Long-lived nuclear spin states in rapidly rotating CH_2D groups

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Abstract

Although monodeuterated methyl groups support proton long-lived states, hindering of the methyl rotation limits the singlet relaxation time. We demonstrate an experimental case in which the rapid rotation of the CH_2D group extends the singlet lifetime but does not quench the chemical shift difference between the CH_2D protons, induced by the chiral environment. Proton singlet order is accessed using Spin-Lock Induced Crossing (SLIC) experiments, showing that the singlet relaxation time T_S is over 2 minutes, exceeding the longitudinal relaxation time T_1 by a factor of more than 10. This result shows that proton singlet states may be accessible and long-lived in rapidly rotating CH_2D groups.

Keywords: long-lived states, singlet state, methyl group, rotamer

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1. Introduction

Systems of spin-1/2 pairs support a nuclear singlet state, which is antisymmetric with respect to particle exchange, and three nuclear triplet states, which are exchange-symmetric. The population imbalance between the singlet state and the triplet states is called *singlet order* and is protected against many common relaxation mechanisms [1–15]. The relaxation time constant for singlet order is called T_S and often exceeds the conventional longitudinal relaxation time T_1 by a large factor [16–22]. Applications of singlet order to hyperpolarized NMR experiments have been proposed [8, 23–28].

Access to nuclear singlet order requires a symmetry-breaking interaction, such as a chemical shift difference, or differential couplings to other nuclear spins. In monodeuterated methyl groups, a small chemical shift difference $\Delta\delta$ may exist between the two protons, providing that: (1) the rotamer populations of the CH_2D group are not exactly equal, and (2) the local molecular environment is chiral, so that a significant chemical shift difference exists between the protons in a given rotamer. These conditions have been shown to be satisfied in a variety of molecular systems [29–31].

We recently demonstrated that the finite value of $\Delta\delta$ in N-CH_2D-2-methylpiperidine allows access to CH_2D nuclear singlet order [32]. A relatively low relaxation time ratio $T_S/T_1 \simeq 3.1$ was observed in this case. This was attributed to slow rotational jumps of the CH_2D moiety between three rotational conformers, combined with a non-equilateral effective geometry for the two protons and the deuteron [32].

A much larger ratio of T_S to T_1 is expected in the case of rapid CH_2D rotation [32]. However, it has been unclear whether rapid CH_2D rotation is compatible with a sufficiently large chemical shift difference $\Delta\delta$, required for access to the nuclear singlet order. In this paper we show that rapid CH_2D rotation is not *a priori* incompatible with a finite chemical shift difference. Long-lived nuclear singlet order is accessed in a rapidly-rotating CH_2D system, and displays a relatively large relaxation time ratio, $T_S/T_1 \simeq 11.3$.

To the best of our knowledge, chemical inequivalence between CH_2D protons has only been described so far in three chemical compounds [29–31]. Of these, the one expected to provide rapid CH_2D rotation is (α-deuterio-*o*-chlorotoluene)chromium tricarbonyl (**I**), see Figure 1. A small chemical shift difference of $\Delta\delta \simeq 8.0$ ppb between the CH_2D protons has been observed in this compound, and has been attributed to a significant interaction between the orbitals of the chromium centre and those of the CH_2D carbon, combined with the chiral environment provided by the *ortho*-Cl substituent [31].

2. Experiments

12.58 mg of **I** was dissolved in 0.5 mL of C_6D_6 at a concentration of 0.1 M. Samples were subjected to thorough degassing using 4 standard freeze-pump-cycles in a Wilmad low pressure/vacuum NMR tube (5 mm outer diameter) to remove the majority of dissolved molecular oxygen. Details of the chemical synthesis are given in the Supplementary Information.

The relevant portion of the proton NMR spectrum of **I**, in the presence of deuteron decoupling (nutation frequency = 500 Hz), is shown in Figure 1. The two central peaks of the AB spectral pattern are unresolved, and the weak

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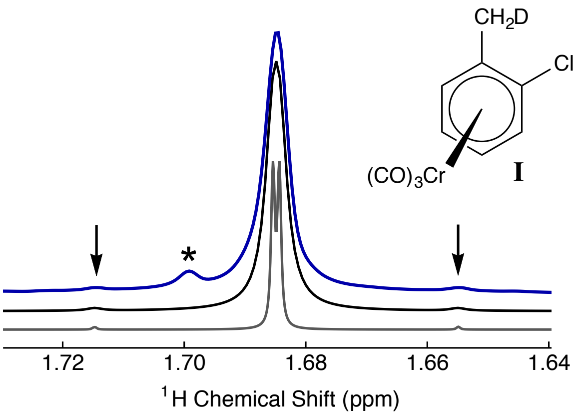

