Hyperpolarized 1H NMR Employing Low Gamma Nucleus as a Spin Order Storage

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Introduction The PASADENA (parahydrogen and synthesis allow dramatically enhanced nuclear alignment) method [2,3,4,5,6] and DNP (Dynamic Nuclear Polarization) [1] efficiently hyperpolarize biologically relevant nuclei such as ^{1}H, ^{31}P, ^{13}C, ^{15}N, etc. Recently, multiple groups have demonstrated the utility of hyperpolarized MR in medicine using hyperpolarized ^{13}C biomarkers with relatively long spin lattice relaxation time T_1, on the order of tens of seconds. However, as hyperpolarized NMR receptivity scales as γ^2 for spin ½ nuclei, NMR detection of low γ 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}H hyperpolarized MR in biomedical applications.

Purpose Here, we demonstrate the utility of ^{13}C for spin storage of hyperpolarization followed by ^{1}H detection shown schematically in Fig. 1, which theoretically can provide up to ~$(\gamma_{1H}/\gamma_X)^2$ gain in sensitivity in hyperpolarized biomedical MR.

Methods We utilized PASADENA to hyperpolarize 1-^{13}C-succinate-d2 at pH=10 [5] and 2,2,3,3-tetrafluoropropyl 1-^{13}C-propionate (TFPP) in D_2O. Both molecules have very long ^{13}C spin lattice relaxation times T_1 of 105 seconds and 67 seconds, respectively, measured using hyperpolarized solution and a series of small angle excitation pulses.

Results Spin order of PASADENA hyperpolarized ^{13}C was transferred to ^{1}H nuclei with 41% efficiency in succinate and 51% efficiency in TFPP utilizing refocused INEPT (rINEPT) (Fig. 2). We find that multiple protons are successfully hyperpolarized (Fig. 2). The ^{13}C nucleus acts as an efficient spin order storage, while ^{1}H nuclei nearby are ideal for detection. The demonstrated method could be potentially applied to these and other potent hyperpolarized ^{13}C metabolic contrast agents *in vivo*. More importantly, using this technique, hyperpolarized ^{15}N MR would become a very attractive biomedical tool due to the much longer spin lattice relaxation time owing to low γ, but now also with advantage of more sensitive detection using proton NMR ($\gamma^2_{15N} \approx \gamma^2_{1H}/100$). Proton detection also has 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 γ at a given gradient strength.

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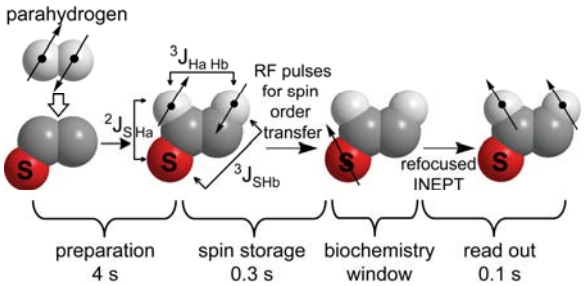

Figure 1. The experimental diagram of molecular cis addition of parahydrogen followed spin order transfer to ^{13}C, spin order storage on ^{13}C (potentially allowing monitoring of biochemical events on the time scale of minutes) followed by spin order transfer back to more sensitive protons for NMR detection.

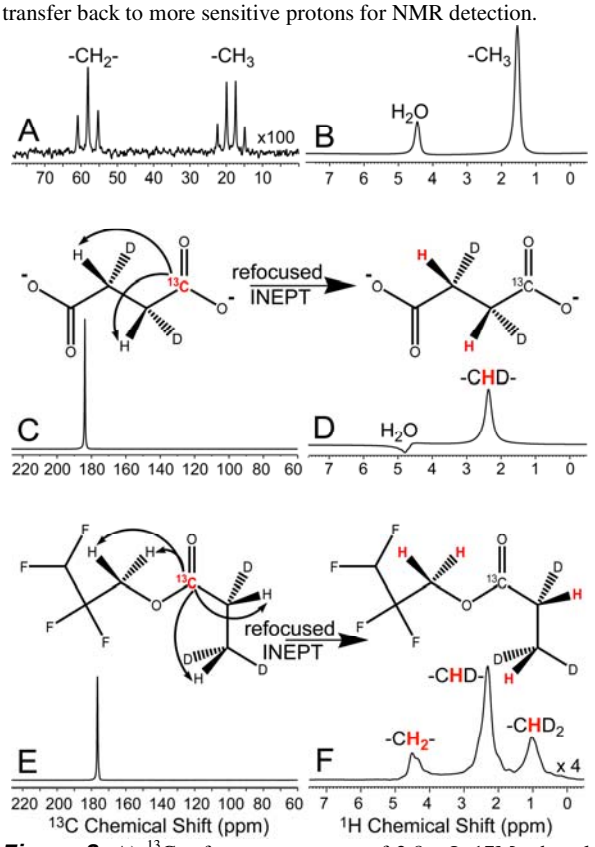

Figure 2. A) ^{13}C reference spectrum of 2.8 mL 17M ethanol, with 188 mM ^{13}C concentration per site, B) ^{1}H spectrum of 2.8 mL 3M sodium ^{13}C-acetate in D_2O, C) ^{13}C spectrum of hyperpolarized 6.2 mM 1-^{13}C-succinate-$d_{2,3}$, ^{13}C polarization of 5.5% after being stored for 70 s, spectrum acquired with 12° excitation pulse, D) ^{1}H spectrum of hyperpolarized 6.2 mM 1-^{13}C-succinate-$d_{2,3}$, ^{1}H net signal enhancement by 1,350 fold with 41% spin order transfer efficiency, E) ^{13}C spectrum of hyperpolarized 2.9 mM TFPP, ^{13}C polarization of 9.5% after being stored for 24s, spectrum acquired with 12° excitation pulse, F) ^{1}H spectrum of hyperpolarized 2.9 mM TFPP, ^{1}H net signal enhancement by 2,930 fold with 51% efficiency.