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Equilibrium and Kinetic Studies of Lanthanide Complexes of Macrocyclic Polyamino Carboxylates

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The stability constants (log K_{LnL}) of lanthanide complexes of macrocyclic polyamino carboxylates, LnL (where Ln is Ce^{3+}, Gd^{3+}, and Lu^{3+} and L is DO3A = 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid and HP-DO3A = 10-(hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid), have been determined at 25.0 ± 0.1 °C and $\mu = 0.1$ ($(CH_3)_4NCl$). The stability constants of lanthanide complexes of DO3A increase with the decreasing ionic radii or increasing charge density of Ln^{3+}. For L = HP-DO3A, the stability constant of GdL is greater than that of CeL; however the stability constants of GdL and LuL are similar. The protonation constants, K_H (M^{-1}), of the LnL complexes have been determined at 25.0 ± 0.1 °C and $\mu = 1.0$ (NaCl), and the values are 18 ± 3 for Ce(DO3A), 115 ± 8 for Gd(DO3A), 11 ± 1 for Ce(HP-DO3A), and 240 ± 25 for Gd(HP-DO3A). The rates of acid-assisted dissociation of the protonated complexes, ML(H), have been measured at 25.0 ± 0.1 °C and $\mu = 1.0$ (NaCl). Direct, k_d (s^{-1}), and acid-assisted, k_1 ($M^{-1}\ s^{-1}$), dissociation rate constants are $k_d = (1.8 \pm 0.8) \times 10^{-3}$ and $k_1 = (1.12 \pm 0.04) \times 10^{-1}$ for Ce(DO3A) and $k_d = (1.4 \pm 0.2) \times 10^{-4}$ and $k_1 = (2.00 \pm 0.04) \times 10^{-3}$ for Ce(HP-DO3A). The rates of dissociation of the other complexes are first order in acid at low $[H^+]$, but the rates saturate at high $[H^+]$. The calculated equilibrium constants, K_1 (M^{-1}), for the formation of the diprotonated species, $LnL(H_2)$, and their dissociation rate constants, k_2 (s^{-1}), are 3.6 ± 0.4 and $(7.4 \pm 0.4) \times 10^{-3}$ for Gd(DO3A), 7.7 ± 1.8 and $(3.6 \pm 0.1) \times 10^{-3}$ for Lu(DO3A), and 1.0 ± 0.1 and $(6.4 \pm 0.3) \times 10^{-4}$ for Gd(HP-DO3A), respectively. Evidence of a direct dissociation pathway for Gd(DO3A)(H) is also observed with a rate constant, k_d (s^{-1}), of $(4.4 \pm 0.1) \times 10^{-4}$. A linear correlation of log k_{obsd} with charge density for dissociation of Ln(DO3A) complexes in 0.1 M HCl was observed.

Introduction

There has been considerable interest in thermodynamic[1] and kinetic[2] studies of lanthanide (Ln) complexes because of their coordination chemistry and their use as contrast agents in magnetic resonance imaging (MRI)[3,4] and ion-selective reagents in analytical chemistry.[5] Several factors influence the stability and the rates and mechanisms of acid-assisted dissociation of Ln complexes of linear polyamino carboxylates.[6-9] These factors are the size of the metal ion, charge density, and rigidity. Two types of trends in the stability constants of lanthanide complexes of linear polyamino carboxylates are observed: (1) The stability constants increase linearly with increasing charge density of the lanthanide ion. (2) The stability constants increase for lighter lanthanides, and then they either become constant or decrease with increasing charge density with a break at gadolinium. The kinetic inertia also increases with increasing charge density of the metal ion[8,9] for Ln complexes of linear polyamino carboxylates. Macrocyclic polyamino carboxylates, however, have some additional features which affect the stability and their acid-assisted dissociation rates. These include internal cavity size,[10] conformation,[11] and preorganization[12] of the free ligand.

Recent studies[13] on the lanthanide complexes of polyamino polyoxa carboxylates (K21DA and K22DA) demonstrated the unusual charge density and cavity size dependence of the stability and dissociation rates. Brucher and Sherry[14] reported the formation and dissociation rates of Ce^{3+}, Gd^{3+}, and Er^{3+} complexes of the 9-membered macrocyclic polyamino carboxylate NOTA (1,4,7-triazacyclononane-1,4,7-triacetic acid). The formation rates of these complexes were independent of the size of the metal ion; however dissociation rates varied with the size of the metal ion. NOTA is smaller than the 12-membered macrocyclic polyamino carboxylate ligands, and the results for the latter type of ligands could differ. Additional studies on dissociation of Ce^{3+} and Gd^{3+} complexes of DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetracaetic acid) were also reported.[15,16] In these studies, the dissociation of LnL by an acid-assisted path was suggested, but no conclusions were drawn regarding the effect of the size of the metal ion on the dissociation rates. The studies were performed under highly acidic conditions, $[H^+] = 0.02–2.0$ M, and we suspected the involvement of protonated species[17] in the acid-assisted dissociation of these complexes.

We initiated the present study with the following goals: (1) to understand the effect of the number of ligand donor atoms, the size of the macrocyclic ligand cavity, and the charge density of the metal ion on the stability and acid-assisted dissociation rates of the lanthanide complexes; (2) to understand the mechanisms of dissociation of the complexes; and (3) to investigate the possible involvement of the protonated complex species in the

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(1) Choppin, G. R. *J. Less-Common Met.* **1985**, *112*, 193.
(2) Margerum, D. W.; Cayley, G. A.; Weatherburn, D. C.; Pagenkopf, G. K. In *Coordination Chemistry, Vol. 2*; Martell, A. E., Ed.; ACS Monograph 174; American Chemical Society: Washington, D.C., 1978; p 1.
(3) Lauffer, R. B. *Chem. Rev.* **1987**, *87*, 901.
(4) Tweedle, M. F. In *Lanthanide Probes in Life, Chemical and Earth Sciences*; Bunzli, J.-C. G., Choppin, G. R., Eds.; Elsevier: Amsterdam, 1989.
(5) Marcus, Y.; Kertes, A. S. *Ion Exchange and Solvent Extraction of Metal Complexes*; Wiley-Interscience: London, 1969.
(6) Tse, P. K.; Powell, J. E. *Inorg. Chem.* **1985**, *24*, 2727.
(7) Cacheris, W. P.; Nickel, S. K.; Sherry, A. D. *Inorg. Chem.* **1987**, *26*, 958.
(8) Nyssen, G. A.; Margerum, D. W. *Inorg. Chem.* **1970**, *9*, 1814.
(9) De Jonghe, M.; D'Olieslager, W. *Inorg. Chim. Acta* **1985**, *109*, 7.
(10) Lehn, J.-M.; Sauvage, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6700.
(11) Dale, J. *Isr. J. Chem.* **1980**, *20*, 3.
(12) Artz, S. P.; Cram, D. J. *J. Am. Chem. Soc.* **1984**, *106*, 2160.
(13) (a) Chang, C. A.; Ochaya, V. O.; Chandra Sekhar, V. *J. Chem. Soc., Chem. Commun.* **1985**, 1724. (b) Chandra Sekhar, V.; Chang, C. A. *Inorg. Chem.* **1986**, *25*, 2061.
(14) Brucher, E.; Sherry, A. D. *Inorg. Chem.* **1990**, *29*, 1555.
(15) Brucher, E.; Laurenczy, G.; Makara, Z. S. *Inorg. Chim. Acta* **1987**, *139*, 141.
(16) Wang, X.; Tianzhu, J.; Comblin, V.; Lopez-Mut, A.; Merciny, E.; Desreux, J. F. *Inorg. Chem.* **1992**, *31*, 1095.
(17) For protonation of metal complexes of DOTA, see: (a) Kumar, K.; Magerstadt, M.; Gansow, O. A. *J. Chem. Soc., Chem. Commun.* **1989**, 145. (b) Baron, C. J.; Cox, J. P. L.; Craig, A. S.; Kataly, R.; Parker, D. A.; Harrison, A.; Randall, A. M., Ferguson, G. *J. Chem. Soc., Perkin Trans. 2* **1991**, 87.

