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[15] Assuming that the metal ions and **1** are present only as complexed species within a trinuclear complex **1**-M_3 and that the binding of the second and third metal ion is independent of the contents of the ligands in **1**-M and **1**-M_2, then **1**-Zn_2Cu is theoretically present in 44% in a statistical mixture together with **1**-Zn_3 (30%), **1**-$ZnCu_2$ (22%), and **1**-Cu_3 (4%). Moreover, two complexes with the composition **1**-Zn_2Cu (44%) can exist, that is, **1**-ZnZnCu and **1**-ZnCuZn in theoretical amounts of 29 and 15%. When considering the catalytic activity by pure **1**-ZnZnCu or **1**-ZnCuZn over **1**-Zn_3, the enhanced activity is much higher than the factor of 1.3 for **1**-Zn_2Cu shown in Table 1 and Figure 1.

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A Novel pH-Sensitive MRI Contrast Agent[**]

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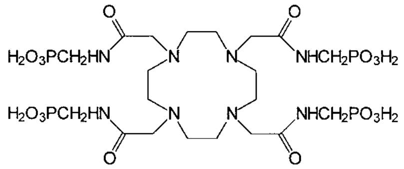
Most gadolinium complexes enhance relaxation of water protons by rapid exchange of inner-sphere water molecules with bulk solvent.[1] However, recent kinetic results have shown that the lifetime of an inner-sphere water molecule in Gd^{III} complexes can range from 0.84 ns for aqueous Gd^{III}, 208 ns for $[Gd(dota)]^-$, (dota = 1,4,7,10-tetraazacyclododecane-*N*,*N'*,*N''*,*N'''*-tetraacetate) to over 19000 ns in the tetraamide analogue, [Gd(**2**)].[1d, 2, 3] Recently reported examples of gadolinium-based contrast agents that are sensitive to enzyme activity[4a] and Ca^{2+}[4b] has stimulated synthesis of new cyclen-based ligands bearing different types of pendant arms. Given that tetraamide derivatives of cyclen have been reported to form both thermodynamically stable and kinetically inert complexes with Gd^{III} in aqueous solution,[3, 5, 6] we have been exploring tetraamide-based ligands with extended phosphonate or carboxylate noncoordinating side chains with the intent of generating new systems with specific ion-pairing capabilities. In characterizing one new derivative in this series, we observed that the water proton R_1 relaxivity of [Gd(**1**)] has an unusual pH dependence, increasing between pH 4 and 6, reaching a maximum near pH 6, gradually decreasing to a minimum near pH 8.5, then remaining relatively insensitive to pH 10.5 before increasing once again at higher pH values (Figure 1). This feature is quite different from that of [Gd(**2**)] whose R_1 is essentially independent of pH between 2 and 8 before increasing at higher pH values.[3] Similarly, the R_1 of $[Gd(dotp)]^{5-}$ (dotp is the tetraphosphonate analogue of dota) is independent of pH over an extended pH range (3–13).[7]



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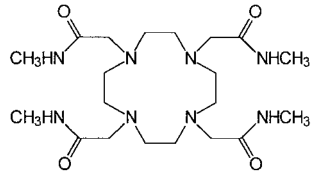

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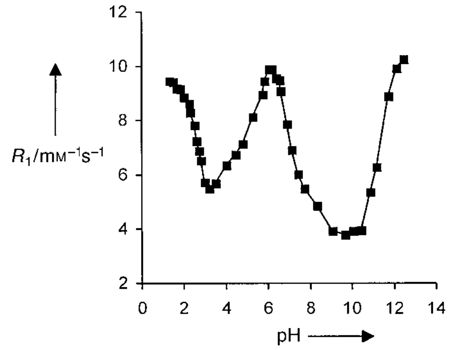

Figure 1. The pH dependence of the water proton relaxivity of [Gd(**1**)] at 20 MHz, 25 °C. The solid line is included to guide the eye and does not represent a fit of these data to theory.

To provide further insight into the unusual relaxation behavior of [Gd(**1**)], we examined the solution structures of various [Ln(**1**)] complexes by NMR spectroscopy. ^{31}P NMR spectra of all [Ln(**1**)] complexes (except Gd^{III}) had single resonances with chemical shifts not dramatically different from that of the free ligand. In comparison with the highly shifted ^{31}P resonances in the analogous $[Ln(dotp)]^{5-}$ complexes,[8] this indicated that the four phosphonate groups of [Ln(**1**)] are situated relatively far from the paramagnetic center, likely not coordinated to the central ion. ^1H and ^{13}C NMR spectra of [Ln(**1**)] were all consistent with one main molecular species having high stereochemical rigidity. The hyperfine shifts of the macrocyclic protons of [Yb(**1**)] mirrored those of $[Yb(dotp)]^{5-}$,[8] $[Yb(dota)]^-$,[9] and

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$[Yb(dotma)]^-$,[10] indicating that the Yb^{3+} is chelated by the four amide oxygens and four macrocyclic nitrogens (dotma = 1,4,7,10-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetra(2-propionate). After correction for bulk susceptibility effects, no shift was observed in the ^{17}O NMR resonance of bulk water at 25 °C upon addition of [Dy(**1**)] but a sizable shift was observed at 75 °C (Figure 2). The slope of the line through the 75 °C data indicated that one inner-sphere water molecule in [Dy(**1**)] was in exchange with bulk water.[11] The insensitivity of the ^{17}O water resonance to [Dy(**1**)] at 25 °C suggests that water exchange is slow at this temperature. The temperature dependence of the ^{17}O linewidth verified that water exchange in this complex is indeed slow below ≈67 °C (Figure 2). A fit of that data to theory[12] gave a water exchange lifetime (τ_M) of 21 ± 1.2 µs for [Dy(**1**)] at 25 °C, identical to the value reported for [Gd(**2**)].[1d, 3] Interestingly, τ_M for water exchange in [Dy(**1**)] was independent of pH from 5.9 to 9.5, so the changes in R_1 over this pH range do not reflect changes in water molecule exchange.

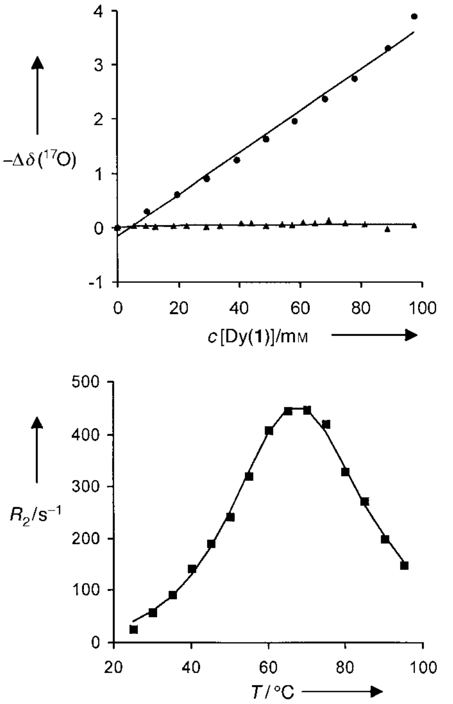

Figure 2. Top: ^{17}O NMR chemical shift of bulk water as a function of [Dy(**1**)] at 25 °C (▲) and 75 °C (●). Bottom: ^{17}O NMR linewidth of the bulk water resonance in the presence of 46 mM [Dy(**1**)] as a function of temperature at pH 9.5. The curve shows the fit of the data to theory as described in Pubanz et al.[12]

The water proton relaxivity R_1 of [Gd(**1**)] increased ≈2.6-fold between pH 10.5 and 12. The R_1 of [Gd(**2**)] is also pH sensitive in this range,[3] although in this complex R_1 begins increasing at pH ≈ 8 and increases ≈2.2-fold by pH 11. This has been ascribed to OH^--catalyzed prototropic exchange of the bound water protons in this complex.[3] To quantitatively analyze the R_1 changes above pH 10.5, we followed the lead of Aime et al.[3] and assumed that τ_M is proportional to $1/(k_1 + k_2[OH^-])$. Given that $k_1 = 4.76 \times 10^4\,s^{-1}$ ($= 1/\tau_M$ as determined by ^{17}O NMR), a fit of the high pH relaxivity data to this equation gave $k_2 = 8.09 \times 10^7\,M^{-1}s^{-1}$. This value is significantly smaller than k_2 reported for [Gd(**2**)][3] ($1.4 \times 10^{10}\,M^{-1}s^{-1}$), showing that higher concentrations of base are necessary to catalyze prototropic exchange in [Gd(**1**)] than in [Gd(**2**)]. This may reflect protection of the coordinated water molecule in [Gd(**1**)] by the extended side-arms of the ligand.

Potentiometric titrations of [Gd(**1**)] showed that the complex undergoes five protonations between pH 9 and 2 ($\lg K_n$ = 8.70, 7.28, 6.55, 6.02, and 3.38). In comparison to the protonation constants of uncomplexed ligand **1** in this same pH range ($\lg K_n$ = 7.30, 6.64, 6.11, and 2.39), it is tempting to assign the highest constant ($\lg K_1 = 8.70$) of the complex to the bound water (the pK_a of the bound water molecule of [Gd(**2**)][3, 6] is reportedly 7.9). However, the fluorescence lifetime of [Eu(**1**)] was insensitive to pH in this range and the ^{31}P NMR chemical shift of [Eu(**1**)] showed pH dependent changes consistent with protonation of a phosphonate beginning above pH 9. Thus, the ≈2.6-fold increase in water relaxivity catalyzed by [Gd(**1**)] over the pH range 9 to 6 seems to largely parallel protonation of the extended phosphonate groups. This suggests that the H-bonding network created by protonation of the phosphonates provides a catalytic pathway for exchange of the bound water protons with protons of bulk water. Interestingly, the maximum in the R_1 curve near pH 6 indicates that prototropic exchange is maximized after ≈3–4 phosphonates are protonated and that further protonation at these sites interferes with the H-bonded exchange network. The subsequent increase in R_1 below pH 3 suggests that strong acid also catalyzes prototropic exchange of the bound water protons, as first suggested by Aime et al.[3] for [Gd(**2**)]. Unlike recent data reported for [Gd(**2**)],[6] however, we find no evidence for release of free Gd^{III} (as detected by colorimetric indicators) from [Gd(**1**)] even after storage in 2.5 M HNO_3 for 2 months, so the increase in R_1 below pH 3 does not reflect release of the aqua-ion. Interestingly, the minimum in R_1 observed between pH 8.5–10.5 (3.8 $mM^{-1}s^{-1}$) does not correspond to pure outer-sphere relaxation typical of other Gd^{III} complexes at this field (ca. 2–2.4 $mM^{-1}s^{-1}$). This indicates a small prototropic exchange contribution (≈50 %) remains in this pH range catalyzed either by partial deprotonation of the bound water molecule or by the fully deprotonated phosphonate groups.

The unique sensitivity of the water relaxivity of [Gd(**1**)] indicates that this complex could be used in a magnetic resonance imaging (MRI) experiment to monitor changes in pH. T_1 weighted proton images of phantoms containing 0.2 mM $[Gd(dtpa)]^{2-}$ at pH 6 and 9 and [Gd(**1**)] at pH 6 and 9 were recorded on a 4.7 T imaging system (images not shown). Using a spin-echo sequence and parameters typical of those used for T_1 weighted imaging (TR/TE = 300/12 ms), we observed a 50 % increase in average pixel intensity for the [Gd(**1**)] sample at pH 6 compared to the sample at pH 9, while the average pixel intensity of the corresponding $[Gd(dtpa)]^{2-}$ (dtpa = diethylenetriamine-*N*,*N*,*N*′,*N*″,*N*‴-pentaacetate) samples decreased by ≈10 %. This demonstrates that [Gd(**1**)] can produce MRI contrast that is exquisitely sensitive to pH. Although other approaches to preparing gadolinium complexes with relaxivities that are sensitive to pH near physiological values have been proposed,[13] the present results demonstrate that it may be possible to modulate prototropic exchange by pendant arms in ligands such as **1** to design a series of contrast agents with differing pH sensitivities.

