Hyperpolarization quenching in ^{13}C nuclei bound to fast relaxing quadrupolar ^{14}N mediated by scalar coupling relaxation in amide groups exposed to Earth's magnetic field

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Introduction

Magnetic resonance spectroscopic imaging (MRSI) with hyperpolarized substances is one of the most promising molecular imaging methods. This approach has the potential to overcome the main drawback of the ^{13}C-MRS/MRI technique, namely the low absolute sensitivity that results from the low gyromagnetic ratio and low natural isotopic abundance of ^{13}C. The possibility of using hyperpolarized agents in either MR spectroscopy or in MR imaging is strictly dependent on their relaxation time. Glutamine is an important metabolite, its utilization is greatly enhanced and linked to the energetic metabolism in tissues where a proliferative state is activated (e.g injuries, tumor)[1]. Working with [5- ^{13}C] glutamine for this purpose, a rapid polarization loss was observed after completing the dissolution process, yielding an almost zero signal in the resulting NMR spectrum (Fig. 1). The same behavior has been observed in [^{13}C]urea. To the best of our knowledge no one has described and explained a similar transient fast relaxation phenomenon. The significant T_1 shortening that is observed can be explained in terms of the scalar coupling relaxation (2nd kind) contribution to relaxation due to the fast relaxing quadrupolar ^{14}N nucleus coupling with the ^{13}C nucleus. This contribution is efficient at the low environmental magnetic field present in the laboratory. In fact, the use of an auxiliary magnetic field of about 0.2 T from a permanent magnet during sample transfer to the MRI scanner reduced the T_1 shortening; using this method, a sufficient level of liquid-state polarization was obtained for both molecules to enable their use as DNP probes.

Methods

The spin–lattice relaxation time T_1 is determined by contributions from different and independent mechanisms:

$$R_1 = \sum_i R_i = R_d + R_{para} + R_{csa} + R_{sr} + R_q + R_{sc}$$

- Dipolar interaction, Quadrupolar interaction, Spin rotation(R_d, R_q, R_{sr}) → No Field Dependence
- Paramagnetic dipolar interaction → $R_1 \propto 1/B_0$ but only when using nitroxide radicals[2]
- Chemical shift anisotropy relaxation (c.s.a) → $R_1 \propto B_0^2$
- Scalar coupling relaxation (s.c): → $R_1 \propto 1/B_0^2$ through $\omega=\gamma B_0$

$$(1)\quad R_{sc} = \frac{8\pi^2 J^2}{3} I(I+1) \frac{T_1{}^{14N}}{1+(\omega_{13C}-\omega_{14N})^2 (T_1{}^{14N})^2}$$

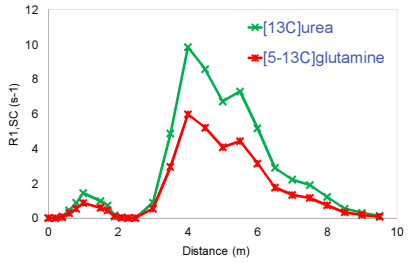

Fig. 2: Estimated SC contribution profile to ^{13}C relaxation rate obtained from the Eq. 1. $T_1{}^{14N} = 10^{-3}$ s $J_{C\text{-}N} = 14$ Hz $B_0 = 20\mu T$ $2mT$ during transfer

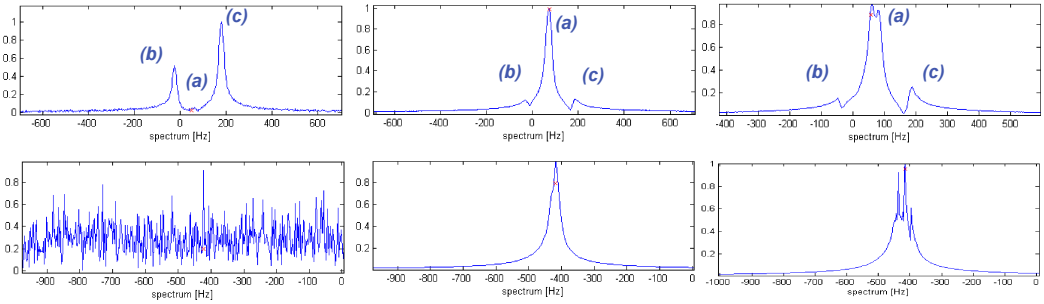

Fig. 1: Hyperpolarized spectra of [5-^{13}C]glutamine (above) and [^{13}C]urea (below): first column, samples transferred at low field magnetic field (<1mT); second column, samples transferred with a 0.2 T auxiliary magnetic field; third column ^{15}N labeled samples transferred at low magnetic field (<1mT). Glutamine signal is indicated as (a); (b) and (c) are assigned to [5-^{13}C] glutamate and [5-^{13}C] pyroglutamate, respectively;