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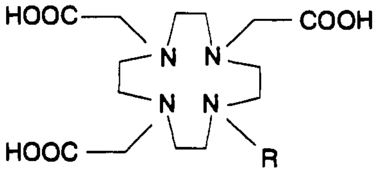
acid-assisted dissociation of lanthanide complexes of macrocyclic polyamino carboxylates in general, and DOTA in particular.

We report herein a systematic equilibrium and kinetic study of lanthanide (Ln = Ce^{3+}, Gd^{3+}, Lu^{3+}) complexes of DO3A (1,4,7,10-tetrazacyclododecane-1,4,7-triacetic acid, structure I) and HP-DO3A (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, structure II).



I. R = H DO3A
II. R = $CH_2CH(CH_3)OH$ HP-DO3A

Experimental Section

Chemicals and Reagents. The ligands DO3A, HP-DO3A, and DOTA and their Gd^{3+} complexes were synthesized and characterized by published methods.[18,19] The standard solutions of $CeCl_3$, $GdCl_3$, and $LuCl_3$ were prepared from solid samples (Research Chemicals, Inc.). The concentration of the sample solutions was determined by EDTA titrations using Xylenol Orange or Arsenazo-III indicators.[20] Stock solutions of Ce^{3+} and Lu^{3+} complexes of DO3A, HP-DO3A, and DOTA were prepared in situ by mixing the ligand with a slight excess of $CeCl_3$ or $LuCl_3$ and raising the pH of the mixture to 7 very slowly. The sample was then filtered through a 0.22-μ Millipore filter to remove the $Ce(OH)_3$ or $Lu(OH)_3$ precipitate. The clear colorless sample solutions of CeL were characterized using their UV/vis spectral characteristics: 310 nm (ϵ = 350 M^{-1} cm^{-1}), 318 nm (ϵ = 580 M^{-1} cm^{-1}), and 320 nm (ϵ = 630 M^{-1} cm^{-1}) for DO3A, HP-DO3A, and DOTA complexes of Ce^{3+}, respectively. However LuL samples did not have significant absorbance or fluorescence and were used as prepared. Arsenazo-III (Aldrich), sodium acetate, acetic acid (Fisher), and tetramethylammonium chloride (Aldrich) were used as received. Sodium chloride (Alfa) was used for ionic strength control in all kinetics studies. Distilled deionized water and reagent grade buffers, acids, and bases were used in these studies.

Methods. Solution pH values were measured with an Orion combination glass electrode and Orion pH meter, Model SA 720. All spectrophotometric and kinetic measurements were made with the use of an HP-8452A spectrophotometer interfaced with an HP-310 data station. The formation of LnL (Ln = Ce, Gd, Lu; L = DO3A, HP-DO3A) was very slow, and a direct potentiometric titration technique could not be used to determine the stability constants. Consequently, a spectrophotometric method was used with Arsenazo-III as the indicator.[7,21]

The formation constants for the 1:1 (β_{LnAz}) and 1:2 (β_{LnAz_2}) complexes of the lanthanide with Arsenazo-III at pH 4.0 ($[OAc]_T$ = 50 mM), μ = 0.1 $(CH_3)_4NCl$), 25.0 ± 0.1 °C were determined by a spectrophotometric titration. Arsenazo-III solution (2.02×10^{-4} M) was added to the buffered $LnCl_3$ solution (usually (2.00–2.10) $\times 10^{-5}$ M) in a curvette such that the Az:Ln ratio reached 1.5–2.0. Titration data consisting of the absorbance of the mixture of LnAz and $LnAz_2$ (at 656 nm for Ce^{3+}, 660 nm for Gd^{3+}, and 652 for Lu^{3+}) vs volume of Aresenazo-III added were used to calculate[7] the values of β_{LnAz}, β_{LnAz_2}, ϵ_{LnAz}, and ϵ_{LnAz_2}. The calculated values of extinction coefficients (M^{-1} cm^{-1}) of 1:1 (ϵ_{LnAz}) and 1:2 (ϵ_{LnAz_2}) complexes of Arsenazo-III were 26 000 and 56 000 for Ce^{3+}, 38 000 and 50 000 for Gd^{3+}, and 36 000 and 38 000 for Lu^{3+}, respectively. The stability constants of 1:1 and 1:2 complexes of Arsenazo-III were calculated: 6.8 and 11.2 for Ce^{3+}, 6.6 and 12.8 for Gd^{3+}, and 6.8 and 12.3 for Lu^{3+}. Batch solutions of mixtures of Ln^{3+} ((1.05–1.10) $\times 10^{-5}$ M) and Arsenazo-III (3.03×10^{-5} M) were prepared with variable amounts of the ligand such that the L:Ln ratio reached as high as 3.0–3.30. As described by Sherry and co-workers,[7] the solutions were maintained at 60 °C in sealed vials for 18 h, followed by additional room-temperature equilibration for 6–12 h. The change in absorbance due to displacement of Arsenazo-III by the ligand and the values of the extinction coefficients and the stability constants of Arsenazo-III complexes were used to calculate the conditional equilibrium constant at pH 4.0 for each complex.[7]

The stability constants (K_{LnL}) for the complexes were calculated from the conditional stability constant, K_{LnL}(Cond), at pH 4.0 and the ligand protonation constants.[22] The accuracy of this technique was verified by measuring the thermodynamic stability constants for the lanthanide complexes with ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA).[7,21]

All kinetic studies were carried out at 25.0 ± 0.1 °C, at a constant ionic strength (μ = 1.0), and under pseudo-first-order conditions with large excesses of $[H^+]$. The temperature of the reaction mixture was maintained at 25.0 ± 0.1 °C with the use of a Lauda RMS circulatory water bath. The reactions were followed for at least 4 half-lives. Pseudo-first-order rate constants (k_{obsd}, s^{-1}) were calculated from the absorbance or intensity vs time data using a first-order model.[23] A SIMPLEX[24,25] program was used to fit these data. All calculations were completed on a Dell-200 desk-top personal computer.

The rates of acid-assisted dissociation of lanthanide complexes were slow, and conventional absorbance or fluorescence measurements were used to monitor the progress of the reactions. In the case of dissociation of CeL or LuL, a multicell transport was used to study more than one reaction at a time. The progress of the dissociation reactions of CeL was monitored by following the absorbance decrease at 310 and 318 nm for Ce(DO3A) and Ce(HP-DO3A), respectively. The fluorescence intensity measurements for GdL complexes were made with a Hitachi F-2000 or an SPEX-OMIB with SPEX-Fluorolog spectrofluorimeter with 274- and 312-nm excitation and emission wavelengths, respectively. In the case of Gd(HP-DO3A), the experiments were also carried out by removing free Gd^{3+} from the reaction mixture using ion-exchange resin (Dowex 50W-X8 in Na^+ form) and by measuring the fluorescence intensity of the sample as a function of time. The calculated k_{obsd} values in the presence or absence of the ion-exchange resin were in excellent agreement. The chelates, LuL (L = DO3A, HP-DO3A, DOTA), do not show appreciable UV/vis absorption or fluorescence; here Cu^{2+} was used as the scavenger for the free ligand.[8,13] In the copper method, the ligand released due to the dissociation of the Lu complex was monitored at 290 nm as the formation of CuL. To evaluate the driving force of the reactions of LuL (L = DO3A, HP-DO3A, DOTA) with Cu^{2+}, the stability constants of copper complexes of these ligands were determined from the potentiometric titrations. The values are 22.6 (DO3A), 22.6 (HP-DO3A), and 22.2 (DOTA). No dissociation reaction was observed for Lu(HP-DO3A) or $Lu(DOTA)^-$ by this method. The progress of the dissociation reaction of Lu(DO3A) was also monitored by the copper method. A large excess of Cu^{2+} (8–9-fold) was used to complete the reaction.

Results and Discussion

Equilibrium Constants for the Formation of Lanthanide Complexes of DO3A, HP-DO3A, and DOTA. The stability constants of the complexes formed between the macrocyclic polyamino carboxylates (DO3A, HP-DO3A, DOTA) and the lanthanide ions (Ce, Gd, Lu) determined in this work and elsewhere[7,21] are summarized in Table I. A comparison of the stability constants of the lanthanide complexes of macrocyclic polyamino carboxylates demonstrates the order DOTA > HP-DO3A > DO3A. X-ray crystal structure studies[21] of free ligands demonstrate that the conformations of the macrocyclic ligands are identical; therefore, the stability differences between the complexes of heptadentate DO3A and octadentate HP-DO3A and DOTA are due to the differences in the number and type of donor atoms and the number of chelate rings formed. Replacement of the neutral hydroxypropyl coordinating group in HP-DO3A by the ionizable carboxylate group in DOTA increases the stability by 2 orders of magnitude. As expected, the additional negative charge on DOTA provides additional stability of Ln complexes, which

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(18) Dischino, D. D.; Delaney, E. J.; Emswiler, J. E.; Gaughan, G. A.; Prasad, J. S.; Srivastava, S. K.; Tweedle, M. F. *Inorg. Chem.* **1991**, *30*, 1265.

(19) Desreux, J. F. *Inorg. Chem.* **1980**, *19*, 1319.

(20) Vogel, A. I. *A Text Book of Quantitative Inorganic Analysis*, 3rd ed.; Longman: London, 1961.

(21) Kumar, K.; Chang, C. A.; Francesconi, L. F.; Dischino, D.; Mailley, M.; Gougoutas, J. Z.; Tweedle, M. *Inorg. Chem.*, to be submitted for publication.

(22) The ligand protonation constants in 0.1 $((CH_3)_4NCl)$ and at 25.0 ± 0.1 °C are[21] 11.59 ± 0.03, 9.24 ± 0.03, 4.43 ± 0.07, 3.48 ± 0.01 for DO3A, 11.96 ± 0.02, 9.43 ± 0.01, 4.30 ± 0.04, 3.26 ± 0.01 for HP-DO3A, and 11.73 ± 0.03, 9.40 ± 0.02, 4.50 ± 0.04, 4.19 ± 0.06 for DOTA.

(23) Espenson, J. H. *Chemical Kinetics and Reaction Mechanisms*; McGraw-Hill: New York, 1981.

(24) Caceci, M. S.; Catheris, W. P. *Byte* **1984**, *9*, 340.

(25) Yarboro, L. A.; Deming, S. N. *Anal. Chim. Acta* **1974**, *73*, 391.

Table I. Formation Equilibrium Constants (log K_{LnL}) and Protonation Equilibrium Constants (log K_{H})[a]

equilibrium	L: DO3A	L: HP-DO3A	L: DOTA
Ce + L ↔ CeL	19.7 ± 0.4	21.2	23.0[b]
CeL + H$^+$ ↔ CeL(H)$^+$	1.25 ± 0.20	1.04 ± 0.09	c
Gd + L ↔ GdL	21.0 ± 0.2[d]	23.8 ± 0.8[d]	25.3 ± 0.6[d] 24.6[b]
GdL + H$^+$ ↔ GdL(H)$^+$	2.06 ± 0.1	2.38 ± 0.3	2.8 ± 0.5
Lu + L ↔ LuL	23.0 ± 0.2	23.3 ± 0.3	25.5[b]

[a] log K_{LnL} at 25.0 ± 0.1 °C, μ = 0.1 ((CH$_3$)$_4$NCl); log K_{H} at 25.0 ± 0.1 °C, μ = 1.0 (NaCl). [b] Reference 7. [c] Not observed. [d] Reference 21.

