Natural-Abundance Solid-State H-2 NMR Spectroscopy at High Magnetic Field

ARTICLE *in* THE JOURNAL OF PHYSICAL CHEMISTRY A · JUNE 2011

Impact Factor: 2.69 · DOI: 10.1021/jp202810k · Source: PubMed

5 AUTHORS, INCLUDING:

Abil E Aliev
University College London
269 PUBLICATIONS **1,643** CITATIONS
SEE PROFILE

Dinu Iuga
The University of Warwick
38 PUBLICATIONS **607** CITATIONS
SEE PROFILE

THE JOURNAL OF PHYSICAL CHEMISTRY A

ARTICLE

pubs.acs.org/JPCA

Natural-Abundance Solid-State ^{2}H NMR Spectroscopy at High Magnetic Field

Abil E. Aliev,*[,†] Sam E. Mann,[†] Dinu Iuga,[‡] Colan E. Hughes,[§] and Kenneth D. M. Harris*[,§]

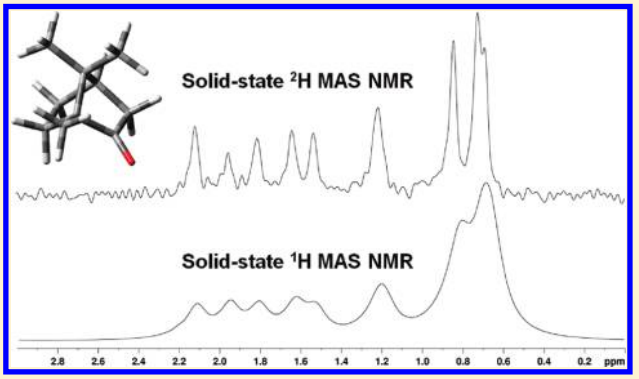
[†]Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, U.K.

[‡]Department of Physics, University of Warwick, Coventry CV4 7AL, U.K.

[§]School of Chemistry, Cardiff University, Park Place, Cardiff CF10 3AT, Wales, U.K.

Supporting Information

ABSTRACT: High-resolution solid-state ^{2}H NMR spectroscopy provides a method for measuring ^{1}H NMR chemical shifts in solids and is advantageous over the direct measurement of high-resolution solid-state ^{1}H NMR spectra, as it requires only the application of routine magic angle sample spinning (MAS) and routine ^{1}H decoupling methods, in contrast to the requirement for complex pulse sequences for homonuclear ^{1}H decoupling and ultrafast MAS in the case of high-resolution solid-state ^{1}H NMR. However, a significant obstacle to the routine application of high-resolution solid-state ^{2}H NMR is the very low natural abundance of ^{2}H, with the consequent problem of inherently low sensitivity. Here, we explore the feasibility of measuring ^{2}H MAS NMR spectra of various solids with natural isotopic abundances at high magnetic field (850 MHz), focusing on samples of amino acids, peptides, collagen, and various organic solids. The results show that high-resolution solid-state ^{2}H NMR can be used successfully to measure isotropic ^{1}H chemical shifts in favorable cases, particularly for mobile functional groups, such as methyl and $-N^+H_3$ groups, and in some cases phenyl groups. Furthermore, we demonstrate that routine ^{2}H MAS NMR measurements can be exploited for assessing the relative dynamics of different functional groups in a molecule and for assessing whole-molecule motions in the solid state. The magnitude and field-dependence of second-order shifts due to the ^{2}H quadrupole interaction are also investigated, on the basis of analysis of simulated and experimental ^{1}H and ^{2}H MAS NMR spectra of fully deuterated and selectively deuterated samples of the α polymorph of glycine at two different magnetic field strengths.



1. INTRODUCTION

Knowledge of isotropic ^{1}H NMR chemical shifts can provide wide-ranging information about structural properties of solids, including insights into specific intermolecular interactions. However, recording high-resolution ^{1}H NMR spectra for solids is associated with significant experimental challenges, arising from the requirement to average the strong anisotropic *homonuclear* ^{1}H−^{1}H dipole−dipole interactions. Recently, a number of ingenious multiple-pulse sequences have been devised for this purpose,[1] allowing high-resolution solid-state ^{1}H NMR spectra to be recorded for solid materials and allowing information on isotropic ^{1}H chemical shifts to be accessed and exploited. However, in this paper we explore a much simpler approach for accessing information on ^{1}H chemical shifts in solids, based on the fact that ^{1}H and ^{2}H chemical shifts are essentially the same (except for small second-order shifts that can be readily estimated and which become less significant at high magnetic field). Thus, in principle, ^{1}H chemical shifts can be accessed via the measurement of ^{2}H chemical shifts in high-resolution solid-state ^{2}H NMR spectra. The more routine nature of this approach emanates from the fact that to record high-resolution ^{2}H NMR spectra for solids only requires averaging of the anisotropic *heteronuclear* ^{2}H−^{1}H dipole−dipole interactions, which is readily achieved using standard ^{1}H decoupling techniques. Furthermore, *homonuclear* ^{2}H−^{2}H dipole−dipole interactions are very weak and are readily averaged by magic-angle sample spinning (MAS). Thus, in principle, the measurement of high-resolution ^{2}H NMR spectra for solids should be significantly more routine than the measurement of high-resolution ^{1}H NMR spectra. However, the major drawback of ^{2}H NMR is the inherently low sensitivity of this technique (the natural isotopic abundance of ^{2}H is only ca. 0.0115%[2]). For this reason, ^{2}H NMR studies of solids are virtually always carried out on isotopically enriched (i.e., deuterated) materials, which clearly imposes limitations with regard to materials synthesis and preparation. In order to overcome such limitations and thus to enable the advantages of high-resolution

Received: March 25, 2011
Revised: April 28, 2011
Published: May 12, 2011

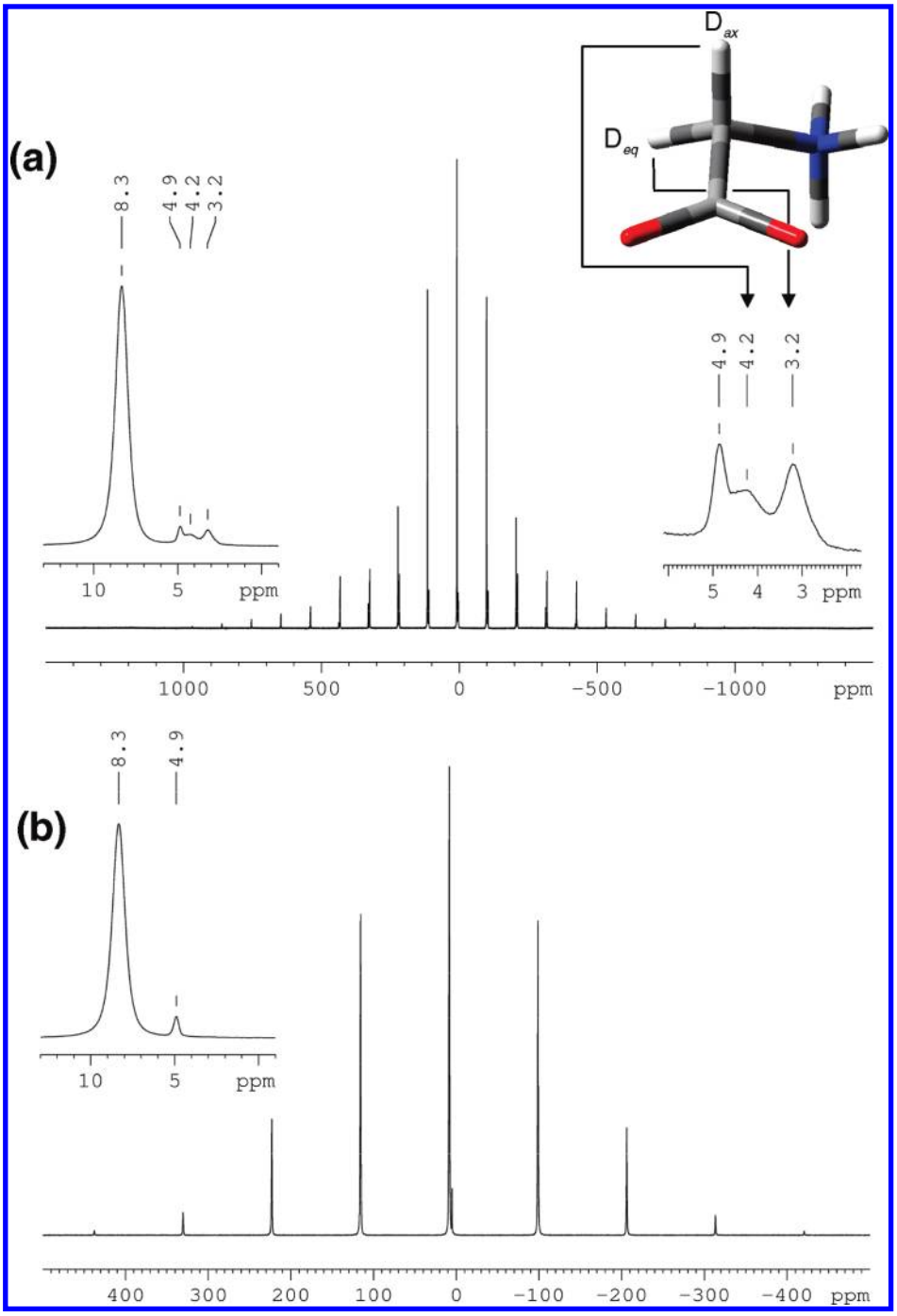


Figure 1. (a) ^{2}H MAS NMR spectrum of glycine-d_5 (130.51 MHz; recycle delay, 20 s; number of scans, 8). (b) ^{2}H MAS NMR spectrum of glycine-d_3 (130.51 MHz; recycle delay, 20 s; number of scans, 8). The peak at 4.9 ppm in each case is due to an unidentified impurity.

solid-state ^{2}H NMR spectroscopy to be fully exploited, it would be highly desirable to be able to carry out ^{2}H NMR studies on solid materials with natural isotopic abundances.

