5

Interpreting Your Spectrum

We should perhaps make a few important points before going any further – the title of this chapter is highly ambitious! We certainly cannot promise to turn you, the reader into expert interpreters in the time it takes you to read this section. Experience is essential and to become really proficient in this area, you need to critically examine literally *thousands* of spectra. However, be that as it may, by establishing some sound principles and cultivating a critical approach to the spectra you encounter, this book should prove useful in helping you along the way.

It might be worth considering at this stage, what we really mean by the term 'spectral interpretation'. What do we consider to be acceptable criteria for the interrogation of spectral data? Is a cursory glance sufficient if you are also holding a mass spectrum in your other hand that shows a parent ion of the correct mass for your desired compound? Or should you throw every known NMR technique at all your compounds irrespective of how trivial the chemical change being attempted? These questions should be pondered in the light of the fact that an NMR spectrum should never be regarded in itself as an *absolute* proof of structure. If this is what is required, then you had better practise your crystal-growing skills because you will be needing the services of an X-ray crystallography department. That having been said, NMR data can certainly provide the next best thing – in the right hands.

Our initial observations are aimed at improving your understanding of 1-D proton spectra, though many of the principles we will try to establish will be equally applicable to other nuclei too. We will discuss issues specific to ^{13}C interpretation in Chapter 9.

As we mentioned in the Introduction, it is ironic that one of the major problems encountered when dealing with NMR spectra, is the sheer quantity of information that you are presented with. Unless you are practiced in the art of interpretation, you may find yourself swamped by it. Clearly, a methodical and universally applicable approach would be advantageous. There is not necessarily a 'right' or a 'wrong' way to approach a spectrum, but some ways are probably better than others! These are our 'top ten' recommendations, for what they are worth.

1. Take a moment to survey the spectrum and ask yourself if it is fit for purpose? Of course, if you have run it yourself, then it should be fine but this may not always be so with walk-up systems. Is the line shape and resolution up to standard? Has the spectrum been phased correctly? Is the vertical scale well adjusted so that you can see the tops of all the peaks (except perhaps, obvious

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singlets)? Are the integrals well displayed? If the horse is dead, don't flog it – get a new one. Note: a good walk-up system will run day and night, producing quality results for the vast majority of samples. However, the occasional spectrum may 'come off the rails' for no obvious reason, but remember that there are dozens of processes that must run correctly in the background before a high quality spectrum drops into the collection tray and a slight hiccup in any of them can spoil the end result. Some of these problems (vertical scaling, phasing and integration) can be rectified by reprocessing the acquired data and some cannot as the 'raw' data itself may have been corrupted (poor signal/noise and sub-standard shimming).

2. If the spectrum is satisfactory, you can get to work on it. Can you identify any obvious impurities or solvents that might be present? Crossing them off at this stage is a valuable exercise in data reduction and clears the way ahead so that you can concentrate on the important peaks.
3. Does your proposed structure exhibit any special features likely to have a significant effect on your spectrum? (e.g., chiral centres, sites of potential restricted rotation, abnormal stereochemistry, etc.)
4. Can you identify a signal that gives a clear integration for a known number of protons?
5. Now work from left to right, assigning each signal, or groups of signals that you observe, to protons in your proposed structure. (If there is logic in starting at the left of the spectrum, it is that most molecules have some aromatic or heterocyclic core, to which, various alkyl functions are attached. If there is a problem with the core, then you will at least discover it promptly and be able to relate it to the alkyl components of the molecule.)
6. Interrogate each and every signal in your spectrum to check that they conform to the expected values for the *three* crucial NMR parameters: (1) chemical shift, (2) coupling pattern and (3) integration. And this, in a very real sense, must form the basis of our working definition of 'interpretation.' In the words of the song by Meatloaf 'two out of three ain't bad.' In NMR, however, two out of three isn't good enough! Obviously, in order for you to match your observed values for chemical shifts and couplings, to expected values, you will need a great deal of data at your disposal and this will be provided in the following chapters.
7. If you note an obvious mismatch between observed and predicted data, might you have overlooked something in (3) above? Interpretation is essentially an iterative process. Try to maintain a degree of flexibility in your approach – without being *too* flexible! Achieving this balance takes practise! If there is still no way of reconciling observations with predictions, you must accept the strong probability that your proposed structure is incorrect.
8. If so, propose an alternative structure and start the whole process again. Alternatively, could your sample be a mixture? If so, might your sample benefit from a chromatographic investigation at this stage or is it possible to qualify and quantify the components directly?
9. If you have any reasonable cause for doubt (e.g., because some key signals in your spectrum are obscured, etc.), would the acquisition of more NMR data be helpful? If so, consider exactly what you wish to achieve and select the appropriate technique and gather the data.
10. Re-evaluate all data again and again until you are as happy as possible with all aspects of your spectrum. Guard against complacency! Is it watertight? Check on this by asking yourself if you would be happy to stand up in a court of law and defend your efforts.

Adherence to all these points might seem to make the whole process of interpretation incredibly convoluted and unappealing but in reality, it should eventually becomes 'second nature'. Developing the theme further, you will hopefully soon get used to mentally synthesising the spectra of compounds you look at and matching these against what you see before you. The degree of deviation between the two

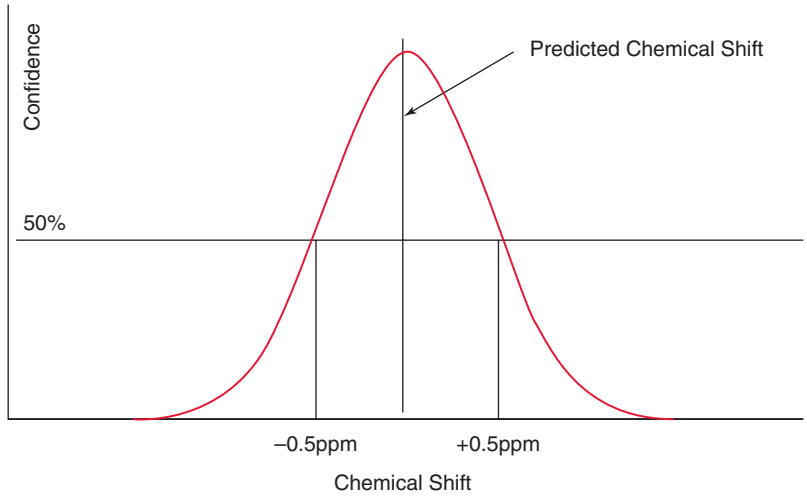


Figure 5.1 The confidence curve.

will be critical and we will explore this a little later. Should you be lucky enough to have a job which involves you looking at literally, *thousands* of spectra, then mental shortcuts will evolve and you will find yourself taking-in and digesting certain patterns almost subliminally in the same way that you read the words on this page. This is perfectly valid but *always* be on your guard against complacency! Take pride in your craft. *Make* yourself revisit that splitting pattern. There is nothing worse than falling into an obvious trap!

Of course, we do not mean to imply any kind of moral imperative here. For example, if you were checking out some dubious looking starting material that supposedly contained a given functionality (e.g., Ar-$\mathbf{CH_2}$-Br with no ortho substituent on the aryl ring and no other obvious steric clash between this aryl system and any other), then it would be quite acceptable – and even desirable – to exploit some obvious 'handle' in the form of a 'cutdown interpretation'. In this case for example, if there is no two-proton singlet (or AB system if the molecule is chiral) at around 4.6–4.3 ppm, then you can reasonably conclude that the stuff is not what you wanted. Job done. Move on.

We discussed earlier the concept of mentally synthesising a spectrum and trying to match it with real, observed data. This might sound like a task that a computer would be very good at – but this is certainly not the case in the field of proton NMR! We will discuss this in detail in a later chapter dealing with software issues. Our synthesised spectrum will need to be based on hard data. For example, in the case above, just how much leeway can you allow yourself in predicting the chemical shift of the Ar-$\mathbf{CH_2}$-Br protons? +/– 0.1 ppm? +/– 0.2 ppm? More? Instinctively, of course, the closer our observed signals are to our predicted ones, the better we will feel about them and vice versa. We have tried to portray this in Figure 5.1. "The Confidence Curve".

Whilst this might seem to state the obvious, it begs a number of very important questions. Ultimately, and perhaps after the expenditure of a great deal of mental effort, the bottom-line of an interpretation boils down to a simple question: Does this spectrum support this putative structure or doesn't it? Yes or no? The question is clearly black or white but the answer has plenty of scope for shades of grey! The yes/no question will have to be answered on the back of a great many other questions regarding the 'goodness of fit' of all the signals in the spectrum. Let's return to the simple case of Ar-$\mathbf{CH_2}$-Br above,

and consider how far the observed shift can be allowed to deviate from our predicted position. At what stage must we reject the structure? After all, how can we be sure that it isn't Ar-**CH_2**-Cl instead? Or what if the aryl ring is further substituted? What would you expect to see if there was a -NO_2 ortho to the -CH_2-Br? Or what about a para -NR_2?

Hopefully, we make our point. The confidence curve is NOT fashioned out of granite – it has to be applied with understanding and circumspection. It will always have the same basic shape but we have to be prepared to take a view on how wide it should be in every individual situation! Matters become a great deal more complex when we come up against structures that are sterically crowded (i.e., structures where bond constraints force various moieties into close proximity with one another).

Note also that the concept of the 'confidence curve' is equally applicable when considering coupling data. That is: What size coupling should I be looking for in this system or that? Is it too big? Too small?

Unfortunately, it is impossible to cover all the potential pitfalls that wait for the unwary. Many more will come to light in the following chapters but for now we will concentrate on supplying you with useful proton NMR chemical shift data . . . We have done this by collating various types of protons into convenient 'groups,' but first, let's clear the wood from the trees and deal with commonly encountered solvents and impurities in the regularly used NMR solvents.

