Observation of anomalously long-lived hyperpolarized C13 states in parahydrogen-induced polarization

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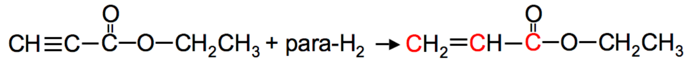
Introduction: Hyperpolarized contrast media based on nuclei such as ^{13}C yield significant enhancements of signal-to-noise ratio in MRI (1). These agents are beginning to show promise for a variety of applications, including real-time metabolic imaging (2) and cancer imaging (3). One challenge to the widespread application of these agents is the relatively short spin-lattice (T_1) relaxation time of the hyperpolarized nucleus. Even with the use of low-gamma nuclei that are isolated from protons, spin-lattice relaxation generally limits the useful lifetime of these agents to a few minutes. Recent observations (4,5) have shown that certain quantum-mechanical spin states can have lifetimes significantly longer than T_1 when they are stored at low field, or at high field under continuous radiofrequency irradiation. Using techniques such as parahydrogen-induced polarization (PHIP) (6), it may be possible to prepare hyperpolarized versions of these states, thereby obtaining long-lived hyperpolarized contrast media. However, it is unlikely that long-lived states of short-T_1 nuclei such as protons will be longer-lived than simple polarized states of long-T_1 nuclei such as ^{13}C. To date, measurements of candidate long-lived states involving ^{13}C have not demonstrated substantial lifetime enhancements (5). Here we present a set of observations in PHIP-polarized ethyl acrylate containing natural abundance ^{13}C that demonstrate the existence of an anomalously long-lived heteronuclear spin state involving both protons and ^{13}C. The long lifetime occurs only when the sample is stored in a very low field of a few milligauss. Remarkably, the long-lived state involves a ^{13}C nucleus that is directly bound to a proton and would therefore be expected to have rapid relaxation resulting from strong dipolar interactions. By contrast, the carbonyl ^{13}C nucleus, which possesses the longest T_1 at high field, exhibits a very short relaxation time at low field.

Methods: Enriched parahydrogen gas was prepared by cooling hydrogen gas to liquid nitrogen temperature in the presence of an Iron(III) oxide catalyst. Samples consisting of deuterated acetone, 600 millimolar ethyl propiolate, and approximately 2 mg of a rhodium-based hydrogenation catalyst ([1,4-Bis(diphenylphosphino)butane](1,5-cyclooctadiene)rhodium(I) tetrafluoroborate) were placed into 5 mm NMR tubes with septum caps. All reagents were obtained from Sigma-Aldrich, St. Louis, MO. The samples were polarized by introducing parahydrogen at a pressure of roughly 3 bars followed by vigorous shaking of the tubes. The hydrogenation scheme is illustrated in Figure 1. Following hydrogenation, the samples were transferred to a shielded solenoid situated inside a three-layer mu-metal shield (Mushield, Manchester, NH). Initially, the solenoid produced a magnetic field comparable to the earth's field. After introduction of the sample, the solenoid was abruptly turned off, reducing the field to roughly 5 mG and bringing the polarized protons into strong coupling with nearby natural-abundance ^{13}C nuclei (7). After a waiting period of 30 to 180 seconds at low field, the field was adiabatically increased, and the samples were transported to a 400 MHz NMR spectrometer (Unity INOVA, Varian, Palo Alto, CA). ^{13}C spectra were obtained immediately following transport. Six minutes later, an equilibrium proton spectrum was acquired to measure the yield of the hydrogenation reaction. The ^{13}C signal strengths of the carbonyl (C=O), CH, and CH_2 carbon nuclei indicated in red in Figure 1 were normalized to the reaction yield and plotted as a function of the waiting time at low field. The conventional high-field T_1 relaxation times of these nuclei were measured using a saturation-recovery method at 400 MHz.



$$CH{\equiv}C{-}\overset{O}{\overset{\|}{C}}{-}O{-}CH_2CH_3 + \text{para-}H_2 \rightarrow CH_2{=}CH{-}\overset{O}{\overset{\|}{C}}{-}O{-}CH_2CH_3$$

Figure 1: Hydrogenation of ethyl propiolate to form ethyl acrylate.

