

# Effect of Ligand Basicity on the Formation and Dissociation Equilibria and Kinetics of Gd<sup>3+</sup> Complexes of Macrocyclic Polyamino Carboxylates

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The effect of nitrogen basicity on the formation and dissociation equilibria and kinetics of Gd(III) complexes of macrocyclic polyamino carboxylates, GdL (L is HE-DO3A = 10-(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, HP-DO3A = 10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, and HIP-DO3A = 10-(2-hydroxyisopropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid), is studied in the present work. The stability constants of the gadolinium complexes ( $\log K_{\text{GdL}}$ ) have been determined at  $25.0 \pm 0.1$  °C and at  $\mu = 0.1$  ((TMA)Cl) and have the following order: HIP-DO3A > HP-DO3A > HE-DO3A. The formation and dissociation reaction rates of the chelates have been measured at  $25.0 \pm 0.1$  °C and at  $\mu = 1.0$  (NaCl). The proposed mechanism for the formation reactions involves the formation of an intermediate with stability constant,  $K_{\text{Gd}}^{\text{HL}}$ , and its base-assisted rate constant of reorganization,  $k_{\text{OH}}$ . The calculated stability constants of the intermediate,  $\log K_{\text{Gd}}^{\text{HL}}$ , are 8.4 (HE-DO3A), 8.9 (HP-DO3A), and 8.2 (HIP-DO3A). The second-order rate constants for the base-assisted reorganization ( $\log k_{\text{OH}}$ ) depend on the nitrogen basicity ( $\log K_1$ ) with a linear correlation as follows:  $\log k_{\text{OH}} = -(0.37 \pm 0.05) \log K_1 + (11.6 \pm 0.6)$  ( $r^2 = 0.98$ ). The protonation constants of GdL ( $\log K_{\text{GdL(H)}}$ ) and the stability constants ( $\log K_{\text{GdL(HL)}}$ ) of the protonated species of GdL are determined, and the values are as follows: 2.04, 13.3 (HE-DO3A); 2.38, 14.2 (HP-DO3A); 2.23, 13.6 (HIP-DO3A). The rate of the acid-assisted dissociation of the protonated GdL is first-order in the limiting reagent,  $[\text{GdL}]_{\text{T}}$ , and the rate saturates at higher  $[\text{H}^+]$ . The equilibrium constants,  $K_{\text{GdL(H}_2)}$  ( $\text{M}^{-1}$ ), for the formation of the diprotonated species, GdL(H<sub>2</sub>), and their dissociation rate constants ( $10^3 k_2$ ,  $\text{s}^{-1}$ ) are as follows:  $9 \pm 2$  and  $1.9 \pm 0.2$  for HE-DO3A,  $0.35 \pm 0.03$  and  $1.66 \pm 0.09$  for Gd(HP-DO3A) and  $0.6 \pm 0.1$  and  $0.64 \pm 0.05$  for Gd(HIP-DO3A). Evidence of a direct dissociation pathway for Gd(HIP-DO3A)(H) is also observed with a rate constant,  $k_d$  ( $\text{s}^{-1}$ ), of  $(0.2 \pm 0.1) \times 10^{-4}$ . A comparison of the measured first-order rate constants for acid-assisted dissociation of GdL in 0.1 M HCl,  $10^5 k_{\text{obsd}}$  ( $\text{s}^{-1}$ ), 46.6 (HE-DO3A), 6.4 (HP-DO3A), and 5.8 (HIP-DO3A), suggests that the rate of dissociation depends on the basicity of nitrogen and the stability constant of the chelate.

## Introduction

Several factors are known to influence the thermodynamics, kinetics, and mechanisms of formation and dissociation of lanthanide complexes of macrocyclic polyamino carboxylates, including charge density, ring size, number of donor atoms, and ring and side arm substituents.<sup>1–11</sup> Macrocyclic polyamino carboxylates offer several variations which include preorganization of the free ligand,<sup>12</sup> conformation,<sup>13</sup> cavity size,<sup>14</sup> ligand basicity, and rigidity.<sup>11</sup> Recent studies have demonstrated that for

lanthanide complexes of macrocyclic polyamino carboxylates, with seven and eight donor atoms, stability and kinetic inertia increase with increasing charge density of the metal ion.<sup>9,10</sup> While Sherry and co-workers reported independence of the formation rate on the charge density of metal ion,<sup>6</sup> we studied the effect of variation in the ligand on the formation rate of macrocyclic polyamino carboxylates.<sup>10,11</sup> The proposed mechanism involves the formation of an intermediate (precursor) in an equilibrium step, followed by its base-assisted reorganization.<sup>11</sup> For a series of preorganized ligands with similar conformation and cavity size, we observed a strong dependence of the formation rate on the basicity of the nitrogen atoms and the rigidity of the ligand.<sup>11</sup>

