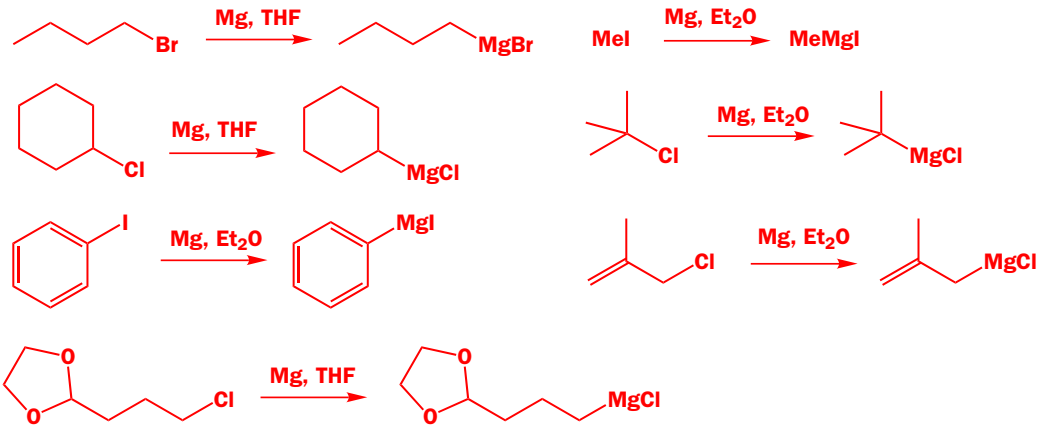
The true structure of organolithiums and Grignard reagents is rather more complicated!

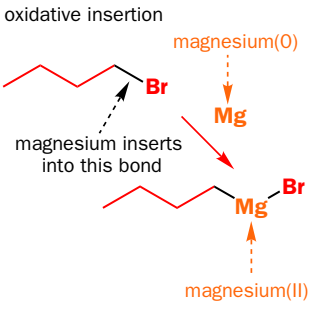
Even though these organometallic compounds are extremely reactive with water and oxygen, and have to be handled under an atmosphere of nitrogen or argon, a number have been studied by X-ray crystallography in the solid state and by NMR in solution. It turns out that they generally form complex aggregates with two, four, six, or more molecules bonded together, often with solvent molecules. In this book we shall not be concerned with these details, and it will suffice always to represent organometallic compounds as simple monomeric structures.

Making organometallics

How to make Grignard reagents

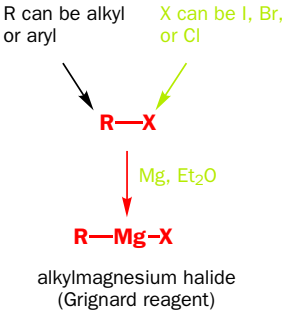
Grignard reagents are made by reacting magnesium turnings with alkyl halides in ether solvents to form solutions of alkylmagnesium halide. Iodides, bromides, and chlorides can be used, as can both aryl and alkyl halides, though they cannot contain any functional groups that would react with the Grignard reagent once it is formed. Here are some examples.



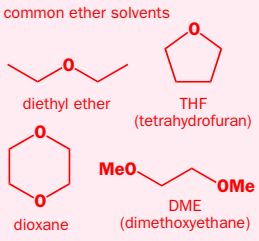


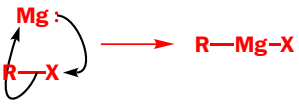
The reaction scheme is easy enough to draw, but what is the mechanism? Overall it involves an *insertion* of magnesium into the new carbon–halogen bond. There is also a change in oxidation state of the magnesium, from Mg(0) to Mg(II). The reaction is therefore known as an **oxidative insertion** or **oxidative addition**, and is a general process for many metals such as Mg, Li (which we meet shortly), Cu, and Zn.

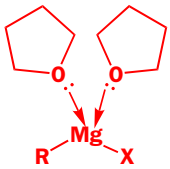
The mechanism of the reaction is not completely understood but a possible (but probably not very accurate) way of writing the mechanism is shown here: the one thing that is certain is that the first interaction is between the metal and the halogen atom.



▶ Diethyl ether (Et_2O) and THF are the most commonly used solvents, but you may also meet others such as dimethoxyethane (DME) and dioxane.

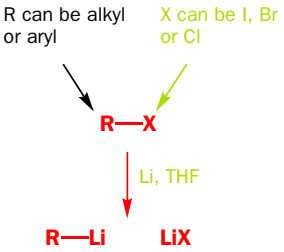






complex between Lewis-acidic metal atom and lone pairs of THF

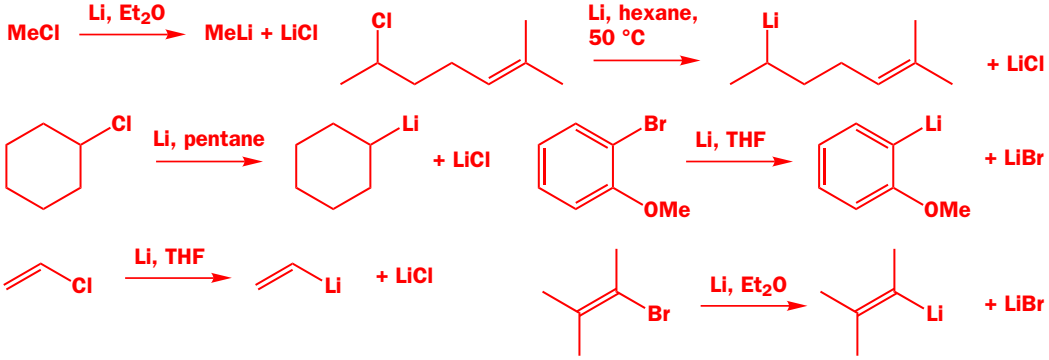
The reaction takes place not in solution but on the surface of the metal, and how easy it is to make a Grignard reagent can depend on the state of the surface—how finely divided the metal is, for example. Magnesium is usually covered by a thin coating of magnesium oxide, and Grignard formation generally requires 'initiation' to allow the metal to come into contact with the alkyl halide. Initiation can be accomplished by adding a small amount of iodine or 1,2-diiodoethane, or by using ultrasound to dislodge the oxide layer. The ether solvent is essential for Grignard formation because (1) ethers (unlike, say, alcohols or dichloromethane) will not react with Grignards and, more importantly, (2) only in ethers are Grignard reagents soluble. In Chapter 5 you saw how triethylamine forms a complex with the Lewis acid BF_3, and much the same happens when an ether meets a metal ion such as magnesium or lithium: the metals are Lewis-acidic because they have empty orbitals (2p in the case of Li and 3p in the case of Mg) that can accept the lone pair of the ether.



alkylithium plus lithium halide

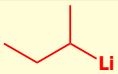
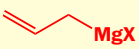
How to make organolithium reagents

Organolithium compounds may be made by a similar oxidative insertion reaction from lithium metal and alkyl halides. Each inserting reaction requires two atoms of lithium and generates one equivalent of lithium halide salt. As with Grignard formation, there is really very little limit on the types of organolithium that can be made this way.



Some Grignard and organolithium reagents are commercially available

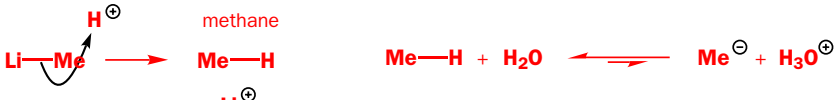
Most chemists (unless they were working on a very large scale) would not usually make the simpler organolithiums or Grignard reagents by these methods, but would buy them in bottles from chemical companies (who, of course, *do* use these methods). The table lists some of the most important commercially available organolithiums and Grignard reagents.

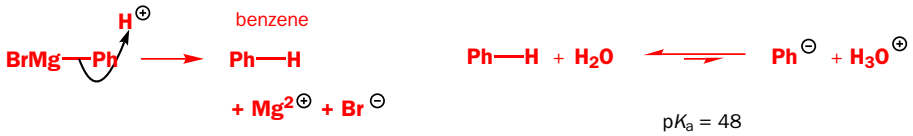
Commercially available organometallics	
methyllithium (MeLi)	methylmagnesium chloride, bromide, and iodide (MeMgX)
n-butyllithium (*n*-BuLi or just BuLi) 	ethylmagnesium bromide (EtMgBr)
sec-butyllithium (*sec*-BuLi or *s*-BuLi) 	butylmagnesium chloride (BuMgCl)
tert-butyllithium (*tert*-BuLi or *t*-BuLi) 	allylmagnesium chloride and bromide 
phenyllithium (PhLi)	phenylmagnesium chloride and bromide (PhMgCl or PhMgBr)

Organometallics as bases

Organometallics need to be kept absolutely free of moisture—even moisture in the air will destroy them. The reason is that they react very rapidly and highly exothermically with water to produce

alkanes. Anything that can protonate them will do the same thing. If we represent these protonation reactions slightly differently, putting the products on the left and the starting materials (represented, just for effect, as 'carbanions') on the right, you can see that that they are acid–base equilibria from the last chapter. The organometallic acts as a base, and is protonated to form its conjugate acid—methane or benzene in these cases.

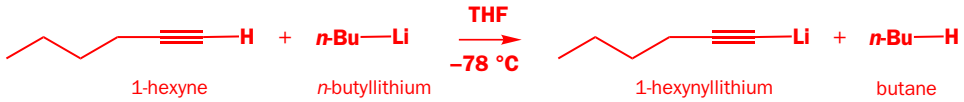


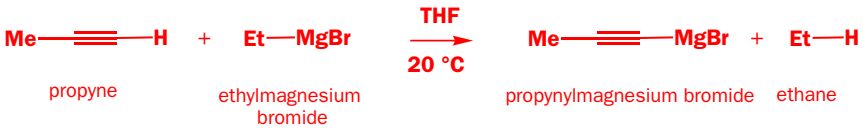


The equilibria lie vastly to the left: the pK_a values indicate that methane and benzene are extremely weak acids and that methyllithium and phenylmagnesium bromide must therefore be extremely strong bases. Some of the most important uses of organolithiums—butyllithium, in particular—are as bases and, because they are so strong, they will deprotonate almost anything. That makes them very useful as reagents for making *other* organolithiums.

Making organometallics by deprotonating alkynes

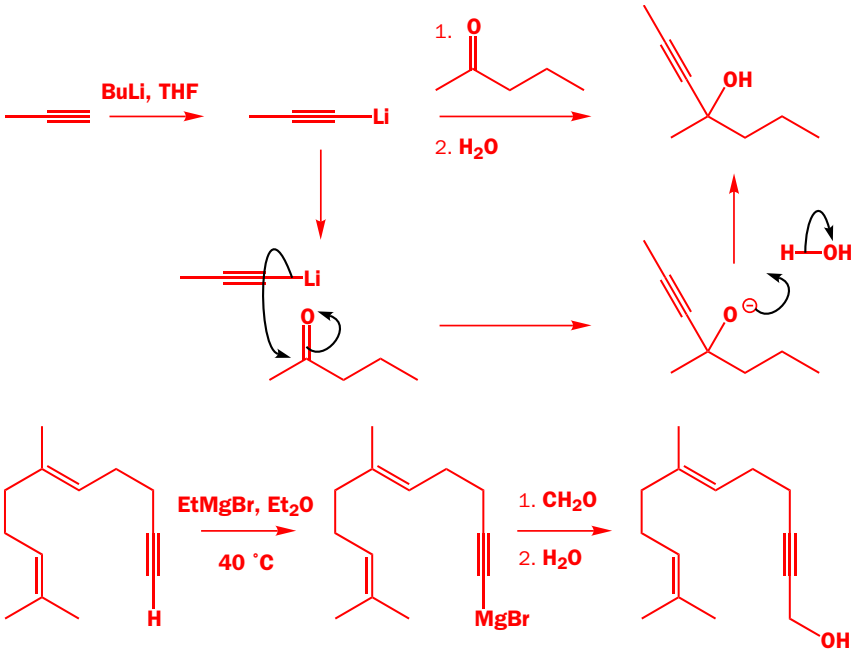
In Chapter 8 (p. 000) we talked about how hybridization affects acidity. Alkynes, with their C–H bonds formed from sp orbitals, are the most acidic of hydrocarbons, with pK_as of about 25. They can be deprotonated by more basic organometallics such as butyllithium or ethylmagnesium bromide. Alkynes are sufficiently acidic to be deprotonated even by nitrogen bases, and another common way of deprotonating alkynes is to use $NaNH_2$ (sodium amide), obtained by reacting sodium with liquid ammonia. An example of each is shown here: we have chosen to represent the alkynyllithium and alkynylmagnesium halide as organometallics and the alkynyl sodium as an ionic salt. Propyne and acetylene are gases, and can be bubbled through a solution of the base.





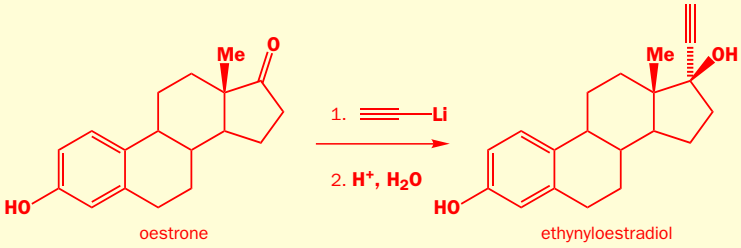


The metal derivatives of alkynes can be added to carbonyl electrophiles as in the following examples. The first (we have reminded you of the mechanism for this) is the initial step of an important synthesis of the antibiotic, erythronolide A, and the second is the penultimate step of a synthesis of the widespread natural product, farnesol.



Ethynyloestradiol

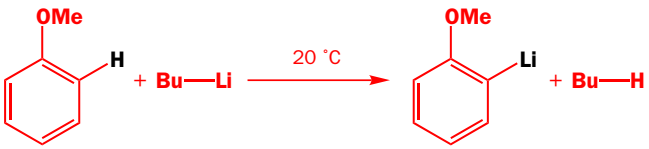
The ovulation-inhibiting component of many oral contraceptive pills is a compound known as ethynyloestradiol, and this compound too is made by an alkynyllithium addition to the female sex hormone oestrone. A range of similar synthetic analogues of hormones containing an ethynyl unit are used in contraceptives and in treatments for disorders of the hormonal system.



oestrone ethynyloestradiol

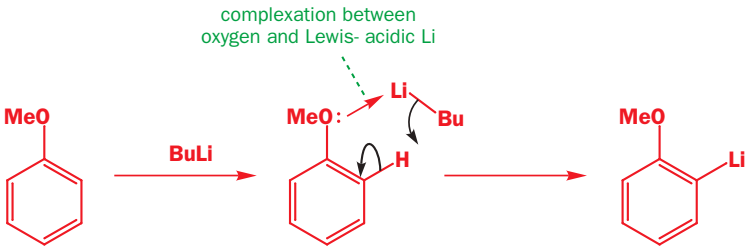
Making organometallics by deprotonating aromatic rings: ortholithiation

Look at the reaction below: in some ways it is quite similar to the ones we have just been discussing. Butyllithium deprotonates an sp^2 hybridized carbon atom to give an aryllithium. It works because the protons attached to sp^2 carbons are more acidic than protons attached to sp^3 carbons (though they are a lot less acidic than alkyne protons).

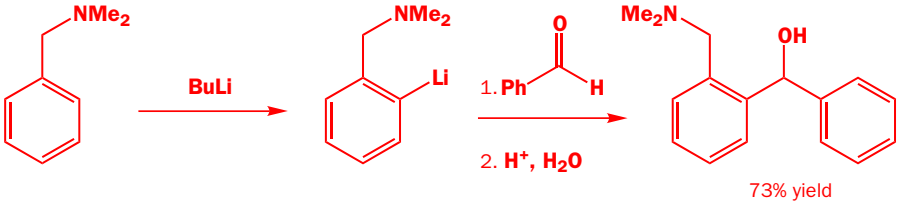


But there is another factor involved as well. There has to be a functional group containing oxygen (sometimes nitrogen) next to the proton to be removed. This functional group 'guides' the butyllithium, so that it attacks the adjacent protons. It does this by forming a complex with the Lewis-acidic lithium atom, much as ether solvents dissolve Grignard reagents by complexing their Lewis-acidic metal ions. This mechanism means that it is only the protons *ortho* to the functional group that can be removed, and the reaction is known as an **ortholithiation**.