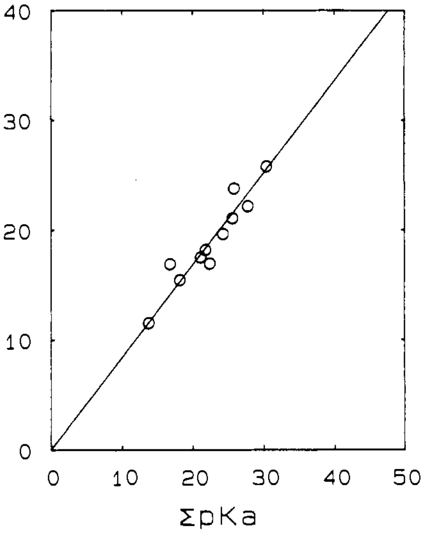

Figure 1. Plot of log K_{GdL} vs the sum of the pK_a values of the neutral forms of some linear and macrocyclic polyamino carboxylates.

supports the preference of ionic binding of lanthanides. This is supported by an excellent correlation of log K_{GdL} vs $\sum$pK_a of the neutral form of the ligand as shown in Figure 1 for linear and macrocyclic polyamino carboxylates which form 5-membered chelate rings. (The stability constants for the Gd^{3+} complexes of linear polyamino carboxylates are taken from the literature.[26])

Protonation Equilibria of DO3A, HP-DO3A, and DOTA Complexes of Ce^{3+} and Gd^{3+}. Mixing equal volumes of CeL or GdL with a known concentration of acid showed a small but instantaneous absorbance (*A*) or fluorescence intensity (*I*) decrease, respectively, which depended on the concentration of acid, followed by a slow dissociation reaction of the complex. As observed previously[17] in the case of Pb(DOTA)$^{2-}$, the instantaneous absorbance or fluorescence intensity decrease was attributed to the formation of a protonated species, LnL(H) (eq 1).

$$\mathrm{LnL + H^+ \leftrightarrow LnL(H)^+} \qquad (1)$$

The instantaneous absorbance change (ΔA) or fluorescence intensity change (ΔI) as a function of [H$^+$] for LnL was measured and used to plot eq 2. Derivation of the equation is given in the

$$[\mathrm{LnL}]_{\mathrm{T}}/\Delta I = \{1/b(\Delta\epsilon)K_{\mathrm{H}}[\mathrm{H}^+]\} + \{1/b(\Delta\epsilon)\} \qquad (2)$$

Appendix. The ratio of the intercept and the slope gave the protonation equilibrium constant, K_{H} (M^{-1}), for LnL. For example, a value of K_{H} for Gd(DO3A) was determined as 115 ± 8 M^{-1} from the plot of eq 2 shown in Figure 2. In eq 2, [LnL]$_{\mathrm{T}}$ is the sum of the concentrations of protonated and unprotonated complex and ΔI and $\Delta\epsilon$ are the differences in the absorbance or fluorescence intensity and extinction or emission coefficients of the protonated and unprotonated forms of the complex, respectively. Similarly, the protonation equilibrium constants for other complexes were also determined, and the values are given in Table I. Desreux and co-workers[16] studied the acid-assisted dissociation of Gd(DOTA)$^-$ under strongly acidic conditions; i.e. [H$^+$] was varied from 0.02 to 0.23 M. They did not observe the formation of protonated species. However from the fluorescence intensity decrease as a function of [H$^+$], we determined a value for the protonation constant of Gd(DOTA)$^-$: 575 ± 110 M^{-1}. This value is similar to the value determined previously for Pb(DOTA)$^{2-}$ (K_{H} = 465 ± 26).[17] Experiments with Ce(DOTA)$^-$ failed due to the limited change in the absorbance of the complex on protonation. Lu complexes did not have appreciable absorbance or fluorescence; consequently K_{H} values for these complexes could not be determined. In contrast to the observations made in this work, no evidence of the protonated species was observed in the case of NOTA complexes.[14]

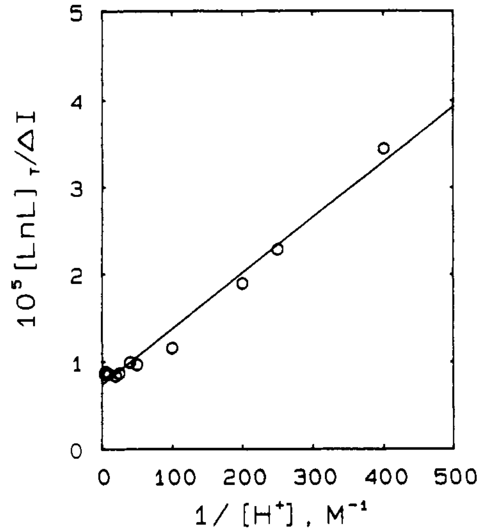

Figure 2. Determination of the protonation equilibrium constant of Gd(DO3A). [GdL] = 5.0 × 10^{-4} M; μ = 1.0 (NaCl).

The protonation of lanthanide complexes of linear polyamino carboxylates has been reported in the solid state and in solution.[27-33] The site of the protonation in LnL(H) is presumably carboxylic oxygen. This assumption is supported by solid-state IR studies of Ln(EDTA)(H) complexes and X-ray crystallography of La(EDTA)(H), respectively, which have demonstrated protonation of the carboxylate oxygen.[28,29] Solution NMR studies of Ln(EDTA)$^-$ and several kinetic studies of lanthanide and actinide complexes of linear polyamino carboxylates have also proposed protonated carboxylate oxygens.[2,8,14,32,34,35]

The protonation constants of the lanthanide complexes of linear polyamino carboxylates either were constant[28,30,31] or were decreasing[32,33] as the size of the lanthanide ion decreased. This trend in the protonation constants of the complexes was consistent with the formation of stronger complexes with heavier lanthanides, which are more difficult to protonate.[32,33] The values of the protonation constants of the lanthanide complexes of macrocyclic polyamino carboxylates are either similar to or lower in magnitude than the literature values for linear polyamino carboxylate complexes. In contrast to the literature data,[28,30-32] the protonation

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(26) Martell, A. E.; Smith, R. M. *Critical Stability Constants*; Chemical Society: London, 1989; Vols. 5 and 6.

(27) Moeller, T.; Moss, F. A. J.; Marshall, R. H. *J. Am. Chem. Soc.* **1955**, *77*, 3182.

(28) Kolat, R. S.; Powell, J. E. *Inorg. Chem.* **1962**, *1*, 485.

(29) Lind, M. D.; Byungkook, L.; Hoard, J. L. *J. Am. Chem. Soc.* **1965**, *87*, 1611.

(30) Moeller, T.; Thompson, L. C. *J. Inorg. Nucl. Chem.* **1962**, *24*, 499.

(31) Moeller, T.; Hseu, T. M. *J. Inorg. Nucl. Chem.* **1962**, *24*, 1635.

(32) Brucher, E.; Kukri, G. E.; Zekany, L. *J. Inorg. Nucl. Chem.* **1974**, *36*, 2620.

(33) Mioduski, T. *J. Radioanal. Chem.* **1979**, *53*, 25.

(34) References 8 and 9 in ref 32.

(35) Muscatello, A. C.; Choppin, G. R.; D'Olieslager, W. *Inorg. Chem.* **1989**, *28*, 993.