Results & Discussion

The hyperpolarized signal is strongly enhanced by the presence of an auxiliary magnetic field during the transfer, as well as by the use of ^{15}N labeled amides (Fig. 1). No polarization preserving effect was observed when a radical scavenger (sodium ascorbate 5mM) was added to the dissolution agent (Tab. 1). The observed low field relaxation behavior for ^{14}N-^{13}C amides suggested that, in such conditions (relatively strong J coupling, short ^{14}N nucleus T_1 and weak magnetic field), a new relaxation mechanism becomes dominant. Scalar coupling (type II) is known to be an efficient relaxation mechanism in closely resonant nuclei (^{79}Br-^{13}C). Its contribution to relaxation has been theoretically estimated[3] using eq. 1 and has been found to be equivalent to an averaged R_1 of 1.5±0.1 s^{-1} (Fig. 2). This polarization quenching has been successfully overcome by keeping the hyperpolarized sample close to a permanent magnet (0.2 T). Alternatively, ^{15}N labeling of the substrates appeared to be effective and may be a safer solution. This phenomenon should be taken into account during the design of a DNP-MRI laboratory, either by locating the polarizer in the stray field of the MR scanner or by connecting it to the MR scanner with a suitable sustained magnetic field transfer system.

Experimental

- 20 µL [^{13}C]urea ($^{14}N/^{15}N_2$ – 8M), 25 mM OX063 Trityl radical, 2.5mM Dotarem;
- 100 µL [5-^{13}C]glutamine (5-$^{14}N/^{15}N$ – 0.6M), 45 mM OX063 Trityl radical 5mM Dotarem;
- Glassing agent: Glycerol;
- Dissolution agent: 5ml Tris (30mM) buffered D_2O;
- Final concentration: 32 and 12 mM, [^{13}C]urea and [5-^{13}C]glutamine, respectively;
- Hypersense 3.35T polarizer for 1h at 94.115 and 94.105 GHz, [^{13}C]urea and [5-^{13}C]glutamine, respectively;
- Transfer time: 16 - 18 sec;
- 3T GE Signa HDx scanner set up with a purpose-built solenoid ^{13}C coil;
- Small flip angle pulses sequence (5° for the [^{13}C]/[^{13}C,^{15}N] urea and 10° for the [5-^{13}C]/[^{13}C,^{15}N] glutamine samples);
- Thermal polarization: 2048 scan averaged measurement on the sample after adding 4% v/v Dotarem (90°, TR 1s);
- Liquid polarization calculated from the integrated hyperpolarized and the thermal spectrum, a thermal Boltzmann distribution was assumed for the thermal measurement;
- Polarization values not corrected for the T_1 decay since the T_1 at low field was markedly different from the one measured at 3 T.

Table 1. Polarization values and relaxation times of [^{13}C]urea and [5-^{13}C]glutamine, measured at 3T.

	T_1(s) at 3 T	Transport in earth's magnetic field	Sample attached to 0.2 T permanent magnet during transport	Transport in earth's magnetic field, ascorbate added as radical scavenger
		Liquid Pol (%)	Liquid Pol (%)	Liquid Pol (%)
[^{13}C,$^{14}N_2$]urea	78±4	$3\cdot10^{-3}$±$1\cdot10^{-3}$	13±1	$3\cdot10^{-3}$±$1\cdot10^{-3}$
[^{13}C,$^{15}N_2$]urea	85±7	30±2	25±1	- - -
[5-^{13}C, ^{14}N]glutamine	8.0±0.1	$0.02\pm5\cdot10^{-3}$	0.7±0.1	$0.05\pm5\cdot10^{-3}$
[5-^{13}C, ^{15}N]glutamine	7.7±0.4	0.7±0.2	0.8±0.1	- - -

References

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