Dynamics-based selective 2D $^1\text{H}/^1\text{H}$ chemical shift correlation spectroscopy under ultrafast MAS conditions

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Dynamics plays important roles in determining the physical, chemical, and functional properties of a variety of chemical and biological materials. However, a material (such as a polymer) generally has mobile and rigid regions in order to have high strength and toughness at the same time. Therefore, it is difficult to measure the role of mobile phase without being affected by the rigid components. Herein, we propose a highly sensitive solid-state NMR approach that utilizes a dipolar-coupling based filter (composed of 12 equally spaced 90° RF pulses) to selectively measure the correlation of ^1H chemical shifts from the mobile regions of a material. It is interesting to find that the rotor-synchronized dipolar filter strength decreases with increasing inter-pulse delay between the 90° pulses, whereas the dipolar filter strength increases with increasing inter-pulse delay under static conditions. In this study, we also demonstrate the unique advantages of proton-detection under ultrafast magic-angle-spinning conditions to enhance the spectral resolution and sensitivity for studies on small molecules as well as multi-phase polymers. Our results further demonstrate the use of finite-pulse radio-frequency driven recoupling pulse sequence to efficiently recouple weak proton-proton dipolar couplings in the dynamic regions of a molecule and to facilitate the fast acquisition of $^1\text{H}/^1\text{H}$ correlation spectrum compared to the traditional 2D NOESY (Nuclear Overhauser effect spectroscopy) experiment. We believe that the proposed approach is beneficial to study mobile components in multi-phase systems, such as block copolymers, polymer blends, nanocomposites, heterogeneous amyloid mixture of oligomers and fibers, and other materials. © 2015 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4921381>]

I. INTRODUCTION

Molecular dynamics in materials plays an important role in determining the physical, chemical, and functional properties such as the mechanical performance of graphene,¹ stability of pharmaceuticals,² and the behavior around glass transition temperatures of polymers.³ In polymers, the mobile components could change the topological constraints imposed by the crystallites, rendering the material to be stiff while at the same time being tough.^{4,5} The chain diffusion and helical jump are important for the ultrahigh drawability of polymers as well as the α -relaxation behavior.⁶ The mobility of polyethylene oxide (PEO) exerts vital influence on the conductivity of the alkali metal polymer electrolyte.^{7–9} Also, it is well demonstrated that dynamics of a protein directly affects its function such as ion transportation across the cell membrane¹⁰ and protein folding/unfolding/misfolding events.¹¹ Therefore, developing new high-resolution techniques to fully understand the role of dynamics in materials is of considerable importance; at the same time, it is a major challenge, particularly, to study non-crystallizable and/or amorphous materials for which the most commonly used solution NMR techniques and X-ray crystallography may not be applied.

Solid-state NMR spectroscopy is a powerful tool that can provide atomic-level insights into the structure and dynamics of various solids, such as bone,^{12,13} polymers,¹⁴

pharmaceuticals,¹⁵ inorganic materials,^{16,17} and membrane proteins.^{18–22} For high-throughput utilization of solid-state NMR spectroscopy, ^1H NMR experiments are always desired due to the high natural-abundance and large gyromagnetic ratio of protons that render high sensitivity of detection. However, the proton spectral resolution is poor due to the presence of strong ^1H - ^1H dipolar couplings, which severely restricts the applications of proton-based NMR studies of solid-state systems. Fortunately, recent development of magic-angle-spinning (MAS) probe technology has enabled a spinning rate of 65 kHz with a 1.3 mm sample rotor, and even a very impressive speed of 120 kHz with a 0.75 mm rotor. Ultrafast-MAS NMR experiments demonstrated the suppression of large ^1H - ^1H anisotropic dipolar coupling interactions to dramatically enhance the spectral resolution.^{23–26} These developments are significantly impacting the applications of various proton-detected solid-state NMR experiments, which also provide additional significant enhancement in signal-to-noise ratio.^{16,26–36} In fact, under ultrafast MAS, the introduction of ^1H - ^1H dipolar recoupling sequence becomes necessary for controlling and utilizing the dipolar-coupling-based spin diffusion process to accomplish through-space correlation of chemical shifts.^{37–41} In this study, we propose a dipolar filter (or the dipolar-coupling filter) based pulse sequence to selectively detect correlation of ^1H isotropic chemical shifts from mobile regions of a system under ultrafast MAS conditions. The performance of the rotor-synchronized dipolar filter was first examined for different inter-pulse delays, i.e., for different dipolar filter periods.

