

Homonuclear Decoupling in ^1H NMR of Solids by Remote Correlation

Pinelopi Moutzouri, Federico M. Paruzzo, Bruno Simões de Almeida, Gabriele Stevanato, and Lyndon Emsley*

Abstract: The typical linewidths of ^1H NMR spectra of powdered organic solids at 111 kHz magic-angle spinning (MAS) are of the order of a few hundred Hz. While this is remarkable in comparison to the tens of kHz observed in spectra of static samples, it is still the key limit to the use of ^1H in solid-state NMR, especially for complex systems. Here, we demonstrate a novel strategy to further improve the spectral resolution. We show that the anti- z -COSY experiment can be used to reduce the residual line broadening of ^1H NMR spectra of powdered organic solids. Results obtained with the anti- z -COSY sequence at 100 kHz MAS on thymol, β -AspAla, and strychnine show an improvement in resolution of up to a factor of two compared to conventional spectra acquired at the same spinning rate.

Extracting useful structural information from ^1H NMR spectra of solids is a challenge. At natural isotopic abundance, strong ^1H - ^1H dipolar interactions typically produce linewidths of several kHz which more often than not mask the underlying chemical shifts, making resonance assignment impossible. The possibility to acquire high-resolution ^1H spectra would significantly strengthen the role of solid-state NMR in the field of structural characterization. Magic-angle spinning (MAS)^[1] can be used to average out homonuclear dipolar interactions, improving the resolution of ^1H NMR spectra by typically about two orders of magnitude as compared to those acquired from static samples. However, even at the fastest MAS rates available today (around 100–150 kHz),^[2] proton linewidths are still on the order of a few hundred Hz, which, in many cases, is still insufficient to resolve ^1H resonances. In comparison, ^1H linewidths in solution NMR spectra are typically of the order of 1 Hz.

In principle, further homonuclear decoupling can be achieved with approaches involving combined rotation and multi-pulse spectroscopy (CRAMPS).^[3] These use the simultaneous application of MAS and pulse sequences designed to suppress homonuclear dipolar couplings while retaining

isotropic chemical shifts, and nowadays they produce linewidths narrower than those in conventional MAS spectra at spinning rates up to 65 kHz.^[4] However, at MAS rates > 65 kHz, little to no advantage has been reported so far with CRAMPS approaches, and the resolution of spectra from pure MAS experiments at 100 kHz is comparable to that from CRAMPS experiments at lower spinning rates. While there are now many examples where fast MAS or CRAMPS have proven to yield important structural information, resolution is still the main bottleneck to a more widespread use.

All the strategies described above rely on a coherent averaging of the homonuclear dipolar Hamiltonian by rapid controlled rotations of the sample or of the spin operators. Recently, alternative strategies to further increase ^1H resolution have been considered, most notably involving delayed acquisition^[5] or the use of constant-time strategies that remove homogeneous broadening from the spectra,^[6] but such alternative approaches have so far received very limited attention. Here, we show how narrower ^1H spectra are obtained from a simple 2D scheme that exclusively generates correlations in which the coupling partners have all flipped their spin states, that is, correlations between so-called remote transitions. Specifically, we show that the residual broadening under MAS in a multi-spin system with different chemical shifts is due to a combination of higher-order shifts and

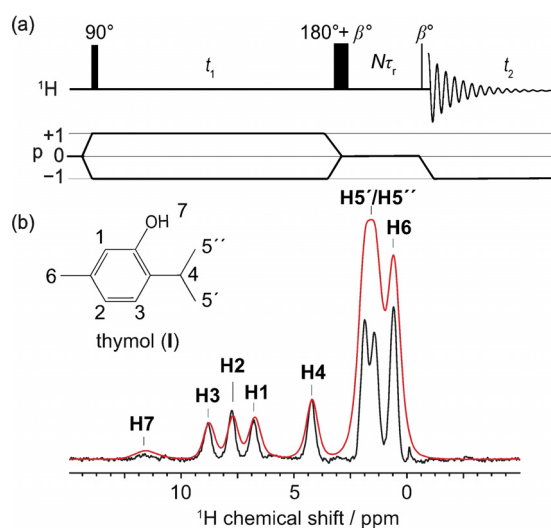


Figure 1. a) Anti- z -COSY pulse sequence and coherence-transfer pathway, where β indicates a low-flip-angle pulse. b) Echo-detected spectrum (red) and a 45° projection of an anti- z -COSY spectrum with a flip angle of 5° (black) of thymol (I) acquired with 100 kHz MAS. Further details are given in the Supporting Information.

[*] Dr. P. Moutzouri, Dr. F. M. Paruzzo, B. Simões de Almeida, Dr. G. Stevanato, Prof. L. Emsley
Institut des Sciences et Ingénierie Chimiques
École Polytechnique Fédérale de Lausanne (EPFL)
1015 Lausanne (Switzerland)
E-mail: lyndon.emsley@epfl.ch

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splittings, and that these splittings are removed in a 45° projection of an anti-z-COSY spectrum.

