Conservation of Hyperpolarized Long-Lived States in Low Field: Theory and Experiment

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Introduction

Recent work has shown that singlet-states in two-spin and multi-spin systems can possess lifetimes exceeding the T1 relaxation time, provided that the system is kept under conditions that minimize the effects of the chemical shift Hamiltonian(1-3). These conditions can be achieved in low field or under application of suitable radiofrequency irradiation. Such states are expected to have a variety of applications in NMR and biomedical imaging. In particular, long-lived spin states may dramatically enhance the usefulness of hyperpolarized contrast media. These media, which can be imaged with a sensitivity many orders of magnitude greater than is possible using conventional techniques, are currently being investigated as tools for angiography, perfusion imaging, and metabolic studies aimed at cancer diagnosis (4,5). However, because the spin-lattice relaxation times of existing hyperpolarized agents are comparatively short (on the order of tens of seconds to a minute), they can only be applied to the study of rapid processes that take place over timescales on the order of minutes. By combining long-lived states with hyperpolarization, it may be possible to dramatically extend the range of applications for hyperpolarized magnetic resonance imaging (6). Although the dynamics underlying the long lifetimes of these states are well understood in the case of two-spin systems, the corresponding dynamics in systems containing more spins is still under investigation. Recently a quantum-mechanical selection rule governing intramolecular dipolar relaxation in low field was derived that may account for the observed lifetime enhancements (7). Here we present results of a theory of long-lived states in systems containing three or four spins, and discuss examples of states that are immune or partially immune to intramolecular dipolar relaxation and that are therefore expected to be long lived. We show experimental observations of a long-lived state prepared by PHIP and compare the late-time NMR spectrum of this state with theoretical predictions.

Materials and Methods

A solution of ethyl propiolate was hydrogenated with parahydrogen to form hyperpolarized ethyl acrylate. Details of the parahydrogen source and hydrogenation method have been given elsewhere (8). The polarized material was stored in a weak magnetic field of approximately 5 Gauss for varying periods of time and subsequently *adiabatically* transferred to a 400 MHz Varian spectrometer. The FID following a 45 degree RF pulse was acquired. Computer simulations were used to test various forms of the low-field late-time density matrix against the data.

Results

Under low field conditions 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, which is the major interaction at low field, where the chemical shift differences are smaller than scalar couplings. Three spin systems have total of 8 states: two doublets with j=1/2 and one quadruplet with 3/2 (Figure 1). Because parahydrogen has zero nuclear spin, immediately after hydrogenation only the j=1/2 states are occupied.

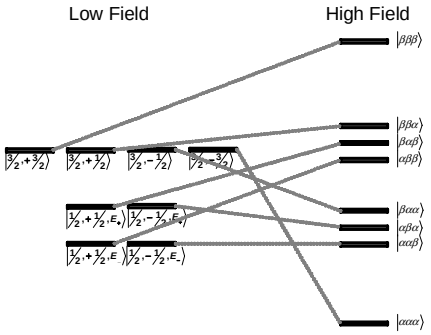

Figure1. *Schematic energy level diagram of three-spin system in low and high magnetic fields. The dotted lines indicate adiabatic transformation of the energy levels from low to high field.*

Recently we have derived a quantum mechanical selection rule governing dipolar interactions in low field that forbids mixing between states with j=1/2 (7). As a result, some relaxation pathways that would be available to the system at high field may become forbidden at low field. In such cases equilibrium can only be achieved via higher order relaxation pathways. If, in addition, one or more of the allowed transitions along these pathways is slow, it can lead to the creation of "bottlenecks" where some of the states decay significantly more slowly than the others, and hence are long-lived. The degree of enhancement will vary depending upon the geometry and scalar couplings of the system. Small spin systems, i.e. three and four spins, can be parameterized in terms of their geometry and a single scalar function of the *j*-couplings, and can be analyzed analytically. In the three-spin case, states with zero dipolar decay are only found in systems where the spins are collinear. In the four-spin case, more general geometries possess such states. Once a long-lived state has been identified, one can predict the NMR spectrum of this state as a function of flip angle.

To verify the theoretical preidictions, spectra of hyperpolarized ethyl acrylate were acquired after storage at low field for increasing periods of time (Figures 2 and 3). After about 60 seconds in low field the spectrum approaches a highly symmetric non-equilibrium form that can be still observed after 600 seconds. This spectrum corresponds to the high field density matrix of the form $I_z^1 I_z^3 - I_z^1 I_z^2 + I_z^2 I_z^3$. Computer simulations were used to identify which low field density matrix component leads to this high field form after the adiabatic transport. This low-field state has populations in one of j=1/2 doublet states only, and *zero* population in other states. The lifetime of this non-thermal state is very long: about 70s, while the T_1 of the constituent protons is about 10 seconds (Figure 3). A detailed theoretical analysis of relaxation dynamics in ethyl acrylate at low field shows that this j=1/2 state is indeed is long-lived.

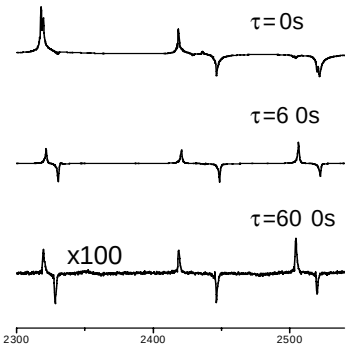

Figure 2. *Hyperpolarized spectra as a function of the evolution period at the low field.*

Conclusions

We have illustrated the preparation of a long-lived hyperpolarized state by means of parahydrogen-induced polarization. By storing the compound at low field following hydrogenation, the lifetime of the hyperpolarized signal can be extended by nearly an order of magnitude relative to the high-field T_1 relaxation time. These data qualitatively support the picture of long-lived states in multi-spin systems that was derived in Ref. (7). The selection rule for intramolecular dipolar relaxation in combination with 'bottlenecks' in the relaxation process may give rise to long-lived states.

The analysis presented here may help to develop a protocol for the extension of hyperpolarized signal lifetimes for *in-vitro* and *in-vivo* studies. The spectral lineshapes depend on the molecular structure and the experimental details of the PHIP experiment. Hence, in the future, imaging sequences for these agents can be tailored for better utilization of hyperpolarized signals.

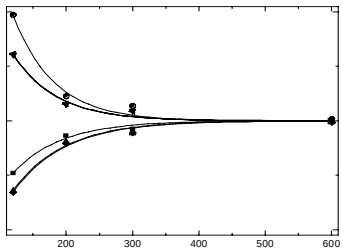

Figure 3. The decay of the anti-phase signals as a function of the evolution period at low field

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