This issue was first explored by us in 1994, when we demonstrated[3] that natural-abundance solid-state ^{2}H NMR represents a feasible approach for establishing ^{1}H chemical shifts of solids. In particular, we showed that the signals from inequivalent sites in organic solids could be successfully resolved in natural-abundance solid-state ^{2}H MAS NMR and ^{2}H CPMAS NMR spectra, the latter involving ^{1}H→^{2}H cross-polarization (CP) (we note that it is implicit throughout this paper that the acquisition of ^{2}H NMR spectra for natural-abundance samples involves the application of high-power ^{1}H decoupling). In some favorable cases, chemical shift differences as small as 0.1 ppm could be resolved, and it was shown that relative peak intensities could be used in peak assignment in a similar manner to the analysis of routine solution-state ^{1}H NMR spectra.

In order to address the low sensitivity of ^{2}H NMR, we carried out studies of ^{1}H→^{2}H CP dynamics for natural-abundance samples, leading to the first demonstration that ^{2}H CPMAS NMR experiments can provide sensitivity enhancements in comparison with single-pulse ^{2}H MAS NMR experiments

dx.doi.org/10.1021/jp202810k |J. Phys. Chem. A 2011, 115, 5568–5578

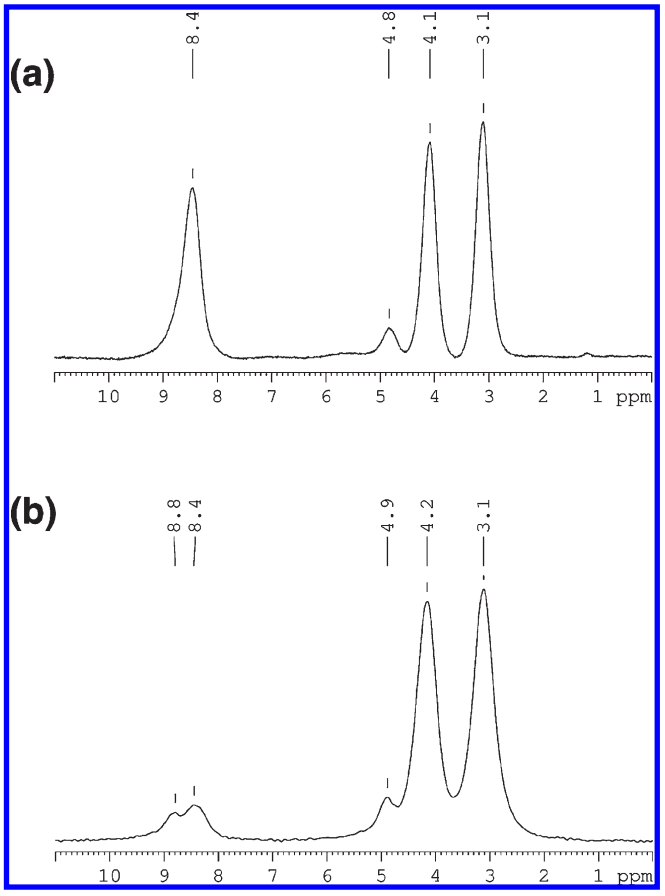


Figure 2. (a) ^{1}H MAS NMR spectrum of glycine-d_5 ($D_3N^+CD_2COO^-$; recycle delay, 10 s) recorded at 850.22 MHz. The peak at 4.8 ppm is due to an unidentified impurity. (b) ^{1}H MAS NMR spectrum of glycine-d_5 ($D_3N^+CD_2COO^-$; recycle delay, 10 s) recorded at 300.13 MHz. The peak at 4.9 ppm is due to an unidentified impurity. By analogy with the field-dependent (^{13}C,^{14}N) residual dipolar coupling,[17] the additional splitting of the peak due to the $-N^+HD_2$ proton at ca. 8.5 ppm in the ^{1}H MAS NMR spectrum recorded at low field (300.13 MHz) is attributed to (^{1}H,^{14}N) residual dipolar coupling.

(enhancements of between 3- and 6-fold were achieved using ^{1}H→^{2}H CP in comparison with single-pulse experiments on the same natural-abundance materials). In another paper,[4] we showed that natural-abundance solid-state ^{2}H NMR spectra can be recorded for rotator phase solids, as well as for the rigid phases of the same materials below their rotator-phase transition temperatures. The application of natural-abundance solid-state ^{2}H NMR to a rigid solid was also reported subsequently by Mizuno et al.[5] Other applications of natural-abundance solid-state ^{2}H NMR have been restricted to solid materials with motionally averaged ^{2}H quadrupole interactions.[6−9] Overall, however, very few natural-abundance solid-state ^{2}H NMR studies have been reported,[10] and there is a clear need to assess the wider potential of this technique. Another less explored feature of natural-abundance solid-state ^{2}H NMR is that the measured spectra are expected to reflect motional averaging effects with frequencies on the order of 10^5-10^7 Hz (i.e., on the order of the ^{2}H quadrupole interaction), thus providing efficient means for assessing dynamics in solid materials.

The availability of high-field solid-state NMR instrumentation provides an opportunity to extend the previous work on natural-abundance solid-state ^{2}H NMR, as measurements at high field should give significant improvements in both sensitivity and resolution in comparison with previous measurements.[3,4,6−10] Here we report solid-state ^{2}H NMR studies of various organic solids, using the high-field 850 MHz UK solid-state NMR facility, allowing an assessment of the feasibility of exploiting natural-abundance solid-state ^{2}H NMR measurements to establish ^{1}H chemical shifts in solids and to assess aspects of molecular dynamics in the solid state.

2. EXPERIMENTAL SECTION

Solid materials used in this work were purchased from Acros Organics, Alfa Aesar, Fluka Chemika, and Sigma-Aldrich and were used without further purification. Selectively deuterated glycine-d_3 (i.e., $D_3N^+CH_2COO^-$) was prepared by dissolving glycine (1.02 g) in D_2O (20 mL) with the solution then concentrated in vacuo. This process was repeated three times and the residue was dried under high vacuum for 18 h to give glycine-d_3 (1.06 g) as a white crystalline solid. Powder X-ray diffraction indicated that the sample of glycine-d_3 was a monophasic sample of the α polymorph of glycine. The sample of glycine-d_5 studied here was also shown, by powder X-ray diffraction, to be a monophasic sample of the α polymorph. Selectively deuterated glycine-d_2 (i.e., $H_3N^+CD_2COO^-$) was prepared in a similar way by dissolving glycine-d_5 in H_2O. Powder X-ray diffraction indicated that the sample of glycine-d_2 was virtually a monophasic sample of the α polymorph (with evidence for a very small component of an unidentified impurity phase).

As our natural-abundance sample of the α polymorph of glycine, we used a sample of glycine obtained from Sigma which was shown (by powder X-ray diffraction) to be a monophasic sample of the α polymorph. To prepare a natural-abundance sample of the γ polymorph,[11] the sample of glycine (α polymorph) supplied by Sigma was recrystallized from aqueous solution and left for a period of time under damp conditions. Powder X-ray diffraction confirmed that the resultant material was a monophasic sample of the γ polymorph.

Solid-state ^{1}H and ^{2}H NMR spectra were recorded at ambient probe temperature at 850.22 and 130.51 MHz, respectively, on a Bruker AVANCE III 850 spectrometer at the UK 850 MHz Solid-State NMR Facility at the University of Warwick. All samples were studied as polycrystalline powders in zirconia rotors (4 mm external diameter). For all samples, high-resolution solid-state ^{2}H NMR spectra were recorded using a single-pulse sequence, with the sample subjected to MAS and with ^{1}H decoupling applied during acquisition using the SPINAL-64 sequence.[12] The MAS frequency was 14 kHz (stability better than ca. ±5 Hz). Typical operating conditions were ^{2}H 90° pulse duration, 5 μs; recycle delay, 0.5−80 s; number of scans, 8−14 000; acquisition time, 20−300 ms. The total acquisition time for recording natural-abundance ^{2}H MAS NMR spectra was between 1 h (for the α polymorph of glycine) and 5 h (for collagen). For adamantane and glycine-d_3, ^{2}H CPMAS NMR spectra were also recorded using ^{1}H→^{2}H CP (CP contact time, τ_{CP}, in the range 0.5−50 ms) together with MAS (14 kHz) and ^{1}H decoupling (SPINAL-64).[12] Solid-state ^{1}H and ^{2}H chemical shifts were calibrated using deuterated chloroform (99.96% atom D) as a secondary reference (δ_H = 7.26 ppm relative to tetramethylsilane).

