Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supplementary Information

Long-Lived Nuclear Spin States in Monodeuterated Methyl Groups

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Contents

1. Synthesis

1.1 2-Methyl-1-(methyl-d)piperidine

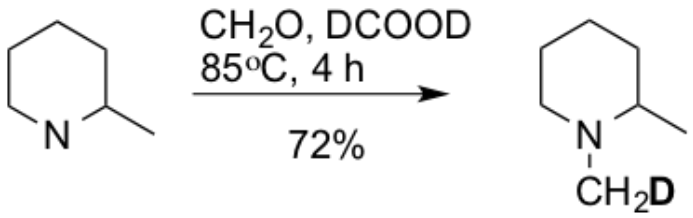

Figure S1: Synthetic route to 2-Methyl-1-(methyl-d)piperidine.

To 2-methylpiperidine (844 mg, 1 mL, 8.51 mmol) was added formaldehyde (37 wt.% in H_2O, 767 mg, 2.07 mL, 25.53 mmol, 3 equiv.) followed by careful addition of formic acid-d_2 (95% in D_2O, 1.72 g, 1.41 mL, 34.04 mmol, 4 equiv.), and the reaction heated at 85°C (using a water bath) for 3 h. The reaction was cooled to room temperature, water (2 mL) added and the acidic aqueous reaction was extracted with pet. ether. The aqueous layer was basified to pH 12 using 6 M NaOH and extracted with Et_2O (x5). The combined Et_2O extractions were dried ($MgSO_4$) and concentrated on a rotary evaporator with no vacuum (bath temp = 40°C) to give a pale yellow oil. Purification by Kugelrohr distillation (oven temperature 150°C - 160°C) to gave the title compound as a clear oil (696 mg, 6.09 mmol, 72%).

1.2 1-(methyl-d)-2-(methyl-d_3)piperidine

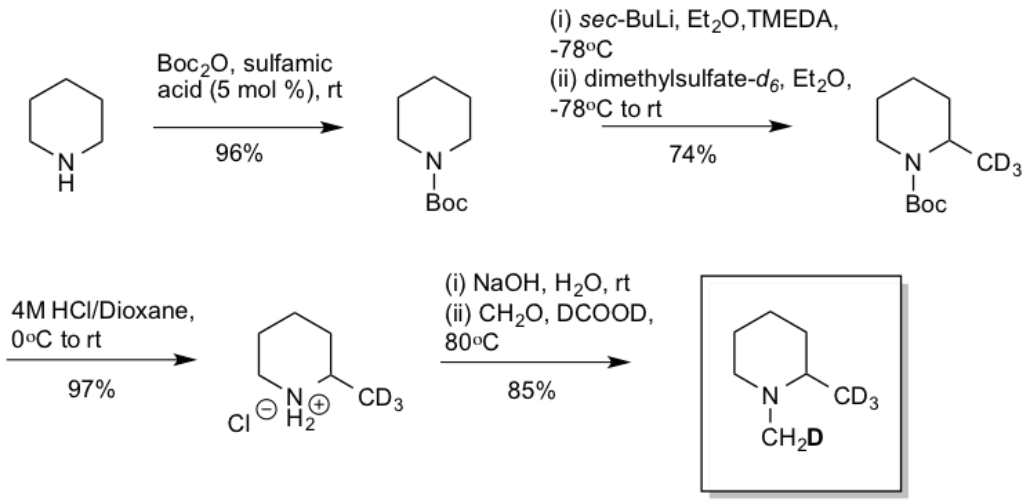

Figure S2: Synthetic route to 1-(methyl-d)-2-(methyl-d_3)piperidine.

tert-Butyl piperidine-1-carboxylate:
Boc anhydride (6.78 g, 31.0 mmol) and sulfamic acid (150 mg, 1.5 mmol, 5 mol%) were mixed together neat and warmed to 28°C - 30°C to melt the $(Boc)_2O$. Piperidine (3.2 mL, 2.77 g. 32.0 mmol) was added and the resulting mixture was stirred at room temperature for 15 minutes. The reaction was diluted with Et_2O, washed with H_2O (x 2) and brine (x 2) and dried ($MgSO_4$). Removal of the solvents in vacuo (no heat) gave the title product as a pale yellow oil (5.51 g, 29.8 mmol, 96%).

tert-Butyl 2-(methyl-d3)piperidine-1-carboxylate:
A solution of tert-butyl piperidine-1-carboxylate (2.5 g, 13.51 mmol) in Et_2O (30 mL) was cooled to -78°C and treated with TMEDA (2.63 mL, 17.56 mmol) dropwise over 10 minutes. sec-BuLi (1.4 M in cyclohexane, 12.5 mL, 17.56 mmol) was added dropwise over 20 minutes. The pale yellow mixture was stirred for 5 h at -78°C. and then treated with a solution of dimethyl sulfate-d_6 (3.20 g, 24.32 mmol) in Et_2O (12 mL). The mixture was warmed to room temperature and stirred for 12 h. The reaction was concentrated in vacuo to give a crude colorless oil which was purified by column chromatography on silica gel eluting with 2% - 5% Et_2O: pet. ether. This afforded the title product as a clear oil (2.03 g, 10.0 mmol, 74%).

