# Proton nuclear magnetic resonance

# 11

## Connections

**Building on:**

- **X-ray crystallography, mass spectrometry, $^{13}$C NMR and infrared spectroscopy ch3**

**Arriving at:**

- **Proton (or $^{1}$H) NMR spectroscopy**
- **How $^{1}$H NMR compares with $^{13}$C NMR**
- **How 'coupling' in $^{1}$H NMR provides most of the information needed to find the structure of an unknown molecule**

**Looking forward to:**

- **Using $^{1}$H NMR with other spectroscopic methods to solve structures rapidly ch15**
- **Using $^{1}$H NMR to investigate the detailed shape (stereochemistry) of molecules ch32**
- **$^{1}$H NMR spectroscopy is referred to in most chapters of the book as it is the most important tool for determining structure; you must understand this chapter before reading further**

## The differences between carbon and proton NMR

■
Three prongs: $^{13}$C NMR; infrared spectroscopy; mass spectrometry.

We used $^{13}$C NMR in Chapter 3 as part of a three-pronged attack on the problem of determining molecular structure. Important though these three prongs are, we were forced to confess at the end of Chapter 3 that we had delayed the most important technique of all—proton ($^{1}$H) NMR—until a later chapter because it is more complicated than $^{13}$C NMR. This is that delayed chapter and we must now tackle those complications. We hope you will see $^{1}$H NMR for the beautiful and powerful technique that it surely is. The difficulties are worth mastering for this is the chemist's primary weapon in the battle to solve structures.

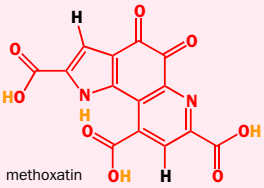
▶
$^{1}$H NMR and proton NMR are interchangeable terms. Chemists often use 'proton' to mean not only $H^+$ but also the nucleus of a hydrogen atom forming part of a molecule. This is how it will be used in this chapter.

Proton NMR differs from $^{13}$C NMR in a number of ways.

- $^{1}$H is the major isotope of hydrogen (99.985% natural abundance), while $^{13}$C is only a minor isotope (1.1%)
- $^{1}$H NMR is quantitative: the area under the peak tells us the number of hydrogen nuclei, while $^{13}$C NMR may give strong or weak peaks from the same number of $^{13}$C nuclei
- Protons interact magnetically ('couple') to reveal the connectivity of the structure, while $^{13}$C is too rare for coupling between $^{13}$C nuclei to be seen
- $^{1}$H NMR shifts give a more reliable indication of the local chemistry than that given by $^{13}$C spectra

▶ **An instance where $^{1}$H NMR was *not* useful**

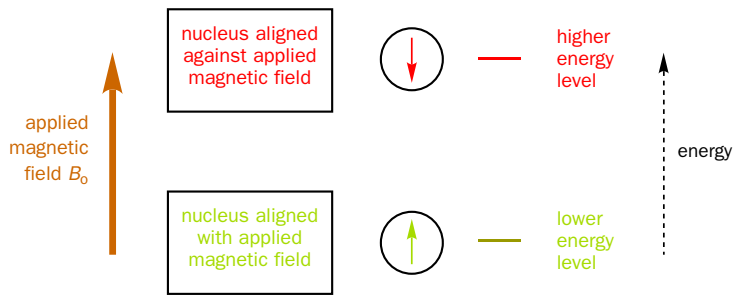
In Chapter 3 you met methoxatin. Proton NMR has little to tell us about its structure as it has so few protons (it is $C_{14}H_6N_2O_8$). Carbon NMR and eventually an X-ray crystal structure gave the answer. There are four OH and NH protons (best seen by IR) and only two C-H protons. The latter protons are the kind that proton NMR reveals best. Fortunately, most compounds have lots more than this.



methoxatin

We shall examine each of these points in detail and build up a full understanding of proton NMR spectra. The other spectra remain important, of course.

Proton NMR spectra are recorded in the same way as $^{13}$C NMR spectra: radio waves are used to study the energy level differences of nuclei, but this time they are $^{1}$H and not $^{13}$C nuclei. Hydrogen nuclei have a nuclear spin

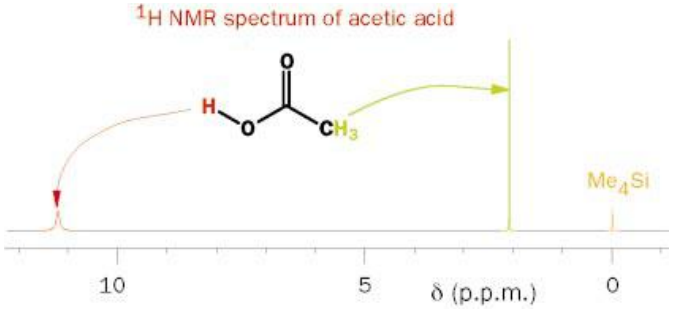



▶
The number of energy levels available to a nucleus of spin $I$ is $2I + 1$.

of a half and so have two energy levels: they can be aligned either with or against the applied magnetic field.

The spectra look much the same: the scale runs from right to left and the zero point is given by the same reference compound though it is the proton resonance of $Me_4Si$ rather than the carbon resonance that defines the zero point. You will notice at once that the scale is much smaller, ranging over only about 10 p.p.m. instead of the 200 p.p.m. needed for carbon. This is because the variation in the chemical shift is a measure of the shielding of the nucleus by the electrons around it. There is inevitably less change possible in the distribution of two electrons around a hydrogen nucleus than in that of the eight valence electrons around a carbon nucleus. Here is a simple $^1H$ NMR spectrum.

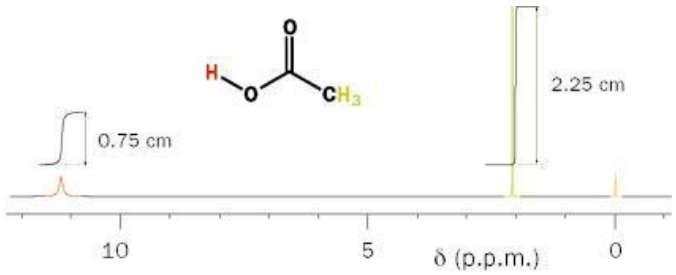
▶ This 10 p.p.m. scale is not the same as any part of the $^{13}C$ NMR spectrum. It is at a different frequency altogether.




## Integration tells us the number of hydrogen atoms in each peak

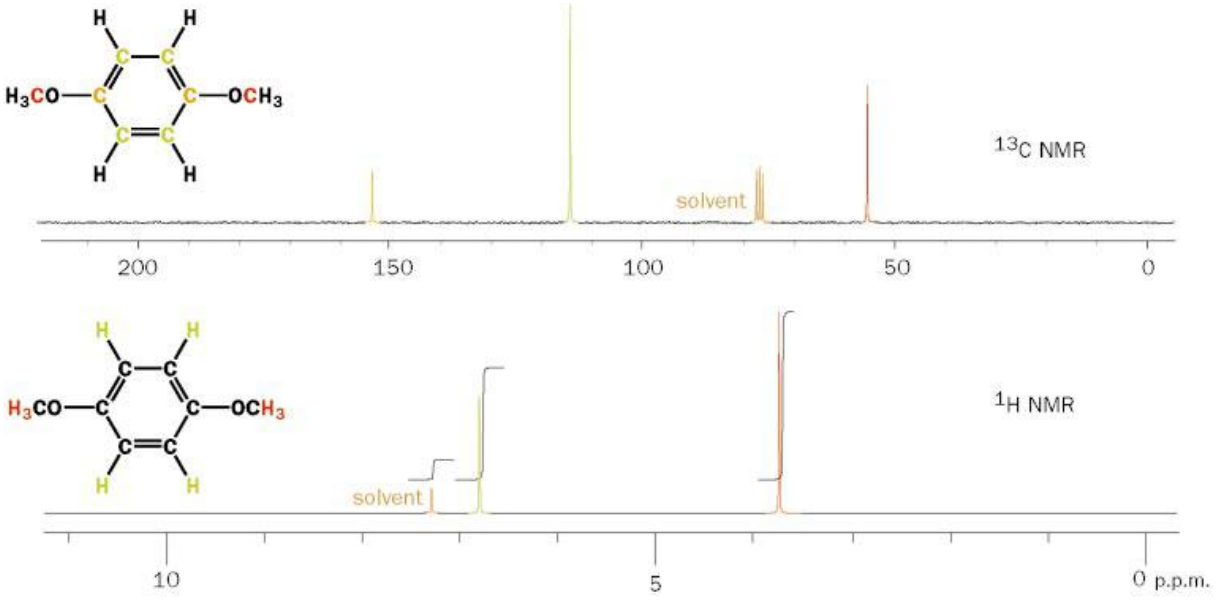
The chemical shift of the twelve hydrogen atoms of the four identical methyl groups in $Me_4Si$ is defined as zero. The methyl group in the acid is next to the carbonyl group and so slightly deshielded at about δ 2.0 p.p.m. and the acidic proton itself is very deshielded at δ 11.2 p.p.m. The same factor that makes this proton acidic—the O–H bond is polarized towards oxygen—also makes it resonate at low field. So far things are much the same as in carbon NMR. Now for a difference. Notice that the ratio of the peak heights in this spectrum was about 3:1 and that that is also the ratio of the number of protons. In fact, it's not the peak height but the area under the peaks that is exactly proportional to the number of protons. Proton spectra are normally **integrated**, that is, the area under the peaks is computed and recorded as a line with steps corresponding to the area, like this.

■ It is not enough simply to measure the relative heights of the peaks because, as here, some peaks might be broader than others. Hence the area under the peak is measured.

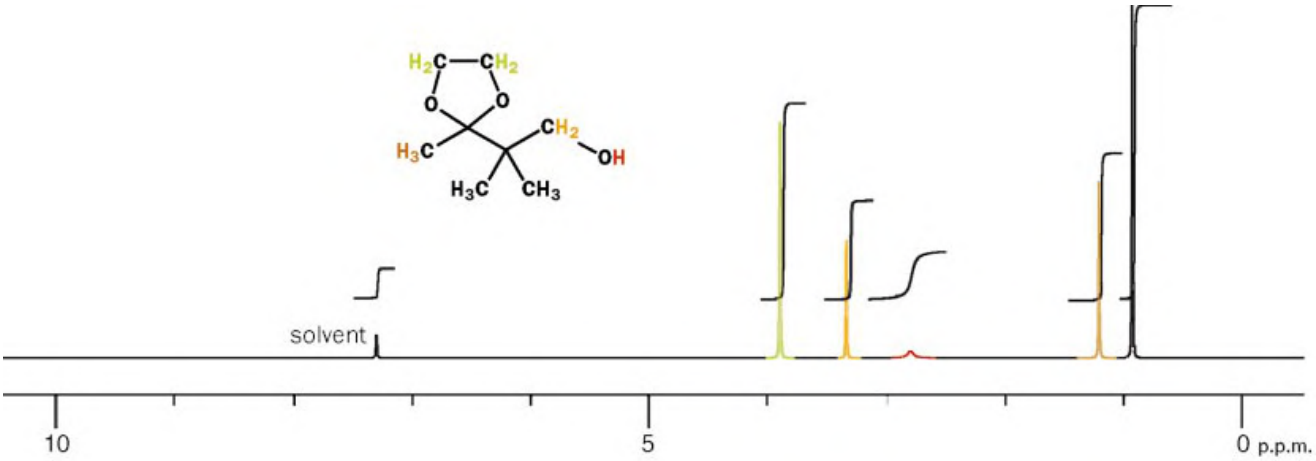



Simply measuring the height of the steps with a ruler gives you the *ratio* of the numbers of protons represented by each peak. Knowing the atomic composition from the mass spectrum, we also know the distribution of protons of various kinds. Here the heights are 0.75 and 2.25 cm, a ratio of about 1:3. The compound is $C_2H_4O_2$ so, since there are 4 H atoms altogether, the peaks must contain $1 \times H$ and $3 \times H$, respectively.

In the spectrum of 1,4-dimethoxybenzene, there are just two signals in the ratio of 3:2. This time the compound is $C_8H_{10}O_2$ so the true ratio must be 6:4. Assigning the spectrum requires the same attention to symmetry as in the case of $^{13}C$ spectra.



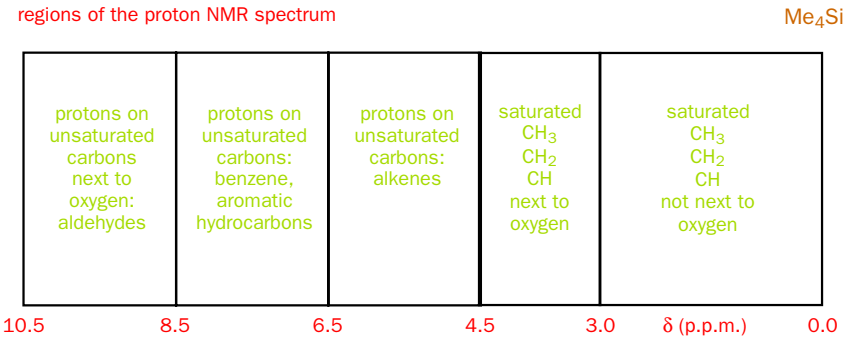

In this next example it is easy to assign the spectrum simply by measuring the steps in the integral. There are two identical methyl groups ($CMe_2$) having 6 Hs, one methyl group by itself having 3 Hs, the OH proton (1 H), the $CH_2$ group next to the OH (2 Hs), and finally the $CH_2CH_2$ group between the oxygen atoms in the ring (4 Hs).




Proton NMR spectra are generally recorded in solution in deuterochloroform ($CDCl_3$)—that is, chloroform with the $^{1}$H replaced by $^{2}$H. The proportionality of the size of the peak to the number of protons tells you why: if you ran a spectrum in C*H*$Cl_3$, you would see a vast peak for all the solvent Hs because there would be much more solvent than the compound you wanted to look at. Using C*D*$Cl_3$ cuts out all extraneous protons.

## Regions of the proton NMR spectrum

The integration gives useful—indeed essential—information, but it is much more important to understand the reasons for the exact chemical shift of the different types of proton. In the last example you can see one marked similarity to carbon spectra: protons on saturated carbon atoms next to oxygen are shifted downfield to larger δ values (here 3.3 and 3.9 p.p.m.). The other regions of the proton NMR spectrum are also quite similar in general outline to those of $^{13}$C spectra. Here they are.




These regions hold for protons attached to C: protons attached to O or N can come almost anywhere on the spectrum. Even for C–H signals, the regions are approximate and overlap quite a lot. You should use the chart as a basic guide, but you will need a more detailed understanding of proton chemical shifts than you did for $^{13}C$ chemical shifts. To achieve this understanding, we now need to examine each class of proton in more detail and examine the reasons for particular shifts. It is important that you grasp these reasons. An alternative is to learn all the chemical shifts off by heart (not recommended).

## Protons on saturated carbon atoms

### Chemical shifts are related to the electronegativity of substituents

▶ In this chapter you will see a lot of numbers—chemical shifts and differences in chemical shifts. We need these to show that the ideas behind $^1H$ NMR are securely based in fact. You do *not* need to learn these numbers. Comprehensive tables can be found at the end of Chapter 15, which we hope you will find useful for reference while you are solving problems. Again, do not attempt to learn the numbers!

We shall start with protons on saturated carbon atoms. If you study Table 11.1 you will see that the protons in a methyl group are shifted more and more as the atom attached to them gets more electronegative.

**Table 11.1** Effects of electronegativity

| Atom | Electronegativity | Compound | $^1H$ NMR shift, p.p.m. |
|---|---|---|---|
| Li | 1.0 | $CH_3$–Li | –1.94 |
| Si | 1.9 | $CH_3$–$SiMe_3$ | 0.0 |
| N | 3.0 | $CH_3$–$NH_2$ | 2.41 |
| O | 3.4 | $CH_3$–OH | 3.50 |
| F | 4.0 | $CH_3$–F | 4.27 |

When we are dealing with simple atoms as substituents, these effects are straightforward and more or less additive. If we go on adding electronegative chlorine atoms to a carbon atom, electron density is progressively removed from it and the carbon nucleus and the hydrogen atoms attached to it are progressively deshielded.

▶ The second two compounds, dichloromethane $CH_2Cl_2$ and chloroform $CHCl_3$, are commonly used as solvents and their shifts will become familiar to you if you look at a lot of spectra.

| | $CH_3Cl$ | $CH_2Cl_2$ | $CHCl_3$ |
|---|---|---|---|
| $^1H$ NMR shift, p.p.m. | 3.06 | 5.30 | 7.27 |
| $^{13}C$ NMR shift, p.p.m. | 24.9 | 54.0 | 77.2 |

### Proton chemical shifts tell us about chemistry

▶ You have seen δ used as a symbol for chemical shift. Now that we have two sorts of chemical shift—in the $^{13}C$ NMR spectrum and in the $^1H$ NMR spectrum—we need to be able to distinguish them. $\delta_H$ means chemical shift in the $^1H$ NMR spectrum, and $\delta_C$ chemical shift in the $^{13}C$ NMR spectrum.

The truth is that shifts and electronegativity are not perfectly correlated. The key property is indeed electron withdrawal but it is the electron-withdrawing power of the whole substituent in comparison with the carbon and hydrogen atoms in the CH skeleton that matters. Methyl groups joined to the same element, say, nitrogen, may have very different shifts if the substituent is an amino group ($CH_3$–$NH_2$ has $\delta_H$ for the $CH_3$ group = 2.41 p.p.m.) or a nitro group ($CH_3$–$NO_2$ has $\delta_H$ 4.33 p.p.m.). A nitro group is much more electron-withdrawing than an amino group.

What we need is a quick guide rather than some detailed correlations, and the simplest is this: all functional groups except very electron-withdrawing ones shift methyl groups from 1 p.p.m. (where you find them if they are not attached to a functional group) downfield to about 2 p.p.m. Very electron-withdrawing groups shift methyl groups to about 3 p.p.m.

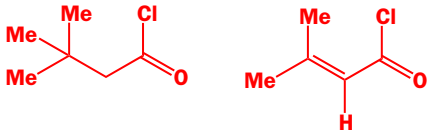
**Approximate chemical shifts for methyl groups**

| No electron-withdrawing functional groups | Less electron-withdrawing functional groups X | More electron-withdrawing functional groups X |
|---|---|---|
| Me at about 1 p.p.m. | MeX at about 2 p.p.m. (i.e. add 1 p.p.m.) | MeX at about 3 p.p.m. (i.e. add 2 p.p.m.) |
| aromatic rings, alkenes, alkynes | carbonyl groups: acids ($CO_2H$), esters ($CO_2R$), ketones (COR), nitriles (CN) | oxygen-based groups: ethers (OR), esters (OCOR) |
| | amines (NHR) | amides (NHCOR) |
| | sulfides (SR) | sulfones ($SO_2R$) |

Rather than trying to fit these data to some atomic property, even such a useful one as electronegativity, we should rather see these shifts as a useful measure of the electron-withdrawing power of the group in question. The NMR spectra are telling us about the chemistry. Among the largest shifts possible for a methyl group is that caused by the nitro group, 3.43 p.p.m., at least twice the size of the shift for a carbonyl group. This gives us our first hint of some important chemistry: one nitro group is worth two carbonyl groups when you need electron withdrawal. You have already seen that electron withdrawal and acidity are related (Chapter 8) and in later chapters you will see that we can correlate the anion-stabilizing power of groups like carbonyl, nitro, and sulfone with proton NMR.

## Methyl groups give us information about the structure of molecules

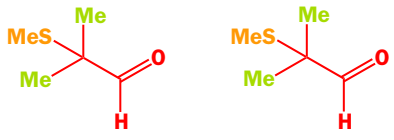
It sounds rather unlikely that the humble methyl group could tell us much that is important about molecular structure—but just you wait. We shall look at four simple compounds and their NMR spectra—just the methyl groups, that is. The first two are the acid chlorides on the right.

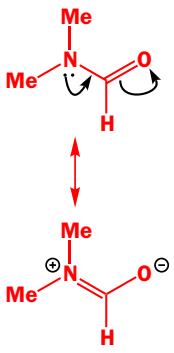



The first compound shows just one methyl signal containing 9 Hs at $\delta_H$ 1.10 p.p.m.. This tells us two things. All the protons in each methyl group are the same; and all three methyl groups in the tertiary butyl (*t*-butyl, or $Me_3C$–) group are the same. This is because rotation about C–C single bonds, both about the $CH_3$–C bond and about the $(CH_3)_3C$–C bond, is fast. Though at any one instant the hydrogen atoms in one methyl group, or the methyl groups in the *t*-butyl group, may differ, on average they are the same. The time-averaging process is fast rotation about a σ bond. The second compound shows two 3H signals, one at 1.99 and one at 2.17 p.p.m. Now rotation is slow—indeed the C=C double bond does not rotate at all and so the two methyl groups are different. One is on the same side of the alkene as (or '*cis* to') the –COCl group while the other is on the opposite side (or '*trans*').

▶ Rotation about single bonds is generally very fast (you are about to meet an exception); rotation about double bonds is generally very, very slow (it just doesn't happen). This was discussed in Chapter 7.

The second pair of compounds contain the CHO group. One is a simple aldehyde, the other an amide of formic acid: it is DMF, dimethylformamide. The first has two sorts of methyl group: a 3H signal at $\delta_H$ 1.81 p.p.m. for the SMe group and a 6H signal for the $CMe_2$ group. The two methyl groups in the 6H signal are the same, again because of fast rotation about a C–C σ bond.



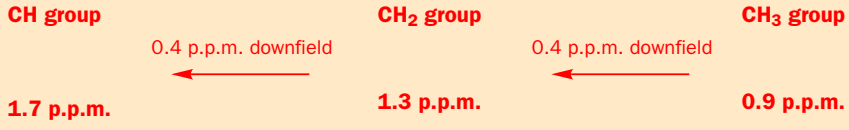




The second compound also has two methyl signals, at 2.89 and 2.98 p.p.m., each 3H, and these are the two methyl groups on nitrogen. Restricted rotation about the N–CO bond must be making the two Me groups different. You will remember from Chapter 7 (p. 000) that the N–CO amide bond has considerable double bond character because of conjugation: the lone pair electrons on nitrogen are delocalized into the carbonyl group.

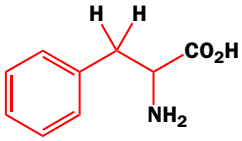
## Chemical shifts of $CH_2$ groups

Shifts of the same order of magnitude occur for protons on $CH_2$ groups and the proton on CH groups, but with the added complication that $CH_2$ groups have *two* other substituents and CH groups *three*. A $CH_2$ (methylene) group resonates at 1.3 p.p.m., about 0.4 p.p.m. further downfield than a comparable $CH_3$ group (0.9 p.p.m.), and a CH (methine) group resonates at 1.7 p.p.m., another 0.4 p.p.m. downfield. Replacing each hydrogen atom in the $CH_3$ group by a carbon atom causes a small downfield shift as carbon is slightly more electronegative (C 2.5 p.p.m.; H 2.2 p.p.m.) than hydrogen and therefore shields less effectively.

**Chemical shifts of protons in CH, $CH_2$, and $CH_3$ groups with no nearby electron-withdrawing groups**




δ($CH_2$) ~3.0 p.p.m.

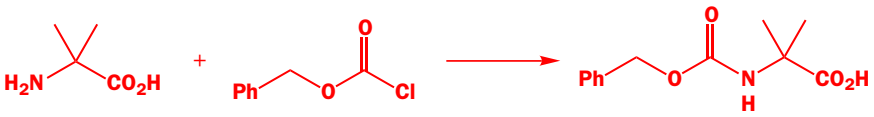



phenylalanine

The benzyl group ($PhCH_2$–) is very important in organic chemistry. It occurs naturally in the amino acid phenylalanine, which you met in Chapter 2. Phenylalanine has its $CH_2$ signal at 3.0 p.p.m. and is moved downfield from 1.3 p.p.m. mostly by the benzene ring.

Amino acids are often protected as the 'Cbz' derivatives (Carboxybenzyl) by reaction with an acid chloride.

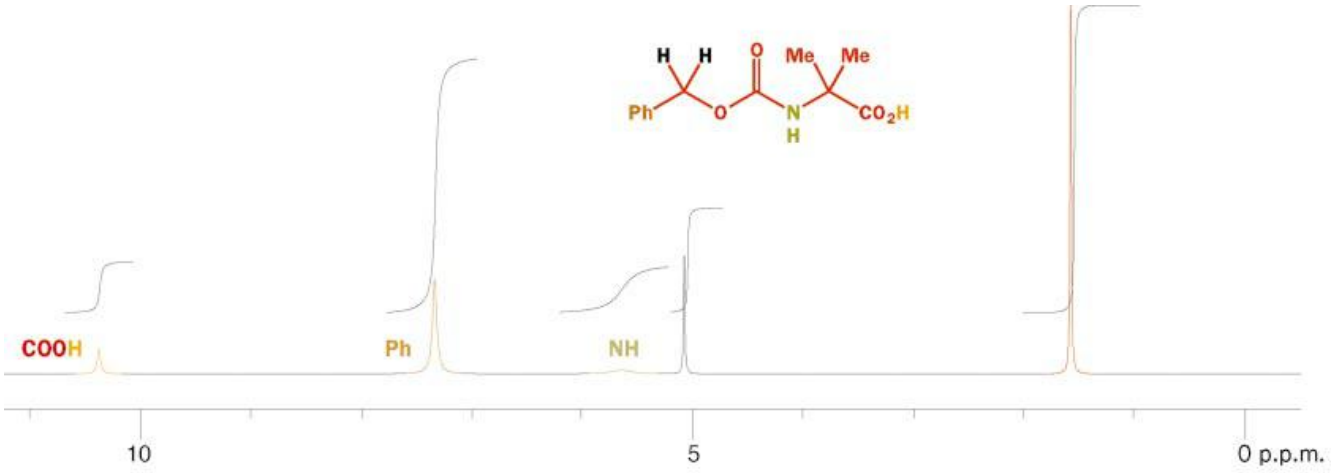
Here is a simple example together with the NMR spectrum of the product. Now the $CH_2$ group has gone further downfield to 5.1 p.p.m. as it is next to both oxygen and phenyl.




amino acid

"Cbz chloride" (benzyl chloroformate)

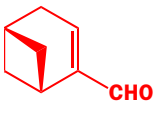
"Cbz protected" amino acid



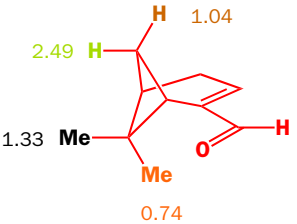

■

You'll meet this reaction in the next chapter, and we shall discuss protection and protecting groups in Chapter 24. For the moment, just be concerned with the structure of the product.

Like double bonds, **cage structures** prevent bond rotation, and can make the two protons of a $CH_2$ group appear different. There are many flavouring compounds from herbs that have structures like this. In the example here—myrtenal, from the myrtle bush—there is a four-membered ring bridged across a six-membered ring. The $CH_2$ group



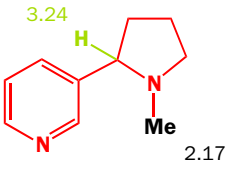

myrtenal



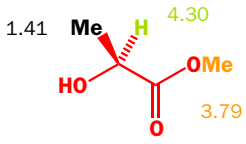
on the bridge has two different hydrogen atoms—one is over a methyl group and the other is over the enal system. No rotation of any bonds in the cage is possible, so these hydrogens are always different and resonate at different frequencies (1.04 and 2.49 p.p.m.). The methyl groups on the other bridge are also different for the same reason.

## Chemical shifts of CH groups

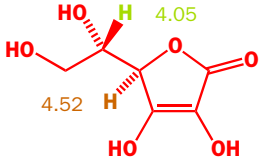
A CH group in the middle of a carbon skeleton resonates at about 1.7 p.p.m.—another 0.4 p.p.m. downfield from a $CH_2$ group. It can have up to three substituents and these will cause further downfield shifts of about the same amount as we have already seen for $CH_3$ and $CH_2$ groups. Here are three examples from nature: nicotine, the compound in tobacco that causes the craving (though not the death, which is doled out instead by the carbon monoxide and tars in the smoke), has one hydrogen atom trapped between a simple tertiary amine and an aromatic ring at 3.24 p.p.m. Lactic acid has a CH proton at 4.3 p.p.m.. You could estimate this with reasonable accuracy by taking 1.7 (for the CH) and adding 1.0 (for C=O) plus 2.0 (for OH) = 4.7 p.p.m. Vitamin C (ascorbic acid) has two CHs. One at 4.05 p.p.m. is next to an OH group (estimate 1.7 + 2.0 for OH = 3.7 p.p.m.) and one next to a double bond and an oxygen atom at 4.52 p.p.m. (estimate 1.7 + 1 for double bond + 2 for OH = 4.7 p.p.m.).



nicotine

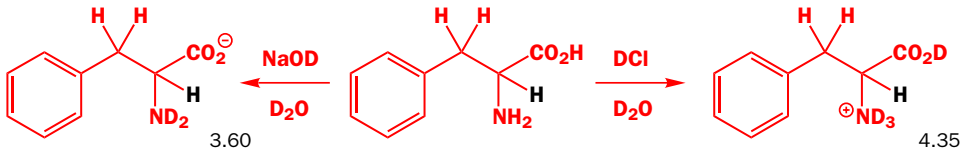


methyl ester of lactic acid



vitamin C (ascorbic acid)

An interesting case is the amino acid phenylalanine whose $CH_2$ group we looked at a moment ago. It also has a CH group between the amino and the carboxylic acid groups. If we record the $^1H$ NMR spectrum in $D_2O$, either in basic (NaOD) or acidic (DCl) solutions we see a large shift of that CH group. In basic solution the CH resonates at 3.60 p.p.m. and in acidic solution at 4.35 p.p.m. There is a double effect here: $CO_2H$ and $NH_3^+$ are both more electron-withdrawing than $CO_2^-$ and $NH_2$ so both move the CH group downfield.

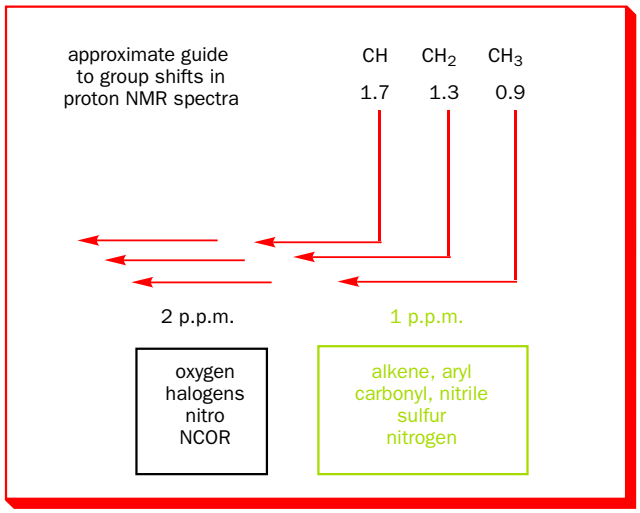


phenylalanine

▶ $D_2O$, NaOD, and DCl have to be used in place of their $^1H$ equivalents to avoid swamping the spectrum with $H_2O$ protons. All acidic protons are replaced by deuterium in the process — more on this later.

## Your simple guide to chemical shifts

We suggest you start with a very simple (and therefore oversimplified) picture, which should be the basis for any further refinements. Start methyl groups at 0.9, methylenes ($CH_2$) at 1.3, and methines (CH) at 1.7 p.p.m. Any functional group is worth a *one* p.p.m. downfield shift except oxygen and halogen which are worth *two* p.p.m. This diagram summarizes the basic position.

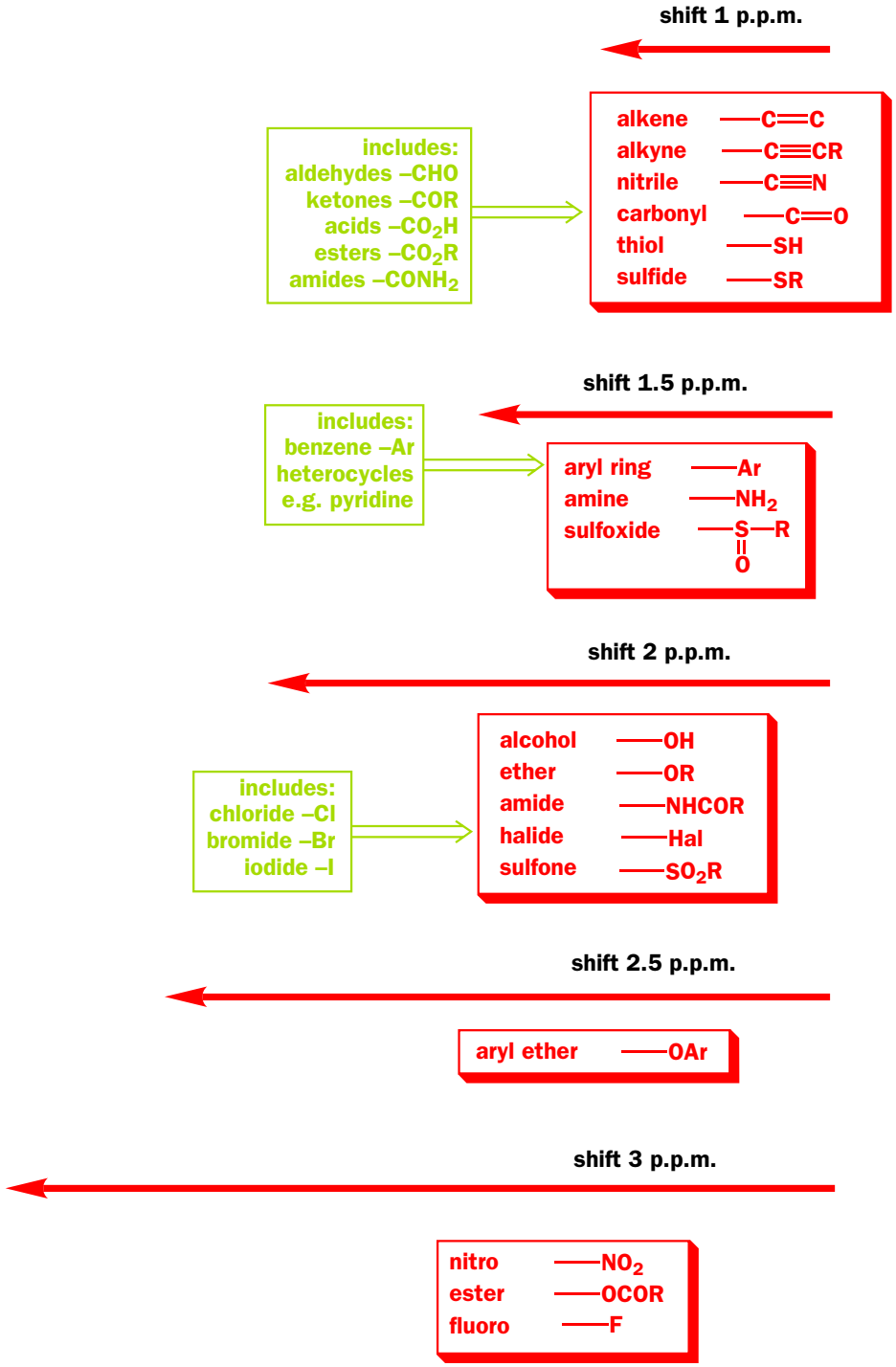


If you want more detailed information, you can refer to the tables in Chapter 15 or better still the more comprehensive tables in any specialized text.

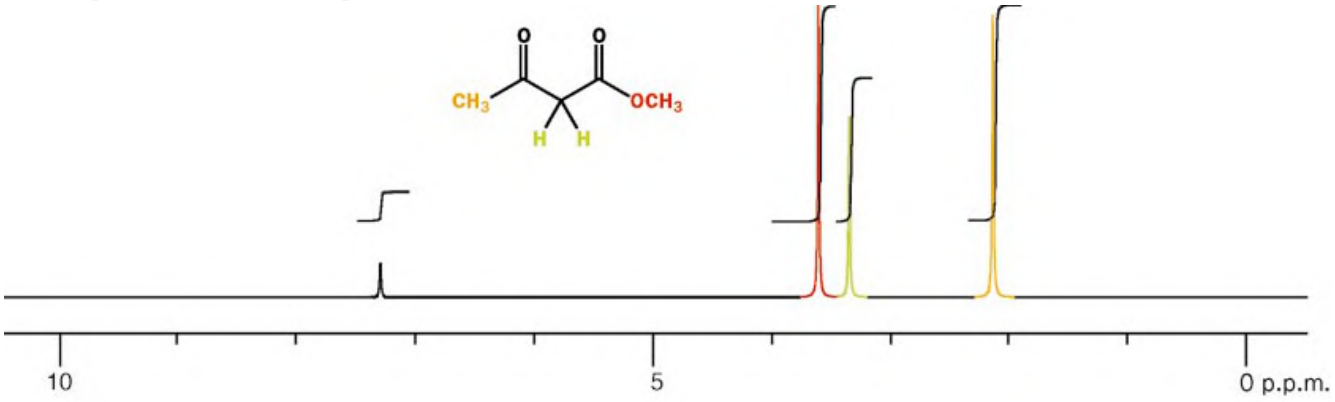
This is a very rough and ready guide and you can make it slightly more accurate by adding subdivisions at 1.5 and 2.5 p.p.m. and including the very electron-withdrawing groups (nitro, ester, fluoride), which shift by 3 p.p.m. This gives us the summary chart on this page, which we suggest you use as a reference.

## Summary chart of proton NMR shifts

values to be added to 0.9 for $CH_3$, 1.3 for $CH_2$ or 1.7 for CH



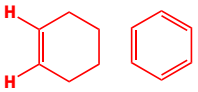
Answers deduced from this chart won't be very accurate but will give a good guide. Remember—these shifts are additive. Take a simple example, the ketoester below. There are just three signals and the integration alone distinguishes the two methyl groups from the $CH_2$ group. One methyl has been shifted from 0.9 p.p.m. by about 1 p.p.m., the other by more than 2 p.p.m. The first must be next to C=O and the second next to oxygen. More precisely, 2.14 p.p.m. is a shift of 1.24 p.p.m. from our standard value (0.9 p.p.m.) for a methyl group, about what we expect for a methyl ketone, while 3.61 p.p.m. is a shift of 2.71 p.p.m., close to the expected 3.0 p.p.m. for an ester joined through the oxygen atom. The $CH_2$ group is next to an ester and a ketone carbonyl group and so we expect it at 1.3 + 1.0 + 1.0 = 3.3 p.p.m., an accurate estimate, as it happens. We shall return to these estimates when we look at spectra of unknown compounds.




## The alkene region and the benzene region

In $^{13}C$ NMR, one region was enough for both of these, but see how different things are with proton NMR.

The two carbon signals are almost the same (1.3 p.p.m. difference < 1% of the total 200 p.p.m. scale) but the proton signals are very different (1.6 p.p.m. difference = 16% of the 10 p.p.m. scale). There must be a fundamental reason for this.



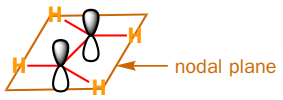
| | | |
|---|---|---|
| $^{13}C$ shift, p.p.m. | 127.2 | 128.5 |
| $^{1}H$ shift, p.p.m. | 5.68 | 7.27 |

### The benzene ring current causes large shifts for aromatic protons

A simple alkene has an area of low electron density in the plane of the molecule because the π orbital has a node there, and the carbons and hydrogen nuclei lying in the plane gain no shielding from the π electrons.

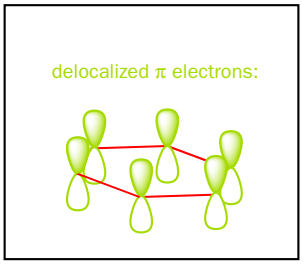
The benzene ring looks similar at first sight, and the plane of the molecule is indeed a node for all the π orbitals. However, benzene is 'aromatic'—it has extra stability because the six π electrons fit into three very stable orbitals and are delocalized round the whole ring.

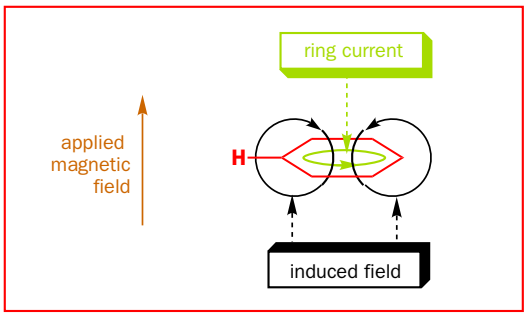
The applied field sets up a ring current in these delocalized electrons that produces a local field rather like the field produced by the electrons around a nucleus. Inside the benzene ring, the induced field opposes the applied field but, outside the ring, it reinforces the applied field. The carbon atoms are in the ring itself and experience neither effect, but the hydrogens are outside the ring, feel a stronger applied field, and appear less shielded.




■ Chapter 7 was devoted to a discussion of aromaticity and delocalization.

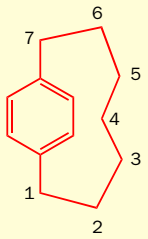
▶ Magnetic fields produced by circulating electrons are all around you: electromagnets and solenoids are exactly this.



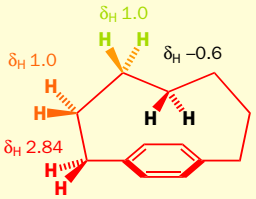



## Cyclophanes and annulenes

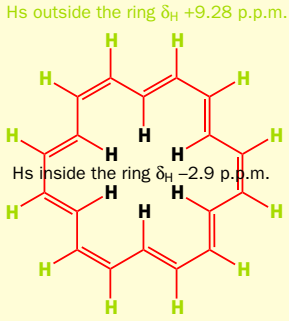
You may think that it is rather pointless imagining what goes on inside an aromatic ring as we cannot have hydrogen atoms literally *inside* a benzene ring. However, we can get close. Compounds called cyclophanes have loops of saturated carbon atoms attached at both ends to the same benzene rings. You see here a structure for [7]*para*-cyclophane, which has a string of seven $CH_2$ groups attached to the *para* positions of the same benzene ring. The four protons on the benzene ring itself appear as one line at a normal δ 7.07 p.p.m. The two $CH_2$ groups joined to the benzene ring (C1) are deshielded by the ring current at δ 2.64 p.p.m. The next two sets of $CH_2$ groups on C2 and C3 are neither shielded nor deshielded at δ 1.0 p.p.m. The middle $CH_2$ group in the chain (C4) must be pointing towards the ring in the middle of the π system and is heavily shielded by the ring current at negative δ (–0.6 p.p.m.).



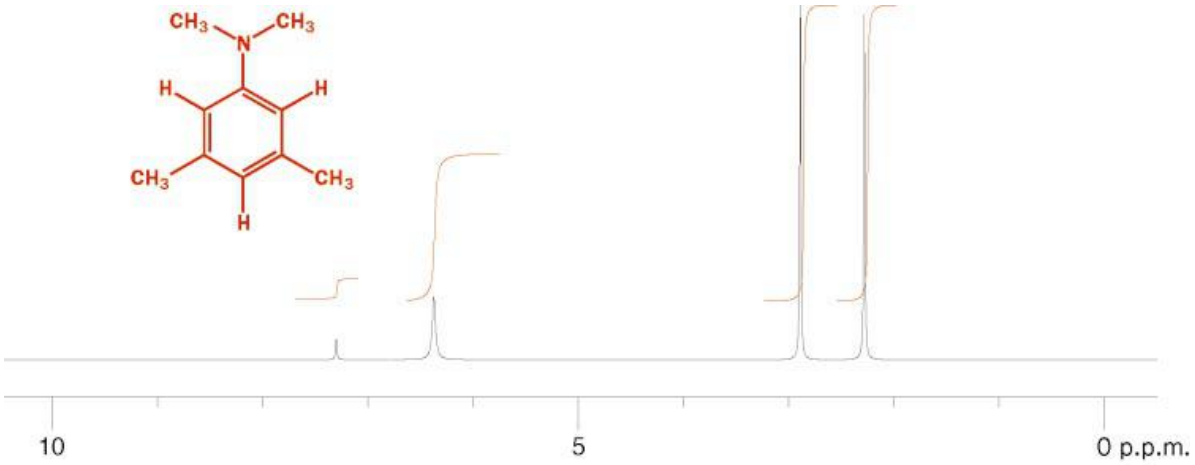

[7]-*para*-cyclophane



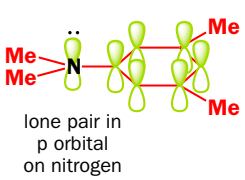

With a larger aromatic ring, it *is* possible actually to have hydrogen atoms inside the ring. Compounds are aromatic if they have $4n + 2$ delocalized electrons and this ring with nine double bonds, that is, 18 π electrons, is an example. The hydrogens outside the ring resonate in the aromatic region at rather low field (9.28 p.p.m.) but the hydrogen atoms inside the ring resonate at an amazing –2.9 p.p.m. showing the strong shielding by the ring current. Such extended aromatic rings are called annulenes: you met them in Chapter 7.

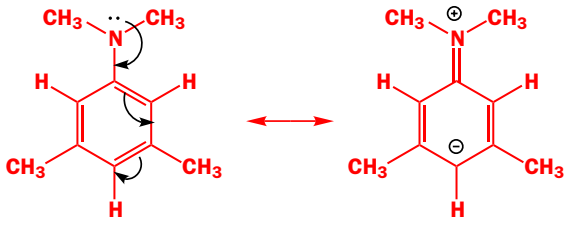



## Uneven electron distribution in aromatic rings

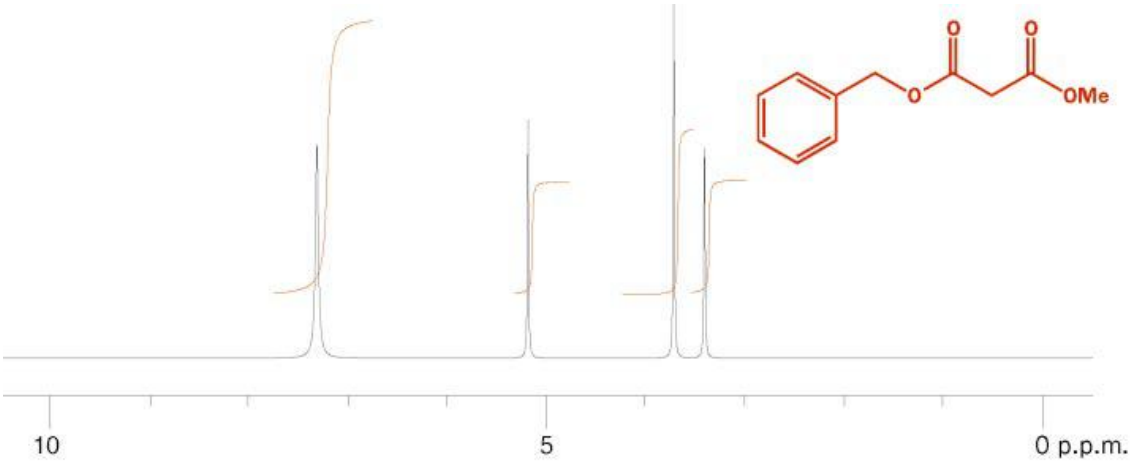



The NMR spectrum of this simple aromatic amine has three peaks in the ratio 1:2:2 which must be 3H:6H:6H. The 6.38 p.p.m. signal clearly belongs to the protons round the benzene ring, but why are they at 6.38 and not at 7.27 p.p.m.? We must also distinguish the two methyl groups at 2.28 p.p.m. from those at 2.89 p.p.m. The chart on p. 000 suggests that these should both be at about 2.4 p.p.m., close enough to 2.28 p.p.m. but not to 2.89 p.p.m. The solution to both these puzzles is the distribution of electrons in the aromatic ring. Nitrogen feeds electrons into the π system making it electron-rich: the ring protons are more shielded and the nitrogen atom becomes positively charged and its methyl groups more deshielded. The peak at 2.89 p.p.m. belongs to the $NMe_2$ group.



Other groups, such as simple alkyl groups, hardly perturb the aromatic system at all and it is quite common for all five protons in an alkyl benzene to appear as one signal instead of the three we might expect. Here is an example with some nonaromatic protons too: there is another on p. 000—the Cbz-protected amino acid.



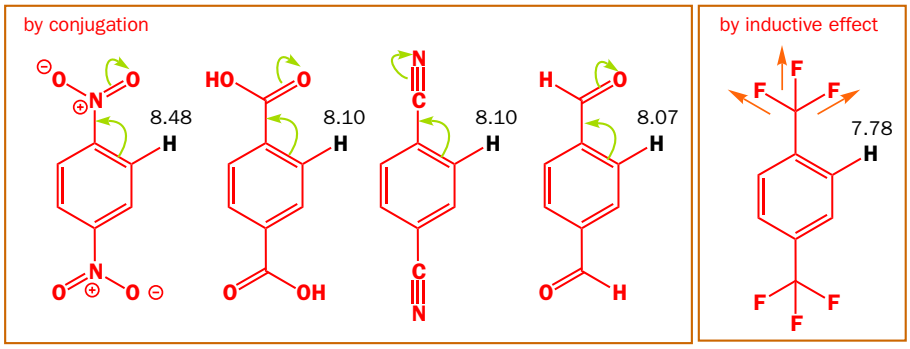

The five protons on the aromatic ring all have the same chemical shift. The $OCH_3$ group is typical of a methyl ester (the chart on p. 000 gives 3.9 p.p.m.). One $CH_2$ group is between two carbonyl groups (cf. δ 3.35 p.p.m. for the similar $CH_2$ group on p. 000). The other is next to an ester and a benzene ring: we calculate 1.3 + 1.5 + 3.0 = 5.8 p.p.m. for that—reasonably close to the observed 5.19 p.p.m.

## How electron donation and withdrawal change chemical shifts

We can get an idea of the effect of electron distribution by looking at a series of 1,4-disubstituted benzenes. This pattern makes all the remaining hydrogens in the ring the same. The compounds are listed in order of chemical shift: largest shift (lowest field) first. Benzene itself resonates at 7.27 p.p.m. Conjugation is shown by the usual curly arrows, and inductive effects by a straight arrow by the side of the group. Only one effect and one hydrogen atom are shown; in fact, both groups exert the same effect on all four identical hydrogen atoms.

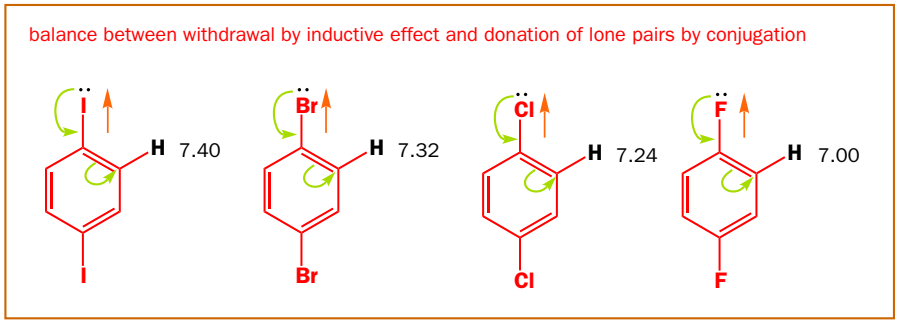
▶ Conjugation, as discussed in Chapters 7 and 10, is felt through π bonds, while inductive effects are the effects of electron withdrawal or donation felt simply by polarization of the σ bonds of the molecule. See p. 000.

**electron-withdrawing groups**



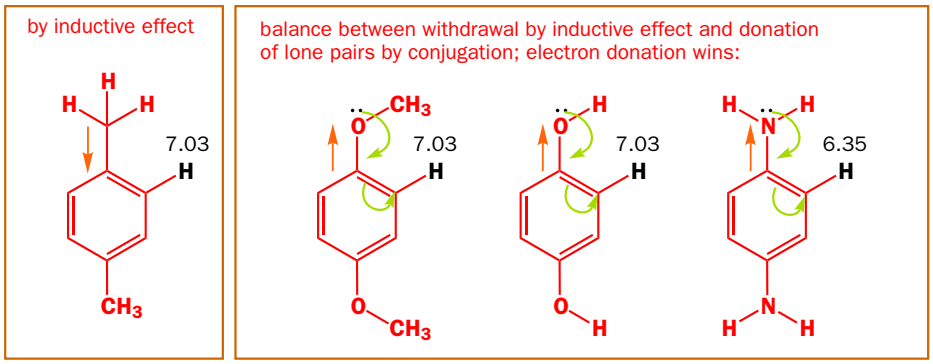

The largest shifts come from groups that withdraw electrons by conjugation. Nitro is the most powerful—this should not surprise you as we saw the same in nonaromatic compounds both in $^{13}C$ and $^{1}H$ NMR spectra. Then come the carbonyl groups and nitrile followed by the few groups showing simple inductive withdrawal. $CF_3$ is an important example of this kind of group—three fluorine atoms combine to exert a powerful effect.

**electron-donating and -withdrawing groups**



In the middle, around the position of benzene itself at δ 7.27 p.p.m., come the halogens whose inductive electron withdrawal and lone pair donation are nearly balanced.

**electron-donating groups**




▶ This all has very important consequences for the reactivity of differently substituted benzene rings: their reactions will be discussed in Chapter 22.

Alkyl groups are weak inductive donators and at the smallest shift we have the groups that, on balance, donate electrons to the ring and increase the shielding at the carbon atoms. Amino is the best of these. So a nitrogen-based functional group ($NO_2$) is the best electron withdrawer while another ($NH_2$) is the best electron donor.

▶ Proton NMR is, in fact, a better guide to the electron density at carbon than is carbon NMR.

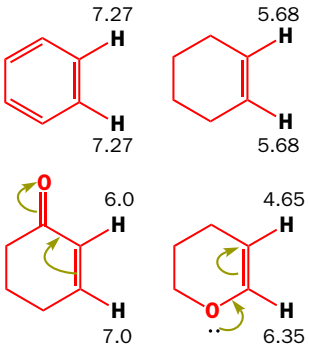
As far as the donors with lone pairs are concerned, two factors are important—the size of the lone pairs and the electronegativity of the element. If we look at the four halides (central box above) the lone pairs are in 2p(F), 3p(Cl), 4p(Br), and 5p(I) orbitals. In all cases the orbitals on the benzene ring are 2p so the fluorine orbital is of the right size and the others too large. Even though fluorine is the most electronegative, it is still the best donor.

Now comparing the groups in the first row of the p block elements. F, OH, $NH_2$, all have lone pairs in 2p orbitals so electronegativity is the only variable. As you would expect, the most electronegative element, F, is now the weakest donor.

| Element | Electronegativity | $\delta_H$, p.p.m. | Shift from 7.27 |
|---|---|---|---|
| F | 4.1 | 7.00 | –0.27 |
| O | 3.5 | 6.59 | –0.68 |
| N | 3.1 | 6.35 | –0.92 |

## Electron-rich and electron-deficient alkenes

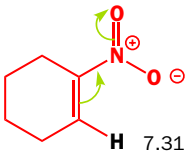
The same sort of thing happens with alkenes. We'll concentrate on cyclohexene so as to make a good comparison with benzene. The six identical protons of benzene resonate at 7.27 p.p.m.; the two identical alkene protons of cyclohexene resonate at 5.68 p.p.m. A conjugating and electron-withdrawing group such as a ketone removes electrons from the double bond as expected—but unequally. The proton nearer the C=O group is only slightly downfield from cyclohexene but the more distant one is over 1 p.p.m. downfield. The curly arrows show the electron distribution, *which we can deduce* from the NMR spectrum.



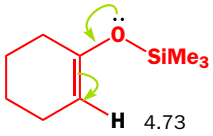

▶ In Chapter 10 we used $^{13}C$ NMR to convince you that a carbonyl group polarized a conjugated alkene; we hope you find the $^{1}H$ NMR data even more convincing. Conjugate addition occurs to those very atoms whose electron deficiency we can measure by proton NMR.

Oxygen as a conjugating electron donor is even more dramatic. It shifts the proton next to it downfield by the inductive effect but pushes the more distant proton upfield again by a whole p.p.m. by donating electrons. The separation between the two protons is nearly two p.p.m.

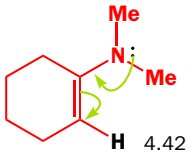
For both types of substituent, the effects are more marked on the more distant (β) proton. If these shifts reflect the true electron distribution, we can deduce that nucleophiles will attack the electron-deficient site in the nitroalkene, while electrophiles will be attacked by the electron-rich sites in silyl enol ethers and enamines. These are all important reagents and do indeed react as we predict, as you will see in later chapters. Look at the difference—there are nearly 3 p.p.m. between the nitro compound and the enamine!




electron-deficient nitroalkene




electron-rich silyl enol ether



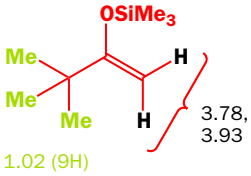

electron-rich enamine

### Structural information from the alkene region

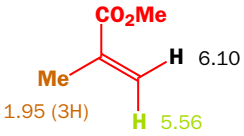
Alkene protons on different carbon atoms can obviously be different if the carbon atoms themselves are different and we have just seen examples of that. Alkene protons can also be different if they are on the same carbon atom. All that is necessary is that the substituents at the other end of the double bond should themselves be different. The silyl enol ether and the unsaturated ester below both fit into this category. The protons on the double bond must be different, because each is *cis* to a different group. The third compound is an interesting case: the different shifts of the two protons on the ring prove that the N–Cl bond is at an angle to the C=N bond. If it were in line, the two hydrogens would be identical. The other side of the C=N bond is occupied by a lone pair and the nitrogen atom is trigonal ($sp^2$ hybridized).

▶ DMF is similar: as we saw earlier (p. 000), it has two different methyl groups because of the double bond.

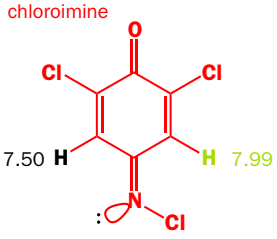
silyl enol ether




unsaturated ester



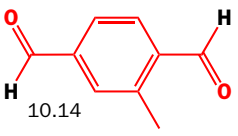

chloroimine



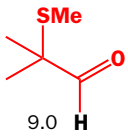

## The aldehyde region: unsaturated carbon bonded to oxygen

The aldehyde proton is unique. It is directly attached to a carbonyl group—one of the most electron-withdrawing groups that exists—and is very deshielded, resonating with the largest shifts of any CH protons in the 9–10 p.p.m. region. The examples below are all compounds that we have met before. Two are just simple aldehydes—aromatic and aliphatic. The third is the solvent DMF. Its CHO proton is less deshielded than most—the amide delocalization that feeds electrons into the carbonyl group provides some extra shielding.

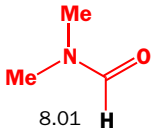
▶ **Aliphatic** is a catch-all term for compounds that are not aromatic.




an aromatic aldehyde

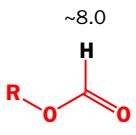



an alphatic aldehyde

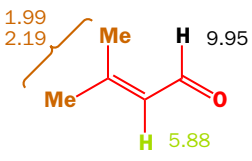



DMF

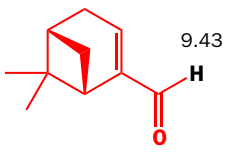
Conjugation with an oxygen atom has much the same effect—formate esters resonate at about 8 p.p.m.—but conjugation with π bonds does not. The simple conjugated aldehyde below and myrtenal both have CHO protons in the normal region (9–10 p.p.m.).




a formate ester




3-methylbut-2-enal

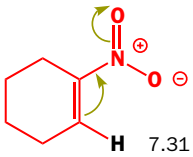



myrtenal

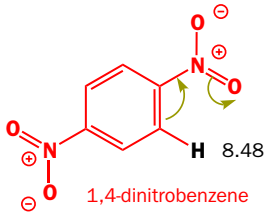
Two other types of protons resonate in this region: some aromatic protons and some protons attached to heteroatoms like OH and NH. The first of these will provide our discussion on structural information and the second will be the subject of the section following that discussion.

## Structural information from the aldehyde region

Protons on double bonds, even very electron-deficient double bonds like those of nitroalkenes, hardly get into the aldehyde region. However, some benzene rings with very electron-withdrawing groups do manage it because of the extra downfield shift of the ring current, so beware of nitrobenzenes as they may have signals in the 8–9 p.p.m. region.

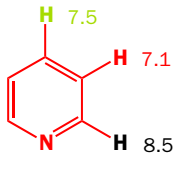



electron-deficient nitroalkene

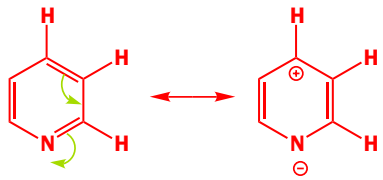



1,4-dinitrobenzene

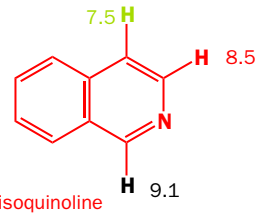
More important molecules with signals in this region are the aromatic heterocycles such as pyridine, which you met in Chapter 7. The NMR shifts clearly show that pyridine is aromatic and we discussed its basicity in Chapter 8. One proton is at 7.1 p.p.m., essentially the same as benzene, but the others are more downfield and one, at C2, is in the aldehyde region. This is not because pyridine is 'more aromatic' than benzene but because nitrogen is more electronegative than carbon. Position C2 is like an aldehyde—a proton attached to $sp^2$ C bearing a heteroatom—while C4 is electron-deficient by conjugation (the electronegative nitrogen is electron-withdrawing). Isoquinoline is a pyridine and a benzene ring fused together and has a proton even further downfield at 9.1 p.p.m.—this is an imine proton that experiences the ring current of the benzene ring.




pyridine



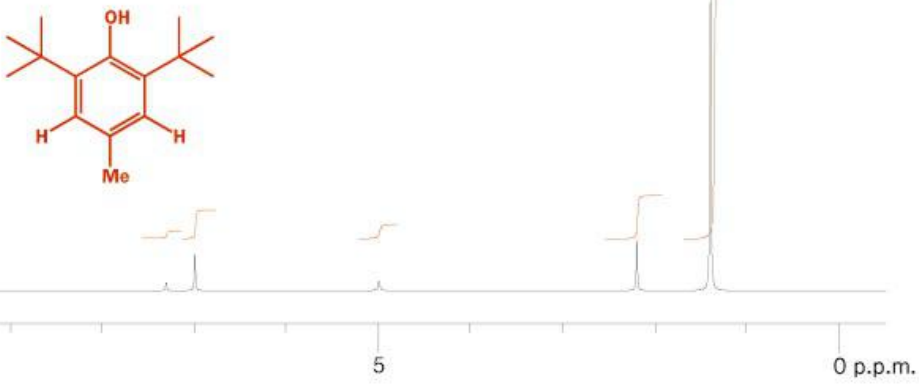

conjugation in pyridine




isoquinoline

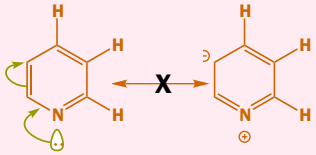
## Protons on heteroatoms are more variable than protons on carbon

Protons directly attached to O, N, or S (or any other heteroatom, but these are the most important) also have signals in the NMR spectrum. We have avoided them so far because the positions of these signals are less reliable and because they are affected by exchange.



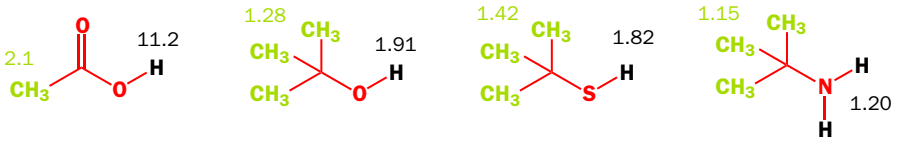

In Chapter 3 we looked at the $^{13}C$ NMR spectrum of BHT. Its proton NMR is very simple, consisting of just four lines with integrals 2, 1, 3, and 18. The chemical shifts of the *t*-butyl group, the methyl group on the benzene ring, and the two identical aromatic protons should cause you no surprise. What is left, the 1H signal at 5.0 p.p.m., must be the OH. Earlier on in this chapter we saw the spectrum of acetic acid $CH_3CO_2H$, which showed an OH resonance at 11.2 p.p.m. Simple alcohols such as *t*-butanol have OH signals in $CDCl_3$ (the usual NMR solvent) at around 2 p.p.m. Why such differences?

▶ Please note that the alternative 'conjugation' shown in this figure is wrong. The structure with two adjacent double bonds in a six-membered ring is impossible and, in any case, as you saw in Chapter 8, the lone pair electrons on nitrogen are in an $sp^2$ orbital orthogonal to the p orbitals in the ring. There is no interaction between orthogonal orbitals.




incorrect delocalization

impossible structure

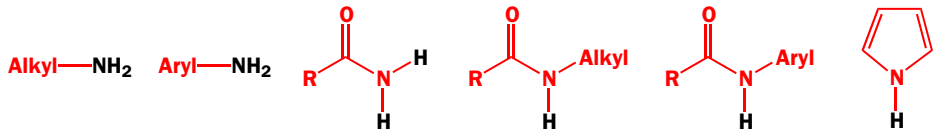



This is a matter of acidity. The more acidic a proton is—that is, the more easily it releases $H^+$ (this is the definition of acidity from Chapter 8)—the more the OH bond is polarized towards oxygen. The more the RO–H bond is polarized, the closer we are to free $H^+$, which would have no shielding electrons at all, and so the further the proton goes downfield. The OH chemical shifts and the acidity of the OH group are very roughly related.

| Functional group | Alcohol ROH | Phenol ArOH | Carboxylic acid $RCO_2H$ |
|---|---|---|---|
| $pK_a$ | 16 | 10 | 5 |
| $\delta_H$(OH), p.p.m. | 2.0 | 5.0 | >10 |

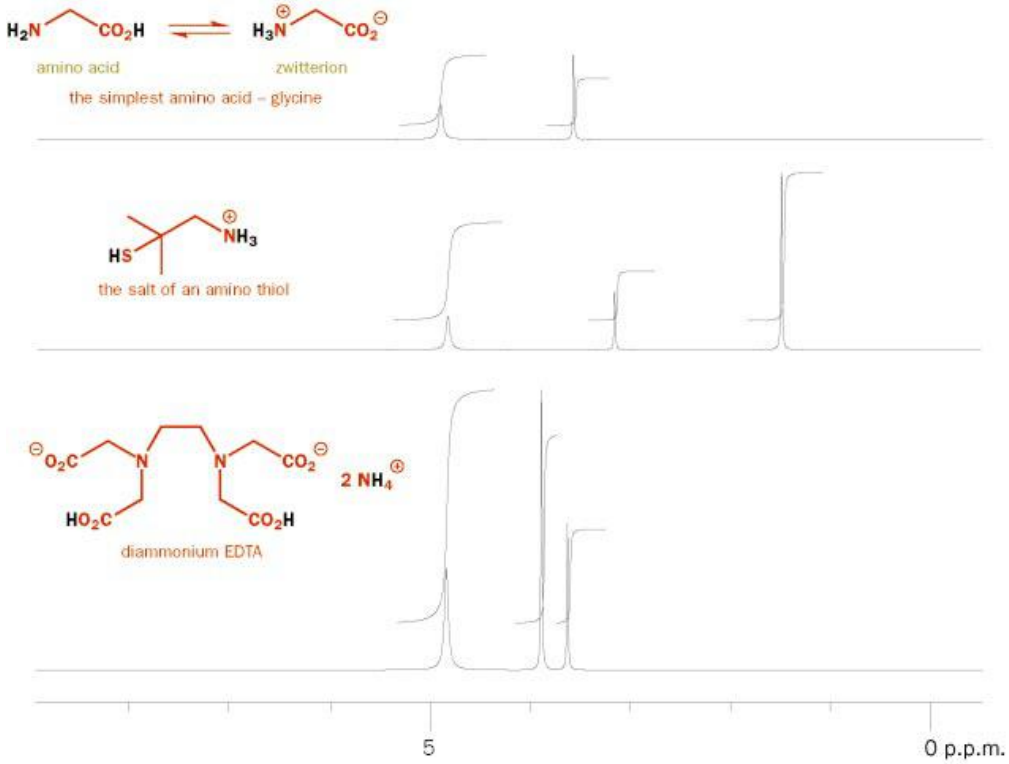
Thiols (RSH) behave in a similar way to alcohols but are not so deshielded, as you would expect from the smaller electronegativity of sulfur (phenols are all about 5.0 p.p.m., PhSH is at 3.41 p.p.m.). Alkane thiols appear at about 2 p.p.m. and arylthiols at about 4 p.p.m. Amines and amides show a big variation, as you would expect for the variety of functional groups involved, and are summarized below. Amides are slightly acidic, as you saw in Chapter 8, and amide protons resonate at quite low fields. Pyrroles are special—the aromaticity of the ring makes the NH proton unusually acidic and they appear at about 10 p.p.m.

chemical shifts of NH protons




## Exchange of acidic protons is revealed in proton NMR spectra

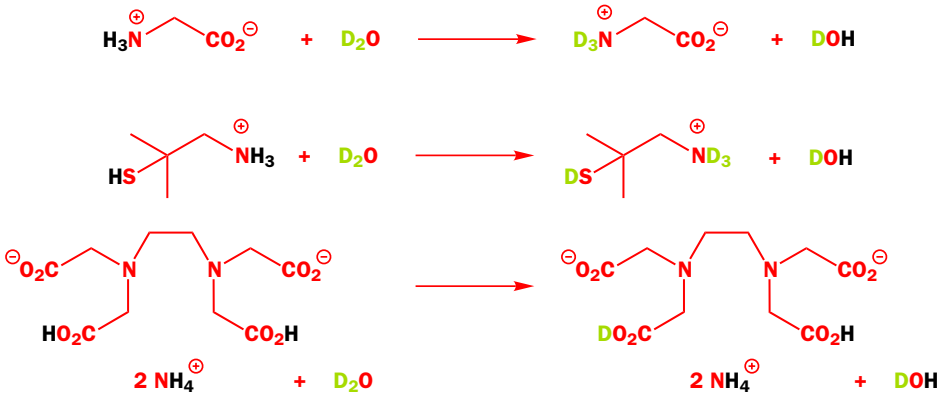
Compounds with very polar groups often dissolve best in water. NMR spectra are usually run in $CDCl_3$, but heavy water, $D_2O$, is an excellent NMR solvent. Here are some results in that medium.




▶ EDTA is ethylenediamine tetraacetic acid, an important complexing agent for metals. This is the salt formed with just two equivalents of ammonia.

Glycine is expected to exist as a zwitterion (Chapter 8, p. 000). It has a 2H signal for the $CH_2$ between the two functional groups, which would do for either form. The 3H signal at 4.90 p.p.m. might suggest the $NH_3^+$ group, but wait a moment before making up your mind. The aminothiol salt has the $CMe_2$ and $CH_2$ groups about where we would expect them, but the SH and $NH_3^+$ protons appear as one 4H signal. The double salt of EDTA has several curious features. The two $CH_2$ groups in the middle are fine, but the other four $CH_2$ groups all appear identical as do all the protons on both the $CO_2H$ and $NH_3^+$ groups.

The best clue to why this is so involves the chemical shifts of the OH, NH, and SH protons in these molecules. They are all the same within experimental error: 4.90 p.p.m. for glycine, 4.80 p.p.m. for the aminothiol, and 4.84 p.p.m. for EDTA. They all correspond to the same species: HOD. Exchange between XH (where X = O, N, or S) protons is extremely fast, and the solvent, $D_2O$, supplies a vast excess of exchangeable *deuteriums*. These immediately replace all the OH, NH, and SH protons in the molecules with D, forming HOD in the process. Recall that we do not see signals for deuterium atoms (that's why deuterated solvents are used). They have their own spectra at a different frequency.




The same sort of exchange between OH or NH protons with each other or with traces of water in the sample means that the OH and NH peaks in most spectra in $CDCl_3$ are rather broader than the peaks for CH protons.

Two questions remain. First, can we tell whether glycine is a zwitterion in water or not? Not really: the spectra fit either or an equilibrium between both. Other evidence leads us to prefer the zwitterion in water. Second, why are all four $CH_2CO$ groups in EDTA the same? This we can answer. As well as the equilibrium exchanging the $CO_2H$ protons with the solvent, there will be an equally fast equilibrium exchanging protons between $CO_2H$ and $CO_2D$. This makes all four 'arms' of EDTA the same.

You should leave this section with an important chemical principle firmly established in your mind.

**Protons exchange fast**

**Proton exchange between heteroatoms, particularly O, N, and S, is a *very fast* process in comparison with other chemical reactions, and often leads to averaged peaks in the $^1H$ NMR spectrum.**

You will need this insight as you study organic mechanisms.

## Coupling in the proton NMR spectrum

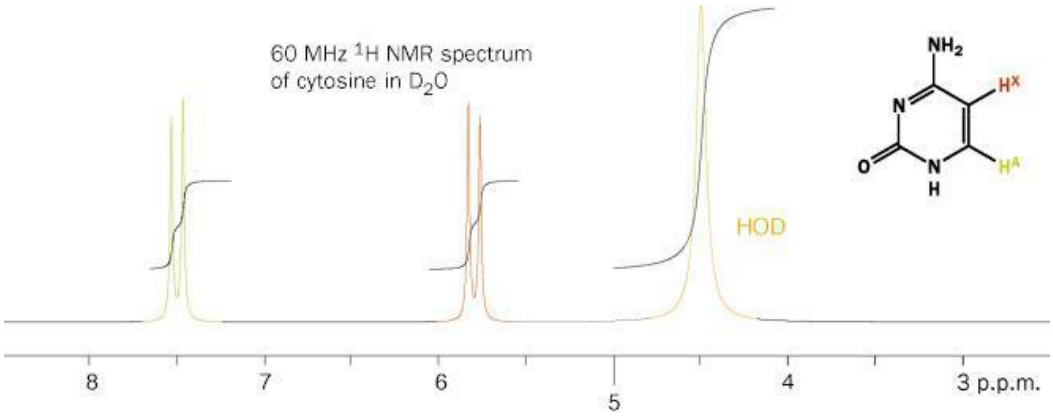
### Nearby hydrogen nuclei interact and give multiple peaks

So far proton NMR has been not unlike carbon NMR on a smaller scale. However, we have yet to discuss the real strength of proton NMR, something more important than chemical shifts and

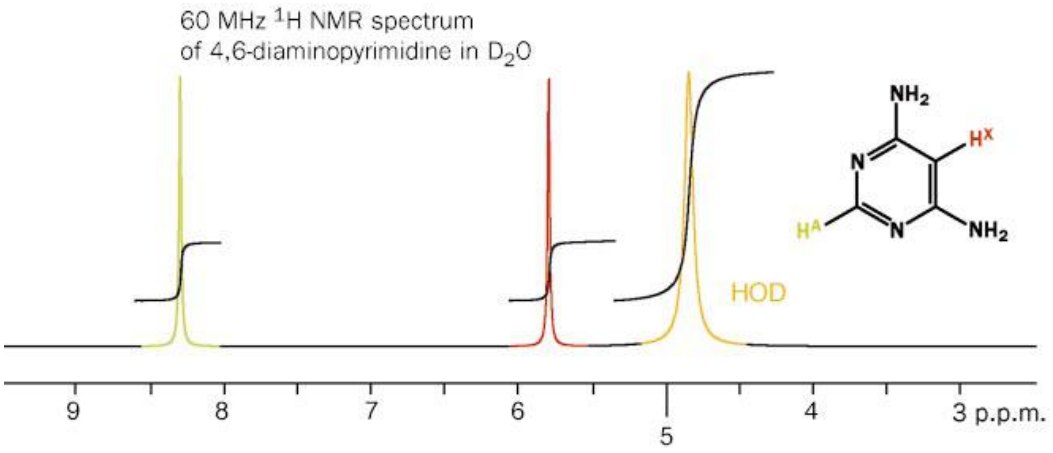
something that allows us to look not just at individual atoms but also at the way the C–H skeleton is joined together. This is the result of the interaction between nearby protons known as **coupling**.

An example we could have chosen in the last section is the nucleic acid component, cytosine, which has exchanging $NH_2$ and NH protons giving a peak for HDO at 4.5 p.p.m. We didn't choose this example because the other two peaks would have puzzled you. Instead of giving just one line each, they give two lines each—doublets as you will learn to call them—and it is time to discuss the origin of this 'coupling'.

▶ Cytosine is one of the four bases that, in combination with deoxyribose and phosphate, make up DNA. It is a member of the class of heterocycles called **pyrimidines**. We come back to the chemistry of DNA towards the end of this book, in Chapter 49.

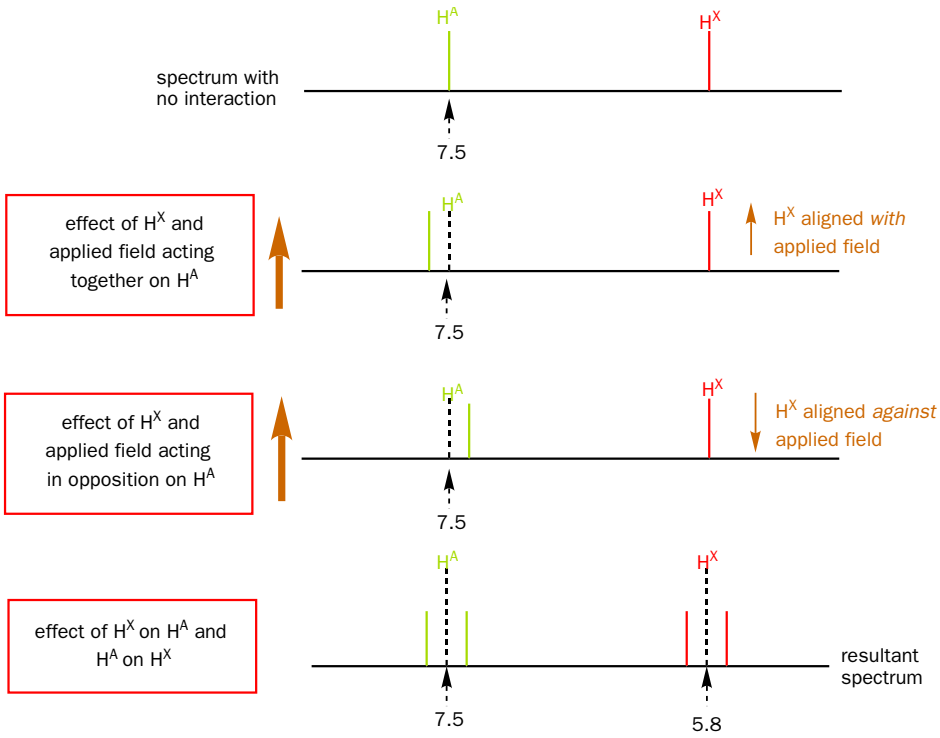



You might have expected a spectrum like that of the heterocycle below, which is also a pyrimidine. It too has exchanging $NH_2$ protons and two protons on the heterocyclic ring. But these two protons give the expected two lines instead of the four lines in the cytosine spectrum. It is easy to assign the spectrum: proton $H^A$ is attached to an aldehyde-like C=N and so comes at lowest field. The proton $H^X$ is *ortho* to two electron-donating $NH_2$ groups and so comes at high field for an aromatic proton (p. 000). These protons do not couple with each other because they are too far apart. They are separated by five bonds whereas the ring protons in cytosine are separated by just three bonds.



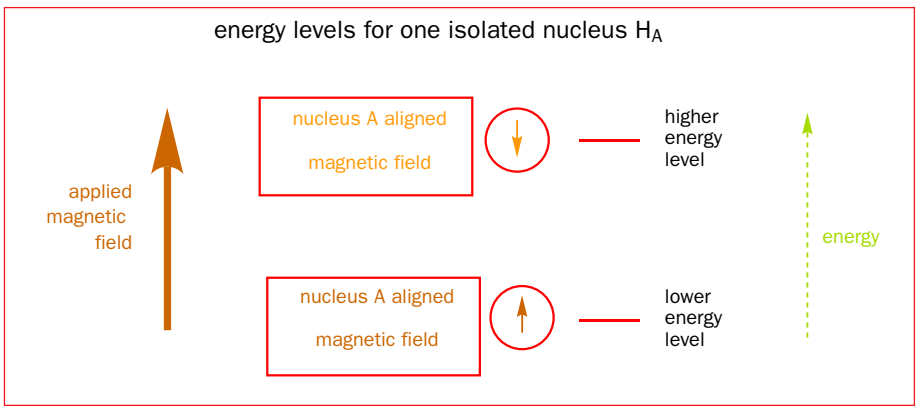

Understanding this phenomenon is so important that we are going to explain it in three different ways—you choose which appeals to you most. Each method offers a different insight.

The pyrimidine spectrum has two single lines (**singlets** we shall call them from now on) because each proton, $H^A$ or $H^X$, can be aligned either with or against the applied magnetic field. The cytosine spectrum is different because each proton, say, $H^A$, is near enough to experience the small magnetic field of the other proton $H^X$ as well as the field of the magnet itself. The diagram shows the result.

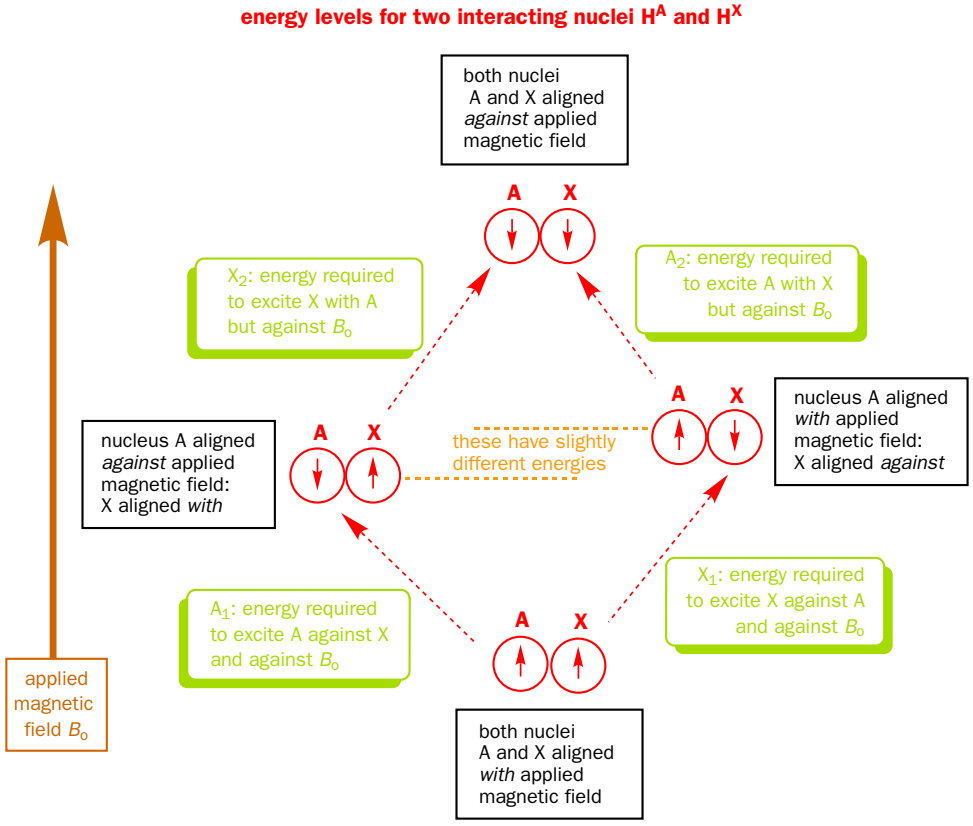



If each proton interacted only with the applied field we would get two singlets. But proton $H^A$ actually experiences two slightly different fields: the applied field *plus* the field of $H^X$ or the applied field *minus* the field of $H^X$. $H^X$ acts either to increase or to decrease the field experienced by $H^A$. The position of a resonance depends on the field experienced by the proton so these two situations give rise to two slightly different peak—a **doublet** as we shall call it. And whatever happens to $H^A$ happens to $H^X$ as well, so the spectrum has two doublets, one for each proton. Each couples with the other. The field of a proton is a very small indeed in comparison with the field of the magnet and the separation between the lines of a doublet is very small. We shall discuss the size of the coupling later (p. 000).

The second explanation takes into account the energy levels of the nucleus. In Chapter 4, when we discussed chemical bonds, we imagined electronic energy levels on neighbouring atoms interacting with each other and splitting to produce new molecular energy levels, some higher in energy and some lower in energy than the original atomic energy levels. When hydrogen *nuclei* are near each other in a molecule, the nuclear energy levels also interact and split and produce new energy levels. If a single hydrogen nucleus interacts with a magnetic field, we have the picture on p. 000 of this chapter: there are *two* energy levels as the nucleus can be aligned with or against the applied magnetic field, there is one energy jump possible, and there is a resonance at one frequency. This you have now seen many times and it can be summarized as shown below.



The spectrum of the pyrimidine on p. 000 showed two protons each independently in this situation. Each had two energy levels, each gave a singlet, and there were two lines in the spectrum. But, in the cytosine molecule, each proton has another hydrogen nucleus nearby and there are now *four* energy levels. Each nucleus $H^A$ and $H^X$ can be aligned with or against the applied field. There is one most stable energy level where they are both aligned with the field and one least stable level where they are both aligned against. In between there are two different energy levels in which one nucleus is aligned with the field and one against. Exciting $H^A$ from alignment with to alignment against the applied field can be done in two slightly different ways, shown as $A_1$ and $A_2$ on the diagram. The result is two resonances very close together in the spectrum.

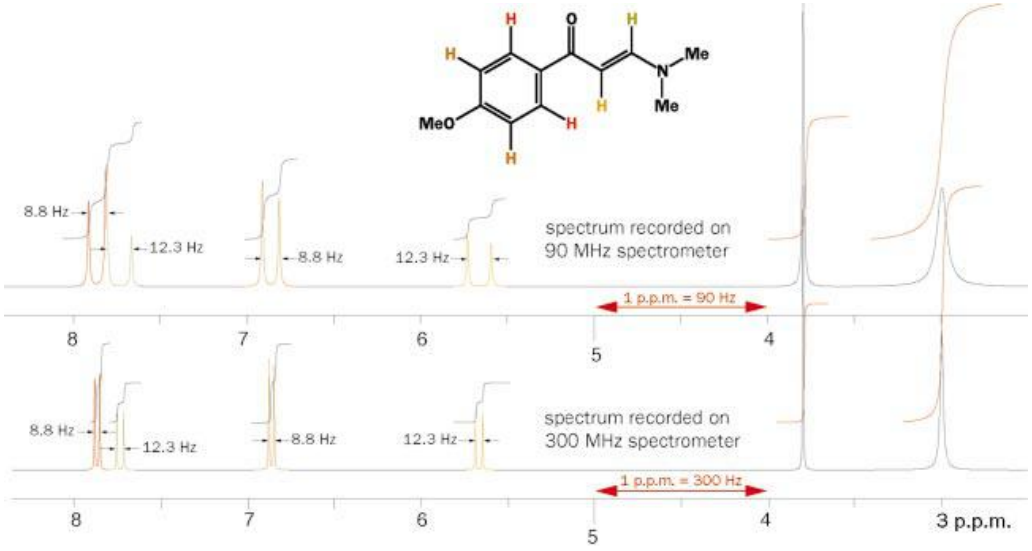



Please notice carefully that we cannot have this discussion about $H^A$ without discussing $H^X$ in the same way. If there are two slightly different energy jumps to excite $H^A$, there must also be two slightly different energy jumps to excite $H^X$. The difference between $A_1$ and $A_2$ is exactly the same as the difference between $X_1$ and $X_2$. Each proton now gives two lines (a doublet) in the NMR spectrum and the splitting of the two doublets is *exactly the same*. We describe this situation as **coupling**. We say 'A and X are coupled' or 'X is coupled to A'(and vice versa, of course). We shall be using this language from now on and so must you.

Now look back at the spectrum of cytosine at the beginning of this section. You can see the two doublets, one for each of the protons on the aromatic ring. Each is split by the same amount (this is easy to check with a ruler) and the separation of the lines is the **coupling constant** and is called *J*. In this case $J = 4$ Hz. Why do we measure *J* in hertz and not in p.p.m.? We measure chemical shifts in p.p.m. because we get the same number regardless of the rating of the NMR machine in MHz. We measure *J* in Hz because we also get the same number regardless of the machine.

### ▶ Measuring coupling constants in hertz

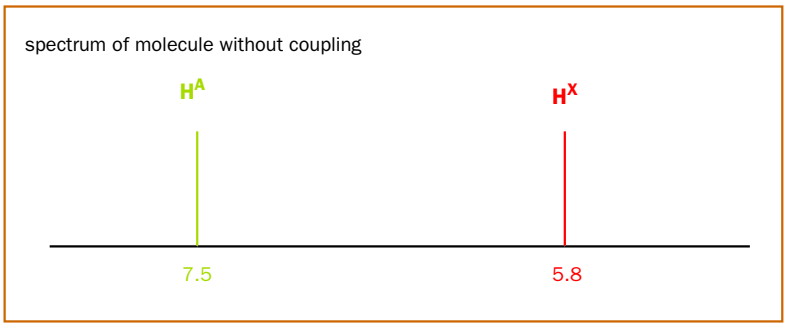
To measure a coupling constant it is essential to know the rating of the NMR machine in MHz (MegaHertz). This is why you are told that each illustrated spectrum is, say, a '250 MHz $^1$H NMR spectrum'. To measure the coupling, measure the distance between the lines by ruler or dividers and use the horizontal scale to find out the separation in p.p.m. The conversion is then easy—to turn parts per million of megahertz into hertz you just leave out the million! So 1 p.p.m. on a 300 MHz machine is 300 Hz. On a 90 MHz machine it would be 90 Hz.



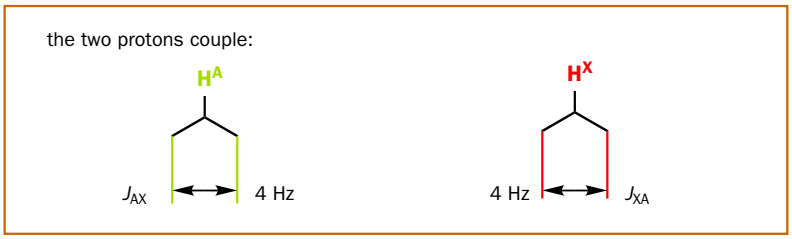

### ● Spectra from different machines

**When you change from one machine to another, say, from an 80 MHz to a 500 MHz NMR machine, chemical shifts (δ) stay the same in p.p.m. but coupling constants (*J*) stay the same in Hz.**

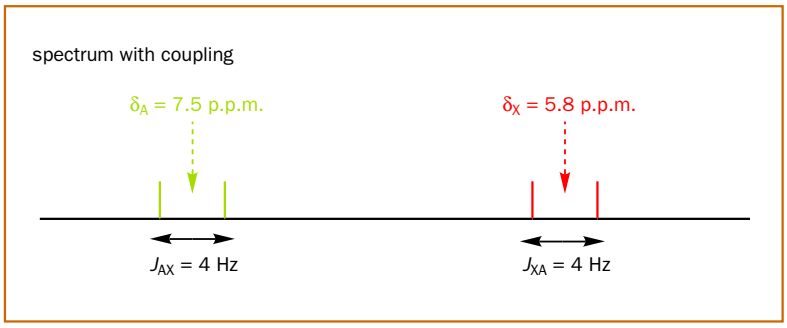
Now for the third way to describe coupling. If you look again at what the spectrum would be like without interaction between $H^A$ and $H^X$ you would see this, with the chemical shift of each proton clearly obvious.




But you don't see this because each proton couples with the other and splits its signal by an equal amount either side of the true chemical shift.



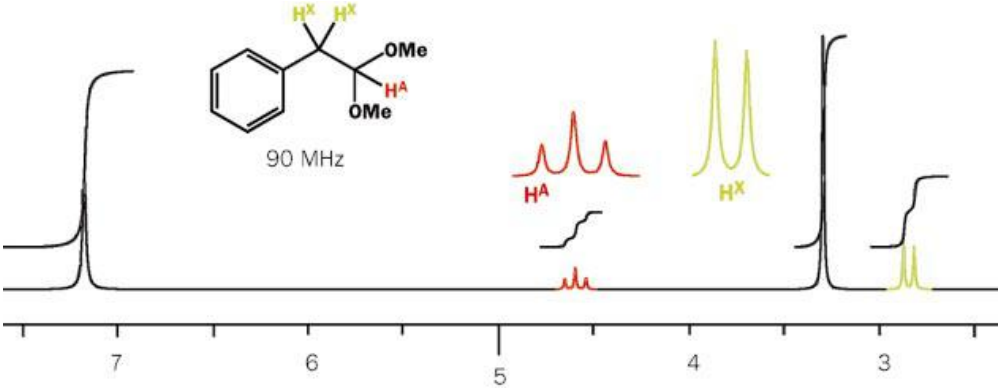

The true spectrum has a pair of doublets each split by an identical amount. Note that no line appears at the true chemical shift, but it is easy to measure the chemical shift by taking the midpoint of the doublet.




So this spectrum would be described as $\delta_H$ 7.5 (1H, d, *J* 4 Hz, $H^A$) and 5.8 (1H, d, *J* 4 Hz, $H^X$). The main number gives the chemical shift in p.p.m. and then, in brackets, comes the integration as the number of Hs, the shape of the signal (here 'd' for doublet), the size of coupling constants in Hz, and the assignment, usually related to a diagram. The integration refers to the combined integral of both peaks in the doublet. If the doublet is exactly symmetrical, each peak integrates to half a proton. The combined signal, however complicated, integrates to the right number of protons.

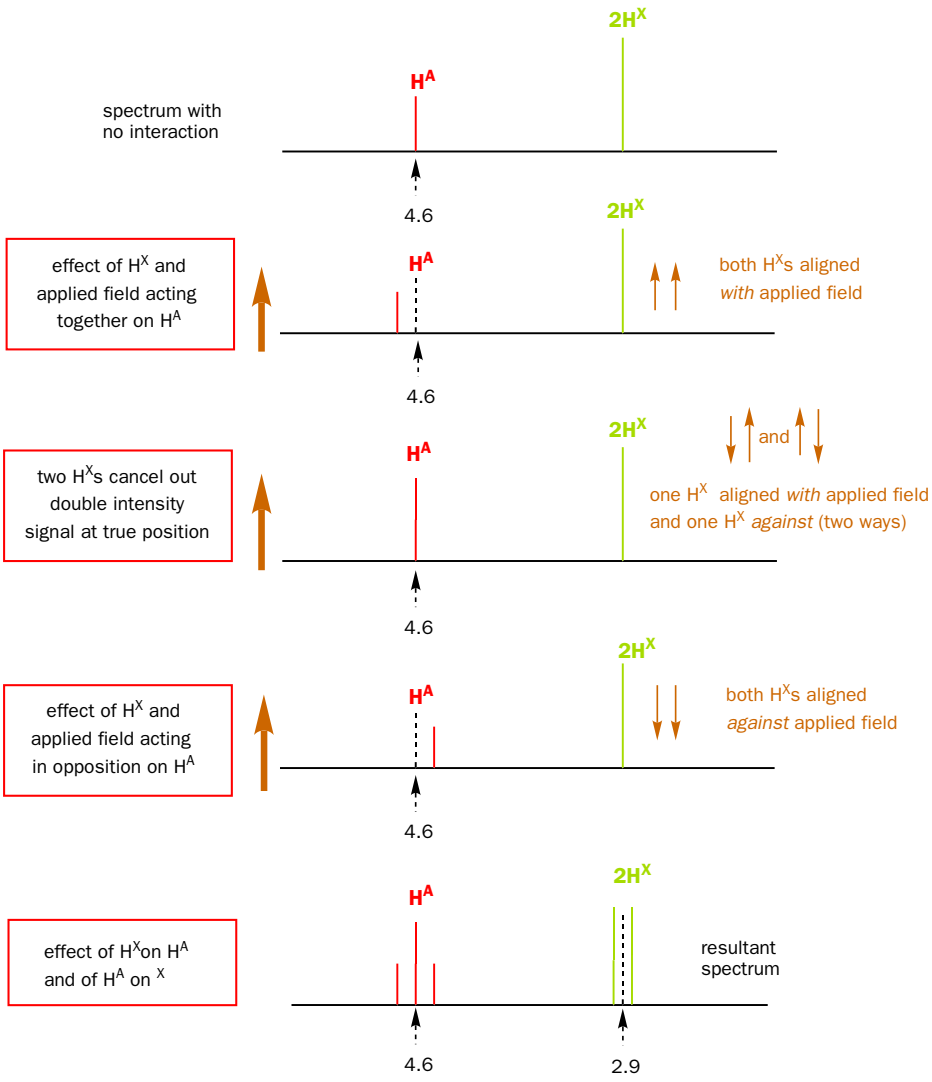
We have described these protons as A and X with a purpose in mind. A spectrum of two equal doublets is called an **AX spectrum**. A is always the proton you are discussing and X is a proton with a very different chemical shift. The alphabet is used as a ruler: nearby protons (on the chemical shift scale—not necessarily nearby in the structure!) are called B, C, etc. and distant ones are called X, Y, etc. You will see the reason for this soon.

If there are more protons involved, the splitting process continues. Here is the NMR spectrum of a famous perfumery compound supposed to have the smell of 'green leaf lilac'. The compound is an acetal with five nearly identical aromatic protons at the normal benzene position (7.2–7.3 p.p.m.) and six protons on two identical OMe groups.

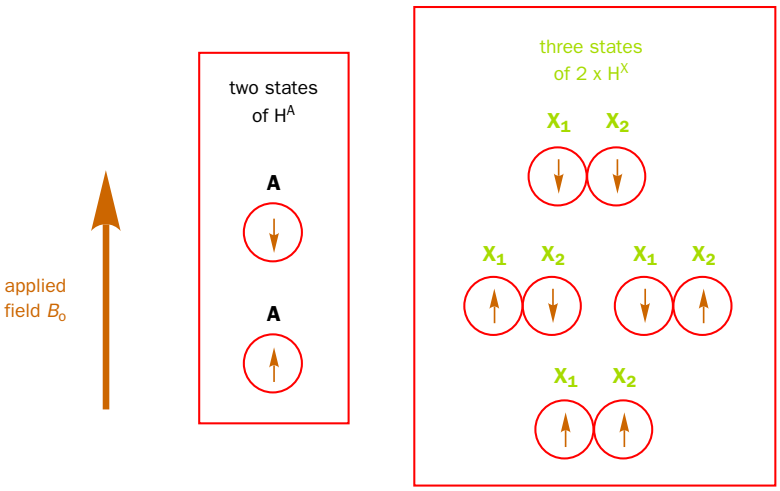



It is the remaining three protons that interest us. They appear as a 2H doublet at 2.9 p.p.m. and a 1H *triplet* at 4.6 p.p.m. In NMR talk, **triplet** means three equally spaced lines in the ratio 1:2:1. The triplet arises from the three possible states of the two identical protons in the $CH_2$ group.

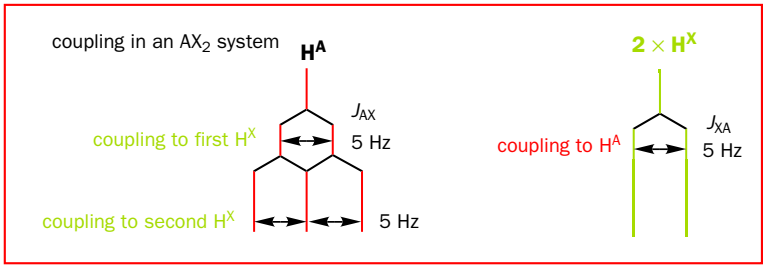
If one proton $H^A$ interacts with two protons $H^X$ , it can experience three states of proton $H^X$. Both protons $H^X$ can be aligned with the magnet or both against. These states will increase or decrease the applied field just as before. But if one proton $H^X$ is aligned with, and one against the applied field, there is no net change to the field experienced by $H^A$ and there are two possibilities for this (see diagram). We therefore see a signal of double intensity for $H^A$ at the correct chemical shift, one signal at higher field and one at lower field. In other words, a 1:2:1 triplet.

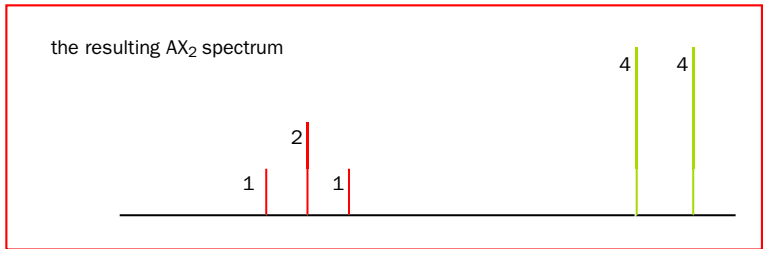



We could look at this result by our other methods too. There is one way in which both nuclei can be aligned with and one way in which both can be aligned against the applied field, but two ways in which they can be aligned one with and one against. Proton $H^A$ interacts with each of these states. The result is a 1:2:1 triplet.

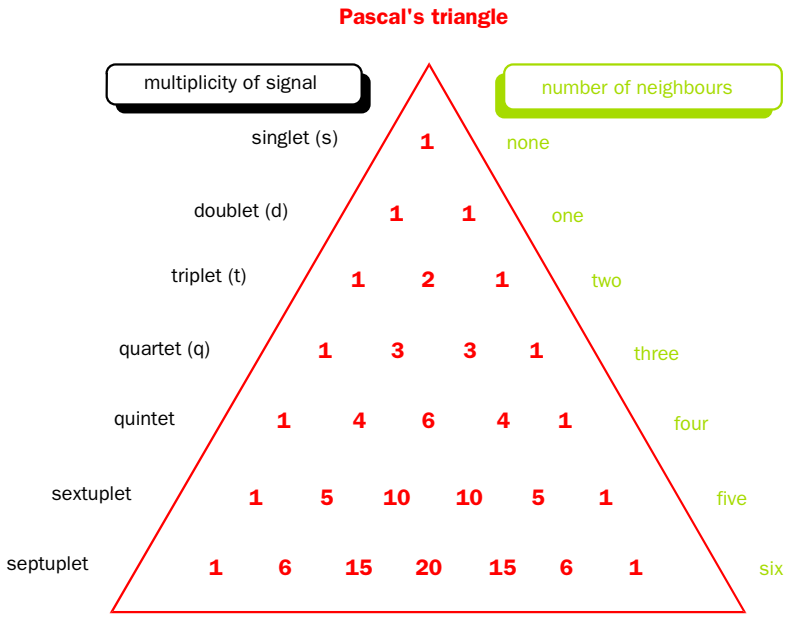


Using our third way to see how the triplet arises, we can look at the splitting as it happens.




If there are more protons involved, we continue to get more complex systems, but the intensities can all be deduced simply from Pascal's triangle, which gives the coefficients in a binomial expansion. If you are unfamiliar with this simple device, here it is.




**▶ Constructing Pascal's triangle**

Put '1' at the top and then add an extra number in each line by adding together the numbers on either side of the new number in the line above. If there is no number on one side, that counts as a zero, so the lines always begin and end with '1'.

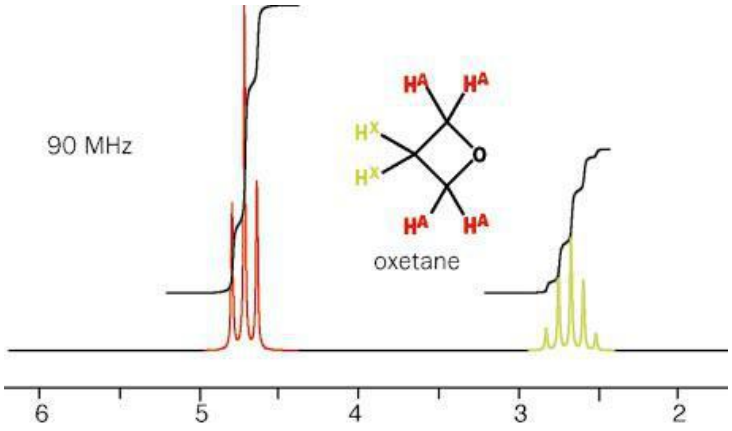
You can read off from the triangle what pattern you may expect when a proton is coupled to $n$ equivalent neighbours. There are always $n + 1$ peaks with the intensities shown by the triangle. So far, you've seen 1:1 doublets (line 2 of the triangle) from coupling to 1 proton, and 1:2:1 triplets (line 3) from coupling to 2. You will often meet ethyl groups ($CH_3$–$CH_2X$) where the $CH_2$ group appears as a 1:3:3:1 quartet and the methyl group as a 1:2:1 triplet and isopropyl groups $(CH_3)_2CHX$ where the methyl groups appear as a 6H doublet and the CH group as a septuplet. The outside lines of a septuplet are so weak (1/20th of the middle line) that it is often mistaken for a quintet. Inspection of the integral should put you on the right track.

Here is a simple example, the four-membered cyclic ether oxetane. Its NMR spectrum has a 4H triplet for the two identical $CH_2$ groups next to oxygen and a 2H quintet for the $CH_2$ in the middle. Each proton $H^X$ 'sees' four identical neighbours ($H^A$) and is split equally by them all to give a

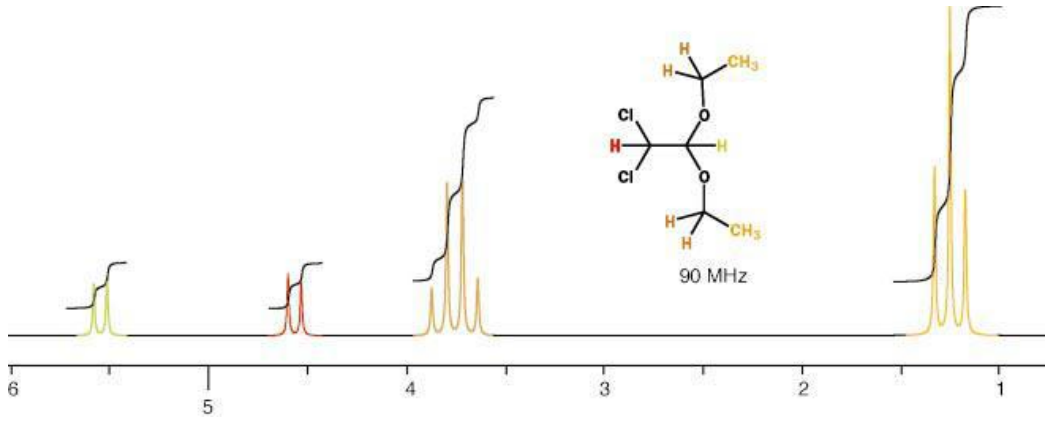
**Constructing Pascal's triangle**

Remember, the coupling comes from the *neighbouring* protons: it doesn't matter how many protons form the signal itself (2 for $H^X$, 4 for $H^A$)—it's how many are next door (4 next to $H^X$, 2 next to $H^A$) that matters. It's *what you see* that counts not *what you are*.

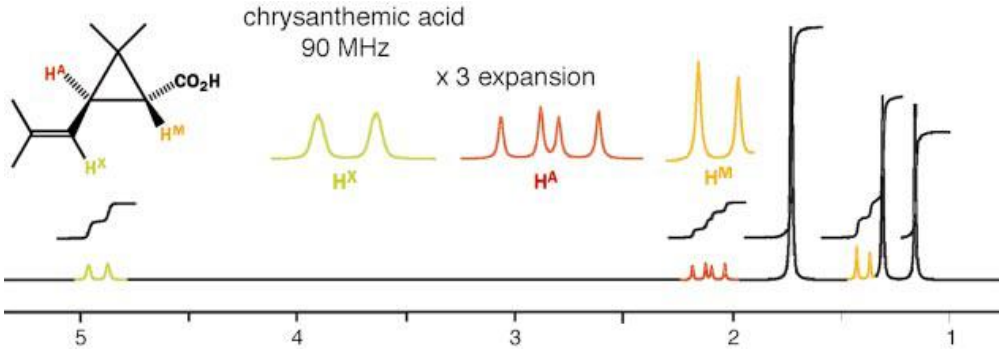
1:4:6:4:1 quintet. Each proton $H^A$ 'sees' two identical neighbours $H^X$ and is split into a 1:2:1 triplet. The combined integral of all the lines in the quintet together is 2 and of all the lines in the triplet is 4.



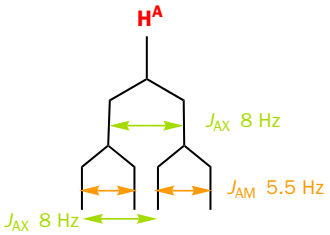

A slightly more complicated example is the diethyl acetal below. It has a simple AX pair of doublets for the two protons on the 'backbone' (red and green) and a typical ethyl group (2H quartet and 3H triplet). An ethyl group is attached to only one substituent through its $CH_2$ group, so the chemical shift of that $CH_2$ group tells us what it is joined to. Here the peak at 3.76 p.p.m. can only be an OEt group. There are, of course, two identical $CH_2$ groups in this molecule.




So far, we have seen situations where a proton has several neighbours, but the coupling constants to all the neighbours have been the same. What happens when coupling constants differ? Chrysanthemic acid, the structural heart of the natural pyrethrin insecticides, gives an example of the simplest situation—where a proton has two different neighbours.



This is an interesting three-membered ring compound produced by pyrethrum flowers (Chapter 1). It has a carboxylic acid, an alkene, and two methyl groups on the three-membered ring. Proton $H^A$ has two neighbours, $H^X$ and $H^M$. The coupling constant to $H^X$ is 8 Hz, and that to $H^M$ is 5.5 Hz. The splitting pattern looks like this.




**Abbreviations used for style of signal**

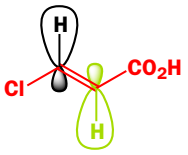
| Abbreviation | Meaning | Comments |
|---|---|---|
| s | singlet | might be 'broad' |
| d | doublet | equal in height |
| t | triplet | should be 1:2:1 |
| q | quartet | should be 1:3:3:1 |
| dt | double triplet | other combinations too, such as dd, dq, tq... |
| m | multiplet | avoid if possible but sometimes necessary to describe complicated signals |

The result is four lines of equal intensity called a **double doublet** (or sometimes a doublet of doublets), abbreviation dd. The smaller coupling constant can be read off from the separation between lines 1 and 2 or between lines 3 and 4, while the larger coupling constant is between lines 1 and 3 or between lines 2 and 4. You could see this as an imperfect triplet where the second coupling is too small to bring the central lines together: alternatively, look at a triplet as a special case of a double doublet where the two couplings are identical.

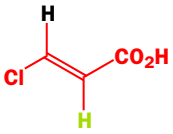
▶ Coupling constants to two identical protons must be identical but, if the protons differ, the coupling constants must also be different (though sometimes by only a very small amount).

## Coupling is a through bond effect

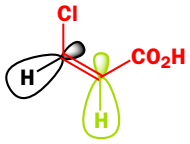
Neighbouring nuclei might interact through space or through the electrons in the bonds. We know that coupling is in fact a 'through bond effect' because of the way coupling constants vary with the shape of the molecule. The most important case occurs when the protons are at either end of a double bond. If the two hydrogens are *cis*, the coupling constant *J* is typically about 10 Hz but, if they are *trans*, *J* is much larger, usually 15–18 Hz. These two chloro acids are good examples.



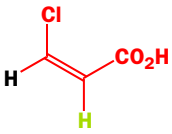

H atoms distant
orbitals parallel




hydrogens are *trans*
*J* = 15 Hz



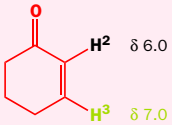

H atoms close
orbitals not parallel



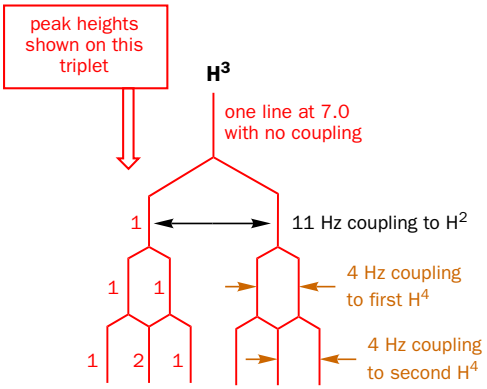

hydrogens are *cis*
*J* = 9 Hz

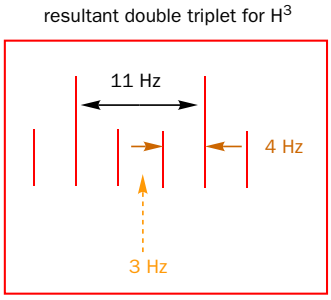
If coupling were through space, the nearer *cis* hydrogens would have the larger *J*. In fact, coupling occurs *through the bonds* and the more perfect parallel alignment of the orbitals in the *trans* compound provides better communication and a larger *J*.

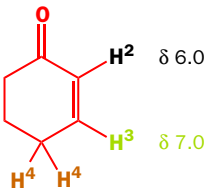
▶ For the same reason—orbital overlap—this *anti* arrangement of substituents is also preferred in chemical reactions such as elimination (Chapter 19) and fragmentation (Chapter 38).



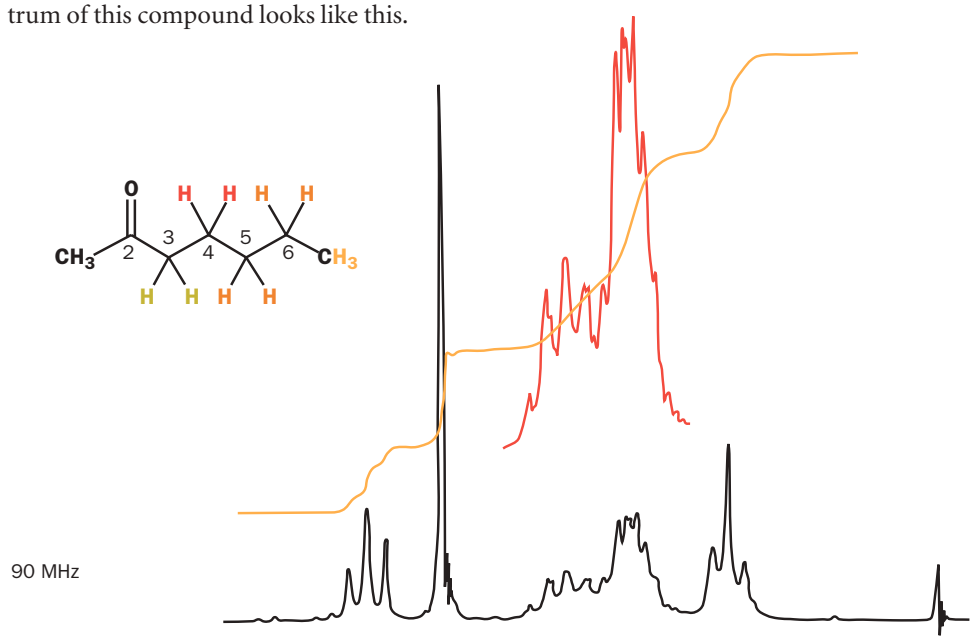

Coupling is at least as helpful as chemical shift in assigning spectra. When we said that the protons on cyclohexenone had the chemical shifts shown, how did we know? It was coupling that told us the answer. The proton next to the carbonyl group has one neighbour and appears as a doublet with *J* = 11 Hz, just right for a proton on a double bond with a *cis* neighbour. The proton at the other end appears as a double triplet. Inside each triplet the separation of the lines is 4 Hz and the two triplets are 11 Hz apart. This means the following diagramatically.



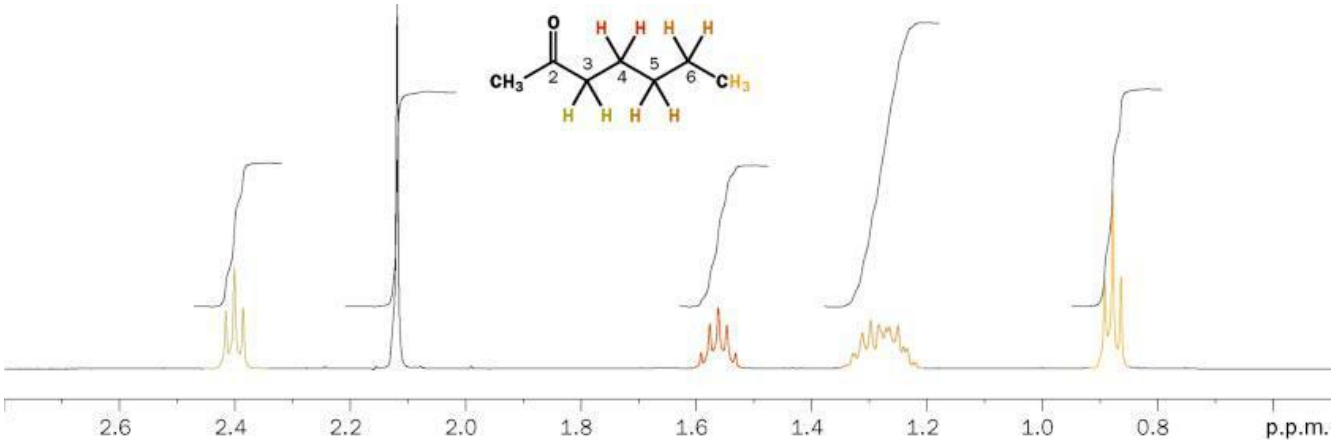



This is what happens when a proton couples to different groups of protons with different coupling constants. Many different coupling patterns are possible, many can be interpreted, but others cannot. However, machines with high field magnets make the interpretation easier. As a demonstration, let us turn back to the bee alarm pheromone that we met in Chapter 3. An old 90 MHz NMR spectrum of this compound looks like this.




You can see the singlet for the isolated black methyl group and just about make out the triplets for the green $CH_2$ group next to the ketone (C3) at about 2.5 p.p.m. and for the orange methyl group at 0.9 p.p.m. (C7) though this is rather broad. The rest is frankly a mess. Now see what happens when the spectrum is run on a more modern 500 MHz spectrometer.




Notice first of all that the chemical shifts have not changed. However, all the peaks have closed up. This is because *J* stays the same in Hz and the 7 Hz coupling for the methyl group triplet was 7/90 = 0.07 p.p.m. at 90 MHz but is 7/500 = 0.014 p.p.m. at 500 MHz. In the high field spectrum you can easily see the singlet and the two triplets but you can also see a clear quintet for the red $CH_2$ group at C4, which couples to both neighbouring $CH_2$ groups with the same *J* (7 Hz). Only the two $CH_2$ groups at C5 and C6 are not resolved. However, this does not matter as *we know they are there from the coupling pattern.* The triplet for the orange methyl group at C7 shows that it is next to a $CH_2$ group, and the quintet for the $CH_2$ group at C4 shows that it is next to two $CH_2$ groups. We know about one of them, at C5, so we can infer the other at C6.

## Coupling constants depend on three factors

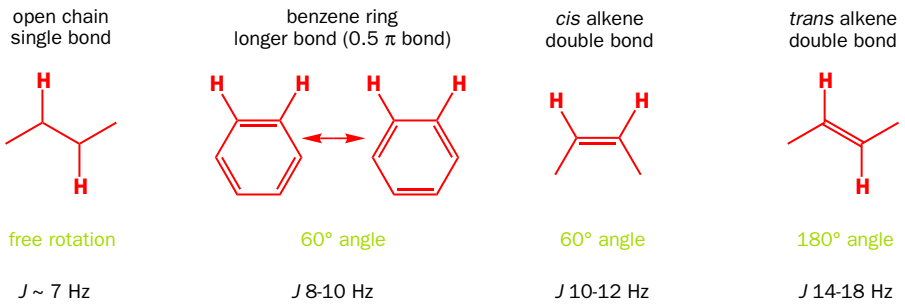
In heptanone all the coupling constants were about the same but in cyclohexenone they were quite different. What determines the size of the coupling constant? There are three factors.

- Through bond distance between the protons
- Angle between the two C–H bonds
- Electronegative substituents

The coupling constants we have seen so far are all between hydrogen atoms on neighbouring carbon atoms. The coupling is through three bonds (H–C–C–H) and is designated $^3J_{HH}$. These coupling constants $^3J_{HH}$ are usually about 7 Hz in an open-chain, freely rotating system such as we have in heptanone. The C–H bonds vary little in length but the C–C bond might be a single or a double bond. In cyclohexenone it is a double bond, significantly shorter than a single bond. Couplings ($^3J_{HH}$) across double bonds are usually larger than 7 Hz (11 Hz in cyclohexenone). $^3J_{HH}$ couplings are called **vicinal** couplings because the protons concerned are on neighbouring carbon atoms.

Something else is different too: in an open-chain system we have a time average of all rotational conformations. Across a double bond there is no rotation and the angle between the two C–H bonds is fixed because they are in the same plane. In the plane of the alkene, the C–H bonds are either at 60° (*cis*) or at 180° (*trans*) to each other. Coupling constants in benzene rings are slightly less than those across *cis* alkenes because the bond is longer (bond order 1.5 rather than 2).

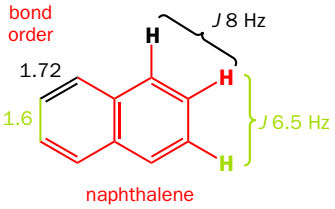
$^3J_{HH}$ coupling constants



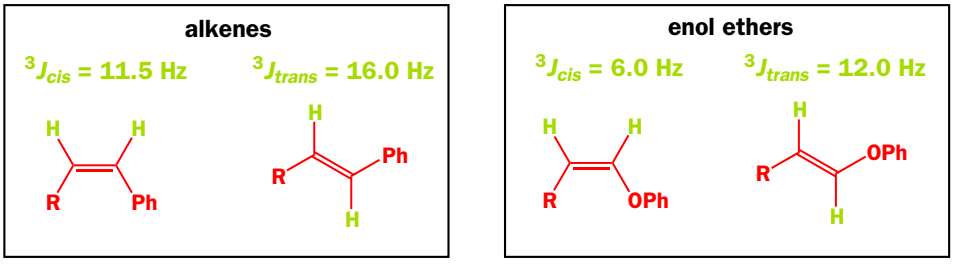

In naphthalenes, there are unequal bond lengths around the two rings. The bond between the two rings is the shortest, and the lengths of the others are shown. Coupling across the shorter bond (8 Hz) is significantly stronger than coupling across the longer bond (6.5 Hz).

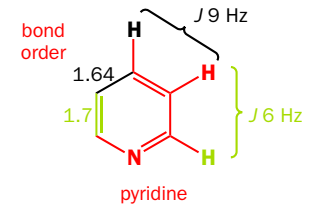
The effect of the third factor, electronegativity, is easily seen in the comparison between ordinary alkenes and enol ethers. We are going to compare two series of compounds with a *cis* or a *trans* double bond. One series has a phenyl group at one end of the alkene and the other has an OPh group. Within each box, that is for either series, the *trans* coupling is larger than the *cis*, as you would now expect. But if you compare the two series, the enol ethers have much smaller coupling constants. The *trans* coupling for the enol ethers is only just larger than the *cis* coupling for the alkenes. The electronegative oxygen atom is withdrawing electrons from the C–H bond in the enol ethers and weakening communication through the bonds.

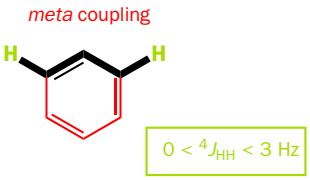
■ Conjugation in naphthalene was discussed in Chapter 7, p. 000.

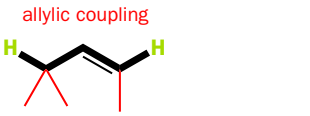



**effect of electronegative substituents on $^3J_{HH}$ – alkenes and enol ethers**





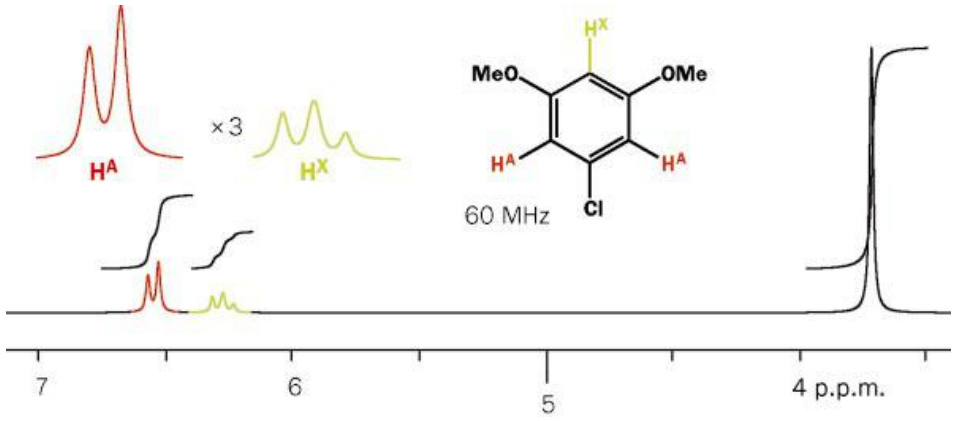



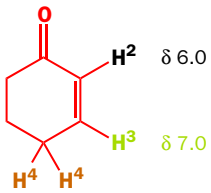

Another good example is the coupling found in pyridines. Though the bond order is actually slightly less between C3 and C4, the coupling constants are about normal for an aromatic ring (compare naphthalene above), while coupling constants across C2 and C3, nearer to the electronegative nitrogen, are smaller.

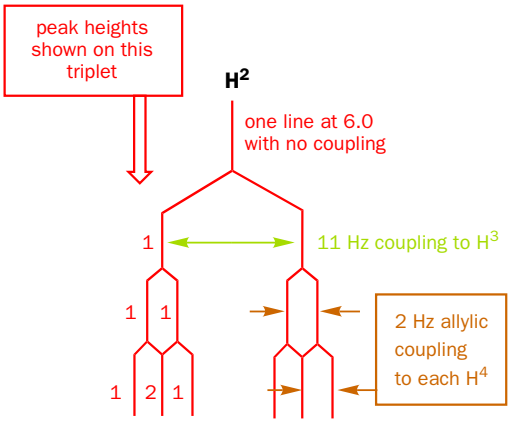
When the through bond distance gets longer, coupling is not usually seen. To put it another way, four-bond coupling $^4J_{HH}$ is usually zero. However, it is seen in some special cases, the most important being *meta* coupling in aromatic rings and allylic coupling in alkenes. In both, the orbitals between the two hydrogen atoms can line up in a zig-zag fashion to maximize interaction. This arrangement looks rather like a letter 'W' and this sort of coupling is called **W-coupling**. Even with this advantage, values of $^4J_{HH}$ are usually small, about 1–3 Hz.

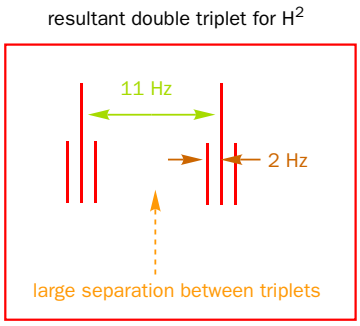
*Meta* coupling is very common when there is *ortho* coupling as well, but here is an example where there is no *ortho* coupling because none of the aromatic protons have immediate neighbours—the only coupling is *meta* coupling. There are two identical $H^A$s, which have one *meta* neighbour and appear as a 2H doublet. Proton $H^X$ between the two MeO groups has two identical *meta* neighbours and so appears as a 1H triplet. The coupling is small ($J \sim 2.5$ Hz).

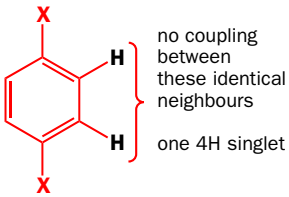



We have already seen a molecule with allylic coupling. We discussed in some detail why cyclohexenone has a double triplet for $H^3$. But it also has a less obvious double triplet for $H^2$. The triplet coupling is less obvious because $J$ is small (about 2 Hz) because it is $^4J_{HH}$—allylic coupling to the $CH_2$ group at C4. Here is a diagram of the coupling, which you should compare with the earlier one for cyclohexenone.



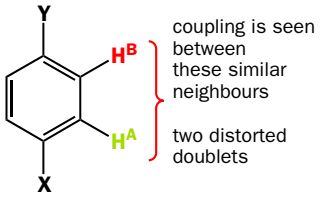



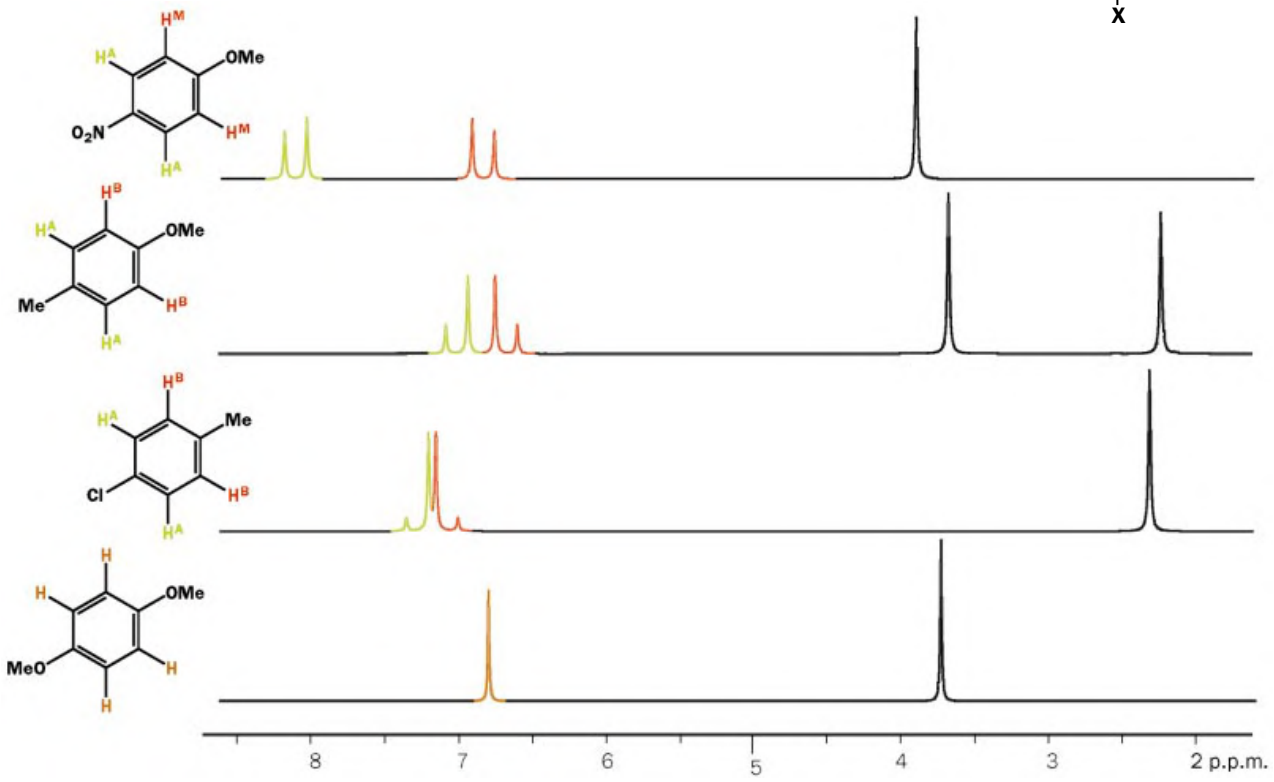




## Coupling between similar protons

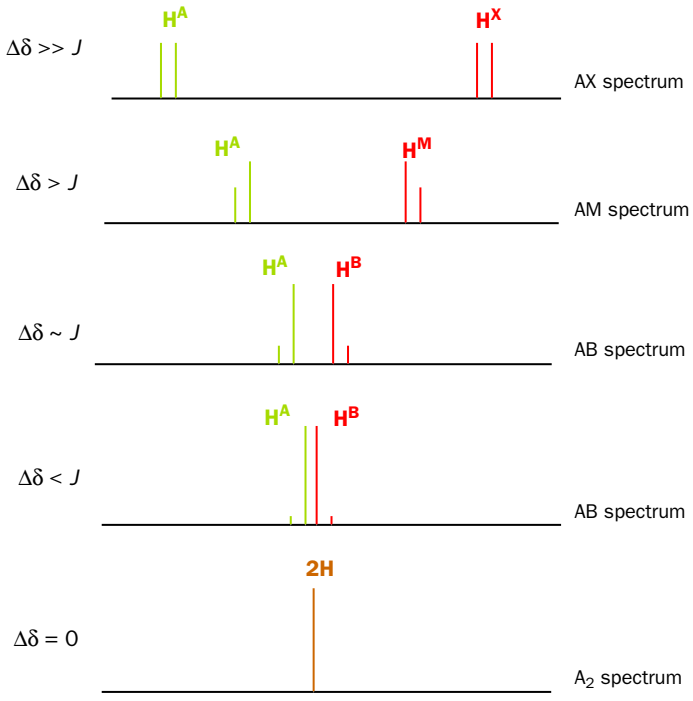
We have already seen that identical protons do not couple with each other. The three protons in a methyl group may couple to some other protons, but *never* couple with each other. They are an $A_3$ system. Identical neighbours do not couple either. In the *para*-disubstituted benzenes we saw on p. 000, all the protons on the aromatic rings were singlets.

We have also seen how two different protons forming an AX system give two separate doublets. Now we need to see what happens to protons in between these two extremes. What happens to two similar neighbours? Do the two doublets of the AX system suddenly collapse to the singlet of the $A_2$ system? You have probably guessed that they do not. The transition is gradual. Suppose we have two different neighbours on an aromatic ring. The spectra show what we see.



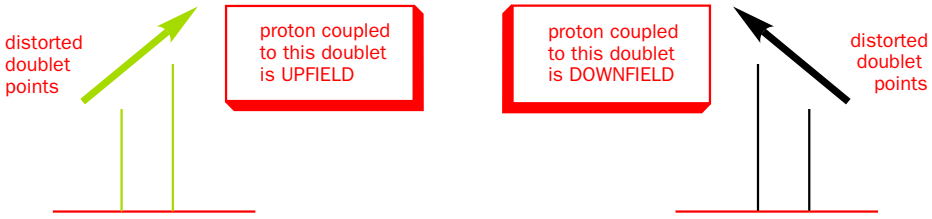

The critical factor is how the difference between the chemical shifts of the two protons ($\Delta\delta$) compares with the size of the coupling constant ($J$) for the machine in question. If $\Delta\delta$ is much larger than $J$ there is no distortion: if, say, $\Delta\delta$ is 4 p.p.m. at 250 MHz (= 1000 Hz) and the coupling constant is a normal 7 Hz, then this condition is fulfilled and we have an AX spectrum of two 1:1 doublets. As $\Delta\delta$ approaches $J$ in size, so the inner lines of the two doublets increase and the outer lines decrease until, when $\Delta\delta$ is zero, the outer lines vanish away altogether and we are left with the two superimposed inner lines—a singlet or an $A_2$ spectrum. You can see this progression in the diagram.



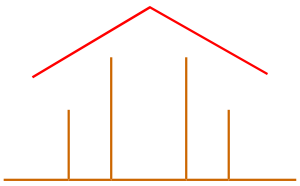
▶ You may see this situation described as an 'AB quartet'. It isn't! A quartet is an exactly equally spaced 1:3:3:1 system arising from coupling to three identical protons, and you should avoid this usage.

We call the last stages, where the distortion is great but the protons are still different, an **AB spectrum** because you cannot really talk about $H^A$ without also talking about $H^B$. The two inner lines may be closer than the gap between the doublets, or the four lines may all be equally spaced. Two versions of an AB spectrum are shown in the diagram—there are many more variations.

It is a generally useful tip that a distorted doublet 'points' towards the protons with which it is coupled.

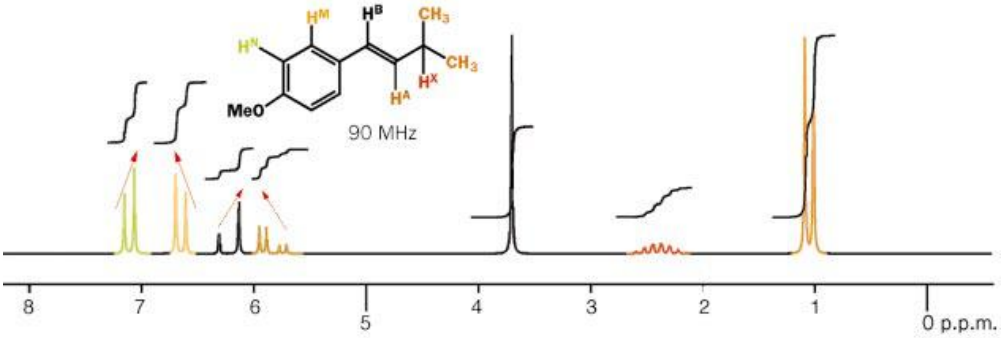



doublets with a roof over their heads



Or, to put it another way, the AB system is 'roofed' with the usual arrangement of low walls and a high middle to the roof. Look out for doublets (or any other coupled signals) of this kind.

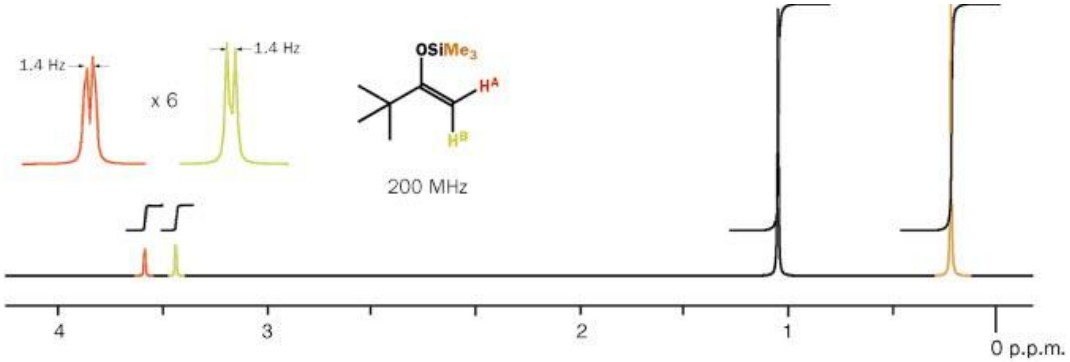
We shall end this section with a final example illustrating *para*-disubstituted benzenes and roofing as well as an ABX system and an isopropyl group.




The aromatic ring protons form a pair of distorted doublets (2H each) showing that the compound is a *para*-disubstituted benzene. Then the alkene protons form the AB part of an ABX spectrum. They are coupled to each other with a large (*trans*) $J = 16$ Hz and one is also coupled to another distant proton. The large doublets are distorted (AB) but the small doublets within the right-hand half of the AB system are equal in height. The distant proton X is part of an *i*-Pr group and is coupled to $H^B$ and the six identical methyl protons. Both *J*s are nearly the same so it is split by seven protons and is an octuplet. It looks like a sextuplet because the intensity ratios of the lines in an octuplet would be 1:7:21:35:35:21:7:1 (from Pascal's triangle) and it is hardly surprising that the outside lines disappear.

## Coupling can occur between protons on the same carbon atom

We have seen cases where protons on the same carbon atom are different: compounds with an alkene unsubstituted at one end. If these protons are different (and they are certainly near to each other), then they should couple. They do, but in this case the coupling constant is usually very small. Here you see the example we met on p. 000.

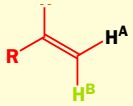


The small 1.4 Hz coupling is a $^2J_{HH}$ coupling between two protons on the same carbon that are different because there is no rotation about the double bond. $^2J_{HH}$ coupling is called **geminal** coupling.

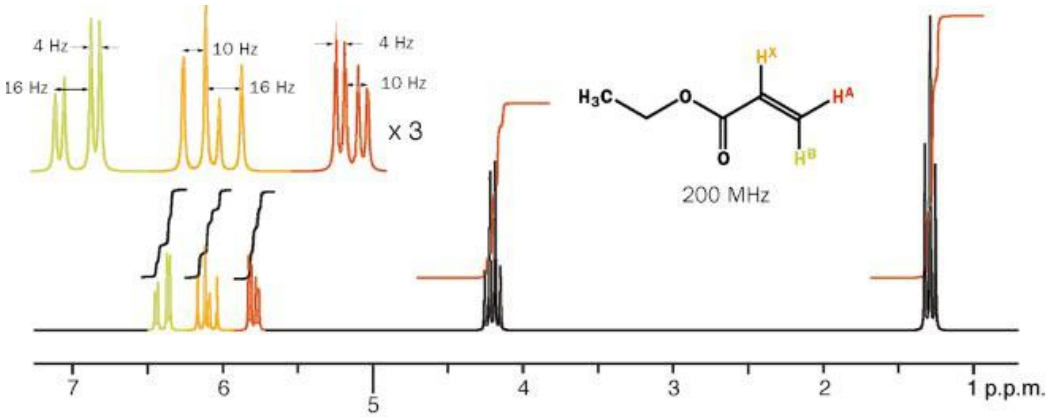
This means that a monosubstituted alkene will have very characteristic signals for the three protons on the double bond. The three different coupling constants are very different so that this ABX system is unusually clear.

Here is an example of such a vinyl compound, ethyl acrylate (ethyl propenoate, a monomer for the formation of acrylic polymers). The spectrum looks rather complex at first, but it is easy to sort out using the coupling constants.

**Proton NMR spectrum of a VINYL group**

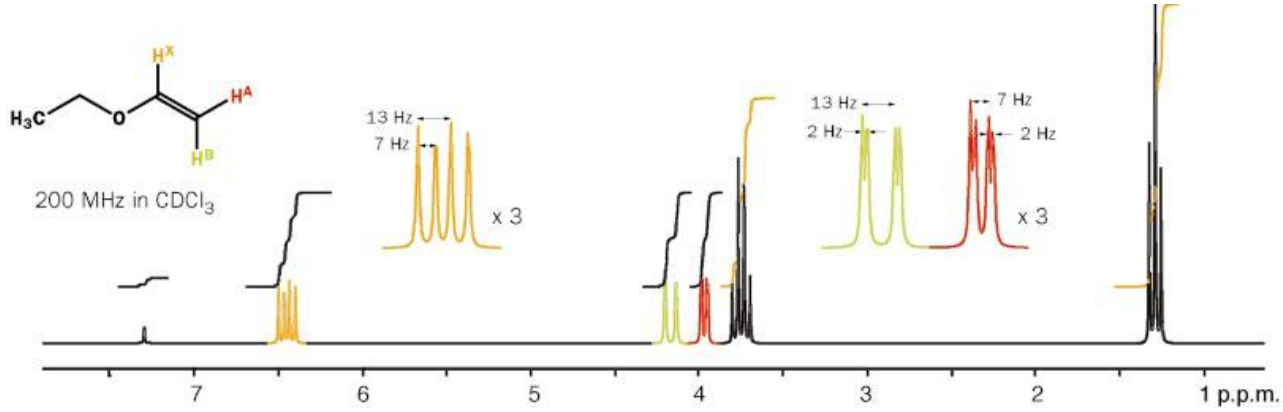



$J_{AB}$ very small (0–2 Hz)
$J_{AX}$ (*cis*) large (10–13 Hz)
$J_{BX}$ (*trans*) very large (14–18 Hz)



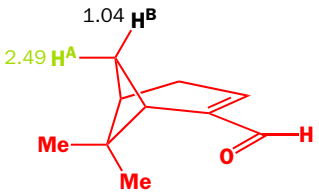

The largest $J$ (16 Hz) is obviously between X and B (*trans* coupling), the medium $J$ (10 Hz) is between X and A (*cis* coupling), and the small $J$ (4 Hz) must be between A and B (geminal). This assigns all the protons: A, 5.80 p.p.m.; B, 6.40 p.p.m.; X, 6.11 p.p.m. Rather surprisingly, X comes between A and B in chemical shift. Assignments based on coupling are more reliable than those based on chemical shift alone.

