Nucleophilic addition to the carbonyl group

6

Connections

Building on

- Functional groups, especially the C=O group 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 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

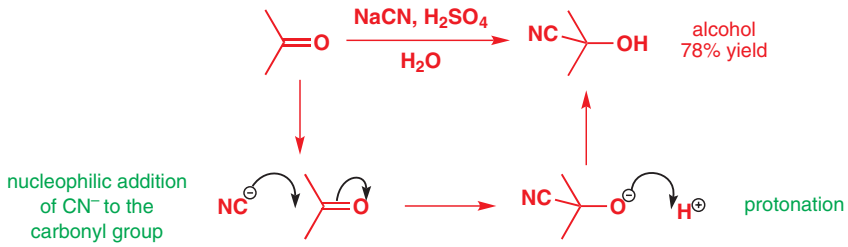
Looking forward to

- Additions of organometallic reagents ch9
- Substitution reactions of the C=O group's oxygen atom ch11
- How the C=O group in derivatives of carboxylic acids promotes substitution reactions ch10
- C=O groups with an adjacent double bond ch22

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 pp. 115 and 121, where we showed you how cyanide reacts with aldehydes to give an alcohol. As a reminder, here is the reaction again, this time with a ketone, with its mechanism.



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.

■ 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 above and below the arrow across the top tell you how you might carry out the reaction, and the pathway shown underneath tells you how it actually works.

Online support. The icon in the margin indicates that accompanying interactive resources are provided online to help your understanding: just type **www.chemtube3d.com/clayden/123** into your browser, replacing **123** with the number of the page where you see the icon. For pages linking to more than one resource, type **123-1, 123-2** etc. (replacing **123** with the page number) for access to successive links.

- **Additions to carbonyl groups generally consist of two mechanistic steps:**
  - **nucleophilic attack on the carbonyl group**
  - **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.

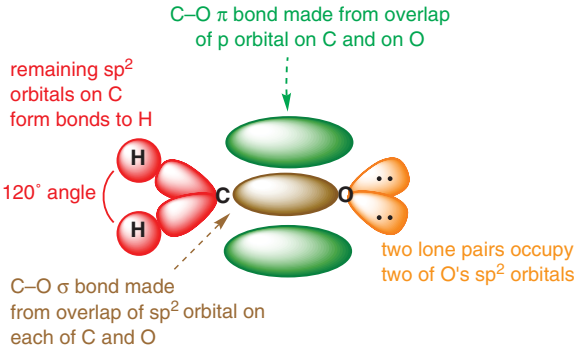
Why does cyanide, in common with many other nucleophiles, attack the carbonyl group? And why does it attack the *carbon* atom of the carbonyl group? To answer these questions we need to look in detail at the structure of carbonyl compounds in general and the orbitals of the C=O group in particular.

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.

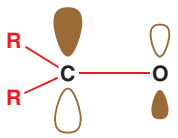
Interactive bonding orbitals in formaldehyde

formaldehyde (methanal, CH_2O)

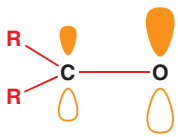
viewed from a slight angle



You were introduced to the polarization of orbitals in Chapter 4 and we discussed the case of the carbonyl group on p. 104.



empty, antibonding π* orbital



filled σ orbital

When we introduced the bonding in the carbonyl group in Chapter 4 we explained how polarization in the π bond means it is skewed towards oxygen, because oxygen is more electronegative than carbon. Conversely, the unfilled π* antibonding orbital is skewed in the opposite direction, with a larger coefficient at the carbon atom. This is quite hard to represent with the π bond represented as a single unit, as shown above, but becomes easier to visualize if instead we represent the π and π* orbitals using individual p orbitals on C and O. The diagrams in the margin show the π and π* orbitals represented in this way.

Electronegativities, bond lengths, and bond strengths

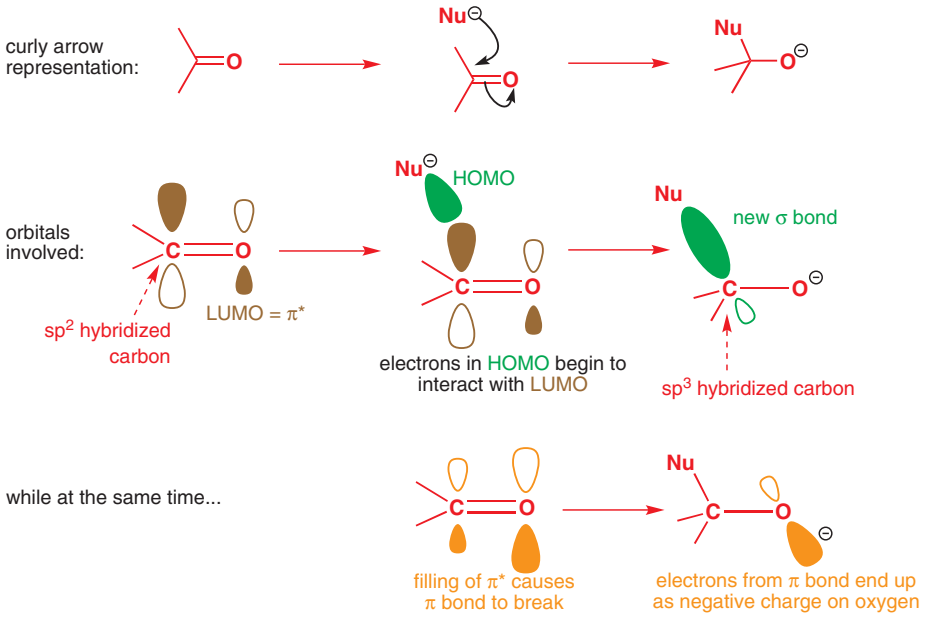
Representative bond energy, kJ mol^{-1}		Representative bond length, Å		Electronegativity	
C–O	351	C–O	1.43	C	2.5
C=O	720	C=O	1.21	O	3.5

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 the case of cyanide) 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.

