



Second Order Effects: High-field vs. Low-field NMR Spectroscopy

Introduction

The analysis of NMR spectra is one of the skills that synthetic chemists have to quickly learn in order to characterize their products. Chemical shifts, integration areas and coupling constants provide invaluable information about the connectivity in a molecule or the progress of reactions. In this Application Note we are going to focus on coupling constants. First order spectra can be roughly described as the ones you can look at and visually extract the coupling information. Second, and higher order effects mean that while the information is still contained in the spectra, it may be too convoluted to be extracted manually. Second order effects appear when the difference in chemical shifts ($\Delta\nu$ [in Hz]) of two resonances have similar values to the corresponding scalar coupling (J [Hz]) of those signals. This can be expressed by equation (1), which can be easily transformed to equation (2).^[1]

$$\frac{\Delta\nu}{J} \approx 1 \text{ or } \frac{\Delta\nu}{J} < 5 \quad (1)$$

$$\Delta\nu \approx J \text{ or } \Delta\nu < 5J \quad (2)$$



Simulated Spectra

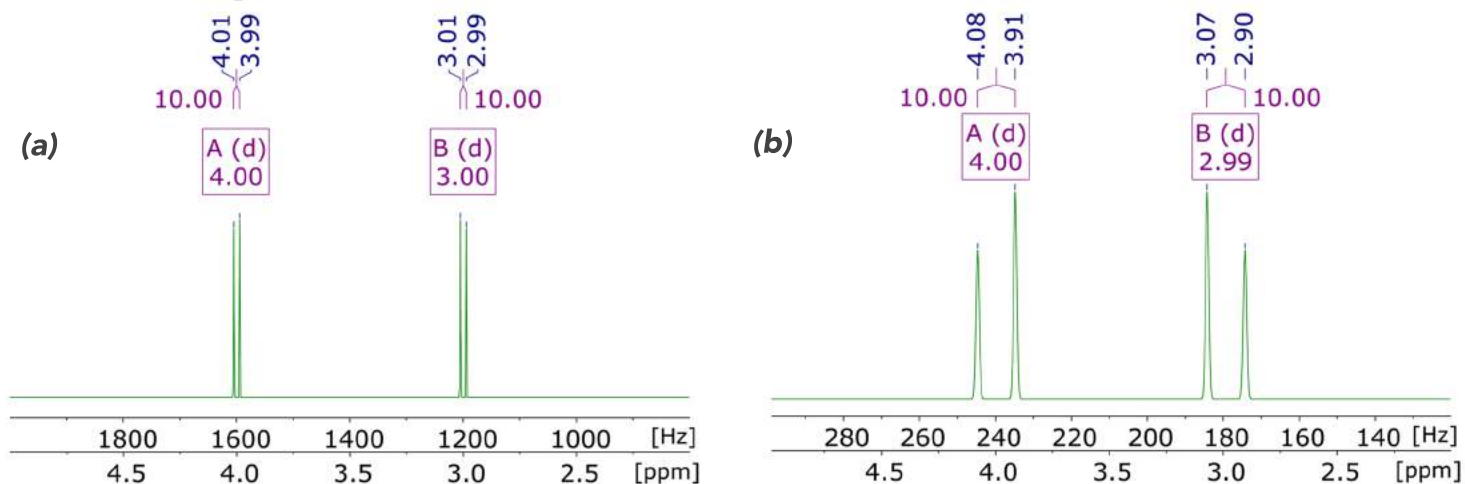


Figure 1: Simulated spectra $\Delta\delta = 1$ ppm; $J = 10$ Hz at (a) 400 MHz; and (b) 60 MHz.

Before examining experimental spectra, simulated spectra will be used to demonstrate how second order effects vary with field strength. Figure 1 shows the simulated spectra of two protons that appear as doublets at 400 (left) and 60 (right) MHz. In both spectra the chemical shift (δ) of the protons were chosen to be 4.00 and 3.00 ppm. Therefore, the difference in chemical shift ($\Delta\delta$) is 1 ppm in both cases. When the chemical shift is converted into frequency units the difference in chemical shift ($\Delta\nu$) is 400 Hz at 400 MHz whereas at 60 MHz the difference in chemical shift is only 60 Hz. With an arbitrarily chosen scalar coupling (J) of 10 Hz, the ratio $\Delta\nu/J$ is 40 for the high field spectrum while in the case of the low field spectrum the $\Delta\nu/J$ ratio is 6. Clearly, the high field spectrum shows a first order spectrum; however, in the low field spectrum the $\Delta\nu/J$ value is very close to the aforementioned threshold and second order effects start to manifest in the form of asymmetric peaks. The intensities of the lines are no longer the same and the area of each peak are no longer equivalent. The signals in the periphery become smaller while the inner lines become larger. This is traditionally referred as the "roofing effect" and it becomes more pronounced as the $\Delta\nu/J$ ratio becomes smaller.