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Our results demonstrate the advantage of ultrafast MAS to obtain a high-resolution ^1H chemical shift spectrum of polystyrene-polybutadiene-polystyrene (SBS) triblock copolymers, especially the rigid benzene signals that are generally not observable under slow MAS. We also demonstrate the use of a finite-pulse radio-frequency driven recoupling (fp-RFDR) sequence^{37,42} to reintroduce ^1H - ^1H dipolar couplings proved to be beneficial for fast acquisition of a 2D $^1\text{H}/^1\text{H}$ isotropic chemical shift correlation spectrum within an 8 ms mixing time.

II. PULSE SEQUENCE

The MAS solid-state NMR pulse sequence used in this study is shown in Fig. 1. A dipolar-filter sequence (Fig. 1(a)) consisting of twelve 90° RF pulses^{43–45} is used to select the ^1H magnetization from a mobile component, which has a long transverse relaxation time than the rigid components of the system under investigation. In principle, the proton transverse relaxation time in solid systems is mainly determined by the ^1H - ^1H dipolar couplings, which means that the proton signals experiencing strong dipolar couplings will be filtered out first. Because of this reason, the 12-pulse dipolar filter sequence has been utilized in the investigation of the mobility of adsorbed ligands on the surface of nanoparticles,^{46,47} to measure the domain size in a multiphase system,^{44,48,49} and the chain interpenetration and compatibility in polymer glasses.^{50,51} In order to overcome the destructive interferences between MAS averaging and RF-pulses of the dipolar filter, here we utilized a rotor-synchronized dipolar filter with CN_n^v symmetry to filter out signals from rigid components of the system.⁵² To selectively observe the 2D $^1\text{H}/^1\text{H}$ isotropic chemical shift correlation spectrum from the mobile components in a system, a dipolar filter is inserted right before the first and final 90° read pulse as shown in Fig. 1(b). The two dipolar filters in the pulse sequence ensure that peaks in both F1 and F2 dimensions arise only from the mobile components of the molecule. On the other hand, if only one of the dipolar filters is used, either before the first 90° RF pulse or before the final 90° RF pulse, then signal from rigid components can also appear in proton

spectra along F1 or F2 dimension. Generally, a short delay around a few microseconds between the dipolar filter and 90° read pulse could be inserted to remove residual transverse magnetization. During the mixing time, fp-RFDR was used for ^1H - ^1H dipolar recoupling to enable longitudinal magnetization transfer among protons through spin diffusion. XY4¹₄ phase cycling scheme, which has been proved to have the best performance for ^1H - ^1H dipolar recoupling and magnetization transfer under ultrafast MAS conditions, was chosen for the fp-RFDR pulse of 2D $^1\text{H}/^1\text{H}$ correlation experiment in the present study.^{53,54}

III. EXPERIMENTAL

A. Samples

Uniformly, ^{13}C , ^{15}N -L-alanine was purchased from Isotec (Champaign, IL), while PS-PB-PS (polystyrene-polybutadiene-polystyrene), i.e., SBS triblock copolymer (Mw = 140 000 g/mol, PI = 1.2) was purchased from Aldrich Chemical Co. where the weight fraction of styrene is around 32 wt. %.⁵⁵ All samples were used as received without any further purification.

B. Solid state NMR experiments

All solid state NMR experiments were performed on an Agilent/Varian VNMRS 600 MHz solid-state NMR spectrometer operating with a ^1H resonance frequency of 599.8 MHz. A 1.2 mm triple-resonance ultrafast MAS probe was used. The sample/rotor volume was about 2 μl and the 90° pulse width was 1.4 μs . ^1H chemical shifts were reference to L-alanine by setting the chemical shift frequency of the CH_3 group at 1.32 ppm. For the 2D experiment on L-alanine, 16 t_1 increments with a spectral width of 12 kHz were applied for the indirect dimension. For SBS sample, 320 t_1 increments with a spectral width of 12 kHz were applied due to the rather high mobility of the PB component. A recycle delay of 3 s and 4 scans for each t_1 increment were used for all the experiments. For the 2D experiment, n in the pulse sequence (Fig. 1(a)) was set to