5.1 Common Solvents and Impurities

As we pointed out earlier, it is a good idea if you can eliminate peaks from common solvents and impurities before getting into the real interpretation (note how chemical shifts can vary in different solvents – another factor which helps define the breadth of the confidence curve). Table 5.1 can be very helpful in this regard.

Table 5.1 The proton chemical shifts of common solvents and impurities.

Impurities	$CDCl_3$	DMSO	D_2O	MeOD
Acetic acid	2.13	1.95	2.16	1.99
Acetone	2.17	2.12	2.22	2.15
Acetonitrile	1.98	2.09	2.05	2.03
Benzene	7.37	7.40	7.44	7.33
Bromoform	6.85	7.75	insoluble	7.42
n-Butanol	3.67(t,6)	3.41(t,6)	3.60(t,6)	3.54(t,6)
	0.94(t,7)	0.89(t,7)	0.89(t,7)	0.93(t,7)
t-Butyl alcohol	1.28	1.14	1.23	–
Chloroacetic acid	4.14	4.28	4.25	–
Chloroform	7.27	8.35	Insoluble	7.88
Cyclohexane	1.43	1.42	Insoluble	1.45
1,2-Dibromoethane	3.63	3.84	3.79	3.72
Dichloroacetic acid	5.98	6.68	6.21	–
1,2-Dichloroethane	3.73	3.93	3.92	3.78
Dichloromethane	5.30	5.79	Insoluble	5.48
Diethyl ether	3.48(q,7)	3.42(q,7)	3.56(q,7)	3.48(q,7)
	1.20(t,7)	1.13(t,7)	1.17(t,7)	1.17(t,7)

Table 5.1 (Continued)

Impurities	$CDCl_3$	DMSO	D_2O	MeOD
Diisopropyl ether	1.12(d,6)	1.04(d,6)	1.12(d,6)	–
Dimethylacetamide	3.01	2.99	3.05	3.05
	2.94	2.82	2.89	2.91
	2.08	1.99	2.08	2.07
Dimethylformamide	8.01	7.98	7.91	7.98
	2.95	2.92	3.00	2.99
	2.88	2.76	2.86	2.85
Dimethyl sulfoxide	2.62	2.52	2.70	2.65
Dioxan	3.70	3.61	3.75	3.65
Ethanediol	3.76	3.42	3.66	–
Ethanol	3.72(q,7)	3.49(q,7)	3.64(q,7)	3.60(q,7)
	1.24(t,7)	1.09(t,7)	1.16(t,7)	1.17(t,7)
Ethyl acetate	4.12(q,7)	4.08(q,7)	4.14(q,7)	4.09(q,7)
	2.04	2.02	2.08	2.01
	1.25(t,7)	1.21(t,7)	1.23(t,7)	1.23(t,7)
Ethyl formate	8.04	8.23	8.16	–
	4.22(q,7)	4.17(q,7)	4.28(q,7)	–
	1.29(t,7)	1.24(t,7)	1.29(t,7)	–
Formic acid	8.02	8.18	8.22	–
Isobutyl methyl ketone	2.12	2.08	2.19	2.11
	0.92(d,6)	0.88(d,6)	0.88(d,6)	0.91(d,6)
Isopropyl acetate	2.02	2.00	Insoluble	1.99
	1.22(d,6)	1.21(d,6)		1.22(d,6)
Isopropyl alcohol	1.2(d,6)	1.06(d,6)	1.18(d,6)	1.14(d,6)
	4.03(m)			3.92(m)
Methanol	3.48	3.20	3.35	3.35
Methyl acetate	3.67	3.61	3.68	–
	2.05	1.92	2.09	
Methyl iodide	2.16	2.21	Insoluble	2.15
Morpholine	3.69(m)	3.52(m)	3.70(m)	3.64(m)
	2.85(m)	2.68(m)	2.79(m)	2.79(m)
Nitromethane	4.32	4.44	4.41	–
Petroleum spirit	1.28	1.28	Insoluble	1.30
(60°–80°)	0.90	0.89		0.88
Potassium Acetate	Insoluble	1.60	1.91	–
Propanol	3.60(t,7)	1.45(m)	3.61(t,7)	3.49(t,7)
	1.60(m)	0.87(t,7)	1.57(m)	1.54(m)
	0.93(t,7)		0.89(t,7)	0.92(m)
Proprionic acid	2.42(q,7)	2.26(q,7)	2.47(q,7)	–
	1.18(t,7)	1.03(t,7)	1.10(t,7)	–
Pyridine	8.60(m)	8.61(m)	8.50(m)	8.53(m)
	7.69(m)	7.83(m)	7.90(m)	7.84(m)
	7.28(m)	7.40(m)	7.46(m)	7.43(m)
Succinimide	2.75	2.63	2.78	–
Tetrahydrofuran	3.74(m)	3.63(m)	3.75(m)	3.72(m)
	1.85(m)	1.78(m)	1.88(m)	1.87(m)

Note: The peaks listed are singlets, unless described as doublets (d), triplets (t), quartets (q), or multiplets (m). Coupling constants (in Hz) are given in parentheses.

5.2 Group 1 – Exchangeables and Aldehydes

Of all the protons you may encounter in an NMR spectrum, exchangeables (any protons that exist in a state of dynamic equilibrium with any free water that might be present in the solvent, i.e., -OH, -NHR, -SH, -COOH, etc.) can be the least predictable – both with regard to their shape, and their position. A guide to their typical chemical shift ranges and any notable features is given in Table 5.2. An alkyl -OH or -NHR, for example, may be sharp and uncoupled, sharp and coupled, or broad and partially coupled. In a molecule with numerous exchangeables, they may appear distinct, or they may combine with each other, and with any water present – watch out for it particularly in D_6-DMSO solutions! Remember also that exchangeable protons will not be present in spectra of compounds run in D_4-MeOH, or D_2O solutions because they will have exchanged for deuterium. This forms the basis of a useful method for the identification of exchangeable protons which we will discuss in Chapter 7.

The origin of this unpredictability lies in the fact that they are relatively acidic, and can undergo exchange in solution. The appearance of the signals we observe is governed by the rate at which this process occurs, the rate being greatly influenced by the nature of the solvent, its water content, pH, temperature, and concentration of the compound.

Table 5.2 Typical exchangeable protons.

Exchangeable	Typical shift (ppm)	Remarks
Alkyl-OH	5–1	Can appear sharp and are capable of coupling to adjacent protons in dry aprotic solvents. Easily exchanged by shaking with D_2O.
Phenolic-OH	11–5	Often broad. Easily exchanged.
Phenolic-OH (H-bonded)	17–11	Can be broad but more usually sharp as proton exchange is slowed by need to break both bonds. Can therefore be more difficult exchange. Warm if necessary.
Alkyl-COOH	12–6	Usually broad but can be extremely broad! Very easily exchanged.
Aryl-COOH	14–8	As for alkyl-COOH.
Alkyl-NH_2/NHR	5–1	Generally similar to alkyl-OH but maybe somewhat broader even in dry solutions and less likely to couple to adjacent protons. Ability to protonate nitrogen tends to broaden protons and displace to lower field. Easily exchanged.
Aryl-NH_2/NHR	11–6	Usually broad. Easily exchanged.
Alkyl-$CONH_2$/-CONHR	9–7	Often broad but frequently couple. Primary amides often appear as two broad signals due to partial double bond character of amide bond. Often slow to exchange and may require warming/mild base
Aryl-$CONH_2$/-CONHR	13–7	As for alkyl-$CONH_2$/-CONHR
Alkyl-SH	5–1	Usually sharp and couple to adjacent protons. May need mild base to exchange (e.g., drop of $NaHCO_3/D_2O$ solution) Beware easy oxidation to -S-S-. Therefore important to locate!
Aryl-SH	7–3	Somewhat broader and easier to exchange than alkyl-SH. Again, an important one to find!
Alkyl/aryl-SO_3H	14–6	Similar to corresponding -COOH

A discussion of the kinetics of the process is outside the scope of this book because it won't help you to interpret your spectrum, but it is worth considering the two extremes of exchange, and the all-important region which lies between these extremes, as this might give you an insight into the seemingly fickle behaviour of exchangeable protons.

If you take a pure sample of ethanol, and run its NMR spectrum in dry $CDCl_3$, the hydroxyl proton will appear as a well-defined triplet, which couples to the adjacent -CH_2-, rendering it a multiplet. This is because the hydroxyl proton remains on the oxygen for relatively long periods of time, as there is nothing in the solution to entice it off, i.e., exchange (if any) is said to be very slow on the NMR timescale (less than about 1 s).

The presence of a trace of acid and water however, causes collapse of the hydroxyl-OH to a singlet (at lower field), the proton can now protonate, and de-protonate the oxygen very rapidly, as the process is catalysed by the acid, i.e., exchange is said to be fast on the NMR timescale (less than about 10^{-6} s).

In practise, one often encounters exchangeable protons which are exchanging at an intermediate rate, which leads to broadening of their signals, and only partial coupling (which can manifest itself as a mere broadening of the exchangeable proton and any they couple to). The actual position of the centre of a broad exchangeable signal, is dependant on how much water (or alternative exchange site) is present, and on the difference in the chemical shifts of the proton in the two environments. For example, a carboxylic acid proton, in a very dry solvent, may occur at about 12 ppm. A similar molar quantity of water in DMSO would absorb at around 3.5 ppm, and in such a solution, the carboxylic acid proton may well appear as a very broad signal, centred between these positions.