Solid-state ^{1}H and ^{2}H MAS NMR spectra were also recorded (at 300.13 and 46.06 MHz, respectively) at ambient probe temperature on a Bruker MSL300 spectrometer using zirconia

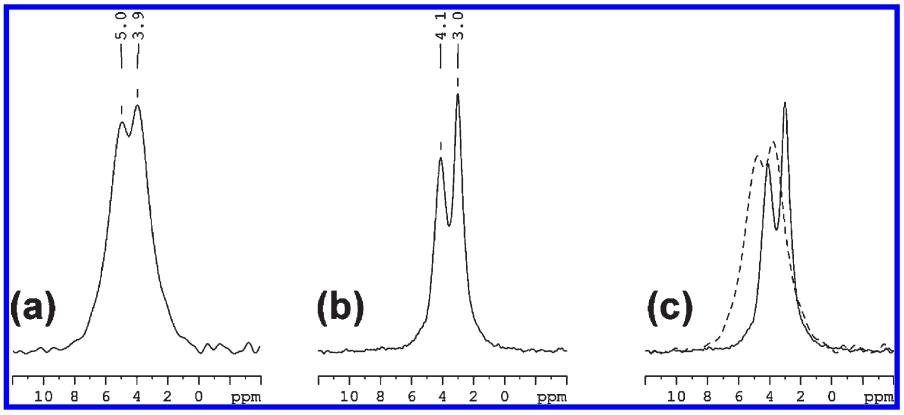


Figure 3. (a) The isotropic region of the ^{2}H MAS NMR spectrum of glycine-d_2 recorded at 46.06 MHz (recycle delay, 60 s; number of scans, 64). (b) The isotropic region of the ^{2}H MAS NMR spectrum of glycine-d_2 recorded at 130.51 MHz (recycle delay, 60 s; number of scans, 16). (c) Overlay of the ^{2}H MAS NMR spectra of glycine-d_2 recorded at 46.06 MHz (dashed line) and 130.51 MHz (solid line).

rotors (7 mm external diameter). High-resolution solid-state ^{2}H NMR spectra were recorded using a single-pulse sequence, with the sample subjected to MAS (5.3 kHz; stability better than ca. ±5 Hz) and continuous wave (CW) ^{1}H decoupling. Typical operating conditions were ^{2}H 90° pulse duration, 5.5 μs; recycle delay, 2−360 s; number of scans, 8−150 000; acquisition time, 30−300 ms. ^{2}H CPMAS NMR spectra were also recorded for the natural-abundance sample of the α polymorph of glycine using ^{1}H→^{2}H CP (^{1}H 90° pulse duration, 6.0 μs; CP contact time, 5 ms; recycle delay, 3.3 s) together with MAS (5.3 kHz) and ^{1}H decoupling (CW). ^{1}H and ^{2}H NMR chemical shifts were again calibrated using deuterated chloroform as a secondary reference.

Solution-state ^{1}H NMR spectra were recorded at 298 K for materials dissolved in $CDCl_3$ on a Bruker AVANCE III 600 NMR spectrometer equipped with a Bruker 5 mm cryoprobe. The ^{1}H NMR chemical shifts were calibrated using the residual solvent peak at 7.258 ppm in $CDCl_3$. Data acquisition and processing were performed using standard Bruker TopSpin (version 2.1) software.

Powder X-ray diffraction was carried out on a Bruker D8 diffractometer using Ge-monochromated Cu Kα_1 radiation with a Vå ntec detector (2θ range, 4°−50°; step size, 0.017°; data collection time, 25 min; foil sample holder).

3. RESULTS AND DISCUSSION

3.1. ^{2}H MAS NMR of ^{2}H-Labeled Samples of Glycine. Initially, ^{2}H MAS NMR spectra were recorded for fully deuterated (glycine-d_5, $D_3N^+CD_2COO^-$) and selectively deuterated (glycine-d_3, $D_3N^+CH_2COO^-$) samples of glycine (Figure 1), both of which were monophasic samples of the α polymorph of glycine. Three isotropic peaks are resolved for glycine-d_5, assigned to the $-N^+D_3$ (at 8.3 ppm) and $>CD_2$ (at 3.2 and 4.2 ppm) groups. The two deuterons of the $>CD_2$ group are denoted "axial" (D_{ax}) and "equatorial" (D_{eq}) on the basis of their orientation relative to the plane of the COO^- group in the crystal structure of the α polymorph[13] (Figure 1). Previous single-crystal ^{2}H NMR measurements on the α polymorph of glycine[14] indicate that the isotropic resonance for the axial deuteron is at higher frequency. A low-intensity peak observed at 4.9 ppm for glycine-d_5 is attributed to an unidentified impurity[15] (there are no spinning sidebands associated with this peak, unlike the peaks due to glycine). The observed ^{2}H NMR chemical shifts for glycine-d_5 are consistent with those observed for the natural-abundance sample of the α polymorph discussed below. Although the high-resolution solid-state ^{1}H NMR spectrum of glycine has been reported previously[16] (in a study focused on methodology for ^{1}H homonuclear decoupling), the observed ^{1}H chemical shifts were not stated explicitly, and the specific polymorph of glycine studied was not actually indicated.

We have also recorded ^{1}H MAS NMR spectra for glycine-d_5 (Figure 2). As expected, the high level of dilution of the ^{1}H spins in glycine-d_5 is such that there is negligible line broadening due to homonuclear ^{1}H−^{1}H dipole−dipole interactions, and all peaks are well-resolved. Interestingly, the peak resolution in our ^{1}H MAS NMR spectrum for glycine-d_5 is similar to that observed in the ^{1}H MAS NMR spectrum of a natural-abundance sample of glycine recorded at 500 MHz using homonuclear ^{1}H decoupling techniques and ultrafast MAS at 65 kHz.[16]

In the crystal structure of the α polymorph of glycine, determined from neutron diffraction data,[13] the two hydrogens in the $>CH_2$ group are inequivalent. One hydrogen atom [H(4) in the original notation, corresponding to D_{ax} in Figure 1] has two close oxygen neighbors with H···O distances of 2.39 and 2.45 Å, whereas the other hydrogen atom [H(5) in the original notation, corresponding to D_{eq} in Figure 1] has no close contacts. On the basis of the expected chemical shifts of ^{1}H nuclei in the vicinity of oxygen atoms, the peaks at 4.2 and 3.2 ppm in our ^{2}H MAS NMR spectrum of glycine-d_5 are assigned as D_{ax} and D_{eq}, respectively. The relatively large difference in chemical shifts may be a consequence of an intermolecular C−H···O hydrogen bond involving D_{ax}, although further computational studies would be required to verify the significance of this noncovalent interaction.

3.2. Assessment of Second-Order Shifts in ^{2}H MAS NMR Spectra. To investigate the field dependence of second-order effects on ^{2}H NMR chemical shifts, which arise from the quadrupolar interaction of the ^{2}H nuclei, ^{2}H MAS NMR spectra of glycine-d_2 (α polymorph) were recorded at 46.06 and 130.51 MHz (Figure 3). As the two deuterons in the CD_2 group are inequivalent, we consider the center of gravity of the peaks for the two deuterons, the position of which is 4.45 ppm at 46.06 MHz and 3.55 ppm at 130.51 MHz. Thus, the position of the center of gravity shifts to higher frequency by 0.9 ppm as the field strength is decreased from 20 T (130.51 MHz) to 7.05 T (46.06 MHz). The overlay of the ^{1}H and ^{2}H MAS NMR spectra recorded for glycine-d_5 and glycine-d_2, shown in Figure S1 (Supporting Information), also indicates the

