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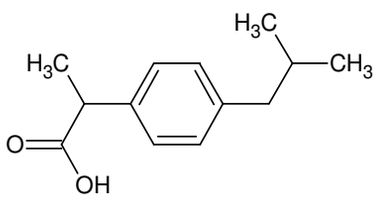
Ibuprofen

Example of benchtop NMR on small organic molecules

Ibuprofen ($C_{13}H_{18}O_2$) is a non-steroidal antiinflammatory drug (NSAID) and is commonly used for pain relief, fever reduction and against inflammation.



The ^{1}H NMR spectrum of 200 mM ibuprofen 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.

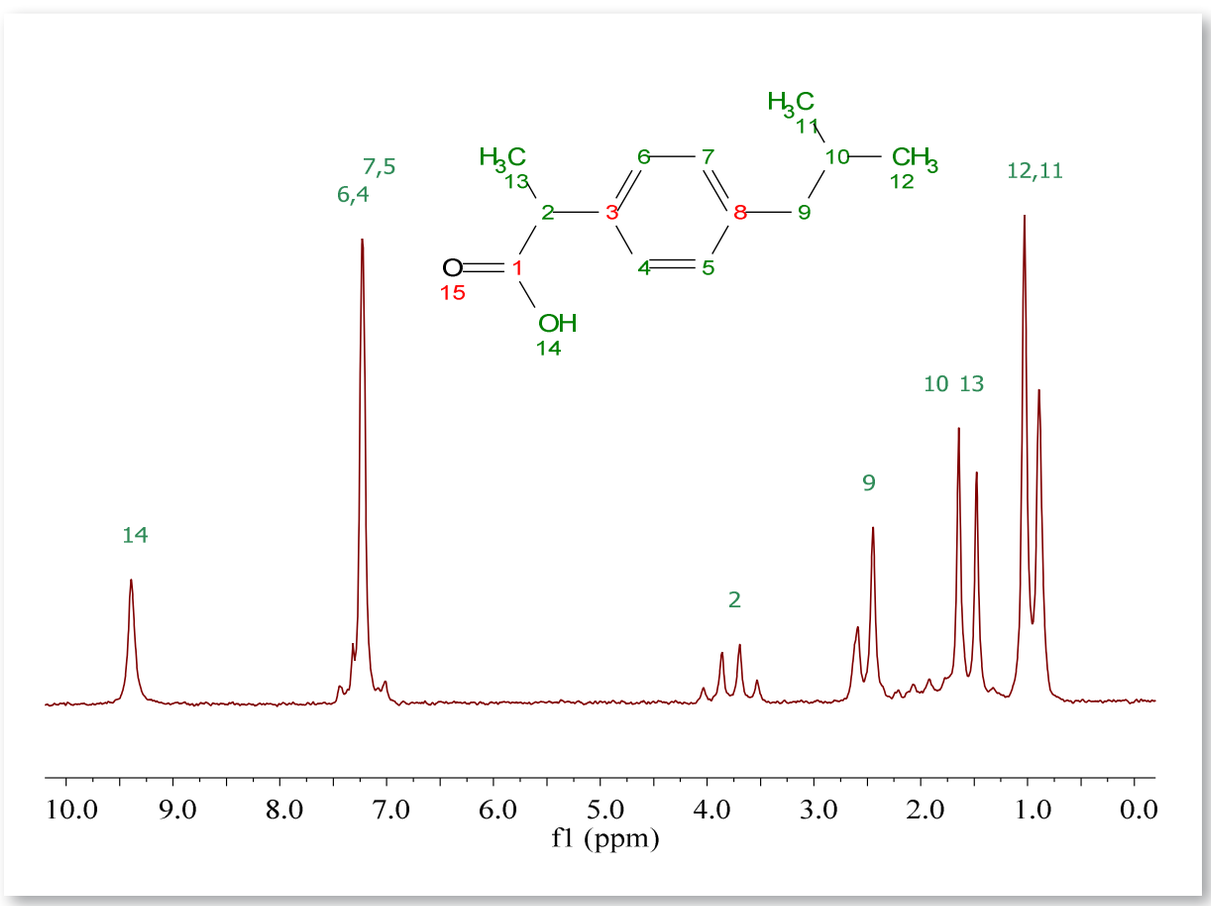


Figure 1: Proton NMR spectrum of 200 mM ibuprofen in $CDCl_3$.