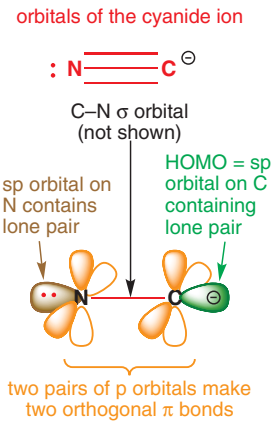
■ The HOMO of the nucleophile will depend on what the nucleophile is, and we will meet examples in which it is an sp or sp^3 orbital containing a lone pair, or a B–H σ orbital or metal–carbon σ orbital. We shall shortly discuss cyanide as the nucleophile; cyanide's HOMO is an sp orbital on carbon.

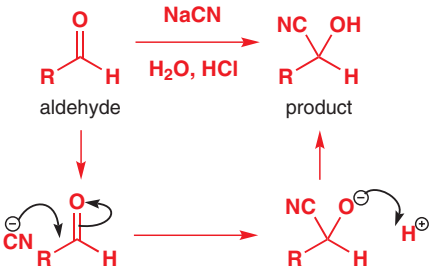


Notice how the trigonal, planar sp^2 hybridized carbon atom of the carbonyl group changes to a tetrahedral, sp^3 hybridized state in the product. For each class of nucleophile you meet in this chapter, we will show you the HOMO–LUMO interaction involved in the addition reaction. These interactions also show you how the orbitals of the starting materials change into the orbitals of the product as they combine. Most importantly here, the lone pair of the nucleophile combines with the π* of the carbonyl group to form a new σ bond in the product.

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. This reaction appeared first in Chapter 5.

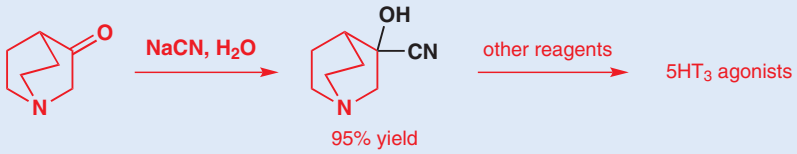




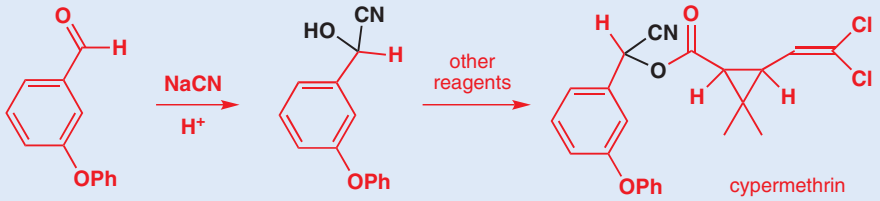
Interactive mechanism for cyanohydrin formation

Cyanohydrins in synthesis

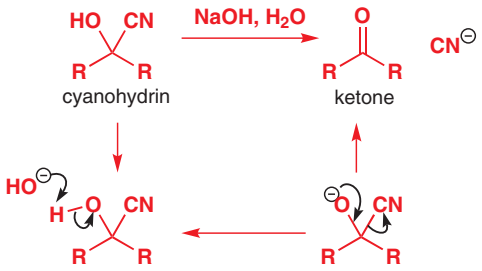
Cyanohydrins are important synthetic intermediates, for example the cyanohydrin formed from this cyclic amino ketone is the first intermediate in a synthesis of some medicinal compounds known as $5HT_3$ agonists, which were designed to reduce nausea in chemotherapy patients.

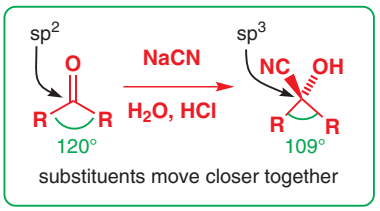


Cyanohydrins are also components of many natural and industrial products, such as the insecticide cypermethrin (marketed as 'Ripcord' and 'Barricade').

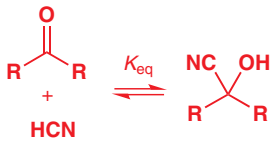


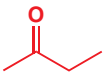
Cyanohydrin formation is reversible: just dissolving a cyanohydrin in water can give back the aldehyde or ketone you started with, and aqueous base usually decomposes cyanohydrins completely. This is because cyanide is a good *leaving group*—we'll come back to this type of reaction in more detail in Chapter 10.





Some equilibrium constants



aldehyde or ketone	K_{eq}
PhCHO	212
	28

Cyanohydrin formation is therefore an equilibrium between starting materials and products, and we can get good yields only 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 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.

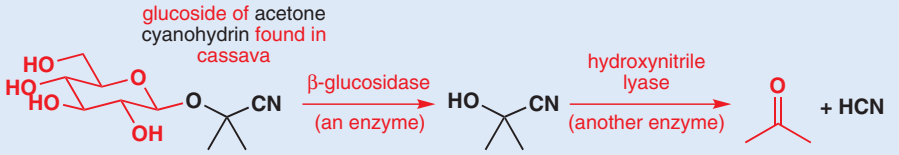
Steric hindrance

The size of substituents plays a role in very many organic reactions—it's the reason aldehydes (with an H next to the C=O group) are more reactive than ketones, for example. Steric hindrance affects reaction rates, but also makes molecules react by completely different mechanisms, as you will see in the substitution reactions in Chapter 15. You will need to get used to thinking about whether the presence of large substituents, with all their filled C–H and C–C bonds, is a factor in determining how well a reaction will go.

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.