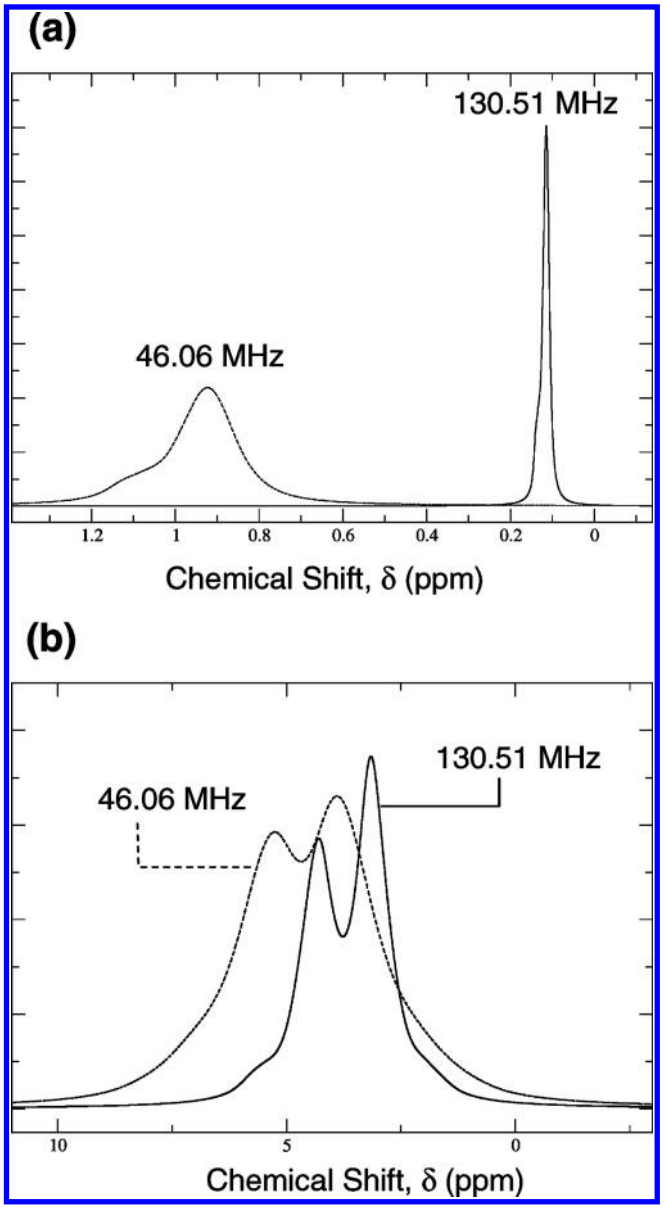


Figure 4. Overlay of ^{2}H MAS NMR spectra simulated (a) for a single ^{2}H nucleus and (b) for two ^{2}H nuclei in a tetrahedral >CD_2 group at 46.06 MHz (dashed line) and 130.51 MHz (solid line). The spectra were calculated using SPINEVOLUTION (version 3.4.2).[18] Parameters used in spectra a were: quadrupole coupling constant, 160 kHz; asymmetry parameter, 0; isotropic chemical shift, 0 ppm; MAS frequency, 10 kHz; line broadening, 0.1 ppm at 46.06 MHz, 0.01 ppm at 130.51 MHz. Parameters used in spectra b were: internuclear ^{2}H−^{2}H distance, 1.763 Å; quadrupole coupling constants, 160 kHz (D_{ax}), 169.4 kHz (D_{eq});[14] asymmetry parameters, 0.043 (D_{ax}), 0.085 (D_{eq}); isotropic chemical shifts, 3.1 ppm (D_{ax}), 4.1 ppm (D_{eq}); MAS frequency, 5.3 kHz at 46.06 MHz, 14 kHz at 130.51 MHz; line broadening, 50 Hz at 46.06 MHz, 80 Hz at 130.51 MHz. The ^{2}H chemical shift anisotropy was assumed to be 0 ppm in both a and b. Calculations using typical values and orientations of the ^{2}H chemical shift tensor[14] showed no significant change in the line shapes and intensities of the peaks for the values of MAS frequency and Larmor frequency used.

second-order shifts observed in the ^{2}H NMR spectra relative to the ^{1}H NMR spectra and, in particular, illustrates the fact that the magnitude of these shifts is reduced significantly at higher magnetic field.

The field dependence of the second-order shift predicted from theoretical calculations (Figure 4a) is in agreement, both in sign and magnitude, with that observed experimentally (Figure 3c). For the quadrupole interaction parameters used in the theoretical calculations (quadrupole coupling constant, 160 kHz; asymmetry parameter, 0), the predicted second-order shift is +1.00 ppm at 7.05 T and +0.12 ppm at 20 T (where "+" represents a shift to higher frequency). In addition, and perhaps of more importance, the theoretical calculations demonstrate (Figure 4a) that line widths are significantly narrower at 20 T than at 7.05 T, emphasizing the advantage of recording ^{2}H MAS NMR spectra at high magnetic field for better resolution, especially when the ^{2}H quadrupole coupling constant is close to its static value.

As shown in Figure 3, the line shape for the CD_2 deuterons in glycine-d_2 resembles a Pake-like pattern for a dipolar coupled ^{2}H−^{2}H pair, with the line width reduced significantly by the application of MAS. This MAS-narrowed Pake-like pattern is indicative of relatively strong ^{2}H−^{2}H dipolar coupling, arising from the close proximity of the two inequivalent CD_2 deuterons (internuclear distance, 1.76 Å) and the fact that the >CD_2 group is not mobile in glycine-d_2. This type of interference between the ^{2}H quadrupole interaction and the homonuclear ^{2}H−^{2}H dipole−dipole interaction, leading to a characteristic line shape of spinning sidebands in ^{2}H MAS NMR spectra, has also been observed[19] for the selectively deuterated transition metal dihydride $OsD_2Cl_2(CO)(P^iPr_3)_2$, which has an unusually short distance (0.96 Å) between two equivalent deuterons. In that case, theoretical analysis showed[19] that the characteristic line shape of the spinning sidebands depends on the strength of the ^{2}H−^{2}H dipole−dipole interaction and the relative orientations of the ^{2}H quadrupole interaction tensors for the two deuterons. The present work on the >CD_2 group in glycine-d_2 (Figure 3) demonstrates that interference between these two types of anisotropic interaction can also arise for a relatively large value of the ^{2}H quadrupole coupling constant (ca. 160−170 kHz, in comparison with ca. 50−100 kHz for the metal hydrides studied previously[19]) and for significantly larger ^{2}H−^{2}H internuclear distance. Our spectral simulations taking into consideration both the ^{2}H quadrupole interactions and homonuclear ^{2}H−^{2}H dipole−dipole interactions of the CD_2 deuterons (Figure 4b) reproduce all the features in the experimental ^{2}H MAS NMR line shapes, recorded at two different field strengths, for the CD_2 group in glycine-d_2 (Figure 3).

3.3. Assessment of ^{1}H→^{2}H Cross-Polarization. To assess the feasibility of ^{1}H→^{2}H CP measurements, solid-state ^{2}H MAS NMR spectra were recorded for glycine-d_3 under conditions chosen to approximate those to be used in our studies of natural isotopic abundance samples. In particular, recognizing the magnitude of the ^{2}H quadrupole coupling constant (ca. 170 kHz), a relatively high MAS frequency (14 kHz, which is close to the maximum MAS frequency for 4 mm rotors) was used. However, for both short (2 s) and long (80 s) recycle delays (Figure S2, Supporting Information), no gain in sensitivity was observed in comparison with the single-pulse ^{2}H MAS NMR spectrum. For the same total acquisition time, the single-pulse ^{2}H MAS NMR spectrum has higher signal intensity by a factor of ca. 13 in comparison with the ^{2}H CPMAS NMR spectrum. In the ^{2}H CPMAS NMR spectrum, the intensity of the peak for the $-N^+D_3$ group increases significantly on increasing the recycle delay from 2 to 80 s, confirming that the ^{1}H spin−lattice relaxation time (T_1) for glycine-d_3 is very long.

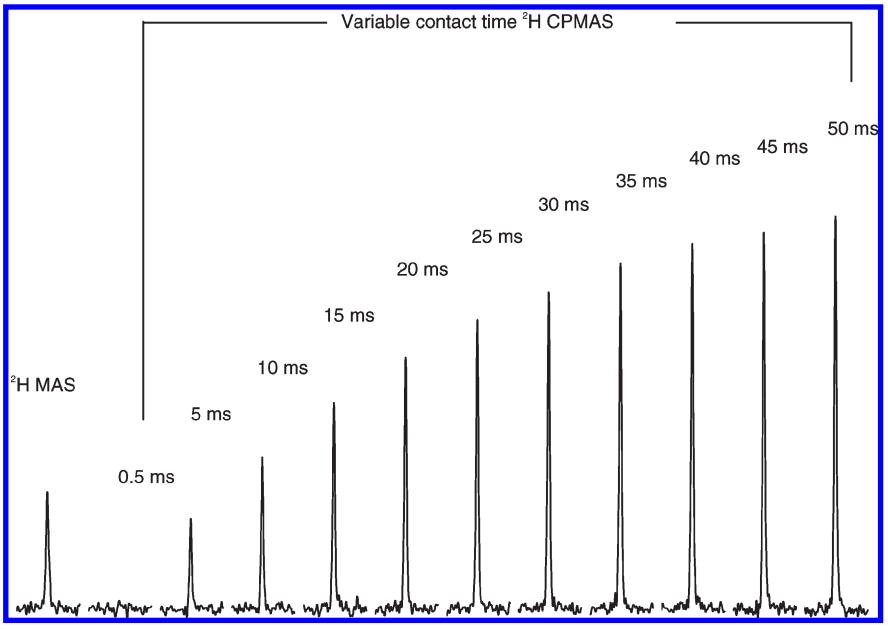


Figure 5. Signal intensities in ^{2}H CPMAS NMR spectra of adamantane as a function of CP contact time (recycle delay, 5 s; number of scans, 32; MAS frequency, 14 kHz). For reference, the single-pulse ^{2}H MAS NMR spectrum is also shown (left).

The dependence of ^{1}H→^{2}H CP on the contact time τ_{CP} (at MAS frequency 14 kHz) was studied using a natural-abundance sample of adamantane, for which a sufficiently strong signal is obtained from 32 acquisitions with 5 s recycle delay in both single-pulse ^{2}H MAS NMR and ^{2}H CPMAS NMR experiments (Figure 5). Signal enhancement was achieved in the ^{2}H CPMAS NMR spectra, relative to the single-pulse ^{2}H MAS NMR spectrum, for CP contact times greater than ca. 10 ms. The highest observed signal enhancement factor was 3.4 for τ_{CP} = 50 ms. However, as long CP contact times can have adverse effects on spectrometer hardware, no spectra were recorded for τ_{CP} values higher than 50 ms.

