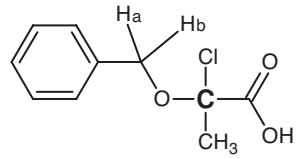
6

Delving Deeper

6.1 Chiral Centres

It's fair to say, that if all molecules were flat and lacked chiral centres, the interpretation of their NMR spectra would be far easier than it actually is but it would be a whole lot less fun too! In moving on to discuss more interesting chiral compounds, we have an opportunity to deal with some commonly held misconceptions and urban myths that can severely limit understanding of the subject.

A good working knowledge of stereo-chemistry is certainly a big advantage when looking at the spectra of chiral molecules. Let's start by considering Structure 6.1.



Structure 6.1 A chiral molecule.

Clearly, the highlighted carbon is a chiral centre (it has four different groups attached to it). For this reason, the two protons Ha and Hb can never be in the same environment. The fact that there is free rotation around all the single bonds in the molecule is irrelevant. This can best be appreciated by building a model of the molecule. Having done so, look down the molecule from left to right as drawn and rotate the C-O bonds so that Ha and Hb rotate. It should now be clear why these two protons can never occupy the same space and are therefore not equivalent.

Now for the next big step forward: if they are not equivalent, then there is no reason for them to have the same chemical shift. Another big step: and if they have different chemical shifts, they will couple to each other. In fact, in molecules of this type (i.e., that have an isolated CH_2 in the region of a chiral centre) the likelihood is that the CH_2 will be observed as a pair of doublets (see Spectrum 6.1).

How close they are to each other, or how far apart, is not something that can be easily estimated as it depends on the through-space interactions (anisotropies) of both protons with all the other groups in the molecule. That having been said, the two doublets are likely to be within 1 ppm of each other and

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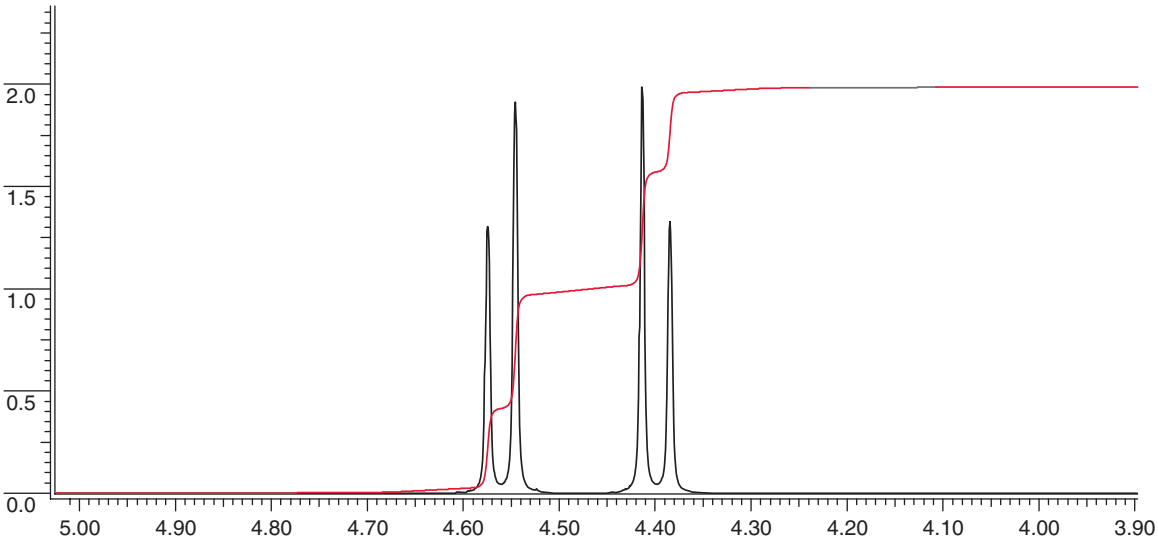


Spectrum 6.1 An AB system.

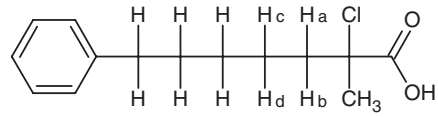
are therefore likely to be clearly 'roofed' to each other. Spectroscopists use the term 'AB system' to describe this type of arrangement. All it means is that the spin system contains two protons which are relatively close to each other in chemical shift terms, (but not equivalent to each other), HA and HB, and they couple to each other and nothing else.

Geminal couplings of this type are typically in the region of 12–14 Hz, though interestingly, they can be as large as 19 Hz between protons that are alpha to an alkene or carbonyl function. This can be a useful interpretive 'handle' if you are looking for a starting point in a complex assignment. (Take a look at a spectrum of camphor if you need convincing! Spot any huge geminal couplings?)

Of course, it is quite possible, though statistically unlikely, that you might encounter a molecule of this type in which the chemical shifts of the two protons, Ha and Hb just happen to be identical. Under these circumstances, there will be no splitting observed and you will just observe a singlet as if there were no chiral centre in the molecule at all. But beware! Should you run the sample in a different solvent, or even in the same solvent but at a different concentration, the singlet would be likely to re-present itself as an AB system. *Note*: The degree of separation between Ha and Hb reflects the anisotropic influences the different groups on the chiral centre exert on the two protons. If these groups were all very similar in nature (e.g., an ethyl, propyl and butyl) there would be very little 'difference' engendered in Ha and Hb, and for this reason, we could reasonably expect the chemical shift difference between these two protons to be small.

You might consider there to be an issue in predicting the chemical shift of a signal that is split into an AB system in this way but in reality, we have found it safe to treat the prediction as the midpoint between the two doublets of the AB.

So in summary, the presence of a chiral centre in a molecule can render nearby geminal pairs of protons non-equivalent. 'Nearby' is not an exact term and varies according to circumstance. Let's consider our molecule again, but this time, replace the -CH_2- with an alkyl chain (Structure 6.2).



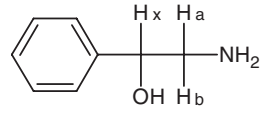
Structure 6.2 A chiral molecule with an alkyl chain.

In this case, it should be clear that Ha and Hb are just as non-equivalent as before. And because they are non-equivalent, it stands to reason that the next pair of protons, Hc and Hd must also be non-equivalent – and the next pair and the next pair. And so it is. In terms of the spectral lines observed, complexity will certainly be the name of the game! Not only will Ha and Hb couple to each other but they will obviously both couple to Hc and Hd. What will not necessarily be so obvious is that the size of the splittings between Ha and Hc and between Ha and Hd will very likely be different! This is because although there is free rotation about all single bonds, the chiral centre will place certain steric constraints upon the molecule such that it will tend to adopt a conformation that will minimise these constraints. This means that the time-averaged dihedral angles between H_a and H_c and H_a and H_d will not be the same – and neither will be the corresponding couplings. All of a sudden, in this welter of complex, overlapped, heavily roofed multiplets, Pascal's triangle starts to look woefully inadequate, doesn't it?

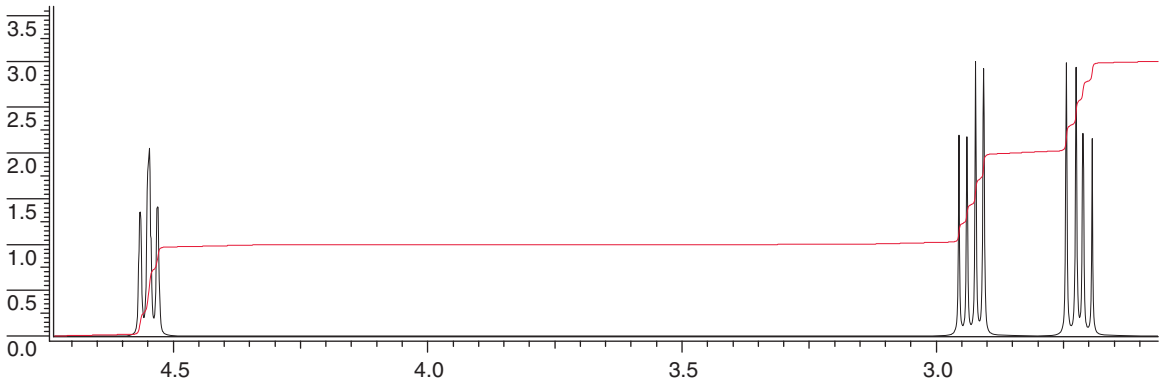
In practise, of course, we find that the further away from the chiral centre we go, the smaller the difference in chemical shift between corresponding geminal protons is likely to be. By the time we move three or four carbons down the chain, the likelihood is that corresponding pairs will be approximately equivalent, so for example, in the case above, we might expect the $-CH_2-$ next to the phenyl ring to be just a fairly normal, slightly broadened, roofed triplet rather than a pair of complex multiplets. It is not impossible, however for a molecule to wrap itself up in certain conditions such that the a geminal pair of protons are brought near to a chiral centre in the molecule – even though they may be many, many bonds away from it. It is important to remember that this is a 'through space' effect rather than a 'through bond' effect.

The convention of appending letters of the alphabet to protons in order to describe spin systems is commonly used in two more important cases. Structure 6.3 shows a molecule likely to exhibit a classic ABX system (see Spectrum 6.2).

As before, the chiral centre renders H_a and H_b non-equivalent and for the reasons already covered, H_x will couple to both with all three couplings (H_a-H_b, H_a-H_x and H_b-H_x) likely to be different. So the classical presentation of an ABX system is that of three multiplets, each of four lines. (Note that in Spectrum 6.2, the size of the H_a-X and the H_b-X couplings are almost identical so the X proton appears as an approximate triplet. This is quite common.). The AB part indicates that the geminal pair are likely to be relatively close in terms of chemical shift, whilst the X proton is someway distant from both. Obviously, the scope for variation in the appearance of ABX systems is enormous. The difference in chemical shift between H_a and H_b is a major factor in this but we have also come across ABX systems



Structure 6.3 A molecule likely exhibiting a classic ABX system.



Spectrum 6.2 A typical ABX system.

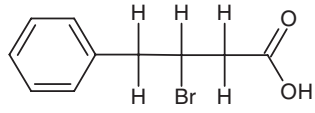
constrained within five-membered rings where all three splittings happen to be the same size. In such cases, we observe three triplets. Another possibility is for A and B to be accidentally equivalent in which case we observe something approximating to a simple doublet for H_a and H_b and a triplet for H_x.

It is also quite common to see molecules in which the X proton is actually the X of two distinct ABX systems. Structure 6.4 and Spectrum 6.3 show an example of such a molecule.

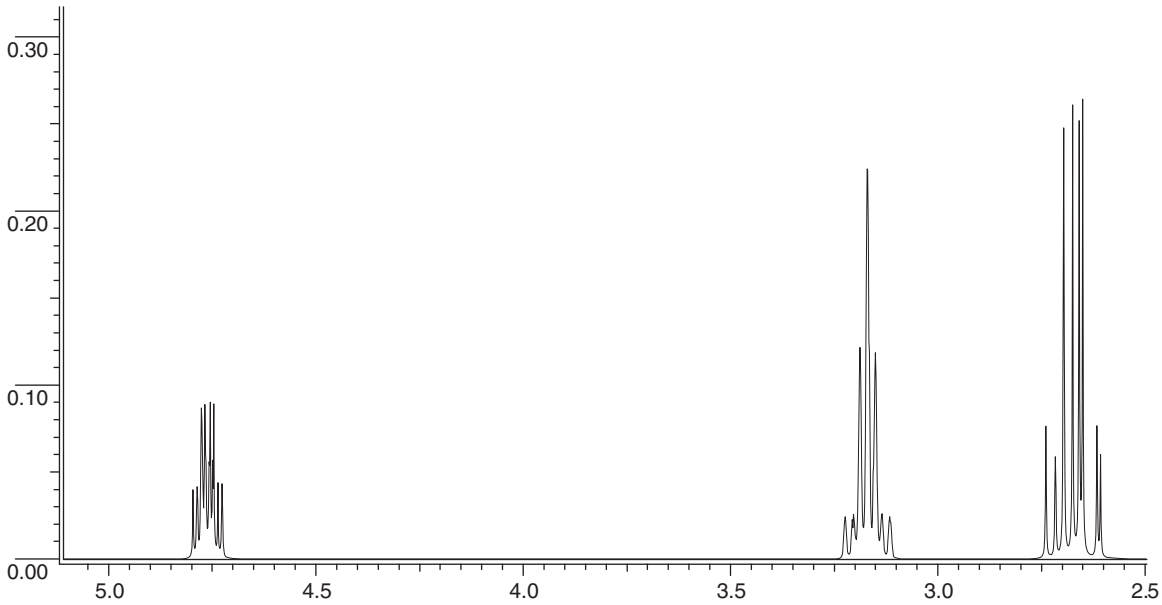
In a molecule like this, it would be theoretically possible for H_x to present as a 16-line multiplet but it is extremely unlikely that you would be able to count this many as there would almost certainly be a considerable overlap between them. Then of course, it is would be quite possible for the two AB parts to overlap. Be flexible in your approach and alert to the possibilities . . .

Moving on to some wider stereochemical considerations, just as enantiomers are indistinguishable as far as their physical and chemical properties are concerned (except, of course, as regards their reactions with other optically active reagents) so their spectra, acquired under normal conditions, are identical. The NMR spectrometer does not differentiate between optically pure samples and racemic ones. *Note*: there is a way of differentiating between enantiomers by NMR but it involves using certain chiral reagents which we'll discuss in detail later.

So much for one chiral centre. The problems really begin when you come up against molecules which have two or more chiral centres! With two chiral centres, we can construct four possible stereoisomers. These can be separated into two enantiomeric pairs (indistinguishable by NMR). But, (*key sentence coming up*) if we compare one member of each of these enantiomeric pairs, we will find that they may be distinguished from each other by NMR, because they are diastereoisomers. Diastereoisomers are stereoisomers which are not mirror images of each other – they are different compounds with distinct physical and chemical properties. See Figure 6.1 if this isn't clear.



