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Proton detection of MAS solid-state NMR spectra of half-integer quadrupolar nuclei

Amrit Venkatesh[a,b], Michael P. Hanrahan[a,b], Aaron J. Rossini[a,b,*]

[a] Iowa State University, Department of Chemistry, Ames, IA 50011, USA
[b] US DOE Ames Laboratory, Ames, IA 50011, USA

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ABSTRACT

Fast magic angle spinning (MAS) and proton detection has found widespread application to enhance the sensitivity of solid-state NMR experiments with spin-1/2 nuclei such as ^{13}C, ^{15}N and ^{29}Si, however, this approach is not yet routinely applied to half-integer quadrupolar nuclei. Here we have investigated the feasibility of using fast MAS and proton detection to enhance the sensitivity of solid-state NMR experiments with half-integer quadrupolar nuclei. The previously described dipolar hetero-nuclear multiple quantum correlation (D-HMQC) and dipolar refocused insensitive nuclei enhanced by polarization transfer (D-RINEPT) pulse sequences were used for proton detection of half-integer quadrupolar nuclei. Quantitative comparisons of signal-to-noise ratios and the sensitivity of proton detected D-HMQC and D-RINEPT and direct detection spin echo and quadrupolar Carr-Purcell Meiboom-Gill (QCPMG) solid-state NMR spectra, demonstrate that one dimensional proton detected experiments can provide sensitivity similar to or exceeding that obtainable with direct detection QCPMG experiments. 2D D-HMQC and D-RINEPT experiments provide less sensitivity than QCPMG experiments but proton detected 2D hetero-nuclear correlation solid-state NMR spectra of half-integer nuclei can still be acquired in about the same time as a 1D spin echo spectrum. Notably, the rarely used D-RINEPT pulse sequence is found to provide similar, or better sensitivity than D-HMQC in some cases. Proton detected D-RINEPT benefits from the short longitudinal relaxation times (T_1) normally associated with half-integer quadrupolar nuclei, it can be combined with existing signal enhancement methods for quadrupolar nuclei, and t_1-noise in the indirect dimension can easily be removed by pre-saturation of the ^{1}H nuclei. The rapid acquisition of proton detected 2D HETCOR solid-state NMR spectra of a range of half-integer quadrupolar nuclei such as ^{17}O, ^{27}Al, ^{35}Cl and ^{71}Ga is demonstrated.

1. Introduction

Solid-state nuclear magnetic resonance (NMR) spectroscopy is an extremely powerful probe of structure and dynamics for both crystalline and disordered/amorphous solid materials [1–7]. NMR spectroscopy is hindered by intrinsically poor sensitivity due to a very small polarization of the nuclear spin states at ambient temperature. Low sensitivity often prevents the application of solid-state NMR spectroscopy to many materials and biological systems, even when isotopic labeling is used. This has spurred the development of different methods/techniques capable of increasing the sensitivity of solid-state NMR. These include cooling the sample to cryogenic temperatures [8–10], using dynamic nuclear polarization (DNP) [11] to transfer the high polarization of unpaired electrons to spin active nuclei at cryogenic temperatures [10,12–14], transferring polarization from hyper-polarized noble gases such as ^{129}Xe [15–17], and combining fast magic angle spinning (MAS) with proton detection [18–24]. Of these various techniques, fast MAS and proton detection are the most straightforward and routine to implement into solid-state NMR.

While it has long been known that proton detection provides a large gain in sensitivity in solution NMR [25], the development and widespread use of ^{1}H detection in solid-state NMR is much more recent. ^{1}H solid-state NMR spectra are usually substantially broadened by homonuclear dipolar couplings. Efficient indirect detection is only possible if ^{1}H NMR signals can be narrowed and this requires MAS frequencies above ca. 30 kHz in rigid protonated solids. In their seminal work, Ishii and Tycko demonstrated that appreciable net gains in sensitivity could be obtained with fast MAS and ^{1}H detection [18]. They demonstrated that with (what are now considered) moderate MAS frequencies of ca. 30 kHz, ^{1}H NMR peak widths were narrowed enough to provide sensitivity gains by proton detection (ξ) of 1.5 to 3.3 for ^{13}C and ^{15}N solid-state NMR experiments [18]. The subsequent development of

* Corresponding author at: Iowa State University, Department of Chemistry, Ames, IA 50011, USA.
E-mail address: arossini@iastate.edu (A.J. Rossini).

