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Long-Lived ^1H Singlet Spin States Originating from Para-Hydrogen in Cs-Symmetric Molecules Stored for Minutes in High Magnetic Fields

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S Supporting Information

ABSTRACT: Nuclear magnetic resonance (NMR) is a very powerful tool in physics, chemistry, and life sciences, although limited by low sensitivity. This problem can be overcome by hyperpolarization techniques dramatically enhancing the NMR signal. However, this approach is restricted to relatively short time scales depending on the nuclear spin–lattice relaxation time T_1 in the range of seconds. This makes long-lived singlet states very useful as a way to extend the hyperpolarization lifetimes. Para-hydrogen induced polarization (PHIP) is particularly suitable, because para- H_2 possesses singlet symmetry. Most PHIP experiments, however, are performed on asymmetric molecules, and the initial singlet state is directly converted to a NMR observable triplet state decaying with T_1 , in the order of seconds. We demonstrate that in symmetric molecules, a long-lived singlet state created by PHIP can be stored for several minutes on protons in high magnetic fields. Subsequently, it is converted into observable high nonthermal magnetization by controlled singlet–triplet conversion via level anticrossing.

Para-hydrogen induced polarization (PHIP), which involves a catalytic reaction where hydrogen in the para-state (pH_2) is added to an unsaturated precursor, has become a promising technique to boost the low sensitivity in NMR experiments, since the first pioneering work by Bowers and Weitekamp.¹ The resulting hyperpolarization of nuclear spins can reach several orders of magnitude. One of the limitations of this technique and all other hyperpolarization methods, however, is the limited lifetime of hyperpolarized states. This calls for careful selection of the spin states created in the experiments. One solution relies on the creation of long-lived singlet states to sustain the lifetime.^{2–4} Indeed, it was shown that the lifetimes of spin-singlet states can be longer than the spin–lattice relaxation times of the constituent spins up to a factor of 37.⁵ These long-lasting states require a pair of isolated (strongly coupled) magnetically equivalent spins $I = 1/2$. Because of the singlet symmetry, the conventional relaxation mechanisms are inactive, but at the same time the singlet state is NMR silent. It is particularly beneficial to generate such singlet states involving two protons, as their signal is highest among the nuclei usually applied in NMR and their relaxation times are rather short at ambient conditions. The magnetic equivalence of the nuclei can be easily fulfilled at low-magnetic fields where chemical shift differences are naturally vanishing.^{2,4,6,7} In high magnetic fields,

which have the advantage of high spectral resolution and thus site selectivity, this magnetic equivalence is more difficult to achieve and requires the use of dedicated pulse sequences to minimize the evolution of the spin system due to the chemical shift.^{3,6,8} As the pH_2 molecule itself forms a singlet state, the hydrogenation reaction in PHIP not only produces enhanced polarization but can also generate long-lived proton singlet states making it an excellent candidate for many applications in the natural sciences.^{9–11} Indeed, such long-lived PHIP states have been exploited in low or even zero magnetic fields.^{7,12,13} The majority of the PHIP experiments require the breaking of the initial singlet state symmetry to observe the enhanced nonequilibrium magnetization. Therefore, in order to accomplish observation, systems were chosen, where the two pH_2 protons occupy magnetically nonequivalent sites after the reaction. However, as first reported by Haacke et al., enhanced hyperpolarized signals can even be observed when the pH_2 protons occupy symmetrical positions in a Cs-symmetric molecule.¹⁴ However, a convincing explanation of the observed enhanced signal after the hydrogenation of acetylene dicarboxylic acid dimethylester was not given. Recently we provided a comprehensive treatment of this problem and found that long-range J -couplings can promote singlet–triplet conversion via level anticrossing at well-defined magnetic fields,¹⁵ thus leading to the observed hyperpolarized signals.

In the present report this new understanding is used to store long-lived pH_2 singlet states in high magnetic fields and later convert them to observable highly polarized triplet states via controlled level anticrossing, by simply changing the position of the sample. With this, it is possible to measure the pH_2 singlet state lifetime T_s at high magnetic fields for the first time.