Table II. Pseudo-First-Order Rate Constants for Acid-Assisted Dissociation[a]

$[H^+]$, M	10^3k_{obsd}, s^{-1}	$[H^+]$, M	10^3k_{obsd}, s^{-1}
1. Ce(DO3A)[b]			
0.005	0.47 ± 0.09	0.010	0.69 ± 0.09
0.015	0.85 ± 0.02	0.020	1.20 ± 0.01
0.025	1.42 ± 0.09	0.030	1.90 ± 0.01
0.038	2.4 ± 0.1	0.040	2.63 ± 0.03
0.050	3.5 ± 0.2	0.075	5.9 ± 0.2
0.100	8.43 ± 0.04	0.125	10.8 ± 0.4
0.150	14.2 ± 0.4	0.200	17.9 ± 2.3
0.250	25.4 ± 1.4	0.300	31.0 ± 1.2
0.350	38.8 ± 1.3	0.400	40.3 ± 1.1
2. Ce(HP-DO3A)[c]			
0.099	0.165 ± 0.002	0.198	0.387 ± 0.002
0.396	0.772 ± 0.008	0.594	1.15 ± 0.02
0.792	1.52 ± 0.02	0.990	1.97 ± 0.03
3. Gd(DO3A)[d]			
0.010	0.36 ± 0.02	0.010	0.48 ± 0.01
0.02	0.76 ± 0.02	0.025	0.87 ± 0.02
0.030	0.81 ± 0.03	0.030	0.88 ± 0.02
0.04	0.96 ± 0.04	0.04	1.08 ± 0.02
0.050	1.1 ± 0.1	0.06	1.33 ± 0.07
0.10	2.37 ± 0.02	0.15	2.92 ± 0.01
0.25	3.88 ± 0.02	0.30	4.20 ± 0.07
0.40	4.52 ± 0.07		
4. Gd(HP-DO3A)[e]			
0.042	0.024 ± 0.001	0.05	0.024 ± 0.001
0.050	0.031 ± 0.001	0.10	0.07 ± 0.02
0.101	0.0648 ± 0.008	0.20	0.119 ± 0.004
0.202	0.088 ± 0.001	0.25	0.14 ± .01
0.252	0.123 ± 0.002	0.30	0.153 ± 0.004
0.303	0.142 ± 0.003	0.34	0.16 ± 0.01
0.404	0.176 ± 0.006	0.50	0.23 ± 0.05
0.505	0.21 ± 0.03	0.606	0.23 ± 0.06
0.707	0.27 ± 0.06	0.808	0.29 ± 0.06
0.909	0.31 ± 0.05		
5. Lu(DO3A)[f]			
0.0025	0.061 ± 0.01	0.005	0.129 ± 0.01
0.0075	0.199 ± 0.001	0.010	0.268 ± 0.02
0.0125	0.32 ± 0.01	0.015	0.37 ± 0.01

[a] At 25.0 ± 0.1 °C and $\mu = 1.0$ (NaCl). [b] [Ce(DO3A) = 5.0×10^{-4} M. [c] [Ce(HP-DO3A)] = 2.5×10^{-4} M. [d] [Gd(DO3A)] = 5.0×10^{-4} M. [e] [Gd(HP-DO3A)] = 5.0×10^{-4} M. [f] [Lu(DO3A)] = 5.0×10^{-4} M. $[Cu^{2+}] = 4.37 \times 10^{-4}$ M.

constants of CeL are 10–20-fold lower than the protonation constants of GdL complexes. Electrostatic repulsion between metal and the incoming $[H^+]$ cannot explain this trend because (1) the charge density on Gd^{3+} is higher than that on Ce^{3+} and consequently an opposite trend is expected, (2) the metal ion is inside the cavity of the ligand and the incoming proton should not experience significant repulsion, and (3) the protonation constants were determined at high ionic strength ($\mu = 1.0$), where such effects are less important. The difference in the protonation constants for Ce^{3+} and Gd^{3+} complexes suggests the formation of stronger ion pairs in the secondary coordination sphere of the metal. For example, the stability constants ($\log K_{LnL}$) of Ce^{3+} complexes are 1–2 orders of magnitude smaller than those of Gd^{3+} complexes. The M–O bonds are expected to be weaker in the complexes of Ce^{3+} than in those of Gd^{3+}, and coordinated oxygens probably have more residual negative charge in the complexes of Ce^{3+}. This would provide a stronger Na^+ ionic environment around Ce^{3+} complexes, which would lead to more difficult protonation of CeL.

Dissociation Kinetics of Protonated Chelates, LnL(H). The rates of dissociation reactions of Ln^{3+} complexes of DO3A and HP-DO3A were measured in 0.005–1.0 M HCl solutions under pseudo-first-order conditions (chelate was the limiting reagent) (Table II) at a constant ionic strength ($\mu = 1.0$) and at 25.0 ± 0.1 °C. Although, at low $[H^+]$, LnL is the major species, LnL(H) is assumed to be the reactive species. This assumption was made for the following reasons: (1) There was no appreciable dissociation of the complexes at neutral pH for several months, even for years in some cases, while from the rate and equilibrium constants (vide infra) one would expect appreciable dissociation at pH 7.0. (2) Under the experimental conditions, except for Ce(DO3A), a large percentage of the complexes is in the protonated form (50–99%). (3) The protonated species probably has one less coordinated group and consequently will be less stable and more reactive. For example, Gd(DO3A) is easier to dissociate than Gd(HP-DO3A) or $Gd(DOTA)^-$ (vide infra). Relative concentrations of these species can be calculated from the protonation equilibrium constant of the complexes given in Table I.

The reactions were first-order in the limiting reagent, and the following observations were made regarding the order dependence in other reactants: (1) A plot of k_{obsd} vs $[H^+]$ was linear for Ce^{3+} complexes with a positive intercept. (2) For Gd^{3+} complexes, the value of k_{obsd} increased linearly with increasing acid concentration. However, at high acid concentration, k_{obsd} values were independent of acid concentration. This behavior indicates saturation kinetics or the existence of a rapid preequilibrium step (e.g. the formation of the diprotonated species, $LnL(H_2)$) prior to its dissociation in the rate-determining step. The plot of k_{obsd} vs $[H^+]$ gave a positive intercept for the Gd(DO3A) reaction. (3) The rate of dissociation of Lu(DO3A) was independent of copper concentration, suggesting no appreciable copper ion attack on the Lu^{3+} complex. The concentration of Cu^{2+} was varied by a factor of 4, and k_{obsd} values were within 3% of the average value of k_{obsd} at a given $[H^+]$. Such an independence of $[Cu^{2+}]$ has been observed by other workers in the dissociation kinetics of lanthanide complexes.[8,9,13] The k_{obsd} value increased linearly with $[H^+]$; however, saturation kinetics behavior was observed for this reaction also. The observed results may be expressed by eqs 3–5, where k_d is

