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Enhanced sensitivity in high-resolution ^{1}H solid-state NMR spectroscopy with DUMBO dipolar decoupling under ultra-fast MAS

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ABSTRACT

The solid-state NMR ^{1}H homonuclear decoupling sequences in the DUMBO family are shown to be effective at ultra-fast MAS rates of up to 65 kHz. The sequences are applied to model compounds glycine and [2-^{13}C]-L-alanine as well as the dipeptide β-L-Asp-L-Ala in windowed and continuous phase-modulated versions. They are shown to achieve especially impressive resolution when implemented in a 2D constant-time experiment. At 65 kHz MAS, ^{1}H resolution using homonuclear decoupling is similar to that obtained at lower MAS rates, but peak intensity, and therefore spectral sensitivity, is improved by a factor of 5 over homonuclear-decoupled spectra at 10 kHz MAS.

1. Introduction

One of the frontiers of development in solid-state NMR is ^{1}H homonuclear dipolar decoupling. This area aims to remove the broadening of ^{1}H spectra caused by homonuclear dipolar couplings sufficiently to obtain resolved peaks and thereby obtain site-specific information from ^{1}H NMR. This is relevant to many areas of NMR [1–5] and in particular is the principal barrier to the application of natural abundance NMR crystallography [6,7] to more complex molecules or materials of increasing pharmaceutical relevance. Progress in ^{1}H homonuclear decoupling has been rapid recently [8], with pulse sequences in the DUMBO family [9–11] and the PMLG scheme [12–16] being well established and widely used for several years. Interesting symmetry-based pulse sequences have also been developed in parallel [17–21]. The most widely used of these pulse sequences are today the DUMBO and PMLG families, and they have been used with success at sample spinning rates up to 30–35 kHz [10,22,23]. However, spectrometer and probe hardware has been improving recently, with ultra-fast magic-angle spinning (MAS) probes capable at spinning at speeds of at least 65 kHz now available. These probes have opened up a wide range of potential new applications and experiments, and even though residual proton linewidths are expected to decrease linearly as the inverse of the spinning frequency decreases, the linewidths obtained under conditions of ultra-fast MAS alone are still far from the limiting resolution [24–26].

At first sight, the application of homonuclear dipolar decoupling sequences under ultra-fast MAS potentially presents difficulties for homonuclear decoupling sequences not specifically developed for such a fast-spinning regime. The original DUMBO scheme [9] and PMLG [12] were both developed in an implicitly static limit. Indeed, they are part of the large class of pulse sequences that were developed in the so-called (Combined Rotation And Multiple-Pulse Sequences) CRAMPS approach, which assumes that the spinning speed is slow compared to the cycle time of the pulse sequence [27–29], and the experiment is thus performed in the 'quasi-static' regime, where it can be assumed that the two averaging effects operate independently [30,31]. Thus, averaging of homonuclear dipolar couplings is considered to be performed consecutively by the application of the rf pulses and then MAS. Under very fast MAS, the cycle time of the MAS spinning is often of the same order of magnitude as the rf cycle time induced by the homonuclear decoupling sequence, and the two averaging effects may no longer be independent: the 'quasi-static' regime is no longer relevant. Here we demonstrate that, despite this potential barrier, homonuclear decoupling sequences belonging to the DUMBO family lead to high-resolution ^{1}H spectra at high spinning rates (ν_R = 65 kHz). We show that a significant enhancement in resolution is obtained when compared to fast MAS alone. We describe the synchronization behavior of the sequences, and most notably, we show that resolution is maintained at ultra-fast MAS rates while sensitivity is significantly enhanced, using glycine, [2-^{13}C]-L-alanine, and the dipeptide β-L-Asp-L-Ala as model compounds.