Structure 6.4 X proton belonging to two distinct ABX systems.



Spectrum 6.3 A complex double ABX system.

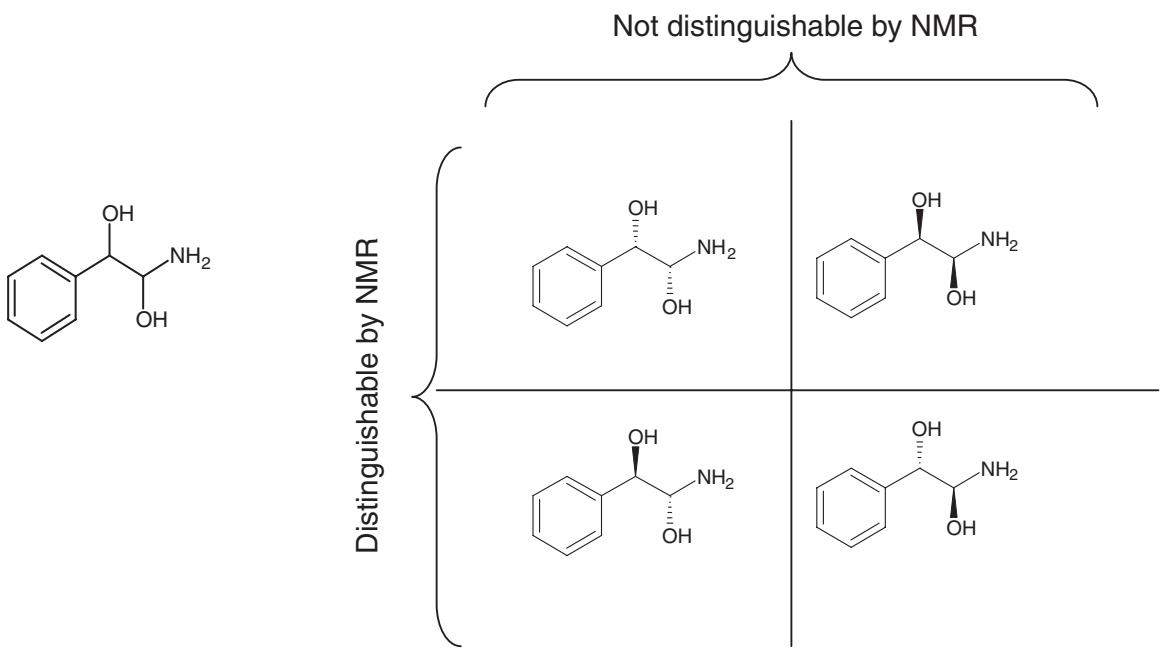
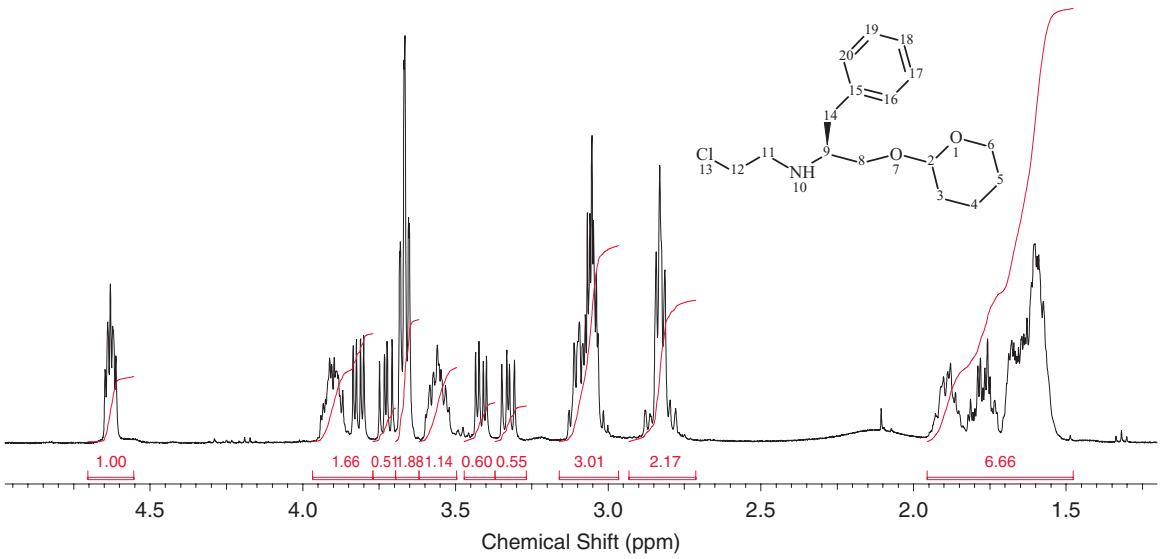


Figure 6.1 NMR and the relationship between enantiomers and diastereoisomers.



Spectrum 6.4 A mixture of diastereoisomers.

Differences in the spectra of diastereoisomers are generally most noticeable in the region of the chiral centres. Spectrum 6.4 shows a typical example.

Note how two sets of signals are clearly visible, for the protons labelled '8' above. These present as two pairs of protons, i.e., two AB parts of two ABX systems at 3.30–3.45 and 3.70–3.85 ppm, each integrating for approximately half a proton with respect to the unresolved parts of the spectrum. You certainly wouldn't expect *all* the signals of a pair of diastereoisomers to resolve (e.g., protons 3, 4 and 5 in the example above) but some will almost certainly do so. In some cases, the differences in the spectra of diastereoisomers can be quite spectacular, with chemical shift differences of 0.5 ppm or more.

With more than two unspecified chiral centres, problems multiply rapidly – three chiral centres yield eight stereoisomers, and thus four possible sets of signals and so on. From this, it follows that n chiral centres give rise to 2^n chiral entities of which $2^n/2$ will be distinguishable by NMR.

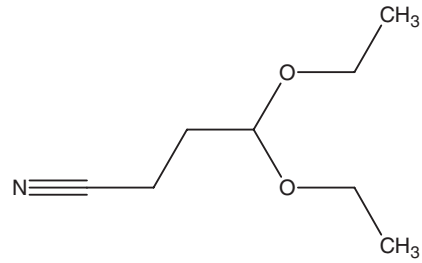
A final point on this phenomenon – nitrogen can sometimes act as a chiral centre. This topic is explored in some detail in Section 6.6.6.

6.2 Enantiotopic and Diastereotopic Protons

Consider ethanol (*key sentence coming up*). If you were to replace each of the methylene protons in turn with some other group, Z, you would end up with a pair of enantiomers. We call this, 'the Z test.' For this reason, the protons (or whatever groups may be involved, in molecules of the type: X-CA_2-Y) are described as *enantiotopic*. This is of no consequence in the spectrometer, because as we have mentioned, enantiomers are not distinguishable by NMR under normal conditions.

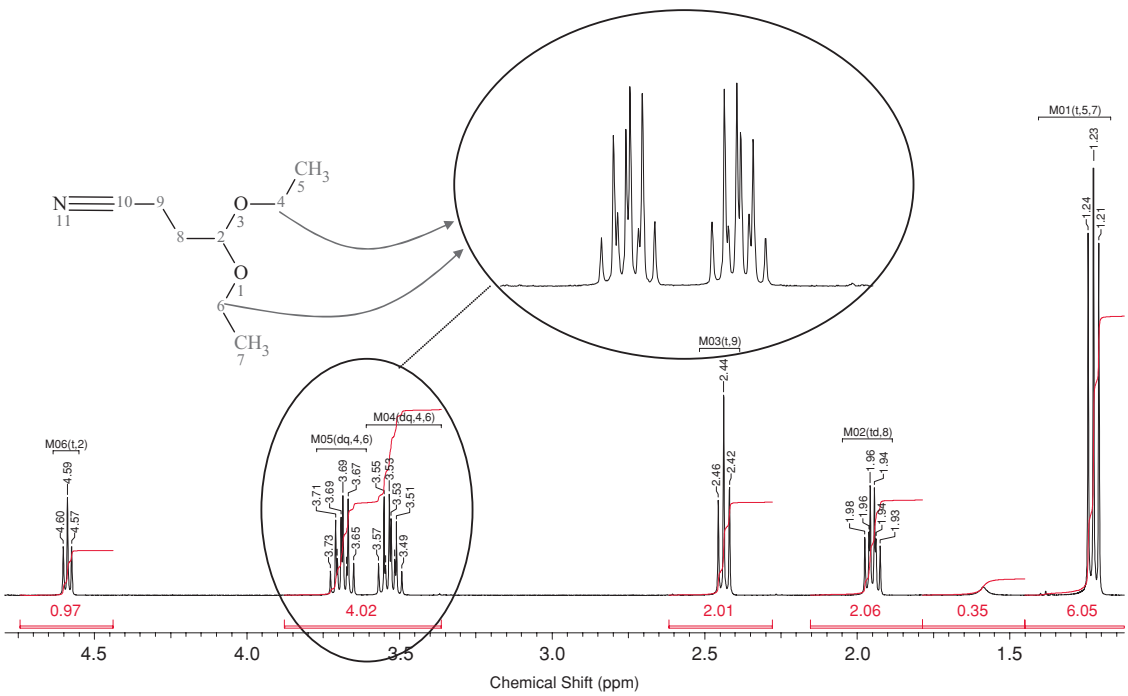
So far so good. Now consider the molecule in Structure 6.5.

The molecule clearly does not contain any chiral centres and so should give a perfectly straightforward spectrum. Now take a look at the Spectrum 6.5.



Structure 6.5 A diastereotopic molecule.

On close examination, it is clear that the methylene protons of the -OEt groups (H4, H6), do not give the nice simple quartet which we might reasonably expect. Close examination of the methylene signal shows it to be a complex multiplet. But why? Try applying the 'Z test' to the methylene protons. Straight away, the difference between this molecule and ethanol becomes apparent. Whereas ethanol would yield a pair of enantiomers in response to the test, this molecule would yield a pair of diastereoisomers as a second chiral centre would be generated at the branch point (C2)! For this reason, the methylene protons in this molecule would be described as *diastereotopic*. Such protons are not equivalent and therefore exhibit further splittings as they couple to each other – hence the complexity.

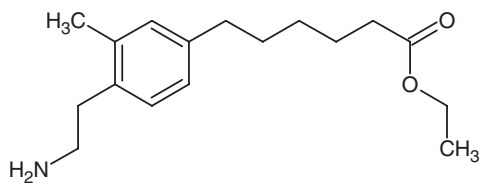


Spectrum 6.5 Diastereotopic protons.

Some confusion can arise over use of the term 'prochiral' to describe various sites within molecules and is perhaps best avoided for this reason. The term means literally, one step removed from being chiral (i.e., swap one of the protons for 'Z' and you have a full chiral centre). The methylene in ethanol for example, would be a good example. What we have in the di-ethoxy molecule above is one prochiral centre acting in combination with another to render a pair of protons non-equivalent.

6.3 Molecular Anisotropy

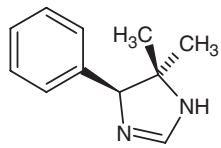
There are two factors that determine chemical shifts – electron distribution and molecular anisotropy. We have already seen how electronics define chemical shifts in previous sections. When we use Table 5.4 to estimate shifts around an aromatic ring, for example, the predictions we arrive at are based on the known electron withdrawal or supply of the various substituents on the ring. No allowance is made for unusual anisotropy. Similarly, predictions of chemical shifts of alkyl protons using Table 5.8 will be calculated on the basis of electronic factors only as it would be impossible to vector anisotropy into the prediction since it varies in each individual molecule. They will be reasonably accurate in molecules where electronic factors predominate and molecular anisotropy has little or no influence. A typical example of such a molecule is shown in Structure 6.6. Note the lack of steric crowding in the structure.



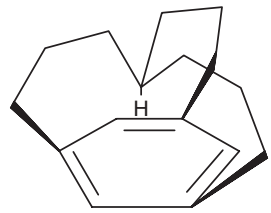
Structure 6.6 Typical molecule where electronic factors predominate.

However, in molecules where groups are constrained for whatever steric reasons, molecular anisotropy can play a large part in determining chemical shifts. Take for example, the molecule in Structure 6.7.

When confronted by a molecule like this, we can be sure that whatever conformation it adopts in solution, the likelihood is that the two methyl groups will not be equivalent! The driving force for their non-equivalence will of course be the aromatic ring. One of the methyl groups will be on the same face of the five-membered ring as the phenyl group and the other will not (once again, building a model is a good idea). In terms of through-bond electronics, both methyls enjoy much the same environment but the magnetic field that each will experience in terms of their proximities to the phenyl ring will be very different. And this, in essence, is what molecular anisotropy is all about – non-uniform distribution of electrons within groups, inducing significant chemical shift changes in parts of molecules by the



Structure 6.7 Molecule displaying molecular anisotropy.



Structure 6.8 An extreme example of anisotropy.

introduction of localised magnetic fields. In Structure 6.7 above, for example, it would be likely that the phenyl ring would interact with the methyl group *cis* to it (i.e., on same face of five-membered ring) in such a way as to minimise contact. In order to do this, it would probably spend most of its time at right-angles to the plane of the paper, i.e., sticking up vertically out of the page. This would position the *cis* methyl over the phenyl ring's pi-cloud which would induce an upfield shift in this methyl and cause it to be higher field than you might expect. The *trans* methyl would be relatively unaffected.

Structure 6.8 demonstrates a most extreme example of anisotropy. In this unusual metacyclophane, the predicted chemical shift (Table 5.8) of the methine proton that is suspended above the aromatic ring would be 1.9 ppm. In fact, the observed shift is –4 ppm, i.e., 4 ppm *above* TMS! The discrepancy between these values is all down to the anisotropic effect of the benzene ring and the fact that the proton in question is held very close to the delocalised 'p' electrons of the pi cloud.