FIG. 1. Dipolar filter based proton-detected MAS experiments. (a) Rotor-synchronized dipolar filter sequence for selecting resonances only from mobile components of the system under investigation. The dipolar filter efficiency is determined by the inter-pulse delay τ as well as the number of dipolar filter cycles, N_{cycle} . Under a constant τ_{DF} , the dipolar filter strength increases with N_{cycle} . (b) Two-dimensional $^1\text{H}/^1\text{H}$ correlation experiment with fp-RFDR to recouple ^1H - ^1H dipolar couplings and dipolar filter to select the resonance signals from only mobile components. XY4¹₄ phase cycling scheme (i.e., 0101 1212 2323 3030) was used for the fp-RFDR sequence.

FIG. 2. Dipolar filtered signal intensity as a function of total dipolar filter time. (a) ^1H NMR spectra of a powder sample of $\text{U-}^{13}\text{C-}^{15}\text{N}$ -labeled L-alanine under different MAS rates: 10 (cyan), 20 (pink), 40 (blue), and 60 (red) kHz from bottom to top. Signal intensities of (b) NH_3^+ , (c) CH, and (d) CH_3 groups as a function of dipolar filter time under different dipolar filter periods. The dipolar filter time is calculated as $n \cdot \tau_R \cdot N_{\text{cycle}}$. All the dipolar filter time is increased by increasing the value of N_{cycle} under a constant value of n .

11, corresponding to a dipolar filter period of $\tau_{\text{DF}} = 183.33 \mu\text{s}$ under 60 kHz MAS and an inter-pulse delay $\tau = 13.88 \mu\text{s}$.

IV. RESULTS AND DISCUSSION

In this study, the performance of the dipolar filter as well as the 2D $^1\text{H}/^1\text{H}$ chemical shift correlation experiments under ultrafast MAS conditions is demonstrated on powder samples of a small molecular crystalline solid, L-alanine, as well as on triblock copolymer, SBS, which contains rigid PS and mobile PB components. The experimental results on L-alanine are shown in Figs. 2 and 3. The efficiency of MAS in suppressing ^1H - ^1H dipolar couplings increases with the increasing MAS rate as demonstrated in Fig. 2(a). Beyond a spinning rate of 40 kHz, the three proton peaks from alanine are completely resolved. Also, it is important to examine the performance of the dipolar filter with increasing N_{cycle} under different values of n (the dipolar filter period $\tau_{\text{DF}} = n \cdot \tau_R$), which is

the key parameter in the dipolar filter sequence. The rotor-synchronized dipolar filter has a symmetry of $C6_n^3$ with the basic element $90^\circ_x - \tau - 90^\circ_{-x} - \tau$.⁵² Therefore, n should not be an integer multiple of 3, as it would recouple the ^1H - ^1H dipolar couplings causing a relatively rapid decay of signals from both rigid and mobile components as shown in Figs. 2(c) and 2(d) with $n = 6, 9, 15$. The $n = 12$ case is different, under which condition each 90° pulse is rotor-synchronized, and instead of recoupling, the dipolar couplings are largely averaged in this rotor period (as the 90° pulse length ($1.4 \mu\text{s}$) is much less than the rotor period ($16.7 \mu\text{s}$) under 60 kHz MAS). Furthermore, to the first-order approximation, the dipolar filter Hamiltonian with $C6_n^3$ symmetry for an I_2S spin system can be described as⁵²

$$\begin{aligned} \bar{H}^{(1)} = & \kappa_{0010}^C (\Omega_{I_1}^0 I_{1z} + \Omega_{I_2}^0 I_{2z} + 2\pi J_{I_1S} I_{1z} S_z \\ & + 2\pi J_{I_2S} I_{2z} S_z) + 2\pi J_{I_1I_2} I_{1z} I_{2z} + \Omega_S^0 S_z, \end{aligned} \quad (1)$$

FIG. 3. Dipolar filtered ^1H spectra of alanine. (a) ^1H NMR spectra acquired using the pulse sequence given in Fig. 1(a) with different dipolar filter strength values (varied by increasing N_{cycle}) under 60 kHz MAS, where the amide-proton signal quickly decayed while the CH_3 and CH signals remain even after 54 dipolar-filter cycles. (b) 2D $^1\text{H}/^1\text{H}$ isotropic chemical shift correlation spectrum showing signals only from CH_3 and CH, with $N_{\text{cycle}} = 60$, $n = 11$, by completely filtering out the signal from NH_3^+ protons.

