Published in final edited form as:

J Magn Reson. 2013 September ; 234: 141–146. doi:10.1016/j.jmr.2013.06.018.

High-Resolution Proton CRAMPS NMR Using Narrowband Analog Filters and Postponed Data Acquisition

Liyang Wang^{a,b} and Donghua H. Zhou^{a,*}

^aDepartment of Physics, Oklahoma State University, Stillwater, OK 74078, USA

^bState Key Laboratory of Magnetic Resonance and Atomic Molecular Physics, Wuhan Center for Magnetic Resonance, Key Laboratory of Magnetic Resonance in Biological Systems, Wuhan Institute of Physics and Mathematics, Chinese Academy of Sciences, Wuhan 430071, China

Abstract

Proton linewidths decrease with increasing magic-angle spinning (MAS) rates. However, without spin dilution by deuteration, even with the fastest MAS rates available today, the narrowest proton linewidths are obtained by using the combined rotation and multiple pulse spectroscopy (CRAMPS) method. Direct observation under windowed CRAMPS typically introduces several tens of times more noise, partly because wideband analog filters (e.g. 5 MHz) must be used or sometimes even bypassed. Here we report that it is possible to keep using narrowband analog filters (about 50 kHz cutoff frequency) in CRAMPS by taking advantage of the time delay caused by the filters, which is inversely proportional to the cutoff frequency. This delay coincides with typical CRAMPS cycle times, enabling acquisition of the data point in the next detection window. The noise of such CRAMPS spectra is only about 5 times larger than MAS-only spectra. This new method allows CRAMPS to be performed on systems that lack wideband hardware (wideband filters and fast ADCs), for example, older spectrometers originally intended for solution NMR.

Keywords

high resolution proton spectra; CRAMPS proton NMR; magic-angle spinning NMR; audio filter; postponed data sampling; noise reduction

1. Introduction

High-resolution solid-state proton NMR spectroscopy is a powerful method for characterization of molecular structure and dynamics of organic and hydrogen-containing inorganic materials [1–8]. To obtain narrow proton linewidths, the strong dipolar interactions among the proton networks are often reduced by three techniques: proton dilution, fast magic angle spinning (MAS), and homonuclear dipolar decoupling. Proton dilution is realized by substituting hydrogens with deuterium atoms either synthetically or biologically [9–12]. MAS averages the spatial parts of the interaction, resulting in narrowed proton linewidths inversely proportional to the MAS frequency [13–19]. Homonuclear decoupling averages the spin parts of the interaction by applying special rf pulse patterns

© 2013 Elsevier Inc. All rights reserved.

*Corresponding author. Tel: 405-744-3277, Fax: 405-744-6811, donghua@okstate.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

[20]. Proton dilution and its combination with fast MAS resulted in the recent development of highly sensitive proton-detected multi-dimensional pulse sequences and structure elucidation for several proteins [21–28]. For fully protonated samples, the combination of MAS and homonuclear decoupling, i.e., combined rotation and multiple pulse spectroscopy (CRAMPS) [29–31], provides lines narrower than MAS alone even at very high spinning frequencies (> 60 kHz) [31–37]. Among the many implementations of CRAMPS techniques, frequency-switched Lee-Goldberg (FSLG) [38], phase-modulated Lee-Goldberg (PMLG) [32], decoupling using mind-boggling optimization (DUMBO) [34], and an experimentally optimized version eDUMBO [33] are widely used. For direct acquisition of homonuclear decoupled proton signals, narrow detection windows of a few microseconds are inserted between rf pulses, resulting in windowed CRAMPS such as wPMLG [39] and wDUMBO [40].

Direct observation under windowed CRAMPS typically introduces several tens of times more noise, partly because wideband, rather than narrowband, analog filters must be used or sometimes even bypassed. In MAS-alone experiments, the 3 dB cutoff frequency (f_c) of receiver analog filters is set slightly larger than half of the required spectral width, requiring f_c of about 30 kHz. These filters introduce a time delay about 30 μ s, which is inversely proportional to the cutoff frequency [41]. Such a big time displacement of the signals cannot be tolerated for CRAMPS with narrow detection windows. Instead, another set of analog filters with large bandwidth (e.g. 5 MHz) are used to reduce the filter delay to less than 1 μ s. However, the actual spectral width in CRAMPS is not determined by the filter bandwidth, rather by the CRAMPS cycle time (e.g. spectral width 50 kHz for 20 μ s cycle time, requiring about 30 kHz cutoff frequency in non-CRAMPS experiments). Noise in the wide bandwidth is aliased into the spectral window, resulting in 13 times more noise using the exemplary numbers and assuming white noise distribution (square root of the ratio of the cutoff frequencies for CRAMPS and normal experiments).

