

# Thermodynamics, PMR, and Fluorescence Studies for the Complexation of Trivalent Lanthanides, $\text{Ca}^{2+}$ , $\text{Cu}^{2+}$ , and $\text{Zn}^{2+}$ by Diethylenetriaminepentaacetic Acid Bis(methylamide)

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$^1\text{H-NMR}$  shift data were measured for the diamagnetic  $\text{La}^{3+}$  and  $\text{Lu}^{3+}$  complexes with diethylenetriaminepentaacetate- $N,N'$ -bis(methylamide) (DTPA-BMA) at different temperatures. Quartet splitting of the methylene protons of the terminal acetate groups and of the amide groups upon complexation with metal ions is indicative of long-lived metal-nitrogen bonds and short-lived metal-oxygen bonds. The observation of two quartets for the terminal acetates and the splitting of the  $N$ -methyl singlet upfield is attributed to the presence of more than one conformation in solution. Thermodynamic data indicate that DTPA-BMA acts as an octadentate ligand toward lanthanide ions and possibly as a hexadentate ligand toward  $\text{Ca}^{2+}$ ,  $\text{Cu}^{2+}$ , and  $\text{Zn}^{2+}$  ions. Fluorescence data for the  $\text{Eu}^{3+}$  complex support the octadentate behavior of the ligand toward lanthanides and indicate that the complex contains one coordinated water molecule.

## Introduction

Paramagnetic lanthanide chelates, particularly those of  $\text{Gd}^{3+}$ , have a pronounced influence on the  $T_1$  and  $T_2$  relaxation rates of protons in  $\text{H}_2\text{O}$ . This property has led to their use in improving the contrast enhancement in magnetic resonance imaging.<sup>1</sup> Ligands designed for use in such complexes must provide large thermodynamic and kinetic stabilities to minimize exchange of metal ions with physiological ligands and also must have inner-sphere hydration. The complexes formed by some polyamino carboxylate ligands<sup>2</sup>—especially those of diethylenetriaminepentaacetic acid (DTPA) and its derivatives—have been found to fit these criteria. An understanding of the factors which influence thermodynamic and kinetic stabilities of the  $\text{Gd}(\text{III})$  complexes as well as the hydration of the complexes in solution is of importance for the development of improved imaging agents.

In an earlier report,<sup>3</sup> the acute chemotoxicity of some gadolinium complexes of EDTA, DTPA, DTPA-BP (diethylenetriamine- $N,N',N''$ -triacetic- $N,N''$ -bis(2-methylpyridine)), and DTPA-BMA (diethylenetriaminepentaacetic- $N,N'$ -bis(methylamide)) (see structures in Figure 1) has been correlated to the selectivity constant of the ligand (a function of its stability constant with  $\text{Gd}^{3+}$  and other metal ions). The acute toxicity was found to correlate directly with the amount of gadolinium released in vivo. This release of gadolinium presumably occurs through a metal exchange mechanism involving the  $\text{Zn}^{2+}$ ,  $\text{Cu}^{2+}$ , and/or  $\text{Ca}^{2+}$  ions present in the biological fluid.

In the present paper, we report measurements of the  $^1\text{H-NMR}$  spectra of  $\text{Na}(\text{I})$ ,  $\text{La}(\text{III})$ , and  $\text{Lu}(\text{III})$  complexes, the fluorescence lifetimes ( $\text{Eu}(\text{III})$  complex), and the complexation thermodynamics of DTPA-BMA systems with divalent  $\text{Ca}$ ,  $\text{Cu}$ , and  $\text{Zn}$  and trivalent lanthanides. The purpose of the study was to obtain a sufficient understanding of the solution structure of these complexes that they can serve as models for the behavior of a variety of complexes of other bis(amide) derivatives of DTPA.

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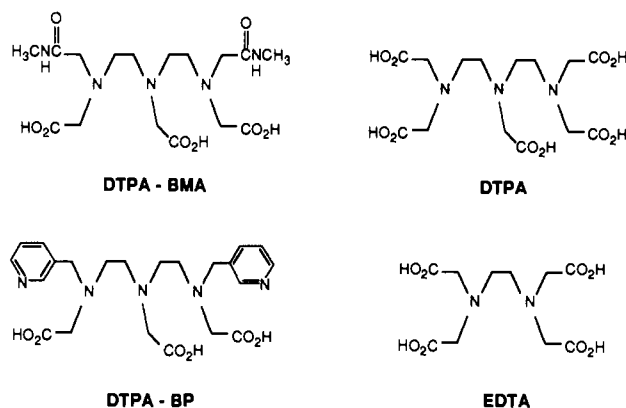


Figure 1. Structures of DTPA-BMA and other related ligands.