2-(methyl-d_3)piperidin-1-ium chloride:
To tert-butyl 2-(methyl-d_3)piperidine-1-carboxylate (1.0 g, 5.0 mmol) at 0°C was added 4M HCl in dioxane (4mL, 16 mmol) and the reaction stirred at room temperature for 30 minutes. Et_2O (20 mL) was added producing a white solid. The reaction was concentrated in vacuo and Et_2O (20 mL) added, the resultant white solid was filtered and washed with Et_2O (2 x 10 mL) and dried in vacuo to give the desired white salt (0.67 g, 4.84 mmol, 97%) which was used directly in the next reaction.

1-(methyl-d)-2-(methyl-d_3)piperidine:
2-(methyl-d_3)piperidin-1-ium chloride (0.63 g, 4.55 mmol) was dissolved in a solution of sodium hydroxide (182 mg, 4.55 mmol) in H_2O (2 mL) and stirred for 10 minutes at room temperature. To this mixture was added formaldehyde (37 wt.% in H_2O, 410 mg, 1.10 mL, 13.65 mmol, 3 equiv.) resulting in a cloudy white solution. Formic acid-d_2 (95% in D_2O, 0.86 mL, 22.75 mmol, 5 equiv.) was carefully added and the reaction heated at 85°C

(using a water bath) for 4 h. The reaction was cooled to room temperature, water (2 mL) added and the acidic aqueous reaction was extracted with pet. ether. The aqueous layer was basified to pH 12 using 6 M NaOH and extracted with Et_2O (x5). The combined Et_2O extractions were dried ($MgSO_4$) and concentrated on a rotary evaporator with no vacuum (bath temp = 40°C) to give the title compound as a clear oil (455 mg, 3.89 mmol, 85%).

2. NMR spectra

2.1 Sample preparation

Solutions were prepared in Wilmad low pressure/vacuum NMR tubes with a 5 mm OD. 6.2 μL of (N-CH_2D)-2-methylpiperidine was dissolved in 0.5 mL of choice solvent at a concentration of 0.1 M. Samples were subjected to thorough degassing using 6 standard freeze-pump-thaw cycles to remove the majority of dissolved molecular oxygen.

2.2 ^{1}H spectrum

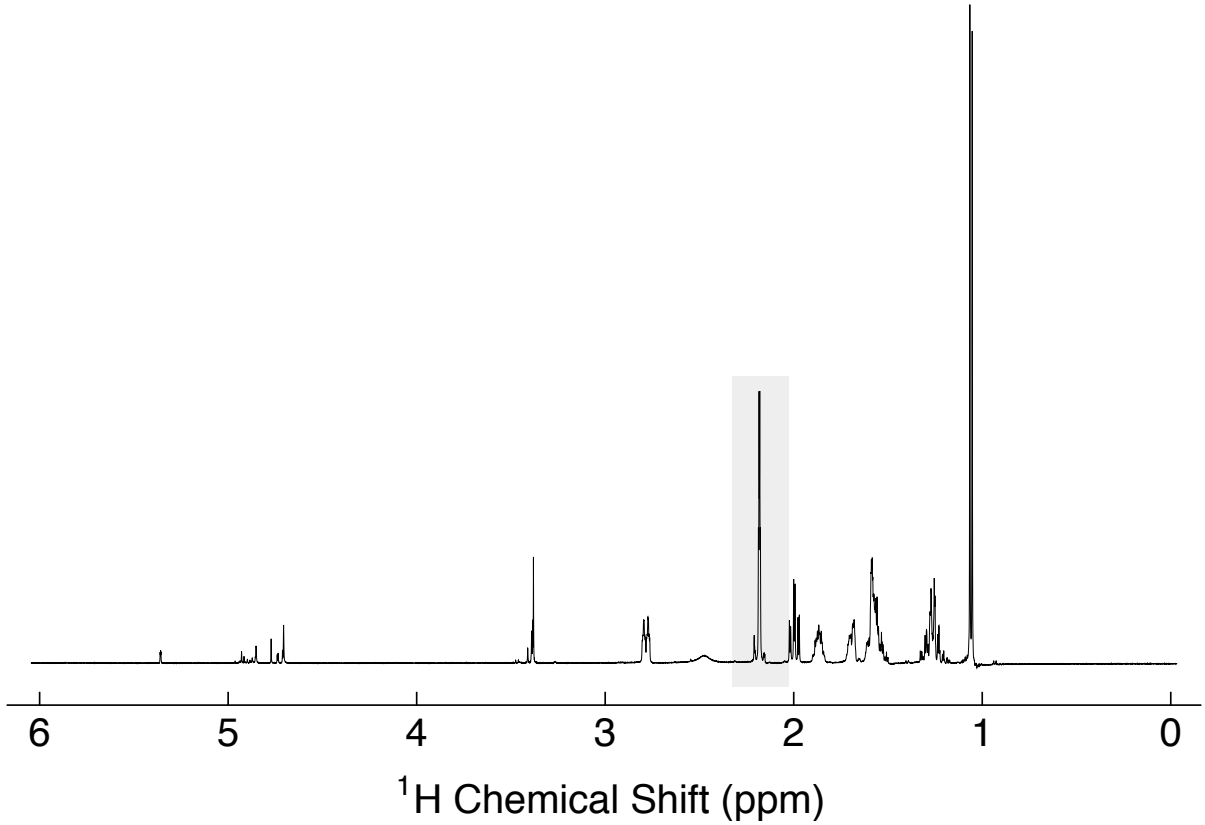

Figure S3: Experimental ^{1}H spectrum of (N-CH_2D)-2-methylpiperidine in CD_2Cl_2 solution acquired at 11.7 T (500 MHz) with a single transient. The grey region shows the CH_2D resonances.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 2.80 - 2.76 (m, 1H, NCH_2), 2.18 (d, 2H, JH,D = 0.98 Hz, CH_2D), 2.01 - 1.95 (m, 1H, NCH_2), 1.88 - 1.80 (m, 1H, $NCHCH_3$), 1.70 - 1.48 (m, 4H, CH_2), 1.29 - 1.16 (m, 2H, CH_2), 1.04 (d, JH,H = 6.1 Hz, 3H).