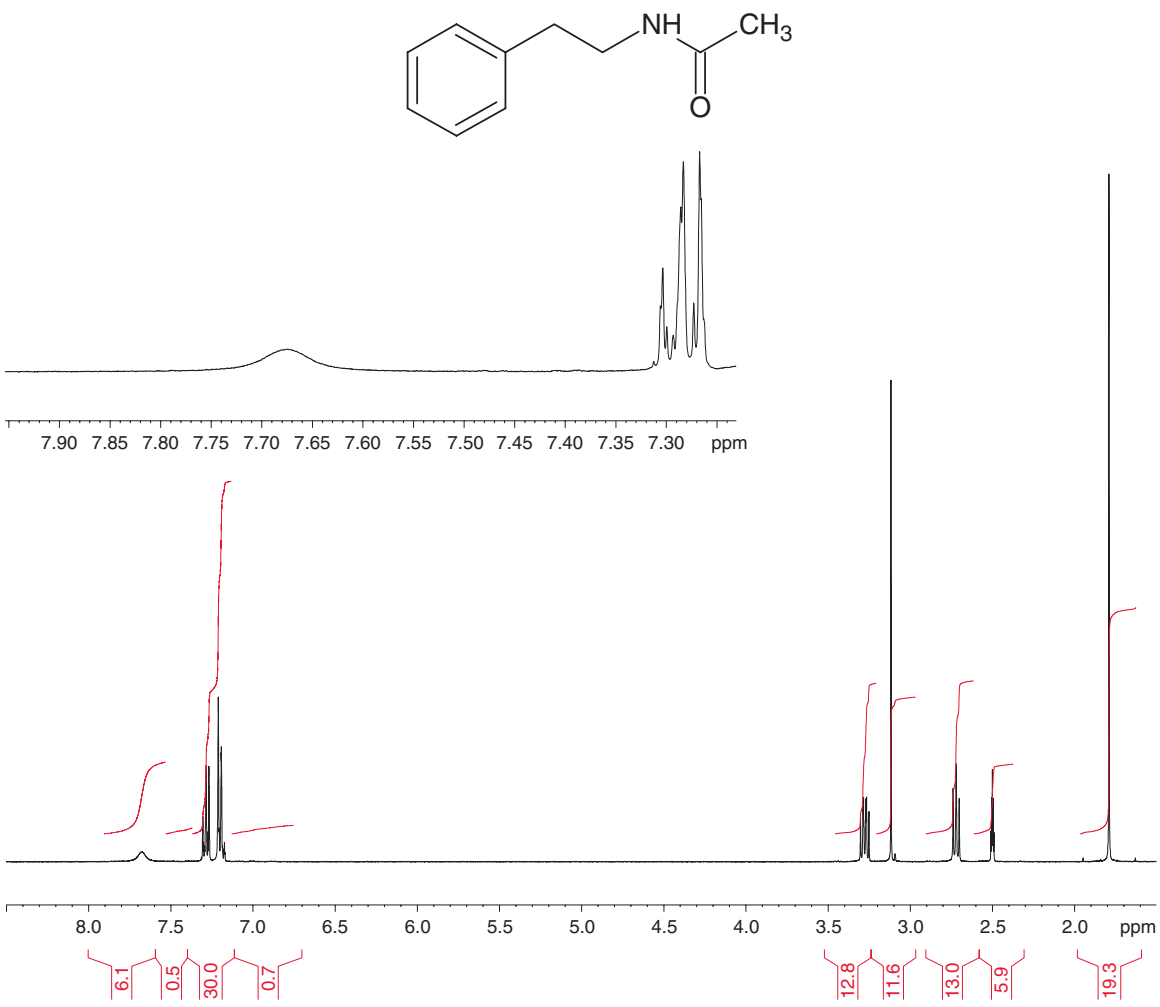
It is worth mentioning that >NH protons may often appear somewhat broader than their -OH counterparts, for another reason: >NH protons have another relaxation mechanism available to them (quadrupole relaxation) because the ^{14}N nucleus has an electric quadrupole moment. This extra relaxation capability can lead to a shorter relaxation time for >NH protons, and since the natural linewidth of a peak is inversely proportional to the relaxation time of the proton(s) giving rise to it, a shorter relaxation time will give rise to a broader peak.

This can lead to cases where an >NH of an amide, for example, couples to a -CH_2- adjacent to it, without *appearing* to show a reciprocal coupling itself, which as we know, is impossible! What happens is that its coupling becomes lost in the broadness of the signal – consider the compound shown with its spectrum (Spectrum 5.1).

Should your spectrum contain a very broad signal, such as the carboxylic acid proton of 4-fluoro benzoic acid shown in Spectrum 5.2 below and you aren't sure whether it's there at all, or whether your eyes are deceiving you, try looking along the baseline. Any slight lump which could be a signal will be seen more easily in this way. Of course if you are operating the spectrometer yourself, you only have to turn up the vertical gain but if you are looking at a walk-up spectrum, this trick might be useful.

As we have mentioned already, a very useful tool when trying to identify exchangeables is to exchange them for deuterium, which removes them from the spectrum. This will be covered in detail in Chapter 7 but don't be in too much of a hurry to do this – they are part of the spectrum and hold valuable information. If they are sharp enough, they may become potentially useful targets for NOE experiments which we will discuss later.

Finally, a brief word about aldehydes. They are included at the end of this group for convenience only and should be spotted easily. Aldehydes bound to aromatic rings give sharp singlets at 10.2–9.9 ppm, whilst in alkyl systems, they give sharp signals at 10.0–9.7 ppm, which couple to adjacent alkyl protons with a relatively small coupling constants (2–4 Hz).



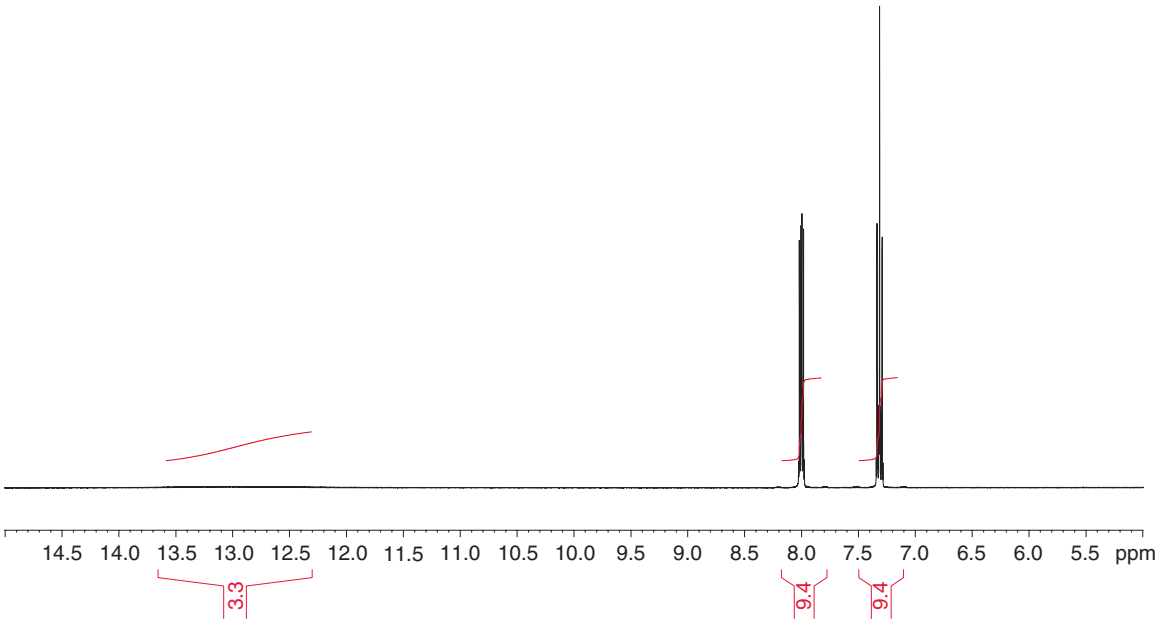
Spectrum 5.1 An amide NH (7.68 ppm) appearing to show no coupling to -CH_2 (3.28 ppm).

5.3 Group 2 – Aromatic and Heterocyclic Protons

Protons on aromatic rings are generally fairly predictable, both as regards to their position, and shape. The effects of substituents on a benzene ring are shown in Table 5.4.

They are applicable to compounds in the common NMR solvents – but not in D_6-benzene (or D_5-pyridine). The substituent effects are additive, but don't place too much reliance on chemical shifts predicted using the table, in compounds where more than two groups are substituted next to each other, as steric interactions between them can cause large deviations from expected values. Note that Table 5.4, like all others, does not cater for solvent shifts, etc!

A number of features become apparent on running an eye over these figures. Firstly, one saturated carbon in a substituent between the benzene ring and another group (e.g., -CH_2-OH) is sufficient to



Spectrum 5.2 A very broad carboxylic acid signal.

virtually isolate the ring from the influence of that other group, i.e., in this case, the -OH. This assumes that there are no abnormal 'through space' effects, of course, which we'll touch on later.

Secondly, groups which withdraw electrons (e.g., -NO_2, -COR, -COOR) cause shifts of the aromatic protons to lower field, to varying extents around the ring (the ortho-protons are generally the most influenced by a substituent, followed by the para-protons, and the meta-protons being the least influenced). But some groups which are known to be electron-withdrawing in alkyl systems, such as -OH, -OR, -NR actually bring about upfield shifts in aromatic systems. This is because, whilst these groups withdraw electrons inductively, they more than make up for this by supplying electrons, mesomerically. This effect is almost exactly balanced in the case of -Cl, which has very little influence on aromatic protons.

As for spin coupling around the benzene ring, Table 5.3 shows the expected ranges and typical values.

Note that: (1) in saturated systems proton–proton couplings are seldom observed beyond three bonds, but (2) in aromatic and heterocyclic systems, four- and even five-bond coupling is commonplace. This is because spin coupling is transferred by electrons. Where you have extended conjugation, you can expect to observe coupling over a greater number of bonds.