■ The terms *ortho*, *meta*, and *para* were defined on p. 000.



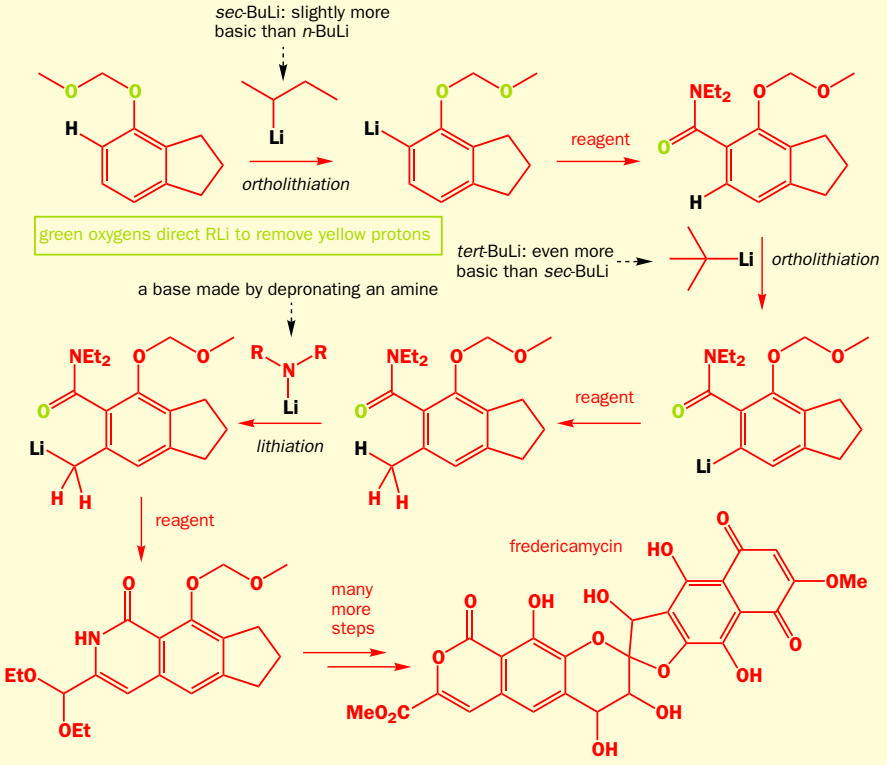
The example below shows an organolithium formed by ortholithiation being used to make a new C–C bond. Here it is a nitrogen atom that directs attack of the butyllithium.



Ortholithiation is useful because the starting material does not need to contain a halogen atom. But it is much less general than the other ways we have told you about for making organolithiums, because there are rather tight restrictions on what sorts of groups the aromatic ring must carry.

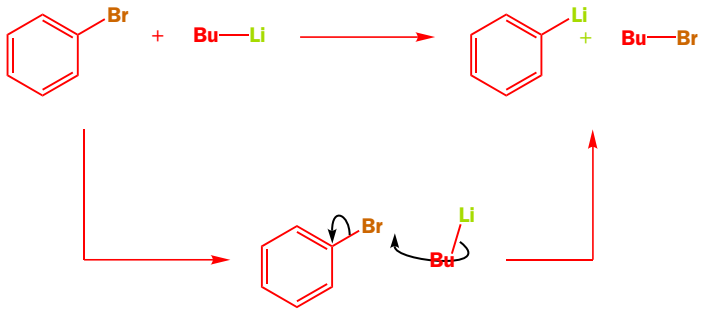
Fredericamycin

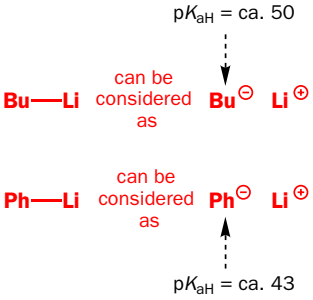
Fredericamycin is a curious aromatic compound extracted in 1981 from the soil bacterium *Streptomyces griseus*. It is a powerful antibiotic and antitumour agent, and its structure is shown below. The first time it was made in the laboratory, in 1988, the chemists in Boston started their synthesis with three consecutive lithiation reactions: two are ortholithiations, and the third is slightly different. You needn't be concerned about the reagents that react with the organolithiums; just look at the lithiation reactions themselves. In each one, an oxygen atom (colour-coded green) directs a strongly basic reagent to remove a nearby proton (colour-coded black). As it happens, none of the steps uses *n*-BuLi itself, but instead its more reactive cousins, *sec*-BuLi and *tert*-BuLi (see the table on p. 000). The third lithiation step uses a different kind of base, made by deprotonating an amine (pK_a about 35). The yellow proton removed in this third lithiation is more acidic because it is next to an aromatic ring (p. 000).



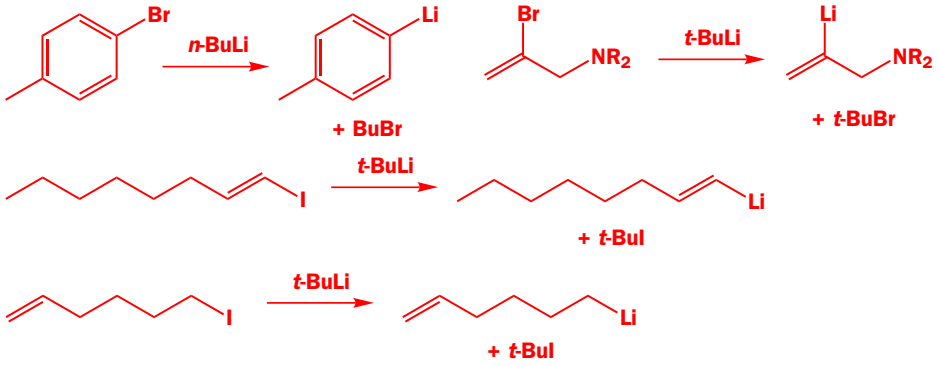
Halogen–metal exchange

Deprotonation is not the only way to use one simple organometallic reagent to generate another more useful one. Organolithiums can also remove halogen atoms from alkyl and aryl halides in a reaction known as **halogen–metal exchange**. Look at this example and you will immediately see why.

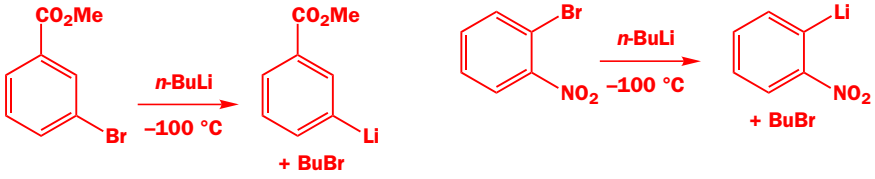




The bromine and the lithium simply swap places. As with many of these organometallic processes, the mechanism is not altogether clear, but can be represented as a nucleophilic attack on bromine by the butyllithium. But why does the reaction work? The key, again, is pK_a. The reaction works because the organolithium that is formed (phenyllithium, which protonated would give benzene, pK_a about 43) is less basic (more stable) than the organolithium we started with (BuLi, which protonated would give butane, pK_a about 50). The following reactions are also successful halogen–metal exchanges, and in each case the basicity of the organolithium decreases.

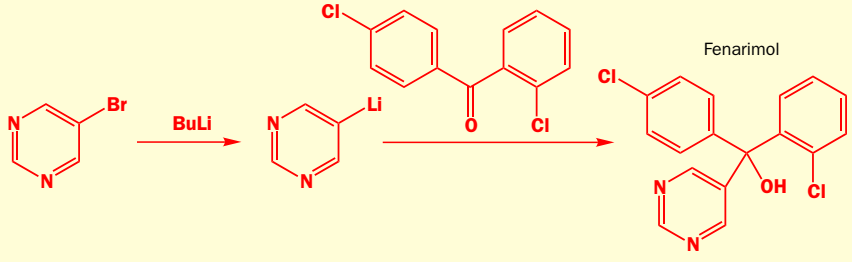


Iodides, bromides, and chlorides can all be used, but the reactions are fastest with iodides and bromides. In fact, halogen–metal exchange can be so fast that, at very low temperature (–100 °C and below), it is even occasionally possible to use compounds containing functional groups that would otherwise react with organolithiums, such as esters and nitro compounds.



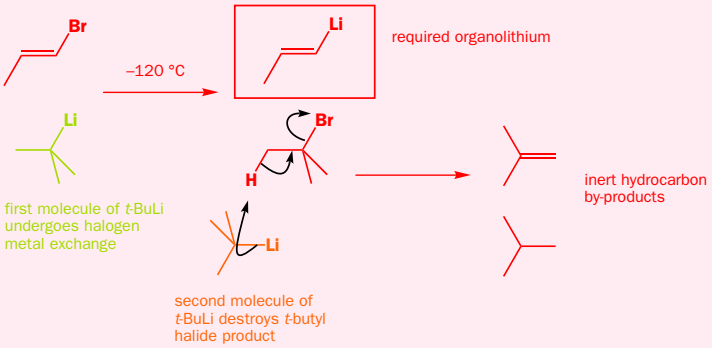
Fenarimol

Fenarimol is a fungicide that works by inhibiting the fungus's biosynthesis of important steroid molecules. It is made by reaction of a diarylketone with an organolithium derived by halogen–metal exchange.



▶ *tert*-Butyllithium

Alkyl substituents are slightly electron-donating, so more substituted organolithiums are less stable because the carbon atom is forced to carry even more of a negative charge. Instability reaches a peak with *tert*-butyllithium, which is the most basic of the commonly available organolithium reagents, and so is particularly useful for halogen exchange reactions. (It is so unstable that even in solution it will spontaneously catch fire in contact with air.) Its importance is enhanced by a subtlety in its reactions that we have not yet mentioned: a problem with halogen–metal exchanges is that the two products, an organolithium and an alkyl halide, sometimes react with one another in a substitution (Chapter 17) or elimination (Chapter 19) reaction. This problem is overcome provided two equivalents of *t*-BuLi are used. The first takes part in the halogen–metal exchange, while the second immediately destroys the *t*-butyl bromide produced by the exchange, preventing it from reacting with the organolithium product.

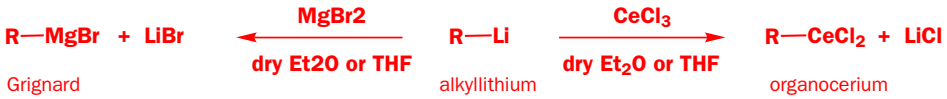


Do not be concerned about the mechanism at this stage: we will come back to this sort of reaction in Chapter 19.

Transmetallation

Organolithiums can be converted to other types of organometallic reagents by **transmetallation**—simply treating with the salt of a less electropositive metal. The more electropositive lithium goes into solution as an ionic salt, while the less electropositive metal (magnesium and cerium in these examples) takes over the alkyl group.

■ You will see several examples of transmetallation with copper salts in the next chapter.

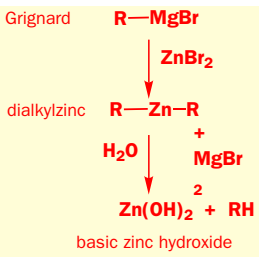


But why bother? Well, the high reactivity—and in particular the basicity—of organolithiums, which we have just been extolling, sometimes causes unwanted side-reactions. You saw in Chapter 8 that protons next to carbonyl groups are moderately acidic (pK_a about 20), and because of this organolithiums occasionally act as bases towards carbonyl compounds instead of as nucleophiles. Organoceriums, for example, are rather less basic, and may give higher yields of the nucleophilic addition products than organolithiums or Grignard reagents.

■ You met the idea that carbonyl groups, and aromatic rings, acidify adjacent protons in Chapter 8 (p. 000).

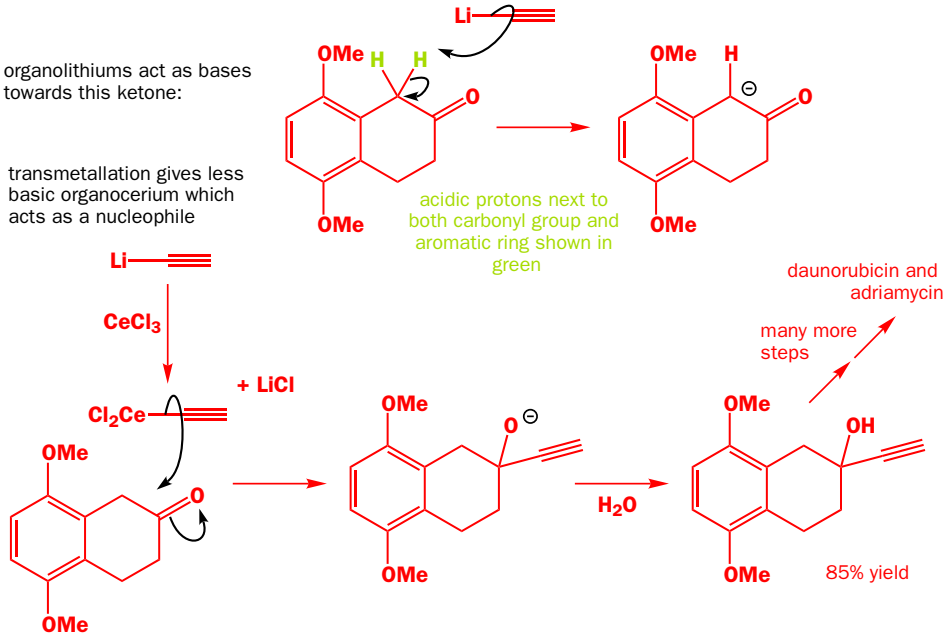
An instance where transmetallation is needed to produce another organometallic, which does act as a base but not as a nucleophile!

Dialkylzincs are stable, distillable liquids that can be made by transmetallating Grignard reagents with zinc bromide. They are much less reactive than organolithium or organomagnesium compounds, but they are still rather basic and react with water to give zinc hydroxides and alkanes. They are used to preserve old books from gradual decomposition due to acid in the paper. The volatile dialkylzinc penetrates the pages thoroughly, where contact with water produces basic hydoxides that neutralize the acid, stopping the deterioration.



Acidic protons were a major problem in several syntheses of the anticancer compounds, daunorubicin and adriamycin, which start with a nucleophilic addition to a ketone with a pair of particularly acidic protons. Organolithium and organomagnesium compounds remove these pro-

tons rather than add to the carbonyl group, so some Japanese chemists turned to organocerium compounds. They made ethynylcerium dichloride ($HC{\equiv}CCeCl_2$) by deprotonating acetylene, and then transmetallating with cerium trichloride. They found that it reacted with the ketone to give an 85% yield of the alcohol they wanted.



Using organometallics to make organic molecules

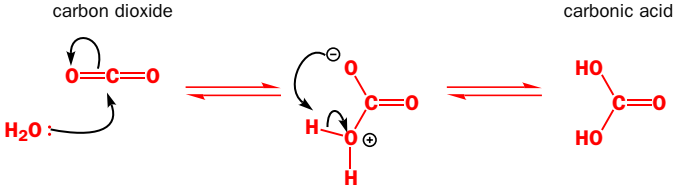
Now that you have met all of the most important ways of making organometallics (summarized here as a reminder), we shall move on to consider how to use them to make molecules: what sorts of electrophiles do they react with and what sorts of products can we expect to get from their reactions? Having told you how you can make other organometallics, we shall really be concerned for the rest of this chapter only with Grignard reagents and organolithiums. In nearly all of the cases we shall talk about, the two classes of organometallics can be used interchangeably.

Ways of making organometallics

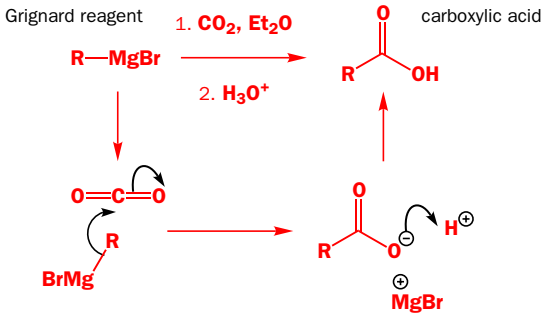
- Oxidative insertion of Mg into alkyl halides
- Oxidative insertion of Li into alkyl halides
- Deprotonation of alkynes
- Ortholithiation of functionalized benzene rings
- Halogen–metal exchange
- Transmetallation

Making carboxylic acids from organometallics and carbon dioxide

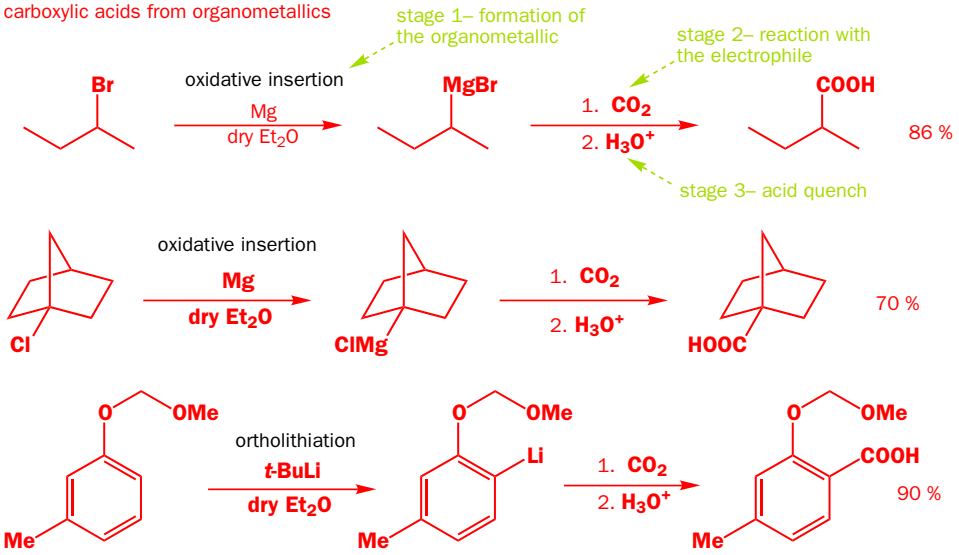
Carbon dioxide is a carbonyl compound, and it is an electrophile. It reacts slowly with water, for example, to form the unstable compound carbonic acid—you can think of this as a hydration reaction of a carbonyl group.



Carbon dioxide reacts with organolithiums and Grignard reagents to give carboxylate salts. Protonating the salt with acid gives a carboxylic acid with one more carbon atom than the starting organometallic. The reaction is usually done by adding solid CO_2 to a solution of the organolithium in THF or ether, but it can also be done using a stream of dry CO_2 gas.

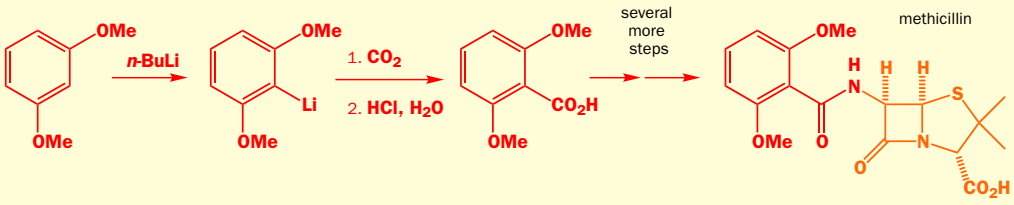


The examples below show the three stages of the reaction: (1) forming the organometallic; (2) reaction with the electrophile (CO_2); and (3) the acidic work-up or **quench**, which protonates the product and destroys any unreacted organometallic left over at the end of the reaction. The three stages of the reaction have to be monitored carefully to make sure that each is finished before the next is begun—in particular it is absolutely essential that there is no water present during either of the first two stages—water must be added only at the end of the reaction, when the organometallic has all been consumed by reaction with the electrophile. You may occasionally see schemes written out without the quenching step included—but it is nonetheless always needed.



Methicillin synthesis

Methicillin is an important antiobiotic compound because it works even against bacteria that have developed resistance to penicillin, whose structure is quite similar. It can be made from an acid obtained by reaction of carbon dioxide with an organolithium. In this case the organolithium is made by an ortholithiation reaction of a compound with two oxygen atoms that direct removal of the proton in between them.

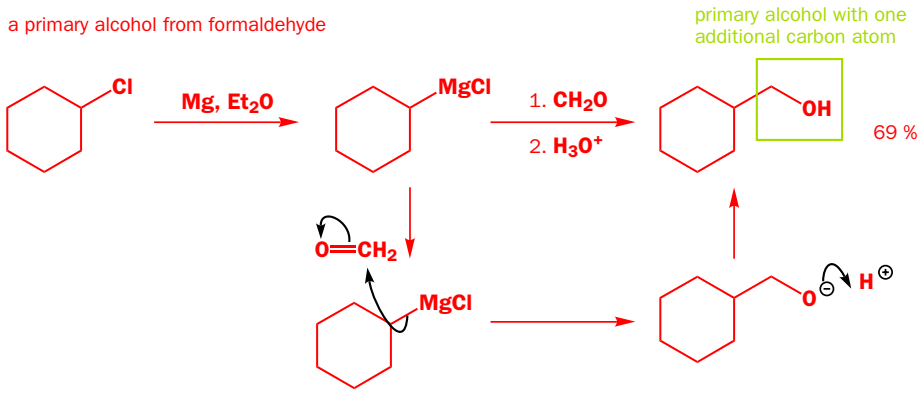


Making primary alcohols from organometallics and formaldehyde

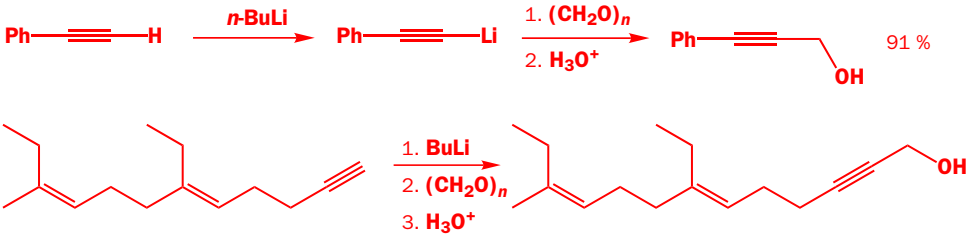
You met formaldehyde, the simplest aldehyde, in Chapter 6, where we discussed the difficulties of using it in anhydrous reactions: it is either hydrated or a polymer (paraformaldehyde, $(CH_2O)_n$) and, in order to get pure, dry formaldehyde, it is necessary to heat ('crack') the polymer to

■ Primary, secondary, and tertiary are defined on p. 000.

decompose it. But formaldehyde is a remarkably useful reagent for making **primary** alcohols, in other words, alcohols that have just one carbon substituent attached to the hydroxy-bearing C atom. Just as carbon dioxide adds one carbon and makes an acid, fomaldehyde adds one carbon and makes an alcohol.

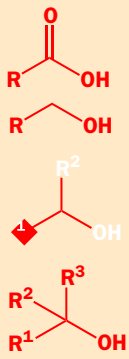


In the next examples, formaldehyde makes a primary alcohol from two deprotonated alkynes. The second reaction here (for which we have shown organolithium formation, reaction, and quench simply as a series of three consecutive reagents) forms one of the last steps of the synthesis of *Cecropia* juvenile hormone whose structure you met right at the beginning of the chapter.



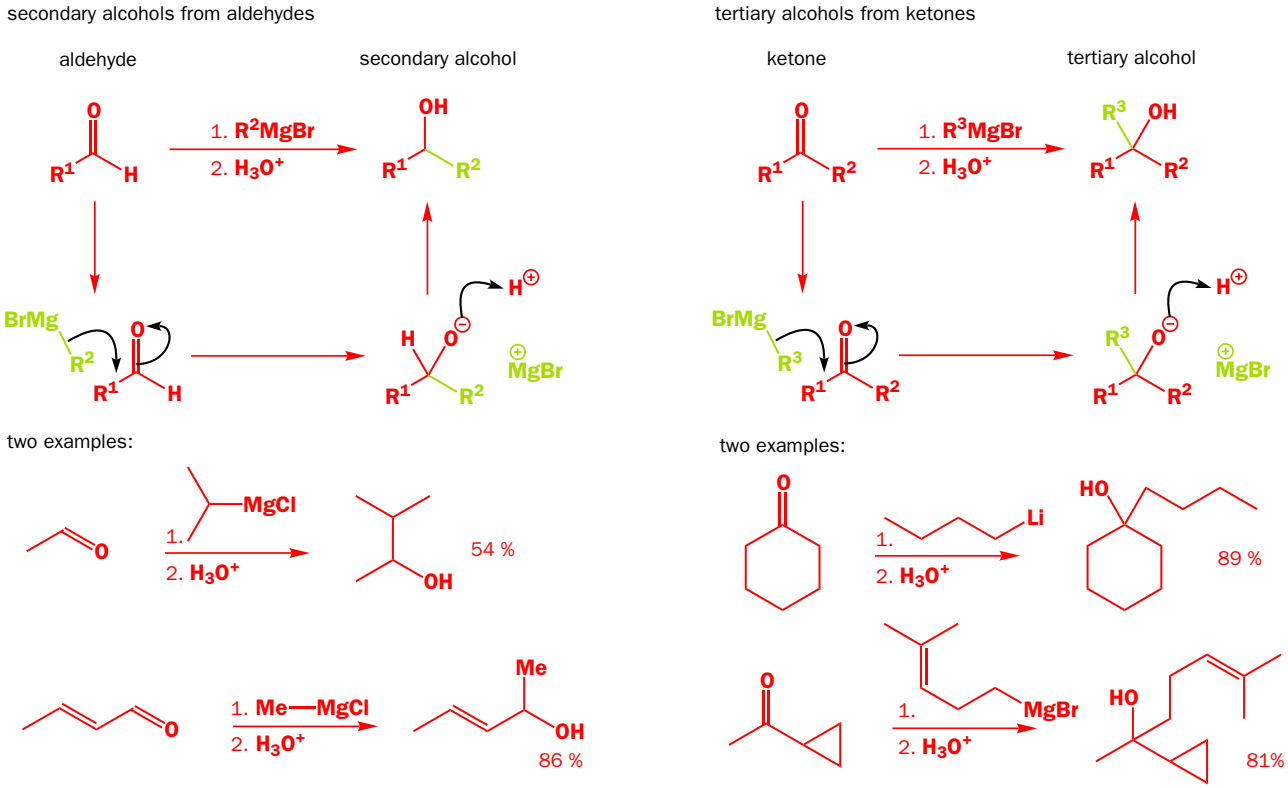
● **Something to bear in mind with all organometallic additions to carbonyl compounds is that the addition takes the oxidation level *down one*. In other words, if you start with an aldehyde, you end up with an alcohol. More specifically,**

- **Additions to CO_2 give carboxylic acids**
- **Additions to formaldehyde (CH_2O) give primary alcohols**
- **Additions to other aldehydes (RCHO) give secondary alcohols**
- **Additions to ketones give tertiary alcohols**

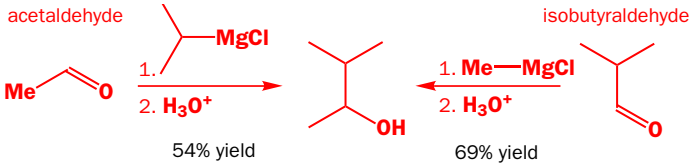


Secondary and tertiary alcohols: which organometallic, which aldehyde, which ketone?

Aldehydes and ketones react with Grignard or organolithium reagents to form secondary and tertiary alcohols, respectively, and some examples are shown with the general schemes here.



To make any secondary alcohol, however, there is often a choice of two possible routes, depending on which part of the molecule you choose to make the organometallic and which part you choose to make the aldehyde. For example, the first example here shows the synthesis of a secondary alcohol from isopropylmagnesium chloride and acetaldehyde. But it is equally possible to make this same secondary alcohol from isobutyraldehyde and methyllithium or a methylmagnesium halide.

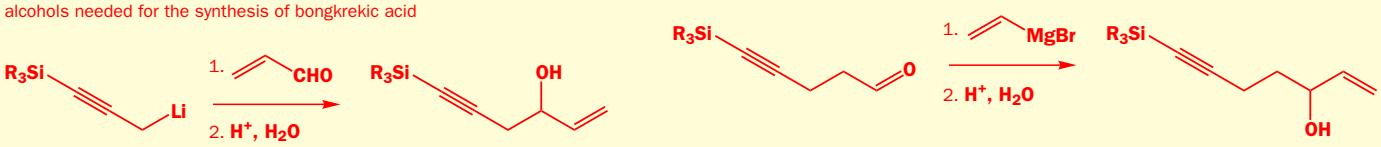


Indeed, back in 1912, when this alcohol was first described in detail, the chemists who made it chose to start with acetaldehyde, while in 1983, when it was needed as a starting material for a synthesis, it was made from isobutyraldehyde. Which way is better? The 1983 chemists probably chose the isobutyraldehyde route because it gave a better yield. But, if you were making a secondary alcohol for the first time, you might just have to try both in the lab and see which one gave a better yield. Or you might be more concerned about which uses the cheaper, or more readily available, starting materials—this was probably behind the choice of methylmagnesium chloride and the unsaturated aldehyde in the second

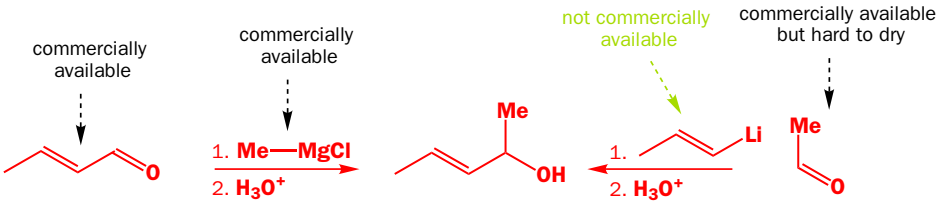
Flexible alcohol synthesis

As an illustration of the flexibility available in making secondary alcohols, one synthesis of bongkrekic acid, a highly toxic compound that inhibits transport across certain membranes in the cell, required both of these (very similar) alcohols. The chemists making the compound at Harvard University chose to make each alcohol from quite different starting materials: an unsaturated aldehyde and an alkyne-containing organolithium in the first instance, and an alkyne-containing aldehyde and vinyl magnesium bromide in the second.

alcohols needed for the synthesis of bongkrekic acid

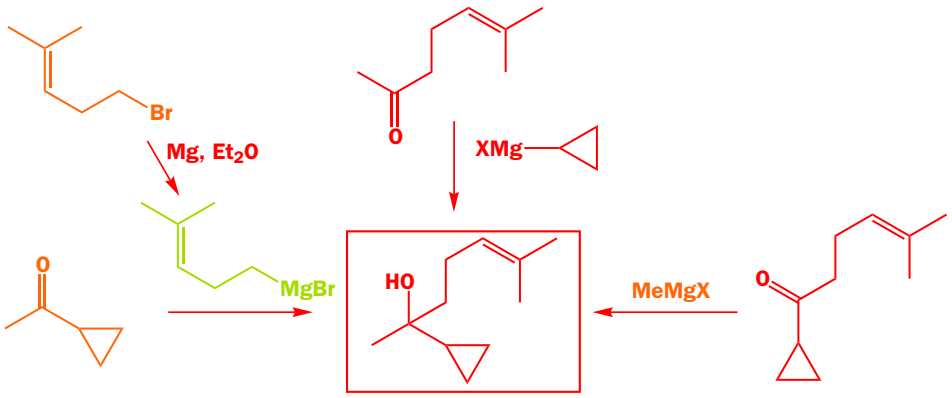


example. Both can be bought commercially, while the alternative route to this secondary alcohol would require a vinyllithium or vinylmagnesium bromide reagent that would have to be made from a vinyl halide, which is itself not commercially available, along with difficult-to-dry acetaldehyde.



With tertiary alcohols, there is even more choice. The last example in the box is a step in a synthesis of the natural product, nerolidol. But the chemists in Paris who made this tertiary alcohol could in principle have chosen any of these three routes.

three routes to a tertiary alcohol

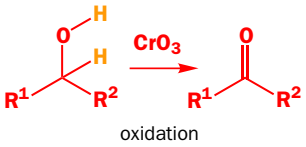


■ Note we have dropped the aqueous quench step from these schemes to avoid cluttering them.

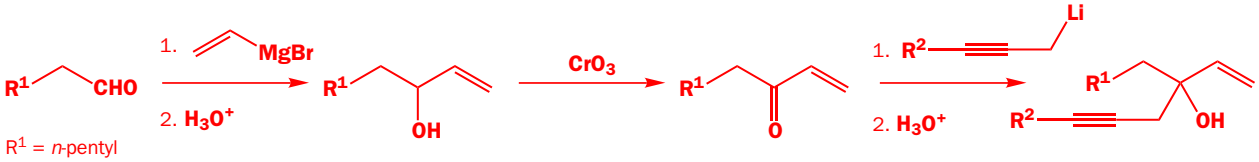
Only the reagents in orange are commercially available, but, as it happens, the green Grignard reagent can be made from an alkyl bromide, which is itself commercially available, making the route on the left the most reasonable.

Now, do not be dismayed! We are not expecting you to remember a chemical catalogue and to know which compounds you can buy and which you can't. All we want you to appreciate at this stage is that there are usually two or three ways of making any given secondary or tertiary alcohol, and you should be able to suggest alternative combinations of aldehyde or ketone and Grignard reagent that will give the same product. You are not expected to be able to assess the relative merits of the different possible routes to a compound. That is a topic we leave for a much later chapter on retrosynthetic analysis, Chapter 30.

Ketones by oxidation of secondary alcohols



Tertiary alcohols can be made from ketones, and secondary ones from aldehydes, but we should now show you that ketones can be made from secondary alcohols by an oxidation reaction. There are lots of possible reagents, but a common one is an acidic solution of chromium trioxide. We will look in much more detail at oxidation later, when we will discuss the mechanism of the reaction, but for now take it from us that secondary alcohols give ketones on treatment with CrO_3. Note that you can't oxidize tertiary alcohols (without breaking a C–C bond). The link between secondary alcohols and ketones means that the ketones needed for making tertiary alcohols can themselves ultimately be made by addition of organometallics to carbonyl compounds. Here, for example, is a sequence of reactions leading to a compound needed to make the drug viprostol.

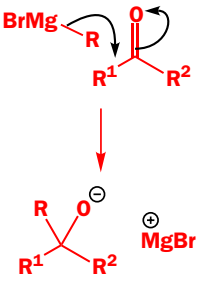


R1 = *n*-pentyl

A closer look at some mechanisms

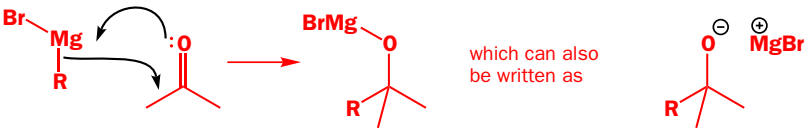
We finish this chapter with some brief words about the mechanism of the addition of organometallics to carbonyl compounds. The problem with this reaction is that no-one really knows precisely what happens during the addition reaction. We know what the organic products are because we can isolate them and look at them using NMR and other spectroscopic techniques. But what happens to the metal atoms during the reaction?

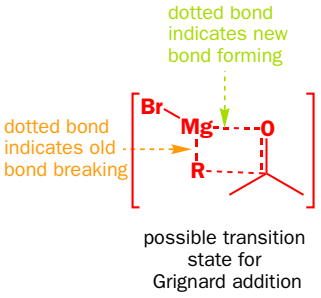
You will have noticed that we always write the addition reaction with the metal atom just falling off the organometallic as it reacts, and then appearing near to the anionic oxygen atom of the product. In other words, we have not been specific about what the metal atom is actually doing during the addition; in fact, we have been deliberately vague so as not to imply anything that may not be true. But there is one thing that is certain about this process, and before we discuss it we need to remind you of something we talked about in Chapter 6: the effect of acid on the addition of nucleophiles to carbonyl groups. We said that acid tends to catalyse addition reactions by protonating the carbonyl group, making it positively charged and therefore more electrophilic.



Now, of course, in our organometallic addition reactions we have no acid (H^+) present, because that would destroy the organometallic reagent. But we do have *Lewis-acidic* metal atoms—Li or Mg—and these can play exactly the same role. They can coordinate to the carbonyl's oxygen atom, giving the carbonyl group positive charge and therefore making it more electrophilic. In one possible version of the mechanism, a four-centred mechanism allows coordination of the magnesium to the oxygen while the nucleophilic carbon atom attacks the carbonyl group. The product ends up with a (covalent) Mg–O bond, but this is just another way of writing $RO^- MgBr^+$.

■ Lewis acids were introduced in Chapter 5.



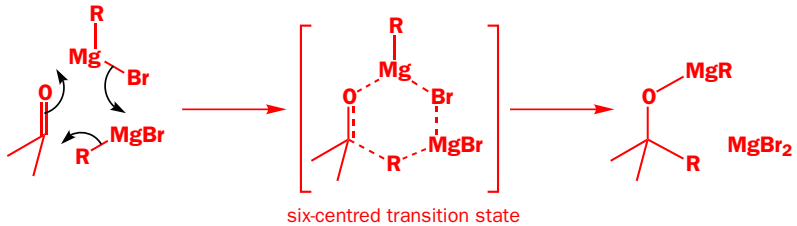


The four-centred mechanism is quite hard to visualize just with curly arrows: what they are saying is that the O–Mg interaction is forming at the same time as the new C–C bond, and that simultaneously the old C–Mg bond and C=O π bond are breaking. A neat way of representing all of this is to draw what we might see if we took a snapshot of the reaction halfway through, using dotted lines to represent the partially formed or partially broken bonds. It would look something like this, and such a snapshot is known as the **transition state** for the reaction.

▶ The term 'transition state' has, in fact, a more precise definition, which we will introduce in Chapter 13.

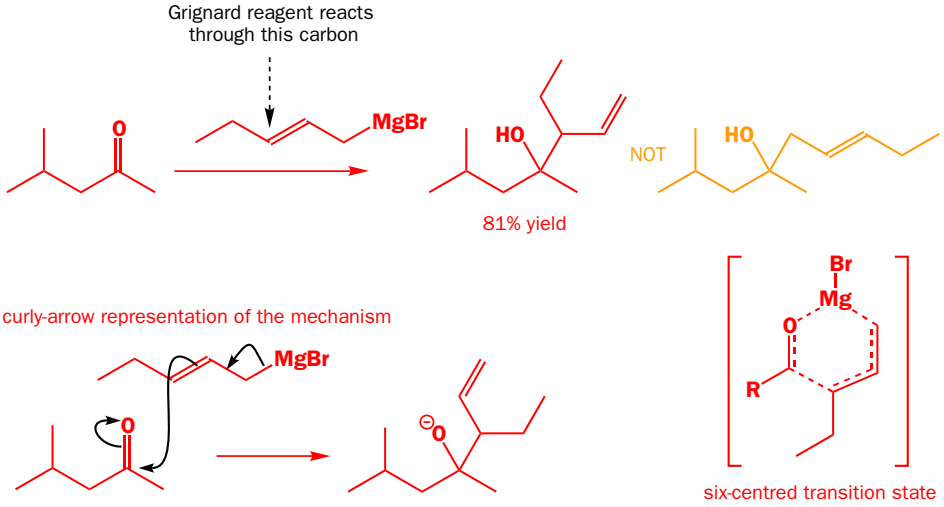
An alternative possibility is that two molecules of the Grignard reagent are involved, and that the transition state is a six-membered ring. We are telling you all this not because we want to confuse you but because we want to be honest: there is genuine uncertainty about the mechanism, and this arises because, while it is easy to determine the products of a reaction using spectroscopy, it is much harder to determine mechanisms.

■ We shall devote two chapters entirely to mechanism and how it is studied: Chapters 13 and 41.

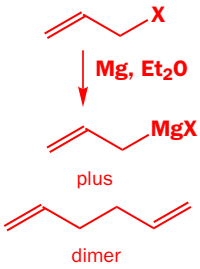


But, for one type of Grignard reagent, it is certain that the addition proceeds through a six-membered ring. Here is a reaction between an allylic Grignard reagent and a ketone. The product is a tertiary alcohol, but perhaps not the tertiary alcohol you would expect. The Grignard reagent appears to

have attached itself via the wrong carbon atom. We can explain this by a six-membered transition state, but one involving only one molecule of Grignard reagent.

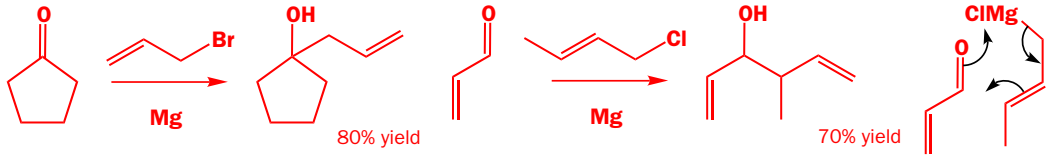


■ Barbier was Victor Grignard's PhD supervisor.



Allylic Grignard reagents are unusual for more than one reason, and it turns out that they are, in fact, quite hard to make in good yield from allyl halides. The problem is that the allyl halide is highly reactive towards the Grignard reagent as it forms, and a major by-product tends to be a dimer. The way round this problem is to make the Grignard reagent actually in the presence of the carbonyl compound. This method works in a number of cases, not just with allylic Grignards, and is often called the Barbier method.

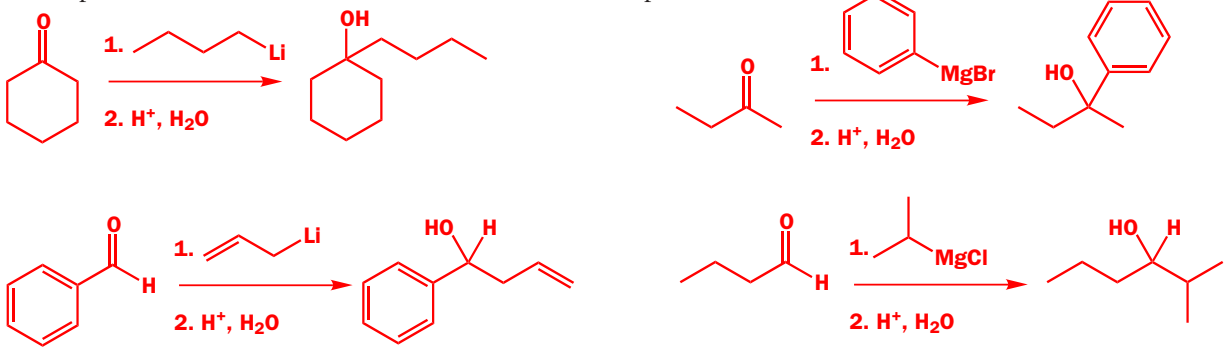
For example, it is a straightforward matter to make these three alcohols, provided the allylic halide, aldehyde, and magnesium are all mixed together in one flask. The Grignard reagent forms, and immediately reacts with the aldehyde, before it has a chance to dimerize. In the second example, notice again that the allylic Grignard reagent must have reacted through a six-membered transition state because the allyl system has 'turned around' in the product.



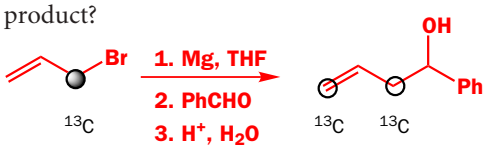
The last reaction above leads us nicely into the next chapter where we will look at an alternative way for such unsaturated aldehydes to react—by *conjugate addition*.

Problems

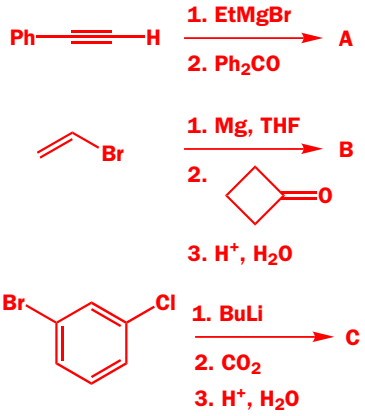
1. Propose mechanisms for the first four reactions in the chapter.



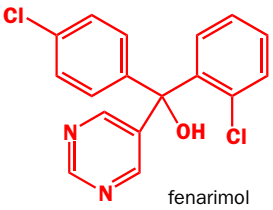
2. When this reaction is carried out with allyl bromide labelled as shown with ^{13}C, the label is found equally distributed between the ends of the allyl system in the product. Explain how this is possible. How would you detect the ^{13}C distribution in the product?



3. What products would be formed in these reactions?



4. Suggest alternative routes to fenarimol—that is, different routes from the one shown in the chapter.



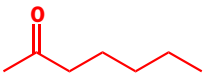
fenarimol

5. The synthesis of the gastric antisecretory drug rioprostil requires this alcohol.



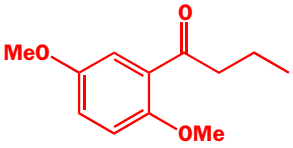
(**a**) Suggest possible syntheses starting from ketones and organometallics and (**b**) suggest possible syntheses of the ketones in part (**a**) from aldehydes and organometallics (don't forget about CrO_3 oxidation!).

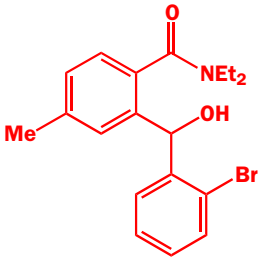
6. Suggest two syntheses of the bee pheromone heptan-2-one.



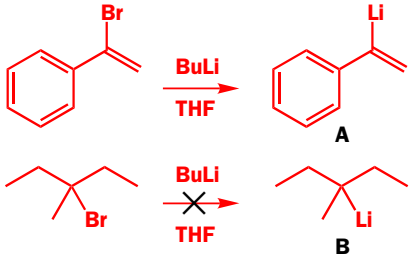
heptan-2-one

7. How could you prepare these compounds using ortholithiation procedures?

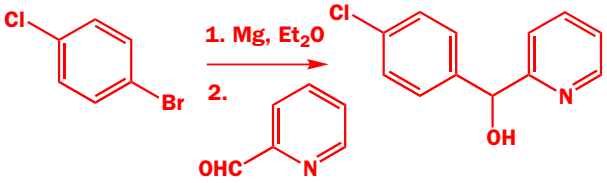




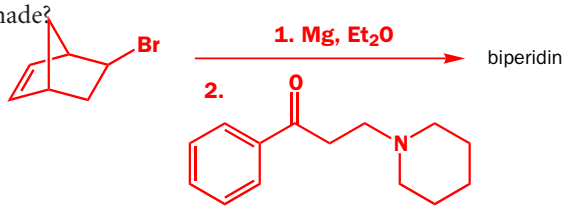
8. Why is it possible to make the lithium derivative A by Br/Li exchange, but not the lithium derivative B?

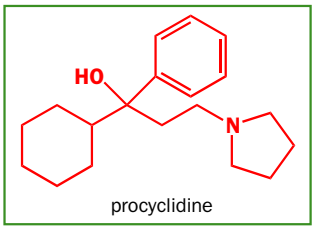


9. Comment on the selectivity (that is, say what else might have happened and why it didn't) shown in this Grignard addition reaction used in the manufacture of an antihistamine drug.



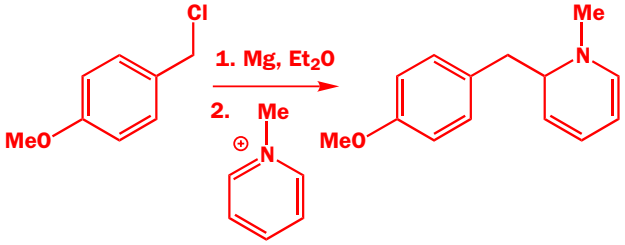
10. The antispasmodic drug biperidin is made by the Grignard addition reaction shown here. What is the structure of the drug? Do not be put off by the apparent complexity of the compounds—the chemistry is the same as that you have seen in this chapter. How would you suggest that the drug procyclidine should be made?



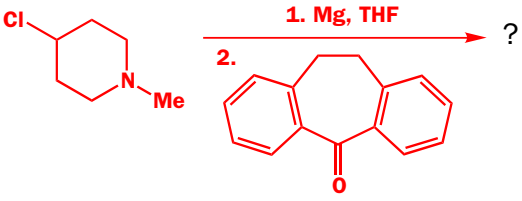


procyclidine

11. Though heterocyclic compounds, such as the nitrogen ring system in this question, are introduced rather later in this book, use your knowledge of Grignard chemistry to draw a mechanism for what happens here. It is important that you prove to yourself that you can draw mechanisms for reactions on compounds that you have never met before.



12. What product would be formed in this reaction between a chloro compound and a seven-membered ring ketone?



Conjugate addition

10

Connections

Building on:

- Reactions of C=O groups ch6 & ch9
- Conjugation ch7

Arriving at:

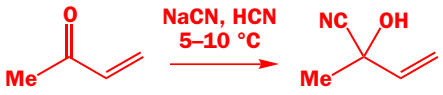
- How conjugation affects reactivity
- What happens to a C=O group when it is conjugated with a C=C bond
- How the C=C double bond becomes electrophilic, and can be attacked by nucleophiles
- Why some sorts of nucleophiles attack C=C while others still attack the C=O group

Looking forward to:

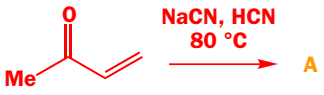
- Conjugate addition in other electrophilic alkenes ch23
- Conjugate addition with further types of nucleophiles ch29
- Alkenes that are *not* conjugated with C=O ch20

Conjugation changes the reactivity of carbonyl groups

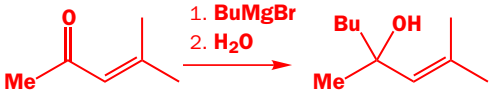
To start this chapter, here are four reactions of the same ketone. For each product, the principal absorptions in the IR spectrum are listed. The pair of reactions on the left should come as no surprise to you: nucleophilic addition of cyanide or a Grignard reagent to the ketone produces a product with no C=O peak near 1700 cm^{-1}, but instead an O–H peak at 3600 cm^{-1}. The 2250 cm^{-1} peak is C≡N; C=C is at 1650 cm^{-1}.



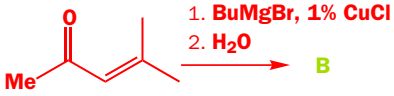
IR: 3600 (broad), 2250, 1650
no absorption near 1700



IR: 2250, 1715
no absorption at 3600



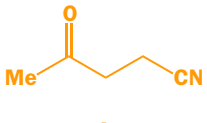
IR: 3600 (broad), 1640
no absorption near 1700



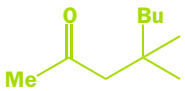
IR: 1710
no absorption at 3600

■ If you need to review IR spectroscopy, turn back to Chapter 3. Chapter 6 dealt with addition of CN^- to carbonyl compounds, and Chapter 9 with the addition of Grignard reagents.

But what about the reactions on the right? Both products A and B have kept their carbonyl group (IR peak at 1710 cm^{-1}) but have lost the C=C. Yet A, at least, is definitely an addition product because it contains a C≡N peak at 2200 cm^{-1}.



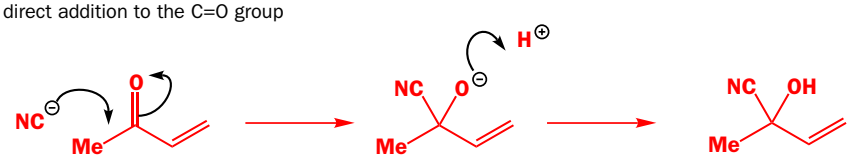
A



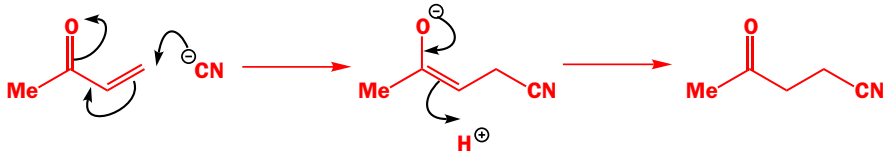
B

Well, the identities of A and B are revealed here: they are the products of addition, not to the carbonyl group, but to the C=C bond. This type of reaction is called conjugate addition, and is what this chapter is all about. The chapter will also how explain how such small differences in reaction conditions (temperature, or the presence of CuCl) manage to change the outcome completely.

direct addition to the C=O group



conjugate addition to the C=C double bond



Conjugate addition to the C=C double bond follows a similar course to direct addition to the C=O group, and the mechanisms for both are shown here. Both mechanisms have two steps: addition, followed by protonation. Conjugate additions only occur to C=C double bonds next to C=O groups. They don't occur to C=C bonds that aren't immediately adjacent to C=O (see the box on p. 000 for an example).

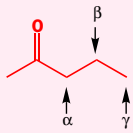
Compounds with double bonds adjacent to a C=O group are known as **α,β-unsaturated carbonyl compounds**. Many α,β-unsaturated carbonyl compounds have trivial names, and some are shown here. Some *classes* of α,β-unsaturated carbonyl compounds also have names such as 'enone' or 'enal', made up of 'ene' (for the double bond) + 'one' (for ketone) or 'ene' + 'al' (for aldehyde).

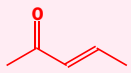
an α,β-unsaturated aldehyde (an enal) | an α,β-unsaturated ketone (an enone) | an α,β-unsaturated acid | an α,β-unsaturated ester



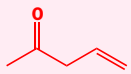
propenal (trivial name = acrolein) | but-3-en-2-one (trivial name = methyl vinyl ketone) | propenoic acid (trivial name = acrylic acid) | ethyl propenoate (trivial name = ethyl acrylate)

▶ The α and β refer to the distance of the double bond from the C=O group: the α carbon is the one next to C=O (*not* the carbonyl carbon itself), the β carbon is one further down the chain, and so on.





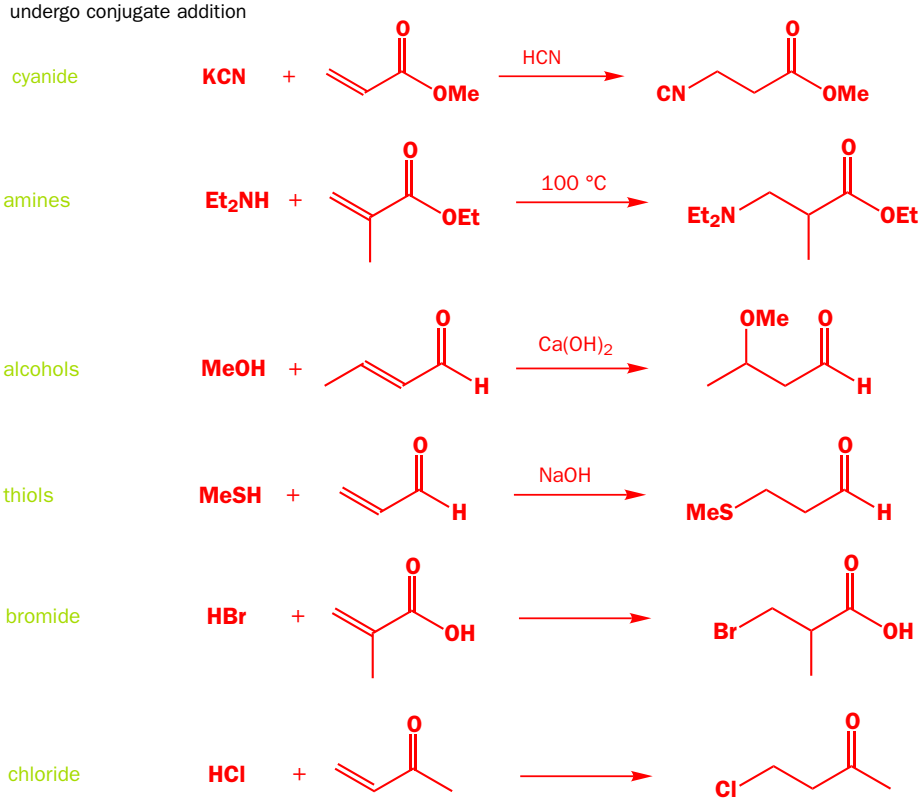
α,β-unsaturated ketone



β,γ-unsaturated ketone

A range of nucleophiles will undergo conjugate additions with α,β-unsaturated carbonyl compounds, and six examples are shown below. Note the range of nucleophiles, and also the range of carbonyl compounds: esters, aldehydes, acids, and ketones.

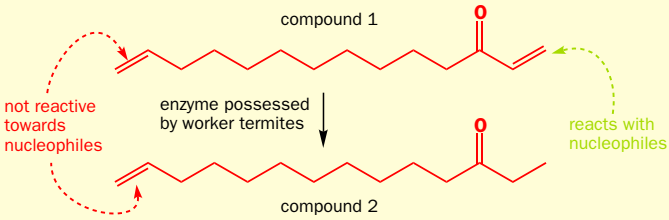
types of nucleophile which undergo conjugate addition



The reason that α,β-unsaturated carbonyl compounds react differently is conjugation, the phenomenon we discussed in Chapter 7. There we introduced you to the idea that bringing two π systems (two C=C bonds, for example, or a C=C bond and a C=O bond) close together leads to a stabilizing interaction. It also leads to modified reactivity, beacuse the π bonds no longer react as independent functional groups but as a single, conjugated system.

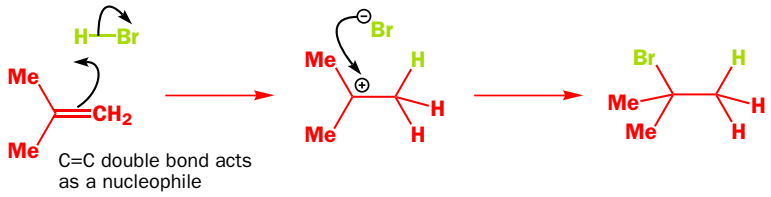
Termite self-defence and the reactivity of alkenes

Soldier termites of the species *Schedorhinotermes lamanianus* defend their nests by producing this compound, which is very effective at taking part in conjugate addition reactions with thiols (RSH). This makes it highly toxic, since many important biochemicals carry SH groups. The worker termites of the same species—who build the nests—need to be able to avoid being caught in the crossfire, so they are equipped with an enzyme that allows them to reduce compound 1 to compound 2. This still has a double bond, but the double bond is completely unreactive towards nucleophiles because it is not conjugated with a carbonyl group. The workers escape unharmed.

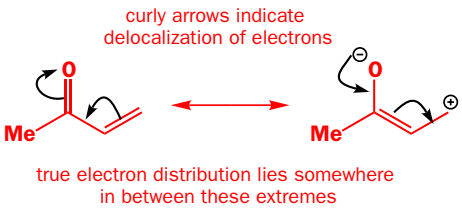


Alkenes conjugated with carbonyl groups are polarized

You haven't met many reactions of alkenes yet: detailed discussion will have to wait till Chapter 20. But we did indicate in Chapter 5 that they react with electrophiles. Here is the example from p. 000: in the addition of HBr to isobutene the alkene acts as a nucleophile and H–Br as the electrophile.

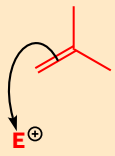


This is quite different to the reactivity of a C=C double bond conjugated with a carbonyl group, which, as you have just seen, reacts with nucleophiles such as cyanide, amines, and alcohols. The conjugated system is different from the sum of the isolated parts, with the C=O group profoundly affecting the reactivity of the C=C double bond. To show why, we can use curly arrows to indicate delocalization of the π electrons over the four atoms in the conjugated system. Both representations are extremes, and the true structure lies somewhere in between, but the polarized structure indicates why the conjugated C=C bond is electrophilic.

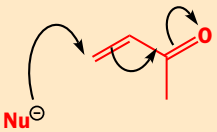


Conjugation makes alkenes electrophilic

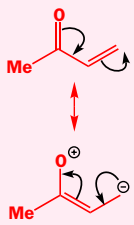
- Isolated C=C double bonds are nucleophilic



- C=C double bonds conjugated with carbonyl groups are electrophilic



▶ You may be asking yourself why we can't show the delocalization by moving the electrons the other way, like this.



Think about electronegativities: O is much more electronegative than C, so it is quite happy to accept electrons, but here we have taken electrons away, leaving it with only six electrons. This structure therefore cannot represent what happens to the electrons in the conjugated system.

Polarization is detectable spectroscopically

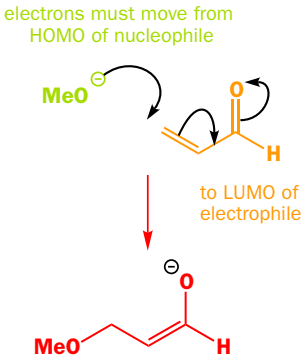
IR spectroscopy provides us with evidence for polarization in C=C bonds conjugated to C=O bonds. An unconjugated ketone C=O absorbs at 1715 cm^{-1} while an unconjugated alkene C=C absorbs

(usually rather weakly) at about 1650 cm^{-1}. Bringing these two groups into conjugation in an α,β-unsaturated carbonyl compound leads to two peaks at 1675 and 1615 cm^{-1}, respectively, both quite strong. The lowering of the frequency of both peaks is consistent with a weakening of both π bonds (notice that the polarized structure has only single bonds where the C=O and C=C double bonds were). The increase in the *intensity* of the C=C absorption is consistent with polarization brought about by conjugation with C=O: a conjugated C=C bond has a significantly larger dipole moment than its unconjugated cousins.

The polarization of the C=C bond is also evident in the ^{13}C NMR spectrum, with the signal for the sp^2 carbon atom furthest from the carbonyl group moving downfield relative to an unconjugated alkene to about 140 p.p.m., and the signal for the other double bond carbon atom staying at about 120 p.p.m.

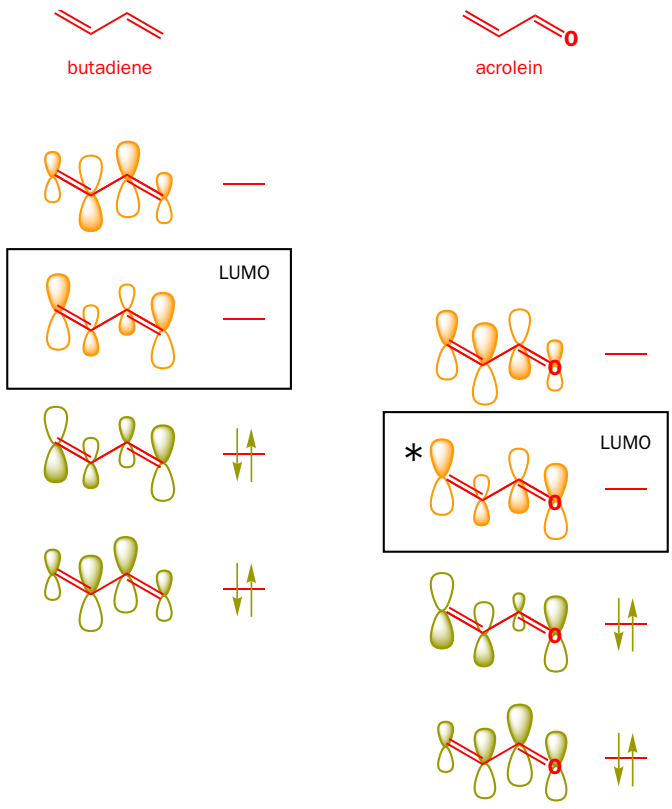


Molecular orbitals control conjugate additions



We have spectroscopic evidence that a conjugated C=C bond is polarized, and we can explain this with curly arrows, but the actual bond-forming step must involve movement of electrons from the HOMO of the nucleophile to the LUMO of the unsaturated carbonyl compound. The example in the margin has methoxide (MeO^-) as the nucleophile.

