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# Optimisation of $^1\text{H}$ PMLG homonuclear decoupling at 60 kHz MAS to enable $^{15}\text{N}$ – $^1\text{H}$ through-bond heteronuclear correlation solid-state NMR spectroscopy†‡

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The Lee–Goldburg condition for homonuclear decoupling in  $^1\text{H}$  magic-angle spinning (MAS) solid-state NMR sets the angle  $\theta$ , corresponding to  $\arctan$  of the ratio of the rf nutation frequency,  $\nu_1$ , to the rf offset, to be the magic angle,  $\theta_m$ , equal to  $\tan^{-1}(\sqrt{2}) = 54.7^\circ$ . At 60 kHz MAS, we report enhanced decoupling compared to MAS alone in a  $^1\text{H}$  spectrum of  $^{15}\text{N}$ -glycine with PMLG $^{\text{xx}}$  at  $\theta = 30^\circ$  for a  $\nu_1$  of  $\sim 100$  kHz at a  $^1\text{H}$  Larmor frequency,  $\nu_0$ , of 500 MHz and 1 GHz, corresponding to a high chemical shift scaling factor ( $\lambda_{\text{CS}}$ ) of 0.82. At 1 GHz, we also demonstrate enhanced decoupling compared to 60 kHz MAS alone for a lower  $\nu_1$  of 51 kHz, *i.e.*, a case where the nutation frequency is less than the MAS frequency, with  $\theta = 18^\circ$ ,  $\lambda_{\text{CS}} = 0.92$ . The ratio of the rotor period to the decoupling cycle time,  $\Psi = \tau_r/\tau_c$ , is in the range 0.53 to 0.61. Windowed PMLG $^{\text{xx}}$  decoupling using the optimised parameters for a  $\nu_1$  of  $\sim 100$  kHz also gives good performance in a  $^1\text{H}$  spin-echo experiment, enabling implementation in a  $^1\text{H}$ -detected  $^{15}\text{N}$ – $^1\text{H}$  cross polarisation (CP)-refocused INEPT heteronuclear correlation NMR experiment. Specifically, initial  $^{15}\text{N}$  transverse magnetisation as generated by  $^1\text{H}$ – $^{15}\text{N}$  CP is transferred back to  $^1\text{H}$  using a refocused INEPT pulse sequence employing windowed PMLG $^{\text{xx}}$   $^1\text{H}$  decoupling. Such an approach ensures the observation of through-bond N–H connectivities. For  $^{15}\text{N}$ -glycine, while the CP-refocused INEPT experiment has a lower sensitivity ( $\sim 50\%$ ) as compared to a double CP experiment (with a 200  $\mu\text{s}$   $^{15}\text{N}$  to  $^1\text{H}$  CP contact time), there is selectivity for the directly bonded  $\text{NH}_3^+$  moiety, while intensity is observed for the  $\text{CH}_2$   $^1\text{H}$  resonances in the double CP experiment. Two-dimensional  $^{15}\text{N}$ – $^1\text{H}$  correlation MAS NMR spectra are presented for the dipeptide  $\beta$ -AspAla and the pharmaceutical cimetidine at 60 kHz MAS, both at natural isotopic abundance. For the dipeptide  $\beta$ -AspAla, different build-up dependence on the first spin-echo duration is observed for the NH and  $\text{NH}_3^+$  moieties demonstrating that the experiment could be used to distinguish resonances for different  $\text{NH}_x$  groups.

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## 1. Introduction

Direct  $^1\text{H}$  detection is increasingly important for solid-state NMR study of pharmaceuticals<sup>1–4</sup> and biological molecules.<sup>5–8</sup> The availability of ever faster Magic Angle Spinning (MAS) frequencies reduces line broadening due to  $^1\text{H}$  homonuclear dipolar couplings.<sup>9–14</sup> In particular,  $^1\text{H}$  detection is advantageous

for the identification of specific correlations to nuclei with low gyromagnetic ratio,  $\gamma$ , such as the two natural-abundant isotopes of nitrogen,  $^{14}\text{N}$  and  $^{15}\text{N}$ . Our focus here is on the spin  $I = 1/2$   $^{15}\text{N}$ , though it is to be noted that there is increasing application of  $^{14}\text{N}$ – $^1\text{H}$  experiments for the much higher natural abundance (99.6%) spin  $I = 1$  nucleus.<sup>15–22</sup> The low sensitivity of  $^{15}\text{N}$ , associated with its low natural abundance and gyromagnetic ratio, can be overcome by the use of  $^{15}\text{N}$ – $^1\text{H}$  correlation experiments with proton acquisition, thanks to the high natural abundance and  $\gamma$  that characterise protons, provided that fast MAS can achieve sufficient  $^1\text{H}$  line narrowing.<sup>23–26</sup> We note that an  $^{15}\text{N}$ -detected MAS- $J$ -HMQC  $^1\text{H}$ – $^{15}\text{N}$  two-dimensional spectrum has also been recorded at natural abundance and 12.5 kHz MAS using Frequency Switched Lee–Goldburg (FSLG)  $^1\text{H}$  homonuclear decoupling.<sup>27</sup>

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$^1\text{H}$ -detected heteronuclear  $^{15}\text{N}$ - $^1\text{H}$  correlation experiments can be achieved by inverse polarization, CP, as applied to small molecules<sup>23,25,26,28–30</sup> and  $^{15}\text{N}$ -labelled proteins as a hNH experiment.<sup>31–33</sup> An alternative to CP-based dipolar-mediated through-space transfer is a  $J$  coupling mediated through-bond refocused INEPT solid-state NMR experiment.<sup>34–37</sup> Specifically, we consider the CP-refocused INEPT correlation experiment,<sup>38,39</sup> whereby  $J$  coupling mediated  $^{15}\text{N}$ - $^1\text{H}$  back-transfer, following CP to give maximum initial  $^{15}\text{N}$  magnetisation, ensures only the observation of peaks due to through-bond transfer in a  $^{15}\text{N}$ - $^1\text{H}$  spectrum.<sup>26</sup> However, fast dephasing due to strong  $^1\text{H}$  homonuclear dipolar couplings shortens  $^1\text{H}$  coherence lifetimes, reducing sensitivity, making  $J$  coupling based experiments challenging. Even 60 kHz MAS is not sufficient to completely average out  $^1\text{H}$  homonuclear dipolar couplings.<sup>40</sup> The application of  $^1\text{H}$  homonuclear decoupling<sup>41–44</sup> under fast MAS during the  $^{15}\text{N}$ - $^1\text{H}$  coherence transfer improves sensitivity sufficiently for refocused INEPT transfer.<sup>26,39</sup>

While a large number of  $^1\text{H}$  homonuclear decoupling schemes have been optimised under static conditions for operation at low (5–10 kHz) and moderate ( $\sim 15$  kHz) MAS frequencies,<sup>41–54</sup> there have only been a few papers presenting  $^1\text{H}$  homonuclear decoupling at faster MAS frequencies of (35+ kHz)<sup>55,56</sup> and (60+ kHz).<sup>57–62</sup>  $^1\text{H}$  homonuclear decoupling is clearly not being applied under quasi-static conditions under such fast MAS and the performance is dependent upon the ratio between the rotor period,  $\tau_r$ , and the cycle time of the  $^1\text{H}$  homonuclear decoupling,  $\tau_c$ . Lee–Goldburg<sup>45,46,49,59</sup> and DUMBO<sup>50,62</sup> based decoupling are characterized by short cycle times which makes them compatible with faster MAS implementations. Nevertheless, a short cycle time means high  $^1\text{H}$  nutation frequencies,  $\nu_1$ , for the scheme which can be demanding on the instrumentation. In this work, we consider the application of phase-modulated Lee–Goldburg (PMLG)<sup>49</sup> in a 1D  $^1\text{H}$  Combined Rotation and Multiple-Pulse Sequence (CRAMPS)<sup>63</sup> experiment at 60 kHz MAS using relatively low nutation frequencies. The performance of PMLG depends on multiple factors such as the type of PMLG-block, frequency offset, and  $^1\text{H}$  nutation frequency.<sup>41,42,53,54</sup>  $^1\text{H}$  homonuclear decoupling sequences are usually evaluated through three principal parameters: the chemical shift scaling factor ( $\lambda_{\text{CS}}$ ),<sup>57,58,64</sup> and linewidth improvement reflected in sensitivity and resolution determined through observation of the chemical shift evolution,<sup>62</sup> and extended coherence lifetimes as observed through spin-echo experiments.<sup>57</sup> A bimodal Floquet theory analysis shows that  $^1\text{H}$  homonuclear decoupling requires a fine optimization at MAS above 40 kHz owing to the considerable number of zero- and first-order degeneracies.<sup>65</sup> The two types of degeneracy arise when  $n\nu_r + k\nu_c = 0$ , where  $\nu_r$  is the MAS spinning frequency and  $\nu_c$  is the cycle frequency of the decoupling block, and  $n$  and  $k$  are integers. When these conditions are met, degeneracies occur within the diagonal block of the Floquet Hamiltonian and the effective Hamiltonian<sup>66</sup> leading to dipolar line-broadening.

In this paper, we first demonstrate, at 60 kHz MAS, enhanced decoupling compared to MAS alone in a  $^1\text{H}$

solid-state NMR spectrum of  $^{15}\text{N}$ -glycine for an angle  $\theta$ , corresponding to arctan of the ratio of the rf nutation frequency,  $\nu_1$ , to the rf offset, that is far from the ideal magic angle,  $\theta_m$ , equal to  $\tan^{-1}(\sqrt{2}) = 54.7^\circ$ . Moreover, the application of windowed PMLG $5_{\text{mm}}^{\text{xx}}$  decoupling with parameters based on those optimised for the one-pulse spectrum gives enhanced dephasing times in a  $^1\text{H}$  spin-echo experiment. In this way, we systematically investigate the  $^1\text{H}$  homonuclear decoupling parameters that affect sensitivity in the  $^{15}\text{N}$ - $^1\text{H}$  CP-refocused INEPT experiment under  $^1\text{H}$  homonuclear decoupling and fast MAS. It is shown that optimized decoupling enables the recording of two-dimensional through-bond  $^{15}\text{N}$ - $^1\text{H}$  MAS NMR correlation spectra for moderately sized organic molecules such as the dipeptide  $\beta$ -AspAla and the pharmaceutical cimetidine.

## 2. Experimental

$^{15}\text{N}$ -Labelled glycine, and natural abundance (NA) glycine,  $\beta$ -AspAla and cimetidine were purchased from Sigma Aldrich or Bachem ( $\beta$ -AspAla) and packed as received into 1.3 mm zirconia rotors.  $^{15}\text{N}$ -Glycine was packed into a restricted volume in the centre of the rotor using silicone spacers.  $^{15}\text{N}$ -Labelled glycine was used to optimise  $^1\text{H}$  homonuclear decoupling in 1D and 2D correlation experiments and the 2D  $^{15}\text{N}$ - $^1\text{H}$  CP-refocused INEPT experiment. Glycine,  $\beta$ -AspAla and cimetidine, all at natural abundance, were used to test the  $^{15}\text{N}$ - $^1\text{H}$  natural abundance CP-refocused INEPT correlation experiment.

The experiments were performed on a Bruker Avance III (500 MHz) or Avance NEO (600 MHz, 1 GHz) spectrometer operating at a  $^1\text{H}$  Larmor frequency of  $\nu_{\text{OH}} = 500.13$  MHz (11.7 T), 599.45 MHz (14.1 T), 1000.40 MHz (23.5 T) and sample spinning using a Bruker 1.3 mm HXY probe at 60 kHz. The  $90^\circ$  pulse duration of 2.5  $\mu\text{s}$  ( $\nu_1 = 100$  kHz) for  $^1\text{H}$  and 4  $\mu\text{s}$  ( $\nu_1 = 62.5$  kHz) or 3.5  $\mu\text{s}$  ( $\nu_1 = 71.4$  kHz, cimetidine) for  $^{15}\text{N}$  was calibrated using a one-pulse experiment and a CP followed by a  $90^\circ$  pulse experiment, respectively. A recycle delay of 3 s or 5 s (cimetidine) was used.

$^1\text{H}$  chemical shifts are externally referenced with respect to tetramethylsilane (TMS) *via* L-alanine at natural abundance as a secondary reference (1.1 ppm for the  $\text{CH}_3$   $^1\text{H}$  resonance) corresponding to adamantane at 1.85 ppm.<sup>67,68</sup>  $^{15}\text{N}$  chemical shifts are referenced relative to liquid  $\text{CH}_3\text{NO}_2$  at 0 ppm,<sup>69</sup> using the  $\text{NH}_3^+$  peak of glycine (at natural abundance) at  $-347.4$  ppm as a secondary reference. To convert to the chemical shift scale frequently used in protein NMR, where the alternative IUPAC reference (see Appendix 1 of ref. 70) is liquid ammonia at  $-50^\circ\text{C}$ , it is necessary to add 379.5 to the given values.<sup>71</sup>  $^1\text{H}$  and  $^{15}\text{N}$  chemical shifts can be experimentally determined to an accuracy of  $\pm 0.2$  and  $\pm 0.1$  ppm, respectively. The  $^{15}\text{N}$  RF transmitter frequency was centred at  $-304.5$  ppm (or  $-291.5$  ppm cimetidine). Where the  $^1\text{H}$  resonance offset is referred to, 0 kHz refers to on-resonance with the  $\text{NH}_3^+$  peak of glycine at 8.4 ppm, with a positive resonance offset referring to a move of the RF transmitter frequency to higher ppm.



