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Communication

Symmetry-based recoupling of proton chemical shift anisotropies in ultrahigh-field solid-state NMR

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Abstract

A two-dimensional NMR experiment for estimating proton chemical shift anisotropies (CSAs) in solid powders under magic-angle spinning conditions is demonstrated in which ^{1}H CSAs are reintroduced with a symmetry-based recoupling sequence while the individual proton sites are resolved according to their isotropic chemical shifts by magic-angle spinning (MAS) or combined rotation and multiple pulse (CRAMPS) homonuclear decoupling. The experiments where carried out on an ultrahigh-field solid-state NMR instrument (900 MHz ^{1}H frequency) which leads to increased resolution and reliability of the measured ^{1}H CSAs. The experiment is expected to be important for investigating hydrogen bonding in solids.

Keywords: Proton MAS NMR; Chemical shift anisotropy; Recoupling; CRAMPS; Hydrogen bonding

1. Introduction

Hydrogen bonding is a key interaction in chemistry and biology, playing a central role in determining the structure and properties of many materials as well as in life processes [1]. Proton nuclear magnetic resonance (NMR) spectroscopy is an attractive technique for probing hydrogen bonds since the chemical shift interaction is sensitive to local electronic environments; for instance, a relationship between isotropic chemical shifts and hydrogen bond lengths has been demonstrated [2–5]. Solid-state NMR can potentially investigate local structure and bonding in great detail since the complete chemical shift tensor is available for measurement. However, high resolution solid-state NMR of protons is challenging due to poor spectral resolution arising from the small chemical shift range and the dominant ^{1}H–^{1}H homonuclear dipolar interactions present in most materials. These challenges are being met by advances in magic-angle spinning (MAS) technology, the development of advanced pulse sequences (and the hardware to implement them), and the availability of high magnetic fields.

Isotropic chemical shifts of protons in hydrogen bonds can be obtained from high resolution ^{1}H spectra acquired using fast MAS or combined rotation and multiple pulse (CRAMPS) homonuclear decoupling [4]. However, measurements of ^{1}H chemical shift anisotropy (CSA) are limited to static powders and single-crystal spectra of simple carboxylic acids obtained with multiple pulse homonuclear decoupling [6,7], analysis of spinning sidebands in CRAMPS spectra [8], and ^{1}H–^{2}H dipolar NMR of residual protons in deuterated crystalline hydrate powders [9]. Extending these approaches to more complex systems is not feasible since most materials of interest are limited to powder samples, have a multitude of proton sites whose isotropic resonances and spinning sidebands cannot be sufficiently resolved, and are not conducive to isotopic dilution of protons.

Here, we demonstrate an approach for measuring ^{1}H CSAs in powders that circumvents these limitations. The experiment (see Fig. 1) is a two-dimensional (2D) experiment in which the anisotropy of the ^{1}H chemical shift

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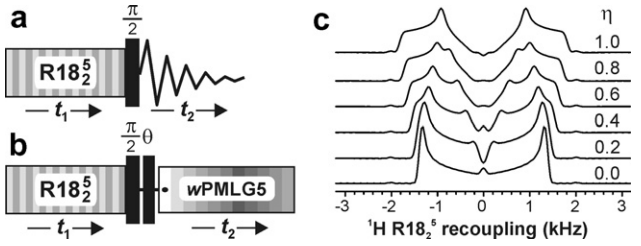

Fig. 1. 2D pulse sequences for ^{1}H CSA recoupling in t_1 with R18$_2^5$ symmetry sequence and correlation to isotropic chemical shifts in t_2 under (a) regular MAS conditions and (b) *w*PMLG5 multiple pulse homonuclear decoupling [11]. (c) simulated ^{1}H R18$_2^5$ CSA recoupled lineshapes as a function of the asymmetry parameter η with $|\delta_{aniso}| = 10$ ppm, 16.103 kHz MAS frequency.

tensor is observed in the indirect dimension by means of a symmetry-based [10] recoupling sequence while the individual proton sites are resolved according to their isotropic chemical shifts in the direct dimension by MAS alone (Fig. 1a) or with a multiple pulse homonuclear decoupling sequence [11,12] (Fig. 1b). Furthermore, the experiments were carried out on an ultrahigh-field NMR instrument (21.1 T, 900 MHz ^{1}H frequency) leading to increased resolution and increased reliability of the estimated ^{1}H CSA values since the chemical shift interaction is proportional to the magnetic field strength.

