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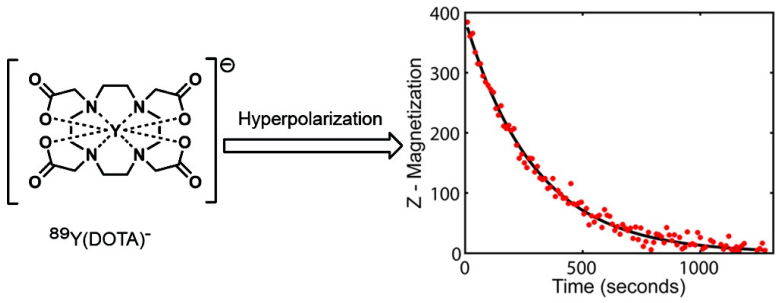

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Hyperpolarized ^{89}Y Offers the Potential of Direct Imaging of Metal Ions in Biological Systems by Magnetic Resonance

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Hyperpolarization of nuclear spins can produce a dramatic increase in sensitivity for NMR active nuclei. Although the idea of transferring spin polarization from electrons to nuclei by dynamic nuclear polarization (DNP) to create a hyperpolarized NMR sample has been around since the mid-1950s, applications of this technology for study of liquid samples have appeared only recently. In 2003, Ardenkjaer-Larsen et al.[1] developed an automated method to polarize ^{13}C nuclei at low temperatures in the presence of a stable trityl radical then bring the sample to room temperature very quickly to perform NMR measurements.[1,2] Obviously, this method was most practical for long T_1 ^{13}C nuclei such as non-protonated carbonyl or carboxyl carbons in rapidly tumbling small molecules, which yielded NMR signal enhancements of 10 000-fold or higher. One of the more exciting applications of this technology was reported shortly thereafter by Golman et al.[3] who demonstrated that it is practical to do real time metabolic imaging of [1-^{13}C]pyruvate, [1-^{13}C]lactate, and [1-^{13}C]alanine in live animals using ^{13}C chemical shift imaging (lactate and alanine are quickly formed from the injected hyperpolarized pyruvate through single-enzyme catalyzed steps).

A commercial DNP device based on this technology now offers new opportunities for imaging nuclei that have not ordinarily been considered possible in the past. One attractive NMR nucleus for polarization is ^{89}Y because this nucleus is difficult to detect at thermal Boltzmann polarization levels owing to its small magnetic moment, low receptivity, and long T_1 relaxation times. ^{89}Y does however have a favorable spin quantum number ($^1/_2$), sharp NMR linewidths (3−5 Hz), and a long T_1, so this makes ^{89}Y attractive as a potential in vivo imaging and spectroscopy probe. Another isotope of yttrium, ^{90}Y (half-life = 2.7 days), is an attractive radioisotope for cancer therapy because it emits high energy β electrons (average β energy = 0.93 MeV) that provide relatively deep tissue penetration necessary for the treatment of larger tumors.[4,5] To date, the only approved targeted ^{90}Y radiopharmaceutical is Zevalin, used for treatment of non-Hodgkin's lymphomas.[6] A second drug, ^{90}Y-DOTA-D-Phe^1-Tyr^3-octreotide (^{90}Y-DOTATOC), is in phase I/II studies in Europe for somatostatin receptor positive tumors[7] and others will likely follow. Thus, a long-lived, hyperpolarized ^{89}Y analogue might be attractive for imaging the biodistribution of such drugs.

