The Spin-Lattice Relaxation of Hyperpolarized 89Y Complexes

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INTRODUCTION

The intrinsically low sensitivity of NMR can be overcome by dynamic nuclear polarization (DNP),[1] However, a fundamental limitation in the use of hyperpolarized materials is the signal decay due to T_1 relaxation. Among NMR-active nuclei, ^{89}Y offers a number of attractive features. It is 100% abundant, it has spin ½, and it has a long T_1, up to 10 min.[2] ^{89}Y is potentially valuable in medical imaging because in chelated form, pH-sensitive agents can be developed.[3] Further, ^{90}Y in a monoclonal antibody is therapeutically useful and the ability to directly image biodistribution of the ^{89}Y analogue would be valuable. A long T_1 and T_2 (up to 15 seconds) also makes ^{89}Y suitable for fast CSI techniques using flyback gradients. The development of new ^{89}Y complexes with even longer T_1 values is desirable. The design of such complexes relies upon understanding the mechanism(s) responsible for longitudinal relaxation. However, measuring such long relaxation times with thermally polarized ^{89}Y requires days or weeks, rendering such an approach inefficient. We have observed that the accuracy of T1 measurements in hyperpolarized ^{89}Y solutions strongly depends upon appropriate choice of experimental parameters. Here we report an approach to T_1 measurements. This method enabled an analysis of relaxation mechanisms by selective deuteration of the ligand backbone, the solvent or both. Initial results are reported for both open chain and macrocyclic Y(III) complexes that can be used for *in vivo* applications. The ligands examined are DTPA, EDTA, uniformly deuterated EDTA, and DOTA (Figure 1).

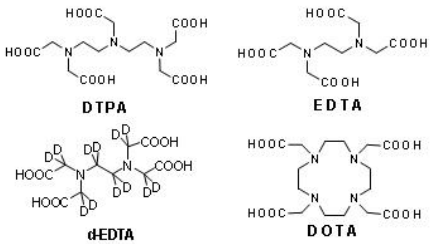

Figure 1. Ligands used in this work

METHODS

T_1 measurements of hyperpolarized ^{89}Y samples were conducted at room temperature in a 9.4T field using a Varian VNMRS console and 10mm probe tuned to ^{89}Y (19.6 MHz). Samples were polarized using an Oxford DNP HyperSense operating at 1.4° K and 3.35T, subject to 94.125 GHz of CW irradiation at 100 mW power. 160 µL samples comprised of either 160 mM DTPA, 158 mM EDTA, 158 mM deuterated EDTA, or 394 mM DOTA plus 16 mM trityl radical dissolved in a 75/25 H_2O/glycerol mixture were hyperpolarized. To ensure proper glassing of the mixture, necessary to achieve optimum polarization levels, samples were pre-frozen outside of the HyperSense in liquid N_2. Dissolution was performed with H_2O, except for the case of EDTA and d-EDTA, in which case D_2O was also used.

RESULTS

Data was acquired on only 1 mL of the 4 mL of hyperpolarized solution ejected from the HyperSense to ensure confinement of the sample strictly within the vertical height of the coil. This subjects all of the spins within the sample to the same rf amplitude (ie., flip angle). If the sample were to extend beyond the dimensions of the coil, diffusion of fresh magnetization into the coil would artificially lengthen the measured T_1. To examine the influence of flip angle on the accuracy of T_1 measurements, a series of both 5° and 20° hard pulses, each with a repletion time of 20 seconds, were employed. The recorded data was fit to the equation in Figure 2 where M_p represents the initial magnetization, TR the repetition time, and θ the flip angle (in degrees). If a shallow flip angle is administered (≤5°), only a small fraction of the hyperpolarized magnetization is destroyed per pulse, rendering the dominant loss of magnetization to T_1 decay, rather than rf. On the contrary, if spins are subjected to a large flip angle (≥15°), a significant fraction of the magnetization is destroyed per pulse, placing greater emphasis on rf calibration than on T_1 decay. In the latter case, the accuracy of the hyperpolarized T_1 measurement can be compromised. An illustration of this is shown in Figure 2, where the T_1 of hyperpolarized d-YEDTA in H_2O solvent is measured using a series of 5° and 20° hard pulses. It is clear that the decay resulting from a 20° flip angle is heavily weighted by the destruction of Z-magnetization by pulsing, rather than T_1 relaxation, as the measured value is reduced by almost 35% in comparison to that derived from the 5° pulse. Another problem with the use of large flip angles is that even small errors in pulse width calibrations can propagate into extremely large errors in the measured T_1. To illustrate this point, a 15% error in pulse width was imposed upon the fitting of the two decay curves shown in Figure 2, such that a 6° flip angle was substituted in place of the 5°, and 23° in place of the 20° pulse (fits not shown). There was only about a 5% change in the extrapolated T_1 for the shallow flip angle scenario, while an almost 50% change resulted in the case of the large pulse width!

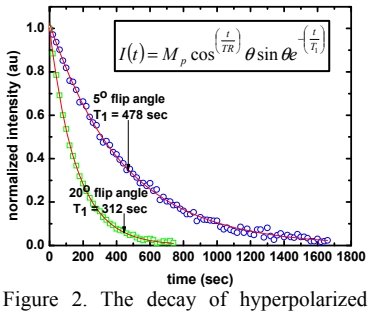

Figure 2. The decay of hyperpolarized magnetization resulting from a series of 5° (○) and 20° (□) hard pulses, along with their corresponding T_1 values.

complex	T_1 *(sec)*
YDTPA	398
YEDTA (H_2O)	418
YEDTA (D_2O)	431
d-YEDTA (H_2O)	469
d-YEDTA (D_2O)	521
YDOTA (H_2O)	471

Table 1. T_1 values for hyperpolarized YDTPA, YEDTA, d-YEDTA, and YDOTA, measured using a 5° pulse and 20 sec TR.

Using 5° pulses, the T_1 of hyperpolarized YDTPA, YEDTA, d-YEDTA, and YDOTA were measured to gain insight into the dominant mechanism responsible for relaxation. For the case of YEDTA, we independently examined the effect of deuteration on the ligand backbone and the solvent. It is evident from Table 1 that the T_1s of the open chain complexes are comparable, while the macrocyclic YDOTA has a slightly larger value. An important observation is the increase in T_1 with the presence of ^{2}H. According to dipolar relaxation theory, the dipole moments of nearby nuclei provide a source of oscillating magnetic field, necessary to induce relaxation. The effect of ^{2}H substitution significantly reduces the dipolar coupling due to the much smaller magnetic moment of ^{2}H. Although the percent change in Table 1 is small when water is substituted with D_2O as the dissolution solvent, the effect is more pronounced when the complex itself is deuterated. The effect of substituting D_2O for the three metal-bound water molecules in YEDTA was smaller than expected, which may be due to the chemical exchange between the bound water and bulk water pools.

CONCLUSIONS

We have demonstrated that the accuracy of hyperpolarized T_1 measurements depends strongly on the choice of flip angle – the smaller, the better. By making accurate T_1 measurements, we have been able to clearly observe the dependence on deuteration of both the ligand and solvent. The increased T_1 from this combination implies that the development of longer T_1 molecules for hyperpolarization experiments should involve the use of zero spin (^{12}C for example) or extremely low gamma nuclei in the vicinity of the hyperpolarized nucleus of observation. These results are also extremely encouraging for *in vivo* applications since they suggest that the presence of bound water will not play a major role in the reduction of T_1 for carefully engineered ^{89}Y complexes.

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