2. Pulse sequence

In order to obtain high-resolution solid-state NMR spectra, MAS is required to resolve isotropic chemical shifts. However, the gain in resolution comes at the expense of a loss in information as anisotropic nuclear spin interactions such as dipole–dipole couplings and CSA are averaged out by MAS. However, with an appropriately designed pulse sequence, it is possible to interfere with the averaging of MAS and selectively reintroduce or "recouple" desired nuclear spin interactions. For ^{1}H CSA recoupling experiments, it is crucial that the CSA interactions are selectively recoupled while the homonuclear ^{1}H–^{1}H interactions are suppressed.

Levitt and co-workers have developed symmetry principles for designing MAS recoupling pulse sequences [10]. A set of RN$_n^v$ pulse sequence symmetries for recoupling heteronuclear dipolar interactions while suppressing homonuclear dipolar interactions have been described [13]. It has been noted that, since heteronuclear dipolar and CSA interactions share the same symmetry properties with respect to rotations and r.f. pulses, these symmetries also recouple the CSA of the nuclei to which the sequence is applied [13,10]. It is this property that is exploited in the present work.

The sequence used is denoted R18$_2^5$ and consists of a continuous series of 180° pulses that alternate in phase between $\pm$ 50°, timed such that 18 such pulses are applied over two sample rotations about the magic-angle. According to the first order selection rules [10] derived from average Hamiltonian theory, the sequence suppresses homonuclear dipolar interactions, isotropic chemical shifts and heteronuclear *J*-coupling interactions, but recouples terms with $(l,m,\lambda,\mu) = (2,2,1,-1)$ and $(2,-2,1,1)$ which include both CSA and heteronuclear dipolar interactions, as well as homonuclear *J*-coupling interactions with $(l,m,\lambda,\mu) = (0,0,0,0)$. The sequence is γ-encoded (each m term is associated with a single value of μ), therefore the signal arising from a powder sample depends only on two of the three crystallite orientations, leading to larger oscillations in the time domain signal and more defined singularities upon Fourier transformation compared to non-γ-encoded sequences. As the numerical simulations in Fig. 1c show, Fourier transformation of a signal obtained as a function of the R18$_2^5$ recoupling time gives a "CSA recoupled lineshape" whose breadth reflects the magnitude of the CSA, $|\delta_{aniso}|$, and whose shape reflects the asymmetry parameter, η.

This 2D anisotropic-isotropic chemical shift correlation experiment is similar in principle to previously described approaches [14–18], but has the very important distinction that the homonuclear dipolar interactions are completely suppressed (to first order in average Hamiltonian theory) which is crucial for application to strongly coupled protons. For instance, the CSA recoupling sequences presented by Tycko and co-workers [15,18] have the symmetry C3$_3^1$ and recouple both CSA and homonuclear dipolar interactions. These sequences have an advantage that a basic C element can be chosen such that the CSA recoupled lineshapes have the same shape as a static powder pattern. However it is not possible to fully remove the homonuclear dipolar interactions. For the four π-pulse sequence [15], the scaling factors for the homonuclear dipolar interactions are zero only for infinitely short π pulses, a condition that obviously cannot be achieved experimentally. For the ROCSA sequence [18], the basic C element has been designed to reduce the scaling factors of homonuclear dipolar interactions; however these interactions are not completely suppressed. This reduction is sufficient for ^{13}C CSA recoupling in the presence of ^{13}C–^{13}C homonuclear dipolar interactions but not sufficient for ^{1}H CSA recoupling in the presence of much stronger ^{1}H–^{1}H dipolar interactions.

To test the homonuclear decoupling capability of the R18$_2^5$ CSA recoupling sequence, a series of numerical simulations were carried out for protons in typical environments with both CSA and ^{1}H–^{1}H dipolar interactions. As Fig. 2 demonstrates, the ^{1}H CSA recoupled lineshapes are not significantly influenced by the presence of ^{1}H–^{1}H homonuclear dipolar couplings. The simulations for the CH_2 group are particularly indicative of this property as the recoupling of a 4 ppm CSA (3.6 kHz at 900 MHz) is not significantly perturbed by the much stronger homonuclear dipolar coupling constant of −22 kHz.

