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Unusually Sharp Dependence of Water Exchange Rate versus Lanthanide Ionic Radii for a Series of Tetraamide Complexes

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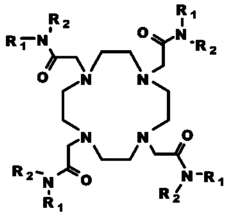
Relaxation of bulk water by gadolinium-based MRI contrast agents (CA's) relies upon rapid exchange of metal ion-bound water molecules with bulk water.[1] A different design approach was recently demonstrated by Gd(**1**),[2,3] a complex with slow water molecule exchange but fast prototropic exchange catalyzed by the four appended phosphonate groups. This feature gives Gd(**1**) an unusual pH-dependent water relaxivity that may prove useful for measuring extracellular pH in vivo. Water exchange seems to be even slower for Eu^{3+} complexes of DOTA-tetraamides, in many cases (ligands **2**−**7**, Scheme 1)[3−7] slow enough to observe a separate Eu^{3+}-bound water resonance in their high resolution spectra. This feature may prove useful for implementing a new type of water CA based upon transfer of saturated spins from a highly shifted bound water resonance to bulk water.[8] Such systems are now referred to as MT agents[8] or CEST agents.[9]

A recent study of Eu(**7**) and Yb(**7**) indicated that water exchange was ca. 500-fold faster in the later complex ($\tau_M{}^{298} = 278\ \mu s$ for Eu(**7**) and 0.5 μs for Yb(**7**)).[6] This was ascribed to a change in structure from square-antiprism for Eu(**7**) to twisted square-antiprism for Yb(**7**), even though square-antiprismatic crystals of Yb(**7**) were isolated. Preliminary estimates of the bound water lifetimes ($\tau_M{}^{298}$) in Eu(**2**) and Eu(**3**) indicated that water exchange was about 2-fold slower than in the corresponding Gd^{3+} complexes,[3,7] even though Eu^{3+} and Gd^{3+} complexes are normally assumed to be isostructural due to the similar ionic radii of these two ions.

The solid-state structures of Eu(**3**)[7] and Tb(**3**) (unpublished) are nearly identical square antiprismatic structures (often referred to as the **M** isomer). Interestingly, the twist angle between N4 and O4 planes is slightly smaller in Tb(**3**) (38.0°) than in Eu(**3**) (38.5°) consistent with a slightly longer $Tb-O_{water}$ (2.427 Å) bond distance ($Eu-O_{water} = 2.414$ Å). This trend, an increase in $Ln-O_{water}$ bond distance with smaller ionic radii, is opposite that reported for other DOTA-like complexes: for $LnDOTA^-$ crystals, $Eu-O_{water}$ (2.480 Å[10] 2.483 Å[11]) > $Gd-O_{water}$ (2.463 Å[12]) > $Y-O_{water}$ (2.435 Å,[12] 2.424 Å[13]) > $Lu-O_{water}$ (2.416 Å[14]); for LnHP-DO3A crystals, $Gd-O_{water}$ (2.50 Å[15]) > $Y-O_{water}$ (2.49 Å[15]); and for Ln(**5**) crystals, $Gd-O_{water}$ (2.461 Å[16]) > $Dy-O_{water}$ (2.427 Å[5]). Furthermore, an analysis of the ^1H and ^{17}O lanthanide induce shifts (LIS) for Ln(**3**) complexes indicated that they are isostructural (again, consistent with the **M** isomer) both in acetonitrile and in water along the Ln^{3+} series (see Supporting Information, Figures S1 and S2). This anomaly between varying water exchange rates for isostructural complexes stimulated an evaluation of $\tau_M{}^{298}$ for the remaining Ln(**3**) complexes.