2. Experimental

The DUMBO family of homonuclear dipolar decoupling pulse sequences consists of constant-amplitude pulses subject to a periodic continuous phase modulation $\varphi(t)$ of the form [11]

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$$\varphi(t) = \sum_{n=1}^{6}[a_n \cos(2nx_c t) + b_n \sin(2nx_c t)] \quad \text{if } 0 \le t < \tau_c/2,$$
$$\varphi(t) = \pi + \varphi(\tau_c - t) \quad \text{if } \tau_c/2 \le t < \tau_c,$$

where $x_c = 2\pi/\tau_c$ and τ_c is the period, approximately equal to a 6π pulse. The two sequences used here are denoted eDUMBO-1_{22} [11] and DUMBO-1 [9], and the Fourier coefficients (a_n, b_n) used to describe their phases are described in reference [11]. The DUMBO-1 sequence was originally developed for the static case by numerically optimizing the Fourier coefficients to obtain the best homonuclear decoupling possible, beginning from random starting points [9], while the coefficients of the eDUMBO-1_{22} sequence were experimentally optimized on a spinning sample from the values of the DUMBO-1 scheme [11]. These two sets of coefficients have been used here without further optimization.

In the ^{1}H spectra shown here, windowed sequences were used to obtain 1D homonuclear-resolved spectra with ^{1}H direct detection, and windowless sequences were used to obtain 2D correlation spectra with ^{1}H homonuclear decoupling applied only in the indirect dimension of acquisition (Fig. 1). Both approaches are relevant to practical applications. Both decoupling schemes were implemented with an rf pulse amplitude of 170 kHz. The length of the period τ_c was found by optimization to give maximum signal for $\tau_c = 20$ μs, which is slightly longer than a 6π pulse. When windowed DUMBO was applied (Fig. 1a), three repeated cycles of a DUMBO sequence, each with $\tau_c = 20$ μs, were separated from the next three blocks of the DUMBO sequence by a detection window of 7.6 μs. The pre-pulse length θ and phase angle ϕ were optimized as described in [10] to remove rf artifacts without recourse to supercycling [23]: the only phase cycling used in the 1D experiment was CYCLOPS [32] to remove quadrature images.

All experiments were performed on a Bruker 500 MHz Avance III NMR spectrometer with a ^{1}H operating frequency of 500.17 MHz and a ^{13}C frequency of 125.75 MHz using a double tuned 1.3 mm CPMAS probe. Samples were restricted to the central millimeter of a 1.3 mm rotor in order to maximize rf homogeneity; less than 1 mg of sample was used. The glycine ^{1}H MAS spectrum was acquired in four scans, the β-L-Asp-L-Ala ^{1}H MAS spectrum was acquired in two scans, and the homonuclear-decoupled 1D ^{1}H spectra in 16 scans.

Two-dimensional ^{1}H–^{1}H correlation spectra acquired using the pulse sequence shown in Fig. 1b [10,12] were acquired in just over one hour each, using 4 scans per t_1 increment, an un-scaled spectral width in the indirect dimension of 10 kHz (i.e. before correction for the homonuclear decoupling scaling factor), and 400 t_1 points. 2D constant-time ^{1}H–^{1}H correlation experiments [33] were acquired using the pulse sequence in Fig. 1c, with an un-scaled spectral width in the indirect dimension of 12.5 kHz and 48 scans per increment. No homonuclear decoupling was applied in the direct acquisition dimension of these experiments. In both cases, pure phase spectra were obtained using the States-TPPI method in t_1 [34].