It should also be noted that a ^{1}H CSA recoupling sequence has previously been reported [19], but has been employed for spectra editing purposes rather than ^{1}H CSA measurements.

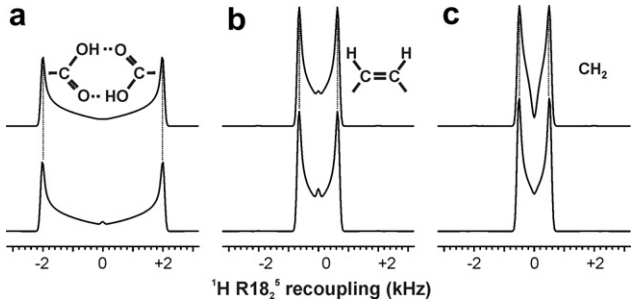

Fig. 2. Comparison of ^{1}H $R18_2^5$ CSA recoupled lineshapes for numerical simulations with (*upper*) and without (*lower*) ^{1}H–^{1}H dipolar interactions for (a) carboxylic acid dimer ($|\delta_{aniso}| = 15$ ppm, $b_{HH}/2\pi = -6.5$ kHz), (b) H–C=C–H olefinic or aromatic fraction ($|\delta_{aniso}| = 5$ ppm, $b_{HH}/2\pi = -9.2$ kHz), (c) CH_2 group ($|\delta_{aniso}| = 4$ ppm, $b_{HH}/2\pi = -22.0$ kHz). The MAS frequency was 16.103 kHz and the asymmetry parameter was $\eta = 0$ in each case.

3. Experimental

Experiments were performed on a Bruker AVANCE-II 900 MHz NMR spectrometer operating at a magnetic field of 21.1 T and using a narrow-bore double resonance 2.5 mm MAS NMR probe. The MAS frequency in all experiments was 16.103 kHz. At this spinning frequency, the $R18_2^5$ symmetry sequence was achieved by applying a train of 180° pulses of 6.9 μs (corresponding to a 72.5 kHz ^{1}H nutation frequency) in succession with phases alternating between ± 50°. The r.f. power level was set to 72.5 kHz according to a careful calibration of the ^{1}H nutation frequency with 2D ^{1}H nutation experiments performed on adamantane.

Directly detected high-resolution ^{1}H spectra were obtained with a windowed phase-modulated Lee–Goldberg (*w*PMLG-5) homonuclear decoupling sequence [11] with a ^{1}H nutation frequency of 109 kHz and sampling windows of 3 μs. The tip angle and phase of second pulse were experimentally optimized on a 1D ^{1}H spectrum to minimize the zero-frequency artifact and had values near 54.7° and 270° for the tip angle and phase, respectively.

All experiments employed presaturation pulses consisting of twenty 90° pulses separated by 10 ms prior to the recycle delay. For maleic acid, the recycle delay was 60 s and 64 t_1 increments each with eight scans were acquired. For citric acid, the recycle delay was 120 s and 50 t_1 increments each with eight scans were acquired. The indirect CSA recoupling dimension, t_1, was acquired with increments of eight 180° pulses, giving a t_1 dwell time of 8×6.9 μs = 55.2 μs.

The ^{1}H chemical shifts are referenced to TMS using the proton resonance in the ^{1}H MAS (10 kHz) NMR spectrum of adamantane (1.74 ppm) as a secondary reference. The chemical shift scales for citric acid spectra acquired with the *w*PMLG-5 sequence have been corrected with scaling factor of 0.589 which was experimentally determined by comparing the 1D *w*PMLG-5 spectrum to the ^{1}H 30 kHz MAS NMR spectrum. The isotropic value, anisotropy, and asymmetry parameter for the chemical shift interaction are related to the principal elements of the shift tensor according to $\delta_{iso} = (\delta_{11} + \delta_{22} + \delta_{33})/3$, $\delta_{aniso} = \delta_{33} - \delta_{iso}$, $\eta = (\delta_{22} - \delta_{33})/\delta_{aniso}$, where the principal elements are labeled and ordered according to $|\delta_{33} - \delta_{iso}| \geqslant |\delta_{11} - \delta_{iso}| \geqslant |\delta_{22} - \delta_{iso}|$.

