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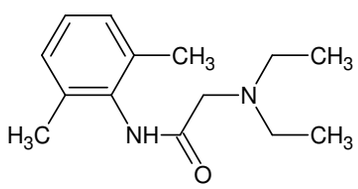
Lidocaine

Example of benchtop NMR on small organic molecules

Lidocaine ($C_{14}H_{22}N_2O$) is a common local anaesthetic and antiarrhythmic drug. It is used topically to relieve itching, burning and pain from skin inflammations. As anaesthetic it is injected for dental or other minor surgery.



The ^{1}H NMR spectrum of 200 mM lidocaine in $CDCl_3$ is shown in Figure 1. The spectrum was recorded in a single scan, taking 7 seconds to acquire. All peaks and ^{1}H-^{1}H couplings are well resolved, and can be assigned to the molecular structure.

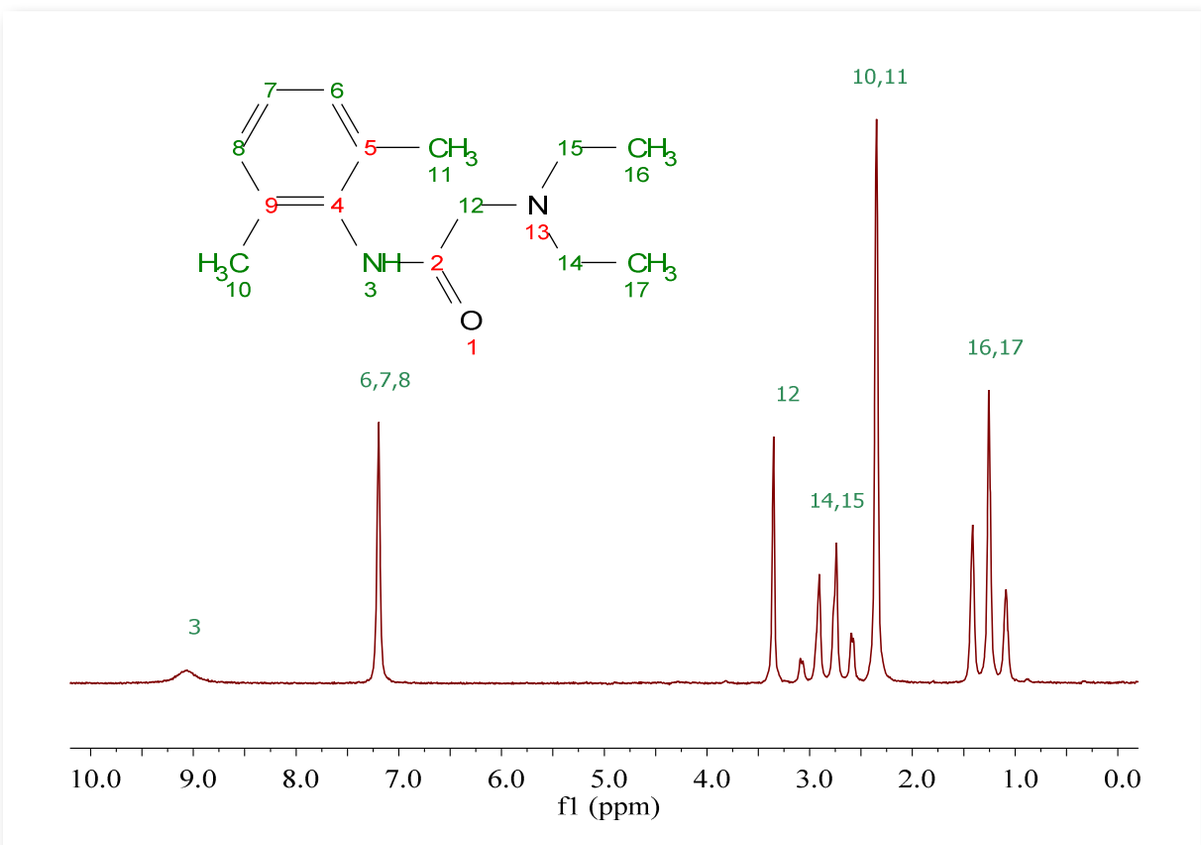


Figure 1: Proton NMR spectrum of 200 mM lidocaine in $CDCl_3$.

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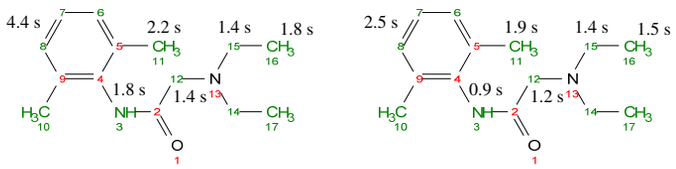
^{1}H NMR RELAXATION

The relaxation time measurements are shown in Figures 2 - 4. Note that the relaxation times are longest for the CH protons and shortest for the CH_2 protons. The amplitude of the first data point scales with the number of protons for the corresponding peak.



Proton T_1 (left) and T_2 (right) relaxation time for each proton position of the molecule

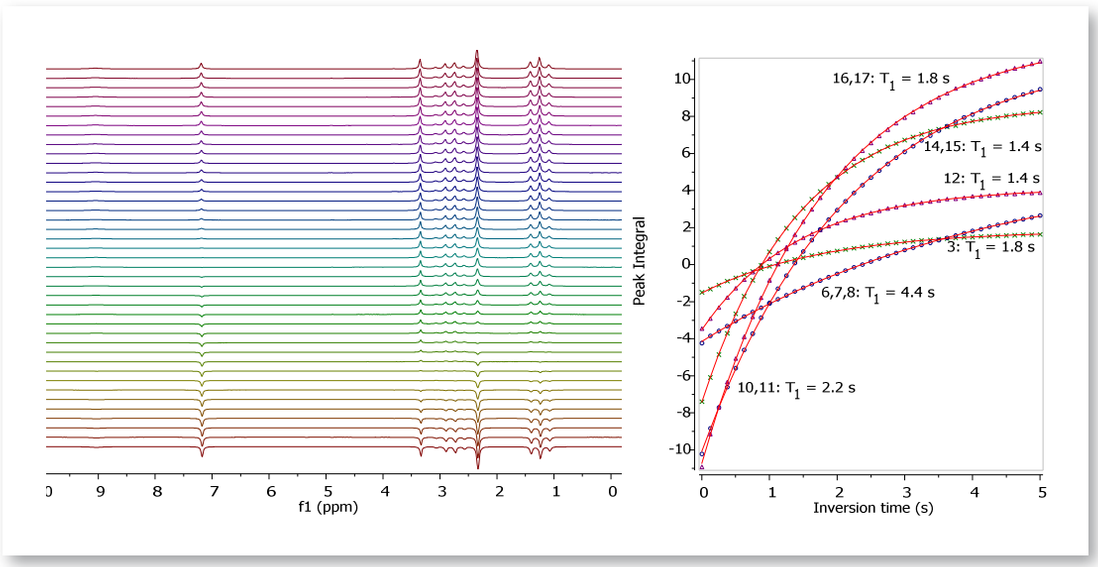


Figure 2: Proton T_1 relaxation time measurement of 200 mM lidocaine in $CDCl_3$.

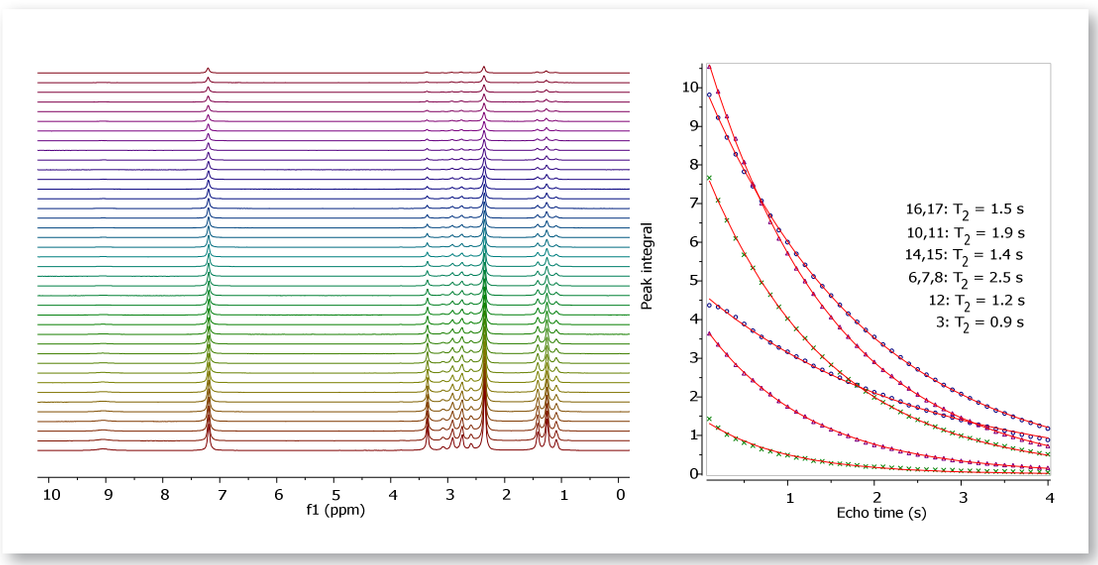
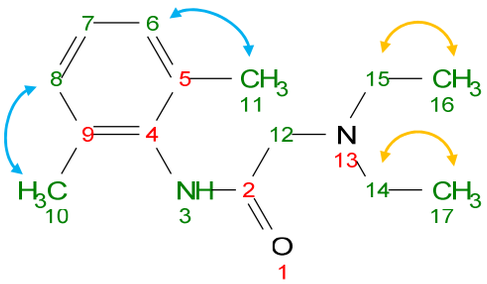


Figure 3: Proton T_2 relaxation time measurement of 200 mM lidocaine in $CDCl_3$.

2D COSY

The 2D COSY spectrum is shown in Figure 4. It clearly shows two spin systems (6,7,8) to (10,11) and (14,15) to (16,17). For example, the methyl groups at positions 16 an 17 only couple to the ethylene groups at positions 14 and 15, whilst the methyl groups at positions 10 and 11 couple to aromatic protons at positions 6 and 8. There is no coupling of positions (6,7,8) to either (14,15) or (16,17).