Table 5.3 Spin coupling around the benzene ring.

Position	Range (Hz)	Typical value
Ortho	6.0–9.4	About 8.0 Hz
Meta	1.2–3.1	About 2.5 Hz
Para	0.2–1.5	Negligible!

Table 5.4 Aromatic protons – the common substituent effects.

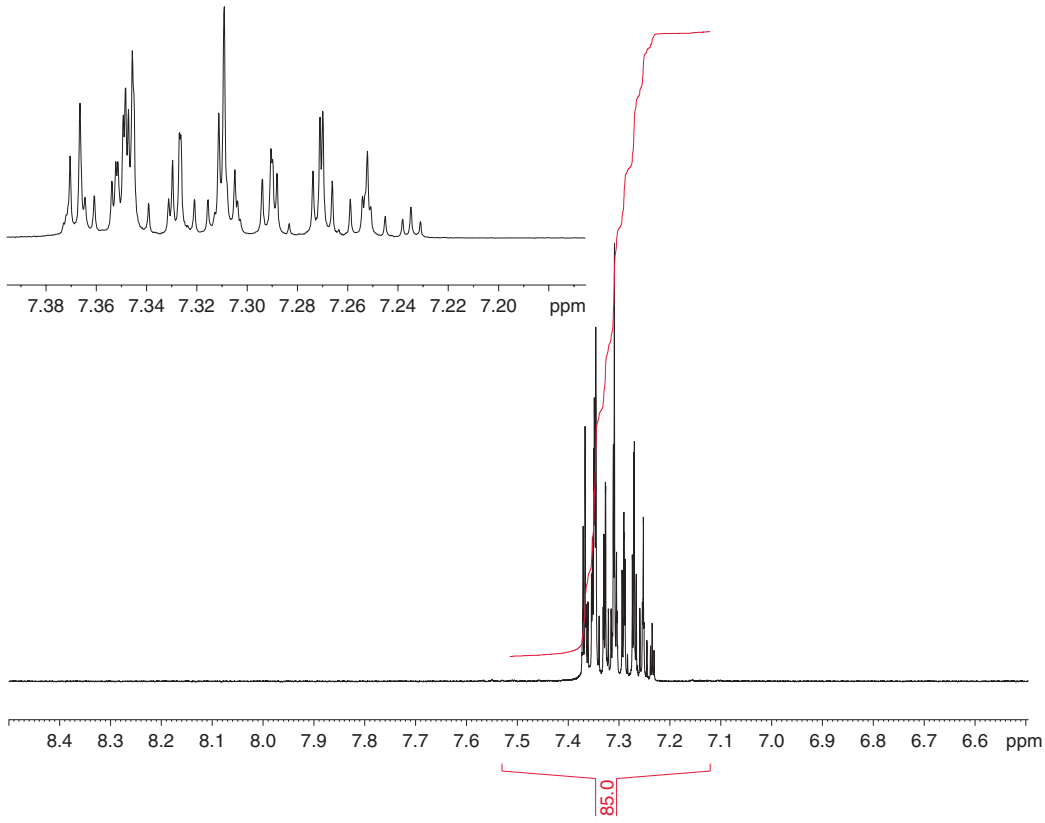
	Change in chemical shift (in ppm) relative to benzene (7.27)		
Substituent	Ortho	Meta	Para
-NO_2	0.95	0.17	0.33
-CHO	0.58	0.21	0.27
-COCl	0.83	0.16	0.30
-COOH	0.80	0.14	0.20
-$COOCH_3$	0.74	0.07	0.20
-$COCH_3$	0.64	0.09	0.30
-CN	0.27	0.11	0.30
-Ph	0.18	0.00	−0.08
–CCl_3	0.80	0.20	0.20
–$CHCl_2$	0.10	0.06	0.10
–CH_2Cl	0.00	0.01	0.00
–CH_3	−0.17	−0.09	−0.18
–CH_2CH_3	−0.15	−0.06	−0.18
–$CH(CH_3)_2$	−0.14	−0.09	−0.18
–$C(CH_3)_3$	0.01	−0.10	−0.10
–CH_2OH	−0.10	−0.10	−0.10
–CH_2NH_2	0.00	0.00	0.00
–F (couples!)	−0.30	−0.02	−0.22
–Cl	0.02	−0.06	−0.04
–Br	0.22	−0.13	−0.03
–I	0.40	−0.26	−0.03
–OCH_3	−0.43	−0.09	−0.37
–$OCOCH_3$	−0.21	−0.02	0.00
–OH	−0.50	−0.14	−0.40
–NH_2	−0.75	−0.24	−0.63
–SCH_3	−0.03	0.00	0.00
–$N(CH_3)_2$	−0.60	−0.10	−0.62

Note: A positive sign denotes a *downfield* shift (i.e., a shift to larger delta number; signal moves to the left).

In the light of this information, we can now consider a few examples of frequently encountered benzene-substitution patterns.

5.3.1 Monosubstituted Benzene Rings

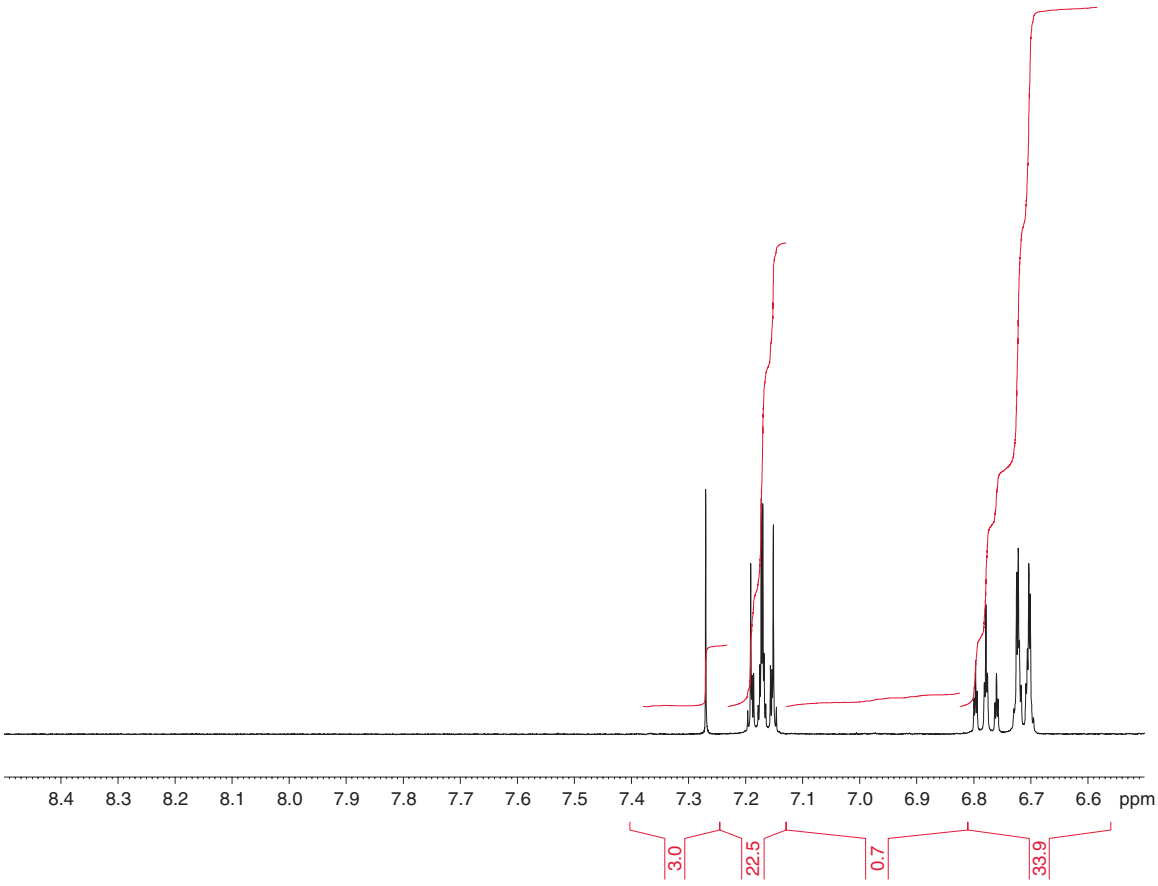
Spectrum 5.3 shows a typical pattern for a benzene ring monosubstituted with a relatively 'electron neutral' group. In this case, it's plain old chlorobenzene but similar patterns can be expected for any relatively neutral substituents, i.e., groups that neither donate nor withdraw electrons to or from the ring to any great extent (e.g., alkyl substituents). As the group has only a slight effect on the aromatic protons, they all resonate at quite close chemical shifts, giving anything from what can essentially be a singlet with small 'fringy bits' at its base, through to broader, heavily roofed multiplets as in this case though the exact appearance will of course vary considerably with spectrometer frequency. The complexity of the multiplet observed is dependant on two phenomena. The first, non-first-order behaviour, we will



Spectrum 5.3 A benzene ring bearing a single fairly neutral substituent.

discuss below. The second, magnetic non-equivalence, we will discuss in Section 5.3.2, which covers multisubstituted benzene rings.

Splitting patterns of signals are nice and predictable, only as long as the protons coupling to each other are separated by a chemical shift which is large relative to the size of the coupling between them. Notice for example, how the triplet and quartet of an ethyl signal are almost perfectly symmetrical. However, when signals coupled to each other are much closer together in the spectrum so that the difference between their chemical shifts and the size of their coupling is comparable, non-first-order effects can be expected. The closer they are, the more distorted (more non-first-order) they will be. In cases where signals are *very* close together, energy levels become mixed, and to quote L.M. Jackman: 'We find multiplicity rules no longer hold. Usually, more lines appear, and simple patterns of spacings and intensities are no longer found.' Such complex patterns can, in some cases, be subjected to mathematical analysis and the coupling information they contain extracted, but this practise has thankfully virtually died out with the advent of high-field spectrometers, or at least become a job for the computer! Our chlorobenzene example would look far less resolved (and thus more complex) than it does had it been run on an old 90 MHz instrument! Understanding, or at least recognising 'non-first-orderness' is very important and relevant to interpreting the spectra you will encounter.

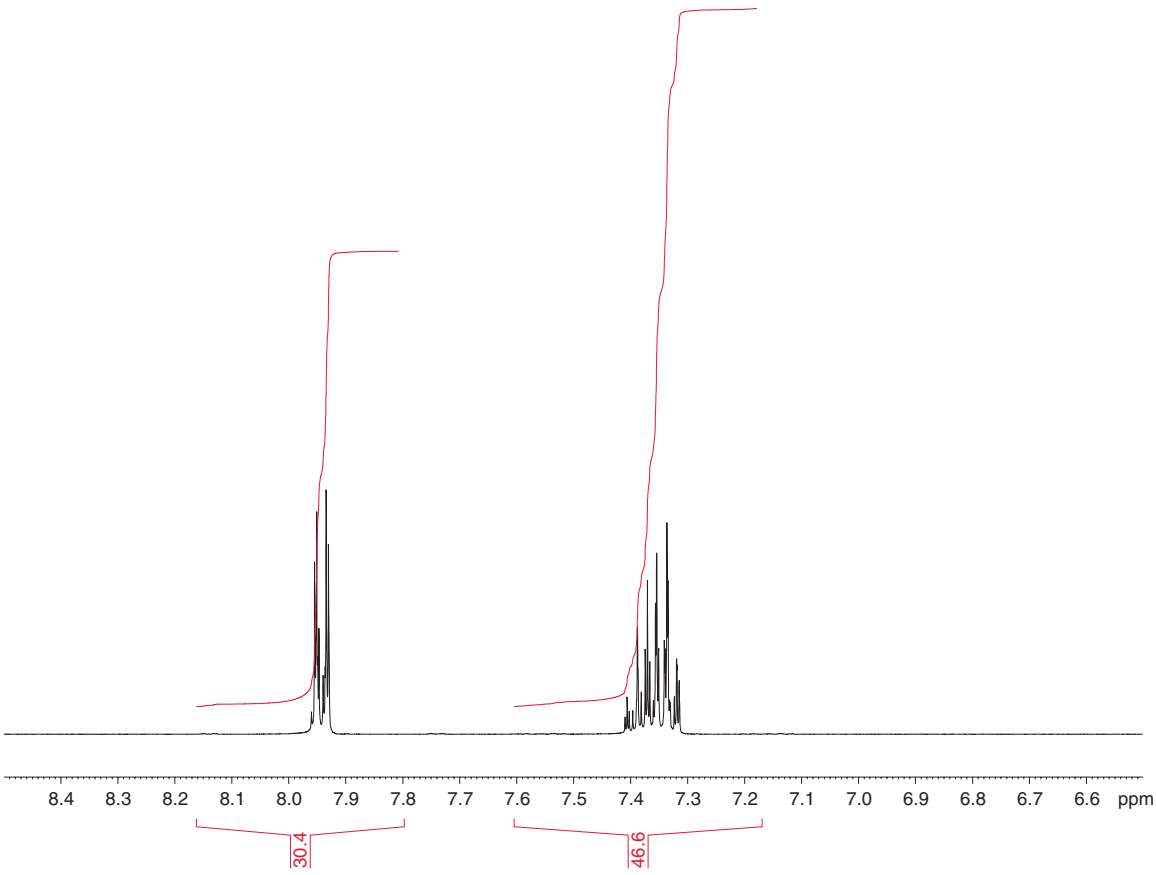


Spectrum 5.4 A benzene ring bearing a single electron-donating substituent.

Spectrum 5.4 shows a typical pattern of a benzene ring monosubstituted with an electron donating group (in this case, it's $-NH_2$).

Of the five aromatic protons, notice from the integration that two of them are below 7 ppm, occupying a position only slightly upfield of benzene itself, whilst the other three have been shifted upfield, above 7 ppm. A glance at Table 5.4 will show that these high-field signals can be assigned to the ortho, and para protons. The meta protons have been 'left behind', as it were. This shielding at the ortho and para positions is characteristic of simple electron-donating substituents.

These observations are of course underpinned by spin coupling observations. The meta protons both experience two ortho couplings of about 8 Hz which should yield a triplet (or more correctly, a doublet of doublets – note that a proton coupled to two other protons, which are different from each other, gives a doublet of doublets – when the two couplings are the same size, the signal appears as a triplet). What we actually observe is a very distorted 'triplet', the intensity of its lines being nothing like the 1:2:1 you might expect if you took Pascal's triangle too seriously! This distortion is referred to as 'roofing', and is the initial manifestation of the non-first-order behaviour just discussed.



Spectrum 5.5 A benzene ring bearing a single electron-withdrawing substituent.

The ortho- protons are shielded to the greatest extent and appear as a 'roofed' doublet of doublets whilst the less shielded para- proton presents as a triplet of triplets constructed from two large ortho- couplings and two small meta- ones. In cases where the electron donating substituent is oxygen-based (i.e., -OH or -OR), para- shielding can be as large as the ortho- shielding so that the ortho- and para- protons may have very similar chemical shifts. The consequence of this will be explored further in the next section.

Spectrum 5.5 shows the effect of a single deshielding substituent (carboxylic acid) on the benzene ring.

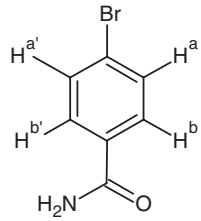
This time, we observe a pronounced downfield shift of the protons ortho- to the deshielding substituent and note that the signal is dominated by the large ortho-coupling and that it also bears a smaller meta- one. The signal is however both 'roofed' and is composed of more lines than you might naively expect.

The meta and para protons themselves appear as one ill defined multiplet, but on closer inspection, you can see that they are just resolved from each other. The para proton is slightly more deshielded than the meta protons and is centred at 7.39 ppm and is in fact a heavily 'roofed' triplet of triplets.

Note that Spectra 5.3, 5.4 and 5.5 are all plotted on the same scale to give you a feeling for the range of shifts that are typically encountered when looking at aromatic protons.

5.3.2 Multisubstituted Benzene Rings

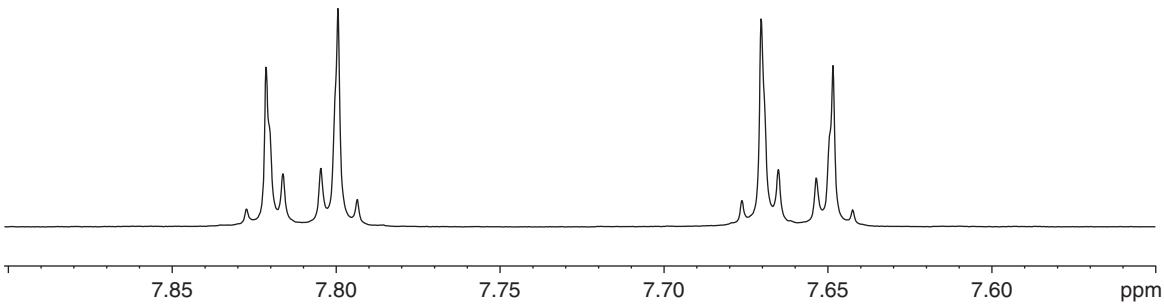
Moving on to multisubstituted aromatic systems, the real value of Table 5.4 soon becomes apparent. In dealing with such systems, it will not be long before you encounter a 1,4 di-substituted benzene ring. This substitution pattern (along with the 1,2 symmetrically di-substituted systems) gives rise to an NMR phenomenon that merits some explanation – that of *chemical* and *magnetic* equivalence and the difference between them. Consider the 1,4 di-substituted aromatic compound shown in Structure 5.1.



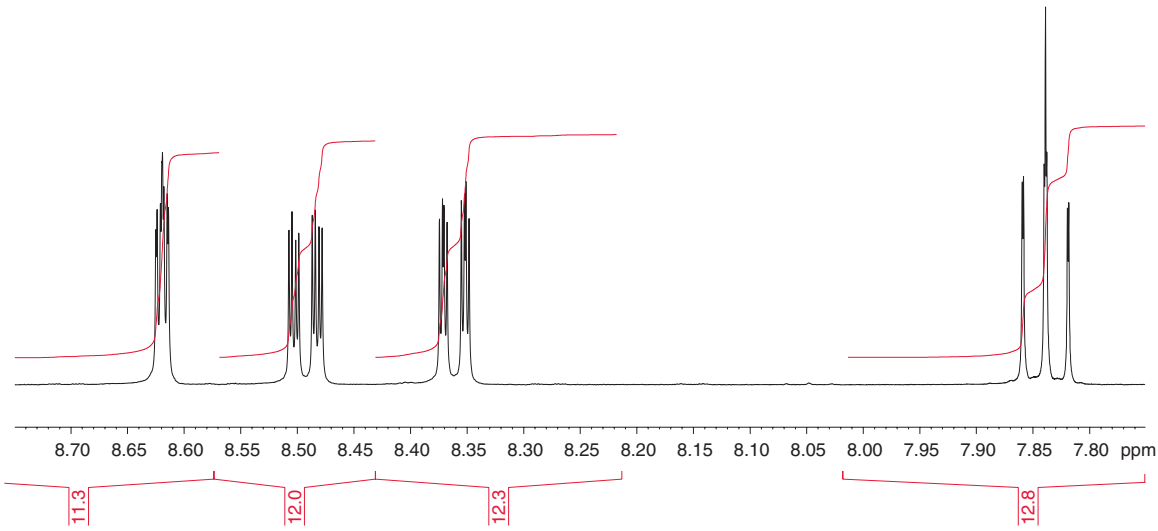
Structure 5.1 4-Bromobenzamide.

