11

Some of the Other Nuclei

As we have already pointed out in the section dealing with heteronuclear coupling that it is not always necessary to confirm the presence of a particular hetero atom by acquiring the NMR spectrum of that nucleus. More often than not, the hetero atom will have a clear signature in the proton or carbon spectrum. Fluorine and phosphorus are both examples of nuclei that couple to protons over two, three, four and even more bonds.

If you have suitable hardware, any of the 60+ NMR-sensitive nuclei can be observed, though some are more suitable than others and in terms of organic synthesis, many are largely irrelevant. The most suitable nuclei for observation have three characteristics in common – high natural abundance (ensuring good sensitivity), a spin quantum number of $^1/_2$ (ensuring that an uncoupled signal will appear as a singlet) and no quadrupole (ensuring that line shape will be naturally sharp). Both fluorine and phosphorus tick all three boxes, making them two of the more important 'also rans.'

11.1 Fluorine

There are cases where coupling from the hetero atom to neighbouring protons is not observed for some reason. Consider the examples in Structure 11.1.

In terms of proton NMR, these two compounds would give remarkably similar spectra. The solitary fluorine on the 1,4 di-substituted ring would certainly couple to the protons both ortho- and meta- to it but the fluorines of the -CF$_3$ group would not show any discernable coupling to the ring protons and neither would the fluorines of the fully substituted ring. Yes, you could certainly discriminate between the two by ^{13}C NMR but if you only had a mg. of each, you would be really struggling for sufficient signal/noise to observe the key carbons – even if you had a top of the range spectrometer at your disposal. By ^{19}F NMR, however, the distinction would be easily made.

There are a number of features regarding ^{19}F NMR that are worthy of special note. Firstly, spectra may be acquired that are either proton-decoupled, or un-decoupled. We recommend acquiring both if you can. A comparison between the two can yield valuable information regarding neighbouring protons and other fluorines. Secondly, the range over which fluorine resonances occur is very large indeed and a sweep width of about 400 ppm (–300 to +100 relative to CFCl$_3$) is required to capture all the organofluorine resonances that can be expected. When such a large sweep width is plotted on a single sheet, it effectively
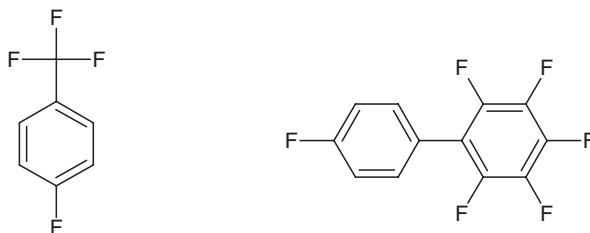
Structure 11.1   Fluorinated compounds.

compresses any couplings, making them almost unnoticeable. For this reason, expansion of peaks is recommended in coupled spectra.

Another consequence of the large sweep width needed for ^{19}F acquisition is that the electronics of the instrument are pushed to the limit: it is difficult to generate uniform r.f. irradiation over such a large frequency range and for this reason it may be necessary to acquire spectra in different spectral ranges, depending on the expected fluorine environment. This is particularly so in the case of high-field (>400 MHz) spectrometers.

There seems to be no universal reference standard in ^{19}F NMR as there is in proton NMR and this can cause confusion. Chemical shifts may be quoted relative to $CFCl_3$ or to CF_3COOH and there maybe a

Table 11.1 ^{19}F chemical shifts of some typical fluorinated compounds (relative to $CFCl_3 = 0$ ppm).

few other standards in use as well for all we know. If you are following some literature data, always check which reference standard was used. In Table 11.1, we try to give a brief overview of ^{19}F chemical shifts in some of the more commonly encountered fluorine environments. The tables we quote are relative to CF_3Cl where the chemical shift of the fluorine is set at 0 ppm. Note that all shifts have negative values when using this standard.

11.2 Phosphorus

^{31}P is another nucleus which can be useful to the organic chemist. Many of the comments we have made about ^{19}F are also relevant to ^{31}P. Once again, compounds containing phosphorus are likely to show a clear ^{31}P 'signature' in their proton and carbon spectra and once again the chemical shift range for this nucleus is extremely large – as you might imagine, given the variable oxidation state of the element – typically from –200 to +230 ppm.

