

Solid-state ^{15}N polarimetry of hyperpolarized $^{15}\text{N}_2\text{O}$ based on the modeling of NMR spectral patterns

Nicholas N. Kuzma¹, Pär Håkansson², Rajat K. Ghosh¹, Huseyin Kara^{1,3}, Mehrdad Pourfathi¹, Stephen J. Kadlecik¹, Giuseppe Pileio², Malcolm H. Levitt², and Rahim R. Rizi¹

¹Radiology, University of Pennsylvania, Philadelphia, PA, United States, ²School of Chemistry, Southampton University, Southampton, Hampshire, United Kingdom, ³Astronomy and Physics, University of Pennsylvania, Philadelphia, PA, United States

Introduction: MRI signals can be enhanced by several orders of magnitude utilizing *ex-vivo* hyperpolarization methods such as dynamic nuclear polarization (DNP). This enables *in-vivo* MR imaging of even the trace amounts of hyperpolarized molecules and their metabolism. However, hyperpolarized agents typically exhibit relatively short magnetization life-time due to fast T_1 relaxation (typically less than a minute). This severely restricts the storage and transportation of hyperpolarized molecules, and limits the physiological time scales accessible with this technique. An emerging development demonstrated long-lived polarization storage in quantum-mechanical singlet states of a scalar-coupled, homo-nuclear two-spin system, if the two nuclei exhibit different chemical shifts [1]. Doubly labeled $^{15}\text{N}_2\text{O}$, a non-toxic anesthetic gas, constitutes an example of such a system. A recent relaxation study of $^{15}\text{N}_2\text{O}$ reports singlet relaxation times of many minutes in liquid solutions [2]. At this conference we are reporting the first successful dynamic nuclear polarization (DNP) of $^{15}\text{N}_2\text{O}$ at 1.5 K and a magnetic field of 5 T [3]. Here we present our theoretical model of the solid-state ^{15}N NMR spectrum in an isotropic $^{15}\text{N}_2\text{O}$ /1-proponal/trityl-radical mixture, which makes it possible to calculate ^{15}N polarization solely from the powder-spectrum shape of the measured ^{15}N NMR peaks.

Materials and methods: Our home-built hybrid DNP/NMR system is based on an Oxford TMR7/88/15 Teslatron^{MR} superconducting magnet with an integrated ^4He -cooled variable-temperature insert monitored by an Oxford ITC-503 controller. A computer-controlled primary microwave source (Giga-tronics SNY-0410-510-01) operating at 7.78 GHz and 18.3 dBm was followed by a $\times 18$ frequency multiplier integrated with a narrow-band 140 GHz/70 mW microwave amplifier (ELVA DCOIMA-06/140/70). Our custom-made probe supported an overmoded cylindrical aluminum microwave chamber (~ 5 cm in height and diameter), which was directly coupled to an overmoded circular stainless-steel waveguide. It contained a two-turn copper NMR saddle coil wrapped around a PEEK sample holder which accommodated a vertical 5-mm sample tube. $^{15}\text{N}_2\text{O}$ NMR spectra were acquired using a home-built broadband NMR spectrometer at 21.565-MHz ^{15}N NMR frequency

using small ($1.9\text{--}10^\circ$) flip-angle pulses followed by a $7.5\text{--}8\ \mu\text{s}$ dead time delay. The free-induction decay signals (FIDs) were base-line adjusted, Fourier transformed, and subjected to a zero-order phase correction. The spectra were modeled using SpinDynamica software [4] for various trial values of ^{15}N polarization and spin parameters. The FIDs were simulated in the time domain assuming that the spin Hamiltonian parameters are time independent. The simulation assumes isotropically-distributed orientations of the $^{15}\text{N}_2\text{O}$ molecules in the solid. The $^{15}\text{N}_2\text{O}$ spectra can be described with the following spin Hamiltonian:

$$H = H_{CS} + H_{CSA} + H_{DD} \quad (1)$$

$$H_{CS} = \sum_{j=1}^2 \omega_{CS}^j \hat{I}_{jZ} \quad (2)$$

$$H_{CSA} = \sum_{j=1}^2 \omega_{CSA}^j D_{00}^{(2)}(\Omega_{PL}) \hat{I}_{jZ} \quad (3)$$

$$H_{DD} = \omega_{DD} D_{00}^{(2)}(\Omega_{PL}) \left(-\frac{1}{2\sqrt{6}} (\hat{I}_1^- \cdot \hat{I}_2^+ + \hat{I}_1^+ \cdot \hat{I}_2^-) + \sqrt{\frac{2}{3}} \hat{I}_{1Z} \cdot \hat{I}_{2Z} \right) \quad (4)$$