In terms of *chemical* equivalence, (or more accurately, *chemical shift* equivalence) clearly, H^a is equivalent to $H^{a'}$. But it is not *magnetically* equivalent to $H^{a'}$ because if it was, then the coupling between H^a and H^b would be the same as the coupling between $H^{a'}$ and H^b. Clearly, this cannot be the case since H^a is ortho to H^b but $H^{a'}$ is para to it. Such spin systems are referred to as AA′BB′ systems (pronounced *A-A dashed B-B dashed*). The dashes are used to denote magnetic non-equivalence of the otherwise chemically equivalent protons. What this means in practise is that molecules of this type display a highly characteristic splitting pattern which would be described as a pair of doublets with a number of minor extra lines and some broadening at the base of the peaks (Spectrum 5.6).

These extra lines are often mistakenly thought to be impurity peaks. An in-depth understanding of how they may arise is not really necessary for the purpose of interpretation. What is important is that you instantly recognise the appearance of such spin systems. Check that the system integrates correctly and check that the two halves of the system are symmetrical. *Note*: This phenomenon has nothing whatsoever



Spectrum 5.6 A typical aromatic AA′BB′ system (4-bromobenzamide).



Spectrum 5.7 Methyl 3-nitrobenzoate.

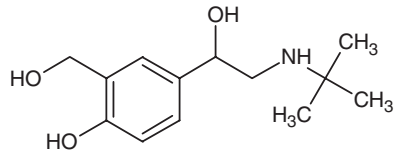
to do with chiral centres and is purely a function of the spatial arrangement of the protons involved as described above.

Spectrum 5.6 also shows a good example of 'roofing', which we touched on earlier. If you imagine the simple case of a pair of doublets well separated from each other, then all four of their lines will be of almost equal intensity. But when coupled doublets get closer together, they become distorted so that their inner lines become more intense, and their outer lines less intense. This is the onset of 'non-first-orderness'. The closer a pair of coupled doublets are to each other, the more extreme the effect becomes. It is worth noting that the phenomenon can sometimes be a useful interpretive tool, as the roofing can indicate which doublet is coupled to which other one, in spectra where you encounter two or more systems of this type: doublets which are coupled to each other, always roof towards a point between them, as shown.

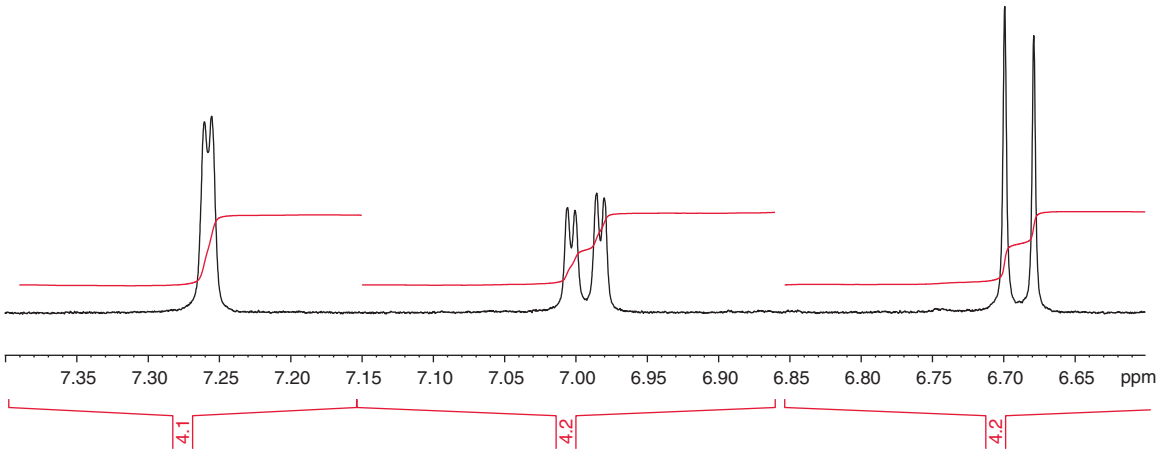
Obviously, there are too many possible combinations of groups for us to show a comprehensive collection of them but Spectrum 5.7 shows a nice example of a 1,3 di-substituted pattern featuring two strongly deshielding groups (a nitro group and a methyl ester) and serves to demonstrate the limitations of Table 5.4.

Predicting the chemical shift of the proton between the two substituents using Table 5.4 suggests a figure of 8.96 ppm. The observed figure is in fact 8.62 ppm. Very low field for sure, but significantly not as low as predicted. We find that this sort of error is quite commonplace in ring systems containing two or more very deshielding groups. Naively, it's as if the first group withdraws so much electron density from the ring that there is not much left for the second group to withdraw so the combined effect is less than expected. Be that as it may, Table 5.4 at least succeeds in predicting the correct *relative* positions of the protons, even if the actual values are a little off the mark.

And finally, Structure 5.2 and Spectrum 5.8 show a classic example of a 1,2,4 tri-substituted benzene ring, (a well known anti-asthma drug, salbutamol). Obviously, the scope for variation in these systems is vast!



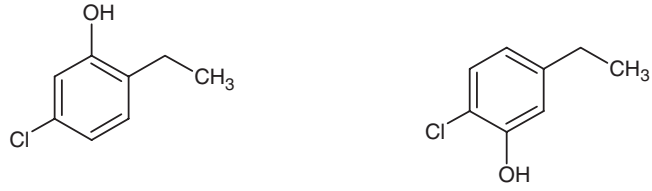
Structure 5.2 Salbutamol.



Spectrum 5.8 Aromatic region of salbutamol.

As a closing observation, it is difficult to say just how close you can reasonably expect predicted and observed values to be, even discounting highly sterically interactive systems mentioned earlier. A crude observation would be that the more substituents on the ring, the less accurate your predictions are likely to be. For what it's worth however, a rough working guide would be an expectation of, shift predictions within 0.3 ppm for multi-substituted rings in the absence of strong steric interactions between groups.

A final word of caution on aromatic systems – the electron donating groups (notably those in which oxygen is the shielding entity) can cause problems, because their ortho- and para- effects are so similar. Consider the following example – you are presented with a sample known to be one of the two isomers shown in Structure 5.3:



Structure 5.3 Two possible isomers.

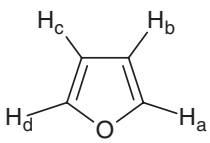
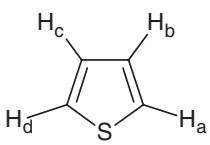
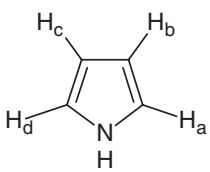
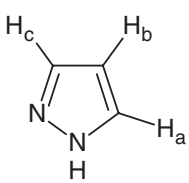
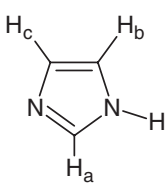
The two compounds will give very similar spectra and you would not be able to tell which isomer your sample is without an authentic spectrum of at least one of the isomers, for comparison. The only unambiguous way to tell these isomers apart, in the absence of an authentic spectrum, would be

by a nuclear Overhauser experiment (NOE), which we'll discuss later. Without performing such an experiment, you'd be ill-advised to chance your arm! Any chemical shift differences would be far too small to exploit with any certainty whatsoever!

5.3.3 Heterocyclic Ring Systems (Unsaturated) and Polycyclic Aromatic Systems

Heterocyclic systems resemble aromatic systems in some respects, but are more varied and interesting. We'll outline a few of these interesting features and then provide some useful chemical shift and coupling data in Table 5.5. It is not really feasible to provide information as in Table 5.4, as every heterocycle would need its own specific table and there are a great many heterocycles out there!

Table 5.5 Chemical shifts and couplings in some common heterocyclic and polycyclic aromatic systems.

Compound	Chemical shift (ppm)	Typical couplings (Hz) in parent *or* derivative
	a/d 7.4 b/c 6.3	a-b 1.8 b-c 3.5 a-c 0.8 a-d 1.6
	a/d 7.19 b/c 7.04	a-b 4.7 b-c 3.4 a-c 1.0 a-d 2.9
	a/d 6.62 b/c 6.05	a-b 2.6 b-c 3.4 a-c 1.1 a-d 2.2
	a/c* 7.55 b 6.25 * Note that tautomerism renders 'a' and 'c' equivalent in the parent NH compound.	a-b* 2.9 b-c* 1.6 a-c* 0.7 * Couplings measured in nontautomeric alkylated derivatives.
	a 7.7 b/c* 7.14 * Note that tautomerism renders 'b' and 'c' equivalent in the parent NH compound.	b-c 1.6 a-b ≈ a-c 0.8-1.5

(*continued*).