FIG. 4. Dipolar filtered 1H spectra of SBS. (a) Schematic molecular structure for the SBS triblock polymer. (b) 1H single pulse NMR spectra of SBS acquired under different spinning rates of 10, 20, 30, 40, 50, and 60 kHz as shown from bottom to top. It is clearly seen that with increasing the spinning rate, the benzene proton signals (indicated in green dashed rectangular box) are gradually resolved from the rest of the peaks in the spectrum, while proton peaks from polybutadiene are all well resolved due to its high molecular mobility. (c) 1H NMR spectra acquired with increasing dipolar filter strength under 60 kHz MAS (N_{cycle} corresponds to 0, 10, 20, 30, 40, and 50 from top to bottom), where the benzene signals are quickly decayed while other mobile PB signals remain appearing in the spectra.

where Ω^0 , J , and κ_{0010}^C are the isotropic chemical shift, J -coupling, and the scaling factor, respectively; I_i ($i = 1$ or 2) and S_i are the components of angular momentum operators I and S . However, this first-order average Hamiltonian is not sufficient to describe the spin dynamics during the dipolar filter when the magnitude of 1H - 1H dipolar couplings is large compared to $1/n\tau_R$.⁵² Under such a condition, the higher-order terms of the dipolar coupling Hamiltonian could not be ignored. Indeed, the rigid signal decay is mainly resulted from the higher-order dipolar coupling Hamiltonian. Conversely, when the magnitude of 1H - 1H dipolar coupling is small compared to $1/n\tau_R$, the first-order Hamiltonian dominates the spin dynamics resulting in a rather slow decay of mobile signals as the 1H - 1H J couplings commute with the total angular momentum along z -direction, $[I_{1z} + I_{2z}, J_{I_1 I_2} I_1 \cdot I_2] = 0$. Therefore, the value of n directly determines the performance of the dipolar filter in filtering out signals from rigid parts and keeping signals from the mobile ones. Indeed, it is interesting to find that with increasing n , the rigid signal from the NH_3^+ group (strong 1H - 1H dipolar couplings among protons) decays slower with the increasing the dipolar filter time, where the decay rate is quite similar for $n = 11, 12, 13$, and 14 as shown in Fig. 2(b). While for the CH and CH_3 group, the decay rate is the slowest when $n = 11$ or 12 as shown in Figs. 2(c) and 2(d). In Figs. 2(c) and 2(d), when n is below 12, except $n = 6$ or 9 , the signal decay is slower with increasing n because it takes longer time to complete a dipolar filter cycle with increasing n . When n is ≥ 12 , the inter-pulse delay τ is greater than or close to the rotor period τ_R ; therefore, the efficient dephasing time is actually around $|\tau - \tau_R|$, as the dipolar couplings are averaged to zero in a rotor period. So, the signal does not decay faster with increasing n beyond 12. This observation is quite opposite to the dipolar filter under static conditions, where the dipolar filter strength increases (resulting in faster signal decay) with increasing the inter-pulse delay.^{48,49} However, for the rotor-synchronized dipolar filter, the dipolar filter strength decreases with increasing the inter-pulse delay (i.e., increasing n with $n \leq 12$ and $n \neq 3k$) due to the MAS interference. According

to the decay rate of signals from the rigid NH_3^+ and the most mobile CH_3 given in Fig. 2, a large value of n around 11 is recommended because the rigid NH_3^+ has almost decayed to zero for $n = 11$, while most of the CH_3 signal intensity remains for a reasonable dipolar filter time. Finally, it is also worth noting that, in addition to ultrafast MAS, the $C6_n^3$ symmetry of the pulse sequence also suppresses the proton chemical shift anisotropy (CSA), though 1H CSA is small for most systems.⁵² Therefore, the proton CSAs, even at ultra-high magnetic fields, should not contribute to the observed signal decay. However, the higher order CSA Hamiltonian may play a role when the dipolar filter time becomes sufficiently long, as shown by the simulated results given in the supplementary material, Fig. S1.⁵⁶