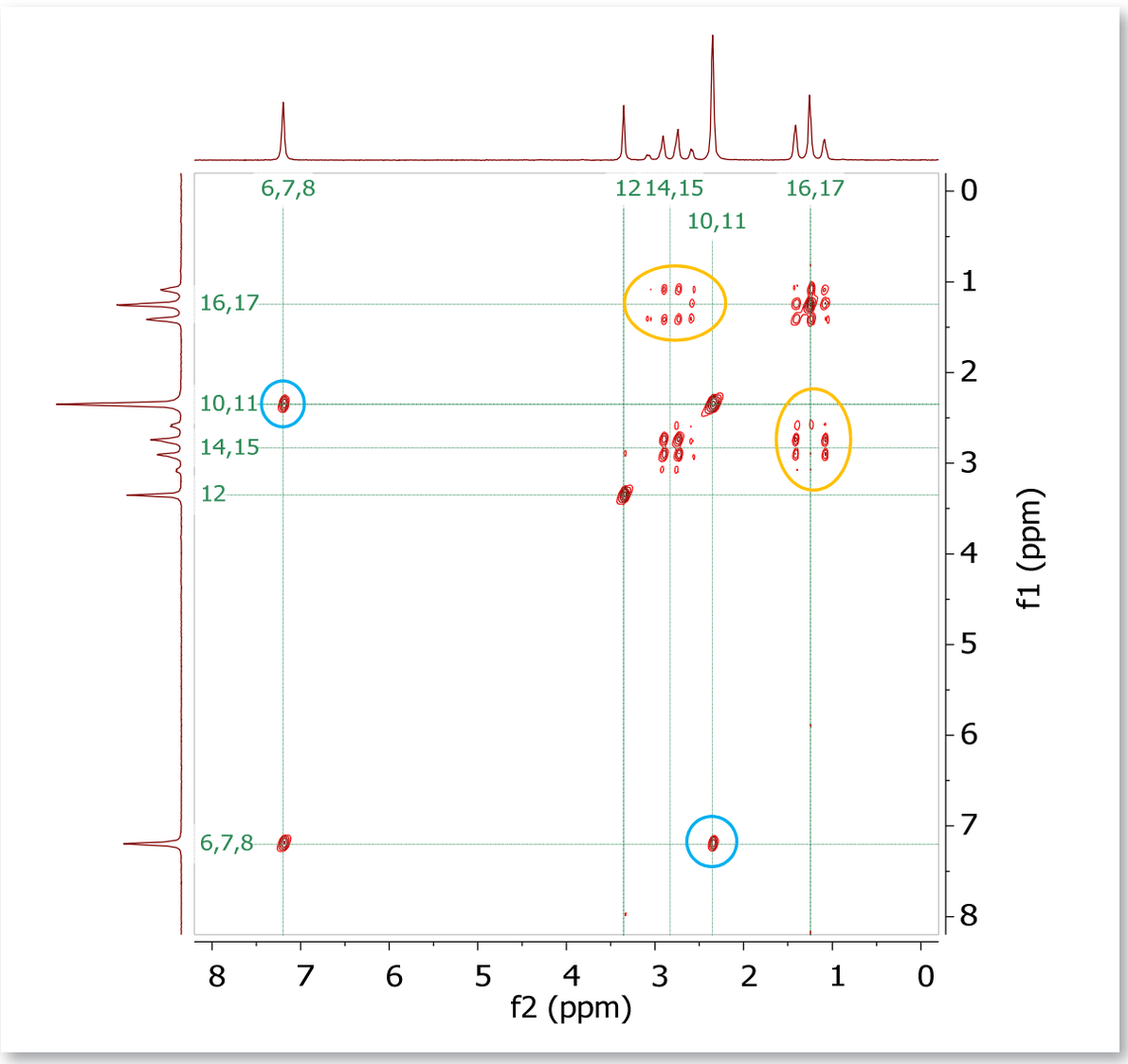


Figure 4: COSY spectrum of 200 mM lidocaine in $CDCl_3$. The cross-peaks and corresponding exchanging protons are marked by colour-coded ellipses and arrows.

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2D HOMONUCLEAR J-RESOLVED SPECTROSCOPY

In the 2D homonuclear *j*-resolved spectrum the chemical shift is along the direct (f2) direction and the effects of proton-proton coupling along the indirect (f1) dimension. This allows the full assignment of chemical shifts of overlapping multiplets, and can allow otherwise unresolved couplings to be measured. The projection along the f1 dimension yields a “decoupled” 1D proton spectrum. Figure 5 shows the 2D homonuclear *j*-resolved spectrum of lidocaine, along with the 1D proton spectrum as blue line. The vertical projection shows how the multiplets collapse into a single peak, which greatly simplifies the 1D spectrum. Vertical traces through the peaks in the 2D spectrum yield the peak multiplicities, as shown by the green lines in Figure 5, and enables the measurement of proton-proton coupling frequencies. By comparing the coupling frequencies between different peaks, it is possible to extract information about which peaks are coupled to each other.
For example, both the triplet at 1.23ppm and the quartet at 2.80 ppm have a splitting of 7.21 Hz, suggesting that these groups are coupled to each other. The size of the coupling frequency provides information about the coupling strength.
For example, the small splitting of 1.26 Hz of the peak at 2.35 ppm is probably due to the long range coupling to aromatic protons at positions 6 and 8. These couplings confirm the findings of the COSY experiment in Figure 4.