Experimental ^{1}H spectrum of (N-CH_2D)-2-methylpiperidine in CD_2Cl_2 solution acquired at 11.7 T (500 MHz) with a single transient. The CH_2D peak is at 2.18ppm, highlighted by the shaded area. All peaks were referenced with respect to the CD_2Cl_2 solvent resonance = 5.32ppm. Traces of ether are observed beyond 3ppm.

2.3 ^{13}C spectrum with ^{1}H decoupling

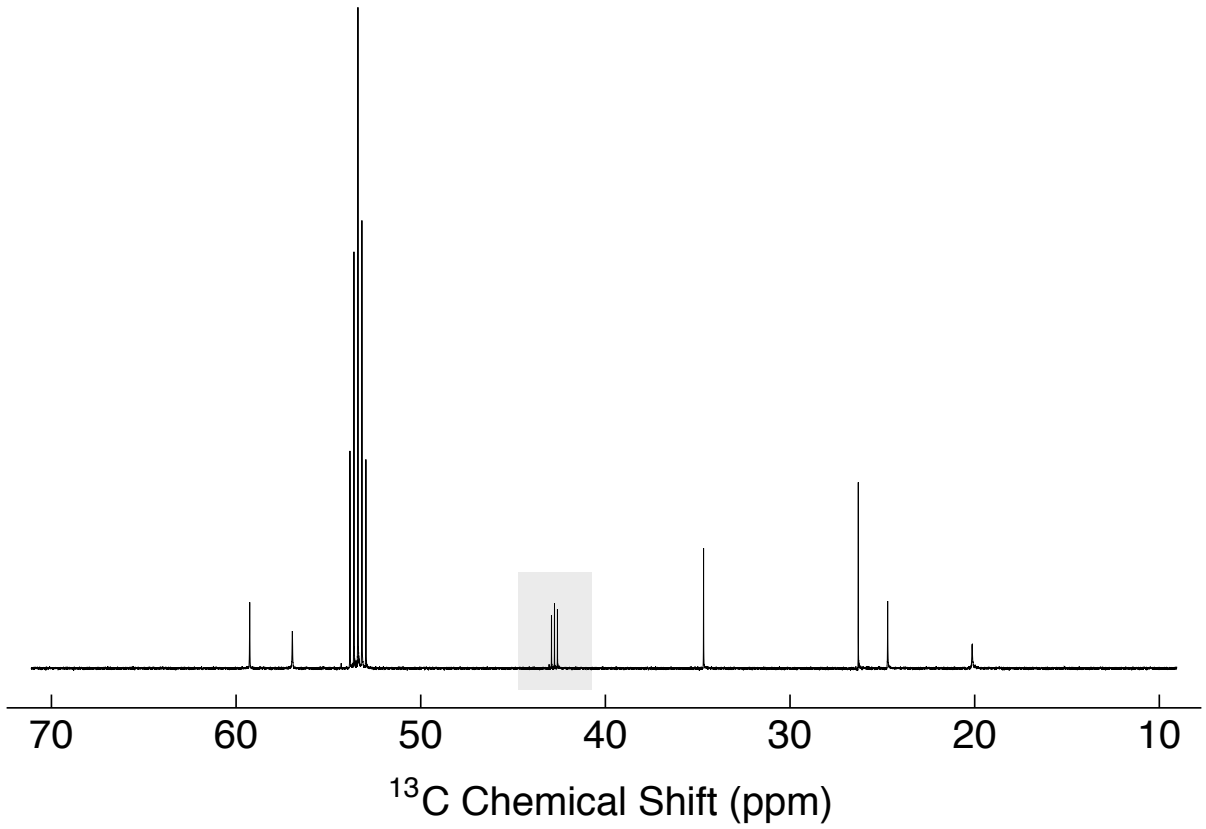

Figure S4: Experimental ^{13}C spectrum with 0.5 kHz ^{1}H decoupling of (N-CH_2D)-2-methylpiperidine in CD_2Cl_2 solution acquired at 11.7 T (500 MHz) with 1024 transients. The grey region shows the CH_2D resonance.

^{13}C{H} NMR (125 MHz, CD_2Cl_2): δ = 59.27 (CH), 56.98 (NCH_2), 42.92 (t, JD,C = 20.54 Hz, CH_2D), 34.57 (CH_2), 26.14 (CH_2), 24.51 (CH_2), 20.23 (CH_3).

Experimental ^{13}C spectrum with 0.5 kHz ^{1}H decoupling of (N-CH_2D)-2-methylpiperidine in CD_2Cl_2 solution acquired at 11.7 T (500 MHz) with 1024 transients. The CH_2D peak is at 42.92ppm, highlighted by the shaded area. The $J_{D,C}$-coupling is 20.54 Hz. All peaks were referenced with respect to the CD_2Cl_2 solvent resonance = 54.00ppm.

2.4 ^2H spectrum

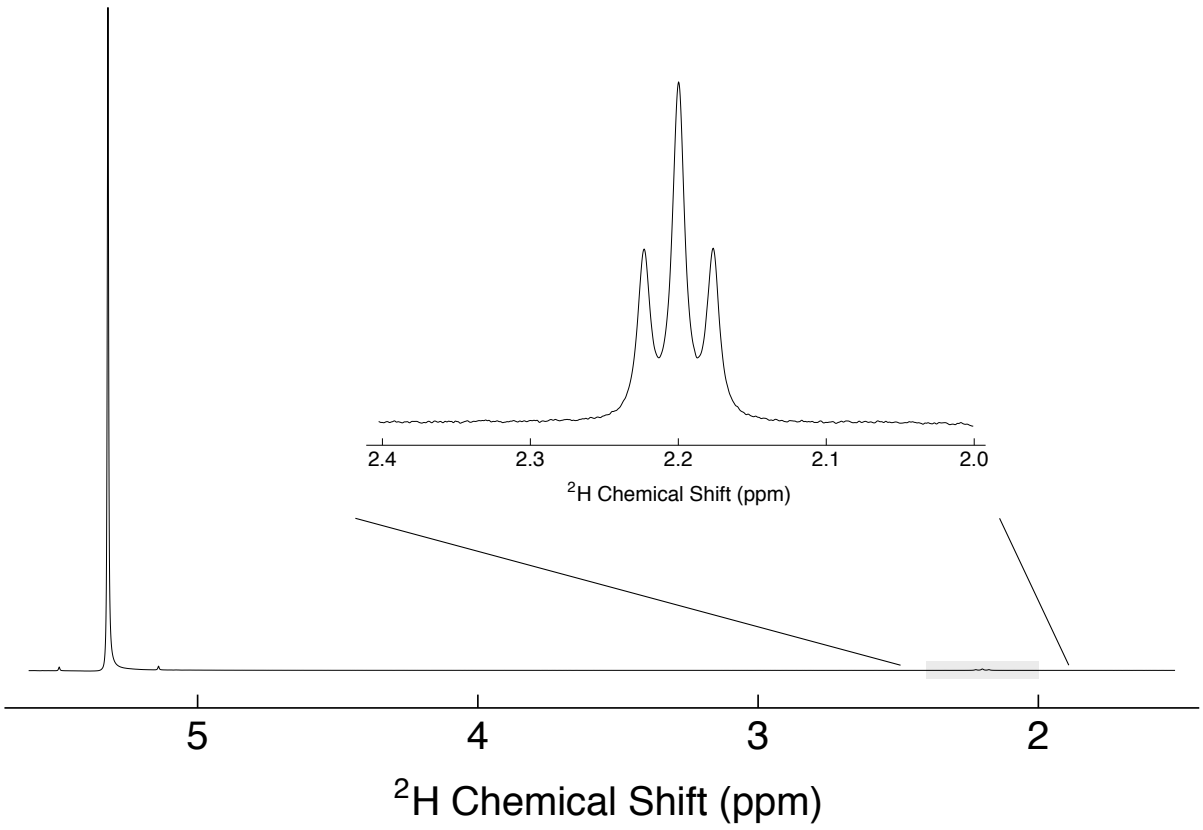

Figure S5: Experimental ^{2}H spectrum of (N-CH_2D)-2-methylpiperidine in CD_2Cl_2 solution acquired at 11.7 T (500 MHz) with a 64 transients.

^{2}H NMR (76.8 MHz, CD_2Cl_2): $\delta = 2.20$ (t, JH,D = 1.8 Hz, CH_2D).

Experimental ^{2}H spectrum of (N-CH_2D)-2-methylpiperidine in CD_2Cl_2 solution acquired at 11.7 T (500 MHz) with a 64 transients. The CH_2D peak is at 2.20ppm, highlighted by the shaded area and shown in the inset. The $J_{H,D}$-coupling is 1.8 Hz. The CH_2D peak was referenced with respect to the CD_2Cl_2 solvent resonance = 5.32ppm.

3. NMR relaxation measurements

3.1 Experimental

Experiments were performed on a Bruker Avance III 500 MHz spectrometer with a TBO probe running *TopSpin 3.2* software. Samples were left to thermally equilibrate for 30 minutes before additional shimming at every temperature increment. Constant air flow across the sample space ensured a fixed sample temperature throughout each relaxation measurement. Spinning at 20 Hz minimised the effects of temperature gradients and convection at increased temperatures.

