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Ultra-wideline ¹⁴N NMR spectroscopy as a probe of molecular dynamics[†]

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We show that ultra-wideline solid-state ¹⁴N NMR can be used as a quantitative probe of molecular dynamics. Jump rates for the molecular flipping mechanism in crystalline urea are determined at various temperatures and are shown to be in good agreement with other NMR techniques.

Solid-state nuclear magnetic resonance is a powerful technique for studying molecular dynamics over a wide range of timescales.¹ In particular, ²H NMR is commonly used for quantifying motional correlation times as well as identifying dynamic mechanisms. Deuterium is well suited to this task due to its integer spin number (I = 1) and the dominance of the first-order quadrupolar interaction (OI), which causes anisotropically-broadened powder lineshapes. The QI is a coupling of the nuclear electric quadrupole moment with the surrounding electric field gradient (EFG), and its magnitude is denoted by the quadrupolar coupling constant $C_{\rm O}$, measured in Hz. The shape of the static ²H NMR powder pattern is sensitive to any dynamics which modulate the EFG on a timescale similar to $1/C_{\rm O}$. The common strategy for measuring such dynamics is to use a spin echo experiment to record the powder pattern and then to fit the lineshape to simulations generated using particular correlation times and dynamic models.² Such experiments can access timescales of ca. 10^{-4} to 10^{-8} s, a range that can be extended by several orders of magnitude in both directions using magic angle spinning,³ the QCPMG⁴ acquisition protocol,⁵ or both. Much faster correlation times can also be studied via an analysis of partially relaxed lineshapes obtained using inversion recovery experiments.⁶ ²H NMR continues to be used to examine a diverse range of materials, and more recently efforts have shifted to extending the same principles to study dynamics using half-integer quadrupolar nuclei.⁷ While the importance of such nuclei is not in doubt, there remains one very significant spin-1 nucleus that, for various reasons, has gone relatively overlooked.

Like ²H, ¹⁴N is a spin-1 nucleus in which the first-order QI dominates the NMR spectra in the solid state. It has a very high natural abundance (99.6%), but unfortunately also has a much larger quadrupole moment than ²H, which means that ¹⁴N powder patterns are broadened over much wider frequency ranges (commonly many MHz) and have traditionally been considered as being beyond the detection limits of

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solid-state NMR. To exacerbate matters, the small gyromagnetic ratio of ¹⁴N also results in a relatively low inherent signal strength. For these reasons, this nucleus is considered as one of the most challenging in solid-state NMR. In this communication, we show that these disadvantages can be overcome using a combination of a high magnetic field strength (21.1 T) and state-of-the-art ultra-wideline NMR methods. Such methods have recently been demonstrated to allow the acquisition of ¹⁴N spectra from samples with C_{OS} of *ca*. 1 MHz at 9.4 T in relatively short experimental times compared with other techniques.⁸ Herein, we demonstrate that much larger C_{OS} can be studied at a higher field and that, much like ²H spectra, ultra-wideline ¹⁴N lineshapes are sensitive to molecular dynamics and can provide both qualitative and quantitative information on motional processes occurring over a range of timescales.

The WURST-QCPMG pulse sequence⁹ combines the broadband excitation capabilities of frequency-swept WURST pulses¹⁰ with the dramatic signal enhancement available from the QCPMG protocol,⁴ and is currently the most efficient method available for recording ultra-wideline NMR spectra from quadrupolar nuclei.^{8,9} The QCPMG protocol involves an excitation pulse followed by a repeating loop containing a refocusing pulse and an acquisition period, and is used to acquire a train of spin echoes, thus sampling the NMR signal over the full timescale of the transverse relaxation (a process characterized by the spin–spin relaxation time T_2). This pulse sequence was used to record the ¹⁴N spectrum from a deuterated, crystalline sample of urea (Aldrich). A deuterated sample was not essential for this work, but was chosen to eliminate ¹⁴N–¹H dipolar couplings and thus maximize T_2 .

