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Boosting Dissolution Dynamic Nuclear Polarization by Cross Polarization

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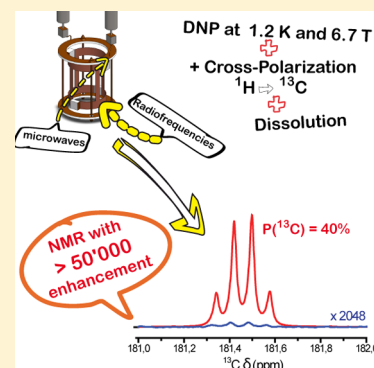
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ABSTRACT: The efficiency of dissolution dynamic nuclear polarization can be boosted by Hartmann–Hahn cross polarization at temperatures near 1.2 K. This enables high throughput of hyperpolarized solutions with substantial gains in buildup times and polarization levels. During dissolution and transport, the ¹³C nuclear spin polarization $P(^{13}\text{C})$ merely decreases from 45 to 40%.



SECTION: Spectroscopy, Photochemistry, and Excited States

Dissolution dynamic nuclear polarization (DNP)^{1,2} consists of enhancing nuclear polarization of a substance of interest in a frozen glassy matrix containing radicals by saturating the EPR transitions at very low temperatures and extracting the resulting hyperpolarized substance by rapid heating to room temperature with a burst of superheated water. DNP is commonly used to boost the polarization $P(S) = (n_\alpha - n_\beta)/(n_\alpha + n_\beta)$ of nuclei S with low gyromagnetic ratios γ_S . DNP is usually performed in fairly low magnetic fields, most frequently $B_0 = 3.35$ T, at temperatures in the vicinity of $T = 1.2$ K. This approach can provide highly polarized solutions for in vitro NMR spectroscopy and for in vivo MRI studies but suffers from long buildup times on the order of hours if one relies on the direct transfer from electron spins to low- γ nuclei at low temperatures. Acceleration of the DNP process is particularly desirable in a clinical context, where the injection of hyperpolarized pyruvate allows one to monitor its metabolism, which is greatly enhanced in prostate cancer. The throughput of DNP can be improved by using multiple samples.³ By transferring polarization from the electron spins to protons, followed by Hartmann–Hahn cross polarization (CP)^{4–7} to low- γ nuclei, the DNP process can be greatly accelerated, while much higher levels of polarization can be achieved. Batel et al.⁸ have very recently achieved $P(^{13}\text{C}) \geq 5\%$ in the liquid state

after polarizing at 3.35 T. Against initial expectations, the efficiency could be further boosted at high fields.⁹ In this Letter, we show that polarization enhanced by CP can be preserved during dissolution from $T = 1.2$ to 300 K and transfer, thus yielding a ¹³C polarization in solution of $P(^{13}\text{C}) \geq 40\%$ after buildup in a record time $\tau_{\text{DNP}}(^1\text{H} \rightarrow ^{13}\text{C}) = 810$ s. Our method is applicable to arbitrary molecules polarized by conventional dissolution DNP. We illustrate its performance by two examples, that is, ¹³C-enriched acetate and pyruvate.

Figure 1 shows the buildup of ¹³C polarization at $T = 1.2$ K and $B_0 = 6.7$ T in five 10 μL frozen beads of a 3 M frozen solution of 1-¹³C-enriched sodium acetate in a deuterated water/ethanol mixture (67:33 v/v) doped with 50 mM TEMPO, with or without CP, followed by relaxation toward thermal equilibrium in solution at ~ 300 K at 7.05 T (300 MHz for protons) after rapid dissolution with 5 mL of D₂O heated to $T_{\text{diss}} = 400$ K at a pressure $p_{\text{diss}} = 1.2$ MPa. Five 10 μL frozen beads of a 3 M solution of ascorbate (vitamin C) were also loaded on top of the DNP sample.¹⁰ The ascorbate is intimately mixed with the hyperpolarized sample during dissolution and

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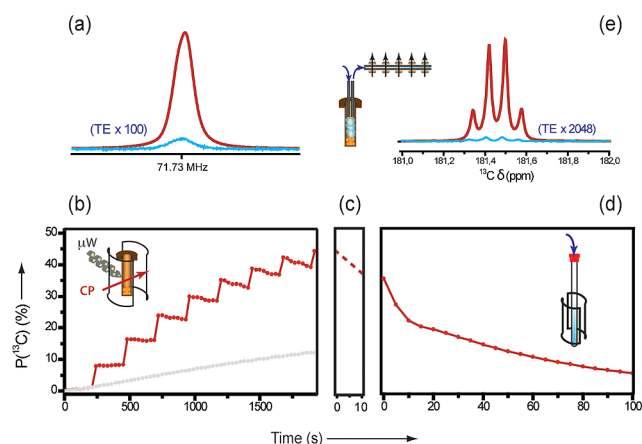


Figure 1. (a) Signals of ^{13}C NMR of 50 μL of a 3 M frozen solution of 1- ^{13}C -enriched sodium acetate in a deuterated water/ethanol mixture (67:33 v/v) doped with 50 mM TEMPO measured without CP (blue) at thermal equilibrium ($T = 4.2$ K and $B_0 = 6.7$ T, scaled by a factor 100) and with CP-DNP (red) ($P_{\mu\text{W}} = 120$ mW at $f_{\mu\text{W}} = 188.3$ GHz). (b) ^{13}C DNP buildup with (red) and without (gray) CP measured every 30 s with $\beta = 5^\circ$ pulses. CP was performed every 240 s with the pulse sequence described in Figure 2 with $B_1 = 15$ kHz, $t_{\text{chirp}} = 250$ μs , and $t_{\text{HH}} = 0$. (c) The dissolution and transfer process requires $t_{\text{diss}} = 10.7$ s. (d) Relaxation of ^{13}C in solution at $\sim T = 300$ K after transfer to a magnetic field $B_0 = 7.05$ T, measured with $\beta = 5^\circ$ pulses at 5 s intervals. (e) Signals of 1- ^{13}C sodium acetate immediately after dissolution (red) and at thermal equilibrium (blue, scaled by a factor 2048).

transfer and efficiently scavenges the TEMPO radicals, thus extending the lifetimes of the enhanced polarization.

The experiment was performed in a home-built DNP polarizer^{9,11–13} operating at 6.7 T, equipped with a novel dissolution-compatible triple-resonance DNP insert composed of a microwave shield coupled to an oversized circular waveguide for high-frequency microwave irradiation at $f_{\mu\text{W}} = 188$ GHz \pm 500 MHz and $P_{\mu\text{W}} = 120$ mW and a doubly resonant NMR coil of 0.5 cm^3 inner volume (^{13}C and ^1H resonating at 71.73 and 285.23 MHz) with a Helmholtz configuration, parallel to the static field to enable rapid dissolution. An ELVA (VCOM 10/94/400) microwave source operating at $f_{\mu\text{W}} = 94$ GHz \pm 250 MHz up to $P_{\mu\text{W}} = 400$ mW was coupled to a VDI doubler (D200) with $\sim 30\%$ power conversion efficiency. Thermal mixing (TM) efficiently generates very high ^1H polarization that can readily be transferred by CP to a low- γ nucleus. The highest nuclear spin polarization can be accumulated by multiple CP contacts at regular intervals, as shown in Figure 2. In solid 1- ^{13}C -enriched acetate at 1.2 K, the ^{13}C polarization rapidly builds up to $P(^1\text{H} \rightarrow ^{13}\text{C}) \approx 45\%$ after eight CP steps. Each CP step leads to a transfer from ^1H to ^{13}C , at the price of a partial depletion of the ^1H polarization. The efficiency of polarization transfer and the extent of depletion strongly depend on the rf field intensity that can be achieved. In our case, moderate fields $B_1 = 15$ kHz on both nuclei result in a fairly low efficiency and a moderate depletion. The ^1H polarization is partly restored by DNP between subsequent CP contacts. The final ^{13}C polarization is enhanced by a Boltzmann factor $e_{\text{KT}} = 250$, a DNP factor $e_{\text{DNP}} = 184.5$, and a CP factor $e_{\text{CP}} = 1.7$, yielding $e_{\text{KT}}e_{\text{DNP}}e_{\text{CP}} = 78400$, assuming that DNP and observation are carried out in the same static field of 6.7 T. (If the observation

