9

Carbon-13 NMR Spectroscopy

9.1 General Principles and 1-D ^{13}C

^{13}C NMR gives us a another vast area of opportunity for structural elucidation and is incredibly useful in many cases where compounds contain relatively few protons, or where those that are available are not particularly diagnostic with respect to the proposed structures. Before we delve into any detail, there are certain general observations which we need to make regarding ^{13}C NMR and the fundamental differences that exist between it, and proton NMR.

For a start, we must be mindful of the fact that ^{13}C is only present as 1.1 % of the total carbon content of any organic compound. This, in combination with an inherently less sensitive nucleus, means that signal to noise issues will always be a major consideration in the acquisition of ^{13}C spectra – particularly 1-D ^{13}C spectra which we will restrict the discussion to for the moment. (Note that the *overall* sensitivity of ^{13}C, probe issues aside, is only about 0.28 % that of proton because the nucleus absorbs at a far lower frequency – in a 400 MHz instrument, ^{13}C nuclei resonate at around 100 MHz.). So it takes a great deal longer to acquire ^{13}C spectra than it does proton spectra. More material is obviously an advantage but can in no way make up for a 350-fold inherent signal to noise deficiency!

Another important aspect of ^{13}C NMR is that the signals are never normally integrated. The reason for this is that some carbon signals have quite long relaxation times. In order to make NMR signals quantitative, acquisition must allow for a relaxation delay (delay period between acquisition pulses) of at least five times the duration of the slowest relaxing nuclei in the compound being considered. With relaxation times of the order of 10–20 s, it is therefore obvious why we cannot obtain quantitative ^{13}C data! The inherent insensitivity of the ^{13}C nucleus often demands thousands of scans to achieve acceptable signal to noise so we can ill afford 100 s relaxation delays between pulses! The only thing that we can say is that methine, methylene and methyl carbons *generally* appear to be more intense than quaternary carbons (see below for explanation).

Yet another significant difference with ^{13}C NMR is that we do not observe coupling between neighbouring nuclei as we do in proton NMR. This is not by virtue of any decoupling technology – it is purely a matter of statistics. As the natural abundance of ^{13}C is only 1.1 %, the chances of having two ^{13}C atoms sitting next to each other is statistically small (it would occur in only 1.1 % of that 1.1% in fact) and so ^{13}C–^{13}C coupling just isn't an issue. It should be noted that with the extra sensitivity of cryoprobes, it is

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becoming possible to observe ^{13}C–^{13}C couplings and these can be used to solve tricky regiochemistry problems.

^{1}H–^{13}C coupling however, *would* be a serious issue – if it were allowed to occur. 1-D ^{13}C spectra are always normally acquired with full proton decoupling. There are a number of good reasons for this. First, the already meagre signal/noise would be further eroded by splitting the signal intensities into doublets, triplets, etc. Furthermore, identifying individual signals would be extremely difficult in compounds having many carbons in a similar chemical environment – particularly in view of the large couplings that exist between protons and ^{13}C nuclei. The potential overlap of signals would make spectra horrifically complex.

Another good reason for fully decoupling protons from ^{13}C is that the ^{13}C sensitivity, to some extent benefits from Overhauser enhancement (from proton to ^{13}C which comes about as a result of decoupling the protons). This explains why quaternary carbons appear less intense than those attached to protons – they lack the Overhauser enhancement of the directly bonded proton.

So far, it might seem that ^{13}C spectroscopy is just a long list of disadvantages. Here we have a technique that is extremely insensitive and thus time-consuming to acquire. It is largely nonquantitative, since we can't integrate the signals and to gild the lily, we can't relate carbon to carbon by means of spin coupling as we have no coupling information to assist us in our assignments. Just about the only commodity we have left at our disposal is the chemical shift – but how do you go about interpreting a spectrum that is composed entirely of singlets? We will explore this a bit later. (Note that although all ^{1}H–^{13}C couplings are decoupled, couplings between ^{13}C and other hetero atoms such as fluorine and phosphorus will *not* be decoupled and splitting of ^{13}C signals will be observed in molecules where these hetero atoms are found in environments that are conducive to coupling.)

So if this all sounds a bit bleak, what's the *good* news? Well, strangely, there is quite a lot. For a start, let's not forget that had the ^{13}C nucleus been the predominant carbon isotope, the development of the whole NMR technique itself would have been held back massively and possibly even totally overlooked as proton spectra would have been too complex to interpret. Whimsical speculation aside, chemical shift prediction is far more reliable for ^{13}C than it is for proton NMR and there are chemical shift databases available to help you that are actually very useful (see Chapter 14). This is because ^{13}C shifts are less prone to the effects of molecular anisotropy than proton shifts as carbon atoms are more internal to a molecule than the protons and also because as the carbon chemical shifts are spread across approximately 200 ppm of the field (as opposed to the approx. 13 ppm of the proton spectrum), the effects are proportionately less dramatic. This large range of chemical shifts also means that it is *relatively* unlikely that two ^{13}C nuclei are exactly coincident, though it does happen.

Other good news comes in the shape of the ^{13}C nucleus having a spin quantum number of $^{1}/_{2}$. This means that ^{13}C signals are generally sharp as there are no line-broadening quadrupolar relaxation issues to worry about and we don't have to deal with any strange multiplicities.

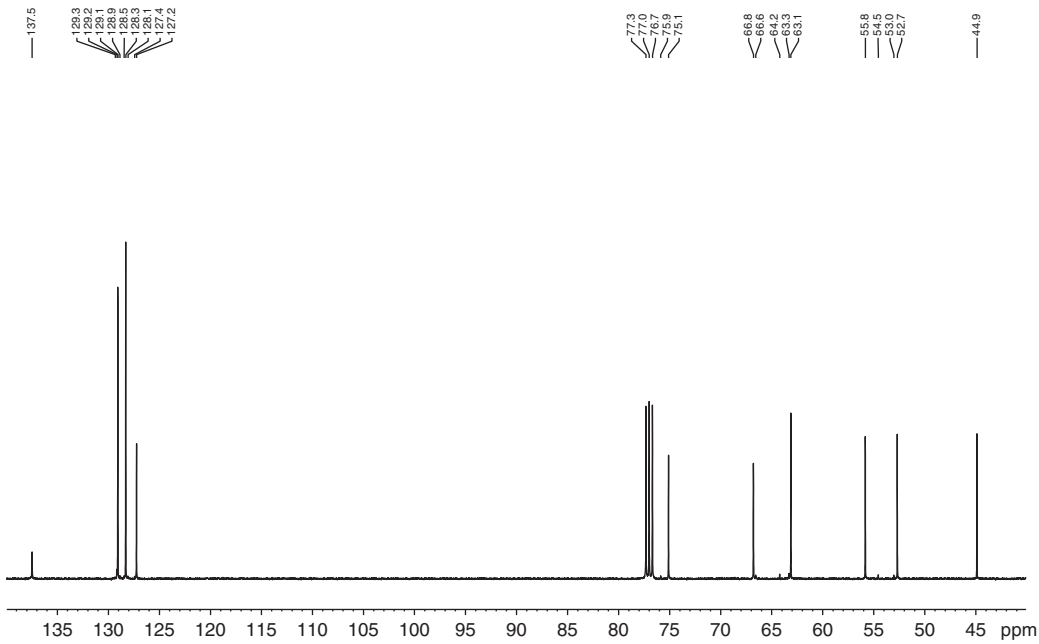
So to a large extent, 1-D ^{13}C NMR interpretation is a case of matching observed singlets to predicted chemical shifts. These predictions can be made by reference to one of the commercially available databases that we've mentioned, or it can be done the hard way – by a combination of looking up reference spectra of relevant analogues and using tables to predict the shifts of specific parts of your molecule (e.g., aromatic carbons). We have included some useful ^{13}C shift data at the end of the chapter but it is by necessity, very limited.

^{13}C prediction software is certainly the preferred option but it should always be used with circumspection. It generally works by using a combination of library data to generate an estimate of the chemical shifts of all the carbons in your proposed structure but it is inevitable that these estimates will be prone

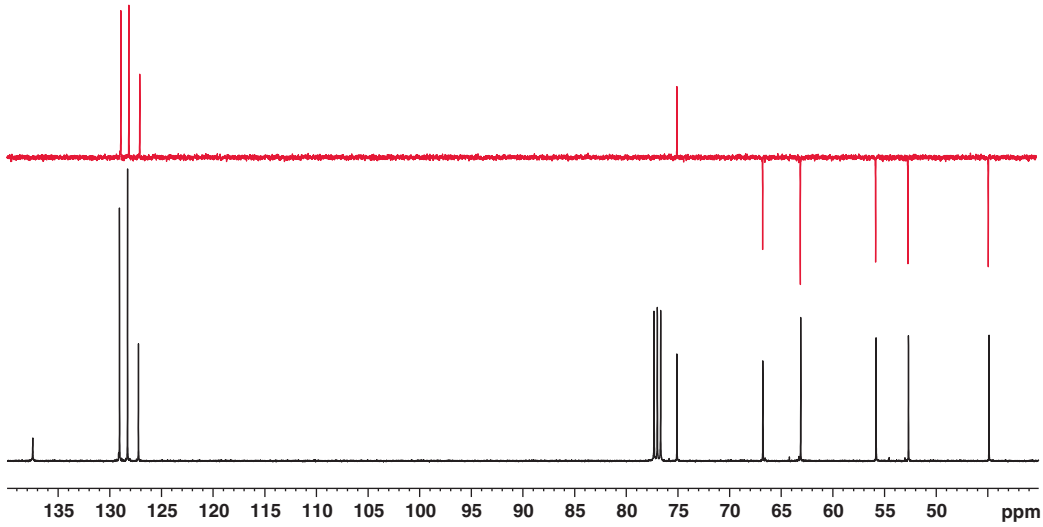
to error. It is important to realise that some shift estimates will be far better than others – even within the same molecule. It is also important to note that whilst these packages may give a measure of confidence with each prediction, these limits must be viewed critically as they may be either unduly pessimistic or (worse) unduly optimistic. We would always recommend that if your prediction software allows you to browse the *actual* compounds used in the predictions, you do so! This will enable you to 'personalise' the predictions to some extent as you will be able to lean more towards the shifts of the compounds in the database that are more similar to your proposed structure. For example, if you are working with steroids and you are trying to predict the shift of a certain carbon in your molecule, it would be wise to pay more heed to the shifts of carbons in similar environments *in other steroids* as opposed to analogous carbons in completely different types of molecule.

From a purely pragmatic point of view, and some purists may take issue with this, it is perhaps not essential that you unambiguously assign every carbon to a *specific* peak as this can be virtually impossible in cases where there are many carbons with similar shifts and all you have to guide you is a mediocre prediction. What *is* important, is that the total number of peaks observed match the number of carbons in your proposed structure and that all their chemical shifts are at least plausible. We shall see presently that there are other tools available which can be used to yield unambiguous assignments in many cases. Consider the carbon spectrum of our familiar morpholine compound (Spectrum 9.1) which demonstrates this point. The chemical shifts of the two carbons in the morpholine ring next to oxygen are pretty close. So too are the carbons next to the nitrogen.

The first of these tools is the *d*istortionless *e*nhancement by *p*olarization *t*ransfer (DEPT) pulse sequence. There are a number of versions of this experiment which can be very useful for distinguishing the different types of carbons within a molecule. Of these, we have found the DEPT 135 sequence to be the most useful. In this experiment, the quaternary carbons are edited out of the spectrum altogether.



Spectrum 9.1 1-D ^{13}C spectrum of *the* morpholine compound.



Spectrum 9.2 1-D ^{13}C spectrum of *the* morpholine compound with DEPT-135 plotted above it.

Methyl and methine protons naturally phase at 180° relative to the methylene carbons and the spectra are usually plotted with methyls and methines positive. (Note that should you encounter a signal that you cannot confidently assign to either a methyl or methine carbon, the DEPT 90 sequence may well be of use as it differentiates these carbons – methines appear positive and methyls are edited out of the spectrum but this technique can be considered obsolete if you have access to any of the 2-D proton–carbon correlated experiments discussed in Section 9.2.)

This is demonstrated once more with our familiar morpholine compound in Spectrum 9.2. The DEPT sequences are of course, still relatively insensitive, though they are probably a little more sensitive than the standard 1-D, fully decoupled ^{13}C spectrum. We find it convenient, particularly with complex molecules, to combine the 1-D ^{13}C spectrum with the DEPT-135 spectrum, which is plotted above it at the same expansion, of course! This enables you to differentiate the different types of carbon in your spectrum at a glance.

9.2 2-D Proton–Carbon (Single Bond) Correlated Spectroscopy

The most powerful techniques of all are undoubtedly the 2-D proton–carbon experiments (*H*eteronuclear *M*ultiple *Q*uantum *C*oherence/*H*eteronuclear *S*ingle *Q*uantum *C*oherence, or HMQC/HSQC; and *H*eteronuclear *M*ultiple *B*ond *C*orrelation, or HMBC) as they provide an opportunity to dovetail proton and carbon NMR data directly.

Taking the HMQC and HSQC first, both these techniques establish one-bond correlations between the protons of a molecule and the carbons to which they are attached. Both techniques are considerably more sensitive than a 1-D ^{13}C spectrum, which might seem strange when you consider that the whole 2-D matrix is composed of a considerable number of ^{13}C spectra. The secret of the superior signal/noise performance of these methods lies in the fact that they are both ‘indirect detection’ techniques. This means that the carbon signals are detected (indirectly) by the transfer of their magnetisation to the much more sensitive protons! A typical data matrix for an HMQC or HSQC might be composed of 256

increments in the carbon domain, each of 2 k points in the proton domain. For a 5–10 mg sample of typical 200–400 molecular weight, reasonable signal/noise could be achieved with about 16–32 scans per increment in a 400 MHz instrument which means that you could easily achieve a good quality spectrum in about 1–2 h.

In terms of choosing between the two, bear in mind that the choice available on the spectrometer you use may well be limited by the hardware itself. Historically, the HMQC looked like the better bet at first, as it was more robust. The HSQC technique was fine – but the large number of 180° pulses in the sequence, require accurate pulse calibration if severe cumulative errors are to be avoided. In other words, if the probe tuning was not optimised, you could expect very poor signal/noise or even no signal at all. Probe tuning and matching is not the sort of thing you can reasonably expect the average walk-up user to get involved with and for this reason, HSQC was a nonstarter. HMQC was the way to go but times and hardware move on and nowadays, most modern instruments *can* deal with HSQC routinely without the need for any poking around under the magnet with a nonmagnetic tweaking stick!

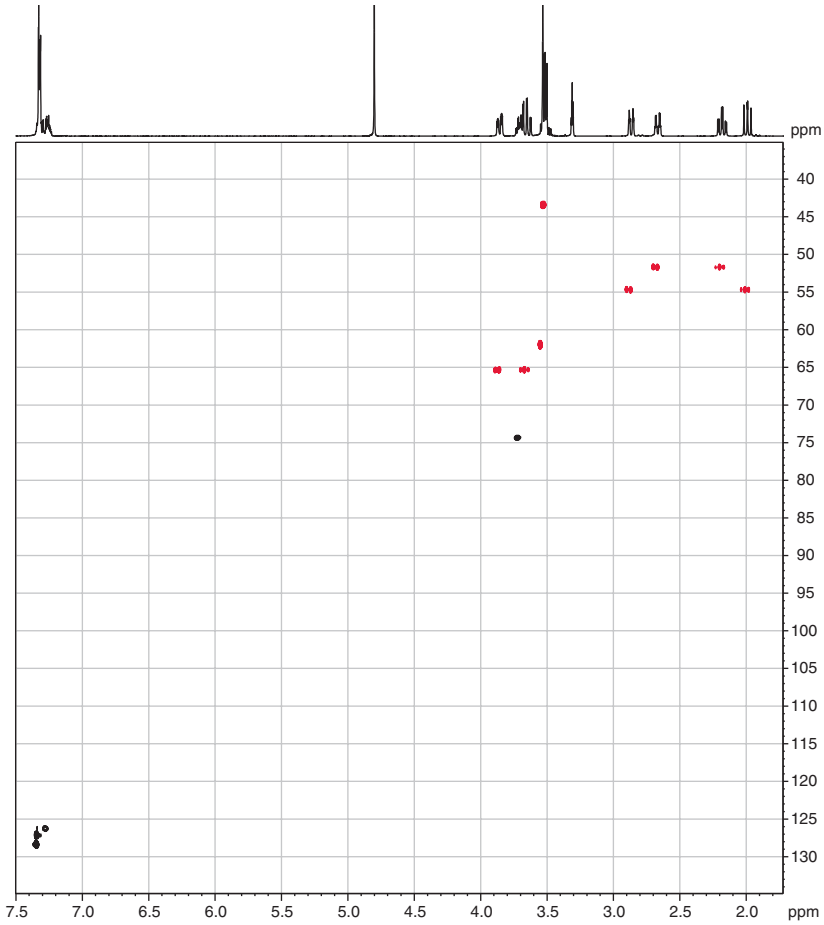
The two developments responsible for this are 'automatic probe tuning and matching', and 'adiabatic pulses.' Automatic probe tuning and matching enables optimal probe tuning to be achieved for every sample in an automated run, regardless of solvent. Adiabatic pulses solve the problem in a different way – by removing the need for accurate pulse calibration. Solving this problem enables us to routinely enjoy the benefits of HSQC over HMQC which include fewer spectral artefacts and slightly better resolution in the carbon domain.