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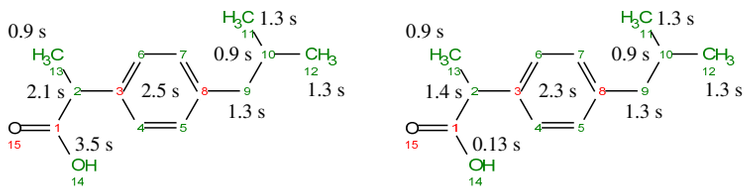
^{1}H NMR RELAXATION

The relaxation time measurements are shown in Figures 2 - 4. Note the long T_1 and short T_2 value of the exchanging hydroxyl proton. 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

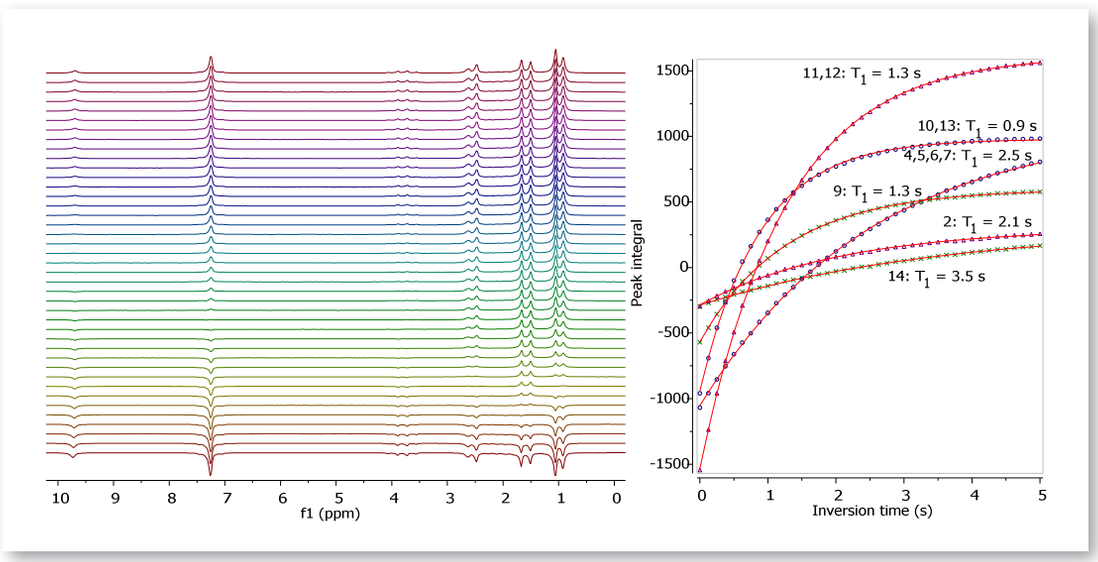


Figure 2: Proton T_1 relaxation time measurement of 200 mM ibuprofen in $CDCl_3$.

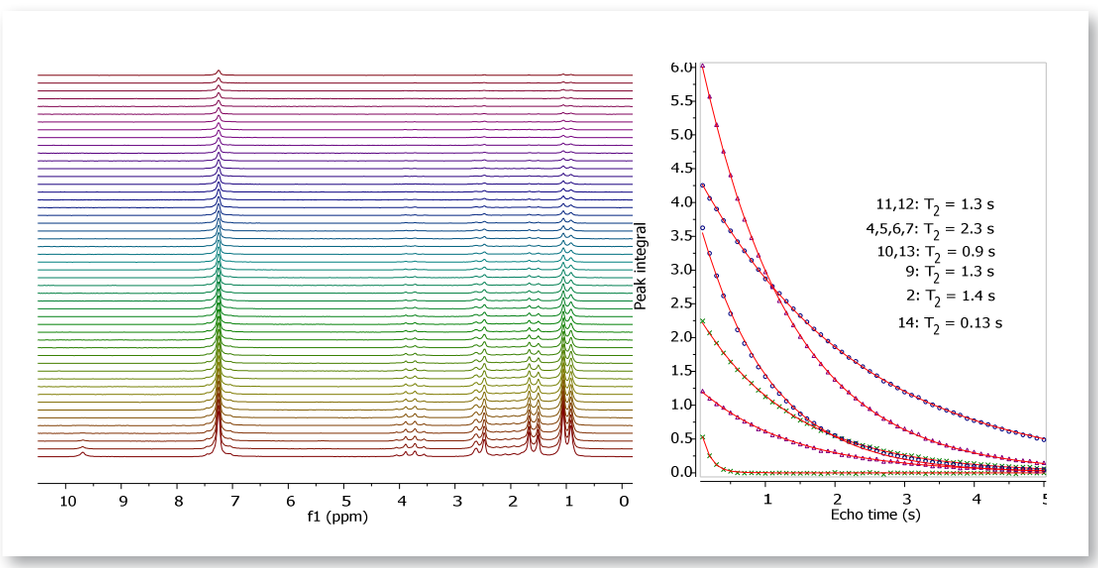
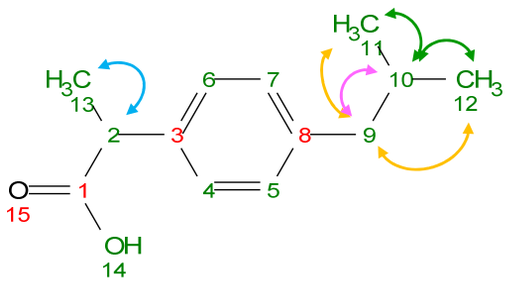


Figure 3: Proton T_2 relaxation time measurement of 200 mM ibuprofen in $CDCl_3$.