Table 5.5 (Continued)

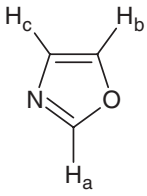
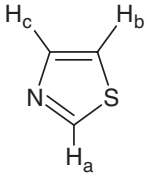
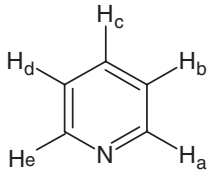
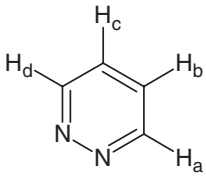
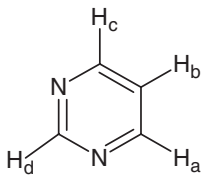
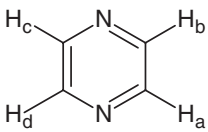
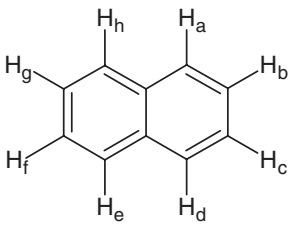
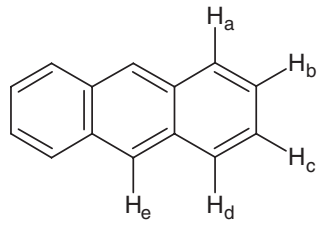
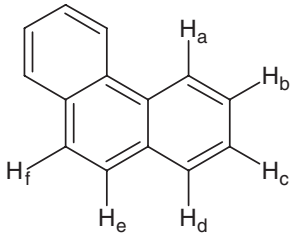
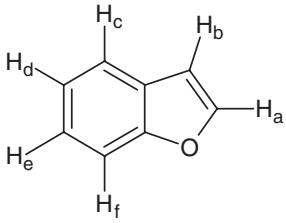
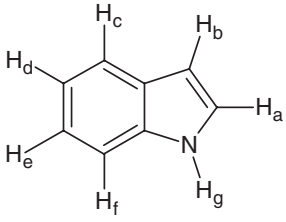
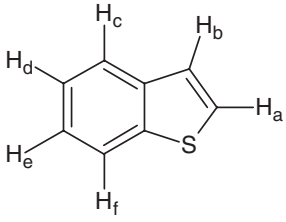
Compound	Chemical shift (ppm)	Typical couplings (Hz) in parent *or* derivative
	a 7.95 b 7.69 C 7.09	b-c 0.8 a-b 0.5 a-c 0.0
	c 8.88 b 7.41 C 7.98	b-c 3.1–3.6 a-b 1.9 a-c 0.0
	a/e 8.6 b/d 7.28 c 7.69	a-b 4.0–6.0 b-d 7.0–9.0 a-c 0–2.5 a-e 0–0.6 b-d 0.5–2.0 a-d 0–2.5
	a/d 9.17 b/c 7.68	a-b 5.0 b-c 8.4 a-c 2.0 a-d 3.5
	a/c 8.6 b 7.1 d 9.15	a-b 5.0 a-d 0 a-c 2.5 b-d 1.5
	a/b/c/d 8.5	a-b 1.8–2.0 a-d 0.5 a-c 1.5
	a/d 7.67 b/c 7.32	a-b 8.0–9.0 b-c 5.0–7.0 a-c 1.0–2.0 a-d ≈ 1.0 a-e ≈ 1.0

Table 5.5 (Continued)

Compound	Chemical shift (ppm)	Typical couplings (Hz) in parent *or* derivative
	a/d 7.98 b/c 7.44 e 8.40	Very similar to naphthalene above.
	a 8.65 b 7.61 c 7.57 d 7.86 e 7.70	a-b 8.4 b-c 7.2 e-f 9.0 a-c ≈ b-d 1.2 a-d ≈ 0.7
	a 7.5 b 6.66 c 7.5 d 7.13 e 7.2 f 7.4	a-b 2.5 c-d 8.0 d-e 7.3 e-f 8.4 c-f 0.8 b-f ≈ 1.0
	a 7.26 b 6.45 c 7.55 d 7.0 e 7.1 f 7.4 g 9.0–12.0 (very solvent dependant!)	a-b 3.0 c-d ≈ e-f 8.0 d-e 7.0 c-e ≈ d-f 1.3 b-f 0.7 c-f ≈1 b-f 0.7 g-a 2.5 g-b 2
	a 7.44 b 7.34 c 7.83 d 7.36 e 7.34 f 7.9	a-b 5.5 c-d ≈ d-e ≈ e-f 7.0–8.0 c-e ≈ e-f ≈1.0 b-f 0.8

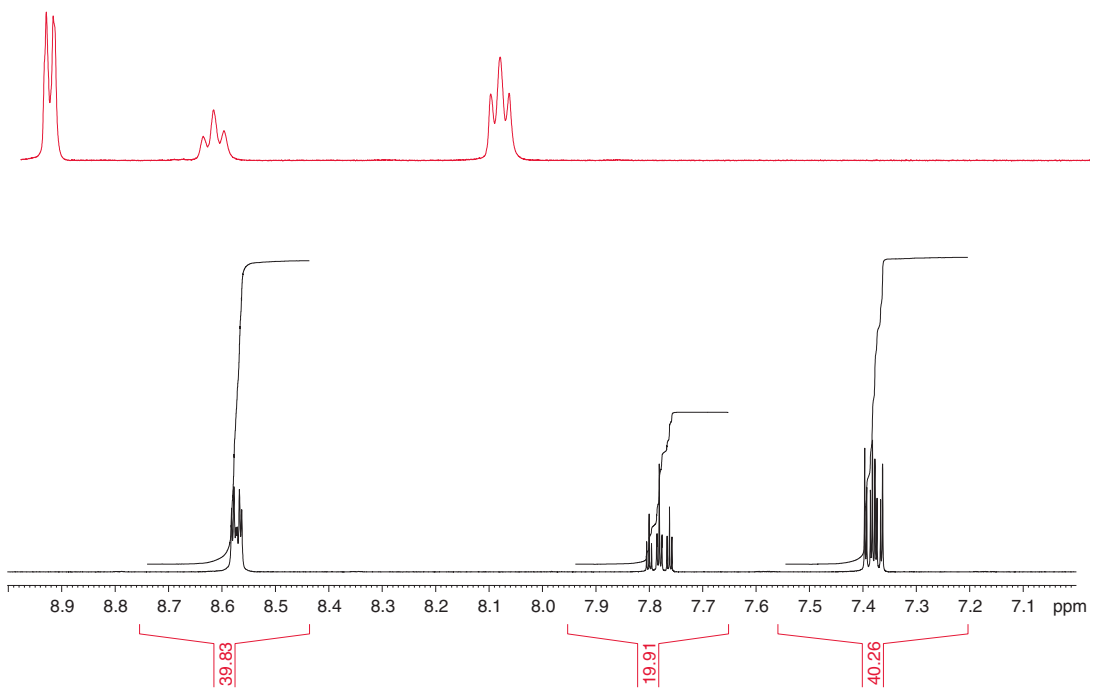
So when confronted with a problem involving an unsaturated heterocycle, our advice is to make yourself aware of the shifts and couplings of the parent compound (Table 5.5) and then use the known effects of substituents from Table 5.4 and 'superimpose' them. This will give you a rough guide only and your 'confidence curve' will need to be adjusted accordingly as the magnitude of the induced shifts are usually somewhat different and may vary within the heterocycle. In a 3-substituted furan, or thiophene, for example, the magnitudes of the ortho effects to the 2′, and 4′ protons are different – sometimes, considerably so!

One other, perhaps even more dramatic and common example concerns compounds like 2′ and 4′ hydroxy- and amino-pyridines. These compounds exhibit tautomeric behaviour and tend to exist in solution as the corresponding pyridone and imine. This reduces the familiar pyridine-like properties of the ring system, accentuating the effects of these substituents (in terms of induced chemical shifts) and at the same time, radically increasing the expected couplings 2′–3′ couplings.

The size of couplings around heterocyclic rings can also vary dramatically. Ortho- couplings in five-membered heterocycles such as furan and thiophene for example, are much smaller than in normal aromatic rings. Note also that even within a given heterocycle, there can be substantial variation in the size of ortho couplings themselves! As with any spectroscopic phenomenon, this should not be regarded as just another complication, but as an important part of your spectroscopic armour, or indeed, as part of your spectroscopic offensive weaponry for attacking problems of substitution etc.

Nitrogen-containing heterocycles are sometimes basic enough to protonate and form salts in acidic conditions and this leads to substantial changes in chemical shifts of their protons – see Spectrum 5.9 (pyridine alone, pyridine + DCl)

Note also that fluorine couplings to protons in heterocyclic systems can be well outside intuitive expectations! See Section 6.5.2 for an example!



Spectrum 5.9 Pyridine in DMSO solution (bottom) and with one drop DCl (top).

One last word on heterocycles. Very small couplings (<1 Hz) have been found to exist between some protons on *different* rings of bicyclic heterocycles. For example, in indole, there is a 3-7 coupling of about 0.7 Hz. In practise however, these very small couplings may only manifest themselves as a broadening of the signals concerned.

Obviously, this table is far from exhaustive but it establishes the typical shifts and couplings found in some of the more commonly encountered heterocycles.

5.4 Group 3 – Double and Triple Bonds

In this section, we will look at alkene, imine, enol ether and alkyne protons. It's convenient to consider the first three at this stage as they usually absorb in the 8-5 delta region and the alkyne is included here for convenience.

Alkene chemical shifts can be estimated using Table 5.6. Use this table with the same circumspection as you would all other tables of this type. It's a useful guide, not gospel.

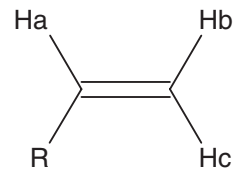
Substitute the additive values in Table 5.6 into the following equation:

$$\text{Approximate chemical shift of proton (ppm)} = 5.25 + Z_{\text{gem}} + Z_{cis} + Z_{trans}$$

Table 5.6 Estimation of chemical shifts for alkene protons.