The goal of this study was to examine the stability and inertia of gadolinium complexes of several ligands with approximately the same rigidity but with different basicity of the nitrogen atoms. In the ligand design, we selected an electron-donating group, e.g. methyl, to influence the basicity of the adjacent nitrogen. Presumably, the presence of the methyl group off the side chain would not alter any other parameters such as the degree of preorganization and conformation. This study contributes to the understanding of the coordination chemistry of lanthanide complexes of macrocyclic polyamino carboxylates and also to the design of metal chelates for medical applications and lanthanide selective reagents in analytical chemistry.<sup>9,15–18</sup> For example,

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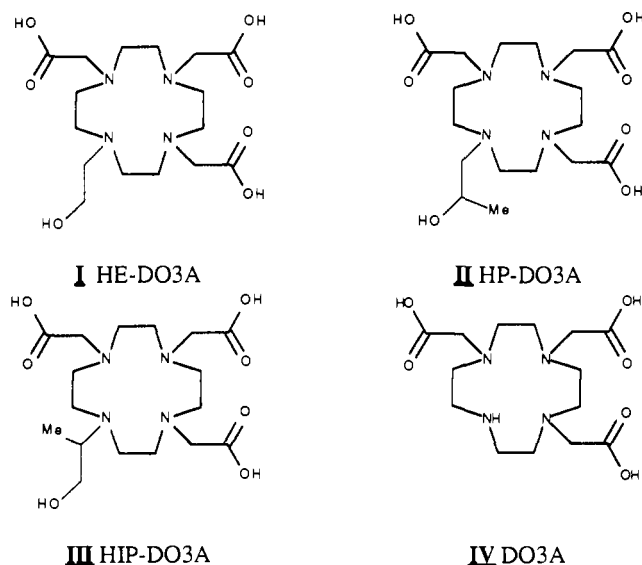
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Chart 1



among the chelates studied, Gd(HP-DO3A) is a well-known MRI contrast agent.<sup>9</sup>

We report herein the results of a systematic equilibrium and kinetic study of a series of Gd(III) complexes of macrocyclic polyamino carboxylates (structures I–III) (Chart 1), e.g. HE-DO3A = 10-(2-hydroxyethyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, HP-DO3A = 10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, and HIP-DO3A = 10-(2-hydroxyisopropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid).

### Experimental Section

**Chemicals and Reagents.** The ligand HE-DO3A was synthesized from the reaction of 2-bromoethanol and DO3A. In the procedure, 3.46 g of DO3A (0.01 mol) was dissolved in 25 mL of water. The pH of the solution was adjusted to 10.5 with sodium hydroxide, followed by cooling the mixture to 5 °C. Three equivalents of bromoethanol (2.1 mL) were added, and the solution was brought to room temperature and then heated at 80 °C for 5 h. The pH of the reaction mixture was adjusted to 10.5 and heating at 80 °C was continued for additional 24 h, while the progress of the reaction was monitored by an HPLC method. The crude material was purified by an ion exchange (AG 50W-X8 in H<sup>+</sup> form) column. After the column was loaded, it was first washed with distilled water to remove bromide and unreacted 2-bromoethanol. The desired product was eluted with 0.5 M ammonium hydroxide. All fractions with pH < 5 were collected and concentrated to a yellowish solid by lyophilization. The sample was dried under vacuum at 80 °C. A 1.1-g amount of the product was recovered (yield = 25.8%). The purity of the compound was checked by elemental and mass spectral analysis.

Anal. Calcd for C<sub>16</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub>·0.5NH<sub>3</sub>·1.5H<sub>2</sub>O: C, 45.84; H, 8.05; N, 14.28. Found: C, 46.02; H, 8.15; N, 14.28. FAB Mass: *m/e* at 391 [(m + H)<sup>+</sup>], 347 [(m - CO<sub>2</sub> + H)<sup>+</sup>], and 333 [(m - CH<sub>2</sub>COO + H)<sup>+</sup>].

More HE-DO3A was recovered by washing the column with 1.0 M ammonium hydroxide. The column wash was evaporated to dryness by rotary evaporation leaving a sticky hygroscopic compound. Addition of ethanol and further evaporation gave 1.2 g of a fluffy product (yield = 28%). The isolated product was the desired compound as confirmed by mass and elemental analysis.

Anal. Calcd for C<sub>16</sub>H<sub>30</sub>N<sub>4</sub>O<sub>7</sub>·0.25NH<sub>3</sub>·1.36H<sub>2</sub>O: C, 45.17; H, 8.04; N, 14.81. Found: C, 44.98; H, 8.28; N, 14.79. FAB Mass: *m/e* at 429 [(m + K)<sup>+</sup>], 391 [(m + H)<sup>+</sup>], 347 [(m - CO<sub>2</sub> + H)<sup>+</sup>], and 333 [(m - CH<sub>2</sub>COO + H)<sup>+</sup>]. HP-DO3A and HIP-DO3A were synthesized and characterized by literature procedures.<sup>19</sup>

Stock solutions of the ligands were prepared and standardized either by a potentiometric or by a back titration method using arsenazo-III as the indicator. The Gd(III) complexes of HP-DO3A and HIP-DO3A were prepared and analyzed by literature procedures.<sup>19</sup> A stock solution of Gd(HE-DO3A) was prepared in situ by mixing equimolar amounts of GdCl<sub>3</sub> and HE-DO3A and raising the pH very slowly to 7.0. The final solution was filtered through a 0.22- $\mu$ m filter.

A solid sample of GdCl<sub>3</sub>, purchased from Research Chemicals (Phoenix, AZ), was used without further purification. The sample solution was standardized by a complexometric titration with arsenazo-III as the indicator. Arsenazo-III (Aldrich), sodium chloride (Alfa), sodium acetate and acetic acid (Fisher), tetramethyl ammonium chloride, and tetramethylammonium hydroxide (Aldrich) were used as received. Standardization of tetramethylammonium hydroxide solution was carried out using dried potassium hydrogen phthalate (KHP) as the primary standard and phenolphthalein as the indicator. Tetramethylammonium chloride and sodium chloride were used for the ionic strength control in thermodynamic and kinetic studies, respectively. Distilled deionized water was used for all solution preparations.

**Methods.** Solution pH values were measured with an Orion combination glass electrode and an Orion Model 720A pH meter. Potentiometric titrations for the determination of the ligand protonation constants were carried out at a constant ionic strength of 0.1 M [(CH<sub>3</sub>)<sub>4</sub>NCl] as given elsewhere.<sup>20</sup> Titrations were performed with an automatic titrator/pH meter (Brinkmann 670 titroprocessor, precision  $\pm 0.002$  pH unit), equipped with a thermostated (25.0  $\pm$  0.1 °C) glass-jacketed titration cell fitted with a combination glass electrode and a Metrohm piston buret with a capillary tip placed below the surface. The pH meter–electrode system was calibrated with standard buffers. All pH values were converted to  $-\log [H^+]$  or p[H] correcting the measured pHs. The correction factor was established either from measured pH values of known analytical concentrations of hydrochloric acid solutions or from those of standard acid–base titrations at 25.0  $\pm$  0.1 °C and at a desired ionic strength. The ligand concentration was 0.001–0.002 M. Precautions were taken to avoid CO<sub>2</sub> absorption by the base solution. In the case of very basic pK<sub>a</sub> values for tertiary amines, the constant was confirmed by spectrophotometric methods.

The pH-metric titration data were used to calculate<sup>21</sup> the stepwise ligand protonation constants defined in eq 1, where  $n = 1-4$  depending on the ligand.

$$K_n = [H_nL]/[H_{n-1}L][H^+] \quad (1)$$

A direct potentiometric titration technique could not be used to determine the stability constants of the Gd(III) complexes because formation and equilibration of Gd(III) complexes are very slow. Consequently, a literature spectrophotometric method using the indicator arsenazo-III was used.<sup>3,20</sup> The formation reactions were slow and the progress of the reactions was monitored by conventional methods. Since complexed or uncomplexed Gd<sup>3+</sup> does not have significant absorbance, formation reaction kinetics were studied in weakly buffered medium (acetate/acetic acid) by monitoring the decrease in pH ( $\Delta$ pH  $\sim$  0.1) with the use of indicators.<sup>7,11</sup> The amount of the buffer in these reactions was sufficient to ensure small change in the pH. For example, in the formation reaction of Gd(HE-DO3A) the lowest calculated concentration of acetate was 1.42 mM at pH 4.07 and the concentration of H<sub>2</sub>L<sup>-</sup>, the reactive form of the ligand (vide infra), was only 0.048 mM. The remaining ligand is in the unreactive tri- and tetraprotonated forms of the ligand, H<sub>3</sub>L and H<sub>4</sub>L. The ratio, [OAc<sup>-</sup>]/[H<sub>2</sub>L<sup>-</sup>] > 15, suggests that the change in pH is < 0.1. In practice the change in pH was observed < 0.1. The rates of acid-assisted dissociation of gadolinium complexes were slow, and the progress of the reaction was monitored by conventional fluorescence intensity measurements<sup>10</sup> with the use of a Hitachi F-2000 with 274-nm excitation and 312-nm emission wavelengths, respectively. All spectrophotometric and kinetic measurements were made with an HP-8452A spectrophotometer interfaced with an HP-310 data station. A multicell transport was used for monitoring the progress of more than one reaction at a time. The temperature of the reaction mixture was maintained at 25.0  $\pm$  0.1 °C with a Lauda RMS circulatory water bath.

All kinetic studies were carried out at a constant ionic strength ( $\mu = 1.0$ ) and under pseudo-first-order conditions with large excess of Gd(III)

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**Table 1.** Ligand Protonation Constants and Stability Constants of Gd<sup>3+</sup> Complexes of Macrocyclic Polyamino Carboxylates<sup>a</sup>

constant	HE-DO3A	HP-DO3A <sup>b</sup>	HIP-DO3A	DO3A <sup>b</sup>	DO3MA <sup>c</sup>
log $K_1$	11.01 ± 0.11 (9.37 ± 0.08)	11.96 ± 0.02 (9.24 ± 0.05)	12.4 ± 0.17 (9.58 ± 0.04), 12.53 ± 0.04 <sup>d</sup>	11.59 ± 0.03 (10.51 ± 0.01)	13.38 (10.82), 13.46 <sup>d</sup>
log $K_2$	9.28 ± 0.09 (9.28 ± 0.08)	9.43 ± 0.01 (9.27 ± 0.02)	9.48 ± 0.13 (9.07 ± 0.01)	9.24 ± 0.03 (9.08 ± 0.09)	9.15 (8.42)
log $K_3$	4.50 ± 0.09 (4.54 ± 0.07)	4.30 ± 0.04 (4.45 ± 0.11)	4.3 ± 0.2 (4.51 ± 0.04)	4.43 ± 0.03 (4.36 ± 0.13)	5.30 (4.98)
log $K_4$	3.49 ± 0.11 (3.67 ± 0.07)	3.26 ± 0.01	3.41 ± 0.07 (3.55 ± 0.02)	3.48 ± 0.07	4.07
log $K_{GdL}$	22.3 ± 0.2	23.8 ± 0.8	23.9 ± 0.1	21.0 ± 0.2	25.3
log $K_{GdL}^e$	16.7	17.1	16.7	14.5	17.6

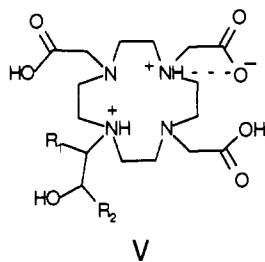
<sup>a</sup> At  $\mu = 0.1$  ((TMA)Cl) and at 25.0 ± 0.1 °C; the numbers in parentheses are at  $\mu = 0.1$  (NaCl) and at 25.0 ± 0.1 °C. <sup>b</sup> Data taken from ref 20. <sup>c</sup> Data taken from ref 40. <sup>d</sup> Determined by spectrophotometry. <sup>e</sup> Conditional stability constant at pH 7.4.

and [H<sup>+</sup>] for the formation and dissociation reactions, respectively. The reactions were followed for at least 4 half-lives. Pseudo-first-order rate constants ( $k_{obsd}$ , s<sup>-1</sup>) were calculated from the absorbance or intensity vs time data using a first-order model<sup>22</sup> and a SIMPLEX<sup>23</sup> fitting program. All calculations were completed on a Dell-486 DX or an IBM AT desktop personal computer.