The anti-z-COSY pulse sequence (Figure 1) was first introduced by Oschkinat et al.^[7] to probe correlations between connected and remote transitions, and then implemented by Pell et al.^[8] for broadband homonuclear J decoupling in liquid-state NMR. The experiment produces phase-sensitive COSY-like 2D spectra in which, in the limit where the pulse angle β tends to zero, the fine structure of the diagonal peaks only contains correlations between the remote transitions, that is, transitions in which the passive spins (the coupling partners) have inverted their spin state between t_1 and t_2 . These transitions lead to peaks that lie along an anti-diagonal position at the center of gravity of the splitting.

Figure 1 shows the one-dimensional ^1H spectrum obtained from a 45° projection across the diagonal peaks in an anti-z-COSY experiment^[7,8] on a sample of powdered thymol (**I**) in comparison to the conventional echo-detected MAS experiment. Both spectra were obtained at 100 kHz MAS. The anti-z-COSY spectrum yields resonances that are narrower up to a factor of two. The effect of MAS on dipolar coupled nuclear spins has been the subject of many studies. A review is out of scope here, but most pertinent to our work are the articles by Nakai and McDowell^[9] as well as Levitt et al.,^[10] who both treated the case of two inequivalent dipolar coupled spins in the AB regime. They showed that MAS leads to a removal of the splitting caused by the dipolar coupling, but there will be a residual shift (ΔR) in the position of the resonances away from the isotropic values. There are no residual splittings. The shift depends on both the chemical shift and coupling tensors. This is illustrated in Figure 2a.

The average Hamiltonian to third order for an arbitrary ABC spin system^[12] (see the Supporting Information for details) shows [Eq. (S6)] that now both I_z and the two-spin $I_x I_x$ terms survive MAS. The resulting spectrum consists of resonances that are also shifted from the isotropic value (by ΔR) and are additionally split, in general, into a doublet of doublets, as illustrated in Figure 2b. Both the residual shifts and the splittings depend on all the spin-system parameters, and they are predicted to decrease with $1/\omega_r^2$, as shown in Figure 2c. The effect of the anti-z-COSY pulse sequence on these spectra is to remove the residual splittings but retain the residual shifts, and this is the underlying cause of the narrowing observed experimentally in Figure 1. This is supported by numerical simulations for single orientations shown in Figure 2d–f and by powder simulations for four- and five-spin systems (Figures S6,S7 in the Supporting Information). The ratio between the desired anti-diagonal peaks and

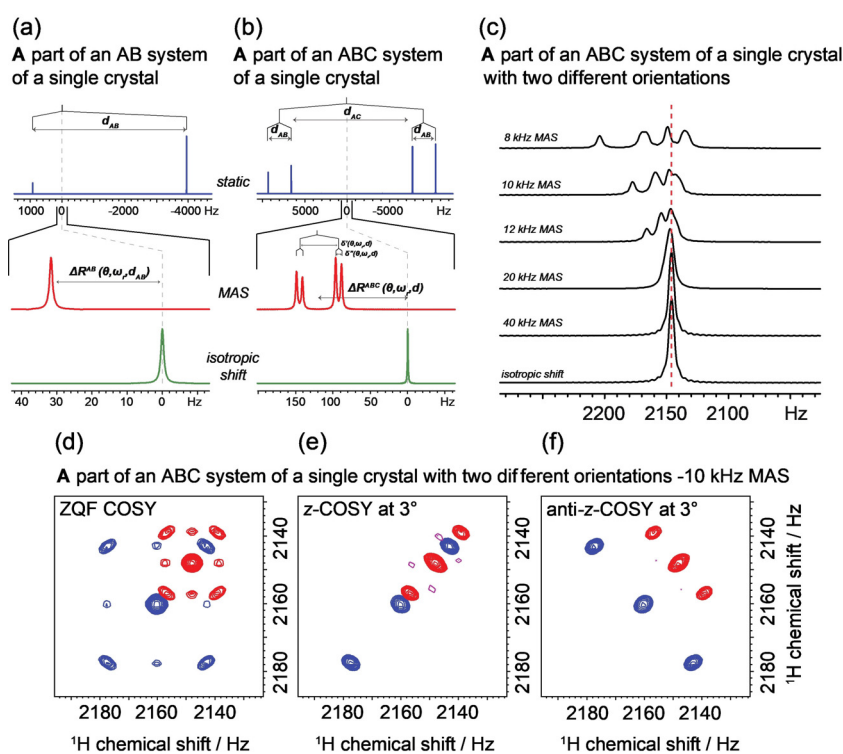


Figure 2. a) The A part of the spectrum of an AB system, and b) the A part of the spectrum of an ABC system for a single orientation simulated using SPINACH^[11] for (top) a static sample, (middle) under MAS, and (bottom) only the isotropic shift. c) The A part of the spectrum of an ABC system for two orientations as a function of the MAS rate. d)–f) Contour plots of the A diagonal-peak region in the 2D spectra of an ABC system for two different orientations (red and blue) in case of d) ZQF-COSY, e) z-COSY and f) anti-z-COSY experiments. All simulation methods and parameters are detailed in the Supporting Information.