Our observations for glycine-d_3 and adamantane suggest that routine ^{2}H CPMAS NMR measurements may be hampered by relatively long ^{1}H spin−lattice relaxation times and the requirement for long ^{1}H→^{2}H CP contact times. For this reason, all subsequent studies of materials with natural isotopic abundances used single-pulse ^{2}H MAS NMR measurements (except for one measurement at MAS frequency 5.3 kHz on the 300 MHz instrument described in section 3.4). Nevertheless, further assessment and optimization of advanced CP experiments[20] is clearly merited for future research.

3.4. ^{2}H MAS NMR of Natural-Abundance Samples of Glycine. Next, we discuss ^{2}H MAS NMR spectra for samples of the α and γ polymorphs of glycine with natural isotopic abundances (Figure 6). In spite of the very low natural abundance of ^{2}H, an isotropic signal was observed in less than 3 min of acquisition for the α polymorph, and the ^{2}H MAS NMR spectrum for the α polymorph shown in Figure 6 was acquired in 1 h. The peak at 8.3 ppm is attributed to deuterons in the $-N^+H_2D$ group. No signals were detected for deuterons in >CHD groups. On increasing the recycle delay from 0.5 to 10 s, no new peaks were observed within 1 h of acquisition. Similarly, no signals were detected for deuterons in >CHD groups for the γ polymorph after 15 h of acquisition with a recycle delay of 20 s. We note that the ^{2}H quadrupole coupling constant is expected to be higher for deuterons in >CHD groups than for deuterons in $-N^+H_2D$ groups, as rapid rotation of the $-N^+H_2D$ groups occurs about the C−N bond,[21] leading to a 3-fold reduction of the ^{2}H quadrupole coupling. In contrast, no large-amplitude motions occur for the >CHD groups. Furthermore, deuterons in >CHD groups are likely to have longer ^{2}H spin−lattice relaxation times than deuterons in $-N^+H_2D$ groups, again due to the dynamics in the latter case. Nevertheless, by recording a ^{2}H CPMAS NMR spectrum (CP contact time, 5 ms) for a very long time (more than 5 days) at relatively low MAS frequency (5.3 kHz) on the 300 MHz instrument, together with a large sample volume (7 mm diameter rotor), it was possible to detect a signal for the >CHD deuterons (Figure S3, Supporting Information).

The ^{2}H MAS NMR spectrum for the γ polymorph is similar to that for the α polymorph (Figure 6), but with a slight shift (ca. +0.3 ppm) of the isotropic peak for the $-N^+H_2D$ deuterons to higher frequency, which might be interpreted in terms of the deuterons of the $-N^+H_2D$ group in the γ polymorph being involved in stronger hydrogen bonding.[22−25]

The line width at half-height for the peak due to the $-N^+H_2D$ group in the ^{2}H MAS NMR spectrum also differs significantly between the α and γ polymorphs (70 and 180 Hz, respectively), probably reflecting differences in the frequency of rotation of the $-N^+H_2D$ groups in the two polymorphs (see also the discussion for L-alanine below). In particular, the frequencies of rotation of the $-N^+H_3$ group about the C−N bond in the α and γ polymorphs at 298 K are estimated[21] to be 77 and 3 GHz, respectively. The slower rate of motion for the γ polymorph is consistent with the greater observed line width and with the suggestion that the $-N^+H_3$ group is engaged in stronger hydrogen bonding in this polymorph.

Our results suggest that ^{2}H NMR chemical shifts provide a straightforward means of identifying the α and γ polymorphs of glycine, and we note that the ^{2}H NMR chemical shift for the $-N^+H_2D$ group in the natural-abundance sample of the α polymorph is consistent with those observed for the $-N^+D_3$ groups in the samples of glycine-d_5 (Figure 1) and glycine-d_3 (Figure 1) discussed above (which were shown independently by

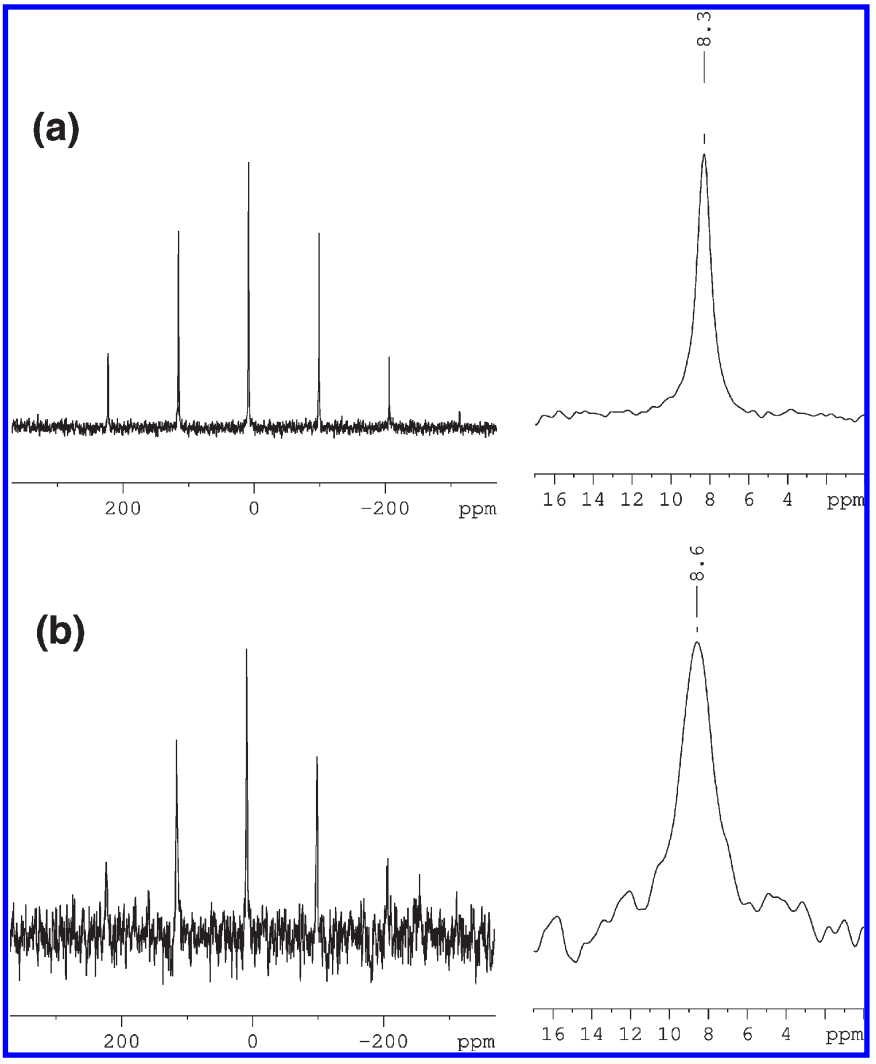


Figure 6. (a) Natural-abundance ^{2}H MAS NMR spectrum of the α polymorph of glycine recorded at 130.51 MHz (recycle delay, 0.5 s; number of scans, 7444). (b) Natural-abundance ^{2}H MAS NMR spectrum of the γ polymorph of glycine recorded at 130.51 MHz (recycle delay, 20 s; number of scans, 2628). The expansions of isotropic peaks are shown on the right of each spectrum.

powder X-ray diffraction to be monophasic samples of the α polymorph).

3.5. ^{2}H MAS NMR of Other Amino Acids, Small Peptides, and Collagen. In the ^{2}H MAS NMR spectra recorded for natural-abundance samples of L-alanine, L-alanylglycine (Ala-Gly), and glycyl-L-alanine (Gly-Ala), signals are observed for deuterons in $-N^+H_2D$ and $-CH_2D$ groups (Figure 7). Such groups are expected to undergo rotational dynamics at the temperature of the measurement. However, the signal for the $-N^+H_2D$ group in L-alanine is significantly broader (ca. 700 Hz) than those for the $-N^+H_2D$ groups in the α and γ polymorphs of glycine, making it difficult to measure the chemical shift accurately. From activation parameters reported previously,[21] the frequency of rotation of the $-N^+H_3$ group about the C−N bond in L-alanine is 7 MHz at 298 K. The significant line broadening observed in the ^{2}H MAS NMR spectrum may be due to the fact that the rotational frequency approaches the same order of magnitude as the static ^{2}H quadrupole coupling constant in this case.

In the natural-abundance ^{2}H MAS NMR spectra for L-alanine, Ala-Gly, and Gly-Ala, no signals are observed for deuterons bonded to the α carbon atom. For the hydrochloride of DL-alanine methyl ester, on the other hand, peaks are observed at 1.6 and 3.7 ppm (Figure 7) and are assigned to deuterons in β-CH_2D and $-OCH_2D$ groups, respectively. The intensity ratio for the isotropic peaks at 3.7 ppm (OCH_2D) and 1.6 ppm (β-CH_2D) is 1:3, but changes to 1:2 for the corresponding first-order spinning sidebands (Figure S4, Supporting Information). This change suggests that the motionally averaged quadrupole coupling constant for the $-OCH_2D$ deuterons is higher than that for the β-CH_2D deuterons. The line widths of the peaks for both the $-OCH_2D$ and β-CH_2D groups are similar, from which we may infer that the rotation of both of these methyl groups occurs at frequencies faster than ca. 10^8 Hz.