$$LnL(H) \rightarrow \text{product} \qquad k_d \tag{3}$$

$$LnL(H) + H^+ \leftrightarrow LnL(H_2) \qquad K_1 = k_1/k_{-1} \tag{4}$$

$$LnL(H_2) \rightarrow \text{product} \qquad k_2 \tag{5}$$

the direct-dissociation rate constant, k_1 is the acid-assisted dissociation rate constant, and k_{-1} is the reverse rate constant for eq 4 and K_1 and k_2 are equilibrium constants for the formation of the diprotonated species, $LnL(H_2)$, and its rate of dissociation, respectively. For CeL complexes, no evidence was observed for the formation of $LnL(H_2)$. A steady-state approximation in $LnL(H_2)$ can be used to derive a rate expression[36] given in eq 6,

$$-d[LnL]_T/dt = k_{obsd}[LnL]_T = [k_d + \{k_1k_2[H^+]/(k_{-1} + k_2)\}][LnL(H)]$$

$$k_{obsd}\{(1 + K_H[H^+])/K_H[H^+]\} = k_d + \{k_1k_2[H^+]/(k_{-1} + k_2)\} \tag{6}$$

where $[LnL]_T$ is the sum of the concentrations of unprotonated and protonated forms of the complex. Since no appreciable concentration of the diprotonated species was observed for the reaction of CeL(H) with acid, $k_{-1} \ll k_2$ and eq 6 becomes eq 7.

$$k'_{obsd} = k_{obsd}(1 + K_H[H^+])/K_H[H^+] = k_d + k_1[H^+] \tag{7}$$

A plot of eq 7 is shown in Figure 3, in which k'_{obsd} is plotted against $[H^+]$. The calculated values of k_d and k_1 are given in Table III.

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(36) Wilkins, R. G. *The Study of Kinetics and Mechanism of Reactions of Transition Metal Complexes*; Allyn and Bacon: Boston, MA, 1974; p 27.

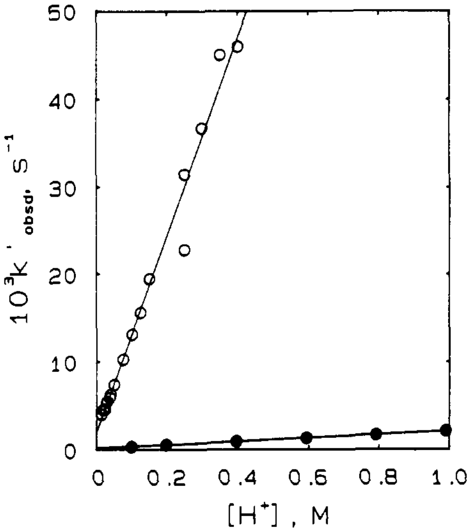


Figure 3. Acid dependence of pseudo-first-order rate constants, k'_{obsd} (corrected for the fraction of LnL(H)), for dissociation of Ce^{3+} complexes of DO3A and HP-DO3A: O, for Ce(DO3A); ●, for Ce(HP-DO3A). Solid curves are calculated from the resolved values of rate and equilibrium constants.

For GdL complexes, saturation kinetics behavior suggests the formation of $LnL(H_2)$ in appreciable concentrations, and this is expressed by eqs 8 and 9. The k'_{obsd} values for dissociation of

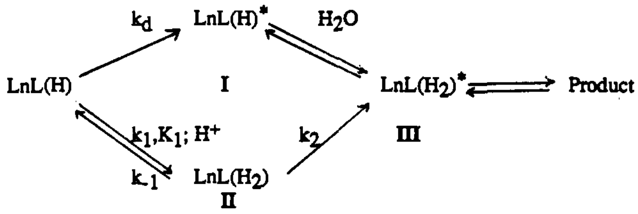
$$-d[LnL]_T/dt = k_{obsd}[LnL]_T = [k_d + \{k_2K_1[H^+]/(1 + K_1[H^+])\}][LnL(H)] \quad (8)$$

$$k'_{obsd} = k_{obsd}\{(1 + K_H[H^+])/K_H[H^+]\} = k_d + \{k_2K_1[H^+]/(1 + K_1[H^+])\} \quad (9)$$

Gd^{3+} and Lu^{3+} complexes were fitted to eq 9 by a SIMPLEX procedure, and the resolved values of equilibrium and rate constants are given in Table III. While Gd(DO3A) showed evidence of direct dissociation of LnL(H) species ($k_d = 4.4 \times 10^{-4}\ s^{-1}$), no such path was observed in the case of Gd(HP-DO3A) or Lu(DO3A). Figure 4 shows a plot of the left-hand side of eq 9 (k'_{obsd} vs $[H^+]$) for dissociation of protonated Gd(DO3A) and Gd(HP-DO3A). The solid curves drawn in Figure 4 are the calculated curves based on the resolved rate and equilibrium constants (Table III).

Since the value of the protonation constant of Lu(DO3A) was not measurable, the k_{obsd} values could not be adjusted for the fraction of LnL(H) before calculation. The values of K_H for GdL were 10–20-fold larger than those for CeL. By analogy, the value of the protonation constant for Lu(DO3A) would be predicted to be >1000, and in the acid concentration range of the study most of the complex (>70–95%) would be in the protonated form.

Dissociation of the protonated lanthanide complexes is consistent with the mechanism proposed by Brucher and Sherry.[14] A scheme is given below for ready reference. Depending on the lanthanide ion, LnL(H) could convert to LnL(H)* (I) via a direct-dissociation path in the rate-determining step, followed by the rapid formation and dissociation of $LnL(H_2)^*$ (III) to the product. The reactant LnL(H) could also convert to $LnL(H_2)$ (II) by a parallel acid-assisted pathway in the equilibrium step, followed by a rate-determining conversion to $LnL(H_2)^*$, which dissociates rapidly to the product. For the complexes of the heavier lanthanides, the formation of $LnL(H_2)$ was observed with an equilibrium constant, K_1. For the lighter lanthanide, Ce^{3+}, no evidence was observed for the formation of $LnL(H_2)$. The second proton in $LnL(H_2)$ presumably associates with the second oxygen of the carboxylate. As proposed previously,[14] in the protonated species, the metal ion moves out of the macrocyclic cavity to a position where three oxygens and fewer nitrogens are coordinated. The slow rate-determining step in the dissociation of LnL(H) is the direct or acid-dependent rearrangement which includes metal–nitrogen bond breakage. Proton transfer from these two oxygens to the nitrogen then occurs. This proton transfer, as a result of electrostatic repulsion, assists removal of the metal ion from the macrocyclic cavity.