## Experimental Section

All chemicals were reagent grade. DTPA-BMA was synthesized according to the published procedure.<sup>4</sup> The purity of the ligand was checked by elemental analysis, pH titration, and PMR measurements, which were all consistent with purity  $\geq 99.5\%$ .

Lanthanide perchlorate solutions were prepared by dissolving the oxides (American Potash and Chemical Corp.) in the minimum amount of perchloric acid. The solutions were evaporated to near dryness to remove excess acid and diluted to volume with water. This produced solutions of pH 2-3 which could be adjusted further with standard  $\text{NaOH}$  or  $\text{HClO}_4$  solutions. The exact concentration was determined by EDTA titration to the end point of Xylenol Orange (acetate buffer).<sup>5</sup> The perchlorates of  $\text{Ca}^{2+}$ ,  $\text{Cu}^{2+}$ , and  $\text{Zn}^{2+}$  were prepared and standardized in a similar way in the presence of a suitable indicator (Erichrome Black T for  $\text{Ca}^{2+}$  and  $\text{Zn}^{2+}$  and Murexide for  $\text{Cu}^{2+}$ ).<sup>5</sup>

For the NMR measurements, stoichiometric amounts of the lanthanide cation and of the ligand solutions were mixed, evaporated, and redissolved in  $\text{D}_2\text{O}$ . The evaporation and dissolution in  $\text{D}_2\text{O}$  were repeated several times to eliminate water before dilution to proper volume with  $\text{D}_2\text{O}$  (plus some  $\text{NaOD}$  if necessary to adjust the pD). Working solutions for fluorescence measurements were prepared with various ratios of europium

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**Table I.** Thermodynamics of Stepwise Protonation of DTPA-BMA ( $I = 0.10 \text{ M (NaClO}_4\text{)}$ ;  $T = 298 \text{ K}$ )

species	log $K$	$-\Delta H$ , kJ mol $^{-1}$	$\Delta S$ , J K $^{-1}$ mol $^{-1}$
HL	9.37 $\pm$ 0.01	30.4 $\pm$ 1.7	77 $\pm$ 6
H <sub>2</sub> L	4.38 $\pm$ 0.01	3.9 $\pm$ 0.3	71 $\pm$ 1
H <sub>3</sub> L	3.31 $\pm$ 0.04	7.1 $\pm$ 0.7	40 $\pm$ 2
H <sub>4</sub> L	1.43 $\pm$ 0.12		

and ligand. The solutions used in all the measurements had a final ionic strength of 0.1 M adjusted with NaClO<sub>4</sub>.

The pH titrations were carried out with an automatic titration system of a Fisher digital pH meter fitted with a Corning combined electrode, a Metrohm digital autoburette, and a PC computer.<sup>6</sup> The electrode was calibrated with standard commercial buffers of pH 4.00 and 7.00. In all measurements the titrant used was 0.100 M HCl and the temperature was maintained at 25  $\pm$  0.1 °C. In this study, as in similar studies of metal-amino carboxylate systems (e.g., EDTA, HEDTA, DCTA, DTPA), there was no evidence for species such as M<sub>2</sub>X or MX<sub>2</sub> forming in measurable quantities from the potentiometric, calorimetric, and NMR data analyses at our concentrations.

Stability constants of the divalent Zn, Cu, and Ca complexes were determined by direct titration of equimolar amounts of metal and ligand (3–5 mM) adjusted to pH 7 with known amounts of sodium hydroxide and back-titrated with the titrant. The stability constants of the lanthanide complexes were determined by a ligand competition titration in which EDTA was the competing ligand. Such a competitive method eliminates the possibility of Ln<sub>2</sub>X or LnX<sub>2</sub> formation, and no evidence for LnXY was found in the data analyses.

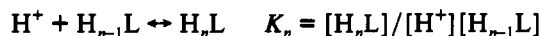
Enthalpy data were obtained with a titration calorimeter interfaced to a PC.<sup>7</sup> The protonation enthalpies were determined by titration of the trisodium salt of the ligand (50 mL, 5.4 mM) with perchloric acid (0.10 M). For the enthalpies of complexation, ligand buffer (0.01 M) was titrated into a solution of the metal (50 mL, 5–15 mM) under the same conditions, 0.10 M (NaClO<sub>4</sub>) ionic strength and 25 °C, as in the potentiometric study. The experimental heat values were corrected for heats of dilution determined in separate experiments. Each metal–ligand system was titrated a minimum of two times.

The proton magnetic resonance measurements were performed in the pulsed Fourier transform mode with a deuterium lock on the Bruker 500-MHz spectrometer of the Florida State University NMR Laboratory. The spectra of the complexes in solutions of pD values between 7 and 8 were recorded at 5 °C, ambient (ca. 25 °C) temperature, and 85 °C, whereas those of the free ligand were obtained at ambient temperature only. The chemical shifts were recorded relative to sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as an internal standard.

Fluorescence measurements were performed in the FSU Laser Laboratory with a pulse laser beam at 395 nm whose energy was typically 3 mJ and whose pulse width was in the nanosecond range. The emission was analyzed by a LeCroy 6103 amplifier fitted with a Hamamatsu R955 photomultiplier tube and a LeCroy TR 8828C transient recorder. The whole system was interfaced to a PC computer through a LeCroy 8901A GPIB.<sup>8</sup>

## Results

The potentiometric titration curve of the free ligand shows two distinct buffer regions with a sharp inflection between pH 5.5 to 9.0. The data were processed to solve for the protonation constants associated with the following equilibria ( $n = 1-3$ )



NMR measurements of the free ligand indicated that the addition of the first three protons occurs at the nitrilo centers. Values of the constants obtained and the respective enthalpies are listed in Table I.

The stability constants for the metal complexes were obtained by solving the following mass balance equations:

$$C_L = A[\text{L}] + (\beta_{101} + \beta_{111}[\text{H}^+])[\text{M}][\text{L}]$$

$$C'_L = B[\text{L}'] + \beta'_{101}[\text{M}][\text{L}']$$

$$C_M = [\text{M}] + (\beta_{101} + \beta_{111}[\text{H}^+])[\text{M}][\text{L}] + \beta'_{101}[\text{M}][\text{L}']$$

$$C_H = [\text{H}^+] + C[\text{L}] + D[\text{L}'] + \beta_{111}[\text{M}][\text{H}][\text{L}]$$

Here

$$A = \sum_{i=0}^3 [\text{H}^+]^i \beta_{0i1} \quad B = \sum_{i=0}^4 [\text{H}^+]^i \beta'_{0i1}$$

$$C = \sum_{i=1}^3 i[\text{H}^+]^i \beta_{0i1} \quad D = \sum_{i=1}^4 i[\text{H}^+]^i \beta'_{0i1}$$

The  $\beta_{0i1}$  and  $\beta'_{0i1}$  are the overall protonation constants of the DTPA-BMA (L) and the auxiliary ligand (L'), respectively.  $\beta_{101}$  and  $\beta'_{101}$  are the formation constants of the normal complexes with the respective ligands, and  $\beta_{111}$  is the formation constant of the protonated DTPA-BMA complex. The constants for EDTA from Martell, et al.<sup>9</sup> were used in the lanthanide competitive titration data analysis.

Data processing used the program "BETA",<sup>6</sup> which minimizes the sum of the error squares,  $S$ , over all the titration points:

$$S = \sum_{i=1}^N [H_i(\text{calc}) - C_{H_i}(\text{exp})]^2$$

Under the present experimental conditions, only the ML complexes formed for the trivalent lanthanides, while both ML and MHL species formed for the other cations.

Enthalpies of complexation were computed by fitting the heat changes, after correction for dilution heats, to the equation

$$Q_{\text{corr}} = \sum Q_{\text{H}_n\text{L}} + Q_{\text{ML}} + Q_{\text{MHL}}$$

$$= \sum (\Delta X_{\text{H}_n\text{L}}) \Delta H_{0n1} + (\Delta X_{\text{ML}}) \Delta H_{101} + (\Delta X_{\text{MHL}}) \Delta H_{111}$$

where  $\Delta X_i$  is the change in the number of moles of the species  $i$  between additions of titrant. The best fit was obtained by minimizing the residual error  $E$

$$E = \sum_{i=1}^N [Q_i(\text{calc}) - Q_i(\text{corr})]^2$$

Table II presents a sample set of calorimetric data for the complexation of Sm<sup>3+</sup> ion. The concentrations of [Sm<sup>3+</sup>], [L<sup>3-</sup>], and [H<sup>+</sup>] are those of the free ions. A summary of all the thermodynamic parameters is given in Table III. The error limits, which represent 3 standard deviations, are the propagated errors calculated from the deviations of both the stability and enthalpy parameters from several runs.