All groups have a certain measure of anisotropy associated with them so that any protons forced abnormally close to *any* group are likely to exhibit some deviation from expected chemical shifts but the most notable are the aromatic/heterocyclic groups, carbonyls and alkenes. Expect abnormal shifts in molecules where steric crowding forces groups into close contact with each other. Build models and try to envisage the likely (lowest energy) conformations of your molecules. How will various groups within your molecules align themselves with respect to the anisotropic moieties? Remember that aromatic/heterocyclic rings shield groups that are held *above* or *below* their plane but de-shield groups that are held *in* their plane and that groups held near the 'oxygen end' of a carbonyl group will be de-shielded.

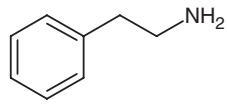
It is anisotropy that is the ultimate cause of the chemical shift differences between the geminal protons in AB and ABX systems. And indirectly, it is changes in anisotropy that bring about differences in observed chemical shifts for the same sample that is run in different solvents. The unknown extent of the anisotropy term in defining chemical shifts make it difficult (or perhaps impossible?) to devise a prediction tool, computer-based or otherwise, that can accurately predict the shifts of all protons regardless of environment. You may be wondering why the extent of the anisotropy term should be unknown. This is because in order to calculate it, we would first need to know the exact shape of the molecule in question – in solution. Molecular modelling packages deal with single molecules in a vacuum. This is nothing like variable concentrations in a variety of organic solvents with varying water content!

Molecular anisotropy affects proton chemical shifts to a far greater extent than ^{13}C chemical shifts. This is because the protons occupy the outer extremities of a molecule whilst the carbon framework is far more internal and to a large extent, removed from the influences of anisotropy.

Always be aware of anisotropy but as with all NMR phenomena, avoid becoming obsessed with it!

6.4 Accidental Equivalence

Accidental equivalence is a fairly self explanatory term used to describe situations where different signals happen to be coincidental. In most cases, this will come as no great surprise, and should cause no great problem. As you run through the mental exercise of estimating the chemical shifts of all the protons in your spectrum in order to create a hypothetical spectrum, don't forget to consider the possibilities of signals sharing exactly the same chemical shifts. There is no mysterious force acting to 'repel' chemical shifts away from each other and it is quite possible for chemical shifts to be coincidental. Take for example, the simple molecule of the type shown in Structure 6.9.



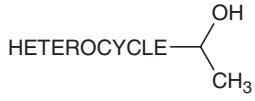
Structure 6.9 An example of accidental equivalence.

Checking the chemical shifts for the alkyl chain *as a free base*, would lead us to conclude that the -CH_2- next to the aromatic ring should absorb at a slightly lower field (approx. 2.9 ppm, making allowance for the short chain length and slight beta de-shielding effect of the -NH_2 group) than the -CH_2- next to the -NH_2 function (should be approx. 2.6 ppm). However, should the nitrogen be protonated by an acid, then the -CH_2- next to the -NH_3^+ would have the lower chemical shift (approx. 3.4 ppm) and those next to the aromatic ring, approx. 3.1 ppm (due to enhanced beta de-shielding). The act of protonation causes the shift of one -CH_2- to 'overtake' the other, as they both move downfield. But at a certain intermediate acid concentration, both CH_2-s will have exactly the same chemical shift and will present as a four-proton singlet. If confronted with a situation like this, your first thought might be: 'This cannot be right!' But your second thought should be: 'Ah! Maybe the nitrogen has been partially protonated by exposure to some acid?' And your third thought should be: 'OK. So what am I going to do to prove this?'

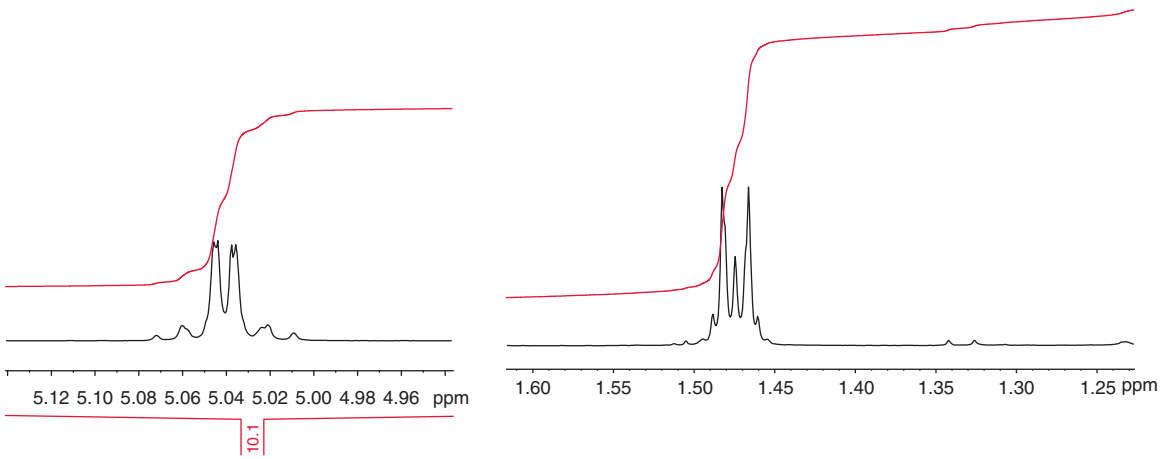
As we have already seen, accidental equivalence could be responsible for the theoretically non-equivalent protons of an AB system presenting as a singlet and for the more complex ABX system presenting as a simple doublet and triplet. But occasionally, even more interesting manifestation of accidental equivalence can be observed. Consider the molecule below (Structure 6.10) and its spectrum (Spectrum 6.6) which shows only the regions of interest to us – expanded and with the intervening region removed.

The complex multiplet centred at 5.04 ppm results from the overlap of the methine and -OH protons (i.e., they are 'accidentally equivalent') whilst the equally complex methyl signal is centred at 1.48 ppm. Because of this overlap, their lines are indistinguishable and so the -OH is said to be 'virtually coupled' to the methyl group. Virtual coupling is another potential consequence of non-first order behaviour.

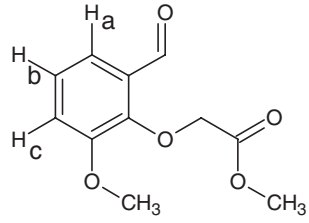
And for a final example, consider the molecule in Structure 6.11 and Spectrum 6.7. Please note: Spectrum 6.7 has been simulated on account of no compound being available at the time of writing. The



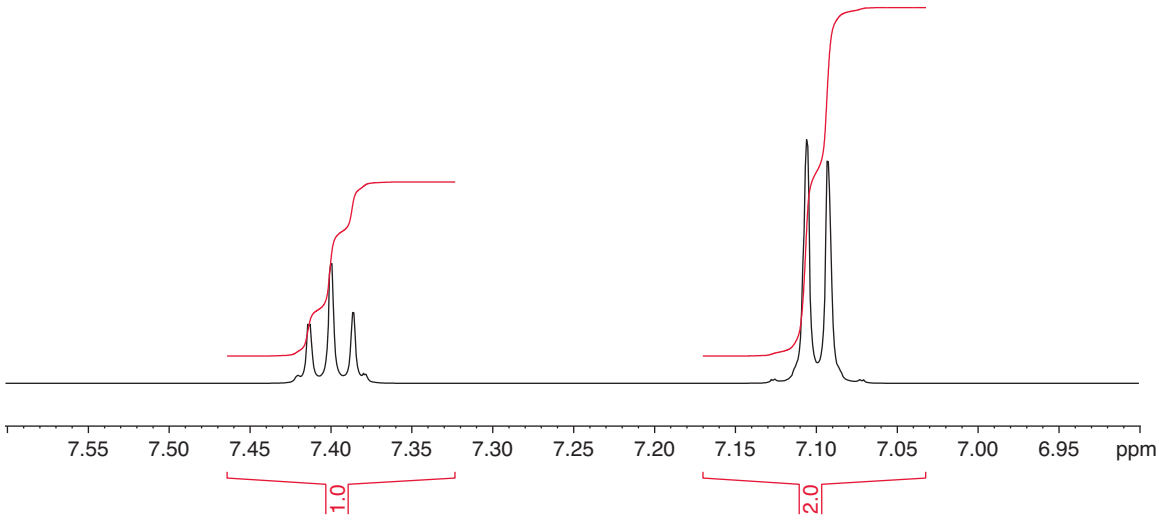
Structure 6.10 An example of vitrual coupling.



Spectrum 6.6 Virtual coupling.



Structure 6.11 A deceptively simple molecule.



Spectrum 6.7 Deceptive simplicity.

chemical shifts and splitting values were taken from an actual spectrum published in *Laboratory Guide to Proton NMR Spectrocopy* (see Introduction).

When we look at this 'deceptively simple' spectrum, it soon becomes clear that two of the aromatic protons must be isochronous since we see only two multiplets with the appropriate integration of 2 : 1 for the three protons. The lowest field of the aromatic protons must be 'Ha' as it is ortho to the de-shielding aldehyde function and therefore it must be the slightly higher-field protons 'Hb' and 'Hc' which are accidentally equivalent to each other as they are either ortho or para to the electron-donating (upfield-shifting) oxygen atoms. Were it not for the fact that 'Hb' and 'Hc' share the same chemical shift, we would expect to see them couple to 'Ha' with couplings of about 7.5 and 2.5 Hz, respectively. What we see in reality is an approximate triplet/doublet structure with an apparent splitting of about 5 Hz! This is clearly too large to be a meta- coupling and too small to be an ortho- coupling. Note that the small additional lines flanking the doublet and triplet are real and part of the signals in question. They can be explained by the magnetic non-equivalence of 'Hb' and 'Hc' and are a manifestation of non-first order behaviour.

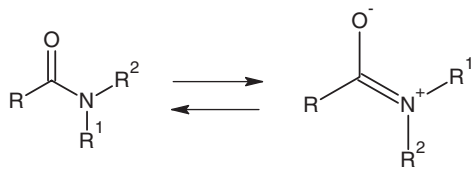
It is in effect a hybrid splitting; literally, an average of the two expected couplings. The two protons become indistinguishable from each other and both appear to exist in some hybrid ortho/meta state! The term 'deceptive simplicity' is quite apt to describe such a spin system. It might look simple, but it isn't. It's non-first order splitting at its most beguiling! Don't bother trying to find this sort of thing in your spectra. It is a rare phenomenon (and the more powerful your magnet, the rarer it is) and you won't find it. But it's good to be aware of it because if you look at enough spectra, one day *it* might find *you*.

6.5 Restricted Rotation

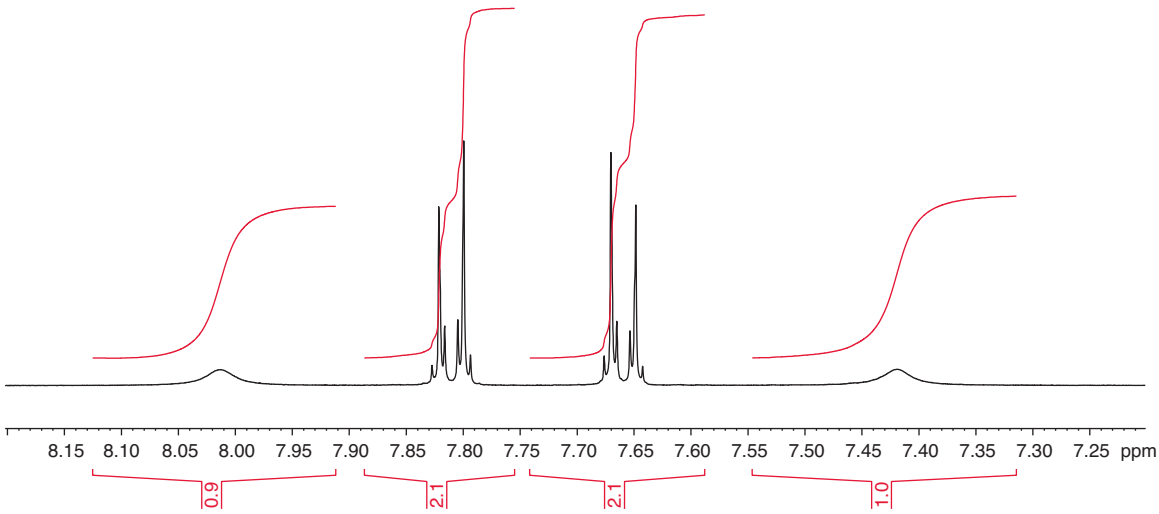
Certain types of bond, whilst nominally being considered as 'single', have in fact, sufficient 'double bond character', to render rotation about their axis, 'restricted'. The one you are most likely to encounter, is the amide bond. Partial double bond character exists between the carbonyl, and the nitrogen, and may be represented as in Structure 6.12:

This can lead to problems in NMR spectra. The magnitude of the energy barrier to the rotation determines what the effect on the spectrum will be. (For the thermodynamically-minded, we are talking about energy barriers of the order of 9–20 Kcal mol.)

Should the energy barrier be substantially lower than this, then restriction will be slight, and rotation will be relatively fast on the NMR time scale, and therefore, we may only see a slight broadening of signals in the region of the site of restricted rotation. Conversely, should the energy barrier be relatively high, rotation will be slow enough for us to see two distinct sets of signals. The worse case scenario



Structure 6.12 Partial double bond character.



Spectrum 6.8 4-Bromobenzamide showing typical appearance of primary amide protons as two non-equivalent broad signals separated by about 0.6 ppm.

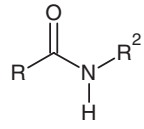
is that of rotation which is of intermediate pace on the NMR timescale, as this gives rise to broad semi-coalesced signals that are impossible to interpret.