## 1D CRAMPS

The acquisition window was optimized to acquire 40 complex data points, each corresponding to 0.1  $\mu\text{s}$ , with a ringdown delay of 1.0  $\mu\text{s}$  and a deadtime optimized to be 2.2  $\mu\text{s}$ , corresponding to a total acquisition window,  $\tau_w$ , of 7.2  $\mu\text{s}$ . The total acquisition time was 15 ms. Both PMLG $5_{\text{mm}}^{\text{xx}}$  and PMLG $9_{\text{mm}}^{\text{xx}}$   $^1\text{H}$  homonuclear decoupling schemes were optimized over a  $^1\text{H}$  nutation frequency,  $\nu_1(^1\text{H})$ , range from  $\sim 10$  to  $\sim 120$  kHz.

## 2D $^{15}\text{N}$ - $^1\text{H}$ CP-refocused INEPT

Cross polarization (CP) from  $^1\text{H}$  to  $^{15}\text{N}$  was used for the initial excitation of  $^{15}\text{N}$  transverse magnetisation, where the  $^1\text{H}$  nutation frequency was  $\sim 80$  kHz (or  $\sim 95$  kHz for cimetidine) using a zero-quantum (ZQ) match condition;<sup>72,73</sup> and a  $^{15}\text{N}$  nutation frequency of  $\sim 20$  kHz (or  $\sim 25$  kHz for cimetidine) with a linear ramp<sup>74</sup> (70–100%) on the  $^{15}\text{N}$  channel (glycine and  $\beta$ -AspAla) or  $^1\text{H}$  (cimetidine). A CP contact time of 2 ms (or 4 ms for cimetidine) was used. The MISSISSIPPI suppression scheme<sup>75</sup>

was applied with a spinlock nutation frequency of  $\sim 30$  kHz for four intervals of 2 ms (or 5 ms for cimetidine) to remove residual  $^1\text{H}$  transverse magnetisation. Low-power<sup>76</sup> heteronuclear  $^1\text{H}$  and  $^{15}\text{N}$  decoupling was applied during  $t_1$  evolution and  $^1\text{H}$  acquisition, respectively, using WALTZ64<sup>77,78</sup> at a nutation frequency of  $\sim 10$  kHz. The pulse sequence used corresponds to a modified version of that presented by Althaus *et al.* (Fig. 1b).<sup>26</sup>

Each  $^1\text{H}$ -detected FID was acquired for 30 ms with a spectral width of 80 ppm (or 40 ppm for cimetidine). The  $^{15}\text{N}$  dimension was acquired with 96 (glycine NA and  $\beta$ -AspAla) or 64 (cimetidine)  $t_1$  FIDs with a dwell time of 300  $\mu\text{s}$  (glycine NA) or 142  $\mu\text{s}$  ( $\beta$ -AspAla) or 160  $\mu\text{s}$  (cimetidine), corresponding to a  $^{15}\text{N}$  spectral width of 66 ppm (glycine NA) or 138 ppm ( $\beta$ -AspAla) or 102 ppm (cimetidine) and a maximum  $t_1$  of 15 ms (glycine NA), 6.9 ms ( $\beta$ -AspAla), or 5.1 ms (cimetidine). The States-TPPI method was employed to achieve sign discrimination in the indirect dimension.

## 3. Results and discussion

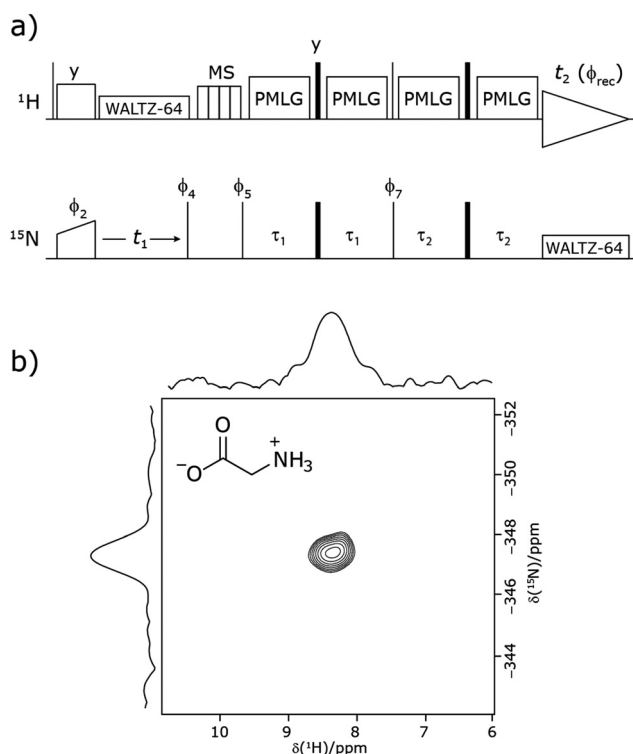
### 3.1 $^{15}\text{N}$ - $^1\text{H}$ CP-refocused INEPT – pulse sequence and product operator analysis

Our implementation of the  $^{15}\text{N}$ - $^1\text{H}$  CP-refocused INEPT experiment at 60 kHz MAS is shown in Fig. 1a. Note that the pulse sequence in Fig. 1a corresponds to a modified version of that used by Althaus *et al.* at  $\nu_r = 40$  kHz.<sup>26</sup> The pulse sequence begins with an initial  $^1\text{H}$  to  $^{15}\text{N}$  CP transfer to provide the largest pool of polarization possible for the low- $\gamma$  and natural abundance  $^{15}\text{N}$  nucleus. The  $^{15}\text{N}$  transverse magnetisation is allowed to evolve during  $t_1$ . The desired magnetisation is stored during a z-filter period, in which  $^1\text{H}$  magnetisation suppression using the MISSISSIPPI sequence<sup>75</sup> is implemented to remove the background proton signals. A  $^{15}\text{N}$ - $^1\text{H}$  refocused INEPT element is used to transfer the magnetization back to proton for acquisition. INEPT utilizes the  $^1\text{H}$ - $^{15}\text{N}$   $J$  couplings to restrict the signals observed to those with direct one-bond H-N connections. Each spin-echo duration should be an integer number of rotor periods to ensure that the chemical shift anisotropy is completely averaged by MAS. Homonuclear  $^1\text{H}$  decoupling, here PMLG,<sup>49</sup> is applied during the two spin-echoes of the refocused INEPT element. Under fast MAS, at a spinning frequency of 60 kHz in this work, low power heteronuclear decoupling,<sup>76</sup> specifically WALTZ-64<sup>78</sup> decoupling, is applied on  $^1\text{H}$  and  $^{15}\text{N}$  during  $t_1$  and  $t_2$ , respectively. The resulting spectrum is a 2D  $^{15}\text{N}$ - $^1\text{H}$  through-bond correlation spectrum, as illustrated in Fig. 1b for natural abundance glycine.

For a  $^{15}\text{N}$ - $^1\text{H}$  spin pair, a product-operator analysis (see Section S1, ESI†) shows a product of sine terms dependence on the heteronuclear  $^{15}\text{N}$ - $^1\text{H}$   $J_{\text{IS}}$  coupling active during the two spin-echo ( $\tau$ - $\pi$ - $\tau$ ) durations,  $\tau_1$  and  $\tau_2$ :

$$(\text{NH}) \quad \sin(2\pi J_{\text{IS}}\tau_2)\sin(2\pi J_{\text{IS}}\tau_1) \quad (1)$$

*i.e.*, this predicts maximum transfer, for  $\sin(\pi/2)$ , *i.e.*,  $\tau = 1/(4J_{\text{IS}})$ , *i.e.*, 2.7 ms, for a one-bond  $^{15}\text{N}$ - $^1\text{H}$  scalar coupling ( $\sim 90$  Hz) for fast MAS alone. When the proton magnetization is along the



**Fig. 1** (a) Pulse sequence for the  $^{15}\text{N}$ - $^1\text{H}$  CP-refocused INEPT experiment utilised in this paper. Narrow lines and filled black rectangles represent  $\pi/2$  and  $\pi$  pulses, respectively. Where not stated, the phase of a pulse is  $x$ . The following phase cycle is applied:  $\phi_2 = \{x^*2, -x^*2\}$ ,  $\phi_4 = \{-y^*4, y^*4\}$ ,  $\phi_5 = \{y^*8, -y^*8\}$ ,  $\phi_7 = \{x, -x\}$  and acquisition  $\phi_{\text{rec}} = \{x, -x, -x, x, -x, x, x, -x, x, -x, -x, x\}$ . States-TPPI is implemented on  $\phi_4$ . (b) A  $^{15}\text{N}$ - $^1\text{H}$  ( $\nu_0 = 500$  MHz) 2D CP (contact time = 2 ms)-refocused INEPT MAS ( $\nu_r = 60$  kHz) NMR correlation spectrum with skyline projections of natural abundance glycine and its molecular structure. PMLG $9_{\text{mm}}^{\text{xx}}$  was applied at a  $^1\text{H}$  nutation frequency of 106 kHz ( $\tau_{\text{LG}} = 2.92$   $\mu\text{s}$ ) during both  $\tau_1 = 2.091$  ms ( $179\tau_c$ ) and  $\tau_2 = 0.993$  ms ( $85\tau_c$ ) at a  $^1\text{H}$  transmitter offset of  $-2.6$  kHz, with a zero offset corresponding to being on resonance with the  $\text{NH}_3^+$  peak. 192 transients were coadded for each of 96  $t_1$  FIDs, corresponding to a total experimental time of 16 hours. The base contour is at 40% of the maximum intensity.



transverse plane, for example as  $\hat{I}_y\hat{S}_z$  during  $\tau_2$ , the  $^1\text{H}$ - $^1\text{H}$  dipolar couplings shorten the coherence lifetime compared to when the  $^1\text{H}$  magnetization is longitudinal, as during  $\tau_1$ .<sup>39</sup> As expanded upon below, the different influence of the interactions is evident in the optimum length of the  $\tau_1$  and  $\tau_2$  periods: the spectrum in Fig. 1b was recorded with  $\tau_2$  (1.0 ms) shorter than  $\tau_1$  (2.1 ms); as discussed further below, note that  $^1\text{H}$  homonuclear decoupling scales the  $J$  coupling.<sup>79–81</sup>

Analogously to the case of  $^{29}\text{Si}$ - $^1\text{H}$   $J$ -couplings in  $\text{SiH}_n$  moieties,<sup>82–84</sup> there is a different dependence on the first spin-echo duration,  $\tau_1$ , for a  $\text{NH}_3$  moiety:

$$(\text{NH}_3) \quad \sin(2\pi J_{\text{IS}}\tau_2)[\sin(2\pi J_{\text{IS}}\tau_1) + \sin(6\pi J_{\text{IS}}\tau_1)] \quad (2)$$

As discussed below, a consequence of this is that different signal build-up with respect to  $\tau_1$  for a  $\text{NH}$  and a  $\text{NH}_3$  moiety (and also for a  $\text{NH}_2$  which has a  $\sin(2\pi J_{\text{IS}}\tau_2)\sin(4\pi J_{\text{IS}}\tau_1)$  dependence).

### 3.2 $^1\text{H}$ PMLG homonuclear decoupling under fast MAS

As noted in the above discussion of Fig. 1a, PMLG  $^1\text{H}$  homonuclear decoupling is employed during the two spin-echo durations of the refocused INEPT pulse sequence element that transfers magnetisation from  $^{15}\text{N}$  to  $^1\text{H}$ . Lee–Goldburg decoupling<sup>45</sup> can be considered to be analogous to MAS where the sample is rotated around an axis inclined at the magic angle,  $\theta_m$ , equal to  $\tan^{-1}(\sqrt{2})$ , to the external magnetic field in that the ratio of the nutation frequency,  $\nu_1$ , to the resonance offset,  $\Delta\nu_{\text{LG}}$ , is also set equal to  $\tan^{-1}(\sqrt{2})$ . This leads to an effective field,  $\nu_{\text{eff, LG}}$ , that is given by Pythagoras' theorem, as:

$$\nu_{\text{eff, LG}} = \sqrt{\nu_1^2 + \Delta\nu_{\text{LG}}^2}. \quad (3)$$

For fixed  $\nu_1$ , the Lee–Goldburg condition is satisfied as:

$$\tan(\theta_m) = \frac{\nu_1}{\Delta\nu_{\text{LG}}} = \sqrt{2}, \quad (4)$$

i.e.,  $\Delta\nu_{\text{LG}} = \frac{\nu_1}{\sqrt{2}}$  and  $\nu_{\text{eff, LG}} = \sqrt{\frac{3}{2}}\nu_1$ . In the PMLG implementation<sup>49</sup> of the LG condition, rf irradiation is applied on resonance for a duration,  $\tau_{\text{LG}}$ , that is the inverse of  $\nu_{\text{eff, LG}}$

$$\tau_{\text{LG}} = \frac{1}{\nu_{\text{eff, LG}}} = \sqrt{\frac{2}{3}} \frac{1}{\nu_1}, \quad (5)$$

but with an equivalent sweep (in discrete jumps) of the rf phase from  $0^\circ$  to  $\phi_{\text{last}}^\circ$  over the duration,  $\tau_{\text{LG}}$ , whereby  $\phi_{\text{last}}$  depends on  $\Delta\nu_{\text{LG}}$  according to:

$$\begin{aligned} \phi_{\text{last}} &= 360^\circ \cdot \Delta\nu_{\text{LG}} \cdot \tau_{\text{LG}} = 360^\circ \cdot \frac{\nu_1}{\sqrt{2}} \cdot \sqrt{\frac{2}{3}} \frac{1}{\nu_1} = \frac{360^\circ}{\sqrt{3}} \\ &= 207.8^\circ. \end{aligned} \quad (6)$$

An overall rotation,  $\xi_{\text{LG}}$ , of  $360^\circ$  around the effective field is achieved:

$$\xi_{\text{LG}} = 360^\circ \cdot \nu_{\text{eff, LG}} \cdot \tau_{\text{LG}} = 360^\circ. \quad (7)$$

In the experimental implementation of PMLG under MAS, the duration over which the phase is swept (as discrete steps) from  $0^\circ$  to the ideal  $\phi_{\text{last}}$  value of  $207.8^\circ$ ,  $\tau_{\text{LG, expt}}$ , can vary from the

ideal value,  $\tau_{\text{LG}}$ . In this way, the equivalent resonance offset,  $\Delta\nu_{\text{expt}}$ , changes from the ideal value,  $\Delta\nu_{\text{LG}}$ , to satisfy:  $\phi_{\text{last}} = \frac{360^\circ}{\sqrt{3}} = 360^\circ \cdot \Delta\nu_{\text{LG, expt}} \cdot \tau_{\text{LG, expt}}$ , so that  $\Delta\nu_{\text{LG, expt}} = \frac{1}{\sqrt{3}\tau_{\text{LG, expt}}}$ .