2D COSY

The 2D COSY spectrum is shown in Figure 4. It clearly shows two spin systems (2,13) and (9,10,11,12). For example, the methyl group at position 13 only couples to the CH group at position 2, whilst the methyl groups at positions 11 and 12 couple to CH and CH_2 groups at positions 10 and 9. There is no coupling of positions (9,10,11,12) to either 2 or 13.



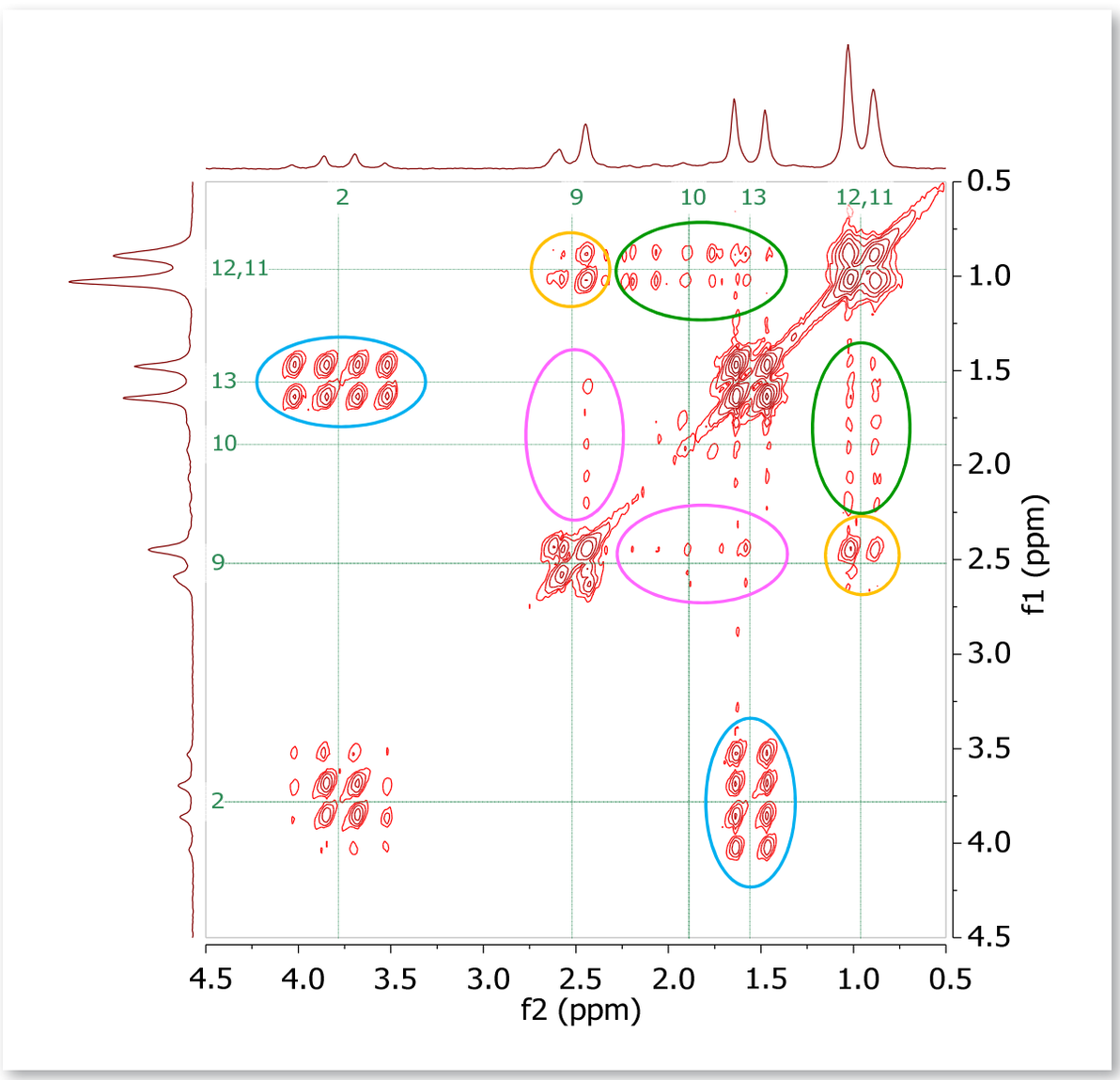


Figure 4: COSY spectrum of 200 mM ibuprofen in $CDCl_3$. The cross-peaks and corresponding exchanging protons are marked by colour-coded ellipses and arrows.

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 ibuprofen, 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 multiplet at 1.90 ppm and the doublet at 3.78 ppm have a splitting of 6.5 Hz, suggesting that these groups are coupled to each other. These couplings confirm the findings of the COSY experiment in Figure 4.