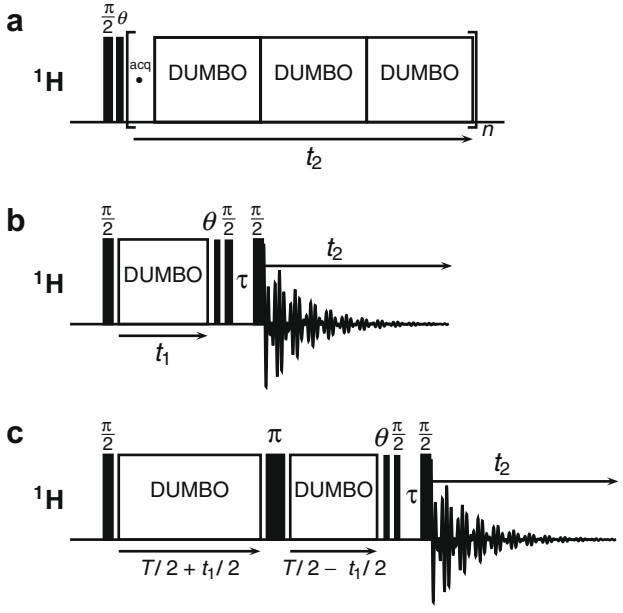


Fig. 1. CRAMPS pulse sequences: (a) 1D windowed pulse sequence for obtaining a directly detected high-resolution ^{1}H spectrum [15], (b) standard 2D experiment in which a high-resolution ^{1}H dimension is correlated with a MAS dimension [10,12], and (c) constant-time 2D experiment (with constant time T) in which a high-resolution ^{1}H spectrum showing refocused ^{1}H linewidths is correlated with a MAS dimension [33]. The pulses with flip angle θ have phase ϕ.

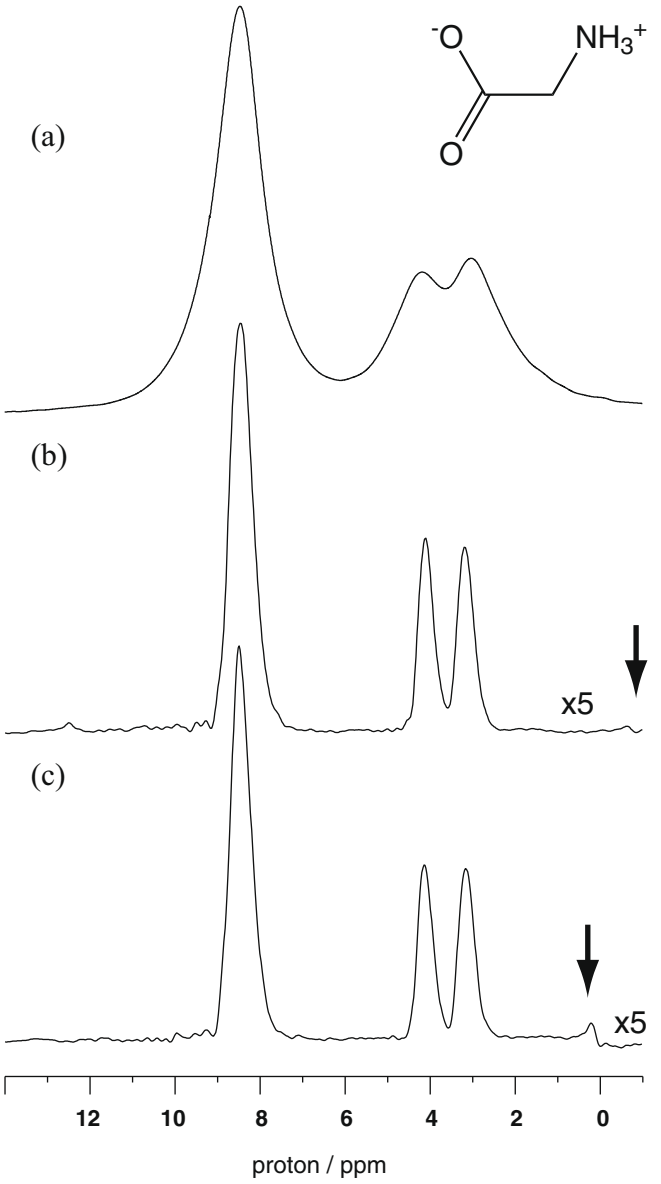


Fig. 2. Directly detected 1D ^{1}H spectra of glycine under MAS at 65 kHz. (a) MAS spectrum. (b) Homonuclear-decoupled spectrum using the windowed DUMBO-1 sequence. (c) Homonuclear-decoupled spectrum using the windowed eDUMBO-1_{22} sequence. The transmitter offset frequency is indicated with arrows in the homonuclear-decoupled spectra.

In the ^{13}C CPMAS spectra, the windowless decoupling sequences were applied during acquisition using the same parameters as above. Low-power double-quantum cross-polarization was used [35,36], with a ^{13}C rf field amplitude of about 40 kHz and a 50% ramp applied with an average rf field amplitude of 25 kHz on the ^{1}H channel during a 2 ms CP contact time, acquired using 64 scans.

