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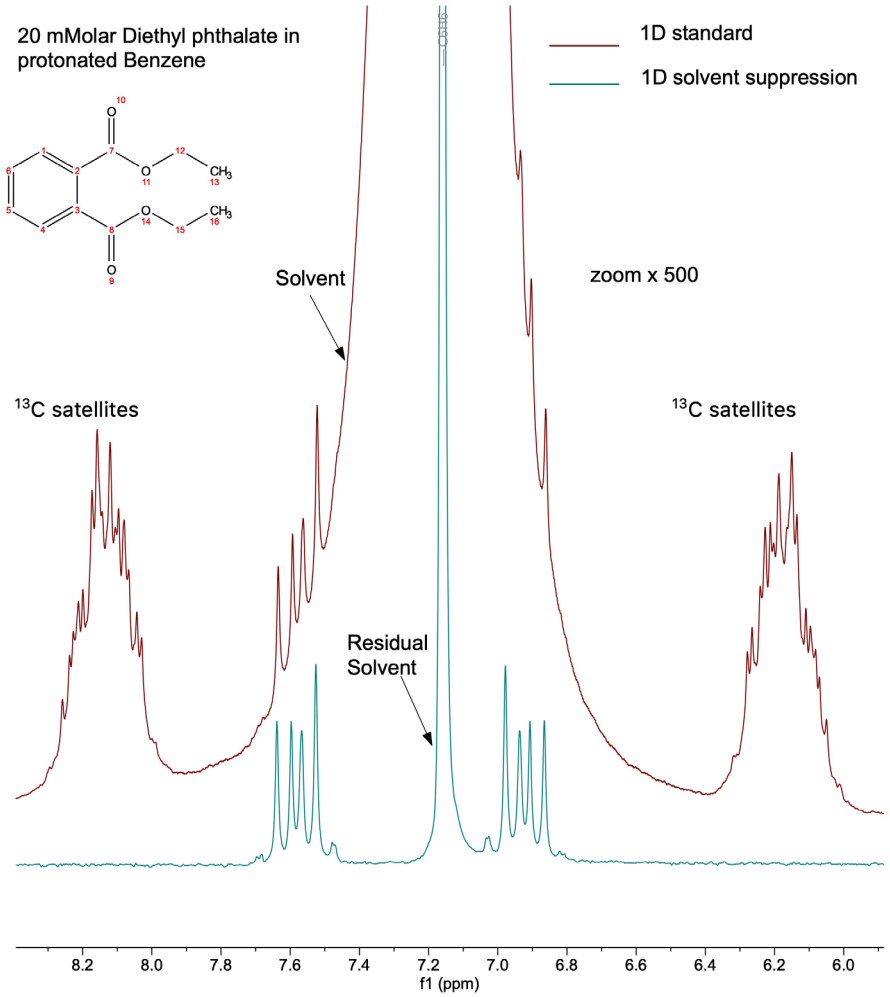
Spinsolve

Lifting the curtain of undesired solvent signals

How solvent suppression and ^{13}C decoupling remove the signals of regular protonated solvents from ^{1}H NMR spectra to eliminate sample work-up before analysis.



A chemist´s dream to have a fast and reliable analytical tool that does not require tedious sample preparation and is available within the lab for reaction analysis might have come true with the implementation of efficient solvent suppression methods on mobile benchtop NMR spectrometers. As these instruments use compact permanent magnets, they do not require cryogenic liquids and can be made small in size to fit on the bench of the chemistry lab. With the rise of the Spinsolve benchtop NMR spectrometers, more and more application fields benefit from NMR spectroscopy as the samples do not have to be taken to the NMR facilities to be analyzed. Moreover, as the measurements are quick and simple, NMR spectroscopy can be used to monitor processes like chemical reactions in the presence of regular solvents.

In this case study, we demonstrate the performance of the WET solvent suppression method implemented on a Spinsolve 80 ULTRA to attenuate the signals of some of the most common organic solvents. The high homogeneity of the Spinsolve ULTRA models make it possible to significantly attenuate the solvent peaks by two to three orders of magnitude. In this way, the overlapping of the analyte and solvent signals is reduced to the point where the analytes can be detected baseline-separated after applying the WET sequence.

With the possibility to install the Spinsolve benchtop NMR spectrometers in the chemistry labs, samples can now be analyzed immediately during the synthesis process. As the external hardware lock of the Spinsolve does not require deuterated solvents, samples can be measured directly in protonated solvents without requiring tedious sample work-ups to replace the regular solvents used in the reactor for their deuterated counterparts. A remaining limitation imposed by protonated solvents is that their large signals tend to cover a large fraction of the proton spectrum, overlapping with the signals of the products dissolved in the sample. Since benchtop NMR systems operate at magnetic fields lower than the conventional superconducting magnets, this limitation is enhanced. A powerful strategy to strongly attenuate the solvent signals uses highly selective solvent suppression methods, like PRESAT or WET. These methods are very successful in high field magnets, but they are a challenge for benchtop systems because a high magnetic field homogeneity is required to achieve an efficient solvent suppression. To remove this limitation Magritek introduced a few years ago the ULTRA version of the Spinsolve models. The superior homogeneity of these magnets boosted the performance of the suppression methods to a point where the residual signals of the protonated solvents after the suppression got comparable to the signal of the residual protons of the deuterated solvents.

For our investigation we selected common organic solvents in their protonated form and dissolved different chemical moieties at concentrations of about 20 mmol/L in each of them. Each 1D ^{1}H NMR measurement was collected in a total measurement time of roughly 3 minutes. Due to the large concentration difference between the protonated solvent and the analytes of interest, only the solvent peaks are visible when the spectra are plotted in full scale (Figure 1).