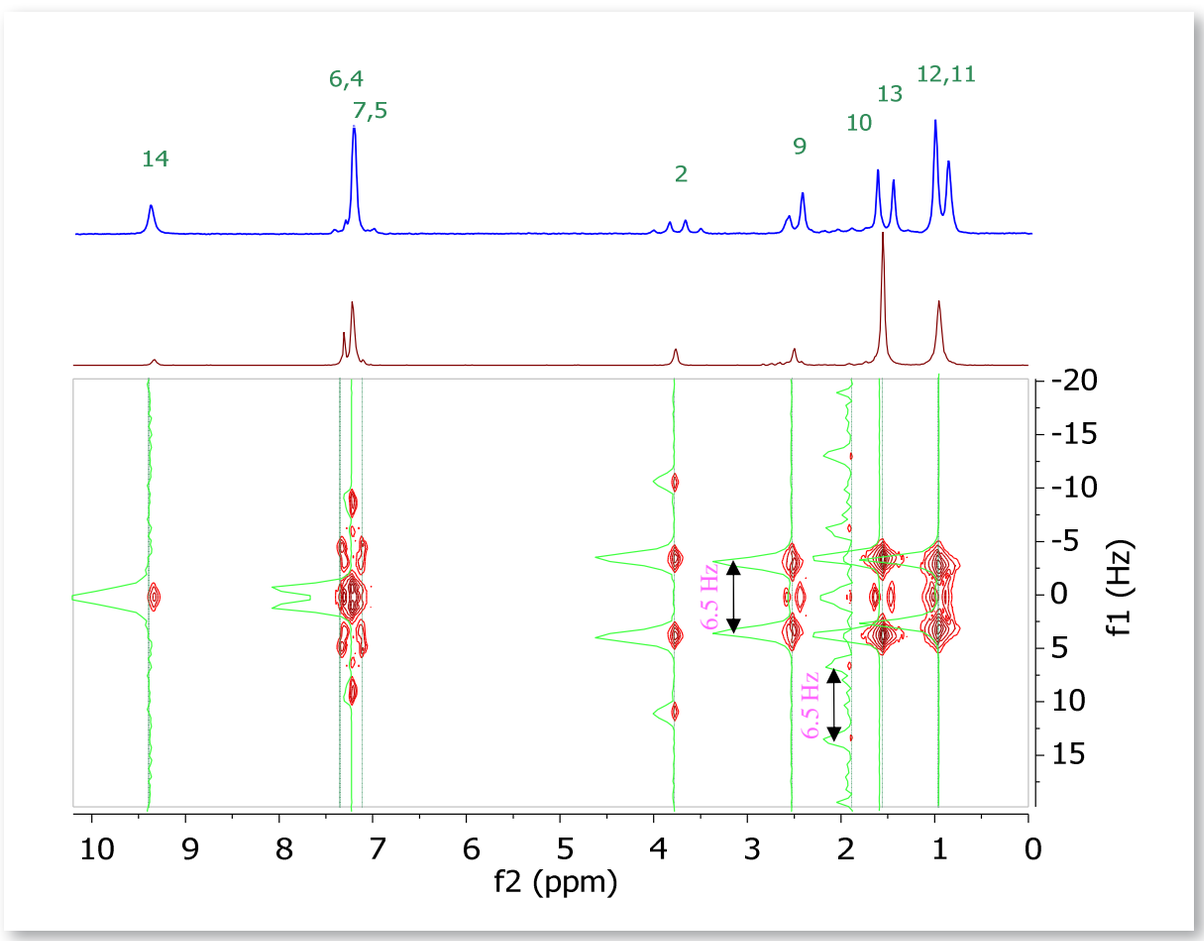
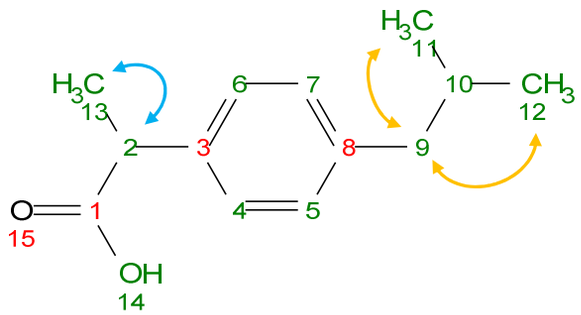


Figure 5: Homonuclear *j*-resolved spectrum of 200 mM ibuprofen in $CDCl_3$. The multiplet splitting frequencies for different couplings are colour-coded as in Figure 4.

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.