Experimental Section

Diethyl aminomethylphosphonate[14] was treated with bromoacetyl bromide to give diethyl bromoacetamidomethylphosphonate. The latter compound (2.88 g, 0.01 mol) was stirred with cyclen (0.43 g, 0.0025 mol) and potassium carbonate (1.5 g, 0.011 mol) in acetonitrile (10 mL) at 60–70 °C for 6 h. After removal of salts by filtration, the ester of **1** was isolated as a pale-yellow solid (2.48 g). The ethyl esters were deprotected in 30 % HBr in glacial acetic acid (8 mL) by stirring overnight at room temperature. Pure **1** was precipitated from methanol using diethyl ether to yield a white solid: 0.53 g, 85.5 %. ^{1}H NMR (D$_2$O): $\delta = 3.72$ (br., 8H; NCH$_2$CO), 3.52 (d, 8H; CH$_2$P), 3.25 (br., 16H; NCH$_2$CH$_2$N); ^{13}C NMR (D$_2$O): $\delta = 170.65$ (CO), 56.50 (N*C*H$_2$CO), 51.83 (NCH$_2$CH$_2$N), 38.24 (d, CH$_2$P). Satisfactory C, H, N analysis.

[Ln(**1**)] complexes were prepared in water by mixing a LnX$_3$ solution with ligand **1** at pH ~ 9. All NMR spectra were recorded at 11.7 T on a Varian INOVA 500 spectrometer using either a 5 mm inverse probe (^{1}H) or a 5 mm tunable broadband probe (^{17}O, ^{13}C and ^{31}P). *tert*-Butyl alcohol was used as an internal chemical shift reference for ^{1}H and ^{13}C while 85 % H$_3$PO$_4$ was used as an external reference for ^{31}P experiments. The sample of [Dy(**1**)] used for the ^{17}O experiments contained 5 % dioxane for purposes of correcting the observed water shifts for bulk susceptibility shifts. Water proton relaxation measurements were performed under temperature control using a MRS-6 NMR analyzer operating at 20 MHz (Institut Jozef Stefan, Ljubljana, Slovenija). ^{1}H images were collected using a GE (Bruker) Omega 4.7 T imaging system and a 20 mm Helmholtz coil. Potentiometric titrations were performed in 0.1 M NMe$_4$Cl at 25 °C under a N$_2$ atmosphere using an Accumet 925 pH meter, an Orion 8103 Ross combination electrode, and a Brinkmann/Metrohm 665 Dosimat titrator. The resulting activity versus volume titration curves were analyzed by using a spreadsheet program described previously.[15]

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Gold(I) and Gold(0) Complexes of Phosphinine-Based Macrocycles[**]

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In the vast majority of gold complexes (organometallic, coordination, and catalytic species) the metal center has an oxidation state from +1 to +3.[1] Indeed, monomeric zerovalent gold complexes, as their Group 11 congeners (complexes of Cu or Ag),[2] eluded isolation for a long time, and are still rare.[3] In any case, these gold(0) complexes appear thermodynamically too unstable to be used in chemical transformations. Carbonyl derivatives [Au(CO)$_n$] ($n = 1-3$) were obtained by cryochemical methods and characterized in matrices at low temperatures; they decompose above 77 K.[4] In this context, the synthesis of new and more stable Au^0 species is a topical and challenging field of investigation.

Recently, we reported on the synthesis of silacalix[*n*]phosphinines, a new class of macrocycles incorporating sp^2-hybridized phosphorus atoms.[5] In view of the adequate electronic balance between σ-donating and π-accepting properties in phosphinines, we proposed that these cavities

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