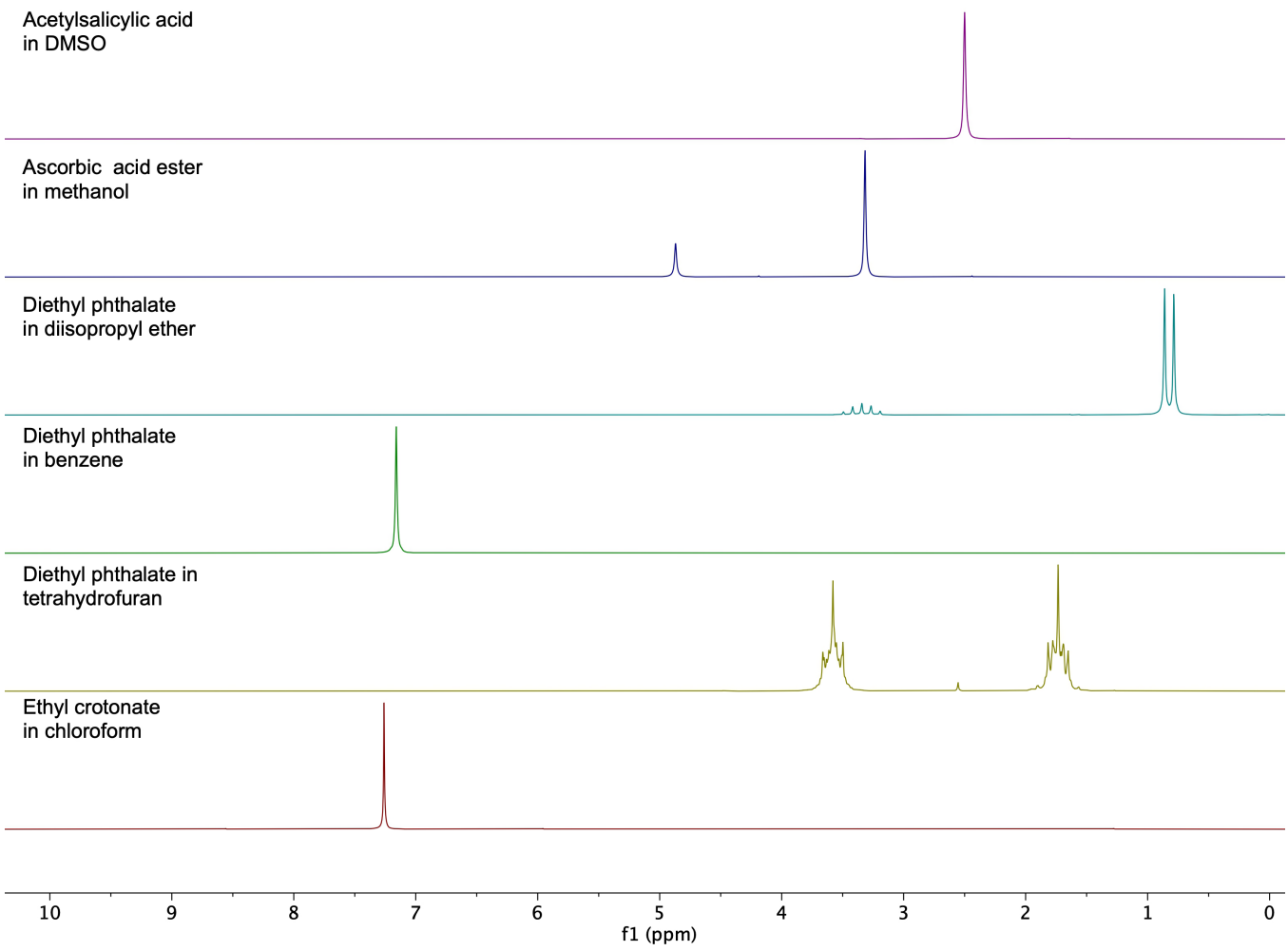


Figure 1: Stacked plot of 1D ^{1}H NMR of analytes in common protonated organic solvents (16 scans, 10 s rep., 90 pa).

Tetrahydrofuran

As a first example, the measurement of diethyl phthalate in tetrahydrofuran (THF) is described in more detail. Figure 2 shows a convenient zoom of the spectrum adjusted to visualize the peaks of interest. The symmetric ethyl ester groups of diethyl phthalate appear as a quartet at 4.25 ppm and a triplet at 1.27 ppm in the aliphatic region. Obviously, none of these functional groups is clearly visible due to a strong overlap with both THF signals and its ^{13}C satellites (red spectrum). Only its aromatic protons at 7.54 ppm are visible when using protonated THF as a solvent (spectrum recorded without carbon decoupling nor solvent signal suppression).