The possibility of proton transfer from the carboxylate oxygens to partially coordinated nitrogen cannot be ruled out.[37,38] Certainly, protonation of fully coordinated nitrogen is not possible, as it requires pentavalent nitrogen. Direct proton transfer to partially coordinated nitrogen involves the presence of nitrogen in the first coordination sphere of lanthanides. We favor a partly bonded species, as opposed to the species in which the metal–nitrogen bond is completely broken. It is very difficult to account for variation in the dissociation rates of Ce, Gd, and Lu complexes of DO3A if rearrangement of the macrocyclic ligand controls the rate. On the other hand, if metal is partly bound to the nitrogen, the difference in bond lengths could account for the variation in the rates. Also, protonation of unbound nitrogen would be fast while observed reactions are slow.

Table III gives a summary of equilibrium and rate constants for dissociation of various Ce^{3+}, Gd^{3+}, and Lu^{3+} complexes of linear and macrocyclic polyamino carboxylates. Direct dissociation of the protonated species, LnL(H), was observed either for Ce^{3+} complexes or for Gd(DO3A); however, no such path was observed for more stable Gd^{3+} and Lu^{3+} complexes, e.g. Gd(HP-DO3A) and Lu(DO3A). Dissociation of macrocyclic polyamino carboxylate complexes of lanthanides differs in several ways from that of the linear polyamino carboxylates, such as EDTA and CyDTA. The rate of dissociation of the complexes of the linear class is much faster than that of the complexes of macrocyclic class. This phenomenon has been rationalized by rapid unraveling of the linear complexes. In the macrocyclic class, dissociation of complexes of lighter lanthanides differs considerably from that of the complexes of heavier lanthanides. No significant differences were observed for the complexes of linear polyamino carboxylates. Finally, the variation in the calculated k_{obsd} in 0.1 M HCl for lanthanide (Ce–Lu) complexes of the linear class (e.g. CyDTA) is 3500; for the macrocyclic class it is only 5.

It is very difficult to compare in detail the rate constants (k_d, k_1, etc.) for dissociation of lanthanide complexes of various macrocyclic polyamino carboxylates given in Table III due to the involvement of the different protonated and unprotonated species and their relative dissociation rates. We have compared the relative kinetic inertness of the Gd^{3+} complexes in 0.1 M HCl and observed the order DOTA > HP-DO3A > DO3A > NOTA. While the first three ligands are 12-membered macrocyclic polyamino carboxylates, NOTA is a carboxylate derivative of a 9-membered macrocyclic amine and the size of the cavity of NOTA is too small for lanthanides. Consequently, the complexes of NOTA are relatively labile. The difference in the relative kinetic lability of the first three complexes is as expected on the basis of the nature and number of donor atoms.

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(37) Read, R. A.; Margerum, D. W. *Inorg. Chem.* **1981**, *20*, 3143.
(38) Grahm, P. G.; Weatherburn, D. C. *Aust. J. Chem.* **1981**, *34*, 291.

Table III. Summary of Kinetic Characteristics of Lanthanide Complexes of Linear and Macrocyclic Polyamino Carboxylates[a]

complex	k_d, s^{-1}	k_1, $M^{-1}\,s^{-1}$	K_1, M^{-1}	k_2, s^{-1}
Ce(DO3A)	$(1.8 \pm 0.8) \times 10^{-3}$	$(1.12 \pm 0.04) \times 10^{-1}$	*b*	*b*
Gd(DO3A)	$(4.4 \pm 0.1) \times 10^{-4}$	*b*	3.6 ± 0.9	$(7.4 \pm 0.4) \times 10^{-3}$
Lu(DO3A)	*b*	*b*	7.7 ± 1.8	$(3.6 \pm 0.1) \times 10^{-3}$
Ce(HP-DO3A)	$(1.4 \pm 0.2) \times 10^{-4}$	$(2.00 \pm 0.04) \times 10^{-3}$	*b*	*b*
Gd(HP-DO3A)	*b*	*b*	1.0 ± 0.1	$(6.4 \pm 0.3) \times 10^{-4}$
Ce(DOTA)[c]	*b*	$(8 \pm 2) \times 10^{-4}$	*b*	*b*
Gd(DOTA)[d]	*b*	$(8.4 \pm 0.4) \times 10^{-6}$	*b*	*b*
Ce(NOTA)[e]	2.5×10^{-5}	$(4.3 \pm 0.5) \times 10^{-2}$	*b*	*b*
Gd(NOTA)[e]	8.0×10^{-6}	$(2.3 \pm 0.3) \times 10^{-2}$	*b*	*b*
Ce(EDTA)[f]	2.0×10^{-4}	2.9×10^{3}	*b*	*b*
Ce(CyDTA)[g]	2.0×10^{-4}	60 ± 2	*b*	*b*
Gd(CyDTA)[g]	1.0×10^{-5}	1.3	*b*	*b*
Lu(CyDTA)[g]	1.1×10^{-7}	0.017	*b*	*b*

[a] This work at 25.0 ± 0.1 °C, $\mu = 1.0$ (NaCl); in this table k_d and k_H are direct and acid-assisted dissociation of the monoprotonated chelate and K_1 and k_2 are the equilibrium and rate constants for the formation and dissociation of the diprotonated species, $LnL(H_2)$, respectively. [b] Not observed. [c] Reference 15; a second-order dependence in $[H^+]$ with a third-order rate constant $(2.0 \pm 0.5) \times 10^{-3}\ M^{-2}\,s^{-1}$ was also observed. [d] Reference 16. [e] Reference 14. [f] Laurenczy, G.; Raddics, L.; Brucher, E. *Inorg. Chim. Acta* **1983**, *75*, 219. [g] Reference 8.

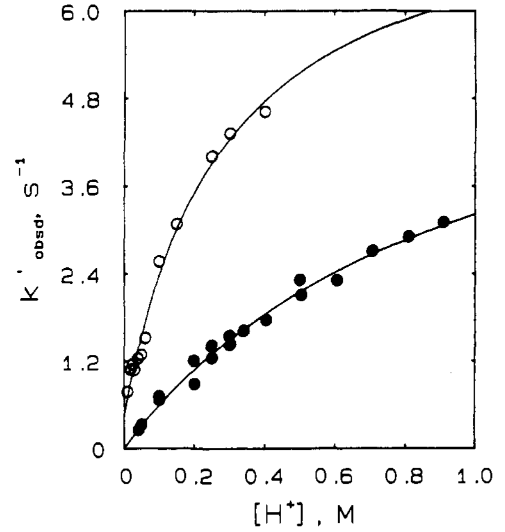

Figure 4. Acid dependence of pseudo-first-order rate constants, k'_{obsd} (corrected for the fraction of LnL(H)), for dissociation of Gd^{3+} complexes of DO3A and HP-DO3A: O, for Gd(DO3A); ●, for Gd(HP-DO3A). Solid curves are calculated from the resolved values of rate and equilibrium constants.