## Results and Discussion

**Protonation Constants of the Ligands.** Acid–base titrations of HE-DO3A, HP-DO3A,<sup>20</sup> and HIP-DO3A were carried out in 0.1 M tetramethylammonium chloride ((TMA)Cl). Excess hydrochloric acid was added to the ligand solutions to determine the lower protonation constants. The calculated ligand protonation constants are given in Table 1 along with the protonation constants for DO3A and DO3MA. The first protonation of tertiary nitrogen in the ligand, HIP-DO3A, occurs at much higher pH than in the case of HE-DO3A or HP-DO3A. A calculated value is 12.4 ± 0.2. The value of the constant is high enough that it cannot be accurately determined using the pH-metric titration technique. Consequently absorbance measurements (at 220 and 230 nm) at variable concentrations of tetramethylammonium hydroxide ((TMA)OH) and at a constant ionic strength of 0.1 ((TMA)Cl) were used to calculate a value of log  $K_1 = 12.53 ± 0.04$  (Table 1).

As proposed previously in the case of other macrocyclic polyamino carboxylates, e.g. DO3A,<sup>20</sup> HP-DO3A,<sup>20</sup> and DOTA,<sup>24</sup> the first two protonation constants are assigned to the protonation of *transannular* nitrogens to minimize electrostatic repulsion. Hydrogen bonding is presumed to the adjacent carboxylate. The third and fourth protonation constants are assigned to the protonation of the two carboxylate oxygens which are not associated with the protonated nitrogens (structure V). This



conclusion is based on the following: (1) there is no positive charge in the vicinity of these carboxylate groups, and (2) the protonation constants are close to the protonation constant of acetic acid (log  $K = 4.6$ ). Protonation of more nitrogens or carboxylates probably occurs at lower pH where the pH electrode is not very sensitive.

The tertiary nitrogen in HE-DO3A which has attached an alcoholic group is less basic than the tertiary nitrogens in other macrocyclic polyamino carboxylates e.g. DO3A. The presence of an alcohol group is known to reduce the basicity of an associated

nitrogen. For example, the nitrogen atoms in ethylamine are more basic than in ethanolamine.<sup>25</sup> A comparison of the first protonation constants of deprotonated ligands follows the order HIP-DO3A > HP-DO3A > HE-DO3A. This order suggests that (1) the first protonation takes place on the tertiary nitrogen to which alcoholic group is attached (structure V: R<sub>1</sub> = R<sub>2</sub> = H, HE-DO3A; R<sub>1</sub> = H, R<sub>2</sub> = CH<sub>3</sub>, HP-DO3A; R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = H, HIP-DO3A) and (2) the presence and proximity of an electron-donating methyl group plays an important role. Interestingly the displacement of the methyl group closer to the nitrogen atom has very little effect on the second protonation constant of HIP-DO3A relative to HP-DO3A.

The ligand protonation constants of the ligands, HE-DO3A, HP-DO3A, and HIP-DO3A, were also determined at  $\mu = 0.1$  (NaCl) (Table 1). The first protonation constant of the ligand (log  $K_1$ ) is reduced considerably by the presence of Na<sup>+</sup> presumably due to the coordination of Na<sup>+</sup> ion with the ligand. This observation is consistent with prior reports on linear and macrocyclic polyamino carboxylates.<sup>20,25,26</sup>

**Stability Constants.** The equilibrium constant for the reaction of the mixture of Gd<sup>3+</sup> and arsenazo-III (Gd<sup>III</sup>(arsenazo)<sub>n</sub> complex) with the ligand at pH 4.0 was determined by a spectrophotometric method.<sup>3</sup> This equilibrium constant and the stability constants of the arsenazo-III complexes allowed the calculation of the conditional stability constant of the complex, GdL, at pH 4.0. By using eq 2, where  $\alpha_L^{-1} = (1 + K_1[H^+] +$

$$K_{GdL(Therm)} = K_{GdL(Cond)} \alpha_L^{-1} \quad (2)$$

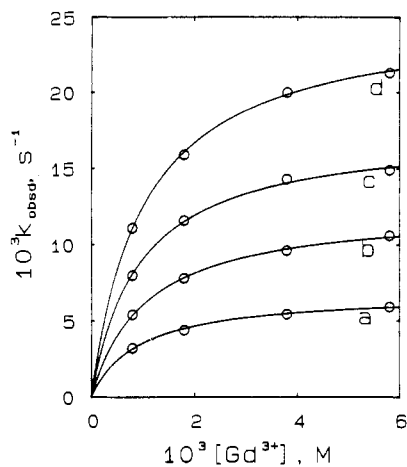
$K_1K_2[H^+]^2 + \dots + K_n[H^+]^n$ ) and  $K_1, K_2, K_3, \dots, K_n$  are the stepwise protonation constants of the ligand, the thermodynamic stability constants (log  $K_{GdL}$ ) (Table 1) for Gd(HE-DO3A), Gd(HP-DO3A),<sup>11</sup> and Gd(HIP-DO3A) were calculated from the conditional or apparent formation constants.

The stability constants for Gd(HE-DO3A), Gd(HP-DO3A), and Gd(HIP-DO3A) are all slightly lower than that of Gd(DOTA)<sup>-</sup> complex as expected on the basis of the charge difference. The crystal structures of the lanthanide complexes of this ligand class, including Gd(HP-DO3A), indicate that they are octadentate ligands. The lower stability of the monoalcohol chelate when compared to DOTA chelate is assigned to the charge difference, the well-known weaker donor ability of the alcoholic group, and the lower basicity of the nitrogen atoms. A comparison of the stability constants of the complexes indicates an order HIP-DO3A > HP-DO3A > HE-DO3A, which appears to correlate with the basicity ( $\sum pK_a$ ) of the ligands.

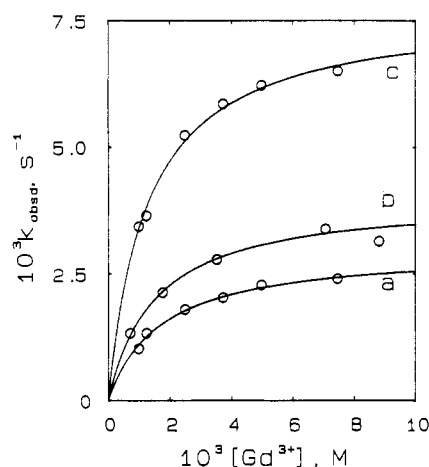
A knowledge of the conditional formation constants (log  $K_{GdL}^e$ ) of Gd(III) complexes under physiological conditions (pH 7.4) is

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**Figure 1.** Dependence of pseudo-first-order rate constants on the concentration of excess reagent for the reaction of  $\text{Gd}^{3+}$  with HE-DO3A. The conditions used are as follows:  $[\text{HE-DO3A}] = 2.0 \times 10^{-4} \text{ M}$ ;  $-\log [\text{H}^+] = 4.07\text{--}4.67$ . The  $-\log [\text{H}^+]$  values for different curves are as follows:  $a = 4.07$ ;  $b = 4.27$ ;  $c = 4.47$ ;  $d = 4.67$ . The solid curves are calculated from the resolved values of the equilibrium and the rate constants (Table 2) for the formation of the intermediate and its reorganization.



**Figure 2.** Dependence of pseudo-first-order rate constants on the concentration of excess reagent for the reaction of  $\text{Gd}^{3+}$  with HIP-DO3A. The conditions used are as follows:  $[\text{HIP-DO3A}] = 1.0 \times 10^{-4} \text{ M}$ ;  $-\log [\text{H}^+] = 4.26\text{--}4.61$ . The  $-\log [\text{H}^+]$  values for different curves are as follows:  $a = 4.26$ ;  $b = 4.38$ ;  $c = 4.61$ . The fourth curve at  $-\log [\text{H}^+] = 4.38$  is not shown as it was too close to the curve at  $-\log [\text{H}^+] = 4.38$ . The solid curves are calculated from the resolved values of the equilibrium and the rate constants (Table 2) for the formation of the intermediate and its reorganization.

useful in the context of biological studies.<sup>27</sup> The conditional stability constant can be calculated by using eq 2. Under physiological conditions there is a significant proton competition depending on the basicity of the ligand, which differs among the ligands (Table 1).