So to sum up, if you have the luxury of modern equipment with all the go faster boxes at your disposal, go for HSQC. If you are stuck with an older instrument and you're not keen on grovelling around under the magnet, an HMQC is for you.

Our preferred experiment of this type is the so called 'DEPT-edited HSQC' which is both relatively artefact-free and sensitive. It also has one other major advantage up its sleeve. This experiment is not an 'absolute value' technique like most of the others, but it allows for discrimination between different types of carbons. Methyl and methine carbons give crosspeaks that are phased opposite to the methylene carbons and so the results are best plotted on a colour plotter which can portray this clearly by plotting positive and negative cross peaks in different colors.

A brief note on the phasing of the DEPT-edited HSQC spectra – because the technique is 'phase sensitive' (as opposed to 'absolute value'), these spectra require phasing. This is usually done under automation in walk-up systems and usually done well. (Note that phasing has to be performed in *both* dimensions) Sometimes, you may find a signal at one end of your spectrum which is clearly not phased, despite the fact that all the neighbouring signals appear perfectly phased. The likely reason for this will be that the size of the ^{1}H–^{13}C coupling for the carbon in question is abnormally large or small and there is not much that can be done about it. (Attempts to phase such signals correctly will result in the phasing of all the other signals suffering!) Instruments are typically set up to give a maximum sensitivity for couplings of around 145 Hz. This figure is a compromise between the generally smaller couplings found in alkyl systems and the slightly larger ones encountered in aryl systems. The larger the deviations of the one-bond ^{1}H–^{13}C couplings from this value, the greater will be the phasing inaccuracies encountered. Typical problem carbons are those of the nitrogen-bearing heterocycles where couplings approaching 200 Hz are quite common.

Interpreting HMQC/HSQC spectra is relatively straightforward as you can see from the HSQC spectrum of *the* morpholine compound (Spectrum 9.3). Basically, it's a case of lining up the proton signal with the contour, and reading off the ^{13}C chemical shift. The technique is extremely powerful – particularly when used in combination with HMBC as we'll see later. In examples like this one, it

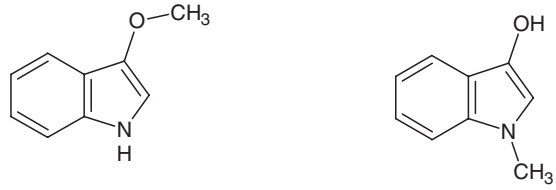


Spectrum 9.3 DEPT-edited HSQC of *the* morpholine compound.

enables you to identify geminal pairs of protons at a glance as you can see which protons are attached to the same carbons. As a philosophical aside, we should always be on our guard against using proton data to 'hammer' the ^{13}C data to fit. Although the 2-D techniques tie the data sets together, we must still interrogate them separately. In other words, if a correlation flags up an implausible shift in one domain or the other, the whole structure should be reconsidered.

HMQC/HSQC spectra can be extremely useful in resolving problems where there is a significant carbon chemical shift precedent that could be used to support one putative structure over another – for example, in dealing with cases of O- versus N- alkylation. Take for example the two methylated indoles in Structure 9.1.

How could you be certain of which site had alkylated? Any judgement based on proton chemical shift would be foolhardy as there would be little to choose between them. (Note that in molecules where the lone pair of electrons on a nitrogen are effectively 'removed' from the nitrogen for whatever reason – in this case, by donation into the aromatic ring - the nitrogen becomes more electron-deficient and thus more 'oxygen-like.' The chemical shift of alkyl groups substituted onto such nitrogens therefore become



Structure 9.1 Two methylated indoles.

very similar to those of analogous O-alkylated compounds and distinction between them on the basis of proton chemical shift becomes unreliable!) The methyl groups in both molecules might be expected to give Overhauser enhancements to their nearest aryl protons but in order to make use of this, you would have to be absolutely certain of the assignment of the aryl protons themselves! ^{13}C data would be unambiguous here. A methyl singlet with a carbon shift in the range, 35–45 ppm and you are looking at N-methylation. If the carbon shift of the methyl is in the region of 55–65 ppm, it's the oxygen that has been methylated.

If interpreting the single-bond correlation experiments is easy, the multiple bond experiment (HMBC) can be considerably less so . . .

9.3 2-D Proton–Carbon (Multiple Bond) Correlated Spectroscopy

Potentially even more useful, is the HMBC experiment. In this experiment, correlations are obtained between carbon atoms and protons that are separated by two and three bonds. Of course, the actual number of bonds separating the protons from the carbons is something of a red herring. What the spectrometer records are carbon-proton correlations for carbons that have protons couplings of specified magnitude. The sensitivity of the spectrometer to various sizes of proton-carbon coupling is controlled by one of the delays in the HMBC pulse sequence. This delay is selected on the basis of $1/2J$, where J is the coupling you wish to optimise for. A proton–carbon coupling of 10 Hz is a fairly typical value for the experiment, and thus the relevant delay would be set at $1/2 \times 10$, or 0.05 s. This means that the spectrometer sensitivity would be optimised for carbons with proton couplings of around 10 Hz. It does not mean that it will not detect carbons with smaller or larger proton couplings, just that the response shown will not be as intense.

