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Long-lived spin states as a source of contrast in magnetic resonance spectroscopy and imaging

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ABSTRACT

A method is proposed to create Long-Lived spin States (LLSs) from longitudinal spin magnetization, which is based on adiabatic switching of a Radio-Frequency (RF) field with proper frequency. The technique is simple to implement with standard Nuclear Magnetic Resonance (NMR) equipment, providing an excellent conversion of population from the triplet T_+ (or T_-) state to the singlet state of a pair of spins and back. The method has been tested for the amino acid tyrosine and its partially deuterated isotopomer; for the deuterated compound, we have achieved a LLS lifetime, which exceeds the longitudinal relaxation time by a factor of 21. Furthermore, by slightly modifying the method, an enhanced contrast with respect to LLSs in NMR spectra is achieved; contrast enhancements of more than 1200 are feasible. This enables efficient suppression of longitudinal spin magnetization in NMR allowing one to look selectively at LLSs. Using this method we have demonstrated that not only spectral but also spatial contrast can be achieved: we have obtained spatial NMR images with strongly improved contrast originating from the difference of LLS lifetimes at different positions in the sample.

1. Introduction

Long-Lived spin States (LLSs) is an important new concept in Nuclear Magnetic Resonance (NMR) [1,2]. An LLS has been first discovered [3] about 10 years ago in a system of two scalar coupled spins, which was placed at low magnetic field. In such a situation, the singlet state of the two spins is an eigen-state of the time-independent Hamiltonian of the system, $\widehat{H}_0$; when dipolar relaxation is the dominant source of relaxation this state does not relax, i.e., it becomes long-lived. This is because the dipole–dipole interaction of two spins is symmetric with respect to exchange of the two spins; consequently, it does not induce symmetry-breaking singlet–triplet transitions. In the first work on LLSs the reported ratio of the LLS relaxation time and the T_1-relaxation time, T_{LLS}/T_1, was about 6 [3] for the 2,3-dibromothiophene molecule. Later T_{LLS}/T_1 ratios of about 45 were found in other systems [4,5]; also extremely long T_{LLS} times have been reported for molecules such as $^{15}N_2O$ (T_{LLS} of the two ^{15}N spins was 26 min at ambient conditions) [6]. Very recently, a special molecule has been designed [7], which has an LLS of two ^{13}C nuclei with a lifetime of more than one hour at room temperature.

LLSs have already found several promising applications, such as storing non-thermal spin polarization (spin hyperpolarization) for NMR signal enhancement [8–13], probing molecular geometry [14], studying slow diffusion [15–17], slow molecular motions [18] as well as motions and interactions in biomolecules [19], investigating protein folding and unfolding [20] and weak ligand–protein interactions [21]. There are several ways of forming LLSs, sustaining them and observing them. LLSs can be prepared from longitudinal spin magnetization using special pulse sequences [1,16,22] or in the course of a hyperpolarization process [4,5,23–26]; for sustaining LLSs one can bring the sample to low magnetic field [3], introduce a strong resonant RF-field, a spin-locking field [27], or deal with systems, in which an LLS is nearly an eigen-state at high magnetic field [11,24,28]. Except for systems of nearly equivalent spins, observation of LLSs, i.e., conversion of the singlet state population into observable magnetization, requires a symmetry switching step [1], which is usually performed by switching the external magnetic field or the spin-locking field or, in some cases, by using chemical reactions, which change the symmetry of the spin system [29].

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In this work, we propose a new technique of creating LLSs from the initial longitudinal spin magnetization of a thermally polarized spin system, which is based on a recently proposed method [30] for manipulating spin hyperpolarization. In this method a spin system is polarized in the presence of a spin-locking RF-field, which is subsequently turned off in an adiabatic fashion. It has been demonstrated theoretically and experimentally that the technique enables complete conversion of population of the singlet spin state (in the presence of the RF-field) and one of the Zeeman states (in the absence of the RF-field) of the spin system; moreover, by varying the RF-frequency one can select the desired Zeeman state and over-populate it (or under-populate it). Since adiabatic transitions are reversible, they can be utilized also to over-populate or under-populate the singlet state starting with net spin magnetization, then turning on an RF-field in an adiabatic fashion. Here we show that this idea can be used to create an LLS and to convert it back to observable magnetization. Specifically, with this method it is possible to create an LLS for the β-CH_2 protons of the amino acid tyrosine, fully protonated or partially deuterated; the LLS lifetimes achieved are up to 21 times longer than the longitudinal relaxation times. We also develop the method further by elaborating a special procedure for editing the NMR spectrum, i.e., getting rid of other (not long-lived) signals and obtaining the spectrum of only those spins, which have an LLS. We also show that such spectral editing opens a way to new exciting NMR experiments: here we demonstrate the feasibility of Magnetic Resonance Imaging (MRI) with T_{LLS} used as a source of contrast. Other possible applications of our method are also discussed.

2. Methods

2.1. Compounds and samples

As samples we used two solutions. 1. Solution of 50 mM L-tyrosine (Tyr) in D_2O. 2. Solution of 50 mM (α,2,3,5,6)-L-tyrosine-d_5 in D_2O (Tyr-d_5). Both solutions also contained about 5 mM of ethylenediamine tetra-acetic acid (EDTA), have pH* 12.9, and were bubbled by argon for 10 min to remove dissolved oxygen. At pH above all the pK_a's of tyrosine, the molecules exist in the dianionic form shown in Chart 1.