Let's return to our amides. In primary amides, where R′ and R″ are both just protons, we can expect to see them as two, distinct, broad signals (Spectrum 6.8).

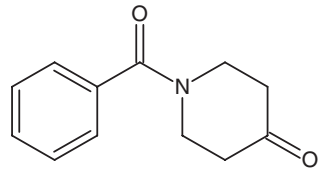
This is because the two protons do not occupy the same environment. Though they do exchange their positions with each other, the process is 'slow on the NMR timescale.' This means that during the time in which a single transient is acquired, there will have been relatively little exchange and for this reason, the spectrometer will 'see' the two amide protons in two distinct environments and you will observe two distinct broad humps separated typically by about 0.6 ppm. Anisotropy of the carbonyl group ensures that the lower-field of the two humps corresponds to the proton that is *cis* to the carbonyl oxygen at the time of the acquisition and the higher field hump, to the proton *trans* to the carbonyl oxygen. No other signals in the spectrum of a primary amide will be broadened by restricted rotation about the primary amide bond.

Secondary amides, on the other hand, generally do not exhibit two rotametric forms (that is not to say that rotation about the amide bond in secondary amides doesn't occur at all – just that secondary amides spend most of their time with the two large groups, R and R^2, *trans* to each other (Structure 6.13).

For this reason, secondary amides do not generally cause any spectroscopic headaches.



Structure 6.13 A secondary amide.



Structure 6.14 First example of restricted rotation.

It is the tertiary amides that tend to be the most problematic in terms of proton NMR. They usually exhibit two rotametric forms, the relative proportion of each being determined by both electronic factors and by the relative sizes of the two groups, R^1 and R^2. *Note*: this in no way implies that the rotameric forms of a tertiary amide could ever be physically separated as the inter-conversion rate between the two forms is generally in the order of seconds. A 50/50 ratio of rotamers is only guaranteed where $R^1=R^2$ (as in the case of a primary amide where $R^1=R^2=H$). Consider the two compounds in Structures 6.14 and 6.15.

In the case of the molecule in Structure 6.14, only the protons of the piperidone ring would be affected by restricted rotation about the amide bond. As far as the aromatic protons are concerned, there is no anisotropic difference in the environment they experience, because the piperidone has a plane of symmetry through it.

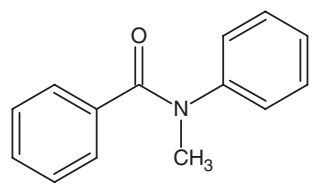
Now consider Structure 6.15. In this case, there is no such symmetry and so *all* the signals of the spectrum of this compound would be expected to be broadened or duplicated! Always consider the symmetry of the molecule in anticipation of the extent of rotameric complexity.

We will see later on, that we can often overcome rotational energy barriers (providing they are not too high) and thus simplify our spectra by running our samples at high temperature. Note that in cases where there is a large difference in the ratio of the rotamers, the coalescence point will not just be midway between the positions of the two rotamers, but will be closer to the position of the major rotamer. Note also that in cases where the amide function is sterically constrained, rotamers may *not* be observed as one rotameric form might be of significantly lower energy than the other and therefore may predominate, perhaps totally in a molecule like the one in Structure 6.16.

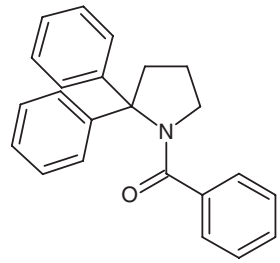
Another group which is well known for restricted rotation is the nitrovinyl group (Structure 6.17).

This time, the alkene nominal double bond has sufficient single bond character to permit a certain amount of rotation, as resonance forms can be drawn (e.g., Structure 6.18).

Another group that frequently – and perhaps surprisingly, in view of secondary amide characteristics – exhibits rotameric behaviour is the secondary carbamate (R-COO-NHR^1), though the energy barrier to rotation tends to be a little lower than in the amide case.



Structure 6.15 Second example of restricted rotation.



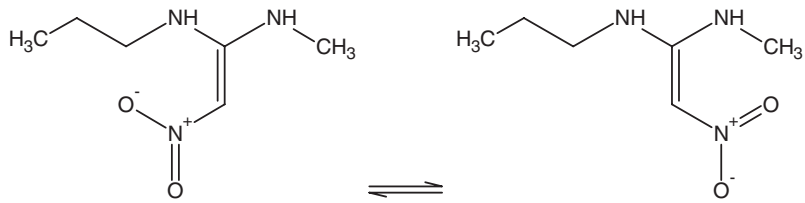
Structure 6.16 Amide function sterically constrained.

Finally, it's worth mentioning the formamide group. Although this looks like a special case of a secondary amide, rotamers of different intensity are often seen. Compounds with a formamide attached to an aromatic ring can give particularly complex spectra. Not only does the NH proton couple to the CHO proton, with a coupling of about 2–3 Hz in the *cis* isomer, and 8–9 Hz in the *trans* isomer, but, any aromatic protons ortho to the formamide are also split out in the rotamers!

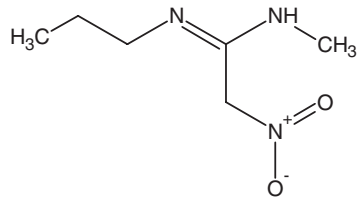
So to sum up, we've seen that restricted rotation can give rise to considerable complexity by broadening or duplication of signals. Indeed, overlap of signals from rotameric pairs is commonplace and can cause further ambiguity. As with any other phenomenon, if it is recognised for what it is, and the spectrum can be interpreted in terms of it, then all well and good. If however, the quality of your spectral information is diminished as a result of it, (and remember that you may have more than one site of restricted rotation in a molecule) to the point where you cannot be confident about determining the structure of your compound, then further action must be taken! (like running your sample hot, or perhaps trying it in D_4-methanol for example – this solvent can reduce rotational energy barriers, probably by eliminating intramolecular H-bonding.)

But don't assume that just because your compound exhibits restricted rotation, you must run it hot, to do it justice. Not so! Sometimes, the barrier to rotation is just too high to allow simplification by heating. Remember – it is easier to deal with a spectrum of two, sharp rotamers than a broad semi-coalesced mess!

It is worth noting that whilst we have restricted discussion in this section to conformational interconversion based on the slow rotation of bonds, the concept of 'the NMR timescale' is equally applicable to other types of interconversion, such as can sometimes be seen in cyclic systems which may exist in two different conformational forms.



Structure 6.17 Nitrovinyl group.



Structure 6.18 Resonance form.

6.6 Heteronuclear Coupling

So far, we've considered spin coupling in considerable detail, but only proton–proton coupling. There are in fact, over 60 elements having nuclei of one or more of their naturally occurring isotopes which have magnetic moments. This means that they not only have their own NMR spectra (e.g., ^{19}F, ^{31}P, which can be recorded with a suitable spectrometer) but also the capability of coupling with protons. The most notable and obvious feature of heteronuclear coupling, is that no reciprocal coupling is observed in the proton spectrum – because it exists in the spectrum of the heteroatom, of course. In this section, we'll have a look at the hetero-atoms of importance, which you are quite likely to encounter, and one or two others, which are less commonly encountered. It might be tempting to think that if your compound contains a heteroatom there should be an imperative to acquire a spectrum for that specific nucleus – but this is not so. The proton spectrum often contains all the confirmation of the hetero atom that you need, as the size and nature of the couplings observed can be quite specific.

We will deal with the spectroscopy of a few of these nuclei in later sections but for now, we will restrict ourselves to the consequences of hetero atoms seen in proton spectroscopy.

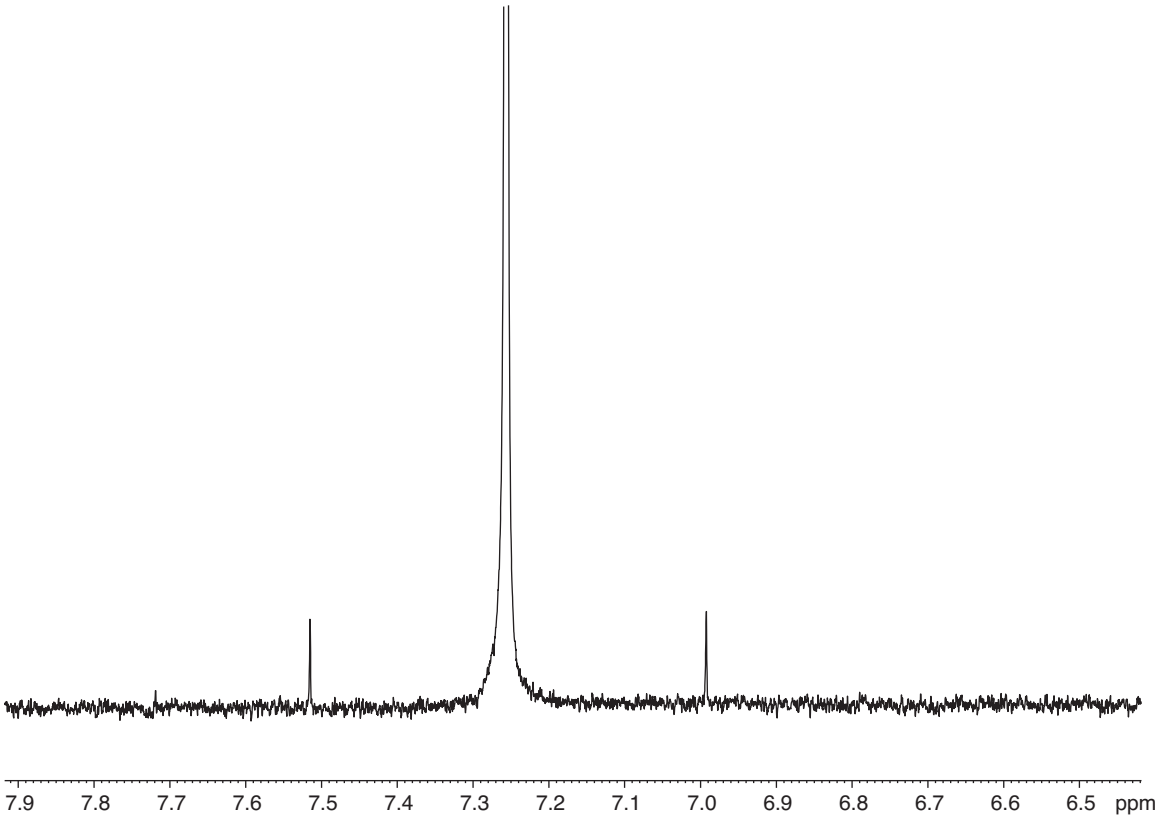
6.6.1 Coupling between Protons and ^{13}C

Consider Spectrum 6.9 which shows a $CHCl_3$ singlet plotted at very high intensity.

On each side of the signal, a number of minor peaks may be seen, one pair of which are the '^{13}C satellites.' (We'll discuss spinning side bands a little later). Since the ^{13}C nucleus has a magnetic moment, it couples to proton signals, but as its natural abundance is only 1.1 %, the ^{13}C satellites are very small, each satellite accounting for only 0.55 % of the intensity of the peak to which it belongs. The only time you might notice them, is when you have a very strong singlet in your spectrum, such as a tertiary butyl.

The ^{13}C nucleus, like the proton, has a nuclear spin quantum number (I) of 1/2, so there are only two permitted energy states of the nucleus with respect to the external magnetic field. This means of course, that there are only two satellite peaks, i.e., the 1.1 % of the protons that are attached to ^{13}C nuclei are split by the ^{13}C nucleus into a doublet (and the 98.9 % that are attached to ^{12}C, are not). If you measure the coupling (from satellite to satellite), you'll find that it's 210 Hz – though the size of ^{13}C-H couplings vary considerably, depending on the type of function the carbon is incorporated into. This coupling may seem very large, but don't forget it is a one-bond coupling.

These days, improvements in magnet design and consequent greater field homogeneity have made it quite common practise to run NMR experiments, nonspinning. Indeed, many of the two-dimensional experiments should definitely *not* be run spinning (see Chapter three for more discussion about spinning vs. non spinning). However, for one-dimensional spectra, the best resolution is likely to be obtained



Spectrum 6.9 $CHCl_3$ singlet plotted at high intensity.

by spinning your samples at about 20 Hz. If you do this, you *may* encounter spinning side bands. These should never be a problem in a well shimmed instrument operating to record spectra at typical levels of gain but it is possible to observe them occasionally as small peaks on either side of very strong peaks (most notable singlets) such as t-butyl singlets. Their relative intensities are not fixed as with ^{13}C satellites but can vary with the state of the high-order shims and with the quality of the NMR tubes you use. *Note*: Should spinning side-bands ever exceed the size of the ^{13}C satellites, you should seriously consider a major shim of your instrument! Should you be looking for some very minor constituent of your sample, ^{13}C satellites, and spinning side bands may get in the way. Spinning side bands can be moved by altering the spin rate of the sample tube but you can't do anything about the satellites. Notice that the separation of the first spinning side band, (if seen) from the main peak, when measured in Hz, gives the spinning speed (also in Hz of course). Notice too, that the phase of a second spinning sideband, if present, is always 'out' with respect to all the other peaks – a useful diagnostic feature.

^{13}C satellites can actually be quite useful sometimes, as they give a ready-made visual comparator for the quality of spectrometer high-order shimming and for trace impurities that you may be trying to quantify, since we know that each satellite will have an intensity of 0.55 % of the peak it is associated with.

Two final interesting points relating to ^{13}C satellites . . . Whilst they are generally, evenly spaced on either side of the major peak, they do not have to be *exactly* symmetrically disposed about it. It is

quite possible to observe a small isotopic shift so that the proton chemical shift of the ^{13}C species is fractionally different from the major ^{12}C species. Also, if you do observe ^{13}C satellites, they will only ever be the product of one-bond ^{13}C-proton coupling. Two- and three-bond couplings between ^{13}C and protons certainly exist (and indeed are pivotal in the HMBC technique as we will see later) but such couplings do not generally manifest themselves in 1-D proton spectra as any satellites thus produced would be too close to the major peak to observe. ^{13}C satellites themselves are never seen to be split further by ^{13}C–^{13}C coupling simply because the statistical chance of finding two ^{13}C atoms next to each other is extremely small in terms of NMR sensitivity.