Nishiyama *et al.*<sup>57</sup> have shown that this deviation from the ideal condition can be expressed in terms of how the angle,  $\theta$ , deviates from the magic angle,  $\theta_m$ :

$$\theta = \tan^{-1}\left(\frac{\nu_1}{\Delta\nu_{\text{LG, expt}}}\right) = \tan^{-1}\left(\nu_1 \cdot \tau_{\text{LG, expt}} \cdot \sqrt{3}\right). \quad (8)$$

The actual effective field,  $\nu_{\text{eff, LG, expt}}$ , that is calculated by Pythagoras' theorem as  $\sqrt{(\nu_1^2 + \Delta\nu_{\text{LG, expt}}^2)}$  is not equal to  $1/\tau_{\text{LG, expt}}$  and also deviates from the ideal value,  $\nu_{\text{eff, LG}}$ . As a consequence, the overall rotation about the actual effective field,  $\xi_{\text{LG, expt}}$ , also deviates from  $\xi_{\text{LG}} = 360^\circ$  according to:

$$\begin{aligned} \xi_{\text{LG, expt}} &= 360^\circ \cdot \nu_{\text{eff, LG, expt}} \cdot \tau_{\text{LG, expt}} \\ &= 360^\circ \cdot \sqrt{\nu_1^2 + \frac{1}{3\tau_{\text{LG, expt}}^2}} \cdot \tau_{\text{LG, expt}}. \end{aligned} \quad (9)$$

Note that Nishiyama *et al.* refer to this rotation angle as  $\Psi$ , but this symbol is used in this paper to denote the ratio of the rotor period to the cycle time (see later discussion), according to Leskes *et al.*<sup>65</sup>

Following the notation of Leskes *et al.*<sup>85</sup> a PMLG block is specified as  $\text{PMLG}n_R^\phi$ , where: first,  $n$  is the number of finite pulses for each LG cycle, with  $n$  equal to 5 or 9 investigated here; second,  $R$  is the sense of the initial rotation for the phase steps,  $m$  for clockwise and  $p$  for counter-clockwise; and third, the initial phase,  $\phi$ , is usually  $x$  or  $-x$  (denoted  $\bar{x}$ ). As stated above (see eqn (7)) and as shown in Fig. 2a and b,  $\tau_{\text{LG, expt}}$  is the time to sweep the phase over  $n$  discrete steps, i.e., as  $n$  finite pulses, from  $0^\circ$  to  $207.8^\circ$ . A single PMLG block,  $\text{PMLG}n_R^\phi$ , is of duration  $2\tau_{\text{LG}}$  with a  $180^\circ$  jump after  $n$  finite pulses in the first  $\tau_{\text{LG}}$  followed by  $n$  finite pulses in the second  $\tau_{\text{LG}}$ , whereby the phase steps are in the opposite direction. This corresponds to changing the sign of the equivalent resonance offset, as in the frequency-switched (FS) LG experiment, where rf irradiation is alternated between  $+\Delta\nu_{\text{LG}}$  and  $-\Delta\nu_{\text{LG}}$ .<sup>46,86,87</sup> As further shown by Leskes *et al.*<sup>85</sup> supercycling can be achieved as  $\text{PMLG}n_{\text{RR}}^{\phi\phi}$ . Specifically, in this work, we use the  $\text{PMLG}5_{\text{mm}}^{\bar{x}x}$  and  $\text{PMLG}9_{\text{mm}}^{\bar{x}x}$  implementations.

In the windowed implementation of  $\text{PMLG}^{88}$  acquisition windows of duration  $\tau_w$  are placed between the  $\text{PMLG}n_R^\phi$  blocks (see Fig. 2b and e). In addition, tilt pulses of duration  $\tau_{\text{tilt}}$  can be used.<sup>53,54,89–91</sup> The cycle time for a complete  $\text{PMLG}5_{\text{mm}}^{\bar{x}x}$  or  $\text{PMLG}9_{\text{mm}}^{\bar{x}x}$  supercycle,  $\tau_c$ , is:

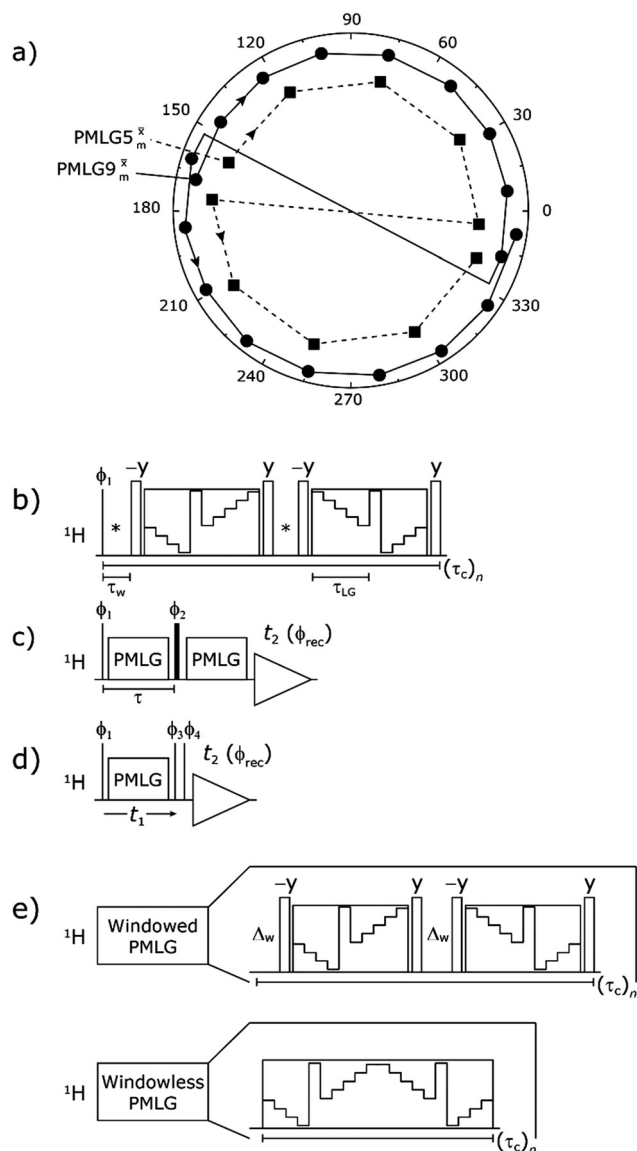
$$\tau_c = 2\tau_w + 4\tau_{\text{LG, expt}} + 4\tau_{\text{tilt}}. \quad (10)$$

### 3.3 Optimisation of $\text{CH}_2$ and $\text{NH}_3$ signal intensity in a 1D CRAMPS experiment of $^{15}\text{N}$ -glycine

The optimization of the  $^1\text{H}$  nutation frequency and  $\tau_{\text{LG, expt}}$  is performed differently for windowless and windowed







**Fig. 2** (a) Representation of the phase rotation for  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  (dashed line, squares) and  $\text{PMLG9}_{\text{mm}}^{\text{xx}}$  (solid line, circles). The phase increments are calculated according to  $\phi_{\text{last}} = 207.8^\circ$  (see eqn (6)), divided by the number of steps. The starting point for both is  $-x$ . Pulse sequence for (b) a  $^1\text{H}$  1D CRAMPS experiment with supercycled  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$ , where the asterisk represents an acquisition window,  $\tau_w$ , (c) a  $^1\text{H}$  spin-echo and (d) a 2D  $^1\text{H}$ - $^1\text{H}$  correlation experiment. Thin lines and filled rectangles represent  $90^\circ$  and  $180^\circ$  pulses, respectively, while open rectangles denote tilt pulses. In (c) and (d), the block named PMLG can accommodate either (a and e) windowed, where  $\tau_w$  is an equivalent period of free evolution, or a windowless sequence, whereby there is continuous rf irradiation during  $\text{PMLG}n_{\text{R}}^{\phi}$  blocks, i.e., there are no tilt pulses and  $\tau_w = 0$ . The following phase cycle is applied for (b) 1D CRAMPS:  $\phi_1 = \{x, -x, -x, x\}$ ,  $\phi_{\text{PMLG}} = \{x, -x, -x, x\}$  and acquisition  $\phi_{\text{rec}} = \{x, -x, -x, x\}$ ; (c)  $^1\text{H}$  spin-echo:  $\phi_1 = \{x, -x\}$ ,  $\phi_2 = \{y^*2, x^*2\}$ ,  $\phi_{\text{PMLG}} = \{x, -x\}$  and acquisition  $\phi_{\text{rec}} = \{x, -x, -x, x\}$ ; (d)  $^1\text{H}$ - $^1\text{H}$  homonuclear correlation:  $\phi_1 = \{x, -x\}$ ,  $\phi_3 = \{-x^*2, x^*2\}$ ,  $\phi_4 = \{x^*4, y^*4\}$ ,  $\phi_{\text{PMLG}} = \{x, -x\}$  and acquisition  $\phi_{\text{rec}} = \{x, -x, -x, x, y, -y, -y, y\}$ .

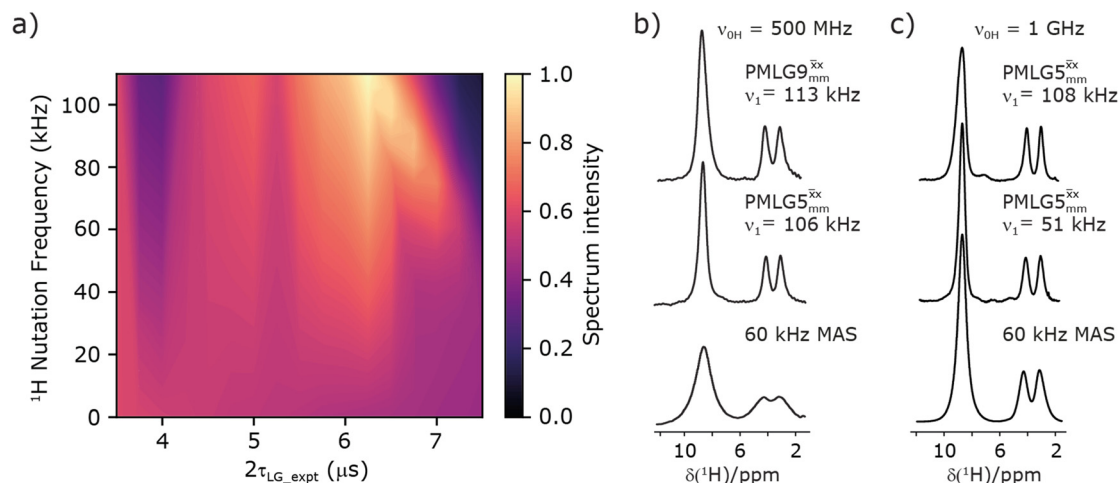
sequences. In this paper, our focus is on windowed sequences that were optimized with a 1D CRAMPS experiment which gives both the chemical shift scaling factor  $\lambda_{\text{CS}}$  and the  $^1\text{H}$  linewidths

in a few seconds for a particular combination of parameters. Specifically for windowed  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  and  $\text{PMLG9}_{\text{mm}}^{\text{xx}}$ , a two variable optimization was performed over a range of  $^1\text{H}$  nutation frequencies between 0 and 110–120 kHz and  $\tau_{\text{LG\_expt}}$  between 3.5 and 7.5  $\mu\text{s}$  for  $^{15}\text{N}$  labelled glycine – see Fig. 3a for  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  and Fig. S1 (ESI $^\ddagger$ ) with slices extracted at different peak intensities, hence with different resolution. (Note that the optimisation of the tilt pulses is discussed in Section S3 of the ESI $^\ddagger$ .) For windowless sequences, a coarse optimization was performed, starting from optimised parameters from the 1D CRAMPS experiments, using a  $^1\text{H}$  spin-echo experiment (Fig. 2c) to find good candidate parameters which yield a long  $^1\text{H}$  coherence lifetime. As noted below, the  $^1\text{H}$ - $^1\text{H}$  correlation experiment (Fig. 2d) was used to determine the  $\lambda_{\text{CS}}$  of the candidate windowless sequences, but can only be used sparingly as the experimental time is relatively long ( $\sim 20$  minutes for 4 co-added transients and 96  $t_1$  FIDs for each combination of  $\tau_{\text{LG\_expt}}$  and  $\nu_1$ ).