For both the experimental and simulated data, the indirect dimension was processed by first removing the DC offset (leading to a zero-frequency spike upon Fourier transformation) by subtracting the average of the final 1/8th points in t_1 from all data points, followed by performing a real Fourier transformation to give the CSA-recoupled lineshapes. Processing and fitting were performed using a program written in *Mathematica* version 5.2.

Numerical simulations were performed with the SPINEVOLUTION program [20]. The effects of r.f. inhomogeneity were incorporated into the simulations and fitting procedure as follows. For each value of $|\delta_{aniso}|$ and η, 32 simulations of $R18_2^5$ CSA recoupled lineshapes were carried out with ^{1}H nutation frequencies between 50 and 100 kHz. Each of the simulations was weighted according to the corresponding intensity in the experimental nutation spectrum and then the series of simulations were summed. In order to fit these calculated lineshapes to experimental lineshapes, the vertical scaling factor and Gaussian line broadening were adjusted to minimize the sum of the squared differences between experimental and calculated data points (χ^2). Contour plots of χ^2 were constructed in order to estimate the values of $|\delta_{aniso}|$ and η that give the minimum χ^2, χ^2_{min}, and the uncertainties in these values (estimated from the contour levels at $2 \times \chi^2_{min}$).

4. Results and discussion

Maleic acid was chosen as a suitable test sample since it has protons involved in two types of hydrogen bonds, one intra-molecular and the other inter-molecular, and ^{1}H chemical shift tensor data obtained by single crystal NMR is available [21] for comparison and validation of this method. The 2D spectrum (Fig. 3a) shows three types of protons resolved according to their isotropic chemical shifts having CSAs that are clearly different from one another. In order to fit the CSA recoupled lineshapes, a series of simulations were carried out as function of $|\delta_{aniso}|$ and η (incorporating the r.f. inhomogeneity measured in a nutation experiment) and each of these simulated lineshapes were fit to the experimental lineshape by adjusting the vertical scaling and line broadening to minimize χ^2. The experimental lineshapes are reproduced very well by the best fit simulated lineshapes (Fig. 3b). The χ^2 contour plots (Fig. 3c) provide a means of estimating the uncertainty in $|\delta_{aniso}|$ and η. As shown in Fig. 3c and in Table 1, the values of $|\delta_{aniso}|$ and η estimated from this experiment are in good agreement with those determined in the single crystal study and thus validate this method.

For more complex materials, the resolution of the ^{1}H spectra obtained with MAS alone may not be sufficient

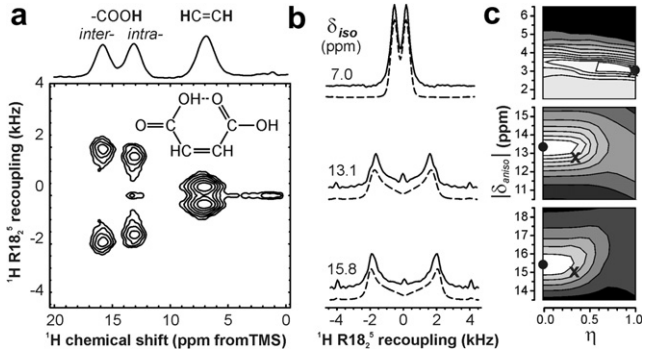

Fig. 3. (a) 2D ^{1}H anisotropic-isotropic chemical shift correlation spectrum of maleic acid obtained at 16.103 kHz MAS frequency using the pulse sequence in Fig. 1a. (b) Experimental CSA recoupled lineshapes obtained from slices at the indicated isotropic chemical shifts (solid lines) with best fit simulations (dashed lines). (c) Contour plots of the quality of fit (χ^2) of simulated to experimental lineshapes as a function of $|\delta_{aniso}|$ and η (the nth contour level is at $2^{n/2} \times \chi^2_{min}$). The dots represent the best fit values of $|\delta_{aniso}|$ and η used for the simulations presented in (b) while x represents the values of $|\delta_{aniso}|$ and η measured in a previous single crystal study [21] (see Table 1).

Table 1
Summary of ^{1}H R18$_2^5$ CSA recoupling results for maleic acid and citric acid

	δ_{iso} (ppm)[a]	$\lvert\delta_{aniso}\rvert$ (ppm)[b]	η [b,c]
Maleic acid (CSA recoupling)			
HC═CH	7.0	3.0 ± 0.5	1.0 (0.0–1.0)
—COOH (inter)	13.1	13.3 ± 0.6	0.0 (0.0–0.4)
—COOH (intra)	15.8	15.4 ± 0.9	0.0 (0.0–0.4)
Maleic acid (single crystal [21])			
HC═CH	7.6	3.0	0.96
—COOH (inter)	14.5	12.7	0.33
—COOH (intra)	16.6	15.1	0.32
Citric acid (CSA recoupling)			
—CH$_2$—	2.4	4.5 ± 0.5	0.6 (0.0–1.0)
—CH$_2$—	3.1	5.5 ± 0.5	0.8 (0.0–1.0)
—OH	5.5	14.0 ± 0.5	0.0 (0.0–0.4)
—COOH	10.0	12.8 ± 0.5	0.3 (0.0–0.5)
—COOH	10.7	12.5 ± 0.4	0.4 (0.0–0.5)
—COOH	13.9	17.9 ± 0.7	0.1 (0.0–0.5)

[a] From MAS spectrum.
[b] Error estimated from χ^2 contour plots.
[c] Estimated error range in parentheses.

to resolve the individual proton sites. However, it is possible to combine the CSA recoupling sequence with a multiple-pulse homonuclear decoupling sequence to improve the resolution of the proton spectra. The results presented for citric acid in Fig. 4 serve to illustrate how this NMR experiment can be extended to more complex materials. Citric acid has eight proton sites and would present a formidable challenge for the previously described methods [6–9] for measuring ^{1}H CSAs. As the 1D spectra in Fig. 4a demonstrate, a homonuclear decoupling sequence is necessary to obtain the highest resolution of ^{1}H isotropic chemical shifts, particularly for the CH$_2$ protons. With this resolution, it was possible to obtain the 2D spectrum shown in Fig. 4 using the pulse sequence in Fig. 1b. Estimates of

