Anatomy of Long-Lived Hyperpolarized States in Parahydrogen-Induced Polarization

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Introduction

Liquid-phase hyperpolarized contrast media promise to open up a range of new applications for MRI. These agents are expected to yield dramatic improvements in perfusion imaging and angiography, and may provide new tools for molecular and metabolic imaging. A key challenge to the widespread application of these agents is the comparatively short spin-lattice relaxation time of the available agents. Even with the use of long T_1 nuclei such as ^{13}C, typical *in vivo* relaxation times are on the order of a minute, implying a useful lifetime on the order of 3 to 5 minutes. Recently it has been noted that under special circumstances (such as in a weak magnetic field) spin-singlet states of two-spin systems can have dramatically enhanced lifetimes, up to an order of magnitude longer than the relaxation times of the constituent nuclei [1-3]. This method has been extended to coherent states of four-spin systems with similar results [4]. The long lifetimes of these states at low field are a consequence of the symmetry of the singlet state that makes it immune to the dominant relaxation mechanism: intramolecular dipole-dipole interactions. If this phenomenon can be extended to generic spin systems, it may provide a mechanism for dramatically extending the useful lifetime of hyperpolarized contrast media. Because parahydrogen is a nuclear spin-singlet state of diatomic hydrogen gas, it is natural to speculate that hyperpolarized states generated in parahydrogen-induced polarization (PHIP) [5] may have similar extended lifetimes. Indeed, in [6] it has been shown that hyperpolarized media prepared by PHIP have lifetimes approximately 3 times longer when they are stored in low field rather than at high field. This is a puzzling phenomenon because the compounds studied in [6] contain several strongly coupled spins and therefore cannot preserve the initial singlet symmetry of the parahydrogen nuclei. Consequently the symmetry arguments invoked to account for the long lifetime of two-spin singlet states are not applicable to these larger systems. Nonetheless, the observation of extended lifetimes in [6] is potentially very significant, and a detailed understanding of the dynamics of these long-lived states is needed in order to fully exploit their benefits.

Here we present a study of a long-lived hyperpolarized state in a simple system where just a single proton is strongly coupled to the parahydrogen protons. Using features of the NMR spectrum at high field, we deduce the form of the longest-lived component of the low-field density matrix and show that it has a surprisingly simple interpretation in terms of the system's low-field energy eigenstates.

Materials and Methods

A solution of ethyl propiolate was hydrogenated with parahydrogen to form hyperpolarized ethyl acrylate as shown in Fig. 1. Details of the parahydrogen source and hydrogenation method have been given elsewhere [7]. The polarized material was stored in a weak magnetic field of approximately 5 Gauss for varying periods of time and subsequently transferred to a 400 MHz Varian spectrometer. The FID following a 45 degree RF pulse was acquired; 45 degree pulses were used to ensure the observability of both linear ($\sim I_z$) and bilinear ($\sim I_{1,z}I_{2,z}$) terms in the density matrix. Computer simulations were used to test various forms of the low-field late-time density matrix against the data.

Results

Spectra of hyperpolarized ethyl acrylate after storage at low field for increasing periods of time are shown in Figure 2. Immediately after the hydrogenation the spectrum has a classic ALTADENA form. The data show that only three protons are involved in the PHIP dynamics; hence we may treat the system as having just three spins. To understand the low-field dynamics that give rise to these spectra, it is convenient to work in terms of the zero field energy eigenstates, which are labeled by energy E, total nuclear spin j and magnetic quantum number m_j, and are denoted by $|E,j,m_j\rangle$. These states are eigenstates of the scalar-coupling Hamiltonian. Three spin systems have states with j=1/2 and 3/2. Because parahydrogen has zero nuclear spin, immediately after hydrogenation only the j=1/2 states (and coherences) are occupied. The corresponding simulated spectrum, which agrees with the data in Fig. 2a, is shown in Fig. 3a. After storage for 3 minutes at low field, the spectrum approaches the highly symmetric form seen in Figure 2b (the data in Fig.2b has been scaled up for clarity). The data are consistent with a high-field density matrix of the form $\rho_{HIGH} = I_z^1 I_z^2 + I_z^1 I_z^3 + I_z^2 I_z^3$. We can determine the longest-lived component of the low-field density matrix by finding a matrix that, when adiabatically transported from low field to high field, yields high field density matrix ρ_{HIGH}.