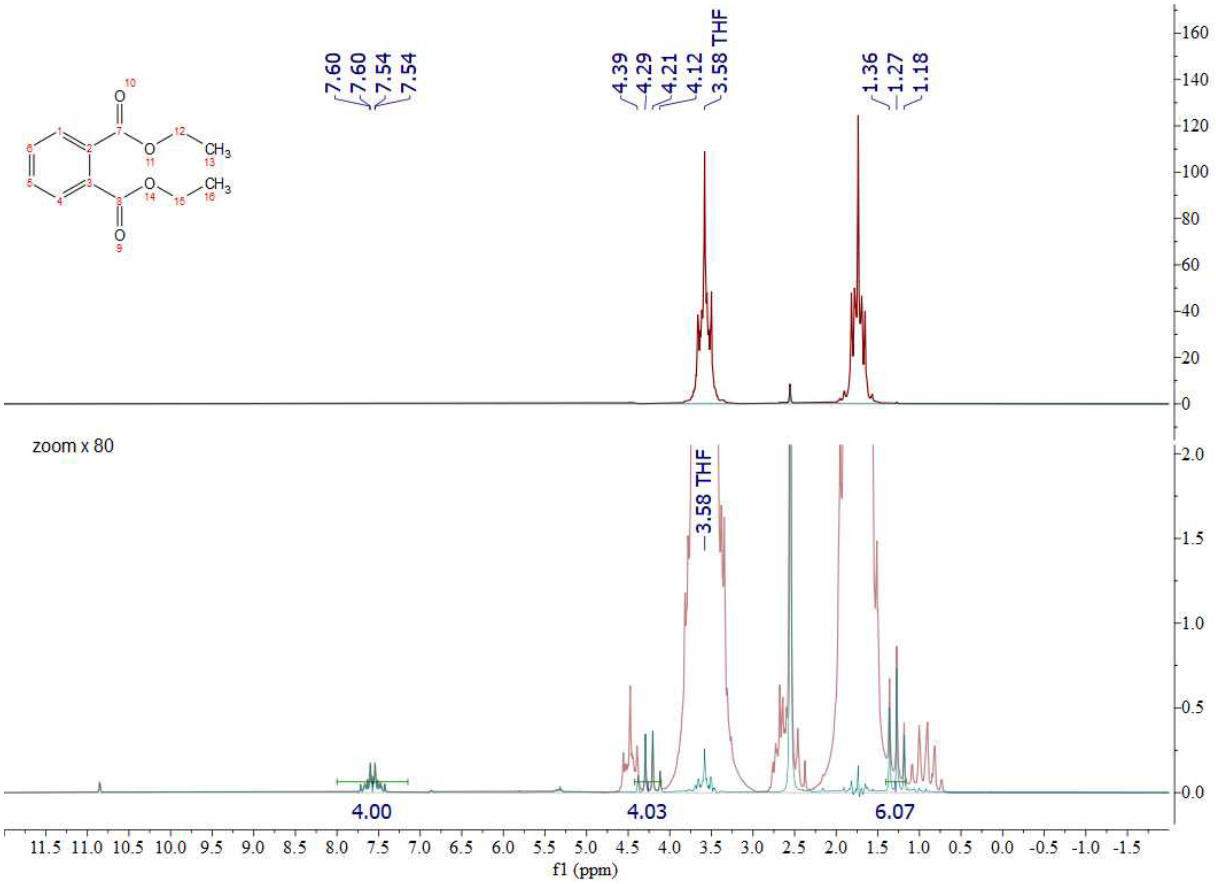


Figure 2: Comparison of a standard 1D 1H NMR spectrum of 20 mMolar diethyl phthalate in THF (red) and the 1D spectrum collected with the WET solvent suppression NMR sequence in the presence of ^{13}C decoupling (cyan).

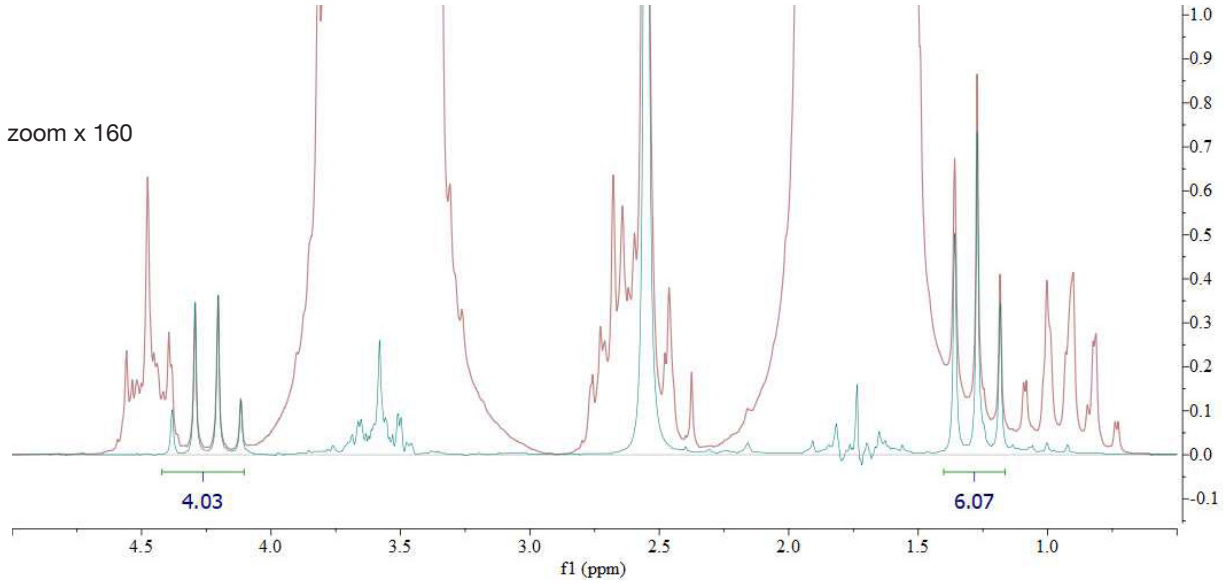


Figure 3: Zoomed comparison of a regular 1D ^{1}H NMR spectrum of 20 mMolar diethyl phthalate in THF (red) and the spectrum collected with the 1D ^{1}H WET solvent suppression protocol with ^{13}C decoupling (cyan).

Benzene

As a second example we explore the option of dissolving diethyl phthalate in an aromatic solvent, like benzene. Due to its lipophilic character, phthalates readily dissolve in aprotic aromatic solvents. By employing benzene as a solvent we eliminate the signal overlap in the aliphatic region, like observed above in the case of THF (see Figure 2). The challenge in this case is to resolve the signals of the aromatic protons of diethyl phthalate within the aromatic region around 7-8 ppm. Figure 4 shows a comparison of the standard ^{1}H spectrum with the spectrum measured after applying the WET suppression sequence and in the presence of ^{13}C decoupling. As expected, the aliphatic region is now clear and both aliphatic proton species at 1.04 ppm and 4.17 ppm can be identified. Unfortunately, in the standard spectrum (red) the aromatic protons of the phthalate are buried beneath the benzene signal at 7.16 ppm. The WET sequence, applied with activated ^{13}C decoupling strongly attenuates the benzene signal and completely removes the carbon satellites to baseline-separate the phthalate signals (cyan spectrum). A zoom of the aromatic region is shown in Fig. 5.