In Figure 2, the two simulated spectra show an unambiguous second order scenario. The distance between the chemical shifts of the two signals are much smaller now. The chemical shifts were set to 3.55 and 3.45 ppm (i.e., $\Delta\delta = 0.1$ ppm) and the scalar coupling was maintained at 10 Hz. This results in a $\Delta\nu/J$ ratio of 4 at 400 MHz and 0.6 at 60 MHz. This time the condition specified in equation 2 is true for both examples and second order effects are expected. Accordingly, a roofing effect was observed in both cases and in the low field spectrum the inner resonances even overlap, resulting in a more pronounced second order effect signal shape. In molecules that contain two isolated protons coupling only to each other (i.e., $^2J_{\text{HH}}$) this is referred as an AB quartet.

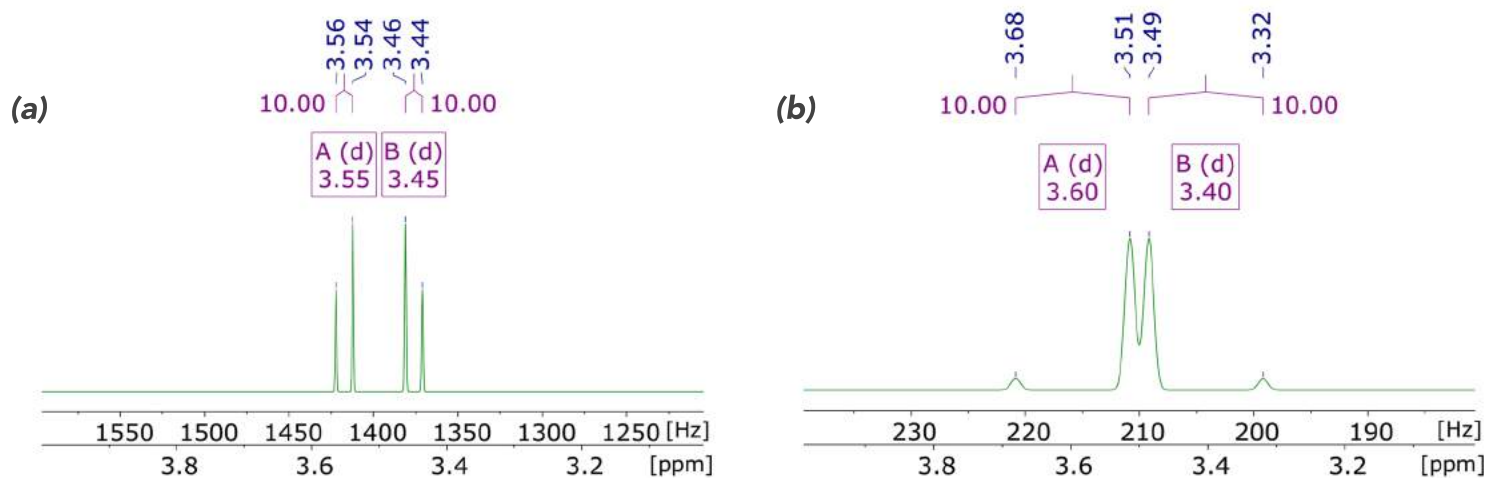


Figure 2: Simulated spectra $\Delta\delta = 0.1$ ppm; $J = 10$ Hz at (a) 400 MHz; and (b) 60 MHz.

As demonstrated in Figures 1 and 2, it is clear that second order effects are more likely to be observed in NMR spectra acquired at lower field strengths because $\Delta\nu$ is inherently smaller compared to NMR spectra recorded on high field instruments. So far, we have demonstrated second order effects with fairly simple simulated spectra. In the next section the second order effect will be discussed using real examples.

Comparison of ^1H NMR Data from High- and Low-field

3,4-dimethoxybenzaldehyde (**1**) is a good example for this discussion because all the aromatic protons are chemically inequivalent (note that aromatic protons usually display second order effects due to magnetic inequivalence)^[3] while dimethylpiperazine (**2**) exhibits a complex coupling pattern with a lot of signal overlap despite its simple chemical structure.

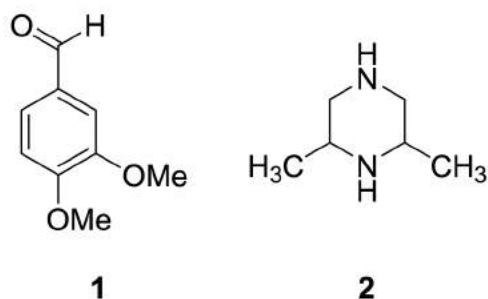


Figure 3: Molecular structure of 3,4-dimethoxybenzaldehyde (**1**) and dimethylpiperazine (**2**).

Figure 4 shows the ^1H NMR spectra of (**1**) at low (60 MHz) and high (400 MHz) magnetic fields. Compound (**1**) can be unambiguously characterized with the low field NMR data. The aldehyde H-atom, as well as the aliphatic methoxy-group signals can be assigned easily (red and purple asterisks in figure 4a). As expected, second order effects were observed in the aromatic region as a roofing effect where the peaks tend to point to each other and the intensity is not quite what you'd expect. Although there is an overlap between signal B (yellow asterisk, $\delta = 7.39$ ppm, s, 1H) and signal A (blue asterisk, $\delta = 7.46$ ppm, dd, $^3J_{\text{HH}} = 7.5$ Hz, $^4J_{\text{HH}} = 1.8$ Hz), the scalar coupling constants of the two signals can still be measured. For signal C (brown asterisk, $\delta = 6.95$ ppm, dd, $^3J_{\text{HH}} = 7.4$, $^4J_{\text{HH}} = 1.8$ Hz, 1H), a second order signal shape was also observed, but again, the integration and J couplings have the right values.

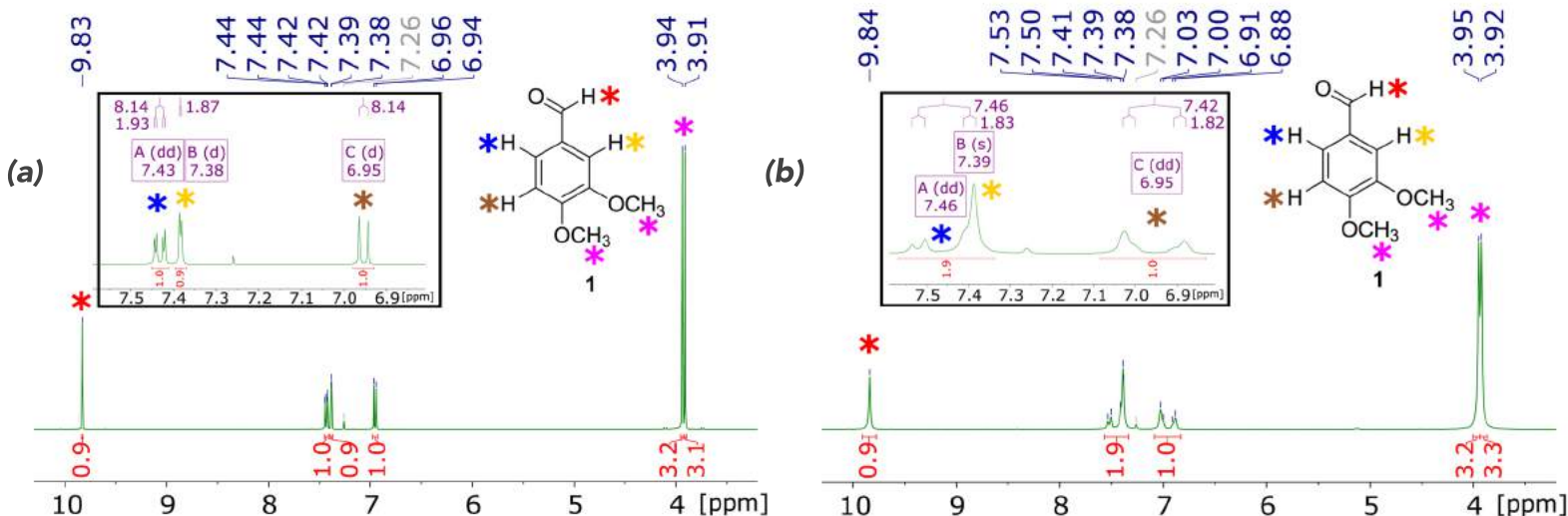


Figure 4: Assigned ^1H NMR spectrum of 3,4-dimethoxybenzaldehyde (**1**) with inset zoom-in of aromatic region at (a) 400 MHz, and (b) 60 MHz.

Although we've encountered second order effects with this substrate, we were able to extract all the pertinent information from the low field spectrum. For comparison, Figure 4a shows the proton NMR spectrum of (**1**) acquired at 400 MHz. In the high field spectrum signals A and B are not overlapping and signal B was revealed to be a doublet instead of a singlet. The $^4J_{\text{HH}}$ coupling was not observed in the low field spectrum and therefore it was observed as a singlet. Resonance C appears as a doublet instead of a doublet of doublets with the 3J coupling constant, as observed at 60 MHz.

The ^1H NMR spectrum of 2,6-dimethylpiperazine (**2**) recorded on a 400 MHz (a) and 60 MHz (b) instrument is displayed in Figure 5 with second order effects clearly observed in the spectrum acquired at low field. Even though the coupling constants of the signal at 2.19 ppm (signal B, dd) can be estimated, it is not possible to analyze multiplet C as a first order signal.

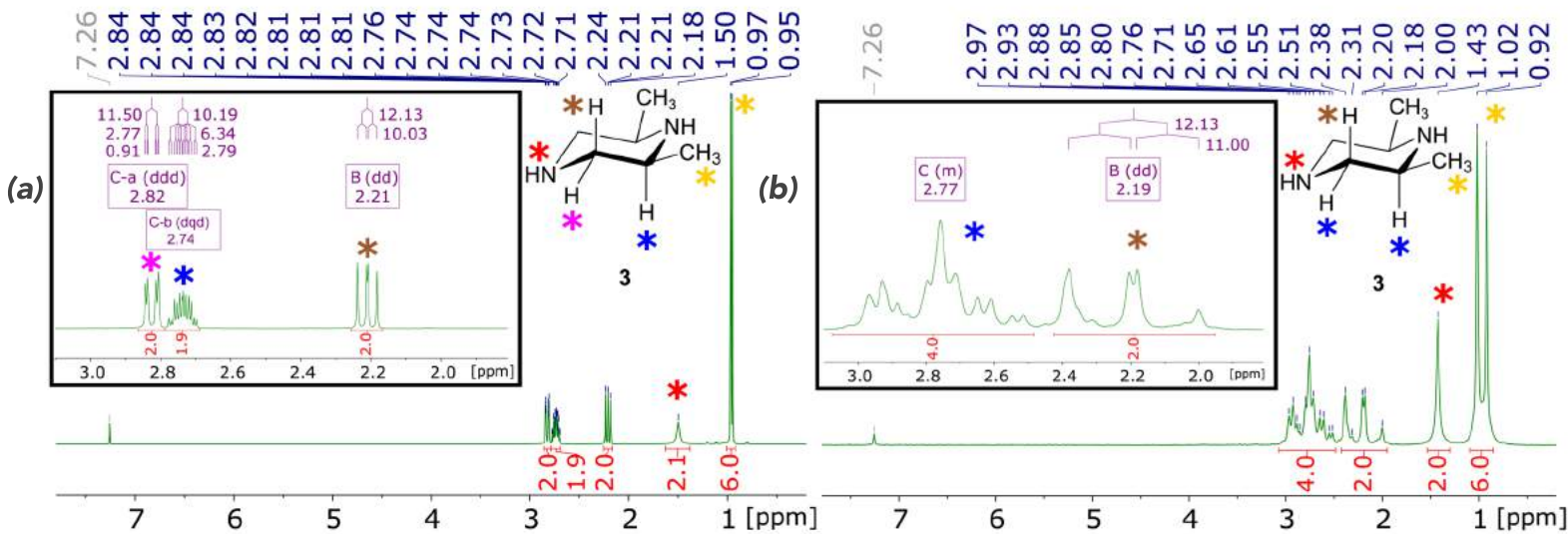


Figure 5: Assigned ^1H NMR spectrum of dimethylpiperazine (**2**) with inset zoom-in of 2.0-3.0 ppm (a) 400 MHz, and (b) 60 MHz.

In the 400 MHz spectrum of (**2**), the signal for B becomes more of a first order signal and the coupling constants are in good agreement with those measured on the low field spectrum. For signal C the higher field results in a well-defined separation of the two multiplets C-a (ddd) and C-b (dqd).

JRes Spectroscopy for analyzing second order

One can also get some more information about the coupling constants in low field by employing JRes spectroscopy.^[4] For this very example the JRes spectrum of 2,6-dimethylpiperazine (**2**) is depicted in Figure 6. Here we can find most of the coupling constants which are in good agreement with the observed multiplets in high field.