Only one ^{89}Y NMR study was reported prior to the 1970s.[8] With the advent of FT spectrometers, a few more reports appeared demonstrating that ^{89}Y salts have unusually long T_1 values and are concentration dependent.[9] More interestingly, Levy et al.[10] were first to show that complexation of $^{89}Y^{3+}$ with crown ethers of various ring size resulted in the lengthening of T_1 about 4-fold over that measured for salts dissolved in DMSO. In 1990, Holz and Horrocks used $^{89}Y^{3+}$ as a Ca^{2+} surrogate and reported that the chemical shift of various chelated forms of Y^{3+} varies widely, ranging from 36.6 ppm when bound at the EF site of parvalbumin to 129.6 ppm in Y(EDTA)$^-$.[11] This was the first demonstration that the chemical shift of $^{89}Y^{3+}$ complexes could be used as a probe of the coordination environment of the ion. Given the potential of hyperpolarized ^{89}Y for molecular imaging of targeted therapeutics, we recently initiated DNP studies of a few Y^{3+} complexes using a commercial polarizer (HyperSense, Oxford Molecular Biotools).

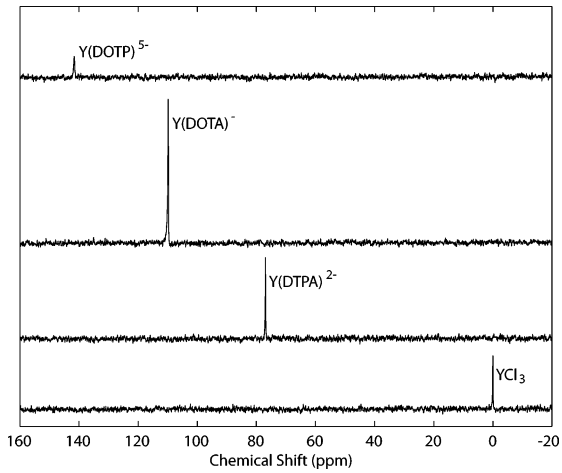

Figure 1. NMR spectra of hyperpolarized ^{89}Y complexes. Each spectrum was obtained on hyperpolarized sample ~30 s after transfer from the polarizer to a 8 mm NMR tube using a single 10° excitation pulse (see Table 1 for sample concentrations). The spectra were collected at 29.4 MHz using a 14.1 T magnet.

Dynamic nuclear polarization of frozen solutions consisting of YCl_3 and three different chelated forms of Y^{3+} in the presence of a common stable trityl radical resulted in polarization enhancements that varied from 246 to 1527-fold above thermal equilibrium at 310 K. Although these polarizations are small compared to recently reported ^{13}C samples where polarizations of 5000−10000-fold have been achieved, they were sufficient to allow easy detection of the ^{89}Y NMR signal using a single 10° pulse (Figure 1). From an experimental standpoint, the necessity of reducing the sample volume by taking only a portion of the effluent from the dissolution process undoubtedly resulted in a loss of some magnetization owing to T_1 processes before the NMR data collection ensued (see Supporting Information). Here, our goal was to measure T_1 values on each sample by following the decay process so the sample volume was limited to 1.5 mL to ensure that the entire volume was sampled with each 10° pulse. If the volume of the sample is not restricted to the sample coil, diffusion will cause erroneous

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Table 1. Hyperpolarized ^{89}Y Data for YCl_3 and Y^{III} Complexes

compound	concn in NMR tube (mM)	measured enhancement	measured T_1 (s)	chemical shift (ppm)
YCl_3	15	246	620	0 (ref)
$Y(DTPA)^{2-}$	7.6	566	451	76
$Y(DOTA)^{-}$	7.9	1527	499	109
$Y(DOTP)^{5-}$	10	298	264	141
$Y(DOTP)^{5-}$	5	1042	277	141

estimates of the T_1 because of the $\cos^{(n-1)}$ term in eq 1 (Supporting Information), making the T_1 appear artificially long. Also, the line width of the trityl radical used here is much too wide to match the Larmor frequency of ^{89}Y at the polarizing field (6.89 MHz), so other more favorable radicals should produce substantially higher polarizations. The polarization time used here (2.5 h) was arbitrary and chosen simply for experimental convenience. In general, the DNP effect is mediated by the electron−nuclear dipolar interactions, and the low gyromagnetic ratio of ^{89}Y means that the polarization time constant is likely very long. Thus, it is likely that higher polarization levels could have been achieved by polarizing the samples for a longer period.