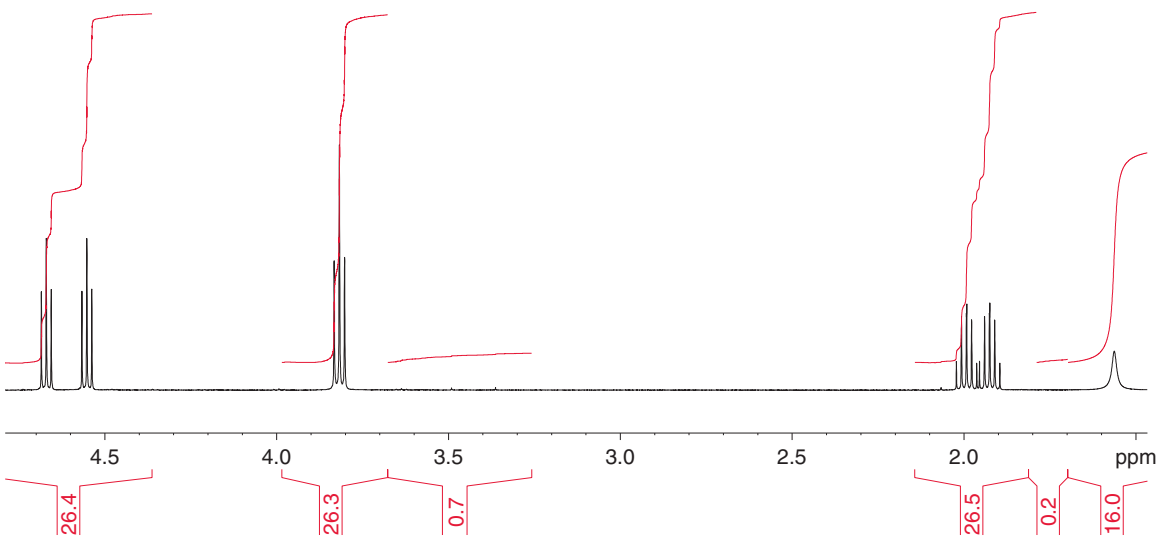
^{13}C coupling has very little significance in everyday proton NMR interpretation, though it has been used in the past to crack specific problems by means of selective enrichment of a specific carbon during synthesis, with a greater than normal percentage of ^{13}C isotope, which makes detection easy.

6.6.2 Coupling between Protons and ^{19}F

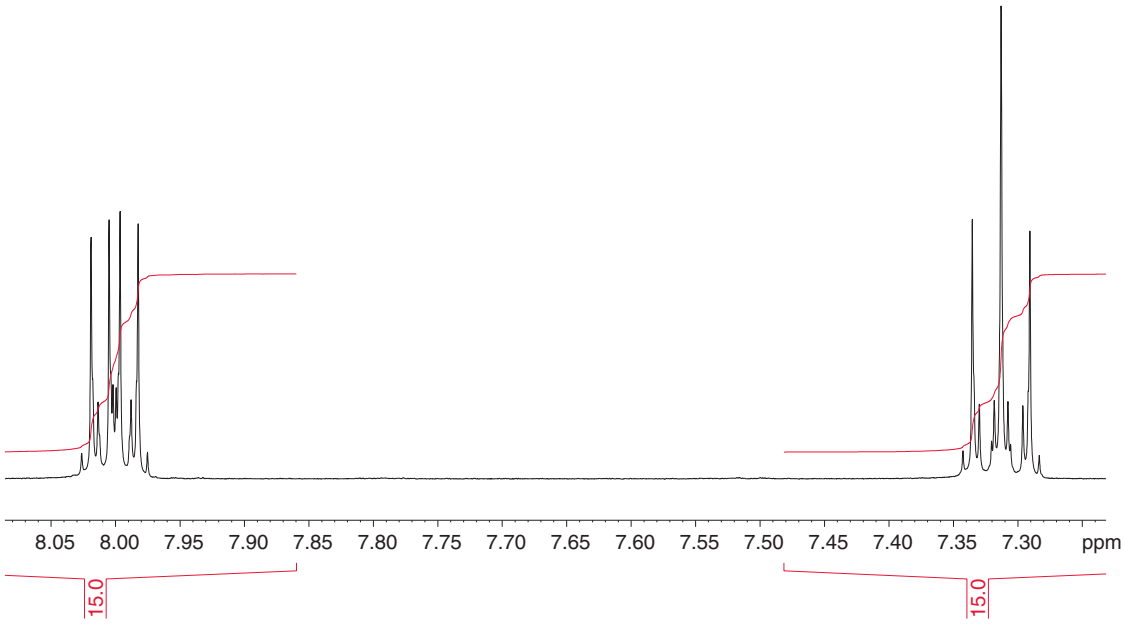
Fluorine usually makes its presence felt in a fairly spectacular fashion, when it is present in a molecule. Once again, I = 1/2, so we only have two allowed states to worry about. Unlike ^{13}C however, fluorine has only one isotope, ^{19}F, and as this of course, has 100 % natural abundance, we see the whole proton signal split, instead of a couple of tiny satellites on either side of our signals!

This point is well illustrated with a spectrum of 3-fluoro propanol (Spectrum 6.10), which shows a fairly dramatic example of fluorine coupling. The F-C**H$_2$**- coupling is about 47 Hz, and the F-CH$_2$-C**H$_2$**- coupling, is 27 Hz. The coupling to the third methylene group is non-existent in this example but can be seen sometimes (0–3 Hz).

Another example of ^{19}F coupling, this time in an aromatic system, (4-fluoro benzoic acid) is shown in Spectrum 6.11. Note how the ^{19}F couplings to the aromatic protons give the AA′BB′ system an



Spectrum 6.10 3-Fluoro propanol.



Spectrum 6.11 4-Fluoro benzoic acid.

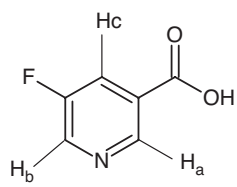
asymmetric appearance. The actual values in this case are 9.0 Hz (ortho) and 5.6 Hz (meta) which are fairly typical.

More useful ^{19}F coupling data is given in Table 6.1.

Fluorine can sometimes throw up some unexpected couplings in certain situations and spectra need to be handled with care! Sometimes, fluorine can be seen to couple over an unfeasible number of bonds (we have seen a seven bond coupling in the past). This is because fluorine is so electron hungry that it can couple through space as well as through-bond!

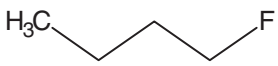
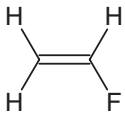
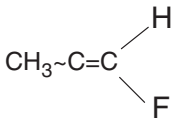
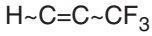
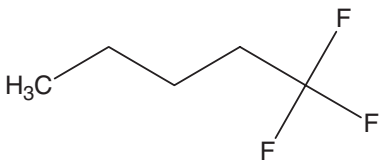
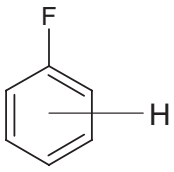
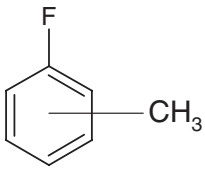
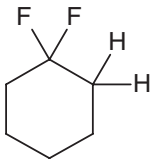
We have also noted some strange behaviour with fluorinated pyridines, for example, 3-fluoro nicotinic acid (Structure 6.19 and Spectrum 6.12). The signal for H_c (approx. 8.1 ppm) clearly shows couplings of 9.1, 2.9 and 1.7 Hz. The 9.1 Hz coupling must be from the fluorine as it does not appear anywhere else in the spectrum and its chemical shift distinguishes it from either of the other two protons.

Of the other two protons, the signal at 8.82 ppm, (H_b) shows only a 2.9 Hz coupling which is also found in H_c, whilst Ha exhibits two small couplings (2.0 and 1.7 Hz), the smallest of these also appearing in H_c. These observations lead to the conclusion that the fluorine–proton couplings in this molecule are as given in Table 6.2.



Structure 6.19 3-Fluoro nicotinic acid.

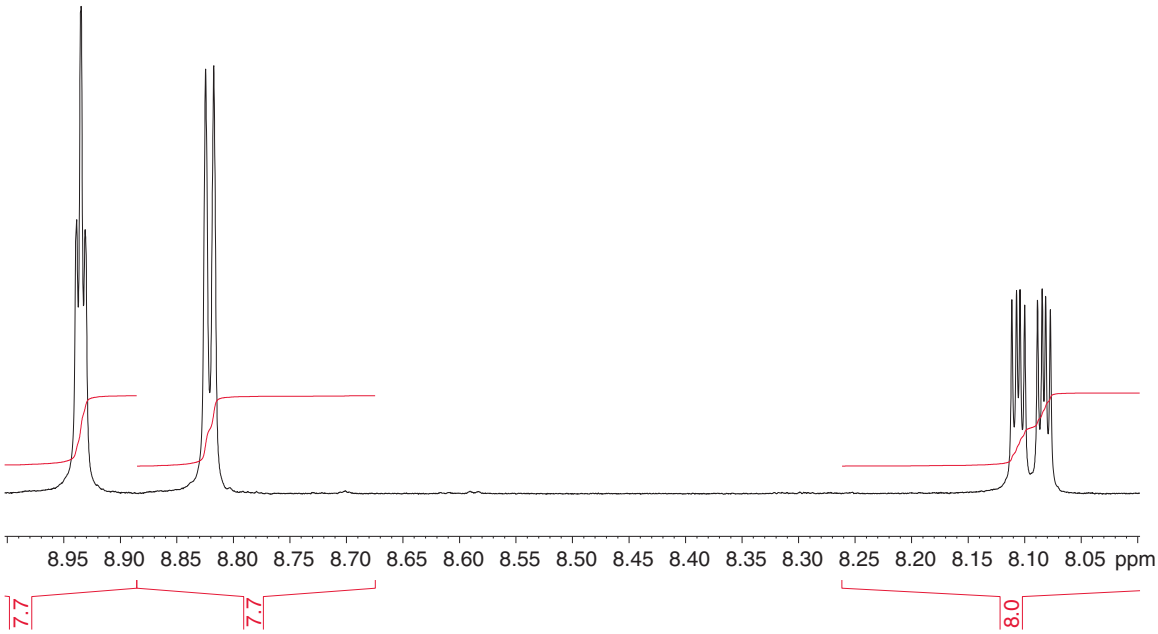
Table 6.1 Some typical ^{19}F–proton couplings.

Structure	^{19}F-^{1}H position	Typical ^{19}F-^{1}H coupling (Hz)
	F-**CH_2**- F-CH_2-**CH_2**- F-CH_2-CH_2-**CH_2**-	45 24 0–3
	F-H (geminal) F-H (*cis*) F-H (*trans*)	85 20 50
	F-CH_3	2–4
	F_3C-H	0-1
	F_3C-CH_2-	8–10
	F-H (ortho) F-H (meta) F-H (para)	6.2–10.3 3.7–8.3 0–2.5
	F-CH_3 (ortho) F-CH_3 (meta) F-CH_3 (para)	2.5 0 1.5
	F_{axial}–H_{axial} F_{axial}–$H_{equatorial}$ $F_{equatorial}$–$H_{equatorial}$	34 11.5 5–8

F-H_c coupling did not surprise and neither did F-H_a coupling. But the F-H_b coupling of less than a single Hz is totally baffling and defies obvious logic!

Having learnt the lessons from this simple little compound, it would seem reasonable to expect similarly surprising couplings in other fluorinated heterocycles.

Tread carefully!



Spectrum 6.12 3-Fluoro nicotinic acid.

Table 6.2 Fluorine–proton couplings in 3-fluoro nicotinic acid.

Position	Coupling (Hz)
F-H_a	2.0
F-H_b	very small, <1.0!
F-H_c	9.1

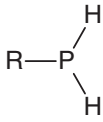
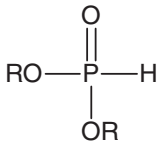
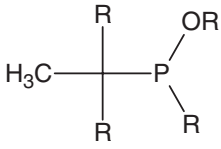
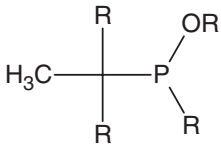
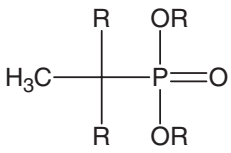
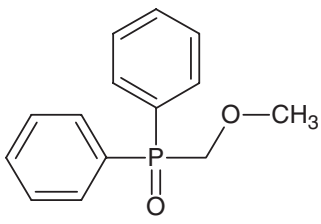
6.6.3 Coupling between Protons and ^{31}P

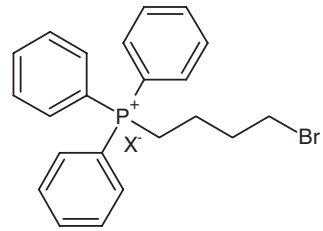
Phosphorus is the other heteroatom of major coupling importance to the organic chemist. Like ^{19}F, ^{31}P has a spin of $^1/_2$ and a 100 % natural abundance, so you know what to expect! The actual size of the couplings observed with ^{31}P can vary considerably, depending on the oxidation state of the ^{31}P atom. You'll find some useful examples in Table 6.3.

^{31}P shows one particularly interesting feature. The size of couplings normally decreases dramatically with the number of intervening bonds, but this is not always the case with ^{31}P (Table 6.3).