Figure 1: Part of the experimental ^{1}H spectrum of (α-deuterio-o-chlorotoluene)chromium tricarbonyl (**I**) in C_6D_6 solution acquired at 11.7 T (500 MHz) with 16 transients, in the presence of deuteron decoupling (500 Hz nutation frequency). Blue line: experimental proton spectrum; Black line: simulation ($|J_{\mathrm{HH}}| = 14.7\,\mathrm{Hz}$, $\Delta\delta = 8.0\,\mathrm{ppb}$), using Lorentzian line broadening (half-width at half-height = 1.5 Hz); Grey line: simulation ($|J_{\mathrm{HH}}| = 14.7\,\mathrm{Hz}$, $\Delta\delta = 8.0\,\mathrm{ppb}$), using Lorentzian line broadening (half-width at half-height = 0.3 Hz). The intensity of the grey spectrum has been artificially reduced. The inner splitting of the grey spectrum is 0.6 Hz. The asterisk indicates a small signal from a non-deuterated impurity, shifted in frequency by a secondary isotope effect. The small outer components of the AB spectral pattern are indicated by arrows. Inset: structure of **I**, indicating the out-of-plane chromium complex.

outer components are only just visible, indicating a very small value of the chemical shift difference relative to the J-coupling. The spectrum may be simulated by using the following parameters: $|J_{\mathrm{HH}}| = 14.7 \pm 0.3\,\mathrm{Hz}$, $\Delta\delta = 8.0 \pm 0.4\,\mathrm{ppb}$. These are consistent with the literature [31].

The small chemical shift difference allows access to the long-lived singlet order of the CH_2D protons, by using radiofrequency pulse techniques which operate in the near-equivalence regime [33–36]. In the current study, we used the SLIC (Spin-Lock Induced Crossing) method [35], as shown in Figure 2. Details of the pulse sequence optimization and the "T_{00} filter" are given elsewhere [32, 35]. The spin-locked magnetization is converted into singlet order through the action of the chemical shift difference, with the conversion complete in a time $\tau_{\mathrm{SLIC}} \simeq 2^{-1/2}\Delta\nu^{-1}$, where $\Delta\nu$ is the chemical shift difference in Hertz, neglecting relaxation and other complications [35]. In the current study, the parameters of the SLIC pulse were chosen to maximise triplet-singlet population conversion: $\omega_{\mathrm{SLIC}}/2\pi = |J_{\mathrm{HH}}| = 14.7$ Hz and $\tau_{\mathrm{SLIC}} = 170\,\mathrm{ms}$. The maximum amplitude of the singlet-filtered ^{1}H NMR signal, relative to that induced by a single 90° pulse, was found to be 0.28. The loss relative to the theoretical maximum of 2/3 [37] is not yet fully understood but is attributed to radiofrequency field imperfections and relaxation.

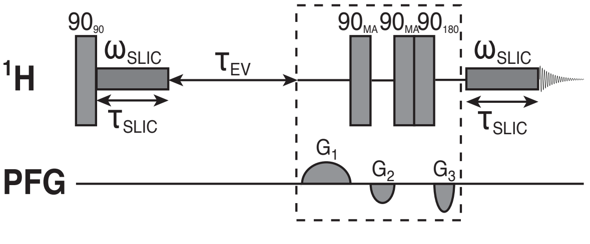

Figure 2: Pulse sequence for preparing long-lived nuclear singlet order in CH_2D groups and monitoring its decay. The experiments used the following parameters: $\omega_{\mathrm{SLIC}}/2\pi = |J_{\mathrm{HH}}| = 14.7$ Hz and $\tau_{\mathrm{SLIC}}/2\pi = 170$ ms. Singlet order is allowed to evolve for a time τ_{EV}. The "T_{00} filter" filters out signals that do not pass through singlet order [32]. "MA" denotes the "magic angle" (54.7°). An interval of 360 s was used between successive transients.

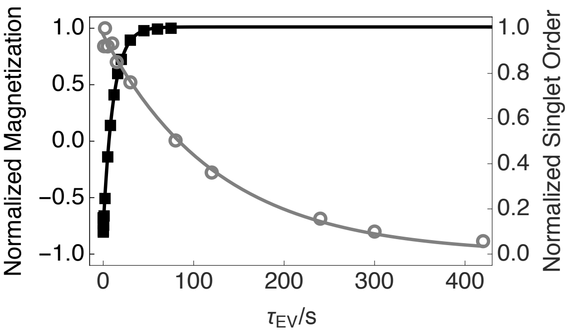

Figure 3: Experimental relaxation curves for the CH_2D protons in 0.1 M **I** in degassed C_6D_6 solvent (proton frequency 500 MHz, temperature 25°C). Open symbols, grey line, and right-hand axis: Decay of long-lived nuclear singlet order measured using the pulse sequence in Figure 2. Filled symbols, black line, and left-hand axis: Spin-lattice relaxation measured by inversion-recovery. All signal amplitudes were normalized to the first point. The fitted curves have a single-exponential form.