But what does this LUMO look like? It will certainly be more complicated than the π* LUMO of a simple carbonyl group. The nearest thing you have met so far (in Chapter 7) are the orbitals of butadiene (C=C conjugated with C=C), which we can compare with the α,β-unsaturated aldehyde acrolein (C=C conjugated with C=O). The orbitals in the π systems of butadiene and acrolein are shown here. They are different because acrolein's orbitals are perturbed (distorted) by the oxygen atom (Chapter 4). You need not be concerned with exactly how the sizes of the orbitals are worked out, but for the moment just concentrate on the shape of the LUMO, the orbital that will accept electrons when a nucleophile attacks.



In the LUMO, the largest coefficient is on the β carbon of the α,β-unsaturated system, shown with an asterisk. And it is here, therefore, that nucleophiles attack. In the reaction you have just seen, the HOMO is the methoxide oxygen's lone pair, so this will be the key orbital interaction

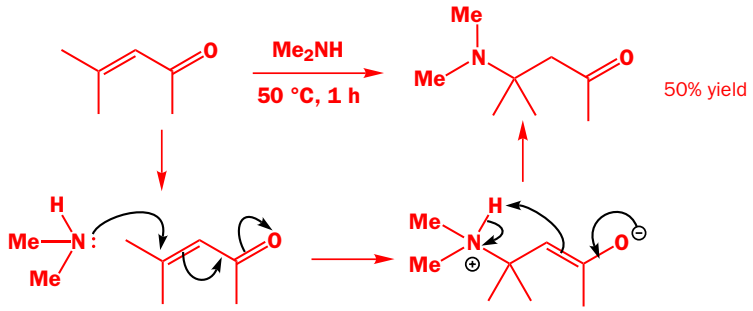
▶ In acrolein, the HOMO is in fact not the highest filled π orbital you see here, but the lone pairs on oxygen. This is not important here, though, because we are only considering acrolein as an electrophile, so we are only interested in its LUMO.

that gives rise to the new bond. The second largest coefficient is on the C=O carbon atom, so it's not surprising that some nucleophiles attack here as well—remember the example right at the beginning of the chapter where you saw cyanide attacking either the double bond or the carbonyl group depending on the conditions of the reaction. We shall next look at some conjugate additions with alcohols and amines as nucleophiles, before reconsidering the question of where the nucleophile attacks.

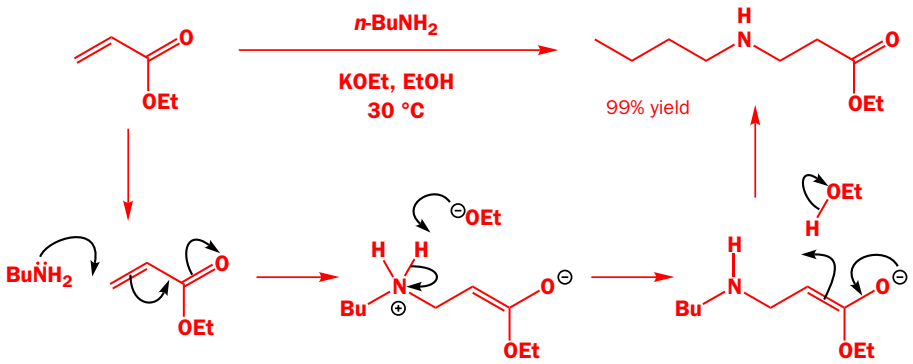


Ammonia and amines undergo conjugate addition

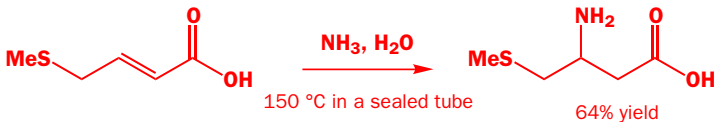
Amines are good nucleophiles for conjugate addition reactions, and give products that we can term **β-amino carbonyl compounds** (the new amino group is β to the carbonyl group). Dimethylamine is a gas at room temperature, and this reaction has to be carried out in a sealed system to give the ketone product.



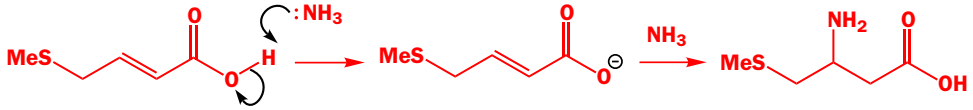
This is the first conjugate addition mechanism we have shown you that involves a neutral nucleophile: as the nitrogen adds it becomes positively charged and therefore needs to lose a proton. We can use this proton to protonate the negatively charged part of the molecule as you have seen happening before. This proton-transfer step can alternatively be carried out by a base: in this addition of butylamine to an α,β-unsaturated ester (ethyl acrylate), the added base (EtO^-) deprotonates the nitrogen atom once the amine has added. Only a catalytic amount is needed, because it is regenerated in the step that follows.



Ammonia itself, the simplest amine, is very volatile (it is a gas at room temperature, but a very water-soluble one, and bottles of 'ammonia' are actually a concentrated aqueous solution of ammonia), and the high temperatures required for conjugate addition to this unsaturated carboxylic acid can only be achieved in a sealed reaction vessel.

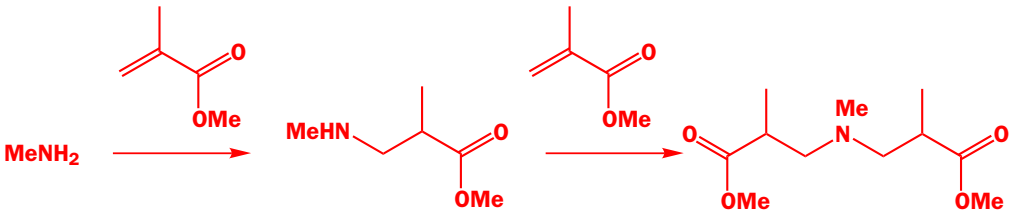


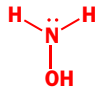
Amines are bases as well as nucleophiles, and in this reaction the first step must be deprotonation of the carboxylic acid: it's the ammonium carboxylate that undergoes the addition reaction. You would not expect a negatively charged carboxylate to be a very good electrophile, and this may well be why ammonia needs 150 °C to react.



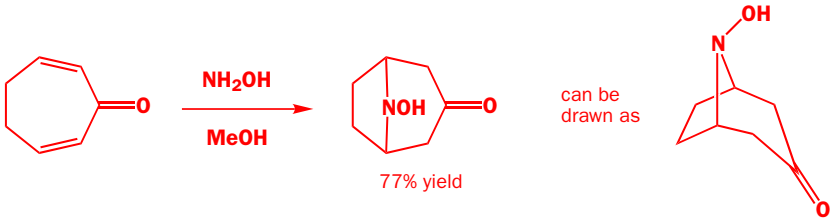
▶ Tertiary amines can't give conjugate addition products because they have no proton to lose.

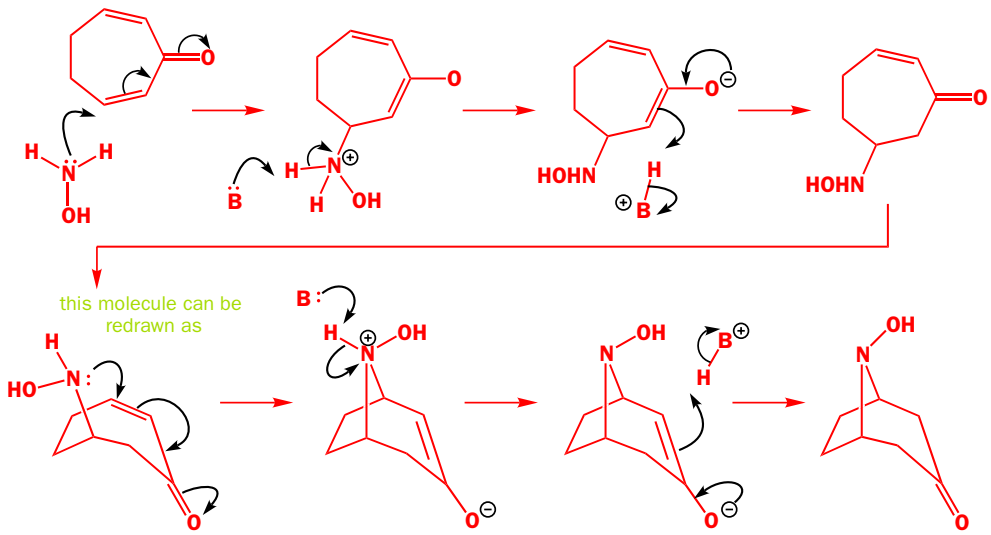
The β-amino carbonyl product of conjugate addition of an amine is still an amine and, provided it has a primary or secondary amino group, it can do a second conjugate addition. For example, methylamine adds successively to two molecules of this unsaturated ester.





Two successive conjugate additions can even happen in the same molecule. In the next example, hydroxylamine is the nucleophile. Hydroxylamine is both an amine and an alcohol, but it always reacts at nitrogen because nitrogen (being less electronegative than oxygen) has a higher-energy (more reactive) lone pair. Here it reacts with a cyclic dienone to produce a bicyclic ketone, which we have also drawn in a perspective view to give a better idea of its shape.

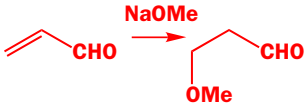




The reaction sequence consists of two conjugate addition reactions. The first is intermolecular, and gives the intermediate enone. The second conjugate addition is intramolecular, and turns the molecule into a bicyclic structure. Again, the most important steps are the C–N bond-forming reactions, but there are also several proton transfers that have to occur. We have shown a base 'B:' carrying out these proton transfers: this might be a molecule of hydroxylamine, or it might be a molecule of the solvent, methanol. These details do not matter.

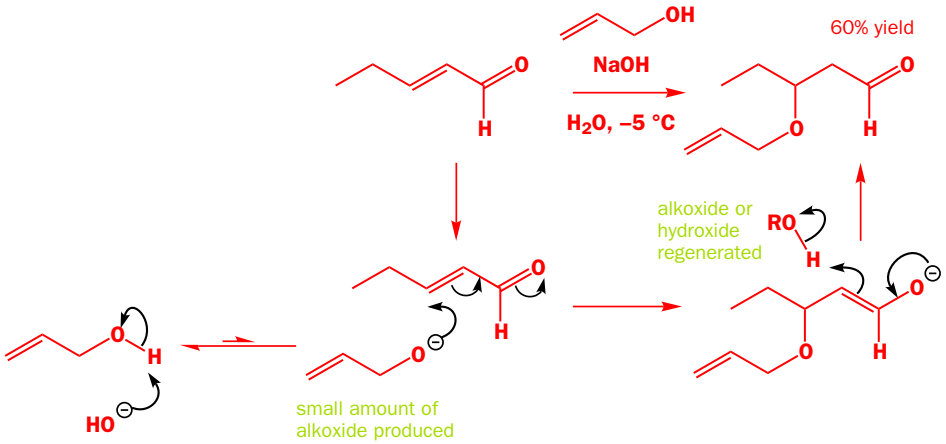
Conjugate addition of alcohols can be catalysed by acid or base

Alcohols undergo conjugate addition only very slowly in the absence of a catalyst: they are not such good nucleophiles as amines for the very reason we have just mentioned in connection with the reactivity of hydroxylamine—oxygen is more electronegative than nitrogen, and so its lone pairs are of lower energy and are therefore less reactive. Alkoxide *anions* are, however, much more nucleophilic. You saw methoxide attacking the orbitals of acrolein above: the reaction in the margin goes at less than 5 °C.



The alkoxide doesn't have to be made first, though, because alcohols dissolved in basic solution are at least partly deprotonated to give alkoxide anions. How much alkoxide is present depends on the pH of the solution and therefore the pK_a of the base (Chapter 8), but even a tiny amount is acceptable because once this has added it will be replaced by more alkoxide in acid–base equilibrium with the alcohol. In this example, allyl alcohol adds to pent-2-enal, catalysed by sodium hydroxide in the presence of a buffer.

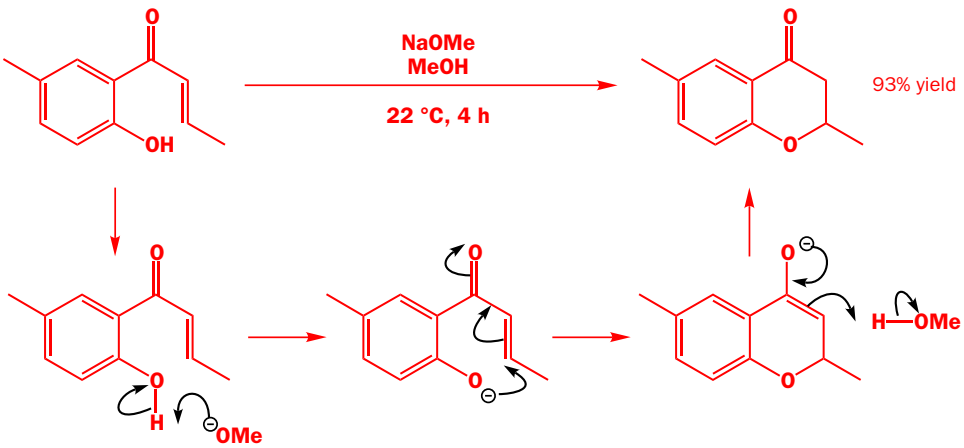
■ In Chapter 6 we discussed the role of base and acid catalysts in the direct addition of alcohols to carbonyl compounds to form hemiacetals. The reasoning—that base makes nucleophiles more nucleophilic and acid makes carbonyl groups more electrophilic—is the same here.



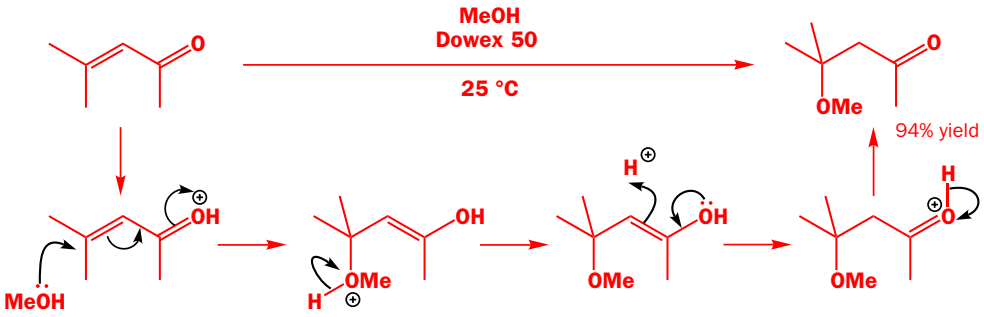
Only a catalytic amount of base is required as the deprotonation of ROH (which can be water or allyl alcohol) in the last step regenerates more alkoxide or hydroxide. It does not matter that sodium hydroxide (pK_{aH} 15.7) is not basic enough to deprotonate an alcohol (pK_a 16–17) completely, since only a small concentration of the reactive alkoxide is necessary for the reaction to proceed.

We can also make rings using alkoxide nucleophiles, and in this example the phenol (hydroxybenzene) is deprotonated by the sodium methoxide base to give a phenoxide anion. Intramolecular attack on the conjugated ketone gives the cyclic product in excellent yield. In this case, the methoxide (pK_{aH} about 16) will deprotonate the phenol (pK_a about 10) completely, and competitive attack by MeO^- acting as a nucleophile is not a problem as intramolecular reactions are usually faster than their intermolecular equivalents.

■ There are some important exceptions to this depending on the size of ring being formed, and some of these are described in Chapter 42.



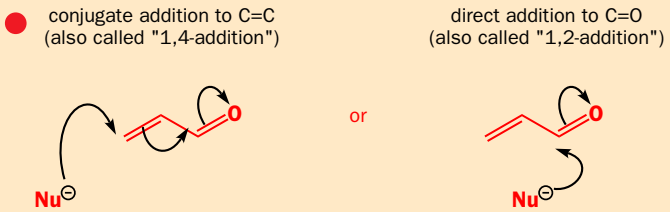
Acid catalysts promote conjugate addition of alcohols to α,β-unsaturated carbonyl compounds by protonating the carbonyl group and making the conjugated system more electrophilic. Methanol adds to this ketone exceptionally well, for example, in the presence of an acid catalyst known as 'Dowex 50'. This is an acidic resin—just about as acidic as sulfuric acid in fact, but completely insoluble, and therefore very easy to remove from the product at the end of the reaction by filtration.



Once the methanol has added to the protonated enone, all that remains is to reorganize the protons in the molecule to give the product. This takes a few steps, but don't be put off by their complexity—as we've said before, the important step is the first one—the conjugate addition.

Conjugate addition or direct addition to the carbonyl group?

We have shown you several examples of conjugate additions using various nucleophiles and α,β-unsaturated carbonyl compounds, but we haven't yet addressed one important question. When do nucleophiles do conjugate addition (also called '1,4-addition') and when do they add directly to the carbonyl group ('1,2-addition')? Several factors are involved—they are summarized here, and we will spend the next section of this chapter discussing them in turn.

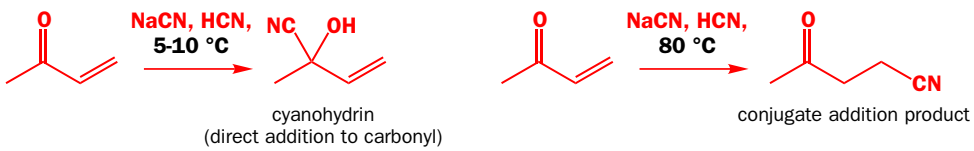


The way that nucleophiles react depends on:

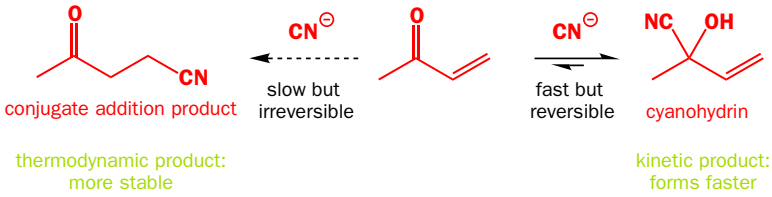
- **the conditions of the reaction**
- **the nature of the α,β-unsaturated carbonyl compound**
- **the type of nucleophile**

Reaction conditions

The very first conjugate addition reaction in this chapter depended on the conditions of the reaction. Treating an enone with cyanide and an acid catalyst at low temperature gives a cyanohydrin by direct attack at C=O, while heating the reaction mixture leads to conjugate addition. What is going on?



We'll consider the low-temperature reaction first. As you know from Chapter 6, it is quite normal for cyanide to react with a ketone under these conditions to form a cyanohydrin. Direct addition to the carbonyl group turns out to be faster than conjugate addition, so we end up with the cyanohydrin.



Now, you also know from Chapter 6 that cyanohydrin formation is reversible. Even if the equilibrium for cyanohydrin formation lies well over to the side of the products, at equilibrium there will still be a small amount of starting enone remaining. Most of the time, this enone will react to form more cyanohydrin and, as it does, some cyanohydrin will decompose back to enone plus cyanide—such is the nature of a dynamic equilibrium. But every now and then—at a much slower rate—the starting enone will undergo a conjugate addition with the cyanide. Now we have a different situation: conjugate addition is essentially an *irreversible* reaction, so once a molecule of enone has been converted to conjugate addition product, its fate is sealed: it cannot go back to enone again. Very slowly, therefore, the amount of conjugate addition product in the mixture will build up. In order for the enone–cyanohydrin equilibrium to be maintained, any enone that is converted to conjugate addition product will have to be replaced by reversion of cyanohydrin to enone plus cyanide. Even at room temperature, we can therefore expect the cyanohydrin to be converted bit by bit to conjugate addition product. This may take a very long time, but reaction rates are faster at higher temperatures, so at 80 °C this process does not take long at all and, after a few hours, the cyanohydrin has all been converted to conjugate addition product.

The contrast between the two products is this: cyanohydrin is formed faster than the conjugate addition product, but the conjugate addition product is the more stable compound.

Typically, kinetic control involves lower temperatures and shorter reaction times, which ensures that only the fastest reaction has the chance to occur. And, typically, thermodynamic control involves higher temperatures and long reaction times to ensure that even the slower reactions have a chance to occur, and all the material is converted to the most stable compound.

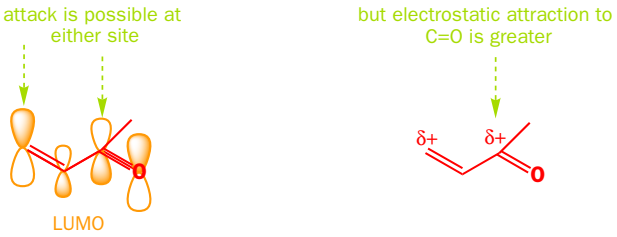
Kinetic and thermodynamic control

- The product that forms faster is called the **kinetic product**
- The product that is the more stable is called the **thermodynamic product**

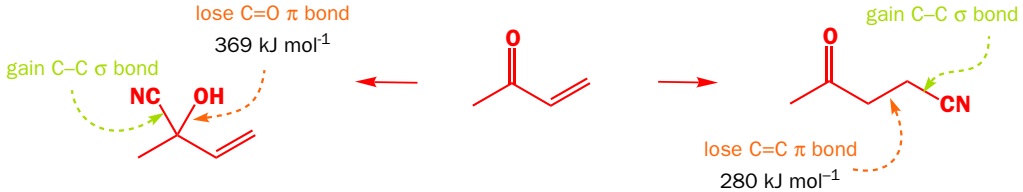
Similarly,

- Conditions that give rise to the kinetic product are called **kinetic control**
- Conditions that give rise to the thermodynamic product are called **thermodynamic control**

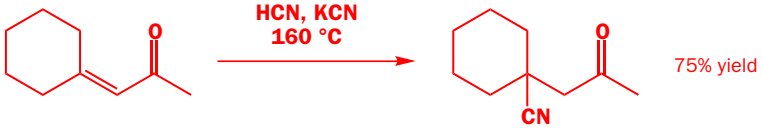
Why is direct addition faster than conjugate addition? Well, although the carbon atom β to the C=O group carries some positive charge, the carbon atom of the carbonyl group carries more, and so electrostatic attraction for the charged nucleophiles will encourage it to attack the carbonyl group directly rather than undergo conjugate addition.

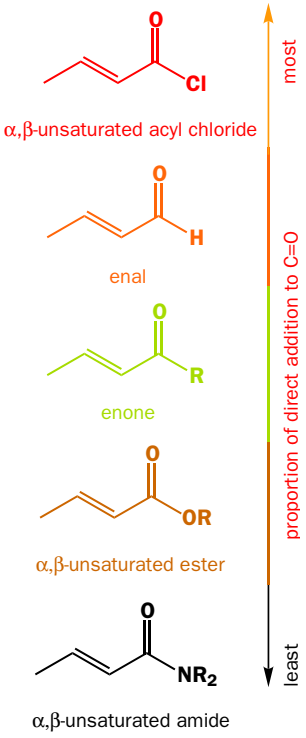


And why is the conjugate addition product the more stable? In the conjugate addition product, we gain a C–C σ bond, losing a C=C π bond, but keeping the C=O π bond. With direct addition, we still gain a C–C bond, but we lose the C=O π bond and keep the C=C π bond. C=O π bonds are stronger than C=C π bonds, so the conjugate addition product is the more stable.



We will return to kinetic and thermodynamic control in Chapter 13, where we will analyse the rates and energies involved a little more rigorously, but for now here is an example where conjugate addition is ensured by thermodynamic control. Note the temperature!

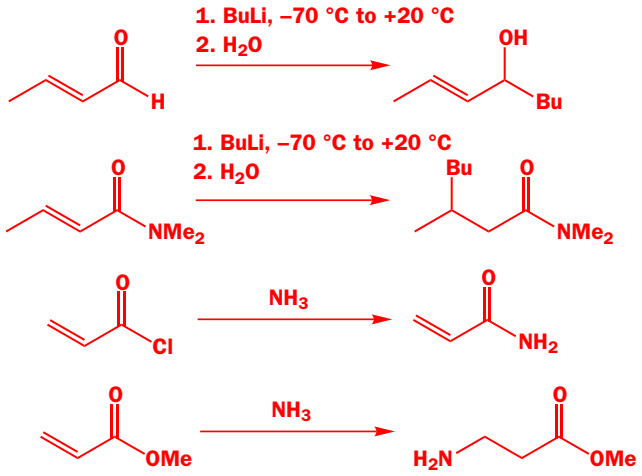




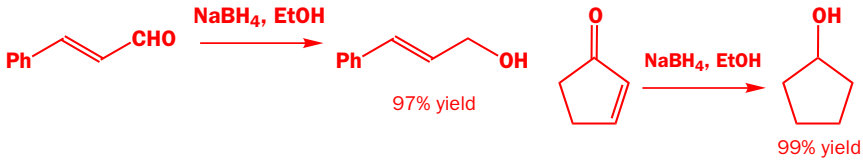
Structural factors

Not all additions to carbonyl groups are reversible: additions of organometallics, for example, are certainly not. In such cases, the site of nucleophilic attack is determined simply by reactivity: the more reactive the carbonyl group, the more direct addition to C=O will result. The most reactive carbonyl groups, as you will see in Chapter 12, are those that are not conjugated with O or N (as they are in esters and amides), and particularly reactive are acyl chlorides and aldehydes. In general, the proportion of direct addition to the carbonyl group follows the reactivity sequence in the margin.

Compare the way butyllithium adds to this α,β-unsaturated aldehyde and α,β-unsaturated amide. Both additions are irreversible, and BuLi attacks the reactive carbonyl group of the aldehyde, but prefers conjugate addition to the less reactive amide. Similarly, ammonia reacts with this acyl chloride to give an amide product that derives (for details see Chapter 12) from direct addition to the carbonyl group, while with the ester it undergoes conjugate addition to give an amine.

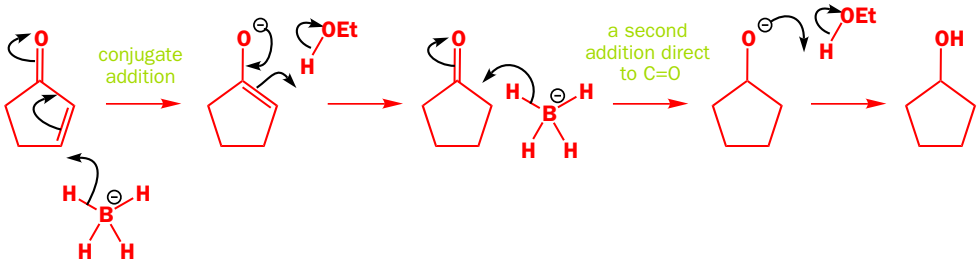


Sodium borohydride is a nucleophile that you have seen reducing simple aldehydes and ketones to alcohols, and it usually reacts with α,β-unsaturated aldehydes in a similar way, giving alcohols by direct addition to the carbonyl group.



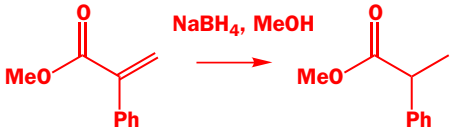
Quite common with ketones, though, is the outcome on the right. The borohydride has reduced

not only the carbonyl group but the double bond as well. In fact, it's the double bond that's reduced first in a conjugate addition, followed by addition to the carbonyl group.



■ This reaction, and how to control reduction of C=O and C=C, will be discussed in more detail in Chapter 24.

For esters and other less reactive carbonyl compounds conjugate addition is the only reaction that occurs.

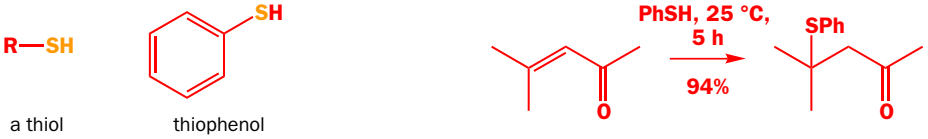


Steric hindrance also has a role to play: the more substituents there are at the β carbon, the less likely a nucleophile is to attack there. Nonetheless, there are plenty of examples where nucleophiles undergo conjugate addition even to highly substituted carbon atoms.

■ The concept of steric hindrance was introduced in Chapter 6.

The nature of the nucleophile: hard and soft

Among the best nucleophiles of all at doing conjugate addition are **thiols**, the sulfur analogues of alcohols. In this example, the nucleophile is thiophenol (phenol with the O replaced by S). Remarkably, no acid or base catalyst is needed (as it was with the alcohol additions), and the product is obtained in 94% yield under quite mild reaction conditions.



a thiol thiophenol

Why are thiols such good nucleophiles for conjugate additions? Well, to explain this, and why they are much less good at direct addition to the C=O group, we need to remind you of some ideas we introduced in Chapter 5. There we said that the attraction between nucleophiles and electrophiles is governed by two related interactions—electrostatic attraction between positive and negative charges and orbital overlap between the HOMO of the nucleophile and the LUMO of the electrophile. Successful reactions usually result from a combination of both, but sometimes reactivity can be dominated by one or the other. The dominant factor, be it electrostatic or orbital control, depends on the nucleophile and electrophile involved. Nucleophiles containing small, electonegative atoms (such as O or Cl) tend to react under predominantly electrostatic control, while nuclophiles containing larger atoms (including the sulfur of thiols, but also P, I, and Se) are predominantly subject to control by orbital overlap. The terms 'hard' and 'soft' have been coined to describe these two types of reagents. **Hard nucleophiles** are typically from the early rows of the periodic table and have higher charge density, while **soft nucleophiles** are from the later rows of the periodic table—they are either uncharged or have larger atoms with higher-energy, more diffuse orbitals.

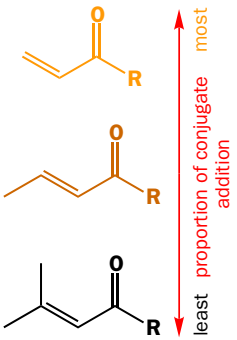


Table 10.1 divides some nucleophiles into the two categories (plus some that lie in between)—but don't try to learn it! Rather, convince yourself that the properties of each one justify its location in the table. Most of these nucleophiles you have not yet seen in action, and the most important ones at this stage are indicated in **bold type**.

Table 10.1 Hard and soft nucleophiles

Hard nucleophiles	Borderline	Soft nucleophiles
F^-, **OH^-**, **RO^-**, SO_4^{2-}, Cl^-,	N_3^-, **CN^-**	**I^-**, **RS^-**, RSe^-, S^{2-}
H_2O, **ROH**, ROR′, RCOR′,	**RNH_2**, **RR′NH**,	**RSH**, RSR′, R_3P
NH_3, **RMgBr**, **RLi**	**Br^-**	alkenes, aromatic rings

Not only can nucleophiles be classified as hard or soft, but electrophiles can too. For example, H^+ is a very hard electrophile because it is small and charged, while Br_2 is a soft electrophile: its orbitals are diffuse and it is uncharged. You saw Br_2 reacting with an alkene earlier in the chapter, and we explained in Chapter 5 that this reaction happens solely because of orbital interactions: no charges are involved. The carbon atom of a carbonyl group is also a hard electrophile because it carries a partial positive charge due to polarization of the C=O bond. What is important to us is that, in general, hard nucleophiles prefer to react with hard electrophiles, and soft nucleophiles with soft electrophiles. So, for example, water (a hard nucleophile) reacts with aldehydes (hard electrophiles) to form hydrates in a reaction largely controlled by electrostatic attraction. On the other hand, water does not react with bromine (a soft electrophile). Yet bromine reacts with alkenes while water does not. Now this is only a very general principle, and you will find plenty of examples where hard reacts with soft and soft with hard. Nonetheless it is a useful concept, which we shall come back to later in the book.

Hard/soft reactivity

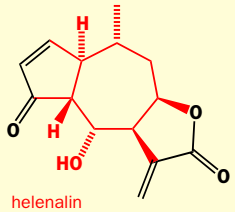
- Reactions of hard species are dominated by charges and electrostatic effects
- Reactions of soft species are dominated by orbital effects
- Hard nucleophiles tend to react well with hard electrophiles
- Soft nucleophiles tend to react well with soft electrophiles

What has all this to do with the conjugate addition of thiols? Well, an α,β-unsaturated carbonyl compound is unusual in that it has two electrophilic sites, one of which is hard and one of which is soft. The carbonyl group has a high partial charge on the carbonyl carbon and will tend to react with hard nucleophiles, such as organolithium and Grignard reagents, that have a high partial charge on the nucleophilic carbon atom. Conversely,the β carbon of the α,β-unsaturated carbonyl system does not have a high partial positive charge but is the site of the largest coefficient in the LUMO. This makes the β carbon a soft electrophile and likely to react well with soft nucleophiles such as thiols.

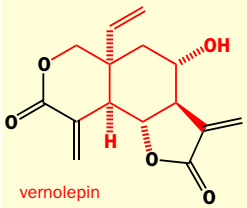
Hard/soft—direct/conjugate addition

- Hard nucleophiles tend to react at the carbonyl carbon (hard) of an enone
- Soft nucleophiles tend to react at the β-carbon (soft) of an enone and lead to conjugate addition

Anticancer drugs that work by conjugate addition of thiols

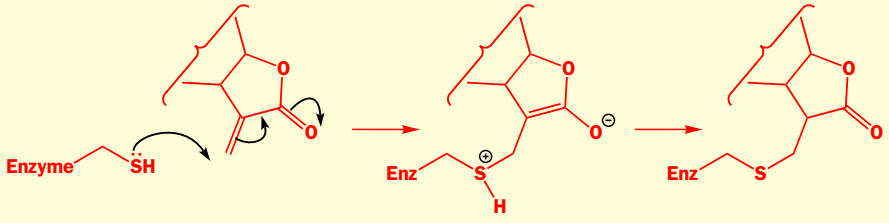


helenalin



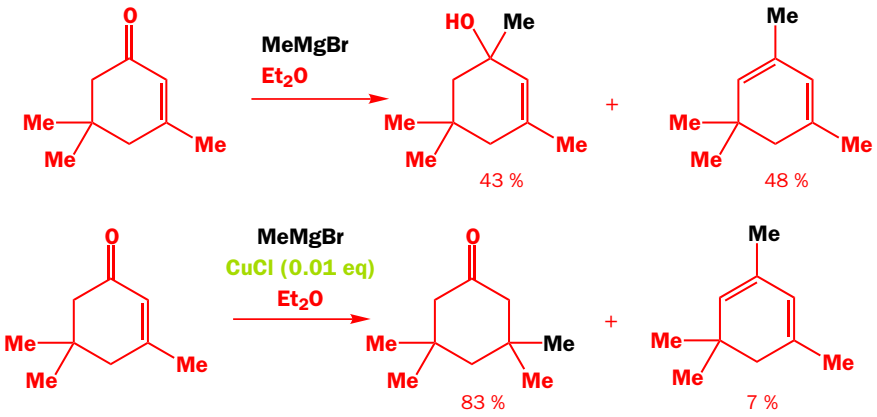
vernolepin

Drugs to combat cancer act on a range of biochemical pathways, but most commonly on processes that cancerous cells need to use to proliferate rapidly. One class attacks DNA polymerase, an enzyme needed to make the copy of DNA that has to be provided for each new cell. Helenalin and vernolepin are two such drugs, and if you look closely at their structure you should be able to spot two α,β-unsaturated carbonyl groups in each. Biochemistry is just chemistry in very small flasks called cells, and the reaction between DNA polymerase and these drugs is simply a conjugate addition reaction between a thiol (the SH group of one of the enzyme's cysteine residues) and the unsaturated carbonyl groups. The reaction is irreversible, and shuts down completely the function of the enzyme.



Copper(I) salts have a remarkable effect on organometallic reagents

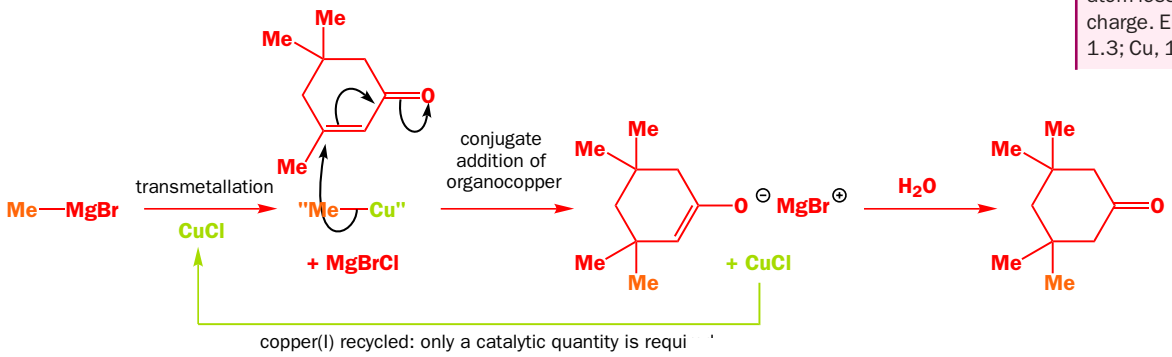
Grignard reagents add directly to the carbonyl group of α,β-unsaturated aldehydes and ketones to give allylic alcohols: you have seen several examples of this, and you can now explain it by saying that the hard Grignard reagent prefers to attack the harder C=O rather than the softer C=C electrophilic centre. Here is a further example—the addition of MeMgI to a cyclic ketone to give an allylic alcohol, plus, as it happens, some of a diene that arises from this alcohol by loss of water (dehydration). Below this example is the same reaction to which a very small amount (just 0.01 equivalents, that is, 1%) of copper(I) chloride has been added. The effect of the copper is dramatic: it makes the Grignard reagent undergo conjugate addition, with only a trace of the diene.



Organocopper reagents undergo conjugate addition

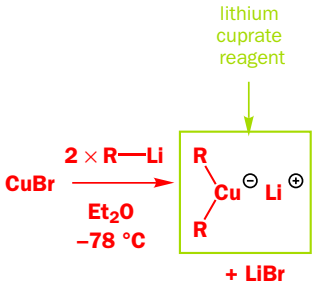
The copper works by transmetallating the Grignard reagent to give an organocopper reagent. Organocoppers are softer than Grignard reagents, and add in a conjugate fashion to the softer C=C double bond. Once the organocopper has added, the copper salt is available to transmetallate some more Grignard, and only a catalytic amount is required.

▶ Organocoppers are softer than Grignard reagents because copper is less electropositive than magnesium, so the C–Cu bond is less polarized than the C–Mg bond, giving the carbon atom less of a partial negative charge. Electronegativities: Mg, 1.3; Cu, 1.9.



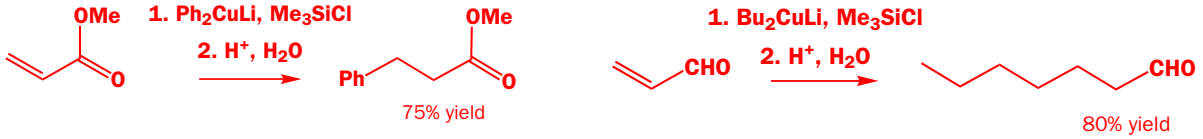
■ We discussed transmetallation in Chapter 9.

The organocopper is shown here as 'Me–Cu' because its precise structure is not known. But there are other organocopper reagents that also undergo conjugate addition and that are much better understood. The simplest result from the reaction of two equivalents of organolithium with one equivalent of a copper (I) salt such as CuBr in ether or THF solvent at low temperature. The lithium cuprates (R_2CuLi) that are formed are not stable and must be used immediately.

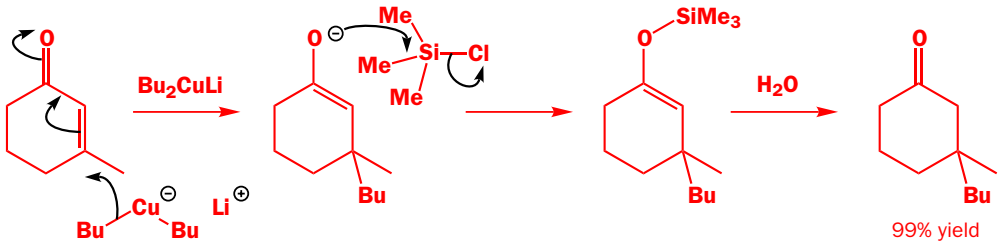


■ As with the organolithiums that we introduced in Chapter 9, the exact structure of these reagents is more complex than we imply here: they are probably tetramers (four molecules of R_2CuLi bound together), but for simplicity we will draw them as monomers.

The addition of lithium cuprates to α,β-unsaturated ketones turns out to be much better if trimethylsilyl chloride is added to the reaction—we will explain what this does shortly, but for the moment here are two examples of lithium cuprate additions.



The silicon works by reacting with the negatively charged intermediate in the conjugate addition reaction to give a product that decomposes to the carbonyl compound when water is added at the end of the reaction. Here is a possible mechanism for a reaction between Bu_2CuLi and an α,β-unsaturated ketone in the presence of Me_3SiCl. The first step is familiar to you, but the second is a new reaction. Even so, following what we said in Chapter 5, it should not surprise you: the oxygen is clearly the nucleophile and the silicon the electrophile, and a new bond forms from O to Si as indicated by the arrow. The silicon-containing product is called a **silyl enol ether**, and we will come back to these compounds and their chemistry in more detail in later chapters.



Conclusion

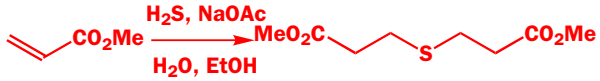
We end with a summary of the factors controlling the two modes of addition to α,β-unsaturated carbonyl compounds, and by noting that conjugate addition will be back again—in Chapters 23 (where we consider electrophilic alkenes conjugated with groups other than C=O) and 29 (where the nucleophiles will be of a different class known as enolates).

Summary

	Conjugate addition favoured by	Direct addition to C=O favoured by
Reaction conditions (for reversible additions):	• thermodynamic control: high temperatures, long reaction times	• kinetic control: low temperatures, short reaction times
Structure of α,β-unsaturated compound:	• unreactive C=O group (amide, ester)	• reactive C=O group group (aldehyde, acyl chloride)
	• unhindered β carbon	• hindered β carbon
Type of nucleophile:	• soft nucleophiles	• hard nucleophiles
Organometallic:	• organocoppers or catalytic Cu(I)	• organolithiums, Grignard reagents

Problems

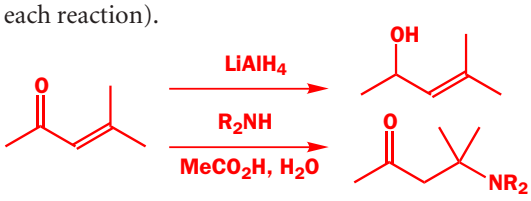
1. Draw mechanisms for this reaction and explain why this particular product is formed.



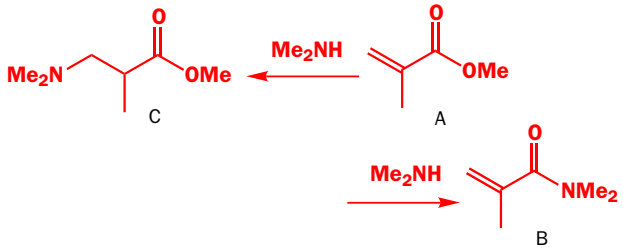
2. Which of the two routes shown here would actually lead to the product? Why?



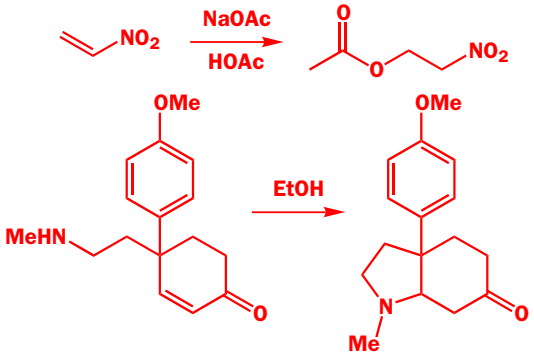
3. Suggest reasons for the different outcomes of the following reactions (your answer must, of course, include a mechanism for each reaction).



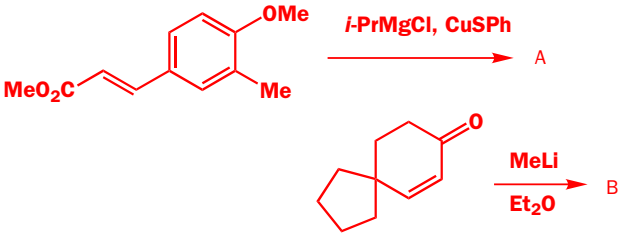
4. Addition of dimethylamine to the unsaturated ester A could give either product B or C. Draw mechanisms for both reactions and show how you would distinguish them spectroscopically.



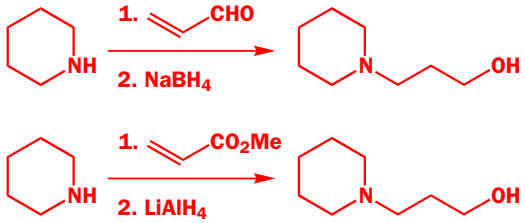
5. Suggest mechanisms for the following reactions.



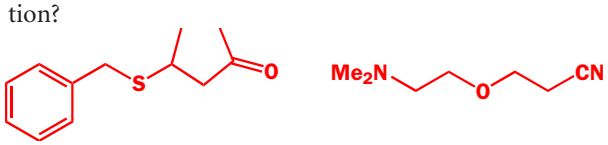
6. Predict the product of these reactions.



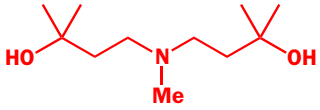
7. Two routes are proposed for the preparation of this amino alcohol. Which do you think is more likely to succeed and why?



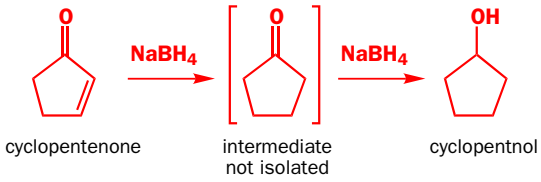
8. How would you prepare these compounds by conjugate addition?



9. How might this compound be made using a conjugate addition as one of the steps? You might find it helpful to consider the preparation of tertiary alcohols as decribed in Chapter 9 and also to refer back to Problem 1 in this chapter.

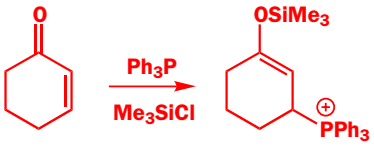


10. When we discussed reduction of cyclopentenone to cyclopentanol, we suggested that conjugate addition of borohydride must occur before direct addition of borohydride; in other words, this scheme must be followed.



What is the alternative scheme? Why is the scheme shown above definitely correct?

11. Suggest a mechanism for this reaction. Why does conjugate addition occur rather than direct addition?



Why is the product shown as a cation? If it is indeed a salt, what is the anion?

12. How, by choice of reagent, would you make this reaction give the direct addition product (route A)? How would you make it give the conjugate addition product (route B)?