All linewidths reported are full linewidths at half height and have been corrected for chemical shift scaling by the homonuclear decoupling sequence applied.

All of the pulse programs used here are available upon request to the authors.

3. Results and discussion

The ability of the DUMBO family of homonuclear decoupling sequences to obtain homonuclear-decoupled directly detected ^{1}H spectra under ultra-fast MAS conditions is shown in Fig. 2. The figure shows spectra obtained for a sample of powdered glycine spinning at 65 kHz. First, it must be noted that the resolution obtained using MAS alone is good (Fig. 2a), but that using DUMBO decoupling (Fig. 2b and c) is dramatically better. Excellent resolution is obtained for the two diastereotopic CH_2 resonances centered at 3.6 ppm (linewidth of 230 Hz (0.47 ppm) for each peak) using the windowed direct-detection pulse sequence shown in Fig. 1a. Comparison of the two DUMBO sequences used shows slightly better resolution obtained using eDUMBO-1_{22} (Fig. 2c) than DUMBO-1 (Fig. 2b), and a larger scaling factor of 0.55 obtained using eDUMBO-1_{22} as compared to 0.47 using DUMBO-1. By contrast, at slower spinning frequencies, the windowed version of DUMBO-1 is generally preferred [11]. Good resolution is also apparent in Fig. 3 which shows a homonuclear-decoupled ^{1}H spectrum of the dipeptide β-L-Asp-L-Ala. The linewidth of the methyl peak of the dipeptide at 1.1 ppm is found to be 160 Hz (0.32 ppm) under application of eDUMBO-1_{22} at an MAS rate of 65 kHz.

Note that because the pre-pulse length θ in the sequence was properly adjusted, the axial peak is almost invisible in the spectra in Figs. 2 and 3, and the transmitter offset can be placed close to resonances in the spectrum. A pulse sequence incorporating the supercycling proposed by Madhu et al. [23,37] to reduce zero-frequency artifacts was, nevertheless, tried in the presence of eDUMBO-1_{22} decoupling (not shown) and found to reduce the scaling

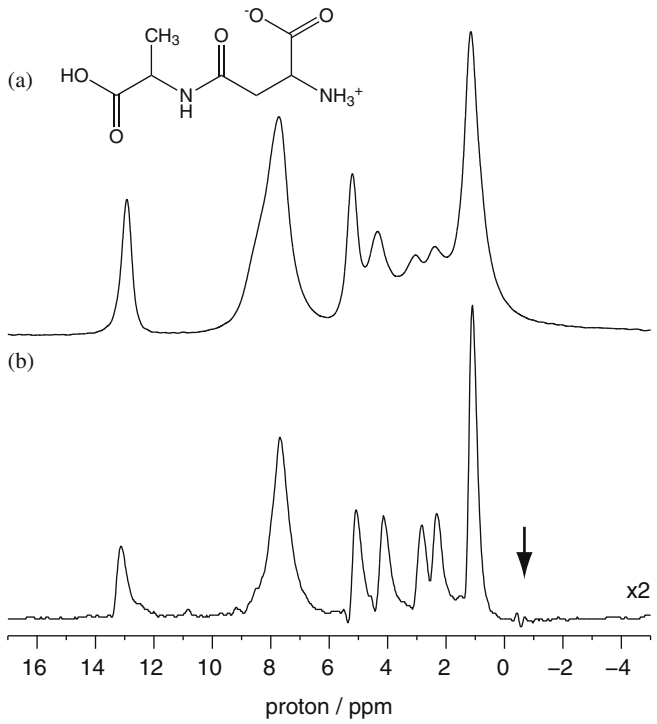


Fig. 3. Directly detected 1D ^{1}H spectra of the dipeptide β-L-Asp-L-Ala under MAS at 65 kHz. (a) MAS spectrum. (b) Homonuclear-decoupled spectrum using the windowed eDUMBO-1_{22} sequence in the directly detected scheme of Fig. 1a. The transmitter offset frequency is indicated with an arrow in the homonuclear-decoupled spectrum.