Fig. 3a reports on the  $\text{NH}_3^+ ^1\text{H}$  resonance, noting its relevance in this paper for the  $^1\text{H}$ - $^{15}\text{N}$  refocused INEPT experiment. Fig. S2 (ESI $^\ddagger$ ) shows that optimum performance for the  $\text{NH}_3^+ ^1\text{H}$  resonance (Fig. S2b, ESI $^\ddagger$ ) is closely matched by that for the  $\text{CH}_2 ^1\text{H}$  resonances (Fig. S2a, ESI $^\ddagger$ ). 1D CRAMPS  $^1\text{H}$  NMR spectra of  $^{15}\text{N}$ -glycine for our best implementations of supercycled windowed  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  and  $\text{PMLG9}_{\text{mm}}^{\text{xx}}$  at  $\nu_0 = 500$  MHz are shown in Fig. 3b, where enhanced resolution compared to MAS alone is evident. Moreover, both  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  and  $\text{PMLG9}_{\text{mm}}^{\text{xx}}$  implemented at  $\nu_0 = 500$  MHz (Fig. 3b) show better resolution than 60 kHz MAS alone at  $\nu_0 = 1$  GHz (Fig. 3c). At  $\nu_0 = 1$  GHz, optimised 1D CRAMPS  $^1\text{H}$  NMR spectra of  $^{15}\text{N}$ -glycine for windowed  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  at a  $^1\text{H}$  nutation frequency of 108 and 51 kHz are presented in Fig. 3c that show enhanced resolution compared to MAS alone. Note that the latter case corresponds to the nutation frequency being less than the MAS frequency.

Table 1 compares the experimentally optimised  $\tau_{\text{LG\_expt}}$  values to the ideal  $\tau_{\text{LG}}$  values: at  $\nu_0 = 500$  MHz, the experimental values are less than half the ideal values, i.e.,  $\tau_{\text{LG\_expt}} = 3.10$   $\mu\text{s}$  and 2.92  $\mu\text{s}$  compared to 7.70  $\mu\text{s}$  and 7.23  $\mu\text{s}$ , respectively. As Table 1 further shows, with the corresponding changes in  $\Delta\nu_{\text{LG\_expt}}$  and  $\nu_{\text{eff\_expt}}$ , the angle  $\theta$  is  $29.7^\circ$ . While a very high nutation frequency of over 200 kHz has been used in the first experimental implementations of PMLG at 65 kHz MAS frequency<sup>59,65</sup> resulting in a  $\theta$  value of  $61^\circ$  for the spectrum presented by Leskes *et al.*,<sup>59</sup> a similar value (of  $31.2^\circ$ ) far from the magic angle has been reported by Nishiyama *et al.* for the implementation of windowed  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  at an MAS frequency of 80 kHz and a  $^1\text{H}$  nutation frequency of 125 kHz.<sup>57</sup> Moreover, the actual rotation,  $\zeta_{\text{LG\_expt}}$  reported by Nishiyama *et al.* of  $243^\circ$  is similar to that of  $239^\circ$  for our implementation of both windowed  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  and  $\text{PMLG9}_{\text{mm}}^{\text{xx}}$  at a MAS frequency of 60 kHz (see Table 1). Table 1 also lists the implementations of  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  by Leskes *et al.* at 10 kHz MAS<sup>85</sup> and Mao & Pruski at 12.5, 19.5, 25.0 and 41.7 kHz MAS;<sup>92</sup> the angle  $\theta$  is seen to vary between  $45^\circ$  and  $64^\circ$ . It is observed that an angle  $\theta$  below and above the magic angle corresponds to an actual rotation,





**Fig. 3**  $^1\text{H}$  MAS ( $\nu_r = 60$  kHz) NMR of  $^{15}\text{N}$ -labelled glycine. (a) PMLG5 $^{xx}_{mm}$  1D CRAMPS (see Fig. 2b,  $\tau_{\text{tilt}} = 0.54$   $\mu\text{s}$ ,  $\Omega = -0.6$  kHz) two-variable optimization ( $\nu_0 = 500$  MHz) of both  $\tau_{\text{LG\_expt}}$  (in steps of 0.25  $\mu\text{s}$ ) and the  $^1\text{H}$  nutation frequency,  $\nu_1$  (0–110 kHz) for the  $\text{NH}_3^+$  peak intensity. (b) Comparison between  $^1\text{H}$  ( $\nu_0 = 500$  MHz) 1D CRAMPS MAS NMR spectra acquired with windowed PMLG9 $^{xx}_{mm}$  ( $\nu_1 = 113$  kHz,  $\tau_{\text{LG\_expt}} = 2.92$   $\mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.82$   $\mu\text{s}$ ,  $\Omega = -0.6$  kHz), windowed PMLG5 $^{xx}_{mm}$  ( $\nu_1 = 106$  kHz,  $\tau_{\text{LG\_expt}} = 3.1$   $\mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.54$   $\mu\text{s}$ ,  $\Omega = -0.6$  kHz), and a one-pulse MAS-alone experiment. (c) Comparison between  $^1\text{H}$  ( $\nu_0 = 1$  GHz) 1D CRAMPS MAS NMR spectra acquired with windowed PMLG9 $^{xx}_{mm}$  ( $\nu_1 = 108$  kHz,  $\tau_{\text{LG\_expt}} = 3.10$   $\mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.18$   $\mu\text{s}$ ,  $\Omega = -7.0$  kHz), windowed PMLG5 $^{xx}_{mm}$  ( $\nu_1 = 52$  kHz,  $\tau_{\text{LG\_expt}} = 3.63$   $\mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.70$   $\mu\text{s}$ ,  $\Omega = -8.6$  kHz), and a one-pulse MAS-alone experiment. 8 (a) or 32 (b and c) co-added transients were added for a recycle delay of 3 s. For all experiments,  $\tau_w = 7.20$   $\mu\text{s}$ .

**Table 1** Implementation of PMLG5 $^{xx}_{mm}$  and PMLG9 $^{xx}_{mm}$   $^1\text{H}$  homonuclear decoupling: variation from the ideal Lee–Goldburg condition for this work and previous publications

Decoupling	$\nu_r$ (kHz)	$\nu_1$ (kHz)	$\tau_{\text{LG}}$ ( $\mu\text{s}$ )	$\tau_{\text{LG\_expt}}$ ( $\mu\text{s}$ )	$\theta_m$ (deg)	$\theta$ (deg)	$\Delta\nu_{\text{LG}}$ (kHz)	$\Delta\nu_{\text{LG\_expt}}$ (kHz)	$\nu_{\text{eff\_LG}}$ (kHz)	$\nu_{\text{eff\_LG\_expt}}$ (kHz)	$\zeta_{\text{LG}}$ (deg)	$\zeta_{\text{LG\_expt}}$ (deg)
Windowed PMLG5 $^{xx}_{mm}$ <sup>a</sup> (500 MHz)	60.0	106	7.70	3.10	54.7	29.7	75.0	186.2	129.8	214.3	360.0	239.2
Windowless PMLG5 $^{xx}_{mm}$ <sup>b</sup> (500 MHz)	60.0	106	7.70	3.10		29.7	75.0	186.2	129.8	214.3		239.2
Windowed PMLG9 $^{xx}_{mm}$ <sup>a</sup> (500 MHz)	60.0	113	7.23	2.92		29.7	79.9	197.7	138.4	227.7		239.4
Windowless PMLG9 $^{xx}_{mm}$ <sup>b</sup> (500 MHz)	60.0	113	7.23	2.92		29.7	79.9	197.7	138.4	227.7		239.4
Windowed PMLG5 $^{xx}_{mm}$ <sup>c</sup> (1 GHz, $\nu_1 = 108$ kHz)	60.0	108	7.56	3.10		30.1	76.4	186.2	132.3	215.3		240.3
Windowed PMLG5 $^{xx}_{mm}$ <sup>c</sup> (1 GHz, $\nu_1 = 51$ kHz)	60.0	51	16.01	3.63		17.6	36.1	159.3	62.4	167.2		218.2
<b>Literature parameters</b>												
PMLG5 $^{xx}_{pp}$ <sup>d</sup>	80.0	125	6.53	2.80	54.7	31.2	88.4	206.2	153.1	241.1	360.0	243.1
PMLG5 $^{xx}_{mm}$ <sup>e</sup>	65.0	216	3.78	4.80		60.9	152.7	120.3	264.5	247.2		427.2
PMLG5 $^{xx}_{mm}$ <sup>f</sup>	41.7	155	5.27	3.75		45.2	109.6	154.0	189.8	218.5		294.9
PMLG5 $^{xx}_{mm}$ <sup>f</sup>	41.7	155	5.27	7.75		64.3	109.6	74.5	189.8	172.0		479.8
PMLG5 $^{xx}_{mm}$ <sup>f</sup>	12.5	78	10.47	12.50		59.4	55.2	46.2	95.5	90.6		407.9
PMLG5 $^{xx}_{mm}$ <sup>f</sup>	19.5	126	6.48	8.00		60.2	89.1	72.2	154.3	145.2		418.2
PMLG5 $^{xx}_{mm}$ <sup>f</sup>	25.0	162	5.04	6.25		60.3	114.6	92.4	198.4	186.5		419.6
PMLG5 $^{xx}_{mm}$ <sup>g</sup>	10.0	95	8.59	7.25		50.0	67.2	79.6	116.4	124.0		323.5
PMLG5 $^{xx}_{mm}$ <sup>h</sup>	65.0	250	3.27	5.00		65.2	176.8	115.5	306.2	275.4		495.7

<sup>a</sup> Parameters from this work for Fig. 3b and Table 3. <sup>b</sup> Parameters from this work for Fig. S3 (ESI). <sup>c</sup> Parameters from this work for Fig. 3c and Table 3. <sup>d</sup> Values extracted from Nishiyama *et al.* Fig. 2 and 3.<sup>57</sup> <sup>e</sup> Values extracted from Leskes *et al.* Table 1.<sup>59</sup> <sup>f</sup> Values extracted from Mao and Pruski,<sup>92</sup> Fig. 3 and 2. <sup>g</sup> Values extracted from Leskes *et al.* Fig. 2.<sup>85</sup> <sup>h</sup> Simulated values extracted from Leskes *et al.* Fig. 2.<sup>65</sup>

$\zeta_{\text{LG\_expt}}$ , less than and more than the ideal  $360^\circ$ , respectively. For the good decoupling performance observed at  $\nu_0 = 1$  GHz with windowed PMLG5 $^{xx}_{mm}$  for a  $^1\text{H}$  nutation frequency of only 51 kHz (see Fig. 3c), the angle  $\theta$  is only  $17.6^\circ$ .