the other peaks in the multiplet should increase as β decreases.^[8] However, the overall intensity of the correlations also decreases with decreasing β . Usually, an angle between 5° and 20° gives the best compromise between spectral resolution and sensitivity.

Figure 3a–c shows the difference in the 2D line shapes observed experimentally for thymol in a ZQF-COSY (that is, the 90° experiment), a z-COSY, and an anti-z-COSY experiment. The strong flip-angle dependence is confirmed in Figure 3d–g, which shows the linewidths for thymol for β angles from 90° to 3°. In the spectrum with $\beta = 3^\circ$, for H1, H2, H3, and H4 of thymol, we measured linewidths of 208, 194, 245 and 218 Hz, respectively, as compared to 359, 336, 350, and 346 Hz, respectively, in the $\beta = 90^\circ$ spectra. This corresponds to an increase in resolution by a factor of 1.4 to 1.7. The method is also demonstrated for microcrystalline powder samples of β -AspAla (**II**) and strychnine (**III**). Figure 4 shows projections extracted from anti-z-COSY spectra of β -AspAla which show the same decoupling effect as observed for thymol above. Again, in this sample, the linewidths are reduced by almost a factor of two for most protons. Figure 5 shows the 1D spectrum for strychnine extracted from the 2D anti-z-COSY spectrum acquired with an 8° flip angle, which is again significantly narrowed.

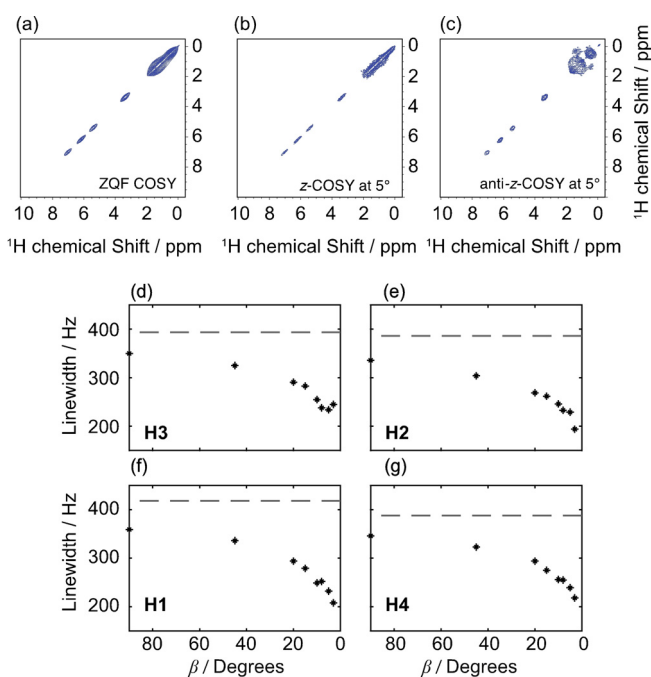


Figure 3. Contour plots of a) ZQF COSY, b) z-COSY, and c) anti-z-COSY spectra of thymol acquired at a MAS rate of 100 kHz. (b) and (c) were obtained with $\beta = 5^\circ$. d)–g) Measured full linewidths at half height of the resonances of protons H1–H4 from anti-z-COSY spectra of thymol as a function of β acquired at a MAS rate of 100 kHz. The dashed lines denote the proton linewidths measured in the conventional spin-echo spectrum.

All three samples used here yield clean anti-z-COSY spectra. In solution, these experiments can be compromised by artifacts due to the appearance of cross-peaks in the spectrum as well as zero-quantum transfers within the diagonal peaks, and additional measures are required to actively suppress them.^[8,13] However, we note that such unwanted peaks appear in anti-phase with respect to the couplings, and have no net integral. The numerous couplings and the comparatively broader lines expected in the solid-state mean that these unwanted peaks are likely to largely cancel themselves out, with no further action required. Additionally, the orientation distributions present in the powder leads to different sizes of the residual couplings and might act in a similar manner to the active measures usually taken to suppress artifacts. Indeed, the cross-peaks we observe here are weak in intensity (see Figure S2).

