Hyperpolarized Singlet State of Nitrous Oxide

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Introduction: Recent advances in hyperpolarized MRI has enabled new methods to observe metabolic pathways in both normal and diseased tissues in real time. These advances include performing real time metabolic studies using hyperpolarized carbon-13 and nitrogen-15 compounds *in vitro* and *in vivo*. However the potential of hyperpolarization is hindered due to the decay of spin polarization on the time scale of T_1. Recently, progress has been made to extend the spin lifetime by storing the polarization in singlet states, which are either immune to or display a significantly decreased sensitivity to the typical relaxation processes [1]. Here, we report the first creation of a singlet state of hyperpolarized doubly ^{15}N-labeled N_2O, where spin lifetimes are extended by over an order of magnitude. The singlet state of N_2O is especially long-lasting in blood, which will allow injection and monitoring *in-vivo* [2]. Potential applications include use as a hyperpolarized blood perfusion tracer, and as an agent to determine cerebral blood flow [3].

Methods: A custom built DNP/NMR system based on an Oxford TMR7/88/15 Teslatron^{MR} superconducting magnet was used to polarize DNP samples. It was integrated with a ^{4}He cooled variable temperature insert, which was monitored by an Oxford ITC-503 controller. Samples were irradiated by microwaves at 21.56GHz. Microwaves were supplied by a Giga-tronics SNY-0410-510-01 microwave source operating at 7.78 GHz and 18.3 dBm, which was fed into a x18 frequency multiplier and a 140GHz/70mW narrow band microwave amplifier (ELVA DCOIMA-06/140/70). Microwaves were coupled to an overmoded cylindrical chamber via stainless steel waveguide. Samples were prepared utilizing a retractable hermetically sealed stirrer to mix 3mg of Trityl radical (Finland acid) dissolved in 97mg of 1-propanol in a 3:1 ratio (by volume) with liquid N_2O (Cambridge isotopes labs 98% purity). Samples were mixed at 195K in an ethanol/dry ice bath under 1.75 atm of N_2O gas pressure. The DNP samples were then transported to an 11.7 T Varian vertical bore magnet in a glass dewar containing an ethanol/dry ice bath and surrounded by a 1.1 T portable Halbach magnet.

The N_2O singlet state was populated using a two-step process. First, a 3.3 ms square π pulse centered on the terminal ^{15}N resonance was applied. The pulse length was chosen to have a node at the central ^{15}N frequency in order to leave it unaffected. Subsequent adiabatic transport of the NMR tube from the bore of the 11.7 T magnet to a region of low magnetic field adjacent to the magnet resulted in over population of the m=0 singlet state. The sample was then reintroduced into the 11.7 T magnet. A non-selective $\pi/2$ pulse was applied to both nuclei to determine the polarization, as shown in figure 1a. Singlet lifetimes were determined by allowing the sample to reach thermal polarization and by repeating the above procedure while varying the wait time in the low field region, as depicted in figure 1b. Systematic error in overestimating the amplitude of the peaks utilizing the Lorentzian fit was reduced by integrating correlations between points in the spectra separated by the well-measured J-coupling prior to fitting to a single Lorentzian lineshape.

Results and Discussion: Typical spin up times for DNP were 26.6±1.6 hours, as shown in figure 1c. Polarization of N_2O in excess of 20% was achieved, see figure 1d. Additionally surrounding the sample by a portable magnet during transportation minimized low field relaxation due to interaction of the N_2O with the paramagnetic Trityl radicals. An enhancement of ~450 over the thermal polarization in the 11.7 T magnet was observed. For comparison a brute force Boltzmann polarization from the 1.4K Oxford magnet would result in an enhancement of ~80 over thermal signal in the 11.7 T vertical bore magnet. The transfer efficiency to the singlet state is limited by the time required to insert and remove the sample during the conversion to the singlet state using adiabatic transport. A more efficient transfer system utilizing M2S pulse sequences would increase the transfer efficiency, but would require accurate determination of the scalar coupling in the liquid state of N_2O. The singlet lifetime appears to be largely unaffected by the paramagnetic trityl radical, see figure 1b. Measurements of N_2O samples dissolved in 1-propanol were similar to that exhibited by the sample containing the radical. In both cases the lifetimes were accurately predicted assuming the lifetime of the singlet state of nitrous oxide is largely dominated by relaxation due to the spin rotation interaction (SR) at low magnetic fields of approximately 1G and are ~11.1mins.

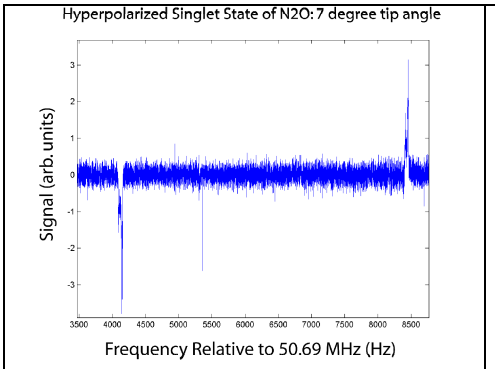

Figure 1a) Hyperpolarized Singlet state of $^{15}N_2O$ dissolved in 1-propanol in an 11.7 Tesla vertical bore magnet. Tip angle is ~7 degrees. The asymmetrical pattern is indicative of the singlet character of the spectra

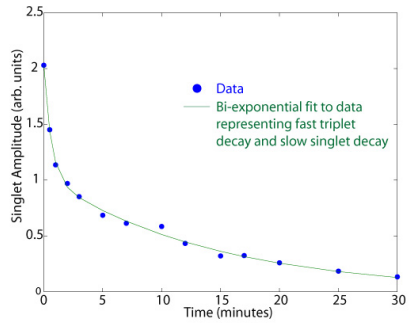

Figure 1b) Lifetime of the spin polarization is unaffected by the minute presence of Finland acid radical. The singlet lifetime is ~11.1 minutes.

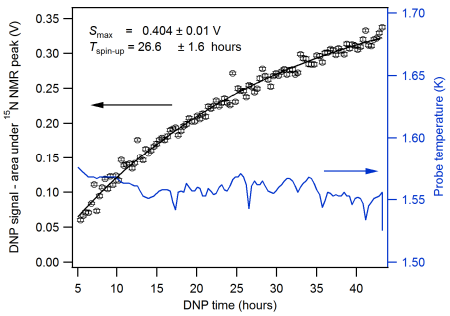

Figure 1c) Spin up time for DNP of $^{15}N_2O$ at 1.4 K and 5 Tesla for $^{15}N_2O$ sample mixed with Finland acid radical and 1-propanol.

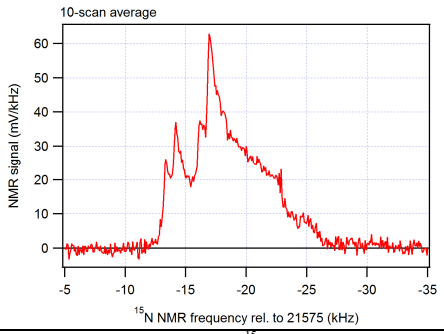

Figure 1d) DNP polarization of $^{15}N_2O$ at 1.4 K and 5 Tesla. Polarization ~10-20%

Conclusion: Hyperpolarization of N_2O to over 20% has been achieved on a custom built DNP system which can in principle be scaled for large production rates. Subsequent transport and conversion to the singlet state allows for over an order of magnitude increase in the spin polarization lifetime. Contrary to earlier concerns the lifetime of the singlet state appears to be unaffected by the small amount of trityl radical mixed in the sample. The first hyperpolarized singlet state of N_2O has been achieved. Application to measurements of blood perfusion and cerebral blood flow are being developed for imaging *in-vivo*.

References: [1] Giuseppe Pileio, Marina Carravetta, Eric Hughes and Malcolm H. Levitt, J. Am. Chem. Soc., 2008, 130 (38), pp 12582–1258
[2] R.K.Ghosh, S.J.Kadlecek, J.H.Ardenkjaer-Larsen, B.M.Pullinger, G.Pileio, M.H.Levitt, N.N.Kuzma, R.R.Rizi, Magn.Reson.Med., 2011, 66 (4), pp 1177-1180. [3] S.S.Kety and C.F. Schmidt, Journal Clin Invest., 1948 July, 27(4) pp 476-483.