The polarization enhancements reported in Table 1 were determined by comparison of the intensity of the polarized ^{89}Y signal after the first 10° pulse to a 3 M YCl_3 standard (single 90° pulse). Comparison of the signal from hyperpolarized samples after full relaxation (thermal polarization) was impossible at these concentrations (mM). The polarization predicted for a sample cooled to 1.4 K is 221 times greater than the Boltzmann thermal value at 310 K. The measured enhancements of YCl_3 and $Y(DOTP)^{5-}$ were only slightly above this value, so the effect due to DNP is only marginal in those cases. The remaining samples had polarizations well above that predicted for a cooled sample. It is interesting to note that the more highly charged species (Y^{3+} and $Y(DOTP)^{5-}$) show the lowest polarization and, as the charge is reduced ($Y(DTPA)^{2-}$ > $Y(DOTA)^{-}$), polarization increases. This may reflect less than optimal glass formation at 1.4 K with the more highly charged species.

The T_1s were measured by fitting the polarization decay curves (Figure 2) to eq 1 (Supporting Information). The T_1 values reported previously for $Y(NO_3)_3$ on thermally polarized samples varied from 63 to 270 s depending upon concentration (1 M samples gave longer T_1 values than 3 M samples).[10] Our estimates of T_1 obtained by following the decay of hyperpolarized ^{89}Y are even longer than those reported by Levy et al. by another factor of ∼2.3, but the concentration of the hyperpolarized sample was also lower by a factor of ∼67, so the trend reported by Levy et al. appears to hold over a very wide concentration range. It is unclear however whether this is simply an effect due to concentration or whether it partially reflects the experimental difficulty in measuring such long T_1 values for such an insensitive nucleus. In general, the T_1 values of the ^{89}Y-chelates were found to be lower than that of the YCl_3 sample, also in contradiction to earlier results.[10] One possible explanation for this observation is the higher B_0 field used here (14.1 T) may have an additional chemical shift anisotropy contribution to the T_1 relaxation mechanism in the asymmetric environment of the chelates. It is also possible that other ligand spins in these samples (^{14}N, ^{31}P) contribute to the relaxation of ^{89}Y.

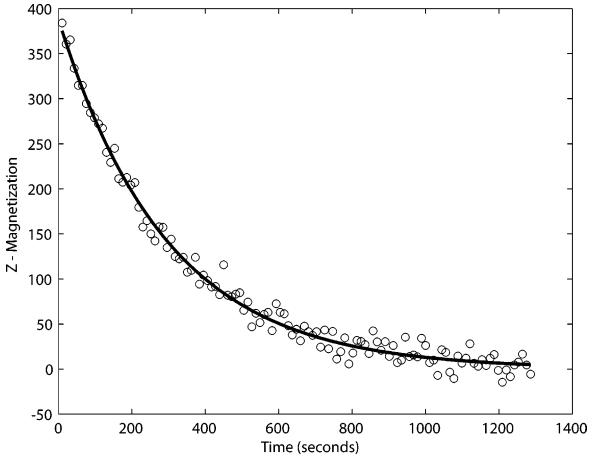

Figure 2. NMR signal of $^{89}Y(DOTA)^{-}$ collected as a function of time after the sample was ejected from the polarizer, then inserted into the magnet. Total time following dissolution until the first acquisition was 30 s. The pH was 7, and final concentration of $Y(DOTA)^{-}$ in the NMR tube was 7.9 mM. The fitted line gave a T_1 of 499 s.

In conclusion, hyperpolarization of ^{89}Y salts and ^{89}Y complexes is feasible with currently available commercial hardware. The long T_1's of ^{89}Y make its application as an MR imaging probe quite promising. In addition, the wide chemical-shift range for ^{89}Y means that contrast agents sensitive to a variety of biological/chemical milieu could serve as exquisite sensors of important biological events.

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Supporting Information Available: Experimental procedures as well as the equation used to fit the NMR data to obtain T_1. This material is available free of charge via the Internet at http://pubs.acs.org.

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