Here we report that it is possible to keep using narrowband analog filters (with cutoff frequency f_c set to about 50 kHz) in CRAMPS by taking advantage of the time delay caused by the filters. The filter delay has been exploited by Hoult to remove the baseline artifacts with a carefully chosen receiver dead time [41]. In our method, the filter delays are chosen to be close to CRAMPS cycle times, shifting the data point to the next detection window for sampling. This method allows CRAMPS to be performed on systems lacking wideband hardware (wideband filters and fast ADCs), such as older spectrometers previously dedicated to solution NMR, while achieving significant noise reduction at the same time.

2. Experimental

Powder glycine sample was purchased from Research Products International Corporation (Mt. Prospect, Illinois) and used without further purification. The sample was filled to the full volume (~ 9 μ L) of a 1.6 mm NMR rotor. The solid-state NMR experiments were performed on a 600 MHz Varian INOVA spectrometer with a FastMAS HXY probe operating in ^1H - ^{13}C - ^{15}N triple resonance mode. For quadrature detection, the spectrometer was equipped with two 500-kHz ADCs and two programmable 8-pole quasi-elliptic analog filters with 256-kHz maximum bandwidth. Proton 90° pulse width was 1.2 μ s. PMLG decoupling [39] was implemented on a waveform generator. Experimental temperature was regulated at 10 $^\circ\text{C}$. Data were zero-filled and apodized with 10 Hz Lorentzian linewidth prior to Fourier transform. Other experimental details are included in the main text and figure captions.

3. Results and discussion

3.1 Filter impulse response

To aid informed selection of a filter bandwidth that produces a time delay close to a desired CRAMPS cycle time, temporal responses to finite impulses were measured for receiver analog filters by direct NMR experiments (Fig. 1). Any liquid sample with a single slow decaying proton signal can be used for this purpose. In our experiment, a 1.6 mm rotor containing 99% D₂O was spun at 10 kHz. Optimized shimming gave 5 Hz line width at half maximum, along with a weak and broad base. The fast-decaying base component was removed by a T₂ filter in the pulse sequence ($\tau = 2$ ms, Fig. 1a). The receiver gate was only engaged for a specified duration (τ_{rcv}), sending a nearly square pulse of the on-resonant proton free induction decay (FID) to the analog filters. However, data sampling was continued after the receiver was turned off (Fig. 1a). The time domain signal acquired in such a manner was phased and its real component displayed, giving the impulse responses for the filter (Fig. 1b).

The impulse responses were measured at filter cutoff frequency $f_c = 59$ kHz for several receiver gating times (Fig. 1b). For the long impulse with $\tau_{\text{rcv}} = 38.8 \mu\text{s}$ in Fig. 1b, the response curve has overshoots on both edges. It seems reasonable to define the filter delay ($t_{fd} = 15.4 \mu\text{s}$ in Fig. 1b) at 50% amplitude on the rising edge, because the time span between this and the other 50% point on the descending edge approximately equals to the impulse width. The t_{fd} values (in μs) were measured for several cutoff frequencies f_c (in kHz) between 30 and 100 kHz, and the data (not shown) were nicely fit by Eq. (1), which shows the standard errors for the coefficients.

$$t_{fd} = (0.804 \pm 0.003) \cdot 1000/f_c + (1.37 \pm 0.08) \quad (1)$$

For relatively short impulses, the response signal started to fall before reaching the first overshooting peak (Fig. 1b). Consequently only one peak was observed. The peak height and position depend on the width of the input impulse. For impulse width of $10.8 \mu\text{s}$, the response peak height is 103%, with its full width at half height (FWHH) roughly the same as the impulse width. The peak height decreases with impulse width. For impulse width of $2.8 \mu\text{s}$, the response peak height decreases to 54%. The peak positions for these short impulses agree very well with the sum of t_{fd} and half of the impulse width

$$t_p = t_{fd} + \tau_{\text{rec}}/2 \quad (2)$$

Therefore, the filter delay t_{fd} can also be interpreted as the time difference between the peak of the response and the center of the impulse.

