

^1H and ^{17}O NMR Detection of a Lanthanide-Bound Water Molecule at Ambient Temperatures in Pure Water as Solvent

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Lanthanide complexes of a tetra-amide derivative of DOTA (structure **4** in text) with four extended carboxymethyl esters have been characterized by X-ray crystallography and multinuclear NMR spectroscopy. $[\text{Eu}(\mathbf{4})(\text{H}_2\text{O})](\text{triflate})_3$ crystallized from water in the monoclinic, $P_{21/c}$ space group ($a = 10.366 \text{ \AA}$, $b = 22.504 \text{ \AA}$, $c = 23.975 \text{ \AA}$, and $\beta = 97.05^\circ$). The Eu^{3+} cation is bound to four macrocyclic nitrogen atoms (mean $\text{Eu}-\text{N} = 2.627 \text{ \AA}$) and four amide oxygen atoms (mean $\text{Eu}-\text{O}_{\text{amide}} = 2.335 \text{ \AA}$) in a square antiprismatic geometry with a twist angle of 38.5° between the N4 and O4 planes. A single bound water molecule ($\text{Eu}-\text{O}_\text{W} = 2.414 \text{ \AA}$) occupies a typical monocapped position on the O4 surface. In pure water, resonances corresponding to a single Eu^{3+} -bound water molecule were observed in the ^1H (53 ppm) and ^{17}O (-897 ppm) NMR spectra of $[\text{Eu}(\mathbf{4})(\text{H}_2\text{O})](\text{triflate})_3$ at 25°C . A fit of the temperature-dependent Eu^{3+} -bound ^1H and ^{17}O water resonance line widths in acetonitrile- d_3 (containing 4% v/v ^{17}O enriched water) gave identical lifetimes (τ_{m}^{298}) of $789 \pm 50 \mu\text{s}$ (in water as solvent; a line shape analysis of the Eu^{3+} -bound water resonance gave a $\tau_{\text{m}}^{298} = 382 \pm 5 \mu\text{s}$). Slow water exchange was also evidenced by the water proton relaxivity of $\text{Gd}(\mathbf{4})$ ($R_1 = 2.2 \text{ mM}^{-1} \text{ s}^{-1}$, a value characteristic of pure outer-sphere relaxation at 25°C). With increasing temperature, the inner-sphere contribution gradually increased due to accelerated chemical exchange between bound water and bulk water protons. A fitting of the relaxation data (T_1) to standard SBM theory gave a water proton lifetime (τ_{m}^{298}) of $159 \mu\text{s}$, somewhat shorter than the value determined by high-resolution ^1H and ^{17}O NMR of $\text{Eu}(\mathbf{4})$. Exchange of the bound water protons in $\text{Gd}(\mathbf{4})$ with bulk water protons was catalyzed by addition of exogenous phosphate at 25°C (R_1 increased to $10.0 \text{ mM}^{-1} \text{ s}^{-1}$ in the presence of 1500-fold excess HPO_4^{2-}).

Relaxation of bulk water by gadolinium-based MRI contrast agents (CA) relies upon rapid exchange of metal ion-bound, inner-sphere water molecules with bulk water.¹ Efforts are now underway to design agents wherein the transfer of this paramagnetic relaxation effect to bulk solvent can be turned on or off in response to some biological or physiological event. The first two examples of responsive agents were reported by Meade and colleagues, one responsive to Ca^{2+} and another to β -galactosidase activity.^{2,3} Both systems were designed to *exclude* water from the inner-sphere of a GdDOTA^- derivative in the inactive form and then *expose* bulk water to a single, rapidly exchanging water site on the gadolinium in the active form. Similar approaches have been used to design gadolinium-based agents that are sensitive to solution pH.^{4–7} These design

approaches are limited to some extent by the difference in water relaxivity of the inactive versus active forms.

A different design approach was recently demonstrated by $\text{Gd}(\mathbf{3})$,⁸ a complex having a single inner-sphere water molecule that exchanges so slowly with bulk water that prototropic exchange is the dominant mechanism for enhancing bulk water relaxation. Protonation of the extended phosphonate groups in $\text{Gd}(\mathbf{3})$ initiates prototropic exchange of the bound water protons, and this results in a substantial increase in water relaxivity. Several other Eu^{3+} -tetraaza-tetraamide complexes have been now reported to exhibit slow water exchange. Aime et al. were first to observe an ^1H NMR signal for a bound water molecule in $\text{Eu}(\mathbf{1})$ in CD_3CN .⁹ Similar observations have been reported for other tetraamide derivatives including the methyl (**2**)¹⁰ and

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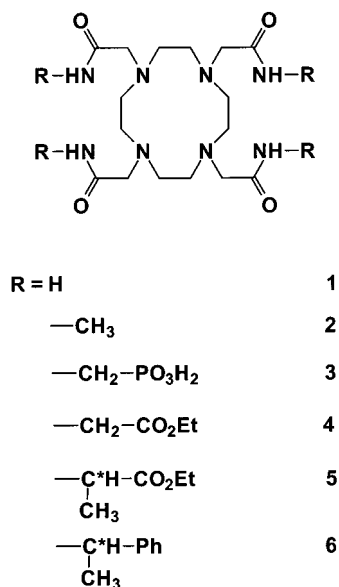
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Scheme 1



dimethyl amides¹⁹ and the more sterically crowded **6** (Scheme 1).¹⁰ For the later complex, the bound water lifetime of the **M** isomer was found to be slightly increased (278 μ s at 298 K)¹⁰ in comparison to that observed for Eu(**1**) (120 μ s at 298 K)^{19,21} and Eu(**2**) (156 μ s at 298 K),¹⁹ all measured in acetonitrile. Interestingly, an ¹H signal of the bound water in Eu(**3**) cannot be detected in mixtures of CD₃OH/H₂O even at -20°C . This suggests that fast prototropic exchange may preclude detection of a bound water signal in Eu(**3**), either due to the appended phosphonate groups or to the protic solvents required to solubilize this complex. To test these possibilities further, we turned our attention to a ligand having four extended, nonprotic carboxy ester groups (structure **4**). Complexes formed between lanthanide triflates and ligand **4** were soluble in both protic (methanol and water) and aprotic (acetone, acetonitrile, and methyl sulfoxide) solvents, thereby permitting experiments over a broader temperature range. As the extended pendant arms of ligand **4** are uncharged, one might anticipate that prototropic exchange might be slow enough to allow NMR detection of a bound water molecule. This was experimentally verified by detecting the ¹H NMR signals of bound water in several Ln(**4**) complexes (Ln³⁺ = Pr³⁺, Nd³⁺, Sm³⁺, Eu³⁺, Tm³⁺, and Yb³⁺) in CD₃CN over a broad temperature range (-40 to 60°C) and in pure water over a more limited range of temperatures. We report here the crystal structure of Eu(**4**), an analysis of Yb(**4**) hyperfine ¹H shifts, dynamic ¹H and ¹⁷O NMR studies of water exchange in Eu(**4**), and the water relaxation characteristics of Gd(**4**) as a function of temperature and with added exogenous phosphate.

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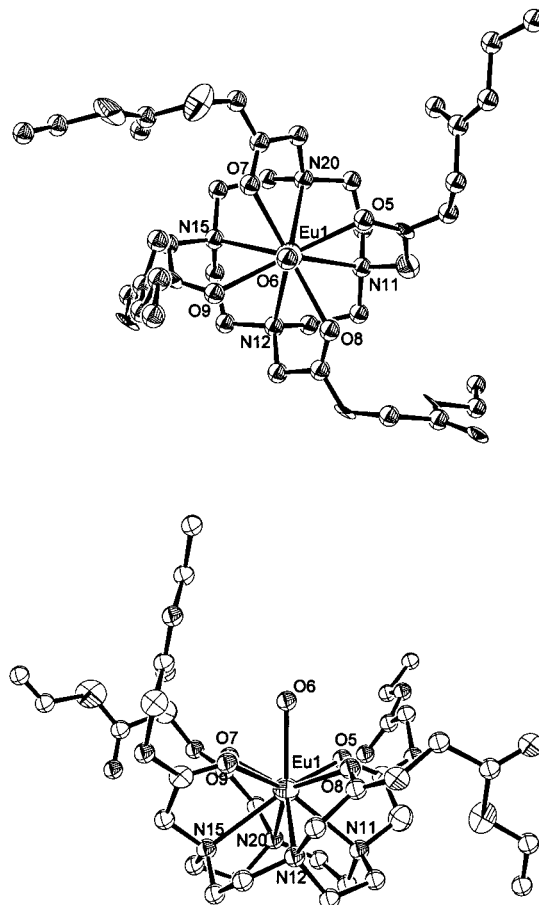


Figure 1. Crystal structure of [Eu(**4**)(H₂O)](triflate)₃, the upper is an overview along the O_w—Eu bond, while the lower is a side view vertical to the O_w—Eu bond. For clarity, both counteranions and protons are omitted. The ORTEP diagram (50% probability) is plotted by using software, ORTEP-III, downloadable from the Internet (<http://www.ornl.gov/ortep/ortep.html>).²⁹

Results and Discussion

Solid State Structure of [Eu(4**)(H₂O)](triflate)₃.** Ln(**4**) complexes were prepared in either acetonitrile or water by mixing stoichiometric amounts of Ln(triflate)₃ and **4**. The complexes were fully formed after several hours (typically overnight) as judged by the absence of free Ln³⁺ (using xylenol orange as indicator). A single crystal suitable for X-ray analysis was obtained by slowly evaporating a concentrated, aqueous solution of Eu(**4**) at 25°C . The crystal structure of [Eu(**4**)(H₂O)](triflate)₃ (Figure 1) revealed that the europium ion is nine-coordinate, bound by four nitrogen atoms (mean Eu—N = 2.627 Å) and four amide oxygen atoms (mean Eu—O = 2.335 Å) of the ligand and one water molecule (Eu—O_w = 2.414 Å). The geometry about the europium ion is a typical monocapped square antiprism. The four nitrogen atoms and four oxygen atoms each are near planarity (N₁₂ is 0.10 Å off-plane from N₁₁N₂₀N₁₅ and O₈ is 0.09 Å off-plane from O₅O₇O₉). The N₄ plane nearly parallels the O₄ plane, and the twist angle between the N₄ and the O₄ squares is 38.5° . The europium ion is positioned closer to the O₄ plane (0.778 Å) than the N₄ plane (1.608 Å), typical of systems where the Eu—N bonds are much longer than those of Eu—O_{amide} bonds. This crystal structure closely resembles those found for Na[Eu(DOTA)(H₂O)]·4H₂O (DOTA = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate acid),^{11,12} [Eu(**1**)(H₂O)](triflate)₃·2CH₃OH (TCMC = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetateamide),¹³ [Dy(**2**)(H₂O)](PF₆)₃·3.5H₂O,¹⁹ and Eu(**5**).⁷ The Eu—O_w bond distance in [Eu(**4**)-

Table 1. Crystallographic Data for [Eu(4)(H₂O)³⁺](triflate⁻)₃

formula	C ₃₅ H ₅₈ Eu F ₉ N ₈ O ₂₂ S ₃
formula weight	1362.02
crystal system	monoclinic
space group	P _{21/c}
unit cell dimension	<i>a</i> (Å) = 10.37(5) <i>b</i> (Å) = 22.50(5) <i>c</i> (Å) = 23.98(5)
vol (Å ³)	5550(10)
Z	4
density (calcd, mg/m ³)	1.630
F(000)	2768
radiation (Mo Kα, Å)	0.709 30
T (°C)	25
reflections (<i>I</i> > 3σ)	8208
refinement method	SIR 92
R indices	<i>R</i> = 0.0517, <i>R</i> _w ² = 0.1730
GOF	6.145

(H₂O)](triflate)₃ (2.414 Å), however, is somewhat shorter in comparison to those found for EuDOTA (2.480 Å,¹¹ 2.483 Å¹²) and Eu(1) (2.422 Å).¹³ Although one triflate anion is positioned relatively close to the bound water (O_W-O_{27(triflate)} = 2.834 Å and O_W-O_{28(triflate)} = 3.154 Å, respectively), a Fourier difference map did not locate the hydrogen atoms attached to the bound water oxygen. It is noteworthy that the four pendent arms of the ligand are nonequivalent in the crystal, with one pendent arm positioned axially (relative to the Eu-O_W bond) and three equatorially.

¹H Hyperfine Shift Analysis. For paramagnetic lanthanide complexes,¹⁴ the chemical shift of a ligand nucleus (Δ_{obs}) consists of a diamagnetic (Δ_{dia}) and a paramagnetic (Δ_p) component. The diamagnetic component can be directly evaluated from the respective shifts of the La³⁺ or Lu³⁺ complexes (here, a Δ_{dia} value of 3 ppm, representing an average of all ¹H shifts in the diamagnetic complexes, was used). The remaining lanthanide induced hyperfine shifts (LIS) may be further separated into contact (Δ_c) and pseudocontact (Δ_{pc}) shift components. Although both terms potentially provide useful structural information, the Δ_{pc} term is more widely used because of its direct relationship to structure (eq 1).

$$\Delta_{pc} = D_1 \left[\frac{3 \cos^2 \theta - 1}{r^3} \right] + D_2 \left[\frac{\sin^2 \theta \cos 2\varphi}{r^3} \right] \quad (1)$$

Here, *D*₁ is proportional to the magnetic susceptibility difference, $\chi_{zz} - 1/3(\chi_{xx} + \chi_{yy} + \chi_{zz})$, *D*₂ is proportional to the susceptibility difference, $\chi_{xx} - \chi_{yy}$, and θ, φ, and *r* are the polar coordinates of each ligand nucleus relative to the highest fold symmetry axis of the complexed Ln³⁺. As hyperfine ¹H NMR shifts in Yb³⁺ complexes are considered to be largely pseudocontact in origin, the observed LIS values may be analyzed directly using eq 1.

A full assignment and hyperfine chemical shift analysis was carried out using the Shift Analysis method described by Forsberg et al.¹⁵ A molecular mechanics minimized (MM+) structure was derived after fixing the Yb³⁺-O_{amide}, Yb³⁺-N and Yb³⁺-O_{water} bond lengths to the corresponding mean values as found experimentally for [Eu(4)(H₂O)](triflate)₃ (Table 2). All remaining atomic distances and bond angles in the molecule were allowed to vary during energy minimization, a method shown to be reliable in a previous study.¹⁶ The macrocyclic amine portion of the energy-minimized MM+ structure was very similar to that seen in the solid state structure of Eu(4). The twist angle between O4 and N4 squares in the Yb(4) was slightly larger (40.3°) than that found experimentally for Eu(4) (38.5°).

Table 2. Selected Bond Distances (Å), Bond Angles (deg), and Torsion Angles (deg) for [Eu(4)(H₂O)³⁺](Triflate⁻)₃

Eu-O ₅	2.343	Eu-N ₁₁	2.611		
Eu-O ₆ (w)	2.414	Eu-N ₁₂	2.603		
Eu-O ₇	2.316	Eu-N ₁₅	2.663		
Eu-O ₈	2.346	Eu-N ₂₀	2.619		
Eu-O ₈	2.335				
O ₇ -Eu-O ₉	81.63	O ₇ -Eu-O ₅	85.34	O ₇ -Eu-O ₈	143.19
O ₇ -Eu-O ₆	69.73	O ₉ -Eu-O ₅	141.07	O ₉ -Eu-O ₈	86.84
O ₉ -Eu-O ₆	69.91	O ₉ -Eu-N ₁₂	74.76	O ₉ -Eu-N ₁₁	142.87
O ₉ -Eu-N ₂₀	130.79	O ₉ -Eu-N ₁₅	66.41	O ₅ -Eu-O ₈	82.03
O ₅ -Eu-O ₆	71.16	O ₅ -Eu-N ₁₂	131.78	O ₅ -Eu-N ₁₁	67.44
O ₅ -Eu-N ₂₀	74.94	O ₅ -Eu-N ₁₅	143.16	O ₈ -Eu-O ₆	73.48
O ₈ -Eu-N ₁₂	66.44	O ₈ -Eu-N ₁₁	72.63	O ₈ -Eu-N ₂₀	140.13
O ₈ -Eu-N ₁₅	131.71	O ₆ -Eu-N ₁₂	127.13	O ₆ -Eu-N ₁₁	129.06
O ₆ -Eu-N ₂₀	126.27	O ₆ -Eu-N ₁₅	126.18	N ₁₂ -Eu-N ₁₁	68.78
N ₁₂ -Eu-N ₂₀	106.57	N ₁₂ -Eu-N ₁₅	68.01	N ₁₁ -Eu-N ₂₀	68.62
N ₁₁ -Eu-N ₁₅	104.76	N ₂₀ -Eu-N ₁₅	68.98		
N ₁₁ -C-C-O ₅	26.0	N ₂₀ -C-C-O ₇	34.7		
N ₁₅ -C-C-O ₈	14.7	N ₁₂ -C-C-O ₉	27.4		
N ₁₁ -C-C-N ₂₀	-56.5	N ₂₀ -C-C-N ₁₅	-60.3		
N ₁₅ -C-C-N ₁₂	-61.3	N ₁₂ -C-C-N ₁₁	-58.3		

Table 3. Experimental and Predicted ¹H Chemical Shifts of [Yb(4)](triflate)₃ in acetonitrile-*d*₃ and [Yb(4)]Cl₃ in D₂O at pH 7.0 and 25 °C

	D ₂ O ^a		acetonitrile- <i>d</i> ₃	
	Δ _{exp}	Δ _{cal}	Δ _{exp}	Δ _{cal}
ethylene-H ₁	-27.1	-33.5 ± 3.1	-30.0	-34.6 ± 1.9
ethylene-H ₂	14.3	7.9 ± 1.8	12.5	8.1 ± 1.1
ethylene-H ₃	17.1	13.2 ± 1.9	15.4	14.1 ± 1.2
ethylene-H ₄	88.6	83.1 ± 3.3	88.9	85.6 ± 2.0
amide-CH ₂ (H ₅)	-49.1	-53.7 ± 3.1	-52.8	-55.3 ± 2.0
amide-CH ₂ (H ₆)	-22.0	-25.7 ± 1.9	-24.9	-26.5 ± 1.2
glycine-CH ₂ (H ₇)	small		-12.8	-10.4 ± 3.7
glycine-CH ₂ (H ₈)	small		-3.3	-7.2 ± 0.5
<i>D</i> ₁		2600.4 ± 77.0		2679.3 ± 48.0
<i>D</i> ₂		23.3 ± 79.0		23.7 ± 49.2
<i>R</i>		1.4%		0.5%

^a Note that the hyperfine shifts of the glycine methylene proton (H₇ and H₈) shifts were too small to be included in a fit of the D₂O data.

The most obvious difference between the two structures was in the position of the extended carboxyethyl sidearms. Unlike in the solid state structure where three equatorial and one axial sidearms were found, all four pendant arms (as required by symmetry) were positioned axially in the energy-minimized structure with no solvent.

A comparison of the experimental and predicted shifts of [Yb(4)](triflate)₃ in acetonitrile-*d*₃ and [Yb(4)]Cl₃ in D₂O at pH 7 and 25 °C is given in Table 3. Only the protons that displayed hyperfine shifts larger than ±2 ppm were included in the calculation. ¹H NMR spectral data in the two solvents were in close agreement, with *D*₁ values of 2679 and 2600 and *D*₂ values near zero as expected for a complex with axial symmetry. This indicates that the solvent and the counteranion have no influence on the conformation of the macrocyclic and amide portions of the complex and that the complex exists as the same coordination isomer in both solvents. However, the glycine ethyl ester arms of the complex appear to be more rigid (as evidenced by greater nonequivalence of the glycine methylene proton resonances) in acetonitrile-*d*₃ than in D₂O and, on average, appear to prefer an axial position in the less polar solvent (as evidenced by the reasonable agreement of the glycine proton shifts with those calculated based upon the energy-minimized structure). This indicates that the average position of the four pendant arms in Ln(4) varies with solvent.

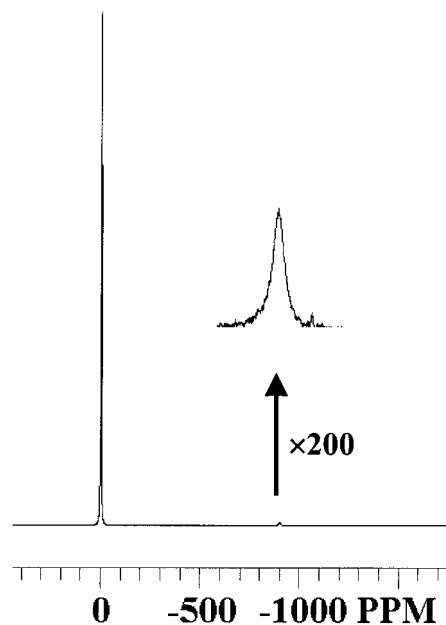


Figure 2. ^{17}O NMR spectrum of $[\text{Eu}(\mathbf{4})(\text{H}_2\text{O})](\text{triflate})_3$ in pure aqueous solution (10% ^{17}O enriched) at 25 °C, $[\text{Eu}(\mathbf{4})] \approx 0.1$ M. (The bulk water was used as the reference at 0 ppm.)

It is well-known that the analogous LnDOTA^- complexes exist in solution as a mixture of two isomeric forms (often referred to as the major (**M**) and minor (**m**) forms). These have been identified as having monocapped square antiprism and twisted monocapped square antiprism structures, respectively.¹⁷ The relative populations of **M** and **m** are sensitive to numerous factors, including lanthanide ion size. YbDOTA^- , for example, typically shows an **M/m** ratio of about 0.3 at pH 7 and 25 °C (our own result) whereas in $\text{Yb}(\mathbf{4})$ it is not clear whether the **m** form is present to any significant extent (<1%). An analysis of the hyperfine shifts¹⁸ of YbDOTA^- (as described above for $\text{Yb}(\mathbf{4})$) gave values of $D_1 = 4022$ and 2585 for **M** and **m** isomers, respectively. Although the D_1 value found here for $\text{Yb}(\mathbf{4})$ is similar in magnitude to that found for the **m** isomer of YbDOTA^- , we conclude that the predominate form of $\text{Yb}(\mathbf{4})$ is actually the **M** form based upon the solid state structure of $\text{Eu}(\mathbf{4})$ and the known propensity of lanthanide complexes of this type to favor the **M** form as the size of the Ln^{3+} decreases along the series.¹⁷ Given this assumption, the small D_1 value found here for $\text{Yb}(\mathbf{4})$ indicates that the four $\text{Yb}^{3+}-\text{O}_{\text{amide}}$ bonds have less effect on the magnetic susceptibility of the Yb^{3+} ion than four $\text{Yb}^{3+}-\text{O}_{\text{carboxylate}}$ bonds. This is reflected by a 34% lower value of D_1 for the **M** form of $\text{Yb}(\mathbf{4})$ compared to the **M** form of YbDOTA^- . This appears to be a common feature of lanthanide complexes formed with DOTA-like amide derivatives.^{15,16,19,20} Interestingly, $\text{Yb}(\mathbf{6})$, thought to exist in solution as the **m** form, crystallized from water as the **M** form.¹⁰

NMR Spectroscopy of $\text{Eu}(\mathbf{4})$. The ^{17}O NMR spectrum of $[\text{Eu}(\mathbf{4})(\text{H}_2\text{O})](\text{triflate})_3$ (dissolved in 10% ^{17}O -enriched water) showed two resonances at 25 °C, one corresponding to bulk water (referenced to 0 ppm) and a second broad, highly shifted peak at -897 ppm (Figure 2). The latter has been assigned to a slowly exchanging Eu^{3+} -bound water resonance on the basis of chemical shift comparisons to a bound water resonance previously observed for $\text{Eu}(\mathbf{1})$ (-1020 ppm dissolved in acetonitrile at -20 °C).²¹ A ^{17}O resonance was also observed for $\text{Eu}(\mathbf{4})$ in acetonitrile at -899 ppm at 25 °C and -995 ppm at -20 °C. The Eu^{3+} -bound ^{17}O water resonance broadened with increasing temperature in both solvents. A line width analysis of the bound water ^1H and ^{17}O resonances of $\text{Eu}(\mathbf{4})$

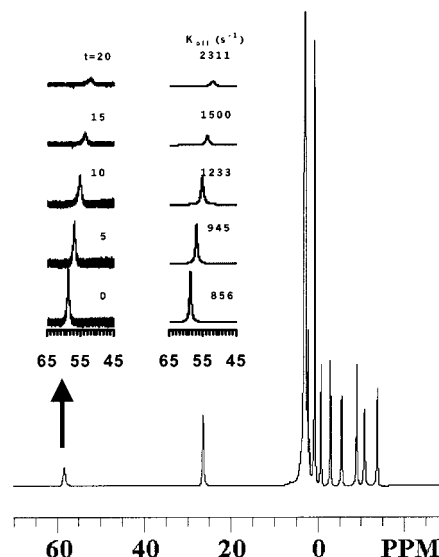


Figure 3. Variable temperature ^1H NMR spectra and the simulated spectra for the bound water of $[\text{Eu}(\mathbf{4})(\text{H}_2\text{O})](\text{triflate})_3$ in aqueous solution, $[\text{Eu}(\mathbf{4})] \approx 0.1$ M. The full spectrum was obtained at 0 °C, where the bulk water was truncated to make other peaks more visible.

dissolved in acetonitrile over the temperature range, -20 to $+50$ °C, gave a bound water lifetime (τ_{M}^{298}) of 789 ± 50 μs (a separate analysis of the ^1H and ^{17}O data gave identical results). This indicates that water exchange in $\text{Eu}(\mathbf{4})$ is significantly slower than in $\text{Eu}(\mathbf{1})$ ($\tau_{\text{M}}^{298} = 120$ μs),^{19,21} $\text{Eu}(\mathbf{2})$ ($\tau_{\text{M}}^{298} = 156$ μs),¹⁹ or $\text{Eu}(\mathbf{6})$ ($\tau_{\text{M}}^{298} = 278$ μs).¹⁰

One broad, highly shifted resonance (53 ppm at 25 °C) also appeared in the ^1H NMR spectrum of $\text{Eu}(\mathbf{4})$ in both water and acetonitrile as solvent. This resonance can be assigned to a Eu^{3+} -bound water molecule on the basis of the following observations: (1) the chemical shift of this resonance is virtually identical to a resonance assigned to the bound water of $\text{Eu}(\mathbf{1})$ in acetonitrile;⁹ (2) the intensity of this resonance decreased when excess bulk water was removed from acetonitrile- d_3 by addition of calcium hydride (spectra not shown); (3) the intensity of the resonance decreased with time after D_2O (~ 10 μL) was added to the sample; (4) the intensity of this resonance decreased when the bulk water signal was selectively saturated; (5) the ^1H hyperfine shift analysis described above predicted (after correcting for paramagnetic differences between Yb^{3+} and Eu^{3+}) that a bound water ^1H resonance would be found near 60 ppm at 25 °C.

Variable temperature ^1H NMR spectra collected over 0 to 80 °C showed that the Eu^{3+} -bound water was in dynamic exchange with bulk water (Figure 3). The analogous ^{17}O NMR experiment was not possible due to limited solubility of $\text{Eu}(\mathbf{4})$ in water at low temperatures. A simple 2-site exchange model with unequal populations was used to fit the ^1H data. The simulated spectra are shown in Figure 3, and the fitting results are summarized in Table 4. The lifetime (τ_{M}^{298}) of the bound water protons was found to be 382 ± 5 μs . Thus, the bound water lifetime of $\text{Eu}(\mathbf{4})$ as determined by ^1H NMR in pure water is about a factor of 2 shorter than the bound water lifetime in acetonitrile (as determined by either ^1H or ^{17}O NMR). Given that the high-resolution NMR spectra of $\text{Yb}(\mathbf{4})$ indicated that the average position of the pendant arms depends on solvent, these data suggest that water exchange in $\text{Eu}(\mathbf{4})$ may be slower in acetonitrile as solvent because the appended glycine ethyl ester groups appear to be more rigid in this solvent and this may hinder release of the bound water molecule.

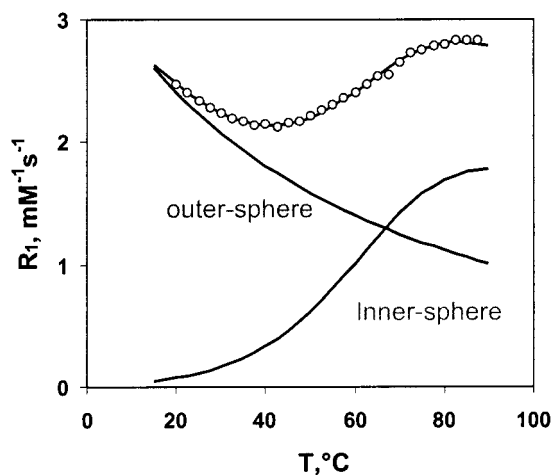


Figure 4. Temperature dependence of the relaxivity of $[\text{Gd}(\text{4})(\text{H}_2\text{O})] \cdot \text{Cl}_3$ aqueous solution, and the best fitted curve to SBM theory, in 0.15 M HEPES/HCl buffer at pH 7.0 and at 20 MHz.

Table 4. Kinetic Parameters for Proton Exchange in $\text{Eu}(\text{4})$ in Water at pH 7.0

	bound \rightarrow bulk	bulk \rightarrow bound
$k_{\text{ex}}^{298}/\text{s}^{-1}$	2618 ± 33	1.9 ± 33
$\tau_{\text{M}}^{298}/\mu\text{s}$	382 ± 5	$534 \text{ } 795 \pm 50 \text{ } 625$
$E_{\text{a}}/\text{kJ mol}^{-1}$	33 ± 4	33 ± 4
$\ln A$	13.9 ± 1.8	21.1 ± 1.8
$\Delta H^{298}/\text{kJ mol}^{-1}$	30.4 ± 4	30 ± 4
$\Delta S^{298}/\text{J mol}^{-1}\text{K}^{-1}$	-77.4 ± 14.9	-137.6 ± 14.9
$\Delta G^{298}/\text{kJ mol}^{-1}$	53.7 ± 0.2	71.4 ± 0.2

It is worth noting that the kinetic parameters, ΔH , ΔS , and ΔG , obtained here for $\text{Eu}(\text{4})$ complex in pure aqueous solution, are notably different from those previously obtained for the $\text{Eu}(\text{1})$ complex in acetonitrile (Table 4).²¹ Especially, ΔS^{298} is a negative value for the $\text{Eu}(\text{4})$ complex, while positive for the $\text{Eu}(\text{1})$ complex. This may imply that the bound water exchanges by different mechanisms for these two complexes. Previously, a dissociative activation mode was suggested for the $\text{Eu}(\text{1})$ complex on the basis of high-pressure NMR experiments.²¹

Water Proton Relaxivity of $\text{Gd}(\text{4})$. $\text{Gd}(\text{4})$ has a water proton relaxivity of $2.2 \text{ mM}^{-1} \text{ s}^{-1}$ in 0.15 M HEPES buffer, pH 7.0, 25 °C, 20 MHz, comparable to other low molecular weight Gd^{3+} complexes at this same frequency when the relaxivity is dominated by outer-sphere effects. Assuming that $\text{Gd}(\text{4})$ has a single, slowly exchanging inner-sphere water molecule like $\text{Eu}(\text{4})$, then water exchange in $\text{Gd}(\text{4})$ must be too slow to contribute to relaxation of bulk water at this temperature. The relaxivity of $\text{Gd}(\text{4})$ is shown as a function of temperature in Figure 4. The curve shows two distinct regions, one below 40 °C where the relaxivity decreases with increasing temperature (largely outer-sphere contribution) and another above 40 °C where the relaxivity increases with increasing temperature (gradually increasing inner-sphere contribution). The temperature dependence of the water proton relaxivities of GdDOTP^{5-} and GdTTHA^{3-} (neither complex has an inner-sphere water molecule) served as useful models for outer-sphere relaxation.^{27,28} These data (Supporting Information) were fit to eq 2 to obtain $R_{\text{1os}}^{298} = 3.43 \pm 0.02 \text{ mM}^{-1} \text{ s}^{-1}$ and $\Delta H_{\text{os}}^{298} = 11.6 \pm 0.2 \text{ kJ mol}^{-1}$ for GdDOTP^{5-} and $R_{\text{1os}}^{298} = 2.34 \pm 0.01 \text{ mM}^{-1} \text{ s}^{-1}$ and $\Delta H_{\text{os}}^{298} = 10.4 \pm 0.2 \text{ kJ mol}^{-1}$ for GdTTHA^{3-} . For Gd^{3+}

$$R_{\text{1os}}^T = R_{\text{1os}}^{298} \times \exp\left[\frac{\Delta H_{\text{os}}^{298}}{R} \left(\frac{1}{298} - \frac{1}{T}\right)\right] \quad (2)$$

Table 5. SBM Fitting Parameters for $\text{Gd}(\text{4})$ in 0.15 M HEPES/HCl Buffer (pH 7.0) at 20 MHz

parameters	values	variable/fixed
$R_{\text{1os}}^{298} (\text{mM}^{-1} \text{ s}^{-1})$	2.232	variable
$\Delta H_{\text{os}} (\text{kJ mol}^{-1})^a$	11.0	fixed
$\tau_{\text{M}}^{298} (\mu\text{s})$	159.0	variable
$\tau_{\text{R}}^{298} (\text{ps})$	220.0	variable
$\tau_{\text{V}}^{298} (\text{ps})$	20.0	variable
$\Delta H_{\text{M}}^{298} (\text{kJ mol}^{-1})$	55.8	variable
$\Delta H_{\text{R}}^{298} (\text{kJ mol}^{-1})$	20.4	variable
$\Delta H_{\text{V}}^{298} (\text{kJ mol}^{-1})$	0.26	variable
$\Delta^2 (\text{s}^{-2})$	1×10^8	variable
$r_{\text{GdH}} (\text{\AA})^b$	2.90	fixed
AF	0.6%	variable

^a An average value was obtained from data fitting of T_1 data for GdDOTP^{5-} and GdTTHA^{3-} , two systems that are considered representative of outer-sphere complexes (see Supporting Information). ^b The value was obtained by MM+ minimization of $\text{Gd}(\text{4})$ after fixing the bond distances of $\text{Gd}-\text{N}$, $\text{Gd}-\text{O}_{\text{amide}}$, and $\text{Gd}-\text{O}_{\text{w}}$ to the corresponding mean found in the solid state structure of $\text{Eu}(\text{4})$.

complexes with similar size, the relative diffusion rate of these complexes is similar, so the temperature dependence of the relaxivity should yield similar activation enthalpies ($\Delta H_{\text{os}}^{298}$). As this seems to be true for GdDOTP^{5-} and GdTTHA^{3-} , the outer-sphere contribution in $\text{Gd}(\text{4})$ was assumed to have an activation enthalpy ($\Delta H_{\text{os}}^{298}$) of 11.0 kJ mol^{-1} .

The inner-sphere contribution can be described in simplest terms by Solomon–Bloembergen–Morgan (SBM) theory,¹ and the temperature dependence of τ_{M} , τ_{R} , and τ_{V} was expressed by the Eyring relationship (eq 3):

$$(\tau_j)_T^{-1} = (\tau_j)^{298,15} \times \frac{T}{298.15} \times \exp\left[\frac{\Delta H_j^{298}}{R} \left(\frac{1}{298.15} - \frac{1}{T}\right)\right] \quad (3)$$

$$\text{AF} = \left[\frac{\sum (R_{\text{1predicted}} - R_{\text{1exptl}})^2}{\sum (R_{\text{1exptl}})^2} \right]^{1/2} \quad (4)$$

where j refers to several different dynamic processes involved ($j = \text{M}, \text{R}, \text{and V}$) and ΔH_j^{298} is the corresponding activation enthalpy.

The data of Figure 4 were fit to the standard SBM equations, plus eqs 2 and 3 by minimizing the residual difference between experimental and predicted relaxivities (eq 4). The resulting fit gave the parameters listed in Table 5 with an agreement factor (AF) of 0.6%. The bound water proton lifetime (τ_{M}^{298}) in $\text{Gd}(\text{4})$ was predicted to be $159 \mu\text{s}$ in HEPES/HCl buffer solution at pH 7.0, again about a factor of 2 shorter than the proton lifetime measured for $\text{Eu}(\text{4})$ by ^1H NMR. The τ_{R} and τ_{V} values obtained in this fit are typical of other low molecular weight Gd^{3+} complexes.^{1e}

Prototropic Exchange Is Catalyzed by Exogenous Phosphate. Given that water proton exchange is slow in $\text{Gd}(\text{4})$,

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exogenous agents known to catalyze prototropic exchange of water protons^{22,23} were added to solutions of Gd(4) at constant pH and 25 °C. The water proton relaxivity gradually increased from 2.2 to 10 mM⁻¹ s⁻¹ with addition of a 1500-fold excess of solid phosphate (KH₂PO₄/Na₂HPO₄ added in a ratio of 2:1) to a solution of Gd(4) maintained at pH 6.0 (Supporting Information). This *R*₁ value is similar to that of Gd(3) at pH 6.0 in which the prototropic exchange is efficiently catalyzed by the appended phosphate groups in the complex itself. This experiment demonstrates that prototropic exchange in slow water exchange systems such as Gd(4) can be modulated by exogenous anions and buffers.

Another experiment also supports this explanation that exogenous phosphate may have a catalyzed effect upon the bound water prototropic exchange, namely, the resonance of the bound water of Eu(4) complex became broader and finally disappeared when a large amount of phosphate salt was added into the NMR sample of Eu(4) in aqueous solution at a constant pH and temperature (see Supporting Information for ¹H NMR spectra of Eu(4) in the presence of different amount of phosphate).

Conclusions

A tetraamide derivative of DOTA (ligand 4) forms complexes with the trivalent lanthanide cations in either water or acetonitrile as solvent. The resulting Ln(4) complexes have many features in common with other tetraamide complexes reported previously, most notable being slow water exchange. Water exchange in Eu(4) proved to be so slow that a Eu³⁺-bound water signal was detected by both ¹H and ¹⁷O NMR at 25 °C, even in pure water solvent. The bound water lifetime (τ_M^{298}) in Eu(4) proved to be solvent dependent, measuring 789 μ s in acetonitrile (measured by both ¹H and ¹⁷O NMR) and 382 μ s in water (measured by ¹H NMR only). We attribute this difference largely to the average position of the extended glycine ethyl ester groups of the complex in the two solvents. High-resolution ¹H NMR spectra of Yb(4) indicate that the side-chain groups are more rigid and on average positioned parallel to the Eu–O_w bond in acetonitrile as solvent, thereby restricting dissociative release of the Ln³⁺-bound water. Consistent with this, [Eu(4)(H₂O)](triflate)₃ crystals obtained from water had unequally positioned sidearms with three extended perpendicular to the Eu–O_w axis and one positioned nearly parallel. Otherwise, Eu(4) in the solid state has the typical square antiprismatic structure found for other cyclen-based complexes with a twist angle of 38.5° between the N₄/O₄ planes, similar to other reported tetraamide systems.^{7,10,13,19} The Eu³⁺–O_w bond length, however, was somewhat shorter (2.414 Å) than that in other tetraamide systems.

Slow water exchange was also evidenced by the water relaxivity of Gd(4) at 25 °C (an *R*₁ of 2.2 mM⁻¹ s⁻¹ at 20 MHz essentially corresponds to pure outer-sphere water relaxation). The inner-sphere contribution to *R*₁ gradually increased with temperature up to 80 °C. Above this temperature, *R*₁ decreased with further increases in temperature, characteristic of a fast water exchange system. A fit of the relaxation data to SBM theory gave a bound water lifetime (τ_M^{298}) of 159 μ s, about 2-fold shorter than that measured for Eu(4) in pure water. Addition of exogenous phosphate accelerated prototropic exchange in Gd(4), leading to a substantially enhanced relaxivity even at 25 °C. This illustrates that prototropic exchange in these slow water-exchange systems can be modulated by exogenous anions, buffers, etc., similar to that reported recently for Gd(3).⁸ This suggests that a new class of slow water-exchange

MRI functional contrast agents might be developed wherein tissue relaxivity is determined by prototropic exchange rather than water molecule exchange and thereby can be easily modulated by endogenous biological anions and buffers.

Experimental Section

Materials. ¹⁷O-Enriched water (10%) was purchased from Cambridge Isotope Laboratories, Inc. (Andover, MA). All other chemicals were obtained from Aldrich Chemical Co. (Milwaukee, WI) and used without further purification.

Ligand and Complex Syntheses. Ethyl Bromoacetamidoacetate. Glycine ethyl ester hydrochloride (28.0 g, 0.2 mol) was dissolved in 4 M NaOH (100 mL) at 0 °C, to which 1,2-dichloroethane (200 mL) was added. Bromoacetyl bromide (40.4 g, 0.2 mol) was added dropwise at the same temperature. The mixture was stirred at 0 °C for 1 h and at room temperature overnight. The organic layer was separated and the water layer was extracted with ethyl ether (3 × 50 mL). The combined organic layer was dried over sodium sulfate overnight. The solvent was removed and the residue was purified by silica gel column chromatography (ethyl ether/chloroform, 1:1) to afford a white solid, 30.6 g, 68.3%. ¹H NMR (CDCl₃) δ 7.26 (br, 1H, NH), 4.24 (q, 2H, OCH₂), 4.06 (d, 2H, CH₂CO₂), 3.933 (s, 2H, BrCH₂), 1.300 (t, 3H, CH₃); ¹³C NMR (CDCl₃) δ 169.11 (CO), 166.01 (CO), 61.48 (OCH₂), 41.70 (NHCH₂), 28.33 (BrCH₂), 13.91 (CH₃).

1,4,7,10-Tetraazaacyclododecane-1,4,7,10-tetrakis(ethyl-acetamidoacetate) (4). A mixture of cyclen (0.86 g, 0.005 mol), ethyl bromoacetamidoacetate (4.48 g, 0.02 mol), and potassium carbonate (3.0 g, 0.022 mol) in acetonitrile (20 mL) was heated at 60–70 °C for 6 h. The solid was filtered off and solvent was removed by evaporation. The residue was dissolved in chloroform and heated to reflux. The precipitate that formed was removed by filtration and the solvent evaporated to give 3.72 g of a pale yellow solid. This was used to form complexes with Ln³⁺ without further purification. ¹H NMR (CDCl₃) δ 7.60 (br, 4H, NH), 4.16 (q, 8H, OCH₂), 3.98 (d, NHCH₂), 3.16 (NCH₂), 2.749 (NCH₂CH₂N), 1.272 (t, 12H, CH₃); ¹³C NMR (CDCl₃) δ 171.51 (CO), 170.060 (CO), 61.329 (OCH₂), 59.145 (NCH₂), 53.175 (NCH₂CH₂N), 40.799 (NHCH₂), 14.064 (CH₃).

[Eu(4)](triflate)₃. A solution of europium trifluoromethanesulfonate (0.15 g, 0.25 mmol) and ligand 4 (0.25 g, ~0.25 mmol) was refluxed for 3 h in dry acetonitrile (20 mL). After the solvent was removed by rotary evaporation, ~0.2 mL of deuterated acetonitrile was added, and the sample was vacuum-dried to give 0.44 g of a light-yellow powder; ~300 mg, dissolved in 0.7 mL of H₂O, yielded colorless crystals by slow evaporation at 25 °C. The same crystals used for crystallography were later dissolved into ¹⁷O-enriched (10%) water for NMR analysis. [Eu(4)(H₂O)](triflate)₃. Anal. Calcd for C₃₅H₅₈EuF₉O₂₂S₃: C, 30.86; H, 4.26; N, 8.23. Found: C, 30.46; H, 4.25; N, 8.06. ¹H NMR (500 MHz, CD₃CN plus 10 mL of H₂O, 25 °C): δ 53.8 (brs, 2H, bound water), 25.0 (s, 4H, cyclen ring CH₂ axial), 3.7 (s, 8H, OCH₂), 2.2 (s, 8H, NHCH₂COO), 2.0 (s, 12H, CH₃), 0.9 (s, 4H, NH), -1.8 (s, 4H, ring CH₂ equatorial), -3.6 (s, 4H, ring CH₂ equatorial), -7.5 (s, 4H, ring CH₂ axial), -8.1 (s, 4H, CH₂CON), -11.5 (s, 4H, CH₂CON). ¹³C NMR (the same sample, 25 °C): δ 195.9 (brs, CON), 170.2 (s, COO), 108.9 (brs, NCH₂CON), 91.5 (brs, NCH₂CH₂N), 78.3 (brs, NCH₂CH₂N), 62.2 (s, OCH₂CH₃), 37.9 (brs, NCH₂COO), 14.1 (s, CH₃).

[Gd(4)(H₂O)]Cl₃. GdCl₃ (0.2 M) was added to ligand 4 (60 mg, ca. 10% excess ligand) to give a solution of 30 mM of Gd(4). This solution was stirred at room temperature overnight to ensure full complexation. When necessary, a small amount of concentrated NaOH was added to maintain the pH near 7 until free Gd³⁺ could no longer be detected using xylenol orange as colorimetric indicator (in 1 M NaAc/HAc buffer solution at pH 5.3). This stock solution was diluted into a 0.15 M HEPES/HCl buffer to maintain a constant pH of 7 for the water *T*₁ measurements.

[Yb(4)](triflate)₃ and [Yb(4)(H₂O)]Cl₃ were prepared using analogous procedures as described above for [Eu(4)](triflate)₃ and [Gd(4)(H₂O)]Cl₃.

NMR Spectroscopy, X-ray Crystallography, and Data Analysis Methods. Water proton longitudinal relaxation measurements were performed under temperature control using a MRS-6 analyzer operating

at 20 MHz (Institut Jozef Stefan, Ljubljana, Slovenia) by means of the inversion–recovery technique (15 experiments, 8 scans). The temperature was controlled by an airflow heater equipped with a copper thermocouple and measured with an Omega CN76000 microprocessor-based temperature/processor controller with an uncertainty of 0.5 °C. The NMR sample was allowed to equilibrate in the probe for 10 min at each temperature before data acquisition.

Variable temperature ^1H , ^{13}C , and ^{17}O NMR spectra were recorded on a Varian INOVA-500 spectrometer at 500, 125.6, and 67.8 MHz, respectively. Similarly, NMR samples were allowed to stand in the probe for at least 10 min at each the temperature before data acquisition. The temperature error was estimated to be within 0.5 °C. ^1H NMR band shape of bound and bulk water was fitted by using a program written in Fortran 77 for a 2-site exchange system with unequal populations.²⁴ The molar ratios of bound water to bulk water were read directly from the relative integration in ^1H NMR spectra at low temperature. Proton lanthanide induced hyperfine shifts measured in the spectra of Yb(4) were analyzed by using the Shift Analysis program developed by Forsberg and colleagues.¹⁵ Molecular mechanic minimizations were performed by using the MM+ force field in HyperChem (Release 5.01) as described in the text. All other data analyses were performed using the Solver feature of Microsoft Excel.

A single-crystal X-ray diffraction experiment was carried out at 298 K on a ENRAF-NONIUS CAD4 diffractometer using graphite-monochromated Mo K α radiation ($\lambda = 0.70930 \text{ \AA}$). The structure was solved by direct methods using the SIR92 program refined by full-matrix least squares against F_o .²⁵ All non-H atoms were refined with anisotropic displacement parameters, while all H atoms were added in calculated position and refined isotropically. A Fourier difference map ($F_o - F_c$) was performed in an attempt to locate the water hydrogens but they were not found. Experimental data and selected bond distances, bond angles, and torsion angles are listed in Tables 1 and 2, respectively.

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Supporting Information Available: Figures for the temperature dependence of relaxivity of GdDOTP and GdTTHA, the enhanced relaxivity of Gd(4) by exogenous phosphate, ^1H NMR spectra of Eu(4) in the presence of different amount of exogenous phosphate, and CIF data for the [Eu(4)(H₂O)](triflate)₃ crystal. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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