The reference of choice for this nucleus is either H_3PO_4 or $(CH_3O)_3PO$. When H_3PO_4 is chosen, it is generally used as an external reference (80–85 % solution) on account of its high acidity. The number and variety of possible organophosphorus compounds combined with the large chemical shift range over which the nucleus resonates make the inclusion of any useful NMR data somewhat problematic. We would refer you to more specialised texts or articles and also to some useful web sites offering some enlightenment on the subject.
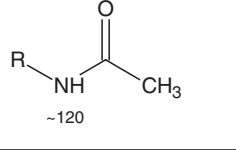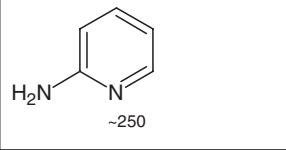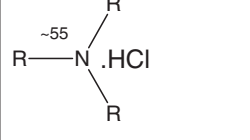
11.3 Nitrogen
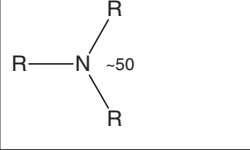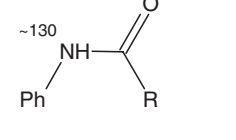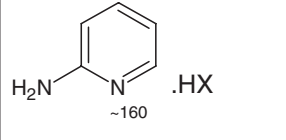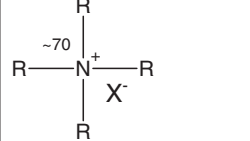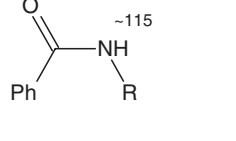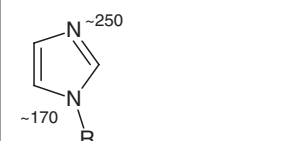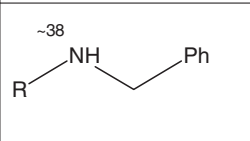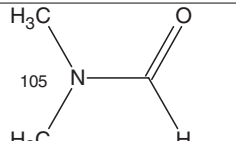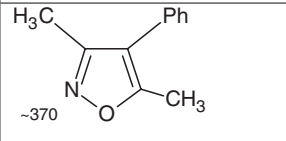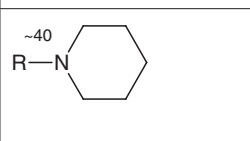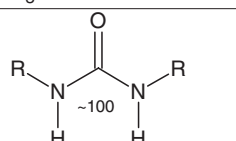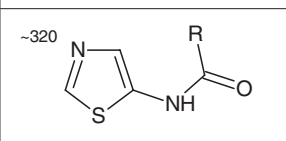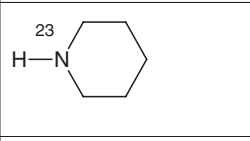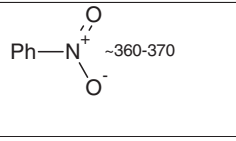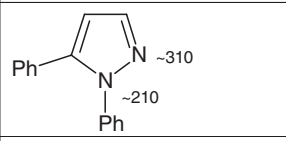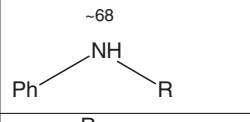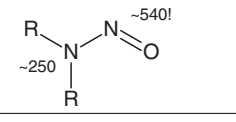
The ^{15}N nucleus is potentially extremely useful, particularly when dealing with nitrogen-rich hetero-cycles but as its natural abundance is so low (0.36 %) it is a nucleus that you would never chose to observe directly without a very good reason! It can really come into its own via the proton–nitrogen HMBC experiment that we have already mentioned. As the number of nitrogen atoms in a small organic molecule is likely to be relatively low – seldom more than half a dozen – in a sense, the ability to accurately predict nitrogen chemical shifts is perhaps a little less pivotal than you might 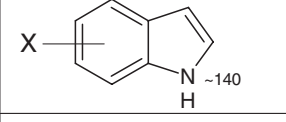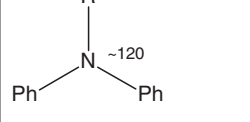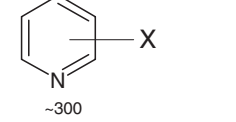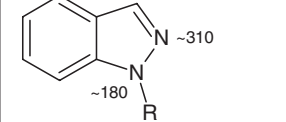think. Observed ^{1}H–^{15}N correlations should define which nitrogen is which in an unknown compound. The real power of the technique lies in using it to establish connectivities in unknown compounds to settle stereochemical issues. Nevertheless, we have included some useful chemical shift information in Table 11.2
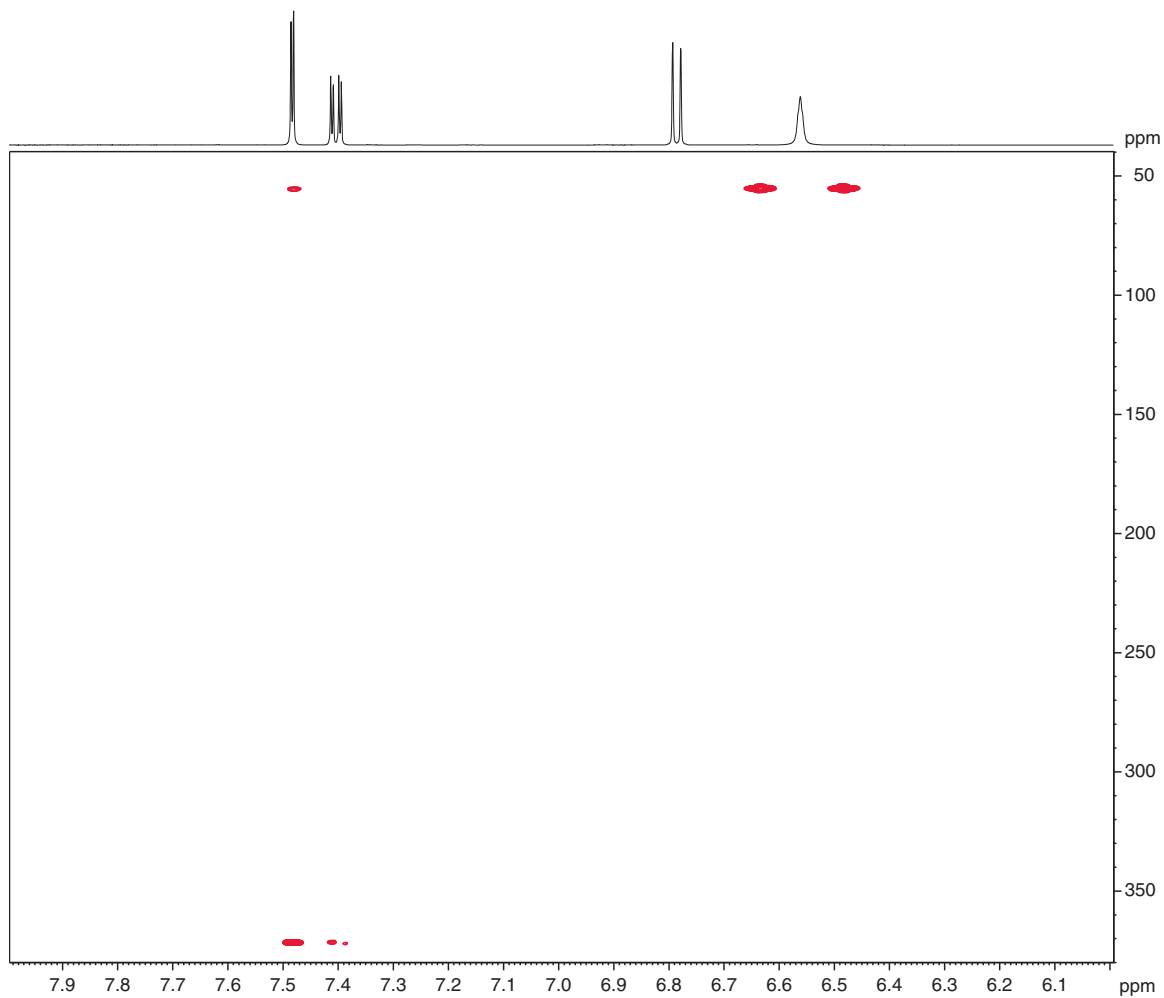
Spectrum 11.1, which was recorded on a 600 MHz instrument fitted with a cryoprobe, shows an example of a ^{15}N HMBC. The compound in question is of the type shown in Structure 11.2.