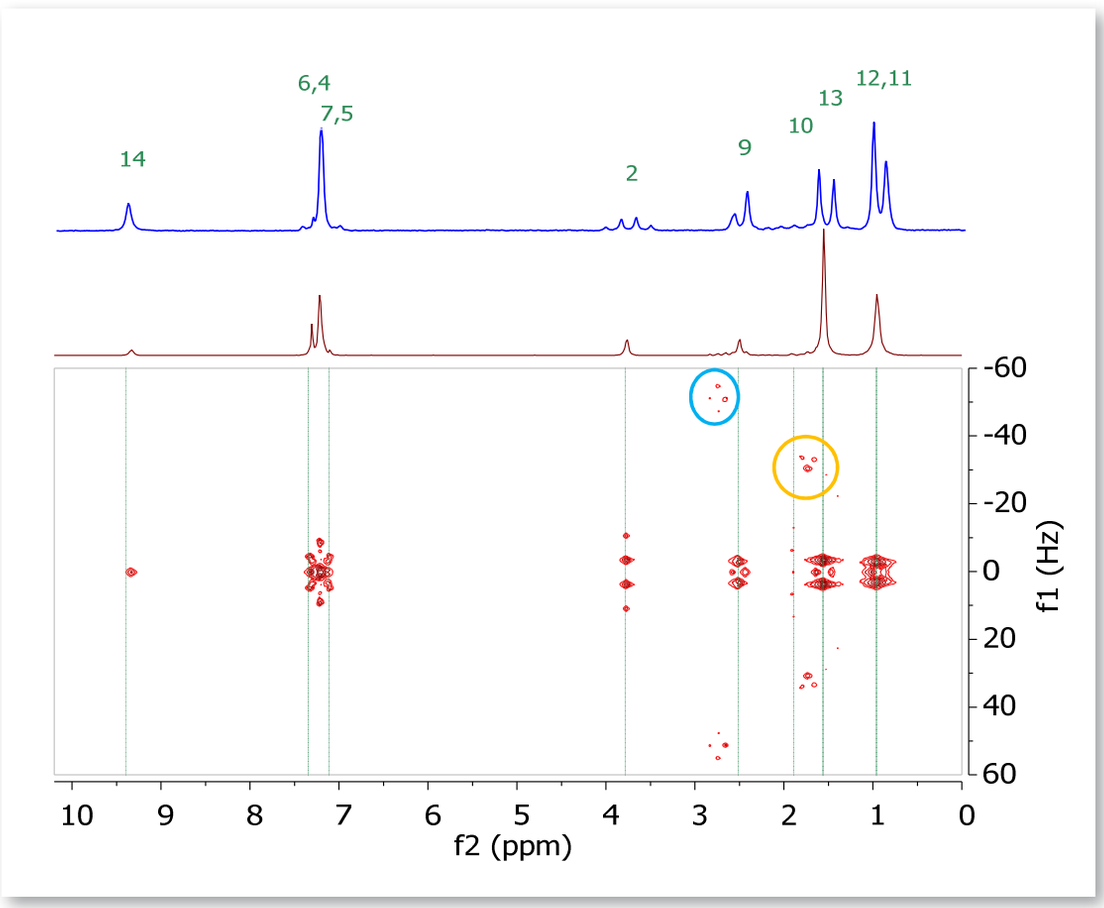
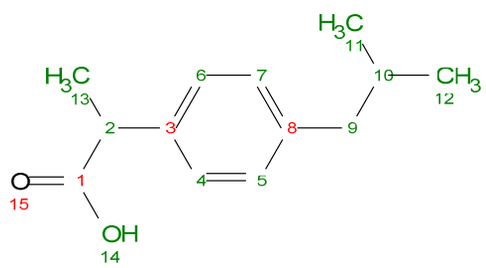


Figure 6: Homonuclear *j*-resolved spectrum of 200 mM ibuprofen in $CDCl_3$ showing the extra peaks due to strong couplings.

1D ^{13}C SPECTRA

The ^{13}C NMR spectra of 2 M ibuprofen in $CDCl_3$ are shown in Figure 7. The 1D Carbon experiment is sensitive to all ^{13}C nuclei in the sample. It clearly resolves 9 resonances; the small triplet between 70 and 80 ppm is from the solvent. 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 181, 140 and 137 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. Through linear combination of the three DEPT spectra one can produce subspectra of the CH_3, CH_2 and CH groups alone, as shown in Figure 7. An interesting feature evident in these subspectra is that the peak at 45 ppm is made up of a CH and a CH_2 resonance with identical chemical shifts.



