Early Experience with Simple Methods for Parahydrogen-Induced Hyperpolarization

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Introduction: Many applications of MRI are hampered by the relatively low signal-to-noise ratio obtainable on clinical scanners. These limitations derive in part from the very small nuclear magnetization that can be evoked by the main magnetic field of the scanner. A variety of hyperpolarization techniques, such as dynamic nuclear polarization [1] and parahydrogen-induced polarization [2], can be used to produce contrast media [3,4] whose nuclear polarization is several orders of magnitude larger than that available in conventional clinical scanners. These hyperpolarized agents can be imaged with very high sensitivity. Furthermore, by polarizing nuclei such as ^{13}C and ^{15}N, it is possible to obtain media with *in vivo* T_1 relaxation times on the order of a minute [3,4] and virtually no endogenous background signal. Here we describe some initial experience with parahydrogen-induced polarization. We have developed a relatively simple scheme for obtaining polarized samples, which in turn provides a means of assessing the chemistry and spin physics of various compounds that are candidates for PHIP-based contrast agents. Our methods are based in part on work described in [5,6,7]. We illustrate the experiments using natural abundance ^{13}C spectra of ethyl propiolate [7].

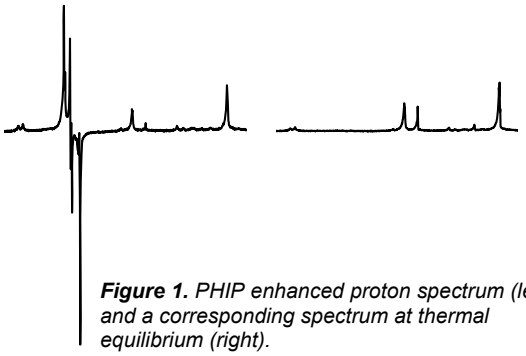
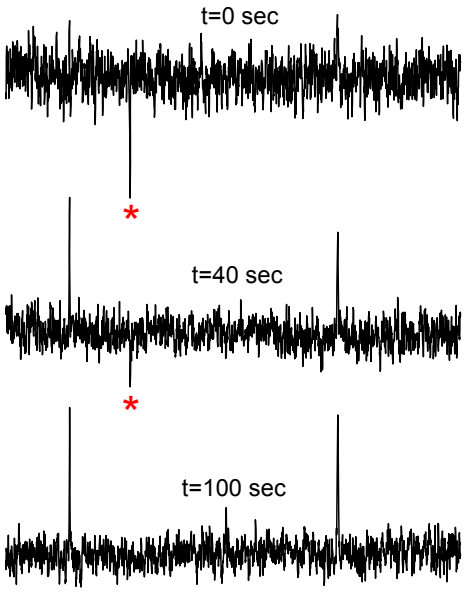


Figure 1. *PHIP enhanced proton spectrum (left) and a corresponding spectrum at thermal equilibrium (right).*

Methods: Parahydrogen-induced polarization is obtained by hydrogenating a substrate compound using hydrogen gas containing an enhanced fraction of the spin-singlet (or 'para') nuclear spin isomer [2]. We obtained hydrogen by electrolysis of water. The resulting gas was dried over silica gel and introduced into a copper tube that was immersed in liquid nitrogen and was filled with an iron-oxide based ortho-para catalyst (hydrated Iron(III) oxide, Sigma-Aldrich, St. Louis, MO) that accelerates the thermal equilibration of the ortho- and para- spin isomers. After an equilibration period of an hour or more, small quantities of cold hydrogen gas were transferred to 5 mm NMR tubes with septum caps. Additional hydrogen was driven into the tube using a syringe, resulting in a pressure of approximately 3 bars. The PHIP substrate compound, ethyl propiolate, was mixed with 0.5 mL of deuterated acetone to a concentration of approximately 250 mM, and 2 mg of the hydrogenation catalyst [Rh(DPPB)(COD)] (Sigma-Aldrich) was dissolved in the resulting solution. The solution was injected through the septum cap of the NMR tube, and the tube was manually shaken for approximately 3 seconds to thoroughly mix the solution with the hydrogen gas. Proton spectra of the sample were obtained by immediately transferring it to a 400 MHz NMR spectrometer (Unity INOVA, Varian, Palo Alto, CA) using a standard air elevator. Alternatively, polarization was transferred to natural abundance ^{13}C by abruptly placing the sample in a very weak (< 50 nT) magnetic field, bringing it back into the fringe field of the magnet over a period of several seconds, and finally placing the sample into the spectrometer [5]. By placing the sample in a weak magnetic field, the parahydrogen protons and ^{13}C nuclei can be brought into strong coupling, resulting in large ^{13}C polarization. The magnetic field cycling was achieved by placing the sample inside a magnetic shield consisting of three concentric cylinders of mu-metal (MuShield, Manchester, NH) containing a solenoid that can be abruptly turned off using a mechanical switch.

Figure 2. *Natural abundance ^{13}C spectra obtained from single readouts 0, 40 and 100 seconds after inserting the sample into the spectrometer. The inverted pre-polarized line is indicated with an asterisk.*



Results and Discussion: A representative parahydrogen-enhanced proton spectrum of the sample is shown in Figure 1. On the left is a spectrum obtained approximately 6 seconds after the sample was hydrogenated. On the right is a spectrum obtained several minutes later, after the initial magnetization decayed away. In Figure 2 we display a series of proton-decoupled ^{13}C spectra obtained after field cycling. The spectra were obtained using a flip angle of approximately 30 degrees. The pre-polarized spectral line is clearly visible in a single scan, in spite of the small (approximately 1%) natural abundance of ^{13}C. In addition, one can observe the buildup of the acetone solvent's natural magnetization over time following placement in the magnet, implying that the initially visible line is indeed the result of interactions with the parahydrogen nuclei, rather than equilibrium magnetization. Note that in equilibrium the line is practically invisible, indicating a significant initial polarization, albeit at low concentration.

Conclusions: Although these results clearly are not optimized for maximal polarization, they nonetheless illustrate that many aspects of PHIP can be investigated using a comparatively simple and inexpensive apparatus. This opens up the possibility of conducting a broad range of experiments to assess the feasibility of various combinations of PHIP substrate compounds, solvents, and hydrogenation catalysts. Experiments on a variety of such combinations are currently underway.

References: [1] See, e.g., Slichter CP, *Principles of Magnetic Resonance* (Springer-Verlag, Berlin, 1990). [2] Bowers RB and Weitekamp DP, Phys Rev Lett 57;1986:2645. [3] Johansson E *et al.,* Magn Reson Med 52;2004:1043. Golman K *et al.,* Magn Reson Med 46;2001:1. [4] Johansson E *et al.,* Magn Reson Med 51;2004:464. Svensson J *et al.,* Magn Reson Med 60;2003:256. [5] Johannesson H *et al.*, C. R. Physique 5;2004:315. [6] Stephan M *et al.*, Magn Reson Chem 40;2002:157. [7] Jonischkeit T and Woelk K*, Adv Synth Catal* 346;2004:960.