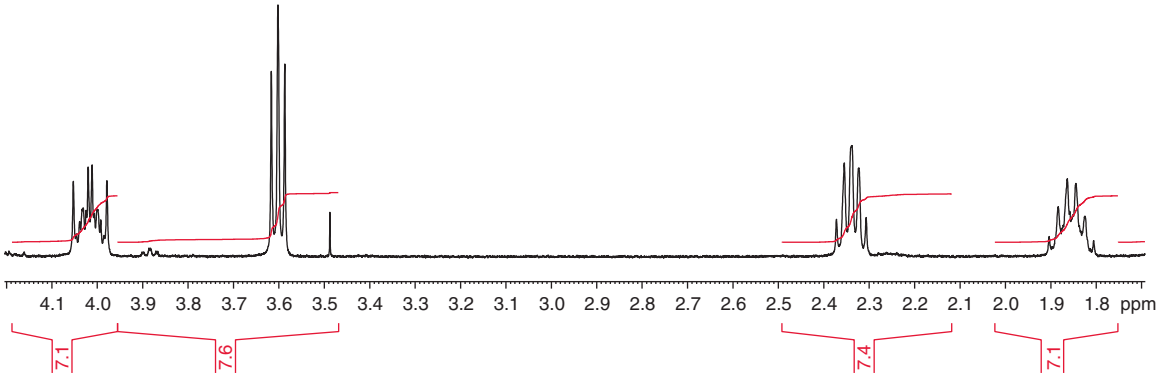
A proton directly bonded to a ^{31}P atom can be split by an enormous coupling of as much as 700 Hz (depending on the oxidation state of the phosphorus)! That means that the two parts of such a signal would be separated by almost 3 ppm at 250 MHz! So huge is this coupling that you could easily fail to recognise or accept it as a coupling at all, if you came across it. Structure 6.20 and Spectrum 6.13 show an example of ^{31}P-^{1}H coupling.

Table 6.3 Some typical ^{31}P–proton couplings.

Structure	^{31}P-^{1}H relative position	Typical ^{31}P-^{1}H coupling (Hz)
$(CH_3)_3P$	P-CH_3	2.7
$(CH_3)_3P{=}O$	P-CH_3	13.4
$(CH_3)_4P^+I^-$	P-CH_3	14.4
$(CH_3\text{-}CH_2)_3P$	P-$\mathbf{CH_2}$-CH_3 P-CH_2-$\mathbf{CH_3}$	0.5! 13.7!
$(CH_3\text{-}CH_2)_3P{=}O$	P-CH_2- P-CH_3	11.9 16.3
	P-H	180–200
	P-H	630–710
	P-CR_2-$\mathbf{CH_3}$	10.5–18.0
	P-CR_2-$\mathbf{CH_3}$	10.5–18.0
	P-CR_2-$\mathbf{CH_3}$	10.5–18.0
	P-$\mathbf{CH_2}$-	6



Structure 6.20 Compound showing ^{31}P-^{1}H coupling.



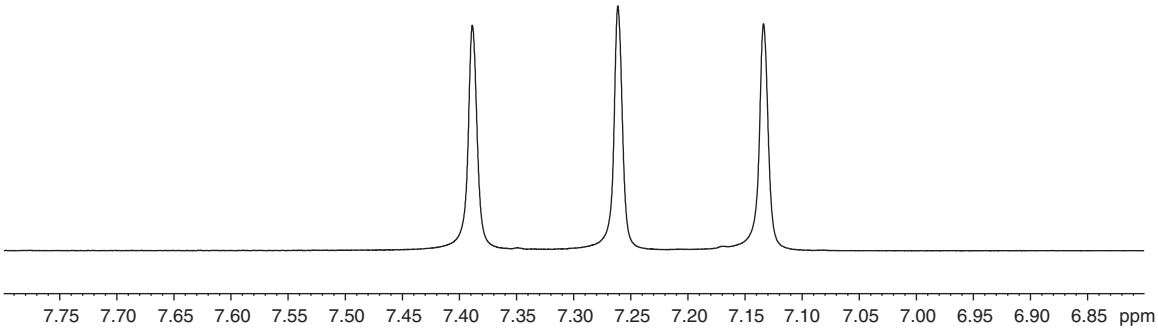
Spectrum 6.13 ^{31}P-^{1}H coupling.

The complex multiplet at 4.02 ppm shows a 13 Hz 2-bond ^{31}P coupling to the first -CH_2 in the chain and spin decoupling enables the 3-bond ^{31}P coupling to the next -CH_2 in the chain (1.86 ppm) to be measured (8 Hz).

6.6.4 Coupling between ^{1}H and other Heteroatoms

If you ever run a sample which is contaminated with an ammonium salt, in DMSO, you will see ^{14}N–proton coupling, as shown in Spectrum 6.14. Note that the three lines of the multiplet are of equal intensity (the middle line is a little bit taller than the outer ones, but this is because of the width of the peaks at their bases. The central signal is reinforced because it stands on the tails of the outer two). This is because ^{14}N has a spin of I = 1, and the allowed states are therefore –1, 0 and +1. This three line pattern with its 51 Hz splitting is highly characteristic and once seen, should never be forgotten.

^{14}N coupling is only observed when the nitrogen atom is quaternary. In all other cases, any coupling is lost by exchange broadening, or quadrupolar broadening, both of which we've discussed before. Two-bond couplings, [e.g., $^{14}\mathbf{N}^{+}$-($\mathbf{CH_2}$)$_4$] are not observed, even when the nitrogen is quaternary, in 'quat salts' such as (*n*-butyl)$_4$N^{+-} Br^{-}, presumably because the coupling is very small. So the phenomenon is only ever observed in the $^{+}$$NH_4$ ion! *Note*: The -CH_2- attached to the quaternary nitrogen in compounds like tetra N-butyl ammonium chloride **does** present as a distorted

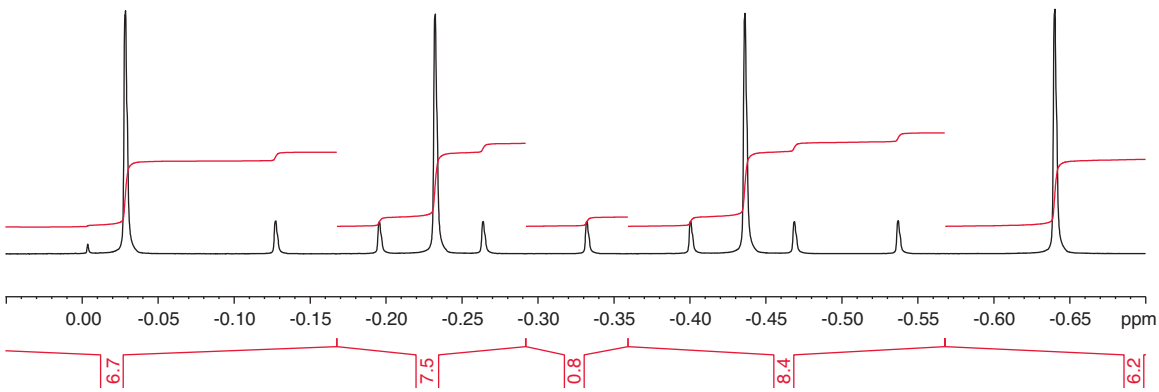


Spectrum 6.14 Typical appearance of $^{+}NH_4$ ion in DMSO.

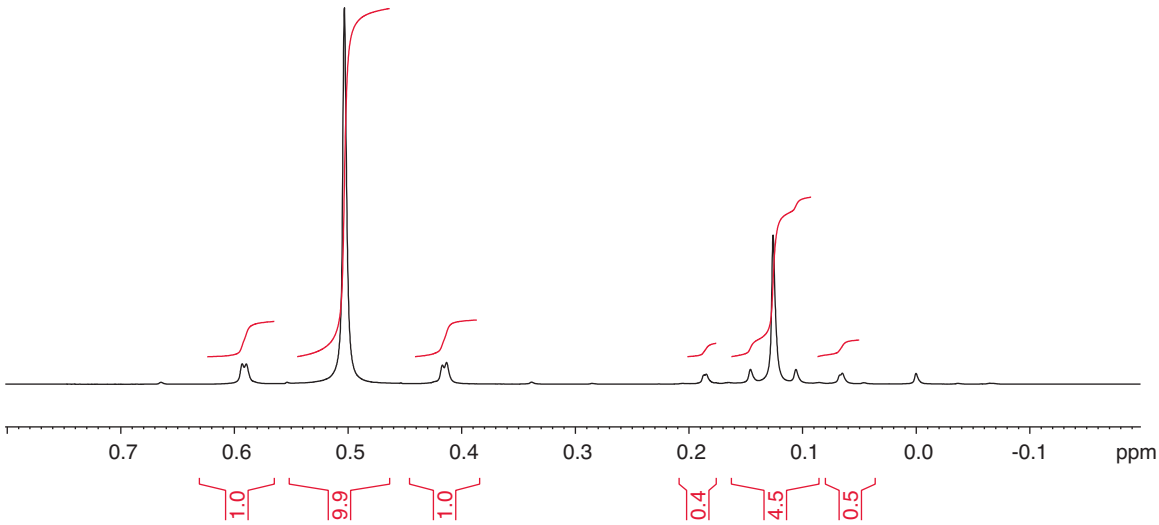
triplet with its central line split into a narrow triplet but this has nothing to do with ^{14}N coupling as the same distortion can sometimes be seen in -CH_2- groups next to certain other moieties, e.g., -SO_2R. It is a non-first order phenomenon caused by slight non-equivalence of the two protons in question.

Boron has two isotopes, both of which have spin! ^{10}B has a natural abundance of 18.8 %, and a spin of I = 3 (allowed spin states –3, –2, –1, 0, +1, +2, +3; i.e., one signal will be split into seven lines of equal intensity), whilst ^{11}B has a natural abundance of 81.2%, and a spin of I = 3/2 (allowed spin states –3/2, –l/2, +1/2, and +3/2; i.e., one signal will be split into four lines of equal intensity).

This gives rise to amazing effects in the borohydride, BH_4^- ion (Spectrum 6.15), which can sometimes be formed accidentally during borohydride reductions. Note that the ^{10}B-H couplings are of a different size to the ^{11}B-H couplings. All 11 lines of the BH_4^- ion are to be found between 0 and –0.7 ppm. Note that, like ^{14}N, ^{11}B has a quadrupolar nucleus, but once again the symmetrical environment of the borohydride ion negates the relaxation pathway that would otherwise cause significant line broadening. Boron coupling is not generally seen in asymmetric environments or over multiple bonds.



Spectrum 6.15 Boron–proton coupling in the borohydride ion.



Spectrum 6.16 Mixture of two organotin compounds.

One other heteroatom worth mentioning is tin as organotin compounds are significant in organic synthesis. Tin has no fewer than ten naturally occurring isotopes, but fortunately, only three of them have nuclear spin. ^{115}Sn has a natural abundance of a mere 0.32 %, which makes it spectroscopically insignificant, of course. The only isotopes of tin that need concern us, are ^{117}Sn (natural abundance 7.67 % and I=1/2), and ^{119}Sn (natural abundance 8.68 %, and also, I=1/2).

These two isotopes are both capable of two-bond and three-bond couplings in alkyl organotin compounds. This is demonstrated in Spectrum 6.16 which shows a mixture of two organotin compounds. The compound with a strong central peak at 0.5 ppm is thought to be $(CH_3)_3$-Sn-OH. The inner satellites result from a ^{117}Sn-CH_3 coupling of 69 Hz and the outer satellites to a ^{119}Sn-CH_3 coupling of 72 Hz.

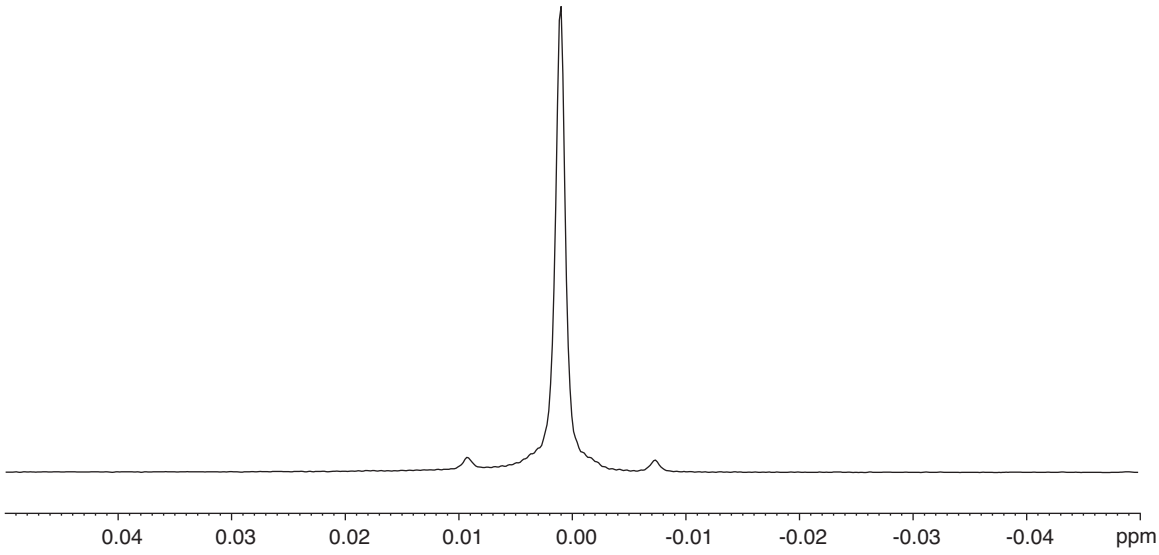
The second compound with the major signal centred at 0.13 ppm is $(CH_3)_3$-Sn-Sn-$(CH_3)_3$. In this case, we see once again, satellites resulting from two-bond couplings but also a second set of inner satellites resulting from smaller three-bond couplings of about 16 Hz for both ^{117}Sn and ^{119}Sn (i.e., **Sn**-Sn-**CH_3**).