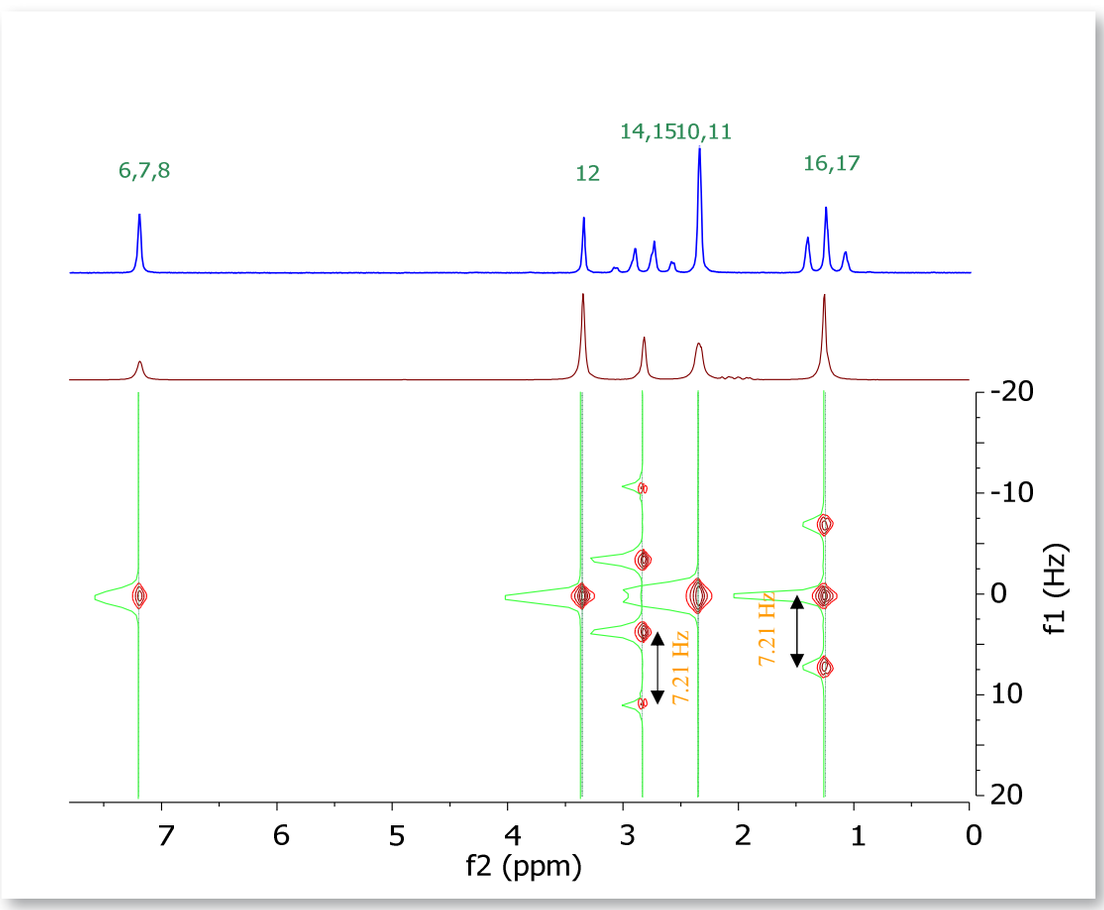
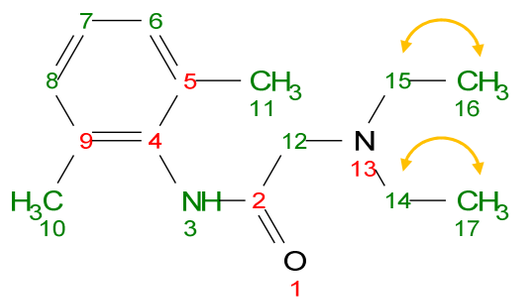


Figure 5: Homonuclear *j*-resolved spectrum of 200 mM lidocaine in $CDCl_3$. The multiplet splitting frequencies for different couplings are colour-coded as in Figure 4.

2D HOMONUCLEAR J-RESOLVED SPECTROSCOPY

One unusual and often neglected feature of this experiment is that second order coupling effects show up in the indirect (f1) direction as extra peaks equidistant from the coupling partners well removed from the zero frequency in the indirect dimension. These peaks are often neglected as artefacts, but provide direct evidence of second order coupling partners. These extra peaks and coupling partners are marked by colour-coded ellipses and arrows in Figure 6.

Note that this spectrum is based on the same data as Figure 5, only the scaling has changed.