The results of the luminescence decay measurements for Eu<sup>3+</sup>, Eu(DTPA)<sup>2-</sup>, and Eu(DTPA-BMA) in aqueous and deuterated media are listed in Table IV. The solutions of the complexes were adjusted to a pH value of ca. 8.5 and had an ionic strength of 0.10 M (NaClO<sub>4</sub>). The error limits are the average deviations from three separate measurements. Since only complexed Eu<sup>3+</sup> is present in the solutions of DTPA and DTPA-BMA, the values of  $n_{\text{H}_2\text{O}}$  ( $\approx 1.2$ ) in Table IV represent the number of water molecules in the primary coordination sphere of complexed Eu<sup>3+</sup>.<sup>10</sup>

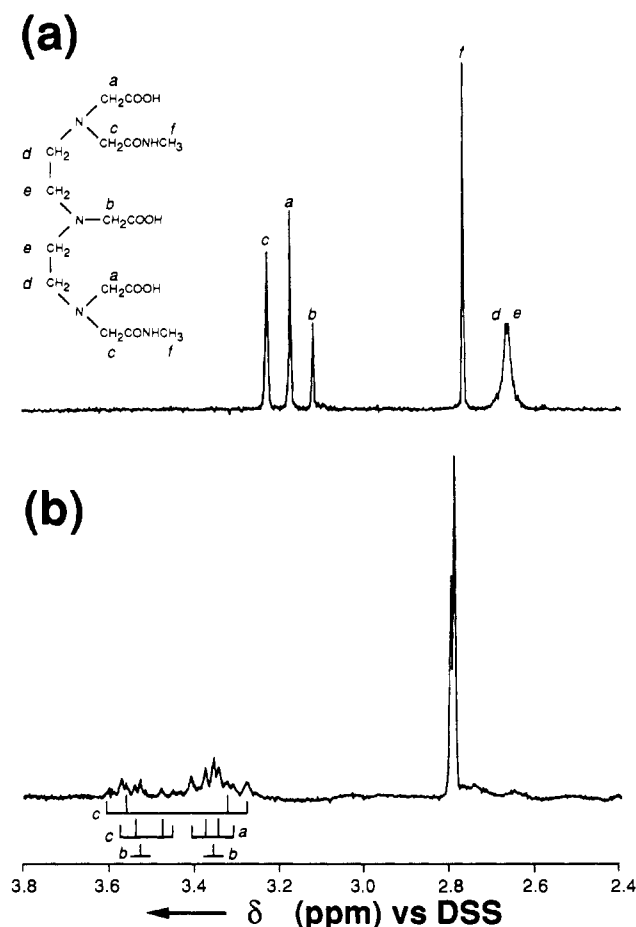
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**Table II.** Calorimetric Titration Data for the Complexation of  $\text{Sm}^{3+}$  by DTPA-BMA ( $I = 0.10 \text{ M}$  ( $\text{NaClO}_4$ );  $T = 298 \text{ K}$ )<sup>a</sup>