An enol ether type of vinyl group is present in ethyl vinyl ether, a reagent used for the protection of alcohols. This time all the coupling constants are smaller because of the electronegativity of the oxygen atom, which is now joined directly to the double bond.




It is still a simple matter to assign the protons of the vinyl group because couplings of 13, 7, and 2 Hz must be *trans*, *cis*, and geminal, respectively. In addition, X is on a carbon atom next to oxygen and so goes downfield while A and B have extra shielding from the conjugation of the oxygen lone pairs (see p. 000).

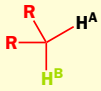
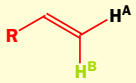
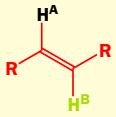
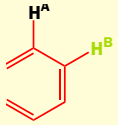
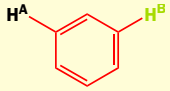
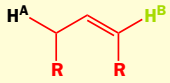
Geminal coupling on saturated carbons can be seen only if the hydrogens of a $CH_2$ group are different. We have seen an example of this on the bridging $CH_2$ group of myrtenal (p. 000). The




myrtenal

coupling constant for the protons on the bridge, $J_{AB}$, is 9 Hz. Geminal coupling constants in a saturated system can be much larger (typically 10–16 Hz) than in an unsaturated one.

**Typical coupling constants**

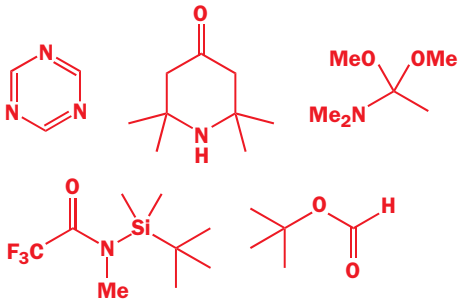
| | | |
|---|---|---|
| **Geminal $^2J_{HH}$** | | |
| saturated |  | 10–16 Hz |
| unsaturated |  | 0–3 Hz |
| **Vicinal $^3J_{HH}$** | | |
| saturated |  | 6–8 Hz |
| unsaturated *trans* |  | 14–16 Hz |
| unsaturated *cis* |  | 8–11 Hz |
| unsaturated aromatic |  | 6–9 Hz |
| **Long-range $^4J_{HH}$** | | |
| *meta* |  | 1–3 Hz |
| allylic |  | 1–2 Hz |

## To conclude

You have now met, in Chapter 3 and this chapter, all of the most important spectroscopic techniques available for working out the structure of organic molecules. We hope you can now appreciate that proton NMR is by far the most powerful of these techniques, and we hope you will be referring back to this chapter as you read the rest of the book. We shall talk about proton NMR a lot, and specifically we will come back to it in detail in Chapter 15, where we will look at using all of the spectroscopic techniques in combination, and in Chapter 32, when we look at what NMR can tell us about the shape of molecules.

# Problems

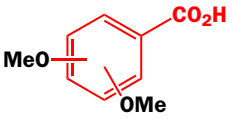
**1.** How many signals will there be in the $^1$H NMR spectrum of each of these compounds? Estimate the chemical shifts of the signals.



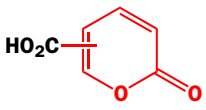
**2.** Comment on the chemical shifts of these three compounds and suggest whether there is a worthwhile correlation with p$K_a$.

| Compound | $\delta_H$, p.p.m. | p$K_a$ |
|---|---|---|
| $CH_3NO_2$ | 4.33 | 10 |
| $CH_2(NO_2)_2$ | 6.10 | 4 |
| $CH(NO_2)_3$ | 7.52 | 0 |

**3.** One isomer of dimethoxybenzoic acid has the $^1$H NMR spectrum 3.85 (6H, s), 6.63 (1H, t, *J* 2 Hz), 7.17 (2H, d, *J* 2 Hz) and one isomer of coumalic acid has the $^1$H NMR spectrum 6.41 (1H, d, *J* 10 Hz), 7.82 (1H, dd, *J* 2, 10 Hz), 8.51 (1H, d, *J* 2 Hz). In each case, which isomer is it? The substituents in black can be on any carbon atoms.

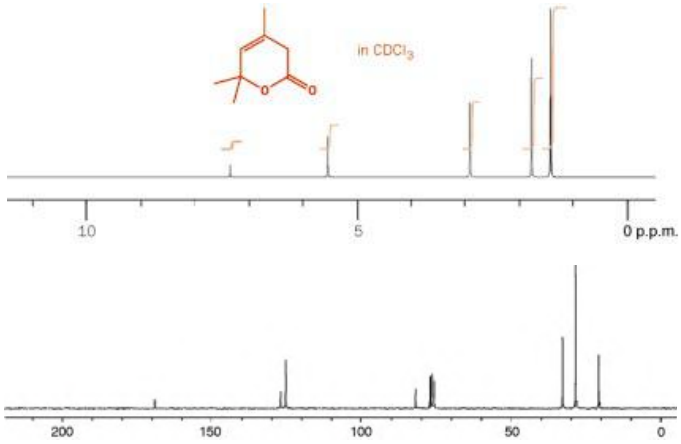


dimethoxybenzoic acid

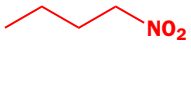


coumalic acid

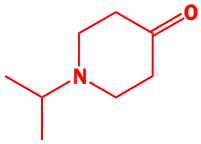
**4.** Assign the NMR spectra of this compound (assign means say which signal belongs to which atom) and justify your assignments.



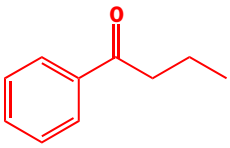

**5.** Assign the $^1$H NMR spectra of these compounds and explain the multiplicity of the signals.



$\delta_H$ 0.97 (3H, t, *J* 7 Hz),
1.42 (2H, sextuplet, *J* 7 Hz),
2.00 (2H, quintet, *J* 7 Hz),
4.40 (2H, t, *J* 7 Hz)

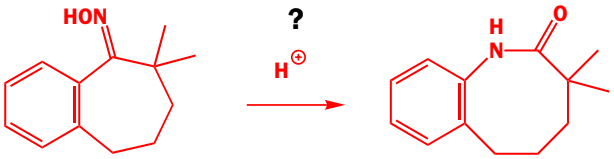


$\delta_H$ 1.08 (6H, d, *J* 7 Hz),
2.45 (4H, t, *J* 5 Hz),
2.80 (4H, t, *J* 5 Hz),
2.93 (1H, septuplet, *J* 7 Hz)



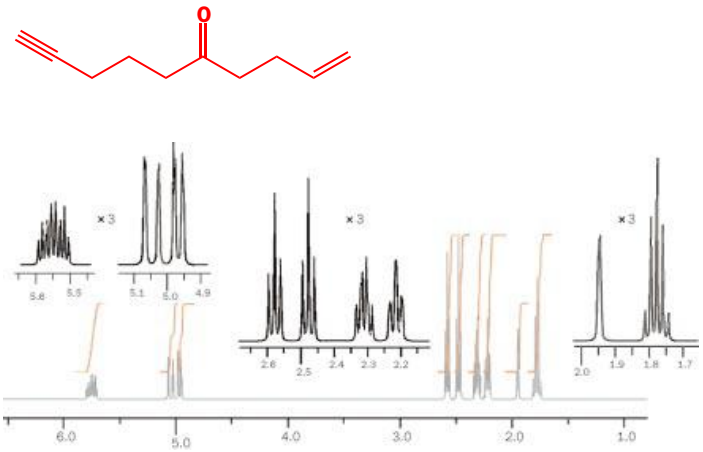
$\delta_H$ 1.00 (3H, t, *J* 7 Hz),
1.75 (2H, sextuplet, *J* 7 Hz),
2.91 (2H, t, *J* 7 Hz),
7.4–7.9 (5H, m)

**6.** The reaction below was expected to give product 6A and did indeed give a product with the correct molecular formula by mass spectrometry. The $^1$H NMR spectrum of the product was however: $\delta_H$ (p.p.m.) 1.27 (6H, s), 1.70 (4H, m), 2.88 (2H, m), 5.4–6.1 (2H, broad s, exchanges with $D_2O$), 7.0–7.5 (3H, m). Though the detail is missing from this spectrum, how can you already tell that this is not the compound expected?

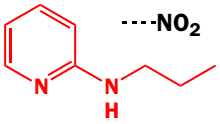


6A

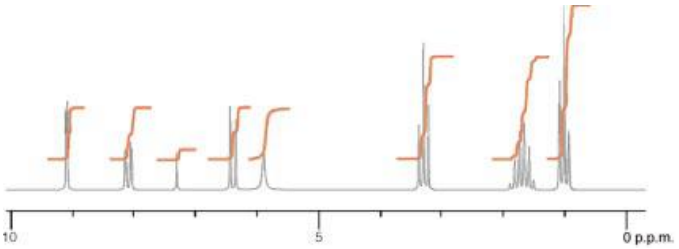
**7.** Assign the 400 MHz $^1$H NMR spectrum of this enynone as far as possible, justifying both chemical shifts and coupling patterns.



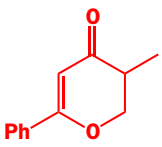
**8.** A nitration product ($C_8H_{11}N_3O_2$) of this pyridine has been isolated which has a nitro ($NO_2$) group somewhere on the molecule. From the 90 MHz $^1$H NMR spectrum, deduce whether the nitro group is (a) on the ring, (b) on the NH nitrogen atom, or (c) on the aliphatic side chain and then exactly where it is. Give a full analysis of the spectrum.




[$NO_2$ somewhere in the molecule]



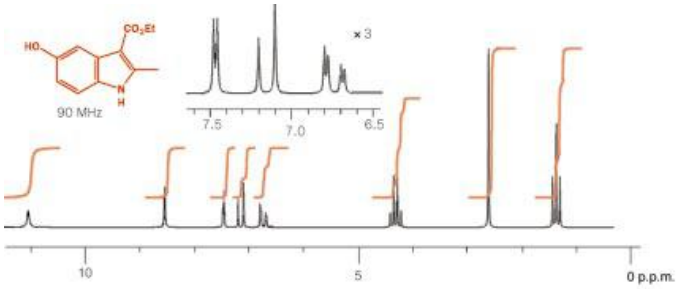

**9.** The natural product bullatenone was isolated in the 1950s from a New Zealand myrtle and assigned the structure 9A. Then compound 9A was synthesized and found not to be identical with natural bullatenone. Predict the expected $^1$H NMR spectrum of 9A. Given the full spectroscopic data available nowadays, but not in the 1950s, say why 9A is definitely wrong and suggest a better structure for bullatenone.



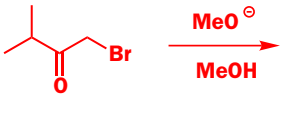

9A
alleged bullatenone

Spectra of bullatenone:
Mass spectrum: m/z 188 (10%) (high resolution confirms $C_{12}H_{12}O_2$), 105 (20%), 102 (100%), and 77 (20%)
Infrared: 1604 and 1705 $cm^{-1}$.
$^1$H NMR: 1.45 (6H, s), 5.82 (1H, s), 7.35 (3H, m), and 7.68 (2H, m).

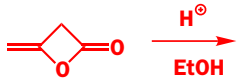
**10.** Interpret this $^1$H NMR spectrum.



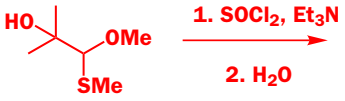

**11.** Suggest structures for the products of these reactions, interpreting the spectroscopic data. You are *not* expected to write mechanisms for the reactions and you should resist the temptation to work out what 'should happen' from the reactions. These are all unexpected products.




A, $C_6H_{12}O_2$
$\nu_{max}$($cm^{-1}$) 1745
$\delta_C$(p.p.m.) 179, 52, 39, 27
$\delta_H$(p.p.m.) 1.20 (9H, s), 3.67 (3H, s)




B, $C_6H_{10}O_3$
$\nu_{max}$($cm^{-1}$) 1745, 1710
$\delta_C$(p.p.m.) 203, 170, 62, 39, 22, 15
$\delta_H$(p.p.m.) 1.28 (3H, t, *J* 7 Hz), 2.21 (3H, s), 3.24 (2H, s), 4.2 (2H, q, *J* 7 Hz)

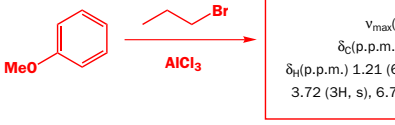



C
m/z 118
$\nu_{max}$($cm^{-1}$) 1730
$\delta_C$(p.p.m.) 202, 45, 22, 15
$\delta_H$(p.p.m.) 1.12 (6H, s), 2.8 (3H, s), 9.8 (1H, s)

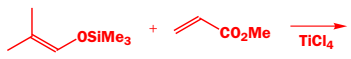
**12.** Precocene is an compound that causes insect larvae to pupate and can also be found in some plants (*Ageratum* spp.) where it may act as an insecticide. It was isolated in minute amounts and has the following spectroscopic details. Propose a structure for precocene.

Spectra of precocene:
Mass spectrum: m/z (high resolution gives $C_{13}H_{16}O_3$), M—15 (100%) and M—30 (weak).
Infrared: CH and fingerprint only.
$^1$H NMR: 1.34 (6H, s), 3.80 (3H, s), 3.82 (3H, s), 5.54 (1H, d, *J* 10 Hz), 6.37 (1H, d, *J* 10 Hz), 6.42 (1H, s), and 6.58 (1H, s ).

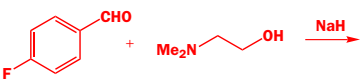
**13.** Suggest structures for the products of these reactions, interpreting the spectroscopic data. Though these products, unlike those in Problem 11, are reasonably logical, you will not meet the mechanisms for the reactions until Chapters 22, 29, and 23, respectively, and you are advised to solve the structures through the spectra.




A, $C_{10}H_{14}O$
$\nu_{max}$($cm^{-1}$) C–H and fingerprint only
$\delta_C$(p.p.m.) 153, 141, 127, 115, 59, 33, 24
$\delta_H$(p.p.m.) 1.21 (6H, d, *J* 7 Hz), 2.83 (1H, septuplet, *J* 7 Hz), 3.72 (3H, s), 6.74 (2H, d, *J* 9 Hz), and 7.18 (2h, d, *J* 9 Hz)

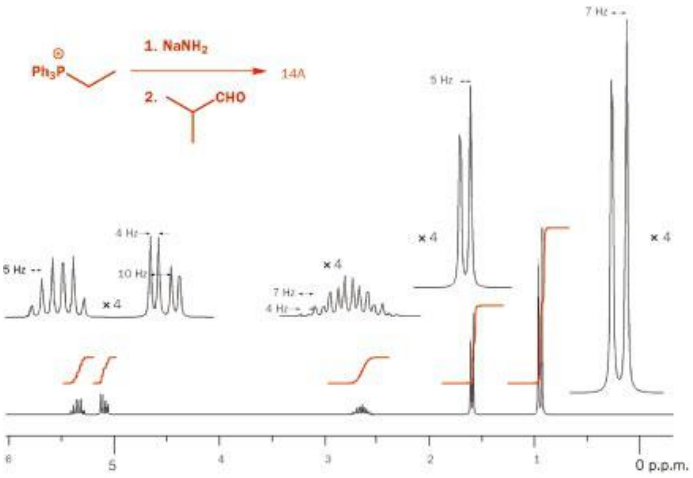



B, $C_8H_{14}O_3$
$\nu_{max}$($cm^{-1}$) 1745, 1730
$\delta_C$(p.p.m.) 202, 176, 62, 48, 34, 22, 15
$\delta_H$(p.p.m.) 1.21 (6H,s), 1.8 (2H, t, *J* 7 Hz), 2.24 (2H, t, *J* 7 Hz), 4.3 (3H, s), 10.01 (1H, s)




C, $C_{11}H_{15}NO_2$
$\nu_{max}$($cm^{-1}$) 1730
$\delta_C$(p.p.m.) 191, 164, 132, 130, 115, 64, 41, 29
$\delta_H$(p.p.m.) 2.32 (6H, s), 3.05 (2H, t, *J* 6 Hz), 4.20 (2H, t, *J* 6 Hz), 6.97 (2H, d, *J* 7 Hz), 7.82 (2H, d, *J* 7 Hz), 9.97 (1H, s)

**14.** The following reaction between a phosphonium salt, base, and an aldehyde gives a hydrocarbon $C_6H_{12}$ with the 200 MHz $^1H$ NMR spectrum shown. Give a structure for the product and comment on its stereochemistry. You are not expected to discuss the chemistry!



# Nucleophilic substitution at the carbonyl (C=O) group

# 12

## Connections

**Building on:**

- Drawing mechanisms ch5
- Nucleophilic attack on carbonyl groups ch6 & ch9
- Acidity and p$K_a$ ch8
- Grignard and RLi addition to C=O groups ch9

**Arriving at:**

- Nucleophilic attack followed by loss of leaving group
- What makes a good nucleophile
- What makes a good leaving group
- There is always a tetrahedral intermediate
- How to make acid derivatives
- Reactivity of acid derivatives
- How to make ketones from acids
- How to reduce acids to alcohols

**Looking forward to:**

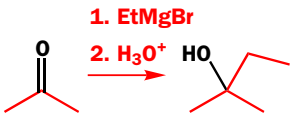
- Loss of carbonyl oxygen ch14
- Kinetics and mechanism ch13
- Reactions of enols ch21, ch26-ch29
- Synthesis in action ch25

You are already familiar with reactions of compounds containing carbonyl groups. Aldehydes and ketones react with nucleophiles at the carbon atom of their carbonyl group to give products containing hydroxyl groups. Because the carbonyl group is such a good electrophile, it reacts with a wide range of different nucleophiles: you have met reactions of aldehydes and ketones with (in Chapter 6) cyanide, water, alcohols, and (in Chapter 9) organometallic reagents (organolithiums and organomagnesiums, or Grignard reagents).

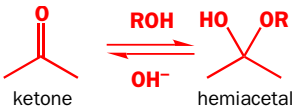
In this chapter and Chapter 14 we shall look at some more reactions of the carbonyl group—and revisit some of the ones we touched on in Chapter 6. It is a tribute to the importance of this functional group in organic chemistry that we have devoted four chapters of this book to its reactions. Just like the reactions in Chapters 6 and 9, the reactions in Chapters 12 and 14 all involve attack of a nucleophile on a carbonyl group. The difference will be that this step is followed by other mechanistic steps, which means that the overall reactions are not just *additions* but also *substitutions*.

## The product of nucleophilic addition to a carbonyl group is not always a stable compound

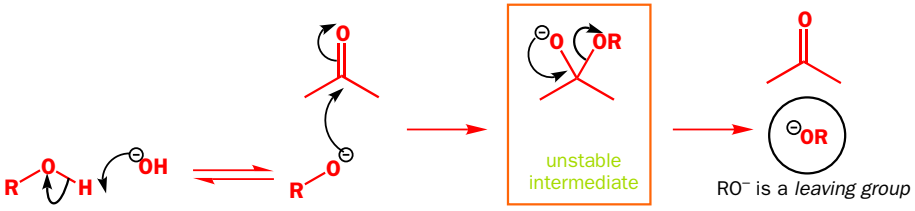
Addition of a Grignard reagent to an aldehyde or ketone gives a stable alkoxide, which can be protonated with acid to produce an alcohol (you met this reaction in Chapter 9).




The same is not true for addition of an alcohol to a carbonyl group in the presence of base—in Chapter 6 we drew a reversible, equilibrium arrow for this transformation and said that the product, a hemiacetal, is only formed to a significant extent if it is cyclic.



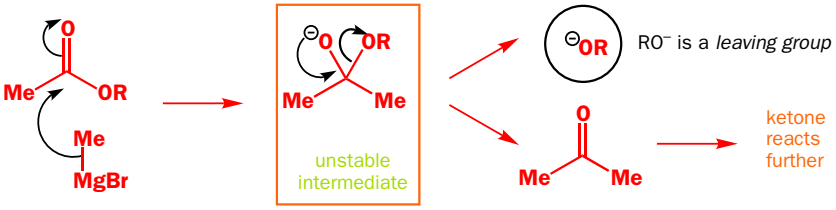

The reason for this instability is that $RO^-$ is easily expelled from the molecule. We call groups that can be expelled from molecules, usually taking with them a negative charge, **leaving groups**. We'll look at leaving groups in more detail later in this chapter and again in Chapter 17.



### Leaving groups

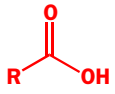
**Leaving groups are anions such as $Cl^-$, $RO^-$, and $RCO_2^-$ that can be expelled from molecules taking their negative charge with them.**

So, if the nucleophile is also a leaving group, there is a chance that it will be lost again and that the carbonyl group will reform—in other words, the reaction will be reversible. The energy released in forming the C=O bond (bond strength 720 kJ $mol^{-1}$) more than makes up for the loss of two C–O single bonds (about 350 kJ $mol^{-1}$ each), one of the reasons for the instability of the hemiacetal product in this case.




Again, it collapses with loss of $RO^-$ as a leaving group. This time, though, we have not gone back to starting materials: instead we have made a new compound (a ketone) by a **substitution reaction**—the OR group of the starting material has been substituted by the Me group of the product. In fact, as we shall see later, this reaction does not stop at this point because the ketone product can react with the Grignard reagent a second time.

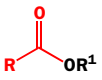
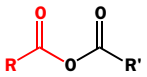
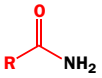
## Carboxylic acid derivatives


carboxylic acid


carboxylic acid derivatives

Most of the starting materials for, and products of, these substitutions will be carboxylic acid derivatives, with the general formula RCOX. You met the most important members of this class in Chapter 3: here they are again as a reminder.

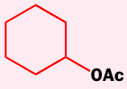
**Carboxylic acid derivatives**

| | | | |
|---|---|---|---|
|  | acid chlorides (acyl chlorides)[a] |  | esters |
|  | acid anhydrides |  | amides |

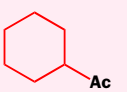
[a]We shall use these two terms interchangeably.

▶ The reactions of alcohols with acid chlorides and with acid anhydrides are the most important ways of making esters, but not the only ways. We shall see later how carboxylic acids can be made to react directly with alcohols. Remember the convenient organic element symbol for 'acetyl', Ac? Cyclohexyl acetate can be represented by 'OAc' but not just 'Ac'.

cyclohexyl acetate can be drawn like this:

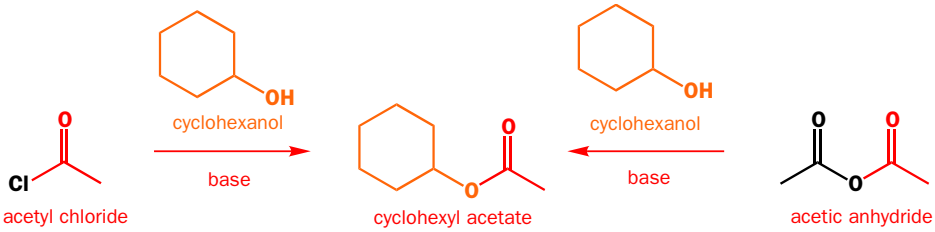


But NOT like this:



### Acid chlorides and acid anhydrides react with alcohols to make esters

Acetyl chloride will react with an alcohol in the presence of a base to give an acetate ester and we get the same product if we use acetic anhydride.

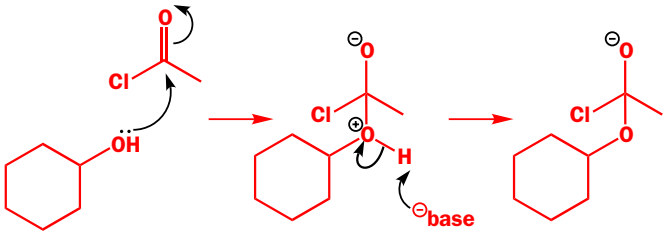



In each case, a substitution (of the black part of the molecule, $Cl^-$ or $AcO^-$, by the orange cyclohexanol) has taken place—but how? It is important that you learn not only the *fact* that

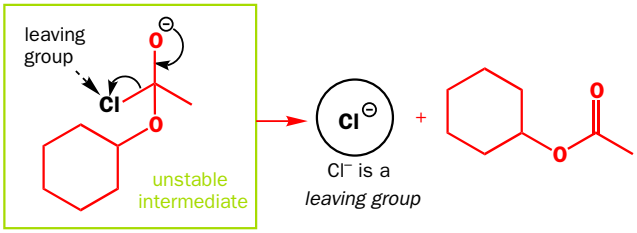
acyl chlorides and acid anhydrides react with alcohols but also the *mechanism* of the reaction. In this chapter you will meet a lot of reactions, but relatively few mechanisms—once you understand one, you should find that the rest follow on quite logically.

▶ You will notice that the terms 'acid chloride' and 'acyl chloride' are used interchangeably.

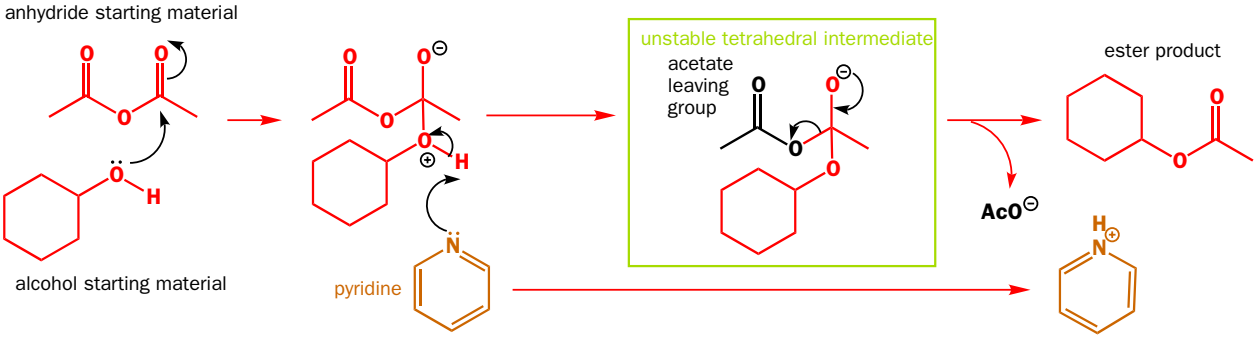
The first step of the reaction is, as you might expect, addition of the nucleophilic alcohol to the electrophilic carbonyl group—we'll take the acyl chloride first.




The base is important because it removes the proton from the alcohol as it attacks the carbonyl group. A base commonly used for this is pyridine. If the electrophile had been an aldehyde or a ketone, we would have got an unstable hemiacetal, which would collapse back to starting materials by eliminating the alcohol. With an acyl chloride, the alkoxide intermediate we get is also unstable. It collapses again by an elimination reaction, this time losing chloride ion, and forming the ester. Chloride is the *leaving group* here—it leaves with its negative charge.



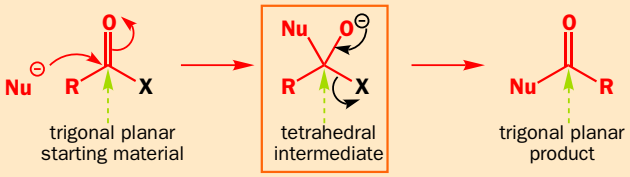

With this reaction as a model, you should be able to work out the mechanism of ester formation from acetic anhydride and cyclohexanol. Try to write it down without looking at the acyl chloride mechanism above, and certainly not at the answer below. Here it is, with pyridine as the base. Again, addition of the nucleophile gives an unstable intermediate, which undergoes an elimination reaction, this time losing a carboxylate anion, to give an ester.




We call the unstable intermediate formed in these reactions the **tetrahedral intermediate**, because the trigonal ($sp^2$) carbon atom of the carbonyl group has become a tetrahedral ($sp^3$) carbon atom.

## Tetrahedral intermediates

**Substitutions at trigonal carbonyl groups go through a tetrahedral intermediate and then on to a trigonal product.**



## More details of this reaction

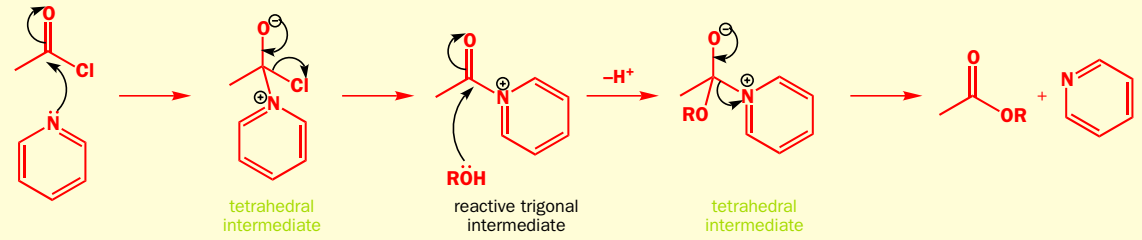
This reaction has more subtleties than first meet the eye. If you are reading this chapter for the first time, you should skip this box, as it is not essential to the general flow of what we are saying. There are three more points to notice.

1 Pyridine is consumed during both of these reactions, since it ends up protonated. One whole equivalent of pyridine is therefore necessary and, in fact, the reactions are often carried out with pyridine as solvent

2 The observant among you may also have noticed that the (weak—pyridine) base catalyst in this reaction works very slightly differently from the (strong—hydroxide) base catalyst in the hemiacetal-forming reaction on p. 000: one removes the proton after the nucleophile has added; the other removes the proton before the nucleophile has added. This is deliberate, and will be discussed further in Chapter 13

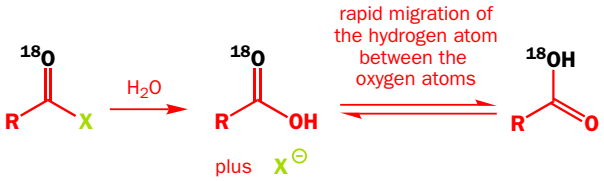
3 Pyridine is, in fact, more nucleophilic than the alcohol, and it attacks the acyl chloride rapidly, forming a highly electrophilic (because of the positive charge) intermediate. It is then this intermediate that subsequently reacts with the alcohol to give the ester. Because pyridine is acting as a nucleophile to speed up the reaction, yet is unchanged by the reaction, it is called a **nucleophilic catalyst**.

Nucleophilic catalysis in ester formation




## How do we know that the tetrahedral intermediate exists?

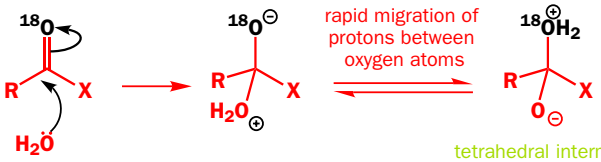
We don't expect you to be satisfied with the bland statement that tetrahedral intermediates are formed in these reactions: of course, you wonder how we know that this is true. The first evidence for tetrahedral intermediates in the substitution reactions of carboxylic acid derivatives was provided by Bender in 1951. He reacted water with carboxylic acid derivatives RCOX that had been 'labelled' with an isotope of oxygen, $^{18}O$.

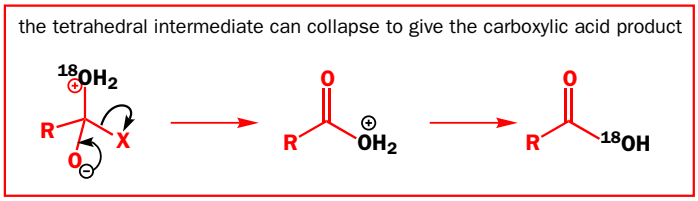


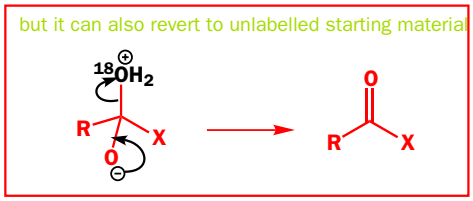

He then reacted these derivatives with water to make labelled carboxylic acids. However, he added insufficient water for complete consumption of the starting material. At the end of the reaction, he found that the proportion of labelled molecules in the *remaining starting material* had decreased significantly: in other words, it was no longer completely labelled with $^{18}O$; some contained 'normal' $^{16}O$.

▶ Non-radioactive isotopes are detected by mass spectrometry (Chapter 3).

This result cannot be explained by direct substitution of X by $H_2O$, but is consistent with the existence of an intermediate in which the unlabelled $^{16}O$ and labelled $^{18}O$ can 'change places'. This intermediate is the *tetrahedral intermediate* for this reaction.



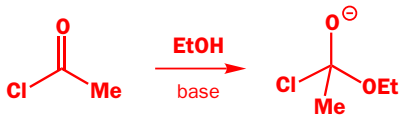




## Why are the tetrahedral intermediates unstable?

The alkoxide formed by addition of a Grignard reagent to an aldehyde or ketone is stable. Tetrahedral intermediates are similarly formed by addition of a nucleophile to a carbonyl group, so why are they *unstable*? The answer is to do with **leaving group ability**.

Once the nucleophile has added to the carbonyl compound, the stability of the product (or tetrahedral intermediate) depends on how good the groups attached to the new tetrahedral carbon atom are at leaving with the negative charge. In order for the tetrahedral intermediate to collapse (and therefore be just an intermediate and not the final product) one of the groups has to be able to leave and carry off the negative charge from the alkoxide anion formed in the addition.

Here once again is the tetrahedral intermediate resulting from addition of an alcohol to an acyl chloride.



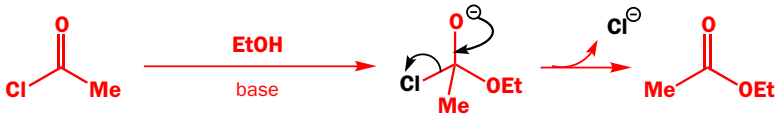

There are three choices of leaving group: $Cl^-$, $EtO^-$, and $Me^-$. We cannot actually make $Me^-$ because it is so unstable, but MeLi, which is about as close to it as we can get (Chapter 9), reacts vigorously with water so $Me^-$ must be a very bad leaving group. $EtO^-$ is not so bad—alkoxide salts are stable, but they are still strong, reactive bases (we shall see below what $pK_a$ has to do with this matter). But $Cl^-$ is the best leaving group: $Cl^-$ ions are perfectly stable and quite unreactive and happily carry off the negative charge from the oxygen atom. You probably eat several grams of $Cl^-$ every day but you would be unwise to eat $EtO^-$ or MeLi.

## $pK_{aH}$ is a useful guide to leaving group ability

It's useful to be able to compare leaving group ability quantitatively. This is impossible to do exactly, but a good guide is $pK_{aH}$. If we go back to the example of ester formation from acyl chloride plus alcohol, there's a choice of $Me^-$, $EtO^-$, and $Cl^-$. The leaving group with the lowest $pK_{aH}$ is the best and so we can complete the reaction.

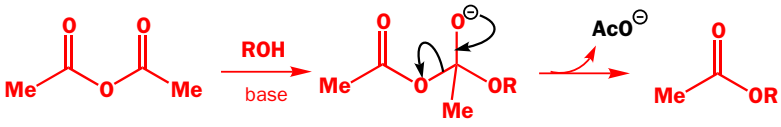
■ Remember that we use the term $pK_{aH}$ to mean '$pK_a$ of the conjugate acid': if you need reminding about $pK_a$ and $pK_{aH}$, stop now and refresh your memory by reviewing Chapter 8.

| Leaving group | $pK_{aH}$ |
|---|---|
| $Me^-$ | 50 |
| $EtO^-$ | 16 |
| $Cl^-$ | –7 |




The same is true for the reaction of acetic anhydride with an alcohol. Possible leaving groups from this tetrahedral intermediate are the following.

| Leaving group | $pK_{aH}$ |
|---|---|
| $Me^-$ | 50 |
| $RO^-$ | 16 |
| $MeCO_2^-$ | 5 |




Again the group that leaves is the one with the lowest $pK_{aH}$.

**● Leaving group ability**

**The lower the $pK_{aH}$, the better the leaving group in carbonyl substitution reactions.**

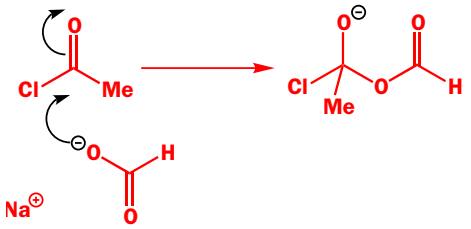
Why should this be so? The ability of an anion to behave as a leaving group depends in some way on its stability—how willing it is to accept a negative charge. $pK_a$ represents the equilibrium between an acid and its conjugate base, and is a measure of the stability of that conjugate base with respect to the acid—low $pK_a$ means stable conjugate base, indicating a willingness to accept a negative charge. So the general trends that affect $pK_a$, which we discussed in Chapter 8, will also affect leaving group ability. However, you must bear in mind that $pK_a$ is a measure of stability only with respect to the protonated form of the anion. Leaving group ability is a fundamentally different comparison between the stability of the negatively charged tetrahedral intermediate and the leaving group plus resulting carbonyl compound. But it still works as a good guide. These five values are worth learning.

increasing $pK_{aH}$ ↑

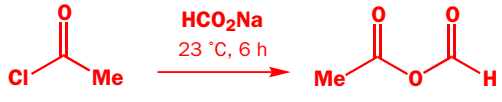
| Leaving group | $pK_{aH}$ |
|---|---|
| $R^-$ | 50 |
| $NH_2^-$ | 35 |
| $RO^-$ | 16 |
| $RCO_2^-$ | 5 |
| $Cl^-$ | –7 |

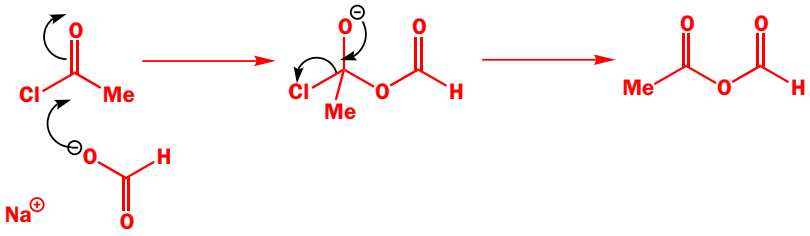
↓ increasing leaving group ability

We can use p$K_a$ to predict what happens if we react an acyl chloride with a carboxylate salt. We expect the carboxylate salt (here, sodium formate, or sodium methanoate, $HCO_2Na$) to act as the nucleophile to form a tetrahedral intermediate, which could collapse in any one of three ways.



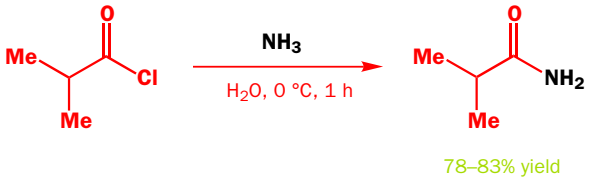
We can straight away rule out loss of $Me^-$ (p$K_{aH}$ 50), but we might guess that $Cl^-$ (p$K_{aH}$ –7) is a better leaving group than $HCO_2^-$ (p$K_a$ about 5), and we'd be right. Sodium formate reacts with acetyl chloride to give 'acetic formic anhydride'.



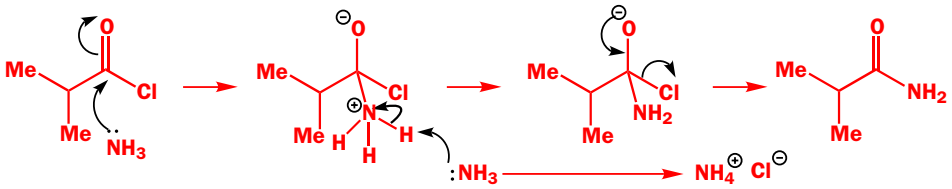



## Amines react with acyl chlorides to give amides

Using the principles we've outlined above, you should be able to see how these compounds can be interconverted by substitution reactions with appropriate nucleophiles. We've seen that acid chlorides react with carboxylic acids to give acid anhydrides, and with alcohols to give esters. They'll also react with amines (such as ammonia) to give amides.

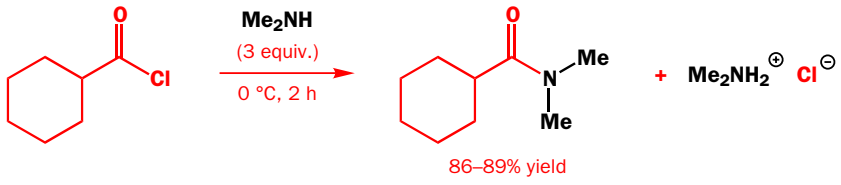



The mechanism is very similar to the mechanism of ester formation.



Notice the second molecule of ammonia, which removes a proton before the loss of chloride ion—the leaving group—to form the amide. Ammonium chloride is formed as a by-product in the reaction.

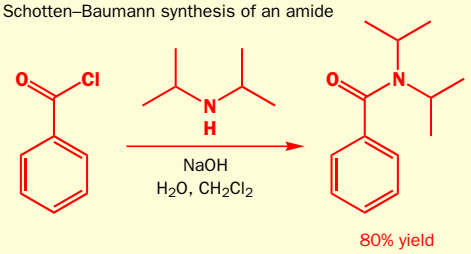
Here is another example, using a secondary amine, dimethylamine. Try writing down the mechanism now without looking at the one above. Again, two equivalents of dimethylamine are necessary, though the chemists who published this reaction added three for good measure.

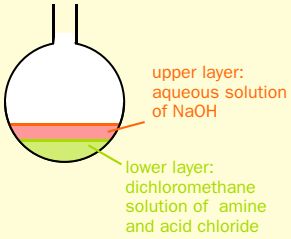


## Schotten–Baumann synthesis of an amide

As these mechanisms show, the formation of amides from acid chlorides and amines is accompanied by production of one equivalent of HCl, which needs to be neutralized by a second equivalent of amine. An alternative method for making amides is to carry out the reaction in the presence of another base, such as NaOH, which then does the job of neutralizing the HCl. The trouble is, $OH^-$ also attacks acyl chlorides to give carboxylic acids. Schotten and Baumann, in the late nineteenth century, published a way round this problem by carrying out these reactions in *two-phase systems* of immiscible water and dichloromethane. (Carl Schotten (1853–1910) was Hofmann's assistant in Berlin and spent most of his working life in the German patent office. (There is more about Hofmann in Chapter 19.) The organic amine (not necessarily ammonia) and the acyl chloride remain in the (lower) dichloromethane layer, while the base (NaOH) remains in the (upper) aqueous layer. Dichloromethane and chloroform are two common organic solvents that are *heavier* (more dense) than water. The acyl chloride reacts only with the amine, but the HCl produced can dissolve in, and be neutralized by, the aqueous solution of NaOH.

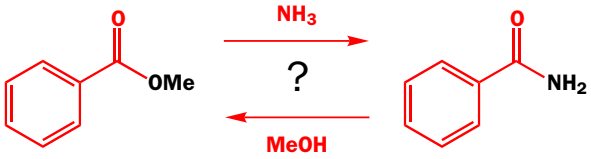
Schotten–Baumann synthesis of an amide



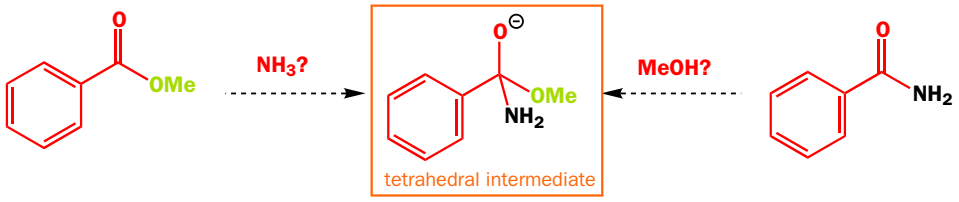




## Using p$K_{aH}$ to predict the outcome of substitution reactions of carboxylic acid derivatives

You saw that acid anhydrides react with alcohols to give esters: they will also react with amines to give amides. But would you expect esters to react with amines to give amides, or amides to react with alcohols to give esters? Both appear reasonable.

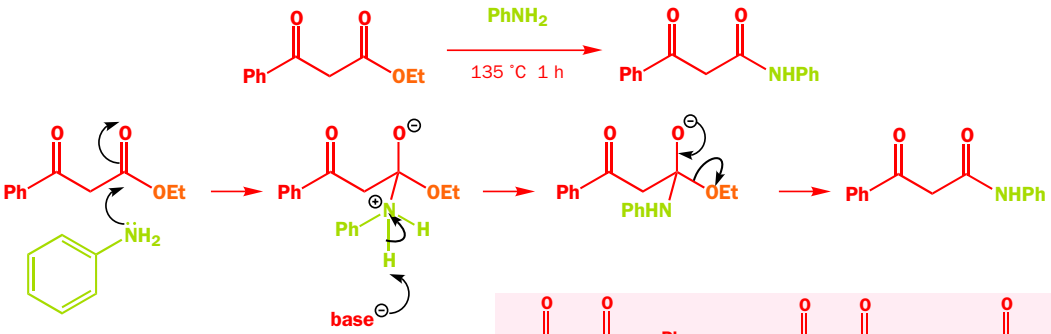


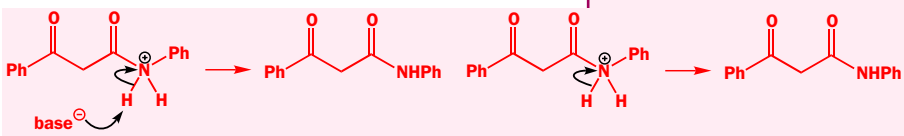

In fact only the top reaction works: amides can be formed from esters but esters cannot be formed from amides. Again, looking at p$K_a$s can tell us why. In both cases, the tetrahedral intermediate would be the same. The possible leaving groups are shown in the table.



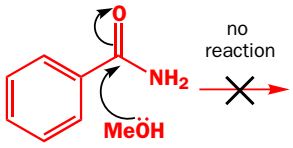

| Possible leaving groups | p$K_{aH}$ |
|---|---|
| $Ph^-$ | 45 |
| $NH_2^-$ | 35 |
| $MeO^-$ | 16 |

So $RO^-$ leaves and the amide is formed. Here is an example. The base may be either the $EtO^-$ produced in the previous step or another molecule of $PhNH_2$.




▶ You will meet many more mechanisms like this, in which an unspecified base removes a proton from an intermediate. As long as you can satisfy yourself that there is a base available to perform the task, it is quite acceptable to write either of these shorthand mechanisms.

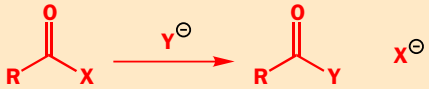



## Factors other than leaving group ability can be important

In fact, the tetrahedral intermediate would simply never form from an amide and an alcohol; the amide is too bad an electrophile and the alcohol not a good enough nucleophile. We've looked at leaving group ability: next we'll consider the strength of the nucleophile Y and then the strength of the electrophile RCOX.

### Conditions for reaction

If this reaction is to go




1. X must be a better leaving group than Y (otherwise the reverse reaction would take place)
2. Y must be a strong enough nucleophile to attack RCOX
3. RCOX must be a good enough electrophile to react with $Y^-$

## $pK_{aH}$ is a guide to nucleophilicity

We have seen how $pK_a$ gives us a guide to leaving group ability: it is also a good guide to how strong a nucleophile will be. These two properties are the reverse of each other: good nucleophiles are bad leaving groups. A species that likes forming new bonds to hydrogen (in other words, the $pK_a$ of its conjugate acid is high) will also like to form new bonds to carbon: it is likely to be a good nucleophile. Bases with high $pK_{aH}$ are bad leaving groups and they are, in general, good nucleophiles towards the carbonyl group. We will come back to this concept again in Chapter 17, where you will see that it does not apply to substitution at saturated carbon atoms.

### Guide to nucleophilicity

*In general*, the higher the $pK_{aH}$, the better the nucleophile.

But just a moment—we've overlooked an important point. When we made acid anhydrides from acid chlorides plus carboxylate salts, we used an anionic nucleophile $RCO_2^-$ but, when we made amides from acid chlorides plus amines, we used a neutral nucleophile $NH_3$, and not $NH_2^-$. For proper comparisons, we should include in our table ROH ($pK_{aH} = -5$; in other words, –5 is the $pK_a$ of $ROH_2^+$) and $NH_3$ ($pK_{aH} = 9$; in other words, 9 is the $pK_a$ of $NH_4^+$).

| Base | $pK_{aH}$ |
|---|---|
| $R^-$ | 50 |
| $NH_2^-$ | 35 |
| $RO^-$ | 16 |
| $NH_3$ | 9 |
| $RCO_2^-$ | 5 |
| ROH | –5 |
| $Cl^-$ | –7 |

increasing $pK_{aH}$ ↑ ; increasing nucleophilicity ↑

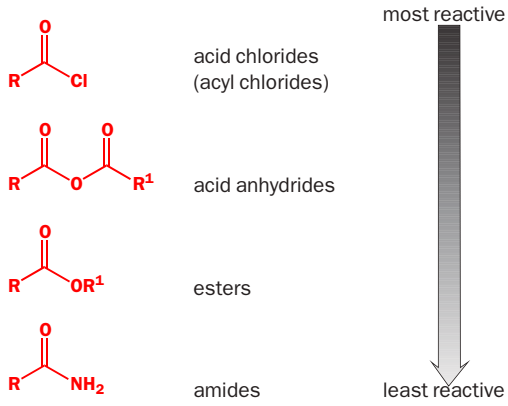
While amines react with acetic anhydride quite rapidly at room temperature (reaction complete in a few hours), alcohols react extremely slowly in the absence of a base. On the other hand, an alkoxide anion reacts with acetic anhydride extremely rapidly—the reactions are often complete within seconds at 0 °C. We don't have to deprotonate an alcohol completely to increase its reactivity: just a catalytic quantity of a weak base can do this job by removing the alcohol's proton *as it adds* to the carbonyl group. All these observations are consistent with our table and our proposition that high $pK_{aH}$ means good nucleophilicity.

■ You saw pyridine doing this on p. 000—it's called **general base catalysis**, and we will talk about it in more detail in Chapter 13.

# Not all carboxylic acid derivatives are equally reactive

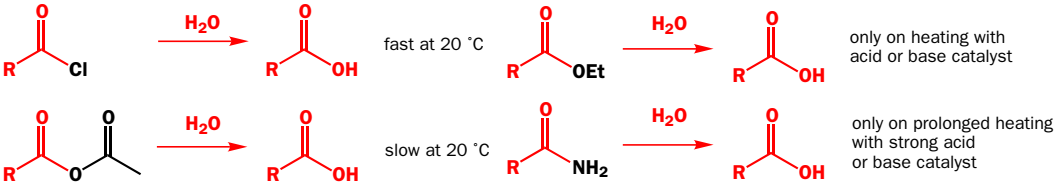
We can list the common carboxylic acid derivatives in a 'hierarchy' of reactivity, with the most reactive at the top and the least reactive at the bottom. Transformations are always possible moving *down*

the hierarchy. We've seen that this hierarchy is partly due to how good the leaving group is (the ones at the top are best), and partly due to how good the nucleophile needed to make the derivative is (the ones at the bottom are best).

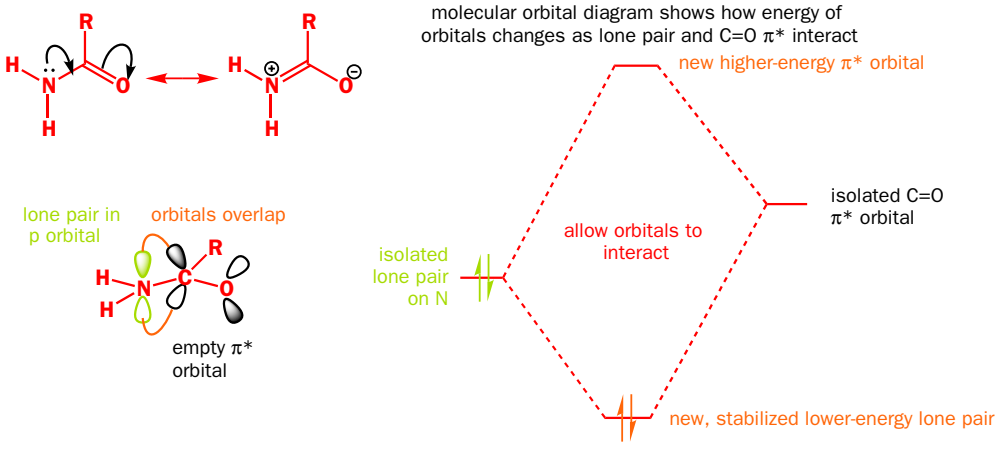



## Delocalization and the electrophilicity of carbonyl compounds

All of these derivatives will react with water to form carboxylic acids, but at very different rates.




Hydrolysing an amide requires boiling in 10% NaOH or heating overnight in a sealed tube with concentrated HCl. Amides are the least reactive towards nucleophiles because they exhibit the greatest degree of delocalization. You met this concept in Chapter 7 and we shall return to it many times more. In an amide, the lone pair on the nitrogen atom can be stabilized by overlap with the π* orbital of the carbonyl group—this overlap is best when the lone pair occupies a p orbital (in an amine, it would occupy an $sp^3$ orbital).

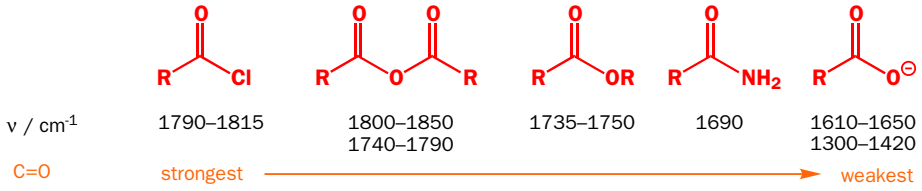



The molecular orbital diagram shows how this interaction both lowers the energy of the bonding orbital (the delocalized nitrogen lone pair), making it neither basic nor nucleophilic, and raises the energy of the π* orbital, making it less ready to react with nucleophiles. Esters are similar but, because the oxygen lone pairs are lower in energy, the effect is less pronounced.

The greater the degree of delocalization, the weaker the C=O bond becomes. This is most clearly

■ We treat this in more detail in Chapter 15. There are two frequencies for the anhydride and the carboxylate because of symmetric and antisymmetric stretching.

evident in the stretching frequency of the carbonyl group in the IR spectra of carboxylic acid derivatives—remember that the stretching frequency depends on the force constant of the bond, itself a measure of the bond's strength (the carboxylate anion is included because it represents the limit of the series, with complete delocalization of the negative charge over the two oxygen atoms).



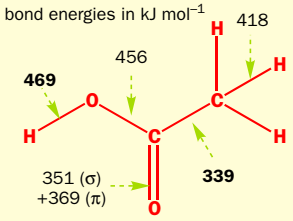

Amides react as electrophiles only with powerful nucleophiles such as $HO^-$. Acid chlorides, on the other hand, react with even quite weak nucleophiles: neutral ROH, for example. They are more reactive because the electron-withdrawing effect of the chlorine atom increases the electrophilicity of the carbonyl carbon atom.

### Bond strengths and reactivity

You may think that a weaker C=O bond should be more reactive. This is not so because the partial positive charge on carbon is also lessened by delocalization and because the molecule as a whole is stabilized by the delocalization. Bond strength is not always a good guide to reactivity!

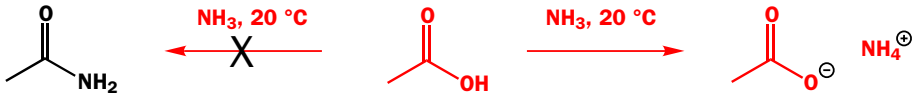
For example, in acetic acid the bond strengths are surprising. The strongest bond is the O–H bond and the weakest is the C–C bond. Yet very few reactions of acetic acid involve breaking the C–C bond, and its characteristic reactivity, as an acid, involves breaking O–H, the strongest bond of them all!

The reason is that polarization of bonds and solvation of ions play an enormously important role in determining the reactivity of molecules. In Chapter 39 you will see that radicals are relatively unaffected by solvation and that their reactions follow bond strengths much more closely.




## Carboxylic acids do not undergo substitution reactions under basic conditions

Substitution reactions of $RCO_2H$ require a leaving group $OH^-$, with $pK_{aH} = 15$, so we should be able to slot $RCO_2H$ into the 'hierarchy' on p. 000 just above the esters $RCO_2R'$. However, if we try to react carboxylic acids with alcohols in the presence of a base (as we would to make esters from acyl chlorides), the only thing that happens is deprotonation of the acid to give the carboxylate anion. Similarly, carboxylic acids react with amines to give not amides but ammonium carboxylate salts, because the amines themselves are basic.



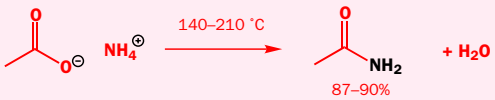

amide not formed

ammonium salt (ammonium acetate)

■ Later in this chapter (p. 000) you will meet about the only nucleophiles that will: organolithium compounds attack lithium carboxylates.

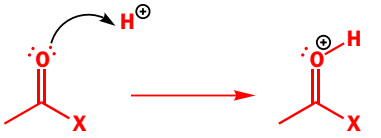
Once the carboxylic acid is deprotonated, substitutions are prevented because (almost) no nucleophile will attack the carboxylate anion. Under neutral conditions, alcohols are just not reactive enough to add to the carboxylic acid but, with *acid* catalysis, esters can be formed from alcohols and carboxylic acids.

▶ In fact, amides *can* be made from carboxylic acids plus amines, but only if the ammonium salt is heated strongly to dehydrate it. This is not usually a good way of making amides!



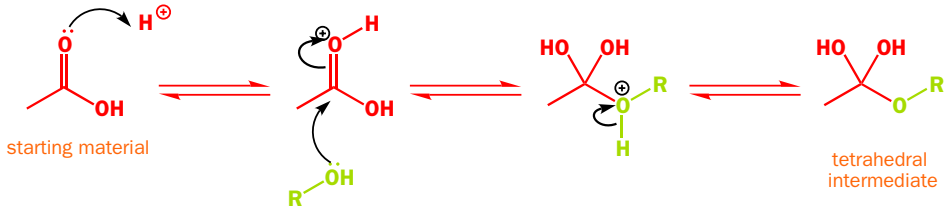

## Acid catalysts increase the reactivity of a carbonyl group

We saw in Chapter 6 that the lone pairs of a carbonyl group may be protonated by acid. Only strong acids are powerful enough to protonate carbonyl groups: the $pK_a$ of protonated acetone is –7, so, for example, even 1M HCl (pH 0) would protonate only 1 in $10^7$ molecules of acetone. However, even proportions as low as this are sufficient to increase the rate of substitution reactions at carbonyl groups enormously, because those carbonyl groups that are protonated become extremely powerful electrophiles.




It is for this reason that alcohols will react with carboxylic acids under acid catalysis. The acid (usually HCl, or $H_2SO_4$) reversibly protonates a small percentage of the carboxylic acid molecules, and the protonated carboxylic acids are extremely susceptible to attack by even a weak nucleophile such as an alcohol.

acid-catalysed ester formation: forming the tetrahedral intermediate



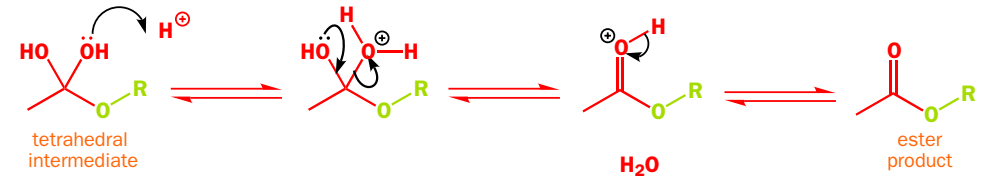

## Acid catalysts can make bad leaving groups into good ones

This tetrahedral intermediate is unstable because the energy to be gained by re-forming a C=O bond is greater than that used in breaking two C–O bonds. As it stands, none of the leaving groups ($R^-$, $HO^-$, or $RO^-$) is very good. However, help is again at hand in the acid catalyst. It can protonate any of the oxygen atoms reversibly. Again, only a very small proportion of molecules are protonated at any one time but, once the oxygen atom of, say, one of the OH groups is protonated, it becomes a much better leaving group ($H_2O$, $pK_{aH}$ –2, instead of $HO^-$, $pK_{aH}$ 15). Loss of ROH from the tetrahedral intermediate is also possible: this leads back to starting materials—hence the equilibrium arrow in the scheme above. Loss of $H_2O$ is more fruitful, and takes the reaction forwards to the ester product.

▶ Average bond strength C=O = 720 kJ mol$^{-1}$. Average bond strength C–O = 351 kJ mol$^{-1}$.

■ We shall discuss the reasons why chemists believe this to be the mechanism of this reaction later in the chapter.

acid-catalysed ester formation (continued)

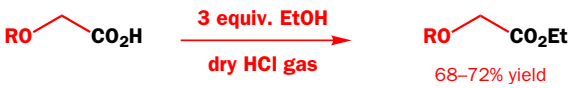



**● Acid catalysts catalyse substitution reactions of carboxylic acids**

1. They increase the electrophilicity of the carbonyl group by protonation at *carbonyl* oxygen
2. They lower the $pK_{aH}$ of the leaving group by protonation there too

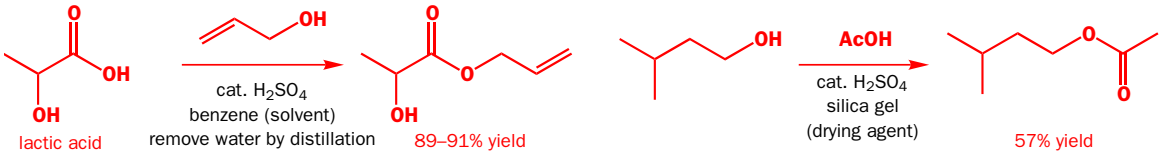
## Ester formation is reversible: how to control an equilibrium

Loss of water from the tetrahedral intermediate is reversible too: just as ROH will attack a protonated carboxylic acid, $H_2O$ will attack a protonated ester. In fact, every step in the sequence from carboxylic acid to ester is an equilibrium, and the overall equilibrium constant is about 1. In order for this reaction to be useful, it is therefore necessary to ensure that the equilibrium is pushed towards the ester side by using an excess of alcohol or carboxylic acid (usually the reactions are done in a solution of the alcohol or the carboxylic acid). In this reaction, for example, using less than three equivalents of ethanol gave lower yields of ester.



■ Lactic acid (the structure is shown in an example on this page) must be handled in solution in water. Can you see why, bearing in mind what we have said about the reversibility of ester formation?

Alternatively, the reaction can be done in the presence of a dehydrating agent (concentrated $H_2SO_4$, for example, or silica gel), or the water can be distilled out of the mixture as it forms.



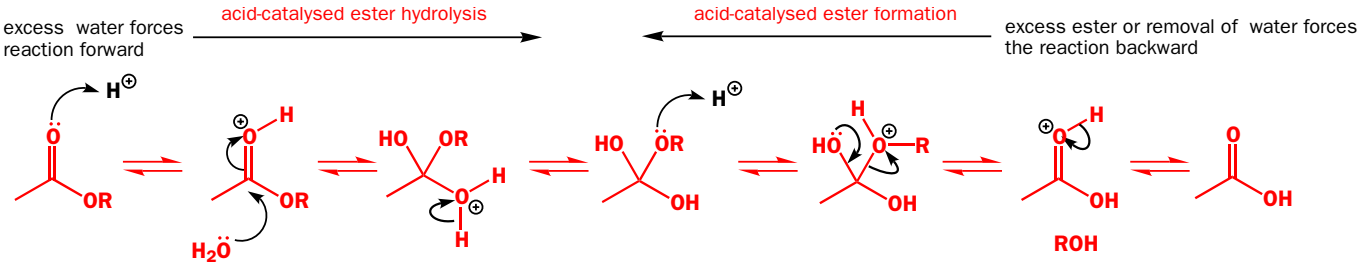

▶ You have now met three ways of making esters from alcohols:

• with acyl chlorides • with acid anhydrides • with carboxylic acids

Try to appreciate that different methods will be appropriate at different times. If you want to make a few milligrams of a complex ester, you are much more likely to work with a reactive acyl chloride or anhydride, using pyridine as a weakly basic catalyst, than to try and distil out a minute quantity of water from a reaction mixture containing a strong acid that may destroy the starting material. On the other hand, if you are a chemist making simple esters (such as those in Chapter 3, p. 000) for the flavouring industry on a scale of many tons, you will prefer the cheaper option of carboxylic acid plus HCl in alcohol solution.

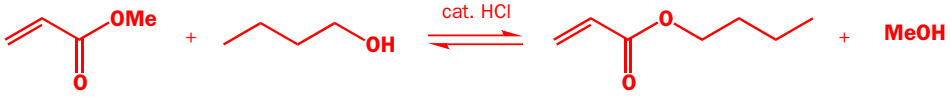
## Acid-catalysed ester hydrolysis and transesterification

By starting with an ester, an excess of water, and an acid catalyst, we can persuade the reverse reaction to occur: formation of the carboxylic acid plus alcohol with consumption of water. Such a reaction is known as a **hydrolysis reaction**, because water is used to break up the ester into carboxylic acid plus alcohol (*lysis* = breaking).

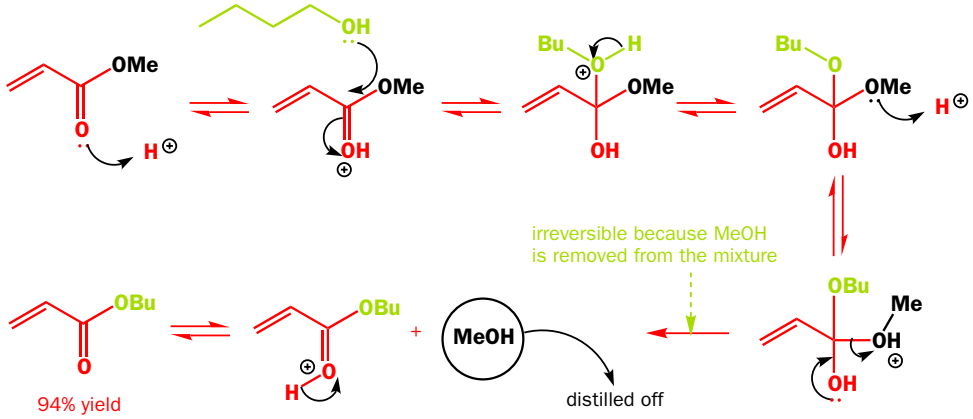



■ The mechanisms of acid-catalysed formation and hydrolysis of esters are extremely important: you *must* learn them, and understand the reason for each step.

Acid-catalysed ester formation and hydrolysis are the exact reverse of one another: the only way we can control the reaction is by altering concentrations of reagents to drive the reaction the way we want it to go. The same principles can be used to convert to convert an ester of one alcohol into an ester of another, a process known as **transesterification**. It is possible, for example, to force this equilibrium to the right by distilling methanol (which has a lower boiling point than the other components of the reaction) out of the mixture.

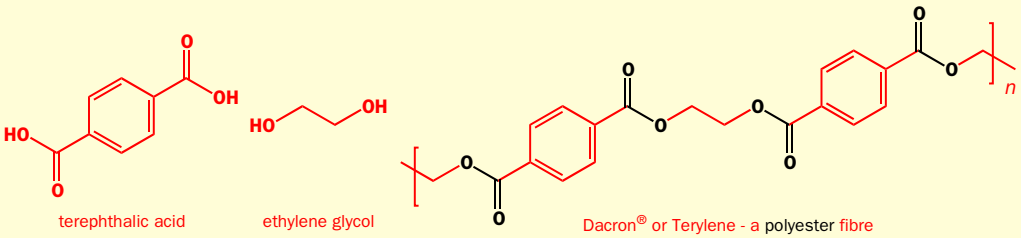



The mechanism for this transesterification simply consists of adding one alcohol (here BuOH) and eliminating the other (here MeOH), both processes being acid-catalysed. Notice how easy it is now to confirm that the reaction is *catalytic* in $H^+$. Notice also that protonation always occurs on the *carbonyl* oxygen atom.

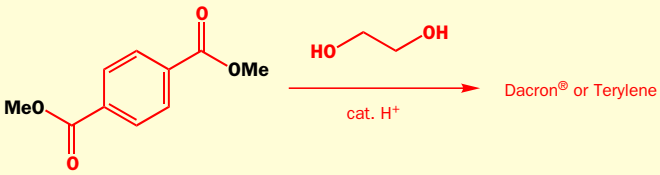


### Polyester fibre manufacture

A transesterification reaction is used to make the polyester fibres that are used for textile production. Terylene, or Dacron, for example, is a polyester of the dicarboxylic acid terephthalic acid and the diol ethylene glycol. Polymers are discussed in more detail in Chapter 52.



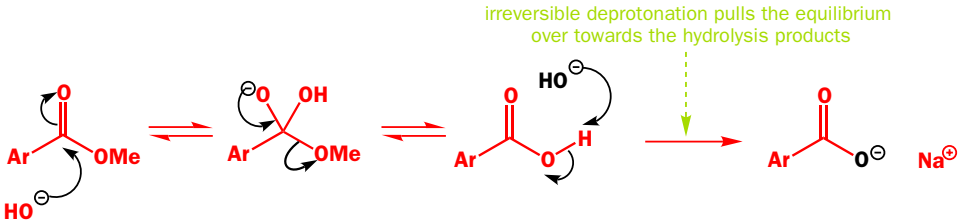

It is made by transesterifying diethyl terephthalate with ethylene glycol in the presence of an acid catalyst, distilling off the methanol as it forms.




## Base-catalysed hydrolysis of esters is irreversible

You can't make esters from carboxylic acids and alcohols under basic conditions because the base deprotonates the carboxylic acid (p. 000). However, you can reverse that reaction and hydrolyse an ester to a carboxylic acid (more accurately, a carboxylate salt) and an alcohol.


This time the ester is, of course, not protonated first as it would be in acid, but the unprotonated ester is a good enough electrophile because $OH^-$, and not water, is the nucleophile. The tetrahedral intermediate can collapse either way, giving back ester, or going forward to acid plus alcohol.




Without an acid catalyst, the alcohol cannot react with the carboxylic acid; in fact, the backward reaction is doubly impossible because the basic conditions straight away deprotonate the acid to make a carboxylate salt (which, incidentally, consumes the base, making at least one equivalent of base necessary in the reaction).

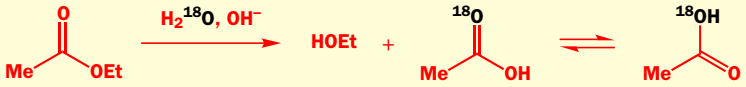
### How do we know this is the mechanism?

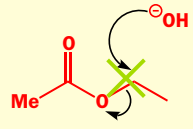
Ester hydrolysis is such an important reaction that chemists spent a lot of time and effort finding out exactly how it worked. If you want to know all the details, read a specialist textbook on physical (mechanistic) organic chemistry. Many of the experiments that tell us about the mechanism involve oxygen-18 labelling. The starting material is synthesized using as a starting material a compound enriched in the heavy oxygen isotope $^{18}O$. By knowing where the heavy oxygen atoms start off, and following (by mass spectrometry—Chapter 3) where they end up, the mechanism can be established.

## How do we know this is the mechanism? (continued)

1 An $^{18}O$ label in the 'ether' oxygen of the ester starting material ends up in the alcohol product


2 Hydrolysis with $^{18}OH_2$ gives $^{18}O$-labelled carboxylic acid, but no $^{18}O$-labelled alcohol



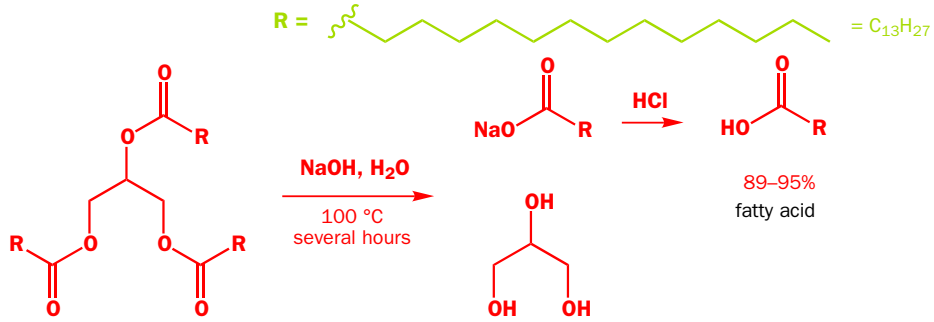




INCORRECT

These experiments tell us that a displacement (substitution) has occurred at the carbonyl carbon atom, and rule out the alternative displacement at saturated carbon.

Having worked this out, one further labelling experiment showed that a tetrahedral intermediate must be formed: an ester labelled with $^{18}O$ in its carbonyl oxygen atom passes some of its $^{18}O$ label to the water. We discussed why this shows that a tetrahedral intermediate must be formed on p. 000.

The saturated fatty acid tetradecanoic acid (also known as myristic acid) is manufactured commercially from coconut oil by base-catalysed hydrolysis. You may be surprised to learn that coconut oil contains more saturated fat than butter, lard, or beef dripping: much of it is the trimyristate ester of glycerol. Hydrolysis with aqueous sodium hydroxide, followed by reprotonation of the sodium carboxylate salt with acid, gives myristic acid. Notice how much longer it takes to hydrolyse this branched ester than it did to hydrolyse a methyl ester (p. 000).

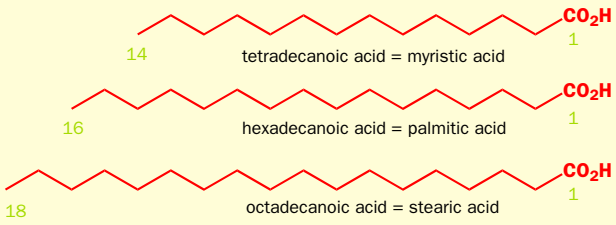



principal component of coconut oil

glycerol

## Saponification

The alkaline hydrolysis of esters to give carboxylate salts is known as **saponification**, because it is the process used to make soap. Traditionally, beef tallow (the tristearate ester of glycerol—stearic acid is octadecanoic acid, $C_{17}H_{35}CO_2H$) was hydrolysed with sodium hydroxide to give sodium stearate, $C_{17}H_{35}CO_2Na$, the principal component of soap. Finer soaps are made from palm oil and contain a higher proportion of sodium palmitate, $C_{15}H_{31}CO_2Na$. Hydrolysis with KOH gives potassium carboxylates, which are used in liquid soaps. Soaps like these owe their detergent properties to the combination of polar (carboxylate group) and nonpolar (long alkyl chain) properties.

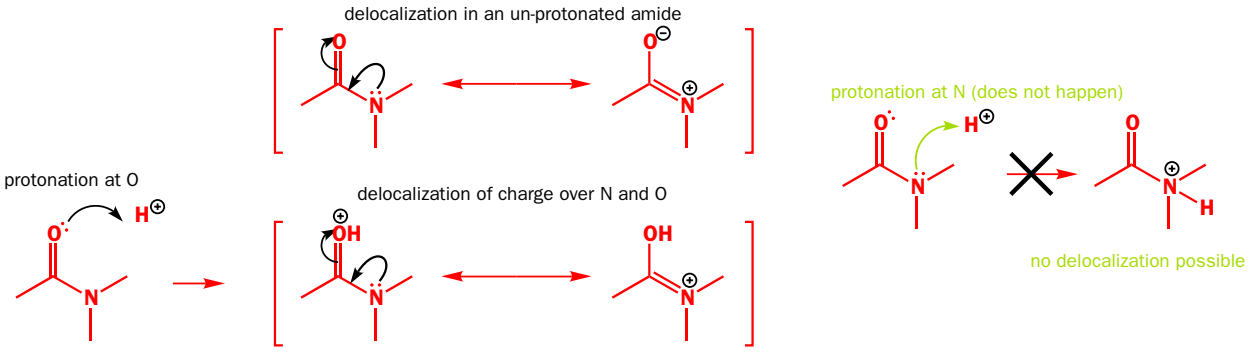



## Amides can be hydrolysed under acidic or basic conditions too

In order to hydrolyse the least reactive of the series of carboxylic acid derivatives we have a choice: we

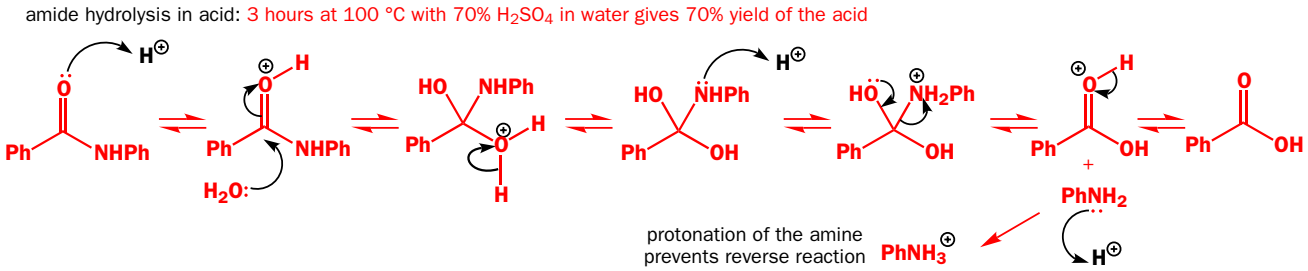
can persuade the amine leaving group to leave by protonating it, or we can use brute force and forcibly eject it with concentrated hydroxide solution.

Amides are very unreactive as electrophiles, but they are also rather more basic than most carboxylic acid derivatives: a typical amide has a p$K_{aH}$ of –1; most other carbonyl compounds have p$K_{aH}$s of around –7. You might therefore imagine that the protonation of an amide would take place on nitrogen—after all, *amine* nitrogen atoms are readily protonated. And, indeed, the reason for the basicity of amides is the nitrogen atom's delocalized lone pair, making the carbonyl group unusually electron-rich. But amides are always protonated on the oxygen atom of the carbonyl group—never the nitrogen, because protonation at nitrogen disrupts the delocalized system that makes amides so stable.

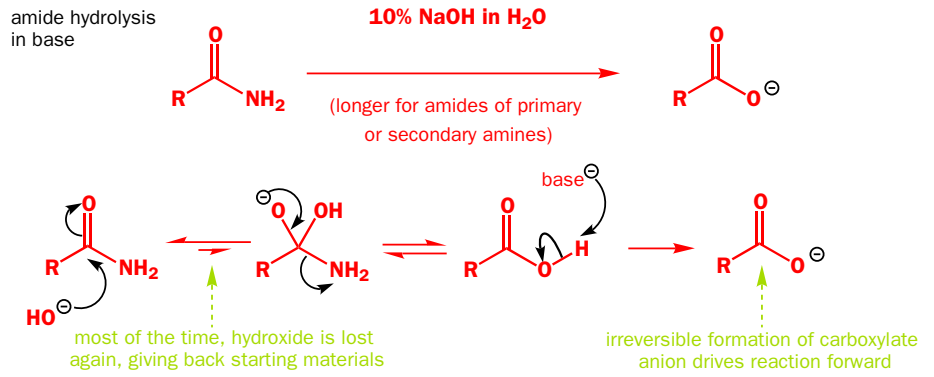



Protonation of the carbonyl group by acid makes the carbonyl group electrophilic enough for attack by water, giving a neutral tetrahedral intermediate. The amine nitrogen atom in the tetrahedral intermediate is much more basic than the oxygen atoms, so now *it* gets protonated, and the $RNH_2$ group becomes really quite a good leaving group. And, once it has left, it will immediately be protonated again, and therefore become completely nonnucleophilic. The conditions are very vigorous—70% sulfuric acid for 3 hours at 100 °C.

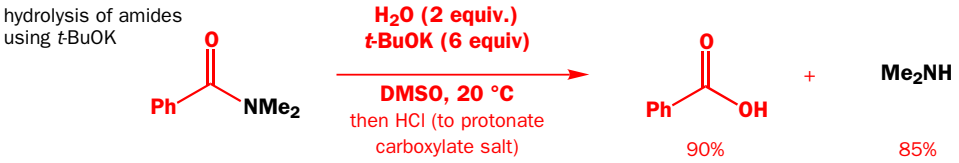
▶ Notice that this means that one equivalent of acid is used up in this reaction—the acid is not solely a catalyst.




Hydrolysis of amides in base requires similarly vigorous conditions. Hot solutions of hydroxide are sufficiently powerful nucleophiles to attack an amide carbonyl group, though even when the tetrahedral intermediate has formed, $NH_2^-$ (p$K_{aH}$ 35) has only a slight chance of leaving when $OH^-$ (p$K_{aH}$ 15) is an alternative. Nonetheless, at high temperatures, amides are slowly hydrolysed by concentrated base.



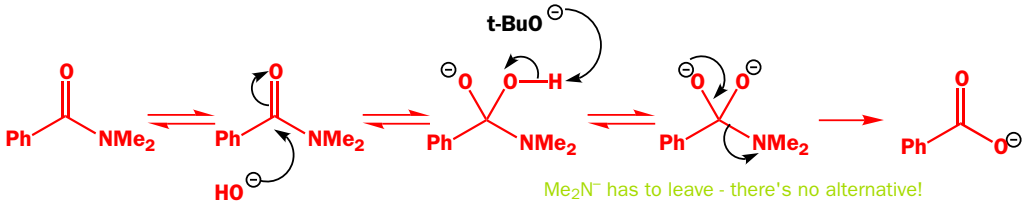
Secondary and tertiary amides hydrolyse much more slowly under these conditions. However, with a slightly different set of reagents, even tertiary amides can be hydrolysed at room temperature.



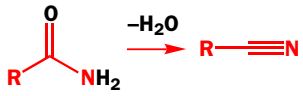

▶ You've not seen the option of $O^{2-}$ as a leaving group before but this is what you would get if you want $O^-$ to leave. Asking $O^{2-}$ to be a leaving group is like asking $HO^-$ to be an acid.

The reason is a change in mechanism. Potassium *tert*-butoxide is a strong enough base ($pK_{aH}$ 18) to deprotonate the tetrahedral intermediate in the reaction, forming a dianion. Now that the choice is between $Me_2N^-$ and $O^{2-}$, the $Me_2N^-$ has no choice but to leave, giving the carboxylate salt directly as the product.

▶ The hydrolysis of some amides in aqueous NaOH probably proceeds by a similar dianion mechanism—see Chapter 13.



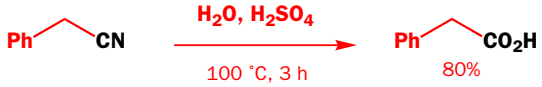

## Hydrolysing nitriles: how to make the almond extract, mandelic acid

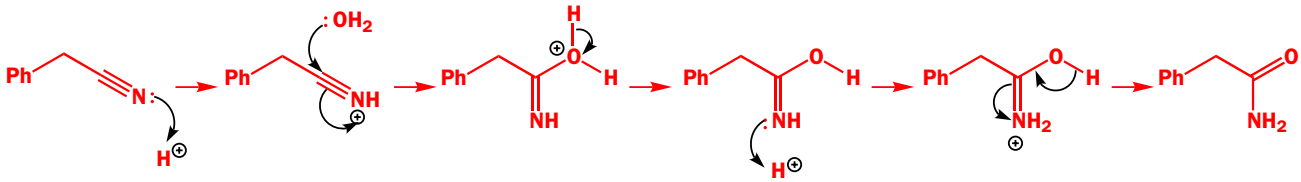



Closely related to the amides are nitriles. You can view them as primary amides that have lost one molecule of water and, indeed, they can be made by dehydrating primary amides.

They can be hydrolysed just like amides too. Addition of water to the protonated nitrile gives a primary amide, and hydrolysis of this amide gives carboxylic acid plus ammonia.

▶ Don't be put off by the number of steps in this mechanism—look carefully, and you will see that most of them are simple proton transfers. The only step that isn't a proton transfer is the addition of water.

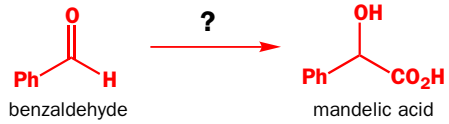


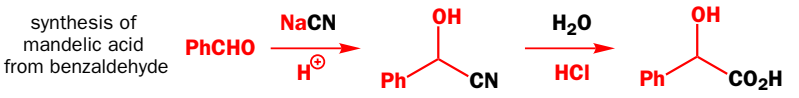

reminder: cyanohydrins from aldehydes


You met a way of making nitriles—from HCN (or NaCN + HCl) plus aldehydes—in Chapter 6: the hydroxynitrile products are known as **cyanohydrins**.

With this in mind, you should be able to suggest a way of making mandelic acid, an extract of almonds, from benzaldehyde.




This is how some chemists did it.



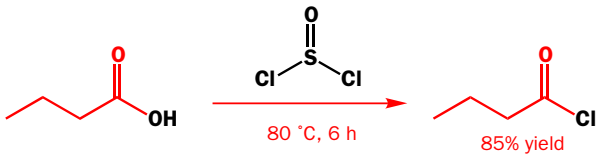

▶ You have just designed your first total synthesis of a natural product. We return to such things much later in this book, in Chapter 31.

## Acid chlorides can be made from carboxylic acids using $SOCl_2$ or $PCl_5$

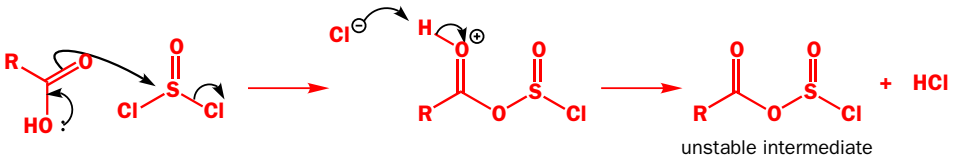
We have looked at a whole series of interconversions between carboxylic acid derivatives and, after this next section, we shall summarize what you should have learned. We said that it is always easy to move down the series of acid derivatives we listed early in the chapter and, so far, that is all we have

done. But some reactions of carboxylic acids also enable us to move upwards in the series. What we need is a reagent that changes the bad leaving group $HO^-$ into a good leaving group. Strong acid does this by protonating the $OH^-$, allowing it to leave as $H_2O$. In this section we look at two more reagents, $SOCl_2$ and $PCl_5$, which react with the OH group of a carboxylic acid and also turn it into a good leaving group. Thionyl chloride, $SOCl_2$, reacts with carboxylic acids to make acyl chlorides.

acid chlorides are made from carboxylic acids with thionyl chloride

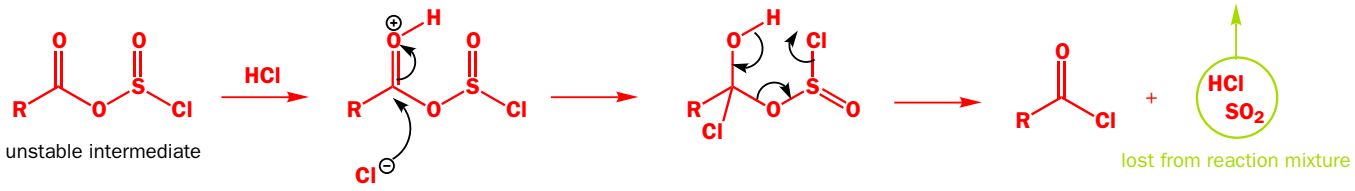



This volatile liquid with a choking smell is electrophilic at the sulfur atom (as you might expect with two chlorine atoms and an oxygen atom attached) and is attacked by carboxylic acids to give an unstable, and highly electrophilic, intermediate.



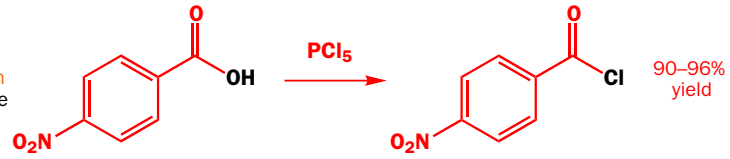

▶ You may be shocked to see the way we substituted at S=O without forming a 'tetrahedral intermediate'. Well, this trivalent sulfur atom is already tetrahedral (it still has one lone pair), and substitution can go by a direct '$S_N2$ at sulfur' (Chapter 17).

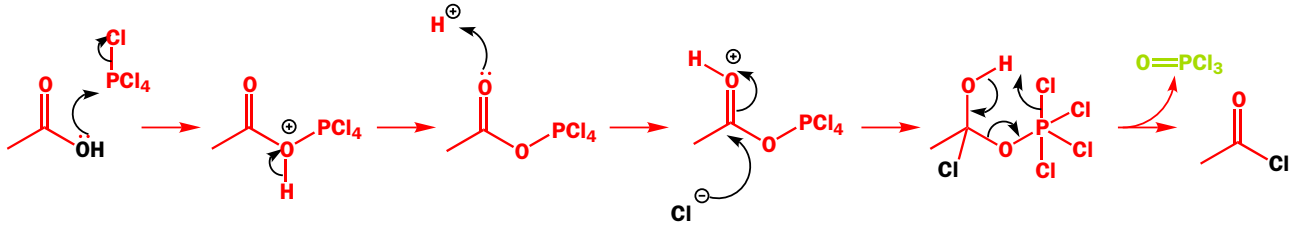
Protonation of the unstable intermediate (by the HCl just produced) gives an electrophile powerful enough to react even with the weak nucleophile $Cl^-$ (low $pK_{aH}$, poor nucleophilicity). The tetrahedral intermediate that results can collapse to the acyl chloride, sulfur dioxide, and hydrogen chloride. This step is irreversible because $SO_2$ and HCl are gases that are lost from the reaction mixture.




Although HCl is involved in this reaction, it cannot be used as the sole reagent for making acid chlorides. It is necessary to have a sulfur or phosphorus compound to remove the oxygen. An alternative reagent for converting $RCO_2H$ into RCOCl is phosphorus pentachloride, $PCl_5$. The mechanism is similar—try writing it out before looking at the scheme below.

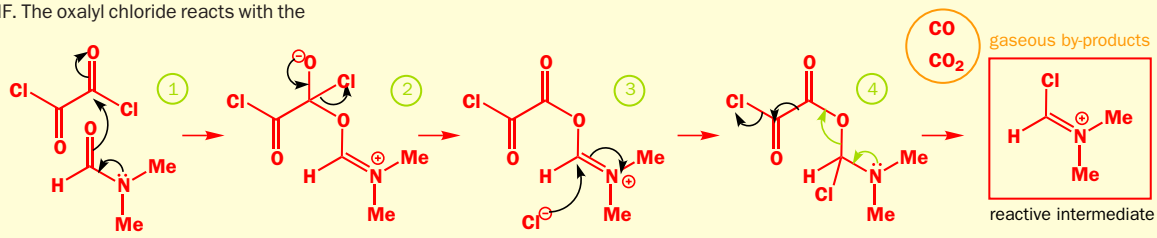
acid chlorides are made from carboxylic acids with phosphorus pentachloride



## An alternative method of making acid chlorides: oxalyl chloride plus DMF

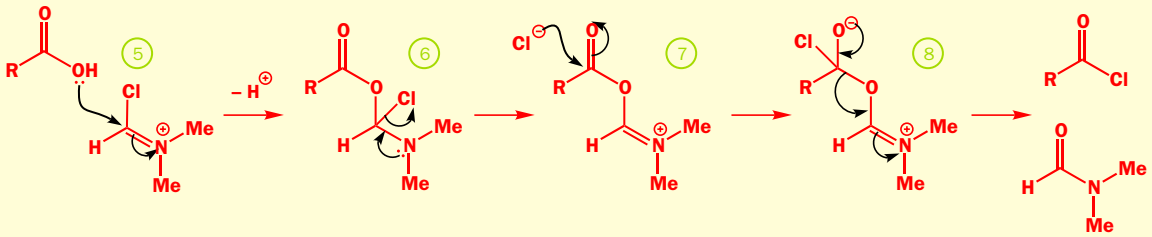
A modification of the thionyl chloride method for making acyl chlorides uses oxalyl chloride plus catalytic DMF. The oxalyl chloride reacts with the DMF in a rather remarkable way to produce a highly electrophilic cationic intermediate, plus CO and $CO_2$—as with the $SOCl_2$ reaction, the by-products are all gases.




A few aspects of this mechanism need comment.

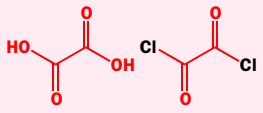
- The first two steps are simply a nucleophilic substitution of Cl at the carbonyl group, going via the now familiar tetrahedral intermediate
- Nucleophiles can attack the C=N bond (step 3) much as they might attack a C=O bond
- The black arrows in step 4 look very odd, but they are the only way we can draw the formation of carbon monoxide

The reactive intermediate is highly electrophilic and reacts rapidly with the carboxylic acid, producing another intermediate which intercepts $Cl^-$ to give the acyl chloride and regenerate DMF.

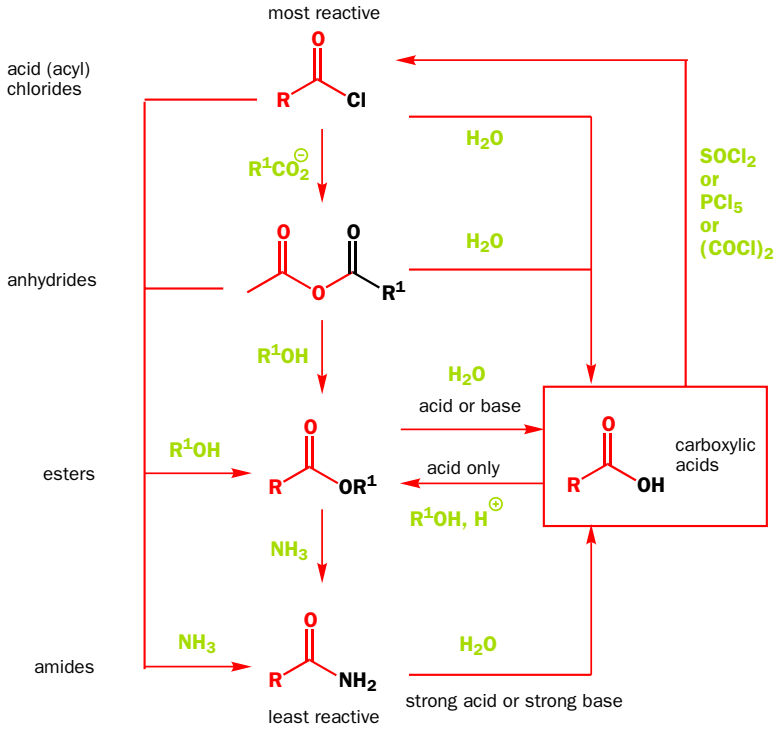



This method is usually used for producing small amounts of valuable acyl chlorides—oxalyl chloride is much more expensive than thionyl chloride. DMF will nonetheless also catalyse acyl chloride formation with thionyl chloride, though on a large scale its use may be ill advised since one of the minor by-products from these reactions is a potent carcinogen. We hope you enjoyed the eight-step mechanism.

▶ Oxalyl chloride, $(COCl)_2$, is the 'double' acid chloride of oxalic acid, or ethane-1,2-dioic acid, the toxic dicarboxylic acid found in rhubarb leaves.




These conversions of acids into acid chlorides complete all the methods we need to convert acids into any acid derivatives. You can convert acids directly to esters and now to acid chlorides, the most reactive of acid derivatives, and can make any other derivative from them. The chart below adds reactions to the reactivity order we met earlier.



All these acid derivatives can, of course, be hydrolysed to the acid itself with water alone or with various levels of acid or base catalysis depending on the reactivity of the derivative. To climb the reactivity order therefore, the simplest method is to hydrolyse to the acid and convert the acid into the acid chloride. You are now at the top of the reactivity order and can go down to whatever level you require.

## Making other compounds by substitution reactions of acid derivatives

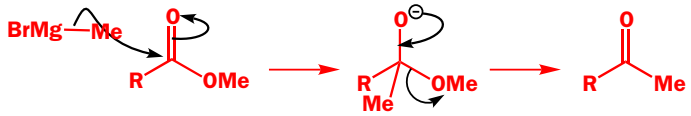
We've talked at length about the interconversions of acid derivatives, explaining the mechanism of attack of nucleophiles such as ROH, $H_2O$, and $NH_3$ on acyl chlorides, acid anhydrides, esters, acids, and amines, with or without acid or base present. We shall now go on to talk about substitution reactions of acid derivatives that take us out of this closed company of compounds and allow us to make compounds containing functional groups at other oxidation levels such as ketones and alcohols.

■ Five 'oxidation levels'—(1) $CO_2$; (2) carboxylic acid; (3) aldehyde and ketone; (4) alcohol; and (5) hydrocarbon—were defined in Chapter 2.

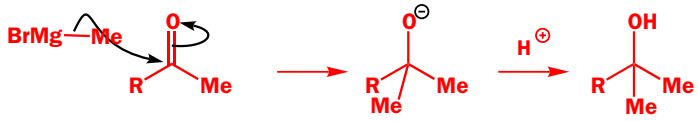
## Making ketones from esters: the problem

Substitution of the OR group of an ester by an R group would give us a ketone. You might therefore think that reaction of an ester with an organolithium or Grignard reagent would be a good way of making ketones. However, if we try the reaction, something else happens.


Two molecules of Grignard have been incorporated and we get an alcohol! If we look at the mechanism we can understand why this should be so. First, as you would expect, the nucleophilic Grignard reagent attacks the carbonyl group to give a tetrahedral intermediate. The only reasonable leaving group is $RO^-$, so it leaves to give us the ketone we set out to make.

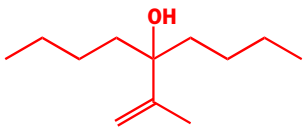



Now, the next molecule of Grignard reagent has a choice. It can either react with the ester starting material, or with the newly formed ketone. Ketones are more electrophilic than esters so the Grignard reagent prefers to react with the ketone in the manner you saw in Chapter 9. A stable alkoxide anion is formed, which gives the tertiary alcohol on acid work-up.

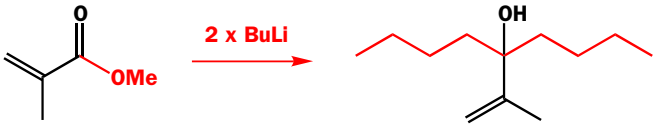



### Making alcohols instead of ketones

In other words, the problem here lies in the fact that the ketone product is more reactive than the ester starting material. We shall meet more examples of this general problem later (in Chapter 24, for example): in the next section we shall look at ways of overcoming it. Meanwhile, why not see it as a useful reaction? This compound, for example, was needed by some chemists in the course of research into explosives.

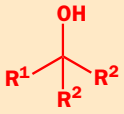



It is a tertiary alcohol with the hydroxyl group flanked by two identical R (= butyl) groups. The chemists who wanted to make the compound knew that an ester would react twice with the same organolithium reagent, so they made it from this unsaturated ester (known as methyl methacrylate) and butyllithium.



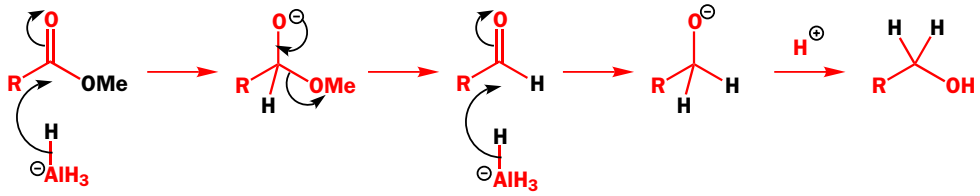

**Tertiary alcohol synthesis**

Tertiary alcohols with two identical $R^2$ groups can be made from ester plus two equivalents of organolithium or Grignard reagent.




This reaction works with R=H too if we use lithium aluminium hydride as the source of $H^-$. $LiAlH_4$ is a powerful reducing agent, and readily attacks the carbonyl group of an ester. Again, collapse of the tetrahedral intermediate gives a compound, this time an aldehyde, which is more reactive than the ester starting material, so a second reaction takes place and the ester is converted (reduced) into an alcohol.

reduction of esters by $LiAlH_4$

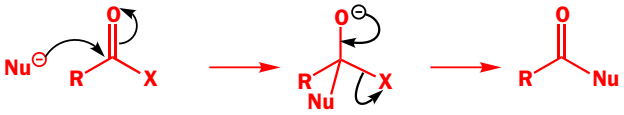



This is an extremely important reaction, and one of the best ways of making alcohols from esters. Stopping the reaction at the aldehyde stage is more difficult: we shall discuss this in Chapter 24.

## Another bit of shorthand

Before we go any further, we should introduce to you another little bit of chemical shorthand that makes writing many mechanisms easier.

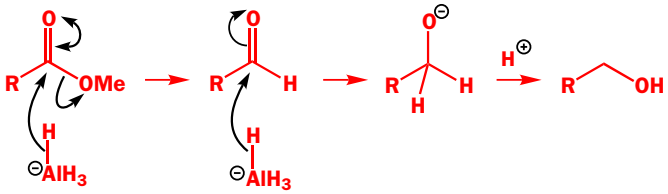
As you now appreciate, all substitution reactions at a carbonyl group go via a tetrahedral intermediate.




A convenient way to save writing a step is to show the formation and collapse of the tetrahedral intermediate in the same structure, by using a double-headed arrow like this.


Now, this is a useful shorthand, but it is not a substitute for understanding the true mechanism. Certainly, you must never ever write


Here's the 'shorthand' at work in the $LiAlH_4$ reduction you have just met.



# Making ketones from esters: the solution

We diagnosed the problem with our intended reaction as one of reactivity: the product ketone is more reactive than the starting ester. To get round this problem we need to do one of two things:

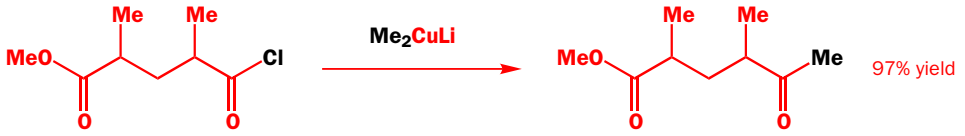
1. make the starting material more reactive *or*
2. make the product less reactive

## Making the starting materials more reactive

A more reactive starting material would be an acyl chloride: how about reacting one of these with a Grignard reagent? This approach can work: for example, this reaction is successful.


Notice how this reaction illustrates the difference in reactivity between an acyl chloride functional group and an ester functional group.

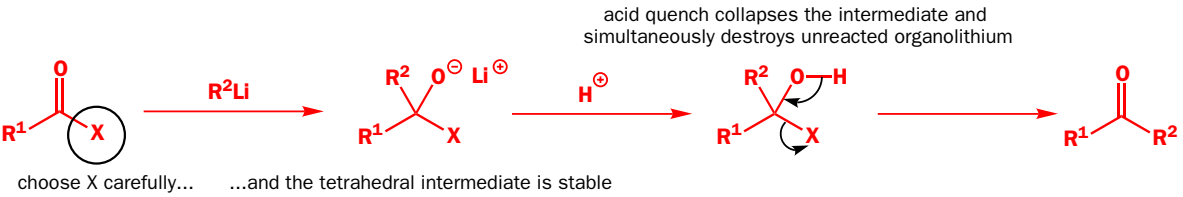
Often, better results are obtained by transmetallating (see Chapter 9) the Grignard reagent, or the organolithium, with copper salts. Organocopper reagents are too unreactive to add to the product ketones, but they react well with the acyl chloride. Consider this reaction, for example: the product was needed for a synthesis of the antibiotic septamycin.



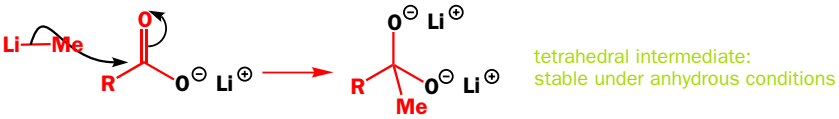

You met organocopper reagents in Chapter 10 where you saw that they did conjugate additions to α,β-unsaturated carbonyl compounds. Other metals, such as cadmium or manganese, can also be used to make ketones from acid chlorides.

## Making the products less reactive

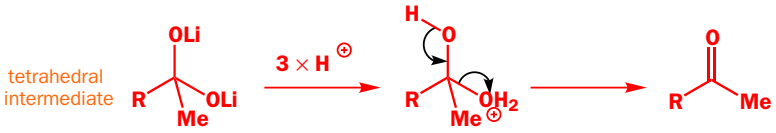
This alternative solution is often better. With the right starting material, the tetrahedral intermediate can become stable enough not to collapse to a ketone during the reaction; it therefore remains completely unreactive towards nucleophiles. The ketone is formed only when the reaction is finally quenched with acid but the nucleophile is also destroyed by the acid and none is left for further addition.




We can illustrate this concept with a reaction of an unlikely looking electrophile, a lithium carboxylate salt. Towards the beginning of the chapter we said that carboxylic acids were bad electrophiles and that carboxylate salts were even worse. Well, that is true, but with a sufficiently powerful nucleophile (an organolithium) it is just possible to get addition to the carbonyl group of a lithium carboxylate.

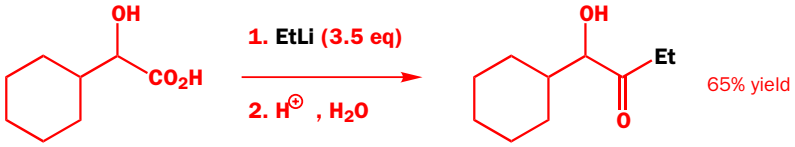



We could say that the affinity of lithium for oxygen means that the Li–O bond has considerable covalent character, making the $CO_2Li$ less of a true anion. Anyway, the product of this addition is a dianion of the sort that we met during one of the mechanisms of base-catalysed amide hydrolysis. But, in this case, there is no possible leaving group, so there the dianion sits. Only at the end of the reaction, when water is added, are the oxygen atoms protonated to give a hydrated ketone, which collapses immediately (remember Chapter 6) to give the ketone that we wanted. The water quench also destroys any remaining organolithium, so the ketone is safe from further attack.




This method has been used to make some ketones that are important starting materials for making cyclic natural products known as **macrolides**.

▶ Notice that three equivalents of organolithium are needed in this reaction: one to deprotonate the acid; one to deprotonate the hydroxyl group; and one to react with the lithium carboxylate. The chemists added a further 0.5 for good measure!




Another good set of starting materials that leads to noncollapsible tetrahedral intermediates is known as the **Weinreb amides**, after their inventor, S.M. Weinreb.


a Weinreb amide
(an *N*-methoxy-*N*-methyl amide)

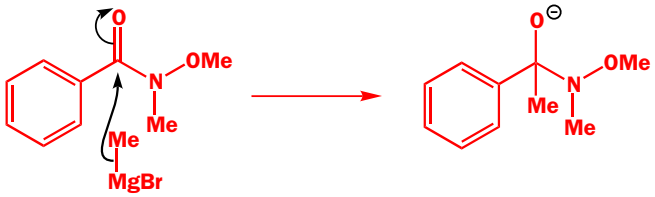
acyl chloride

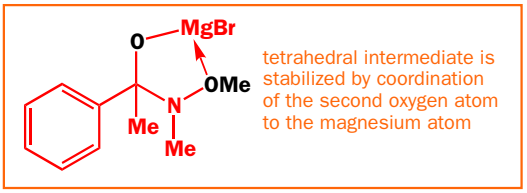
amine

▶ **Chelation** means the coordination of more than one electron-donating atom in a molecule to a single metal atom. The word derives from *chele*, the Greek for 'claw'.

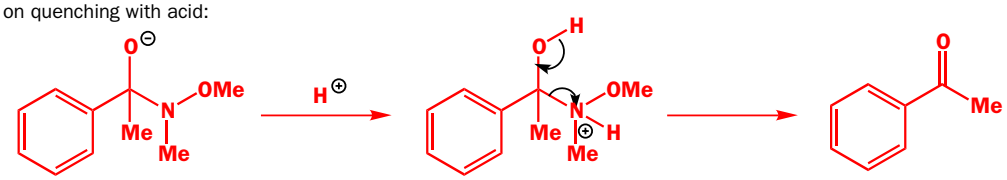
Addition of organolithium or organomagnesium reagents to *N*-methoxy-*N*-methyl amides gives a tetrahedral intermediate that is stabilized by *chelation* of the magnesium atom by the two oxygen atoms. This intermediate collapses, to give a ketone, only when acid is added at the end of the reaction.

during the reaction:

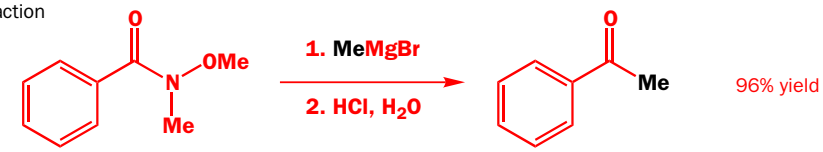


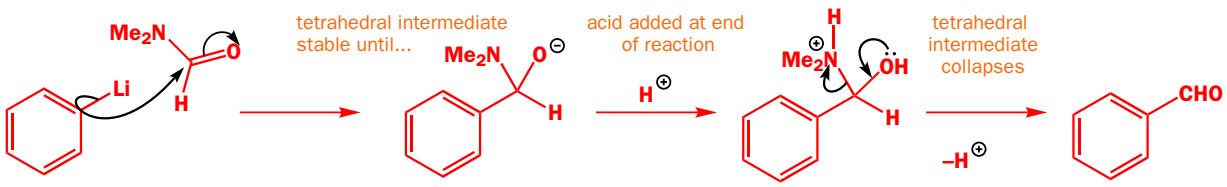

on quenching with acid:



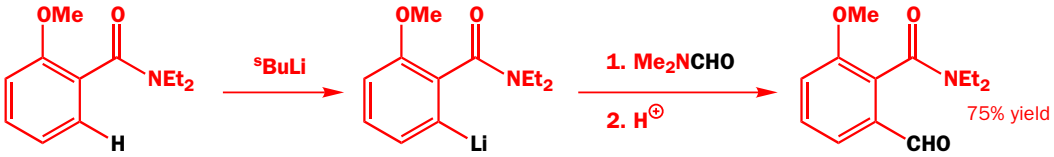

summary of reaction




This strategy even works for making aldehydes, if the starting material is dimethylformamide (DMF, $Me_2NCHO$).

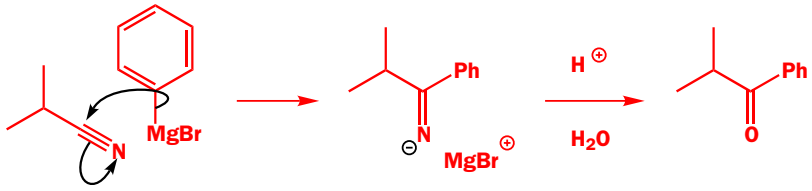


This is an extremely useful way of adding electrophilic CHO groups to organometallic nucleophiles. Here is an example. The first step is an 'ortholithiation' as described in Chapter 9.



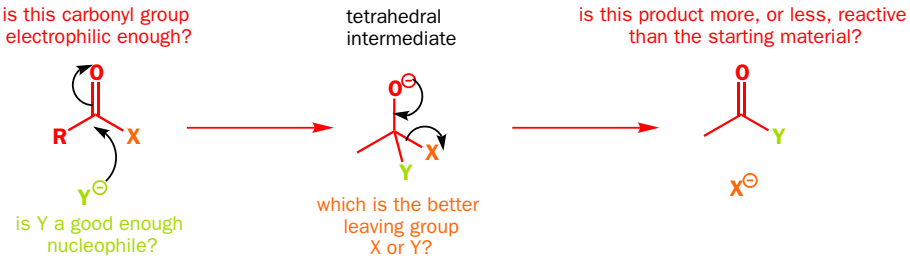

A final alternative is to use a nitrile instead of an ester.


The intermediate is the anion of an imine (see Chapter 14 for more about imines), which is not electrophilic at all—in fact, it's quite nucleophilic, but there are no electrophiles for it to react with until the reaction is quenched with acid. It gets protonated, and hydrolyses (we'll discuss this in the next chapter) to the ketone.




## To summarize...

To finish, we should just remind you of what to think about when you consider a nucleophilic substitution at a carbonyl group.

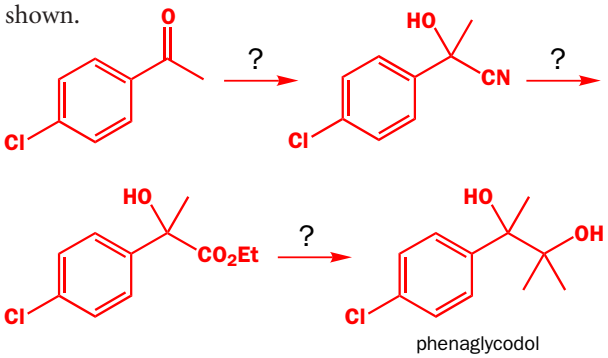



## And to conclude...

In this chapter you have been introduced to some important reactions—you can consider them to be a series of facts if you wish, but it is better to see them as the logical outcome of a few simple mechanistic steps. Relate what you have learned to what you gathered from Chapters 6 and 9, when we first started looking at carbonyl groups. All we did in this chapter was to build some subsequent transformations on to the simplest organic reaction, addition to a carbonyl group. You should have noticed that the reactions of all acid derivatives are related, and are very easily explained by writing out proper mechanisms, taking into account the presence of acid or base. In the next two chapters we shall see more of these acid- and base-catalysed reactions of carbonyl groups. Try to view them as closely related to the ones in this chapter—the same principles apply to their mechanisms.

# Problems

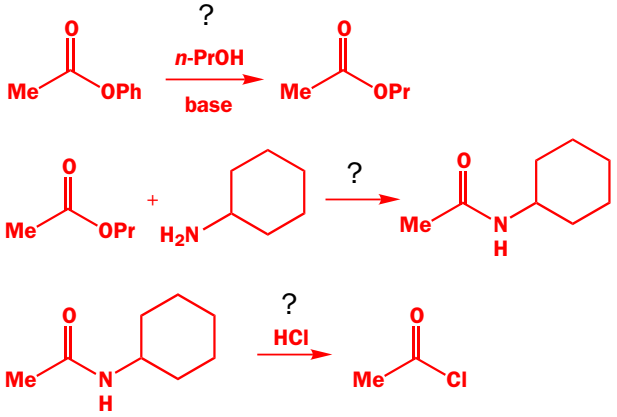
**1.** Suggest reagents to make the drug 'phenaglycodol' by the route shown.



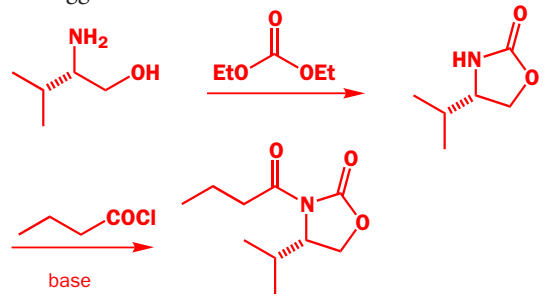

phenaglycodol

**2.** Direct ester formation from alcohols ($R^1OH$) and carboxylic acids ($R^2CO_2H$) works in acid solution but does not work at all in basic solution. Why not? By contrast, ester formation from alcohols ($R^1OH$) and carboxylic acid anhydrides, $(R^2CO)_2O$, or acid chlorides, RCOCl, is commonly carried out in the presence of amines such as pyridine or $Et_3N$. Why does this work?

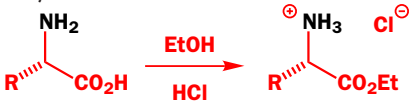
**3.** Predict the success or failure of these attempted nucleophilic substitutions at the carbonyl group. You should use estimated $pK_a$ or $pK_{aH}$ values in your answer and, of course, draw mechanisms.



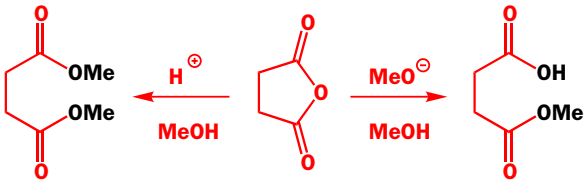

**4.** Suggest mechanisms for these reactions.



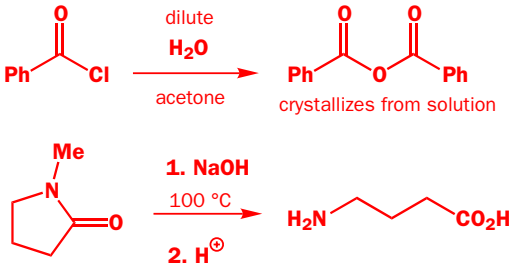

**5.** In making esters of the naturally occurring amino acids (general formula below) it is important to keep them as their hydrochloride salts. What would happen to these compounds if they were neutralized?



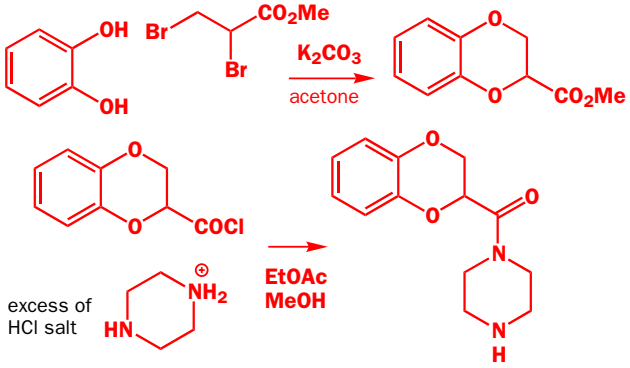

**6.** It is possible to make either the diester or the monoester of butanedioic acid (succinic acid) from the cyclic anhydride as shown. Why does the one method give the monoester and the other the diester?



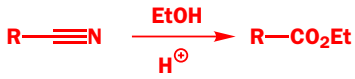

**7.** Suggest mechanisms for these reactions, explaining why these particular products are formed.



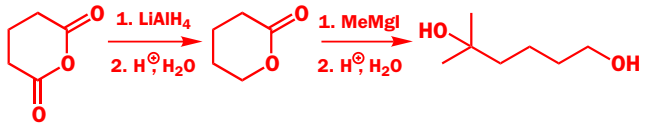

**8.** Here is a summary of part of the synthesis of Pfizer's heart drug Doxazosin (Cordura®). The mechanism for the first step will be a problem at the end of Chapter 17. Suggest reagent(s) for the conversion of the methyl ester into the acid chloride. In the last step, good yields of the amide are achieved if the amine is added as its hydrochloride salt in excess. Why is this necessary?



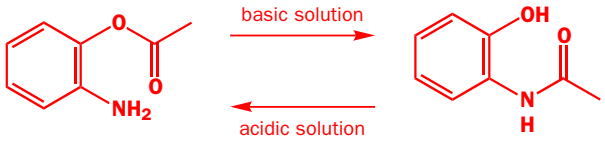
**9.** Esters can be made directly from nitriles by acid-catalysed reaction with the appropriate alcohol. Suggest a mechanism.



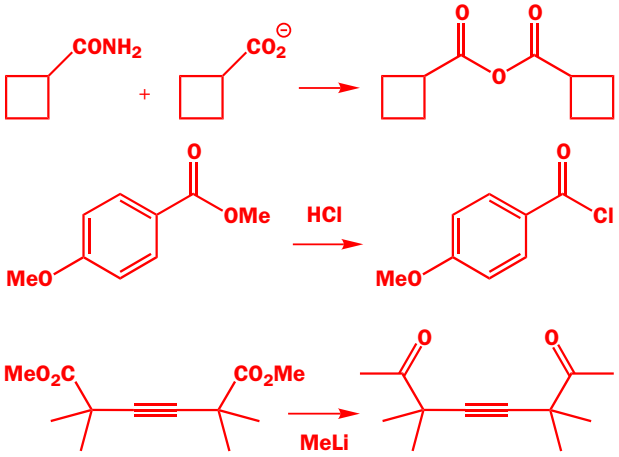

**10.** Give mechanisms for these reactions, explaining the selectivity (or lack of it!) in each case.




**11.** This reaction goes in one direction in acidic solution and in the other direction in basic solution. Draw mechanisms for the reactions and explain why the product depends on the conditions.




**12.** These reactions do not work. Explain the failures and suggest in each case an alternative method that might be successful.



# Equilibria, rates, and mechanisms: summary of mechanistic principles

# 13

## Connections

**Building on:**

- Structure of molecules ch4
- Drawing mechanisms ch5
- Nucleophilic attack on carbonyl groups ch6 & ch9
- Conjugate addition ch10
- Acidity and p$K_a$ ch8

**Arriving at:**

- What controls equilibria
- Enthalpy and entropy
- What controls the rates of reactions
- Intermediates and transition states
- How catalysts work
- Effects of temperature on reactions
- Why the solvent matters

**Looking forward to:**

- Kinetics and mechanism ch41
- Synthesis in action ch25
- How mechanisms are discovered ch41

One purpose of this chapter is to help you understand why chemists use such a vast range of different conditions when performing various organic reactions. If you go into any laboratory, you will see many reactions being heated to reflux; however, you will also see just as many being performed at –80 °C or even lower. You will see how changing the solvent in a reaction can drastically alter the time that a reaction takes or even lead to completely different products. Some reactions are over in a few minutes; others are left for hours under reflux. In some reactions the amounts of reagents are critical; in others large excesses are used. Why such a diverse range of conditions? How can conditions be chosen to favour the reaction we want? To explain all this we shall present some very basic thermodynamics but organic chemists do not want to get bogged down in algebra and energy profile diagrams will provide all the information we need.

■

'One could no longer just mix things; sophistication in physical chemistry was the base from which all chemists—including the organic—must start.' Christopher Ingold (1893–1970)

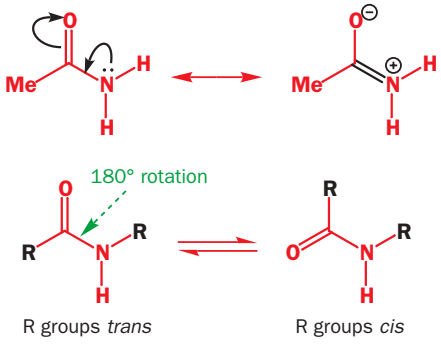
## How far and how fast?

We are going to consider which way (forwards or backwards) reactions go and by how much. We are going to consider how fast reactions go and what we can do to make them go faster or slower. We shall be breaking reaction mechanisms down into steps and working out which step is the most important. But first we must consider what we really mean by the 'stability' of molecules and what determines how much of one substance you get when it is in equilibrium with another.

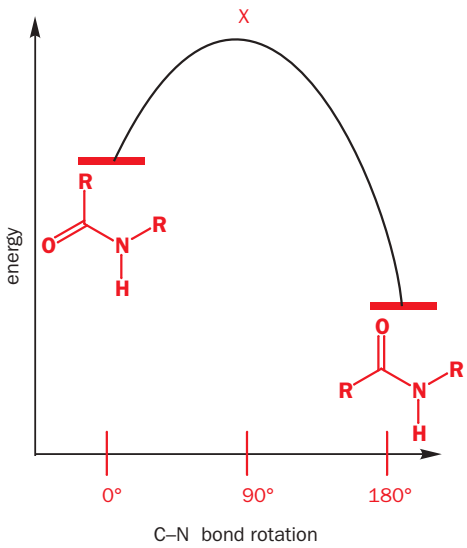
### Stability and energy levels

So far we have been rather vague about the term **stability** just saying things like 'this compound is more stable than that compound'. What we really mean is that one compound has more or less energy than another. This comparison is most interesting when two compounds can interconvert. For example, rotation about the C–N bond of an amide is slow because conjugation (Chapter 7) gives it some double-bond character.

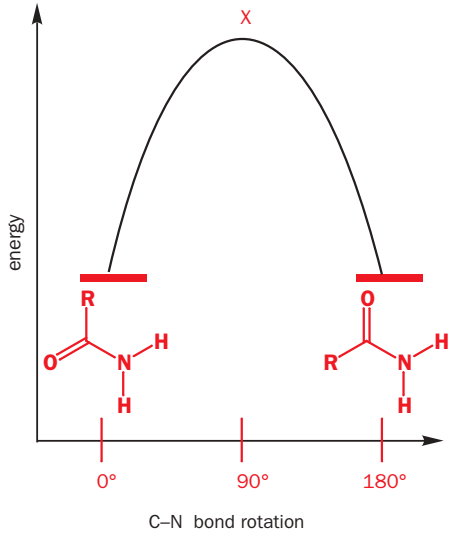
There is rotation, but it can be slow and can be measured by NMR spectroscopy. We can expect to find two forms of an amide of the type RNH–COR: one with the two R groups *trans* to one another, and one with them *cis*.




R groups *trans* R groups *cis*

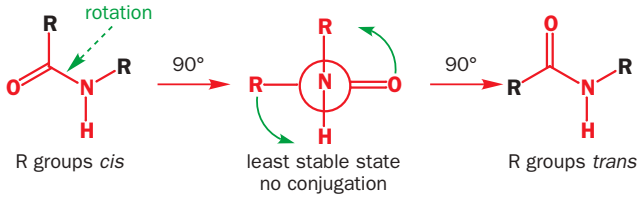



The two red lines show the energies of the molecules and the curved black line shows what must happen in energy terms as the two forms interconvert. Energy goes up as the C–N bond rotates and reaches a maximum at point X when rotation by 90° has removed the conjugation.

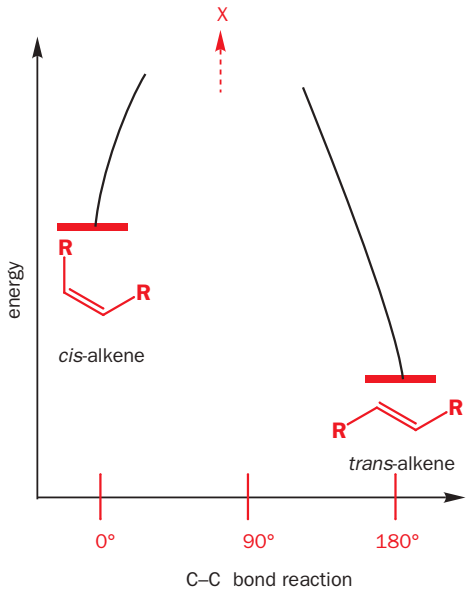



The process is the same but there is now no difference between the two structures and, if equilibrium is reached, there will be an exactly 50:50 ratio of the two arrangements. The equilibrium constant is $K = 1$. In other cases, we can measure the equilibrium constant by NMR spectroscopy. Another limit is reached if the bond is a full double bond as in simple alkenes instead of amides. Now the two states do not interconvert.

Depending on the size of R we should expect one form to be more stable than the other and we can represent this on an **energy profile diagram** showing the relationship between the two molecules in energy terms.

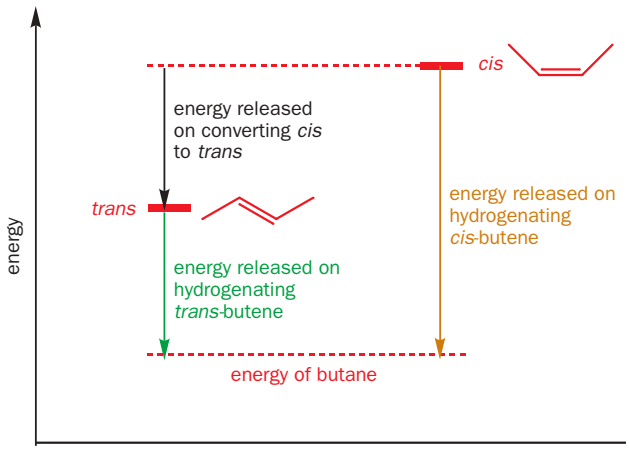


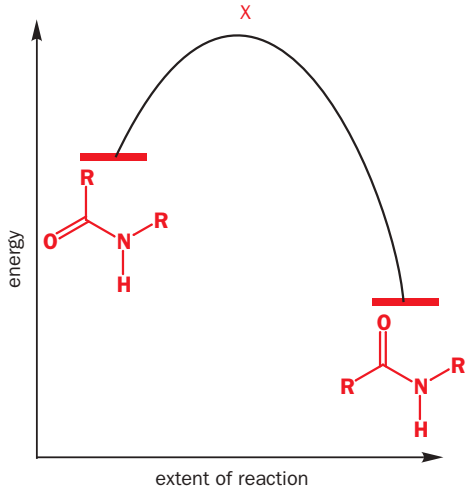

The relative energies of the two states will depend on the nature of R. The situation we have shown, with the *cis* arrangement being much less stable than the *trans*, would apply to large R groups. An extreme case would be if the substituent on nitrogen were H. Then the two arrangements would have equal energies.

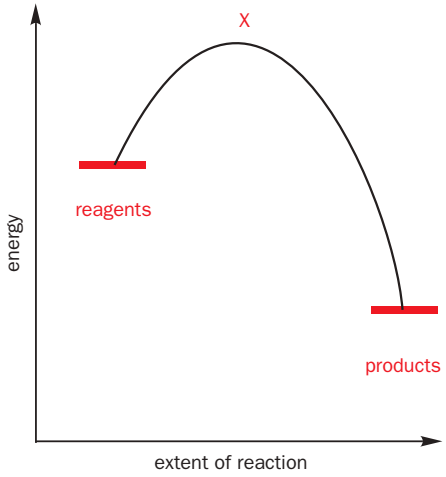


We can measure the energies of the two molecules by measuring the heat of hydrogenation of each isomer to give butane—the same product from both. The difference between the two heats of hydrogenation will be the difference in energy of *cis*- and *trans*-butene.

In more general terms, amide rotation is a simple example of an equilibrium reaction. If we replace 'rotation about the C–N bond' with 'extent of reaction' we have a picture of a typical reaction in which reagents and products are in equilibrium.




## How the equilibrium constant varies with the difference in energy between reactants and products

The equilibrium constant $K$ is related to the energy difference between starting materials and products by this equation

$$\Delta G^\circ = -RT \ln K$$

where $\Delta G^\circ$ (known as the **standard Gibbs energy** of the reaction) is the difference in energy between the two states (in kJ mol$^{-1}$), $T$ is the temperature (in kelvin *not* °C), and $R$ is a constant known as the **gas constant** and equal to 8.314 J K$^{-1}$ mol$^{-1}$.

This equation tells us that we can work out the **equilibrium composition** (how much of each component there is at equilibrium) provided we know the difference in energy between the products and reactants. Note that this difference in energy is not the difference in energy between the starting mixture and the mixture of products but the difference in energy if one mole of reactants had been completely converted to one mole of products.

### Chemical examples to show what equilibria mean

The equilibrium between isobutyraldehyde and its hydrate in water shows the relationship between $\Delta G^\circ$ and $K_{eq}$.

The equilibrium constant may be written to include $[H_2O]$; however, since the concentration of water effectively remains constant at 55.5 mol dm$^{-3}$ (p. 000), it is often combined into the equilibrium constant giving

$$K_{eq} = \frac{[\text{hydrate}]_{eq}}{[\text{aldehyde}]_{eq}}$$

The concentrations of hydrate and aldehyde at equilibrium in water may be determined by measuring the UV absorption of known concentrations of aldehyde in water and comparing these with the absorptions in a solvent such as cyclohexane where no hydrate formation is possible. Such experiments reveal that the equilibrium constant for this reaction in water at 25 °C is approximately 0.5 so that there is about twice as much aldehyde as hydrate in the equilibrium mixture. The corresponding value for $\Delta G°$ is $-8.314 \times 298 \times \ln(0.5) = +1.7$ kJ mol$^{-1}$. In other words, the solution of the hydrate in water is 1.7 kJ mol$^{-1}$ higher in energy than the solution of the aldehyde in water.

We could compare this reaction to the addition of an alkyllithium reagent to the same aldehyde. You met this reaction in Chapter 9.


The difference in energy between the starting materials, the aldehyde and methyllithium, and the products is so great that at equilibrium all we have are the products. In other words, this reaction is irreversible.

## The sign of $\Delta G°$ tells us whether products or reactants are favoured at equilibrium

Consider the equilibrium A⇌B. The equilibrium constant, $K_{eq}$, for this reaction is simply given by the expression

$$K_{eq} = \frac{[B]_{eq}}{[A]_{eq}}$$ where $[A]_{eq}$ represents the concentration of A at equilibrium.

If, at equilibrium, there is more B present than A, then $K$ will be greater than 1. This means that the natural log of $K$ will be positive and hence $\Delta G°$ (given by $-RT\ln K$) will be negative. Similarly, if A is favoured at equilibrium, $K$ will be less than 1, $\ln K$ negative, and hence $\Delta G°$ will be positive. If equal amounts of A and B are present at equilibrium, $K$ will be 1 and, since $\ln 1 = 0$, $\Delta G°$ will also be zero.

■ The sign of $\Delta G°$ for a reaction tells us whether the starting materials or products are favoured at equilibrium, but it tells us nothing about how long it will take before equilibrium is reached. The reaction could take hundreds of years! This will be dealt with later.

**● $\Delta G°$ tells us about the position of equilibrium**

- If $\Delta G°$ for a reaction is *negative*, the *products* will be favoured at equilibrium
- If $\Delta G°$ for a reaction is *positive*, the *reactants* will be favoured at equilibrium
- If $\Delta G°$ for a reaction is *zero*, the equilibrium constant for the reaction will be 1

## A small change in $\Delta G°$ makes a big difference in $K$

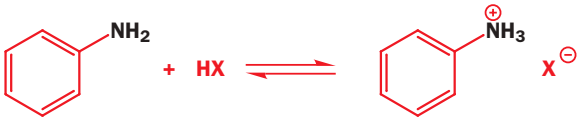
The tiny difference in energy between the hydrate and the aldehyde (1.7 kJ mol$^{-1}$) gave an appreciable difference in the equilibrium composition. This is because of the log term in the equation $\Delta G° = -RT\ln K$: relatively small energy differences have a very large effect on $K$. Table 13.1 shows the equilibrium constants, $K_{eq}$, that correspond to energy differences, $\Delta G°$, between 0 and 50 kJ mol$^{-1}$. These are relatively small energy differences—the strength of a typical C–C bond is about 350 kJ mol$^{-1}$—but the equilibrium constants change by enormous amounts.

In a typical chemical reaction, 'driving an equilibrium over to products' might mean getting, say, 98% of the products and only 2% of starting materials. You can see in the table that this requires an equilibrium constant of just over 50 and an energy difference of only 10 kJ mol$^{-1}$. This small energy difference is quite enough—after all, a yield of 98% is rather good!

**Table 13.1** Variation of $K_{eq}$ with $\Delta G°$

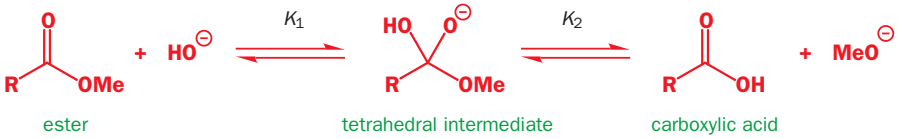
| $\Delta G°$, kJ mol$^{-1}$ | $K_{eq}$ | % of more stable state at equilibrium |
|---|---|---|
| 0 | 1.0 | 50 |
| 1 | 1.5 | 60 |
| 2 | 2.2 | 69 |
| 3 | 3.5 | 77 |
| 4 | 5.0 | 83 |
| 5 | 7.5 | 88 |
| 10 | 57 | 98 |
| 15 | 430 | 99.8 |
| 20 | 3 200 | 99.97 |
| 50 | 580 000 000 | 99.9999998 |

Aromatic amines such as aniline ($PhNH_2$) are insoluble in water. We saw in Chapter 8 that they can be dissolved in water by lowering the pH. We are taking advantage of the equilibrium between neutral amine and its ammonium ion. So how far below the p$K_{aH}$ of aniline do we have to go to get all of the aniline into solution?

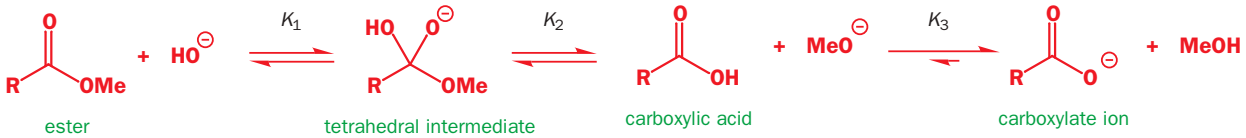



If the pH of a solution is adjusted to its p$K_{aH}$, by adding different acids there will be exactly 50% $PhNH_2$ and 50% $PhNH_3^+$. We need an equilibrium constant of about 50 to get 98% into the soluble form ($PhNH_3^+$) and we need to go only about 2 p$K_a$ units below the p$K_{aH}$ of aniline (4.6) to achieve this. All we need is quite a weak acid though in Chapter 8 we used HCl (p$K_a$ –7) which certainly did the trick!

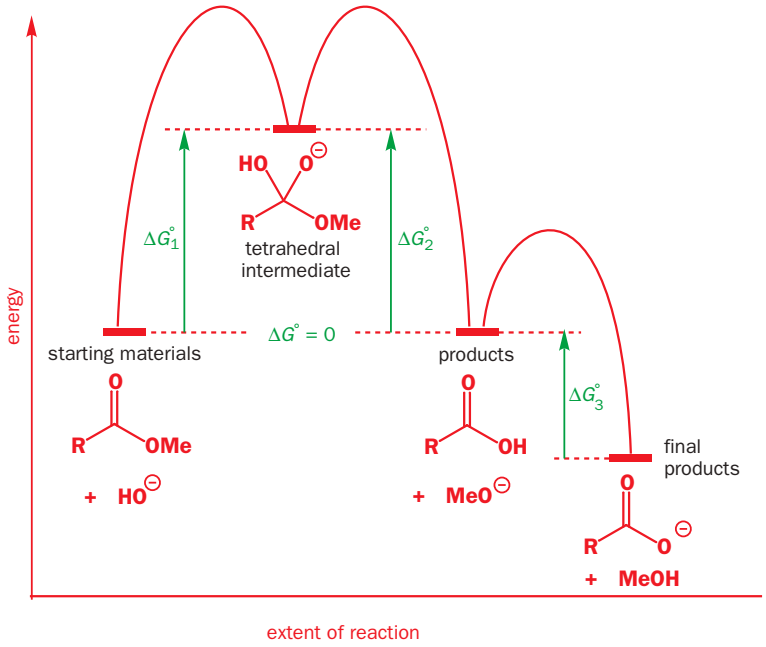
In Chapter 12 (p. 000) we looked at the hydrolysis of esters in basic solution. The decomposition of the tetrahedral intermediate could have occurred in either direction as $HO^-$ (p$K_{aH}$ 15.7) and $MeO^-$ (p$K_{aH}$ 16) are about the same as leaving groups. In other words $K_1$ and $K_2$ are about the same and both equilibria favour the carbonyl compound (ester or carboxylic acid).




This reaction would therefore produce a roughly 50:50 mixture of ester and carboxylic acid if this were the whole story. But it isn't because the carboxylic acid will be deprotonated in the basic solution adding a third equilibrium.




Though $K_1$ and $K_2$ are about the same, $K_3$ is very large (p$K_a$ of $RCO_2H$ is about 5 and p$K_a$ of MeOH is 16 so the difference between the two $K_a$s is about $10^{11}$) and it is this equilibrium that drives the reaction over to the right. For the same reason (because $K_3$ is very large), it is impossible to form esters in basic solution. This situation can be summarized in an energy diagram showing that the energy differences corresponding to $K_1$ and $K_2$ ($\Delta G_1°$ and $\Delta G_2°$) are the same so that $\Delta G°$ between $RCO_2Me$ + $HO^-$, on the one hand, and $RCO_2H$ + $MeO^-$, on the other, is zero. Only the energy difference for $K_3$ provides a negative $\Delta G°$ for the whole reaction.




# How to make the equilibrium favour the product you want

## The direct formation of esters

The formation and hydrolysis of esters was discussed in Chapter 12 where we established that acid and ester are in equilibrium and that the equilibrium constant is about one.

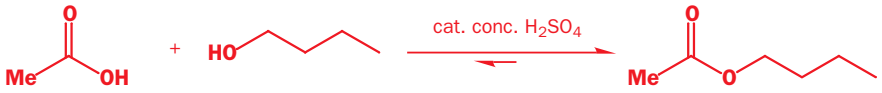

If we stew up equal amounts of carboxylic acid, alcohol, ester, and water and throw in a little acid to catalyse the reaction (we shall see exactly how this affects the reaction profile later), we find that the equilibrium mixture consists of about equal amounts of ester and carboxylic acid. The position of the equilibrium favours neither the starting materials or the products. The question now arises: how can we manipulate the conditions of the reaction if we actually want to make 100% ester?

The important point is that, at any one particular temperature, the equilibrium constant is just that—*constant*. This gives us a means of forcing the equilibrium to favour the products (or reactants) since the ratio of the two must remain constant. Therefore, if we increase the concentration of the reactants (or even that of just one of the reactants), more products must be produced to keep the equilibrium constant. One way to make esters in the laboratory is to use a large excess of the alcohol and remove water continually from the system as it is formed, for example by distilling it out. This means that in the equilibrium mixture there is a tiny quantity of water, lots of the ester, lots of the alcohol, and very little of the carboxylic acid; in other words, we have converted the carboxylic acid into the ester. We must still use an acid catalyst, but the acid must be anhydrous since we do not want any water present—commonly used acids are toluene sulfonic acid (tosic acid, TsOH), concentrated sulfuric acid ($H_2SO_4$), or gaseous HCl. The acid catalyst does not alter the position of the equilibrium; it simply speeds up the rate of the reaction, allowing equilibrium to be reached more quickly.

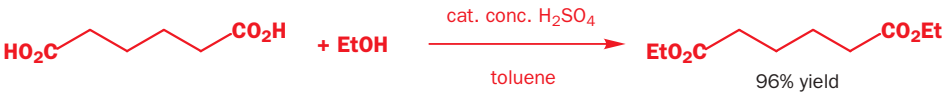
- To make the ester

  Reflux the carboxylic acid with an excess of the alcohol (or the alcohol with an excess of the carboxylic acid) with about 3–5% of a mineral acid (usually HCl or $H_2SO_4$) as a catalyst and distil out the water that is formed in the reaction. For example: butanol was heated under reflux with a

fourfold excess of acetic acid and a catalytic amount of concentrated $H_2SO_4$ to give butyl acetate in a yield of 70%.




It may also help to distil out the water that is formed in the reaction: diethyl adipate (the diethyl ester of hexanedioic acid) can be made in toluene solution using a sixfold excess of ethanol, concentrated $H_2SO_4$ as catalyst, distilling out the water using a Dean Stark apparatus. You can tell from the yield that the equilibrium is very favourable.



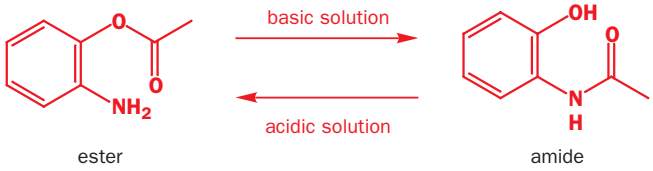

In these cases the equilibrium is made more favourable by using an excess of reagents and/or removing one of the products. The equilibrium constant remains the same. High temperatures and acid catalysis are used to speed up arrival at equilibrium which would otherwise take days.

- To hydrolyse the ester

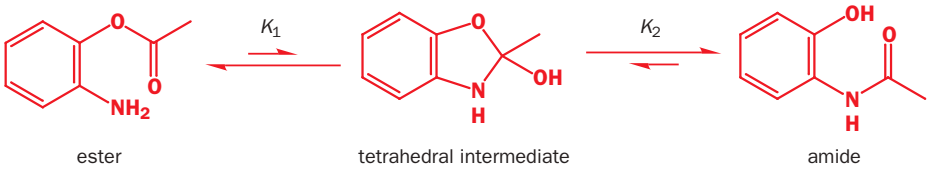
  Simple: reflux the ester with aqueous acid or alkali.

## The equilibrium between esters and amides

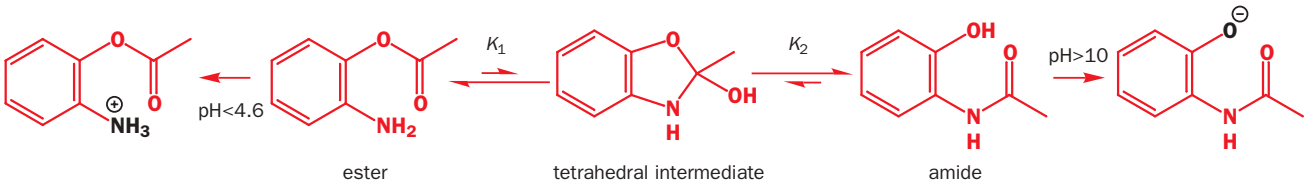
If you solved Problem 12 at the end of the last chapter, you will already know of one reaction that can be driven in either direction by a selection of acidic or basic reaction conditions. The reaction is the interconversion of an ester and an amide and one would normally expect the reaction to favour the amide because of the greater stability of amides due to the more efficient conjugation of the lone pair on nitrogen.



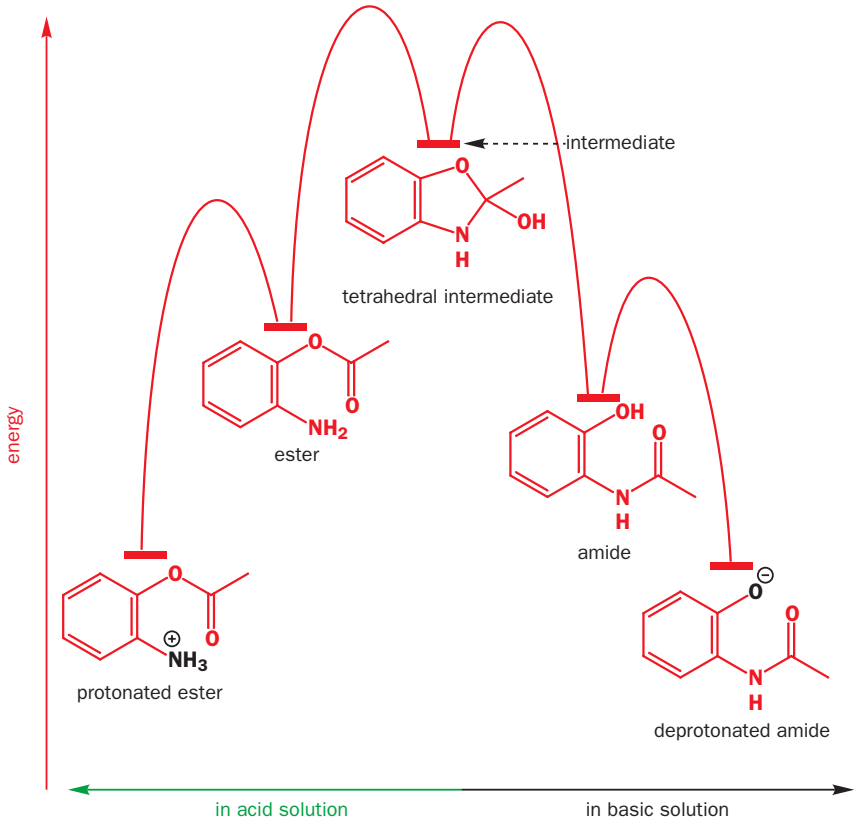

If we examine the mechanism for the reaction it is clear that $ArO^-$ ($pK_{aH}$ ~10) is a better leaving group than $ArNH^-$ ($pK_{aH}$ ~25) and so the equilibria between the two compounds and the tetrahedral intermediate are like this.




The two individual equilibria favour the carbonyl compounds over the tetrahedral intermediate but $K_1 < K_2$ so the overall equilibrium favours the amide. However, two new equilibria must be added to these if the variation of pH is considered too. In acid solution the amine will be protonated and in base the phenol will be deprotonated.




The energy profile for this equilibrium can be studied from either left or right. It is easiest to imagine the tetrahedral intermediate going to the left or to the right depending on the acidity of the solution.




We have shown these last equilibria as reactions because they can be pushed essentially to completion by choosing a pH above 10 if we want the amide or below 4 if we want the ester. This is a relatively unusual situation but there are many other cases where reactions can be driven in either direction by choice of conditions.

## Entropy is important in determining equilibrium constants

The *position* of equilibrium (that is, the equilibrium constant, which tells us in a chemical reaction whether products or reactants are favoured) is determined by the energy difference between the two possible states: in the case of the amide $RCONH_2$, there is no difference so the equilibrium constant is one; in the case of the amide RCONHR with large R groups, the arrangement with R groups *trans* is of lower energy than the state with R groups *cis*, and so the equilibrium constant is in favour of the *trans* isomer.

Even when there is a difference in energy between the two states, we still get some of the less stable state. This is because of entropy. *Why* we get the mixture of states is purely down to entropy—there is greater disorder in the mixture of states, and it is to maximize the overall entropy that the equilibrium position is reached.

### Energy differences: $\Delta G°$, $\Delta H°$, and $\Delta S°$—energy, enthalpy, and entropy

Returning to that all important equation: $\Delta G° = -RT \ln K$, the sign and magnitude of the energy $\Delta G°$ are the only things that matter in deciding whether an equilibrium goes in one direction or another. If $\Delta G°$ is negative the equilibrium will favour the products (the reaction goes) and if $\Delta G°$ is large and negative the reaction goes to completion. It is enough for $\Delta G°$ to be only about $-10$ kJmol$^{-1}$ to get complete reaction. The Gibbs energy, $\Delta G°$, the enthalpy of reaction, $\Delta H°$, and the entropy of reaction, $\Delta S°$, are related via the equation

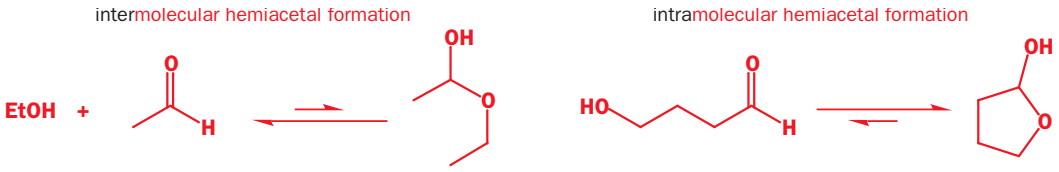
$$\Delta G° = \Delta H° - T\Delta S°$$

The change in enthalpy $\Delta H°$ in a chemical reaction is the heat given out (at constant pressure). Since breaking bonds requires energy and making bonds liberates energy, the enthalpy change gives an indication of whether the products have more stable bonds than the starting materials or not. $T$ is the temperature, in kelvin, at which the reaction is carried out. Entropy, $S$, is a measure of the disorder in the system. A mixture of products and reactants is more disordered than either pure products or pure reactants alone. $\Delta S°$ represents the entropy difference between the starting materials and the products.

The equation $\Delta G° = \Delta H° - T\Delta S°$ tells us that how $\Delta G°$ varies with temperature depends mainly on the entropy change for the reaction ($\Delta S°$). We need these terms to explain the temperature dependence of equilibrium constants and to explain why some reactions may absorb heat (endothermic) while others give out heat (exothermic).

## Enthalpy versus entropy—an example

Entropy dominates equilibrium constants in the difference between inter- and intramolecular reactions. In Chapter 6 we explained that hemiacetal formation is unfavourable because the C=O double bond is more stable than two C–O single bonds. This is clearly an enthalpy factor depending simply on bond strength. That entropy also plays a part can be clearly seen in favourable intramolecular hemiacetal formation of hydroxyaldehydes. The total number of carbon atoms in the two systems is the same, the bond strengths are the same and yet the equilibria favour the reagents (MeCHO + EtOH) in the inter- and the product (the cyclic hemiacetal) in the intramolecular case.




The difference is one of entropy. In the first case two molecules would give one with an increase in order as, in general, lots of things all mixed up have more entropy than a few large things (when you drop a bottle of milk, the entropy increases dramatically). In the second case one molecule gives one molecule with little gain or loss of order. Both reactions have negative $\Delta S°$ but it is more negative in the first case.

There is some discussion of entropy in related reactions in Chapter 6.

## The acidity of chloroacids

In Chapter 8 we saw how increasing the number of electronegative substituents on a carboxylic acid decreased the acid's p$K_a$, that is, increased its acidity. Acid strength is a measure of the equilibrium constant for this simple reaction.


For this equilibrium as for others, the all important equations $\Delta G° = -RT\ln K$ and $\Delta G° = \Delta H° - T\Delta S°$ apply. When the breakdown of $\Delta G°$ for acid ionization was explored, entropy proved to be more important than was expected. Take for example the series $CH_3COOH$, $CH_2ClCOOH$, $CHCl_2COOH$, and $CCl_3COOH$ with p$K_a$s 7.74, 2.86, 1.28, and 0.52, respectively. If the increase in acidity were simply due to the stabilization of the conjugate base $RCO_2^-$ by the electronegative groups (C–Cl bonds), this would be reflected in the enthalpy difference $\Delta H°$ between the conjugate base and the acid. The enthalpy change takes into account the loss of the O–H bond on ionization of the acid and also the difference in solvations between the acid and the ions it produces (H bonds between $RCO_2H$ and water and between $RCO_2^-$ and water). However the data (see table below) show that the difference in equilibrium constant is determined more by entropy than by enthalpy. $\Delta H°$ changes by only 6 kJ mol$^{-1}$ over the whole series while $\Delta S°$ changes by nearly 100 J K$^{-1}$ mol$^{-1}$ and the more directly comparable $T\Delta S$ changes by over 25 kJ mol$^{-1}$.

| Acid | $pK_a$ | $\Delta H°$, kJ mol$^{-1}$ | $\Delta S°$, J K$^{-1}$ mol$^{-1}$ | $-T\Delta S°$, kJ mol$^{-1}$ | $\Delta G°$, kJ mol$^{-1}$ |
|---|---|---|---|---|---|
| $CH_3COOH$ | 4.76 | –0.08 | –91.6 | 27.3 | 27.2 |
| $CH_2ClCOOH$ | 2.86 | –4.6 | –70.2 | 20.9 | 16.3 |
| $CHCl_2COOH$ | 1.28 | –0.7 | –27 | 8.0 | 7.3 |
| $CCl_3COOH$ | 0.52 | 1.2 | –5.8 | 1.7 | 2.9 |

The entropy change depends on the difference in 'order' between the reactants and products. Going from one species (the undissociated acid) to two (the proton and conjugate base) gives an increase in entropy. This in turn makes $\Delta G°$ more negative and so favours the dissociation. But the solvent structure also changes during the reaction. If a species is strongly solvated, it has many solvent molecules tightly associated with it; in other words, the solvent surrounding it is more ordered. As a weakly solvated neutral acid ionizes to two strongly solvated ions, the neighbouring solvent becomes more ordered and the *overall* entropy decreases.

As we expect, the $pK_a$ decreases as more electronegative chlorines are substituted for the hydrogen atoms in acetic acid. However, the enthalpy change for the ionization remains approximately the same—the decrease in $\Delta G°$ is predominantly due to the increase in the entropy change for the reaction. With the increasing numbers of chlorine atoms, the negative charge on the conjugate base is more spread out. The less concentrated the charge, the less order is imposed on the neighbouring solvent molecules and so $\Delta S°$ becomes less negative.

Because such trends in $pK_a$ are often determined by the entropy change of the whole system, the order of $pK_a$s may change in solvents where there is less solvation and be different again in the gas phase where there are no solvent effects at all. For example, whilst the $pK_a$ of water is usually 15.74, in dimethyl sulfoxide (DMSO) it is about 29. This is because, in DMSO, the hydroxide ion is no longer as effectively solvated as it was in water and this makes the base much stronger.

## Equilibrium constants vary with temperature

We have said that the equilibrium constant is a constant only so long as the temperature does not change. Exactly how the equilibrium constant varies with temperature depends on whether the reaction is exothermic or endothermic. If the reaction is **exothermic** (that is, gives out heat) then at higher temperatures the equilibrium constant will be smaller. For an **endothermic** reaction, as the temperature is increased, the equilibrium constant increases. Putting our all important equations $\Delta G° = -RT\ln K$ and $\Delta G° = \Delta H° - T\Delta S°$ together we see that $-RT\ln K = \Delta H° - T\Delta S°$. If we divide throughout by $-RT$ we have

$$\ln K = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R}$$

The equilibrium constant $K$ can be divided into enthalpy and entropy terms but it is the enthalpy term that determines how $K$ varies with temperature. Plotting $\ln K$ against $1/T$ would give us a straight line with slope $-\Delta H°/R$ and intercept $\Delta S°$. Since $T$ (the temperature in Kelvin) is always positive, whether the slope is positive or negative depends on the sign of $\Delta H°$: if it is positive then, as temperature increases, $\ln K$ (and hence $K$) increases. In other words, for an endothermic reaction ($\Delta H$ positive), as $T$ increases, $K$ ([products]/[reactants]) increases which in turn means that more products must be formed.

### Thermodynamics for the organic chemist

- The free energy change $\Delta G°$ in a reaction is proportional to $\ln K$ (that is, $\Delta G° = -RT\ln K$)
- $\Delta G°$ and $K$ are made up of enthalpy and entropy terms (that is, $\Delta G° = \Delta H° - T\Delta S°$)
- The enthalpy change $\Delta H°$ is the difference in stability (bond strength) of the reagents and products
- The entropy change $\Delta S°$ is the difference between the disorder of the reagents and that of the products
- The enthalpy term alone determines how $K$ varies with temperature

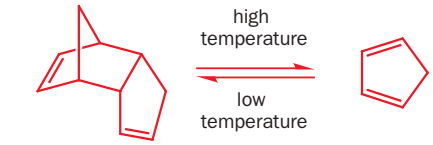
### Le Chatelier's principle

You may well be familiar with a rule that helps to predict how a system at equilibrium responds to a change in external conditions—**Le Chatelier's principle**. This says that if we disturb a system at equilibrium it will respond so as to minimize the effect of the disturbance. An example of a disturbance is adding more starting material to a reaction mixture at equilibrium. What happens? More product is formed to use up this extra material. This is a consequence of the equilibrium constant being, well... constant and hardly needs anybody's principle.

Another disturbance is heating. If a reaction under equilibrium is heated up, how the equilibrium changes depends on whether the reaction is exothermic or endothermic. If is exothermic (that is, gives out heat), Le Chatelier's principle would predict that, since heat is consumed in the *reverse* reaction, more of the starting materials will be formed. Again no 'principle' is needed—this change occurs because the equilibrium constant is smaller at higher temperatures in an exothermic reaction. Le Chatelier didn't know about equilibrium constants or about $-RT\ln K = \Delta H^\circ - T\Delta S^\circ$ so he needed a 'principle'. You know the reasons and they are more important than rules.

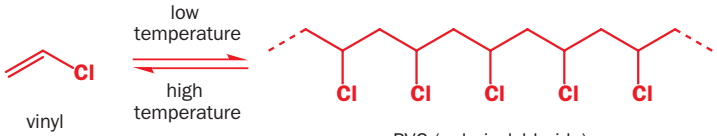
### Some reactions are reversible on heating

Simple dimerization reactions will favour the dimer at low temperatures and the monomer at high temperatures. Two monomer molecules have more entropy than one molecule of the dimer. An example is the dimerization of cyclopentadiene. On standing, cyclopentadiene dimerizes and if monomeric material is needed the dimer must be heated and the monomer used immediately. If you lazily leave the monomer overnight and plan to do your reaction tomorrow, you will return in the morning to find dimer.




cyclopentadiene dimer — cyclopentadiene

This idea becomes even more pointed when we look at polymerization. Polyvinyl chloride is the familiar plastic PVC and is made by reaction of large numbers of monomeric vinyl chloride molecules. There is, of course, an enormous decrease in entropy in this reaction and any polymerization will not occur above a certain temperature. Some polymers can be depolymerized at high temperatures and this can be the basis for recycling.




vinyl chloride — PVC (polyvinylchloride)

■ This chemistry does not appear until Chapter 35 but you do not need to know the mechanism of the reaction to appreciate the idea.

■ Polymerization does not appear until Chapter 52 but you do not need to know the details to appreciate the idea.

▶ Everything decomposes at a high enough temperature eventually giving atoms. This is because the entropy for lots of particles all mixed up is much greater than that of fewer larger particles.

## Making reactions go faster: the real reason reactions are heated

Although in organic laboratories you will see lots of reactions being heated, very rarely will this be to alter the equilibrium position. This is because most reactions are not carried out reversibly and so the ratio of products to reactants is not an equilibrium ratio. The main reason chemists heat up reactions is simple—it speeds them up.

### How fast do reactions go?—activation energies

Using tables of thermodynamic data, it is possible to work out the energy differences for many different reactions at different temperatures. For example, for the combustion of isooctane, $\Delta G^\circ$ (at 298 K) = –1000 kJ mol$^{-1}$.


isooctane

We have seen in Table 13.1 on p. 000 that even a difference of 50 kJ mol$^{-1}$ gives rise to a huge equilibrium constant: –1000 kJ mol$^{-1}$ gives an equilibrium constant of $10^{175}$ (at 298 K), a number too

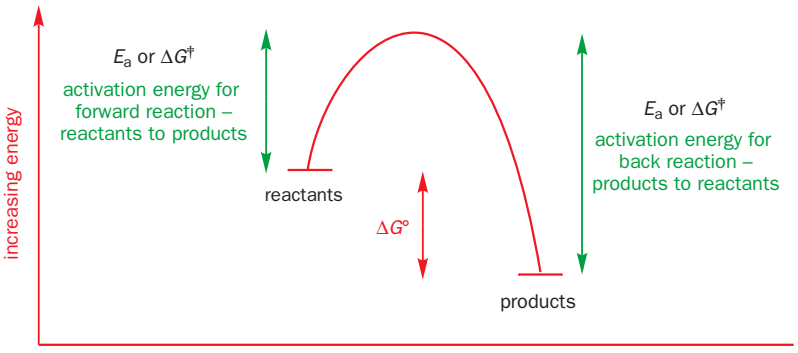
■ Isooctane (2,2,4-trimethylpentane) is a major component of petrol (gasoline). Strictly speaking, if we follow the standard meaning for 'iso' (p. 000), the name isooctane should be reserved for the isomer 2-methylheptane. However, 2,2,4-trimethylpentane is by far the most important isomer of octane and so, historically, it has ended up with this name.

vast to contemplate (there are only about $10^{86}$ atoms in the observable universe). This value of $\Delta G^\circ$ (or the corresponding value for the equilibrium constant) suggests that isooctane simply could not exist in an atmosphere of oxygen and yet we put it into the fuel tanks of our cars every day—clearly something is wrong.

Since isooctane can exist in an atmosphere of oxygen despite the fact that the equilibrium position really is completely on the side of the combustion products, the only conclusion we can draw must be that a mixture of isooctane and oxygen cannot be at equilibrium. A small burst of energy is needed to reach equilibrium: in a car engine, the spark plug provides this energy and combustion occurs. If no such burst of energy is applied, the petrol would continue to exist for a long time. The mixture of petrol and air is said to be *kinetically* stable but *thermodynamically* unstable with respect to the products of the reaction, $CO_2$ and $H_2O$. If the same small energy burst is applied to the products, they do not convert back to petrol and oxygen.

The energy required to overcome the barrier to reaction is called the **activation energy** and is usually given the symbols $E_a$ or $\Delta G^\ddagger$. An energy level diagram for a reaction such as the combustion of isooctane is shown below.

▶ $E_a$ and $\Delta G^\ddagger$ are both used for the activation energy and are almost the same. There are subtle differences that do not concern us here.




Points to notice:

- The products are lower in energy than the reactants as the equilibrium position lies in favour of the products
- The activation energy for the forward reaction is less than the activation energy for the back reaction

If a reaction cannot proceed until the reactants have sufficient energy to overcome the activation energy barrier, it is clear that, the smaller the barrier, the easier it will be for the reaction to proceed. In fact the activation energy is related to how fast the reaction proceeds by another exponential equation

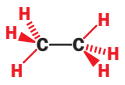
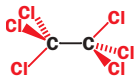
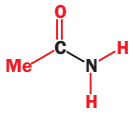
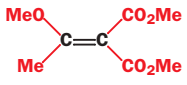
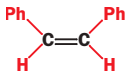
$$k = Ae^{\frac{E_a}{RT}}$$

■ Svante Arrhenius (1859–1927) was one of the founders of physical chemistry. He was based at Uppsala in Sweden and won the Nobel prize in 1903 mainly for his theory of the dissociation of salts in solution.

where $k$ is the rate constant for the reaction, $R$ is the gas constant, $T$ is the temperature (in kelvin), and $A$ is a quantity known as the pre-exponential factor. This equation is called the **Arrhenius equation**. Because of the minus sign in the exponential term, the larger the activation energy, $E_a$, the slower the reaction but the higher the temperature, the faster the reaction.

## Examples of activation energy barriers

A very simple reaction is rotation about a bond. In the compounds in the table, different amounts of energy are needed to rotate about the bonds highlighted in black. See how this activation energy barrier affects the actual rate at which the bond rotates. Approximate values for $k$ have been calculated from the experimentally determined values for the activation energies. The **half-life**, $t_{1/2}$, is just the time needed for half of the compound to undergo the reaction.

| Compound | $E_a$, kJ mol$^{-1}$ | Approximate $k$, 298 K/s$^{-1}$ | $t_{1/2}$ at 298 K |
|---|---|---|---|
|  | 12 | $5\times10^{10}$ | 0.02 ns |
|  | 45 | $8\times10^{4}$ | 10 µs |
|  | 70 | 3 | 0.2 s |
|  | 108 | $7\times10^{-7}$ | 11 days |
|  | 180 | $2\times10^{-19}$ | ca. $10^{11}$ years[a] |

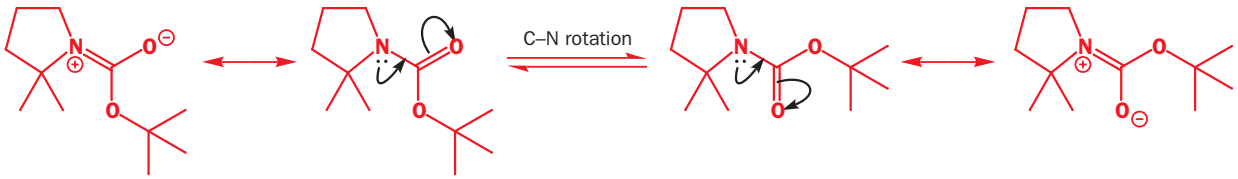
[a] The age of the earth = $4.6\times10^{9}$ years.

We can see how the rate constant varies with temperature by looking at the Arrhenius equation. The pre-exponential factor, $A$, does not vary much with temperature, but the exponential term is a function of temperature. Once again, because of the minus sign, the greater the temperature, the greater the rate constant.

This observation is used in practice when NMR spectra give poor results because of slow rotation about bonds. Amides of many kinds, particularly carbamates, show slow rotation about the C–N bond at room temperature because of the amide delocalization. These amides have bigger barriers to rotation than the 70 kJ mol$^{-1}$ of the example in the table. The result is a poor spectrum with broad signals. In this example, the two sides of the five-membered ring are different in the two rotational isomers and give different spectra.

■ NMR spectra of DMF at high and low temperature are shown on p. 000 of Chapter 7

■ You will see this 'Boc' group used as a protecting group for amines in Chapter 24.




The solution is to run the NMR spectrum at higher temperatures. This speeds up the rotation and averages out the two structures.

A word of warning: heating is not all good for the organic chemist—not only does it speed up the reaction we want, it will also probably speed up lots of other reactions that we don't want to occur! We shall see how we can get round this, but first we shall take a closer look at what determines how fast a reaction takes place.

## Rates of reaction

Suppose we have the very simple reaction of a single proton reacting with a molecule of water in the gas phase

$$H^+(g) + H_2O(g) \rightarrow H_3O^+(g)$$

We saw at the beginning of Chapter 8 that this is essentially an irreversible process, that is, $\Delta G^\circ$ is very large and negative and therefore the equilibrium constant, $K$, is large and positive.

So we know that this reaction goes, but what determines how quickly it can proceed? Since the mechanism simply involves one proton colliding with one molecule of water, then clearly the rate will depend on how often the two collide. This in turn will depend on the concentrations of these species—if there are lots of protons but only a few water molecules, most collisions will be between protons. The reaction will proceed fastest when there are lots of protons and lots of water molecules.

■ This reaction turns two species into one, all in the gas phase. The standard entropy for the reaction must therefore be negative. In order for $\Delta G^\circ$ to be negative, the reaction must give out heat to the surroundings. In other words, this reaction must be highly exothermic, as indeed it is.

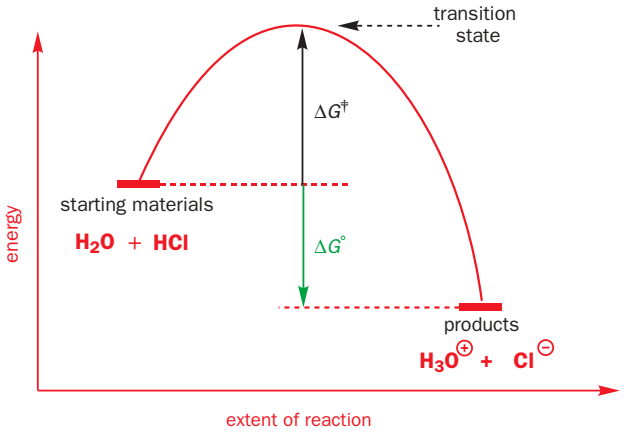
We can express this mathematically by saying that the rate of reaction is proportional to the concentration of protons multiplied by the concentration of water molecules (the square brackets mean 'concentration of').

$$\text{rate of reaction} \propto [H^+] \times [H_2O]$$

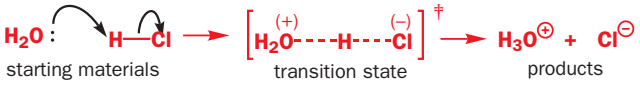
The constant of proportionality, $k$, is known as the **rate constant**.

$$\text{rate of reaction} = k \times [H^+] \times [H_2O]$$

We are not very interested in reactions in the gas phase, but fortunately reactions in solution follow more or less the same laws so the reaction of a proton source like HCl and a water molecule in an inert solvent would have the rate expression: rate = $k \times [HCl] \times [H_2O]$. Expressing the same idea graphically requires an energy profile diagram like those we used for equilibria but concentrating rather more on $\Delta G^{\ddagger}$ than on $\Delta G^{\circ}$.




Note that the products are lower in energy than the starting materials as before. The energy barrier is now marked $\Delta G^{\ddagger}$ and the highest point on the profile is labelled *transition state*. Somewhere between the starting materials and the products there must come a point where the O–H bond is half formed. This is the least stable structure in the whole reaction scheme and would correspond to a structure about halfway between starting materials and products, something like this.




Now notice that the transition state is drawn in square brackets and marked ‡. Note the long dashed bonds not yet completely formed or not yet completely broken and the partial charges (+) and (–) meaning something about half a charge (the products have complete charges shown in circles).

### Transition state

**A transition state is a structure that represents an energy maximum on passing from reactants to products. It is not a real molecule in that it may have partially formed or broken bonds and may have more atoms or groups around the central atom than allowed by valence bond rules. It cannot be isolated because it is an energy maximum and any change in its structure leads to a more stable arrangement. A transition state is often shown by putting it in square brackets with a double-dagger superscript.**

This species is unstable—both the starting materials and the products are lower in energy. This means that it is not possible to isolate this halfway species; if the reaction proceeds just a little more forwards or backwards, the energy of the system is lowered (this is like balancing a small marble on top of a football—a small push in any direction and the marble will fall, lowering its potential energy).

# Kinetics

The value of the rate constant will be different for different reactions. Consider the reaction of HCl and a water molecule discussed in the last section. Even with the same concentrations, the almost identical reaction where hydrogen is replaced by deuterium will proceed at a different rate (Chapter 19). To understand this we need to think again about what needs to happen for a reaction to occur. It is not enough for the two species to simply collide. We know that for this reaction to work the proton must come into contact with the *oxygen* atom in the water molecule, not the hydrogen atoms, that is, there is some sort of steric requirement. We have also seen that most reactions need to overcome an energy barrier. In other words, it is not enough for the two species just to collide for a reaction to proceed, they must collide in the right way and with enough force.

You can see now how the overall rate equation for our example reaction

$$\text{rate of reaction} = k \times [\text{HCl}] \times [\text{H}_2\text{O}]$$

contains all the points needed to work out how fast the reaction will proceed. The most important point concerns the concentrations of the reacting species—which are expressed directly in the rate equation. Other considerations, such as how large the species are or whether or not they collide in the right way with the right energy, are contained in the rate constant, *k*. Notice once again that not only is *k* different for different reactions (for all of the above reasons), but that it also varies with temperature. It is essential when quoting a rate constant that the temperature is also quoted. That part of chemistry that deals with reaction *rates* rather than equilibria is known as **kinetics**.

## Activation barriers

In the same way that we define $\Delta G^{\ddagger}$ to be the difference in energy between the starting materials and the transition state (that is, activation energy), we can define the entropy of activation, $\Delta S^{\ddagger}$, and the enthalpy of activation, $\Delta H^{\ddagger}$, as being the entropy and enthalpy differences between the starting materials and transition sate. These quantities are directly analogous to the entropy and enthalpy of the reaction but instead refer to the difference between starting material and *transition state* rather than starting material and *products*.

In a similar manner, we could also define an equilibrium constant between the reactants and the transition state

$$K^{\ddagger} = \frac{[\text{AB}]}{[\text{A}][\text{B}]}$$

Our all-important thermodynamic equations apply equally well to these activation functions so that we may write

$$\Delta G^{\ddagger} = -RT\ln K^{\ddagger} \text{ and } \Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}.$$

It is possible to relate these functions with the rate constant for the reaction, *k*, by using a model known as **transition state theory**. We will not go into any details here, but the net result is that

$$k = \frac{k_B T}{h} K^{\ddagger}$$

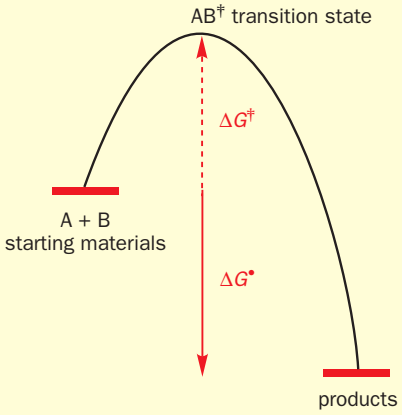
where $k_B$ and *h* are universal constants known as Botlzmann's constant and Planck's constant, respectively

By substituting in the equation $K^{\ddagger} = e^{\frac{-\Delta G^{\ddagger}}{RT}}$ the rearranged form of $\Delta G^{\ddagger} = -RT\ln K^{\ddagger}$) we arrive at an equation, known as the **Eyring equation**, which relates how fast a reaction goes (k) to the activation energy ($\Delta G^{\ddagger}$)

$$k = \frac{k_B T}{h} e^{-\frac{\Delta G^{\ddagger}}{RT}}$$

This can be rearranged and the numerical values of the constants inserted to give an alternative form

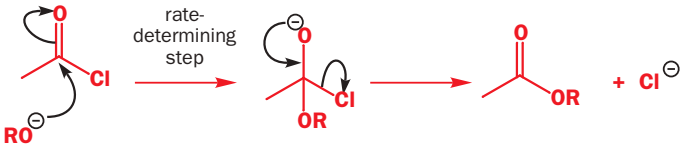
$$\Delta G^{\ddagger} \text{ (in J mol}^{-1}) = 8.314 \times T \times [23.76 + \ln(T/k)]$$

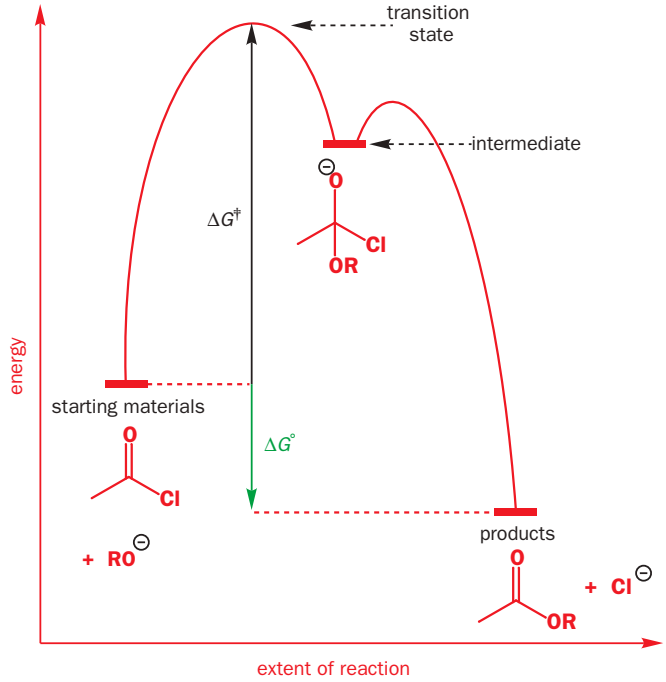



## Kinetics gives us an insight into the mechanism of a reaction

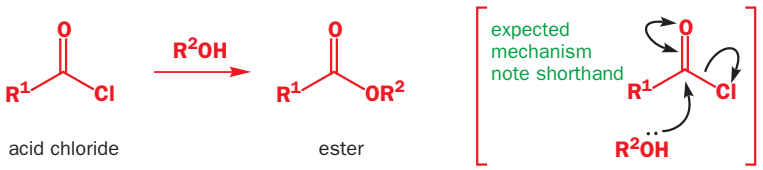
Now for some of the reactions you have seen in the last few chapters. Starting with carbonyl substitution reactions, the first example is the conversion of acid chlorides into esters. The simplest mechanism to understand is that involved when the anion of an alcohol (a metal alkoxide $RO^-$) reacts with an acid chloride. The kinetics are bimolecular: rate = $k$[MeCOCl][$RO^-$]. The mechanism is the simple addition elimination process with a tetrahedral intermediate.

The formation of the tetrahedral intermediate by the combination of the two reagents is the rate-determining step and so the highest transition state will be the one leading from the starting materials to that intermediate.

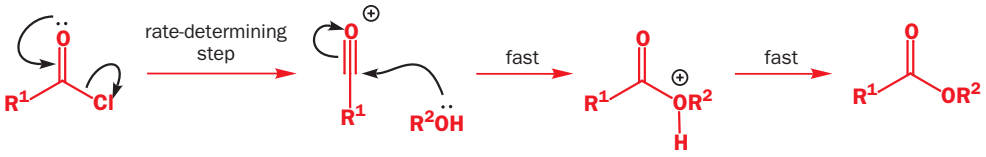





We shall return to this important mechanism in a moment after a brief mention of *first-order kinetics*. The reaction between the acid chloride and the neutral alcohol to give an ester may not have the bimolecular rate expression expected for this mechanism: rate = $k[R^1COCl][R^2OH]$.



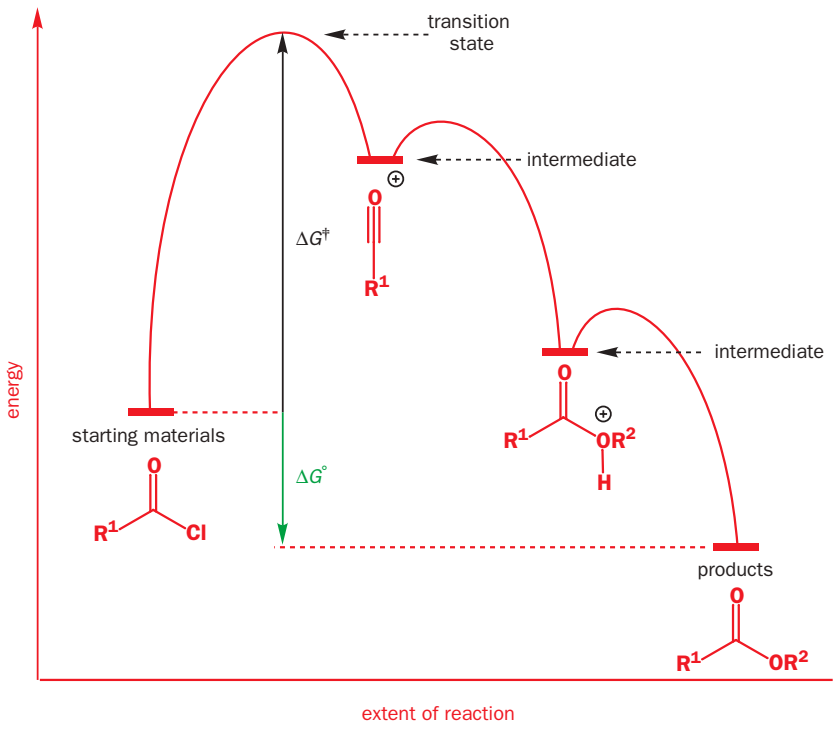

Some such reactions have a simpler rate expression: rate = $k[R^1COCl]$ in which the alcohol does not appear at all. Evidently, no collision between the acid chloride and the alcohol is required for this reaction to go. What actually happens is that the acid chloride decomposes by itself to give a reactive cation (a cation you have already seen in mass spectrometry) with the loss of the good leaving group $Cl^-$.




There are three steps in this reaction scheme though the last is a trivial deprotonation. Evidently, the energy barrier is climbed in the first step, which involves the acid chloride alone. The cation is an intermediate with a real existence and reacts later with the alcohol in a step that does not affect the rate of the reaction. The easiest way to picture this detail is in an energy profile diagram (top right).

Points to notice:

- The products are again lower in energy than the starting materials
- There are three transition states in this reaction
- Only the highest-energy transition state matters in the reaction rate (here the first)
- The step leading to the highest transition state is called the rate-determining step
- The two intermediates are local minima in the reaction profile
- The highest-energy transition state is associated with the formation of the highest-energy intermediate



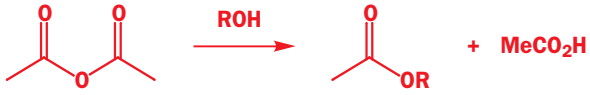

**Intermediates and transition states**

**A transition state represents an energy maximum—any small displacement leads to a more stable product. An intermediate, on the other hand, is a molecule or ion that represents a *localized* energy minimum—an energy barrier must be overcome before the intermediate forms something more stable. As you have seen in Chapter 3, and will see again in Chapter 22, because of this energy barrier, it is even possible to isolate these reactive intermediates ($RCO^+$) and study their spectra.**

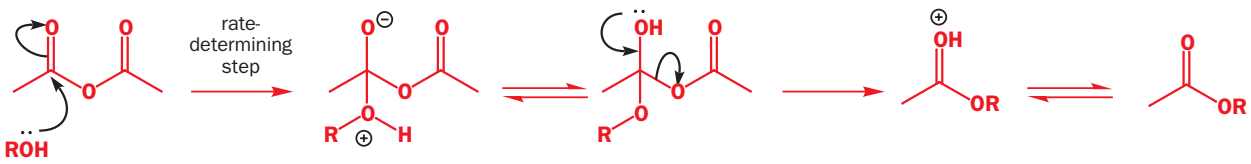
Because the rate-determining step involves just one molecule, the rate equation shows rate = $k[R^1COCl]$, and the reaction is called a **first-order reaction** as the rate is proportional to just one concentration. A first-order reaction involves the unimolecular decomposition of something in the rate-determining step.

## Second-order reactions

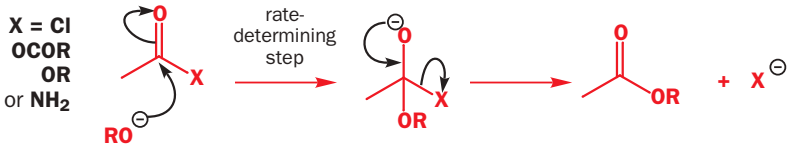
The unimolecular mechanism is unusual for carbonyl substitution reactions. Those in the last chapter as well as the carbonyl addition reactions in Chapter 6 all had nucleophilic addition to the carbonyl group as the rate-determining step. An example would be the formation of an ester from an anhydride instead of from an acid chloride.



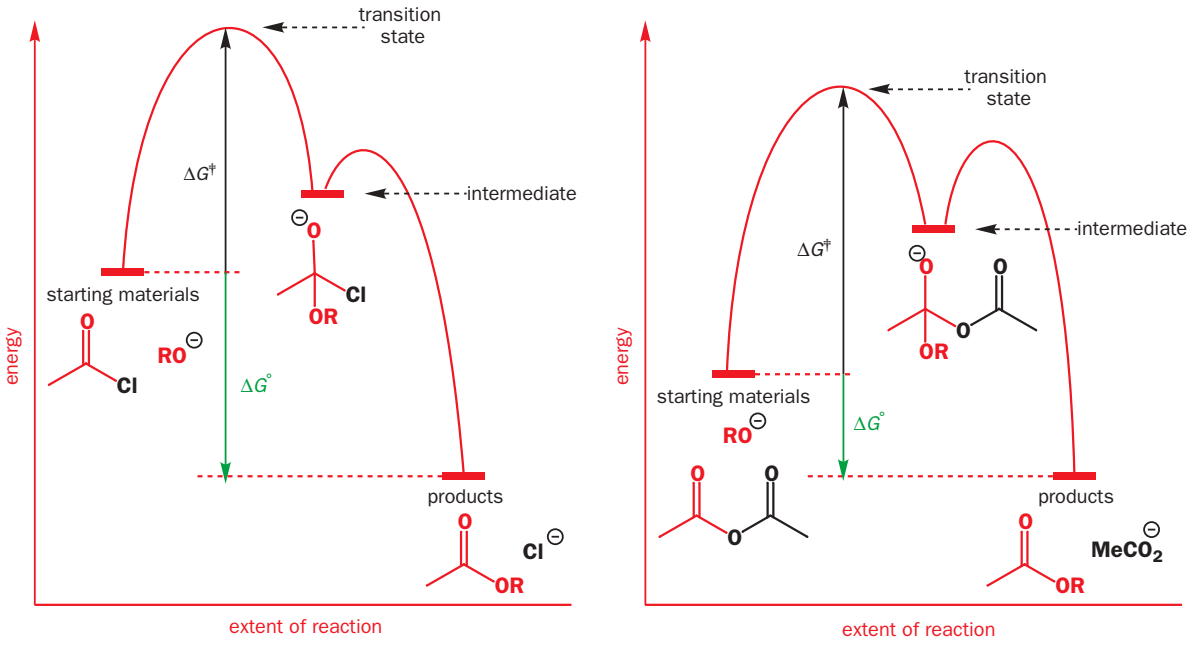

The leaving group ($MeCO_2^-$) is not now good enough ($pK_{aH}$ about 5 instead of –7 for $Cl^-$) to leave of its own accord so the normal *second-order* mechanism applies. The kinetics are bimolecular: rate = $k[(MeCO)_2O][ROH]$ and the rate-determining step is the formation of the tetrahedral intermediate.



All the acid derivatives (acid chlorides, anhydrides, esters, and amides) combine with a variety of nucleophiles in very similar bimolecular mechanisms.




This is the simplest and the most typical bimolecular mechanism with one intermediate, and the energy profile diagrams are correspondingly easier to understand. The reactions with acid chlorides (discussed a few pages back) and anhydrides are straightforward and go in good yield.

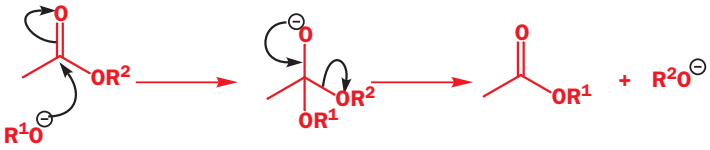



The energy levels of the starting materials, the transition state, and the intermediate are all lower in the anhydride reaction than in the acid chloride reaction. So which goes faster? We know the answer—acid chlorides are more reactive than anhydrides towards nucleophiles. The reason is that the stability of the starting materials is determined by the interaction between the carbonyl group and the substituent attached directly to it. This is a big effect as we know from infrared spectroscopy.

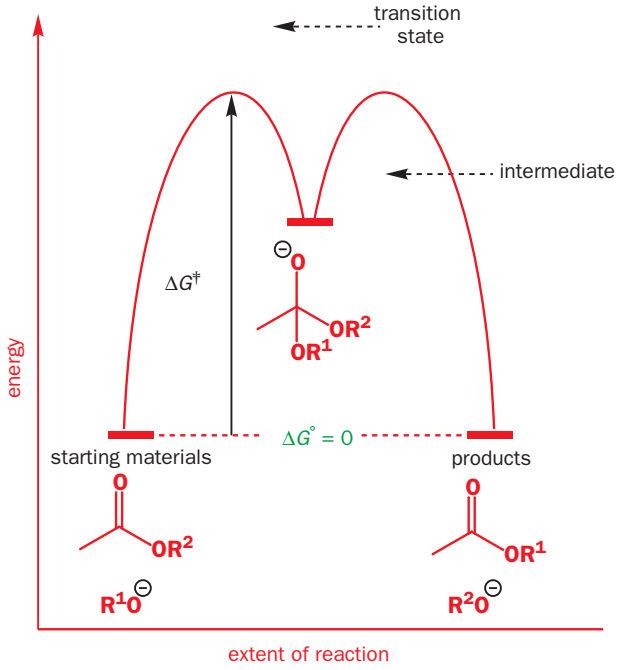
The two intermediates also have different energies depending mainly on the stability of the oxyanion. This too will be affected by the substituents, Cl and OAc, but they are separated from the oxyanion by the tetrahedral carbon atom and there is no conjugation. Substituent effects on the oxyanion are smaller than they are on the starting materials so the two intermediates are similar in energy. Substituent effects on the transition state will be somewhere between the two but the transition state is nearer to the intermediate than to the starting material so substituent effects will be like those on the intermediate. The two transition states also have similar energies. The net result is that $\Delta G^{\ddagger}$ is bigger for the anhydride mainly because the energy of the starting materials is lower. This also explains why $\Delta G^{\circ}$ is smaller.

## The ester exchange reaction

When we move on to esters reacting with alkoxides the chart is a good deal more symmetrical. This is the reaction.



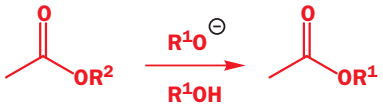
The nucleophile and the leaving group are both alkoxides, the only difference being $R^1$ and $R^2$. If $R^1$ and $R^2$ were the same, the energy profile diagram would be totally symmetrical and small differences between $R^1$ and $R^2$ are not going to affect the symmetry much.




Points to notice:

- The transition states for the two steps are equal in energy
- $\Delta G^{\ddagger}$ is the same for the forward and the back reaction
- $\Delta G^{\circ}$ is zero
- If $R^1 = R^2$, the intermediate has an exactly 50% chance of going forward or backward

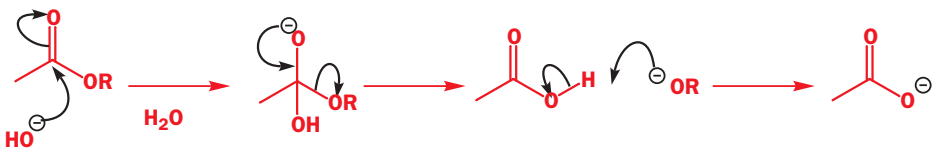
In fact, we now have an equilibrium reaction. If $R^1$ and $R^2$ are different then the reaction is called ester exchange or transesterification and we should drive it in the direction we want by using a large excess of one of the two alcohols. If we carried out the reaction on one ester using an equivalent of the other alkoxide in that alcohol as solvent, the other ester would be formed in good yield.



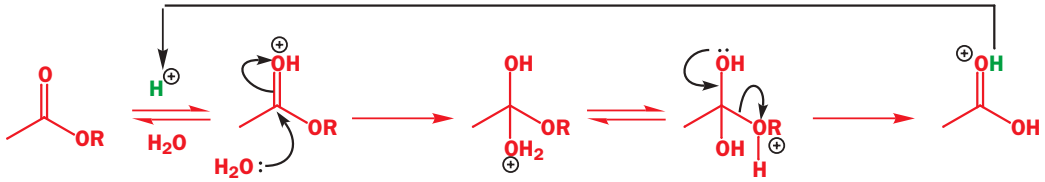

## Catalysis in carbonyl substitution reactions

We don't need the equivalent of alkoxide in ester exchange because alkoxide is regenerated in the second step. We need only catalytic quantities (say, 1–2% of the ester) because the role of the alkoxide is catalytic. It speeds up the reaction because it is a better nucleophile than the alcohol itself and it is regenerated in the reaction.

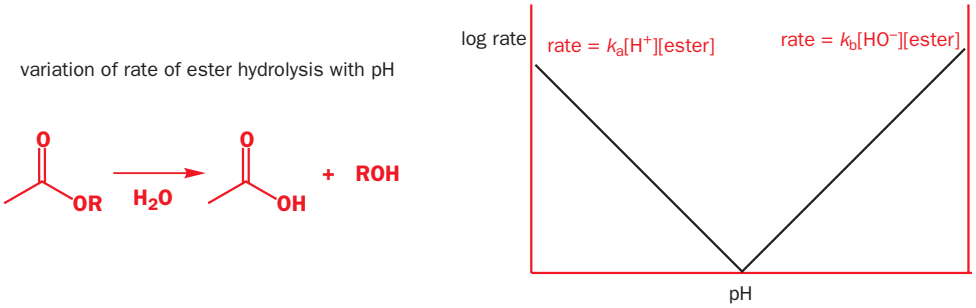

Making a solution more basic speeds up reactions in which alcohols act as nucleophiles because it increases the concentration of the alkoxide ion, which is more nucleophilic than the alcohol itself. The same thing happens in hydrolysis reactions. The hydrolysis of esters is fast in either acidic or basic solutions. In basic solution, hydroxide is a better nucleophile than water.



The mechanism is like that for ester exchange but hydroxide is used up in deprotonating the carboxylic acid produced so a whole equivalent of NaOH is needed. In acidic solution, protonation of the carbonyl oxygen atom makes the ester more electrophilic and attack by the weak nucleophile (water) is made faster but the acid catalyst is regenerated. In both these reactions nucleophilic attack is the rate-determining step.



So, the higher the concentration of protons, the faster the hydrolysis goes and, the higher the concentration of hydroxide ion, the faster the reaction goes. If we plot the (log of the) rate of the reaction against the pH of the solution we shall get two straight lines increasing at high and low pH and each with a slope of one. The lines intersect near neutrality when there are neither protons nor hydroxide ions. This is simple acid and base catalysis.




▶ You will also see rate constants labelled in other ways—this is a matter for choice. A common method is to use $k_1$ for unimolecular and $k_2$ for bimolecular rate constants.

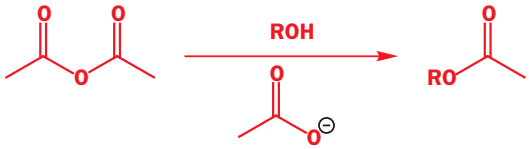
These are bimolecular reactions with bimolecular kinetics and the rate expression in each case includes the concentration of the catalyst. We can label the rate constants $k_a$ and $k_b$ with a suffix 'a' for acid and 'b' for base to show more clearly what we mean.

rate of ester hydrolysis in acid solution (pH < 7) = $k_a[MeCO_2R][H_3O^+]$

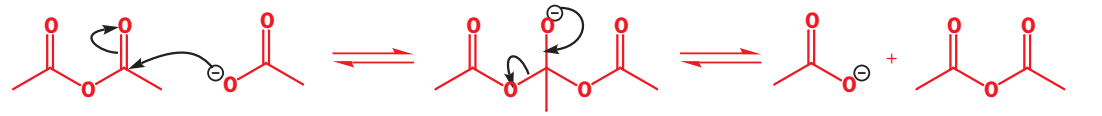
rate of ester hydrolysis in basic solution (pH > 7) = $k_b[MeCO_2R][HO^-]$

## Catalysis by weak bases

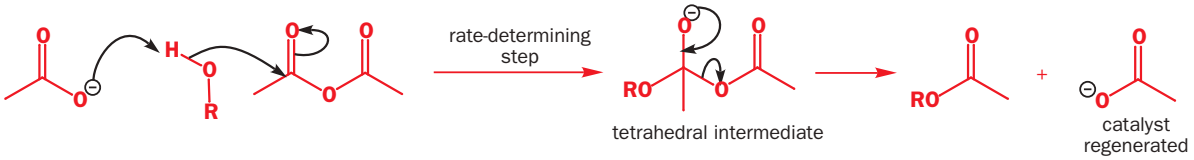
In Chapter 12 pyridine was often used as a catalyst in carbonyl substitution reactions. It can act in two ways. In making esters from acid chlorides or anhydrides pyridine can act as a nucleophile as well as a convenient solvent. It is a better nucleophile than the alcohol and this nucleophilic catalysis is discussed in Chapter 12. But nonnucleophilic bases also catalyse these reactions. For example, acetate ion catalyses ester formation from acetic anhydride and alcohols.



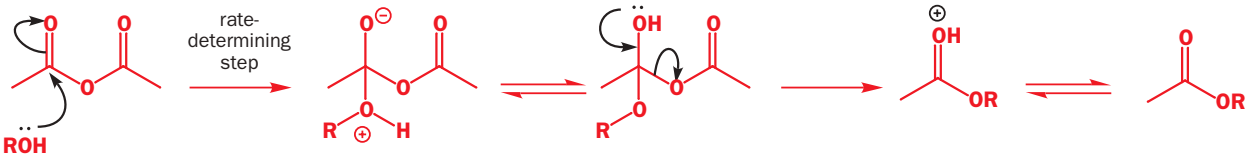

Could this be nucleophilic catalysis too? Acetate can certainly attack acetic anhydride, but the products are the same as the starting materials. This irrelevant nucleophilic behaviour of acetate ion cannot catalyse ester formation.




Can acetate be acting as a base? With a p$K_{aH}$ of about 5 it certainly cannot remove the proton from the alcohol (p$K_{aH}$ about 15) before the reaction starts. What it can do is to remove the proton from the alcohol as the reaction occurs.




This type of catalysis, which is available to any base, not only strong bases, is called **general base catalysis** and will be discussed more in Chapters 41 and 50. It does not speed the reaction up very much but it does lower the energy of the transition state leading to the tetrahedral intermediate since that intermediate is first formed as a neutral compound instead of a dipolar species. Here is the mechanism for the uncatalysed reaction.

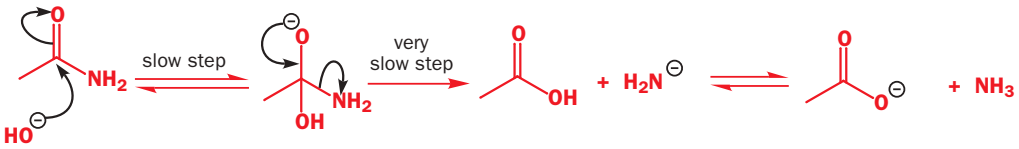



The disadvantage of general base catalysis is that the first, rate-determining, step is termolecular. It is inherently unlikely that three molecules will collide with each other simultaneously and in the next section we shall reject such an explanation for amide hydrolysis. In this case, however, if ROH is the solvent, it will always be present in any collision so a termolecular step is just about acceptable.

## The hydrolysis of amides can have termolecular kinetics

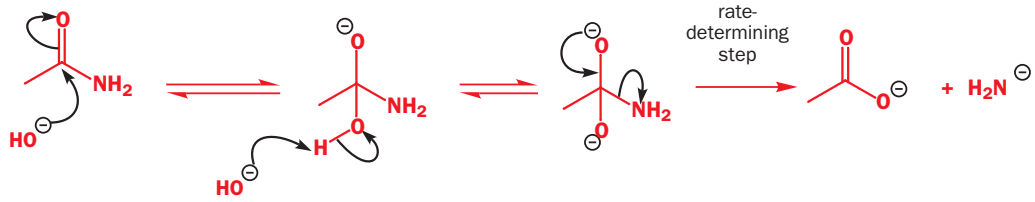
When we come to reactions of amides we are at the bottom of the scale of reactivity. Because of the efficient delocalization of the nitrogen lone pair into the carbonyl group, nucleophilic attack on the carbonyl group is very difficult. In addition the leaving group ($NH_2^-$, p$K_{aH}$ about 35) is very bad indeed.

■ This reaction was first discussed in Chapter 12.




You might indeed have guessed from our previous example, the hydrolysis of esters, where the transition states for formation and breakdown of the tetrahedral intermediate had about the same energies, that in the hydrolysis of amide the second step becomes rate-determining. This offers the opportunity for further base catalysis. If a second hydroxide ion removes the proton from the tetrahedral intermediate, the loss of $NH_2^-$ is made easier and the product is the more stable carboxylate ion.

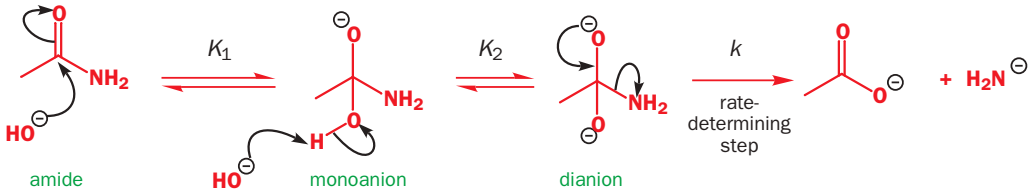
▶ Of course the very basic leaving group ($NH_2^-$, p$K_{aH}$ about 35) instantaneously reacts with water (p$K_{aH}$ about 15) in a fast proton transfer to give $NH_3$ and $HO^-$.



Notice that in the first mechanism the hydroxide is consumed as the product eventually emerges as an anion. In the second mechanism, one hydroxide is consumed but the second is catalytic as the $NH_2^-$ reacts with water to give ammonia and hydroxide ion. The rate expression for the hydrolysis of amides includes a termolecular term and we shall label the rate constant $k_3$ to emphasize this.

$$\text{rate} = k_3[\text{MeCONH}_2][\text{HO}^-]^2$$

Where do the termolecular kinetics come from? It is, of course, extremely unlikely that three species will collide simultaneously, particularly as two of them are mutually repelling anions. The rate-determining step is actually unimolecular—the spontaneous breakdown of a dianion. But the concentration of the dianion is in the rate expression too and that depends on the reactions before the rate-determining step. With a late rate-determining step, the previous steps are in equilibrium and so we can put in some rate and equilibrium constants for each step and label the intermediates like this.




The rate of the reaction is the rate of the rate-determining step

$$\text{rate} = k[\text{dianion}]$$

We don't know the concentration of the dianion but we do know that it's in equilibrium with the monoanion so we can write

$$K_2 = \frac{[\text{dianion}]}{[\text{monoanion}][\text{HO}^-]}$$

$$\text{and so } [\text{dianion}] = K_2[\text{monanion}][\text{HO}^-]$$

In the same way we don't want the unknown [monoanion] in our rate expression and we can get rid of it using the first equilibrium

$$K_1 = \frac{[\text{monoanion}]}{[\text{amide}][\text{HO}^-]}$$

$$\text{and so } [\text{monoanion}] = K_1[\text{amide}][\text{HO}^-]$$

Substituting these values in the simple rate equation we discover that rate = $k$[dianion] becomes

$$\text{rate} = kK_1K_2[\text{amide}][\text{HO}^-]^2$$

The termolecular kinetics result from two equilibria starting with the amide and involving two hydroxide ions followed by a unimolecular rate-determining step, and the 'termolecular rate constant' $k_3$ is actually a product of the two equilibrium constants and a unimolecular rate constant $k_3 = k \times K_1 \times K_2$.

We have now seen examples of unimolecular and bimolecular reactions and also how termolecular kinetics can arise from unimolecular and bimolecular reactions.

Just because a proposed mechanism gives a rate equation that fits the experimental data, it does not necessarily mean that it is the *right* mechanism; all it means is that it is consistent with the experimental facts so far but there may be other mechanisms that also fit. It is then up to the experimenter to design cunning experiments to try to rule out other possibilities.

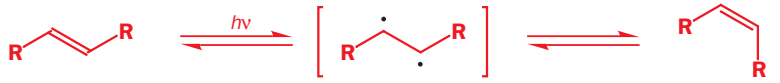
Mechanisms are given throughout this book—eventually you will learn to predict what the mechanism for a given type of reaction is, but this is because earlier experimentalists have worked out the mechanisms by a study of kinetics and other methods (see Chapter 41 for more details on how mechanisms are elucidated). In Chapter 17 you will meet another pair of mechanisms—one first-order and one second-order—following the same pattern as these.

## The *cis–trans* isomerization of alkenes

The fact that a reaction is favourable (that is, $\Delta G°$ is negative) does not mean that the reaction will go at any appreciable rate: the rate is determined by the activation energy barrier that must be

overcome. Returning to the example of the *cis–trans* isomerism of butene, the energy difference between two forms is just 2 kJ mol$^{-1}$; the activation energy barrier is much bigger: 260 kJ mol$^{-1}$. The difference in energy determines the equilibrium position (2 kJ mol$^{-1}$ corresponding to an equilibrium constant of about 2.2, or a ratio of 30:70, *cis*:*trans*; see table on p. 000), whilst the activation energy determines how fast the reaction occurs (260 kJ mol$^{-1}$ means that the reaction does not happen at all at room temperature). A calculation predicts that the half-life for the reaction would be approximately $10^{25}$ years at room temperature, a time interval much greater than the age of the universe. At 500 °C, however, the half-life is a more reasonable 4 hours which just goes to show the power of exponentials! Unfortunately, when most alkenes are heated to these sorts of temperatures, other unwanted reactions occur.

In order to interconvert the *cis* and *trans* isomers we must use a different strategy. One method is to shine light on the molecule. If UV light is used it is of the right wavelength to be absorbed by the C=C π bond exciting one of the π electrons into the antibonding π* orbital. There is now no π bond and the molecule can rotate freely.

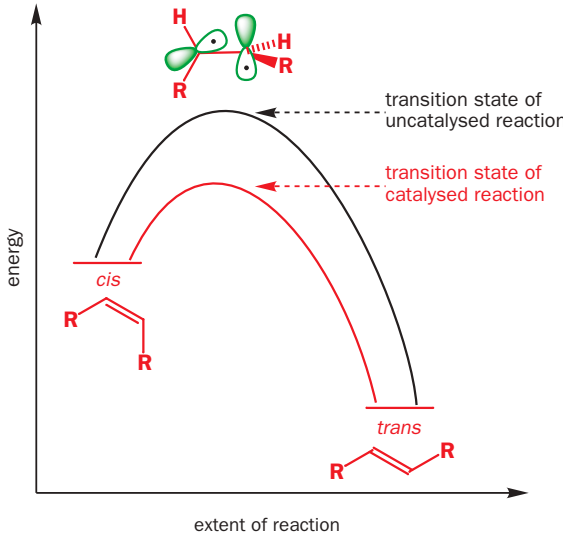



*trans* (*E*-) alkene alkene excited state *cis* (*Z*-) alkene

Another approach to alkene isomerization would be to use a catalyst. Base catalysis is of no use as there are no acidic protons in the alkene. Acid catalysis can work (Chapter 19) if a carbocation is formed by protonation of the alkene.

## How to catalyse the isomerization of alkenes

The rate at which a reaction occurs depends on its activation energy—quite simply, if we can decrease this, then the reaction rate will speed up. There are two ways by which the activation energy may be decreased: one way is to raise the energy of the starting materials; the other is to lower the energy of the transition state. In the *cis/trans* isomerization of alkenes, the transition state will be halfway through the twisting operation—it has p orbitals on each carbon at right angles to each other. It is the most unstable point on the reaction pathway.

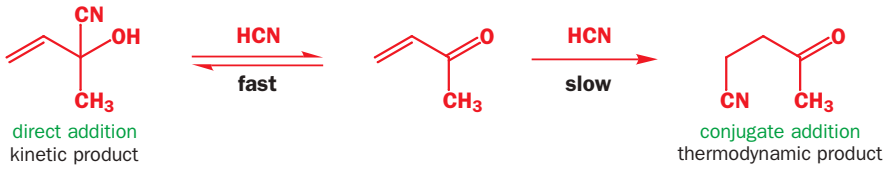



Lowering the energy of the transition state means stabilizing it in some way or other. For example, if there is a separation of charge in the transition state, then a more polar solvent that can solvate this will help to lower the energy of the transition state. Catalysts generally work by stabilizing the transition states or intermediates in a reaction. We shall return to this point when we have introduced kinetic and thermodynamic products.

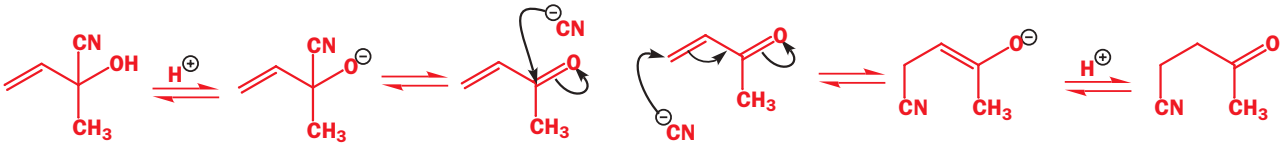
▶ The quantum symbols *hν* are conventionally used for light in a reaction and the excited state diagram is the best we can do for a molecule with one electron in the π orbital and one in the π* orbital.

## Kinetic versus thermodynamic products

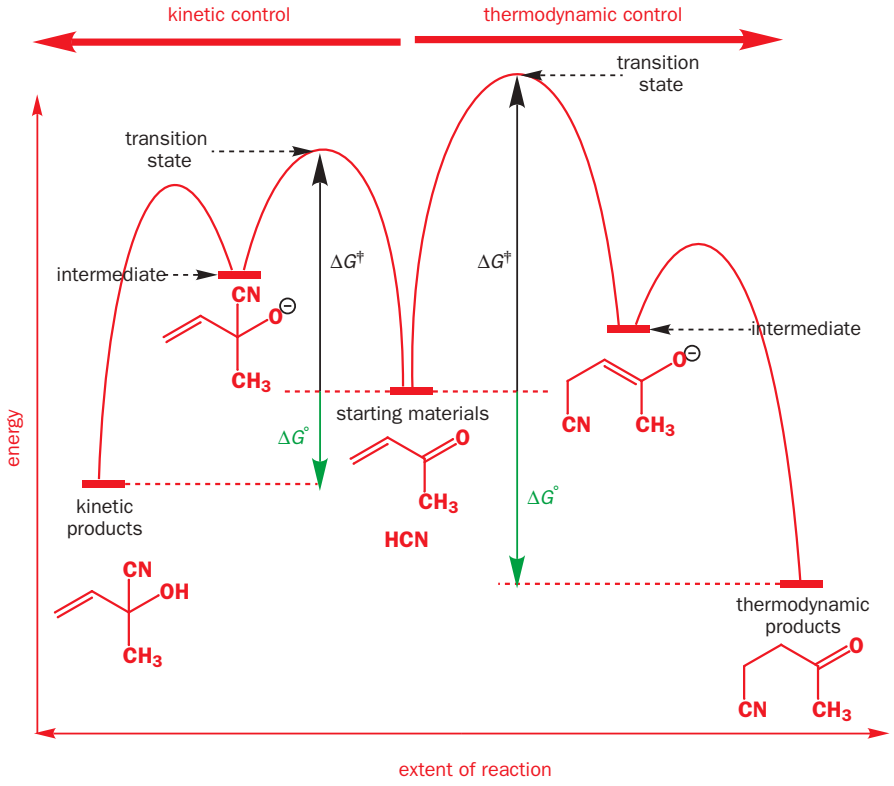
In Chapter 10 we discussed conjugate addition to unsaturated carbonyl compounds in contrast to direct addition to the carbonyl group. A classic illustration is the addition of HCN to butenone. Two products can be formed.




The 'direct' addition to the left means that cyanide ion must attack the carbonyl group directly while the 'conjugate' addition to the right means that it must attack the less electrophilic alkene. The second is a slower reaction but gives the more stable product. Both reactions have an alkoxide anion as an intermediate.




The energy profile diagram for these two reactions is quite complicated. It has the starting material in the middle, as in the mechanism above, and so extent of reaction increases both to the right for thermodynamic control and to the left for kinetic control.



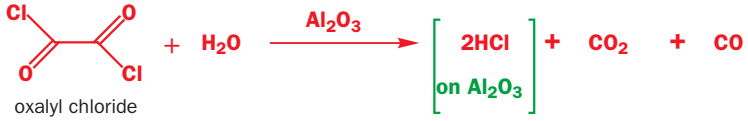

Points to notice:

- The thermodynamic product has a lower energy than the kinetic product
- The highest transition state to the right is higher than the highest to the left
- Initially the reaction will go to the left

- If there is enough energy for the kinetic product to get back to the starting materials, there will be enough energy for some thermodynamic product to be formed
- The energy needed for the thermodynamic product to get back to starting materials is very great
- The kinetic product is formed reversibly; the thermodynamic product irreversibly
- At low temperatures direct addition is favoured, but conjugate addition is favoured at high temperatures

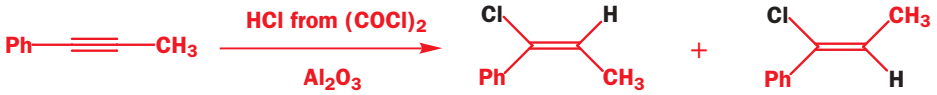
## Kinetic versus thermodynamic control in the isomerization of alkenes

Our catalyst for the isomerization of alkenes is going to be HCl absorbed on to solid alumina (aluminium oxide, $Al_2O_3$) and the isomerization is to occur during a reaction, the addition of HCl to an alkyne, in which the alkenes are formed as products. In this reaction the oxalyl chloride is first mixed with dried alumina. The acid chloride reacts with residual water on the surface (it is impossible to remove all water from alumina) to generate HCl, which remains on the surface.



oxalyl chloride

The treated alumina with HCl still attached is added to a solution of an alkyne (1-phenylpropyne) and an addition reaction occurs to produce two geometrical isomers of an alkene. One results from *cis* addition of HCl to the triple bond, and one from *trans* addition.