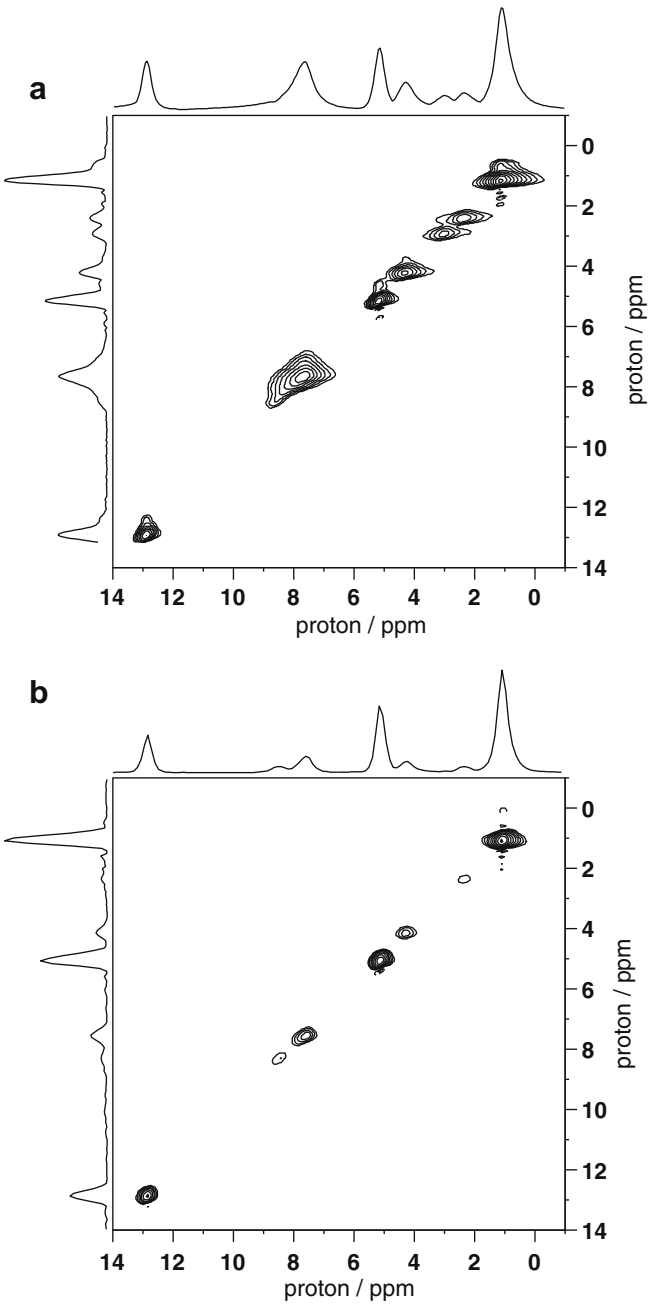
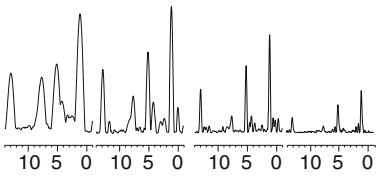


Fig. 4. 2D ^{1}H–^{1}H correlation experiments of the dipeptide β-L-Asp-L-Ala (shown in Fig. 3) acquired at 65 kHz MAS with eDUMBO-1_{22} decoupling in the indirect dimension using (a) the standard 2D experiment pulse sequence in Fig. 1b with total acquisition time in the indirect dimension of 20 ms, and (b) the constant-time pulse sequence in Fig. 1c with constant time $T = 24$ ms. The transmitter offset frequency is at approximately −5 ppm in these spectra. The projections along the direct and indirect dimensions are shown above and to the left of the spectra, respectively. The minimum contour level for each spectrum has 4.5% of the intensity of the most intense peak in that spectrum.

factor to 0.44 from 0.57 for β-L-Asp-L-Ala without significantly improving the quality of the spectrum. Supercycling results in only retaining those components of the effective field aligned with the *z*-axis. Since the DUMBO effective field is not aligned along the *z*-axis, this produces a significantly reduced scaling factor. Furthermore, the homonuclear-decoupled spectra presented in Fig. 2b, c and Fig. 3b show highly linear scaling across the entire ^{1}H chemical shift range (as evaluated from the comparison between the decoupled and the MAS-only spectra), again despite the absence of supercycling.