3.2 Pulse sequences

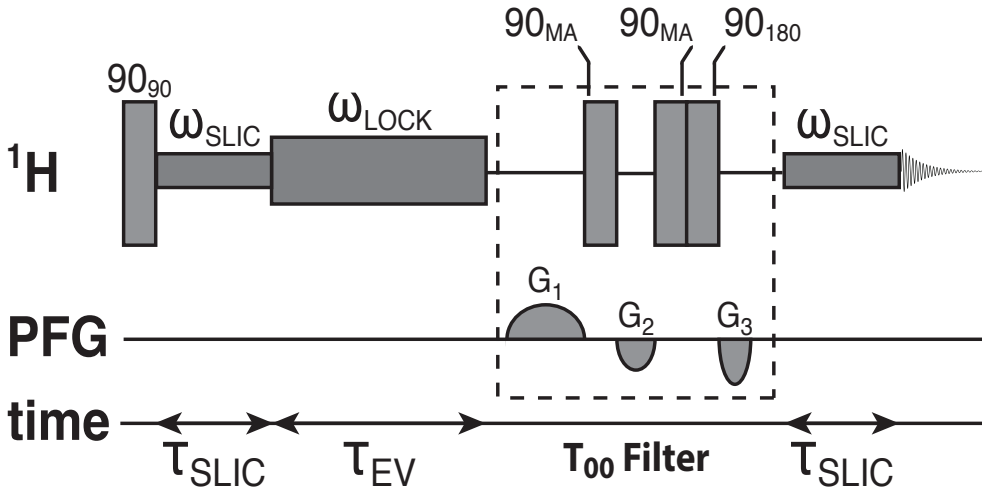

Figure S6: Pulse sequence used for accessing long-lived singlet order in monodeuterated methyl groups and measuring its decay.

The pulse sequence used to monitor long-lived state relaxation is illustrated in Figure S6. The resonance offset was placed in the centre of the CH_2D peak at 2.18ppm. A two-step phase cycle, in which the phase of the 90_{90} pulse and the receiver are simultaneously changed by 180° in successive transients, removes spurious signals generated by longitudinal magnetization generated during the long SLIC pulses.

The singlet state is a magnetically silent arrangement of nuclear spin configurations and is unperturned by the T_{00} filter, which employs the optimized parameters shown in Table S1 to remove signals deriving from residual magnetization.

Table S1: Optimized parameters of T_{00} filter. NMR signals passing through spherical tensors of rank 1 or 2 are destroyed.

PFG	Shape	Strength	Duration
G1	SINE.100	5.0 Gcm^{-1}	4.4 ms
G2	SINE.100	-5.0 Gcm^{-1}	2.4 ms
G3	SINE.100	-7.5 Gcm^{-1}	2.0 ms

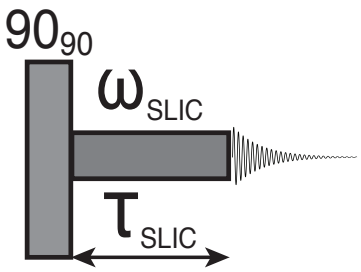

Figure S7: Pulse sequence for optmizing long-lived state access and read-out using SLIC.

The SLIC pulse amplitude and duration were optimized using the pulse sequence given in Figure S7. A two-step phase cycle is used to remove spurious signals generated by longitudinal magnetization accrued during the SLIC pulse. For optimization, one parameter is held constant whilst the other parameter is varied. A reduction in signal amplitude indicates successful conversion of magnetization into NMR-silent singlet order. The results of the SLIC optimization are shown in Figure S8 for the case of degassed CD_2Cl_2 solution at 25°C. (a) $\omega_{\mathrm{SLIC}}/(2\pi) = 11.7$ Hz. (b) $\tau_{\mathrm{SLIC}} = 100$ms (11.7 T, 500 MHz) and $\tau_{\mathrm{SLIC}} = 73$ ms (14.1 T, 600 MHz) (not shown).

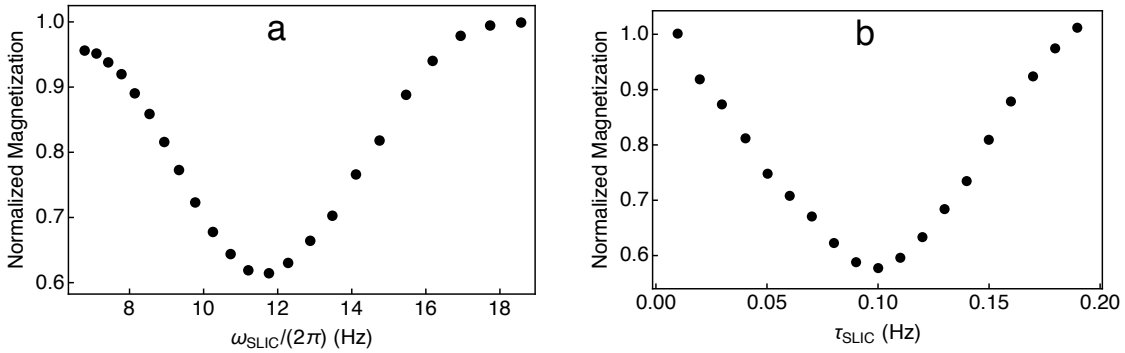

Figure S8: (a) Optimization of SLIC pulse amplitude ($\omega_{\mathrm{SLIC}}/(2\pi)$) and (b) duration ($\tau_{\mathrm{SLIC}}$) for (N-$CH_2$D)-2-methylpiperidine in CD_2Cl_2 solution at 11.7 T (500 MHz). $\omega_{\mathrm{SLIC}}/(2\pi)$ (= 11.7 Hz) and τ_{SLIC} (= 100 ms) are plotted against normalized magnetization.

3.3 Relaxation times

3.3.1 Singlet and longitudinal relaxation

Table S2: The set of singlet relaxation times T_1 and longitudinal relaxation times T_1 for the CH_2D group of (N-CH_2D)-2-methylpiperidine shown in Figure 5 of the main paper. The symbols used in that figure are shown. ▲ denotes (N-CH_2D)-2-(CD_3)-methylpiperidine. All sample concentrations were 0.1 M.

Solvent	Temp.	Magnetic Field	T_S^{-1}/s^{-1}	T_1^{-1}/s^{-1}	Symbol
C_6D_6	25°C	14.1 T (600 MHz)	34.3 ± 0.7	10.9 ± 0.2	● ○
C_6D_6	30°C	14.1 T (600 MHz)	38.2 ± 0.9	11.6 ± 0.2	●
C_6D_6	35°C	14.1 T (600 MHz)	39.9 ± 0.7	12.5 ± 0.3	●
C_6D_6	40°C	14.1 T (600 MHz)	43.8 ± 0.8	13.3 ± 0.2	●
C_6D_6	45°C	14.1 T (600 MHz)	46.1 ± 0.7	14.3 ± 0.3	●
C_6D_6	50°C	14.1 T (600 MHz)	48.9 ± 0.9	15.1 ± 0.3	●
C_6D_6	55°C	14.1 T (600 MHz)	52 ± 1	15.7 ± 0.3	●
C_6D_6	60°C	14.1 T (600 MHz)	55 ± 1	16.7 ± 0.3	●
C_6D_6	25°C	9.4 T (400 MHz)	38 ± 2	12.1 ± 0.4	○
C_6D_6	25°C	11.7 T (500 MHz)	35.2 ± 0.7	11.3 ± 0.3	○ ●
CD_3CN	25°C	11.7 T (500 MHz)	32.8 ± 0.6	10.2 ± 0.2	■
CD_2Cl_2	25°C	11.7 T (500 MHz)	27.0 ± 0.6	8.7 ± 0.1	▲
CD_3OD	25°C	11.7 T (500 MHz)	22.3 ± 0.5	6.9 ± 0.1	◆
CH_2Cl_2	25°C	11.7 T (500 MHz)	20.9 ± 0.8	7.3 ± 0.2	▲
CD_2Cl_2	25°C	11.7 T (500 MHz)	27.1 ± 0.6	8.8 ± 0.2	▲

Longitudinal relaxation times T_1 and singlet relaxation times T_S included in Figure 5 of the main paper for (N-CH_2D)-2-methylpiperidine are shown in Table S2. The experimental conditions are as follows:

(●) 25-60°C temperature (5°C increment), 14.1 T (600 MHz), C_6D_6 solvent
(○) 9.4 T (400 MHz) - 14.1 T (600 MHz) magnetic field (2.35 T (100 MHz) increment), 25°C and C_6D_6 solvent
(●) C_6D_6, (■) CD_3CN, (▲) CD_2Cl_2 and (◆) MeOD solvent, 25°C and 11.7 T (500 MHz)
(▲) 25°C, 11.7 T (500 MHz) and CH_2Cl_2 solvent
(▲) (N-CH_2D)-2-(CD_3)-piperidine at 25°C, 11.7 T (500 MHz) and CD_2Cl_2 solvent.

Data showing the temperature-dependence of the relaxation time constants is given in Figure S9. The increase of T_1 and T_S with increasing T (Figure S9a) indicates that spin-rotation relaxation is not significant in this case. The linear relationship of T_S^{-1} and T_1^{-1} (Figure S9b) indicates a common correlation time for these processes.

Data showing the dependence of T_S^{-1} on the spin-locking field amplitude, expressed as a nutation frequency ω_{LOCK}, is shown in Figure S10. The sharp decrease at low ω_{LOCK} values is due to the suppression of singlet-triplet leakage by the applied rf field. In most

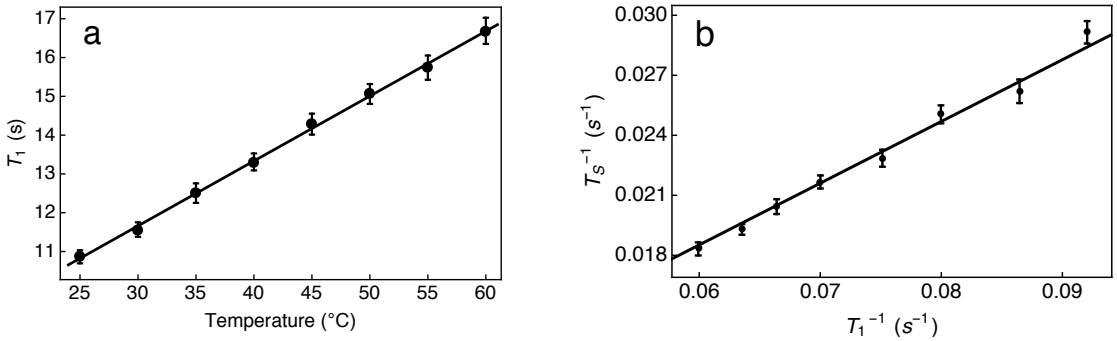

Figure S9: Left: Longitudinal relaxation times (T_1) of 0.1 M (N-CH_2D)-2-methylpiperidine plotted as a function of temperature. Experiments were performed in degassed C_6D_6 solution at 14.1 T (600 MHz). (a) Longitudinal relaxation rates (T_1^{-1}) plotted against singlet relaxation rates (T_S^{-1}) between 25 - 60°C. (b) Singlet relaxation measurements were performed under identical experimental conditions.

experiments we used an rf locking field with amplitude $\omega_{\mathrm{LOCK}}/2\pi = 300\,\mathrm{Hz}$ which is sufficient to suppress singlet-triplet leakage.

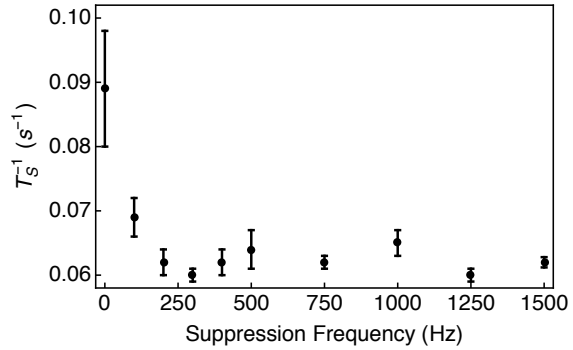

Figure S10: Experimental dependence of T_S^{-1} on the spin-lock rf field strength for 0.1 M (N-CH_2D)-2-methylpiperidine in non-degassed CD_2Cl_2 solvent (proton frequency 500 MHz, temperature 25°C).

3.3.2 ^{13}C relaxation

The measured ^{13}C T_1 values for N-CH_2D-2-methylpiperidine are shown in Table S3 with the ^{13}C numbering scheme shown in Figure S11. These relaxation times were measured by inversion recovery with 0.5 kHz ^{1}H decoupling.

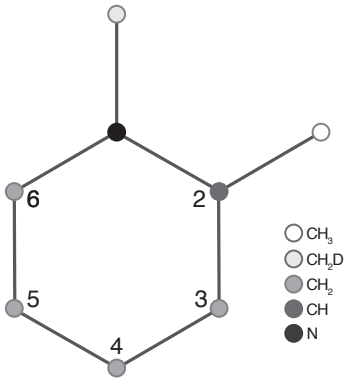

Figure S11: Structure of (N-CH_2D)-2-methylpiperidine, showing the numbering of ^{13}C sites on the (N-CH_2D)-2-methylpiperidine ring.

Table S3: ^{13}C longitudinal relaxation times T_1 for the ring carbons of 0.1 M (N-CH_2D)-2-methylpiperidine in degassed CD_2Cl_2 solution at 11.7 T (500 MHz) and 25°C.

Site	Chemical Shift	T_1/s
2	59 ppm	10.2 ± 0.3
3	34 ppm	6.3 ± 0.5
4	24 ppm	6.2 ± 0.2
5	26 ppm	6.5 ± 0.3
6	56 ppm	6.9 ± 0.4

3.3.3 ^{2}H relaxation

The spin-lattice relaxation time of the CH_2D deuteron $T_1(^2H)$ was measured by inversion recovery to be 0.75 ± 0.01 s at 500 MHz and 25°C in 0.1 M degassed CD_2Cl_2 solution.

4. Relaxation Theory

Consider a H_2D system, comprised by the two protons and the deuterium of a singly deuterated methyl group in solution. The two proton spins are labelled as 1 and 2, the deuteron spin as 3. In this study, relaxation rates are calculated for the longitudinal magnetization of the protons, $I_{1z} + I_{2z}$, and of the deuterium, I_{3z}, as well as the singlet order for the proton pair:

$$\hat{T}_{00}^{12} = \hat{I}_1 \cdot \hat{I}_2 = \hat{I}_{1x}\hat{I}_{2x} + \hat{I}_{1y}\hat{I}_{2y} + \hat{I}_{1z}\hat{I}_{2z}. \tag{S1}$$

An expression of the relaxation superoperator may be derived in the standard semi-classical treatment of spin relaxation [1]. Internal motion is described with a 3-site jump model, with jump rate κ, and a spherical top is assumed for overall motion, with correlation time τ_C. The relaxation superoperator for the dipolar and quadrupolar interactions may be written [2]:

$$\hat{\hat{\Gamma}} = -\sum_{\lambda,\lambda'} c^{\lambda} c^{\lambda'} J_0^{\lambda,\lambda'} \sum_m (-1)^m \hat{T}_{2m}^{\lambda} \hat{T}_{2-m}^{\lambda'}. \tag{S2}$$

The sum is over spin interactions λ. Here we consider the dipolar coupling for each spin pair ij and the quadrupolar interaction for the deuteron (spin 3). The chemical-shielding anisotropy is ignored. c^{λ}, A_{lm}^{λ} and $\hat{T}_{l-m}^{\lambda}$ are given in Table S4. c^{λ} is a real constant. A_{lm}^{λ} and T_{l-m}^{λ} are the spatial and spin tensors for the incoherent Hamiltonian $\hat{H}_{\text{fluc}}$;

$$\begin{aligned} J_0^{\lambda,\lambda'} &= \frac{1}{5} A_{20}^{P,\lambda} A_{20}^{P,\lambda'} \sum_{m_2} \frac{\tau_C}{1 + 3\epsilon_{m_2}\kappa\tau_C} \\ &\quad \times D_{0m_2}^{2*}(\Omega_{PR}^{\lambda}) D_{0m_2}^{2}(\Omega_{PR}^{\lambda'}), \end{aligned} \tag{S3}$$

where

$$\epsilon_0 = 0 \quad \text{and} \quad \epsilon_{\pm 1} = \epsilon_{\pm 2} = 1; \tag{S4}$$

is the spectral density at zero frequency for the correlation between interactions λ and λ';$D_{mm'}^2$ is a component of the Wigner matrix of rank 2; Ω_{PR}^{λ} is the set of Euler angles that describes a transformation from the principal axis system of the interaction P to a rotor frame R fixed with respect to the CH_2D group and with its z-axis aligned with the local 3-fold symmetry axis. This general expression can be used to calculate all auto-correlation and cross-correlation terms for dipolar and quadrupolar interactions.