The 1H spectra of L-alanine obtained under different dipolar filter strengths are shown in Fig. 3(a). Despite that both NH_3^+ and CH_3 groups experience axial rotations, the rotation frequency of NH_3^+ is much slower than that of CH_3 group, resulting in a larger residual 1H - 1H dipolar coupling for NH_3^+ group. In fact, from a single pulse 1H spectrum of an alanine powder sample obtained under 60 kHz MAS, the full width at half maximum (FWHM) measured for the peaks of NH_3^+ , CH , and CH_3 peaks are around 1002, 960, and 846 Hz, respectively, indicating that the NH_3^+ protons experience the strongest homonuclear dipolar couplings. Therefore, with an increase in the dipolar filter strength, the overlapping NH_3^+ proton signals were filtered out, while the slow decaying CH and CH_3 signals contribute to the filtered spectra. The simulated signal decay of NH_3^+ and CH groups with increasing dipolar filter strength is also shown in the supplementary material, Fig. S2⁵⁶ indicating a fast decay of NH_3^+ signals. When the dipolar filter cycle $N_{cycle} > 48$, all the rigid NH_3^+ signals are completely suppressed. Herein, we will consider the CH_3 and CH groups as “mobile,” as they experience weaker dipolar couplings than NH_3^+ protons. Therefore, as shown in Fig. 2(c), by using the pulse sequence given in Fig. 1(b), we were able to obtain the 2D $^1H/^1H$ isotropic chemical shift correlation among the resonances of CH_3 and CH groups. The

FIG. 5. High-resolution fp-RFDR-based ^1H spectrum of SBS. (a) 2D $^1\text{H}/^1\text{H}$ isotropic chemical shift correlation spectrum selectively observed for mobile components of SBS, with $N_{\text{cycle}} = 50$, under which condition the benzene signals are completely filtered out by the dipolar filters in the pulse sequence. The fp-RFDR mixing time was 8 ms. The blue dashed circle indicates the missing of rigid benzene signals. (b) Comparison of ^1H spectra obtained from the single pulse experiment and the sum projection along F2 dimension of Fig. 5(a). The green dashed rectangle clearly indicates that the rigid benzene signals are completely filtered out in the 2D selective $^1\text{H}/^1\text{H}$ correlation experiment.

signal from NH_3^+ protons was completely filtered out from the 2D $^1\text{H}/^1\text{H}$ experiment (Fig. 3(b)), as compared to the 2D $^1\text{H}/^1\text{H}$ total correlation spectrum shown elsewhere.⁵³ These results demonstrate the robust performance of the selective mobile 2D $^1\text{H}/^1\text{H}$ correlation experiment for small molecular solid-state samples. In addition, Hahn-echo⁵⁷ is often used to obtain signals selectively from the mobile chemical groups while filtering out the rigid ones.¹⁴ Therefore, we compared the efficiency of the dipolar filter used in this study with that of Hahn-echo under 60 kHz MAS as shown in the supplementary material, Fig. S3.⁵⁶ Obviously, the dipolar filter has a higher efficiency in retaining the signals from mobile groups while at the same time completely filtering out signals of rigid groups.

A complex model system, SBS, is also used in this study to demonstrate the advantage of ultrafast MAS as well as the robust performance of the 2D $^1\text{H}/^1\text{H}$ correlation experiment. Due to the excellent mechanical performance (high tensile strength, elongation at break, etc.) and processability, SBS triblock copolymers with 60% ~ 80% mobile fraction are one of the main commercial and widely used thermoplastic elastomer.⁵⁸ Because of the significance of mobile phase in controlling and modulating the mechanical performance of SBS, a selective observation of signals from mobile regions is necessary for further understanding its effect on the properties of SBS. The experimental results obtained from SBS are shown in Figs. 4 and 5. The peak assignments for SBS are reported in the supplementary material of Ref. 55. As shown in Fig. 4(b), proton peaks from PB are well resolved due to its high mobility, which greatly suppress the dipolar couplings, whereas the PS component is quite rigid, rendering it difficult to resolve the signal from benzene protons at slow spinning speeds. However, with increasing spinning speed of the sample, signals from benzene protons are better resolved as shown in Fig. 4(b). With increasing the dipolar filter strength, as shown in Fig. 4(c) and Fig. S4 in the supplementary material,⁵⁶ the benzene signals are gradually suppressed and finally filtered out for $N_{\text{cycle}} > 30$.

