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Low-temperature cross polarization in view of enhancing dissolution Dynamic Nuclear Polarization in NMR

Sami Jannin^{a,*}, Aurélien Borner^a, Sonia Colombo^{b,c}, Geoffrey Bodenhausen^{a,d,e,f}^a Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), Batochime, CH-1015 Lausanne, Switzerland^b Centro Ricerche Bracco, Bracco Imaging Spa, Via Ribes 5, I-10010 Colletterto Giacosa (TO), Italy^c Dept. of Experimental Physics, University of Torino, Via P. Giuria 1, I-10100 Torino, Italy^d Département de Chimie, Ecole Normale Supérieure, 24 Rue Lhomond, 75231 Paris Cedex 05, France^e Université Pierre-et-Marie Curie, Paris, France^f CNRS, UMR 7203, Paris, France

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ABSTRACT

Dynamic Nuclear Polarization (DNP) induced by saturation of ESR transitions of TEMPO at 1.2 K and 3.35 T is characterized by build-up rates that are typically 5 times faster for protons than for the carboxylic carbon-13 in acetate. We show that cross polarization from protons to carbon-13 allows one to achieve a polarization $P(^{13}\text{C}) > 20\%$ in less than 10 min, twice as much as has been previously reported, in one-fifth of the time. This should open the way to an unprecedented improvement in the efficiency of dissolution DNP.

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So far, most NMR or MRI studies based on dissolution DNP [1] have focused on nuclear spins such as ^{13}C , ^{15}N , ^{89}Y , etc., that have long nuclear spin–lattice relaxation times T_1 in the liquid state. Long T_1 's are mandatory to study slow chemical reactions [2] or metabolic processes [3]. Unfortunately the polarization build-up times τ_{DNP} of such spins can be excessively long, typically on the order of 10–60 min [4,5]. Although the more abundant protons usually have much shorter τ_{DNP} at low temperatures, they also tend to have much shorter T_1 's in the liquid state, so that protons appear to be of limited interest to monitor slow reactions. However, it has recently been shown that proton hyper-polarization can be stored in the form of Long Lived States (LLS) [6–8] which can have lifetimes on the order of 100 s. This can be achieved by semi-selective inversion using suitable radio-frequency (rf) pulses at high field, followed by shuttling the sample to low field [9]. Nevertheless, since many chemically and biologically relevant molecules cannot support LLS that require a pair of reasonably isolated protons, it may be assumed that molecules containing ^{13}C or ^{15}N spins with long T_1 's as in carbonyl groups will remain popular for dissolution-DNP experiments.

We demonstrate in this Communication that cross polarization (CP) [10] from protons to low-gamma nuclei such as ^{13}C can be carried out efficiently at $T = 1.2\text{ K}$ and $B_0 = 3.35\text{ T}$. Since the build-up of proton polarization by DNP using microwave saturation of the electron spin resonance (ESR) transitions of the

free radical 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) is fast, one can quickly obtain intense ^{13}C signals after cross-polarization. The ESR lineshape of TEMPO displays inhomogeneous broadening dominated by g -anisotropy, $g_{xx} = 2.0096$, $g_{yy} = 2.0065$, $g_{zz} = 2.0023$, so that the ESR linewidth ($2\sqrt{\mu_2} = 230\text{ MHz}$) exceeds NMR Larmor frequencies at $B_0 = 3.35\text{ T}$. With appropriate radical concentrations (ca. 30 mM TEMPO) one obtains large electron–electron dipolar couplings D (ca. 10 MHz) allowing a unique spin temperature to be established in the electron dipolar spin bath. With suitable microwave irradiation ($P_{\text{mw}} = 30\text{ mW}$, $f_{\text{mw}} = 93.9\text{ GHz}$), the dominant DNP build-up mechanism is the so-called Thermal Mixing (TM) effect [11] which ultimately confers a common temperature $T_s \approx 8.5\text{ mK}$ to all nuclear spins with $I = \frac{1}{2}$ in the sample. The nuclear spin polarization is given by:

$$P = \tanh\left(\frac{\hbar\omega_l}{2k_B T_s}\right) \quad (1.1)$$

where ω_l is the nuclear Larmor frequency. A spin temperature $T_s = 8.5\text{ mK}$ is equivalent to polarizations $P(^1\text{H}) \approx 0.4$ and $P(^{13}\text{C}) \approx 0.1$. The build-up rates of DNP are much faster for protons than for low-gamma nuclei [5]. Figure 1 shows DNP build-up curves of ^1H and ^{13}C magnetization, measured at 1.2 K at regular intervals with small flip angle pulses ($\beta = 1^\circ$ and 5° , respectively). A 1 M solution of ^{13}C enriched sodium acetate dissolved in a deuterated water/ethanol mixture (67:33 v/v) was doped with 30 mM TEMPO to form glassy beads in liquid nitrogen. At 1.2 K, the build-up time-constant of the proton magnetization $\tau_{\text{DNP}}(^1\text{H}) = 81\text{ s}$ is ten times less than $\tau_{\text{DNP}}(^{13}\text{C}) = 890\text{ s}$, and, as expected by thermal mixing theory, the steady-state DNP polarization is ca. 4 times

* Corresponding author. Address: Institut des Sciences et Ingénierie Chimiques, Ecole Polytechnique Fédérale de Lausanne (EPFL), BCH 1534 (Bâtiment de chimie UNIL), CH-1015 Lausanne, Switzerland. Fax: +41 21 693 94 35.