Note too from the chemical shifts of these methyl groups that tin has quite a strong shielding effect.

Finally, ^{29}Si is an isotope that you should be aware of – every time you acquire a well prepared sample using TMS as a standard! ^{29}Si satellites (accounting for about 4.7 % of the total signal, J ^{29}Si – -CH_3, 6.6 Hz) should be visible at the base of your TMS peak. The small coupling provides a good test of shimming quality (Spectrum 6.17).

6.6.5 Cyclic Compounds and the Karplus Curve

As we have already mentioned, chemical shifts and couplings are heavily influenced by molecular constraint and for this reason, some guidance in dealing with cyclic (saturated) compounds might well prove useful. We have already seen that in straightforward open-chain alkyl systems, the size of proton-proton couplings is governed by the electronegativity of neighbouring atoms. But the most



Spectrum 6.17 TMS showing ^{29}Si satellites.

important factor which governs the size of couplings between vicinal protons is the dihedral angle between them.

In open-chain systems, this angle is usually averaged by rotation about the C-C single bond, and so is not normally of significance. But in carbocyclic systems, dihedral angles are usually fixed, since the structures are generally rigid. It is therefore vital that we understand how the size of vicinal couplings varies with dihedral angle. This data can be obtained by using the Karplus equation but the information derived from this equation (or equations as there are various versions of it) is more usefully portrayed graphically. A family of curves thus constructed makes additional allowance for factors other than dihedral angles which influence vicinal proton couplings, e.g., localised electronegativities (Figure 6.2) but we have opted for a simplified graph showing only three curves.

Selection of the best curve for a given situation is perhaps rather a matter of trial and error, but is best approached by positively identifying an axial–axial coupling, since this arrangement ensures (in six-membered rings at least) a dihedral angle of 180° between the protons. Choose the curve that best fits the value that you observe for an axial–axial coupling in your molecule. Note that in the absence of any extreme electronic effects, this should give rise to a coupling of about 12 Hz. Similarly, a dihedral angle of 90° gives rise to a coupling of approximately 0 Hz, and where the angle is 0°, we may expect a coupling of about 10 Hz. Making a model of the molecule becomes very important in the case of carbocyclic compounds, as it is important to be able to make fairly accurate estimates of dihedral angles.

Now let us consider Structure 6.21 and Spectrum 6.18 and see how the Karplus curve can be used to aid assignment of the spectrum. (This compound will be referred to from now on as *the* morpholine compound as we will use it to demonstrate several different techniques) Note that the aromatic region has been omitted as it contains little of interest and we wish to concentrate on the carbocyclic region of the spectrum. It was acquired in $CDCl_3$.

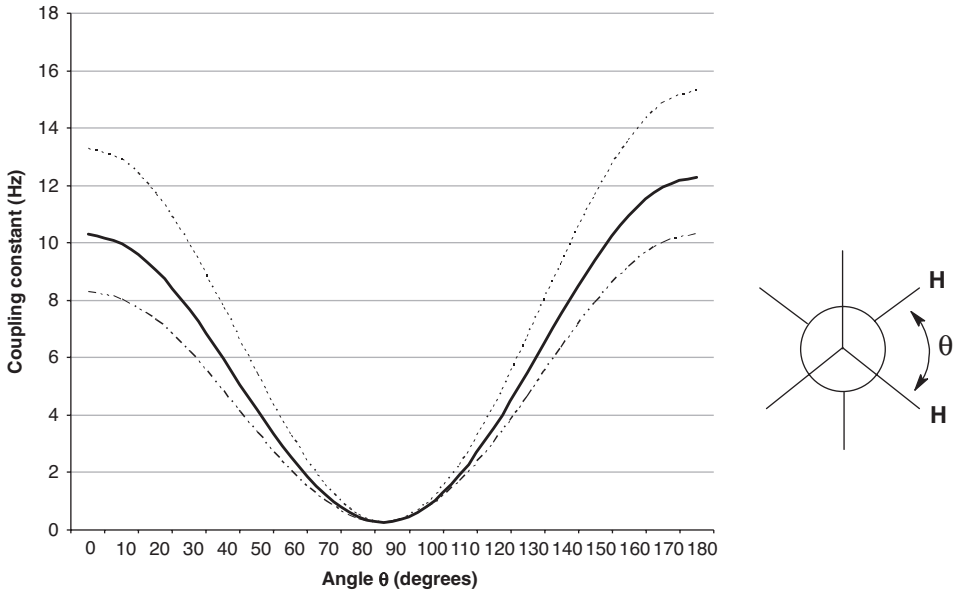
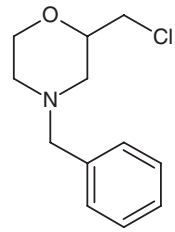


Figure 6.2 The Karplus curve – for relating the observed splitting between vicinal protons to their dihedral angle, θ.

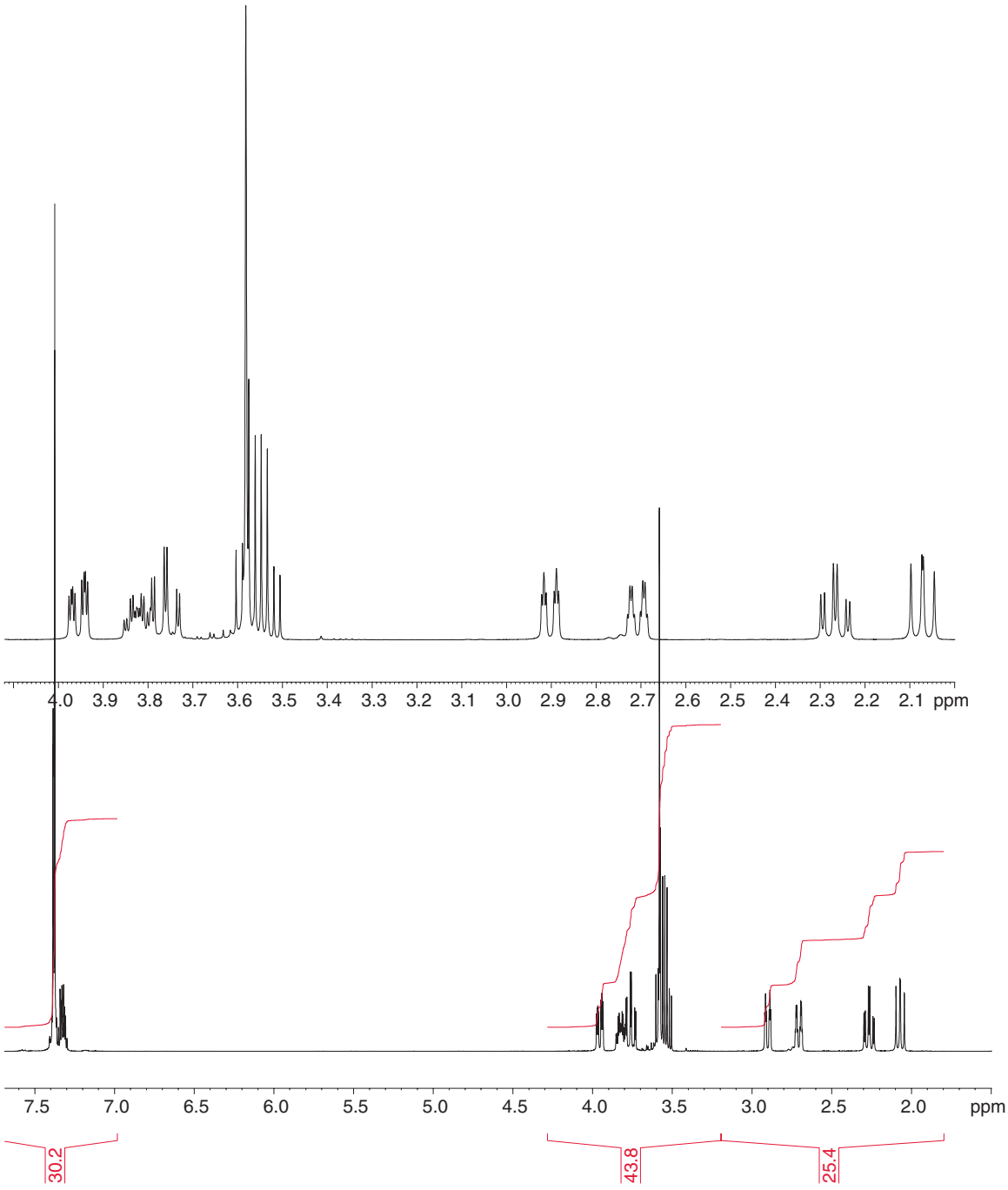
To derive maximum benefit from this exercise, we recommend that you make a model of this molecule, and refer to it as we go through the spectrum. Note that the morpholine ring falls naturally into a 'chair' conformation. Note also that in this example, the -CH_2-Cl function will seek to minimise the morpholine ring energy by occupying an equatorial environment as this minimises steric interactions between it, and protons, and other substituents on the ring. All groups do this. The benzyl function will do likewise by inversion of the nitrogen stereochemistry.

It is also worth noting that nine times out of ten, equatorial protons absorb at somewhat lower field than the corresponding axial protons. This can be reversed in certain cases where the specific anisotropies of the substituents predominate over the anisotropies of the rings themselves but this is relatively rare. The difference is typically 0.5–1.0 ppm, but may be more.

The structure is depicted as a Newman projection below (Figure 6.3). Aromatic protons aside, (they give the expected five-proton multiplet centred at around 7.3–7.4 ppm) the first signal we encounter as



Structure 6.21 *The* morpholine compound.



Spectrum 6.18 *The* morpholine compound in $CDCl_3$ with expansion.

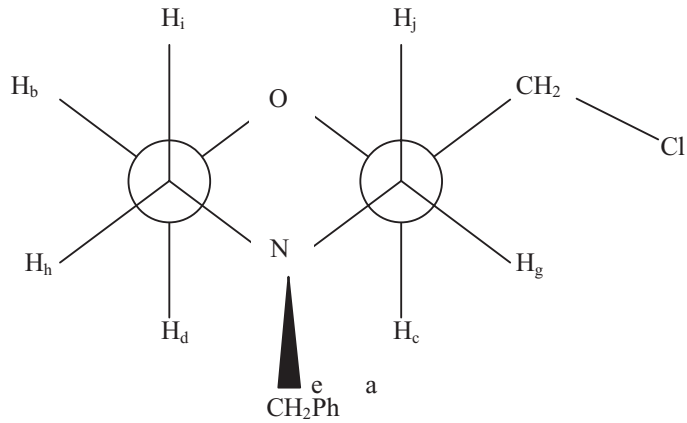


Figure 6.3 *The* morpholine compound shown as a Newman projection.

we work from left to right is a complex multiplet – which is actually, a doublet of doublet of doublets [ddd] – at 3.95 ppm. Careful measurement of the couplings reveals them to be 11.4, 3.4 and 2.0 Hz. Since the multiplet is dominated by one large coupling, we can be safe in the knowledge that it must be an *equatorial* proton.

This is because the dihedral angles between equatorial protons and both their equatorial and axial vicinal partners are always such that they give rise to relatively small couplings (check model and the Karplus curves). The only large coupling (i.e., 10 Hz or more) an equatorial proton can have will always be to its geminal partner – if it has one. So in this case, the 11.4 Hz coupling is clearly a geminal coupling. If we now make the entirely reasonable deductions that the proton giving rise to this signal is likely to be alpha to oxygen rather than nitrogen (on the basis of chemical shift) and that as the -CH_2-Cl will be equatorial (as explained earlier), then this multiplet can only be assigned to the equatorial proton 'b' since there are no other equatorial protons that are alpha to oxygen in the molecule. The other two couplings can be rationalised in terms of the equatorial–axial coupling (3.4 Hz which is reciprocated in the ddd at 2.27 ppm) and the equatorial–equatorial coupling (2.0 Hz which is reciprocated in the dddd at 2.71 ppm). *Note*: methods of unpicking couplings will be discussed at length in later sections. Such methods are very useful when dealing with more complex spin systems like this one.

The degree of roofing of 'b' indicates that its geminal partner must be fairly close to it in terms of chemical shift and sure enough, the six-line multiplet (another ddd) centred at 3.76 ppm satisfies the requirements for this proton ('d'). Note that the second large coupling to this signal is also 11.4 Hz, the axial–axial coupling being the same size as the geminal coupling in this instance. The small remaining coupling (approx. 2 Hz) is reciprocated in the dddd at 2.71 ppm and is an axial–equatorial coupling.

Proton 'c' can be defined by the fact that it is *not* equatorial and it is highly coupled. The multiplet at 3.82 ppm satisfies these requirements. It is in the right ball park for chemical shift and is highly complex in that this proton is already the X part of an ABX system coupled to both protons alpha to the chlorine (the AB part). It is then further coupled with a 10 Hz, axial–axial coupling (reciprocated in the dd at 2.07 ppm) and with a 2 Hz axial–equatorial coupling which is reciprocated in the ddd at 2.90 ppm. Note that 'c' and 'd' are not fully resolved from each other. Such overlap inevitably complicates the issue.

The N-benzyl protons are accidentally equivalent, presenting as a singlet at 3.59 ppm and overlap with the two protons alpha to the chlorine atom which present as the heavily roofed AB part of an ABX system (i.e., eight lines) centred at 3.55 ppm.

Without slavishly dissecting the remaining four signals (2.90, 2.71, 2.27, 2.07 ppm), we hope that the principles of carbocyclic analysis have now been established. You should see at a glance that the 2.90 and 2.71 ppm signals must belong to equatorial protons because they are each dominated by only one large coupling and the remaining two must correspond to their axial partners. You should now be able to verify which equatorial proton belongs to which axial proton just by inspection.