Table 2 states the  $\tau_c$  values, as calculated from  $\tau_{\text{LG\_expt}}$ ,  $\tau_w$  and  $\tau_{\text{tilt}}$  using eqn (10), for the implementations of PMLG5 $^{xx}_{mm}$  and PMLG9 $^{xx}_{mm}$  in this work, as well as that reported in the

literature. An important parameter for predicting decoupling performance is the ratio,  $\Psi$ , of the MAS rotor period,  $\tau_r$ , to the decoupling cycle time,  $\tau_c$ , and *vice versa*, the ratio of the corresponding frequency,  $\nu_c = 1/\tau_c$ , to the MAS frequency,  $\nu_r$ .<sup>65</sup>

$$\Psi = \frac{\tau_r}{\tau_c} = \frac{\nu_c}{\nu_r} \quad (11)$$



**Table 2** Implementation of PMLG $5_{mm}^{xx}$  and PMLG $9_{mm}^{xx}$   $^1\text{H}$  homonuclear decoupling: scaling factors and comparison of rotor period to cycle time for this work and previous publications

	$\tau_{\text{LG\_expt}}$ ( $\mu\text{s}$ )	$\tau_{\text{w}}$ ( $\mu\text{s}$ )	$\tau_{\text{tilt}}$ ( $\mu\text{s}$ )	$\tau_{\text{c}}$ ( $\mu\text{s}$ )	$\tau_{\text{r}}$ ( $\mu\text{s}$ )	$\Psi^k$	$\lambda_{\text{CS\_calc}}$	$\lambda_{\text{CS\_expt}}$
Windowed PMLG $5_{mm}^{xx}$ <sup>a</sup> (500 MHz)	3.10	7.20	0.54	28.96	16.67	0.58	0.76 <sup>j</sup>	0.82
Windowless PMLG $5_{mm}^{xx}$ <sup>b</sup> (500 MHz)	3.10	—	—	12.40	16.67	1.34	0.76 <sup>i</sup>	0.66
Windowed PMLG $9_{mm}^{xx}$ <sup>a</sup> (500 MHz)	2.92	7.20	0.82	29.36	16.67	0.57	0.77 <sup>j</sup>	0.76
Windowless PMLG $9_{mm}^{xx}$ <sup>b</sup> (500 MHz)	2.92	—	—	11.68	16.67	1.43	0.78 <sup>i</sup>	0.60
Windowed PMLG $5_{mm}^{xx}$ <sup>c</sup> (1 GHz, 108 kHz)	3.10	7.20	0.18	27.52	16.67	0.61	0.74 <sup>j</sup>	0.82
Windowed PMLG $5_{mm}^{xx}$ <sup>c</sup> (1 GHz, 51 kHz)	3.63	7.20	0.70	31.70	16.67	0.53	0.90 <sup>j</sup>	0.92
Literature parameters								
PMLG $5_{pp}^{xx}$ <sup>d</sup>	2.80	4.84	—	20.88	12.50	0.60	0.86 <sup>i</sup>	0.82
PMLG $5_{mm}^{xx}$ <sup>e</sup>	4.80	2.70	—	24.60	15.38	0.63	0.40 <sup>i</sup>	0.48
PMLG $5_{mm}^{xx}$ <sup>f</sup>	3.75	—	—	15.00	24.00	1.60	0.50 <sup>i</sup>	0.36
PMLG $5_{mm}^{xx}$ <sup>f</sup>	7.75	—	—	31.00	24.00	0.77	0.19 <sup>j</sup>	0.21
PMLG $5_{mm}^{xx}$ <sup>f</sup>	12.50	—	—	50.00	80.00	1.60	0.26 <sup>i</sup>	—
PMLG $5_{mm}^{xx}$ <sup>f</sup>	8.00	—	—	32.00	51.20	1.60	0.25 <sup>i</sup>	—
PMLG $5_{mm}^{xx}$ <sup>f</sup>	6.25	—	—	25.00	40.00	1.60	0.25 <sup>i</sup>	—
PMLG $5_{mm}^{xx}$ <sup>g</sup>	7.25	4.35	—	37.70	100.00	2.65	0.55 <sup>i</sup>	0.47
PMLG $5_{mm}^{xx}$ <sup>h</sup>	5.00	—	—	20.00	15.38	0.77	0.18 <sup>i</sup>	—

<sup>a</sup> Parameters from this work for Fig. 3b and Table 3. <sup>b</sup> Parameters from this work for Fig. S5 (ESI). <sup>c</sup> Parameters from this work for Fig. 3c and Table 3. <sup>d</sup> Values extracted from Nishiyama *et al.* Fig. 2 and 3. <sup>e</sup> Values extracted from Leskes *et al.* Table 1. <sup>f</sup> Values extracted from Mao and Pruski, <sup>92</sup> Fig. 3 and 2. <sup>g</sup> Values extracted from Leskes *et al.* Fig. 2. <sup>h</sup> Simulated values extracted from Leskes *et al.* Fig. 2. <sup>i</sup>  $\lambda_{\text{CS}}$  is calculated with eqn (15) as stated in this paper, following from Nishiyama *et al.* <sup>57</sup>  $\lambda_{\text{CS}}$  is calculated with eqn (16) as stated in this paper, following from Nishiyama *et al.* <sup>57</sup>  $\Psi$  is calculated with eqn (12), following from Leskes *et al.* <sup>65</sup>

For low to moderate MAS frequencies, small integer values of  $\Psi$  are to be avoided since these values correspond to recoupling rather than decoupling conditions.<sup>53,91,93–95</sup> For fast MAS (of at least 40 kHz), there are more values of  $\Psi$  that need to be avoided.<sup>62,65,92</sup> Specifically, by employing bimodal Floquet theory, Leskes *et al.* have identified values of  $n$  and  $k$  that result in deteriorated decoupling due to zero-order and first-order recoupling conditions, according to:

$$n\nu_{\text{r}} + k\nu_{\text{r}} = 0, \quad (12)$$

where  $n$  takes values 1, 2, 3, 4 while  $-15 \leq k \leq -1$ .<sup>65</sup> While there is a dense set of degeneracies for values of  $\Psi$  below 1.50, there are windows of good decoupling performance that can be found. The  $\Psi$  value of both the windowless sequences, PMLG $5_{mm}^{xx}$  ( $\Psi = 1.34$ ) and PMLG $9_{mm}^{xx}$  ( $\Psi = 1.43$ ), are in line with the value of 1.40–1.60 reported by Mao *et al.* (in Tables 1 and 2 of their paper) for spectra acquired among a range of different spinning frequencies (12.5 kHz to 41.7 kHz) and  $^1\text{H}$  nutation frequencies (78–162 kHz).<sup>92</sup> For windowed sequences, the  $\Psi$  value is usually lower. For the 1D CRAMPS spectra presented in Fig. 3b, Table 2 shows that  $\Psi$  equals 0.58 and 0.57 for windowed PMLG $5_{mm}^{xx}$  and windowed PMLG $9_{mm}^{xx}$ , respectively, at  $\nu_0 = 500$  MHz, and 0.61 and 0.53 at  $\nu_0 = 1$  GHz for a  $^1\text{H}$  nutation frequency of 108 and 51 kHz, respectively. These  $\Psi$  values are similar to the values of 0.60 and 0.63 for the experimental implementation of windowed PMLG $5_{mm}^{xx}$  by Nishiyama *et al.* at an MAS frequency of 80 kHz and a  $^1\text{H}$  nutation frequency of 125 kHz<sup>57</sup> and by Leskes *et al.* at an MAS frequency of 65 kHz and a  $^1\text{H}$  nutation frequency of 216 kHz,<sup>59</sup> respectively.

### 3.4 Windowed and windowless PMLG $^1\text{H}$ decoupling, $^1\text{H}$ spin-echo dephasing and scaling factors

It is well established that the application of rf  $^1\text{H}$  homonuclear decoupling leads to a chemical shift scaling: for a static sample, the chemical shift scaling factor,  $\lambda_{\text{CS}}$ , for perfect decoupling cannot exceed  $\cos^{-1}(\theta_{\text{m}}) = 1/\sqrt{3} = 0.577$ .<sup>64,95,96</sup> The 1D  $^1\text{H}$  CRAMPS spectra presented in Fig. 3b and c have chemical shift axes that have been corrected for this scaling, *i.e.*, a scaling is applied so as to ensure that the chemical shift separation between the  $\text{NH}_3^+$  peak and the lower ppm  $\text{CH}_2$  peak corresponds to the MAS-only  $^1\text{H}$  chemical shifts, *i.e.*, 8.4–3.0 = 5.4 ppm. The full width at half maximum, (FWHM), of the three  $^1\text{H}$  resonances before and after scaling for the spectra presented in Fig. 3b and c are presented in Table 3. Table 3 also states that  $\lambda_{\text{CS}}$  equals 0.82 and 0.76 for windowed PMLG $5_{mm}^{xx}$  and windowed PMLG $9_{mm}^{xx}$ , respectively, at  $\nu_0 = 500$  MHz, and 0.82 and 0.92 at  $\nu_0 = 1$  GHz for a  $^1\text{H}$  nutation frequency of 108 and 51 kHz, respectively. Table 3 also reports, as a measure of decoupling efficiency,  $K$ , given by

$$K = \frac{\text{FWHM}_{\text{MAS}} - \text{FWHM}_{\text{scaled}}}{\text{FWHM}_{\text{MAS}}} \quad (13)$$

$$= \frac{\text{FWHM}_{\text{MAS}} - (\text{FWHM}_{\text{PMLG}}/\lambda_{\text{CS}})}{\text{FWHM}_{\text{MAS}}},$$

where a  $K$  closer to 1 corresponds to better decoupling performance.  $\text{FWHM}_{\text{MAS}}$  is obtained under MAS alone,  $\text{FWHM}_{\text{PMLG}}$  is the linewidth recorded using PMLG, and  $\text{FWHM}$  after scaling,  $\text{FWHM}_{\text{scaled}}$ , is equal to  $\text{FWHM}_{\text{PMLG}}/\lambda_{\text{CS}}$ . High scaling factors that are significantly above 0.577, like those stated in Table 3, have been reported for 60 kHz MAS by Salager *et al.* for an



<sup>d</sup> See spectra in Fig. 3b ( $\nu_0 = 500$  MHz) and Fig. 3c ( $\nu_0 = 1$  GHz) for the pulse sequence in Fig. 2b and experimental parameters in Table 2. <sup>e</sup> Calculated with eqn (13). <sup>f</sup> Calculated with eqn (13). <sup>g</sup> FWHM extracted from the indirect dimension of a 2D  $^1\text{H}$ - $^1\text{H}$  correlation experiment with MAS alone, see Fig. S4 in the ESI.

Fig. 4 compares spin-echo dephasing curves (see pulse sequence in Fig. 2c) for MAS alone to those for windowed and windowless PMLG $5_{\text{mm}}^{\text{xx}}$  and PMLG $9_{\text{mm}}^{\text{xx}}$ , with the values for experimental parameters and extracted  $T_2'$  presented in Table 4. (Note that PMLG $9_{\text{mm}}^{\text{xx}}$  homonuclear decoupling was implemented with a slightly changed nutation frequency of  $\nu_1 = 109$  kHz, as compared to  $\nu_1 = 113$  kHz for the 1D CRAMPS spectrum in Fig. 3b). In windowless PMLG decoupling, there is continuous rf irradiation, *i.e.*, there are no tilt pulses and  $\tau_w = 0$ , while, in the windowed version,  $\tau_w$  is replaced by a delay (Fig. 2e.) Note that the first implementation of PMLG was in the indirect dimension of a two-dimensional  $^1\text{H}$ - $^1\text{H}$  experiment where there is evolution under MAS alone in the direct



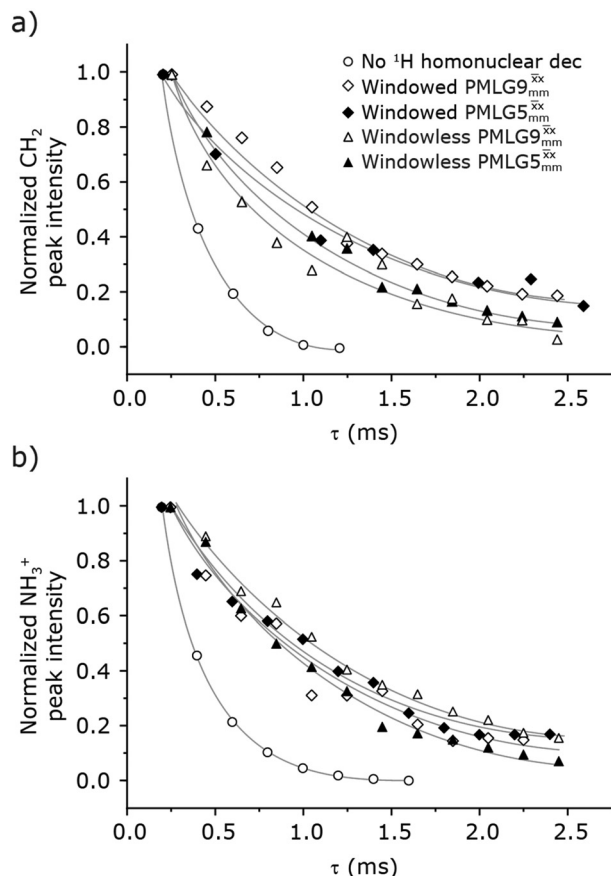


Fig. 4 Dephasing of the  $^{15}\text{N}$ -glycine (a)  $\text{CH}_2$  (the higher ppm  $^1\text{H}$  resonance is considered) and (b)  $\text{NH}_3^+$  proton resonances as a function of the spin-echo (see Fig. 2c) duration,  $\tau$ , with no  $^1\text{H}$  homonuclear decoupling (empty circles), windowed PMLG9 $^{\text{xx}}$  (empty diamonds), windowed PMLG5 $^{\text{xx}}$  (full diamonds), windowless PMLG9 $^{\text{xx}}$  (empty triangles), and windowless PMLG5 $^{\text{xx}}$  (full triangles) for nutation frequencies and resonance offsets as stated in Table 4. Fits to an exponential decay function are shown, with the spin-echo dephasing times,  $T_2'$ , as listed in Table 4. 16 transients were co-added for a recycle delay of 3 s. For all experiments with windowed  $^1\text{H}$  homonuclear decoupling,  $\tau_w = 7.20 \mu\text{s}$ .

dimension.<sup>49</sup> Such a 2D experiment (see Fig. 2d) is used to measure  $\lambda_{\text{CS}}$  for our implementation of windowless PMLG5 $^{\text{xx}}$  and PMLG9 $^{\text{xx}}$ , as reported in Tables 2 and 4 (spectra are presented in Fig. S4, ESI†).