In practise, 3-bond proton couplings tend to be nearer to this value than are the 2-bond couplings and for this reason, the HMBC sequence is usually more sensitive to 3-bond than to 2-bond correlations. This has of course to be viewed within the context of the overall signal/noise for the experiment. If the signal/noise for the whole experiment is less than excellent, it is quite possible for some 2-bond correlations to slip through the net altogether. If you are wondering why the value of $1/2J$ is not used to even-up the response to 2- and 3-bond correlations, there are two important factors to consider. If this value was optimised for, say, 5 Hz proton couplings, then the spectra we would obtain would be further greatly complicated by 4-bond couplings which would start to come through, since the J values for some 4-bond couplings are comparable with 2-bond values. Furthermore, as the value for J gets smaller, so the optimal delay required gets longer so that more and more signal gets lost to relaxation prior to acquisition and overall sensitivity for the experiment is lost. This incidentally partially explains why the technique is not as sensitive as HSQC in the first place (1-bond proton–carbon couplings are typically around 150 Hz, so the delay is extremely short and very little signal is lost.)

So, putting it bluntly, HMBC spectra are more difficult to unpick because there will inevitably be far more correlations recorded than in the corresponding HMQC/HSQC. The problems do not end there, however. For example, it is not immediately obvious by inspection, which are the 2-bond and which are the 3-bond correlations. This has to be reasoned out within the context of whatever molecule you are dealing with. Furthermore, whilst most 4-bond proton–carbon couplings are less than 2 Hz, some are not, allowing unwanted 4-bond correlations we've mentioned through into our spectra, even when we've optimised for 10 Hz couplings! This can be a problem particularly in the case of aromatic, heterocyclic and conjugated compounds where signal to noise is good. These need to be identified for what they are as soon as possible or they will cause confusion!

Unfortunately, the complexity does not stop there. One-bond couplings can also come through in the HMBC experiment, despite filters used to block them. This can be seen in our HMBC spectrum of *the* morpholine compound (Spectrum 9.4) with reference to one of the aromatic signals at 126 ppm. One-bond correlations are characterised by a pair of contours that are symmetrically displayed on either side of the 1-D (proton) projection they relate to, the separation between them giving the proton–carbon coupling, of course. Whilst this is generally not a problem for obvious isolated singlets, it certainly can be a problem in the crowded aromatic region of the spectrum where chemical shifts are relatively tightly packed in both proton and carbon dimensions. Problems can arise where 1-bond contours fall in positions where they line up exactly with peaks from the 1-D proton projection, giving rise to potentially very confusing bogus 'correlations.'

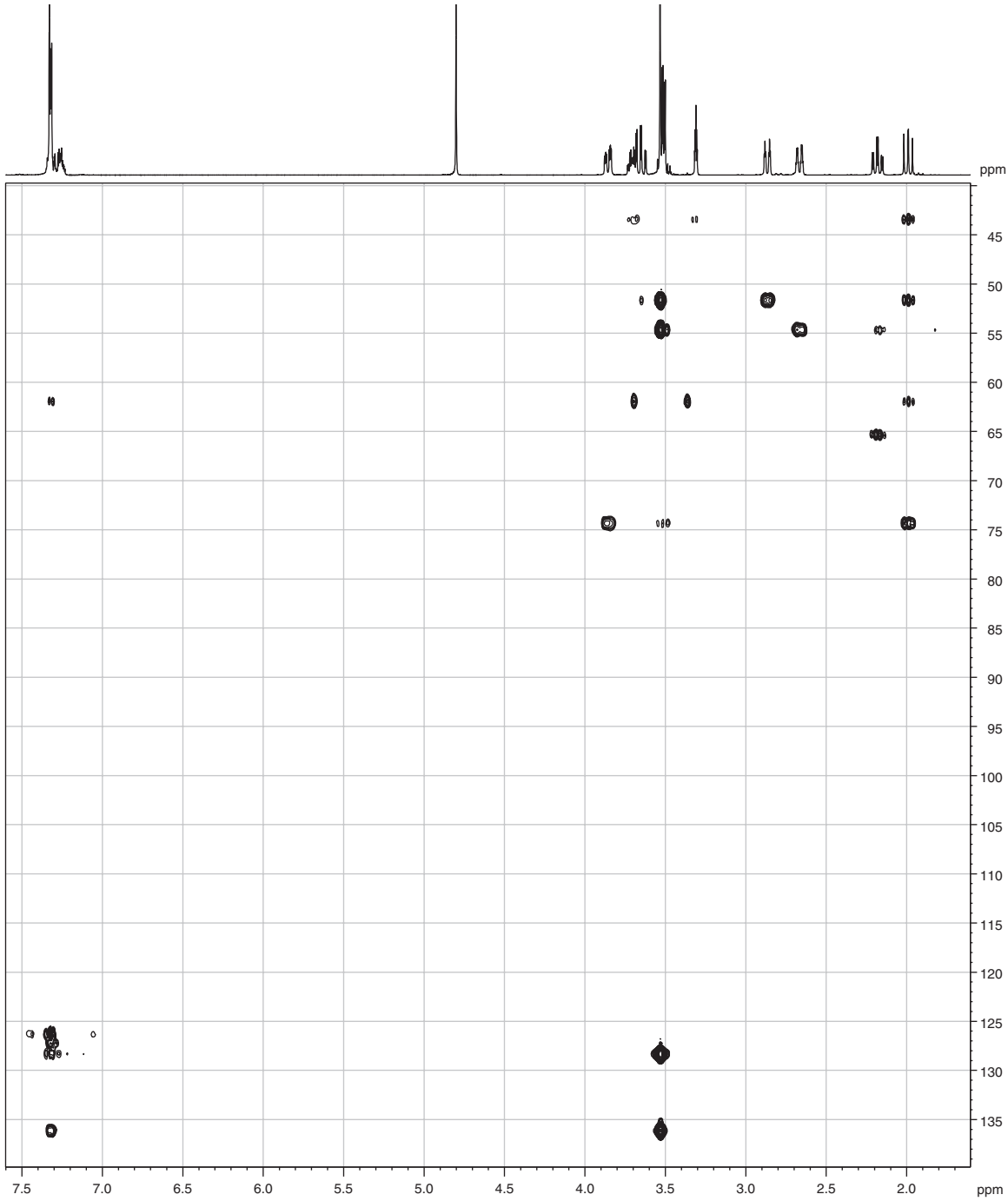
Another feature that is worth being aware of is the so-called 'auto-correlation' phenomenon. These can be observed in molecules which contain moieties such as -N-dimethyl or isopropyl groups. Such groups can give the initially confusing arrangement of three contours in a row. In such cases, the two outer contours are the 1-bond correlation, and the centre correlation, the genuine 3-bond HMBC correlation from the protons of one of the methyl groups to the carbon of the *other* methyl group. Once this pattern has been noted, you will recognise it easily and even make use of it as a quick identifier for these groups.