The efficiency of windowless DUMBO decoupling at ultra-fast MAS is demonstrated in the two ^{1}H–^{1}H correlation spectra shown in Fig. 4, in which eDUMBO-1_{22} is applied in the indirect dimension only to a sample of powdered β-L-Asp-L-Ala. In Fig. 4a, the pulse sequence of Fig. 1b is applied, while in Fig. 4b, the constant-time pulse sequence of Fig. 1c is used. The resolution is again good in both spectra, with a methyl ^{1}H linewidth of 165 Hz obtained for the standard spectrum shown in Fig. 4a; this value is nearly identical to that obtained using windowed eDUMBO-1_{22} in Fig. 2b. The constant-time experiment of Fig. 4b has been shown to give the best possible proton resolution for a given homonuclear decoupling sequence [33]. The constant-time spectrum is indeed better resolved than with the conventional experiment with a methyl linewidth of 120 Hz obtained for a constant time $T = 24$ ms. In this spectrum, the NH and NH_3^+ peaks near 8 ppm are even resolved into two peaks, as has been observed in ^{14}N-decoupled ^{1}H CRAMPS spectra at 500 MHz [38].

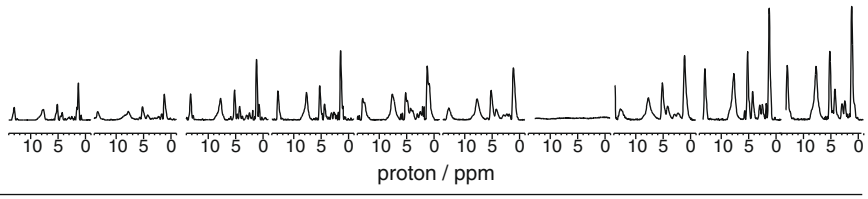
The detailed behavior of DUMBO decoupling as a function of spinning speed is shown in Fig. 5. eDUMBO-1_{22} was applied in the conventional indirect experiment of Fig. 1b for a series of MAS rates ranging from 20 to 65 kHz, using the parameters optimized for a MAS rate of $\nu_r = 65$ kHz ($\tau_c = 20$ μs). Fig. 5 shows the resulting spectra and the measured intensities, linewidths, and scaling factors. The intensities of the spectra show a dependence on the ratio τ_r/τ_c (where $\tau_r = 1/\nu_r$), with clear interference conditions when the decoupling cycle time is synchronized with the rotation period $\tau_r = n\tau_c$ ($n = 1, 2$). It is remarkable that the intensity of the spectrum increases significantly as the spinning frequency is increased. Here this represents a factor of 1.7 improvement in signal intensity between the maximum at 35 kHz, and the maximum at 65 kHz. This is the same behavior as was previously noted in studies of DUMBO during MAS up to 30 kHz [10]. However, while the intensity increases, the $-CH_3$ linewidth remains relatively constant. Furthermore, the intensity of the $-CH_2$ resonances centered at 3.7 ppm increases even more markedly with faster spinning, showing a factor of 2.3 increase between 35 kHz and 65 kHz. These observations suggest that faster spinning increases centerband intensity by decreasing rotational decoupling sideband intensity, without interfering with decoupling efficiency, as long as rotary resonance conditions are avoided. Such a phenomenon has been observed for heteronuclear decoupling in both liquid crystalline samples [39] and in spinning samples [36], and explained using perturbation approaches and numerical simulation [36,39,40]. Unfortunately, the spectral width imposed by the sampling scheme used in homonuclear decoupling experiments prevents us from directly observing the sidebands in a straightforward manner.