The chemical shift of the amine nitrogen is 55 ppm and shows a clear 3-bond correlation to the aromatic proton giving a fine doublet at 7.49 ppm. There is also a strong, and in this case, very useful, 1-bond correlation to this nitrogen from the amine proton itself. Note that whether or not you see 1-bond correlations depends largely on how broad the -NH signal is in the proton domain. The sharper the -NH, the more likely you are to see them. As with ^{13}C HMBC, 2-bond correlations can sometimes be quite weak and that is so in this case as there is no obvious correlation to be seen from the methylene protons adjacent to the amine.
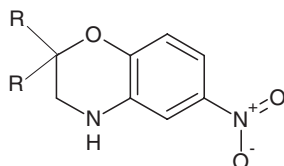
The nitrogen of the nitro group absorbs at 371 ppm and shows 3-bond correlations from both the aromatic protons flanking the group (7.49 and 7.41 ppm). The common correlation from the former signal to both nitrogens confirms the regiochemistry of the structure.

Table 11.2 ^{15}N chemical shifts of some common nitrogen-bearing compounds (relative to $NH_3 = 0\,ppm$).

R—N(R)(R) ~50	R-NH-C(=O)-CH$_3$ ~120	H$_2$N— pyridine-N ~250
R—N(R)(R).HCl ~55	~130 Ph-NH-C(=O)-R	H$_2$N— pyridine-N .HX ~160
R—N$^+$(R)(R)(R) X$^-$ ~70	Ph-C(=O)-NH-R ~115	imidazole N ~250, ~170 R
R-NH-CH$_2$-Ph ~38	(H$_3$C)(H$_3$C)N-C(=O)-H 105	isoxazole H$_3$C, Ph, CH$_3$ ~370
R—N piperidine ~40	R-N(H)-C(=O)-N(H)-R ~100	thiazole ~320, NH-C(=O)-R
H—N piperidine 23	Ph—N$^+$(=O)O$^-$ ~360-370	pyrazole Ph- N ~310, N ~210 Ph
Ph-NH-R ~68	R-N(R)-N=O ~540! ~250	indole X— N—H ~140
Ph-N(R)-Ph ~120	pyridine—X ~300	indazole N ~310, N ~180 R

Spectrum 11.1 ^{15}N HMBC.

Structure 11.2   Example of a molecule examined by ^{15}N HMBC.