Considering Fig. 4 and Table 4, the  $^1\text{H}$  dephasing times,  $T_2'$ , for the  $\text{CH}_2$  (the higher ppm resonance is considered) and  $\text{NH}_3^+$  peaks are 0.22 ms and 0.25 ms for 60 kHz MAS alone. With  $^1\text{H}$  homonuclear decoupling the  $^1\text{H}$  dephasing time for both groups increases. The longest  $\text{CH}_2$  dephasing time is observed for windowed PMLG5 $^{\text{xx}}$ ,  $T_2' = 1.14$  ms, slightly longer than for windowed PMLG9 $^{\text{xx}}$ , where  $T_2'$  is equal to 1.10 ms. However, the scaling by  $\lambda_{\text{CS}}$  needs to be considered and Table 4 reports the product of  $\lambda_{\text{CS}}$  and  $T_2'$  in each case. After this scaling (Table 4), windowed PMLG5 $^{\text{xx}}$  achieves an over 4 fold improvement with respect of MAS alone, compared to the slightly under 4 fold improvement of windowed PMLG9 $^{\text{xx}}$ . A similar comparison can be made for the  $\text{NH}_3^+$  peak, where windowless PMLG9 $^{\text{xx}}$  shows the longest  $T_2'$  equal to 1.15 ms and the longest value of the product,  $\lambda_{\text{CS}} T_2'$  of 0.69 ms, thanks again to the large  $\lambda_{\text{CS}}$ ; this corresponds to a just under 3 fold improvement with respect to MAS alone.

### 3.5 Optimisation of the $^{15}\text{N}$ -glycine $\text{NH}_3^+$ signal intensity in a 1D-filtered CP-refocused INEPT NMR spectrum for PMLG $^1\text{H}$ decoupling at 60 kHz MAS

Under a  $^1\text{H}$  homonuclear decoupling sequence such as PMLG, the proton offset frequency influences the performance;<sup>53,54</sup> this is linked to the overall  $z$ -rotation that the spins need under decoupling to avoid artifacts and RF imperfections.<sup>85</sup> As shown by Leskes *et al.*,<sup>89</sup> the non-supercycled m-block is particularly beneficial in narrowing lines of strong coupled spins, as for the  $\text{CH}_2$  groups of  $^{15}\text{N}$ -glycine, close to the on-resonance position. With the implementation of supercycled PMLG schemes,<sup>90</sup> the sign of the offset is no longer a determining factor as the supercycle brings the effective rotation of the spins closer to the  $z$ -axis.<sup>100</sup> However, the choice of the optimum offset still plays a significant role for achieving good decoupling performance, therefore it is necessary to investigate both positive and negative offsets. Here the optimization was performed directly on the  $^{15}\text{N}$ - $^1\text{H}$  CP-refocused INEPT experiment, where windowed PMLG5 $^{\text{xx}}$  was applied over a wide range of offset values from  $\sim +10$  kHz to  $-12$  kHz, whereby on-resonance corresponds to the  $\text{NH}_3^+$  peak. Fig. 5 shows that the best offsets in term of sensitivity are at +1 kHz and  $-3.5$  kHz, highlighted by dashed vertical lines. Between the two best performing offsets, the

Table 4  $^1\text{H}$  dephasing time,  $T_2'$ , and  $T_2'$  scaled by the experimental  $\lambda_{\text{CS}}$ ,  $\lambda_{\text{CS}} T_2'$ , as determined by a  $^1\text{H}$  spin-echo MAS NMR experiment<sup>a</sup> for  $^{15}\text{N}$ -glycine with optimised rf carrier offset and  $\nu_1$

	Offset (kHz)	$\nu_1$ (kHz)	$\lambda_{\text{CS}}$	$\text{NH}_3^+ T_2'$ (ms)	$\text{NH}_3^+ \lambda_{\text{CS}} T_2'$ (ms)	$\text{CH}_2 T_2'^b$ (ms)	$\text{CH}_2 \lambda_{\text{CS}} T_2'$ (ms)
No decoupling	2	—	1	0.25	0.25	0.22	0.22
Windowed PMLG5 $^{\text{xx}}$	1	106	0.82	1.04	0.85	1.14	0.93
Windowed PMLG9 $^{\text{xx}}$	0.75	109	0.76	0.91	0.69	1.10	0.84
Windowless PMLG5 $^{\text{xx}}$	1	106	0.66	0.86	0.57	0.80	0.53
Windowless PMLG9 $^{\text{xx}}$	$-0.25$	109	0.60	1.15	0.69	0.78	0.47

<sup>a</sup> As implemented at  $\nu_0 = 500$  MHz and  $\nu_r = 60$  kHz, see Fig. 4a for the  $\text{CH}_2$  resonance and Fig. 4b for the  $\text{NH}_3^+$  peak.  $\tau_{\text{tilt}}$  is equal to  $0.54 \mu\text{s}$  for windowed PMLG5 $^{\text{xx}}$  and  $0.82 \mu\text{s}$  for windowed PMLG9 $^{\text{xx}}$ . <sup>b</sup> For the  $\text{CH}_2$  group, the  $T_2'$  of the higher-ppm  $^1\text{H}$  resonance is stated.



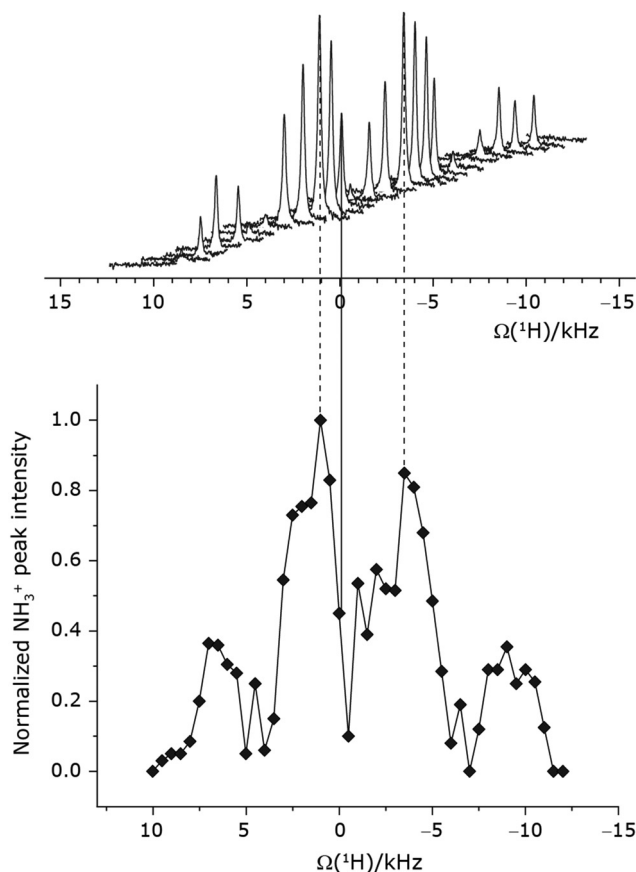


Fig. 5  $^1\text{H}$  RF carrier optimization for a 1D-filtered ( $t_1 = 0$ )  $^{15}\text{N}$ - $^1\text{H}$  ( $\nu_0 = 500$  MHz) CP (contact time = 2 ms)-refocused INEPT MAS ( $\nu_r = 60$  kHz) NMR experiment for  $^{15}\text{N}$ -labelled glycine, whereby windowed PMLG $5_{\text{mm}}^{\text{xx}}$   $^1\text{H}$  homonuclear decoupling was applied with  $\tau_{\text{LG,expt}} = 3.1$   $\mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.54$   $\mu\text{s}$  and a  $^1\text{H}$  nutation frequency,  $\nu_1$ , of 106 kHz during  $\tau_1$  (1.999 ms,  $69\tau_c$ ) and 104 kHz during  $\tau_2$  (1.391 ms,  $48\tau_c$ ). 16 transients were coadded. For all experiments with windowed  $^1\text{H}$  homonuclear decoupling,  $\tau_w = 7.20$   $\mu\text{s}$ . The zero-offset is set with the carrier being on resonance with the  $\text{NH}_3^+$  peak, corresponding to the solid vertical line. Dashed vertical lines indicate the two highest signal intensities at +1 kHz and -3.5 kHz.

sensitivity experiences a fluctuation (Fig. 5) corresponding to the on-resonance position (solid line), dropping to zero for a small negative offset of -0.5 kHz. It is then important to optimize the offset avoiding the on-resonance position. The need for a fine optimization of this parameter is emphasized by

the considerable change in sensitivity that is observed for a small variation of the offset.<sup>53,54,95</sup> For example, the relative sensitivity of the  $\text{NH}_3^+$  peak falls from over 0.8 to 0.5 when switching the offset from  $\sim -3.5$  to  $-2.5$  kHz. In general, in Fig. 5 the offsets close to the on-resonance position yield better sensitivity symmetrically in a range between  $\pm 4$  kHz, in agreement with the rotation improvement brought by the super-cycled  $^1\text{H}$  homonuclear decoupling.<sup>89</sup>

The same offset optimization was carried out on the different PMLG-block types, and similar trends were shown with a better sensitivity in the proximity of the on-resonance position. As stated in Table 4, the offsets which gave the maximum sensitivity were 0.75 kHz for windowed PMLG $9_{\text{mm}}^{\text{xx}}$ , -0.25 kHz for PMLG $9_{\text{mm}}^{\text{xx}}$  and +1 kHz for PMLG $5_{\text{mm}}^{\text{xx}}$  (the same as windowed PMLG $5_{\text{mm}}^{\text{xx}}$ ) (see Fig. S5, ESI†).

The implementation of the  $^1\text{H}$  decoupling scheme into the heteronuclear correlation experiment required the further optimisation of the spin-echo durations during the refocused INEPT transfer. This was carried out separately for  $\tau_1$  and  $\tau_2$  (see pulse sequence in Fig. 1a) because, as stated in Section 3.1, for the two spin echoes, different spins are along the transverse plane,  $^{15}\text{N}$  for the first and  $^1\text{H}$  for the second spin echo. To ensure the best conditions, a double-optimisation of  $^1\text{H}$  homonuclear decoupling nutation frequency vs.  $\tau_1$  and  $\tau_2$  was carried out. Specifically, the two-variable optimisation was performed for  $^{15}\text{N}$ -labelled glycine for windowed or windowless PMLG $5_{\text{mm}}^{\text{xx}}$  and PMLG $9_{\text{mm}}^{\text{xx}}$  for the best offset (see Table 5) and the results are reported in Table 5. The dependence with respect to the second spin-echo duration,  $\tau_2$ , is presented in Fig. 6. Note from eqn (2), a sine dependence is expected from which the scaled  $J$  coupling could be extracted.

Considering Table 5, the  $^1\text{H}$  nutation frequencies are in the range of 102–106 kHz for all the PMLG-block types, with a maximum of 2 kHz difference between that applied in  $\tau_1$  and  $\tau_2$  for the same PMLG block. For  $\tau_1$ , the optimum values for PMLG decoupling are 2.0 or 2.1 ms, as compared to 1.6 ms from MAS alone. However, as discussed in Section 3.4, it is the product  $\lambda_{\text{CS}}\tau$ , that needs to be considered, in which case similar values are obtained as compared to MAS alone. By comparison, a clear difference is observed for  $\tau_2$ , where the evolution of  $^1\text{H}$  coherence is markedly affected by the  $^1\text{H}$ - $^1\text{H}$  dipolar couplings. Indeed, the coherence transfer increases from 0.3 ms for MAS

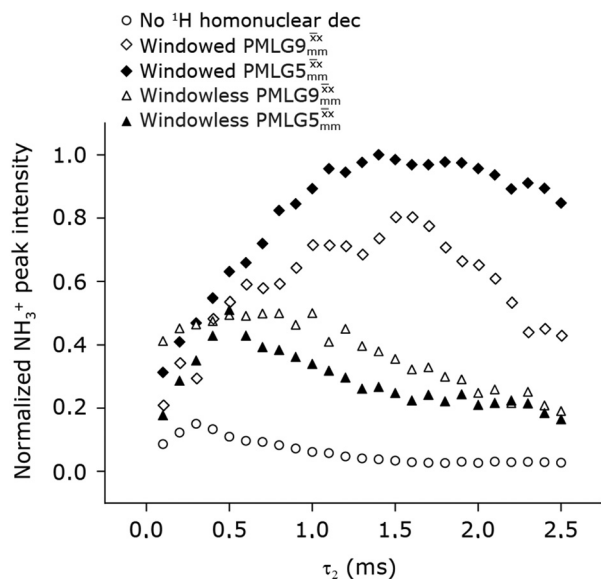
Table 5 Optimised rf carrier offset, spin-echo duration and nutation frequencies for four implementations of PMLG  $^1\text{H}$  homonuclear decoupling and MAS-alone for a  $^{15}\text{N}$ - $^1\text{H}$  CP-refocused INEPT MAS NMR experiment for  $^{15}\text{N}$ -glycine<sup>a</sup>

$^1\text{H}$ homonuclear decoupling	Offset <sup>b</sup> (kHz)	$\lambda_{\text{CS}}$	$\tau_1$ (ms)	$\lambda_{\text{CS}} \tau_1$ (ms)	$\nu_1$ (kHz) for $\tau_1$	$\tau_2$ (ms)	$\lambda_{\text{CS}} \tau_2$ (ms)	$\nu_1$ (kHz) for $\tau_2$	Relative intensity <sup>d</sup>
No decoupling	2.00	1.00	1.600	1.600	—	0.300	0.300	—	0.08
Windowed PMLG $5_{\text{mm}}^{\text{xx}}$	1.00	0.82	1.999 ( $69\tau_c$ )	1.639	106	1.391 ( $48\tau_c$ )	1.140	106	1.00
Windowed PMLG $9_{\text{mm}}^{\text{xx}}$	0.75	0.76	2.085 ( $71\tau_c$ )	1.585	104	1.498 ( $51\tau_c$ )	1.138	106	0.80
Windowless PMLG $5_{\text{mm}}^{\text{xx}}$	1.00	0.66	2.096 ( $169\tau_c$ )	1.383	102	0.496 ( $40\tau_c$ )	0.327	102	0.52
Windowless PMLG $9_{\text{mm}}^{\text{xx}}$	-0.25	0.60	2.091 ( $179\tau_c$ )	1.254	104	1.192 ( $102\tau_c$ )	0.715	102	0.48

<sup>a</sup> As implemented at  $\nu_0 = 500$  MHz and  $\nu_r = 60$  kHz.  $\tau_{\text{tilt}}$  is equal to 0.54  $\mu\text{s}$  for windowed PMLG $5_{\text{mm}}^{\text{xx}}$  and 0.82  $\mu\text{s}$  for windowed PMLG $9_{\text{mm}}^{\text{xx}}$ . See Fig. 6.

