

Hyperpolarized  $^1\text{H}$  NMR Employing Low  $\gamma$  Nucleus as a Spin Order Storage

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The PASADENA (parahydrogen and synthesis allow dramatically enhanced nuclear alignment) [1] and DNP (Dynamic Nuclear Polarization) [2] methods efficiently hyperpolarize biologically relevant nuclei such as  $^1\text{H}$ ,  $^{31}\text{P}$ ,  $^{13}\text{C}$ ,  $^{15}\text{N}$ , etc. Recently, multiple groups have demonstrated the utility of hyperpolarized MR in medicine using hyperpolarized  $^{13}\text{C}$  biomarkers with relatively long spin lattice relaxation time  $T_1$  on the order of tens of seconds. Moreover, hyperpolarized  $^{15}\text{N}$  for biomedical MR has been proposed due to even longer spin lattice relaxations times. However, as NMR receptivity scales as  $\gamma^3$  for spin  $\frac{1}{2}$  nuclei, NMR detection of low  $\gamma$  nuclei results in lower signal-to-noise ratio. While protons are ideal nuclei for detection, short spin lattice relaxation time  $T_1$  prevents direct  $^1\text{H}$  hyperpolarized MR in biomedical applications.

Here, we demonstrate the utility of  $^{13}\text{C}$  for spin storage of hyperpolarization followed by  $^1\text{H}$  detection, which theoretically can provide up to  $\sim(\gamma_{^1\text{H}}/\gamma_{^{13}\text{C}})^2$  gain in sensitivity in hyperpolarized biomedical MR. Specifically, we hyperpolarized the  $^{13}\text{C}$  site of a well studied molecule, 2-hydroxyethyl 1- $^{13}\text{C}$ -2,3,3- $^2\text{H}$ -propionate (HEP), by PASADENA (Fig. 1) using the spin order of parahydrogen [3]. The spin order was then stored on  $^{13}\text{C}$  for 48 s while the sample was transferred from a low magnetic field polarizer operating at 1.8 mT to a 4.7 T animal MR scanner. Spin order on  $^{13}\text{C}$  decayed from 10% to 6% during the sample transfer, after which the refocused INEPT (rINEPT) pulse sequence was used to transfer polarization from  $^{13}\text{C}$  to protons within HEP (Fig. 2). The  $^{13}\text{C}$  nucleus with  $T_1 = 70$  s acts as an efficient spin order storage, while  $^1\text{H}$  nuclei nearby are ideal for detection. We find that multiple protons are successfully hyperpolarized (Fig. 2).

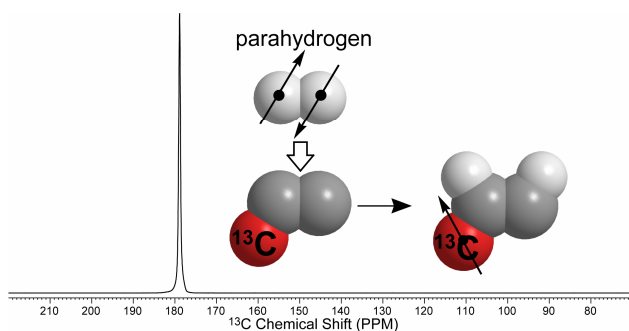
The demonstrated method could be potentially applied to other potent hyperpolarized  $^{13}\text{C}$  metabolic contrast agents *in vivo* including succinate [4, 5] and pyruvate [6]. More importantly, using this technique, hyperpolarized  $^{15}\text{N}$  MR would become a very attractive biomedical tool due to the much longer spin lattice relaxation time owing to low  $\gamma$ , but now also with advantage of more sensitive detection using proton NMR ( $\gamma_{^{15}\text{N}}^2 \approx \gamma_{^1\text{H}}^2/100$ ).

Proton detection has also a very important practical advantage in biomedicine, since clinical MR scanners are typically equipped with proton detection hardware only. Moreover, proton imaging, localized spectroscopy and chemical shift imaging (CSI) allow spatial resolution proportional to  $\gamma$  at a given gradient strength.

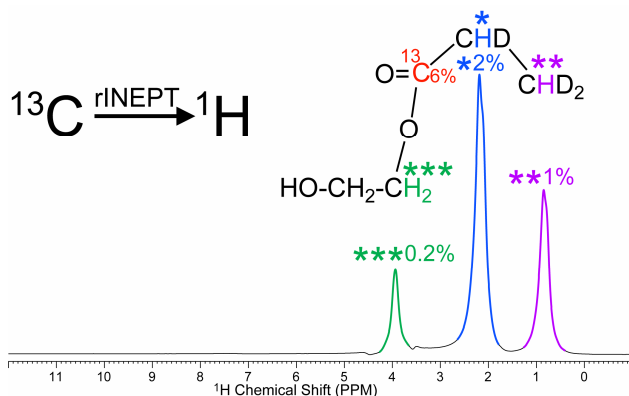
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**Figure 1.** PASADENA hydrogenation scheme of spin order transfer and *in vitro*  $^{13}\text{C}$  spectrum of 6% hyperpolarized 2-hydroxyethyl 1- $^{13}\text{C}$ -2,3,3- $^2\text{H}$ -propionate, 2.8 mL at 4.8 mM. The  $^{13}\text{C}$  spectrum is acquired using a double tuned  $^1\text{H}/^{13}\text{C}$  circuit at 4.7 T. Polarization of 10% on  $^{13}\text{C}$  was produced in a 1.8 mT polarizer and 6% was detected at 4.7 T after 48 seconds.



**Figure 2.** *In vitro*  $^1\text{H}$  spectrum of hyperpolarized 2-hydroxyethyl 1- $^{13}\text{C}$ -2,3,3- $^2\text{H}$ -propionate (HEP), 2.8 mL at 4.8 mM. The experimental polarization percentage is shown for each proton site. The spectrum is acquired using the refocused INEPT sequence. The  $^1\text{H}$  spectrum is acquired using a double tuned  $^1\text{H}/^{13}\text{C}$  circuit at 4.7 T.