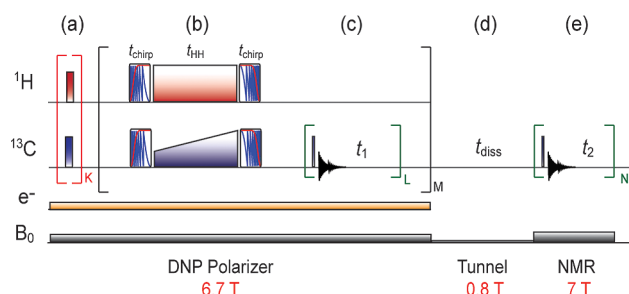


Figure 2. CP sequence used for dissolution DNP. The sample is placed in a polarizer at $T = 1.2$ K and $B_0 = 6.7$ T and subjected to continuous microwave irradiation at $f_{\mu\text{W}} = 188.3$ GHz with $P_{\mu\text{W}} = 120$ mW. (a) A train of $K = 30$ $\pi/2$ pulses is applied to both ^1H and ^{13}C for presaturation. (b) CP is performed using adiabatic half-passage pulses (t_{chirp}) to convert the magnetization components from I_z to I_x and from S_z to S_x and vice versa and adiabatic passage through the Hartmann–Hahn condition (t_{HH}). (c) A sequence of $M = 8$ pulses with $\beta = 5^\circ$ separated by $t_1 = 30$ s is applied to monitor the buildup of the polarization $P(^1\text{H} \rightarrow ^{13}\text{C})$. This CP + NMR scheme is repeated N times until a satisfactory level of ^{13}C polarization is attained. (d) Afterward, the DNP sample is dissolved, transferred through a 3.2 m long “magnetic tunnel” with a magnetic field of $B_{\text{tunnel}} > 0.8$ T, and injected into a 5 mm NMR tube in a 7.05 T NMR spectrometer (300 MHz for protons) in a time $t_{\text{diss}} = 10.7$ s. (e) Finally, the relaxation back to thermal equilibrium can be monitored with $\beta = 5^\circ$ pulses separated by $t_2 = 5$ s.

is in a higher field, e.g., 7.05 T in our system, the gain is reduced by a distinct Boltzmann factor $e_B = 6.7/7.05 = 0.95$).

In an earlier study in the same field $B_0 = 6.7$ T and at the same temperature $T = 1.2$ K,⁹ higher polarization levels $P(^1\text{H} \rightarrow ^{13}\text{C}) > 70\%$ could be achieved with an insert that was not compatible with rapid dissolution. The solenoidal radio frequency (rf) coil used in the first study⁹ was replaced by a Helmholtz coil. It should be possible to achieve higher polarization levels by increasing the microwave power and/or improving the irradiation efficiency by inserting a mirror and/or a horn in the cavity to focus the microwaves onto the sample. The DNP insert, rf coils, sample holder, and dissolution and injection devices are shown in Figure 3. Special attention was given to the design of a reliable rf coil for efficient CP over the entire sample volume with homogeneous B_1 fields. However, because of arcing in superfluid helium at $T = 1.2$ K, the rf fields used for CP were limited to 15 kHz each, using 15 and 25 W on the proton and carbon channels, respectively. Higher CP efficiency should be possible with higher B_1 fields,⁷ as demonstrated in our previous study⁹ where we used a solenoidal coil with $B_1 = 50$ kHz applied to each nucleus. We are investigating strategies for increasing B_1 without arcing.