For our studies we used the following simple example: when acetylenedicarboxylic acid dimethyl ester is hydrogenated with para-hydrogen (Figure 1a) to generate maleic acid dimethyl ester, the pH_2 occupies chemically equivalent vinyl (V) positions in the Cs-symmetric molecule, and both spins remain strongly J -coupled for every magnetic field.

The three protons in each rotating methyl group are magnetically equivalent, and for the purposes of this Communication can, in a good approximation, be replaced by one spin $1/2$. Therefore, the molecule is simplified as two pairs of chemically equivalent spins $1/2$, see Figure 1b. The vinyl group (V,V') corresponds to the former pH_2 molecule, while the pair (M,M') represents the methyl groups. At high magnetic fields the model molecule then represents an AA'XX' spin

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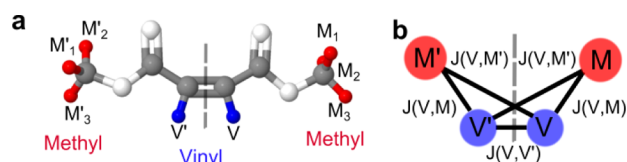


Figure 1. (a) Maleic acid dimethyl ester with labeled protons. (b) Sketch of the J -coupling network. Strong coupling $J(V,V') = 11.6$ Hz and remote couplings $J(V,M)$ and $J(V,M')$, etc., are estimated to be lower than 1 Hz.

system.¹⁶ The vinyl protons, V and V' exhibit a known coupling $J(V,V') = 11.6$ Hz,¹⁴ while the long-range couplings to the methyl protons (M,M') are expected to be smaller by an order of magnitude. In ref 15 it was theoretically and experimentally demonstrated that the energy levels associated with the singlet and the triplet states of the pH_2 in the vinyl group, as a function of the preparation field B_0 , display an anticrossing region at a well-defined magnetic field $B_0 = 0.1$ T. For level anticrossing to happen, $J(V,M) \neq J(V,M')$ is a necessary and sufficient condition (no magnetic equivalence). This 'resonance condition' appears at the field for which the difference between the proton Larmor frequencies of vinyl and methyl protons equals the coupling between the two vinyl protons, $J(V,V')$. Energy level crossings, in which two quantum states cross as a function of an external parameter, are ubiquitous in quantum mechanics. It is well-known that small off-diagonal elements in the Hamiltonian can lead to level anticrossing (or avoided crossing) where the eigenstates are mixed.^{17–21} The existence of an external parameter (in our case B_0) which, when swept in times such that the system traverses the anticrossing regions, enables the transition from one branch to the other and vice versa was first described theoretically by Landau and Zener.^{18,19} This kind of transition was studied experimentally and theoretically in a number of different physical systems, including PHIP and NMR.^{21–28} In our case, such level anticrossing can be used for controlled singlet–triplet conversion by simply moving the sample to the 'resonance

field', $B_0 = 0.1$ T, and subsequently to the desired field of observation. This offers a simple way of generating highly polarized species in high magnetic fields as required in structural elucidation of complex molecules, limited by relaxation of the singlet rather than the triplet state.¹⁵

In order to measure the lifetime of a 1H – 1H singlet state we designed a pulse sequence in which the chemical reaction predominantly takes place at the 7 T high magnetic field where the singlet state is preserved. By subsequently moving the sample to the 'resonance field' we generated a polarized triplet state in a controlled way. As usual, the hydrogenation reaction starts outside the magnet at a low-magnetic field, and then the sample is transported to the observation field. Once the sample is in the observation field, the complete pulse sequence and magnetic field path shown in Figure 2 are applied. In order to avoid any NMR signal resulting from the transportation from the earth field into the observation field, an initial 90° pulse is applied, and the T_2^* relaxation acts as a spoiler before all subsequent parts of the experiments. As the chemical reaction continues, new product molecules are formed at 7 T. When applying a second 90° pulse following the waiting time (T_W), the acquired NMR spectrum shows the thermally polarized methyl protons only, (first spectrum in Figure 2). This is due to the fact that the created singlet state of the vinyl protons itself is silent in magnetic resonance. The second pulse was applied in all the experiments below to destroy signal from spin–lattice relaxation during T_W . Next, the sample is transported to the resonance field (0.1 T) and back to the high detection field, in a transport time T_T of a few seconds. A detailed analysis on the impact of the transportation paths, involved velocities, etc., on the singlet–triplet conversion is presented in ref 15. At the resonance field singlet–triplet conversion occurs, and after arrival of the sample in the observation field, a third 90° pulse allows acquisition of the second spectrum in Figure 2, which exhibits hyperpolarized 180° out-of-phase signals of vinyl and methyl protons. This demonstrates the controlled singlet–triplet conversion. The decisive role of the long-range J -coupling between vinyl and methyl protons is manifested in the