3.2 CRAMPS with postponed acquisition

Fig. 2 shows the implementation of wPMLG5 [39] using narrowband filters and postponed sampling. In our experiments, receiver protection delay $\tau_{rd} = 1.2 \mu\text{s}$, acquisition duration $\tau_{acq} = 0.2 \mu\text{s}$, time to prepare amplifier $\tau_{ad} = 0.6 \mu\text{s}$. According to Eq. 2, the center of the signal created by the activation of the receiver in the first window is shifted to the second detection window by t_{fd} . This is when the peak of the response occurs and data should be sampled at that moment for maximum sensitivity. The time for the center of the second sampling event can be calculated in two different ways, establishing the following equation,

$$\tau_{sd} + \tau_{acq}/2 + \tau_c = \tau_{rd} + \tau_{rcv}/2 + t_{fd} \quad (3)$$

where sampling delay τ_{sd} is used to position the acquisition event in the window and τ_c is the cycle time. Assisted with

$$\tau_{rcv} = \tau_w - \tau_{rd} - \tau_{ad} \quad (4)$$

where τ_w is the width of the detection window, the solution for the sampling delay is

$$\tau_{sd} = t_{fd} - \tau_c + (\tau_w + \tau_{rd} - \tau_{ad} - \tau_{acq})/2 \quad (5)$$

For $\tau_w = 4.8 \mu\text{s}$ and pulse width $\tau_p = 1.2 \mu\text{s}$, $\tau_c = 10 \tau_p + \tau_w = 16.8 \mu\text{s}$ and $t_{fd} = 15.2 \mu\text{s}$ for $f_c = 59 \text{ kHz}$, Eq. (5) predicts sampling delay $\tau_{sd} = 1.0 \mu\text{s}$. In practice, the delay before data sampling was optimized experimentally for the strongest signal (Fig. 3). Direct optimization finds $1.6 \mu\text{s}$ to be best, while values between 1.0 to $2.2 \mu\text{s}$ are all acceptable.

Fig. 4 shows several CRAMPS proton spectra acquired using the postponed sampling method. The related experimental and spectral parameters are listed in Table 1. For comparison, a MAS spectrum acquired at 40 kHz spinning frequency is also shown (Fig. 4a), which has two severely overlapped methylene peaks and a nearly isolated amine peak. The CRAMPS spectra (Fig. 4b–e) are well resolved and their resolution is among the best of glycine proton spectra reported in the literature [31,35,36,42–47]. In the spectrum acquired with a $4.8 \mu\text{s}$ window, 40 kHz spinning, and 145 kHz decoupling strength (Fig. 4b and Table 1), the two methylene peaks are fully resolved. The scaled up linewidths for the amine and methylene protons are 0.62 and 0.51 ppm , respectively. The method is further tested for lower spinning frequency (18 kHz) and decoupling strength (109 kHz) while keeping the same detection window size. The resulting spectrum (Fig. 4e) shows slightly deteriorated but still excellent resolution with 0.71 and 0.62 ppm linewidths for the amine and methylene peaks, respectively. Such spinning frequencies and decoupling strengths are achievable with probes having larger rotors (e.g. 3.2 mm diameter).

For spectra shown in Fig. 4c and Fig. 4d, longer detection windows of 7.6 and $8.1 \mu\text{s}$ were attempted. As expected from the dependence of filter response peak height on the impulse width (Fig. 1), higher resonance peak intensities are observed with longer detection windows (Fig. 4b, c, d and Table 1). The intensities are reported in relation to the intensity of the amine peak in the 40 kHz MAS spectrum (Fig. 4a), which is measured as the product of the peak width and height. For the CRAMPS spectra (Fig. 4b–e), the raw width prior to scaling up (division by the scaling factor) is used in the calculation. The relative intensities are 51% , 88% , and 94% for spectra obtained with 4.8 , 7.6 , and $8.1 \mu\text{s}$ windows, respectively (Table 1). The relative intensity for the spectrum obtained at 18 kHz MAS was 45% . To be fair, this spectrum should have been compared with a MAS spectrum obtained at the same MAS rate, which was unfortunately unresolved. A weaker center band intensity at the lower MAS rate should correct the relative intensity to over 50% .

It is evident that the scaling factor increases with the detection window (Table 1), agreeing with the reported dependence of scaling factor on the ratio of the windowed and rf periods [47]. Slightly lower resolution is observed for longer detection windows (Fig. 4b–d and Table 1). One possible solution is to spin the sample faster in a smaller rotor, since homonuclear decoupling solely relies on MAS during the windowed period.