The 2D $^1\text{H}/^1\text{H}$ correlation spectrum selectively observed for the mobile PB component is shown in Fig. 5(a), where the rigid proton signal around 6.8 ppm is completely filtered out. A clearer demonstration is shown in Fig. 5(b), where peaks from the benzene group are suppressed in the sum projection spectrum along the F2 dimension of Fig. 5(a), as compared to the 1D single pulse spectrum. Another experimental demonstration of the approach proposed in this

study on collagen is given in the supplementary material, Fig. S5.⁵⁶ After the dipolar filter, signals (in 6–10 ppm and the bottom hump between 0 and 6 ppm) from rigid groups are filtered out, and by using an 8 ms fp-RFDR mixing time, the $^1\text{H}/^1\text{H}$ correlation among resonances in the high field region (0–2 ppm) is obtained. However, the $^1\text{H}/^1\text{H}$ correlations between resonances in the high field (0–2 ppm) and low field (3–6 ppm) regions require a longer fp-RFDR mixing time. Here, it is worth mentioning about the advantage of fp-RFDR in recoupling weak homonuclear dipolar couplings from mobile components. By using the fp-RFDR sequence during the mixing time of the 2D experiment, the longitudinal magnetization transfer occurs within a few milliseconds. However, it may take tens of milliseconds or longer for the magnetization transfer to occur in a 2D NOESY (Nuclear Overhauser effect spectroscopy) experiment. The 2D $^1\text{H}/^1\text{H}$ correlation RF pulse sequences for NOESY and fp-RFDR based experiments are shown in the supplementary material, Fig. S6.⁵⁶ The difference in 2D $^1\text{H}/^1\text{H}$ NOESY and fp-RFDR spectra can be seen in Fig. S7,⁵⁶ where the cross peak intensity in fp-RFDR spectrum is stronger than that observed in the NOESY spectrum indicating the efficiency of fp-RFDR in recoupling weak ^1H - ^1H dipolar couplings.

Since spinning at a very high speed heats up the sample, and therefore the molecule mobility and dipolar couplings could be altered, it is important to control the sample temperature by appropriately cooling the sample. In our case, the sample temperature at 60 kHz MAS may be around 60 °C. For the crystalline L-alanine sample, this temperature is much smaller than the melting temperature (~250 °C) and therefore the MAS-induced sample heating may not affect the observed spectral resolution. Similarly, the glass transition temperature of PS in the SBS sample is around 100 °C,⁵⁵ which means that the mobility of PS should not be affected by the elevated spinning speed. Therefore, the enhanced ^1H spectral resolution observed under ultrafast MAS for both alanine and SBS samples only results from the effect of higher spinning speed instead of the elevated sample temperature.

In summary, we have demonstrated a 2D $^1\text{H}/^1\text{H}$ solid-state NMR experiment that correlates the isotropic chemical shifts of protons under ultrafast MAS conditions to selectively obtain the total correlation among the proton resonances originating from mobile components of a solid sample under investigation. A rotor-synchronized dipolar filter was utilized to select proton signals from the mobile regions/groups, where

the dipolar filter strength was found to decrease with increasing inter-pulse delay (i.e., increasing the 12-pulse dipolar filter period) when $n < 12$. Besides, the ultrafast MAS suppressed strong ^1H - ^1H dipolar couplings in solids, enabling the direct detection of protons that rendered an additional sensitivity gain. Our results demonstrate that overlapped proton signals from rigid and mobile components in a system could be resolved using the dipolar filter, which is important for the investigation of mobile/dynamic components in a polymeric mixture or in a heterogeneous amyloid soup that consist of monomers, oligomers, and fibers. We have also demonstrated the efficiency of fp-RFDR for recoupling weak ^1H - ^1H dipolar couplings under ultrafast MAS.

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