T / ms	4	8	16	24
$\Delta_{(CH3)}$ / ppm	1.08	0.55	0.28	0.24
$\Delta_{(CH3)}$ / Hz	540	275	140	120
λ	0.58	0.58	0.58	0.58

Fig. 6. Skyline projections from 2D ^{1}H–^{1}H correlation spectra of the dipeptide β-L-Asp-L-Ala acquired at an MAS rate of 65 kHz with the constant-time pulse sequence in Fig. 1c using eDUMBO-1_{22} decoupling. The constant time T, the full linewidth at half height $\Delta_{(CH_3)}$ of the methyl peaks, and the scaling factor λ of the sequence are given in the table.

The ability of the constant-time implementation of DUMBO [33] decoupling to narrow lines at an MAS rate of 65 kHz is demonstrated in Fig. 6 for a range of constant times T from 4 ms to 24 ms. Line narrowing improves with increased constant time T, as expected, albeit at the expense of intensity, and the limiting linewidth is presumably even narrower than that achieved at $T = 24$ ms here. The improved resolution is obtained since (i) the linewidth in the indirect dimension corresponds only to non-refocusable or antisymmetric interactions and (ii) the experiment favors crystallite orientations having weaker couplings [22,33]. The constant-time linewidths observed here, of around 120 Hz



ω_r / kHz	20	25	30	35	40	45	50	55	60	65
τ_r/τ_c	2.50	2.00	1.67	1.43	1.25	1.11	1.00	0.91	0.83	0.77
$\Delta_{(CH3)}$ / ppm	0.22	0.36	0.29	0.31	0.50	0.50		0.45	0.28	0.33
$\Delta_{(CH3)}$ / Hz	110	180	145	155	250	250		225	140	165
λ	0.56	0.56	0.57	0.59	0.58	0.56		0.56	0.58	0.58
$A_{(CH2)}$ / $A_{(CH3)}$	0.36	0.40	0.39	0.45	0.48	0.49		0.48	0.53	0.54

Fig. 5. Skyline projections (indirect dimension) from 2D ^{1}H–^{1}H correlation spectra of the dipeptide β-L-Asp-L-Ala acquired at the indicated MAS rates with the pulse sequence in Fig. 1b using eDUMBO-1_{22} decoupling. The ratio of the rotation period τ_r to the decoupling cycle time τ_c, the full linewidth at half height, $\Delta_{(CH_3)}$ of the methyl peaks, after correction for the experimentally determined scaling factor λ (also given) of the sequence, and the ratio of the total area of the two CH_2 peaks A_{CH_2} to the area of the CH_3 peak A_{CH_3} are given in the table.

(0.24 ppm) after correction for the scaling factor, are comparable with the limiting linewidths observed previously in experiments at moderate spinning speeds for the dipeptide β-L-Ala-L-Asp using FSLG decoupling (155 kHz) [33], indicating that, as for the case of the ordinary homonuclear-decoupled lineshapes whose lineshapes are shown in Fig. 5, the limiting resolution obtained in the constant-time experiment has not changed greatly as a result of ultra-fast-spinning.

Finally, the efficiency of the two DUMBO decoupling sequences in heteronuclear decoupling is demonstrated in Fig. 7, where both sequences are applied during the acquisition of a ^{13}C CPMAS spectrum of [2-^{13}C]-L-alanine. In this case, the homonuclear decoupling sequences are applied in a windowless fashion using a 20 μs decoupling cycle time τ_c. The quality of the decoupling is reflected in the resolution of the doublet due to ^{1}J-coupling of the CH group, and this in turn will determine the efficiency of multi-dimensional correlation experiments such as J-HMQC [41], J-HSQC [42], or INEPT [43]. The doublet is well resolved using both decoupling sequences, but there is a significant improvement when using eDUMBO-1_{22}, which provides exceptionally good performance under these conditions. These spectra can be compared to spectra recorded under more standard conditions (22 kHz) published previously [11], and we find the spectra at 65 kHz to be certainly no worse than those obtained at slower speeds.