R	Z_{gem} (ppm)	Z_{cis}	Z_{trans}
-H	0.00	0.00	0.00
-Alkyl	0.45	−0.22	−0.28
-CH_2-OR	0.64	−0.01	−0.02
-CH_2-SR	0.71	−0.13	−0.22
-CH_2-halogen	0.70	0.11	−0.04
-CH_2NR_2	0.58	−0.10	−0.08
>C=C< (isolated)	1.00	−0.09	−0.23
>C=C< (conjugated)	1.24	0.02	−0.05
-CN	0.27	0.75	0.55
-C ≡ C-R	0.47	0.38	0.12
>C=O (isolated)	1.10	1.12	0.87
>C=O (conjugated)	1.06	0.91	0.74
-COOH	0.97	1.41	0.71
-COOR	0.80	1.18	0.55
-CHO	1.02	0.95	1.17
-$CONR_2$	1.37	0.98	0.46
-COCl	1.11	1.46	1.01
-OR	1.22	−1.07	−1.21
-OCOR	2.11	−0.35	−0.64
-CH_2-Ar	1.05	−0.29	−0.32
-Cl	1.08	0.18	0.13
-Br	1.07	0.45	0.55
-I	1.14	0.81	0.88
-NR_2	0.80	−1.26	−1.21
-NRCOR	2.08	−0.57	−0.72
-Ar	1.38	0.36	−0.07
-SR	1.11	−0.29	−0.13
-SO_2R	1.55	1.16	0.93

Figure 5.2 shows typical couplings found in alkenes.:



J_{a-b} (*cis* coupling)	7–13 Hz, typically 11 Hz
J_{a-c} (*trans* coupling)	11–18 Hz, typically 16 Hz
J_{b-c} (geminal coupling)	Approximately 1–2 Hz

Figure 5.2 Typical couplings found in alkenes.

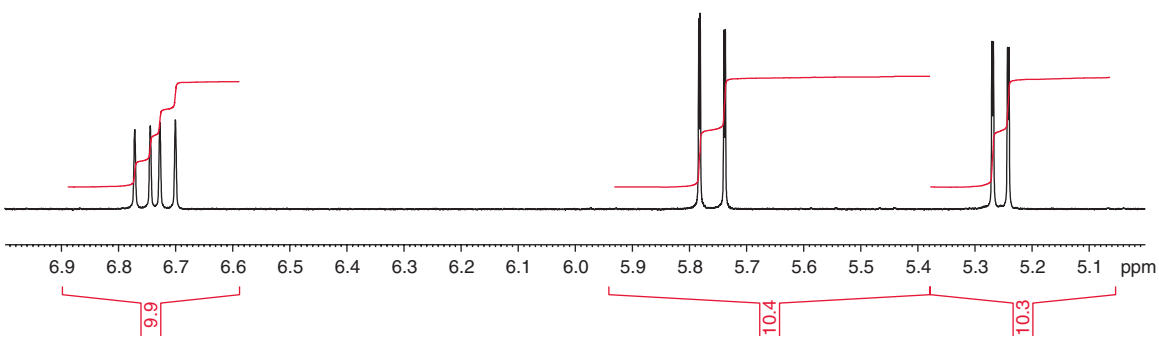
These couplings are exemplified below with reference to styrene (Spectrum 5.10).

Note that small couplings (approx. 1.0–2.5 Hz) would also be expected between the first CH_2 of any alkyl group (R) and both Hb and Hc.

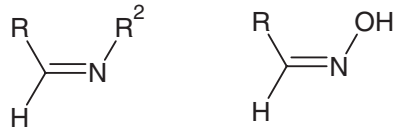
The actual sizes of the observed *cis*- and *trans*- couplings are influenced by the electronegativity of the substituents attached to the double bond. In general, the more electronegative the substituents, the smaller the observed couplings. (There is actually an approximately linear relationship between the size of the coupling and the sum of the electronegativities of the substituents).

It is interesting to note that in cases where an alkene is joined directly to an aromatic ring, the alkene proton geminal to the aromatic ring is invariably at the lowest field of the alkene protons. This is because the alkene bond tends to lie in the same plane as the aryl ring and for this reason, the geminal proton is held in the deshielding zone of the aromatic ring, as is the alkene proton cis to the aromatic ring. This is an example of anisotropy which we will discuss in some detail later on.

Determining whether an alkene is *cis* or *trans* in cases where the alkene is in the middle of a long alkyl chain is usually not possible by ^{1}H NMR as both cis and trans protons have very similar shifts in such circumstances, as do the -CH_2s attached to the alkene. Such a problem can however be dealt with using ^{13}C NMR where the shifts of these CH_2s are diagnostic.



Spectrum 5.10 The alkene protons of styrene (Ph-CH=CH2).

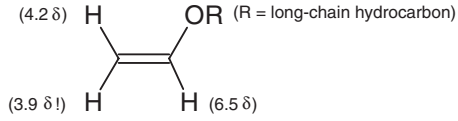


Structure 5.4 Double-bond moieties.

Other double-bond moieties which are often encountered include the imines and oximes (Structure 5.4).

Note that the lack of rotation about the double bond means that 'E' and 'Z' isomers are distinct entities in the same way that *cis* and *trans* isomers are distinct in conventional alkenes. It is not really feasible to give a comprehensive guide to the chemical shifts of these protons but expect them to be somewhat lower field (approx. 1 ppm) than for comparable alkenes, with chemical shifts being driven largely by the anisotropy of the substituents.

Enol ether protons are interesting in that their chemical shifts are unusually high field in comparison with other alkenes on account of lone pair donation into the double bond from oxygen (Structure 5.5). No special precautions are necessary when dealing with them as this is reflected in the values obtained using Table 5.6.



Structure 5.5 An example of an enol ether showing typical shifts.

Whereas alkene protons are relatively de-shielded by the overlapping p electrons of the double bond, alkyne protons are fairly shielded by their electronic environment. In common with alkenes, however, is the possibility of small, long-range coupling through the triple bond. The chemical shifts of alkyne protons are highly influenced by the electronegativity of groups attached to the other end of the triple bond as can be seen from the examples in Table 5.7. It is worth bearing in mind that alkyne protons may exchange in strongly basic solutions.

Table 5.7 The chemical shifts of alkyne protons.

Alkyne	Chemical shift (ppm)	Comments
R-C≡C-**H**	1.9	(R = long-chain hydrocarbon)
Ph-C≡C-**H**	3.1	
Ph-Ph-C≡C-**H**	4.2	(Ph-Ph = biphenyl rings)

5.5 Group 4 – Alkyl Protons

This section must necessarily be brief and general on account of the size of the category and the vast number of case studies we could dissect in detail.

For now, the discussion will be restricted to straightforward systems (open-chain and containing no chiral centres) and adhere to previous practise by supplying chemical shift data (Table 5.8) which will enable you to estimate the chemical shifts of methyl, methylene and methane protons you will typically encounter. Typical three-bond couplings in such systems can be expected in the region of 7–9 Hz, what variations there are being attributable to electronic effects of the substituents. These small variations can sometimes be exploited as a means of verifying which signal is coupled to which other, e.g., in cases where you are up against a molecule with two different -CH_2CH_2- systems. Perhaps we should mention at this stage that the single most significant factor in determining the magnitude of a three-bond (vicinal) coupling is the dihedral angle Φ, between the protons in question (Figure 5.3).

In open chain compounds that lack any chiral centre of course, rotation about all single bonds can be assumed to be both relatively 'free' and fast on the NMR timescale and the 7–9 Hz range quoted is the result of averaging of this angle. The same is of course not true in cyclic systems where structures are rigid and bond angles constrained. We will deal with this topic thoroughly in Section 6.6.5.

Let's stop for a moment, and reflect on what we have dealt with so far. In fact, we've covered quite a lot of ground already. We started by considering some basic theory and background to the

Table 5.8 Estimation of chemical shifts for alkyl protons.

X	C	X	C
-CH_3	0.5	-NR,COR	2.4
-Alkyl	0.6	-NR_2	1.6
>=<	1.3	-$^+NR_3$	2.4
-C≡C-Ar	1.7	-N=C=S	2.9
-C≡C-R	1.4	-Ar	1.8
-CN	1.7	-OCOAr	3.5
-COAr	1.9	-OCOR	3.1
-COCl	1.8	-OAr	3.2
-$CONR_2$	1.6	-OH	2.6
-COOR	1.5	-OR	2.4
-COR	1.6	-OSO_2Ar	3.4
-Cl	2.5	-SAr	2.1
-Br	2.3	-SR	1.9
-I	2.1	-CF_3 *	1.1
-NO_2	3.7	-F *	3.6

*Note: both show coupling to neighbouring alkyl protons.
For methine protons, approx. chemical shift (ppm) will be: 0.1 + CX + CX1 + CX2
For methylene protons, approx. chemical shift will be: 0.3 + CX + CX1
For methyl protons, approx. chemical shift will be: 0.5 + CX
Note: the values 0.1, 0.3 and 0.5 are just 'fudge factors' to give better estimates.
For more extensive shift and coupling data on a wider variety of compounds, we would recommend *Structure Determination of Organic Compounds* by E. Pretsch, P. Bűhlmann and C. Affolter (Springer, ISBN 3-540-67815-8)

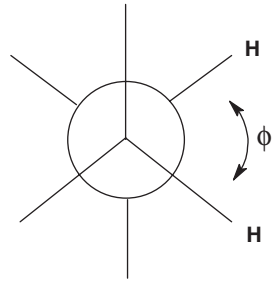


Figure 5.3 Dihedral angle Φ between protons.

subject. We've looked at the very important issues of sample preparation and skimmed the surface of spectrometer set up. We've established a good standard method of dealing with spectra, by partitioning the information available into coherent segments – both with respect to the nature of the information (chemical shift, multiplicity and integration) and also, with respect to the various classes of proton commonly encountered. And finally, we've spent a good deal of time examining these different types of protons in some detail. In fact, it might be tempting to wonder what more needs to be said on the subject of spectral interpretation. After all, you now have in your grasp some pretty powerful tools – tables and so on, which will, if used prudently, give you a good idea of what to expect from relatively simple spectra.

Unfortunately, it's not quite as simple as that. In the next chapter, we'll delve a little deeper and have a look at some possible pitfalls you may encounter in more complex spectra.