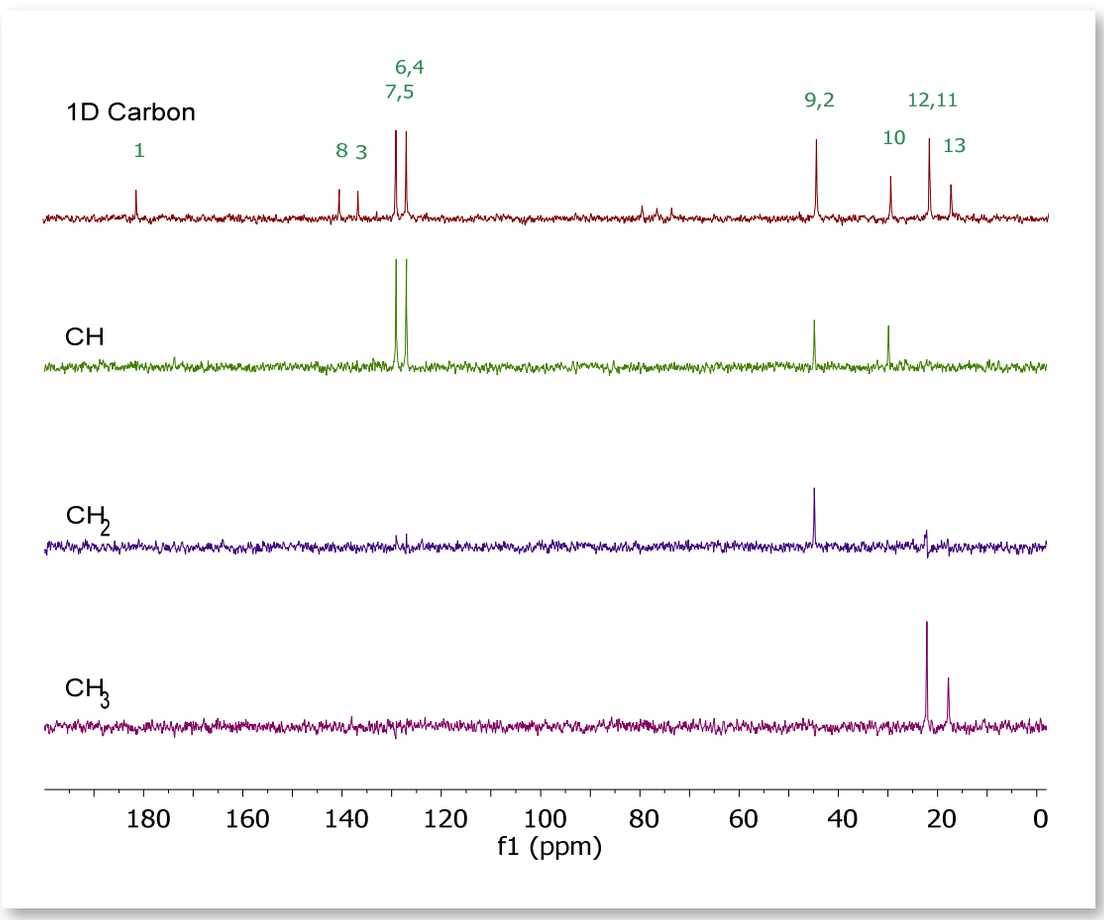


Figure 7: Carbon spectra of 2 M ibuprofen in $CDCl_3$.

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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 2 M ibuprofen 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.