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smaller diameter MAS modules capable of MAS at frequencies above 60 kHz has subsequently enabled further reductions in ^{1}H NMR linewidths and provided further gains in the efficiency of proton detection in solid-state NMR. Proton detected solid-state NMR experiments are now widely applied to bio-molecular systems [21,22,24,26–30], inorganic materials [23,31,32], and organic solids such as polymers and pharmaceuticals [19,33,34]. Recently, probes capable of 100 kHz MAS frequencies have enabled acquisition of multi-dimensional NMR spectra from microgram quantities of proteins [35,36], organic solids [37–39], and inorganic materials [40]. Proton detection is now a widespread and critical tool used to obtain multi-dimensional correlation solid-state NMR spectra of commonly encountered spin-½ nuclei such as ^{13}C, ^{15}N and ^{29}Si.

However, proton detection is less commonly applied for the indirect detection of half-integer quadrupolar nuclei (spin $I > ½$, e.g., ^{23}Na, ^{27}Al, ^{35}Cl, ^{51}V, etc.) and exotic spin-½ nuclei (e.g., ^{77}Se, ^{109}Ag, ^{113}Cd, ^{195}Pt, ^{207}Pb, etc.). This is because proton detection in solid-state NMR is normally accomplished with a double cross-polarization (CP) experiment involving a forward CP step for excitation, then a second back CP step for detection (e.g., ^{1}H→^{13}C(excite), ^{13}C→^{1}H(detect)) [18]. In the case of heavier spin-½ nuclei, indirect detection with CP pulse sequences will likely be hindered by the poor excitation bandwidths of CP pulse sequences and the frequency offsets due to a large isotropic shift range or chemical shift anisotropy (CSA). On the other hand, for half-integer quadrupolar nuclei it is well known that CP experiments are often challenging to setup and/or unproductive due to inefficient spin-locking of central transition (CT) magnetization under MAS [41,42].

Multi-dimensional dipolar HETCOR solid-state NMR spectra of integer spin or half-integer spin quadrupolar nuclei are usually acquired with multiple pulse methods such as TEDOR [46,47], PRESTO [48–50], or dipolar hetero-nuclear multiple quantum coherence (D-HMQC, Fig. 1A) [44,51–53]. The use of HMQC pulse sequences for the indirect detection of ^{14}N (I=1) solid-state NMR spectra was independently demonstrated by Gan and Bodenhausen [54,55]. Application of dipolar recoupling (to the spin-1/2 nucleus) during the coherence build-up/re-conversion periods results in a D-HMQC pulse sequence which allows dipolar (through space) correlations to be observed [44,51–53]. Proton detected D-HMQC (Fig. 1A) is now commonly applied to obtain 2D solid-state NMR spectra of the ^{14}N nucleus [38,52,56–58]. We have recently demonstrated that it is also possible to use a constant time D-HMQC pulse sequence, fast MAS and proton detection to rapidly acquire wideline MAS solid-state NMR spectra of spin-1/2 and half-integer quadrupolar nuclei [59]. Very recently Perras et al. have combined magic angle turning (MAT) with constant time D-HMQC to enable the indirect detection of isotropic HETCOR solid-state NMR spectra of spin-1/2 nuclei with large chemical shift anisotropy (CSA) [60].

Proton detection of half-integer spin quadrupolar nuclei with ^{1}H {X} D-HMQC experiments has only been reported in a few instances [39,59,61–63]. This is likely because proton detected D-HMQC spectra are often hindered by "t_1-noise" in the indirect dimension which occurs due to incomplete cancellation of background ^{1}H NMR signals from uncoupled proton spins [39,53,59,61,64]; this limits the gains in sensitivity that should be realized with proton detection. Subsequently, directly detected X {^{1}H} D-HMQC experiments are sometimes performed because they may give a higher quality 2D correlation spectrum [65,66], despite their lower theoretical sensitivity. Note that direct detection D-HMQC experiments with quadrupolar nuclei can still provide good sensitivity since the large nuclear spins (I) of quadrupolar nuclei enhance sensitivity (see SI for discussion of this point). The longitudinal (T_1) and transverse (T_2') relaxation times of quadrupolar nuclei are also often favorable. However, many quadrupolar nuclei give rise to broad CT powder patterns, necessitating the use of fast MAS to eliminate overlap of isotropic and sideband peaks. In such cases, efficient proton detection could possibly provide a large gain in sensitivity since the proton linewidth will often be much smaller than the linewidth of the quadrupolar nucleus.

The main goal of this study is to explore the possibility of obtaining improved sensitivity by proton detection for solid-state NMR spectroscopy of half-integer quadrupolar nuclei. To the best of our knowledge, there are no systematic comparisons of the sensitivity of direct detection and indirect detection for half-integer quadrupolar nuclei. Therefore, we have compared the sensitivity of proton detected D-HMQC and dipolar refocused INEPT experiments [44] (D-RINEPT, Fig. 1B) to direct detection spin echo (Fig. 1C) and QCPMG experiments (Fig. 1D). We find that proton detection can provide a substantial gain in sensitivity. Proton detection enables acquisition of 2D dipolar HETCOR spectra in experiment times similar to those required for acquisition of a 1D spin echo spectrum. Consistent with previous work [39,53,59,61,64], we observe that the signal-to-noise ratio (SNR) in the indirect dimension of proton detected 2D D-HMQC NMR spectra may be reduced due to the presence of t_1-noise. To address this, we show that the D-RINEPT pulse sequence [44,67] is a viable alternative to D-HMQC for proton detection. Direct excitation D-RINEPT experiments have the advantage that t_1-noise in the indirect dimension can be easily eliminated by ^{1}H pre-saturation and that the recycle delay is governed by T_1 of the quadrupolar nucleus. In the samples examined here, we also find that both constant time D-HMQC and D-RINEPT provide high quality second order MAS central transition (CT) powder patterns. D-RINEPT is shown to be broadly applicable for the rapid acquisition of proton detected 2D HETCOR solid-state NMR spectra from a variety of half-integer quadrupolar nuclei.

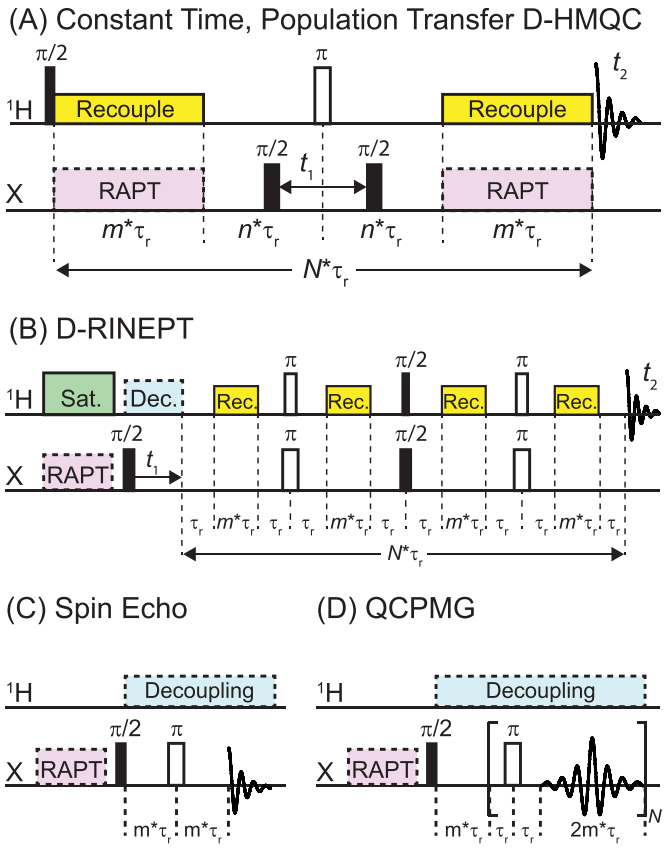

Fig. 1. Pulse sequences used for acquisition of solid-state NMR spectra of half-integer nuclei. (A) Constant time, population transfer ^{1}H{X} D-HMQC, (B) X→^{1}H D-RINEPT, (C) spin echo and (D) QCPMG. Rotor timings are indicated by vertical dashed lines. The symmetry based recoupling sequence supercycled $(S)R4_1^2$ [43], was applied to the ^{1}H nuclei in D-HMQC and D-RINEPT experiments [44,45].