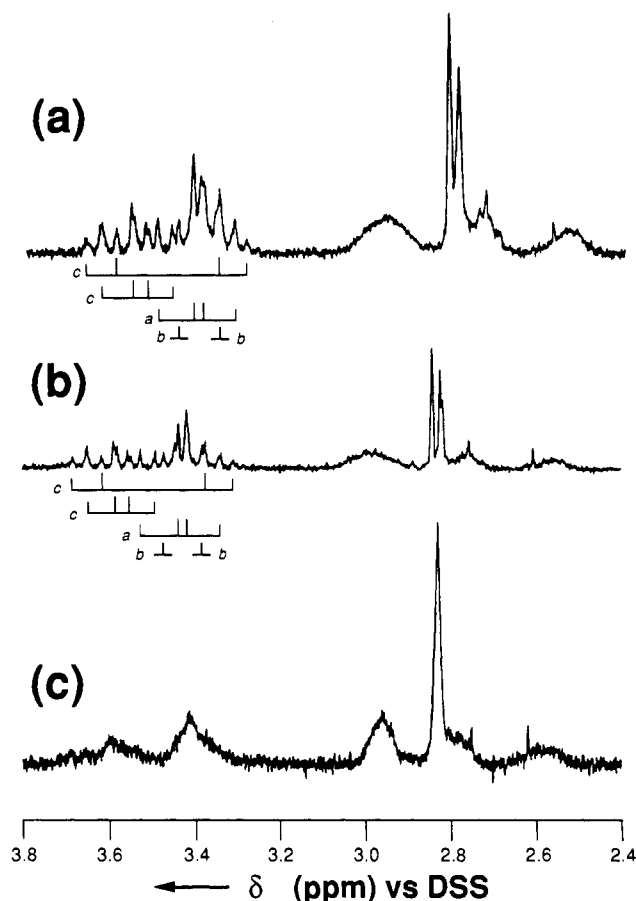
$V, \text{ mL}$	$\Sigma Q_{\text{exp}}, \text{ mJ}$	$-\Sigma Q^b, \text{ mJ}$	$[\text{Sm}^{3+}], \text{ mM}$	$[\text{L}^{3-}], 10^{19} \text{ M}$	$[\text{H}^+], 10^4 \text{ M}$	$\Delta H_{101}, \text{ kJ mol}^{-1}$
0.25		64.4	13.061	0.834	1.853	24.0
0.50	2.3	133.4	12.943	1.675	2.249	24.9
0.75	9.2	207.0	12.827	2.523	2.640	25.7
1.00	20.7	278.2	12.711	3.378	3.028	26.0
1.25	29.8	341.8	12.597	4.239	3.412	25.5
1.50	31.3	406.2	12.484	5.109	3.792	25.2
1.75	33.6	476.9	12.372	5.985	4.168	25.4
2.00	42.1	539.5	12.261	6.869	4.541	25.2
2.25	42.6	607.0	12.151	7.760	4.910	25.2
2.50	48.0	673.4	12.042	8.659	5.276	25.1
2.75	52.3	738.1	11.934	9.565	5.638	25.0
3.00	54.9	806.4	11.827	10.479	5.997	25.1
3.25	61.1	881.4	11.721	11.401	6.353	25.3
3.50	74.0	949.8	11.616	12.331	6.705	25.3
3.75	80.3	1024.5	11.512	13.270	7.054	25.5
4.00	92.9	1093.9	11.409	14.216	7.400	25.5
4.25	100.2	1162.3	11.307	15.170	7.742	25.5
4.50	106.5	1228.4	11.206	16.133	8.081	25.5
4.75	110.5	1301.5	11.106	17.105	8.418	25.5
5.00	121.5	1341.8	11.007	18.084	8.751	25.0
5.25	122.9	1443.8	10.909	19.073	9.081	25.6
5.50	139.6	1514.3	10.811	20.071	9.408	25.7
5.75	147.9	1585.5	10.715	21.077	9.733	25.7
6.00	157.0	1650.6	10.619	22.093	10.054	25.7
	160.0					

<sup>a</sup> Experimental Conditions are as follows. Cup solution:  $[\text{Sm}^{3+}] = 13.180 \text{ mM}$ ;  $C_{\text{H}} = 0.1454 \text{ mM}$ ; volume = 50.0 mL. Titrant:  $C_{\text{L}} = 10.724 \text{ mM}$ ;  $C_{\text{H}} = 8.172 \text{ mM}$ . Constant:  $\Delta H_{101} = -25.3 \pm 0.4 \text{ kJ mol}^{-1}$ .  
<sup>b</sup> Corrected for ligand deprotonation.

**Figure 2.**  $^1\text{H-NMR}$  spectra of (a)  $\text{Na}^+$  salt of DTPA-BMA and (b)  $\text{La}(\text{DTPA-BMA})$  at  $5^\circ\text{C}$ .

On the basis of these values, both ligands are octadentate in the europium complexes.

The proton magnetic resonance spectrum of the ligand sodium

**Figure 3.**  $^1\text{H-NMR}$  spectra of  $\text{LuDTPA}$  at (a)  $5^\circ\text{C}$ , (b) ambient temperature, and (c)  $85^\circ\text{C}$ .

salt ( $\text{Na}_3\text{L}$ ), shown in Figure 2a, displays four singlets at 3.24, 3.18, 3.12, and 2.78 ppm and a multiplet centered at 2.66 ppm with an intensity ratio of 2:2:1:3:4. The assignments of the peaks follows those reported for  $\text{Na}_5\text{DTPA}^{11a}$  in which a multiplet was observed at 2.60 ppm for the D and E protons, a singlet at 3.09 ppm for the B protons, and a singlet at 3.14 ppm for the A protons. The distinction between the  $\text{H}_A$  and  $\text{H}_C$  signals is also supported by the fact that amide groups have a larger inductive effect relative to an  $\alpha$ -carboxylate group.<sup>11b,c</sup> The multiplet associated with the D and E protons was too complex and usually too weak to provide useful analysis and is not discussed further.

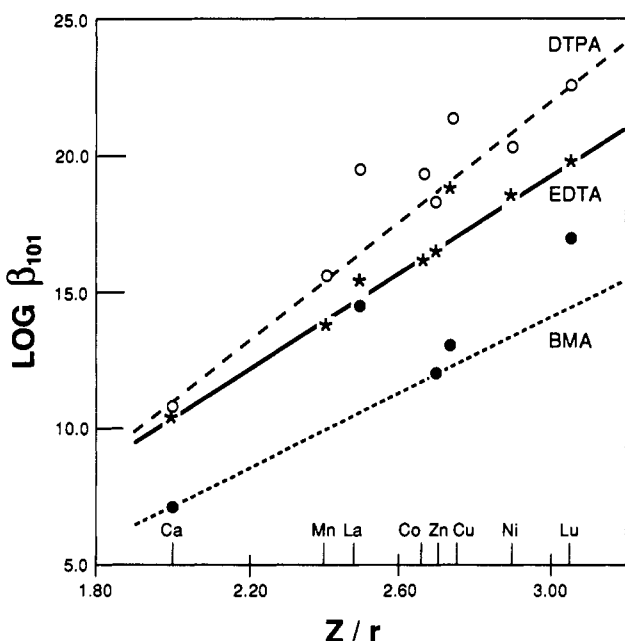
The spectra observed for lanthanum and lutetium complexes (Figures 2b and 3) are more complicated. In the low-temperature ( $5^\circ\text{C}$ ) spectrum of  $\text{La}(\text{DTPA-BMA})$ , the doublet at 2.79 and 2.81 ppm with an intensity ratio of 3:2 is assigned to the *N*-methyl protons. This doublet collapses into a singlet as the temperature increases. The protons of the terminal acetate groups ( $\text{H}_A$ ) gave an AB pattern with the baricenter at 3.36 ppm ( $J = 23 \text{ Hz}$ ) whereas the protons of the amide methylenes ( $\text{H}_C$ ) show two AB quartets with baricenters at 3.45 ppm ( $J = 20 \text{ Hz}$ ) and 3.51 ppm ( $J = 14 \text{ Hz}$ ), respectively. This pattern of splitting implies long metal–nitrogen and short metal–oxygen bond lifetimes.<sup>12</sup>

The spectrum of the lutetium complex at  $5^\circ\text{C}$  resembles closely that of lanthanum with a slight shift downfield as a result of the increase in the charge density. The resonances for the *N*-methyl protons are split into two peaks at 2.81 and 2.83 ppm, the protons of the terminal acetate groups show a quartet pattern with the baricenter at 3.41 ppm ( $J = 38 \text{ Hz}$ ), and the amide methylenes

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**Table III.** Thermodynamics of Complexation of Lanthanide, Ca<sup>2+</sup>, Cu<sup>2+</sup>, and Zn<sup>2+</sup> Ions with DTPA-BMA (*I* = 0.10 M (NaClO<sub>4</sub>); *T* = 298 K)

equil quotient	log β	Δ <i>G</i> , kJ mol <sup>-1</sup>	-Δ <i>H</i> , kJ mol <sup>-1</sup>	Δ <i>S</i> , J K <sup>-1</sup> mol <sup>-1</sup>
[LaL]/[La][L]	14.55 ± 0.05	83.02 ± 0.29	17.3 ± 2.0	221 ± 6
[SmL]/[Sm][L]	16.69 ± 0.05	95.22 ± 0.29	25.1 ± 0.9	235 ± 3
[GdL]/[Gd][L]	16.86 ± 0.05 <sup>a</sup>	96.19 ± 0.29	25.3 ± 0.4	238 ± 1
[DyL]/[Dy][L]	17.90 ± 0.05	102.12 ± 0.29	24.1 ± 0.3	262 ± 1
[LuL]/[Lu][L]	17.06 ± 0.05	97.34 ± 0.29	19.1 ± 1.4	263 ± 4
[CaL]/[Ca][L]	7.17 ± 0.04 <sup>a</sup>	40.91 ± 0.22	25.9 ± 2.1	50 ± 6
[CaHL]/[Ca][HL]	2.20 ± 0.02	12.57 ± 0.11	5.3 ± 0.7	24 ± 2
[CuL]/[Cu][L]	13.05 ± 0.03 <sup>a</sup>	74.46 ± 0.17	56.7 ± 4.0	60 ± 12
[CuHL]/[Cu][HL]	7.04 ± 0.02	40.19 ± 0.11	23.3 ± 1.7	57 ± 5
[ZnL]/[Zn][L]	12.04 ± 0.03 <sup>a</sup>	68.69 ± 0.17	33.3 ± 1.5	119 ± 5
[ZnHL]/[Zn][HL]	6.66 ± 0.02	38.02 ± 0.11	8.1 ± 0.6	100 ± 2