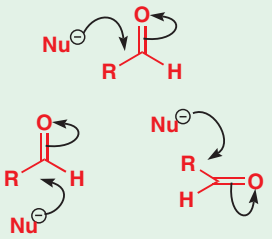
The cassava is now safe to eat but it still contains some glucoside. Some diseases found in eastern Nigeria can be traced to long-term consumption of HCN. Similar glucosides are found in apple pips and the kernels inside the stones of fruit such as peaches and apricots. Some people like eating these,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

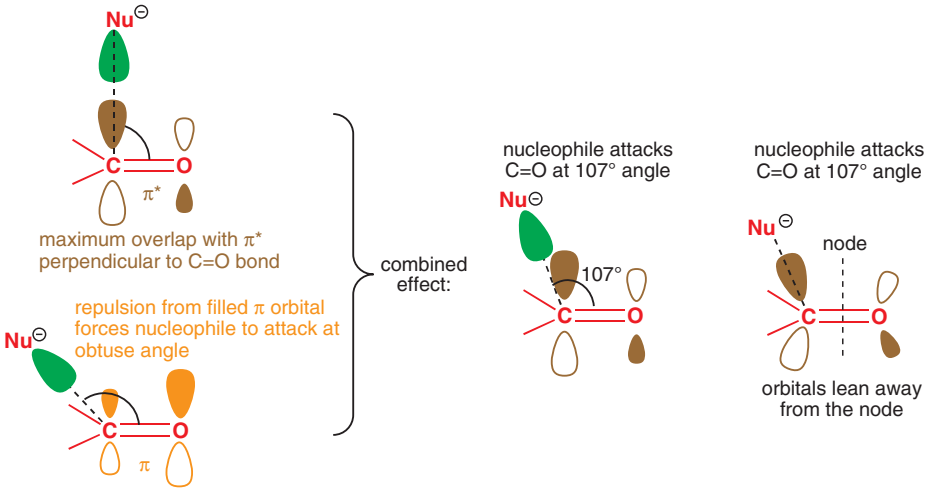
The angle of nucleophilic attack on aldehydes and ketones

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—close to the angle at which the new bond will form. 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. But a better explanation is that π* does not have parallel atomic orbitals as there is a node halfway down the bond (Chapter 4) so the atomic orbitals are already at an angle. The nucleophile attacks along the axis of the larger orbital in the HOMO.

We pointed this out in Chapter 4 on p. 104.

■ 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.



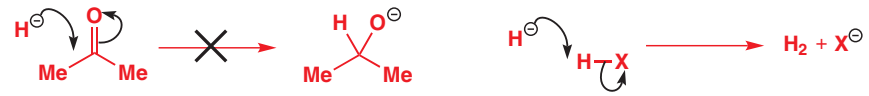


Any other portions of the molecule that get in the way of (or, in other words, that cause *steric hindrance* to) the Bürgi–Dunitz trajectory will greatly reduce the rate of addition and this is another reason why aldehydes are more reactive than ketones. The importance of the Bürgi–Dunitz trajectory will become more evident later, particularly in Chapter 33.

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 described here. Theoretical calculations later gave the same 107° value for the optimum angle of attack.

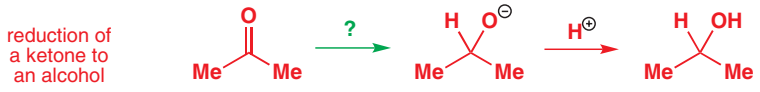
Nucleophilic attack by 'hydride' on aldehydes and ketones

Nucleophilic attack by the hydride ion, H^-, is an almost unknown reaction. This species, which is present in the salt sodium hydride, NaH, 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 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.



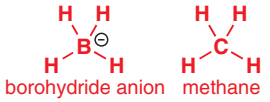
nucleophilic attack by H^- almost *never happens* — H^- almost *always* reacts as a base

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, p. 32) 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.

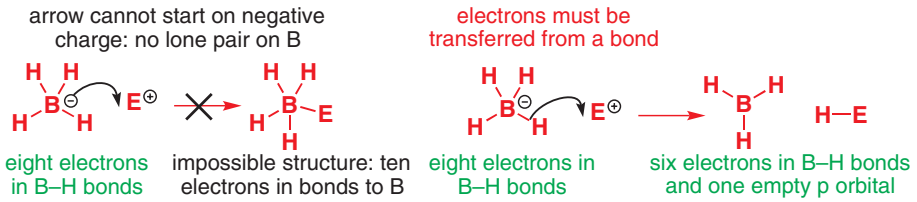


The most important of these compounds is sodium borohydride, $NaBH_4$. This is a water-soluble salt containing the tetrahedral BH_4^- anion, which is isoelectronic with methane but has a negative charge since boron has one less proton in the nucleus than does carbon.

In Chapter 4 we looked at isoelectronic borane BH_3 and the cation CH_3^+. Here we have effectively added a hydride ion to each of them.

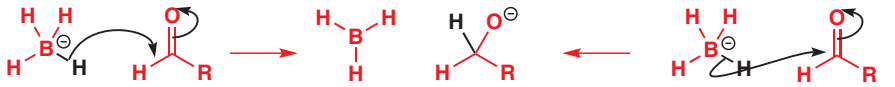


But beware! Remember (p. 115) there is no lone pair on boron: you must not draw an arrow coming out of this negative charge to form another bond. If you did, you would get a pentacovalent B(V) compound, which would have ten electrons in its outer shell. Such a thing is impossible with a first-row element as there are only four available orbitals ($1 \times 2s$ and $3 \times 2p$). Instead, since all of the electrons (including those 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.



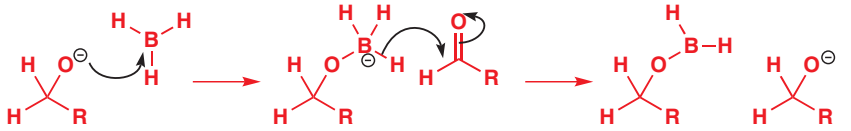
■ Just as we have used Nu^- to indicate any (undefined) nucleophile, here E^+ means any (undefined) electrophile.