1-phenylpropyne

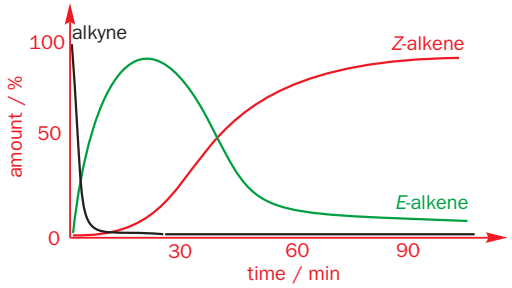
*E*-alkene from *cis* addition of HCl

*Z*-alkene from *trans* addition of HCl

The two alkenes are labelled *E* and *Z* . After about 2 hours the main product is the *Z*-alkene. However, this is not the case in the early stages of the reaction. The graph below shows how the proportions of the starting material and the two products change with time.

Points to note:

- When the alkyne concentration drops almost to zero (10 minutes), the only alkene that has been formed is the *E*–alkene
- As time increases, the amount of *E*-alkene decreases as the amount of the *Z*-alkene increases
- Eventually, the proportions of *E*- and *Z*-alkenes do not change




Since it is the *Z*-alkene that dominates at equilibrium, this must be lower in energy than the *E*-alkene. Since we know the ratio of the products at equilibrium, we can work out the difference in energy between the two isomers

ratio of *E*:*Z* alkenes at equilibrium = 1:35

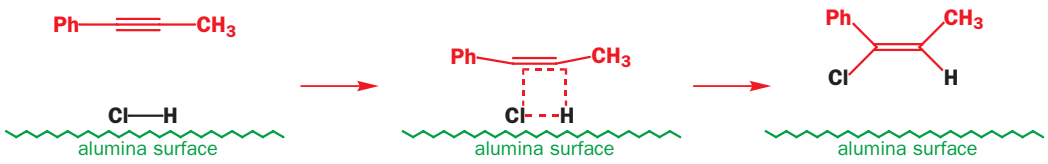
$$K_{eq} = \frac{[Z]}{[E]} = 35$$

$$\Delta G^\circ = -RT \ln K = -8.314 \times 298 \times \ln(35) = -8.8 \text{ kJ mol}^{-1}$$

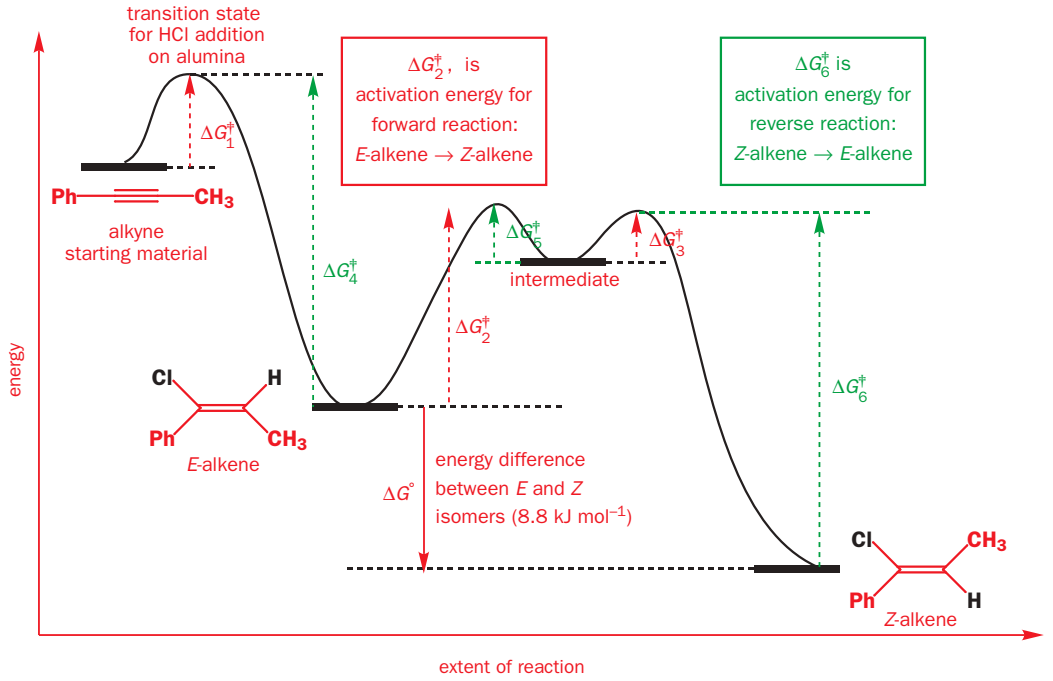
that is, the *Z*-alkene is 8.8 kJ mol$^{-1}$ lower in energy than the *E*-alkene.

Since the *E*-alkene is the quickest to form under these conditions, *cis* addition of HCl must have a smaller activation energy barrier than *trans* addition. This suggests that reaction occurs on the surface of the alumina with both the H and the Cl added to the triple bond simultaneously from the same side rather like *cis*-hydrogenation of triple bonds on a palladium catalyst (p. 000).

▶ You might normally expect an *E*-alkene to be more stable than a *Z*-alkene—it just so happens here that Cl has a higher priority than Ph and the *Z*-alkene has the two largest groups (Ph and Me) *trans*. (See p. 000 for rules of nomenclature.)

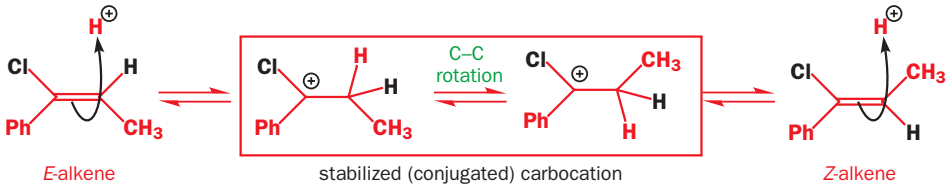



There must then be some mechanism by which the quickly formed *E*-alkene is converted into the more stable *Z*-alkene, presumably through another intermediate that is more stable than the transition state for alkene interconversion. This information is summarized on a reaction profile diagram.




Initially, the alkyne is converted into the *E*-alkene. The activation energy for this step is labelled $\Delta G_1^{\ddagger}$. The *E*-alkene then converts to the *Z* isomer via an intermediate. The activation energy for this step is $\Delta G_2^{\ddagger}$. Overall, the reaction is the addition of HCl to the alkyne to give the *Z*-alkene—we could look on the *E* isomer as just another intermediate. The only difference between the *E*-alkene and the intermediate in the isomerism reaction is the size of the activation energies; it is much easier to isolate the *E*-alkene because the activation energies to be overcome ($\Delta G_2^{\ddagger}$ and $\Delta G_4^{\ddagger}$) are both much larger than those of the intermediate ($\Delta G_5^{\ddagger}$ and $\Delta G_3^{\ddagger}$). The activation energy to be overcome to form the *E*-alkene ($\Delta G_1^{\ddagger}$) is less than that to be overcome to form the *Z*-alkene ($\Delta G_2^{\ddagger}$).

So what is this intermediate in the isomerization reaction? It is a cation from protonation of the alkene by more HCl. The cation is stabilized by delocalization into the benzene ring and can rotate as it has no double-bond character.




### Kinetic and thermodynamic products

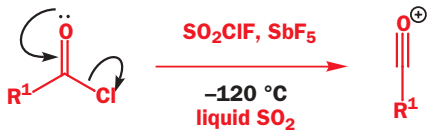
The *E*-alkene is formed faster and is known as the **kinetic product**; the *Z*-alkene is more stable and is known as the **thermodynamic product**.

If we wanted to isolate the kinetic product, the *E*-alkene, we would carry out the reaction at low temperature and not leave it long enough for equilibration. If, on the other hand, we want the thermodynamic product, the *Z*-alkene, we would leave the reaction for longer at higher temperatures to make sure that the larger energy barrier yielding the most stable product can be overcome.

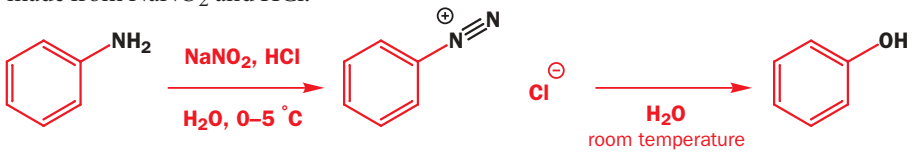
## Low temperatures prevent unwanted reactions from occurring

So far in this chapter we have seen why chemists heat up reaction mixtures (usually because the reaction goes faster) but in the introduction we also said that, in any organic laboratory, an equal number of reactions are carried out at low temperatures. Why might a chemist want to slow a reaction down? Actually, we already hinted at the answer to this question when we said that it is possible to isolate reactive carbocations. It *is* possible to isolate these reactive intermediates but only at low temperatures. If the temperature is too high then the intermediate will have sufficient energy to overcome the energy barrier leading to the more stable products.

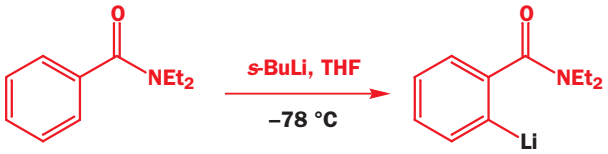
In our discussion of the reactions of acid chlorides, we deduced that a unimolecular reaction to give a cation must be happening. This cation cannot be detected under these conditions as it reacts too quickly with nucleophiles. If we remove reactive nucleophiles from solution, the cation is still too unstable to be isolated at room temperature. But if we go down to –120 °C we can keep the cation alive long enough to run its NMR spectrum.




Lowering the temperature lowers the energies of all of the molecules in the sample. If there are several possible reactions that might occur and if they have different activation energies, we may be able to find a temperature where the population of molecules has only enough energy to surmount the lowest of the alternative energy barriers so that only one reaction occurs. The diazotization of aromatic amines is an example. The reaction involves treating the amine with nitrous acid (HONO) made from $NaNO_2$ and HCl.



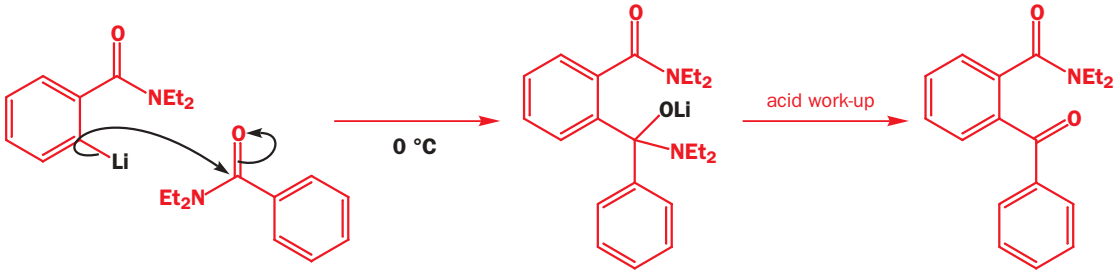

At room temperature the diazonium salt decomposes to the phenol and cannot be used but at 0–5 °C it is stable and can be reacted with other nucleophiles in useful processes discussed in Chapter 23.




Other examples you have met involve lithiated organic molecules. These are always prepared at low temperatures, often at –78 °C. The ortholithiation of aromatic amides was mentioned in Chapter 9.

▶ –78 °C is the convenient temperature of a bath of acetone with solid $CO_2$ dissolved in it.

If the lithiation is carried out at 0 °C, each molecule of lithiated amide attacks another molecule of unlithiated amide in the substitution reaction from Chapter 12.

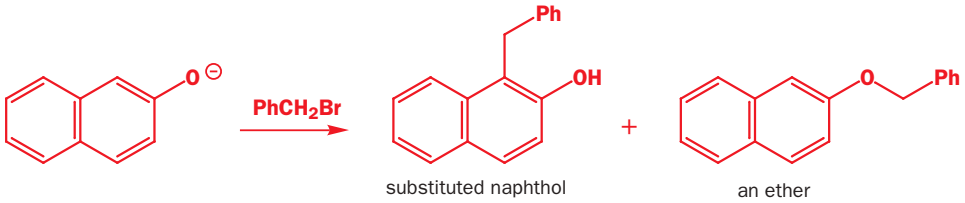


The situation is more critical because of the behaviour of the solvent THF. This cyclic ether is a good solvent for lithiations because it is a good ligand for lithium and it remains liquid at –78 °C. But if lithiations are attempted at higher temperatures, THF also reacts with *s*-BuLi to give surprising by-products discussed in Chapter 35.

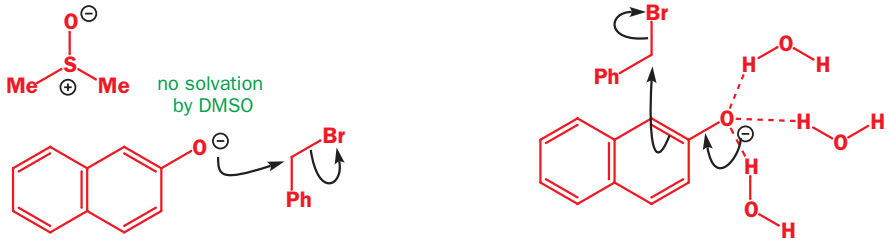

## Solvents

The nature of the solvent used in reactions often has a profound effect on how the reaction proceeds. Often we are limited in our choice of solvent by the solubilities of the reactants and products—this can also be to our advantage when trying to separate products, for example, in ether extractions. We have seen so far in this chapter that THF is a good solvent for lithiations because it coordinates to Li, that water is a good solvent for hydrolyses of carboxylic acids because it is a reagent and because it dissolves the carboxylate anion, and that alcohols are a good solvents in reactions such as transesterifications where mass action is needed to drive equilibria over towards products.

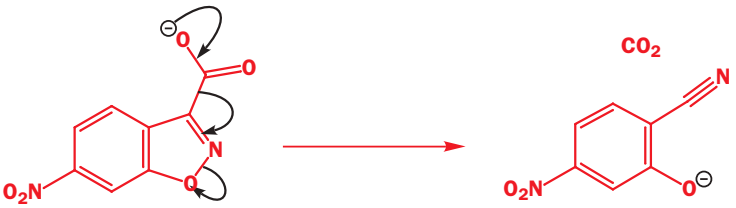
But solvents can affect reactions more drastically; for example, the reaction below gives different products depending on the choice of solvent.




In water the product is almost all benzyl naphthol. However, in DMSO (dimethyl sulfoxide) the major product is the ether. In water the oxyanion is heavily solvated through hydrogen bonds to water molecules and the electrophile cannot push them aside to get close to $O^-$ (this is an entropy effect). DMSO cannot form hydrogen bonds as it has no OH bonds and does not solvate the oxyanion, which is free to attack the electrophile.



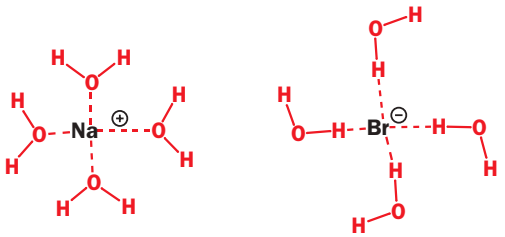

In terms of rates of reaction, where a charged intermediate is formed, a polar solvent will help to stabilize the charge by solvation. Some of this stabilization will already be present in the transition state and solvation will therefore lower the activation energy and speed up the reaction. Turning to a reaction not dealt with elsewhere in the book, an elimination of carbon dioxide, let us see how the rate constant varies with solvent.




■ We shall discuss this type of reaction—fragmentation—in Chapter 38.

These solvents may be divided into three groups—those in which the reaction is slower than in benzene, those in which it is faster, and, of course, benzene itself. The solvents in which the reaction goes relatively slowly all have something in common—they have either O–H or N–H groups. Solvents of this kind are described as **protic solvents**, that is, they are capable of forming hydrogen bonds in solution (though none of these solvents is a good acid). Mechanistically, the important point is that these solvents solvate both cations and anions. The cations are solvated by use of the lone pairs on the oxygen or nitrogen; the anions *via* the hydrogens.

We can illustrate this with a schematic drawing of the solvation of a salt (NaBr) by water.




**Rate of reaction in various solvents**

| Solvent | Rate[a] |
|---|---|
| $H_2O$ | 0.0015 |
| MeOH | 0.052 |
| $HCONH_2$ | 0.15 |
| $C_6H_6$ | 1 |
| acetonitrile, $CH_3CN$ | 600 |
| dimethyl sulfoxide, DMSO, $(CH_3)_2SO$ | 2 100 |
| acetone, $(CH_3)_2CO$ | 5 000 |
| dimethyl formamide, DMF, $HCON(CH_3)_2$ | 7 700 |
| dimethylacetamide, $CH_3CON(CH_3)_2$ | 33 000 |
| hexamethyl phosphoramide, HMPA, $[(CH_3)_2N]_3PO$ | 150 000 |

[a] Relative to reaction in benzene.

**Solubilities of sodium bromide in protic solvents**

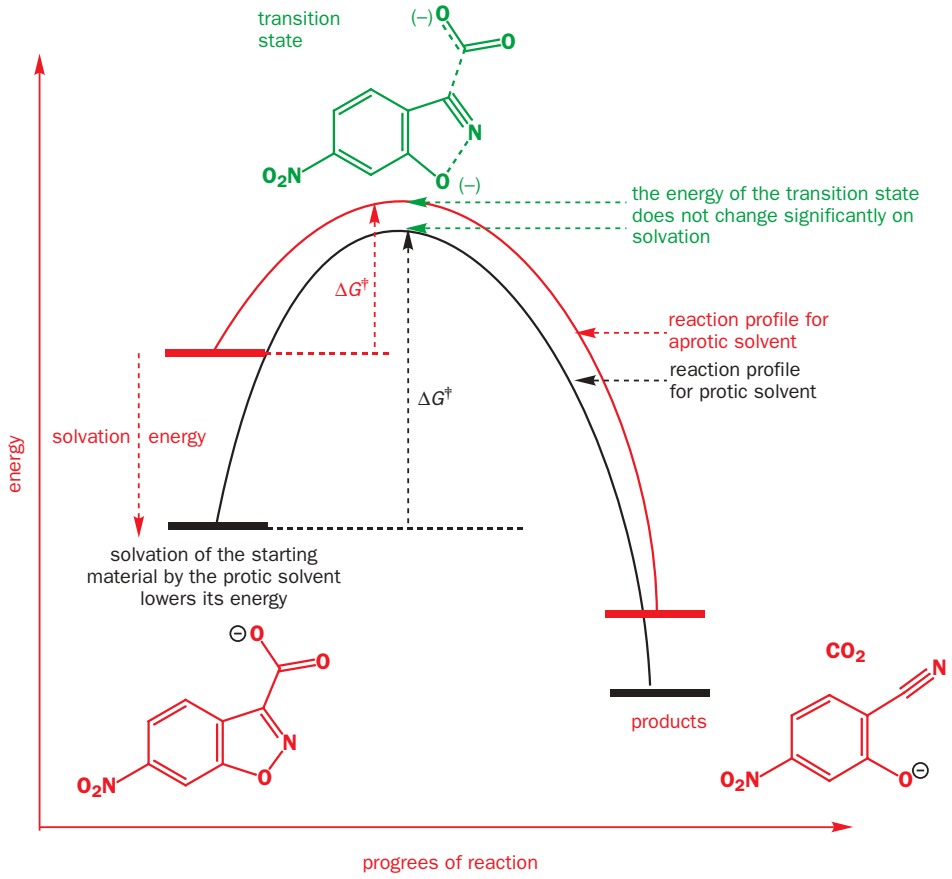
| Solvent | Solubility, g/100 g of solvent |
|---|---|
| $H_2O$ | 90 |
| MeOH | 16 |
| EtOH | 6 |

The solvents in which the reaction proceeds fastest also have something in common—they have an electronegative group (oxygen or nitrogen) but no O–H or N–H bonds. This class is known as polar **aprotic solvents**. Aprotic solvents can still solvate cations but they are unable to solvate anions.

We can now understand the observed trend in the reaction. In the aprotic solvents, the positively charged counterion is solvated and, to some extent, separated from the anion. The anion itself is not solvated and hence is not stabilized; it can therefore react very easily. In protic solvents, such as water, the anion is stabilized by solvation and so is less reactive. We could represent this information on an energy level diagram (overleaf). The main effect of the solvent is on the energy of the starting material—good solvation lowers the energy of the starting material.

The reaction in the aprotic solvent proceeds fastest because the activation energy for this reaction is smallest. This is not because the energy of the transition state is significantly different but because the energy of the starting material has been raised. You might wonder why the energy of the transition state is not stabilized to the same extent as the starting material on changing from an aprotic solvent to a protic solvent. This is because the charge is spread over a number of atoms in the transition state and so it is not solvated to the same extent as the starting material, which has its negative charge localized on the one atom. This is an important point since, if the transition state were stabilized by the same amount as the starting materials, then the reaction would proceed just as quickly in the different solvents since they would then have the same activation energy barriers.

When you meet the new reactions awaiting you in the rest of the book you should reflect that each is controlled by an energy difference. If it is an equilibrium, $\Delta G^\circ$ must be favourable, if a kinetically controlled reaction, $\Delta G^\ddagger$ must be favourable, and either of these could be dominated by enthalpy or entropy and could be modified by temperature control or by choice of solvent.




## Summary of mechanisms from Chapters 6–12

We last discussed mechanisms in Chapter 5 where we introduced basic arrow-drawing. A lot has happened since then and this is a good opportunity to pull some strands together. You may like to be reminded:

1 When molecules react together, one is the *electrophile* and one the *nucleophile*

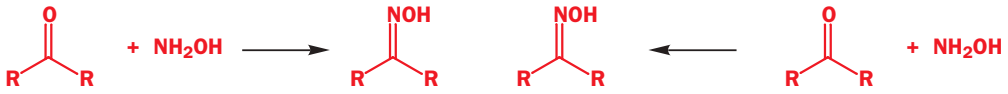
2 In most mechanisms electrons flow from an electron-rich to an electron-poor centre

3 Charge is conserved in each step of a reaction

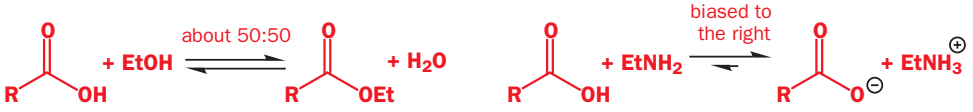
These three considerations will help you draw the mechanism of a reaction that you have not previously met.

### Types of reaction arrows

**1** Simple reaction arrows showing a reaction goes from left to right or right to left



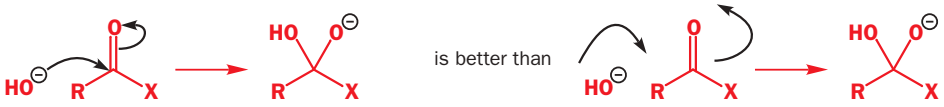

**2** Equilibrium arrows showing extent and direction of equilibrium



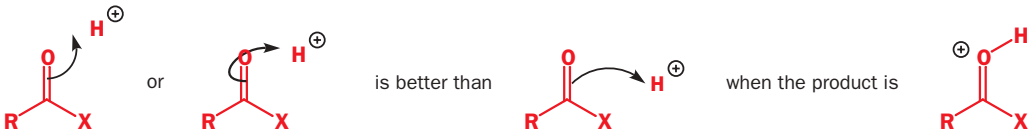
**3** Delocalization or conjugation arrows showing two different ways to draw the same molecule. The two structures ('canonical forms' or 'resonance structures') must differ only in the position of electrons


## Types of curly arrows

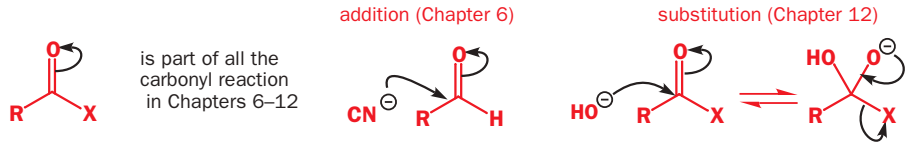
**1** The curly arrow should show clearly where the electrons come from and where they go to




**2** If electrophilic attack on a π or σ bond leads to the bond being broken, the arrows should show clearly which atom bonds to the electrophile

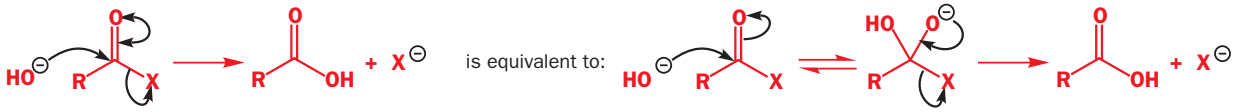



**3** Reactions of the carbonyl group are dominated by the breaking of the π bond. If you use this arrow first on an unfamiliar reaction of a carbonyl compound, you will probably find a reasonable mechanism

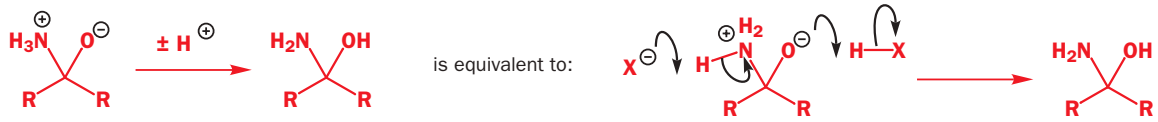



## Short cuts in drawing mechanisms

**1** The most important is the double-headed arrow on the carbonyl group used during a substitution reaction




**2** The symbol $\pm H^+$ is shorthand for the gain and loss of a proton in the same step (usually involving N, O, or S)



# Nucleophilic substitution at C=O with loss of carbonyl oxygen

# 14

## Connections

**Building on:**

- Nucleophilic attack on carbonyl groups ch6
- Nucleophilic substitution at carbonyl groups ch12
- Acidity and p$K_a$ ch8
- Rate and pH ch13

**Arriving at:**

- Replacement of carbonyl oxygen
- Acetal formation
- Imine formation
- Stable and unstable imines
- Reductive amination
- The Strecker and Wittig reactions

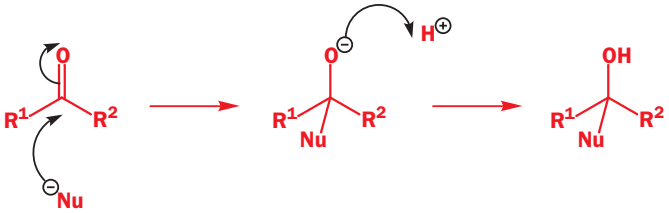
**Looking forward to:**

- Protecting groups ch24
- Synthesis in action ch25
- Acylation of enolates ch28
- Synthesis of amino acids ch49
- Synthesis of alkenes ch31
- Stereochemistry ch16
- Asymmetric synthesis ch45

## Introduction

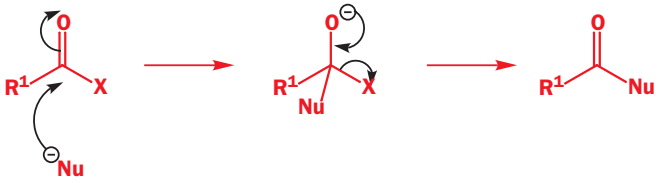
Nucleophiles add to carbonyl groups to give compounds in which the trigonal carbon atom of the carbonyl group has become tetrahedral.

nucleophilic addition to a carbonyl group



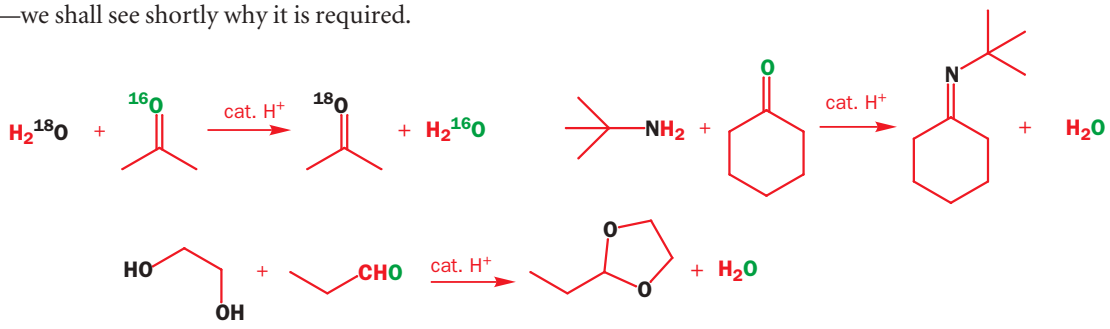

In Chapter 12 you saw that these compounds are not always stable: if the starting material contains a leaving group, the addition product is a **tetrahedral intermediate**, which collapses with loss of the leaving group to give back the carbonyl group, with overall substitution of the leaving group by the nucleophile.

nucleophilic substitution at a carbonyl group

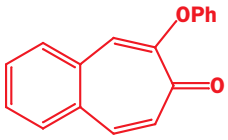



In this chapter, you will meet more substitution reactions of a different type. Instead of losing a leaving group, the carbonyl group loses its oxygen atom. Here are three examples: the carbonyl oxygen atom has been replaced by an atom of $^{18}O$, a nitrogen atom, and two atoms of oxygen. Notice too the acid catalyst—we shall see shortly why it is required.

nucleophilic substitution at a carbonyl group with loss of carbonyl oxygen



You have, in fact, already met some reactions in which the carbonyl oxygen atom can be lost, but you probably didn't notice at the time. The equilibrium between an aldehyde or ketone and its hydrate (p. 000) is one such reaction.

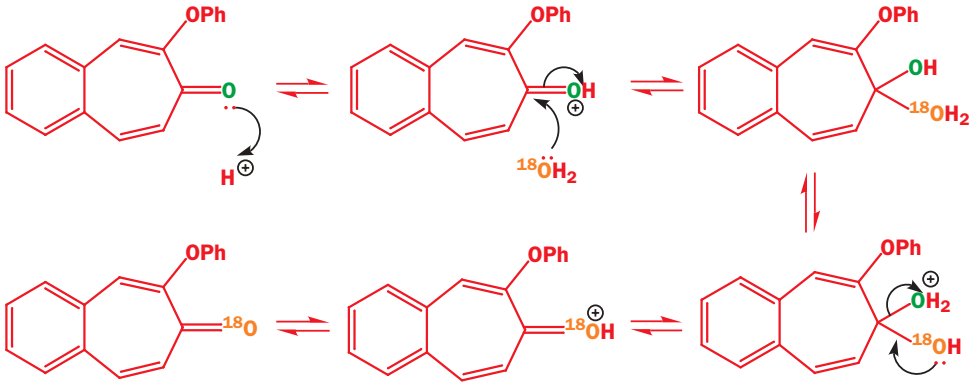




When the hydrate reverts to starting materials, either of its two oxygen atoms must leave: one came from the water and one from the carbonyl group, so 50% of the time the oxygen atom that belonged to the carbonyl group will be lost. Usually, this is of no consequence, but it can be useful. For example, in 1968 some chemists studying the reactions that take place inside mass spectrometers needed to label the carbonyl oxygen atom of this ketone with the isotope $^{18}O$.

By stirring the 'normal' $^{16}O$ compound with a large excess of isotopically labelled water, $H_2{}^{18}O$, for a few hours in the presence of a drop of acid they were able to make the required labelled compound. Without the acid catalyst, the exchange is very slow. Acid catalysis speeds the reaction up by making the carbonyl group more electrophilic so that equilibrium is reached more quickly. The equilibrium is controlled by mass action—$^{18}O$ is in large excess.

■

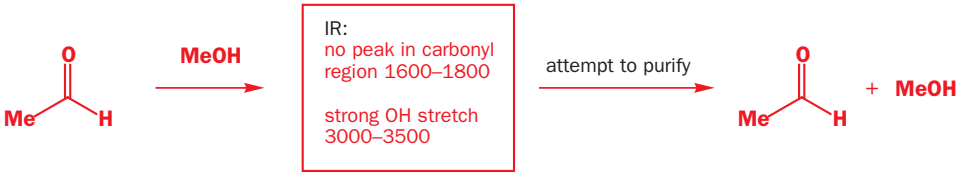
In Chapter 13 we saw this way of making a reaction go faster by raising the energy of the starting material. We also saw that the position of an equilibrium can be altered by using a large excess of one of the reagents. This is often called a **mass action effect**.



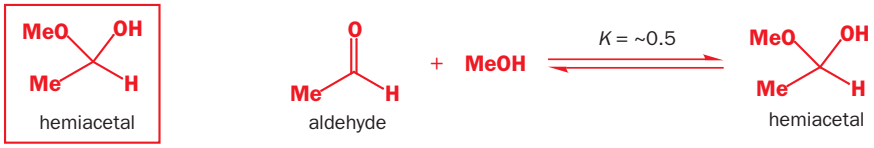

We need now to discuss hemiacetals though you may well wonder why – they retain the carbonyl oxygen and they are unstable. We need to discuss them as a preliminary to the much more important acetals. Hemiacetals are halfway to acetals.

## Aldehydes can react with alcohols to form hemiacetals

When acetaldehyde is dissolved in methanol, a reaction takes place: we know this because the IR spectrum of the mixture shows that a new compound has been formed. However, isolating the product is impossible: it decomposes back to acetaldehyde and methanol.




The product is in fact a hemiacetal. Like hydrates, most hemiacetals are unstable with respect to their parent aldehydes and alcohols: for example, the equilibrium constant for reaction of acetaldehyde with simple alcohols is about 0.5 as we saw in Chapter 13.



This equilibrium constant $K$ is defined as

$$K = \frac{[\text{hemiacetal}]}{[\text{aldehyde}][\text{MeOH}]}$$

So by making [MeOH] very large (using it as the solvent, for example) we can turn most of the aldehyde into the hemiacetal. However, if we try and purify the hemiacetal by removing the methanol, more hemiacetal keeps decomposing to maintain the equilibrium constant. That is why we can never isolate such hemiacetals in a pure form.

■ These are more 'mass action' effects like the $^{18}O$ exchange we have just discussed.

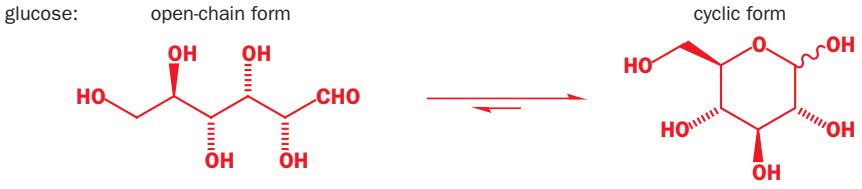
## Only a few hemiacetals are stable

Like their hydrates, the hemiacetals of most ketones (sometimes called **hemiketals**) are even less stable than those of aldehydes. On the other hand, some hemiacetals of aldehydes bearing electron-withdrawing groups, and those of cyclopropanones, are stable, just like the hydrates of the same molecules.

■ We discussed the reasons for this in Chapter 6.


a stable hemiacetal

Hemiacetals that can be formed by intramolecular cyclization of an alcohol on to an aldehyde are also often stable, especially if a five- or six-membered ring is formed. You met this in Chapter 6—many sugars (for example, glucose) are cyclic hemiacetals, and exist in solution as a mixture of open-chain and cyclic forms.




0.003% > 99%

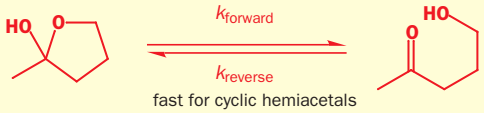
### Why are cyclic hemiacetals stable?

Part of the reason for the stability of cyclic hemiacetals concerns *entropy*. Formation of an acyclic acetal involves a decrease in entropy ($\Delta S°$ negative) because two molecules are consumed for every one produced. This is not the case for formation of a cyclic hemiacetal. Since $\Delta G° = \Delta H° - T\Delta S°$, a reaction with a negative $\Delta S°$ tends to have a more positive $\Delta G°$; in other words, it is less favourable.

Another way to view the situation is to consider the rates of the forward and reverse processes. We can measure the stability of a cyclic hemiacetal by the equilibrium constant $K$ for the ring-opening reaction: a large $K$ means lots of ring-opened product, and therefore an unstable hemiacetal, and a small $K$ means lots of ring-closed product: a stable hemiacetal. After reading Chapter 13 you should appreciate that an equilibrium constant is simply the rate of the forward reaction divided by the rate of the reverse reaction. So, for a stable hemiacetal, we need a fast hemiacetal-forming reaction. And when the hemiacetal is cyclic that is just what we do have: the reaction is intramolecular and the nucleophilic OH group is always held close to the carbonyl group, ready to attack.

equilibrium constant

$$K = \frac{k_{\text{forward}}}{k_{\text{reverse}}}$$

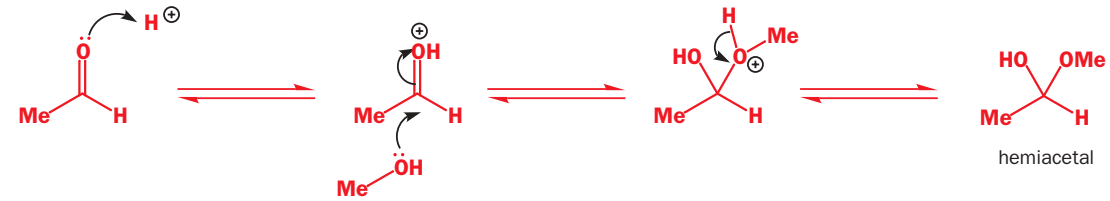



fast for cyclic hemiacetals

## Acid or base catalysts increase the rate of equilibration of hemiacetals with their aldehyde and alcohol parents

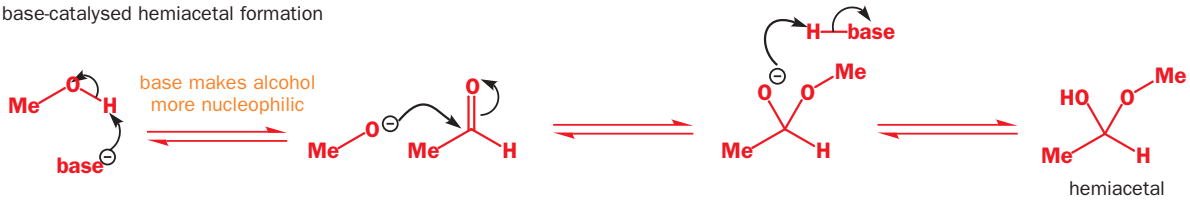
Acyclic hemiacetals form relatively slowly from an aldehyde or ketone plus an alcohol, but their rate of formation is greatly increased either by acid or by base. As you would expect, after Chapters 12 and 13, acid catalysts work by increasing the electrophilicity of the carbonyl group.

acid-catalysed hemiacetal formation



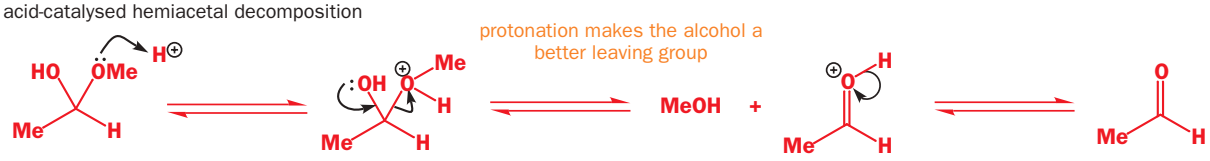

Base catalysts, on the other hand, work by increasing the nucleophilicity of the alcohol by removing the OH proton before it attacks the C=O group. In both cases the energy of the starting materials is raised: in the acid-catalysed reaction the aldehyde is destabilized by protonation and in the base-catalysed reaction the alcohol is destabilized by deprotonation.

base-catalysed hemiacetal formation

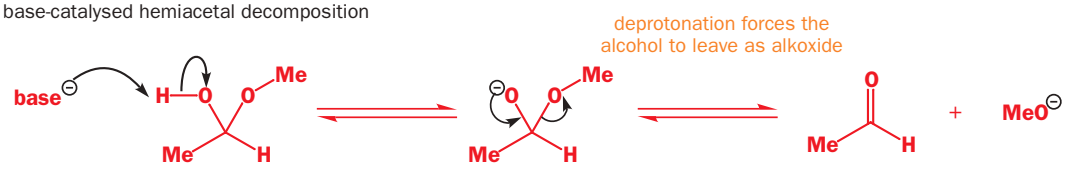



You can see why hemiacetals are unstable: they are essentially tetrahedral intermediates containing a leaving group and, just as acid or base catalyses the formation of hemiacetals, acid or base also catalyses their decomposition back to starting aldehyde or ketone and alcohol. That's why the title of this section indicated that acid or base catalysts increase the rate of equilibration of hemiacetals with their aldehyde and alcohol components—the catalysts do not change the position of that equilibrium!

acid-catalysed hemiacetal decomposition

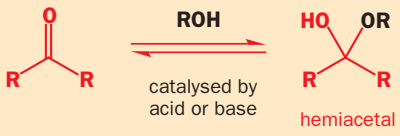



base-catalysed hemiacetal decomposition




**To summarize**

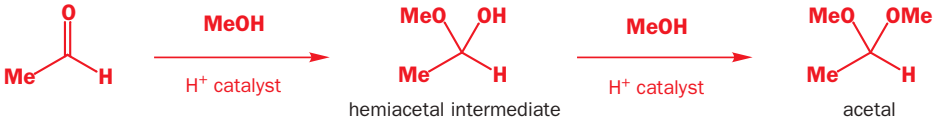
**Hemiacetal formation and decomposition are catalysed by acid or base.**




## Acetals are formed from aldehydes or ketones plus alcohols in the presence of acid

We said that a solution of acetaldehyde in methanol contains a new compound: a hemiacetal. We've also said that the rate of formation of hemiacetals is increased by adding an acid (or a base) catalyst to an alcohol plus aldehyde mixture. But, if we add catalytic acid to our acetaldehyde–methanol

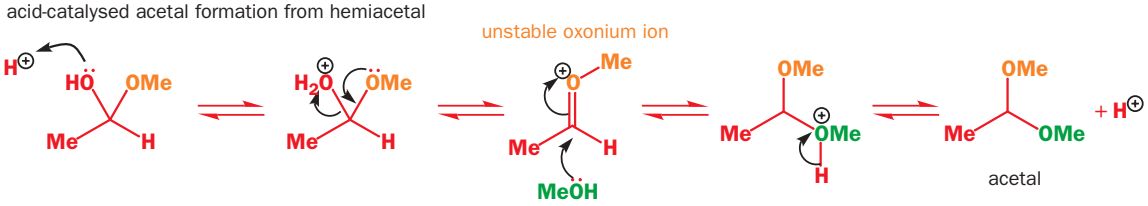
mixture, we find not only that the rate of reaction of the acetaldehyde with the methanol increases, but also that a different product is formed. This product is an **acetal**.




In the presence of acid (but not base!) hemiacetals can undergo an elimination reaction (different from the one that just gives back aldehyde plus alcohol), losing the oxygen atom that once belonged to the parent aldehyde's carbonyl group. The stages are:

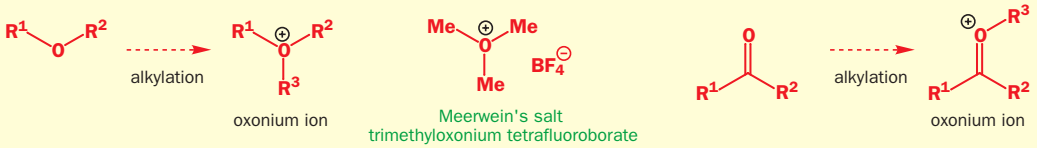
1. Protonation of the hydroxyl group of the hemiacetal
2. Loss of water by elimination. This elimination leads to an unstable and highly reactive oxonium ion
3. Addition of methanol to the oxonium ion (breaking the π bond and not the σ bond, of course)
4. Loss of a proton to give the acetal

acid-catalysed acetal formation from hemiacetal




## Oxonium ions

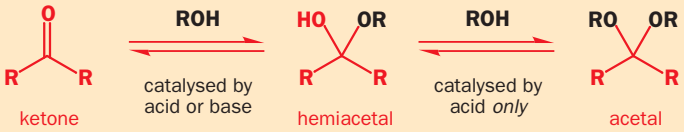
Oxonium ions have three bonds to a positively charged oxygen atom. All three bonds can be σ bonds as in $H_3O^+$ or Meerwein's salt, trimethyloxonium fluoroborate, a stable (though reactive) compound described in Chapter 21, or one bond can be a π bond as in the acetal intermediate. The term 'oxonium ion' describes either of these structures. They are like alkylated ethers or *O*-alkylated carbonyl compounds.




Just as protonated carbonyl groups are much more electrophilic than unprotonated ones, these oxonium ions are powerful electrophiles. They can react rapidly with a second molecule of alcohol to form new, stable compounds known as **acetals**. An oxonium ion was also an intermediate in the formation of hemiacetals in acid solution. Before reading any further, it would be worthwhile to write out the whole mechanism of acetal formation from aldehyde or ketone plus alcohol through the hemiacetal to the acetal, preferably without looking at the fragments of mechanism above, or the answer below.

## Formation of acetals and hemiacetals

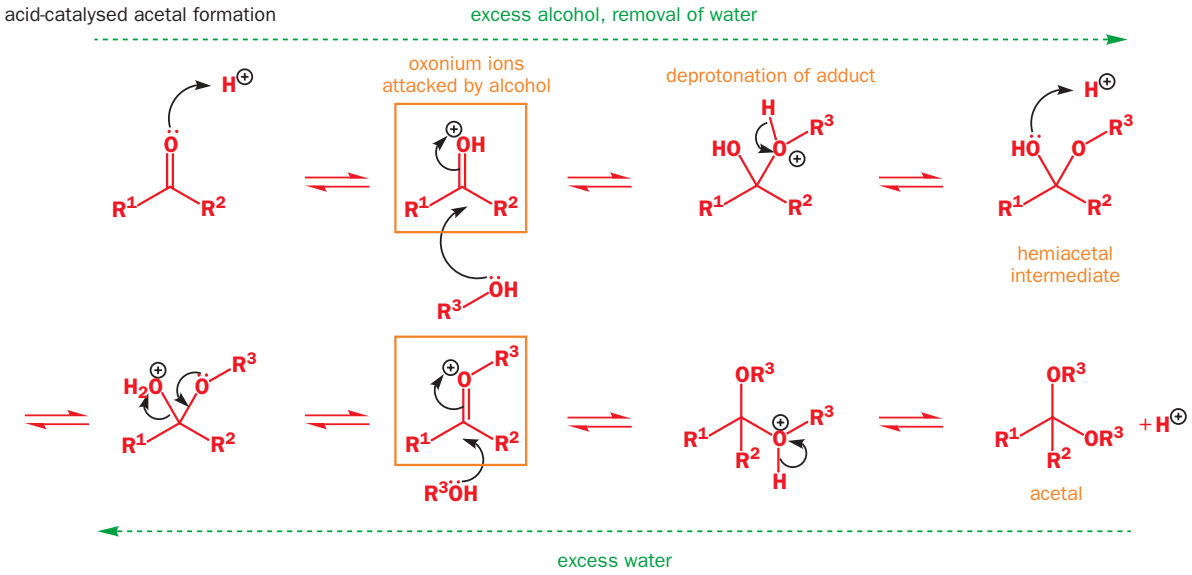
**Hemiacetal formation is catalysed by acid or base, but acetal formation is possible only with an acid catalyst because an OH group must be made into a good leaving group.**




When you look at our version of this complete mechanism you should notice a remarkable degree of similarity in the two halves. The reaction starts with a protonation on carbonyl oxygen and, when

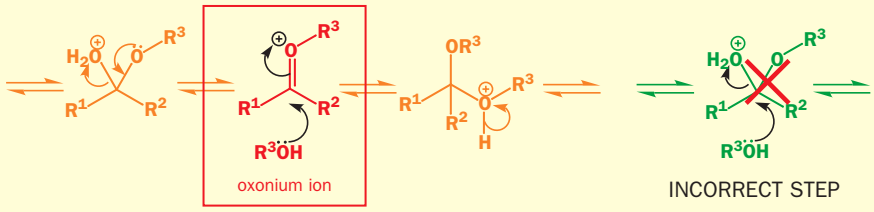
you get to the temporary haven of the hemiacetal, you start again with protonation of that same oxygen. Each half goes through an oxonium ion and each oxonium ion adds the alcohol. The last step in the formation of both the acetal and the hemiacetal is the loss of a proton from the recently added alcohol.

This is about as complex a mechanism as you have seen and it will help you to recall it if you see it in two halves, each very similar to the other. First, form the hemiacetal by adding an alcohol to the C=O π bond; then lose the OH group by breaking what was the C=O σ bond to form an oxonium ion and add a second alcohol to form the acetal. From your complete mechanism you should also be able to verify that acetal formation is indeed catalytic in acid.




**Remember the oxonium ion!**

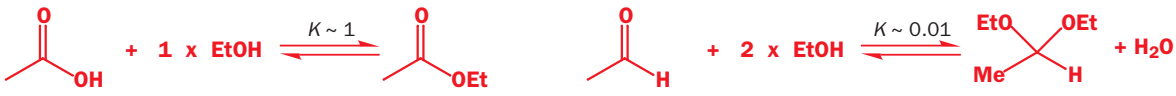
When you wrote out your mechanism for acetal formation, we hope you didn't miss out the oxonium ion! It's easy to do so, but the mechanism most definitely does not go via a direct displacement of water by alcohol.




If you wonder how we know this, consult a specialized book on organic reaction mechanisms. After you have read Chapter 17 in this book, you will be able to spot that this substitution step goes via an $S_N1$ and not an $S_N2$ mechanism.

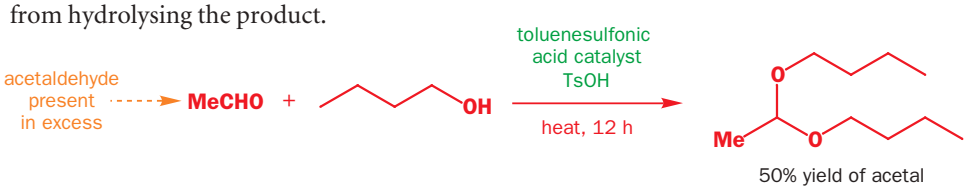
## Making acetals

Just as with the ester formation and hydrolysis reactions we discussed in Chapters 12 and 13, every step in the formation of an acetal is reversible. To make acetals, therefore, we must use an excess of alcohol or remove the water from the reaction mixture as it forms, by distillation, for example.



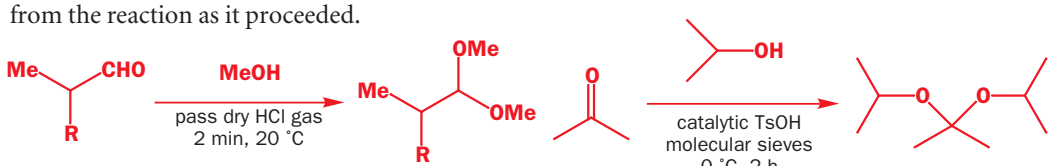

In fact, acetal formation is even more difficult than ester formation: while the equilibrium constant for acid-catalysed formation of ester from carboxylic acid plus alcohol is usually about 1, for

acetal formation from aldehyde and ethanol (shown above), the equilibrium constant is $K = 0.0125$. For ketones, the value is even lower: in fact, it is often very difficult to get the acetals of ketones (these used to be called ketals) to form unless they are cyclic (we consider cyclic acetals later in the chapter). However, there are several techniques that can be used to prevent the water produced in the reaction from hydrolysing the product.




50% yield of acetal

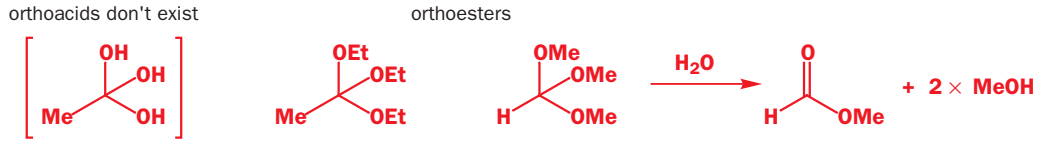
In these two examples, with the more reactive aldehyde, it was sufficient just to have an excess of one of the reagents (acetaldehyde) to drive the reaction to completion. Dry HCl gas can work too. In the second example, with a less reactive ketone, molecular sieves (zeolite) were used to remove water from the reaction as it proceeded.




60% yield 62% yield

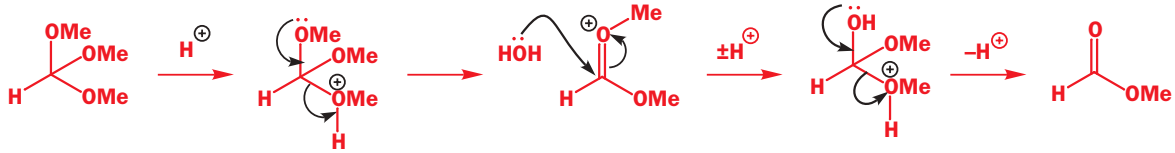
## Overcoming entropy: orthoesters

We have already mentioned that one of the factors that makes acyclic *hemi*acetals unstable is the unfavourable decrease in entropy when two molecules of starting material (aldehyde or ketone plus alcohol) become one of product. The same is true for acetal formation, when three molecules of starting material (aldehyde or ketone plus 2 × alcohol) become two of product (acetal plus $H_2O$). We can improve matters if we tie the two alcohol molecules together in a diol and make a cyclic acetal: we discuss cyclic acetals in the next section. Alternatively, we can use an **orthoester** as a source of alcohol. Orthoesters can be viewed as the 'acetals of esters' or as the triesters of the unknown 'orthoacids'—the hydrates of carboxylic acids. They are hydrolysed by water, catalysed by acid, to ester + 2 × alcohol.

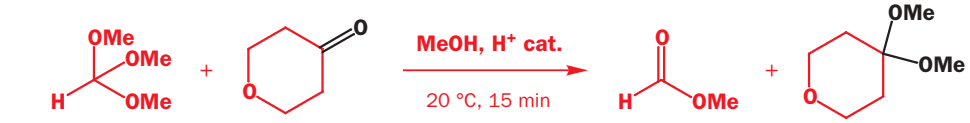



orthoacetic acid triethyl orthoacetate trimethyl orthoformate

Here is the mechanism for the hydrolysis—you should be feeling quite familiar with this sort of thing by now.

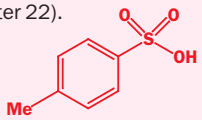



Ketones or aldehydes can undergo **acetal exchange** with orthoesters. The mechanism starts off as if the orthoester is going to hydrolyse but the alcohol released adds to the ketone and acetal formation begins. The water produced is taken out of the equilibrium by hydrolysis of the orthoester.

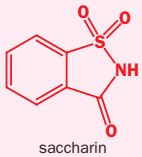



trimethyl orthoformate methyl formate

▶ *para*-Toluenesulfonic acid is commonly used to catalyse reactions of this sort. It is a stable solid, yet is as strong an acid as sulfuric acid. It is widely available and cheap because it is produced as a by-product in the synthesis of saccharin (for more details, see Chapter 22).



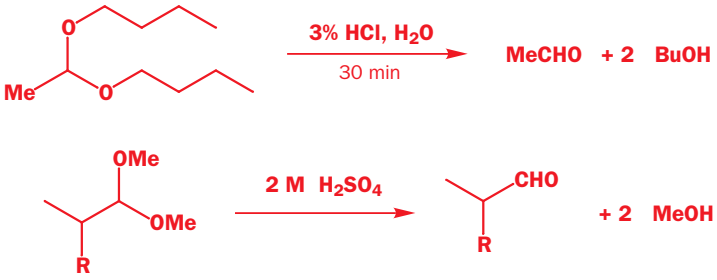

*p*-toluenesulfonic acid




saccharin

## Acetals hydrolyse only in the presence of acid

Just as acetal formation requires acid catalysis, acetals can be hydrolysed only by using an acid catalyst. With aqueous acid, the hydrolysis of acyclic acetals is very easy. Our examples are the two acetals we made earlier.



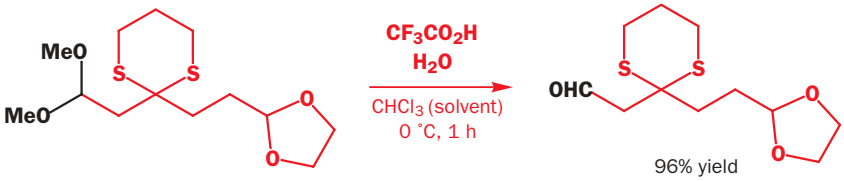

**Acetal hydrolysis**

**Acetals can be hydrolysed in acid but are stable to base.**

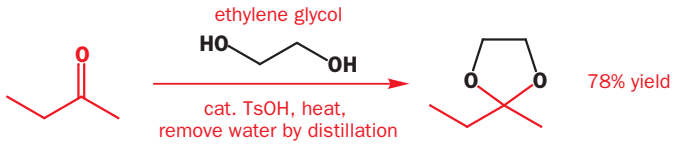
We won't go through the mechanism again—you've already seen it as the reverse of acetal formation (and you have a hint of it in the orthoester hydrolysis just discussed), but the fact that acetals are stable to base is really a very important point, which we will use on p. 000 and capitalize on further in Chapter 24.

## Cyclic acetals are more stable towards hydrolysis than acyclic ones

Of course you want us to prove it: well—

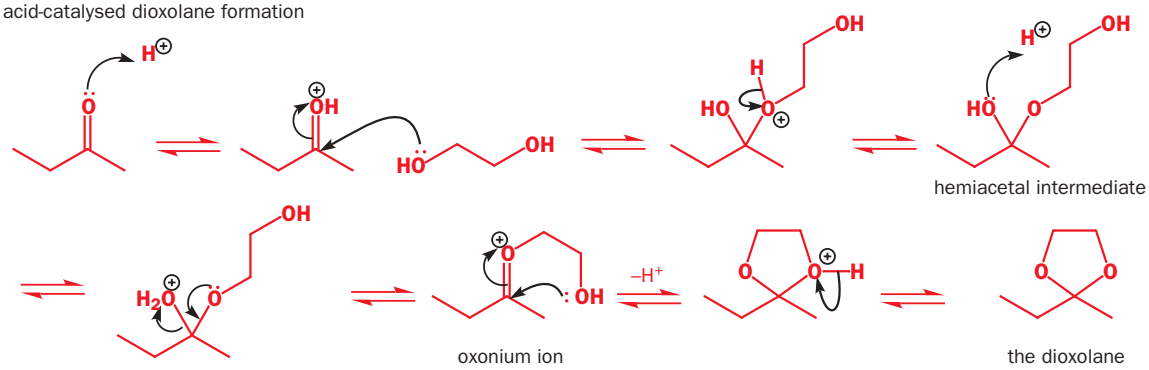



The acetals you have met so far were formed by reaction of two molecules of alcohol with one of carbonyl compound. Cyclic acetals, formed by reaction of a single molecule of a diol, a compound containing two hydroxyl groups, are also important. When the diol is ethylene glycol (as in this example) the five-membered cyclic acetal is known as a **dioxolane**.




Before looking at the answer below, try to write a mechanism for this reaction. If you need it, use the mechanism we gave for the formation of acyclic acetals.

acid-catalysed dioxolane formation




▶ We hope you didn't make the mistake of missing out the oxonium ion step!

Cyclic acetals like this are more resistant to hydrolysis than acyclic ones and easier to make—they form quite readily even from ketones. Again, we have entropic factors to thank for their stability. For the formation of a cyclic acetal, two molecules go in (ketone plus diol) and two molecules come out (acetal plus water), so the usually unfavourable $\Delta S^{\circ}$ factor is no longer against us. And, as for hemiacetals (see the explanation above), equilibrium tends to lie to the acetal side because the intramolecular ring-closing reaction is fast.

Water is still generated, and needs to be got rid of: in the example above you can see that water was distilled out of the reaction mixture. This is possible with these diols because they have a boiling point above that of water (the boiling point of ethylene glycol is 197 °C). You can't distil water from a reaction mixture containing methanol or ethanol, because the alcohols distil too! One very useful piece of equipment for removing water from reaction mixtures containing only reagents that boil at higher temperatures than water is called a **Dean Stark head**: there is a picture of this in Chapter 13.

▶ Don't be confused by this statement! Acetal formation and hydrolysis are invariably carried out under thermodynamic control—what we mean here is that the equilibrium constant for acetal hydrolysis, which is a measure of rate of hydrolysis divided by rate of formation, turns out to be small because the rate of formation is large.

▶ **Dean Stark head**

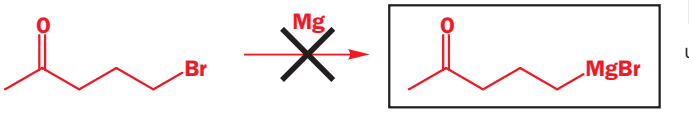
When a mixture of toluene and water boils, the vapour produced is a constant ratio mixture of toluene vapour and water vapour known as an **azeotrope**. If this mixture is condensed, the liquid toluene and water, being immiscible, separate out into two layers with the water below. By using a Dean Stark apparatus, or Dean Stark head, the toluene layer can be returned to the reaction mixture while the water is removed. Reactions requiring removal of water by distillation are therefore often carried out in refluxing toluene or benzene under a Dean Stark head.

## Modifying reactivity using acetals

Why are acetals so important? Well, they're important to both nature and chemists because many carbohydrates are acetals or hemiacetals (see the box below). One important use that chemists have put them to is as *protecting groups*.

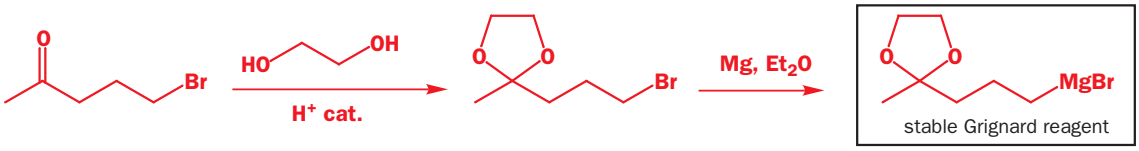
One important synthesis of the steroid class of compounds (about which more later) requires a Grignard reagent with this structure.

■ We shall discuss protecting groups in much more detail in Chapter 24.




unstable structure – impossible to make

Yet this compound cannot exist: it would react with itself. Instead, this Grignard reagent is used, made from the same bromoketone, but with an acetal-forming step.

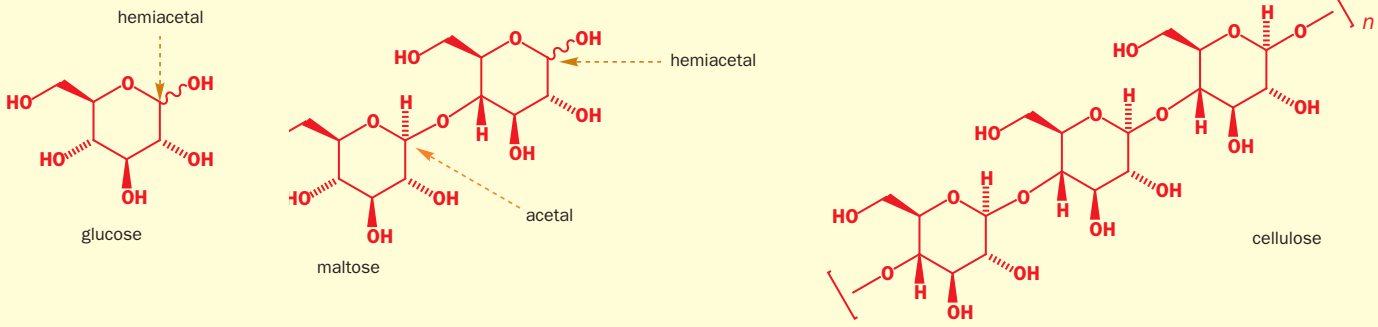



stable Grignard reagent

Acetals, as we stressed, are stable to base, and to basic nucleophiles such as Grignard reagents, so we no longer have a reactivity problem. Once the Grignard reagent has reacted with an electrophile, the ketone can be recovered by hydrolysing the acetal in dilute acid. The acetal is functioning here as

### Acetals in nature

We showed you glucose as an example of a stable, cyclic hemiacetal. Glucose can, in fact, react with itself to form an acetal known as maltose.

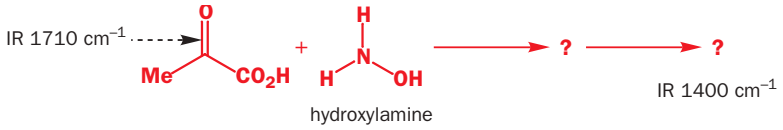


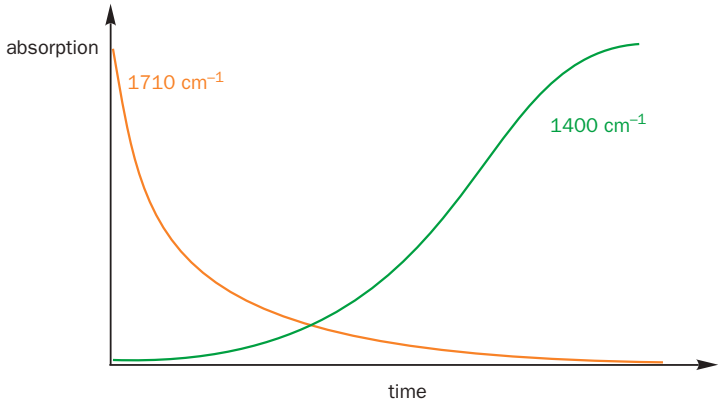

Maltose is a disaccharide (made of two sugar units) produced by the enzymatic hydrolysis of starch or cellulose, which are themselves polyacetals made up of a string of glucose units.

a **protecting group** because it protects the ketone from attack by the Grignard reagent. Protecting groups are extremely important in organic synthesis, and we will return to them in Chapter 24.

## Amines react with carbonyl compounds

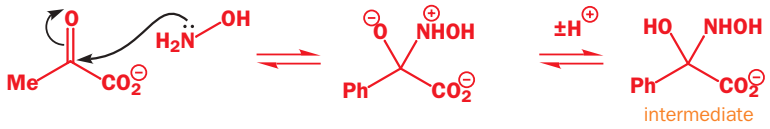
The ketone carbonyl group of pyruvic acid (or 2-oxopropanoic acid) has a stretching frequency of a typical ketone, 1710 $cm^{-1}$. When hydroxylamine is added to a solution of pyruvic acid, this stretching frequency slowly disappears. Later, a new IR absorption appears at 1400 $cm^{-1}$. What happens?



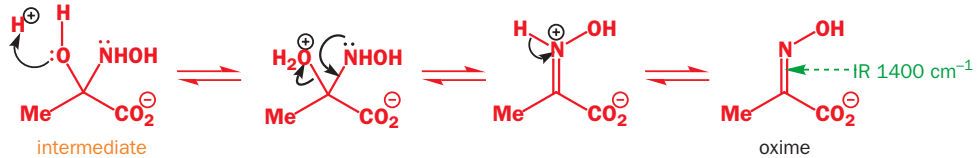

Well, you saw a diagram like this in the last chapter when we were discussing kinetic and thermodynamic products (p. 000) and you can probably also apply something of what you now know about the reactivity of carbonyl compounds towards nucleophiles to work out what is happening in this reaction between a carbonyl compound and an amine. The hydroxylamine first adds to the ketone to form an unstable intermediate such as a hemiacetal.

intermediate formation

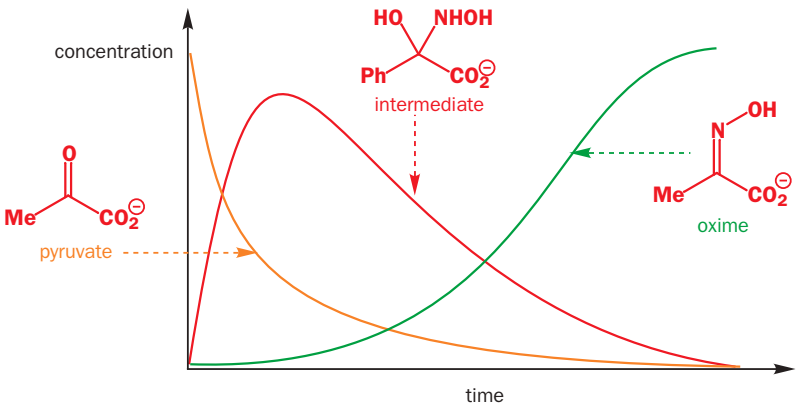



Notice that it is the more nucleophilic nitrogen atom, and not the oxygen atom, of hydroxylamine that adds to the carbonyl group. Like hemiacetals, these intermediates are unstable and can decompose by loss of water. The product is known as an **oxime** and it is this compound, with its C=N double bond, that is responsible for the IR absorption at 1400 $cm^{-1}$.

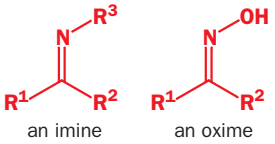
dehydration of the intermediate to give oxime




We know that the oxime is formed via an intermediate because the 1400 $cm^{-1}$ absorption hardly appears until after the 1710 $cm^{-1}$ absorption has almost completely gone. We also know something must be there because, by IR, everything has disappeared. There must really be another curve to show the formation and the decay of the intermediate, the hemiacetal, just like the one in the last chapter (p. 000). The only difference is that the intermediate has no double bond to give an IR absorbance. We come back to oximes later in the chapter.

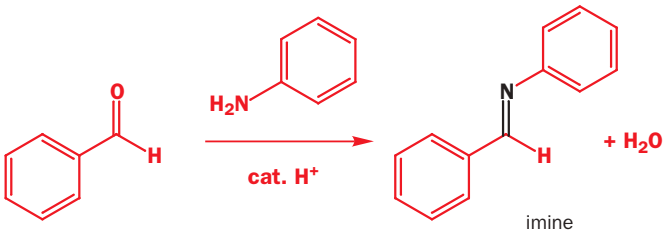



## Imines are the nitrogen analogues of carbonyl compounds

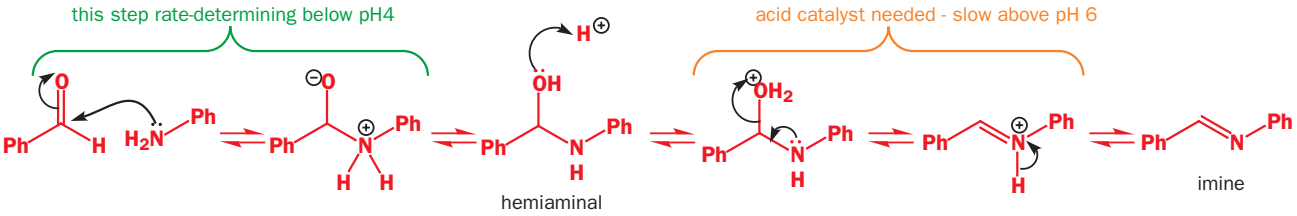



In fact, the oxime formed from a ketone and hydroxylamine is just a special example of an **imine**.

Imines are formed when any primary amine reacts with an aldehyde or a ketone under appropriate conditions: for example, cyclohexylamine and benzaldehyde.