We note that equivalent spins will behave differently. This is simulated for an A_2B system in the Supporting Information. We see in Figure S5 that the 2D line shape has some negative intensity in the anti-z-COSY spectrum, which leads to small negative dips in the 45° projection. This might correspond to the origin of the dips observed for the CH_3 and NH_3^+ peaks in Figures 1 and 4 for small β values. For the anti-z-COSY concept to work properly, it is important that the z magnetization should remain unchanged during the z -filter period. Therefore, any effect that changes any of the spin states during the mixing scheme will lead to a reduction in resolution. Notably, spin diffusion during this period will induce spin flip-flops. While the fast spinning rate slows down

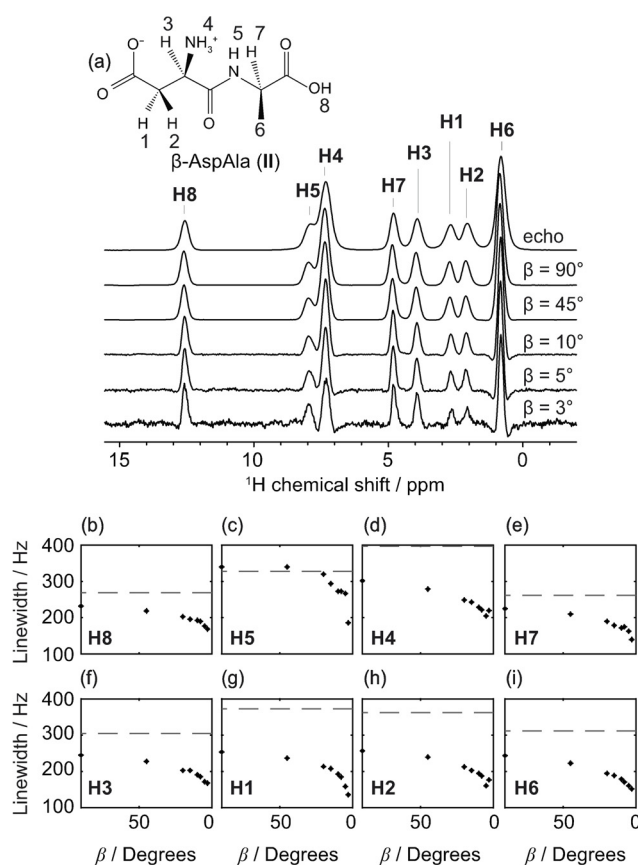


Figure 4. a) Spectra of β -AspAla (II) obtained from 45° integral projections of anti-z-COSY spectra acquired at 100 kHz MAS. The top spectrum was acquired with the conventional spin-echo sequence at the same sample spinning rate. b)–i) Measured linewidths of protons H1–H8 as a function of β . The dashed lines denote the proton linewidths measured in the conventional spin-echo spectrum.

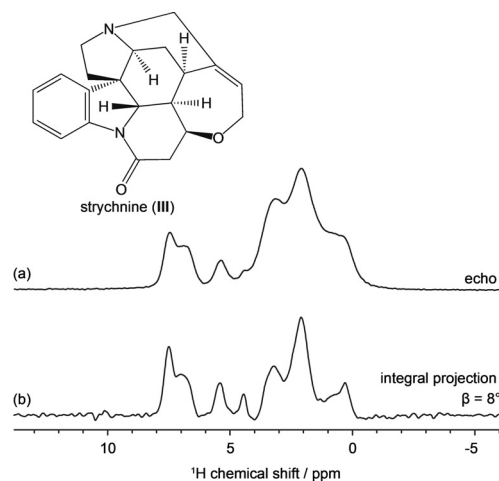


Figure 5. a) Echo-detected 100 kHz MAS spectrum of strychnine (III). b) 1D spectrum extracted as an integral projection from a doubly sheared 2D anti-z-COSY spectrum acquired with a flip angle of $\beta = 8^\circ$ at 100 kHz MAS.

homonuclear spin diffusion, it is important to keep the delay as short as possible. Additionally, any dipolar-recoupling effects caused by the mixing pulses will also induce spin flips.

Here we use a mixing time equal to a single rotor period. These effects and others leading to limiting resolution will be explored further in the future. We finally note that we expect this strategy to also lead to better resolution at lower spinning speeds. This is confirmed in Figure S8, where we show the results for thymol at a MAS rate of 62.5 kHz. In this case, we obtain a gain in resolution of a factor between 1.8 and 2.1.

In conclusion, the simple approach introduced here for achieving homonuclear decoupling in organic solids by exclusively generating remote correlations yields a gain in resolution of up to a factor of two as compared to conventional echo-detected MAS experiments. Smaller flip angles produce spectra with higher resolution at the expense of reduced sensitivity. The factor-two gain in resolution achieved with the concept as introduced here in its most simple form is striking, with clear room for improvement through further development.

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Conflict of interest

The authors declare no conflict of interest.

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