The dominance of the first-order quadrupolar interaction on this spectrum results in a lineshape that is essentially symmetric, thus only one half of the spectrum was acquired and the remaining half was reconstructed by reflection (this strategy is justified in more detail in the ESI⁺). This half-spectrum was acquired in 11 separate pieces (400 scans per piece), spaced 300 kHz apart. 50 µs WURST pulses were used with a 1 MHz sweep range and a recycle delay of 5 s (total experiment time of ca. 6 hours). Other experimental details can be found elsewhere.^{8,11} The resultant spectrum is shown in Fig. 1a. The majority of the spectrum corresponds to a single nitrogen site (the two sites in the molecule are equivalent in the crystal structure)¹² with $C_Q = 3.47$ MHz and asymmetry parameter $\eta_{\rm O} = 0.31$. These parameters are in reasonably good agreement with values predicted using the CASTEP software¹³ ($C_Q = -3.86$ MHz and $\eta_Q = 0.28$, details of these simulations can also be found elsewhere).¹¹ This is by far the widest ¹⁴N NMR spectrum reported to date. The CASTEP calculations also allowed a determination of the EFG tensor

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Fig. 1 (a) ¹⁴N WURST-QCPMG NMR spectrum obtained from urea-d₄ at 21.1 T (for clarity, individual spin echoes were summed prior to Fourier transformation so that the spectrum has a standard, rather than spikelet, appearance), (b) simulations of a two-pulse echo experiment with inter-pulse delays given in µs and molecular flipping at a jump rate of $k = 7 \times 10^3 \text{ s}^{-1}$, and (c) simulations with a fixed echo delay of 127 μ s and jump rates as shown (log k). Simulations are shown with normalized heights.

orientation; the largest principal component V_{33} is perpendicular to the plane of the molecule, and V_{22} is aligned close to the N-C bond. The sharp features at the outermost edges of the ¹⁴N spectrum can only be accounted for by considering the dynamics present in this system.

Urea molecules in the crystal structure exhibit both a flipping of the NH₂ groups around the N-C bonds, and flipping of the whole molecule about the carbonyl bond.¹⁴ The former motion has a relatively high onset temperature (ca. 110 °C), and would not be expected to have any direct influence on the ¹⁴N spectrum since it leaves the EFG tensor unchanged. Thus, this mode is not further considered. The flipping of the full molecule, however, is known to occur at ambient temperature and has been previously characterized by several techniques including NMR.¹⁵ Such a flipping process will alter the nitrogen EFG tensor orientation (relative to the magnetic field B_0 in a way that will differ for each molecular orientation in the powder. The ¹⁴N spins for each orientation will thus experience a unique modulation of the OI, and since this interaction is the dominant relaxation mechanism in this system, T_2 will vary across the powder pattern.

The net result of this process on the NMR spectrum can be seen in the simulations in Fig. 1b and c, which were made using the EXPRESS software.¹⁶ Rather than simulate the full WURST-QCPMG experiment, which would be highly computationally demanding due to the phase-modulated pulses, the length of the acquisition period and the large number of crystal orientations over which the simulations must be averaged, a much simpler two-pulse quadrupolar echo sequence was used. Fig. 1b shows spectra resulting from an increasing inter-pulse delay, and it is clear that the outermost edges of the spectrum exhibit the longest T_2 , thus causing the sharp features observed in the experimental spectrum.

edge of the urea-d₄ pattern at (a) 19, (b) 10 and (c) 0 °C. The top spectra show the Fourier transform of the full QCPMG echo train (in spikelet form), while transforms of individual echoes are shown underneath with EXPRESS simulations (in red) corresponding to twopulse echo experiments with inter-pulse delays shown. Jump rates used in the simulations are (a) 7.0 (\pm 0.5) × 10³, (b) 1.8 (\pm 0.2) × 10³ and (c) 8.0 (\pm 0.1) \times 10² s⁻¹. Uncertainties were estimated visually *via* the quality of fit.

This is easily understood; these regions correspond to orientations where B_0 is perpendicular to the plane of the molecule, thus the flipping process causes no change in the orientation of the EFG tensor relative to B_0 and the effects of the dynamics are essentially absent for these particular nuclei. Fig. 1c shows that the ¹⁴N NMR spectrum of urea is potentially sensitive to this motion for a range of jump rates over six orders of magnitude, and the use of the QCPMG protocol will further extend this range. In the slow motion limit ($k \le 10^3 \text{ s}^{-1}$), the spectrum resembles a regular powder pattern corresponding to the EFG parameters given above. In the fast limit $(k \ge 10^{10} \text{ s}^{-1})$, the spectrum corresponds to an average of the two EFG orientations. The $C_{\rm O}$ (or the total width of the pattern) is unchanged because V_{33} is perpendicular to the flip axis, but η_{O} is reduced to ca. 0.14 by an averaging of the two orientations of V_{22} and V_{11} .