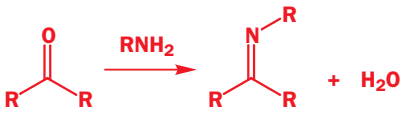

You shouldn't need us to tell you the mechanism of this reaction: even without looking at the mechanism we gave for the formation of the oxime it should come as no surprise to you by now. First, the amine attacks the aldehyde and the intermediate is formed. Dehydration gives the imine.

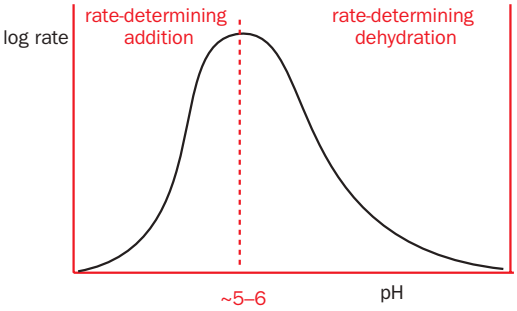



**Imine formation requires acid catalysis.**

Notice that an acid catalyst is normally added for imine formation. Without an acid catalyst, the reaction is very slow, though in some cases it may still take place (oximes, for example, will form without acid catalysis, but form much faster with it). It's important to notice that acid is not needed for the addition step in the mechanism (indeed, protonation of the amine means that this step is very *slow* in strong acid), but *is* needed for the elimination of water later on in the reaction. Imine formation is in fact fastest at about pH 4–6: at lower pH, too much amine is protonated and the rate of the first step is slow; above this pH the proton concentration is too low to allow protonation of the OH leaving group in the dehydration step. Imine formation is like a biological reaction: it is fastest near neutrality.

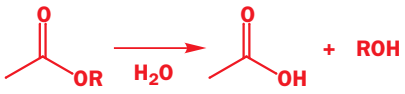
variation of rate of imine formation with pH

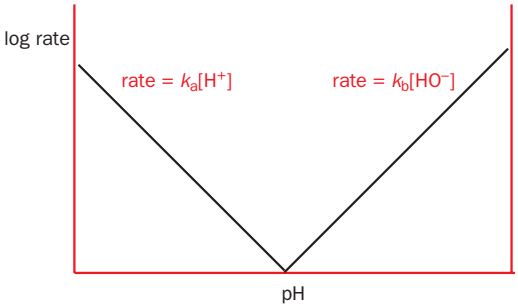



Either side of pH 5–6 the reaction goes more slowly. This is a sign of a change in rate-determining step. Where there is a choice between two rate-determining steps, the *slower* of the two determines the overall rate of the reaction. In the last chapter we saw that ester hydrolysis was a typical example of an organic reaction showing acid and base catalysis. It has a minimum rate at about neutrality showing that the mechanism must change. Where there is a choice of mechanism, the faster of the two operates. The contrast between the two is obvious from the diagrams.

variation of rate of ester hydrolysis with pH



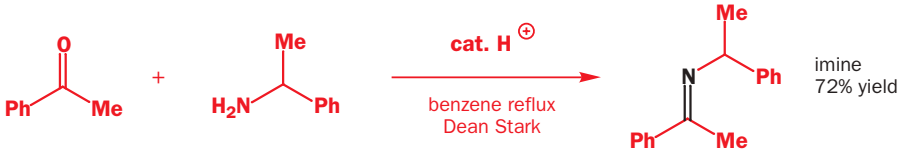

**Multistep reaction rates**

**The overall rate of a multistep reaction is decided by:**

- **The *faster* of two available mechanisms**
- **The *slower* of two rate-determining steps**

## Imines are usually unstable and are easily hydrolysed

Like acetals, imines are unstable with respect to their parent carbonyl compound and amine, and must be formed by a method that allows removal of water from the reaction mixture.

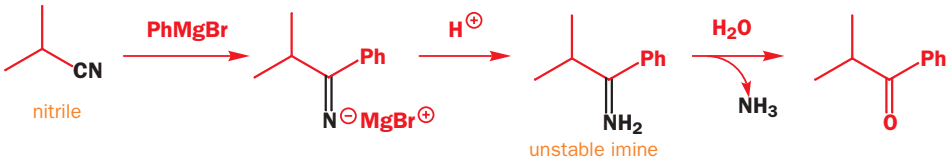



Imines are formed from aldehydes or ketones with most primary amines. In general, they are only stable enough to isolate if either the C or N of the imine double bond bears an aromatic substituent. Imines formed from ammonia are unstable, but can be detected in solution. $CH_2{=}NH_2$, for example, decomposes at temperatures above –80 °C, but PhCH=NH is detectable by UV spectroscopy in a mixture of benzaldehyde and ammonia in methanol.


Imines are readily hydrolysed back to carbonyl compound and amine by aqueous acid—in fact,

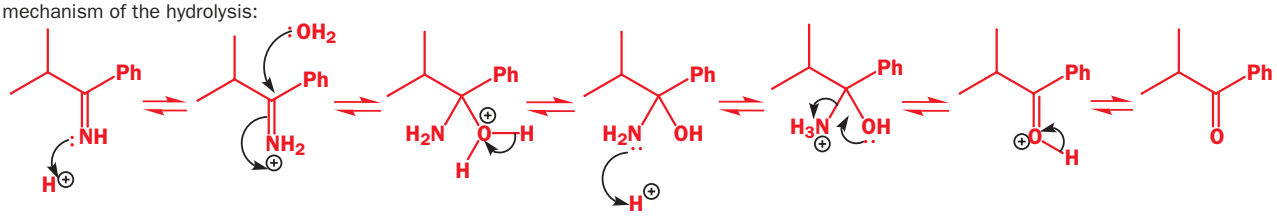
▶ Because it is made from an unsymmetrical ketone, this imine can exist as a mixture of *E* and *Z* isomers, just like an alkene. When it is formed by this method, the ratio obtained is 8:1 *E*:*Z*. Unlike the geometrical isomers of alkenes, however, those of an imine are usually unstable and interconvert quite rapidly at room temperature. The geometrical isomers of oximes, on the other hand, are stable and can even be separated.

except for the particularly stable special cases we discuss on p. 000, most can be hydrolysed by water without acid or base catalysis.



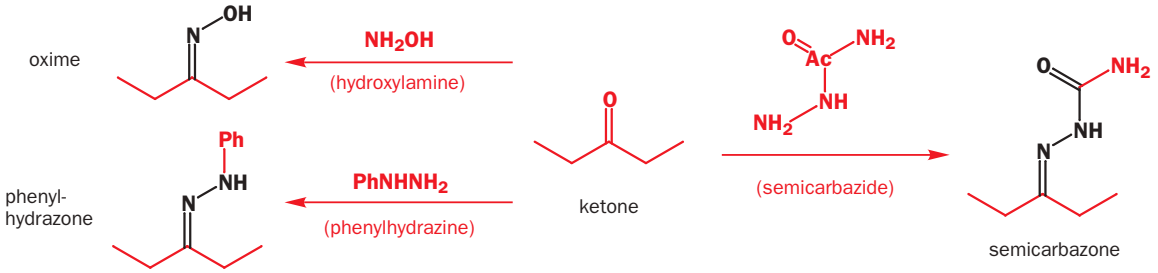

You have, in fact, already met an imine hydrolysis: at the end of Chapter 12 we talked about the addition of Grignard reagents to nitriles. The product is an imine that hydrolyses in acid solution to ketone plus ammonia.

mechanism of the hydrolysis:

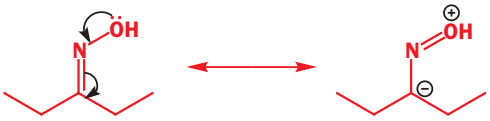



## Some imines are stable

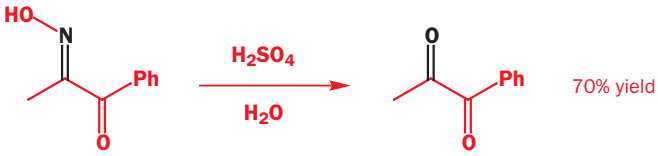
Imines in which the nitrogen atom carries an electronegative group are usually stable: examples include **oximes**, **hydrazones**, and **semicarbazones**.




These compounds are more stable than imines because the electronegative substituent can participate in delocalization of the imine double bond. Delocalization decreases the δ+ charge on the carbon atom of the imine double bond and raises the energy of the LUMO, making it less susceptible to nucleophilic attack.

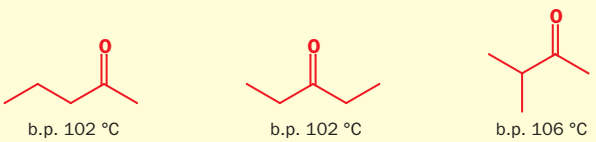



Oximes, hydrazones, and semicarbazones require acid or base catalysis to be hydrolysed.




### Historical note

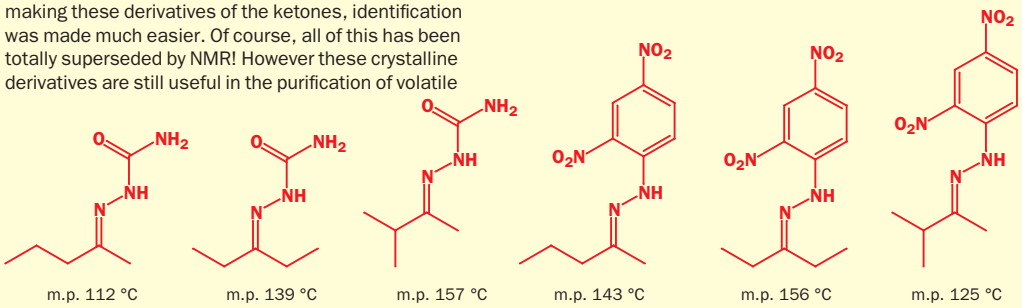
Because the hydrazone and semicarbazone derivatives of carbonyl compounds are often stable, crystalline solids, they used to be used to confirm the supposed identity of aldehydes and ketones. For example, the boiling points of these three isomeric five-carbon ketones are all similar, and before the days of NMR spectroscopy it would have been hard to distinguish between them.




b.p. 102 °C b.p. 102 °C b.p. 106 °C

**Historical note (continued)**

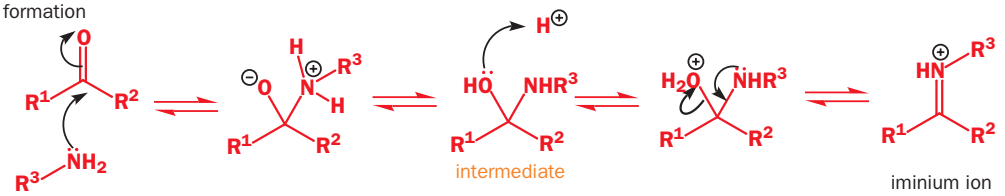
Their semicarbazones and 2,4-dinitrophenylhydrazones, on the other hand, all differ in their melting points. By making these derivatives of the ketones, identification was made much easier. Of course, all of this has been totally superseded by NMR! However these crystalline derivatives are still useful in the purification of volatile aldehydes and ketones and in solving structures by X-ray crystallography.



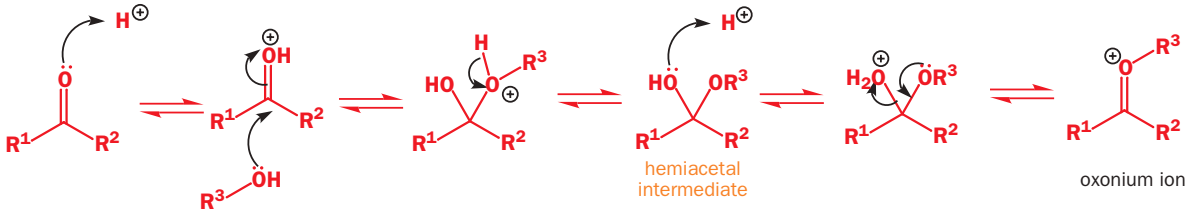

## Iminium ions and oxonium ions

Let's return to the mechanism of imine formation, and compare it for a moment with that of acetal formation. The only difference to begin with is that there is no need for acid catalysis for the addition of the amine but there is need for acid catalysis in the addition of the alcohol, a much weaker nucleophile.

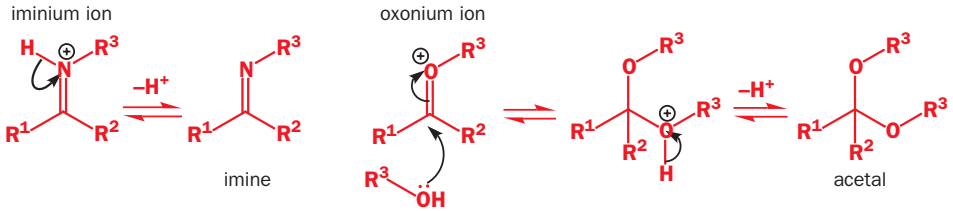
acid-catalysed imine formation




acid-catalysed acetal formation




Up to this point, the two mechanisms follow a very similar path, with clear analogy between the intermediate and hemiacetal and the iminium and oxonium ion. Here, though, they diverge, because the iminium ion carries a proton, which the oxonium ion doesn't have. The iminium ion therefore acts as an acid, losing a proton to become the imine. The oxonium ion, on the other hand, acts as an electrophile, adding another molecule of alcohol to become the acetal.

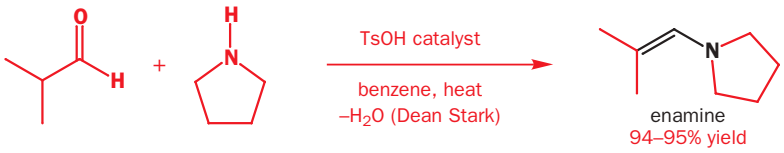



As you might guess, however, iminium ions can be persuaded to act as electrophiles, just like oxonium ions, provided a suitable nucleophile is present. We will spend the next few pages considering reactions in which an iminium ion acts as an electrophile. First, though, we will look at a reaction in which the iminium ion cannot lose an N–H proton because it has none.

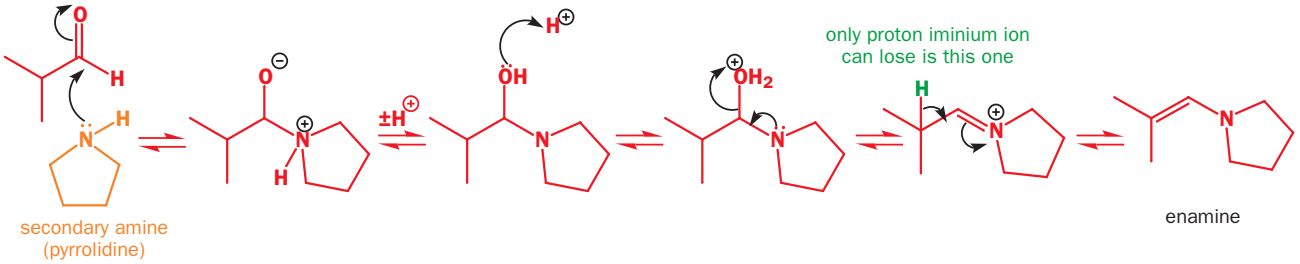
## Secondary amines react with carbonyl compounds to form enamines

Pyrrolidine, a secondary amine, reacts with isobutyraldehyde, under the sort of conditions you would use to make an imine, to give an **enamine**.

■ The name enamine combines 'ene' (C=C double bond) and 'amine'.

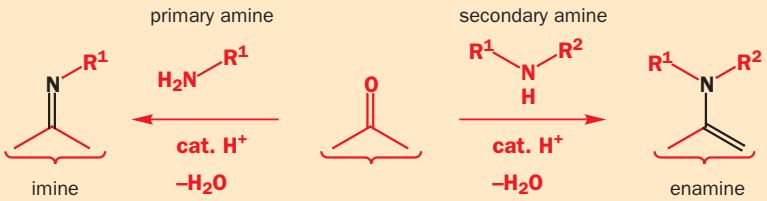



The mechanism consists of the same steps as those that take place when imines form from primary amines, up to formation of the iminium ion. This iminium ion has no N–H proton to lose, so it loses one of the C–H protons next to the C=N to give the enamine. Enamines, like imines, are unstable to aqueous acid. We shall return to them in Chapter 21.

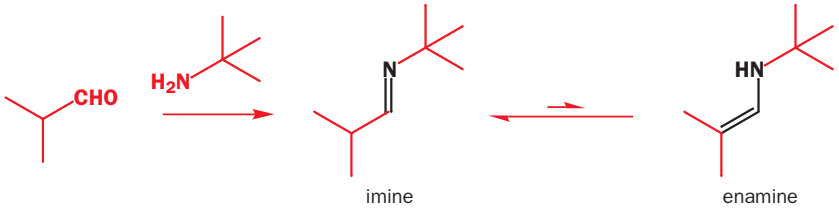



### Imines and enamines

- Imines are formed from aldehydes or ketones with primary amines
- Enamines are formed from aldehydes or ketones with secondary amines
- Both require acid catalysis and removal of water



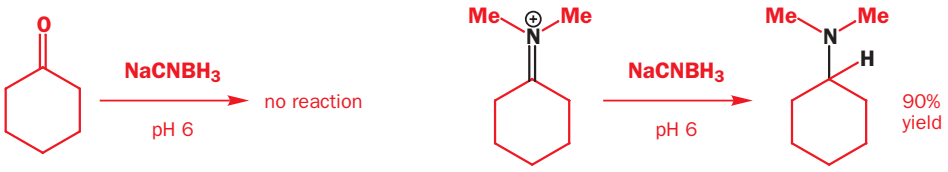

Enamines of primary amines, or even of ammonia, also exist, but only in equilibrium with an imine isomer. The interconversion between imine and enamine is the nitrogen analogue of **enolization**, which is discussed in detail in Chapter 21.




## Iminium ions can react as electrophilic intermediates

We made the point above that the difference in reactivity between an iminium ion and an oxonium ion is that an iminium ion can lose $H^+$ and form an imine or an enamine, while an oxonium ion reacts as an electrophile. Iminium ions can, however, react as electrophiles provided suitable nucleophiles are present. In fact, they are very good electrophiles, and are significantly more reactive than

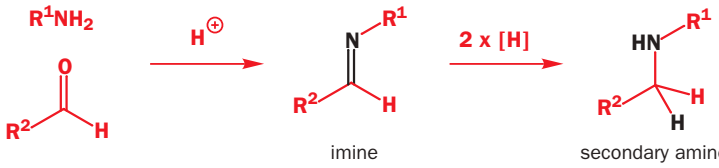
carbonyl compounds. For example, iminium ions are reduced rapidly by the mild reducing agent sodium cyanoborohydride ($NaCNBH_3$), while carbonyl compounds are not.



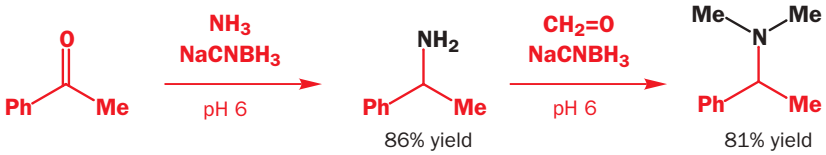

An alternative to $Na(CN)BH_3$ is $NaBH(OAc)_3$ (sodium triacetoxy-borohydride)—somewhat safer because strong acid can release HCN from $Na(CN)BH_3$.

## Amines from imines: reductive amination

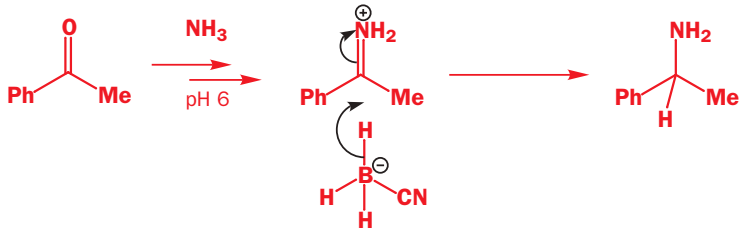
A useful way of making amines is by reduction of imines (or iminium ions). This overall process, from carbonyl compound to amine, is called **reductive amination**. This is, in fact, one of the few successful ways, and the best way, of making secondary amines. This should be your first choice in amine synthesis.




This can be done in two steps, provided the intermediate is stable, but, because the instability of many imines makes them hard to isolate, the most convenient way of doing it is to form and reduce the imine in a single reaction. The selective reduction of iminium ions (but not carbonyl compounds) by sodium cyanoborohydride makes this possible. When $NaCNBH_3$ is added to a typical imine-formation reaction it reacts with the products but not with the starting carbonyl compound. Here is an example of an amine synthesis using reductive amination.




In the first step, the ketone and ammonia are in equilibrium with their imine, which, at pH 6, is partly protonated as an iminium ion. The iminium ion is rapidly reduced by the cyanoborohydride to give the amine. Reactions like this, using ammonia in a reductive amination, are often carried out with ammonium chloride or acetate as convenient sources of ammonia. At pH 6, ammonia will be mostly protonated anyway.

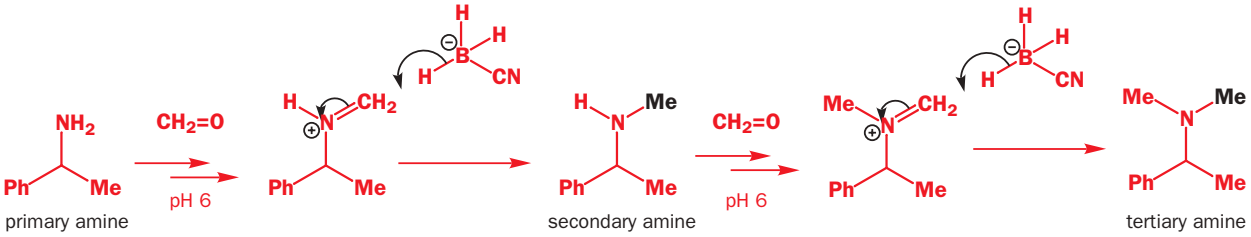



In the second step of the synthesis, amine plus formaldehyde gives an imine, present as its protonated iminium form, which gets reduced. Formaldehyde is so reactive that it reacts again with the secondary amine to give an iminium ion; again, this is reduced to the amine.

▶ Sodium cyanoborohydride contains the cyanoborohydride anion, whose structure is


It is a 'toned down' version of sodium borohydride—the electron-withdrawing cyano group decreases the ease with which hydride is transferred.

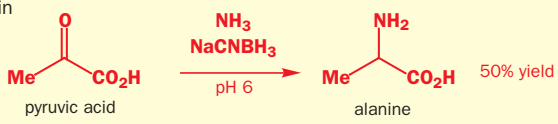
■ You will again meet the highly electrophilic iminium ions produced by reaction of formaldehyde with amines in Chapter 27, where we introduce you to the Mannich reaction.



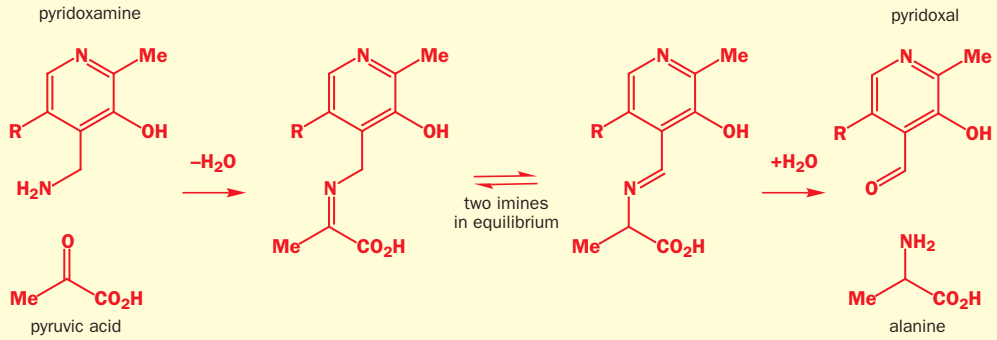

## Living things make amino acids using imines

The amino acid alanine can be made in moderate yield in the laboratory by reductive amination of pyruvic acid.

Living things use a very similar reaction to manufacture amino acids from keto acids—but do it much more efficiently. The key step is the formation of an imine between pyruvic acid and the vitamin $B_6$-derived amine pyridoxamine.

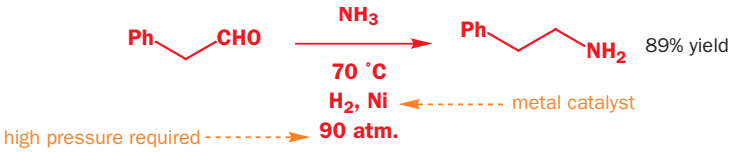



Nature's synthesis of alanine:




This Schiff base (biochemists call imines **Schiff bases**) is in equilibrium with an isomeric imine, which can be hydrolysed to pyridoxal and alanine. These reactions are, of course, all controlled by enzymes, and coupled to the degradation of unwanted amino acids (the latter process converts the pyridoxal back to pyridoxamine). Nature was doing reductive aminations a long time before sodium cyanoborohydride was invented! We will come back to this in Chapter 50.

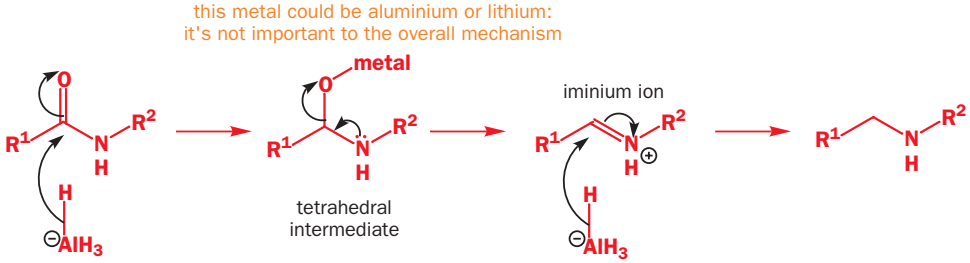
An alternative method for reductive amination uses hydrogenation (hydrogen gas with a metal catalyst) to reduce the imine in the presence of the carbonyl compound.



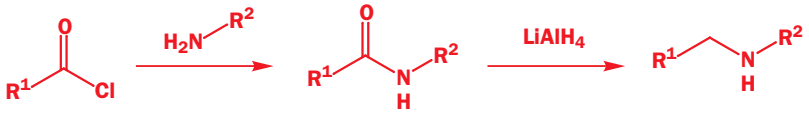

■ Hydrogenation is a good way of reducing a number of different functional groups, but not (usually) carbonyl groups. In Chapter 24 we will look in more detail at reducing agents (and other types of reagent) that demonstrate selectivity for one functional group over another (**chemoselectivity**).

## Lithium aluminium hydride reduces amides to amines

We've talked about reduction of iminium ions formed from carbonyl compounds plus amines. Iminium ions can also be formed by reducing amides with lithium aluminium hydride. A tetrahedral intermediate is formed that collapses to the iminium ion.



The iminium ion, is of course, more electrophilic than the starting amides (amide carbonyl groups are about the least electrophilic of any!), so it gets reduced to the secondary amine. This reaction can be used to make secondary amines, from primary amines and acyl chlorides.

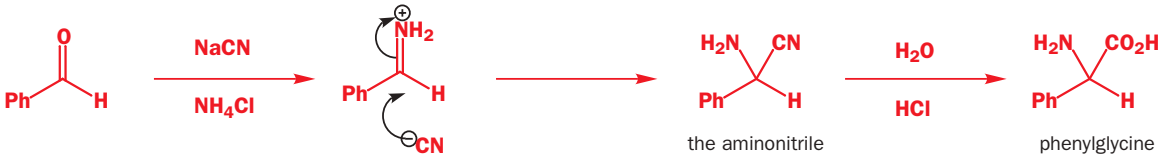



## Cyanide will attack iminium ions: the Strecker synthesis of amino acids

Cyanide will react with iminium ions to form α amino nitriles. Although these compounds are relatively unimportant in their own right, a simple hydrolysis step produces α amino acids. This route to amino acids is known as the Strecker synthesis. Of course, it's not usually necessary to make the amino acids that Nature produces for us in living systems: they can be extracted from hydrolysed proteins.

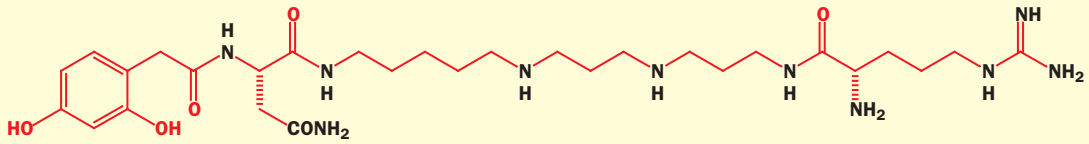
This Strecker synthesis is of phenylglycine, an amino acid not found in proteins. Cyanide reacts more rapidly with the iminium ion generated in the first step than it does with the starting benzaldehyde.

▶ Make sure that you can write a mechanism for the hydrolysis of the nitrile to the carboxylic acid! (If you need reminding, it is given in Chapter 12)

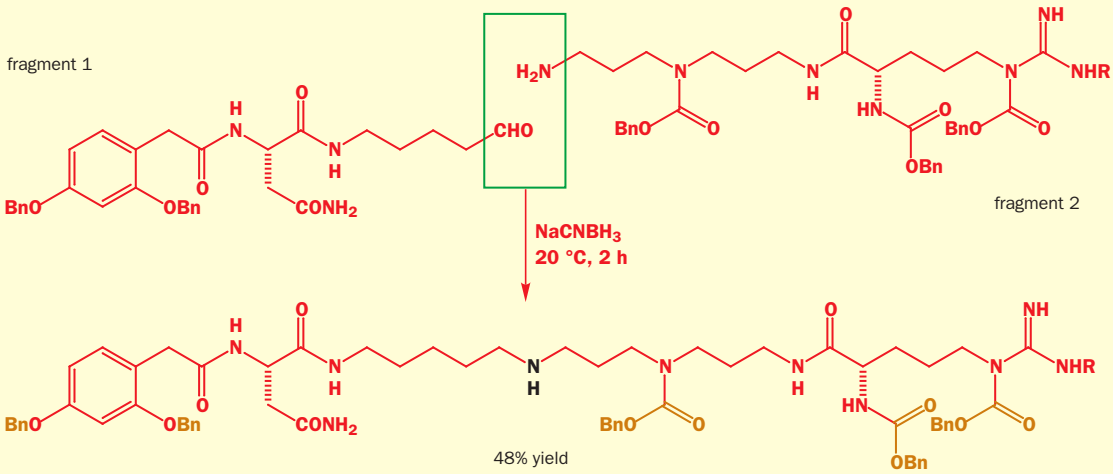



### The synthesis of a spider toxin: reductive amination

This compound is the toxin used by the orb weaver spider to paralyse its prey:

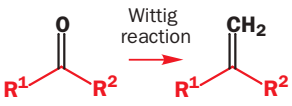



Since the spider produces only minute quantities of the compound, chemists at the University of Bath set about synthesizing it in the laboratory so that they could study its biological properties. The toxin contains several amide and amine functional groups, and the chemists decided that the best way to make it was to link two molecules together at one of the secondary amine groups using a reductive amination.




The compound made by this reaction has almost, but not exactly, the spider toxin structure. The extra groups in brown are protecting groups, and prevent unwanted side-reactions at the other amine and phenol functional groups. We will discuss protecting groups in detail in Chapters 24 and 25.

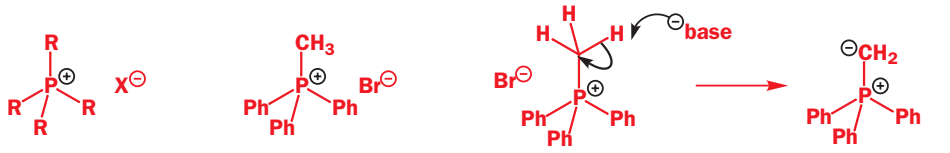
# Substitution of C=O for C=C: a brief look at the Wittig reaction




Before we leave substitution reactions of carbonyl groups, there is one more reaction that we must introduce. It is an important one, and we will come back to it again later in this book, particularly in Chapter 31. It also has a rather different mechanism from most you have met in recent chapters, but we talk about it here because the overall consequence of the **Wittig reaction** is the substitution of a C=C bond for a C=O bond.

We don't normally tell you the name of a reaction before even mentioning how to do it, but here we make an exception because the reagents are rather unusual and need explaining in detail. The Wittig reaction is a reaction between a carbonyl compound (aldehyde or ketone only) and a species known as a **phosphonium ylid**. An ylid (or ylide) is a species with positive and negative charges on adjacent atoms, and a phosphonium ylid carries its positive charge on phosphorus. Phosphonium ylids are made from **phosphonium salts** by deprotonating them with a strong base.

▶ The Wittig reaction is named after its discoverer, the Nobel Prize winner Georg Wittig (1897–1987; Nobel Prize 1979).

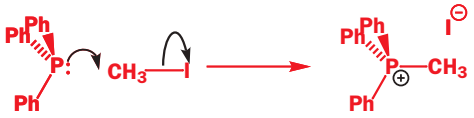



a phosphonium salt

methyltriphenylphosphonium bromide: an example of a phosphonium salt

phosphonium ylid

You have already met phosphonium salts in Chapter 5 where you saw the reaction of a phosphine (triphenylphosphine) with an alkyl halide (methyl iodide).

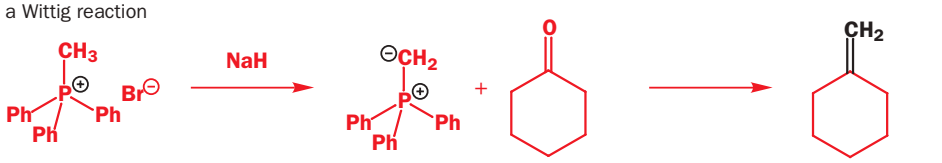



triphenylphosphine

phosphonium salt

So, here is a typical Wittig reaction: it starts with a phosphonium salt, which is treated with sodium hydride, and then with a carbonyl compound; the alkene forms in 85% yield.

a Wittig reaction




phosphonium salt

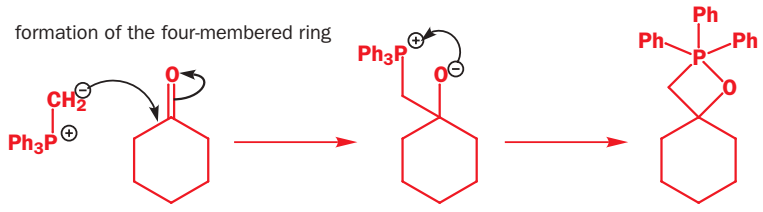
phosphonium ylid

alkene, 85% yield

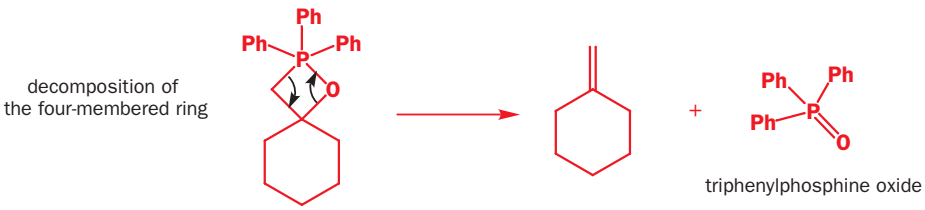
▶ Sodium hydride, $Na^+H^-$, is the conjugate base of $H_2$, and has a $pK_a$ of about 35.

What about the mechanism? We warned you that the mechanism is rather different from all the others you have met in this chapter, but nonetheless it begins with attack on the carbonyl group by a nucleophile; the nucleophile is the carbanion part of the phosphonium ylid. This reaction generates a negatively charged oxygen that attacks the positively charged phosphorus and gives a four-membered ring called an **oxaphosphetane**.

formation of the four-membered ring




Now, this four-membered ring (like most other ones) is unstable, and it can collapse in a way that forms two double bonds. Here are the curly arrows: the mechanism is cyclic, and gives the alkene, which is the product of the reaction along with a **phosphine oxide**.

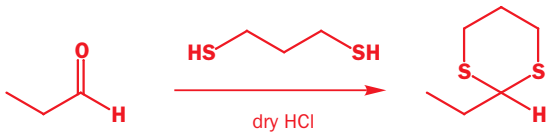



The chemistry of some elements is dominated by one particular property, and a theme running right through the chemistry of phosphorus is its exceptional affinity for oxygen. The P=O bond, with its bond energy of 575 kJ mol$^{-1}$, is one of the strongest double bonds in chemistry, and the Wittig reaction is irreversible and is driven forward by the formation of this P=O bond. No need here for the careful control of an equilibrium necessary when making acetals or imines. We will look at the Wittig reaction again in more detail in Chapter 31.

## Summary

In this chapter, as in Chapter 12, you have met a wide variety of reactions, but we hope you have again been able to see that they are all related mechanistically. Of course, we have not been exhaustive: it would be impossible to cover every possible reaction of a carbonyl group, but having read Chapters 6, 9, 12, and 13 you should feel confident in writing a reasonable mechanism for any reaction involving nucleophilic attack on a carbonyl group. You could try thinking about this, for example.

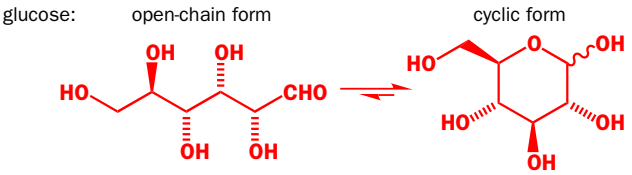
■ *Hint.* Consider sulfur's location in the periodic table.



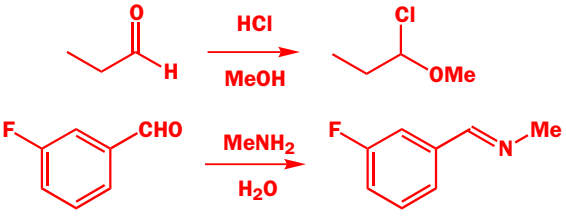

We now take our leave of carbonyl groups until Chapter 21 when we reveal a hidden side to their character: they can be nucleophilic as well as electrophilic. Meanwhile, we shall look some more at NMR spectroscopy and what it can tell us, before applying some of the principles we've used to explain carbonyl reactions to a new type of reaction, substitution at a saturated carbon atom.

## Problems

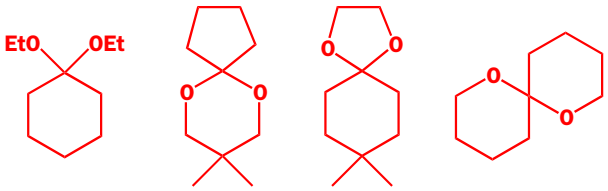
**1.** In the cyclization of the open-chain form of glucose to form the stable hemiacetal, it may be difficult to work out what has happened. Number the carbon atoms in the open-chain form and put the same numbers on the hemiacetal so that you can see where each carbon atom has gone. Then draw a mechanism for the reaction.



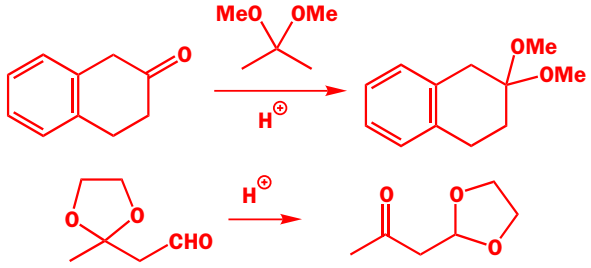

**2.** Draw mechanisms for these reactions, which involve the loss of carbonyl oxygen.




**3.** Each of these molecules is an acetal, that is, a compound made from an aldehyde or ketone and two alcohol groups. Which compounds were used to make these acetals?

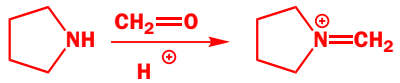


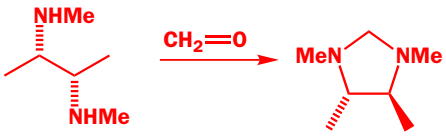

**4.** Each of these reactions leads to an acetal or a closely related compound and yet no alcohols are used in the first two reactions and no carbonyl group in the third. How are these acetals formed?




In the first and third of these two reactions, a compound, different in each case, must be distilled from the reaction mixture if the reaction is to go to completion. What are the compounds and why is this necessary? In the second case, why does the reaction go in this direction?

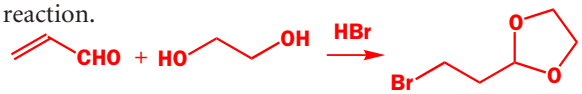
**5.** Suggest mechanisms for these two reactions of the smallest aldehyde, formaldehyde (methanal, $CH_2{=}O$).



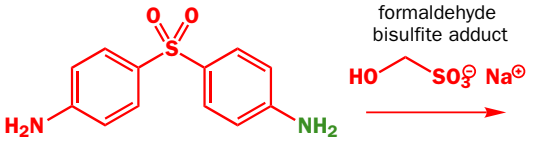




Comment on the stereochemistry of the second example.

**6.** Suggest mechanisms for this reaction. It first appeared in Chapter 3 where we identified the rather unexpected product from its spectra but did not attempt to draw a mechanism for the reaction.



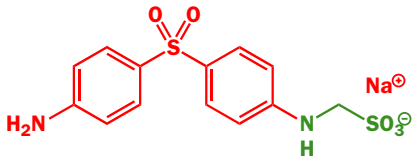

**7.** In Chapter 6 we described how the antileprosy drug dapsone could be made soluble by the formation of a 'bisulfite adduct'. Now that you know about the reactions described in Chapter 14, you should be able to draw a mechanism for this reaction. The adduct is described as a 'pro-drug' meaning that it can give dapsone itself in the human body. How might this happen?




insoluble dapsone

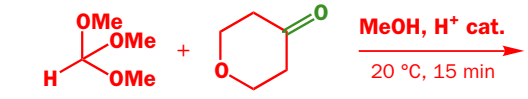
formaldehyde bisulfite adduct



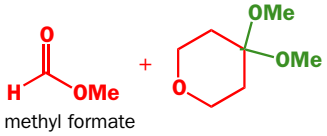




water-soluble 'pro-drug'

**8.** Suggest a detailed mechanism for the acetal exchange used in this chapter to make an acetal of a ketone from an orthoester.

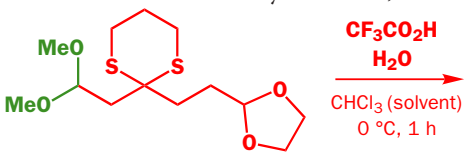


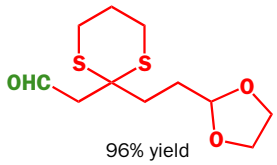

trimethyl orthoformate




methyl formate

**9.** When we introduced cyclic acetals, we showed you this reaction.

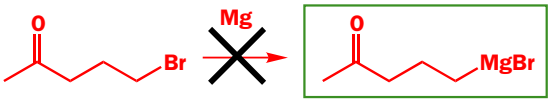



96% yield

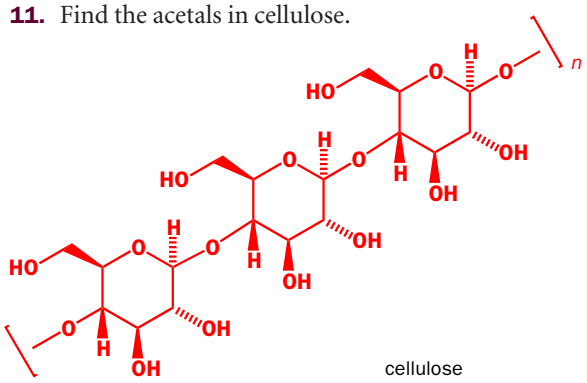
What are the two functional groups not affected by this reaction? How would you hydrolyse them?

**10.** What would actually happen if you tried to make the unprotected Grignard reagent shown here?



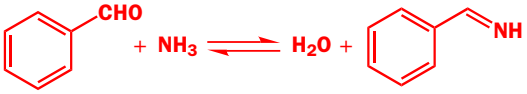

unstable structure – impossible to make

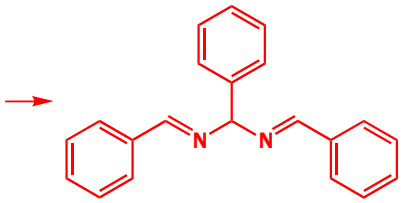
**11.** Find the acetals in cellulose.



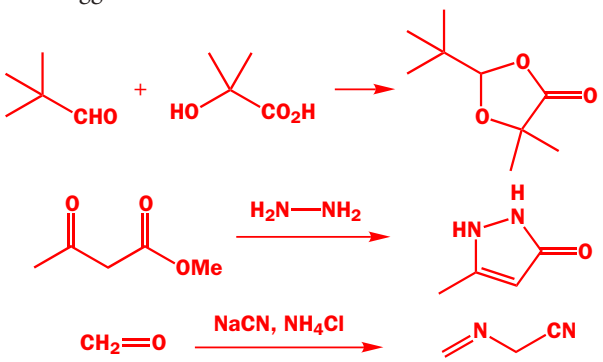

cellulose

**12.** A stable product can be isolated from the reaction between benzaldehyde and ammonia discussed in this chapter. Suggest a mechanism for its formation.



**13.** Suggest mechanisms for these reactions.




**14.** Finally, don't forget the problem at the end of the chapter: suggest a mechanism for this reaction.

# Review of spectroscopic methods 15

## Connections

**Building on:**

- Mass spectrometry ch3
- Infrared spectroscopy ch3
- $^{13}$C NMR ch3
- $^{1}$H NMR ch11

**Arriving at:**

- How spectroscopy explains the reactions of the C=O group
- How spectroscopy tells us about the reactivity of, and reaction products from, conjugated C=C and C=O bonds
- How spectroscopy tells us about the size of rings
- How spectroscopy solves the structure of unknown compounds
- Some guidelines for solving unknown structures

**Looking forward to:**

- A final review of spectroscopy, including what it tells us about the stereochemistry of molecules ch32
- Spectroscopy is an essential tool and will be referred to throughout the rest of the book

This is the first of two review chapters on spectroscopic methods taken as a whole. In Chapter 32 we shall tackle the complete identification of organic compounds including the vital aspect of stereochemistry, introduced in Chapters 16 and 19. In this chapter we gather together some of the ideas introduced in previous chapters on spectroscopy and mechanism and show how they are related. We shall explain the structure of the chapter as we go along.

## There are three reasons for this chapter

1. To review the methods of structure determination we met in Chapters 3 and 11, to extend them a little further, and to consider the relationships between them
2. To show how these methods may be combined to determine the structure of unknown molecules
3. To provide useful tables of data for you to use when you are yourself attempting to solve structure determination problems

The main tables of data appear at the end of the chapter so that they are easy to refer to when you are working on problems. You may also wish to look at them, along with the tables in the text, as you work through this chapter.

We shall deal with points 1 and 2 together, looking first at the interplay between the chemistry of the carbonyl group (as discussed in Chapters 12 and 14) and spectroscopy, solving some structural problems, then moving on to discuss, for example, NMR of more than one element in the same compound, doing some more problems, and so on. We hope that the lessons from each section will help in your overall understanding of structure solving. The first section deals with the assignment of carbonyl compounds to their various classes.

▶ May we remind you that you are *not* intended to *learn* the numbers!

## Does spectroscopy help with the chemistry of the carbonyl group?

As you can guess from the question, it does! Chapters 12 and 14 completed our systematic survey of carbonyl chemistry, the main chemical theme of the book so far (see also Chapters 6, 9, and 10), so this is an appropriate point to put together chemistry and spectroscopy on this most important of all functional groups.

We have divided carbonyl compounds into two main groups.

1 **aldehydes** (RCHO) and **ketones** ($R^1CO{\cdot}R^2$)

2 **acids** ($RCO_2H$) and their derivatives (in order of reactivity):
- **acid chlorides** (RCOCl)
- **anhydrides** ($RCO_2COR$)
- **esters** ($R^1CO_2R^2$)
- **amides** ($RCONH_2$, $R^1CONMe_2$, etc.)

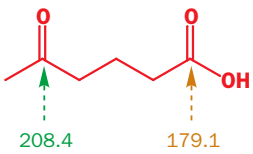
Which spectroscopic methods most reliably distinguish these two groups? Which help us to separate aldehydes from ketones? Which allow us to distinguish the various acid derivatives? Which offer the most reliable evidence on the chemistry of the carbonyl group? These are the questions we tackle in this section.

## Distinguishing aldehydes and ketones from acid derivatives

The most consistently reliable method for doing this is $^{13}C$ NMR.

**$^{13}C$ NMR shifts of carbonyl groups**

| Carbonyl group | $\delta_C$, p.p.m. |
|---|---|
| aldehydes | 195–205 |
| ketones | 195–215 |
| acids | 170–185 |
| acid chlorides | 165–170 |
| acid anhydrides | 165–170 |
| esters | 165–175 |
| amides | 165–175 |



saturated keto-acid

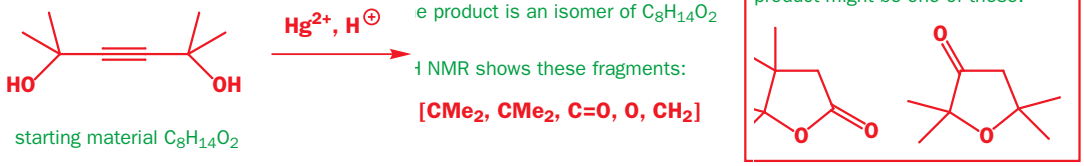
### ● $^{13}C$ NMR distinguishes acid derivatives from aldehydes and ketones

**The carbonyl carbons of all aldehydes and ketones resonate at about 200 p.p.m., while acid derivatives usually resonate at about 175 p.p.m.**

It doesn't much matter whether the compounds are cyclic or unsaturated or have aromatic substituents; they all give carbonyl $^{13}C$ shifts in about the same regions. There is a selection of examples on the facing page which we now discuss. First, look at the shifts arrowed in to the carbonyl group on each structure. All the aldehydes and ketones fall between 191 and 208 p.p.m. regardless of structure, whereas all the acid derivatives (and these are very varied indeed!) fall between 164 and 180 p.p.m. These two sets do not overlap and the distinction is easily made. Assigning the spectrum of the keto-acid in the margin, for example, is easy.

The distinction can be vital in structural problems. The symmetrical alkyne diol below cyclizes in acid with Hg(II) catalysis to a compound having, by proton NMR, the structural fragments shown. The product is unsymmetrical in that the two $CMe_2$ groups are still present, but they are now different. In addition, the chemical shift of the $CH_2$ group shows that it is next to C=O but not next to oxygen. This leaves us with two possible structures. One is an ester and one a ketone. The C=O shift is 218.8 p.p.m. and so there is no doubt that the second structure is correct.

a reaction with an unknown product




■ You need not, at this stage, worry about *how* the reaction works. It is more important that you realize how spectroscopy enables us to work out *what* has happened even before we have any idea *how*. Nonetheless, it is true that the second structure here also makes more sense chemically as the carbon skeleton is the same as in the starting material.

## Distinguishing aldehydes from ketones is simple by proton NMR

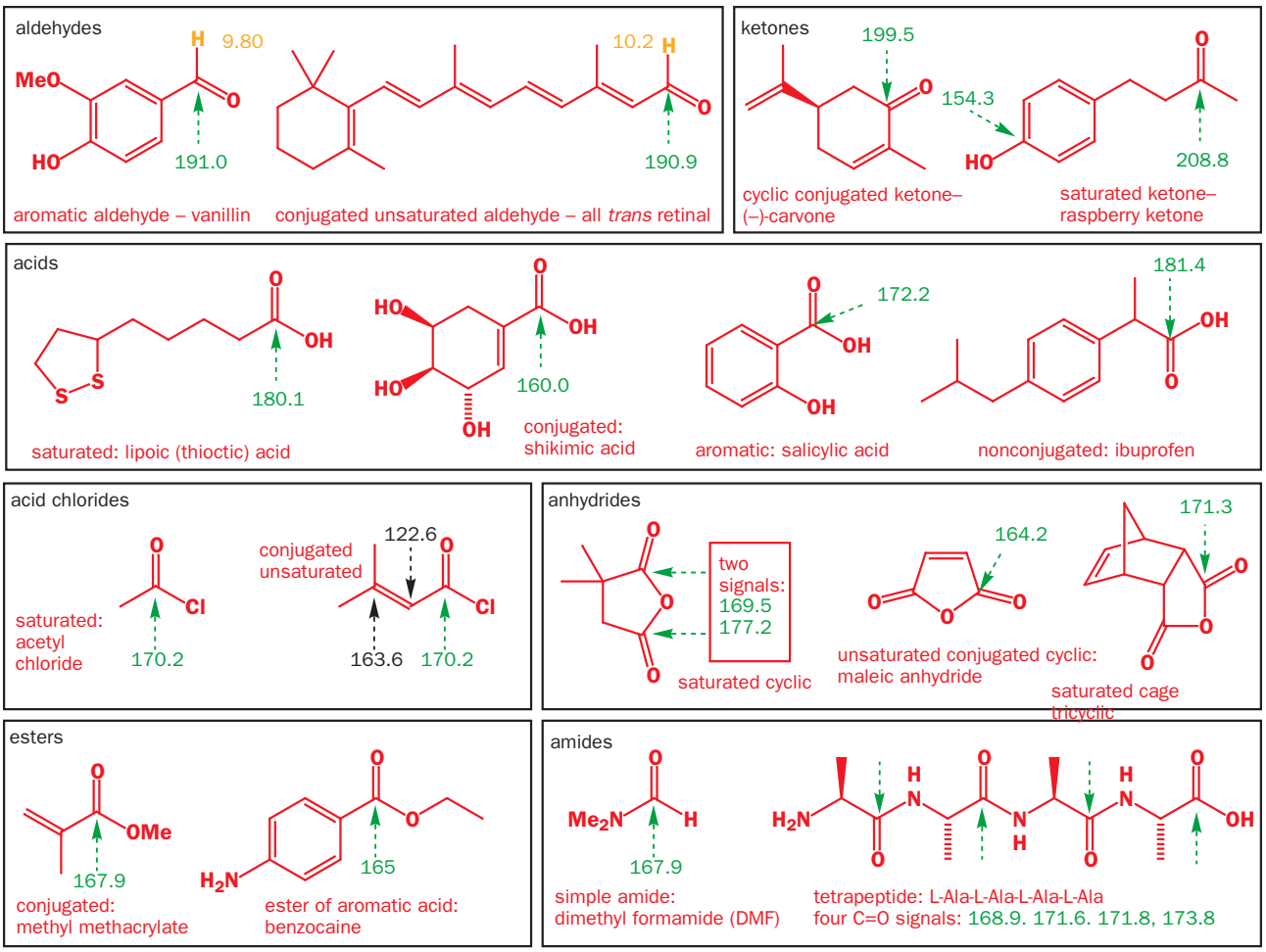
Now look at the first two groups, the aldehydes and ketones. The two aldehydes have smaller carbonyl shifts than the two ketones, but they are too similar for this distinction to be reliable. What distinguishes the aldehydes very clearly is the characteristic proton signal for CHO at 9–10 p.p.m. So you should identify aldehydes and ketones by C=O shifts in carbon NMR and then separate the two by proton NMR.

### ● Aldehyde protons are characteristic

**A proton at 9–10 p.p.m. indicates an aldehyde.**

## Identifying acid derivatives by carbon NMR is difficult

Now examine the other panels on p. 000. The four carboxylic acids are all important biologically or medicinally. Their C=O shifts are very different *from each other* as well as from those of the aldehydes or ketones.




## Aldehydes and ketones

The first aldehyde is vanillin which comes from the vanilla pod and gives the characteristic vanilla flavour in, for example, ice cream. Vanilla is the seed pod of a South American orchid. 'Vanilla essence' is made with synthetic vanillin and tastes slightly different because the vanilla pod contains other flavour components in small quantities. The second aldehyde is retinal. As you look at this structure your eyes use the light reaching them to interconvert *cis* and *trans* retinal in your retina to create nervous impulses. (See also Chapter 31.)

The two ketones are all flavour compounds too. The first, (–)-carvone, is the chief component (70%) of spearmint oil. Carvone is an interesting compound: in Chapter 16 you will meet mirror-image isomers known as enantiomers, and (–)-carvone's mirror image (+)-carvone, is the chief component (35%) of dill oil. Our taste can tell the difference, though an NMR machine can't and both carvones have *identical NMR spectra*. See Chapter 16 for more detail! The second ketone is 'raspberry ketone' and is largely responsible for the flavour of raspberries. It is entirely responsible for the flavour of some 'raspberry' foods. The signal for the aromatic carbon joined to OH is at 154.3 p.p.m. (in the 100–150 p.p.m. region because it is an unsaturated carbon atom joined to oxygen) and cannot possibly be confused with the ketone signal at 208.8 p.p.m. Both ketones have C=O shifts at about 200 p.p.m., and both lack any signals in the proton NMR of $\delta > 8$.

## Acid derivatives

Lipoic acid uses its S–S bond in redox reactions (Chapter 50), while shikimic acid is an intermediate in the formation of compounds with benzene rings, such as phenylalanine, in living things (Chapter 49). Salicylic acid's ethyl ester is aspirin, which is, of course, like the last example ibuprofen, a painkiller.

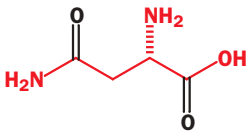
The first acid chloride is a popular reagent for the synthesis of acetate esters and you have seen its reactions in Chapter 12. We used the other as an example in Chapter 11. We have chosen three cyclic anhydrides as examples because they are all related to an important reaction (the Diels–Alder reaction), which you will meet in Chapter 35.

The first ester, methyl methacrylate is a bulk chemical. It is the monomer whose polymerization (Chapter 52) gives Perspex, the rigid transparent plastic used in windows and roofs. The second ester is an important local anaesthetic used for minor operations.

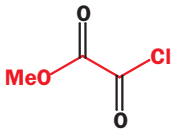
One amide is the now-familiar DMF, but the other is a tetrapeptide and so contains one carboxylic acid group at the end (the 'C-terminus': see Chapter 52) and three amide groups. Though the four amino acids in this peptide are identical (alanine, Ala for short), the carbon NMR faithfully picks up four different C=O signals, all made different by being different distances from the end of the chain.

The first five compounds (two acid chlorides and three anhydrides) are all reactive acid derivatives, and the five esters and amides below them are all unreactive acid derivatives and yet the C=O shifts of all ten compounds fall in the same range. The C=O chemical shift is obviously *not* a good way to check on chemical reactivity.

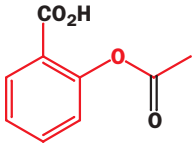
What the carbon NMR fails to do is distinguish these types of acid derivative. There is more variation between the carboxylic acids on display than between the different classes of acid derivatives. This should be obvious if we show you some compounds containing two acid derivatives. Would you care to assign these signals?




amino acid – asparagine
177.1, 176.1




ester/acid chloride
156.1, 160.9



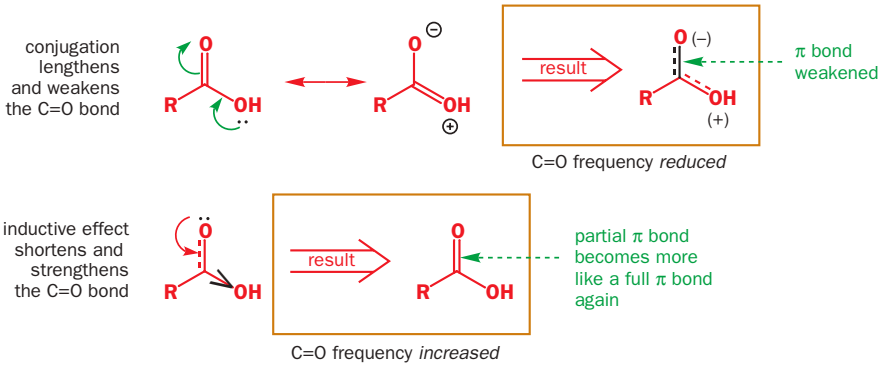

acid/ester – aspirin
165.6, 158.9

No, neither would we. In each case the difference between the carbonyl signals is only a few p.p.m. Though acid chlorides are extremely reactive in comparison with esters or amides, the electron deficiency at the carbon nucleus as measured by deshielding in the NMR spectrum evidently does not reflect this. Carbon NMR reliably distinguishes acid derivatives as a group from aldehydes and ketones as another group but it fails to distinguish even very reactive (for example, acid chlorides) from very unreactive (for example, amides) acid derivatives. So how do we distinguish acid derivatives?

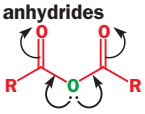
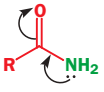
## Acid derivatives are best distinguished by infrared

A much better measure is the difference in IR stretching frequency of the C=O group. We discussed this in Chapter 12 (p. 000) where we noted a competition between conjugation by lone-pair electron donation *into* the carbonyl from OCOR, OR, or $NH_2$ and inductive withdrawal *from* the C=O group because of the electronegativity of the substituent. Conjugation donates electrons into the π* orbital of the π bond and so lengthens and weakens it. The C=O bond becomes more like a single bond and its stretching frequency moves towards the single-bond region, that is, it goes *down*. The inductive effect removes electrons from the π orbital and so shortens and strengthens the π bond. It becomes more like a full double bond and moves *up* in frequency.

■ For a reminder of the distinction between conjugation and inductive effects, see Chapter 7, p. 000.



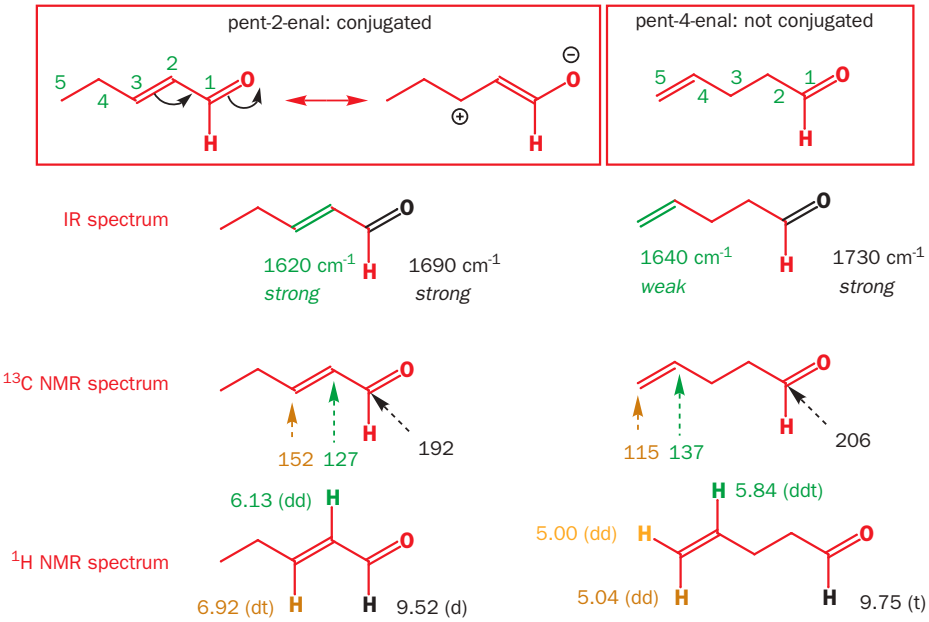

These effects are balanced in different ways according to the substituent. Chlorine is poor at lone-pair electron donation (its lone pair is in an overly large 3p orbital and overlaps badly with the 2p orbital on carbon) but strongly electron-withdrawing so acid chlorides absorb at high frequency, almost in the triple-bond region. Anhydrides have an oxygen atom between two carbonyl groups. Inductive withdrawal is still strong but conjugation is weak because the lone pairs are pulled both ways. Esters have a well balanced combination with the inductive effect slightly stronger (oxygen donates from a compatible 2p orbital but is very electronegative and so withdraws electrons strongly as well). Finally, amides are dominated by conjugation as nitrogen is a much stronger electron donor than oxygen because it is less electronegative.

| acid chlorides | anhydrides | esters | amides |
|---|---|---|---|
|  |  |  |  |
| inductive effect dominates | tug-of-war for lone pair: inductive effect dominates | inductive effect slightly dominates | conjugation strongly dominates |
| 1815 $cm^{-1}$ | two peaks: ~1790, 1810 $cm^{-1}$ | 1745 $cm^{-1}$ | ~1650 $cm^{-1}$ |

The two peaks for anhydrides are the symmetrical and antisymmetrical stretches for the two C=O groups; see Chapter 3, p. 000,

## Conjugation with π electrons or lone pairs affects IR C=O stretches

We need to see how conjugation works when it is with a π bond rather than with a lone pair. This will make the concept more general as it will apply to aldehydes and ketones as well as to acid groups. How can we detect if an unsaturated carbonyl compound is conjugated or not? Well, compare these two unsaturated aldehydes.




The key differences are the frequency of the C=O stretch (lowered by 40 $cm^{-1}$ by conjugation) and the strength (that is, the intensity) of the C=C stretch (increased by conjugation) in the IR. In the $^{13}C$ NMR, C3 in the conjugated enal is moved out of the alkene region just into the carbonyl region, showing how electron-deficient this carbon atom must be. In the proton NMR there are many effects but the downfield shift of the protons on the alkene especially C3 (again!) is probably the most helpful.

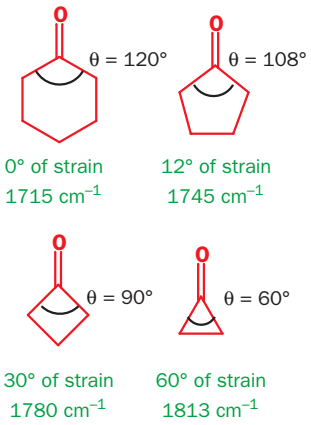
We discussed the way in which conjugation affects reactivity in Chapter 10, and mentioned its spectroscopic effect there as well.

Because the infrared carbonyl frequencies follow such a predictable pattern, it is possible to make a simple list of correlations using just three factors. Two are the ones we have been discussing—conjugation (frequency-lowering) and the inductive effect (frequency-raising). The third is the effect of small rings and this we next need to consider in a broader context.

# Small rings introduce strain inside the ring and higher s character outside it

Cyclic ketones can achieve the perfect 120° angle at the carbonyl group only if the ring is at least six-membered. The smaller rings are 'strained' because the orbitals have to overlap at a less than ideal angle.

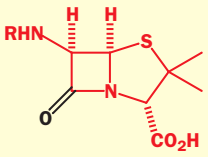
The three-membered ring is, of course, flat. The others are not. Even the four-membered ring is slightly puckered, the five- and especially the six-membered rings more so. This is all discussed in Chapter 18. But you have already met the concept of ring strain in Chapter 6, where we used it to explain why cyclopropanones and cyclobutanones are readily hydrated.



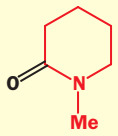

For a four-membered ring, the actual angle is 90°, so there is 120° – 90° = 30° of strain at the carbonyl group. The effects of this strain on five-, four-, and three-membered rings is shown here.

## Lactan C=O stretching frequencies

A further good example is the difference between C=O stretching frequencies in cyclic amides, or **lactams**. The penicillin class of antibiotics all contain a four-membered ring amide known as a β-lactam. The carbonyl stretching frequency in these compounds is way above the 1680 $cm^{-1}$ of the six-membered lactam, which is what you might expect for an unstrained amide.

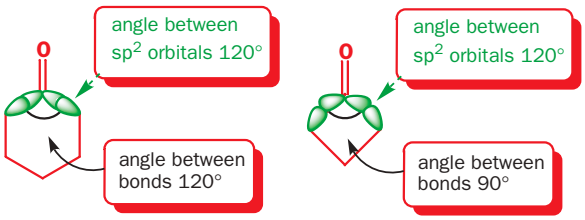



β-lactam in penicillin
1715 $cm^{-1}$

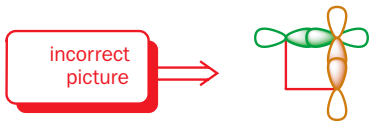



unstrained lactam
1680 $cm^{-1}$

But why should strain raise the frequency of a carbonyl group? It is evidently shortening and strengthening the C=O bond as it moves it towards the triple-bond region (higher frequency), not towards the single-bond region (lower frequency). In a six-membered ring, the $sp^2$ orbitals forming the σ framework around the carbonyl group can overlap perfectly with the $sp^3$ orbitals on neighbouring carbon atoms because the orbital angle and the bond angle are the same. In a four-membered ring the orbitals do not point towards those on the neighbouring carbon atoms, but point out into space.

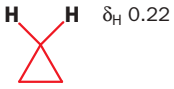


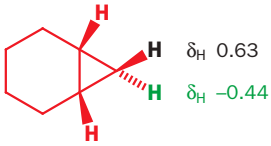

Ideally, we should like the orbitals to have an angle of 90° as this would make the orbital angle the same as the bond angle. In theory it *would* be possible to have a bond angle of 90° if we used pure p orbitals instead of $sp^2$ hybrid orbitals.




σ bonds in a four-membered ring formed with pure p orbitals

If we did we should leave a pure s orbital for the σ bond to oxygen. This extreme is not possible, but a compromise is. *Some* more p character goes into the ring bonds—maybe they become $s^{0.8}p^{3.2}$—and the same amount of extra s character goes into the σ bond to oxygen. The more s character there is in the orbital, the shorter it gets as s orbitals are (much) smaller than p orbitals.



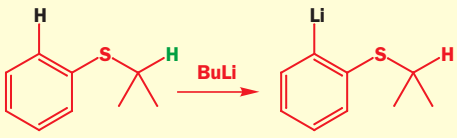




The s-character argument also explains the effects of small rings on proton NMR shifts. These hydrogens, particularly on three-membered rings, resonate at unusually high fields, between 0 and 1 p.p.m. in cyclopropanes instead of the 1.3 p.p.m. expected for $CH_2$ groups, and may even appear at negative δ values. High p character in the framework of small rings also means high s character in C–H bonds outside the ring and this will mean shorter bonds, greater shielding, and small δ values.

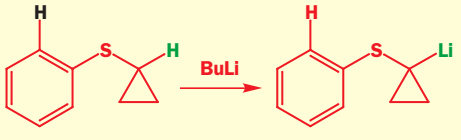
## Three-membered rings and alkynes

You have also seen the same argument used in Chapter 8 to justify the unusual acidity of C–H protons on triple bonds (such as alkynes and HCN), and alluded to in Chapter 3 to explain the stretching frequency of the same C–H bonds. Like alkynes, three-membered rings are also unusually easy to deprotonate in base.

Here is an example where deprotonation occurs at a different site in two compounds identical except for a C-C bond closing a three-membered ring. The first is an ortholithiation of the type discussed in Chapter 9.




deprotonated on benzene ring (ortholithiated)

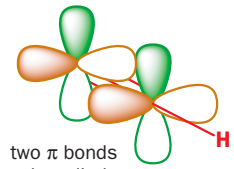



deprotonated on cyclopropyl ring

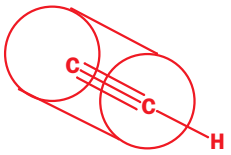
### NMR spectra of alkynes are related to those of small rings

Now what about the NMR spectra of alkynes? By the same argument, protons on alkynes ought to appear in the NMR at quite high field because these protons really are rather acidic (Chapter 8).