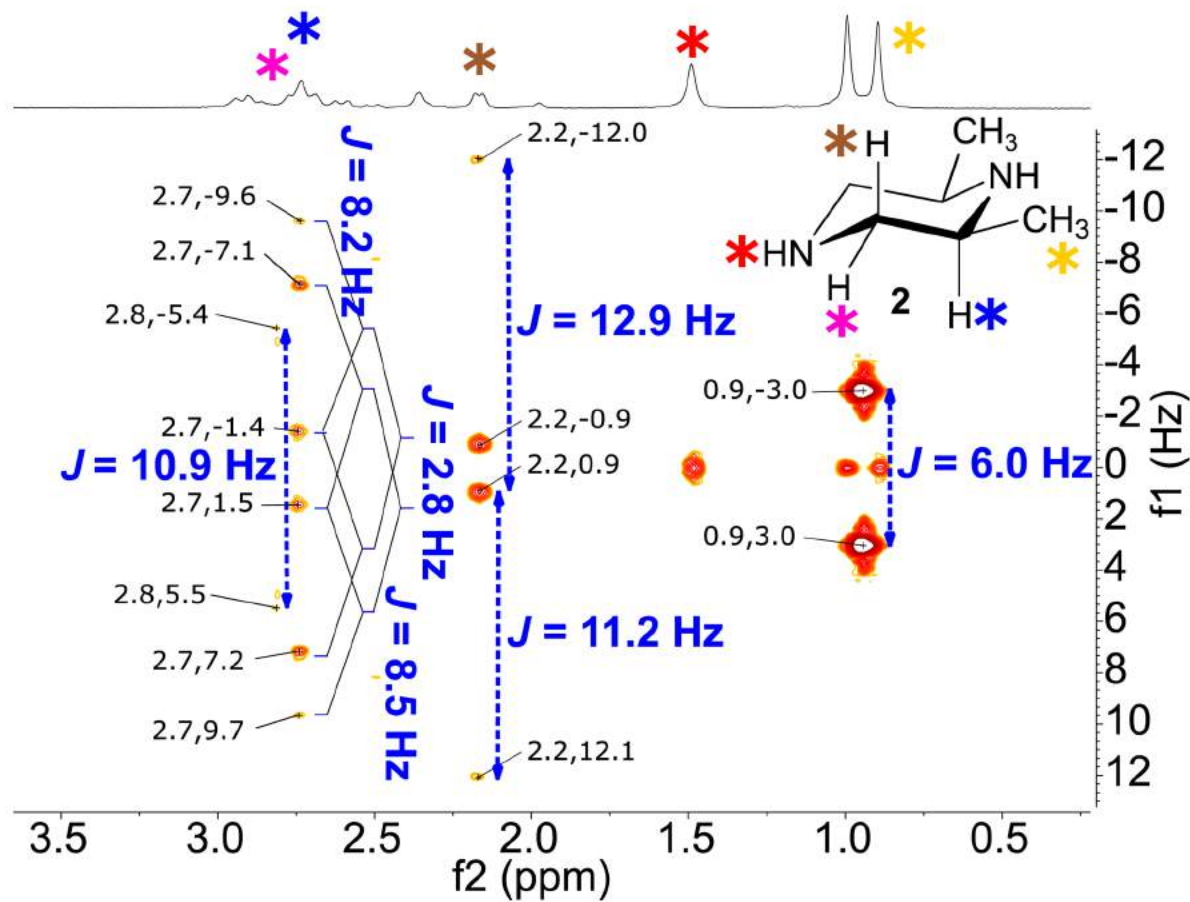


Figure 6: Assigned 60 MHz JRes spectrum of dimethylpiperazine (**2**).

In summary, although low field NMR spectra tend to show second order effects for complex molecules, one still can characterize the substance of interest as well as find most of the relevant coupling constants. JRes experiments are a powerful tool readily available in most benchtop NMR instruments that reveal coupling constants of complex multiplets.

References

^[1]H. J. Reich, Chem 605 - Structure Determination Using Spectroscopic Methods, 2018, University of Wisconsin: <https://www.chem.wisc.edu/areas/reich/nmr/05-hmr-09-2ndorder.htm> (accessed October 2018)

^[2]A. M. Castillo, L. Patiny, J. Wist, *J. Mag. Reson.* **2011**, *209*, 123-130;

^[3]<https://www.nmrdb.org/simulator/index.shtml?v=v2.87.7> (accessed October 2018); Spectra were downloaded as jcamp txt files from the cited website and processed with Mnova.

^[4]https://www.ucl.ac.uk/nmr/NMR_lecture_notes/L3_3_97_web.pdf (accessed October 2018)

^[4]Aue, W.P.; Karhan, H.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 4226.



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