Extending the utility of hyperpolarized compounds by storing polarization in the singlet state

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Introduction: Magnetic resonance has the ability to identify and track a wide array of endogenous and exogenous targets with exciting applications in pharmaceutical development and molecular medicine. Sensitivity is a limitation, but hyperpolarization techniques such as dynamic nuclear polarization (DNP) have been developed to overcome this sensitivity limitation, with much success. Unfortunately, all hyperpolarized states decay with $T_1$, severely limiting the general utility of this method. Almost all the work done has focused on $^{13}$C enriched compounds, due primarily to the longer $T_1$ provided by carbonyl carbons (40s at 14.1 T). Such $T_1$ values are sufficiently long that the labeled and polarized carbons can undergo metabolic reactions before the signal returns to thermal equilibrium and becomes undetectable. While this time scale is acceptable for detecting some metabolic reactions, it is vastly shorter than the lifetime of other metabolic imaging modalities (for example, $^{18}$F PET), providing a fundamental limitation to the general applicability of this technique.

We present a method for storing the hyperpolarized state for times longer than $T_1$, thereby massively increasing the general applicability of hyperpolarized compounds. The method uses chemical reactions in combination with tailored excitations to store the spin polarization for a time $\gg T_1$ in a symmetry protected state. The first demonstration is with labeled diacetyl, but we discuss a range of additional targets in this presentation.

Methods: Thermal experiments were done on an 8.5T vertical bore magnet interfaced to a Bruker Avance console (Bruker BioSpin, Billerica, MA). $^{13}$C-labelled diacetyl (2,3 butanedione, artificial butter flavor) was custom synthesized (Small Molecule Synthesis Facility, Duke University). The $^{13}$C-diacetyl was mixed with water and $D_2$O (Sigma-Aldrich, St. Louis, MO). The downfield peak of the doublet at 210 ppm was inverted using a selective hyperbolic secant pulse followed by a 45º pulse. The hyperpolarized demonstrations of the singlet state used the same $^{13}$C labeled diacetyl (10%) in 50 µl of water and DMSO. The OX63 radical was added to allow for polarization, and the solution was polarized using the Oxford Hypersense (Oxford, UK). The sample was dissolved in 4 ml of water with 25 mM EDTA directly into a 9.4T Oxford magnet interfaced to a JEOL console. The downfield peak of the doublet at 210 ppm was inverted using a selective hyperbolic secant pulse followed by a rapid dilution of the sample to 3:1 acetone:water to shift the equilibrium. Then, a series 45º degree pulses and acquisitions every 10 s were applied for the next 20 minutes. All the data was analyzed using Matlab (MathWorks, Inc, r2008a). The FID showing only the signal from the doublets of the hydrate was extracted by applying a gaussian filter to the spectrum and taking the inverse FT.

Results and Discussion: The dynamics of this reaction are complex and the best way to follow what is going on is to look only at the FID from hydrate peaks (Figure 1). The first FIDs have excess signal at 1/2J (dotted line) from the inversion pulse. This excess dissipates by FID 4 (from the dehydration of the diacetyl), and looks similar to the FID for thermal diacetyl. In FID 14 the excess signal is back, demonstrating a flow of populations from the singlet state into the observable triple state.

Conclusions: We have demonstrated a technique to extend the lifetime of hyperpolarized compounds beyond $T_1$ in vitro. Future work will focus on demonstrating this technique in vivo. One ultimate application of this agent is as a “reporter molecule” in a delivery system such as functionalized liposomes. We believe it can be used to extend the lifetime of many compounds with two equivalent or nearly equivalent adjacent carbons or nitrogens and low coupling to the equivalent nuclei.

References: