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Communication: Dissolution DNP reveals a long-lived deuterium spin state imbalance in methyl groups

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We report the generation and observation of long-lived spin states in deuterated methyl groups by dissolution DNP. These states are based on population imbalances between manifolds of spin states corresponding to irreducible representations of the C_{3v} point group and feature strongly dampened quadrupolar relaxation. Their lifetime depends on the activation energies of methyl group rotation. With dissolution DNP, we can reduce the deuterium relaxation rate by a factor up to 20, thereby extending the experimentally available time window. The intrinsic limitation of NMR spectroscopy of quadrupolar spins by short relaxation times can thus be alleviated. *Published by AIP Publishing.* [<http://dx.doi.org/10.1063/1.4974358>]

Dissolution dynamic nuclear polarization (D-DNP) aims at overcoming the intrinsically low sensitivity of NMR spectroscopy and MRI.^{1–3} This enables an exciting range of previously inaccessible applications.^{4–6} D-DNP relies on the coupling between nuclear and electron spins, as well as on the much larger magnitude of the latter's magnetic moments. By saturating the electron paramagnetic resonance (EPR) transitions of unpaired electrons by microwave (μ w) irradiation, the electron polarization is readily transferred to nearby nuclei, most efficiently to protons.⁷ Other nuclear spins can be enhanced by cross polarization (CP).⁸ In our laboratory polarizations $P(^1\text{H}) > 90\%$ and $P(^{13}\text{C}) > 60\%$ can be achieved routinely at cryogenic temperatures of 1.2 K in a magnetic field strength of 6.7 T. The rapid dissolution of the frozen hyperpolarized sample with overheated water and its transfer in 3–6 s to solution-state 800 or 400 MHz NMR systems allows us to achieve signal enhancements by factors up to 10^4 – 10^5 for ^{13}C nuclei.⁹ The process is schematically depicted in Fig. 1.

Here we highlight a curious and potentially valuable side-effect of hyperpolarisation by D-DNP: the creation of non-equilibrium population distributions in symmetrical deuterated spin systems. The utility of this finding lies in the long-lived nature of these population imbalances, which exhibit lifetimes that can be 20 times longer than the spin-lattice relaxation time $T_1(D_z)$ of the Zeeman polarization D_z of deuterium nuclei (henceforth denoted by $D = ^2\text{H}$) that often relaxes too quickly (typically $0.5 < T_1(D_z) < 2$ s) considering the time required to transfer a hyperpolarized solution to an NMR spectrometer or to an MRI system for spectroscopy or imaging (Fig. 1).

Several related phenomena have been reported in the context of D-DNP: multiplet asymmetries that can be exploited for spin polarimetry (SPY),¹⁰ an imbalance between symmetric and non-symmetric spin states (A/E imbalance) in $^{13}\text{CH}_3$ groups has been discussed by Levitt, Dumez and co-workers,^{11,12} a triplet-singlet imbalance (TSI) has been observed in $^{13}\text{CH}_2$ groups¹³ and a sextet-triplet imbalance (STI) in $^{13}\text{CD}_2$ groups.¹⁴

Here, we report the observation of a spin-state imbalance (SSI) in deuterated methyl groups CD_3 . The lifetime $T_{\text{SSI}}(D_3)$ provides a new way to access of the activation energy of the rotation of methyl groups.

A $^{13}\text{CD}_3$ group comprises an SI_3 system with nuclear spins $S = 1/2$ and $I = 1$. To understand relaxation in $^{13}\text{CD}_3$ groups, it is important to consider the C_{3v} point group symmetry of the time-averaged Hamiltonian by using the symmetry-adapted eigenbasis described by Bernatowicz *et al.*¹⁵ Each of the 27 symmetrized eigenstates of the D_3 subsystem belongs to one of the four manifolds (irreducible representations) A, E1, E2, and B of the C_{3v} point group. Various relaxation pathways between these eigenstates can be identified.

The principal components of the quadrupolar tensors of the three deuterons are aligned along the C—D bonds as shown in Fig. 2. The tensors are assumed to have cylindrical symmetry ($\eta = 0$). Fast 120° jumps of the CD_3 group around its C_{3v} symmetry axis lead to averaging of the quadrupolar tensors so that the three deuterons are no longer distinguishable with respect to quadrupolar relaxation.

Under these conditions a peculiar phenomenon arises: any imbalance generated between the populations that belong to different irreducible representations (A, E1, E2, or B) will persist since its return to thermal Boltzmann equilibrium is inhibited. This is because the flow of populations between these eigenstates is forbidden to first order.

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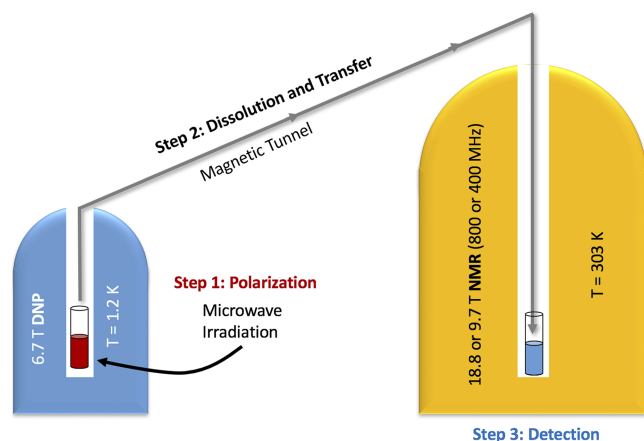


FIG. 1. The principle of dissolution DNP. A sample that contains radicals frozen at 1.2 K in a magnetic field of 6.7 T is hyperpolarized by means of microwave irradiation at 188.2 GHz (left). Subsequent dissolution and transfer to NMR spectrometers at either 400 or 800 MHz (right) yield ^{13}C spectra that can be enhanced by 4 to 5 orders of magnitude.

Quantum states that feature an imbalance between populations belonging to different symmetry manifolds^{13,16} vanish in thermal equilibrium. Here, using both hyperpolarization and a novel type of coherence transfer under radiofrequency pulses, we generated such imbalances in the CD_3 groups of DMSO- d_6 and acetone- d_6 at cryogenic temperatures. Evidence of their existence was then observed in liquid-state ^{13}C NMR spectra after dissolution. In thermal equilibrium, the ^{13}C multiplets feature a symmetric 1:3:6:7:6:3:1 septet pattern due to the scalar couplings $^1J(\text{D}, ^{13}\text{C}) = 18$ Hz to the three equivalent neighboring deuterons with $I = 1$. However, in our experiments, an imbalance between the different symmetry manifolds is produced, which results in an *asymmetric septet*. The lifetime T_{SS1} of the non-equilibrium deuterium spin state imbalance was obtained by monitoring the decay of this asymmetry.^{1,17–19}

In recent work,¹⁴ we described how the hyperpolarization of ^{13}C nuclei in a $^{13}\text{CD}_2$ group can be transferred to the attached deuterium nuclei via multispin order terms like C_2D_z , etc., through side-effects of non-ideal cross-polarization (CP) from protons to ^{13}C . Similar principles apply to $^{13}\text{CD}_3$ groups. During the CP-driven buildup of ^{13}C polarization from the

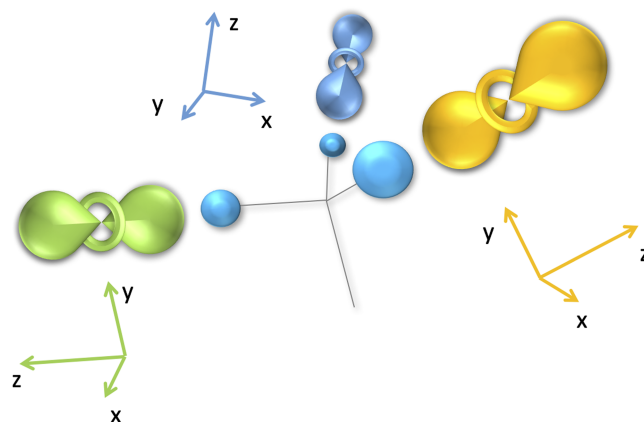


FIG. 2. Sketch of a CD_3 group with its three quadrupolar tensors. The deuterons are represented by blue spheres. In the static limit, the principal components of the Q-tensors (assumed to have axial symmetry) are represented by green, blue, and yellow spherical tensors (analogous to d_{22} orbitals) that are aligned along the three C—D bond axes. The spherical tensors represent the spatially dependent part of the nuclear quadrupole Hamiltonians through the tensor components ($V_{\pm 2}$, $V_{\pm 1}$, V_0) of the electric field gradient at the nucleus.

DNP-polarized *protons* of the frozen solvent, the relatively weak CP irradiation of ^{13}C is insufficient to decouple its dipolar interactions with nearby *deuterons*. Consequently, ^1H - ^{13}C CP leads to multispin carbon-deuterium coherences of the form $n_1\text{C}_2\text{D}_z$, $n_2\text{C}_2\text{D}_z\text{D}_z'$ and $n_3\text{C}_2\text{D}_z\text{D}_z'\text{D}_z''$ (with norms $n_1 = 3^{-1}$, $n_2 = 6^{-1/2}$, and $n_3 = 2^{-1}$) and permutations thereof. After dissolution, these operators project onto long-lived spin state imbalance states that are in antiphase with respect to ^{13}C .¹⁴

These forms of antiphase spin state imbalance feature much longer relaxation times than one would expect, considering the quadrupolar interactions involved. A pictorial representation of the relaxation matrix, Γ_Q , that describes the flow of populations between states of the D_3 subsystem under the influence of quadrupolar couplings is shown in Fig. 3. Each of the 27 symmetry-adapted eigenstates $|1\rangle$ to $|27\rangle$ belongs to one of the four symmetry manifolds, A, E1, E2, and B. States belonging to different irreducible representations are not connected by any off-diagonal matrix elements if methyl group rotation is infinitely fast. This implies that the return to

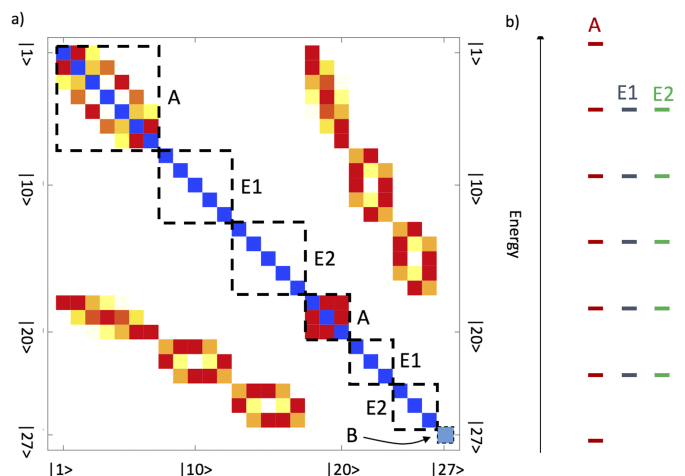


FIG. 3. (a) Pictorial representation of the symmetry-adapted eigenstates and the relaxation matrix of the 27 states of the D_3 subsystem of a $^{13}\text{CD}_3$ group after dissolution, appropriate for the extreme narrowing regime ($\omega_{\perp}\tau_c \ll 1$). Positive relaxation matrix elements are represented by yellow and red boxes and negative elements by blue boxes. Each of the 27 symmetry-adapted states belongs to one of the four symmetry manifolds A, E1, E2, and B. There are no matrix elements that connect different irreducible representations. Therefore, if one considers only quadrupolar relaxation, the populations cannot flow freely between states belonging to different irreducible representations. (b) Energy level diagram associated with the D_3 spin system.

thermal equilibrium of a spin state imbalance between different symmetry manifolds cannot occur via quadrupolar relaxation. The relaxation time of the SSI can be found by evaluating the corresponding matrix elements. The relaxation rates shown in the matrix in Figure 3 were evaluated taking into account the entire Liouville space. This leads to the following expression for the lifetime of the longest-lived spin state imbalance in deuterated methyl groups:

$$T_{\text{SSI}}(D_3) = \left(\frac{\tau_R}{\tau_R + \tau_C} \omega_Q^2 + \frac{2\tau_R}{\tau_R + 4\tau_C} \omega_Q^2 \right)^{-1}, \quad (1)$$

here τ_R denotes the correlation time for rotation around the C_{3v} symmetry axis, while τ_C refers to the overall tumbling. The lifetime $T_{\text{SSI}}(D_3)$ would thus be infinite for infinitely fast methyl group rotation, since τ_R would become zero. $T_{\text{SSI}}(D_3)$ thus provides a measure of the frequency of methyl group rotation and will be short if the activation energy for jumps around the C_{3v} axis is high. However, for infinitely fast rotation around the C_{3v} axis, chemical shift anisotropy (CSA) relaxation of the SSI could still occur in a manner that is analogous to the case described by Dumez *et al.* for protonated methyl groups.¹²

The multiplet of the ^{13}C spins of the $^{13}\text{CD}_3$ groups in DMSO- d_6 at different times after dissolution and transfer to a conventional 400 MHz spectrometer is depicted in Fig. 4. They consist of seven lines numbered L_1 - L_7 . Deuterium populations that are not stored in the form of an imbalance have relaxed to thermal equilibrium. Then, in the first acquired spectrum (at time $t = 0$), the ^{13}C multiplet of the hyperpolarized sample displays a significant asymmetry due to the presence of non-equilibrium deuterium populations that gradually disappears as the multiplet returns to its equilibrium distribution. There are two contributions: on the one hand, the central line L_4 is attenuated, whilst the outer lines L_1 and

L_7 are enhanced. On the other hand, antiphase terms of the form $n_1 C_x D_z$, $n_2 C_x D_z D_z'$, and $n_3 C_x D_z D_z' D_z''$ give rise to the observed tilt of the multiplet in Fig. 4. Simulations with SpinDynamica confirm that the spectra can be reproduced by a superposition of antiphase terms, spin state imbalances, and C_x magnetization.

The observed deviation of the multiplet from equilibrium provides a direct measure of the magnitude of the spin state imbalance between different symmetry manifolds. The asymmetry A can be quantified via the intensities of the individual multiplet components

$$A = (L_1 + L_2 + L_3 - L_5 - L_6 - L_7)/L_4. \quad (2)$$

Note that only fast rotation about the C_{3v} axis can average the three quadrupolar tensors in the CD_3 group. Thus, the faster the rotation of the CD_3 group, the better the separation of the four symmetry manifolds. Hence, a long lifetime $T_{\text{SSI}}(D_3)$ of the asymmetry constitutes an indirect measure of the frequency of rotation of deuterated methyl groups. A similar behaviour has been shown by Levitt and co-workers for CH_3 groups.^{12,20} Werbelow and Grant have given a theoretical treatment of the effects of methyl group rotation on ^{13}C NMR spectra.²¹

Importantly, no asymmetry of the ^{13}C multiplet was observed in direct polarization experiments (without CP), which confirms that the antiphase terms in the solid state that project on spin state imbalances only arise when employing CP.

Fig. 5 shows the experimental asymmetry A defined in Eq. (2) in DMSO- d_6 and acetone- d_6 . The characteristic lifetimes of the multiplet asymmetry, denoted $T_{\text{SSI}}(D_3)$, were found to be 6.8 s in DMSO- d_6 and 12.8 s in acetone- d_6 . The S—O bond in DMSO tends to adopt a zwitterionic character