E-mail address: sami.jannin@epfl.ch (S. Jannin).

Figure 1. DNP build-up curves measured for ^1H and ^{13}C without cross-polarization at $T = 1.2\text{ K}$ and $B_0 = 3.35\text{ T}$ with DNP using $P_{\text{HFW}} = 30\text{ mW}$ and $f_{\text{HFW}} = 93.9\text{ GHz}$. The build-up times are $\tau_{\text{DNP}}(^1\text{H}) = 81\text{ s}$ and $\tau_{\text{DNP}}(^{13}\text{C}) = 890\text{ s}$, and the maximum achieved polarizations are $P(^{13}\text{C}) \approx 0.095$ and $P(^1\text{H}) \approx 0.34$.

greater for protons than for carbon-13, i.e., $P(^1\text{H}) \approx 0.4$ and $P(^{13}\text{C}) \approx 0.1$.

With a custom-built doubly tuned NMR probe coupled to a solid-state Bruker NMR spectrometer allowing simultaneous rf irradiation of ^1H and ^{13}C , CP experiments were carried out using a home-built polarizer [4]. The design of the tuning and matching capacitors and the immersion of the horizontal solenoidal rf coil that contains the DNP sample in the liquid helium bath at 1.2 K provide efficient cooling and high arching limit. It should be noted that the rf circuitry must be very efficient to avoid heating the sample, and should display good rejection between the two channels (higher than 30 dB for both ^1H and ^{13}C in our case). The two transmitters can generate rf field amplitudes of 55 kHz each with only about 14 and 22 W for the ^1H and ^{13}C channels, respectively (both Q factors are equal to 130). Conventional CP has been combined with DNP and magic-angle spinning (MAS) at temperatures near 100 K [12,13]. In the Dissolution DNP approach, one should restore the ^{13}C and ^1H polarizations by flip-back pulses [14] after CP contact to preserve the maximum polarization before dissolution (Figure 2).

Figure 3. DNP build-up of the ^{13}C polarization, measured without CP with short 5° observation pulses (bottom gray curve), and with CP (top red curve) as shown in Figure 2.

Figure 3 shows the DNP build-up curve of the ^{13}C polarization in $1\text{-}^{13}\text{C}$ labeled acetate with and without CP. The latter experiment used 5° pulses repeated every 2 minutes, while CP was performed as shown in Figure 2 with the following parameters: rf field amplitudes $\nu_1(^1\text{H}) = \nu_1(^{13}\text{C}) = 55\text{ kHz}$, contact time $\tau_2 = 1\text{ ms}$, delay prior to short observation pulse $\tau_3 = 50\text{ ms}$, ^{13}C nutation angle $\beta = 5^\circ$, acquisition time 5 ms, and recovery delay $\tau_1 = 0$. A maximum ^{13}C spin polarization of $P(^{13}\text{C}) = 23\%$ was achieved with a build-up time $\tau_{\text{DNP}}^{\text{CP}}(^{13}\text{C}) = 170\text{ s}$ when using CP, whereas without CP only $P(^{13}\text{C}) = 9.5\%$ could be achieved with $\tau_{\text{DNP}}(^{13}\text{C}) = 890\text{ s}$. This result could theoretically be improved, with an optimal CP efficiency, to $P(^{13}\text{C}) = P(^1\text{H}) = 40\%$ and $\tau_{\text{DNP}}^{\text{CP}}(^{13}\text{C}) = \tau_{\text{DNP}}(^1\text{H}) = 81\text{ s}$.

In conclusion, we have demonstrated the virtues of combining cross-polarization (CP) with DNP experiments at low temperatures. The CP scheme provides a way to efficiently polarize ^{13}C nuclear spins from protons which benefit from a rapid DNP build-up. The maximum ^{13}C polarization is more than doubled while the build up rate is enhanced by a factor 5.2. We believe that further improvement in hardware (saddle coils that are better adapted to rapid dissolution, higher rf amplitudes, faster rf power and phase switching times), sample preparation (e.g., partial deuteration of the solvent, optimization of the radical concentration) and pulse sequence design (e.g., adiabatic variants of CP [15]) may lead to higher enhancements. CP for other ^{13}C labeled compounds that are of interest for *in vivo* MRI studies shows similar performances. Thus, $1\text{-}^{13}\text{C}$ sodium pyruvate gives a twofold enhancement with respect to direct DNP of ^{13}C . Dissolution-DNP combined with CP at higher fields [16–18] should yield even higher polarizations $P(^{13}\text{C})$. CP from protons to very low-gamma spins (^{15}N , ^6Li , ^{89}Y , etc.) is also expected to yield substantial enhancements.

Figure 2. CP pulse sequence used for enhancing the ^{13}C spin polarization. Both ^1H and ^{13}C spin polarizations are restored after CP by flip-back pulses [14].

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