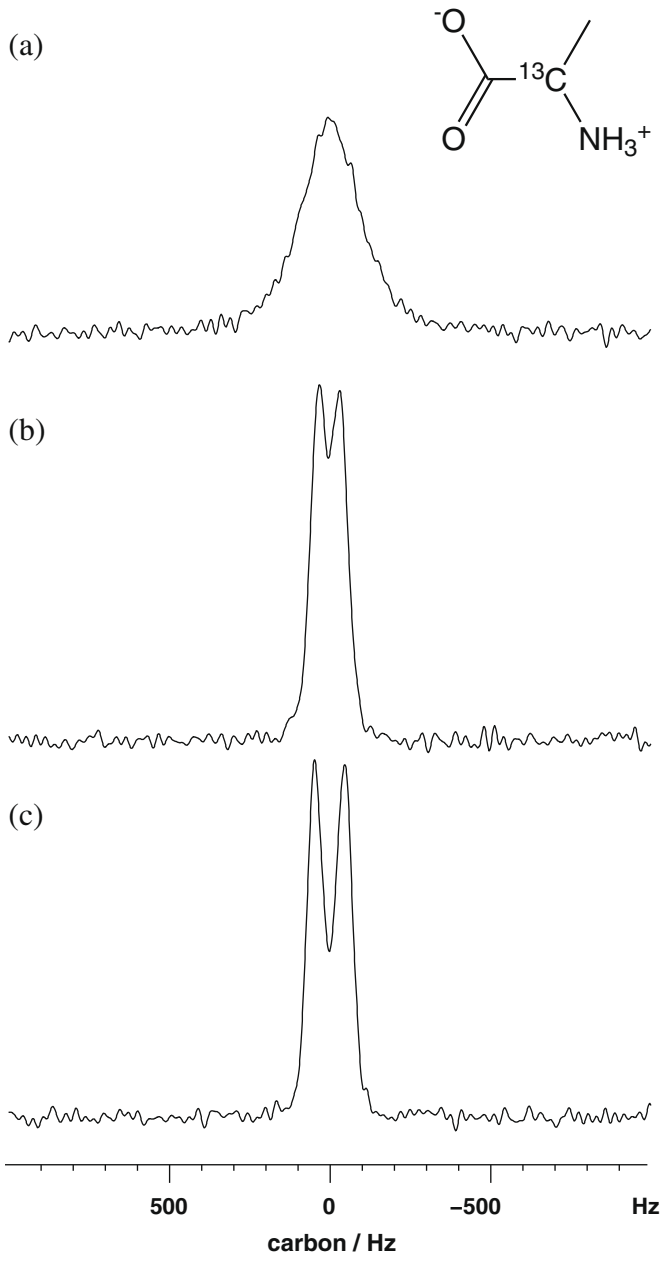


Fig. 7. CPMAS ^{13}C spectrum of the C_2 carbon of [2-^{13}C]-L-alanine obtained with 65 kHz MAS using (a) no proton decoupling and (b) DUMBO-1 and (c) eDUMBO-1_{22} ^{1}H homonuclear decoupling during acquisition.

4. Conclusion

The DUMBO family of homonuclear decoupling pulse sequences has been shown to be effective for efficient homonuclear dipolar decoupling at ultra-fast MAS rates. This is true despite the fact that the DUMBO sequences were developed in the static or moderately fast-spinning regimes, and not in the very fast-spinning regime. Good performance is obtained as long as easily determined interference conditions are avoided. Outside these regimes, no synchronization conditions are required for good homonuclear decoupling performance. Most notably, the sensitivity of these experiments is very significantly improved at ultra-fast MAS. When combined with an increase of a factor of three previously observed between the 'classical' CRAMPS regime of about 10 kHz, and 30 kHz [10], the further increase observed here leads to a factor of more than 5 in sensitivity between classical 10 kHz conditions and the 65 kHz spectra presented here. In contrast to previous results under spinning at ν_R = 12.5 kHz or ν_R = 22 kHz, where DUMBO-1 was the best sequence for windowed acquisition, we find here that eDUMBO-1_{22} is the better decoupling sequence in both windowed and non-windowed applications at 65 kHz MAS.

Finally, we note that our observations open the way to implement at ultra-fast MAS a large set of 2D NMR experiments under conditions of homonuclear decoupling and therefore of high ^{1}H resolution, including homonuclear double-quantum correlation [44] and heteronuclear correlation experiments [42,43].

Acknowledgments

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