Table 1: Relaxation times for the CH_2D protons in 0.1 M **I** in degassed C_6D_6 solution at 11.7 T (500 MHz), for a range of temperatures.

Temperature/°C	T_1/ s	T_S/ s	T_S/T_1
25	11.2 ± 0.6	126 ± 6	11.3 ± 0.8
35	12.6 ± 0.4	131± 10	10.4 ± 0.9
45	14.1 ± 0.5	141 ± 6	10.0 ± 0.6
55	15.6 ± 0.7	144 ± 7	9.3 ± 0.6

3. Results

A decay curve for CH_2D proton singlet order is shown in Figure 3. This shows a single exponential decay with time constant $T_S = 126 \pm 6\,\mathrm{s}$. This is more than eleven times longer than the relaxation time for longitudinal magnetization of the CH_2D protons, $T_1 = 11.2 \pm 0.6\,\mathrm{s}$, as estimated from the inversion-recovery curve, also shown in Figure 3. Without degassing, $T_S = 21.9 \pm 0.8\,\mathrm{s}$ and $T_1 = 5.1 \pm 0.3\,\mathrm{s}$.

Measurements of T_S and T_1 values for the CH_2D protons in **I** at several temperatures between 25°C and 55°C are shown in Table 1. The ratio T_S/T_1 remains reasonably constant over this temperature range. ^{13}C and ^{2}H relaxation times were measured in degassed C_6D_6 solution at 11.7 T (500 MHz) and 25°C. The ^{2}H T_1 of the CH_2D group was $1.2 \pm 0.1\,\mathrm{s}$. The ^{13}C T_1 values for the CH sites of the o-chlorotoluene moiety were $5.3 \pm 0.4\,\mathrm{s}$.

4. Discussion

The observed relaxation time ratio $T_S/T_1 \simeq 11.3$ is much larger than that found for the case of N-CH_2D-2-methylpiperidine, where a ratio of 3.1 was observed [32]. This may be attributed to much faster rotational diffusion of the CH_2D group in **I** around the approximate 3-fold axis. This is physically reasonable since the site adjacent to the CH_2D group in **I** is a sp^2-hybridized carbon, while the adjacent site in the N-CH_2D piperidine derivative is a sp^3-hybridized nitrogen, whose lone pair engages in a hyperconjugation interaction with the deuterated methyl group [29]. Neutron spectroscopy of methyl rotors show that sp^3 hybridization of the neighbouring atom is almost always associated with strong hindering of the methyl rotation, and therefore a small or absent tunneling splitting [38]. It is therefore plausible that the CH_2D group has much greater rotational freedom in **I**, as compared to the N-CH_2D piperidine derivative studied in reference [32].

The torsional potential energy function for a methyl group adjacent to a sp^2 carbon is known to contain periodic components with both 6-fold and 3-fold symmetry [39]. The 3-site jump model for proton singlet relaxation developed in reference [32] is therefore not appropriate to the case of compound **I**. In the discussion below, we use a model in which the CH_2D rotor performs free rotational diffusion, with correlation time τ_R, while the overall rotational diffusion of the molecule in solution is described by a correlation time τ_C. We also assume that the overall correlation time τ_C is short enough relative to the nuclear Larmor period to invoke the extreme narrowing approximation [40]. A model of this kind was used to treat methyl long-lived states and quantum-rotor-induced polarization in γ-picoline [41, 42].

As in reference [32], we assume that the proton relaxation in the CH_2D group is dominated by local dipolar interactions between the protons and the deuteron. These local dipolar interactions are averaged on a fast timescale by rapid vibrational or librational motion, so it is not possible in general to assume that the nuclei can be treated as point dipoles at the vertices of an equilateral triangle [32]. The dipolar coupling constants for the vibrationally-averaged proton-proton interaction and proton-deuteron interactions are denoted ω_{HH} and ω_{HD} respectively. The angle between the unique principal axes of the two vibrationally-averaged ^1H-^2H interaction tensors is denoted 2θ. This angle defines the cross-correlation of the two ^1H-^2H interaction tensors, and is therefore important for the proton singlet relaxation. A point-nucleus equilateral geometry model would lead to the angle $2\theta = \pi/3$, but this value is not assumed in the following discussion [32].