***Scheme 1*. DOTA-Tetraamide Ligands**



R_1 = H	R_2 = $-CH_2PO_3H_2$	1
R_1 = H	R_2 = $-CH_2PO_3Et_2$	2
R_1 = H	R_2 = $-CH_2COOEt$	3
R_1 = H	R_2 = H	4
R_1 = H	R_2 = Me	5
R1 = Me	R2 = Me	6
R_1 = H	R_2 = $-{}^*CH(Me)Ph$	7

In CD_3CN containing 2−4% H_2O (volume ratio) at −40 °C, a bound water signal was detected in the ^1H NMR spectra of the Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Tm^{3+}, and Yb^{3+} complexes of **3** at −60, −45, −4, +80, +700, and +350 ppm, respectively, all relative to bulk water at 0 ppm. Interestingly, the chemical shift of the bound water resonance was ~2-fold larger than the chemical shift of axial H_4 macrocyclic proton in these complexes. This feature was useful in estimating the chemical shift of the bound water molecule in those complexes where it is too broad to be observed. With increasing temperature, the bound water resonance shifted toward bulk water and eventually became too broad to detect. The temperature at which this occurred was ~0, 20, 25, 60, −25, and −15 °C for the Pr^{3+}, Nd^{3+}, Sm^{3+}, Eu^{3+}, Tm^{3+}, and Yb^{3+} complexes, respectively. A ^{17}O NMR signal was observed for bound water in the Pr^{3+}, Nd^{3+}, Eu^{3+}, and Er^{3+} complexes of **3** at +245, +446, −900, and −936 ppm, respectively (at −40 °C). This resonance could not be detected at −40 °C or above for the remaining complexes.

Considering that the ^1H NMR spectra of Sm(**3**) and Eu(**3**) indicated that the water exchange rate in these complexes was similar and slower than that seen in Nd(**3**) and Gd(**3**), it was of particular interest to verify this by ^{17}O NMR. However, ^{17}O NMR spectra of the $Ln_{aq}{}^{3+}$ ions in dry CD_3CN[17] indicated that the ^{17}O contact shift induced by Sm^{3+} is so small that the bound water resonance of Sm(**3**) was likely hidden by the large bulk water resonance. To check this, small amounts of $Er_{aq}{}^{3+}$ or $Nd_{aq}{}^{3+}$ (added as triflate salts) were added to two different samples of Sm(**3**). These cations were chosen for use as "bulk water" shift reagents because they shift the ^{17}O resonance of bulk water in different directions without suffering significant line broadening.[17] A small resonance near −13 ppm appearing in the resulting ^{17}O NMR spectra (Figure 1) was assigned to the bound water resonance of Sm(**3**). A similar experiment successfully resolved the ^{17}O bound water signal of the diamagnetic Y(**3**) complex (ca. 25 ppm), but failed to resolve the bound water resonances of La(**3**) or Lu(**3**).

For complexes where a Ln^{3+}-bound water signal could be directly observed by either ^1H or ^{17}O NMR, $\tau_M{}^{298}$ values were obtained by fitting the temperature dependence of the bound water line width using standard exchange theory.[7] For those complexes where a bound water signal could not be observed (Gd(**3**), Tb(**3**), Dy(**3**),

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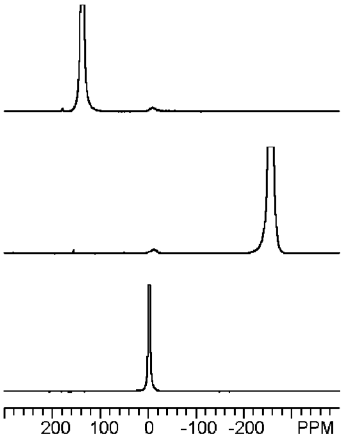

Figure 1. ^{17}O NMR spectra of 30 mg of [Sm(**3**)(H_2O)](triflate)$_3$ in 0.5 mL of CD_3CN plus 10 μL of water (10% ^{17}O enriched) at 25 °C (bottom), after adding 16 mg of Er(triflate)$_3$ as shift reagent (middle), and after adding 29 mg of Nd(triflate)$_3$ to a second sample of Sm(**3**) (top), respectively (the small and sharp peak (around 170 ppm) was assigned to the triflate anion).