Using the relaxation superoperator described in Equation S2, relaxation rates may be calculated as follows for the ^{1}H and ^{2}H longitudinal magnetization and for ^{1}H singlet order:

$$T_{1\text{H}}^{-1} = \frac{\langle \hat{I}_{1z} + \hat{I}_{2z} | \hat{\hat{\Gamma}} | \hat{I}_{1z} + \hat{I}_{2z} \rangle}{\langle \hat{I}_{1z} + \hat{I}_{2z} | \hat{I}_{1z} + \hat{I}_{2z} \rangle}, \tag{S5}$$

$$T_{1\text{D}}^{-1} = \frac{\langle \hat{I}_{3z} | \hat{\hat{\Gamma}} | \hat{I}_{3z} \rangle}{\langle \hat{I}_{3z} | \hat{I}_{3z} \rangle}, \tag{S6}$$

$$T_{\text{S}}^{-1} = \frac{\langle \hat{T}_{00}^{12} | \hat{\hat{\Gamma}} | \hat{T}_{00}^{12} \rangle}{\langle \hat{T}_{00}^{12} | \hat{T}_{00}^{12} \rangle}. \tag{S7}$$

The contribution of the dipole-dipole interaction to ^{2}H longitudinal relaxation is found to be negligible and is not included in Equation 4 of the main text. In practice, the rele-

Table S4: Tensor components of the rank-2 interaction ($l = 2$): the dipole-dipole (DD) interaction for a spin pair ij and the quadrupolar (Q) interaction for a spin i. The T_{2m} tensor components are given in the laboratory frame and the A_{2m} tensor components are given in the principal axis system of the interaction. r_{ij} is the internuclear distance between spin i and spin j, eQ_i is the quadrupole moment and eq_i is the electric field gradient for nucleus i, $\eta_{\lambda,i}$ is the biaxiality of interaction λ.

λ	c^λ	m	A_{2m}	T_{2m}
DD	$-\frac{\mu_0\gamma_i\gamma_j\hbar}{4\pi r_{ij}^3}$	0	$6^{1/2}$	$6^{-1/2}\left(3I_{iz}I_{jz} - I_i \cdot I_j\right)$
		±1	0	$\mp\left(1/2\right)\left(I_{i\pm}I_{jz} + I_{iz}I_{j\pm}\right)$
		±2	0	$\left(1/2\right)I_{i\pm}I_{j\pm}$
Q	$\frac{e^2q_iQ_i}{2I(2I-1)\hbar}$	0	$(3/2)^{1/2}$	$6^{-1/2}\left(3I_{iz}^2 - I(I+1)\right)$
		±1	0	$\mp\left(1/2\right)\left(I_{i\pm}I_{iz} + I_{iz}I_{i\pm}\right)$
		±2	$(1/2)\eta_i$	$\left(1/2\right)I_{i\pm}^2$

vant matrix elements were calculated analytically using the *Mathematica*-based symbolic package *SpinDynamica* [3].

Figure S12 shows the relevant angles for the rates given in Equarion S5-S7. The second Euler angle β_{PR} is equal to $\pi/2$ for the three dipole-dipole interactions. The third Euler angle γ_{PR} is θ for the H_1D interaction and $-\theta$ for the H_2D interaction. For the quadrupolar interaction, the dominant principal axis of the ^2D electric field gradient tensor is assumed to be along the CD bond vector, so that $\beta_{PR} = \theta_Q$, where θ_Q is the angle formed by the 3-fold jump axis and the CD bond.

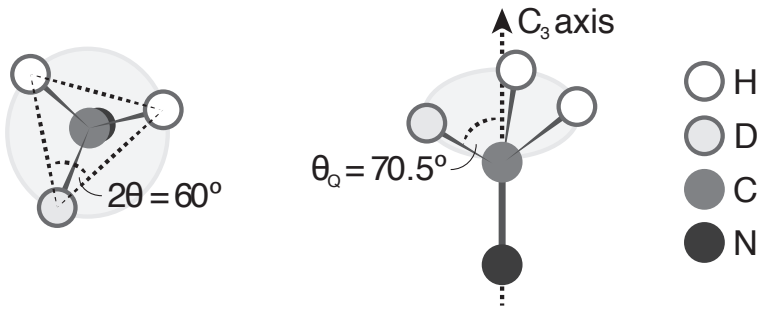

Figure S12: Schematic of a point-particle model with an equilateral triangle geometry perpendicular to and in the plane of the CH_2D group. The light grey disk denotes the plane of the CH_2D group. $2\theta = 60°$ and $\theta_Q = 70.5°$ for an equilateral triangle geometry.

5. References

[1] A.Abragam, *Principles of Nuclear Magnetism*, Clarendon Press, Oxford, 1961.

[2] J. Kowalewski, J. Mäler, *Nuclear Spin Relaxation in Liquids: Theory, Experiments and Applications*, CRC Press, Boca Raton, 2006.

[3] SpinDynamica code for Mathematica, programmed by Malcolm H. Levitt, with contributions by Jyrki Rantaharju, Andreas Brinkmann, and Soumya Singha Roy, available at www.spindynamica.soton.ac.uk.