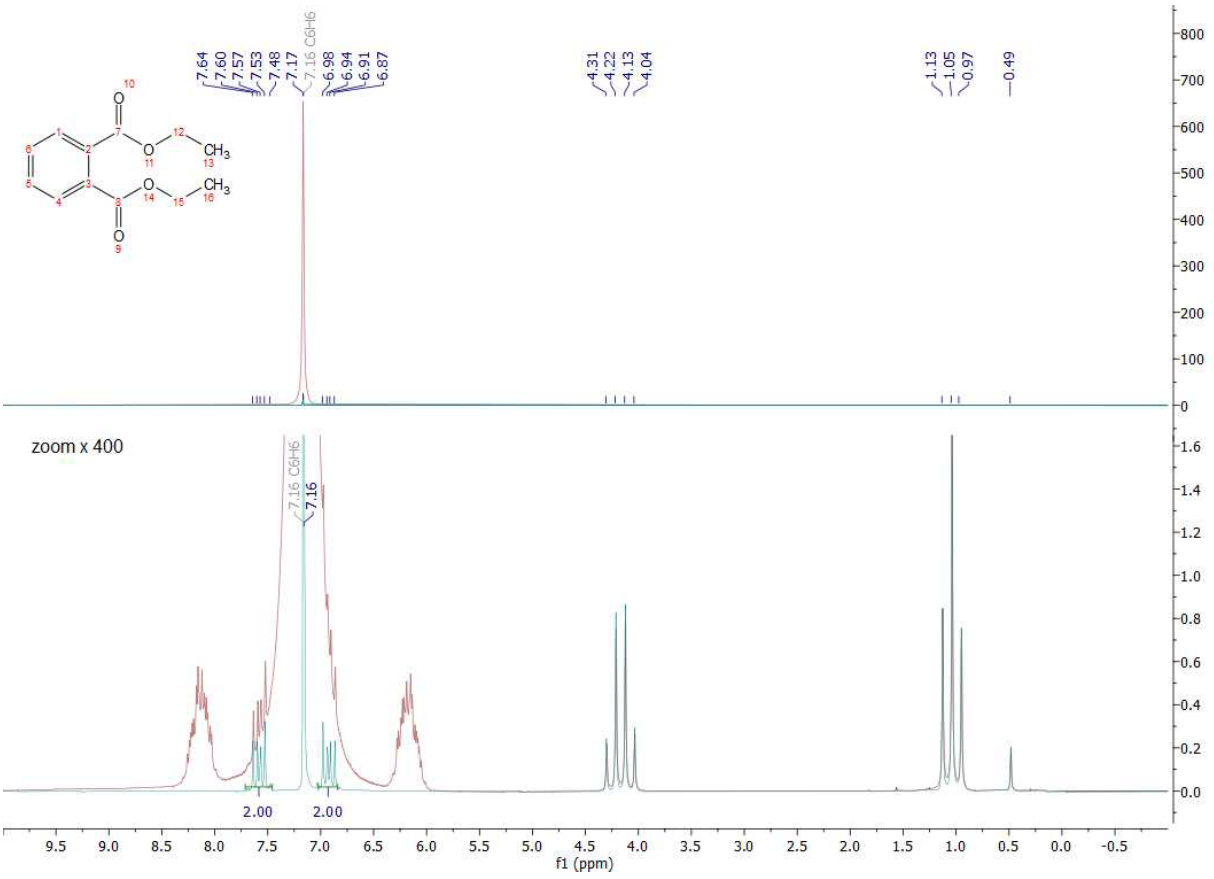


Figure 4: Comparison of a regular 1D ^{1}H NMR of diethyl phthalate in protonated benzene without ^{13}C decoupling and solvent suppression (red) and an applied 1D 1H WET NMR protocol with ^{13}C decoupling and solvent suppression (cyan).

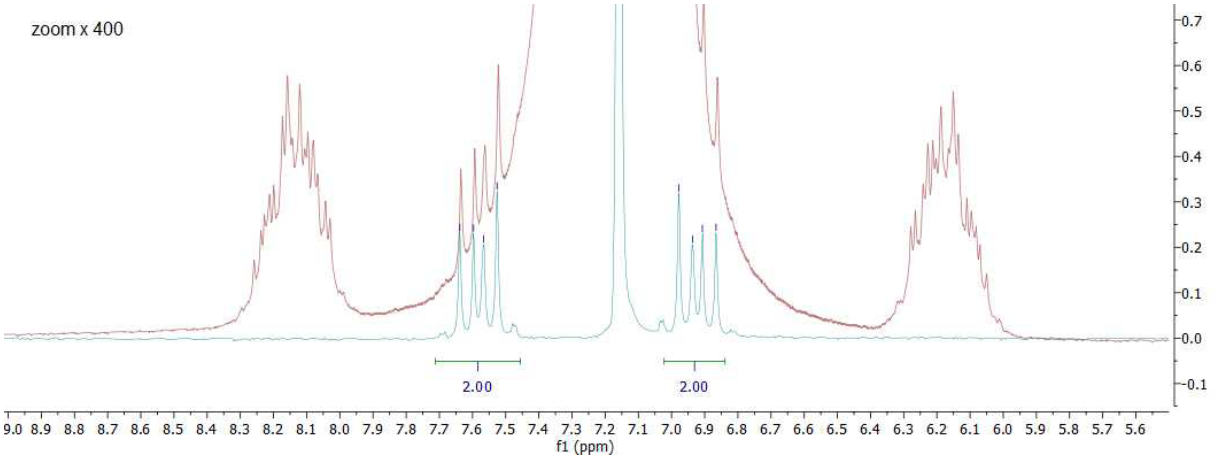


Figure 5: Zoomed comparison of the regular 1D ^{1}H NMR of diethyl phthalate in protonated benzene (red) with the 1D ^{1}H WET NMR spectrum acquired with ^{13}C decoupling (cyan).

Chloroform

As third example the spectrum of ethyl crotonate dissolved in protonated chloroform at a concentration of 20 mM was recorded with and without the WET solvent suppression protocol (Fig. 6). Once more we can observe how the spectrum recorded with the WET sequence (cyan spectrum) delivers baseline separated signals of the unsaturated protons of ethyl crotonate at 5.83 ppm and 6.97 ppm. This example clearly shows how powerful is the combination of a solvent suppression method applied previous to the signal acquisition in the presence of carbon decoupling. In this example, the WET suppression removes the overlapping of the main solvent peak with the signals at 6.97 ppm and ^{13}C decoupling removes the carbon satellites of the solvent signal overlapping with the signal of the proton at 5.83 ppm. The high frequency selectivity of the WET sequence to suppress the solvent peak can be appreciated from the fact that the multiplet of proton 1 at 6.97 ppm remains almost unaffected in the spectrum after the application of the solvent suppression sequence. A zoom of the aromatic region is shown in Fig. 7.