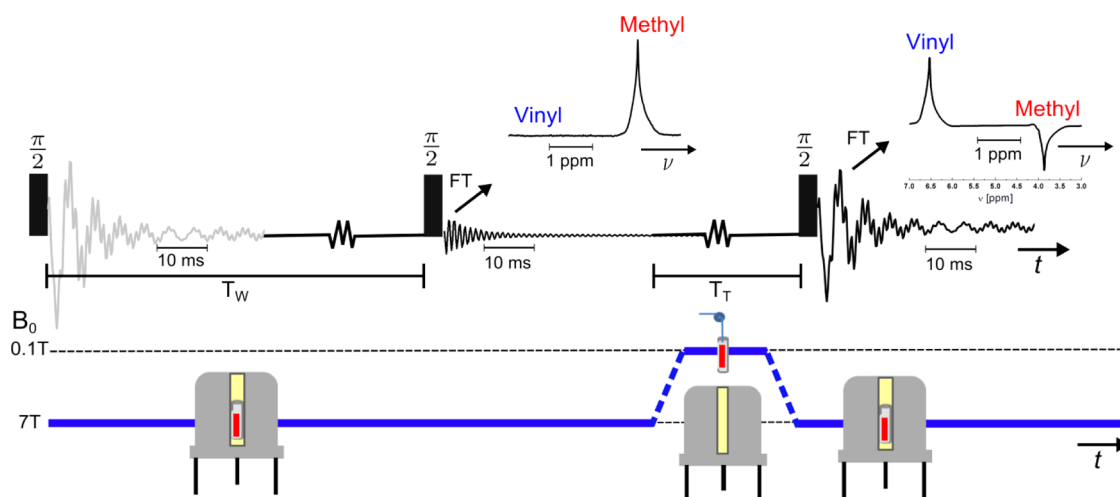


Figure 2. The hydrogenation reaction is started at earth field. The scheme displays the pulse sequence used immediately after the sample is quickly moved to the observation field. In blue, the magnetic field path experienced by the sample is depicted. An initial spoiler 90° pulse is applied at the beginning of the waiting time (T_W) at 7 T. Subsequently, a second 90° pulse is applied and an FID acquired, the corresponding spectrum is also shown. It displays the signal of the methyl groups only. After a transport time T_T to the resonance field and back in the order of seconds, a third 90° pulse and acquisition generate the FID and spectrum in the right part of the figure. It displays the signals of both the vinyl and the methyl groups. For further details see ref 15.

out-of-phase nature of the corresponding NMR signals.¹⁵ It should be noted that the experiments were not optimized for high polarization. The spectral resolution is limited in our setup, but the signals of the two groups are clearly resolved. The slightly lower intensity and the slight asymmetry of the methyl signal are due to destructive interference between the thermal and the hyperpolarized signals. More details on the materials and methods are included as Supporting Information.

