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High field dynamic nuclear polarization at 6.7 T: Carbon-13 polarization above 70% within 20 min

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ABSTRACT

In most applications of dissolution-DNP, the polarization of nuclei with low gyromagnetic ratios such as ^{13}C is enhanced directly by irradiating the ESR transitions of radicals with narrow ESR lines such as Trityl at low temperatures $T = 1.2$ K in polarizing fields $B_0 \leqslant 5$ T. In a field $B_0 = 6.7$ T at $T = 1.2$ K, DNP with TEMPO leads to a rapid build-up of proton polarization $P(^1\mathrm{H}) = 91\%$ with $\tau_{\mathrm{DNP}}(^1\mathrm{H}) = 150$ s. CP at low temperatures yields a polarization $P(^1\mathrm{H} \rightarrow {}^{13}\mathrm{C})$ in excess of 70% within 20 min. After rapid dissolution to room temperature, this is 122 000 times larger than the Boltzmann polarization at 300 K and 6.7 T.

For a variety of reasons, dynamic nuclear polarization (DNP)[1], when it is used to boost the polarization $P(S)$ of nuclei S with low gyromagnetic ratios γ_S prior to rapid heating to room temperature (so-called 'dissolution DNP' [2]), is usually performed in fairly low magnetic fields, most frequently $B_0 = 3.35$ T. Furthermore, DNP is usually carried out at temperatures in the vicinity of $T = 1.2$ K. Under such conditions, the electron spin polarization is close to unity ($P_e = 95\%$). By irradiating the EPR transitions with microwaves, a significant fraction of this polarization can be transferred to the polarization P_S of nuclear spins S such as ^{13}C, which is defined as

$$P_S = \frac{n_\alpha - n_\beta}{n_\alpha + n_\beta}$$

Experimental reports on low temperature dissolution DNP at fields above 3.35 T, i.e., at $B_0 = 4.6$ T using Trityl and at $B_0 = 5$ T using the widely available free radical 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) [3,4] show substantial improvements in polarization levels achieved by direct DNP, i.e., $P(^{13}\mathrm{C}) = 35\%$ at 4.6 T and $P(^{13}\mathrm{C}) = 15\%$ at 5 T, albeit at the price of prohibitively long build-up times: $\tau_{\mathrm{DNP}}(^{13}\mathrm{C}) > 3000$ s with Trityl at 4.6 T and $\tau_{\mathrm{DNP}}(^{13}\mathrm{C}) > 1000$ s with TEMPO at 5 T. On the other hand, the build-up times are usually much shorter for protons than for carbon-13 when TEMPO is used as polarizing agent [5–8]. We have shown recently [9] that the combination of ^{1}H DNP using TEMPO with cross-polarization (CP) to transfer the enhanced magnetization from ^{1}H to ^{13}C allows one to achieve dramatic improvements in both polarization levels and build-up rates.[9] At 3.35 T, polarization levels as high as $P(^1\mathrm{H}) = 40\%$ and $P(^1\mathrm{H} \rightarrow {}^{13}\mathrm{C}) = 25\%$ after CP could be achieved quite rapidly since $\tau_{\mathrm{DNP}}(^1\mathrm{H}) = 90$ s [10]. This approach opens new possibilities by accelerating sample throughput, which should be useful for many *in vivo* and *in vitro* hyperpolarization experiments.

Increasing the magnetic field B_0 beyond 5 T cannot significantly enhance P_e since it is already close to unity at 3.35 T. It is therefore not obvious that an increase of B_0 can yield any improvement in the nuclear spin polarization P_S. However, a closer inspection of the mechanism known as 'thermal mixing' (TM) as described by spin temperature theory[1] reveals that one should expect an improvement in DNP efficiency at higher fields. In this work, it is shown that at $B_0 = 6.7$ T and $T = 1.2$ K, using frozen glassy solutions containing TEMPO as polarizing agent, a polarization $P(^{13}\mathrm{C}) = 36\%$ can be obtained directly, albeit with a slow build-up $\tau_{\mathrm{DNP}}(^{13}\mathrm{C}) = 2000$ s. With Trityl, it might be possible to achieve higher polarization levels $P(^{13}\mathrm{C})$ at $B_0 = 6.7$ T, but the build-up times are likely to be much longer. With TEMPO at $B_0 = 6.7$ T and $T = 1.2$ K, the proton polarization builds up to $P(^1\mathrm{H}) = 91\%$ with a much shorter build-up time $\tau_{\mathrm{DNP}}(^1\mathrm{H}) = 150$ s, i.e., the acceleration factor is $\kappa = \tau_{\mathrm{DNP}}(^{13}\mathrm{C})/\tau_{\mathrm{DNP}}(^1\mathrm{H}) = 13$. Cross polarization (CP) therefore allows one to achieve unprecedented polarization levels $P(^1\mathrm{H} \rightarrow {}^{13}\mathrm{C}) = 71\%$ in a remarkably short time.

The design of the DNP polarizer used in this letter was adapted from the 3.35 T apparatus described previously [11,12] by running a superconducting magnet designed for $B_0 = 7.05$ T (Oxford Instruments) at $B_0 = 6.7$ T, corresponding to an electron frequency $\nu_e = 188$ GHz. The microwave source (ELVA) initially operating at 94 GHz (tuning range ± 250 MHz, $P_{\mu w}^{\max} = 400$ mW) was coupled to a frequency doubler (VDI/D200) to yield 188 GHz (tuning range ± 500 MHz, $P_{\mu w}^{\max} = 120$ mW.) Apart from the tuning and

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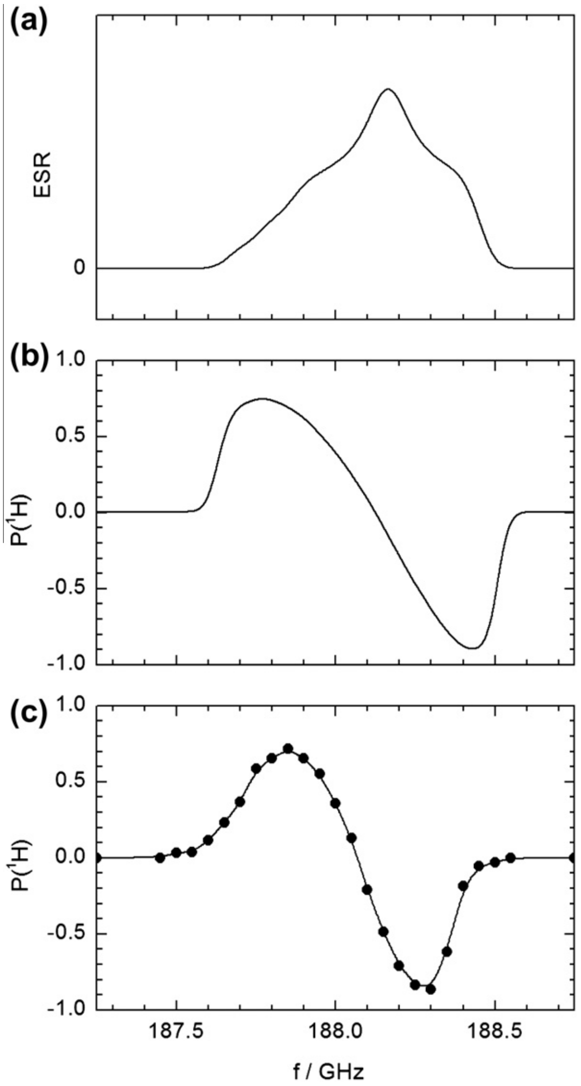

Figure 1. (a) Calculated ESR spectrum of 50 mM TEMPO at $B_0 = 6.7$ T. (b) Proton polarization $P(^1H)$ calculated as a function of the microwave frequency. (c) Experimental polarization $P(^1H)$ as a function of the microwave frequency at $B_0 = 6.7$ T and $T = 1.2$ K in a frozen 3 M solution of ^{13}C-1 enriched sodium acetate in a deuterated water/ethanol mixture (67:33 v/v) doped with 50 mM TEMPO (●). The curve is to guide the eye. For the parameters used to calculate the theoretical curves, see text.

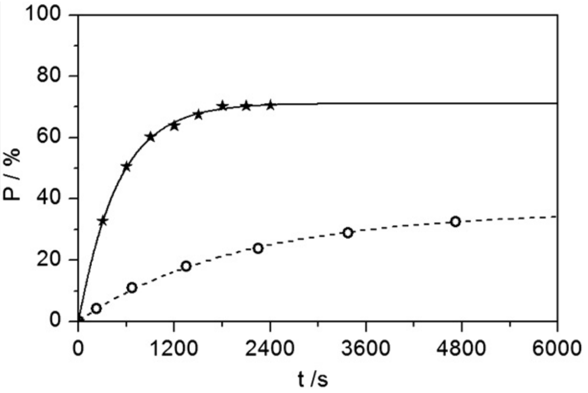

Figure 2. (○) Direct build-up of the polarization $P(^{13}C)$, without using cross-polarization (CP) from ^1H to ^{13}C, using TEMPO at $B_0 = 6.7$ T and $T = 1.2$ K with $f_{\mu w} = 188.3$ GHz and $P_{\mu w} = 120$ mW, leading to $P(^{13}C)^{max} = 36\%$ and $\tau_{DNP}(^{13}C) = 1980$ s. (★) Indirect build-up of the polarization $P(^1H \rightarrow ^{13}C)$ using adiabatic half passage cross-polarization (CP) from ^1H to ^{13}C with contacts of duration $\tau_{CP} = 1$ ms, repeated at intervals $\Delta t_{CP} = 300$ s (see text for details), leading to $P(^1H \rightarrow ^{13}C)^{max} = 71\%$ and $\tau_{DNP}(^1H \rightarrow ^{13}C) = 490$ s for a frozen 3 M solution of ^{13}C-1 enriched sodium acetate in a deuterated water/ethanol mixture (67:33 v/v) doped with 50 mM TEMPO.

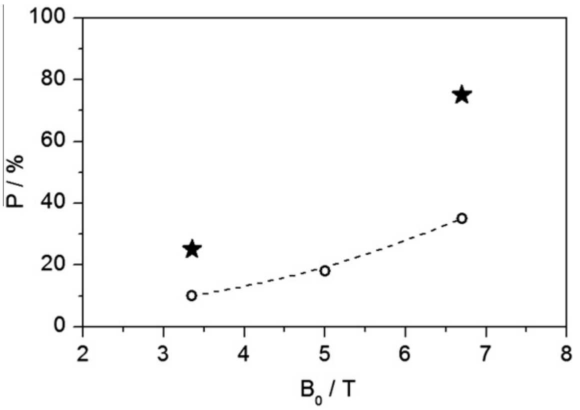

Figure 3. Polarization $P(^{13}C)$ obtained at $T = 1.2$ K in three different magnetic fields ($B_0 = 3.35$, 5.0 and 6.7 T) with frozen 3 M solutions of ^{13}C-1 enriched sodium acetate in a deuterated water/ethanol mixture (67:33 v/v) doped with TEMPO ($C_e = 30$, 50, and 50 mM at 3.35, 5.0 and 6.7 T respectively) (○) by direct DNP and (★) by indirect DNP using cross-polarization [3,9,11]. The curve is to guide the eye.

matching circuitry for $\nu_0(^1H) = 285.23$ MHz and $\nu_0(^{13}C) = 71.73$ MHz, all other components of the DNP polarizer were kept unchanged [11]. While this simple upgrade may appear straightforward, our observation that DNP can actually be dramatically improved at such high fields is far from obvious.

The build-up of $P(^1H)$ is rapid if TM is the dominant mechanism, as occurs with TEMPO. The electron spin resonance (ESR) spectrum of TEMPO has a broad line-width $\Delta\nu_e > \nu_0(^1H)$, because of its relatively large g-anisotropy ($\Delta g > \gamma(^1H)/\gamma_e$). This is not the case for Trityl that is characterized by a narrow ESR line-width $\Delta\nu_e < \nu_0(^1H)$. A broad ESR line $\Delta\nu_e > \nu_0(^1H)$ is a necessary, though not a sufficient, condition for ^1H polarization by TM. According to spin temperature theory [1], the spectral diffusion among electron spins must be fast compared to the electron spin–lattice relaxation ($t_{SD} \ll T_{1e}$). Fast spectral diffusion contributes to establishing a unique spin temperature T_S in the rotating microwave frame [13–15]. This spin temperature is subsequently transferred by thermal contact to all nuclear spins in the sample [12]. The condition $t_{SD} \ll T_{1e}$ can be readily fulfilled by increasing the radical concentration. However, the resulting dipolar broadening δ_d of the ESR spectrum should not mask the inhomogeneous broadening $\nu_e\Delta g$. Since the inhomogeneous line-width $\nu_e\Delta g$ increases with B_0, the radical concentration should be increased with B_0. At 6.7 T and 1.2 K, we empirically determined the optimal radical concentration to be $C_e = 50$ mM, instead of $C_e = 30$ mM at 3.35 T and 1.2 K.

Figure 1 shows (a) the simulated ESR line of 50 mM TEMPO at $B_0 = 6.7$ T calculated with EasySpin[16] with the following parameters: Sys.g = [2.00962.00652.0023]; Sys.Nucs = '14N'; Sys.A = [18.819.4102.4] MHz; Sys.lwpp = 2.7 mT. (b) Corresponding simulated DNP enhanced proton spectrum under partial microwave saturation, as a function of the microwave frequency, assuming that TM is the dominant mechanism [12], taking the ESR spectrum of Figure 1a as input, assuming a microwave field strength $B_1 = 2$ kHz, and a saturation rate $r_s = 40$ Mrad s^{-1} (see [17] for definitions). (c) Experimental DNP enhanced proton signals (●) as a function of the microwave frequency, measured at $B_0 = 6.7$ T and $T = 1.2$ K with a microwave power $P_{\mu w} = 120$ mW

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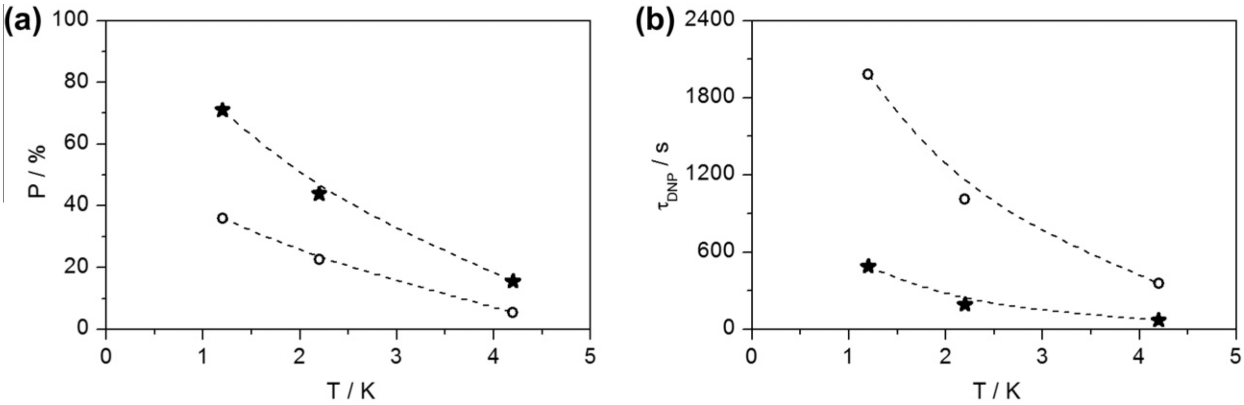

Figure 4. (a) Polarization $P(^{13}C)$ and (b) DNP build-up times $\tau_{DNP}(^{13}C)$, respectively $\tau_{DNP}(^{1}H \rightarrow {}^{13}C)$, obtained (○) by direct DNP and (★) by indirect DNP using cross-polarization at $B_0 = 6.7$ T as a function of temperature $T = 1.2$, 2.2 and 4.2 K with a frozen 3 M solution of ^{13}C-1 enriched sodium acetate in a deuterated water/ethanol mixture (67:33 v/v) doped with 50 mM TEMPO. The curves are to guide the eye.

Table 1
Various polarization levels, enhancements, build-up time constants, and spin–lattice relaxation times (after CP) observed in a field $B_0 = 6.7$ T at three different temperatures $T = 1.2$, 2.2 and 4.2 K for a 3 M frozen solution of ^{13}C-1 enriched sodium acetate in a deuterated water/ethanol mixture (67:33 v/v) doped with 50 mM TEMPO.

T/K	$\tau_{DNP}(^{13}C)$/s	$P(^{13}C)$/%	ε_{DNP}	$\tau_{DNP}(^{1}H)$/s	Δt_{CP}/s	$\tau_{DNP}(^{1}H \rightarrow {}^{13}C)$/s	$P(^{1}H \rightarrow {}^{13}C)$/%	$\varepsilon_{CP\text{-}DNP}$	$T_1(^{13}C)$/s
1.2	1980	36	254.5	150	300	488	71	495.0	1281
2.2	1010	22.5	287.5	52	120	192	43.8	559.8	765
4.2	359	5.5	134.2	25	60	70	15.5	378.2	320

in a frozen 3 M solution of ^{13}C-1 enriched sodium acetate $CH_3{}^{13}COONa$ in a deuterated water/ethanol mixture (67:33 v/v) doped with 50 mM TEMPO.

Proton polarization values as high as $P(^{1}H) = 91\%$ can be readily obtained with $f_{\mu w} = 188.3$ GHz, corresponding to the negative extremum in Figure 1b, with a short build-up time $\tau_{DNP}(^{1}H) = 150$ s. This polarization level is equivalent to a spin temperature as low as $T_S = 4.5$ mK. Under the same conditions, $P(^{13}C)$ builds up much more slowly by direct DNP with $\tau_{DNP}(^{13}C) = 1980$ s towards a level $P(^{13}C) = 36\%$.

Figure 2 demonstrates the use of CP to achieve an unprecedented level of $P(^{1}H \rightarrow {}^{13}C) = 71\%$ with a record build-up time of $\tau_{DNP}(^{1}H \rightarrow {}^{13}C) = 490$ s. This is accomplished by repeating a single-contact adiabatic half-passage cross-polarization (CP) scheme at intervals $\Delta t_{CP} = 300$ s, inspired by preliminary work of Perez-Linde and Köckenberger [18]. In our experiments, each CP contact comprises (a) two frequency-swept pulses applied simultaneously to both ^{1}H and ^{13}C channels, i.e., two CHIRP pulses of duration 175 μs with constant 40 kHz amplitudes on both channels (which must be limited to avoid arcing) and carrier frequencies swept in a linear fashion (from – 100 kHz to ^{1}H or ^{13}C resonance) that convert the longitudinal magnetization $I_z + S_z$ into transverse magnetization $I_x + S_x$, (b) a rectangular pulse with a constant 40 kHz amplitude of duration $\tau_{CP} = 1$ ms applied to the ^{1}H channel, simultaneously with a ramped pulse applied to the ^{13}C channel with an amplitude that is increasing linearly between 36 and 44 kHz,[19] (c) and finally two CHIRP pulses with frequencies that are swept in the opposite sense as in step (a) to bring the magnetization back to $I_z + S_z$, in the manner of flip-back experiments [20]. The overall efficiency of this adiabatic half-passage CP scheme depends on many factors, such as the efficiency of each CP step, the partial depletion of the polarization $P(^{1}H)$ in each CP step, the time constant $\tau_{DNP}(^{1}H)$ of the ^{1}H polarization build-up due to DNP, the T_1 relaxation of $P(^{1}H)$ and $P(^{13}C)$, etc. The optimal repetition time Δt_{CP} and contact time τ_{CP} are best determined empirically. For example, a shorter repetition time $\Delta t_{CP} = 150$ s leads to a faster build-up time constant $\tau_{DNP}(^{1}H \rightarrow {}^{13}C) = 340$ s, but at a price of a lower final polarization level $P(^{1}H \rightarrow {}^{13}C) = 67\%$. Longer contact times τ_{CP} can slightly improve the efficiency of each CP contact, but tend to accelerate the depletion of $P(^{1}H)$ through $T_{1\rho}$ relaxation of the spin-locked proton magnetization. Such losses are more pronounced when the radiofrequency field strength B_1 is not significantly larger than the line-width of the ^{1}H proton spectrum at 1.2 K, which is determined by dipolar broadening.

We advocate the use of TEMPO to rapidly boost the proton polarization $P(^{1}H)$, followed by $^{1}H \rightarrow {}^{13}C$ cross-polarization using adiabatic half-passage methods. Unless one wishes to avoid cross-polarization and prefers direct ^{13}C DNP, TEMPO is actually better than Trityl. Our strategy allows one to obtain higher polarization levels at high fields. Figure 3 shows the improvement of ^{13}C DNP at $T = 1.2$ K (with and without CP) at $B_0 = 6.7$ T compared to $B_0 = 3.35$ and 5 T. Figure 4 shows (a) the maximum ^{13}C polarization obtained and (b) the build-up time constants measured at $B_0 = 6.7$ T and different temperatures $T = 1.2$, 2.2, and 4.2 K, with and without CP. Table 1 collects the polarization levels and build-up times that have been observed and shows relaxation times at $B_0 = 6.7$ T and $T = 1.2$, 2.2, and 4.2 K. In our previous study at $B_0 = 3.35$ T [10], we presented the temperature dependence of direct ^{13}C DNP as a function of microwave irradiation power in the same temperature range $1.2 < T < 4.2$ K. It turned out that, with our microwave system [11], a power $P_{\mu w} > 200$ mW was required to achieve efficient polarization at $T = 4.2$ K. In the present letter, we used a microwave source with a fixed power $P_{\mu w} = 120$ mW at $f_{\mu w} = 188$ GHz. Improvements in microwave transmission and the use of more powerful microwave sources should be greatly beneficial for DNP at $T = 4.2$ K.

In a high field $B_0 = 6.7$ T and at low temperatures $1.2 \leqslant T \leqslant 4.2$ K, in concentrated frozen solutions of 50 mM TEMPO with broad EPR lines, proton DNP occurs mostly through thermal mixing (TM). The enhancements build up much faster for ^{1}H with TEMPO than for ^{13}C with Trityl. Adiabatic half-passage cross-polarization provides polarizations $P(^{1}H \rightarrow {}^{13}C) = 71\%$ that are larger than can be achieved with TEMPO by direct polarization $P(^{13}C) = 36\%$,

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and substantial gains in build-up times with ratios $\kappa = \tau_{DNP}(^{13}C)/\tau_{DNP}(^{1}H \rightarrow {}^{13}C) > 4$. Since the lifetime of CP-enhanced ^{13}C solid state polarization is sufficiently long ($1281 \geqslant T_1(^{13}C) \geqslant 320$ s for $1.2 \leqslant T \leqslant 4.2$ K), dissolution experiments should be straightforward with such highly polarized samples. After acceptance of the manuscript, dissolution experiments were carried out in a new insert, of different geometry, comprising a saddle coil. After dissolution (0.7 s), transfer to a 7.05 T NMR magnet (5 s), injection (3 s), and settling of the sample (1 s), liquid state polarization levels of 39% and 21.5% where achieved with and without CP. This demonstrates that CP-DNP enhanced polarization can be preserved during dissolution and transport.

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