During dissolution with 5 mL of superheated D_2O ($T_{\text{diss}} = 450$ K, $p_{\text{diss}} = 1.2$ MPa), the nuclear spin polarization dropped from $P(^1\text{H} \rightarrow ^{13}\text{C}) \approx 45\%$ in the solid at 1.2 K to $P(^{13}\text{C}) \approx 40\%$ in solution at 300 K. The hyperpolarized solution traveled through a PTFE tube (1.5 mm inner diameter) through a home-built magnetic tunnel of 3.2 m length that was lined with permanent magnets (neodymium iron boron alloy) to sustain a field of $B_{\text{tunnel}} > 0.8$ T. The solution was pushed to an injection device placed inside of the bore of a 7.05 T NMR magnet with helium gas at 0.6 MPa. The injection device was composed of a holding chamber for the hyperpolarized solution that was equipped with a piston moved by a programmable stepper motor (Trinamics Pandrive 57MM PD3-109-57-RS) coupled to a carry-ball screw. Once the sample has settled in the holding

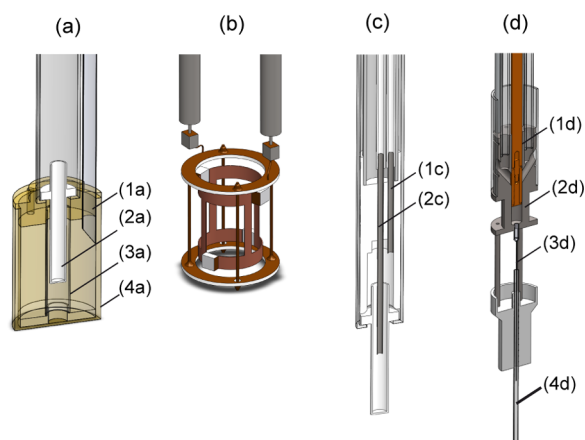


Figure 3. (a) DNP insert, including a waveguide (1a), a 5 mm inner diameter Vespel sample holder (2a), a glass rf coil support together with doubly tuned NMR coil (3a), and a microwave cavity (4a). (b) Resonant rf circuit used for CP, composed of one pair of saddle coils tuned for ^1H and one orthogonal pair for ^{13}C , plus two saddle coils for inductive coupling. (c) Dissolution insert with the sample holder for rapid dissolution: (1c) outlet for the hyperpolarized solution and (2c) inlet for the hot dissolution solvent. (d) Injection device placed in the NMR magnet: (1d) remotely controlled piston that injects the hyperpolarized solution collected in the holding volume (2d) through a capillary (3d) into a 5.0 mm outer diameter NMR tube (4d).

chamber, the piston allowed one to inject a preset volume of hyperpolarized solution (typically 500 μL) into the NMR tube, and NMR measurements could be started after settling for ~ 1 s. The overall delay between the start of the dissolution process and the start of signal acquisition was $t_{\text{diss}} = 10.7$ s. During this delay, relaxation during the voyage¹⁴ would cause a polarization loss of about 16% if $T_1(^{13}\text{C}) \approx 60$ s, thus leaving a theoretical polarization of $P(^{13}\text{C}) = 38\%$ at the start of the NMR measurement. In practice, we measured $P(^{13}\text{C}) = 40\%$. The dissolution step could be automated to improve reproducibility.¹⁵ Exactly the same experiment was applied to ^{13}C -enriched sodium pyruvate and yielded $P(^{13}\text{C}) = 40.5\%$.

Dissolution CP-DNP enables a high throughput of highly polarized solution for in vivo or in vitro studies, without the need for devices with multiple samples.³ CP-DNP is best carried out with inexpensive nitroxide radicals such as TEMPO. CP-DNP should also be applicable to gases such as xenon-129 in combination with sublimation methods,¹⁶ and to other low- γ nuclei such as lithium-6,¹⁷ nitrogen-15,^{2,18} or even yttrium-89^{19,20} as long as the requirement that the rf field intensities should be the same for both nuclei can be fulfilled.

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Notes

The authors declare no competing financial interest.

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