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. Although 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.

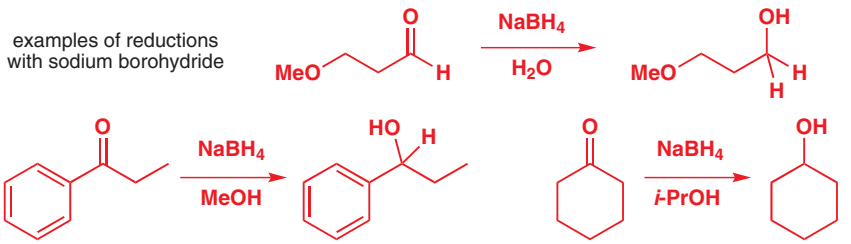


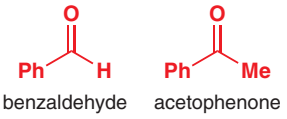
Interactive mechanism for borohydride reduction

You met this reaction in Chapter 5 but there is more to say about it. 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.

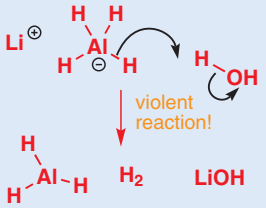


This process can continue so that, in principle, all four hydrogen atoms could be transferred to molecules of aldehyde. In practice the reaction is rarely as efficient as that, but aldehydes and ketones are usually reduced in good yield to the corresponding alcohol by sodium borohydride in water or alcoholic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



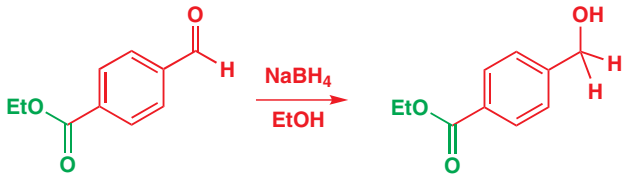


Aluminium is more electropositive (more metallic) than boron and is therefore more ready to give up a hydrogen atom (and the associated negative charge), whether to a carbonyl group or to water. Lithium aluminium hydride reacts violently and dangerously with water in an exothermic reaction that produces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

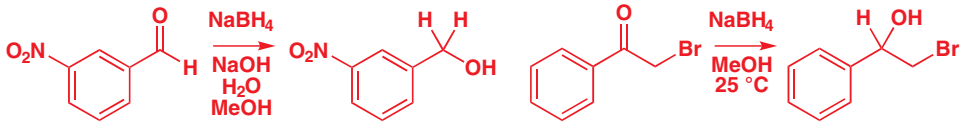


Sodium borohydride is one of the weaker hydride donors. The fact that it can be used in water is evidence of this: more powerful hydride donors such as lithium aluminium hydride, $LiAlH_4$, react violently with water. Sodium borohydride reacts with both aldehydes and ketones, although the reaction with ketones is slower: for example, benzaldehyde is reduced about 400 times faster than acetophenone in isopropanol. This is because of steric hindrance (see above).

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.

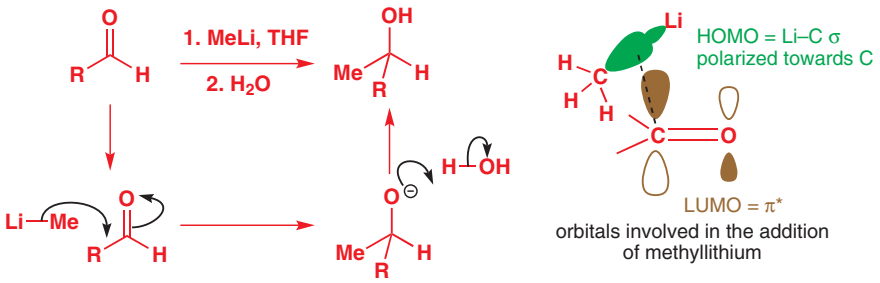


The next two examples illustrate the reduction of aldehydes and ketones in the presence of other reactive functional groups. No reaction occurs at the nitro group in the first case or at the alkyl halide in the second.



Addition of organometallic reagents to aldehydes and ketones

Organometallic compounds have a carbon–metal bond. 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. We explained on p. 113 the polarization of bonds between carbon and more electropositive elements. The relevant electronegativities are C 2.5, Li 1.0, and Mg 1.2 so both metals are much more electropositive than carbon. The orbitals of MeLi are discussed in Chapter 4.



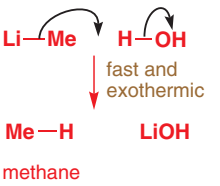
Interactive mechanism for methyllithium addition

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*.

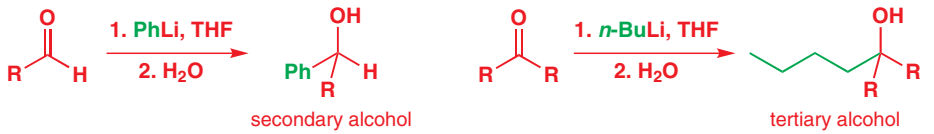
Because they are so reactive, organolithiums are usually used at low temperature, often –78 °C (the sublimation temperature of solid CO_2), in aprotic solvents such as Et_2O or THF. Protic solvents such as water or alcohols have acidic protons but aprotic solvents such as ether do not. Organolithiums 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.

organometallics are destroyed by water



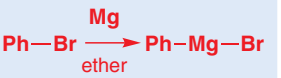
Low-temperature baths

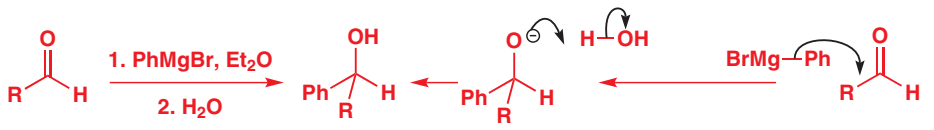
Cooling reaction mixtures is generally the job of a cooling bath of ice and water for around 0 °C, or baths of solid CO_2 in organic solvents such as acetone or ethanol down to about –78 °C. Small pieces of solid CO_2 are added slowly to the solvent until vigorous bubbling ceases. Few chemists then measure the temperature of the bath, which may be anywhere from –50 to –80 °C. The temperature given in publications is often –78 °C, about the lower limit. Lower temperatures require liquid nitrogen. Practical handbooks give details.



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.

Grignard reagents were discovered by Victor Grignard (1871–1935) at the University of Lyon, who got the Nobel prize for his discovery in 1912. They are made by reacting alkyl or aryl halides with magnesium 'turnings'.

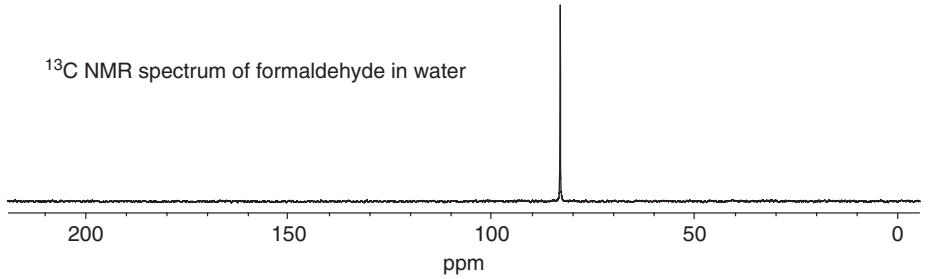




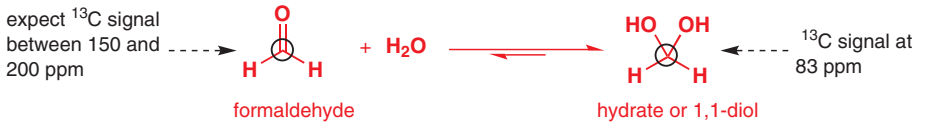
Interactive mechanism for Grignard addition

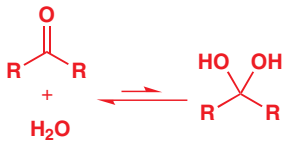
Addition of water to aldehydes and ketones

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 ppm. So where is formaldehyde's carbonyl peak? Instead we have a signal at 83 ppm—where we would expect tetrahedral carbon atoms singly bonded to oxygen to appear.

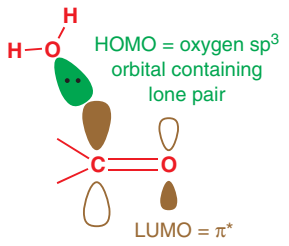


What has happened is that water has added to the carbonyl group to give a compound known as a hydrate or 1,1-diol.





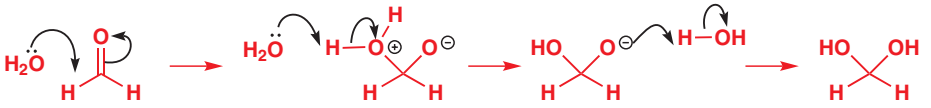
significant concentrations of hydrate are generally formed only from aldehydes



orbitals involved in the addition of water

This reaction, like the addition of cyanide 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 (p. 129) 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. 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. 129). 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.

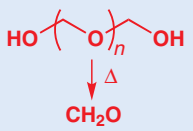


Interactive mechanism for hydrate formation

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.

polymeric 'paraformaldehyde'



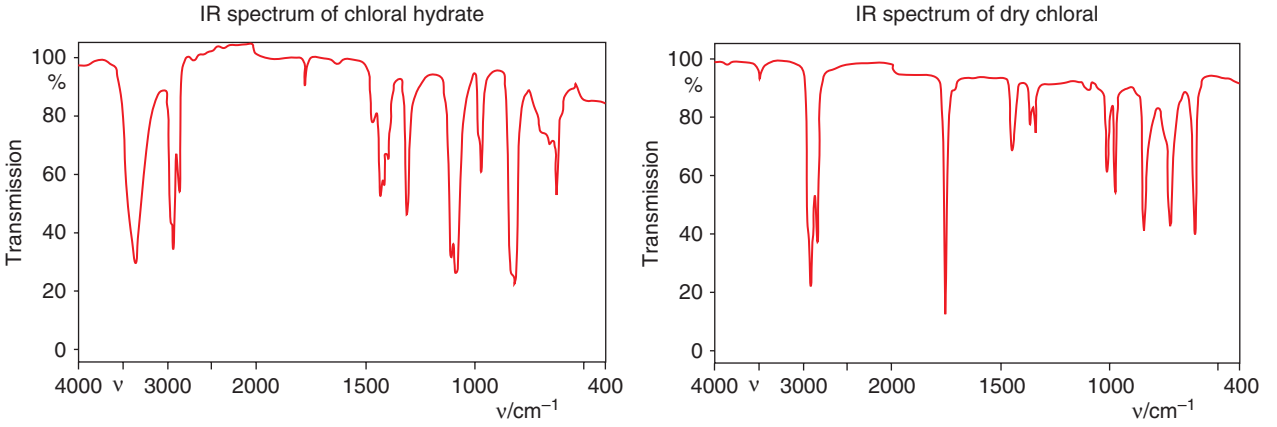
Formaldehyde reacts with water so readily because its substituents are very small: a steric effect. Electronic effects can also favour reaction with nucleophiles—electronegative atoms such as halogens attached to the carbon atoms next to the carbonyl group can increase the extent of hydration by the inductive effect 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 below. 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 'knockout drops' of Agatha Christie or the 'Mickey Finn' of prohibition gangsters.

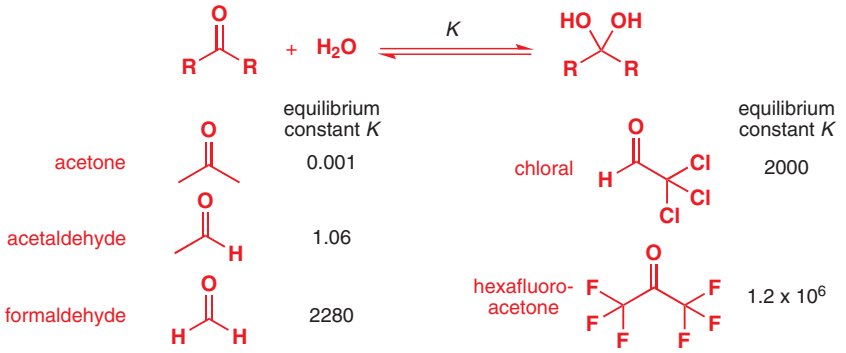
Steric and electronic effects

- **Steric effects** are concerned with the size and shape of groups within molecules.
- **Electronic effects** result from the way that electronegativity differences between atoms affect the way electrons are distributed in molecules. They can be divided into *inductive effects*, which are the consequence of the way that electronegativity differences lead to polarization of σ bonds, and *conjugation* (sometimes called *mesomeric effects*) which affects the distribution of electrons in π bonds and is discussed in the next chapter.

Steric and electronic effects are two of the main factors dominating the reactivity of nucleophiles and electrophiles.

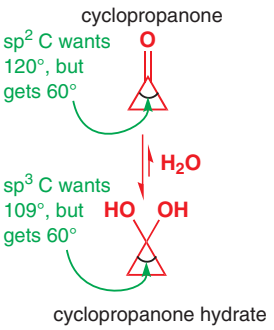


The chart shows the extent of hydration (in water) of a small selection of carbonyl compounds: hexafluoroacetone is probably the most hydrated carbonyl compound possible! The larger the equilibrium constant, the more the equilibrium is to the right.



Interactive structures of carbonyl compounds and hydrates

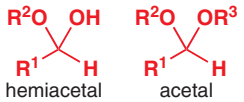
Cyclopropanones—three-membered ring ketones—are also hydrated to a significant extent, but for a different reason. You saw earlier how *acyclic* ketones suffer increased steric hindrance when the bond angle changes from 120° to 109° on moving from sp^2 to sp^3 hybridization. Cyclopropanones (and other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

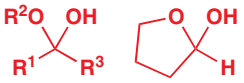


● The same structural features that favour or disfavour hydrate formation are important in determining the reactivity of carbonyl compounds with other nucleophiles, whether the reactions are reversible or not. Steric hindrance and more alkyl substituents make carbonyl compounds less reactive towards 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

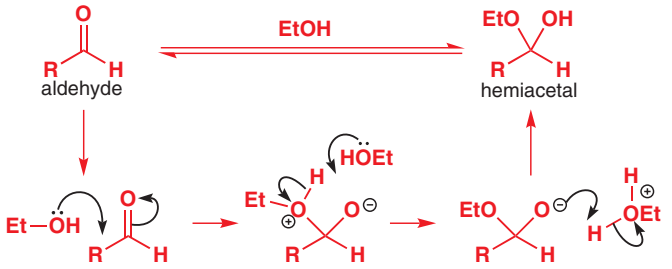




names for functional groups

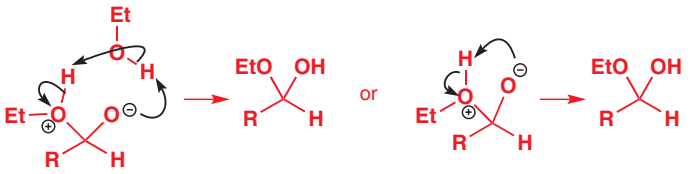
Interactive mechanism for hemiacetal formation

an acetal, a functional group that you met in Chapter 2 (p. 32) and that will be discussed in detail in Chapter 11. The mechanism follows in the footsteps of hydrate formation: just use ROH instead of HOH.



In the mechanism above, as in the mechanism of hydrate formation on p. 134, a proton has to be transferred between one oxygen atom and the other. We have shown a molecule of ethanol (or water) doing this, but it is impossible to define exactly the path taken by any one proton as it transfers between the oxygen atoms. It might not even be the same proton: another possible mechanism is shown below on the left, where a molecule of ethanol simultaneously gives away one proton and takes another. In the simplest case, the proton just hops from one oxygen to another, as shown in the right, and there is no shame in writing this mechanism: it is no more or less correct than the others.

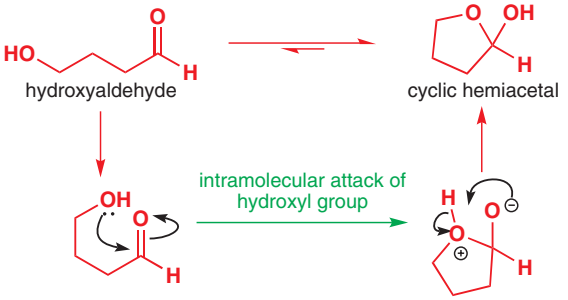
two more (and equally correct) mechanisms for proton transfer between the oxygen atoms:



What is certain is that proton transfers between oxygen atoms are very fast and are reversible, and for that reason we don't need to be concerned with the details—the proton can always get to where it needs to be for the next step of the mechanism. As with all these carbonyl group reactions, what is really important is the addition step, not what happens to the protons.