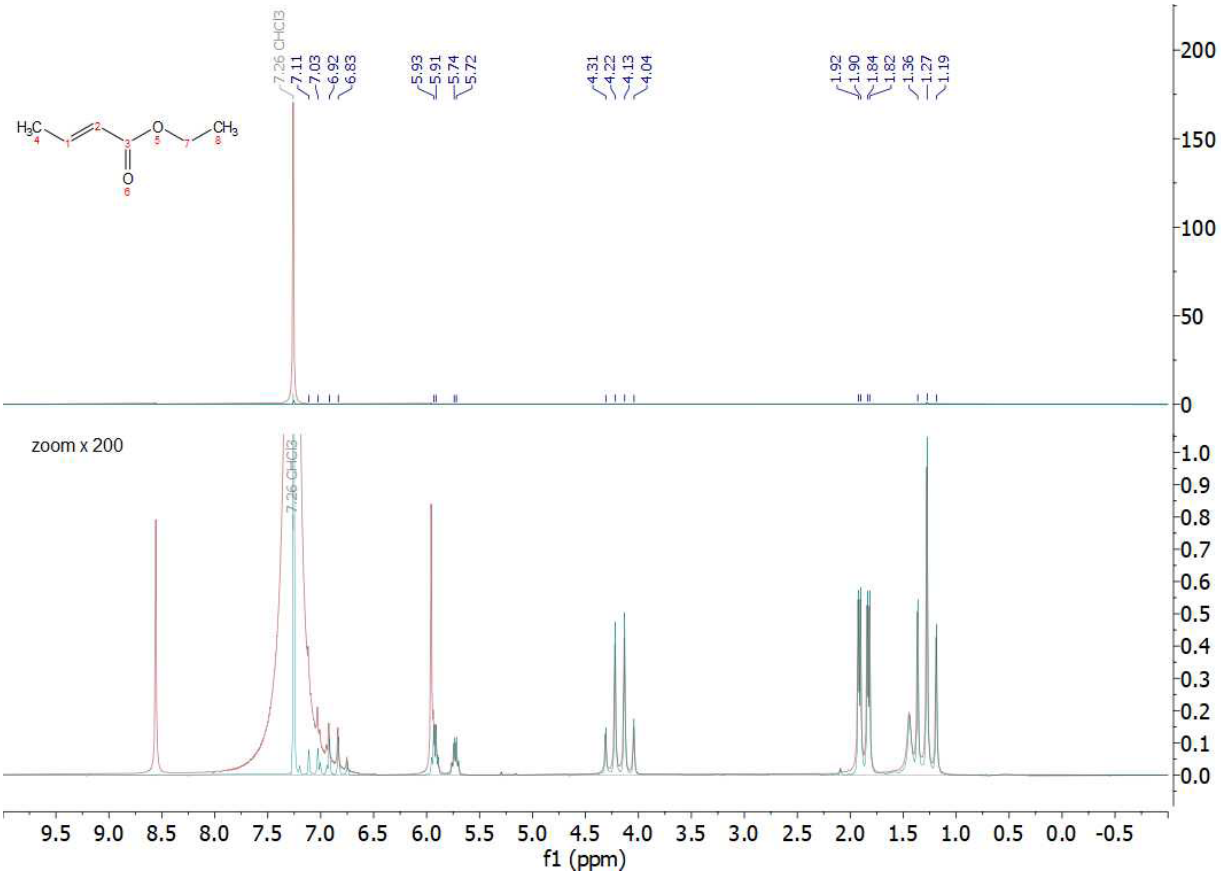


Figure 6: Comparison of a regular 1D ^{1}H NMR of ethyl crotonate in protonated chloroform (red) and the 1D ^{1}H WET solvent suppression protocol with ^{13}C decoupling (cyan).

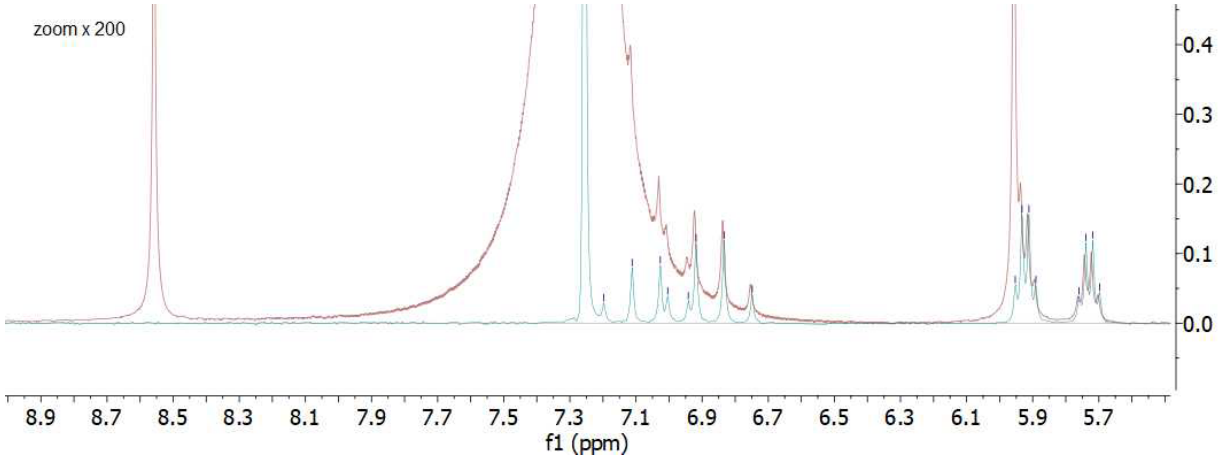


Figure 7: Zoomed comparison of a regular 1D spectrum (red) and the 1D WET spectrum acquired with ^{13}C decoupling (cyan).

Methanol

This solvent has two signals in the aliphatic region. In a first example we dissolved thiamine*HCl at a concentration of 20 mMolar. Figure 8 shows that in the standard 1D spectrum both methanol signals significantly overlap with the signals of the thiamine, making impossible any proper quantification of the desired peaks in the aliphatic region. After applying the WET protocol and acquiring the signal in the presence of ^{13}C decoupling, all four signals of interest show up baseline-separated with correct integration values. The aromatic region is not affected by the chosen solvent so only a zoom is shown separately in the upper left corner.