There is one last coupling which we have not yet mentioned and that is the apparent extra small coupling that can be seen on the equatorial protons alpha to the nitrogen (2.90 and 2.71 ppm). These two signals are in fact coupled to each other by what is known as a W path coupling. These are 4-bond couplings (unusual in saturated systems) which can be seen in situations where all the intervening proton–carbon and carbon–carbon bonds lie in the same plane. You can see from the model which you have next to you (?) that by definition, such protons can only be equatorial. Note that whilst all the assignments in this section have been made purely on the basis of observations of couplings and multiplet appearance, this type of assignment is often simplified by having definitive knowledge of coupling pathways. We will discuss the options available for acquiring this type of data in a later chapter.

Whilst six-membered rings may often give rise to quite complex spectra, they are at least generally rigid and based on the 'chair' conformation. As we have seen, this means that dihedral angles can be relied on and the Karplus curve used with reasonable confidence. Unfortunately however, the same approach will end in tears if applied to other ring systems. Five-membered rings for example, are notoriously difficult to deal with as they have no automatic conformational preference. They are inherently flexible, their conformations driven by steric factors. *Cis* protons on five-membered rings can have dihedral angles ranging from approximately –30° to 0° to +30° and exhibit a range of couplings to match. *Trans* protons on the other hand can range from +90° to +150°. Deductions that can be made on the basis of observed vicinal couplings are therefore limited. If the observed coupling is *very* small, the two protons can only be trans to each other but if it is not, then they may be either *cis* or *trans*. We council against reliance on molecular modelling packages to produce a valid conformation of such structures. The energy difference between potential conformers is often small and could change in different solvents. Modelling packages consider molecules in isolation and thus make no allowances for solvent effects. Stereochemical assignments of such ring systems can only be confidently made on the basis of NOE experiments which we will cover in detail in Section 8.5.

6.6.6 Salts, Free Bases and Zwitterions

Sometimes, misunderstandings can arise when dealing with compounds containing protonatable centres. Hopefully, in this section, we will be able to clarify a few key issues that are relevant to such compounds.

As we have already mentioned, $CDCl_3$ should be avoided as a solvent for salts for two reasons. Firstly, salts are unlikely to be particularly soluble in this relatively nonpolar solvent but more importantly, spectral line shape is likely to be poor on account of relatively slow proton exchange at the protonatable centre. The remedy is simple enough – avoid using $CDCl_3$ and opt for one of the more polar options instead, e.g., deuterated DMSO or MeOH and you should obtain spectra every bit as sharp as those of free bases.

In practical terms, it is invariably a nitrogen atom that is protonated in salt formation. This always leads to a downfield shift for protons on carbons both alpha and beta to the nitrogen concerned. In alkyl amines, the expected shifts would be about 0.7 and 0.3 ppm respectively. Remember that some heterocyclic compounds (e.g., pyridine) contain nitrogen atoms that are basic enough to protonate and comparable downfield shifts can be expected (Spectrum 5.9).

A misconception that we commonly encounter is that a spectrum can be a 'mixture of the salt and the free base.' This is an excuse that is often used by chemists to explain an inconveniently messy looking spectrum! Don't be tempted by this idea – proton transfer is fast on the NMR timescale (or at least, it is when you use a polar solvent!) and because of this, if you have a sample of a compound that contains only half a mole-equivalent of an acid, you will observe chemical shifts which reflect partial protonation and *not* two sets of signals for protonated and free-base forms. It doesn't happen – ever!

Of course, whether a compound forms a salt or not depends on the degree of availability of the lone pair of electrons on any nitrogen atoms in the compound (i.e., their p*K*b values) and on how strong the acids involved in the salt formation (pKas). As a rough rule of thumb, alkyl and aryl amines *do* form salts whilst amides, ureas, most nitrogen-containing heterocycles and compounds containing quaternary nitrogen atoms *do not*.

It should always be remembered of course, that the NMR spectrum reflects a compound's behaviour *in solution*. It is quite possible for a compound and a weak acid to crystallise out as a stoichiometric salt and yet in solution, for the compound to give the appearance of a free base. For this reason, care should be taken in attempting to use NMR as a guide to the extent of protonation. If the acid has other protons that can be integrated reliably, e.g., the alkene protons in fumaric or maleic acid, then there should be no problem but if this is not the case, e.g., oxalic acid, then we would council caution! Do not be tempted to give an estimate of acid content based on chemical shift. With weak acids, protonation may not occur in a *pro rata* fashion though it is likely to in the case of strong acids.

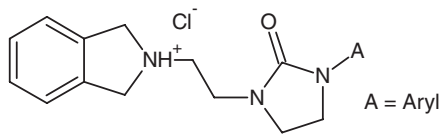
Sometimes, you may encounter compounds which have more than one protonatable centre. It is often possible to work out if either one or more than one are protonated in solution. A good working knowledge of pKbs is useful to help estimate the likely order of protonation with increasing acidity. Assume that the most basic centre will protonate first and assess the chemical shifts of the protons alpha to each of the potentially protonatable nitrogen atoms.

Zwitterionic compounds are worthy of special mention:

$$H_2N{-}R-COOH \leftrightarrow H_3N^+{-}R-COO^-$$

By their very nature, their partial charge separation can make them fairly insoluble and the degree of this charge separation (and hence resultant NMR spectra) tends to be highly dependant on concentration and pH. For these reasons, we recommend dealing with such compounds by 'pushing' them one way or the other, i.e., by adjusting the pH of your NMR solution so that the compound in question is either fully protonated (addition of a drop of DCl) or de-protonated (addition of a drop of saturated sodium carbonate in D_2O):

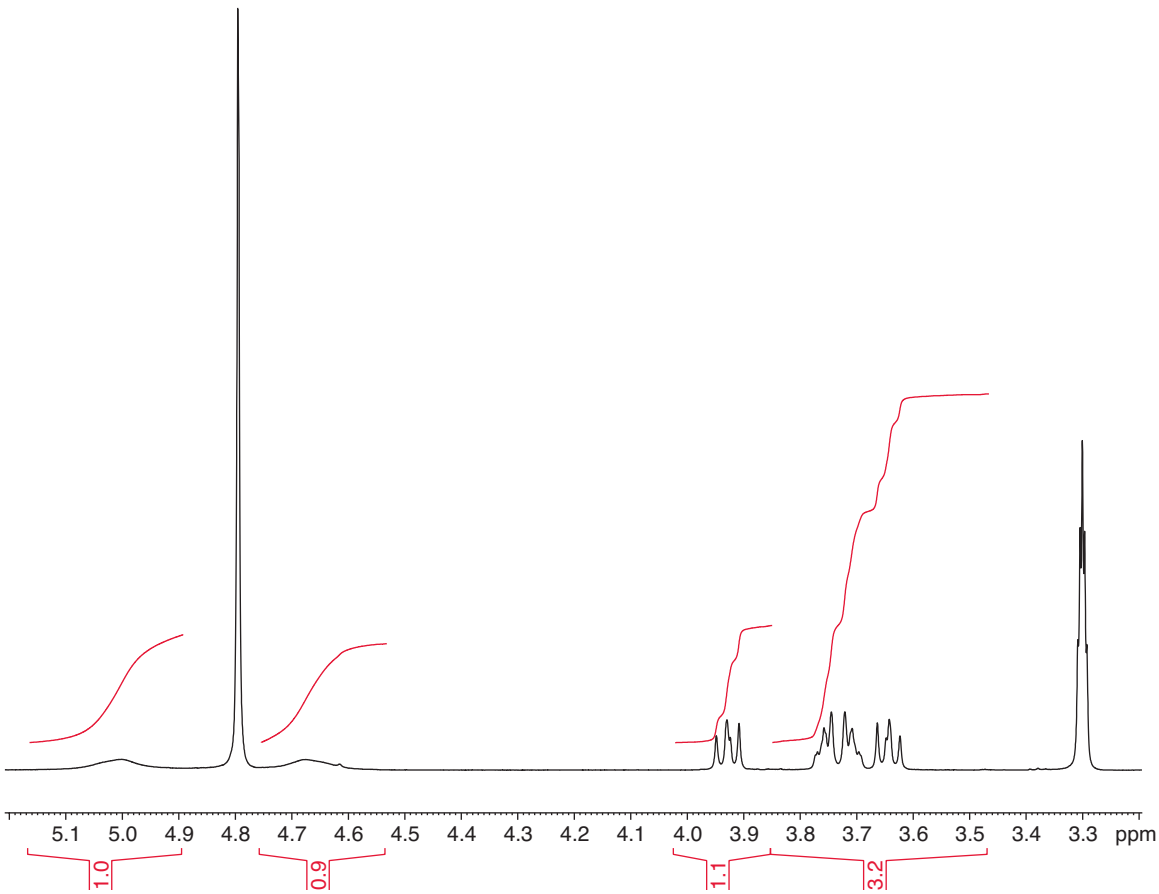
$H_3N^+{-}R-COOH$	$H_2N-R-COO^-$
Fully protonated	Fully de-protonated



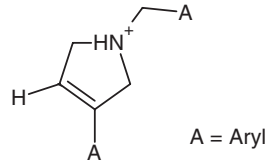
Structure 6.22 A protonation example.

Whilst dealing with protonation issues, it is well worth considering the time dependence of the process in the context of the NMR timescale. A compound of the type shown in Structure 6.22 provides an interesting example.

As a free base, the Ar-CH_2-N protons would present themselves as a simple singlet. The lone pair of electrons on the nitrogen invert very rapidly on the NMR timescale and so the environment of the two protons is averaged and is therefore identical. However, on forming a salt, the whole process of stereochemical inversion at the nitrogen is slowed down dramatically because the sequence of events



Spectrum 6.19 Slow inversion of a protonated tertiary amine nitrogen.



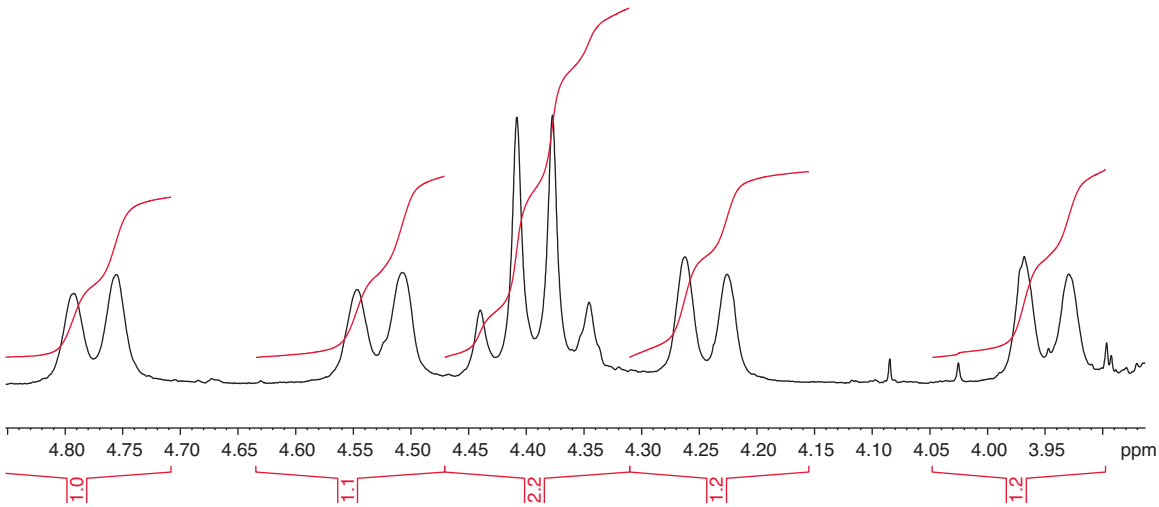
Structure 6.23 Compound showing 'pseudo enantiomeric' behaviour.

would be; de-protonation, inversion and re-protonation. Although as we said earlier, proton transfer is in itself a very fast process on the NMR timescale, it is the time taken for the *entire* process to occur that determines the nature of the spectrum that we observe.

What we actually observe for the Ar-CH_2-N protons of the salt in this molecule is a pair of broad, featureless signals at 4.6 and 5.0 ppm. The explanation for this is simple enough once the concept of time dependency for the inversion sequence has been appreciated. The protons in question find themselves in different environments (within the context of the NMR timescale) and therefore have distinct chemical shifts. The signals are broad because the dynamic exchange process is taking place with a time period comparable to the NMR timescale, the broadening masking the geminal coupling between them (see Spectrum 6.19).

A logical extension of these ideas will lead you to a recognition of the fact that a phenomenon of this type could yield species in solution which appear to behave as if they contain a chiral centre – even when they don't. We have seen 'pseudo enantiomeric' behaviour in compounds of the type shown in Structure 6.23 (when protonated).

All the protons of the CH_2s in a molecule of this type may be non-equivalent (i.e., you observe essentially three AB systems). Note that the coupling from the alkene CH is would be small to both of the cyclic CH_2s when the spectrum is acquired in the presence of HCl (see Spectrum 6.20). When the free



Spectrum 6.20 Protonated nitrogen of a tertiary amine acting as a 'chiral centre'.

base is liberated, all the AB systems collapse to give singlets. The explanation follows on logically from a consideration of the previous example. Protonation of the tertiary amine generates a chiral centre at the nitrogen atom, forcing all the geminal pairs of protons into different environments – hence the three AB systems. But this does not in any way imply that it would be possible to separate out enantiomers of the compound in salt form. These 'pseudo enantiomers' can only be differentiated within the context of a technique which has a timescale of a couple of seconds. Attempting to separate them on an HPLC column for example, would be unsuccessful as this technique has a timescale of several minutes (defined by how long compounds take to travel down the column and enter the detector). During this time, proton exchange and consequent 'enantiomer' interconversion would have occurred many times in the course of the analysis. The only manifestation of this might be a slightly broader than normal (single) peak.

This whole area of spectroscopy touches on many different topics and can only be approached confidently with a reasonable working knowledge of basic NMR, stereochemistry and certain aspects of physical chemistry.