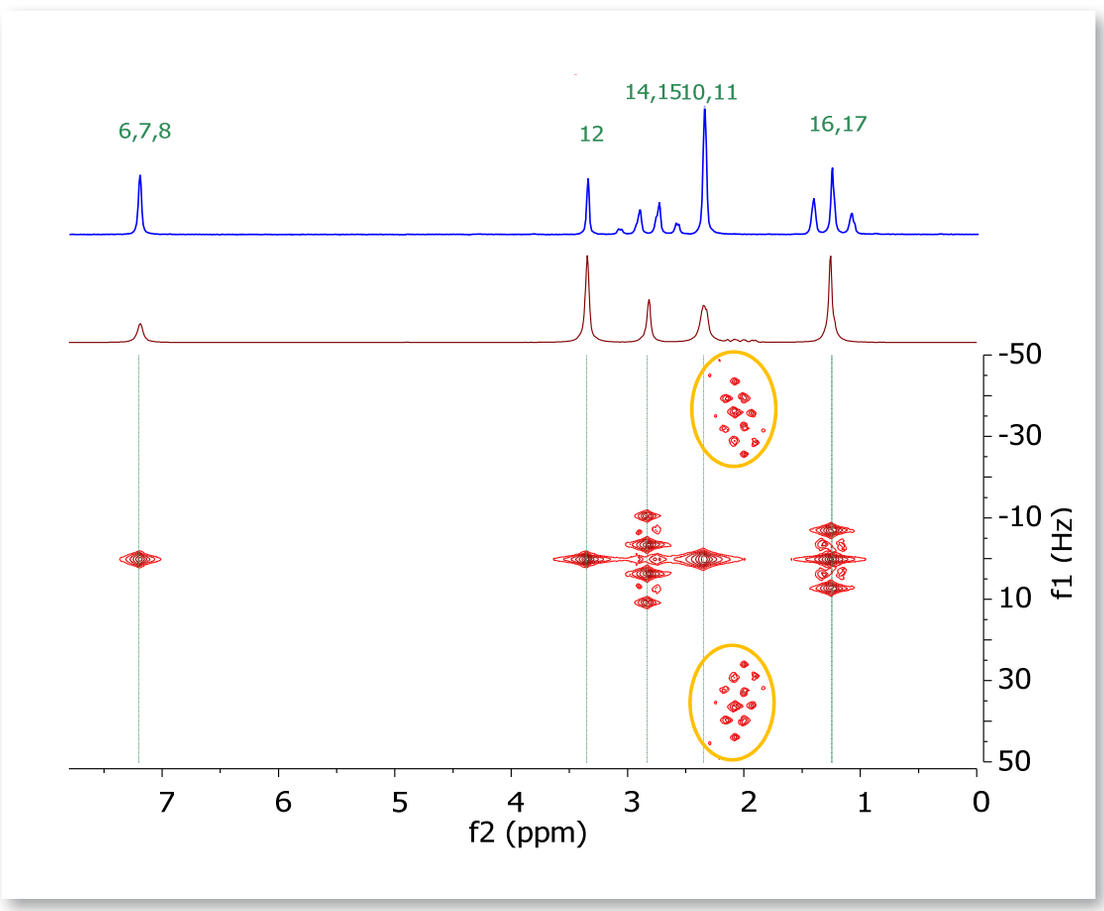
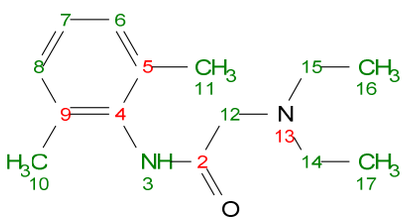


Figure 6: Homonuclear *j*-resolved spectrum of 200 mM lidocaine in $CDCl_3$ showing the extra peaks due to strong couplings.

1D ^{13}C SPECTRA

The ^{13}C NMR spectra of 1 M lidocaine in $CDCl_3$ are shown in Figure 7. The 1DCarbon experiment is sensitive to all ^{13}C nuclei in the sample. It clearly resolves 9 resonances. The ^{13}C DEPT experiment uses polarisation transfer between proton and carbon nuclei and can be used for spectral editing. Only carbons directly attached to protons are visible in these experiments. Since the peaks at 170 and 135 ppm do not show in the DEPT spectra they must belong to quaternary carbons. The DEPT-90 experiment gives only signal of CH groups, whilst the DEPT-45 and DEPT-135 give signals of CH, CH_2 and CH_3 groups, but the CH_2 groups appear as negative peaks in the DEPT-135. It can then be concluded that the peaks between 10 and 20 ppm belong to methyl groups, the ones between 45 and 60 ppm to ethylene, and between 125 and 130 ppm to methyne groups. From the peak intensities the number of contributing carbon atoms can be obtained. For example, there are three CH_2 groups in the molecule, two of which are equivalent (positions 14 and 15). Since the peak at 57.7 ppm is only about half the amplitude of the one at 49.2 ppm, it must come from a single carbon and therefore from position 12. A similar analysis can be performed on the C and CH peaks. The only remaining ambiguity in the assignment would be the CH_3 groups (10,11) and (16,17).



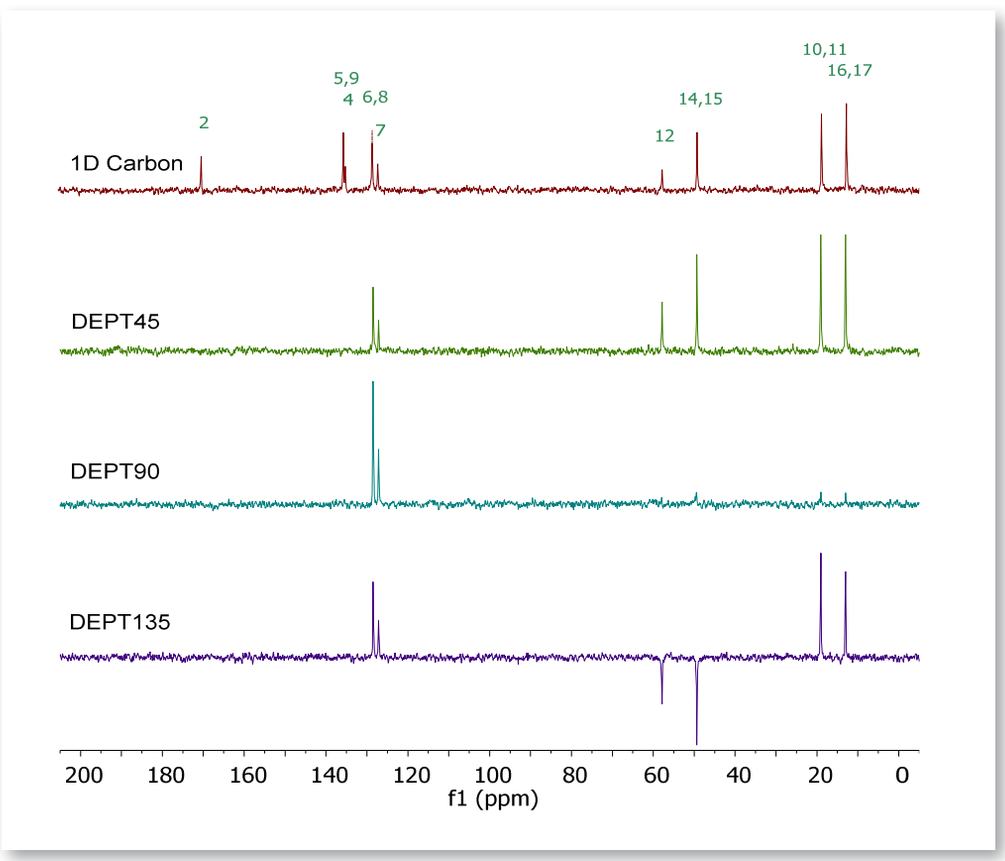


Figure 7: Carbon spectra of 1 M lidocaine in $CDCl_3$.

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HETCOR

Similar to the 2D COSY experiment, which detects proton-proton coupling partners, a series of heteronuclear 2D NMR experiments have been devised to detect coupling partners of different nuclei. The Heteronuclear Correlation (HETCOR) experiment is used to correlate proton resonances to the carbons directly bonded to those protons. The HETCOR experiment detects the carbon signal along the direct dimension and the proton signal along the indirect dimension. The HETCOR spectrum of 1 M lidocaine in $CDCl_3$ is shown in Figure 8, with the 1D proton and carbon spectra from Figures 1 and 7 as vertical and horizontal traces. The peaks in the 2D spectrum show which proton is bonded to which carbon.

This experiment solves the assignment ambiguity from the 1D carbon spectra. The carbon peak at 18.8 ppm is connected to the proton singlet at 2.35 ppm. The singlet structure of the proton peak tells us that this methyl group has no coupling proton partners. Therefore, the carbon peak at 18.8 ppm must be from the carbons at positions 10 and 11.

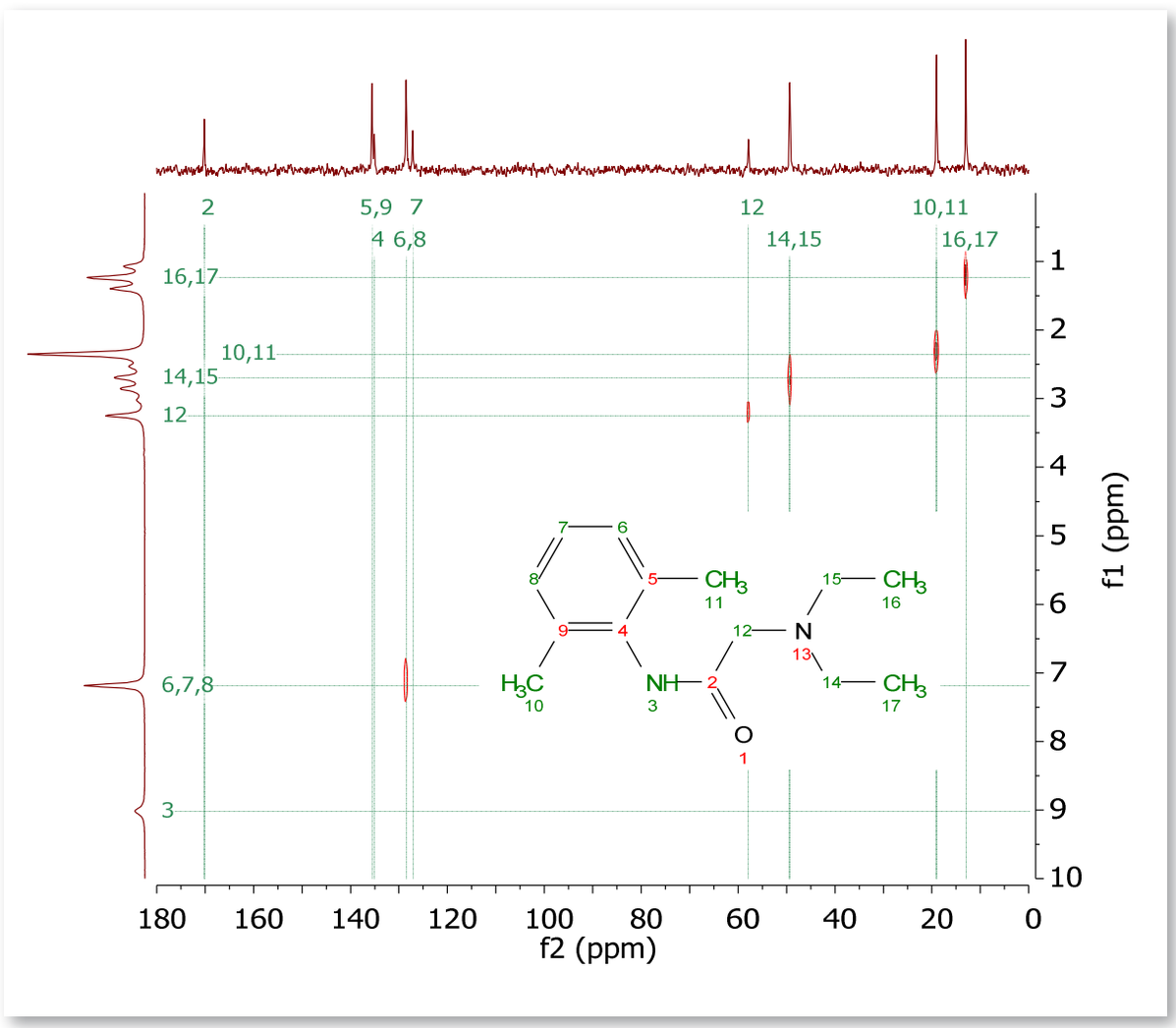

Figure 8: HETCOR spectrum of 1 M lidocaine in $CDCl_3$.