We have also undertaken preliminary natural-abundance ^{2}H NMR measurements for collagen, a solid protein in which one-third of the residues are glycine.[26−28] While collagen has a significantly higher molecular weight (ca. 300 kDa) than the simple amino acids discussed above, we anticipated that noncrystalline materials containing collagen may yield signals in natural-abundance ^{2}H MAS NMR spectra due to higher mobility at the molecular level.[26] As our collagen-containing

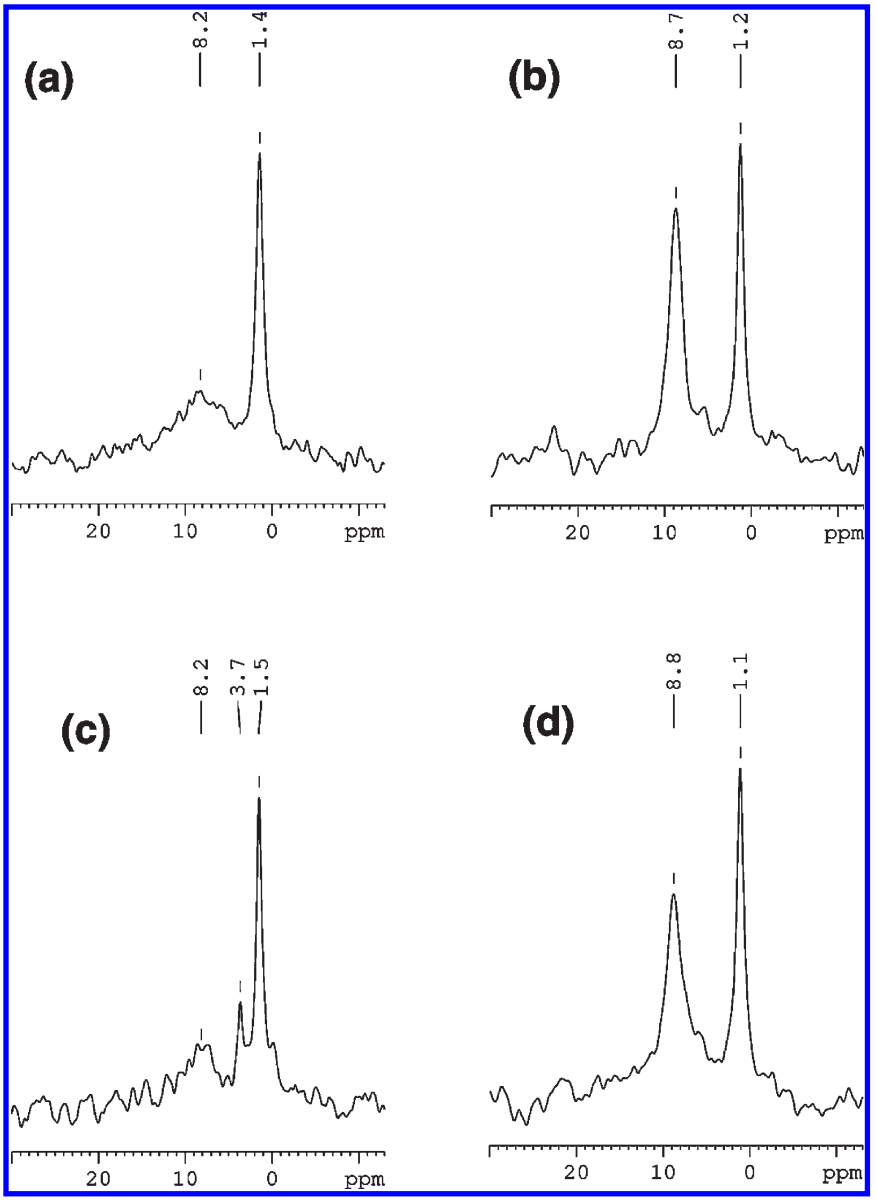


Figure 7. (a) Natural-abundance ^{2}H MAS NMR spectrum of L-alanine recorded at 130.51 MHz (recycle delay, 0.5 s; number of scans, 12 584). (b) Natural-abundance ^{2}H MAS NMR spectrum of L-alanylglycine recorded at 130.51 MHz (recycle delay, 0.5 s; number of scans, 6144). (c) Natural-abundance ^{2}H MAS NMR spectrum of DL-alanine methyl ester hydrochloride recorded at 130.51 MHz (recycle delay, 2 s; number of scans, 3080). (d) Natural-abundance ^{2}H MAS NMR spectrum of glycyl-L-alanine recorded at 130.51 MHz (recycle delay, 0.5 s; number of scans, 15 180). Only the region of the spectrum containing isotropic peaks is shown in each case.

material, we used a new parchment sample (62 mg) made of calf skin, for which solid-state ^{1}H and ^{13}C NMR studies have been reported previously.[27] As shown in Figure 8a, we have successfully recorded a high-resolution solid-state ^{2}H MAS NMR spectrum (acquisition time, 5 h) for the natural-abundance sample of collagen. In this spectrum, the peak at 1.3 ppm is assigned to methyl (CH_2D) groups (e.g., methyl groups of Ala residues, which have a relatively high content in collagen).[27] Peaks due to other aliphatic environments are less intense and are not well resolved. A strong peak is also observed at 8.4 ppm. Although peaks in the region of 8.4 ppm for simple amino acids (as discussed above) may be assigned to $-N^+H_2D$ end-groups, the peak at 8.4 ppm for collagen cannot be assigned to $-N^+H_2D$ end-groups, as the number of such groups per unit mass of collagen is known independently[29] to be very small. It is interesting to note that the ^{2}H MAS NMR spectrum of the sample of collagen studied here (Figure 8a) is significantly different from the ^{1}H MAS NMR spectrum of the same sample (Figure 8b). In particular, the major peak in the ^{1}H MAS NMR spectrum occurs at ca. 4.4 ppm and is assigned to water molecules in collagen.[27] Furthermore, the line width (ca. 360 Hz) of this peak suggests that these water molecules are dynamic. In principle, the significant differences between our ^{1}H and ^{2}H MAS NMR spectra of collagen might reflect differences in the exchange and translational rates of HOH water molecules (which dominate the ^{1}H NMR spectrum) and HOD water molecules (which dominate the ^{2}H NMR spectrum), although much more detailed future studies are essential before a definitive understanding of these differences can be established.

3.6. ^{2}H MAS NMR of Other Organic Solids. We have also recorded natural-abundance ^{2}H MAS NMR spectra for a range of

other organic solids. For some materials that do not contain mobile methyl groups (e.g., the α polymorph of oxalyldihydrazide[30]),

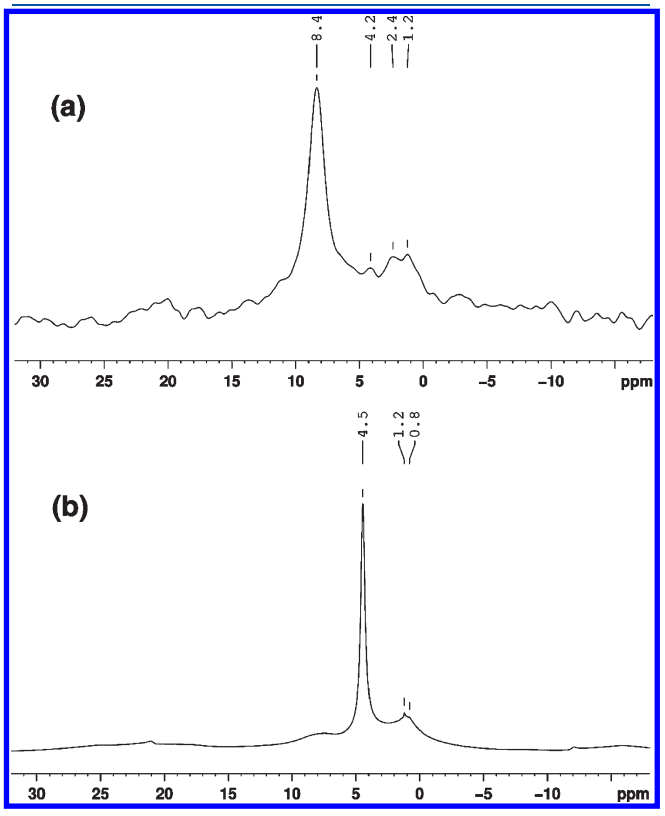


Figure 8. (a) Natural-abundance ^{2}H MAS NMR spectrum of collagen recorded at 130.51 MHz (recycle delay, 1.2 s; number of scans, 13 720). (b) ^{1}H MAS NMR spectrum of collagen recorded at 850.22 MHz (recycle delay, 5 s).

no signal was detected within 1 h of acquisition. For some organic solids with methyl groups, the $-CH_2D$ deuterons are readily detected within several minutes of acquisition, but with no detectable signals for deuterons in methine (CD) or methylene (CHD) groups. For example, the ^{2}H MAS NMR spectrum of tetra-*n*-butylammonium bromide (Figure S5, Supporting Information) has only one isotropic peak at 1.0 ppm (line width ca. 30 Hz). The ^{2}H MAS NMR spectrum of solid cholesterol (Figure S6, Supporting Information) also has only one isotropic peak due to methyl groups (1.0 ppm; line width ca. 30 Hz). Although the cholesterol molecule has five inequivalent methyl environments, the fact that only one peak is observed may be a consequence of the chemical shift differences for different environments being small in the case of methyl deuterons. Indeed, in solution-state ^{1}H NMR spectra of cholesterol in $CDCl_3$, the chemical shifts of the five inequivalent methyl groups span only 0.33 ppm (0.67−1.00 ppm). Furthermore, it is known that the crystal structure of cholesterol has multiple crystallographically independent cholesterol molecules in the asymmetric unit, specifically $Z' = 8$ at ambient temperature[31] (in the phase that exists between 283 and 303 K), implying the existence of a very broad distribution of distinct crystallographic environments for the methyl deuterons in this material. On this basis, it is not surprising that we do not observe individually resolved peaks for crystallographically distinct methyl environments in the ^{2}H MAS NMR spectrum.