Deuterated (α,2,3,5,6)-L-tyrosine-d_5 at pH 12.9 contains only two hydrogen atoms in the β-CH_2 positions, which constitute a two-spin system; it was synthesized in the same way, as previously [5]. L-Tyrosine (99%) was purchased from SigmaAldrich, deuterated water D_2O (99.9% D) was purchased from Astrachem (Russia). The pH was adjusted by addition of NaOD (Sigma–Aldrich). pH* is the reading value of a pH-meter calibrated in protonated water. For the MRI experiments we constructed a simple phantom with two phases separated by a Teflon plug (cf. Section 3.3). The first phase contained 200 μl of Tyr solution; the second phase contained 200 μl of Tyr-d_5 solution. Between the two liquid phases in a 5 mm NMR sample tube we put a plug made out of Teflon and paraffin wax, of about 3 mm in height. During the experiments, there was no mass transport between the two separated phases.

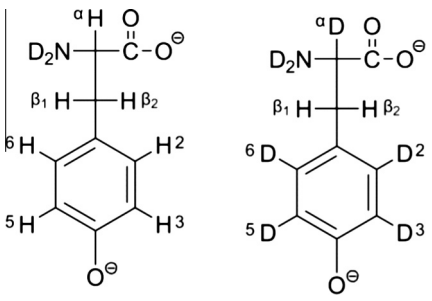

Chart 1. Structure of L-tyrosine (left) and (α,2,3,5,6,)-L-tyrosine-d_5 (right) in strong basic solution of D_2O.

2.2. Spin order conversion by adiabatic switching of the spin-locking field

In the method proposed here we exploit correlation of populations of the adiabatic spin states in the rotating frame. The behavior of spin systems at a high static B_0 field in the presence of a time-dependent RF-field is described by the following Hamiltonian written in the frame rotating with the RF-field (in units of h):

$$\widehat{H}_{rf} = -\sum_{i=1}^{N}\delta\nu_i\widehat{I}_{iz} + \sum_{i\neq j}^{N}J_{ij}(\widehat{\mathbf{I}}_i\cdot\widehat{\mathbf{I}}_j) - \nu_1(t)\sum_{i=1}^{N}\widehat{I}_{ix} \quad (1)$$

Here $\delta\nu_i = (\nu_i - \nu_{rf})$ is the Zeeman interaction of the i-th spin in the rotating frame (with ν_i being its Zeeman interaction with the B_0 field in the lab frame and ν_{rf} being the RF-frequency); $\nu_1(t)$ is the time-dependent RF-field strength; J_{ij} is the constant of scalar spin–spin interaction between the i-th and the j-th spins; $\widehat{I}_{i\alpha}$ is the α-th component of the spin operator of the i-th spin. In the general case, calculating the evolution of the spin density matrix under the action of such a time-dependent Hamiltonian is a complex task; however, it can be drastically simplified in the case of adiabatic variation of $\nu_1(t)$, which means that the eigen-states of the spin system change so slowly that their populations adjust themselves to these changes, i.e., the populations follow the states. In such a situation one can calculate in a simple way the populations of spin states after switching on a strong RF-field (or after switching it off). In the case of two coupled spins, hereafter a and b, one of the eigen-states at strong ν_1 is the singlet state; in the case of negative J_{ab} coupling (which is the case for the β-CH_2 protons in many amino acids) this is the second highest state in energy. The condition of 'strong RF-field' means [30] that the difference $\left(\sqrt{\delta\nu_a^2+\nu_1^2} - \sqrt{\delta\nu_b^2+\nu_1^2}\right)$ is much smaller than J_{ab}. Thus, the singlet state population is the same as that of the second highest energetic state at $\nu_1 = 0$. An important feature of the state correlation in the *rotating frame* is that this state can be different depending on the frequency of the rotating frame. For instance, when $\nu_a > \nu_{rf} > \nu_b$ (for clarity, we always assume that $\nu_a > \nu_b$) this can be either the $\alpha\alpha$-state or the $\beta\beta$-state depending on ν_{rf}; see Ref. [30] for detailed explanation and Fig. 1. As usual, the α-state and β-state are the spin-up and spin-down Zeeman states, respectively. An over-populated $\alpha\alpha$-state or $\beta\beta$-state corresponds to positive or negative net magnetization of the spin system, respectively; thus, our method enables conversion between net magnetization and singlet state population. Hereafter, we use the notation $|\alpha\alpha\rangle = |T_+\rangle$ and $|\beta\beta\rangle = |T_-\rangle$. The specific Zeeman spin state, T_+ or T_-, which exchanges population with the singlet state is chosen by setting an appropriate value of ν_{rf}. Specifically, when $|\nu_a - \nu_{rf}| < |\nu_b - \nu_{rf}|$ conversion is occurring between the S and T_+ states; for $|\nu_a - \nu_{rf}| > |\nu_b - \nu_{rf}|$ we achieve $S \leftrightarrow T_-$ conversion (when in both cases we have $\nu_a > \nu_{rf} > \nu_b$). Hereafter, we will use the following notation for the periods of switching the RF-field on and off. The RF-on periods will be denoted as $T_+ \to S$ or $T_- \to S$ (depending on the ν_{rf} frequency) adiabatic 'pulses'; the RF-off periods will be denoted as $S \to T_+$ or $S \to T_-$ 'pulses'. In this notation we omit the correlation of all other spin states, since they do not involve the long-lived singlet state, see Fig. 1. Further details on the optimization of frequency ν_{rf} are given in Section 3.2.

In this context it is also important to discuss the efficiency of magnetization-to-singlet conversion. In a thermally polarized two-spin system the initial Zeeman state populations are: