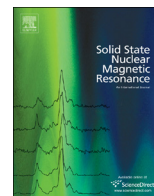




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journal homepage: www.elsevier.com/locate/ssnmrIndirectly detected heteronuclear correlation solid-state NMR spectroscopy of naturally abundant ^{15}N nucleiStacey M. Althaus^{a,b}, Kanmi Mao^{a,b}, John A. Stringer^c,
Takeshi Kobayashi^b, Marek Pruski^{a,b,*}^a U.S. DOE Ames Laboratory, Ames, IA 50011-3020, USA^b Department of Chemistry, Iowa State University, Ames, IA 50011-3020, USA^c Agilent Technologies, 900 South Taft, Loveland, CO 80537, USA

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ABSTRACT

Two-dimensional indirectly detected through-space and through-bond $^1\text{H}\{^{15}\text{N}\}$ solid-state NMR experiments utilizing fast magic angle spinning (MAS) and homonuclear multipulse ^1H decoupling are evaluated. Remarkable efficiency of polarization transfer can be achieved at a MAS rate of 40 kHz by both cross-polarization and INEPT, which makes these methods applicable for routine characterizations of natural abundance solids. The first measurement of 2D $^1\text{H}\{^{15}\text{N}\}$ HETCOR spectrum of natural abundance surface species is also reported.

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1. Introduction

Nitrogen is an important element for spectroscopists due to its ubiquitous presence in organic, catalytic, and biological compounds. Two NMR active isotopes of nitrogen, ^{14}N and ^{15}N , have potential for spectroscopic investigation; however, both have shortcomings and neither has become apparent as the predominant in solid-state (SS) NMR. Detection of ^{14}N , despite a high natural abundance of 99.6%, is challenging due to the integer spin ($I=1$) and the resulting first order quadrupolar broadening (often in excess of 1 MHz), which is detrimental to both sensitivity and resolution. The quadrupolar parameters and chemical shift data can be determined from the analysis of static ^{14}N powder patterns or state-of-the-art magic angle spinning (MAS) spectra obtained under carefully controlled rotor orientation (to $\sim 0.001^\circ$) and ultrastable spinning rate (to ~ 0.1 Hz) [1,2]. The acquisition of high quality wide-line ^{14}N spectra can be further assisted by the use of pulse sequences featuring broadband excitation, multiecho refocusing (using quadrupolar Carr–Purcell–Meiboom–Gill protocol, referred to as QCPMG [3]) and piecewise acquisition schemes [4,5]. Although such spectra can uniquely provide both

electric field gradient and chemical shift tensor parameters, simulations become difficult for complex materials containing multiple nitrogen environments. Recently, two-dimensional (2D) heteronuclear (HETCOR) sequences have been developed wherein detection of the ^{14}N signal occurs indirectly via neighboring spin 1/2 nuclei (^{13}C [6,7] and ^1H [8–11]). These sequences have used precise magic angle setting and rotor synchronization during evolution time (t_1) to average the first order quadrupolar broadening to zero. ^1H detected ^{14}N 2D spectra can be collected with high sensitivity [8,9] despite the low efficiency of polarization transfer. The resulting ^{14}N resonance frequencies depend upon isotropic chemical shifts, quadrupolar induced shifts, and anisotropic contributions due to scaled-down second-order quadrupolar interaction. Isotropic chemical shifts can be determined by separating both contributions, which becomes challenging for unknown compounds.

Notwithstanding the low natural abundance (0.4%), ^{15}N NMR has the advantage of providing direct access to chemical shift information without interference from quadrupolar effects. For the last three decades, 2D ^1H – ^{15}N HETCOR NMR spectra in solution have been measured using the so-called indirect detection via the high- γ ^1H nuclei, primarily using heteronuclear single quantum coherence (HSQC) and heteronuclear multiple quantum coherence (HMQC) schemes, to overcome the sensitivity issues without isotope enrichment [12–14]. In solids however, such approaches were until recently impractical because of the inherently broad ^1H

* Corresponding author at: Ames Laboratory, Iowa State University, 230 Spedding Hall, Ames, IA 50011-3020, USA. Fax: +1 515 294 4709.