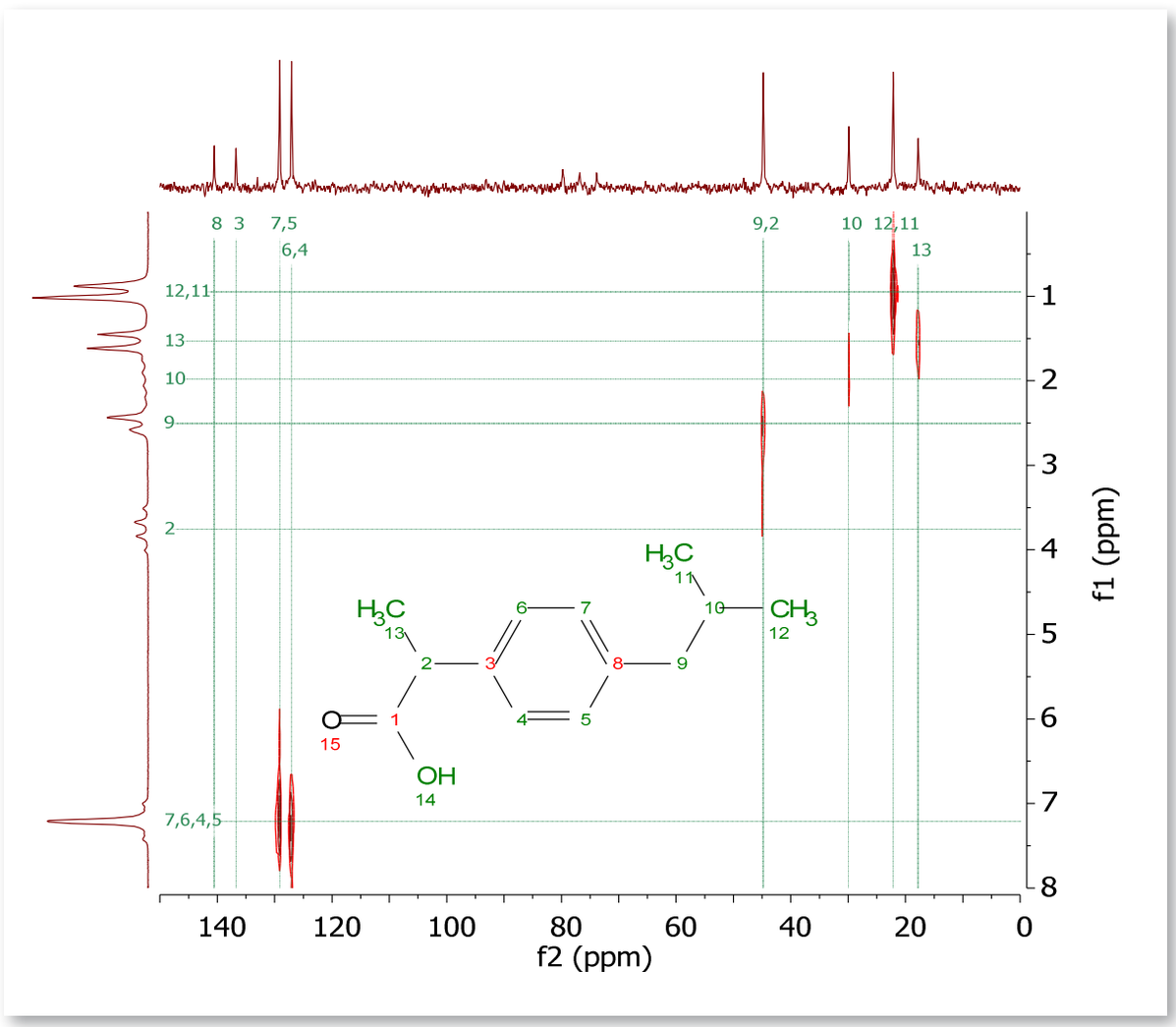


Figure 8: HETCOR spectrum of 2 M ibuprofen in $CDCl_3$.

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 2 M ibuprofen 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.

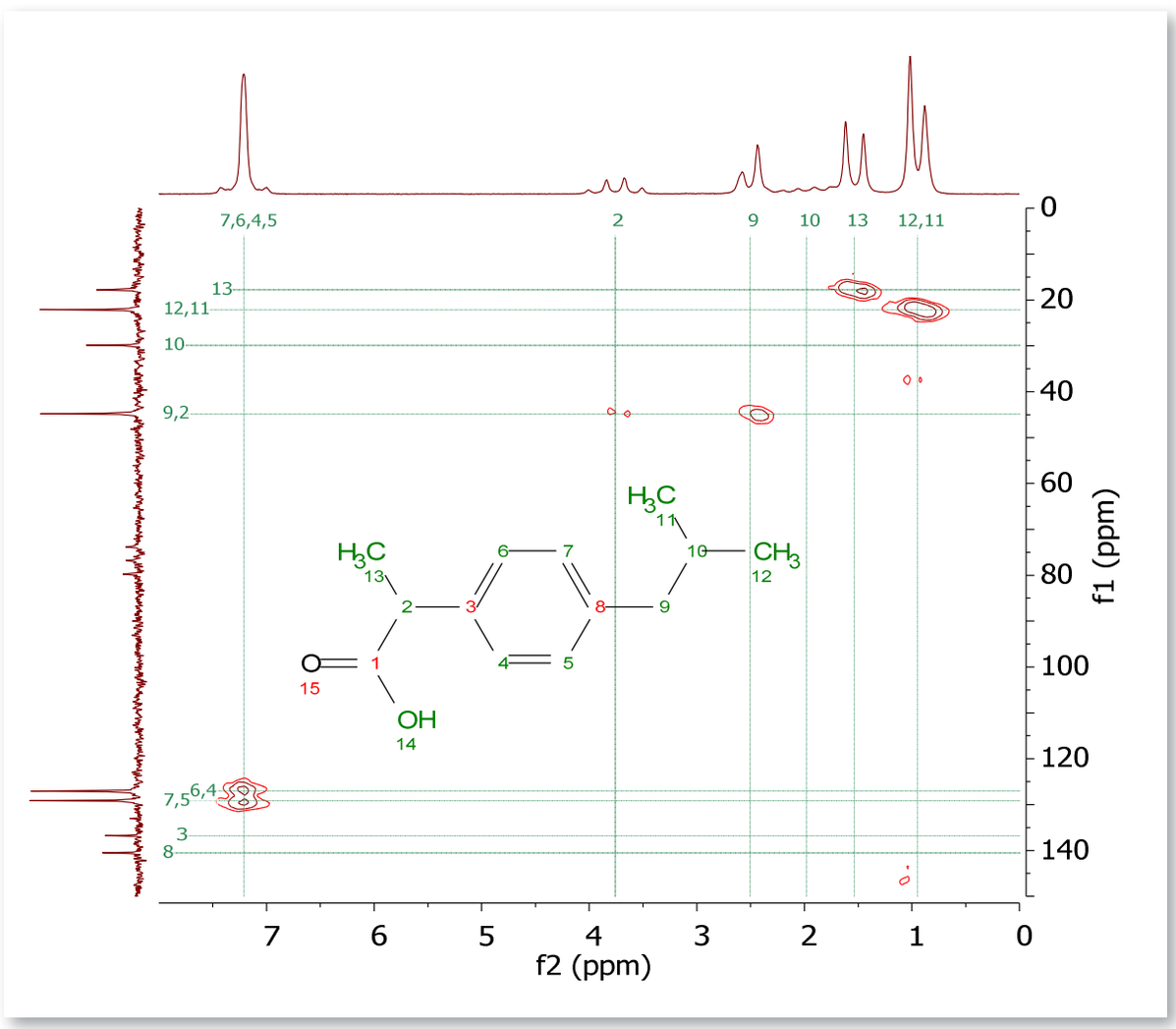
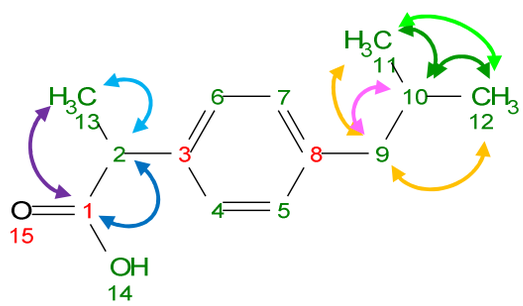