This approach of hyperpolarization is, of course, limited by the lifetime of the singlet state (T_s) in the high magnetic fields (7 T), which can now be measured with the same protocol by varying the waiting time T_w . For every T_w a spectrum was recorded, and in Figure 3 the intensity of the peak

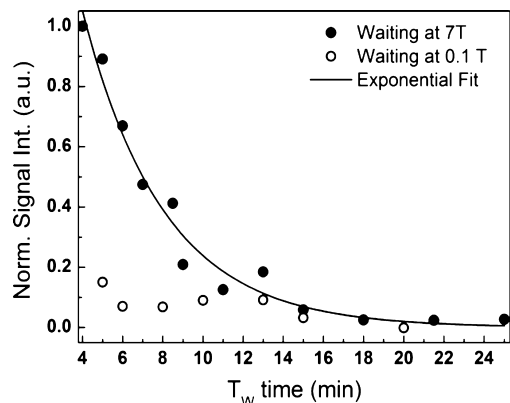


Figure 3. Decay of the long-lived state observed at 7 T (full dots). An exponential decay function with a characteristic time $T_s = 4$ min fit the data. Empty dots were acquired for the case when the waiting time was at the position of the resonance field (0.1 T).

corresponding to the vinyl group is plotted as a function of time. The minimum value $T_w = 4$ min was chosen in order to minimize artifacts arising, e.g., from incomplete chemical reaction. The data were fitted to an exponential decay yielding a relaxation time of the proton singlet state as long as $T_s \sim 4$ min. Experimental parameters, such as the exact amount of pH_2 dissolved in the sample and the reaction rate, can vary from sample to sample and lead to the experimental scatter. Care was taken to control the reproducibility and the spectrum after the spoiler pulse was used for normalization of each point in Figure 3. As a further control, we measured the signals when the chemical reaction was carried out at the position of the resonance field, i.e., where the long-lived state is not preserved. The results plotted as open dots in Figure 3 show that the maximum signal observed in these conditions is only ca. 10% of the maximum signal observed for the same waiting time inside the magnet.

Preserving the long-lived singlet state inside the magnet is needed for applications of hyperpolarization, e.g., in high-resolution liquid-state NMR and biomedical analysis. Vasos et al.²⁹ achieved this by using DNP to create an initial enhanced hyperpolarization magnetization. There, the initial hyperpolarized ^{13}C magnetization was transferred to 1H , converted into a long-lived state, and then read out by partially reconverting it into observable proton magnetization. They extended the protons lifetime by a factor of 7 to $T_s = 16$ s.

The conversion between singlet and triplet states is easier to achieve when the involved spins have different chemical shifts. Then, however, the singlet state which is not a natural state of the system^{2,4} is more difficult to preserve. When the spins

involved are chemically equivalent or nearly equivalent,³⁰ the singlet state is an eigenstate for every magnetic field and the challenge lies in the singlet to triplet conversion for observation. Warren et al.²¹ hyperpolarized a pair of ^{13}C spins occupying chemically equivalent positions in the Cs-symmetrical molecule (2,3- ^{13}C diacetyl). By DNP and rf pulse sequences, a high singlet state population was created in this doubly ^{13}C -labeled system at high field and observed later by subsequently breaking the singlet symmetry via chemical means forming an asymmetric hydrate.

In the present Communication, the initial long-lived proton singlet state is directly generated by PHIP and transformed to a hyperpolarized NMR observable state by well-defined physical means, i.e., level anticrossing. The method of sample movement from a preparation to a detection field is well established in NMR, in particular, in NMR experiments involving hyperpolarization, such as shuttle³¹ and dissolution³² DNP, use of hyperpolarized gases,³³ and PHIP polarization transfer.^{25,26} The time for possible use of the hyperpolarized triplet state of the vinyl protons, exhibiting a relaxation time $T_1 = 15$ s, was prolonged by a factor of 16 to $T_s = 4$ min. Our data show that it is possible to maintain the enhanced signal of protons in high fields for as long as several minutes. Thus, singlet–triplet transition by controlled use of level anticrossing will open up new possibilities for the use of hyperpolarization with high spectral resolution. The ability to prolong hyperpolarization lifetimes opens a range of new possibilities in science using NMR and MRI.^{9,10} Moreover, knowledge of the magnetic fields where level anticrossings can occur is needed, if singlet states are to be used, since crossing these regions will ‘destroy’ the fragile long-lived states.

■ ASSOCIATED CONTENT

Supporting Information

Details on NMR experiments, sample preparation, and parahydrogen generation included. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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