In addition to $-N^+H_3$ and $-CH_3$ groups, aryl rings can also undergo large amplitude motions in the solid state (particularly phenyl groups and *p*,*p*′-disubstituted derivatives of benzene), as demonstrated from previous studies.[32−34] In most cases, aryl rings undergo a two-site 180° flip motion about an axis passing through two carbon atoms in para positions with respect to each other,[32] although continuous rotation of aryl rings has also been observed, leading to considerable averaging of ^{2}H NMR spectra.[35,36] Interestingly, Frey et al. reported[36] that the dynamic

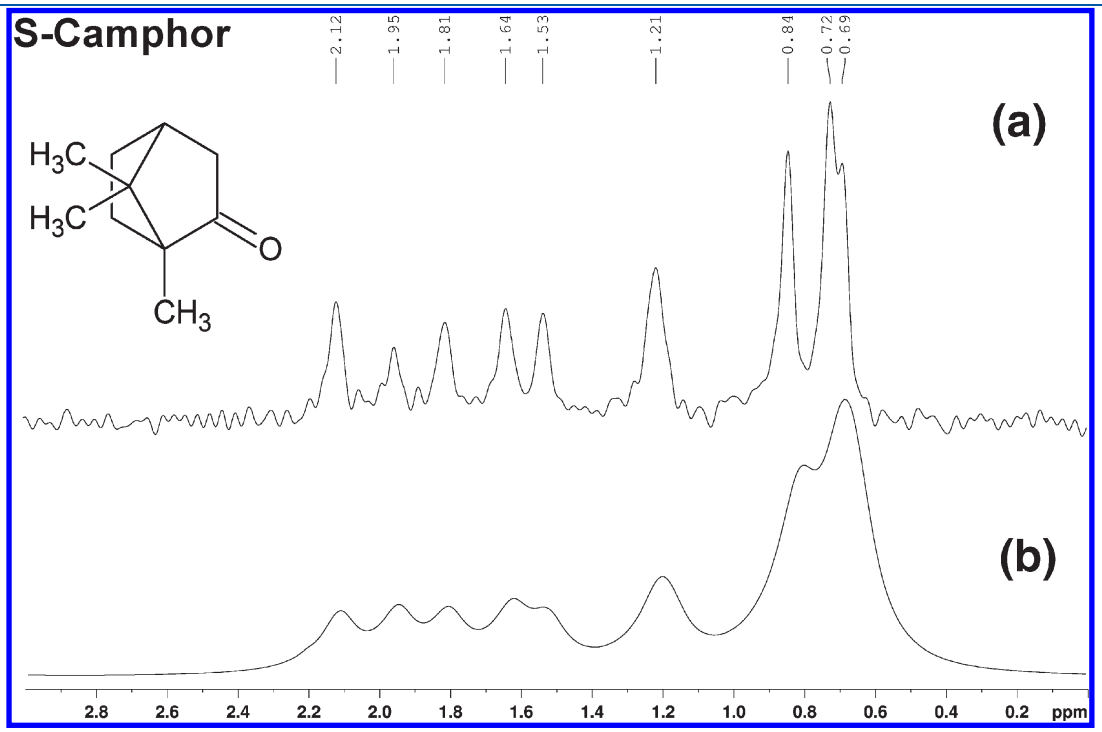


Figure 9. (a) Natural-abundance ^{2}H MAS NMR spectrum of *S*-camphor recorded at 130.51 MHz (recycle delay, 3 s; number of scans, 2344). (b) ^{1}H MAS NMR spectrum of *S*-camphor recorded at 850.22 MHz (recycle delay, 3 s).

dx.doi.org/10.1021/jp202810k |*J. Phys. Chem. A* 2011, 115, 5568–5578

properties of the phenyl ring in phenylalanine differ significantly for samples crystallized from water and from water/ethanol (presumably because different polymorphic forms are produced in each case). In the present work, the natural-abundance ^{2}H MAS NMR spectrum of benzyl triethylchloride (Figure S7, Supporting Information) contains signals assigned to deuterons in the methyl groups (0.9−1.5 ppm) and phenyl group (8.3 ppm). In contrast, the natural-abundance ^{2}H MAS NMR spectrum recorded for *p*-toluenesulfonic acid monohydrate contains only a single peak at 2.5 ppm assigned to deuterons in the methyl group (Figure S8, Supporting Information). The absence of a peak for deuterons in the aryl ring in this case suggests either that the ring is static (giving rise to a long ^{2}H spin−lattice relaxation time) or that it is dynamic with a rotational frequency in the intermediate motion regime with respect to the ^{2}H NMR time scale (i.e., on the order of 10^6 Hz).

In the natural-abundance solid-state ^{2}H MAS NMR spectra recorded for the waxy solids L-menthol (Figure S9, Supporting Information) and *S*-camphor (Figure 9), signals are observed for all ^{2}H environments, including the methine and methylene groups. These samples also show well-resolved peaks in solid-state ^{1}H MAS NMR spectra, but for *S*-camphor, the ^{2}H MAS NMR spectrum has significantly sharper lines than the ^{1}H MAS NMR spectrum. For example, the two peaks for the bridgehead methyl groups, separated by only 0.03 ppm, are resolved in the ^{2}H MAS NMR spectrum (Figure 9). The ^{1}H MAS NMR spectrum of L-menthol has unexpectedly sharp lines, allowing measurement of ^{1}H homonuclear *J*-couplings (2−14 Hz) and measurement of a 2D COSY spectrum (Figures S10 and S11 in Supporting Information). As the melting point of L-menthol is only ca. 36−38 °C, it is important to consider the possibility that the sample may melt when subjected to MAS. However, in the present work, the MAS frequency remained stable at 14 kHz throughout the experiment, suggesting that L-menthol remained as a solid during the measurements.

Relatively sharp peaks are also observed in the natural-abundance solid-state ^{2}H MAS NMR spectrum recorded for a sample of 4-*tert*-butylcyclohexanol comprising a mixture of cis and trans isomers (Figure S12, Supporting Information). From integration of the peaks for the >C*H*(OH) environment at 4.01 ppm (cis isomer) and 3.50 ppm (trans isomer) in the solution-state ^{1}H NMR spectrum for this sample dissolved in $CDCl_3$, the trans:cis ratio is estimated to be 2.46. The peak at 3.4 ppm in the natural-abundance solid-state ^{2}H MAS NMR spectrum is assigned as the >C*D*(OH) deuteron of the predominant trans isomer. Clearly, longer acquisition times would be required to detect the minor cis isomer in this sample.

4. CONCLUDING REMARKS

We have demonstrated that recording solid-state ^{2}H NMR spectra for materials with natural isotopic abundances by employing fast MAS at sufficiently high magnetic field represents a feasible approach for measuring ^{2}H NMR chemical shifts in the solid state and, hence, for accessing ^{1}H NMR chemical shifts. While a high-field (850 MHz) instrument was used in the present work, our experience of carrying out such measurements also on 300[3] and 500 MHz[4] instruments suggests that natural-abundance solid-state ^{2}H MAS NMR spectra can be acquired within a few hours using standard 4 and 7 mm double-resonance probes. Detection of deuterons in functional groups such as methyl, $-N^+H_3$, and some phenyl groups is particularly straightforward, as large amplitude motions of these groups give rise to considerable motional averaging of the ^{2}H quadrupolar interaction and lead to shorter ^{2}H spin−lattice relaxation times. The presence of several equivalent deuteron sites in these groups also contributes significantly toward increasing the signal intensity. These effects combine to provide favorable conditions for detecting signals in high-resolution solid-state ^{2}H NMR spectra for samples with natural isotopic abundances. In the case of rotator phase solids and other materials for which overall motions of molecules lead to considerable reduction of anisotropic interactions, detection of all different ^{2}H environments (including methylene, methine, and hydroxyl groups) is also straightforward, again as a consequence of the ^{2}H quadrupole interaction and spin−lattice relaxation times being reduced by substantial molecular motion. Comparison of ^{1}H and ^{2}H MAS NMR spectra recorded for *S*-camphor shows that considerably sharper lines can be obtained in the ^{2}H MAS NMR spectrum than in the ^{1}H MAS NMR spectrum for the same material, because in the case of ^{2}H MAS NMR, the anisotropic ^{2}H quadrupolar interaction and ^{2}H−^{1}H heteronuclear dipole−dipole interactions are readily averaged using MAS at moderate frequency and ^{1}H decoupling. In the case of ^{1}H MAS NMR, on the other hand, full suppression of line broadening due to homonuclear ^{1}H−^{1}H dipole−dipole interactions would require the application of more advanced techniques than those employed here.

For most crystalline organic solids with natural isotopic abundances, the detection of signals due to deuterons in static functional groups (such as methylene, methine, amino, and hydroxy groups) in solid-state ^{2}H MAS NMR spectra remains problematic and may require the application of ultrafast MAS frequencies, examination and optimization of various ^{1}H→^{2}H CP strategies for ^{2}H signal enhancement, and/or the reduction of ^{1}H and ^{2}H spin−lattice relaxation times (for example, by using paramagnetic dopants). On the positive side, however, this limitation on routine ^{2}H MAS NMR measurements can be exploited as a straightforward approach for assessing the relative dynamics of different functional groups in solids or for assessing the extent of overall motions of molecules in the solid state prior to more detailed multinuclear NMR studies. In principle, natural-abundance solid-state ^{2}H MAS NMR measurements may also successfully complement powder X-ray diffraction studies,[37−39] as dynamically disordered solids are often not readily amenable to structure determination by diffraction-based techniques.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{2}H MAS NMR spectra of solid materials studied in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: A.E.Aliev@ucl.ac.uk (A.E.A.), HarrisKDM@cardiff.ac.uk (K.D.M.H.).

■ ACKNOWLEDGMENT

The UK 850 MHz Solid-State NMR Facility used in this research was funded by EPSRC and BBSRC, as well as the University of Warwick including via part funding through Birmingham Science City Advanced Materials Projects 1 and 2 supported by

Advantage West Midlands (AWM) and the European Regional Development Fund (ERDF).

REFERENCES

(1) Brown, S. P. *Prog. Nucl. Magn. Reson. Spectrosc.* **2007**, *50*, 199.
(2) De Laeter, J. R.; Böhlke, J. K.; De Bièvre, P.; Hidaka, H.; Peiser, H. S.; Rosman, K. J. R.; Taylor, P. D. P. *Pure Appl. Chem.* **2003**, *75*, 683.
(3) Aliev, A. E.; Harris, K. D. M.; Apperley, D. C. *Chem. Phys. Lett.* **1994**, *226*, 193.
(4) Aliev, A. E.; Harris, K. D. M. *Mendeleev Commun.* **1993**, 153.
(5) Mizuno, T.; Nemoto, T.; Tansho, M.; Shimizu, T.; Ishii, H.; Takegoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 9683.
(6) Reichert, D.; Olender, Z.; Poupko, R.; Zimmermann, H.; Luz, Z. *J. Chem. Phys.* **1993**, *98*, 7699.
(7) Poupko, R.; Olender, Z.; Reichert, D.; Luz, Z. *J. Magn. Reson. Ser. A* **1994**, *106*, 113.
(8) Gérardy-Montouillout, V.; Malveau, C.; Tekely, P.; Olender, Z.; Luz, Z. *J. Magn. Reson. Ser. A* **1996**, *123*, 7.
(9) Malveau, C.; Tekely, P.; Canet, D. *Solid State Nucl. Magn. Reson.* **1997**, *7*, 271.
(10) Lesot, P.; Courtieu, J. *Prog. Nucl. Magn. Reson. Spectrosc.* **2009**, *55*, 128.
(11) Hughes, C. E.; Harris, K. D. M. *New J. Chem.* **2009**, *33*, 713.
(12) Fung, B. M.; Khitrin, A. K.; Ermolaev, K. *J. Magn. Reson.* **2000**, *142*, 97.
(13) Jönsson, P.-G.; Kvick, Å. *Acta Crystallogr. Sect. B* **1972**, *28*, 1827.
(14) Müller, C.; Schajor, W.; Zimmermann, H.; Haeberlen, U. *J. Magn. Reson.* **1984**, *56*, 235.
(15) From powder X-ray diffraction, the sample of glycine-d_5 studied in this work was assigned as a monophasic sample of the α polymorph of glycine, with no evidence for any detectable amounts of crystalline impurity phases, suggesting that the impurity observed in the ^{2}H MAS NMR spectrum is either noncrystalline or that the amount of the impurity phase present in the sample is lower than the detection level of this technique. Taking into account the total signal intensity in the ^{2}H MAS NMR spectrum for glycine-d_5 (involving summation of the signal intensity within the spinning sidebands as well as the isotropic peaks) and the observed impurity, the integrated signal ratio of glycine-d_5 to impurity is estimated to be ca. 150:1.
(16) Salager, E.; Stein, R. S.; Steuernagel, S.; Lesage, A.; Elena, B.; Emsley, L. *Chem. Phys. Lett.* **2009**, *469*, 336.
(17) Aliev, A. E.; Harris, K. D. M.; Champkin, P. H. *J. Phys. Chem. B* **2005**, *109*, 23342 and references therein.
(18) Vershtort, M.; Griffin, R. G. *J. Magn. Reson.* **2006**, *178*, 248.
(19) Facey, G.; Gusev, D.; Morris, R. H.; Macholl, S.; Buntkowsky, G. *Phys. Chem. Chem. Phys.* **2000**, *2*, 235.
(20) Murakami, M.; Shimizu, T.; Tansho, M.; Takegoshi, K. *Solid State Nucl. Magn. Reson.* **2009**, *36*, 172.
(21) Gu, Z.; Ebisawa, K.; McDermott, A. *Solid State Nucl. Magn. Reson.* **1996**, *7*, 161.
(22) Aliev, A. E.; Harris, K. D. M. *Struct. Bonding (Berlin)* **2004**, *108*, 1.
(23) In the crystal structures determined from neutron diffraction data at 298 K, the average of the three H···O distances (1.763, 1.828, and 1.960 Å) is 1.850 Å for the γ polymorph[20] and 1.894 Å (1.728, 1.832, and 2.121 Å) for the α polymorph.[15] In addition, the N−H···O angles are somewhat closer to 180° for the γ polymorph (171.3°, 155.8°, 171.9°)[20] than the α polymorph (169.3°, 168.5°, 154.0°).[15] While these structural differences may support the suggestion that the hydrogen bonding of the $-N^+H_3$ group in the γ polymorph may be stronger than that in the α polymorph, as also evidenced by previous NMR studies,[21,25] considerable caution is required in attempting to deduce insights on the relative strengths of hydrogen bonds from small differences in hydrogen-bonding geometries.
(24) Kvick, Å.; Canning, W. M.; Koetzle, T. F.; Williams, G. J. B. *Acta Crystallogr. Sect. B* **1980**, *36*, 115.
(25) Potrzebowski, M. J.; Tekely, P.; Dusausoy, Y. *Solid State Nucl. Magn. Reson.* **1998**, *11*, 253.
(26) Aliev, A. E. *Chem. Phys. Lett.* **2004**, *398*, 522 and references therein.
(27) Aliev, A. E. *Biopolymers* **2005**, *77*, 230.
(28) Odlyha, M.; Cohen, N. S.; Foster, G. M.; Aliev, A.; Verdonck, E.; Grandy, D. *J. Therm. Anal. Calorim.* **2003**, *71*, 939.
(29) Bowes, J. H.; Moss, J. A. *Nature* **1951**, *168*, 514.
(30) Ahn, S.; Guo, F.; Kariuki, B. M.; Harris, K. D. M. *J. Am. Chem. Soc.* **2006**, *128*, 8441.
(31) Shieh, H.-S.; Hoard, L. G.; Nordman, C. E. *Acta Crystallogr. Sect. B* **1981**, *37*, 1538.
(32) Alcobe, X.; Estop, E.; Aliev, A. E.; Harris, K. D. M. *J. Solid State Chem.* **1994**, *110*, 20.
(33) Aliev, A. E.; Harris, K. D. M.; Alcobe, X.; Estop, E. *J. Chem. Soc. Faraday Trans.* **1993**, *89*, 3797.
(34) Kitchin, S. J.; Xu, M.; Serrano-González, H.; Coates, L. J.; Ahmed, S. Z.; Glidewell, C.; Harris, K. D. M. *J. Solid State Chem.* **2006**, *179*, 1335.
(35) Aliev, A. E.; Harris, K. D. M.; Guillaume, F. *J. Phys. Chem.* **1995**, *99*, 1156.
(36) Frey, M. H.; DiVerdi, J. A.; Opella, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 7311.
(37) Harris, K. D. M. *Cryst. Growth Des.* **2003**, *3*, 887.
(38) Harris, K. D. M.; Cheung, E. Y. *Chem. Soc. Rev.* **2004**, *33*, 526.
(39) Harris, K. D. M. *Comput. Mater. Sci.* **2009**, *45*, 16.