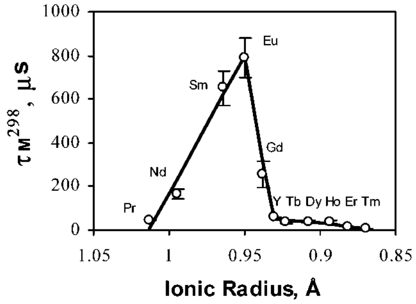

Figure 2. A plot of τ_M^{298} for the Ln(**3**) complexes vs Ln^{3+} ionic radii. The τ_M^{298} values were obtained by fitting the temperature-dependent ^{17}O NMR bound water line widths to standard exchange theory. (The bulk water ^{17}O resonance of Yb(**3**) solution was relatively narrow at all temperatures so no attempt was made to determine τ_M^{298} for this complex from the ^{17}O NMR line width data. However, a fitting of the bound-water ^{1}H NMR line widths gave a τ_M^{298} of 5.8 μs for Yb(**3**), consistent with the trend shown in the figure.)

and Ho(**3**)), the temperature dependence of the bulk water line width was analyzed.[18] ^{1}H and ^{17}O NMR line width fittings gave similar bound water lifetimes (τ_M^{298}) for those complexes where both ^{1}H and ^{17}O bound signals could be fit. The data show that bound water lifetimes in the Ln(**3**) complexes vary dramatically along the series (Figure 2), ranging from several μs to ca. 800 μs for Eu(**3**). It appears that this rather dramatic sensitivity of τ_M^{298} to lanthanide ionic radius does not reflect a change in coordination geometry from square antiprism to twisted square antiprism as suggest before for the Ln(**7**) complexes.[6] Three apparent subdivisions were evident; the Pr−Eu group (r = 1.013−0.950 Å) where τ_M^{298} increases 125 ± 11 μs/0.01 Å, the Eu−Y group (r = 0.950−0.930 Å) where τ_M^{298} falls dramatically with decreasing ionic radii (371 ± 54 μs/0.01 Å), and the Y−Tm group (r = 0.930−0.870 Å) where the change in τ_M^{298} is small (−7 ± 2 μs/0.01 Å). The activation entropies ($\Delta S^{\ddagger}$) for this series of complexes do change sign at Eu(**3**) (see Supporting Information Tables S1 and S2), consistent with an alteration in water exchange mechanism. However, the details of these changes must await further variable-pressure NMR measurements.[18]

The trend shown in Figure 2 is similar to but more dramatic than the changes in τ_M^{298} reported for the LnDTPA-BMA (the bis-methylamide of DTPA) series. Here, τ_M^{298} was found to be largest for the early members of the Ln^{3+} series, then decrease with cation size (1.89, 1.52, 2.32, 0.86, 0.28, and 0.17 μs for Nd^{3+}, Eu^{3+}, Gd^{3+}, Tb^{3+}, Dy^{3+}, and Ho^{3+}, respectively).[18] Activation volumes ($\Delta V^{\ddagger}$) determined from variable-pressure NMR data for this DTPA bis-amide series indicated that the mechanism of water exchange switches from an interchange (I_a) or associative mechanism to a dissociative mechanism along the lanthanide series.[18] The data reported here for the Ln(**3**) complexes show that water exchange is exquisitely fine-tuned in this macrocyclic tetraamide system. Although the exact mechanistic reasons for the dramatic differences shown in Figure 2 will require further kinetic study, the τ_M^{298} shown in the figure will be useful in designing new MT agents that meet the exchange requirement, $\Delta\omega^*\tau_M \geq 1$.[8] These data show that a much richer variety of Ln^{3+} complexes may indeed meet this requirement.

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Supporting Information Available: Figures S1 and S2, ^{17}O and ^{1}H LIS analysis for the Ln(**3**) complexes; Tables S1 and S2, kinetic parameters for water exchange in the Ln(**3**) complexes obtained from ^{17}O and ^{1}H NMR line width fittings (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) ^{17}O NMR chemical shifts (ppm) of the bound water of Ln$_{aq}^{3+}$ (as triflate salts) in dry CD_3CN were measured at 25 °C and 67.7 MHz (externally referred to the pure water δ = 0 ppm): 30 (La^{3+}), 349 (Pr^{3+}), 442 (Nd^{3+}), −10 (Sm^{3+}), −781 (Eu^{3+}), −2385 (Tb^{3+}), ca. −1500 (Dy^{3+}, very broad), −1195 (Ho^{3+}), −1292 (Er^{3+}), −806 (Tm^{3+}), −350 (Yb^{3+}), and 31 (Lu^{3+}), respectively.

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