E-mail address: mpruski@iastate.edu (M. Pruski).

linewidth. Indeed, the first natural abundance ^1H - ^{15}N solid-state spectra of medium-sized organic molecules (tripeptides) used a ^{15}N -detected MAS-J-HMQC scheme with frequency switched Lee Goldburg (FSLG) ^1H homonuclear decoupling [15]. The indirectly detected measurements were initially implemented by perdeuteration of peptides and proteins to enhance the resolution in the ^1H dimension under moderate MAS rates ($\nu_R \leq 30$ kHz) and used dipolar (through-space) cross-polarization (CP) during mixing. This led to sensitivity gain by a factor of 5 to 7 in the 2D and 3D $^1\text{H}\{^{15}\text{N}\}$ spectra of ^{15}N -enriched samples [16–19]. In similar experiments, coherent transfers of dipolar polarization have been implemented at $\nu_R = 30$ kHz utilizing the sequences of rotor-synchronized π pulses [20,21]. The REDOR-type recoupled polarization transfer (REPT) method has been used in the ^1H - ^{15}N - ^1H experiments on ^{15}N -enriched isocytosine derivatives [20]. Remarkably, a related experiment with TEDOR-type magnetization transfer yielded 2D HETCOR spectra, as well as N–H bond length information, in natural abundance L-histidine [21].

The availability of ultrafast MAS, currently with frequencies of up to 110 kHz [22–25], and the resulting boost in ^1H resolution, facilitated further development of multidimensional correlation schemes. Studies have demonstrated that the small rotor volume (< 10 μL) is largely offset by excellent sensitivity per spin and have highlighted other advantages of very fast MAS, including the flexibility in using RF power (e.g., high power for excitation and low power for heteronuclear decoupling) [26,27], reduced transverse T_2^* relaxation [28,29], increased spectral width in rotor-synchronized experiments, and efficient cross-polarization [30–32]. Indeed, 2D HETCOR spectra of naturally abundant biomolecular solids were obtained using the HSQC-type ^1H - ^{15}N - ^1H experiments based on double-transfer CP–CP scheme, where MAS alone provided adequate resolution in ^1H dimension [33]. It has been further demonstrated that through-bond transfers originally developed for solutions can be exploited in these experiments to probe partially mobile surface-bound molecules in mesoporous organic–inorganic hybrid materials [29], where the $\text{X} \rightarrow ^1\text{H}$ step (in this case $\text{X} = ^{13}\text{C}$) utilized refocused INEPT (INEPTR). Fast MAS played a critical role during INEPTR by reducing the magnetization losses due to T_2^* relaxation. This method was extended to fully rigid solids [34] by using ^1H - ^1H homonuclear decoupling during INEPTR [35], which proved efficient under fast MAS [36].

It is somewhat surprising that despite these favorable results the measurements of correlation spectra involving natural abundance ^{15}N species have not become common practice. Herein, we demonstrate that the sensitivity enhancement achieved via indirect detection made it possible, if not routine, to measure CP-based ^{15}N - ^1H HETCOR spectra of several samples, including organically functionalized mesoporous silica. Additionally, we report the first 2D INEPT-based spectra of solids under natural ^{15}N abundance and compare the efficiencies of through-space and through-bond polarization transfers.

2. Experimental

2.1. Sample preparation

Natural abundance samples of *N*-formyl-L-methionyl-L-leucyl-L-phenylalanine-OMe (MLF) and L-histidine H₂O were purchased from Fluka (Sigma-Aldrich). The corresponding ^{15}N -enriched sample of histidine was crystallized from aqueous solution at pH 4.5, which was adjusted by mixing appropriate volumes of 1 M HCl and 1 M NaOH, as described in reference [37]. 1,3,5-Trimethoxybenzene (TMOB) was purchased from Sigma-Aldrich. The sample of 3-(3-phenylureido)propyl attached to the

surface of mesoporous silica nanoparticles (PUP-MSN) was prepared by Dr. Hung-Ting Chen as described in an earlier paper [38]. Glycine with universally labeled ^{13}C and ^{15}N was purchased from Cambridge Isotope Laboratories (CIL).