3.3 Two-dimensional CRAMPS spectra

Fig. 5 shows homonuclear single-quantum correlation 2D spectra of glycine. In Fig. 5a, homonuclear decoupling was applied only to the indirect dimension, with wPMLG5 decoupling parameters identical to those used for Fig. 4b. All three peaks demonstrate much narrower linewidths in the CRAMPS indirect dimension than in the MAS-only direct dimension. In Fig. 5b, wPMLG5 with the same parameters was applied to both dimensions, resulting in a highly resolved spectrum. Spin diffusion of 1 ms was applied between the two evolution periods, creating the off diagonal cross peaks. Two strong cross peaks are observed between the two methylene protons at 3 and 4 ppm, respectively. Two weak cross peaks are also observed between the amine protons and the methylene proton at 4 ppm. Cross peaks between the other methylene proton and the amine protons are 2.7 times weaker and below the plotted contour levels. Based on the fact that the two methylene protons have different chemical shifts, this glycine sample agrees with the α -form crystal structure [3]. In the neutron diffraction crystal structure (Cambridge Structural Database code GLYCIN05) [48], the two methylene protons (H4 and H5 in GLYCIN05) are equally distant from the three amine protons (H1, H2, and H3) in the same molecule. However, H4 is much closer to the amine protons of neighboring molecules than H5. Among the four molecules in the unit cell, there are 12 different H4 to H1/H2/H3 distances, ranging from 3.202 Å to 6.270 Å and having an average of 4.581 Å and a standard deviation of 1.038 Å. The 12 H5 to H1/H2/H3 distances range from 3.857 Å to 6.125 Å, having an average of 5.110 Å and a standard deviation of 0.810 Å. The peak at 4 ppm, which shows stronger cross peaks to the amine protons (Fig. 5b), can be assigned to methylene proton H4.

Comparison of noise measured in regions free of resonances and artifacts indicates that the CRAMPS-CRAMPS 2D (Fig. 5b) is only 5 times noisier than CRAMPS-MAS 2D (Fig. 5a). Both spectra were acquired with 16.8 μ s dwell times in both dimensions, equal to the wPMLG5 cycle time. The maximum evolution time was 7.5 ms in the direct dimension and 6.0 ms in the indirect dimension. However, the filter cutoff frequency was $f_c = 33$ kHz for the spectrum in Fig. 5a, while $f_c = 59$ kHz for Fig. 5b. Use of narrow band analog filters has helped to reduce noise level of CRAMPS spectra by many fold. The spectra are still noisier than MAS-only spectra because rf-induced noise is present during CRAMPS data acquisition.

Under fast MAS, proton detection has been demonstrated to enhance sensitivity of heteronuclear experiments significantly, e.g., by about 4 and 14 times on protein samples at 40 kHz MAS with respect to direct detection on ^{13}C and ^{15}N , respectively [17,49–51]. However, if CRAMPS is applied, the increase of noise by about 5 times overshadows the sensitivity gain for the case of ^{13}C . Therefore, it is still better to directly detect on ^{13}C . For the case of ^{15}N , detection on proton, which is subject to CRAMPS employing narrowband filters as described in this report, is expect to provide a better signal to noise ratio.

4. Conclusions

We demonstrated the feasibility of performing windowed CRAMPS experiments without bypassing narrowband analog filters, contrary to common practice. This is achieved by exploiting the time delay of the signal caused by the filters. The filter delay is carefully controlled to match the CRAMPS cycle time, allowing acquisition of the signal in the following detection window. The analog filters suppress noise from much greater bandwidth, leading to significantly reduced noise level. We notice that direct digital receivers [52] have been adopted in the newest generation of spectrometers. For instance, the Agilent Direct Digital Receiver uses an exceptionally fast ADC (80 MHz) to digitize the NMR signal directly at the intermediate frequency (20 MHz) [53], eliminating the need of any analog filters. Nevertheless, our method allows the direct acquisition of homonuclear

decoupled high-resolution proton spectra on older spectrometers that lack wideband filters and fast ADCs.

Acknowledgments

D.H.Z. is supported by Oklahoma Center for the Advancement of Science and Technology (HR12-050) and National Institutes of Health (R15 GM097713). L.W. is supported by the National Natural Science Foundation of China (No. 21273275). The authors thank Dr. Zhehong Gan (National High Magnetic Field Laboratory, Tallahassee, FL) for helpful discussions. We thank Dr. Margaret A. Eastman (Oklahoma Statewide Shared NMR Facility) for technical assistance.

References

1. Brown SP. Applications of high-resolution ^1H solid-state NMR. *Sol St NMR*. 2012; 41:1–27.
2. Shoji A, Kimura H, Ozaki T, Sugisawa H, Deguchi K. Conformational Study of Solid Polypeptides by ^1H Combined Rotation and Multiple Pulse Spectroscopy NMR. *J Am Chem Soc*. 1996; 118:7604–7607.
3. Kimura H, Nakamura K, Eguchi A, Sugisawa H, Deguchi K, Ebisawa K, Suzuki E-i, Shoji A. Structural study of α -amino-acid crystals by ^1H CRAMPS NMR spectroscopy. *J Mol Struct*. 1998; 447:247–255.
4. Elena B, Emsley L. Powder Crystallography by Proton Solid-State NMR Spectroscopy. *J Am Chem Soc*. 2005; 127:9140–9146. [PubMed: 15969592]
5. Elena B, Pintacuda G, Mifsud N, Emsley L. Molecular Structure Determination in Powders by NMR Crystallography from Proton Spin Diffusion. *J Am Chem Soc*. 2006; 128:9555–9560. [PubMed: 16848494]
6. Pickard CJ, Salager E, Pintacuda G, Elena B, Emsley L. Resolving Structures from Powders by NMR Crystallography Using Combined Proton Spin Diffusion and Plane Wave DFT Calculations. *J Am Chem Soc*. 2007; 129:8932–8933. [PubMed: 17602560]
7. Xue X, Kanzaki M. Proton Distributions and Hydrogen Bonding in Crystalline and Glassy Hydrous Silicates and Related Inorganic Materials: Insights from High-Resolution Solid-State Nuclear Magnetic Resonance Spectroscopy. *J Am Chem Soc*. 2009; 92:2803–2830.
8. Lesage A. Recent advances in solid-state NMR spectroscopy of spin $I = 1/2$ nuclei. *Phys Chem Chem Phys*. 2009; 11:6876–6891. [PubMed: 19652822]
9. McDermott AE, Creuzet FJ, Kolbert AC, Griffin RG. High-resolution magic-angle-spinning NMR-spectra of protons in deuterated solids. *J Magn Reson*. 1992; 98:408–413.
10. Reif B, Griffin RG. ^1H detected ^1H , ^{15}N correlation spectroscopy in rotating solids. *J Magn Reson*. 2003; 160:78–83. [PubMed: 12565053]
11. Chevelkov V, van Rossum BJ, Castellani F, Rehbein K, Diehl A, Hohwy M, Steuernagel S, Engelke F, Oschkinat H, Reif B. ^1H detection in MAS solid-state NMR spectroscopy of biomacromolecules employing pulsed field gradients for residual solvent suppression. *J Am Chem Soc*. 2003; 125:7788–7789. [PubMed: 12822982]
12. Paulson EK, Morcombe CR, Gaponenko V, Dancheck B, Byrd RA, Zilm KW. High-Sensitivity Observation of Dipolar Exchange and NOEs between Exchangeable Protons in Proteins by 3D Solid-State NMR Spectroscopy. *J Am Chem Soc*. 2003; 125:14222–14223. [PubMed: 14624539]
13. Zhou DH, Shah G, Mullen C, Sandoz D, Rienstra CM. Proton-detected solid-state NMR of natural abundance peptide and protein pharmaceuticals. *Angew Chem Int Ed*. 2009; 48:1253–1256.
14. Hafner S, Spiess HW. Advanced solid-state NMR spectroscopy of strongly dipolar coupled spins under fast magic angle spinning. *Conc Magn Reson A*. 1998; 10:99–128.
15. Filip C, Hafner S, Schnell I, Demco DE, Spiess HW. Solid-state nuclear magnetic resonance spectra of dipolar- coupled multi-spin systems under fast magic angle spinning. *J Chem Phys*. 1999; 110:423–440.
16. Zhou DH, Graesser DT, Franks WT, Rienstra CM. Sensitivity and resolution in proton solid-state NMR at intermediate deuteration levels: Quantitative linewidth characterization and applications to correlation spectroscopy. *J Magn Reson*. 2006; 178:297–307. [PubMed: 16289756]