If all these cautionary notes make the technique sound like a complex nightmare, we're not done just yet . . . Just as an unwanted 4-bond correlation can come through to muddy the water and a 2-bond coupling can fail to materialize, so too can a 3-bond coupling fail to register for exactly the same reason – the size of the proton–carbon coupling may be too far from the optimised value to give a sufficient response to be recorded. There can be two possible reasons for this. First, it can just be a question of local electron distribution giving rise to an abnormal value for the 3-bond proton–carbon coupling. One that springs to mind is the lack of a correlation often observed between the 3′ proton and the 4′ carbon in indoles (Structure 9.2).

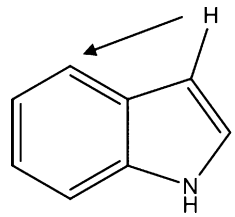
Another reason for not observing expected 3-bond couplings relates to the Karplus equation which we discussed at length in Section 6.6.5. Just as the size of proton–proton vicinal couplings are dependant on the dihedral angle between them, so too are proton–carbon couplings. You can come across molecules where the relevant angle suppresses the coupling and hence a 3-bond proton–carbon coupling can fail to show.

Our advice is that if it is vital to establish such a connectivity, then re-run the experiment optimising for a smaller coupling value (e.g., 5 instead of 10 Hz). Yes, you will take a hit on signal/noise and spectral complexity may well increase as 4-bond couplings start to come through but if you are chasing down one specific coupling, then these things don't really matter.

HMBC experiments are not limited to proton–carbon interaction. With suitable hardware, it is possible to acquire ^{1}H–^{15}N spectra which can be extremely useful for confirming the identity of nitrogen-containing heterocyclic compounds. The sensitivity of this technique is very low, probably only about



Spectrum 9.4 HMBC of *the* morpholine compound.



Structure 9.2 Expected 3-bond correlation often not observed.

one-tenth of the ^{1}H–^{13}C technique but sometimes it can provide that extra, vital piece of the jigsaw. We have provided some basic but useful ^{15}N shift data in Chapter 11.

After digesting this information and noting the many benefits of the 2-D proton–carbon techniques, (providing the pitfalls and complexity of the HMBC technique haven't put you off the idea!) you might be wondering why anybody would ever bother acquiring a simple 1-D ^{13}C spectrum any more. Well, there are two good reasons that spring to mind. First, it is quite possible to encounter a molecule with no protons within a 3-bond range of one or more of its carbon atoms. Such carbons will be 'invisible' to the HMBC technique and will only be visible in a 1-D spectrum.

Second, the resolution achieved in a 2-D experiment, particularly in the carbon domain is nowhere near as good as that in a 1-D spectrum. You might remember that we recommended a typical data matrix size of 2 k (proton) × 256 (carbon). There are two persuasive reasons for limiting the size of the data matrix you acquire – the time taken to acquire it and the shear size of the thing when you have acquired it! This data is generally artificially enhanced by linear prediction and zero-filling, but even so, this is at best equivalent to 2 k in the carbon domain. This is in stark contrast to the 32 or even 64 k of data points that a 1-D ^{13}C would typically be acquired into. For this reason, it is quite possible to encounter molecules with carbons that have very close chemical shifts which do not resolve in the 2-D spectra but will resolve in the 1-D spectrum. So the 1-D experiment still has its place.

9.4 Piecing It All Together

As we've mentioned before, the interpretation of NMR spectra is often made complex by the sheer quantity of information that you are confronted with. This is every bit as true for carbon NMR as it is for proton and when you combine the two, that huge pile of information just gets bigger. . . More important still then that you approach the pile in a logical, methodical manner.

Once your problem takes on a ^{13}C dimension, you are of course, obligated to examine the ^{13}C data with the same level of dispassionate scrutiny that you apply to the proton data. Chemical shifts cannot be fudged and unexpected peaks cannot be glossed over. You have to be able to account for everything you see to have confidence in your product.

We will assume that you have already been through the proton data with a fine-toothed comb and found it wanting in some way, or insufficient to give the level of reassurance that you require. So turning to carbon, a 1-D ^{13}C spectrum of adequate signal/noise would be a luxury, though not an absolute necessity. We'll assume you have one. Strike out the carbons for any known solvents etc. and then count the total number of carbon peaks in the spectrum. Do they match the requirements for your proposed structure? (Don't forget that a para-di-substituted aromatic ring gives four peaks for its six carbons on

Structure 9.3 Our naphthalene problem.

account of its symmetry.) Note also that knowing with certainty, the number of carbons in a structure can be very helpful in narrowing the search for a molecular formula by mass spectroscopy (accurate mass).