Results: ^{13}C spectra obtained after 30, 60, and 90 seconds at 5 mG are shown in Figure 2. The carbonyl and CH_2 carbons exhibit very short relaxation times, while the CH carbon possesses a substantially longer relaxation time. Figure 3 displays an exponential fit to the low-field relaxation time of the CH carbon, which results in an estimate of 60±10 seconds. Saturation recovery measurements of the T_1 relaxation times of the carbonyl, CH, and CH_2 carbons yielded 70±20, 16±1, and 8±1 seconds, respectively.

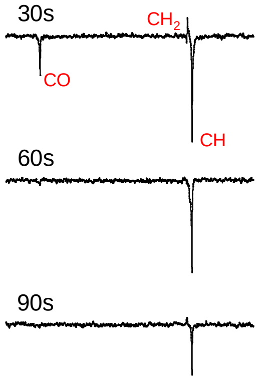


Figure 2: ^{13}C spectra obtained after 30, 60 and 90 seconds at low field (top to bottom).

Discussion: The data presented here show that heteronuclear samples prepared using PHIP and subsequently stored in low (few mG) magnetic fields can exhibit anomalous and somewhat counterintuitive relaxation times. The CH carbon, which has a shorter T_1 relaxation time than the carbonyl at high field, possesses a much longer relaxation time than the carbonyl at low field. Although the low-field lifetime of the CH carbon is slightly shorter than the high-field carbonyl T_1, the anomalous lifetime of this state gives an indication that long-lived, hyperpolarized heteronuclear spin states may be achievable using PHIP. We can gain some understanding of these results by considering the intramolecular dipolar relaxation rates of these states. We first note that, owing to the small (~1%) isotopic abundance of ^{13}C, the samples of ethyl acrylate employed here generally contain at most one ^{13}C nucleus. Referring to Figure 1, we see that acrylate molecules containing a ^{13}C nucleus in one of the red sites will contain a strongly coupled system of three protons and a ^{13}C nucleus. These spins couple very weakly to the spins to the right of the carbonyl. When such molecules are placed in a weak magnetic field, the protons and ^{13}C become strongly coupled, as evidenced by the fact that carbon nuclei at all three sites show enhanced polarization in the spectra of Figure 2. In Ref. (8), it was shown that quantum mechanical selection rules for intramolecular dipolar relaxation can impose a 'botteleneck' on low-field relaxation processes, which slows the relaxation of the spins and gives rise to a long-lived state. We have applied this model to four-spin systems containing a ^{13}C nucleus in each of the three red sites of Figure 1, and found that the model does indeed indicate a longer low-field relaxation time for the CH carbon than for the carbonyl.

These results provide an indication that it may indeed be possible to prepare long-lived hyperpolarized states in heteronuclear spin systems. We are currently investigating a variety of systems to see if further lifetime prolongations may be achieved by these methods.

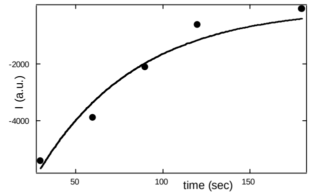


Figure 3: Fit to CH lifetime.

References: 1. See, e.g. Golman *et al*, MRM 2001 45:1. 2. Kohler *et al*, MRM 2007 58:65. 3. Golman *et al,* Cancer Res 2006 66:10855. 4. Carravetta *et al*, Phys Rev Lett 2004 92:153003. 5. Jonischkeit *et al*, J Chem Phys 2006 124:201109. 6. Bowers and Weitekamp, Phys Rev Lett 1986 24:2645. 7. Johannesson *et al,* Comptes Rend. Phys. 2004 17:2359. 8. Vinogradov *et al*, J Mag Res 2007 188:176.