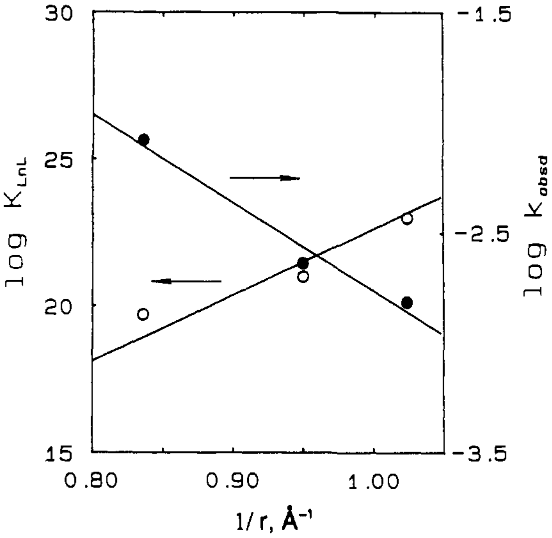

Figure 5. Plots of log K_{LnL} and log k_{obsd} (0.1 M HCl) vs $1/r$ ($Å^{-1}$) for lanthanide complexes of DO3A.

Effect of Charge Density and Structural Changes on the Stability and Rate of Dissociation. The stability constants and kinetic inertia of the lanthanide complexes of the heptadentate ligand, DO3A, increase in the order Ce(DO3A) < Gd(DO3A) < Lu(DO3A), which reflects a decrease in the size or an increase in the charge density of Ln^{3+}. A plot of log K_{LnL} and log k_{obsd} for dissociation of LnL in 0.1 M HCl vs $1/r$ ($Å^{-1}$) (Figure 5) is linear with $r^2 = 0.9999$. Historically the radii for such correlations are taken from ref 39 for 6-coordinate trivalent lanthanide ions. However, hydration numbers as high as 9 for lighter cations (La–Nd) and 8.0 for heavier lanthanides (Dy–Lu) are reported.[40] The values of ionic radii for Ce^{3+} (1.196 Å, 9-coordinate), Gd^{3+} (1.053 Å, 8-coordinate), and Lu^{3+} (0.977 Å, 8-coordinate) are used in Figure 5.[39] Although the results on the variation of kinetic inertia of Ln(DO3A) are in agreement with CyDTA results, variation in the rate of dissociation is not as large as for $Ln(CyDTA)^-$ complexes.[8] These results are in contrast with the results for lanthanide complexes of macrocyclic polyamino polyoxa carboxylates, in which unusual charge density dependence of stability and rate of acid-assisted dissociation was attributed to the size of the metal ion and the ligand cavity.[13]

The observed thermodynamic and kinetic trends in lanthanide complexes of macrocyclic polyamino carboxylates on moving from Ce^{3+} to Lu^{3+} can also be explained in terms of structural changes of the lanthanide complexes. DO3A is a heptadentate ligand, and progressive increase in the stability constant and kinetic inertia may be due to the charge density. In the case of HP-DO3A and DOTA complexes, there is evidence of an increase in the stability of GdL over CeL; however the stability constants of GdL and LuL are similar within the error of the experiments. HP-DO3A and DOTA are octadentate ligands, and carboxylate and/or hydroxypropyl groups of the ligands will have more difficulty finding sufficient room around the lanthanide cation during coordination. This difficulty will increase as we go up the series due to decreasing size and coordination number of the cation. It is not unreasonable to find a point at which one out of four oxygen donors of the macrocyclic ligand cannot coordinate. The octadentate macrocyclic polyamino carboxylates probably have relatively inflexible cavity sizes that are larger than the relatively smaller Lu^{3+}. It appears that these relatively rigid ligands are able to discriminate against cations which are either smaller or larger than their cavity size, since the distortion of a rigid ligand either by contraction or by expansion of the cavity would lead to destabilization. It appears that the cavity sizes of HP-DO3A and DOTA are most suitable for intermediate-size lanthanides, such as Gd^{3+}.

Conclusions

The lanthanide complexes of 12-membered macrocyclic polyamino carboxylates, including DOTA, protonate under acidic conditions. The stability constants and kinetic inertia of lanthanide complexes of macrocyclic polyamino carboxylates (e.g.

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(39) Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751.

(40) Habenschuss, A.; Spedding, F. H. *J. Chem. Phys.* **1979**, *70*, 2797, 3758; **1980**, *73*, 442.

DO3A) increase with increasing charge density of the metal ion, but for the relatively more rigid octadentate ligands HP-DO3A and DOTA, the stability constants of Gd^{3+} and Lu^{3+} are controlled by the cavity size match and/or structural changes.

Both direct and acid-assisted dissociation of the protonated lanthanide complexes of the 12-membered macrocyclic ligands, Ce(DO3A), Ce(HP-DO3A), and Gd(DO3A), are observed. However, with the complexes of increased stability, Gd(HP-DO3A), Lu(DO3A), $Ce(DOTA)^-$, and $Gd(DOTA)^-$, a direct dissociation path is not evident.

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Appendix

An equation to calculate the protonation equilibrium constant from the absorbance or fluorescence data was derived. At any acid concentration, the total concentration of the lanthanide complex, $[LnL]_T$, is the sum of the concentrations of the unprotonated (LnL) and the protonated (LnL(H)) forms of the complex (eq A), and their relative concentrations can be calculated from the protonation equilibrium constant of the complex, K_H (eq B). By a comparison of eqs A and B, $[LnL]_T$ can be expressed in terms of K_H and [LnL(H)] (eq C). Before addition of any acid to the complex, the absorbance (A_1) is due to the unprotonated form of the complex (eq D). On protonation of the complex with acid, a lower absorbance (A_2) is observed which can be expressed in terms of the sum of the absorbances of the protonated and the unprotonated form of the complex (eq E). In eqs D and E, ϵ_1 and ϵ_2 are the molar extinction coefficients of the protonated and unprotonated forms of the complex, LnL, respectively. Subtraction of eq E from eq D and rearrangement give eq F.

$$[LnL]_T = [LnL] + [LnL(H)] \qquad (A)$$

$$K_H[H^+] = [LnL(H)]/[LnL] \qquad (B)$$

$$[LnL]_T = \{(1 + K_H[H^+])/K_H[H^+]\}[LnL(H)] \qquad (C)$$

$$A_1 = b\epsilon_1[LnL]_T \qquad (D)$$

$$A_2 = b\epsilon_1[LnL] + b\epsilon_2[LnL(H)] \qquad (E)$$

$$A_1 - A_2 = \Delta A = b\epsilon_1\{[LnL]_T - [LnL]\} - b\epsilon_2[LnL(H)] \qquad (F)$$

$$\Delta A = b(\epsilon_1 - \epsilon_2)[LnL(H)] = b(\Delta\epsilon)[LnL(H)] \qquad (G)$$

Substitution of eq A into eq F would lead to eq G. Equation G can be expressed in terms of $[LnL]_T$ by replacing [LnL(H)] with the use of eq C, and rearrangement gives the desired equation (2).