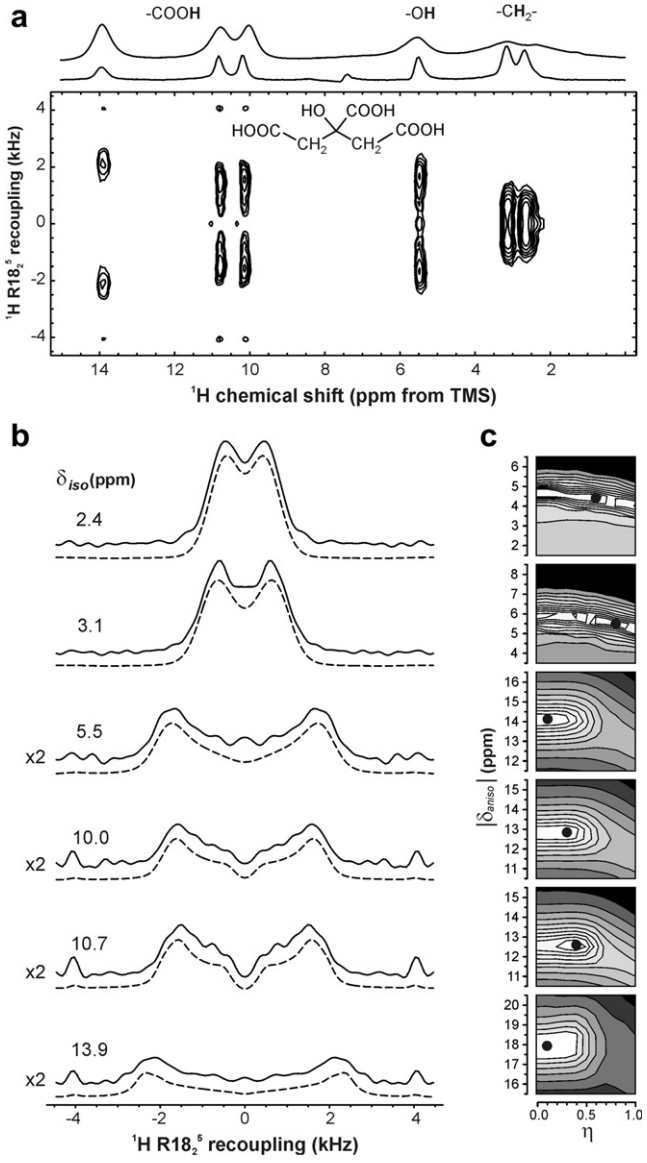

Fig. 4. (a) 2D ^{1}H anisotropic-isotropic chemical shift correlation spectrum of citric acid obtained at 16.103 kHz MAS frequency using pulse sequence in Fig. 1b with wPMLG5 homonuclear decoupling [11] in t_2. The upper 1D spectrum was obtained at 32.000 kHz MAS while the lower was obtained at 16.103 kHz MAS with wPMLG5 decoupling. (b) Experimental CSA recoupled lineshapes obtained from slices at indicated isotropic chemical shifts (solid lines) with best fit simulated lineshapes (dashed lines). (c) Contour plots of the quality of fit (χ^2) of simulated to experimental lineshapes as a function of $|\delta_{aniso}|$ and η (the nth contour level is at $2^{n/2} \times \chi^2_{min}$). The dots represent the best fit values of $|\delta_{aniso}|$ and η used for the simulations (see Table 1).

$|\delta_{aniso}|$ and η were obtained by fitting simulated lineshapes to the experimental lineshapes obtained from slices of the 2D spectrum (Fig. 4b) and these values are listed in Table 1.

According to its single crystal X-ray diffraction structure [22], citric acid forms a highly interlocked hydrogen bond network. The central carboxylic acid group forms a hydrogen bonded dimer with an equivalent group across a center of symmetry and is tentatively assigned to the peak at 13.9 ppm. The other carboxylic groups form a continu-

ous spiral chain of (slightly weaker) hydrogen bonds and are assigned to the peaks at 10.0 and 10.7 ppm. The hydroxyl group (5.5 ppm) forms an additional intramolecular hydrogen bond to the central carboxylic acid group and the experiment indicates quite a large CSA.

Although this method has the advantage of being applicable to complex systems, there are a number of limitations that should be noted. Due to the intrinsic symmetry of the CSA recoupled lineshapes, the sign of δ_{aniso} cannot be ascertained. The lineshapes are sensitive to r.f. errors and inhomogeneity, so, as we have done in this work, care must be taken to calibrate the r.f. power and simulations should account for r.f. inhomogeneity. Although the simulated lineshapes indicate a dependence on η (see Fig. 1c), the uncertainties in η illustrated in the χ^2 contour plots indicate the experimental data is broadened and the dependence on η is obscured. One possible source of broadening could be higher order terms in the average Hamiltonian involving homonuclear dipolar interactions. Lastly, since the $R18_2^5$ sequence recouples heteronuclear dipolar interactions in addition to the ^{1}H CSA, the application to protons near NMR active nuclei such as ^{14}N, ^{15}N, and ^{31}P will require some sort of decoupling or dual channel symmetry sequence [23]. This experiment, in its present form, is therefore limited in application to protons that are located near predominantly NMR inactive nuclei (e.g. carbon and oxygen). We are currently exploring ways to improve the robustness of the CSA recoupling sequence and its dependence on the asymmetry parameter, and to enable its application to protons near NMR active nuclei.

5. Conclusion

We feel that this CSA recoupling experiment and the availability of high-field NMR instruments should open up solid-state NMR studies of ^{1}H chemical shift tensors, particular for protons in hydrogen bonds, to far more complex materials than has been possible thus far. Furthermore, we anticipate that additional data will spur on *ab inito* calculations of ^{1}H chemical shift tensors in order to more fully understand the nature of hydrogen bonding and to employ the predictive powers of these calculations to complement other techniques for structural characterization of materials.

Acknowledgments

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