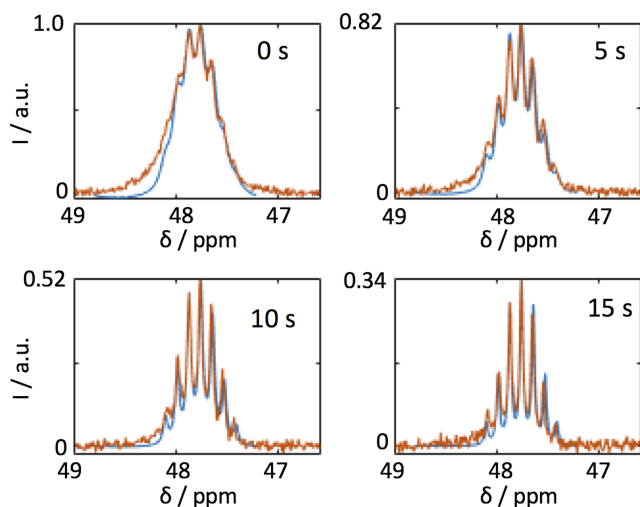


FIG. 4. Experimentally observed signals (orange) of the hyperpolarization of the $^{13}\text{CD}_3$ groups in DMSO- d_6 after DNP, dissolution and transfer to a conventional NMR spectrometer operating at 9.4 T and simulations (blue) obtained with the SpinDynamica software package. Immediately after dissolution ($t = 0$) the septet shows a strong asymmetry. After 15 s the thermal equilibrium distribution is recovered with amplitudes 1:3:6:7:6:3:1. Note that the overall signal intensity decreases as the carbon hyperpolarization decays towards thermal equilibrium with $T_1(^{13}\text{C}) = 19.6$ s (the vertical scale is reduced stepwise from 100 to 82, 52 and 34%).

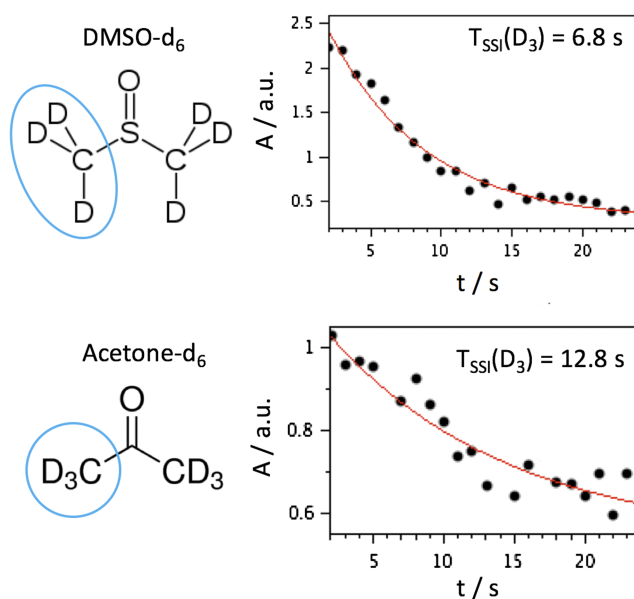


FIG. 5. Decay of the experimentally observed asymmetry A defined in Eq. (2) of the amplitudes of the septet in the $^{13}\text{CD}_3$ groups of DMSO- d_6 (top) and acetone- d_6 (bottom). The characteristic lifetimes $T_{\text{SSI}}(D_3)$ are about 20 times longer than $T_1(D_3)$.

(S^+O^-), in contrast to the neutral double bond ($C=O$) in acetone. Because of the polarity of the CO moiety is lower than in SO, the methyl group rotation in acetone is expected to be faster than in DMSO. The oxygen atom of the carbonyl group constitutes a greater hindrance for the rotation of the deuterons in DMSO than in acetone, thus explaining the differences in $T_{SS1}(D_3)$.²²

It is obvious from Eq. (1) that lower energy barriers for methyl group rotation result in shorter τ_R , therefore leading to increased lifetimes and longer $T_{SS1}(D_3)$. An increased negative charge on the neighboring oxygen, resulting in stronger interactions with the deuterons of the CD_3 moiety and a larger rotational energy barrier, will thus lead to reduced lifetimes $T_{SS1}(D_3)$. These lifetimes therefore provide an indirect measure of the activation energy of rotational jumps in deuterated methyl groups.

As longitudinal relaxation times of deuterons are typically on the order of a few seconds, the long lifetime of the here reported spin-state imbalance prolonging the experimental time window significantly, thus extending the scope of quadrupolar NMR.

The ^{13}C spectra of DMSO- d_6 in natural isotopic 1.1% abundance were observed in a mixture of ethanol:DMSO- d_6 :glycerol- d_8 (v:v:v = 1:2:1). Acetone- d_6 containing samples were prepared in analogy to the DMSO samples. All samples were doped with 50 mM TEMPOL (4-hydroxy-2,2,6,6 tetramethylpiperidine-1-oxyl). Dissolution DNP and NMR experiments are explained in detail in Ref. 14.

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