2.2. NMR measurements and numerical simulations

All experiments were performed at 14.1 T on a Varian 600-MHz NMR System spectrometer using a 1.6-mm FastMAS™ T3 triple resonance probe operated at 599.6 MHz for ^1H , 150.8 MHz for ^{13}C , and 60.8 MHz for ^{15}N . The samples were packed in MAS zirconia rotors and spun at 40 kHz. The pulse sequences employed for 2D $^1\text{H}\{^{15}\text{N}\}$ with CP and INEPTR can be viewed in Fig. 1. These sequences utilize tangentially ramped $^{15}\text{N}\{^1\text{H}\}$ CP to generate initial ^{15}N magnetization, which evolves during t_1 under low power SPINAL-64 [39] ^1H decoupling. The pulse following t_1 stores ^{15}N magnetization along the B_0 field; at the same time, the ^1H magnetization is eliminated using two long pulses with orthogonal phases and whose amplitudes satisfy the rotary resonance recoupling condition [40]. For the through-space sequence, tangential CP is then used again to transfer ^{15}N magnetization back to ^1H , and the data is acquired in t_2 under ^{15}N SPINAL-64 decoupling. In the through-bond sequence, the CP transfer is replaced with the INEPTR sequence of rotor-synchronized pulses to transfer magnetization back to ^1H nuclei. The PMLG_m homonuclear ^1H - ^1H decoupling sequence [41,42] is used during INEPTR transfer to prevent decoherence of ^{15}N and ^1H magnetizations during τ_1 and τ_2 , respectively [34,35]. The phase cycles and optimization strategies were described in more detail in our earlier reports [34,43].

The effect of heteronuclear dipolar coupling during INEPTR polarization transfer under our experimental conditions was studied using the SIMPSON simulation program [44]. The simulations were carried out for an isolated ^1H - ^{15}N spin pair mimicking the δ_1 -NH pair in histidine and for the aromatic ^1H - ^{13}C spin pair of TMOB.

The experimental parameters are shown in figure captions using the following notation: ν_R is the MAS rate, ν_{RF}^X is the magnitude of the RF magnetic field applied to X nuclei, τ_{CP} is the CP contact time, τ_{RR} is the rotary resonance recoupling time, τ_1 is the ^{15}N evolution period in INEPTR, τ_2 is the ^1H evolution period in INEPTR, Δt_1 is the increment of t_1 during 2D acquisition, τ_{RD} is the recycle delay, and AT is the total acquisition time of spectrum. The chemical shifts were referenced relative to ammonia (^{15}N) and tetramethylsilane (^1H and ^{13}C) via secondary references (glycine for ^{15}N and hexamethylbenzene for ^1H and ^{13}C). The data were acquired and processed using Vnmrj 2.2.C software.

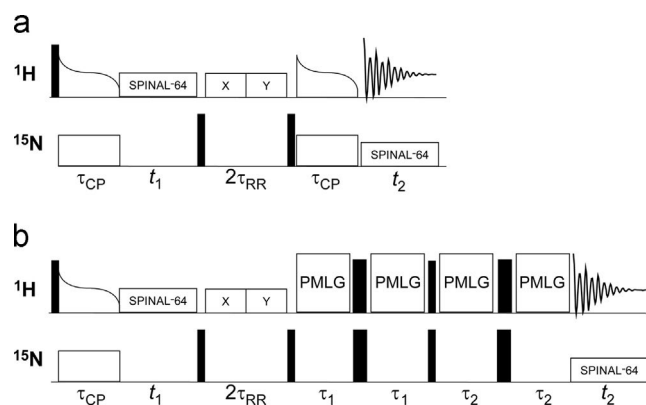


Fig. 1. Pulse sequences for ^1H -detected HETCOR: (a) through-space with $^{15}\text{N} \rightarrow ^1\text{H}$ transfer via CP and (b) through-bond with $^{15}\text{N} \rightarrow ^1\text{H}$ transfer via INEPTR. Narrow and wide black rectangles depict $\pi/2$ and π pulses, respectively. States-TPPI was implemented in these experiments through phase switching of the first $\pi/2$ pulse in the ^{15}N channel.

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