Figure 9: HMQC spectrum of 2 M ibuprofen in $CDCl_3$.

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 ibuprofen 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 2 and 13 to the carbon at position 1, as marked in Figure 10. It is also interesting to note that there is a correlation between carbons (11,12) to protons (11,12). This is due to three-bond coupling from 11 to 12 and vice versa (light green).



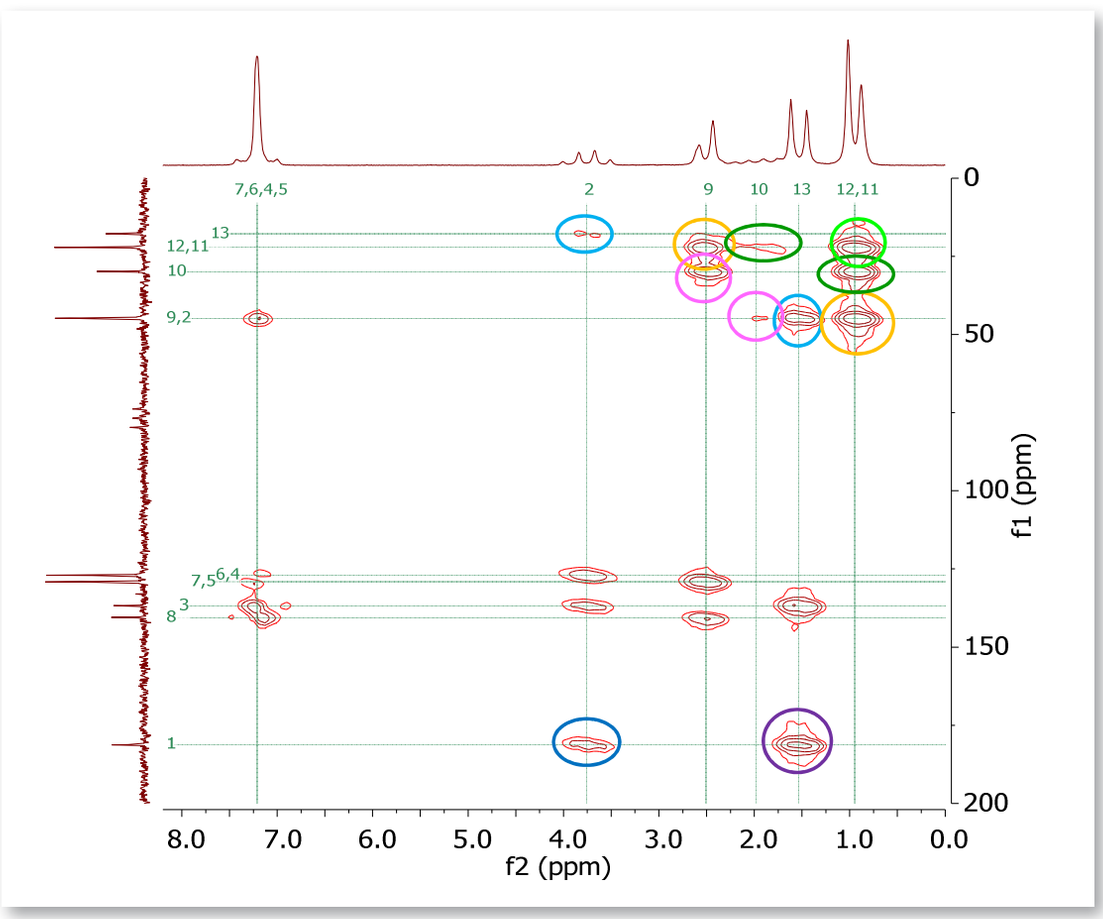


Figure 10: HMBC spectrum of 2M ibuprofen in $CDCl_3$.

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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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- Budget friendly price
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Spinsolve®

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- Relaxation time experiments
- 2D COSY and JRES
- Reaction monitoring

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Professor Frances Separovic, Head of Chemistry, University of Melbourne

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