<sup>b</sup> Relative to the  $\text{NH}_3^+$   $^1\text{H}$  resonance. <sup>c</sup>  $\tau_1 = n\tau_c$ ,  $\tau_2 = m\tau_c$ , where  $n$  and  $m$  are positive integers. <sup>d</sup> See Fig. 7.



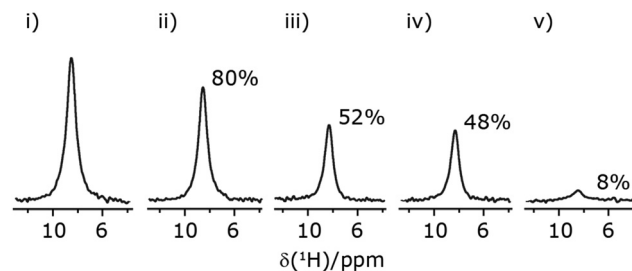


**Fig. 6** Dependence upon the second spin-echo duration,  $\tau_2$ , for  $^{15}\text{N}$ -labelled glycine of the  $\text{NH}_3^+$  peak in a 1D-filtered ( $t_1 = 0$ )  $^{15}\text{N}$ - $^1\text{H}$  ( $\nu_0 = 500$  MHz) CP (contact time = 2 ms)-refocused INEPT MAS ( $\nu_r = 60$  kHz) NMR spectrum for: windowed PMLG5 $_{\text{mm}}^{\text{xx}}$  ( $\tau_{\text{LG-expt}} = 3.1$   $\mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.54$   $\mu\text{s}$ ,  $\nu_1 = 106$  kHz for  $\tau_1$  and 106 kHz for  $\tau_2$  full diamonds), windowless PMLG5 $_{\text{mm}}^{\text{xx}}$  (same conditions but with no tilt pulses, full triangles, with  $\nu_1 = 102$  kHz for  $\tau_1$  and 102 kHz for  $\tau_2$ ), windowed PMLG9 $_{\text{mm}}^{\text{xx}}$  ( $\tau_{\text{LG-expt}} = 2.92$   $\mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.82$   $\mu\text{s}$ ,  $\nu_1 = 104$  kHz for  $\tau_1$  and 106 kHz for  $\tau_2$  empty diamonds), windowless PMLG9 $_{\text{mm}}^{\text{xx}}$  (same conditions but with no tilt pulses, empty triangles, with  $\nu_1 = 104$  kHz for  $\tau_1$  and 102 kHz for  $\tau_2$ ), MAS alone (empty circles). 8 transients were coadded. For all experiments with windowed PMLG,  $\tau_w = 7.20$   $\mu\text{s}$ .

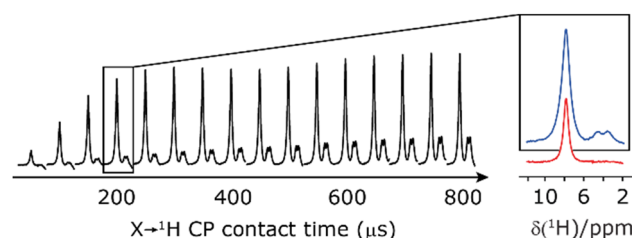
alone to 1.5 ms for windowed PMLG9 $_{\text{mm}}^{\text{xx}}$  and 1.4 ms for windowed PMLG5 $_{\text{mm}}^{\text{xx}}$ . After scaling, the product  $\lambda_{\text{CS}} \tau_2$ , 1.14 ms for both windowed PMLG9 $_{\text{mm}}^{\text{xx}}$  and PMLG5 $_{\text{mm}}^{\text{xx}}$ , are still  $\sim 4$  times longer than the optimum  $\tau_2$  for MAS alone. We note a discrepancy for  $\tau_2$  under windowless PMLG5 $_{\text{mm}}^{\text{xx}}$ , which is considerably shorter (0.3 ms after scaling) with respect to the other  $^1\text{H}$  homonuclear implementations.

In Fig. 7, we compare the different peak intensities for the  $\text{NH}_3^+$  peak of  $^{15}\text{N}$ -labelled glycine for the windowless and windowed implementation of PMLG5 $_{\text{mm}}^{\text{xx}}$  and PMLG9 $_{\text{mm}}^{\text{xx}}$  in a  $^{15}\text{N}$ - $^1\text{H}$  CP-refocused INEPT 1D filtered ( $t_1 = 0$ ) spectrum. The best performance is for our optimum implementation of windowed PMLG5 $_{\text{mm}}^{\text{xx}}$  with a 12.5 times better relative sensitivity compared to MAS alone.

Finally, in this section, we compare the sensitivity and selectivity of the CP refocused INEPT experiment to that of a hNH double CP experiment. Specifically, the right-hand side of Fig. 8 compares 1D-filtered MAS NMR spectra of  $^{15}\text{N}$ -glycine recorded using the CP refocused INEPT experiment (red) or a hNH double CP experiment with a back ( $^{15}\text{N}$  to  $^1\text{H}$ ) CP contact time of 200  $\mu\text{s}$  (blue). In both cases, the  $^1\text{H}$  to  $^{15}\text{N}$  CP contact time is 3.7 ms, *i.e.*, CP is used initially to efficiently generate  $^{15}\text{N}$  transverse magnetisation. While the sensitivity of the CP refocused INEPT spectrum is half that of the double CP experiment, there is no intensity for the  $\text{CH}_2$   $^1\text{H}$  resonances. Fig. 8 also



**Fig. 7** Comparison of the sensitivity of 1D-filtered ( $t_1 = 0$ )  $^{15}\text{N}$ - $^1\text{H}$  ( $\nu_0 = 500$  MHz) CP (contact time = 2 ms)-refocused INEPT MAS ( $\nu_r = 60$  kHz) NMR spectra of  $^{15}\text{N}$ -glycine recorded with the application of different optimised PMLG  $^1\text{H}$  decoupling conditions, (i)–(iv) compared to MAS alone, (v): (i) windowed PMLG5 $_{\text{mm}}^{\text{xx}}$  ( $\tau_{\text{LG-expt}} = 3.1$   $\mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.54$   $\mu\text{s}$ ,  $\tau_1 = 1.999$  ms ( $69\tau_c$ ) with  $\nu_1 = 106$  kHz;  $\tau_2 = 1.391$  ms ( $48\tau_c$ ) with  $\nu_1 = 106$  kHz), (ii) windowed PMLG9 $_{\text{mm}}^{\text{xx}}$  ( $\tau_{\text{LG-expt}} = 2.92$   $\mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.82$   $\mu\text{s}$ ,  $\tau_1 = 2.085$  ms ( $71\tau_c$ ) with  $\nu_1 = 104$  kHz;  $\tau_2 = 1.498$  ms ( $51\tau_c$ ) with  $\nu_1 = 106$  kHz), (iii) windowless PMLG5 $_{\text{mm}}^{\text{xx}}$  ( $\tau_{\text{LG-expt}} = 3.1$   $\mu\text{s}$ ,  $\tau_1 = 2.096$  ms ( $169\tau_c$ ) with  $\nu_1 = 102$  kHz;  $\tau_2 = 0.496$  ms ( $40\tau_c$ ) with  $\nu_1 = 102$  kHz), (iv) windowless PMLG9 $_{\text{mm}}^{\text{xx}}$  ( $\tau_{\text{LG-expt}} = 2.92$   $\mu\text{s}$ ,  $\tau_1 = 2.090$  ms ( $179\tau_c$ ) with  $\nu_1 = 104$  kHz;  $\tau_2 = 1.192$  ms ( $102\tau_c$ ) with  $\nu_1 = 102$  kHz), (v) no decoupling  $\tau_1 = 1.6$  ms ( $96\tau_r$ ) and  $\tau_2 = 0.3$  ms ( $18\tau_r$ ). For all experiments with windowed  $^1\text{H}$  homonuclear decoupling,  $\tau_w = 7.20$   $\mu\text{s}$ . All the spectra were acquired with 16 coadded transients and the corresponding  $^1\text{H}$  transmitter offset reported in Table 5.



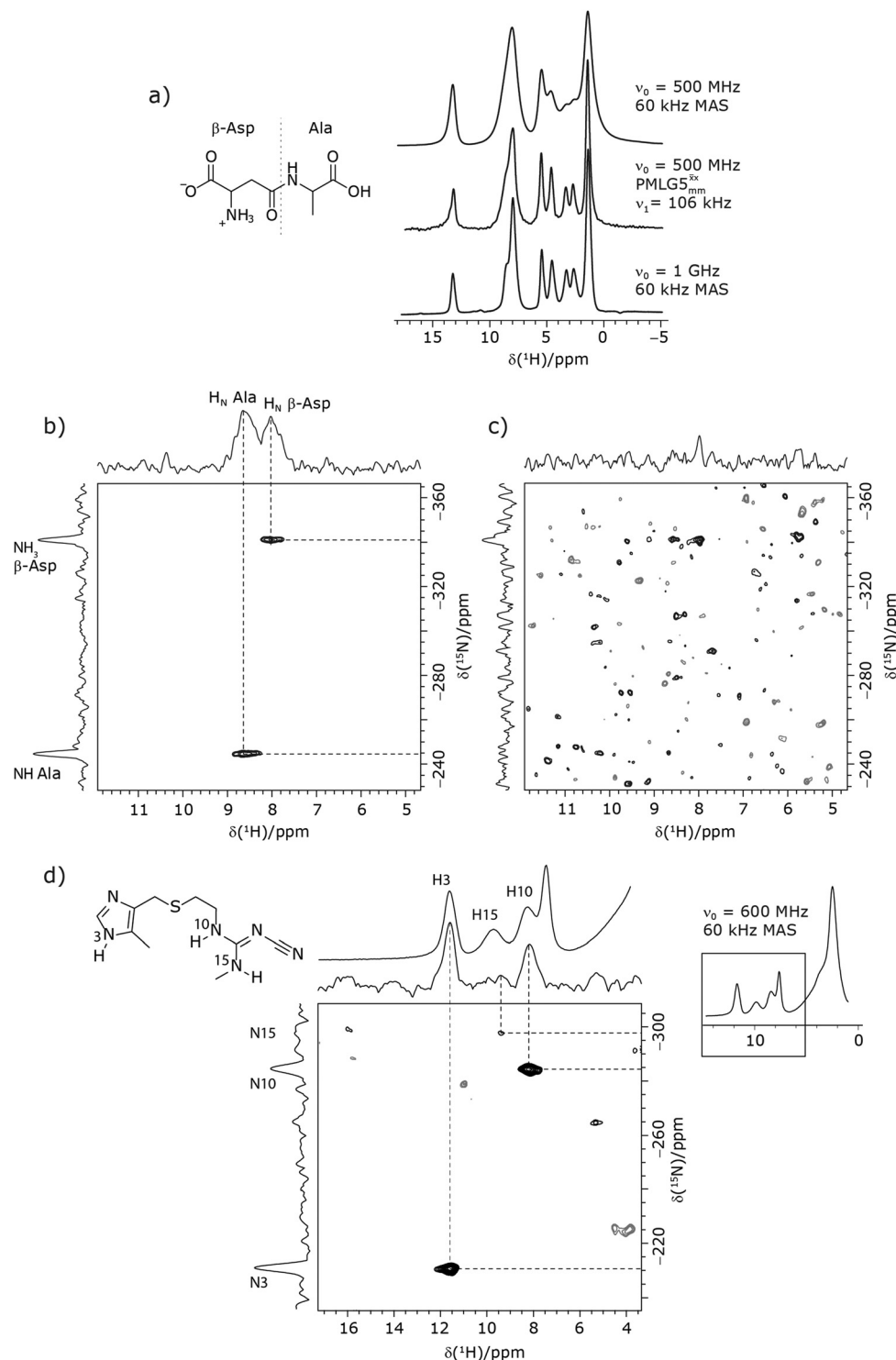
**Fig. 8** Comparison of the sensitivity of 1D-filtered ( $t_1 = 0$ )  $^{15}\text{N}$ - $^1\text{H}$  ( $\nu_0 = 600$  MHz) MAS ( $\nu_r = 60$  kHz) NMR spectra of  $^{15}\text{N}$ -glycine recorded with a double CP experiment (blue) or a CP-refocused INEPT experiment (red). The build-up for the double CP experiment as a function of the  $^{15}\text{N}$  to  $^1\text{H}$  CP contact time is also shown. In both cases, the  $^1\text{H}$  to  $^{15}\text{N}$  CP contact time is 3.7 ms. For refocused INEPT  $^{15}\text{N}$  to  $^1\text{H}$  transfer, windowed PMLG5 $_{\text{mm}}^{\text{xx}}$  ( $\tau_{\text{LG-expt}} = 3.19$   $\mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.5$   $\mu\text{s}$  and  $\tau_w = 7.20$   $\mu\text{s}$ ) is applied at a nutation frequency of 106 kHz for  $\tau_1 = 2.334$  ms ( $140\tau_r$ ) and  $\tau_2 = 1.401$  ms ( $84\tau_r$ ). All the spectra were acquired with 16 co-added transients and a  $^1\text{H}$  transmitter offset of  $-4$  kHz.

shows, for the double CP experiment, the dependence on the back ( $^{15}\text{N}$  to  $^1\text{H}$ ) CP contact time, with a plateau in intensity reached after 200  $\mu\text{s}$ , though note that  $\text{CH}_2$   $^1\text{H}$  resonance signal is already evident from 100  $\mu\text{s}$ .