If you have a DEPT 135 spectrum, now is the time to use it. Categorise all peaks to one of the following types: quaternaries and carbonyls, methines, methylenes and methyls. Now get hold of plausible prediction data for the shifts of your proposed structure. Use HMQC/HSQC spectra to assign the proton-bearing carbons and if satisfactory, move on to assign all the quaternaries and carbonyls by using the HMBC spectrum. Do all the long-range connectivities from the HMBC make sense? Does it all hang together?

As with proton interpretation, this must be considered an iterative process. Try to shoot your proposed structure down. Don't be afraid to tear it up at any stage and start again if some glaring problem becomes apparent. Resist temptation – don't hammer the square peg into a round hole! This is why we do spectroscopy in the first place. If it crashes and burns then it was wrong so shed no tears. If it survives then it's got a good chance of being a winner. Finally, go back again and check that there is no mismatch between any carbon data and any supplementary proton data, e.g., NOE experiments.

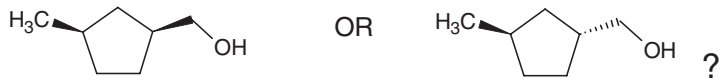
When it *all* sits happily or can at least be explained, the job is done as well as it can be. Not before.

9.5 Choosing the Right Tool

If you have successfully read this far, it might have occurred to you that some problems could well be solved by either an NOE-based approach, or by an HMBC approach and you might be wondering which technique would be preferable under such circumstances. In truth, there may not be a right or wrong answer to this question and each problem should be considered on its merits. The selection of experiment may even be down to personal preference or to the hardware available to you. Questions of positional isomerism can often be resolved by either approach. We have seen how our naphthalene problem could be resolved by using an NOE technique (Structure 9.3).

This problem could also have been resolved by an HMBC approach – you would expect to see a correlation from the protons of either the -CH_2-, or the -CH_3 to one of the quaternary carbons at the junction of the two rings. This same carbon should also show correlations to at least two, and ideally three of the protons on the unsubstituted aromatic ring and one of the protons on the substituted ring.

It is when questions of stereochemistry arise that the NOE techniques come into their own. For example, consider the compounds in Structure 9.4. There would be no chance of resolving these two structures by HMBC, but an NOE technique might well prove successful. (The methyl group would be expected to give an enhancement to either of the -C**H$_2$**-OH protons in one isomer or to the >C**H**-CH_2OH in the other, depending on which face of the ring the two substituents lie relative to each other.)



Structure 9.4 A question of stereochemistry.

As in the case of all NMR problem-solving, the issue is always one of using the most appropriate tool for the job. The two techniques are in no way mutually exclusive. Too much data is not a bad thing if the instrument time is available but taking a chance on insufficient data can be a costly mistake in the long run.

Tables 9.1–9.7 give a useful guide to ^{13}C chemical shifts.

Table 9.1 ^{13}C chemical shifts of some common heterocyclic and fused aryl compounds.

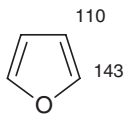
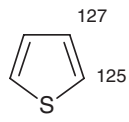
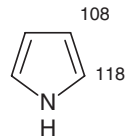
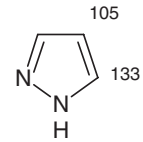
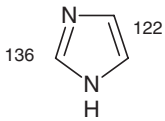
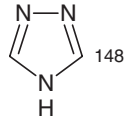
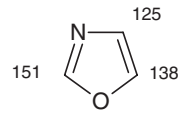
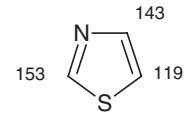
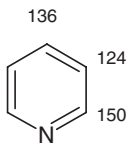
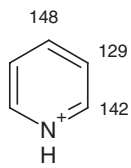
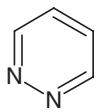
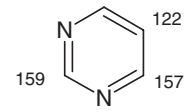
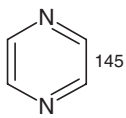
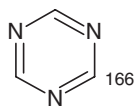
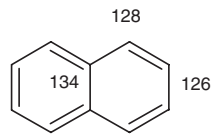
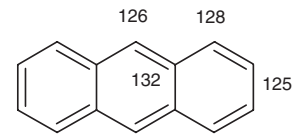
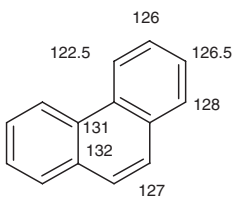
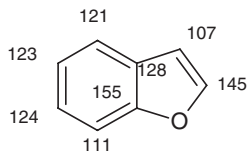
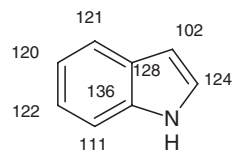
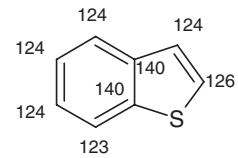
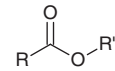
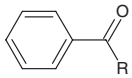
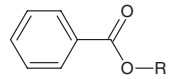
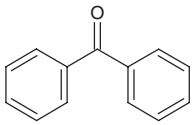
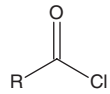
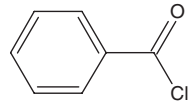
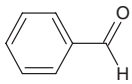
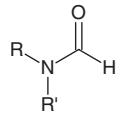
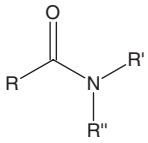
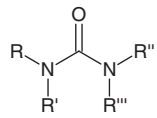
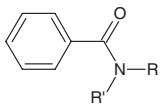
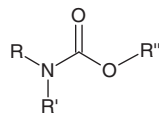
			
			
			
			
			

Table 9.2 ^{13}C chemical shifts of some common carbonyl functions.