In order to extract an accurate measurement of the jump rate k for the flipping motion, the WURST-OCPMG spectrum in Fig. 1a cannot simply be fitted to a simulation of a single echo experiment because the QCPMG protocol records many spin echoes over a wide range of time, and thus effectively represents a weighted average of many different inter-pulse delays. We therefore extracted certain individual echoes from the experimental echo trains and Fourier transformed them individually. These "pseudo echo spectra" were then compared with EXPRESS simulations made using the two-pulse echo sequence with corresponding inter-pulse delays (Fig. 2). This approach should provide a more accurate way of extracting jump rates since the simulated dynamic model can be verified to match the experimental spectrum over a wide range of timescales, rather than just fitting the "average" QCPMG spectrum. Such spectra and simulations, recorded at 19, 10 and 0 °C, are shown in Fig. 2, and the jump rates determined are given in the figure caption. Since this approach requires a

(b)

254

508

76

1016

1270

(c)

508

1016

2540

(a)

635

-20 -2.5 MHz -2.5 -3.0 -2.5 MHz -30 -3.0 -2.0 -2.0 MHz Fig. 2 ¹⁴N WURST-QCPMG spectra recorded at the low-frequency



Fig. 3 A plot of the jump rates k (s⁻¹) determined for the flipping of the urea molecule by various NMR methods, ¹⁵ including that reported herein. Error bars are shown in Fig. S2 (ESI†) for the ¹⁴N and CODEX points.

reasonable signal to noise ratio for each echo, these experiments were run for *ca.* 12 hours each. Importantly, since the height and "tailing off" of the sharp feature at the extremity of the powder pattern is the most sensitive region of the spectrum to these dynamics (at least for slower jump rates), only the experimental piece acquired at this point was considered, thus it was not necessary to acquire the full spectrum in each case.

The measured jump rates are plotted in Fig. 3, alongside values determined using other NMR techniques.¹⁵ Our values agree reasonably well with the other methods. An Arrhenius fit of the three ¹⁴N data points alone yields an activation energy for the flipping motion of $E_A = 75 \pm 15 \text{ kJ mol}^{-1}$, which, given the fact that only three data points were used, is in good agreement with the more recent values found in the literature $(ca. 65 \text{ kJ mol}^{-1})$.¹⁵ More accurate and precise jump rates could potentially be determined via a fit of the full powder patterns, though this would obviously require a significantly increased experimental time. Measurement of jump rates at temperatures higher than 19 °C should be possible in principle, but were not attempted in this instance because of anticipated signal loss due to rapidly decreasing T_2 values as the motional rate enters the intermediate regime (such signal loss is well-known to occur in this regime for spin echo based experiments).

The above work demonstrates the potential of ultrawideline ¹⁴N NMR lineshapes for extracting motional correlation times as a direct analogy of more commonly used ²H echo or QCPMG experiments. ¹⁴N NMR has only been used in this way once before, on choline salts which have extremely small 14 N C_O values (<70 kHz), thus allowing the full 14 N NMR spectrum to be recorded using a conventional spin echo experiment.¹⁷ This was an extremely rare and limiting case, with the vast majority of nitrogen sites exhibiting C_{O} values in excess of 1 MHz. We have shown that dynamics in samples with very large ¹⁴N C_Os can still be studied using the same principles but employing ultra-wideline techniques, and Fig. 2 shows that it is not always necessary to acquire the entire pattern if a certain region is known to exhibit a particularly strong T_2 anisotropy. As an easy-to-implement approach with a long-established theoretical basis and lineshapes that are straightforward to simulate, this technique will provide an attractive alternative to previously reported ¹⁴N methods for studying molecular dynamics, such as hole-burning,¹⁸ which is limited in the qualitative information that it can provide, or

indirectly detected HMQC-type experiments,¹⁹ which are not straightforward and are limited to systems with strong dipolar couplings to "spy" nuclei. It is not difficult to imagine situations where ¹⁴N NMR could provide access to dynamic processes that cannot be probed by ²H. We are currently using ultrawideline ¹⁴N NMR to identify dynamics in systems that are less well-characterized than urea, and further publications will be forthcoming.

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