In extreme narrowing, the isotropic rotational diffusion model leads to the following expressions for the T_1 and T_S relaxation rate constants for the CH_2D protons:

$$T_1^{-1} = \frac{(\tau_R + \tau_C)}{6\,(\tau_R + 4\tau_C)} \left(16\omega_{HD}^2 + 9\omega_{HH}^2\right)\tau_C, \quad (1)$$

$$T_S^{-1} = \frac{8\tau_R \sin^2 2\theta}{(\tau_R + 4\tau_C)}\omega_{HD}^2 \tau_C. \quad (2)$$

The CH_2D deuteron relaxation is assumed to be dominated by the electric quadrupole mechanism, with a rate constant given by:

$$T_1^{-1}(^2H) = \frac{3}{16}\Big(\frac{1}{2}\left(1 + 3\cos 2\theta\right)^2 + \frac{6\tau_R \sin^4\theta}{(\tau_R + 4\tau_C)} + \frac{6\tau_R \sin^2 2\theta}{(\tau_R + \tau_C)}\Big)\omega_Q^2 \tau_C, \quad (3)$$

where ω_Q is the quadrupole coupling frequency of the deuteron [43–45], and tetrahedral effective geometry is assumed. These are similar to the expressions given in equations (1-4) of reference [32] for the 3-site jump model for CH_2D relaxation. The relaxation rate equations given above were derived theoretically using the *SpinDynamica* computation package [46], as described in the Supporting Information.

The experimentally determined T_1 relaxation times for the CH_2D deuteron and for the aromatic ring ^{13}C sites lead to the following estimate of the rotational correlation times at 25°C: $\tau_C = 9.0 \pm 0.6\,\text{ps}$ for the overall tumbling motion and $\tau_R = 2.8 \pm 0.3\,\text{ps}$ for the methyl rotational diffusion. This confirms that the CH_2D group in **I** undergoes local rotational diffusion which is more rapid than the overall rotational tumbling of the molecule. This is different from the case of N-CH_2D-2-methylpiperidine, where the 3-fold jumps of the CH_2D group are slow relative to the overall molecular tumbling [32].

The rotational diffusion model leads to the following expression for the relaxation time ratio T_S/T_1:

$$\frac{T_S}{T_1} = \left(1 + \frac{\tau_C}{\tau_R}\right)\frac{16\omega_{HD}^2 + 9\omega_{HH}^2}{48\omega_{HD}^2 \sin^2 2\theta}. \quad (4)$$

The simplest model of *intra*-CH_2D interactions assumes that the proton and deuteron nuclei are fixed as points on the vertices of an equilateral triangle. Since all internuclear distances are equal, the dipolar couplings are proportional to the gyromagnetic ratios, so that $\omega_{HH}/\omega_{HD} = \gamma_H/\gamma_D = 6.51$, and the angle between the unique principal axes of the two HD dipolar coupling tensors is given by $2\theta = \pi/3$. The estimated correlation times $\tau_C = 9.0 \pm 0.6\,\text{ps}$ and $\tau_R = 2.8 \pm 0.3\,\text{ps}$ lead to a predicted relaxation time ratio $T_S/T_1 = 47 \pm 4$. This is far larger than the observed ratio of $\sim$11.3.

In the case of N-CH_2D-2-methylpiperidine, a good agreement with the observed relaxation time ratio was obtained by adjusting the effective geometry of the CH_2D group to take differential vibrational averaging into account. Moving the effective position of the deuteron by 38.7 pm towards the centre of the CH_2D triangle generated good agreement with experiment [32]. In the current case, the same adjustment of effective geometry leads to a predicted relaxation time ratio $T_S/T_1 = 14.1 \pm 0.4$. This is in better agreement with the experimental result $T_S/T_1 \simeq 11.3$, although a significant discrepancy remains. The remaining discrepancy could be associated with deviations from the free rotational diffusion model, in the direction of a discrete jump model. Additional relaxation mechanisms could also be involved, such as interactions with neighbouring nuclei and spin-rotation interactions. This is plausible since small additional contributions can have a large proportionate effect on the small value of T_S^{-1}. We have not investigated this issue further.

5. Conclusions

In summary, we have shown that rapid CH_2D rotation can extend the proton singlet relaxation time of monodeuterated methyl groups. In the current case, the time constant T_S is more than 10 times longer than T_1, and is consistently longer than 2 minutes. Furthermore, we show that at least in this case, the rapid CH_2D rotation does not completely quench the chemical shift difference between the CH_2D protons, so that the nuclear singlet state is experimentally accessible, as well as being long-lived. These results are encouraging for future applications of long-lived singlet states in monodeuterated methyl groups. We are currently investigating other molecular candidates for providing long-lived CH_2D singlet states.

Acknowledments

This research was supported by the Engineering and Physical Sciences Research Council (UK), grant codes EP/N002482 and EP/L505067/1, the Wolfson Foundation, the Royal Society/CNRS exchange scheme and by Bruker (UK). The authors thank Gabriele Stevanato, Benno Meier, Giuseppe Pileio, Daniel J. O'Leary (Pomona College) and Jay Seigel (Tianjin University) for discussions.

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