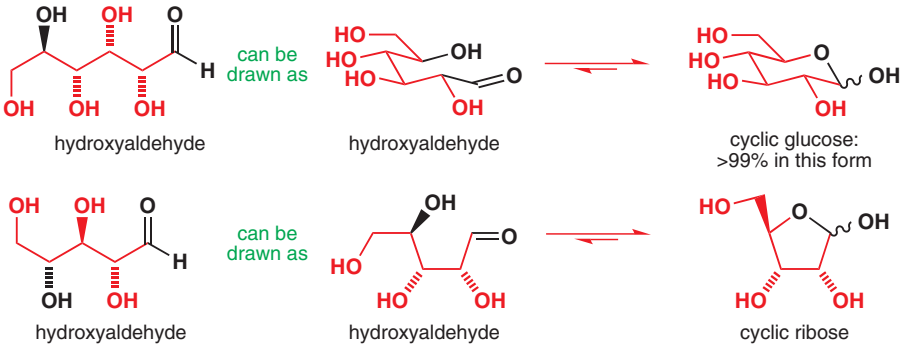
Hemiacetal formation is reversible, and hemiacetals are stabilized by the same special structural features as those of hydrates. However, hemiacetals can also gain stability by being cyclic—when the carbonyl group and the attacking hydroxyl group are part of the same molecule. The reaction is now an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

Intermolecular reactions occur between two molecules. ***Intramolecular*** 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 Chapters 11 and 12.



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

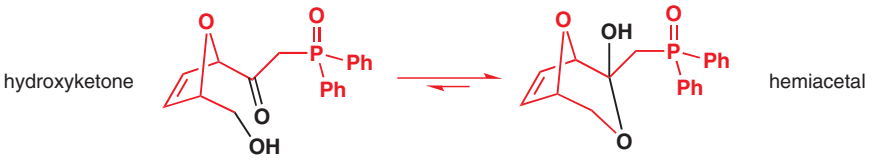
forms, depends on the size of the ring: five- and six-membered rings are free from strain (their bonds are free to adopt 109° or 120° angles—compare the three-membered rings on p. 135), and five- or six-membered hemiacetals are common. Among the most important examples are many sugars. Glucose, for example, 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, although we first mentioned it in Chapter 2: 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 14 to stereochemistry and Chapter 16 to conformation.

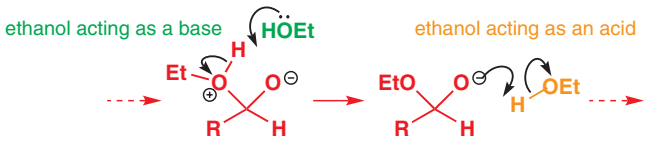
Ketones also form hemiacetals

Hydroxyketones can also form hemiacetals but, as you should expect, they usually do so less readily than hydroxyaldehydes. But we know that this hydroxyketone must exist as the cyclic hemiacetal as it has no C=O stretch in its IR spectrum. The reason? The hydroxyketone is already cyclic, with the OH 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

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. 138 and hydrate formation on p. 134. Both involve proton-transfer steps, which we can choose to draw like this:

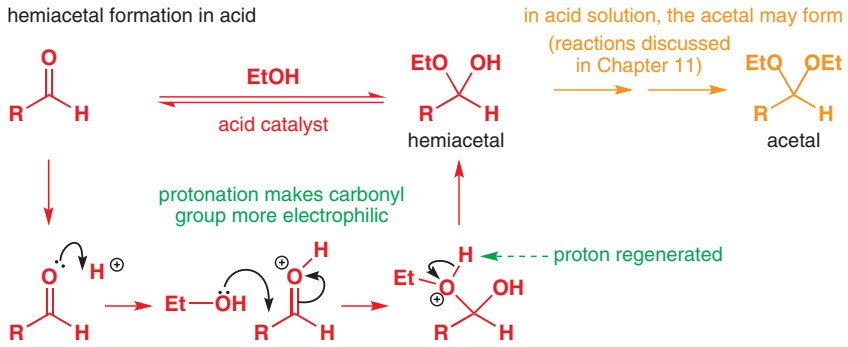


In the first proton-transfer step, ethanol acts as a **base**, removing a proton; in the second it acts as an **acid**, donating a proton. You saw in Chapter 5 how water can also act as an acid or a base. Strong acids or strong bases (for example HCl or NaOH) increase the rate of hemiacetal or hydrate formation because they allow these proton-transfer steps to occur *before* the addition to the carbonyl group.

In acid (dilute HCl, say), the mechanism is different in detail. The first step is now protonation of the carbonyl group's lone pair: the positive charge makes it much more electrophilic

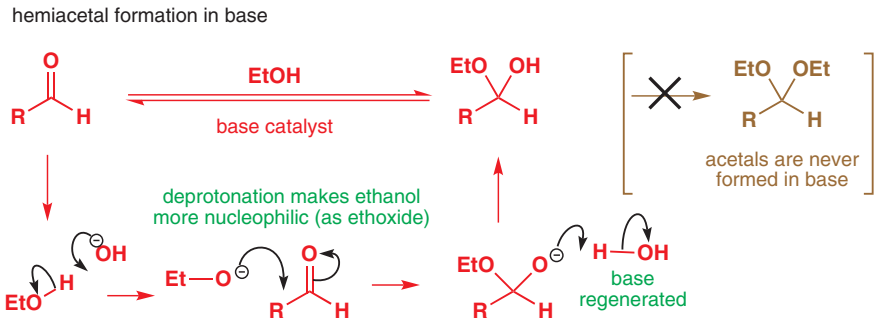
so the addition reaction is faster. Notice how the proton added at the beginning is lost again at the end—it is really a catalyst.

■ In acid it is also possible for the hemiacetal to react further with the alcohol to form an acetal, but this is dealt with in Chapter 11 and need not concern you at present.



The mechanism in basic solution is slightly different again. 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 the last step, making the overall reaction catalytic in base.

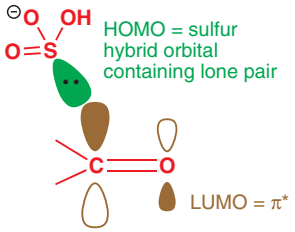
■ As you will see in Chapter 11, the reaction in base always stops with the hemiacetal—acetals never form in base.



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.

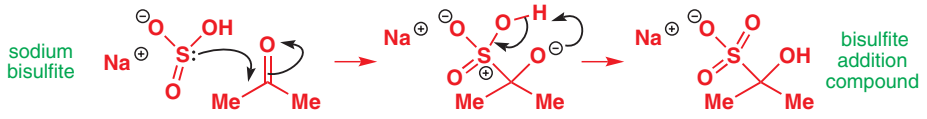
- **For nucleophilic additions to carbonyl groups:**
  - **acid catalysts work by making the carbonyl group more electrophilic**
  - **base catalysts work by making the nucleophile more nucleophilic**
  - **both types of catalysts are regenerated at the end of the reaction.**

Bisulfite addition compounds



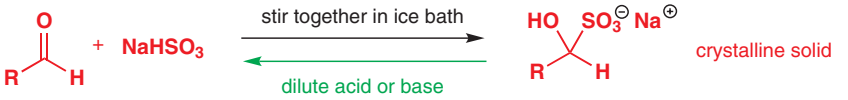
orbitals involved in the addition of bisulfite

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.

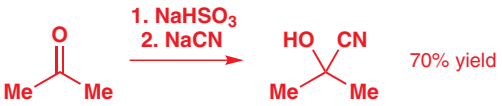


The products are useful for two reasons. They are usually crystalline and so can be used to purify liquid aldehydes by recrystallization. This is of value only because this reaction, like

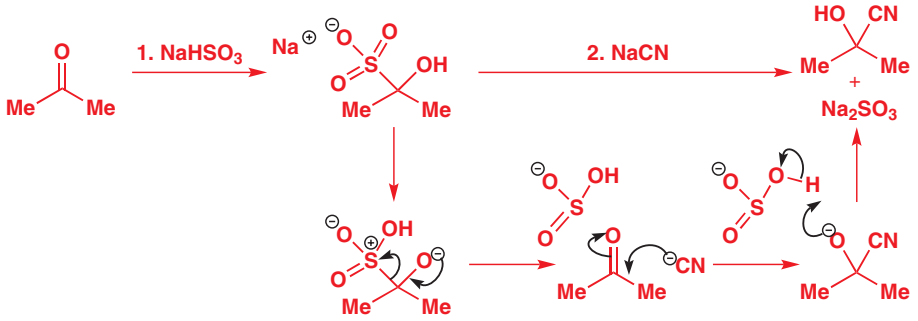
several you have met in this chapter, is reversible. The bisulfite compounds are made by mixing the aldehyde or ketone with saturated aqueous sodium bisulfite in an ice bath, shaking, and crystallizing. After purification the bisulfite addition compound can be hydrolysed back to the aldehyde in dilute 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.



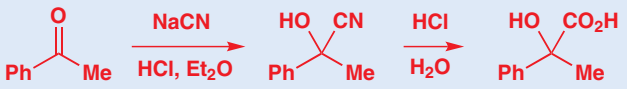
What is happening here? The bisulfite compound forms first, but only as an intermediate on the route to the cyanohydrin. When the cyanide is added, reversing the formation of the bisulfite compound provides the single proton necessary to give back the hydroxyl group at the end of the reaction. No dangerous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



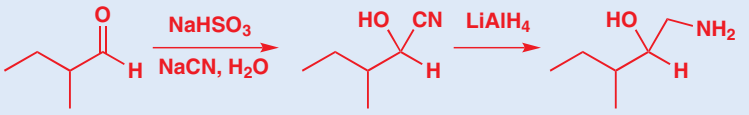
Other compounds from cyanohydrins

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 10 for the details and the mechanisms of the reactions. Note that one cyanohydrin was made by the simplest method—simply 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

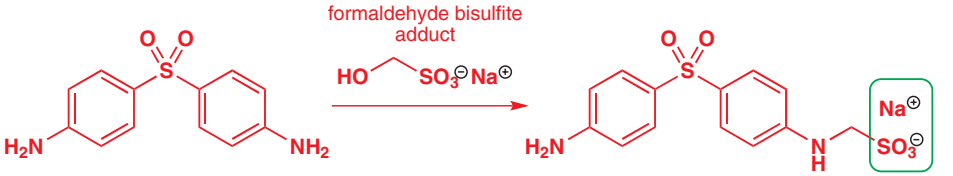


The second reason that bisulfite compounds are useful is that they are soluble in water. Some small (that is, low molecular weight) aldehydes and ketones are water-soluble—acetone is an example. But most larger (more than four or so carbon atoms) aldehydes and ketones are not.

■ 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 'second-row' element (second row of the periodic table, that is) sulfur can have more than just eight electrons—it's all right to have four, five, or six bonds to S or P, unlike, say, B or O. Second-row elements have d orbitals as well as s and p so they can accommodate more electrons.

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 11, 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.

Further reading

Section 1, 'Nucleophilic addition to the carbonyl group' in S. Warren, *Chemistry of the Carbonyl Group*, Wiley, Chichester, 1974, and P. Sykes, *A Guidebook to Mechanism in Organic Chemistry*, 6th edn, Longman, Harlow, 1986, pp. 203–219. For a more theoretical approach, we suggest J. Keeler and P. Wothers, *Why Chemical Reactions Happen*, OUP, Oxford, 2003, especially pp. 102–106.

For further, more advanced, details of the cassava–HCN problem: D. Siritunga, D. Arias-Garzon, W. White, and R. T. Sayre, *Plant Biotechnology Journal*, 2004, **2**, 37. For details of cyanohydrin formation using sodium bisulfite: B. S. Furniss, A. J. Hannaford, P. W. G. Smith, and A. T. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, 5th edn, Longman, Harlow, 1989, pp. 729–730.

Check your understanding

To check that you have mastered the concepts presented in this chapter, attempt the problems that are available in the book's Online Resource Centre at **http://www.oxfordtextbooks.co.uk/orc/clayden2e/**