Type of carbonyl	Typical shift	Type of carbonyl	Typical shift
	205–210		170–180
	195–200		165–170
	~195		170–175
	196–202		~168
	190–195		160–165
	167–173		160–165
	165–172		153–160

Note: thio-carbonyl analogues generally absorb at considerably lower field – sometimes by as much as 40 ppm.

Table 9.3 ^{13}C chemical shifts of some CN functions.

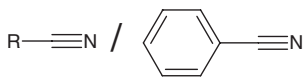
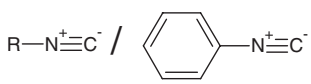
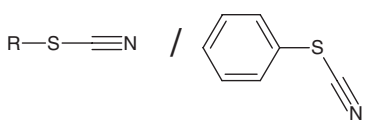
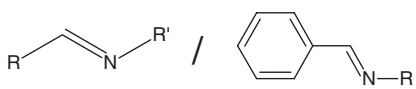
Type of CN function	Typical shift
	115–120
	156–166
	110–115
	155–170

Table 9.4 Data for the estimation of aryl ^{13}C chemical shifts.

Substituent X	C1	C2	C3	C4
-H	0.0	0.0	0.0	0.0
-CH_3	9.2	0.7	0	–3.0
-CH_2-any (approx.)	2–12	–2 (+)2	–2 (+)2	–2 (+)2
-CH=CH_2	9	–2	0	–0.8
-C&ΞC-R (approx.)	–6	4	0	0
-Phenyl	8	–1	0.5	–1
-F	34	–13	1.5	–4
-Cl	5	0	1	–2
-Br	–5	3	2	–1
-I	–31	9	2	–1
-OH/-OR (approx.)	30	–13	1	–7.5
-O-phenyl	28	–11	0	–7
-$OCOCH_3$	22	–7	0	–3
-NH_2/-NR_2 (approx.)	17	–14	1	–10
-NH_3^+/-NR_2H^+ (approx.)	3	–5	2	1
-NO_2	20	–5	1	6
-CN	–16	3.5	1	4
-NC	–2	–2	1	1
-SH/-SR (approx.)	7	0	0	–3.5
-S-phenyl	7	2.5	0.5	–1.5
-SOR	18	–5	1	2
-SO_2R	12	–1	1	5
-SO_2Cl	16	–2	1	7
-SO_3H	15	–2	1	4
-SO_2NH_2	11	–3	0	3
-CHO	8	1	0.5	6
-COR	9	0	0	4
-COOH/-COOR (approx.)	2	1.5	0	4.5
-$CONH_2$/-$CONR_2$ (approx.)	5.5	–1	0	2

Note: substitute values relative to benzene (128 ppm) as follows: chemical shift of C1–C4 = 128 + additive value for C1–C4 from table above.

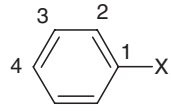


Table 9.5 Data for the estimation of alkene ^{13}C chemical shifts.

Substituent X	C1	C2	Substituent X	C1	C2
-H	0	0	-$OCOCH_3$	18	–27
-alkyl	10–20	–4 to –12	-NR_2	28	–32
-$CH{=}CH_2$	14	–7	-N^+R_3	20	–11
-CH&ΞCH	–6	6	-NO_2	22	–1
-Phenyl	12.5	–11	-CN	–15	14
-F	25	–34	-NC	–4	–3
-Cl	3	–6	-SR	9	–13
-Br	–9	–1	-CHO	15	15
-I	–38	7	-COR	14	5
-OR	28	–37	-COOR	5	10

Note: substitute values relative to ethene (123 ppm) as follows: chemical shift of C1 and C2 = 123 + additive value for C1/C2 from Table 9.4.

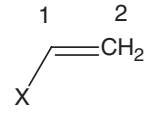


Table 9.6 ^{13}C chemical shifts for alkynes.

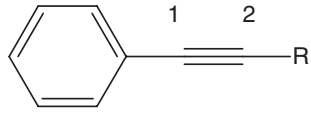
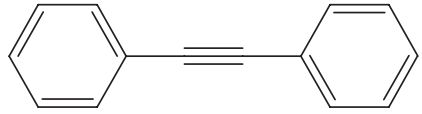
Type of Alkyne	Typical shift
	75–80
	~85(C1) ~80(C2)
	~90

Table 9.7 Data for the estimation of alkyl ^{13}C chemical shifts.

Substituent X	α	β	γ
-H	0	0	0
-alkyl	9	9	–3
-C=C-R_2	20	7	–2
-C≡C-R	4	6	–3
-Phenyl	22	9	–3
-F	70	8	–7
-Cl	31	10	–5
-Br	19	11	–4
-I	–7	11	–2
-OR	49	10	–6
-OCOR	57	7	–6
-NR_2	28	11	–5
-NR^+_3	28	6	–6
-NO_2	62	3	–5
-CN	3	2	–3
-SR	11	11	–4
-SO_2R	30	7	–4
-CHO	30	–1	–3
-COR	23	3	–3
-COOR	20	2	–3
-$CONR_2$	22	3	–3
-COCl	33	8	–3

Note: this table gives only very approximate shift estimates and is intended for use as a rough guide only. The presence of highly branched substituents and atoms bearing multiple halogens, multiple oxygen atoms etc. can cause even more serious deviations rendering the table of questionable value under such circumstances. It is used by summing the substituent effects at each carbon relative to methane (–2.3 ppm). For example, the shift of carbon 'a' below would be estimated as: $-2.3 + 49 + 9 + 9 = 65$ ppm (approx.). Actual value 63ppm.