### 3.6 $2\text{D } ^{15}\text{N}$ - $^1\text{H}$ CP-refocused INEPT NMR spectra with PMLG $^1\text{H}$ decoupling at 60 kHz MAS of a dipeptide and a pharmaceutical at natural abundance

Due to the better sensitivity of windowed PMLG5 $_{\text{mm}}^{\text{xx}}$  observed for glycine, it was selected as the  $^1\text{H}$  homonuclear decoupling sequence for a  $^{15}\text{N}$ - $^1\text{H}$  correlation experiment recorded for the  $\beta$ -AspAla dipeptide at natural isotopic abundance, with the improvement of resolution achieved in the 1D  $^1\text{H}$  CRAMPS compared here with a  $^1\text{H}$  one-pulse recorded at Larmor





**Fig. 9** MAS ( $\nu_r = 60$  kHz) NMR spectra of (a–c) the dipeptide  $\beta$ -AspAla and (d) the pharmaceutical cimetidine, in both cases at natural isotopic abundance, employing windowed PMLG5 $^{\text{xx}}$ <sub>mm</sub> ( $\tau_{\text{LG-expt}} = 3.1$   $\mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.54$   $\mu\text{s}$  and  $\tau_w = 7.20$   $\mu\text{s}$ ). (a) Comparison of a  $^1\text{H}$  1D CRAMPS spectrum acquired with windowed PMLG5 $^{\text{xx}}$ <sub>mm</sub> (at  $\nu_0 = 500$  MHz, with  $^1\text{H}$  one-pulse spectra recorded at  $\nu_0 = 500$  MHz and 1 GHz). (b and c) 2D  $^{15}\text{N}$ - $^1\text{H}$  ( $\nu_0 = 500$  MHz) CP (contact time = 2 ms)-refocused INEPT MAS NMR spectra with (b) windowed PMLG5 $^{\text{xx}}$ <sub>mm</sub>  $^1\text{H}$  homonuclear decoupling during the spin-echo durations used for  $^{15}\text{N}$ - $^1\text{H}$  refocused INEPT coherence transfer or (c) MAS alone. In (b), windowed PMLG5 $^{\text{xx}}$ <sub>mm</sub> was implemented with  $\nu_1(^1\text{H}) = 106$  kHz during  $\tau_1$  (1.999 ms,  $69\tau_c$ ) and  $\nu_1(^1\text{H}) = 106$  kHz during  $\tau_2$  (1.391 ms,  $48\tau_c$ ), with the transmitter frequency centred at 10.3 ppm. For both (b) and (c), 224 transients were co-added for each of 96  $t_1$  FIDs, corresponding to a total experimental time of 23 h with a recycle delay of 3 s. The base contour is at 50% of the respective maximum intensity in (b) and (c). (d) A 2D  $^{15}\text{N}$ - $^1\text{H}$  ( $\nu_0 = 600$  MHz) CP (contact time = 4 ms)-refocused INEPT MAS NMR spectrum with windowed PMLG5 $^{\text{xx}}$ <sub>mm</sub>  $^1\text{H}$  homonuclear decoupling ( $\nu_1(^1\text{H}) = 106$  kHz during  $\tau_1$  (2.491 ms,  $86\tau_c$ ) and  $\nu_1(^1\text{H}) = 106$  kHz during  $\tau_2$  (1.999 ms,  $69\tau_c$ )), with the transmitter frequency centred at 11.0 ppm. 1024 transients were co-added for each of 64  $t_1$  FIDs, corresponding to a total experimental time of 92 h with a recycle of 5 s. The base contour is at 30% of the maximum intensity.





frequency of 500 MHz and 1 GHz (Fig. 9a). Note that a  $^{15}\text{N}$  CP MAS spectrum for the  $\beta$ -AspAla dipeptide has been presented in Tatton *et al.*<sup>22</sup> The  $^{15}\text{N}$ - $^1\text{H}$  CP-refocused INEPT experiment was implemented with the offset and coherence transfer delays optimised for  $^{15}\text{N}$ -labelled glycine, as stated in Table 5, *i.e.*,  $\tau_{\text{LG\_expt}} = 3.1 \mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.54 \mu\text{s}$ ,  $\tau_1 = 2.0 \text{ ms}$  with  $\nu_1 = 106 \text{ kHz}$ ,  $\nu_2 = 1.4 \text{ ms}$  with  $\nu_1 = 106 \text{ kHz}$ , and an offset of +1 kHz. High-performance  $^1\text{H}$  homonuclear decoupling achieved with a finely optimised implementation of windowed  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  enables the recording at natural abundance of a 2D  $^{15}\text{N}$ - $^1\text{H}$  correlation spectrum at 60 kHz MAS with a through-bond back transfer (Fig. 9b). The sensitivity of the windowed  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  implementation is compared to a  $^{15}\text{N}$ - $^1\text{H}$  CP-refocused INEPT spectrum recorded with no decoupling at the optimum  $\tau_1 = 1.6 \text{ ms}$  and  $\tau_2 = 0.3 \text{ ms}$  values in Table 5 for  $^{15}\text{N}$ -labelled glycine; only noise is observed in Fig. 9c.

As noted in Section 3.1, there is a different dependence on the duration of the first spin echo,  $\tau_1$ , for a NH and  $\text{NH}_3^+$  moiety, compare eqn (1) and (2). This is evident from Fig. 10 that shows the build-up of intensity in a 1D-filtered  $^{15}\text{N}$ - $^1\text{H}$  CP-refocused INEPT spectrum of the dipeptide  $\beta$ -AspAla. Two peaks are resolved for the higher-ppm NH and the lower-ppm  $\text{NH}_3^+$  resonances (see deconvolution in Fig. 10b), and it is evident maximum intensity is reached at a shorter spin-echo duration for the lower-ppm  $\text{NH}_3^+$  peak at  $\sim 2.1 \text{ ms}$  as compared to  $\sim 3.5 \text{ ms}$  for the higher-ppm NH peak. As shown in Fig. S7 of the ESI† this is expected as based from a consideration of eqn (1) and (2). Such an experiment could hence be used to distinguish different  $\text{NH}_x$  moieties, as for example has been demonstrated analogously for  $\text{SiH}_x$  groups.<sup>82–84</sup>

Furthermore, windowed  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  was employed to record a 2D  $^{15}\text{N}$ - $^1\text{H}$  CP-refocused INEPT spectrum of the pharmaceutical cimetidine at natural abundance (Fig. 9d), for which  $^1\text{H}$ ,  $^{15}\text{N}$  CPMAS and  $^{14}\text{N}$ - $^1\text{H}$  spectra have been presented in ref. 101 and 102. (For comparison, note that in ref. 101, Tatton *et al.* use a simple  $^{15}\text{N}$ - $^1\text{H}$  heteronuclear spin echo with  $^1\text{H}$  homonuclear decoupling to demonstrate spectral editing.) In this case, spin-echo curves were recorded, because, as discussed above, the optimum  $\tau_1$  and  $\tau_2$  durations in the refocused INEPT pulse sequence element depends both on the  $J$  coupling between the involved nuclei and the  $^1\text{H}$  dephasing  $T_2'$ . The  $^1\text{H}$  coherence lifetime (see Fig. S6 and Table S1 (ESI†) in comparison to Table 4) for two of the protons directly bonded to the nitrogens, N3 and N10, is longer than the  $\text{NH}_3^+$   $T_2'$  of  $^{15}\text{N}$ -glycine acquired with the same windowed  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$   $^1\text{H}$  decoupling. In addition, considering the above discussion of Fig. 10 and eqn (1) and (2), note that for a NH group, a maximum signal is observed at a longer  $\tau_1$  as compared to a  $\text{NH}_3^+$  group. For this reason,  $\tau_1$  and  $\tau_2$  were increased to 2.5 ms and 2.0 ms, respectively. Note that weaker intensity is observed for the proton directly bonded to N15, where the respective  $^1\text{H}$   $T_2'$  is  $\sim 0.5 \text{ ms}$  after scaling (Table S1, ESI†). Further investigation is required to understand the shorter  $T_2'$  for this proton and the very weak signal for the N15-H15 cross peak in the 2D CP-refocused INEPT spectrum in Fig. 9d.

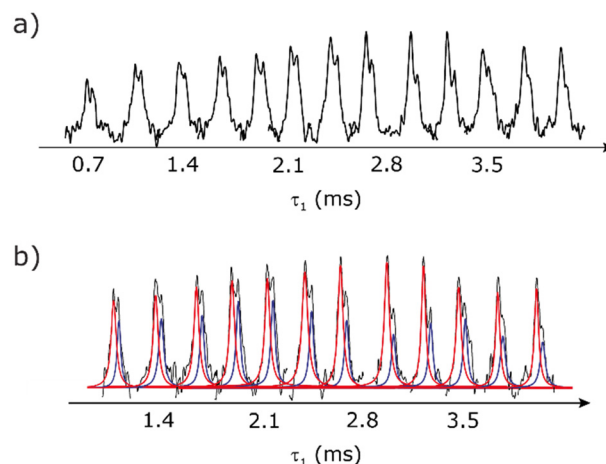


Fig. 10 (a) Dependence upon the first spin-echo duration,  $\tau_1$ , for a 1D-filtered ( $t_1 = 0$ )  $^{15}\text{N}$ - $^1\text{H}$  ( $\nu_0 = 600 \text{ MHz}$ ) CP (contact time = 3.7 ms)-refocused INEPT MAS ( $\nu_r = 60 \text{ kHz}$ ) NMR spectrum for the dipeptide  $\beta$ -AspAla at natural isotopic abundance, recorded using  $^1\text{H}$  homonuclear decoupling ( $\tau_{\text{LG\_expt}} = 3.19 \mu\text{s}$ ,  $\tau_{\text{tilt}} = 0.50 \mu\text{s}$ , with  $\nu_1 = 106 \text{ kHz}$ ) for  $\tau_2 = 2.101 \text{ ms}$  ( $126\tau_r$ ). All the spectra were acquired with 1024 co-added transients and a  $^1\text{H}$  transmitter offset of  $-2 \text{ kHz}$ . A deconvolution of the NH (red) and  $\text{NH}_3^+$  (blue) peaks is shown in (b).

## 4. Conclusions and outlook

This paper has identified  $^1\text{H}$  homonuclear decoupling conditions for the  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  supercycle at 60 kHz MAS that give enhanced resolution in a 1D NMR spectrum as compared to MAS alone. At 1 GHz, we report what we believe to be the first example of effective homonuclear decoupling achieved by using a rf nutation frequency lower than the MAS frequency. The establishing of 2D  $^{15}\text{N}$ - $^1\text{H}$  heteronuclear correlation for natural abundance solids using a  $^1\text{H}$  detected CP-J coupling based refocused INEPT MAS NMR experiment<sup>26,38,39</sup> has been demonstrated at 60 kHz MAS. The application of  $^1\text{H}$  homonuclear decoupling, specifically the  $\text{PMLG5}_{\text{mm}}^{\text{xx}}$  supercycle<sup>26,39,57,85</sup> results in a factor of 12.5 sensitivity enhancement as compared to MAS alone. Notably, in our implementation at 500 MHz, a comparatively low  $^1\text{H}$  nutation frequency, for a 1.3 mm rotor, of 100 kHz was used, with this being associated with a high chemical shift scaling factor of 0.82 and a large deviation from the ideal Lee-Goldburg condition. Future work could further probe the suitability and optimisation of such windowed and windowless decoupling sequences for applications involving spin-echo evolution. In addition, nutation-frequency-selective pulses that reduce rf inhomogeneity could also be explored.<sup>103</sup> The CP-refocused INEPT pulse sequence is complementary to dipolar coupling-based double CP or the use of symmetry-based decoupling to establish  $^{15}\text{N}$ - $^1\text{H}$  heteronuclear correlation under fast MAS.<sup>26,29,30,104</sup> Note that the use of symmetry-based recoupling is more prone to  $t_1$  noise.<sup>105–107</sup> In future work, the extension of our approach to 100+ kHz MAS could be considered, noting an increasing number of applications to pharmaceuticals and other small and moderately sized organic molecules.<sup>9,108–114</sup>



## Conflicts of interest

There are no conflicts to declare.

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