17. Zhou DH, Shah G, Cormos M, Mullen C, Sandoz D, Rienstra CM. Proton-detected solid-state NMR spectroscopy of fully protonated proteins at 40 kHz magic-angle spinning. *J Am Chem Soc.* 2007; 129:11791–11801. [PubMed: 17725352]
18. Marchetti A, Jehle S, Felletti M, Knight MJ, Wang Y, Xu ZQ, Park AY, Otting G, Lesage A, Emsley L, Dixon NE, Pintacuda G. Backbone Assignment of Fully Protonated Solid Proteins by ¹H Detection and Ultrafast Magic-Angle-Spinning NMR Spectroscopy. *Angew Chem Int Ed.* 2012; 51:10756–10759.
19. Zhou DH, Rienstra CM. Rapid analysis of organic compounds by proton-detected heteronuclear correlation NMR spectroscopy at 40 kHz magic-angle spinning. *Angew Chem Int Ed.* 2008; 47:7328–7331.
20. Lee M, Goldburg WI. Nuclear-Magnetic-Resonance Line Narrowing by a Rotating rf Field. *Phys Rev.* 1965; 140:A1261–A1271.
21. Linser R. Side-chain to backbone correlations from solid-state NMR of perdeuterated proteins through combined excitation and long-range magnetization transfers. *J Biomol NMR.* 2011; 51:221–226. [PubMed: 21822966]
22. Zhou DH, Shea JJ, Nieuwkoop AJ, Franks WT, Wylie BJ, Mullen C, Sandoz D, Rienstra CM. Solid-state protein-structure determination with proton-detected triple-resonance 3D magic-angle-spinning NMR spectroscopy. *Angew Chem Int Ed.* 2007; 46:8380–8383.
23. Linser R, Bardiaux B, Higman V, Fink U, Reif B. Structure Calculation from Unambiguous Long-Range Amide and Methyl ¹H ¹H Distance Restraints for a Microcrystalline Protein with MAS Solid-State NMR Spectroscopy. *J Am Chem Soc.* 2011; 133:5905–5912. [PubMed: 21434634]
24. Zhou DH, Nieuwkoop AJ, Berthold DA, Comellas G, Sperling LJ, Tang M, Shah GJ, Brea EJ, Lemkau LR, Rienstra CM. Solid-state NMR analysis of membrane proteins and protein aggregates by proton detected spectroscopy. *J Biomol NMR.* 2012; 54:291–305. [PubMed: 22986689]
25. Linser R. Backbone assignment of perdeuterated proteins using long-range H/C-dipolar transfers. *J Biomol NMR.* 2012; 52:151–158.
26. Akbey U, Lange S, Franks TW, Linser R, Rehbein K, Diehl A, van Rossum BJ, Reif B, Oschkinat H. Optimum levels of exchangeable protons in perdeuterated proteins for proton detection in MAS solid-state NMR spectroscopy. *J Biomol NMR.* 2010; 46:67–73. [PubMed: 19701607]
27. Linser R, Fink U, Reif B. Proton-detected scalar coupling based assignment strategies in MAS solid-state NMR spectroscopy applied to perdeuterated proteins. *J Magn Reson.* 2008; 193:89–93. [PubMed: 18462963]
28. Knight MJ, Webber AL, Pell AJ, Guerry P, Barbet-Massin E, Bertini I, Felli IC, Gonnelli L, Pierattelli R, Emsley L, Lesage A, Herrmann T, Pintacuda G. Fast Resonance Assignment and Fold Determination of Human Superoxide Dismutase by High-Resolution Proton-Detected Solid-State MAS NMR Spectroscopy. *Angew Chem Int Ed.* 2011; 50:11697–11701.
29. Gerstein BC, Pembleton RG, Wilson RC, Ryan LM. High resolution NMR in randomly oriented solids with homonuclear dipolar broadening: Combined multiple pulse NMR and magic angle spinning. *J Chem Phys.* 1977; 66:361–362.
30. Dec SF, Bronnimann CE, Wind RA, Maciel GE. Comparison of the ¹H NMR analysis of solids by the CRAMPS and MAS-only techniques. *J Magn Reson.* 1989; 82:454–466.
31. Madhu PK. High-resolution solid-state NMR spectroscopy of protons with homonuclear dipolar decoupling schemes under magic-angle spinning. *Sol St NMR.* 2009; 35:2–11.
32. Vinogradov E, Madhu PK, Vega S. High-resolution proton solid-state NMR spectroscopy by phase-modulated Lee-Goldburg experiment. *Chem Phys Lett.* 1999; 314:443–450.
33. Benedicte E, de Paepe G, Emsley L. Direct spectral optimisation of proton-proton homonuclear dipolar decoupling in solid-state NMR. *Chem Phys Lett.* 2004; 398:532.
34. Sakellariou D, Lesage A, Hodgkinson P, Emsley L. Homonuclear dipolar decoupling in solid-state NMR using continuous phase modulation. *Chem Phys Lett.* 2000; 319:253–260.
35. Leskes M, Steuernagel S, Schneider D, Madhu PK, Vega S. Homonuclear dipolar decoupling at magic-angle spinning frequencies up to 65 kHz in solid-state nuclear magnetic resonance. *Chem Phys Lett.* 2008; 466:95–99.

36. Salager E, Stein RS, Steuernagel S, Lesage A, Elena B, Emsley L. Enhanced sensitivity in high-resolution ^1H solid-state NMR spectroscopy with DUMBO dipolar decoupling under ultra-fast MAS. *Chem Phys Lett*. 2009; 469:336–341.
37. Amoureux JP, Hu B, Trebosc J. Enhanced resolution in proton solid-state NMR with very-fast MAS experiments. *J Magn Reson*. 2008; 193:305–307. [PubMed: 18502160]
38. Bielecki A, Kolbert AC, Levitt MH. Frequency-switched pulse sequences: Homonuclear decoupling and dilute spin NMR in solids. *Chem Phys Lett*. 1989; 155:341–346.
39. Vinogradov E, Madhu PK, Vega S. Proton spectroscopy in solid state nuclear magnetic resonance with windowed phase modulated Lee-Goldburg decoupling sequences. *Chem Phys Lett*. 2002; 354:193–202.
40. Lesage A, Sakellariou D, Hediger S, Elena B, Charmont P, Steuernagel S, Emsley L. Experimental aspects of proton NMR spectroscopy in solids using phase-modulated homonuclear dipolar decoupling. *J Magn Reson*. 2003; 163:105–113. [PubMed: 12852913]
41. Hoult DI, Chen CN, Eden H, Eden M. Elimination of baseline artifacts in spectra and their integrals. *J Magn Reson*. 1983; 51:110–117.
42. Vinogradov E, Madhu PK, Vega S. A bimodal Floquet analysis of phase modulated Lee-Goldburg high resolution proton magic angle spinning NMR experiments. *Chem Phys Lett*. 2000; 329:207–214.
43. Madhu PK, Vinogradov E, Vega S. Multiple-pulse and magic-angle spinning aided double-quantum proton solid-state NMR spectroscopy. *Chem Phys Lett*. 2004; 394:423–428.
44. Leskes M, Madhu PK, Vega S. A broad-banded z-rotation windowed phase-modulated Lee-Goldburg pulse sequence for ^1H spectroscopy in solid-state NMR. *Chemical Physics Letters*. 2007; 447:370–374.
45. Coelho C, Rocha J, Madhu PK, Mafra L. Practical aspects of Lee-Goldburg based CRAMPS techniques for high-resolution ^1H NMR spectroscopy in solids: Implementation and applications. *J Magn Reson*. 2008; 194:264–282. [PubMed: 18703365]
46. Lafon O, Wang Q, Hu B, Trébosc J, Deng F, Amoureux JP. Proton-proton homonuclear dipolar decoupling in solid-state NMR using rotor-synchronized z-rotation pulse sequences. *J Chem Phys*. 2009; 130:014504. [PubMed: 19140619]
47. Gan Z, Madhu PK, Amoureux JP, Trébosc J, Lafon O. A tunable homonuclear dipolar decoupling scheme for high-resolution proton NMR of solids from slow to fast magic-angle spinning. *Chem Phys Lett*. 2011; 503:167–170.
48. Power LF, Turner KE, Moore FH. The crystal and molecular structure of alpha-glycine by neutron diffraction - a comparison. *Acta Cryst*. 1976; B32:11–16.
49. Ishii Y, Yesinowski JP, Tycko R. Sensitivity enhancement in solid-state ^{13}C NMR of synthetic polymers and biopolymers by ^1H NMR detection with high-speed magic angle spinning. *J Am Chem Soc*. 2001; 123:2921–2922. [PubMed: 11456995]
50. Ishii Y, Tycko R. Sensitivity Enhancement in Solid State ^{15}N NMR by Indirect Detection with High-Speed Magic Angle Spinning. *J Magn Reson*. 2000; 142:199–204. [PubMed: 10617453]
51. Wiench JW, Bronnimann CE, Lin VSY, Pruski M. Chemical Shift Correlation NMR Spectroscopy with Indirect Detection in Fast Rotating Solids: Studies of Organically Functionalized Mesoporous Silicas. *J Am Chem Soc*. 2007; 129:12076–12077. [PubMed: 17877353]
52. Perez P, Santos A. Undersampling to acquire nuclear magnetic resonance images. *Med Eng Phys*. 2004; 26:523–529. [PubMed: 15234688]
53. Direct Digital Receiver. Agilent User Manual: VnmrJ3 Spectroscopy. 2011. p. 382–384.