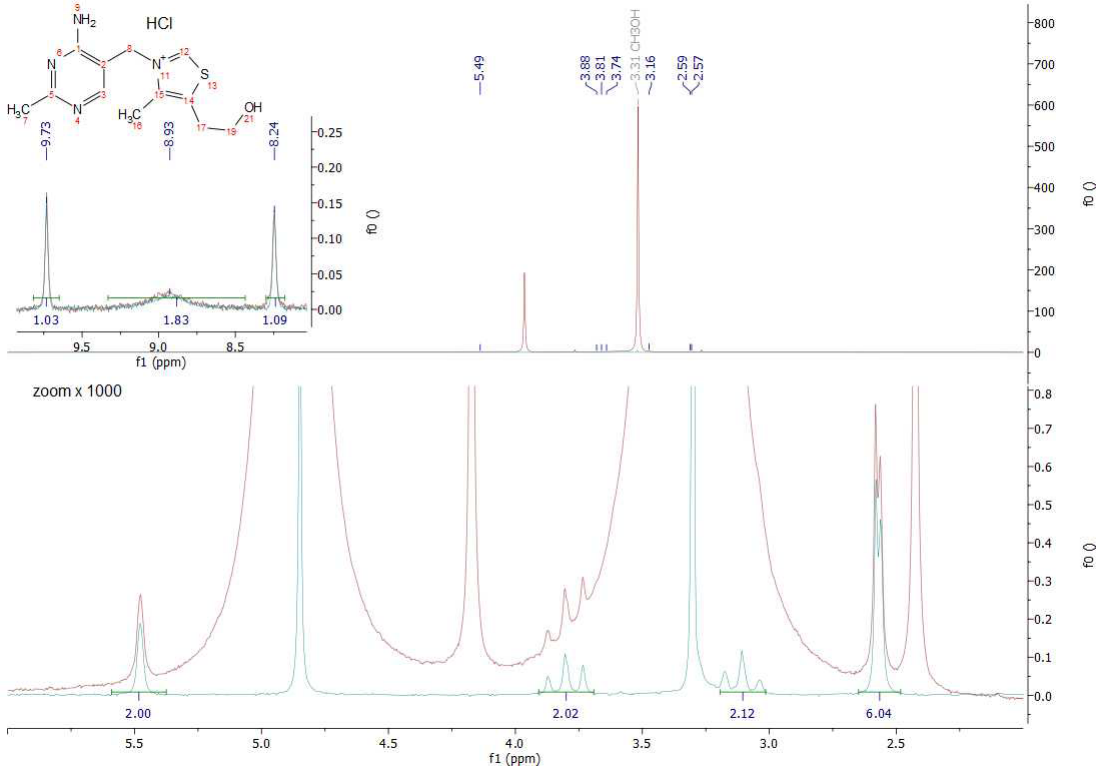


Figure 8: 1D ^{1}H NMR of thiamine*HCl in methanol with (cyan) and without (red) solvent suppression ^{13}C decoupling.

Figure 9 shows the spectra of the open ester form of L-ascorbic acid in methanol. The entire aliphatic region is covered by the methanol signals and only after applying the WET sequence, all the desired signals can be identified (cyan spectrum).

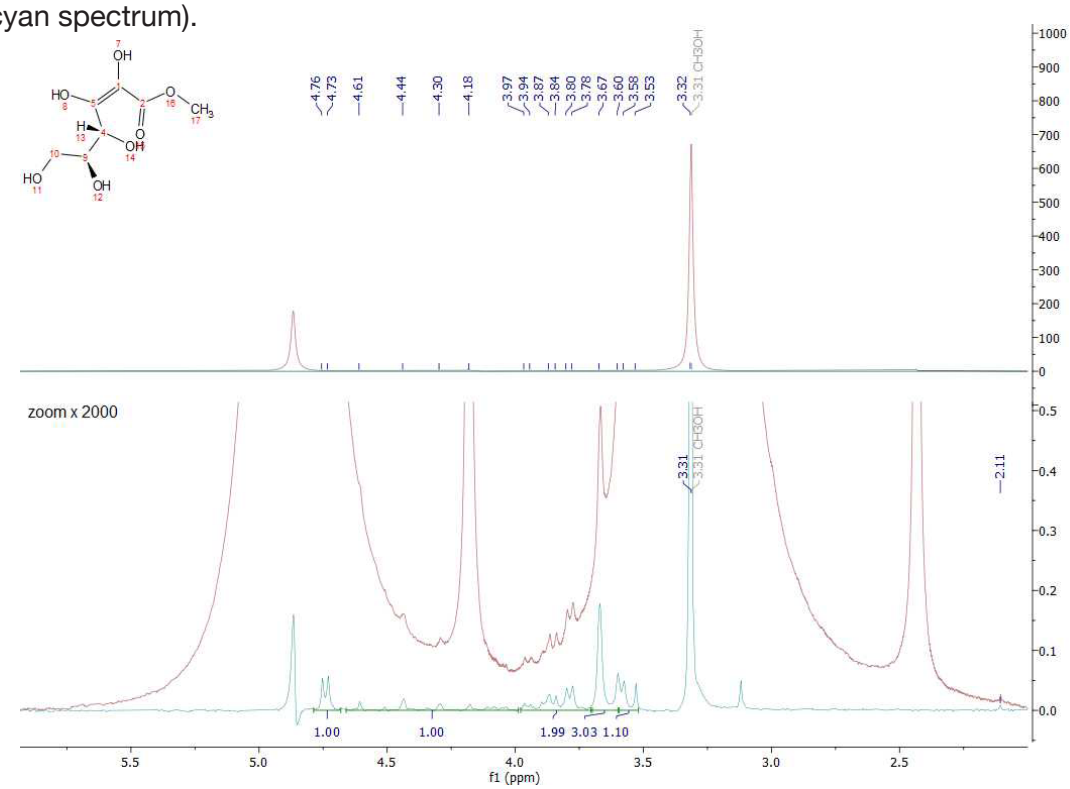


Figure 9: 1D 1H NMR of an ester in in methanol with (cyan) and without (red) 13C decoupling and solvent suppression

Dimethyl sulfoxide

Figure 10 shows the spectra of acetylsalicylic acid dissolved in dimethyl sulfoxide (DMSO). While the aromatic protons are fully resolved at around 7.50 ppm, the signal of the methyl group from the acetyl moiety is only visible after the WET sequence was applied to suppress the signal of DMSO at 2.20 ppm.