Here the index j represents each of the two ^{15}N atoms, Ω_{PL} is the angle between the 5 T field and the molecular axis, and the isotropic, anisotropic chemical shifts and dipole-dipole constant are ω_{CS} , ω_{CSA} and ω_{DD} respectively. The quality of a fit can be quantified using the root-mean square (rms) of the differences between the experimental spectrum and theoretical

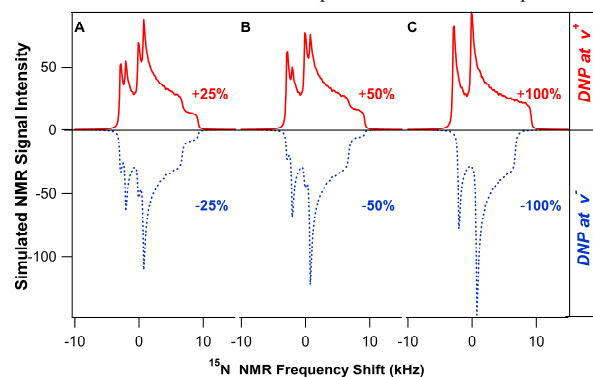


Figure 1. Theoretical line shapes calculated for a range polarizations: A: $\pm 25\%$. B: $\pm 50\%$. C: $\pm 100\%$. Note that due to the asymmetric nature of the couplings in Eqs. 3-4, the positive (solid lines) and negative (dashed lines) polarizations result in the opposite enhancement of different pairs of peaks (i.e., the solid and dashed lines are not mirror images of each other). This dependence of the spectral line shape on polarization is the basis of the polarimetry technique proposed in this work.

line shape as a cost function. Although a single line shape can be calculated in a minute, finding a global minimum of rms as a function of free fit parameters is computationally time consuming. Instead, to fit the spectrum efficiently, we utilize a surrogate cost function [5]. This involves an iterative process where a large number of simulations (the training set where the free fit parameters are evenly spread in their domain) are performed. A Gaussian process (GP) model of the rms as a function of spin Hamiltonian parameters is constructed using the training set. Subsequently the minimum of the GP model is determined and used to simulate the new parameter set and update the training set.

Results and discussion:

Simulated line shapes for a variety of polarizations are shown in Figure 1. The significant dependence of the line shape on the polarization suggests the line shape can be used to determine polarization. The six spin-Hamiltonian parameters were determined using the line shape given in Figure 2, and are given in Table 1.

ω_{CS}^1 (ppm)	ω_{CSA}^1 (ppm)	ω_{CS}^2 (ppm)	ω_{CSA}^2 (ppm)	P (%)	$1/T_2$ (s^{-1})
43.38	320.52	132.70	242.04	11 ± 4	236.5

Table 1. Free-fit parameters determined from fitting the model of Eqs. 1-4 to the spectrum of Fig. 2 (solid line).

Conclusion: The maximum ^{15}N polarization was calculated to be $(11 \pm 4)\%$. Additionally the difference in isotropic chemical shifts is 8% larger in the solid than in the dissolved state [6]. In the future work we will quantify the error bars on the other fit parameters.

References:

- G. Pileio, M. Carravetta, and M. H. Levitt, Proc. Natl. Acad. Sci. USA **107**, 17135 (2010).
- R. K. Ghosh, S. J. Kadlecik, J. H. Ardenkjaer-Larsen, B. M. Pullinger, G. Pileio, M. H. Levitt, N. N. Kuzma, and R. R. Rizi, Magn. Reson. Med. **66**, 1177 (2011).
- N. N. Kuzma *et al.* "Dynamic Nuclear Polarization of doubly-labelled $^{15}\text{N}_2\text{O}$ ", ISMRM (2012).
- SpinDynamica code for Mathematica, <http://www.SpinDynamica.soton.ac.uk/>
- A.J. Keane and P.B. Nair, "Computational Approaches for Aerospace design The pursuit of Excellence", John Wiley & Sons Inc, (2005).
- G.Pileio, M.Carravetta, E.Hughes and M.H.Levitt, J. Am. Chem. Soc. **130**, 12582 - 12583 (2008).

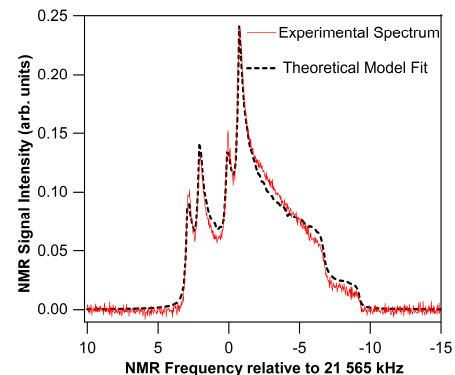


Figure 2. Experimental ^{15}N NMR spectrum recorded with a 1.9° flip angle (—). Theoretical line-shape fit after six-parameter inversion (---). Model parameters that were fitted are the four chemical shifts, the line broadening and the polarization that was determined to be $(11 \pm 4)\%$.