Highlights

Noise reduction for CRAMPS by utilizing narrowband filters.

Exploiting analog filter delay to sample data in the next detection window.

Enabling CRAMPS proton experiments on spectrometers without wideline hardware.

Figure 1.

Measurement of impulse responses for receiver analog filters. (a) The pulse sequence began with a T_2 filter, followed by data acquisition. In the experiments, echo delay $\tau = 2$ ms, dwell time $\tau_{dw} = 2$ μs , receiver protection delay $\tau_{rd} \sim 1.2$ μs (a hardware delay occurred after triggering the T/R switch and before activation of the receiver in order to protect the receiver from pulse ring down), time to sample a pair of quadrature data $\tau_{acq} = 0.2$ μs . The time origin ($t=0$) used for response curves is indicated in the figure. (b) Impulse response curves for receiver analog filters with filter bandwidth set to 59 kHz. Filter delay t_{fd} was measured at 50% amplitude on the rising edge of the response to a long impulse (38.8 μs). Positions of response peaks (t_p) for short impulses are half impulse width from t_{fd} .

Figure 2. wPMLG5 [39] pulse sequence using postponed sampling and narrowband filters. Only the first two wPMLG5 units were shown in the figure. Two-step phase cycle (0° , 180°) was applied for the initial 90° pulse and the receiver.

Figure 3. Sampling delay optimization. In the wPMLG5 experiments for glycine, $\tau_w = 4.8 \mu\text{s}$, $\tau_p = 1.2 \mu\text{s}$, $\tau_{rd} = 1.2 \mu\text{s}$, $\tau_{ad} = 0.6 \mu\text{s}$, $\tau_{acq} = 0.2 \mu\text{s}$, $f_c = 59 \text{ kHz}$, and 40 kHz MAS. Spectra acquired with sampling delay ranging from 0.2 to 3.8 μs were displayed. listed in Table 1.

Figure 4. MAS (a) and wPMLG5 (b)–(e) spectra of glycine. Experimental parameters are listed in Table 1.

Figure 5.

2D ^1H - ^1H single-quantum correlation spectra at 40 kHz MAS. (a) wPMLG5 decoupling was applied only in the indirect dimension, with no homonuclear mixing. (b) wPMLG5 was applied in both dimensions, with homonuclear mixing achieved by 1 ms of spin diffusion. Slices taken along the dotted lines are displayed outside the 2D spectra.

Table 1

Parameters for spectra in Fig. 4.

	τ_w (μs)	τ_p (μs)	f_c (kHz)	τ_R (kHz)	τ_I (kHz)	τ_1 (ppm)	τ_2 (ppm)	f	I (%)
<i>a</i>	-	-	31	40	-	1.8	-	-	100
<i>b</i>	4.8	1.2	59	40	145	0.58	0.47	0.557	51
<i>c</i>	7.6	0.95	59	40	165	0.71	0.63	0.638	88
<i>d</i>	8.1	0.9	58	40	180	0.72	0.65	0.644	94
<i>e</i>	4.8	1.2	59	18	109	0.71	0.62	0.591	45

* Labels in the first column correspond to sub-figure numbers in Fig. 4. For the CRAMPS spectra (b–e), τ_1 and τ_2 are the scaled up linewidths of the amine and methylene peaks, respectively. Detection window (τ_w), wPMLG5 pulse width (τ_p), MAS rate (τ_R), rf strength (τ_I), chemical shift scaling factor (f), and the intensity of the amine peak (I) are listed in other columns.