HMQC

Another heteronuclear 2D correlation experiment is the Heteronuclear Multiple Quantum Coherence (HMQC) experiment. Similar to HETCOR, it is used to correlate proton resonances to the carbons directly bonded to those protons. However, in the HMQC experiment the carbon signal appears along the indirect dimension, and the proton signal along the direct dimension.

The HMQC spectrum of 1 M lidocaine in $CDCl_3$ is shown in Figure 9, with the 1D proton and carbon spectra from Figures 1 and 7 as horizontal and vertical traces. The peaks in the 2D spectrum show which proton is bonded to which carbon. A similar analysis as with the HETCOR spectrum can be performed for conclusive peak assignment.

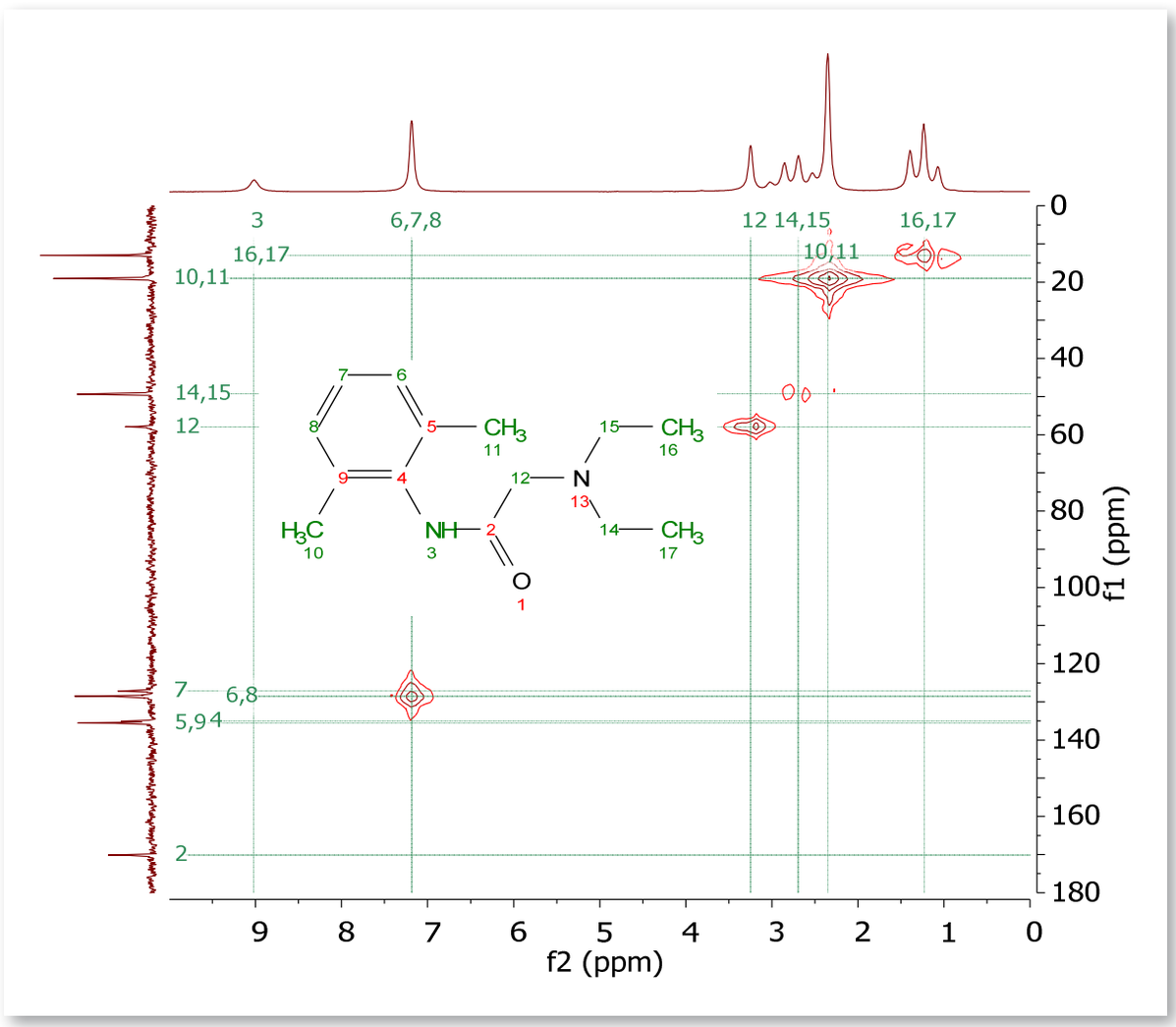

Figure 9: HMQC spectrum of 1 M lidocaine in $CDCl_3$.

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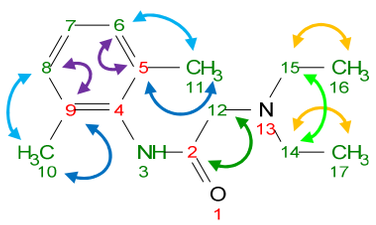
HMBC

The HMQC experiment shown on the previous page was designed to correlate protons and carbons which are connected through a one bond coupling. To obtain long-range protoncarbon correlations through two or three bond couplings, the Heteronuclear Multiple Bond Correlation (HMBC) experiment can be used. Like in the HMQC experiment the carbon signal appears along the indirect dimension, and the proton signal along the direct dimension.

The HMBC spectrum of 1 M lidocaine in $CDCl_3$ is shown in Figure 10, with the 1D proton and carbon spectra from Figures 1 and 7 as horizontal and vertical traces. The peaks in the 2D spectrum show which protons are connected to which carbons via a long-range coupling. The couplings between molecular positions look similar to the ones found from the COSY spectrum, but the HMQC additionally shows couplings to quaternary carbons, which are not visible in the COSY or HMQC. For example, there are clear multibond couplings from the protons at positions (10,11) to the carbons at positions (8,6) and (9,5), as marked in Figure 10. Some other couplings are marked as well. It is interesting to note that there is a correlation between carbons (14,15) to protons (14,15). This is due to three-bond coupling from 14 to 15 and vice versa (light green).



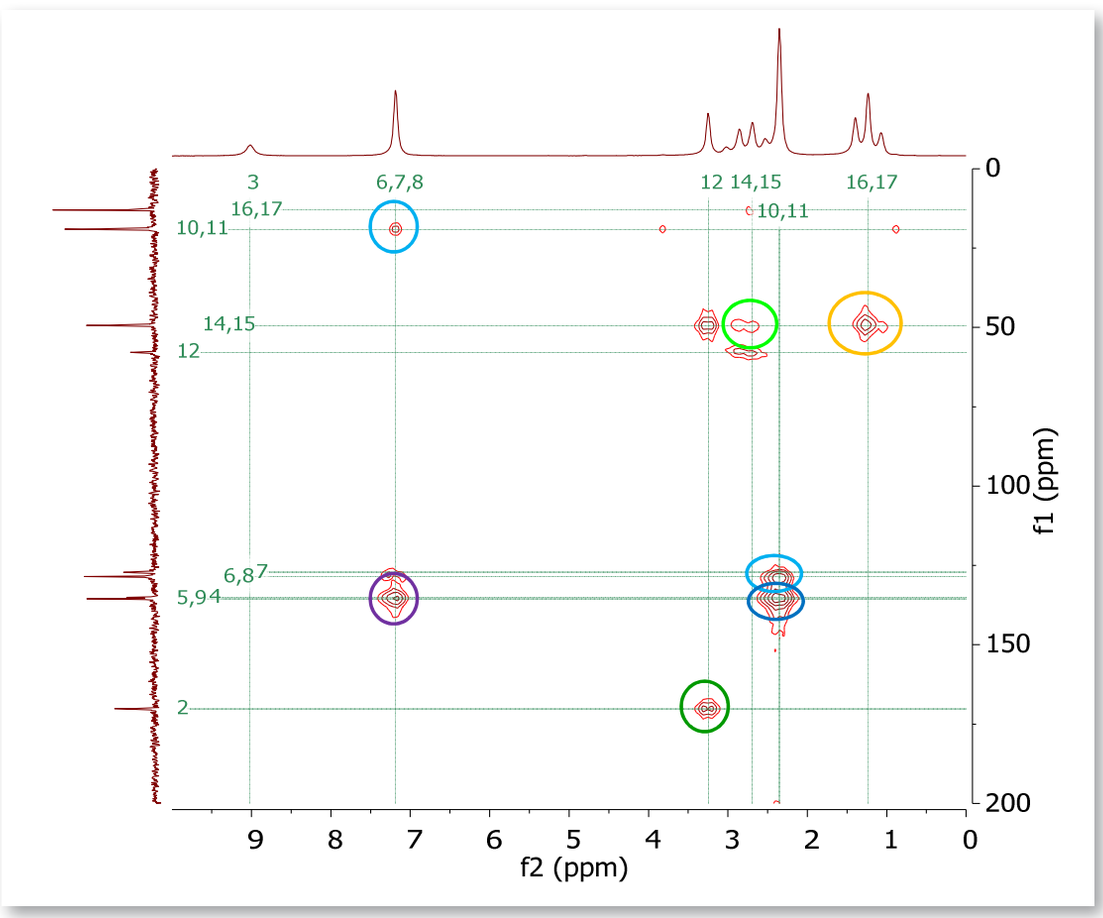


Figure 10: HMBC spectrum of 1 M lidocaine in $CDCl_3$, with some of the long-range couplings marked.

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Specifications

- Frequency: 42.5 MHz Proton, 10.8 MHz Carbon
- Resolution: 50% linewidth < 0.7 Hz (16 ppb)
- Lineshape: 0.55% linewidth < 20 Hz
- Dimensions: 58 x 43 x 40 cm
- Weight: 55 kg
- Magnet: Permanent and cryogen free
- Stray field: < 2 G all around system

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- 1D Proton only system
- Budget friendly price
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- Relaxation time experiments
- 2D COSY and JRES
- Reaction monitoring

"Now the students are able to acquire their own NMR spectra as well as carry out the analysis of the compounds they have made. This makes their undergraduate experiment more applicable to both research and industry settings and increases their enthusiasm for Chemistry."

Professor Frances Separovic, Head of Chemistry, University of Melbourne

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