Performing this calculation*, we find that the low-field density matrix is very simple*: it has equal populations in $|m_j|=1/2$ states, and *zero* population in $|m_j|=3/2$ states. The simulated spectrum resulting from this density matrix is shown in Fig. 3b; it is in very good agreement with the data of Fig. 2b. The lifetime of this non-thermal state is very long: it is readily observable for more than 180 seconds, while the T_1 of the constituent protons is about 17 seconds! The data appear to imply a low-field 'selection rule' that somehow forbids thermal equilibration of states with j=3/2 and $|m_j|=3/2$. While is tempting to postulate a simpler selection rule that forbids mixing of states with different total spin j, such a rule is not supported by the data. We are currently conducting theoretical work in an effort to account for this result, as well as studying time dependence in more complex spin systems. Preliminary data on other compounds suggest that the late-time behavior of the PHIP signal varies qualitatively from one spin system to the next.

Conclusions

We have presented an analysis of a long-lived hyperpolarized state in a simple organic compound. Such states may play an important role in *in vivo* applications of hyperpolarization. This is particularly true if these techniques can be extended to include both protons (as presented here) and long T_1 nuclei such as ^{13}C or ^{15}N. Moreover, these data suggest that it may be desirable to inject hyperpolarized agents at low field, wait for a period of time, and subsequently transfer the patient to high field for imaging.

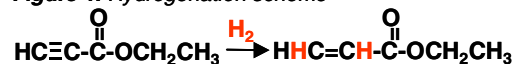**Figure 1.** Hydrogenation scheme

Figure 2. Experimental PHIP spectra acquired (a)immediately and (b) 3 min after hydrogenation
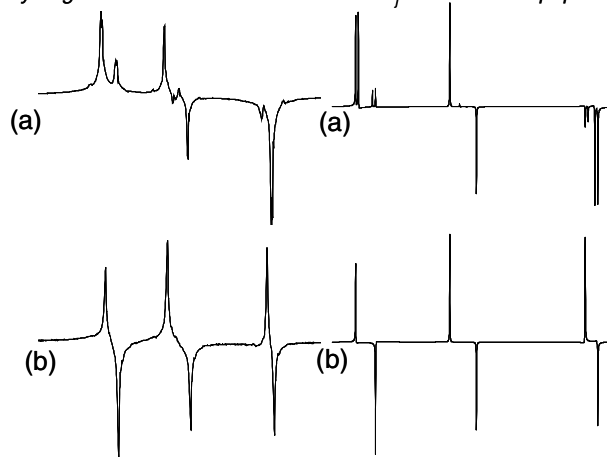

(a)

(b)

Figure 3. Simulated PHIP spectra using density matrix (a)$I_1 \cdot I_2$ and (b) diagonal matrix with $|m_j|=3/2$ states unpopulated

(a)

(b)

References: 1.M.Carravetta, *et.al.*,*JACS***126**,6228(2004); **2.**M.Carravetta, *et.al.*, *PhysRevLett***92**,153003(2004); **3.**M.H.Levitt, *JACS***122**, 214505(2005); **4.**G.Pileio, *et.al., JMR***182**, 353(2006); **5.**C.R.Bowers, *et.al., PhysRevLett***24**, 2645(1986); **6.**T.Jonischkeit, *et.al., JCP***124**, 201109(2006); **7.** A.Grant, *et.al* in *Proc.ISMRM* 14, 2552(2006).