Protons on a typical alkene have $\delta_H$ about 5.5 p.p.m., while the proton on an alkyne comes right in the middle of the protons on saturated carbons at about $\delta_H$ 2–2.5 p.p.m. This is rather a large effect just for increased s character and some of it is probably due to better shielding by the triple bond, which surrounds the linear alkyne with π bonds without a nodal plane.



two π bonds make cylinder of electrons round alkyne

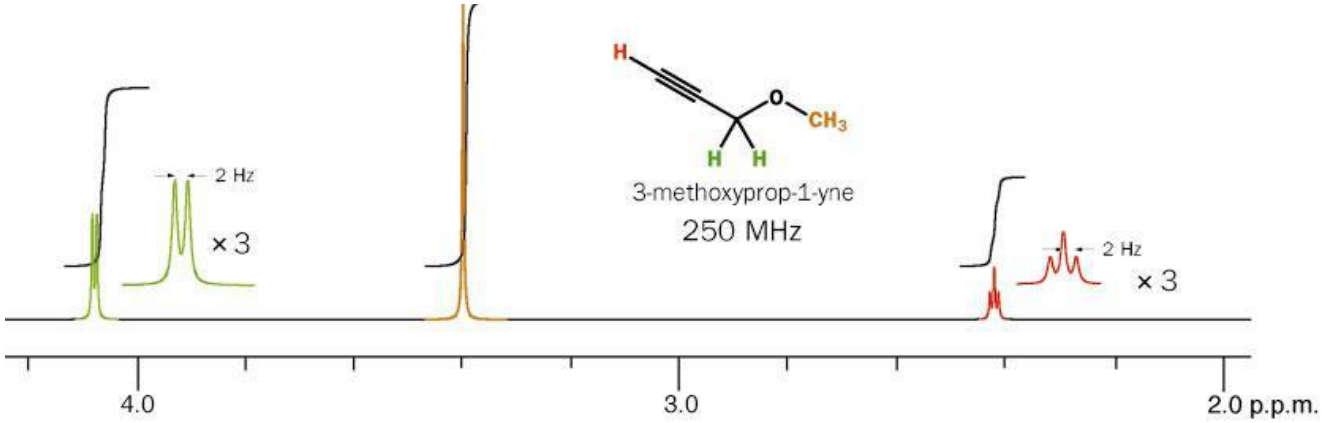


C and H shielded

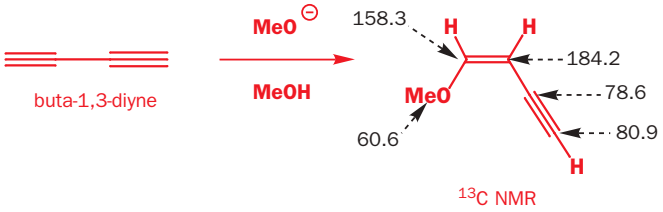
This means that the carbon atoms also appear at higher field than expected, not in the alkene region but from about $\delta_C$ 60–80 p.p.m. The s-character argument is important, though, because shielding can't affect IR stretching frequencies, yet C≡C–H stretches are strong and at about 3300 $cm^{-1}$, just right for a strong C–H bond. The picture is consistent.

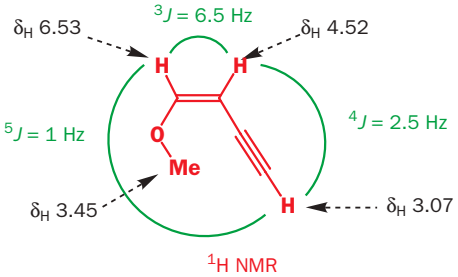
A simple example is the ether 3-methoxyprop-1-yne. Integration alone allows us to assign the spectrum, and the 1H signal at 2.42 p.p.m., the highest field signal, is clearly the alkyne proton. Notice also that it is a triplet and that the $OCH_2$ group is a doublet. This $^4J$ is small (about 2 Hz) and, though there is nothing like a letter 'W' in the arrangement of the bonds, coupling of this kind is often found in alkynes.

▶ In Chapter 11, p. 000, you saw that bonds aligned in a 'W' arrangement can give rise to $^4J_{HH}$ coupling.




A more interesting example comes from the base-catalysed addition of methanol to buta-1,3-diyne (diacetylene). The compound formed has one double and one triple bond and the $^{13}C$ NMR shows clearly the greater deshielding of the double bond.




You may have noticed that we have drawn the double bond with the *cis* (*Z*) configuration. We know that this is true because of the proton NMR, which shows a 6.5 Hz coupling between the two alkene protons (much too small for a *trans* coupling; see p. 000). There is also the longer range coupling ($^4J = 2.5$ Hz) just described and even a small very long range coupling ($^5J = 1$ Hz) between the alkyne proton and the terminal alkene proton.

## Simple calculations of C=O stretching frequencies in IR spectra

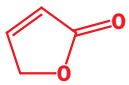
The best way is to relate all our carbonyl frequencies to those for saturated ketones (1715 $cm^{-1}$). We can summarize what we have just learned in a table.

Notice in this simple table (for full details you should refer as usual to a specialist book) that the adjustment '30 $cm^{-1}$' appears quite a lot (–30 $cm^{-1}$ for both alkene and aryl, for example), that the increment for small rings is 35 $cm^{-1}$ each time (30 to 65 $cm^{-1}$ and then 65 to 100 $cm^{-1}$), and that the extreme effects of Cl and $NH_2$ are +85 and –85 $cm^{-1}$, respectively. These effects are additive. If you want to estimate the C=O frequency of a proposed structure, just add or subtract all the adjustments to 1715 $cm^{-1}$ and you will get a reasonable result.

**Effects of substituents on IR carbonyl frequencies**

| Effect | Group | C=O stretch, $cm^{-1}$ | Frequency change[a], $cm^{-1}$ |
|---|---|---|---|
| inductive effect | Cl | 1800 | +85 |
| | OCOR | 1765, 1815 | +50, +100 |
| | OR | 1745 | +30 |
| | H | 1730 | +15 |
| conjugation | C=C | 1685 | –30 |
| | aryl | 1685 | –30 |
| | $NH_2$ | 1630 | –85 |
| ring strain | 5-membered ring | 1745 | +30 |
| | 4-membered ring | 1780 | +65 |
| | 3-membered ring | 1815 | +100 |

[a] Difference between stretching frequency of C=O and stretching frequency of a typical saturated ketone (1715 $cm^{-1}$).



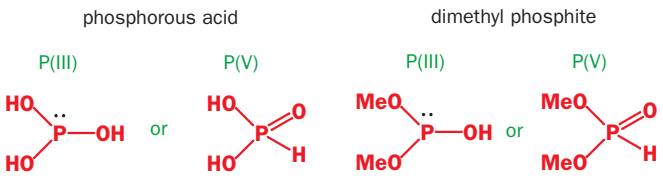
Let us try the five-membered unsaturated (and conjugated) lactone (cyclic ester) in the margin. We must add 30 $cm^{-1}$ for the ester, subtract 30 $cm^{-1}$ for the double bond, and add 30 $cm^{-1}$ for the five-membered ring. Two of those cancel out leaving just 1715 + 30 = 1745 $cm^{-1}$. These compounds absorb at 1740–1760 $cm^{-1}$. Not bad!

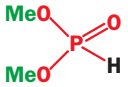
## Interactions between different nuclei can give enormous coupling constants

We have looked at coupling between hydrogen atoms and you may have wondered why we have ignored coupling between other NMR active nuclei. Why does $^{13}C$ not cause similar couplings? In this section we are going to consider not only couplings between the same kind of nuclei, such as two protons, called **homonuclear coupling**, but also coupling between different nuclei, such as a proton and a fluorine atom or $^{13}C$ and $^{31}P$, called **heteronuclear coupling**.

Two nuclei are particularly important, $^{19}F$ and $^{31}P$, since many organic compounds contain these elements and both are at essentially 100% natural abundance and have spin $I = 1/2$. We shall start with organic compounds that have just one of these nuclei and see what happens to both the $^{1}H$ and the $^{13}C$ spectra. In fact, it is easy to find a $^{19}F$ or a $^{31}P$ atom in a molecule because these elements couple to all nearby carbon and hydrogen atoms. Since they can be directly bonded to either, $^{1}J$ coupling constants such as $^{1}J_{CF}$ or $^{1}J_{PH}$ become possible, as well as the more 'normal' couplings such as $^{2}J_{CF}$ or $^{3}J_{PH}$, and these $^{1}J$ coupling constants can be enormous.

We shall start with a simple phosphorus compound, the dimethyl ester of phosphorous acid ($H_3PO_3$). There is an uncertainty about the structure of both the acid and its esters. They could exist as P(III) compounds with a lone pair of electrons on phosphorus, or a P(V) compounds with a P=O double bond.

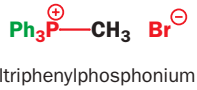


3.80 (6H, d, $^{4}J_{PH}$ 9 Hz)
6.77 (1H, d, $^{1}J_{PH}$ 693 Hz)

In fact, dimethyl phosphite has a 1H doublet with the amazing coupling constant of 693 Hz: on a 250 MHz machine the two lines are over 2 p.p.m. apart and it is easy to miss that they are two halves of the same doublet. This can only be a $^{1}J_{PH}$ as it is so enormous and so the compound has to have a P–H bond and the P(V) structure is correct. The coupling to the methyl group is much smaller but still large for a three-bond coupling ($^{3}J_{PC}$ of 18 Hz).

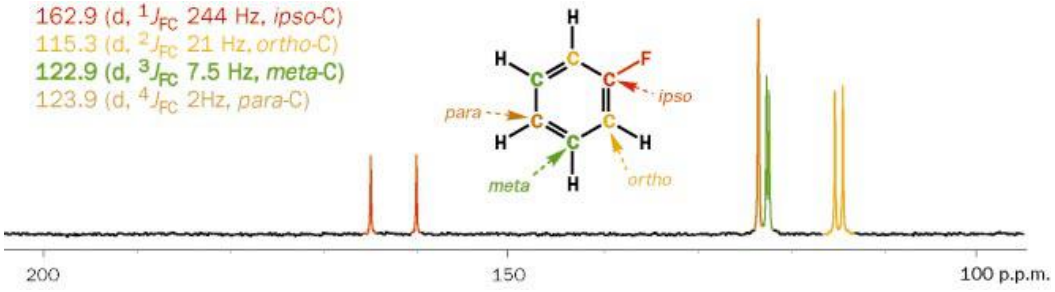
Next, consider the phosphonium salt you met at the end of Chapter 14 for use in the Wittig reaction, turning aldehydes and ketones to alkenes. It has a $^2J_{PH}$ of 18 Hz. There is no doubt about this structure—it is just an illustration of coupling to phosphorus. There is coupling to phosphorus in the carbon spectrum too: the methyl group appears at $\delta_C$ 10.6 p.p.m. with a $^1J_{PC}$ of 57 Hz, somewhat smaller than typical $^1J_{PH}$. We haven't yet talked about couplings to $^{13}C$: we shall now do so.




methyltriphenylphosphonium bromide
aromatic protons and
$\delta_H$ 3.25 (3H, d, $^2J_{PH}$ 18 Hz)

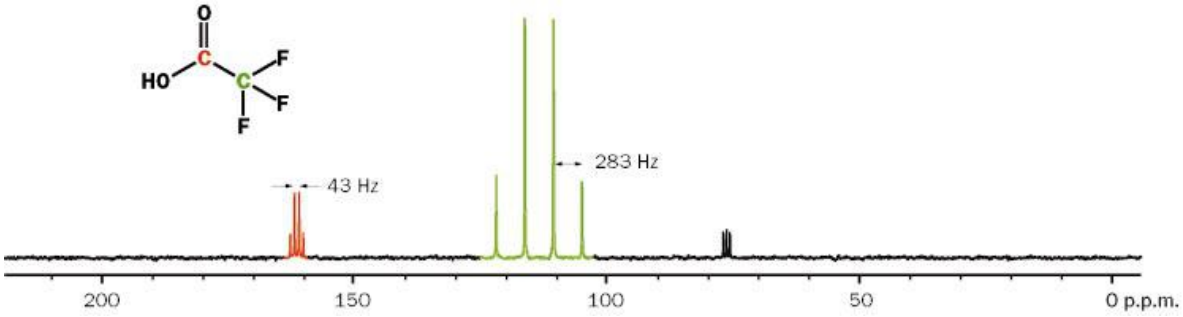
## Coupling in carbon NMR spectra

We shall use coupling with fluorine to introduce this section. Fluorobenzenes are good examples because they have a number of different carbon atoms all coupled to the fluorine atom.




The carbon directly joined to fluorine (the *ipso* carbon) has a very large $^1J_{CF}$ value of about 250 Hz. More distant coupling is evident too: all the carbons in the ring couple to the fluorine in PhF with steadily diminishing *J* values as the carbons become more distant.

Trifluoroacetic acid is an important strong organic acid (Chapter 8) and a good solvent for $^1H$ NMR. The carbon atom of the $CF_3$ group is coupled equally to all the three fluorines and so appears as a quartet with a large $^1J_{CF}$ of 283 Hz, about the same as in PhF. Even the carbonyl group is also a quartet, though the coupling constant is much smaller ($^2J_{CF}$ is 43 Hz). Notice too how far downfield the $CF_3$ carbon atom is!



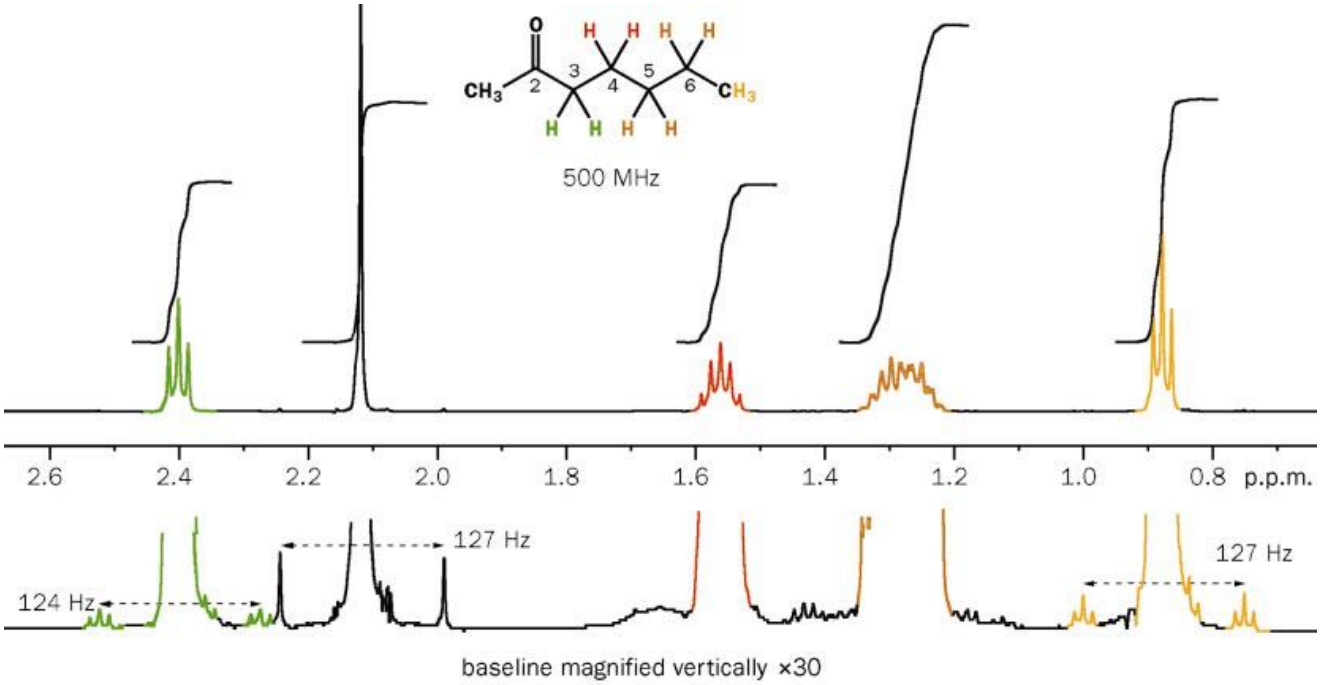

## Coupling between protons and $^{13}C$

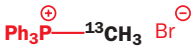
In view of all this, you may ask why we don't apparently see couplings between $^{13}C$ and $^1H$ in either carbon or proton spectra. In proton spectra we don't see coupling to $^{13}C$ because of the low abundance (1.1%) of $^{13}C$. Most protons are bonded to $^{12}C$: only 1.1% of protons are bonded to $^{13}C$. If you look closely at proton spectra with very flat baselines, you may see small peaks either side of strong peaks at about 0.5% peak height. These are the $^{13}C$ 'satellites' for those protons that are bonded to $^{13}C$ atoms.

As an example, look again at the 500 MHz $^1H$ spectrum of heptan-2-one that we saw on p. 000. When the baseline of this spectrum is vertically expanded, the $^{13}C$ satellites may be seen. The singlet due to the methyl protons is actually in the centre of a tiny doublet due to the 1% of protons coupling to $^{13}C$. Similarly, each of the triplets in the spectrum is flanked by two tiny triplets. The two tiny triplets on either side make up a doublet of triplets with a large $^1J$ coupling constant to the $^{13}C$ (around 130 Hz) and smaller $^3J$ coupling to the two equivalent protons.

▶ Note that these spectra with heteronuclear couplings provide the only cases where we can see *one* doublet in the proton NMR. Normally, if there is one doublet, there must be another signal with at least this complexity as all coupling appears twice (A couples to B and so B also couples to A!). If the coupling is to another element (here phosphorus) then the coupling appears once in each spectrum. The Wittig reagent has an $A_3P$ ($CH_3$–P) system: proton A appears as a doublet, while the phosphorus atom appears as a quartet in the *phosphorus* spectrum at a completely different frequency.

▶ *Ipso* can join the list (*ortho*, *meta*, *para*) of trivial names for positions on a substituted benzene ring.



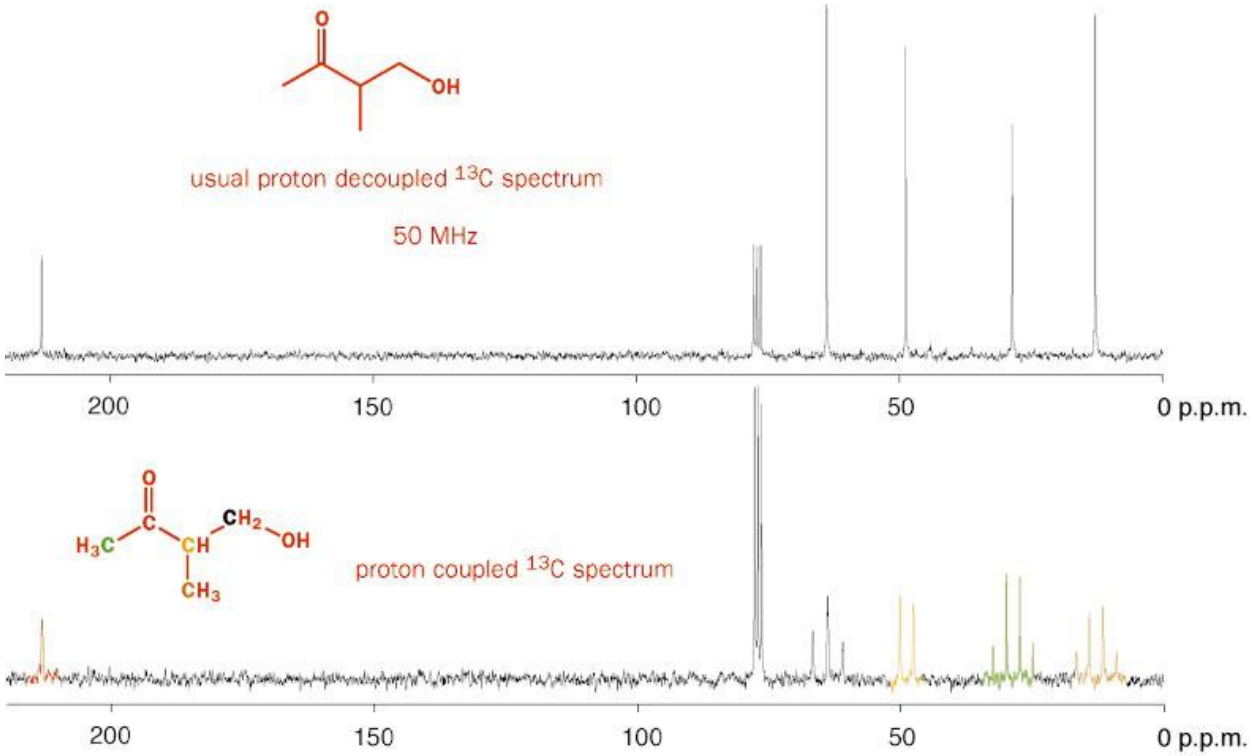
$^{13}$C-labelled phosphonium salt

$\delta_H$ 3.25 (3H, dd, $^1J_{CH}$ 135, $^2J_{PH}$ 18 Hz)

$^{13}$C satellites are usually lost in the background noise of the spectrum and need concern us no further. You do, however, see coupling with $^{13}$C labelled compounds where the $^{13}$C abundance now approaches 100%. The same Wittig reagent we saw a moment ago shows a 3H doublet of doublets with the typically enormous $^1J_{CH}$ of 135 Hz when labelled with $^{13}$C in the methyl group.

## Why is there no coupling to protons in normal $^{13}$C NMR spectra?

We get the singlets consistently seen in carbon spectra because of the way we record the spectra. The values of $^1J_{CH}$ are so large that, if we recorded $^{13}$C spectra with all the coupling constants, we would



get a mass of overlapping peaks. When run on the same spectrometer, the frequency at which $^{13}C$ nuclei resonate turns out to be about a quarter of that of the protons. Thus a '200 MHz machine' (remember that the magnet strength is usually described by the frequency at which the protons resonate) gives $^{13}C$ spectra at 50 MHz. Coupling constants ($^1J_{CH}$) of 100–250 Hz would cover 2–5 p.p.m. and a $CH_3$ group with $^1J_{CH}$ of about 125 Hz would give a quartet covering nearly 8 p.p.m. See the example on previous page.

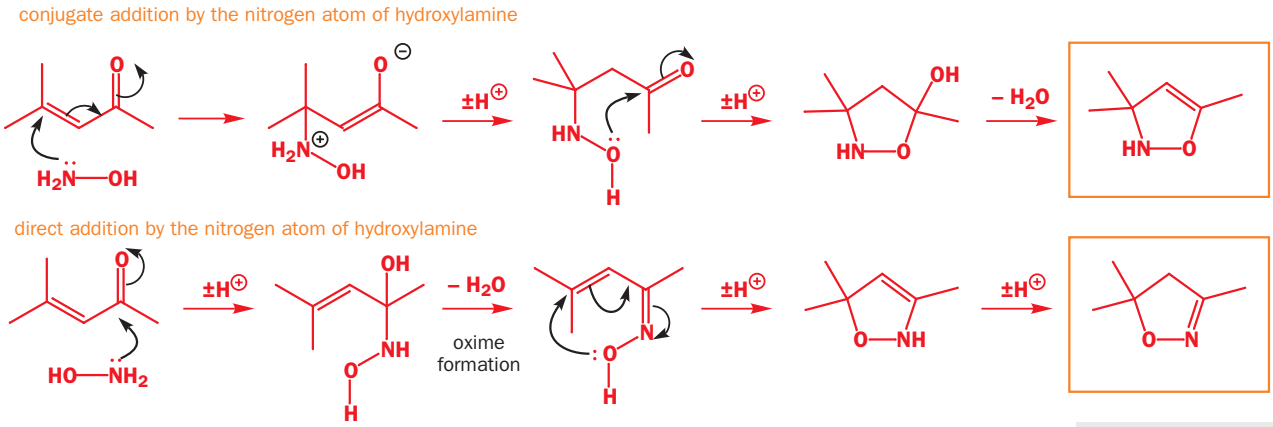
Since the proton coupled $^{13}C$ spectrum can so easily help us to distinguish $CH_3$, $CH_2$, CH, and quaternary carbons, you might wonder why they are not used more. The above example was chosen very carefully to illustrate proton coupled spectra at their best. Unfortunately, this is not a typical example. More usually, the confusion from overlapping peaks makes this just not worthwhile. So $^{13}C$ NMR spectra are recorded while the whole 10 p.p.m. proton spectrum is being irradiated with a secondary radiofrequency source. The proton energy levels are equalized by this process and all coupling disappears. Hence the singlets we are used to seeing.

For the rest of this chapter, we shall not be introducing new theory or new concepts; we shall be applying what we have told you to a series of examples where spectroscopy enables chemists to identify compounds.

# Identifying products spectroscopically

## Conjugate or direct addition?

In Chapter 10 we were discussing the reasons for conjugate addition and direct addition to the carbonyl group. We should now consider how you find out what has happened. A famous case was the addition of hydroxylamine ($NH_2$–OH) to a simple enone. Nitrogen is more nucleophilic than oxygen so we expect it to add first. But will it add directly to the carbonyl group or in a conjugate fashion? Either way, an intermediate will be formed that can cyclize.



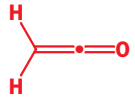

The two possible isomeric products were the subject of a long running controversy. Once the IR and proton NMR spectra of the product were run, doubt vanished. The IR showed no NH stretch. The NMR showed no alkene proton but did have a $CH_2$ group at 2.63 p.p.m. Only the second structure is possible.

We need to look now at a selection of problems of different kinds to show how the various spectroscopic methods can cooperate in structure determination.

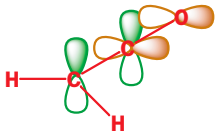
■ Do not be concerned about the details of the mechanisms: note that we have used the '$\pm H^{+}$' shorthand introduced in Chapter 13, and have abbreviated the mechanism where water is eliminated and the oxime formed—the full mechanism of oxime formation can be found in Chapter 14, p. 000. In this chapter, we are much more concerned just with the structure of the products.

## Reactive intermediates can be detected by spectroscopy

Some intermediates proposed in reaction mechanisms look so unlikely that it is comforting if they can be isolated and their structure determined. We feel more confident in proposing an intermediate if we are sure that it can really be made. Of course, this is not necessarily evidence that the intermediate is actually formed during reactions and it certainly does *not* follow that the failure to isolate a given intermediate disproves its involvement in a reaction. We shall use **ketene** as an example.



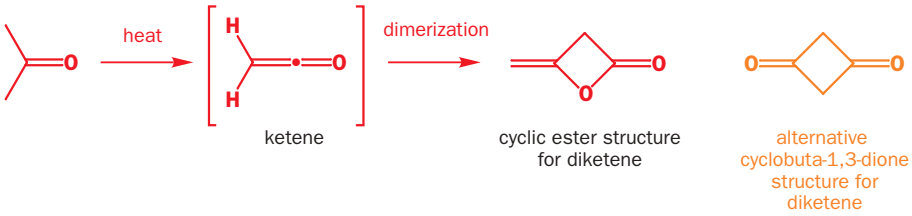
ketene



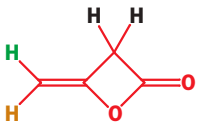
orthogonal π bonds of ketene

■ The structure of *ketene* is loosely analogous to that of *allene*, discussed in Chapter 7, p. 000.

Ketene looks pretty unlikely! It is $CH_2$=C=O with two π bonds (C=C and C=O) to the same carbon atom. The orbitals for these π bonds must be orthogonal because the central carbon atom is sp hybridized with two linear σ bonds and two p orbitals at right angles both to the σ bonds and to each other. Can such a molecule exist? When acetone vapour is heated to very high temperatures (700–750 °C) methane is given off and ketene is supposed to be the other product. What is isolated is a ketene dimer ($C_4H_4O_2$) and even the structure of this is in doubt as two reasonable structures can be written.




The spectra fit the ester structure well, but not the more symmetrical diketone structure at all. There are *three* types of proton (cyclobuta-1,3-dione would have just *one*) with allylic coupling between one of the protons on the double bond and the $CH_2$ group in the ring. The carbonyl group has the shift (185 p.p.m.) of an acid derivative (not that of a ketone which would be about 200 p.p.m.) and all four carbons are different.

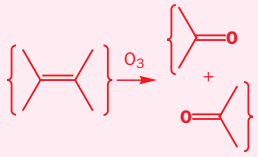


diketone

$^1$H NMR spectrum:
4.85 (1H, narrow t, $J$ ~ 1)
4.51 (1H, s)
3.90 (2H, d, $J$ ~ 1)

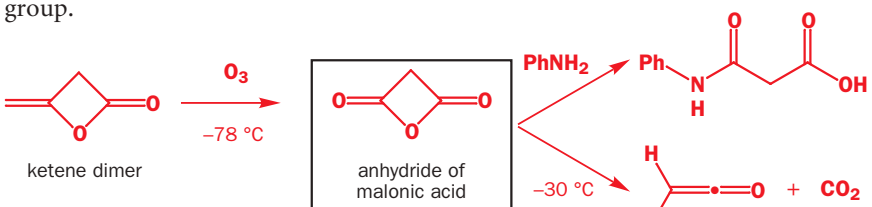
$^{13}$C NMR spectrum:
185.1, 147.7, 67.0, 42.4

▶ **Ozonolysis** or **ozonation** is the cleavage of an alkene by ozone ($O_3$). The reaction and its mechanism are discussed in Chapter 35: the only point to note now is that ozone is a powerful oxidant and cleaves the alkene to make two carbonyl compounds. Again, in this chapter we are concerned only with the structure of the products and how this can be determined.



Ozonolysis of ketene dimer gives a very unstable compound that can be observed only at low temperatures (–78 °C or below). It has two carbonyl bands in the IR and reacts with amines to give amides, so it looks like an anhydride (Chapter 12). Can it be the previously unknown cyclic anhydride of malonic acid?

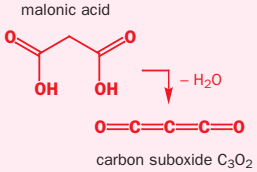
The two carbonyl bands are of high frequency as would be expected for a four-membered ring—using the table on p. 000 we estimate 1715 + 50 $cm^{-1}$ (for the anhydride) + 65 $cm^{-1}$ (for the four-membered ring) = 1830 $cm^{-1}$. Both the proton and the carbon NMR are very simple: just a 2H singlet at 4.12 p.p.m., shifted downfield by two carbonyls, a C=O group at 160 p.p.m., right for an acid derivative, and a saturated carbon shifted downfield but not as much as a $CH_2O$ group.




IR 1820, 1830 $cm^{-1}$
$\delta_H$ 4.12 (2H, s)
$\delta_C$ 160.3, 45.4

IR 2140 $cm^{-1}$
$\delta_H$ 2.24 (2H, s)
$\delta_C$ 193.6

▶ Malonic anhydride cannot be made directly from malonic acid because attempted dehydration of the acid leads to the exotic molecule carbon suboxide $C_3O_2$.




All this is reasonably convincing, and is confirmed by allowing the anhydride to warm to –30 °C when it loses $CO_2$ (detected by the $^{13}$C peak at 124.5 p.p.m.!) and gives another unstable compound with the strange IR frequency of 2140 $cm^{-1}$. Could this be monomeric ketene? It's certainly not either of the possible ketene dimers as we know what their spectra are like, and this is quite different: just a 2H singlet at 2.24 p.p.m. and $^{13}$C peaks at 194.0 and 2.5 p.p.m. It is indeed monomeric ketene.

## Squares and cubes: molecules with unusual structures

Some structures are interesting because we believe they can tell us something fundamental about the nature of bonding while others are a challenge because many people argue that they cannot be made. What do you think are the prospects of making cyclobutadiene, a conjugated four-membered ring, or the hydrocarbons tetrahedrane and cubane, which have, respectively, the shapes of the perfectly symmetrical Euclidean solids, the tetrahedron and the cube?

cyclobutadiene

tetrahedrane

cubane

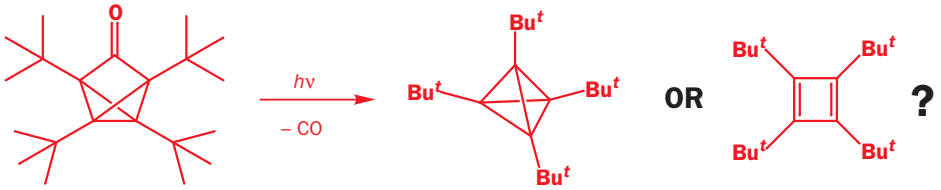
With four electrons, cubane is **anti-aromatic**—it has $4n$ instead of $4n + 2$. You saw in Chapter 7 that cyclic conjugated systems with $4n$ electrons (cyclooctatetraene, for example) avoid being conjugated by puckering into a tub shape. Cyclobutadiene cannot do this: it must be more or less planar, and so we expect it to be very unstable. Tetrahedrane has four fused three-membered rings. Though the molecule is tetrahedral in shape, each carbon atom is nowhere near a tetrahedron, with three bond angles of 60°. Cubane has six fused four-membered rings and is again highly strained.

In fact, cubane has been made, cyclobutadiene has a fleeting existence but can be isolated as an iron complex, and a few substituted versions of tetrahedrane have been made. The most convincing evidence that you have made any of these three compounds would be the extreme simplicity of the spectra. Each has only one kind of hydrogen and only one kind of carbon. They all belong to the family $(CH)_n$.

Cubane has a molecular ion in the mass spectrum at 104, correct for $C_8H_8$, only CH stretches in the IR at 3000 $cm^{-1}$, a singlet in the proton NMR at 4.0 p.p.m.,and a single line in the carbon NMR at 47.3 p.p.m. A very symmetrical molecule and a stable one in spite of all those four-membered rings.

■ You can read more about the synthesis of cubane in Chapter 37 (p. 000), when we discuss the rearrangement reactions that were used to make it.

Stable compounds with a cyclobutadiene and a tetrahedrane core can be made if each hydrogen atom is replaced by a *t*-butyl group. The very large groups round the edge of the molecule repel each other and hold the inner core tightly together. Now another difficulty arises—it is rather hard to tell the compounds apart. They both have four identical carbon atoms in the core and four identical *t*-butyl groups round the edge. The starting material for a successful synthesis of both was the tricyclic ketone below identified by its strained C=O stretch and partly symmetrical NMR spectra. When this ketone was irradiated with UV light (indicated by '*h*ν' in the scheme), carbon monoxide was evolved and a highly symmetrical compound $(t\text{-BuC})_4$ was formed. But which compound was it?




IR 1762 (C=O) $cm^{-1}$
$\delta_H$ 1.37 (18H, s), 1.27 (18H, s)
$\delta_C$ 188.7 (C=O),60.6, 33.2, 33.1, 31.0, 30.2, 29.3

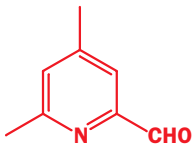
tetra-*t*-butyl tetrahedrane

tetra-*t*-butyl cyclobutadiene

The story is made more complicated (but in the end easier!) by the discovery that this compound on heating turned into another very similar compound. There are only two possible structures for $(t\text{-BuC})_4$, so clearly one compound must be the tetrahedrane and one the cyclobutadiene. The problem simplifies with this discovery because it is easier to distinguish two possibilities when you can make comparisons between two sets of spectra. Here both compounds gave a molecular ion in the mass spectrum, neither had any interesting absorptions in the IR, and the proton NMRs could belong to either compound as they simply showed four identical *t*-Bu groups. So did the carbon NMR, of course, but it showed the core too. The first product had only saturated carbon atoms, while the second had a signal at 152.7 p.p.m. for the unsaturated carbons. The tetrahedrane is formed from the tricyclic ketone on irradiation but it isomerizes to the cyclobutadiene on heating.

## Identifying compounds from nature

The next molecules we need to know how to identify are those discovered from nature—natural products. These often have biological activity and many useful medicines have been discovered this way. We shall look at a few examples from different fields. The first is the sex pheromone of the

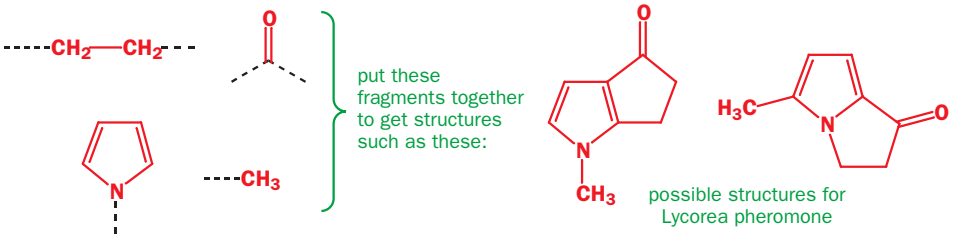


possible structure for *Lycorea* sex pheromone

Trinidad butterfly *Lycorea ceres ceres*. The male butterflies start courtship by emitting a tiny quantity of a volatile compound. Identification of this type of compound is very difficult because of the minute amounts available but this compound crystallized and gave enough for a mass spectrum and an IR. The highest peak in the mass spectrum was at 135. This is an odd number so we might have one nitrogen atom and a possible composition of $C_8H_9ON$. The IR showed a carbonyl peak at 1680 $cm^{-1}$. With only this meagre information, the first proposals were for a pyridine aldehyde.

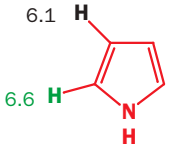
Eventually a little more compound (6 mg!) was available and a proton NMR spectrum was run. This showed at once that this structure was wrong. There was no aldehyde proton and only one methyl group. More positive information was the pair of triplets showing a $–CH_2CH_2–$ unit between two electron-withdrawing groups (N and C=O?) and the pair of doublets for neighbouring protons on an aromatic ring, though the chemical shift and the coupling constant are both rather small for a benzene ring.

If we look at what we have got so far, we see that we have accounted for four carbon atoms in the methyl and carbonyl groups and the $–CH_2CH_2–$ unit. This leaves only four carbon atoms for the aromatic ring. We must use nitrogen too as the only possibility is a pyrrole ring. Our fragments are now those shown below (the black dotted lines show joins to another fragment). These account for all the atoms in the molecule and suggest structures such as these.

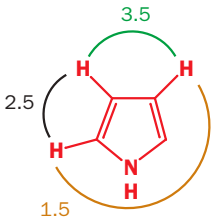


possible structures for Lycorea pheromone

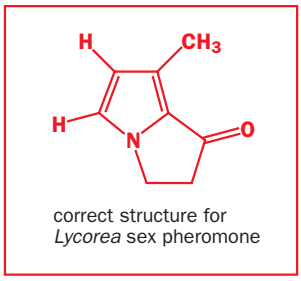
Now we need to use the known chemical shifts and coupling constants for these sorts of molecules. An N–Me group would normally have a larger chemical shift than 2.2 p.p.m. so we prefer the methyl group on a carbon atom of the pyrrole ring. Typical shifts and coupling constants around pyrroles are shown below. Chemists do not, of course, remember these numbers; we look them up in tables. Our data, with chemical shifts of 6.09 and 6.69 p.p.m. and a coupling constant of 2.5 Hz, clearly favour hydrogen atoms in the 2 and 3 positions and suggest this structure for the sex pheromone, which was confirmed by synthesis and is now accepted as correct.



typical chemical shifts for pyrroles



typical coupling constants for pyrroles



correct structure for *Lycorea* sex pheromone

## Tables

The final section of this chapter contains some tables of NMR data, which we hope you may want to use in solving problems. In Chapter 11 there were a few guides to chemical shift—summaries of patterns that you might reasonably be expected to remember. But we have left the main selections of hard numbers—tables that *you are not expected to remember*—until now. There are a few comments to explain the tables, but you will probably want to use this section as reference rather than bedtime reading. The first four tables give detailed values for various kinds of compounds and Table 15.5 gives a simple summary. We hope that you will find this last table particularly useful.

## Effects of electronegativity

Table 15.1 shows how the electronegativity of the atom attached directly to a methyl group affects the shifts of the $CH_3$ protons ($\delta_H$) and the $CH_3$ carbon atom ($\delta_C$)in their NMR spectra.

**Table 15.1** Chemical shifts δ of methyl groups attached to different atoms

| Element | Electronegativity | Compound | $\delta_H$, p.p.m. | $\delta_C$, p.p.m. |
|---|---|---|---|---|
| Li | 1.0 | $CH_3$–Li | –1.94 | –14.0 |
| Si | 1.7 | $CH_3$–$SiMe_3$ | 0.0 | 0.0 |
| I | 2.2 | $CH_3$–I | 2.15 | –23.2 |
| S | 2.4 | $CH_3$–SMe | 2.13 | 18.1 |
| N | 3.1 | $CH_3$–$NH_2$ | 2.41 | 26.9 |
| Cl | 2.8 | $CH_3$–Cl | 3.06 | 24.9 |
| O | 3.5 | $CH_3$–OH | 3.50 | 50.3 |
| F | 4.1 | $CH_3$–F | 4.27 | 75.2 |

## Effects of functional groups

Many substituents are more complicated than just a single atom and electronegativity is only part of the story. We need to look at all the common substituents and see what shifts they cause relative to the CH skeleton of the molecule. Our zero really ought to be at about 0.9 p.p.m. for protons and at 8.4 p.p.m. for carbon, that is, where ethane ($CH_3$–$CH_3$) resonates, and not at the arbitrary zero allocated to $Me_4Si$. In Table 15.2 we give such a list. The reason for this is that the shifts (from $Me_4Si$) themselves are not additive but the shift differences (from 0.9 or 8.4 p.p.m.) are.

**Table 15.2** Chemical shifts δ (p.p.m.) of methyl groups bonded to functional groups

| | Functional group | Compound | $\delta_H$ | $\delta_H$ – 0.9 | $\delta_C$ | $\delta_C$ – 8.4 |
|---|---|---|---|---|---|---|
| 1 | silane | **Me**$_4$Si | 0.0 | –0.9 | 0.0 | –8.4 |
| 2 | alkane | **Me–Me** | 0.86 | 0.0 | 8.4 | 0.0 |
| 3 | alkene | **Me**$_2$C=C**Me**$_2$ | 1.74 | 0.84 | 20.4 | 12.0 |
| 4 | benzene | **Me**–Ph | 2.32 | 1.32 | 21.4 | 13.0 |
| 5 | alkyne | **Me**–C≡C–R[a] | 1.86 | 0.96 | | |
| 6 | nitrile | **Me**–CN | 2.04 | 1.14 | 1.8 | –6.6 |
| 7 | acid | **Me**–$CO_2$H | 2.10 | 1.20 | 20.9 | 11.5 |
| 8 | ester | **Me**–$CO_2$Me | 2.08 | 1.18 | 20.6 | 11.2 |
| 9 | amide | **Me–**CONHMe | 2.00 | 1.10 | 22.3 | 13.9 |
| 10 | ketone | **Me**$_2$C=O | 2.20 | 1.30 | 30.8 | 21.4 |
| 11 | aldehyde | **Me–**CHO | 2.22 | 1.32 | 30.9 | 21.5 |
| 12 | sulfide | **Me**$_2$S | 2.13 | 1.23 | 18.1 | 9.7 |
| 13 | sulfoxide | **Me**$_2$S=O | 2.71 | 1.81 | 41.0 | 32.6 |
| 14 | sulfone | **Me**$_2$$SO_2$ | 3.14 | 2.24 | 44.4 | 36.0 |
| 15 | amine | **Me–**$NH_2$ | 2.41 | 1.51 | 26.9 | 18.5 |
| 16 | amide | MeCONH–**Me** | 2.79 | 1.89 | 26.3 | 17.9 |
| 17 | nitro | **Me**–$NO_2$ | 4.33 | 3.43 | 62.5 | 53.1 |
| 18 | ammonium salt | **Me$_4$**–$N^+$ $Cl^-$ | 3.20 | 2.10 | 58.0 | 49.6 |
| 19 | alcohol | **Me**–OH | 3.50 | 2.60 | 50.3 | 44.3 |
| 20 | ether | **Me**–OBu | 3.32 | 2.42 | 58.5 | 50.1 |
| 21 | enol ether | **Me**–OPh | 3.78 | 2.88 | 55.1 | 46.7 |
| 22 | ester | Me–$CO_2$**Me** | 3.78 | 2.88 | 51.5 | 47.1 |
| 23 | phosphonium salt | $Ph_3P^+$–**Me** | 3.22 | 2.32 | 11.0 | 2.2 |

[a]R = $CH_2OH$; compound is but-2-yn-1-ol..

The effects of groups based on carbon (the methyl group is joined directly to another carbon atom) appear in entries 2 to 11. All the electron-withdrawing groups based on carbonyl and cyanide have about the same effect (1.1–1.3 p.p.m. downfield shift from 0.9 p.p.m.). Groups based on nitrogen (Me–N bond) show a similar progression through amine, ammonium salt, amide, and nitro compound (entries 15–18). Finally, all the oxygen-based groups (Me–O bond) all show large shifts (entries 19–22).

## Effects of substituents on $CH_2$ groups

It is more difficult to give a definitive list for $CH_2$ groups as they have two substituents. In Table 15.3 we set one substituent as phenyl (Ph) just because so many compounds of this kind are available, and give the actual shifts relative to $PhCH_2CH_3$ for protons (2.64 p.p.m.) and $PhCH_2CH_3$ for carbon (28.9 p.p.m.), again comparing the substituent with the CH skeleton.

If you compare the shifts caused on a $CH_2$ group by each functional group in Table 15.3 with the shifts caused on a $CH_3$ group by the same functional group in Table 15.2 you will see that they are broadly the same.

**Table 15.3** Chemical shifts δ (p.p.m.) of $CH_2$ groups bonded to phenyl and functional groups

| | Functional group | Compound | $\delta_H$ | $\delta_H$ – 2.64 | $\delta_C$ | $\delta_C$ – 28.9 |
|---|---|---|---|---|---|---|
| 1 | silane | Ph**$CH_2$**–$SiMe_3$ | ? | ? | 27.5 | –1.4 |
| 2 | hydrogen | Ph**$CH_2$**–H | 2.32 | –0.32 | 21.4 | –7.5 |
| 3 | alkane | Ph**$CH_2$**–$CH_3$ | 2.64 | 0.00 | 28.9 | 0.0 |
| 4 | benzene | Ph**$CH_2$**–Ph | 3.95 | 1.31 | 41.9 | 13.0 |
| 5 | alkene | Ph**$CH_2$**–CH=$CH_2$ | 3.38 | 0.74 | 41.2 | 12.3 |
| 6 | nitrile | Ph**$CH_2$**–CN | 3.70 | 1.06 | 23.5 | –5.4 |
| 7 | acid | Ph**$CH_2$**–$CO_2H$ | 3.71 | 1.07 | 41.1 | 12.2 |
| 8 | ester | Ph**$CH_2$**–$CO_2Me$ | 3.73 | 1.09 | 41.1 | 12.2 |
| 9 | amide | Ph**$CH_2$**–$CONEt_2$ | 3.70 | 1.06 | ? | ? |
| 10 | ketone | $(Ph\mathbf{CH_2})_2C{=}O$ | 3.70 | 1.06 | 49.1 | 20.2 |
| 11 | thiol | Ph**$CH_2$**–SH | 3.69 | 1.05 | 28.9 | 0.0 |
| 12 | sulfide | $(Ph\mathbf{CH_2})_2S$ | 3.58 | 0.94 | 35.5 | 6.6 |
| 13 | sulfoxide | $(Ph\mathbf{CH_2})_2S{=}O$ | 3.88 | 1.24 | 57.2 | 28.3 |
| 14 | sulfone | $(Ph\mathbf{CH_2})_2SO_2$ | 4.11 | 1.47 | 57.9 | 29.0 |
| 15 | amine | Ph**$CH_2$**–$NH_2$ | 3.82 | 1.18 | 46.5 | 17.6 |
| 16 | amide | HCONH–**$CH_2$**Ph | 4.40 | 1.76 | 42.0 | 13.1 |
| 17 | nitro[a] | Ph**$CH_2$**–$NO_2$ | 5.20 | 2.56 | 81.0 | 52.1 |
| 18 | ammonium salt | Ph**$CH_2$**–$NMe_3^+$ | 4.5/4.9 | | 55.1 | 26.2 |
| 19 | alcohol | Ph**$CH_2$**–OH | 4.54 | 1.80 | 65.3 | 36.4 |
| 20 | ether | $(Ph\mathbf{CH_2})_2O$ | 4.52 | 1.78 | 72.1 | 43.2 |
| 21 | enol ether | Ph**$CH_2$**–OAr[b] | 5.02 | 2.38 | 69.9 | 41.0 |
| 22 | ester | $MeCO_2$–**$CH_2$**Ph | 5.10 | 2.46 | 68.2 | 39.3 |
| 23 | phosphonium salt | $Ph_3P^+$–**$CH_2$**Ph | 5.39 | 2.75 | 30.6 | 1.7 |
| 24 | chloride | Ph**$CH_2$**–Cl | 4.53 | 1.79 | 46.2 | 17.3 |
| 25 | bromide | Ph**$CH_2$**–Br | 4.45 | 1.81 | 33.5 | 4.6 |

[a]Data from Kurz, 1978 #9.

[b]Compound is (4-chloromethylphenyoxy)benzene.

## Shifts of a CH group

We can do the same with a CH group, and in the left-hand side of Table 15.4 we take a series of isopropyl compounds, comparing the measured shifts with those for the central proton ($CHMe_3$) or carbon ($CHMe_3$) of 2-methylpropane. We set two of the substituents as methyl groups and just vary the third. Yet again the shifts for the same substituent are broadly the same.

**Table 15.4 Effects of α and β substitution on $^1H$ and $^{13}C$ NMR shifts on $Me_2CHX$[a]**

| | Effects on $C_\alpha$ [$Me_2CH–X$], p.p.m. | | | | Effects on $C_\beta$ [$Me_2CH–X$], p.p.m. | | | |
|---|---|---|---|---|---|---|---|---|
| X | $\delta_H$ | $\delta_H$ – 1.68 | $\delta_C$ | $\delta_C$ – 25.0 | $\delta_H$ | $\delta_H$ – 0.9 | $\delta_C$ | $\delta_C$ – 8.4 |
| Li | | | 10.2 | –14.8 | | | 23.7 | 17.3 |
| H | 1.33 | –0.35 | 15.9 | –9.1 | 0.91 | 0.0 | 16.3 | 7.9 |
| Me | 1.68 | 0.00 | 25.0 | 0.0 | 0.89 | 0.0 | 24.6 | 16.2 |
| $CH=CH_2$ | 2.28 | 0.60 | 32.0 | 7.0 | 0.99 | 0.09 | 22.0 | 13.6 |
| Ph | 2.90 | 1.22 | 34.1 | 9.1 | 1.24 | 0.34 | 24.0 | 15.6 |
| CHO | 2.42 | 0.74 | 41.0 | 16.0 | 1.12 | 0.22 | 15.5 | 7.1 |
| COMe | 2.58 | 0.90 | 41.7 | 16.7 | 1.11 | 0.21 | 27.4 | 19.0 |
| $CO_2H$ | 2.58 | 0.90 | 34.0 | 9.0 | 1.20 | 0.30 | 18.8 | 10.4 |
| $CO_2Me$ | 2.55 | 0.87 | 33.9 | 8.9 | 1.18 | 0.28 | 19.1 | 10.7 |
| $CONH_2$ | 2.40 | 0.72 | 34.0 | 9.0 | 1.08 | 0.18 | 19.5 | 11.1 |
| CN | 2.71 | 1.03 | 20.0 | –5.0 | 1.33 | 0.43 | 19.8 | 11.4 |
| $NH_2$ | 3.11 | 1.43 | 42.8 | 17.8 | 1.08 | 0.18 | 26.2 | 17.8 |
| $NO_2$ | 4.68 | 3.00 | 78.7 | 53.7 | 1.56 | 0.66 | 20.8 | 12.4 |
| SH | 3.13 | 1.45 | 30.6 | 5.6 | 1.33 | 0.43 | 27.6 | 19.2 |
| $SPr^i$ | 3.00 | 1.32 | 33.5 | 8.5 | 1.27 | 0.37 | 23.7 | 15.3 |
| OH | 4.01 | 2.33 | 64.2 | 39.2 | 1.20 | 0.30 | 25.3 | 16.9 |
| $OPr^i$ | 3.65 | 1.97 | 68.4 | 43.4 | 1.12 | 0.22 | 22.9 | 14.5 |
| $O_2CMe$ | 5.00 | 3.32 | 67.6 | 42.6 | 1.22 | 0.32 | 21.4(8) | 17. (0/4) |
| Cl | 4.19 | 2.51 | 53.9 | 28.9 | 1.52 | 0.62 | 27.3 | 18.9 |
| Br | 4.29 | 2.61 | 45.4 | 20.4 | 1.71 | 0.81 | 28.5 | 20.1 |
| I | 4.32 | 2.36 | 31.2 | 6.2 | 1.90 | 1.00 | 21.4 | 13.0 |

[a]There is coupling between the CH and the $Me_2$ groups in the proton NMR; see p. 000.

## Shifts in proton NMR are easier to calculate and more informative than those in carbon NMR

This final table helps to explain something we have avoided so far. Correlations of shifts caused by substituents in proton NMR really work very well. Those in $^{13}C$ NMR work much less well and more complicated equations are needed. More strikingly, the proton shifts often seem to fit better with our understanding of the chemistry of the compounds. There are two main reasons for this.

First, the carbon atom is much closer to the substituent than the proton. In the compounds in Table 15.2, the methyl carbon atom is directly bonded to the substituent, while the protons are separated from it by the carbon atom of the methyl group. If the functional group is based on a large electron-withdrawing atom like sulfur, the protons will experience a simple inductive electron withdrawal and have a proportional downfield shift. The carbon atom is close enough to the sulfur atom to be shielded as well by the lone-pair electrons in the large $3sp^3$ orbitals. The proton shift

caused by S in $Me_2S$ is about the same (1.23 p.p.m.) as that caused by a set of more or less equally strong electron-withdrawing groups like CN (1.14 p.p.m.) or ester (1.18 p.p.m.). The carbon shift (9.7 p.p.m.) is less than that caused by an ester (11.2 p.p.m.) but much *more* than that caused by CN, which actually shifts the carbon upfield (–6.6 p.p.m.).

Second, the carbon shift is strongly affected not only by what is directly joined to that atom (α position), but also by what comes next (β position). The right-hand half of Table 15.4 shows what happens to methyl shifts when substituents are placed on the next carbon atom. There is very little effect on the proton spectrum: all the values are much less than the shifts caused by the same substituent on a methyl group in Table 15.2. Carbonyls give a downfield shift of about 1.2 p.p.m. when directly joined to a methyl group, but only of about 0.2 p.p.m. when one atom further away. By contrast, the shifts in the carbon spectrum are of the same order of magnitude in the two tables, and the β shift may even be greater than the α shift! The CN group shifts a directly bonded methyl group upfield (–6.6 p.p.m.) when directly bonded, but downfield (14.4 p.p.m.) when one atom further away. This is an exaggerated example, but the point is that these carbon shifts must *not* be used to suggest that the CN group is electron-donating in the α position and electron-withdrawing in the β position. The carbon shifts are erratic but the proton shifts give us useful information and are worth understanding as a guide both to structure determination and the chemistry of the compound.

When you use this table and are trying to interpret, say, a methyl group at 4.0 p.p.m. then you have no problem. Only one group is attached to a methyl group so you need a single shift value—it might be a methyl ester for example. But when you have a $CH_2$ group at 4.5 p.p.m. and you are interpreting a downfield shift of 3.2 p.p.m. you must beware. There are *two* groups attached to each $CH_2$ group and you might need a single shift of about 3 p.p.m. (say, an ester again) or two shifts of 1.5 p.p.m., and so on. The shifts are additive.

**Table 15.5** Approximate additive functional group (X) shifts in $^1$H NMR spectra

| Entry | Functional group X | $^1$H NMR shift difference[a], p.p.m. |
|---|---|---|
| 1 | alkene (–C=C) | 1.0 |
| 2 | alkyne (–C≡C) | 1.0 |
| 3 | phenyl (–Ph) | 1.3 |
| 4. | nitrile (–C≡N) | 1.0 |
| 5 | aldehyde (–CHO) | 1.0 |
| 6 | ketone (–COR) | 1.0 |
| 7 | acid (–$CO_2$H) | 1.0 |
| 8 | ester (–$CO_2$R) | 1.0 |
| 9 | amide (–$CONH_2$) | 1.0 |
| 10 | amine (–$NH_2$) | 1.5 |
| 11 | amide (–NHCOR) | 2.0 |
| 12 | nitro (–$NO_2$) | 3.0 |
| 13 | thiol (–SH) | 1.0 |
| 14 | sulfide (–SR) | 1.0 |
| 15 | sulfoxide (–SOR) | 1.5 |
| 16 | sulfone (–$SO_2$R) | 2.0 |
| 17 | alcohol (–OH) | 2.0 |
| 18 | ether (–OR) | 2.0 |
| 19 | aryl ether (–OAr) | 2.5 |
| 20 | ester (–$O_2$CR) | 3.0 |
| 21 | fluoride (–F) | 3.0 |
| 22 | chloride (–Cl) | 2.0 |
| 23 | bromide (–Br) | 2.0 |
| 24 | iodide (–I) | 2.0 |

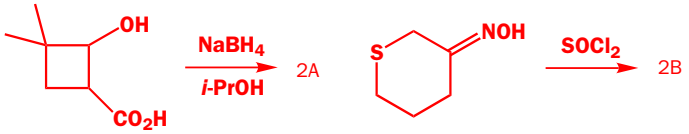
[a]To be added to 0.9 p.p.m. for MeX, 1.3 p.p.m. for $CH_2X$, or 1.7 p.p.m. for CHX.

# Problems

**1.** A compound $C_6H_5FO$ has a broad peak in the infrared at about 3100–3400 $cm^{-1}$ and the following signals in its (proton decoupled) $^{13}C$ NMR spectrum. Suggest a structure for the compound and interpret the spectra.

$\delta_C$ (p.p.m.) 157.38 (doublet, coupling constant 229 Hz), 151.24 (singlet), 116.32 (doublet, coupling constant 7.5 Hz), 116.02 (doublet, coupling constant 23.2 Hz).

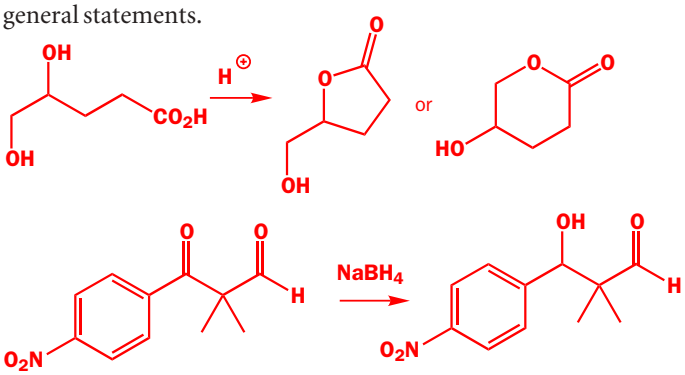
**2.** Suggest structures for the products of these reactions.



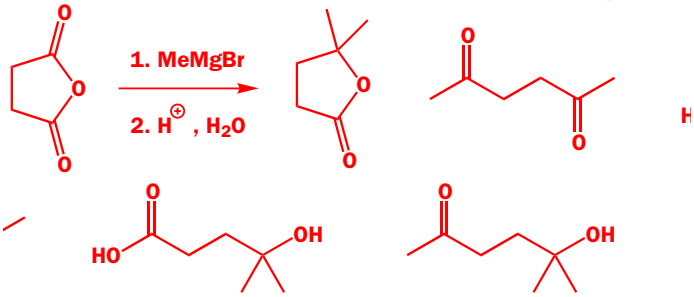

Compound 2A has: $C_7H_{12}O_2$; IR 1725 $cm^{-1}$; $\delta_H$ 1.02 p.p.m. (6H, s), 1.66 p.p.m. (3H, t, *J* 7 Hz), 2.51 p.p.m. (2H, t, *J* 7 Hz), and 3.9 p.p.m. (2H, s).

Compound 2B has: *m/z* 149/151 ($M^+$ ratio 3:1); IR 2250 $cm^{-1}$; $\delta_H$ 2.0 p.p.m. (2H, q, *J* 7 Hz), 2.5 p.p.m. (2H, t, *J* 7 Hz), 2.9 p.p.m. (2H, t, *J* 7 Hz), and 4.6 p.p.m. (2H, s).

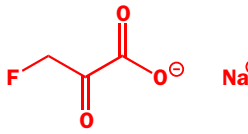
**3.** Two alternative structures are shown for the possible products of the following reactions. Explain in each case how you would decide which product is actually formed. Several pieces of evidence would be required and estimated values are more convincing than general statements.




**4.** The following products might possibly be formed from the reaction of MeMgBr with the cyclic anhydride shown. How would you tell the difference between these compounds using IR and $^{13}C$ NMR spectra? With $^1H$ NMR available as well, how would your task be easier? Draw mechanisms for the formation of these compounds.




**5.** The NMR spectra of sodium fluoropyruvate in $D_2O$ are given below. Are these data compatible with the structure shown? If not, suggest how the compound might exist in this solution.



sodium fluoropyruvate

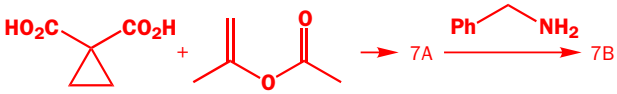
$\delta_H$ 4.43 p.p.m. (2H, d, *J* 47 Hz); $\delta_C$ 83.5 p.p.m. (d, *J* 22 Hz), 86.1 p.p.m. (d, *J* 171 Hz), and 176.1 p.p.m. (d, *J* 2 Hz).

**6.** An antibiotic isolated from a microorganism crystallized from water and formed (different) crystalline salts on treatment with either acid or base. The spectroscopic data were as follows.

Mass spectrum: 182 ($M^+$, 9%), 109 (100%), 137 (87%), and 74 (15%); $\delta_H$ (p.p.m.; in $D_2O$ at pH < 1) 3.67 (2H, d), 4.57 (1H, t), 8.02 (2H, m), and 8.37 (1H, m); $\delta_C$ (p.p.m.; in $D_2O$ at pH < 1) 33.5, 52.8, 130.1, 130.6, 134.9, 141.3, 155.9, and 170.2.

Suggest a structure for the antibiotic.

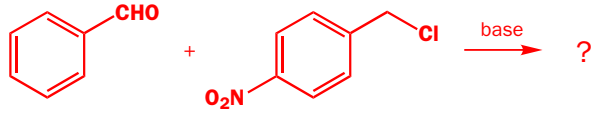
**7.** Suggest structures for the products of these two reactions.




Compound 7A: *m/z* 170 ($M^+$, 1%), 84 (77%), and 66 (100%); IR 1773, 1754 $cm^{-1}$; $\delta_H(CDCl_3)$ 1.82 p.p.m. (6H, s) and 1.97 p.p.m. (4H, s); $\delta_C(CDCl_3)$ 22, 23, 28, 105, and 169 p.p.m. (the signals at 22 and 105 p.p.m. are weak).

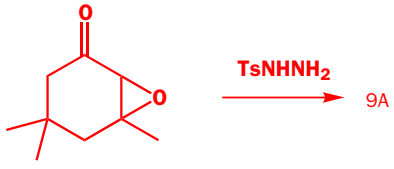
Compound 7B: *m/z* 205 ($M^+$, 40%), 161 (50%), 160 (35%), 106 (100%), and 77 (42%); IR 1670, 1720 $cm^{-1}$; $\delta_H(CDCl_3)$ 2.55 p.p.m. (2H, m), 3.71 p.p.m. (1H, t, *J* 6 Hz), 3.92 p.p.m. (2H, m), 7.21 p.p.m. (2H, d, *J* 8 Hz), 7.35 p.p.m. (1H, t, *J* 8 Hz), and 7.62 p.p.m. (2H, d, *J* 8 Hz); $\delta_C(CDCl_3)$ 21, 47, 48, 121, 127, 130, 138, 170, and 172 p.p.m.

**8.** Treatment of the two compounds shown here with base gives an unknown compound with the spectra given here. What is its structure?



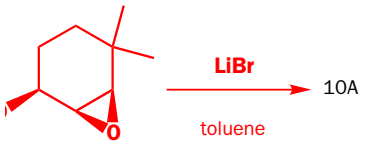

*m/z* 241 ($M^+$, 60%), 90 (100%), 89 (62%); $\delta_H(CDCl_3)$ 3.89 p.p.m. (1H, d, *J* 3 Hz), 4.01 p.p.m. (1H, d, *J* 3 Hz), 7.31 p.p.m. (5H, s), 7.54 p.p.m. (2H, d, *J* 10 Hz), and 8.29 p.p.m. (2H, d, *J* 10 Hz); $\delta_C(CDCl_3)$ 62, 64, 122, 125, 126, 127, 130, 136, 144, and 148 p.p.m. (the last three are weak).

**9.** Treatment of this epoxy-ketone gives a compound with the spectra shown below. What is its structure?



*m/z* 138 ($M^+$, 12%), 109 (56%), 95 (100%), 81 (83%), 82 (64%), and 79 (74%); IR 3290, 2115, 1710 $cm^{-1}$; $\delta_H(CDCl_3)$ 1.12 p.p.m. (6H, s), 2.02 p.p.m. (1H, t, *J* 3 Hz), 2.15 p.p.m. (3H, s), 2.28 p.p.m. (2H, d, *J* 3 Hz), and 2.50 p.p.m. (2H, s); $\delta_C(CDCl_3)$ 26, 31, 32, 33, 52, 71, 82, and 208 p.p.m.

**10.** Reaction of the epoxy-alcohol below with LiBr in toluene gave a 92% yield of compound 10A. Suggest a structure for this compound.



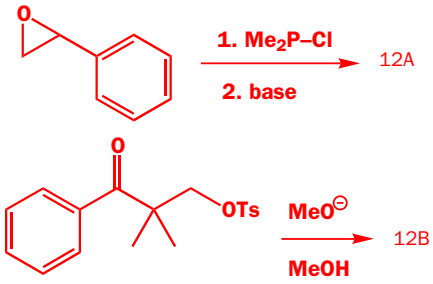

Compound 10A: *m/z* $C_8H_{12}O$; $\nu_{max.}$ ($cm^{-1}$) 1685, 1618; $\delta_H$ (p.p.m.) 1.26 (6H, s), 1.83 (2H, t, *J* 7 Hz), 2.50 (2H, dt, *J* 2.6, 7 Hz), 6.78 (1H, t, *J* 2.6 Hz), and 9.82 (1H, s); $\delta_C$ (p.p.m.) 189.2, 153.4, 152.7, 43.6, 40.8, 30.3, and 25.9.

**11.** Female boll weevils (a cotton pest) produce two isomeric compounds that aggregate the males for food and sex. A few mg of two isomeric active compounds, grandisol and *Z*-Ochtodenol were isolated from 4.5 million insects. Suggest structures for these compounds from the spectroscopic data below. Signals marked * exchange with $D_2O$.

*Z*-Ochtodenol: *m/z* 154 ($C_{10}H_{18}O$), 139, 136, 121, 107, 69 (100%); $\nu_{max}$ ($cm^{-1}$) 3350, 1660; $\delta_H$(p.p.m.) 0.89 (6H, s), 1.35–1.70 (4H broad m), 1.41 (1H, s*), 1.96 (2H, s), 2.06 (2H, t, *J* 6 Hz), 4.11 (2H, d, *J* 7 Hz), and 5.48 (1H, t, *J* 7 Hz).

Grandisol: *m/z* 154 ($C_{10}H_{18}O$), 139, 136, 121, 109, 68 (100%); $\nu_{max}$ ($cm^{-1}$) 3630, 3250–3550, and 1642; $\delta_H$(p.p.m.) 1.15 (3H, s), 1.42 (1H, dddd, *J* 1.2, 6.2, 9.4, 13.4 Hz), 1.35–1.45 (1H, m), 1.55–1.67 (2H, m), 1.65 (3H, s), 1.70–1.81 (2H, m), 1.91–1.99 (1H, m), 2.52* (1H, broad t, *J* 9.0 Hz), 3.63 (1H, ddd, *J* 5.6, 9.4, 10.2 Hz), 3.66 (1H, ddd, *J* 6.2, 9.4, 10.2 Hz), 4.62 (1H, broad s), and 4.81 (1H, broad s); $\delta_C$(p.p.m.) 19.1, 23.1, 28.3, 29.2, 36.8, 41.2, 52.4, 59.8, 109.6, and 145.1.

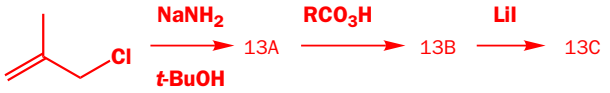
**12.** Suggest structures for the products of these reactions.




Data for compound 12A: $C_{10}H_{13}OP$; IR ($cm^{-1}$) 1610, 1235; $\delta_H$ (p.p.m.) 6.5–7.5 (5H, m), 6.42 (1H, t, *J* 17 Hz), 7.47 (1H, dd, *J* 17, 23 Hz), and 2.43 (6H, d, *J* 25 Hz).

Data for compound 12B: $C_{12}H_{16}O_2$; IR CH and fingerprint only; $\delta_H$ (p.p.m.) 7.25 (5H, s), 4.28 (1H, d, *J* 4.8 Hz), 3.91 (1H, d, *J* 4.8 Hz), 2.96 (3H, s), 1.26 (3H, s), and 0.76 (3H, s).

**13.** Identify the compounds produced in these reactions. Warning! Do not attempt to deduce the structures from the starting materials but use the data! These molecules are so small that you can identify them from $^1H$ NMR alone.

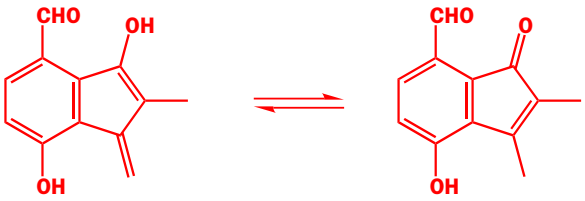



Compound 13A: $\delta_H(C_4H_6)$ 5.35 p.p.m. (2H, s) and 1.00 p.p.m. (4H, s).

Compound 13B: $\delta_H(C_4H_6O)$ 3.00 p.p.m. (2H, s), 0.90 p.p.m. (2H, d, *J* 3 Hz), and 0.80 p.p.m. (2H, d, *J* 3 Hz).

Compound 13C: $\delta_H(C_4H_6O)$ 3.02 p.p.m. (4H, d, *J* 5 Hz) and 1.00 p.p.m. (2H, quintet, *J* 5 Hz)

**14.** The yellow crystalline antibiotic frustulosin was isolated from a fungus in 1975 and it was suggested that the structure was an equilibrium mixture of 14A and 14B. Apart from the difficulty that the NMR spectrum clearly shows one compound and not an equilibrium mixture of two compounds, what else makes you unsure of this assignment? Suggest a better structure. Signals marked * exchange with $D_2O$.




14A 14B

Frustulosin: *m/z* 202 (100%), 187 (20%), 174 (20%); $\nu_{max}$ ($cm^{-1}$) 3279, 1645, 1613, and 1522; $\delta_H$ (p.p.m.) 2.06 (3H, dd, *J* 1.0, 1.6 Hz), 5.44 (1H, dq, *J* 2.0, 1.6 Hz), 5.52 (1H, dq, *J* 2.0, 1.0 Hz), 4.5* (1H, broad s), 7.16 (1H, d, *J* 9.0 Hz), 6.88 (1H, dd, *J* 9.0, 0.4 Hz), 10.31 (1H, d, *J* 0.4 Hz), and 11.22* (1H, broad s); $\delta_C$ (p.p.m.) 22.8, 80.8, 100.6, 110.6, 118.4, 118.7, 112.6, 125.2, 126.1, 151.8, 154.5, and 195.6

*Warning*! This is difficult—after all the original authors initially got it wrong!

*Hint*. How might the DBEs be achieved without a second ring?