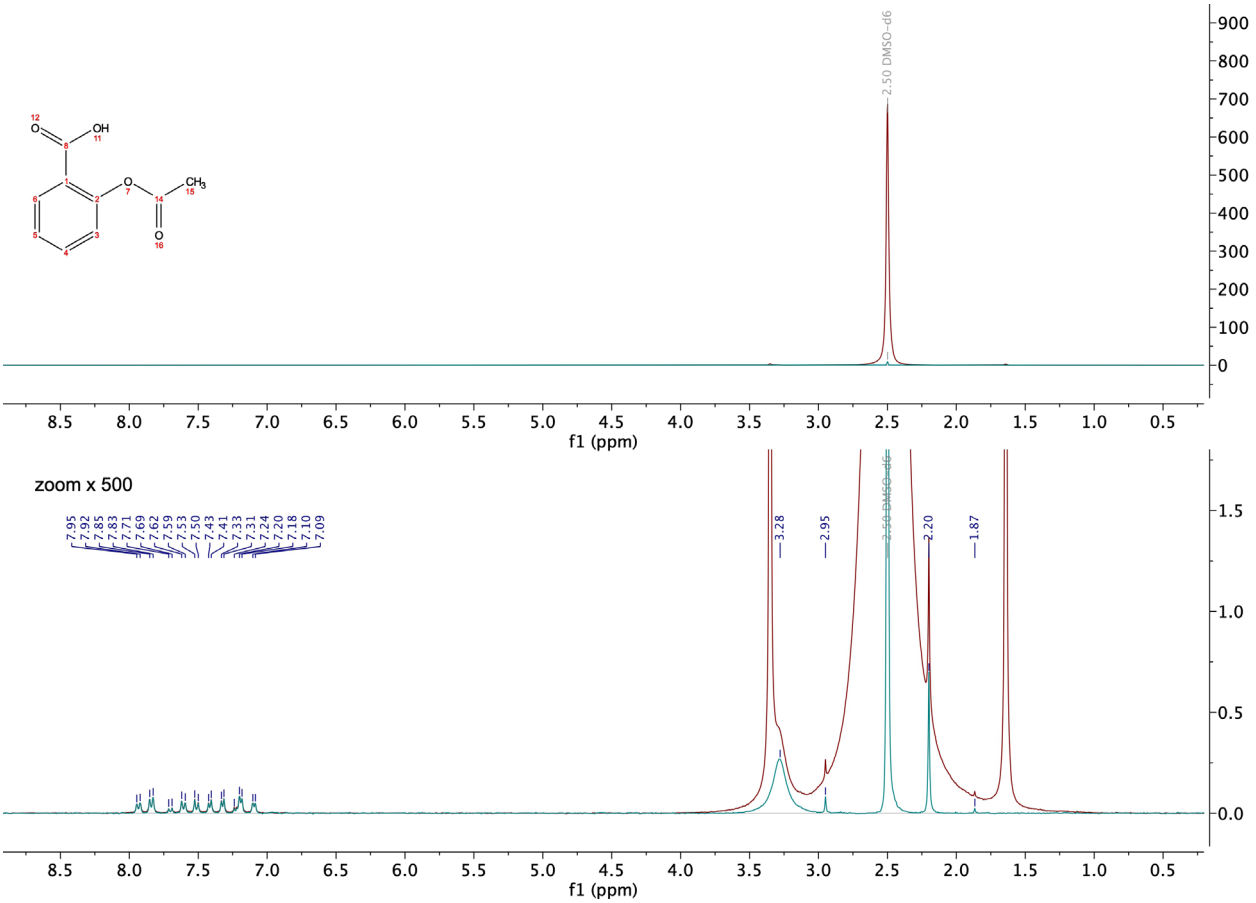


Figure 10: Comparison of a regular 1D ^{1}H NMR of acetylsalicylic acid dissolved in dimethyl sulfoxide (DMSO) (red) and the spectrum acquired with the WET solvent suppression protocol with ^{13}C decoupling (cyan).

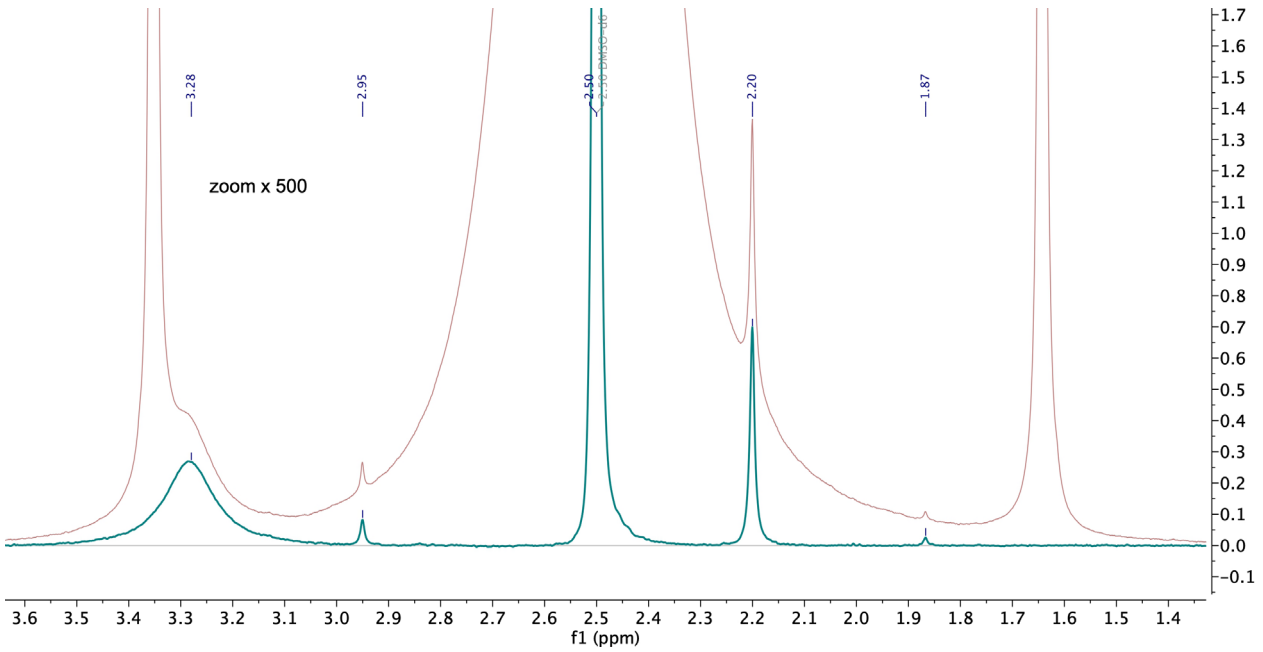


Figure 11: Zoom of the aliphatic region comparing a regular 1D ^{1}H NMR of acetylsalicylic acid dissolved in dimethyl sulfoxide (DMSO) (red) and the spectrum acquired with the WET solvent suppression protocol with ^{13}C decoupling (cyan).

Diisopropyl ether

The next example displays the spectra of diethyl phthalate in diisopropyl ether (Figure 12).