<sup>a</sup> Data from ref 3.**Figure 4.** Correlation of log β<sub>101</sub> and *Z/r* for DTPA-BMA (●), EDTA (\*), and DTPA (○) complexes. The lines are the least-squares correlation of the divalent cation values.**Table IV.** Luminescence Decay Constants for Eu<sup>3+</sup> Complexes and Calculated Number of Primary Coordination Sphere Water Molecules (*I* = 0.10 M (NaClO<sub>4</sub>); *T* = 298 K)

complex	<i>k</i> <sub>H<sub>2</sub>O</sub> , ms	<i>k</i> <sub>D<sub>2</sub>O</sub> , ms	<i>n</i> <sub>H<sub>2</sub>O</sub> <sup>a</sup>
Eu <sup>3+</sup>	8.70 ± 0.10	0.33	8.81 ± 0.10
[Eu(DTPA)] <sup>2-</sup>	1.45 ± 0.10	0.35	1.17 ± 0.10
[Eu(DTPA-BMA)] <sup>0</sup>	1.52 ± 0.03	0.35	1.25 ± 0.03

<sup>a</sup> *n*<sub>H<sub>2</sub>O</sub> = 1.05 (*k*<sub>H<sub>2</sub>O</sub> - *k*<sub>D<sub>2</sub>O</sub>); the error is based on that of the *k* data. It has been estimated that ±0.5 is the uncertainty of this method.<sup>10</sup>

protons have two AB quartets with baricenters at 3.47 ppm (*J* = 33 Hz) and 3.55 ppm (*J* = 34 Hz), respectively. The peaks at 3.45 ppm and 3.36 ppm are assigned to the protons of the middle acetate group (see Figure 3). An uncertainty in our assignments and in the interpretation of Figure 3 is associated with the fact that one of the peaks of the middle acetate of the lutetium complex is 0.08 ppm upfield relative to that of the lanthanum complex. Perhaps this shift reflects a lengthening in the lutetium-carboxylate distance.

Increasing the temperature (Figure 3) to ca. 25 °C results in a slight shift of the Lu(DTPA-BMA) peaks upfield with little broadening. Further increase in temperature (ca. 85 °C) leads to a further small upfield shift and in total collapse of the fine splitting. These changes with temperature probably reflect an increase in the rate of exchange between possible conformers in solution.

## Discussion

<sup>13</sup>C-NMR shift and relaxation measurements of Ln(DTPA-BPA) (DTPA-BPA = diethylenetriaminepentaacetate-bis(propylamide)) indicate that these complexes can exist in solution as eight different enantiomers with the three nitrogens being chiral.<sup>13</sup> In principle, the eight rotamers can interconvert to each other; however, due to the partial double-bond character of the amide C-N bonds, this transformation is slow relative to the NMR time scale. The splitting of the methyl signal in the DTPA-BMA complexes is consistent with the presence of at least two stable conformers. The same model accounts for the splitting of the H<sub>B</sub> protons into two peaks at 3.53 and 3.35 ppm and the collapse into simpler spectra with increased temperature.

Figure 4 is a plot of the values of log β<sub>101</sub> in Table III for Ca<sup>2+</sup>, Cu<sup>2+</sup>, Zn<sup>2+</sup>, La<sup>3+</sup>, and Lu<sup>3+</sup> as a function of the cationic charge density, *Z/r* (i.e., the cationic charge divided by the ionic radius). Data for EDTA and DTPA complexation for Mn<sup>2+</sup>, Co<sup>2+</sup>, and Ni<sup>2+</sup> from ref 9 are included in Figure 4. The Shannon radii<sup>14</sup> were used to calculate the values of *Z/r* (*N* = 6 values were used for the divalent cations and for La<sup>3+</sup> and Lu<sup>3+</sup>, the radii for CN = 9 and 8, respectively). The correlation lines are linear least-squares fits to the divalent Ca, Mn, Co, Zn, and Ni values. The Cu data do not fit these correlations, reflecting the tetragonal distortion observed in these complexes,<sup>15</sup> and are not included in Figure 4. From these correlations, we conclude that Ca<sup>2+</sup>, Cu<sup>2+</sup>, and Zn<sup>2+</sup> are hexacoordinated by the DTPA-BMA ligand with some distortion in the copper complex. It is tempting to suggest that the stronger complexing of La and Lu to DTPA-BMA relative to the M<sup>2+</sup> correlation line reflects Ln-amide interactions not present in the octahedral M<sup>2+</sup> complexes. This would seem to explain also the better agreement of the EDTA complexation. However, if DTPA is octadentate to La and Lu but hexadentate to the M<sup>2+</sup> cations, the complexation of LuDTPA should be above the correlation line.

The NMR data support the behavior of octadentation by the DTPA-BMA ligand in complexation of lanthanum and lutetium. For these cations, the measured log β<sub>101</sub> is larger for DTPA-BMA than predicted by the correlations in Figure 4. This may indicate that the average bond distances in these complexes are somewhat smaller than reflected in the ionic radii of Shannon. log β<sub>101</sub> values for LaEDTA and LaDTPA also fail to fit the correlation lines, while the values for LuEDTA and LuDTPA do.

A linear correlation has been shown to exist between Δ*S*<sub>101</sub> and the number of bound carboxylate groups for lanthanide-amino-polycarboxylate complexation when all the chelate rings are five-membered.<sup>16</sup> For Sm<sup>3+</sup>, this correlation has a slope of ca. 67 ± 3 J K<sup>-1</sup> mol<sup>-1</sup> in 0.1 M ionic strength. This predicts

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$\Delta S_{101} = 67 \times 3 \approx 201 \pm 9 \text{ J K}^{-1} \text{ mol}^{-1}$  for DTPA-BMA compared to the observed value of  $235 \pm 3 \text{ J K}^{-1} \text{ mol}^{-1}$ . The difference in entropy of  $35 \text{ J K}^{-1} \text{ mol}^{-1}$  is attributed to the binding of the two amido groups to the lanthanides.

It was also shown in ref 16 that an enthalpy contribution to  $\Delta H_{101}$  from the Ln-N bonding,  $\delta\Delta H(N)$ , is proportional to the  $\sum pK_a$  of the nitrogen donors. For DTPA-BMA,  $\sum pK_{a(N)}$  refers to the first three values in Table I, which sum to 17.06. At 0.1 M ionic strength, the slope of the linear correlation of  $\delta\Delta H(N)$  and  $\sum pK_{a(N)}$  is 3.33; thus, we estimate  $\delta\Delta H(N) \sim -56.8 \text{ kJ mol}^{-1}$ .  $\Delta H_{101}$  for  $\text{SmAc}^{2+}$  is  $\sim 10.5 \text{ kJ mol}^{-1}$  (from extrapolation of  $\Delta H_{101}$  vs  $\sum pK_a$  using data in refs 18–20). Therefore, according to the treatment in ref 16, we expect for  $\text{Sm(DTPA-BMA)}$   $\Delta H_{101} = \delta\Delta H(N) + n\Delta H(\text{SmAc}^{2+})$  or  $\Delta H_{101} = -56.8 + (3 \times 10.5) = -25.3 \text{ kJ mol}^{-1}$ , which compares very well with the observed value of  $-25.1 \text{ kJ mol}^{-1}$ . The net contribution to  $\Delta H_{101}$  from interaction

with the amido groups is roughly zero (i.e., the exoergic Ln-amido bonds are equally balanced by the associated endoergic dehydration).

#### Conclusion

Lanthanide ions from octadentate complexes with DTPA-BMA, in contrast to the hexadentate complexation by  $\text{Ca}^{2+}$ ,  $\text{Cu}^{2+}$ , and  $\text{Zn}^{2+}$ . In solution, the Ln-N bonds are long-lived (on the NMR time scale) and the Ln-O bonds are short-lived. The  $\text{Ln}^{3+}$  complexes exist in at least two conformer structures in solution with octadentation by the ligand. Analysis of the thermodynamic data indicates that the amido groups bond more weakly to  $\text{Ln}^{3+}$  ions than the carboxylate groups.

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