Producing >60,000-fold room-temperature ^{89}Y NMR signal enhancement

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Introduction

^{89}Y is potentially valuable in medical imaging because in chelated form its chemical shift is highly sensitive to the coordination environment and local factors such as pH. ^{90}Y in a monoclonal antibody is used currently for lymphoma radiotherapy and the ability to directly image its bio-distribution would be valuable. However, ^{89}Y has a low gyromagnetic ratio γ_n and the ^{89}Y NMR signal is hampered by low sensitivity. The NMR signal depends on the number of surplus spins in an upper or lower Zeeman state, i.e. the nuclear spin polarization. An ensemble of ^{89}Y (I = 1⁄2, γ_n=2.0864 MHz/T, 100 % natural isotopic abundance) spins, for instance, has a feeble P=1.578x10^{-4} % nuclear polarization at 9.4 T and 298 K. The low thermal polarization, combined with the long spin-lattice relaxation time T_{1n} (~500 s), makes ^{89}Y one of the most challenging nuclei to detect by NMR. Here we show that we can enhance the room-temperature NMR signal of ^{89}Y up to 65,000 times the thermal signal via fast dissolution dynamic nuclear polarization (DNP). This is a significant advance towards using hyperpolarized ^{89}Y as an MRI agent, in which case, the long T_{1n} translates into a long polarization lifetime.

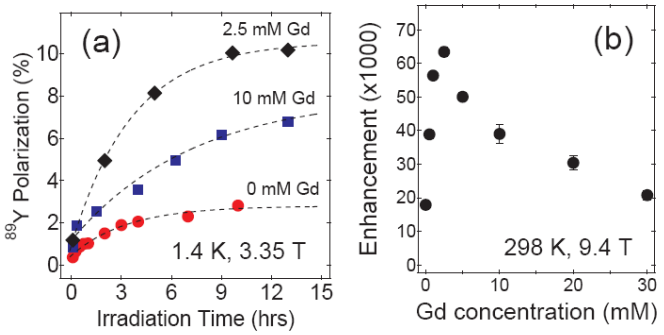
Methods

The samples contained the maximum soluble concentration of the yttrium complex of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (Y-DOTA) and optimum radical concentration dissolved in different glass formers (glycerol, ethylene glycol, propanediol, dimethyl sulfoxide, 18-crown-6, methanol) mixed with 50 % water by volume. Gd doping was done using the commercially available relaxation agent ProHance. For enhancement measurements, 40 uL samples were irradiated with a 100 mW microwave source at the positive polarization peak at 1.4 K and 3.35 T using an Oxford HyperSense polarizer. The dissolved polarized liquid ejected from the polarizer, approximately 3.5 mL in volume, is directly collected in a 10 mm NMR tube inside a 9.4 T high resolution magnet with a transfer time of 8 s. The liquid-state NMR signal enhancement is calculated by taking the ratio of the integrated area of the T_{1n}-corrected hyperpolarized (HP) signal A_{hp} over the thermal equilibrium signal A_{th} of a 3 M YCl_3 sample.

Results

The table below shows a summary of the dependence of room-temperature liquid-state ^{89}Y NMR enhancement ε on the choice of glassing agents and radicals. The more viscous glassing agents (glycerol, crown ether, ethylene glycol, and propanediol) gave the best enhancements. The trityl radical, which has the narrowest ESR linewidth, provides higher polarization than TEMPO and deuterated TEMPO. The NMR enhancement can be improved by increasing the ratio of the glassing agent to water, but this comes at the expense of lower solubility of Y-DOTA. Figures (a) and (b) show that Gd doping increases the ^{89}Y polarization of Y-DOTA samples (solid-state: 0.28 M Y-DOTA, 15 mM trityl in 1:1 glycerol:water matrix) up to 10 % at the optimum Gd doping (2.5 mM). This corresponds to ~65,000-fold enhancement of the thermal ^{89}Y NMR signal at room-temperature in a 9.4 T magnet. The increase of polarization with Gd in the sample may be attributed to the reduction of the Zeeman electronic T_{1e} of the radical which leads to lower spin temperature of the electron spin-spin interaction (SSI) reservoir. By thermal mixing, the electron SSI and nuclear Zeeman reservoirs are in thermal contact and acquire the same spin temperature.

Glassing agent	radical/conc	Y-DOTA conc	ε	$P_{hp}(^{89}Y)$
water	trityl/15 mM	0.48 M	2,200	0.35 %
glycerol	trityl/15 mM	0.28 M	17,700	2.79 %
	TEMPO/40 mM	0.28 M	4,600	0.73 %
	d_8-TEMPO/40 mM	0.28 M	5,400	0.85 %
crown ether	trityl/15 mM	0.27 M	20,400	3.22 %
ethylene glycol	trityl/15 mM	0.24 M	12,600	1.99 %
dimethyl sulfoxide	trityl/15 mM	0.24 M	2,900	0.46 %
propanediol	trityl/15 mM	0.24 M	18,500	2.92 %
methanol	trityl/15 mM	0.24 M	3,000	0.47 %



Conclusion

We have achieved ^{89}Y polarization up to 10 %, which corresponds to 65,000-fold enhancement of the thermal NMR signal at room temperature in a 9.4 T magnet. The increase of ^{89}Y polarization level was achieved through *i*) optimizing the glassing matrix, *ii*) choosing the best radical for DNP, and *iii*) inclusion of an electron T_{1e} relaxation agent. Further improvements could be achieved by decreasing the lattice temperature of the sample. The NMR optimization details here are vital for obtaining higher enhancements for future *in vivo* pH imaging applications using hyperpolarized ^{89}Y complexes.