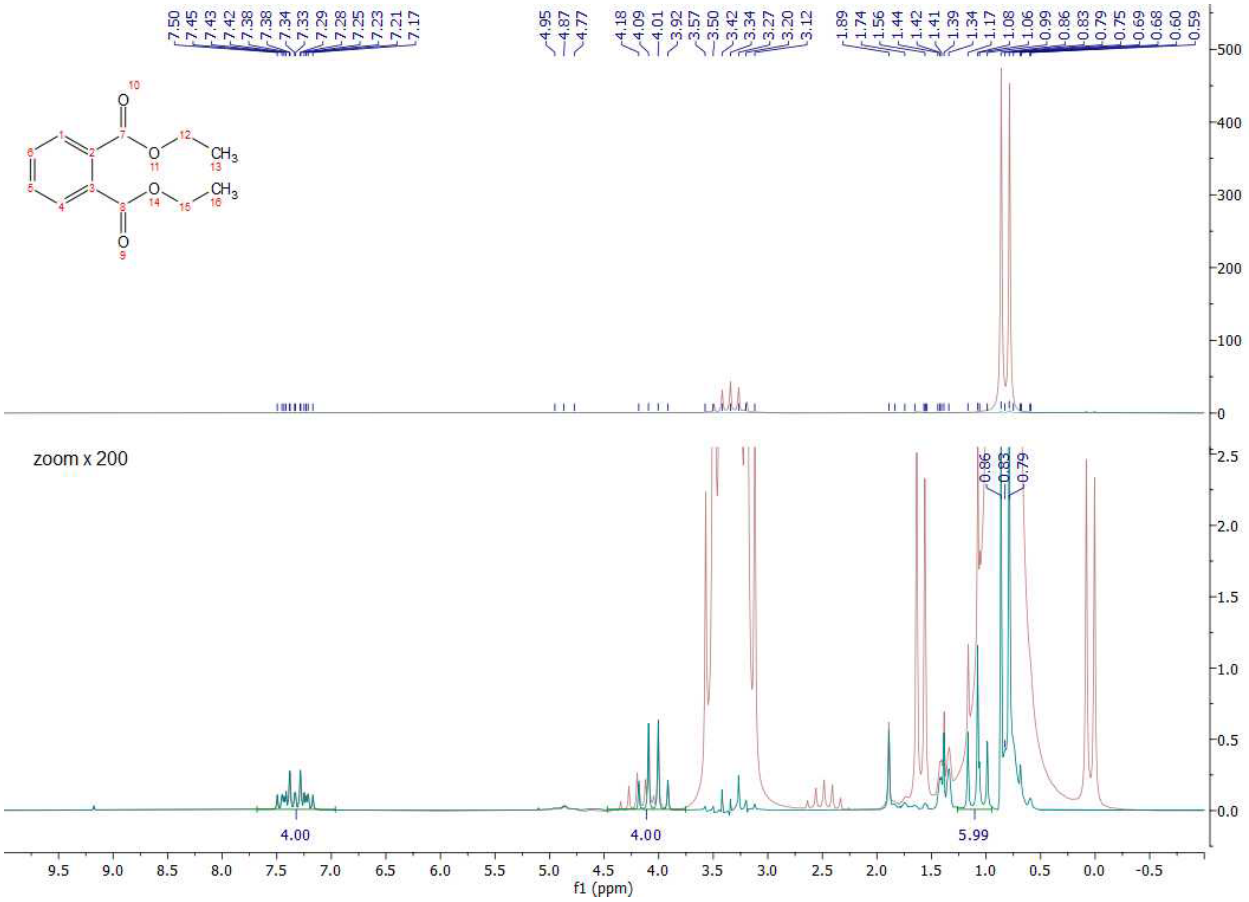


Figure 12: Comparison of a regular 1D ^{1}H NMR spectrum of diethyl phthalate in diisopropyl ether (red) and the spectrum collected with the WET solvent suppression protocol protocol with ^{13}C decoupling (cyan).

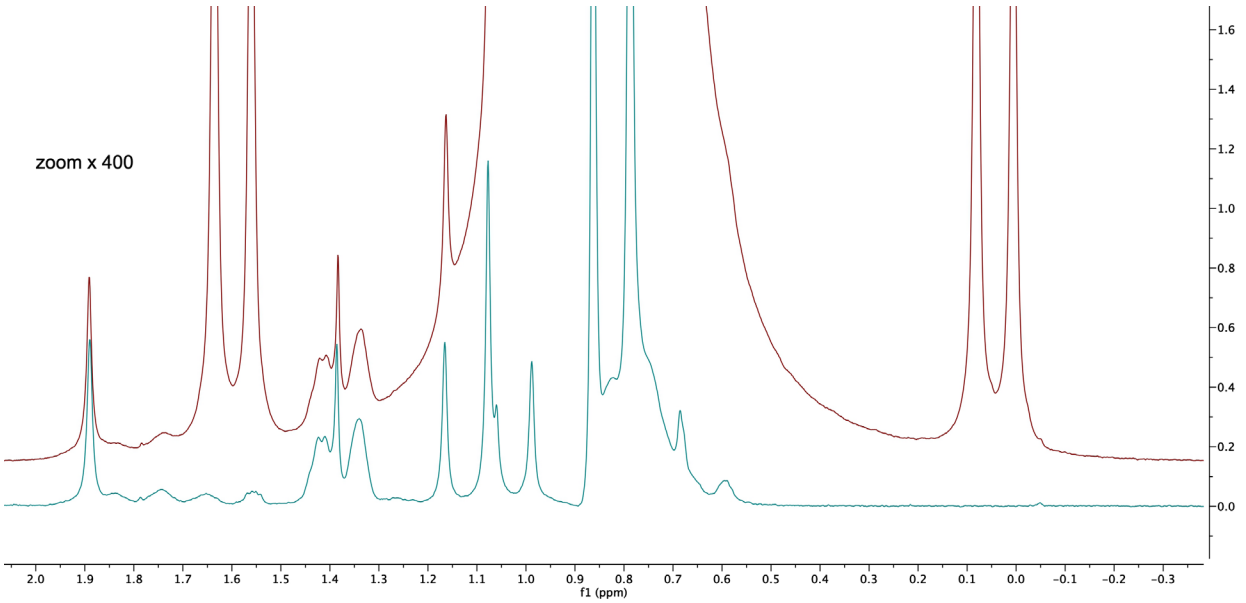


Figure 13: Zoom of the aliphatic region of the spectra of diethyl phthalate in diisopropyl ether. The solvent signal at 0.8 ppm (red) overlaps with the triplet of the methyl group of diethyl phthalate. The spectrum collected with the WET solvent suppression protocol with ^{13}C decoupling (cyan) shows the triplet baseline resolved and allows one to identify some impurities most likely present in the protonated solvent.

In summary, the WET sequence including the ^{13}C decoupling implemented on the Spinsolve ULTRA models allows one to collect NMR spectra from samples dissolved in protonated solvents without requiring time consuming and tedious work-ups. This is particularly advantageous to monitor chemical reactions online or at different stages of the synthesis as part of the quality control of the process, and not just at the end of the process to control the quality of the final product.