**Formation Kinetics and Mechanisms.** The formation reaction of  $\text{Gd}^{3+}$  complexes of HE-DO3A, HP-DO3A,<sup>11</sup> and HIP-DO3A was studied under pseudo-first-order conditions in a lightly buffered medium with  $\text{Gd}^{3+}$  in large excess. Each individual run gave an excellent fit to the first-order model.<sup>22</sup> The  $k_{\text{obsd}}$  values increased with increasing  $[\text{Gd}^{3+}]$  and saturated at high  $\text{Gd}^{3+}$  concentration (Table SI).<sup>28</sup> The data were fitted to a saturation kinetics model (Figures 1 and 2). The observed rates follow eq

3, where  $[\text{L}]_{\text{T}}$  is the concentration of the various protonated forms

$$d[\text{GdL}]/dt = k_{\text{obsd}}[\text{L}]_{\text{T}} \quad (3)$$

of the ligand and  $k_{\text{obsd}}$  is a pseudo-first-order rate constant, expressed by eq 4.<sup>29</sup> As reported,<sup>11</sup> this observation can be

$$k_{\text{obsd}} = kK^*[\text{Gd}^{3+}]/(1 + K^*[\text{Gd}^{3+}]) \quad (4)$$

rationalized in terms of a precursor (intermediate) complex formation in the equilibrium step,  $K^*$ , followed by its reorganization in the rate-determining step,  $k$ . From the observed rate constants,  $k_{\text{obsd}}$ , at a given pH (Table SI,<sup>28</sup> Figures 1 and 2), the values of  $k$  ( $\text{s}^{-1}$ ) and  $K^*$  ( $\text{M}^{-1}$ ) were obtained from a nonlinear least-squares regression analysis of  $k_{\text{obsd}}$  vs  $[\text{Gd}^{3+}]$  data using the "SIMPLEX" procedure (Table 2). The resolved values of  $K^*$  ( $\text{M}^{-1}$ ) were independent of pH while the values of  $k$  ( $\text{s}^{-1}$ ) were pH dependent. An average value of  $K^*$  is given in Table 2 along with published values<sup>10</sup> for the DO3A complex of  $\text{Gd}^{3+}$ . In Figures 1 and 2, the  $[\text{Gd}^{3+}]$  dependence of  $k_{\text{obsd}}$  is plotted; the solid curves are calculated from the resolved values of  $K^*$  and  $k$ . As proposed earlier,<sup>11</sup>  $K^*$  is the equilibrium constant for the formation of an intermediate in which  $\text{Gd}^{3+}$  is coordinated to all of the oxygens and at least one nitrogen. The overall stability constant of the intermediate,  $\text{Gd}^*(\text{HL})$ , defined by eq 5<sup>11</sup> was calculated from

$$K_{\text{Gd}^*(\text{HL})} = [\text{Gd}^*(\text{HL})]/[\text{Gd}^{3+}][\text{HL}^{2-}] \quad (5)$$

$$K_{\text{Gd}^*(\text{HL})} = K^*\alpha_{\text{HL}}^{-1} \quad (6)$$

the value of  $K^*$ , apparent or conditional formation constant at a pH, the ligand protonation constants, and eq 6. In eq 6,  $\alpha_{\text{HL}}^{-1}$  is  $1 + K_2[\text{H}^+] + K_2K_3[\text{H}^+]^2 + \dots + K_n[\text{H}^+]^n$  and  $K_2$ ,  $K_3$ , and  $K_4$  are the ligand protonation constants for the formation of  $\text{H}_2\text{L}^-$ ,  $\text{H}_3\text{L}$ , and  $\text{H}_4\text{L}^+$  forms of the ligand.

The calculated values of  $\log K_{\text{Gd}^*(\text{HL})}$  for the HE-DO3A, HP-DO3A, HIP-DO3A, and DO3A intermediate are comparable (Table 2). In our previous report<sup>11</sup> an enhancement in the value of the stability constant for the DO3MA intermediate was observed and assumed to be due to the presence of three methyl groups in the  $\alpha$  position relative to the carboxylates and the nitrogen atoms. The presence of an  $\alpha$  methyl group in HIP-DO3A led us to expect a similar effect. However, no significant increase in the value is seen over the value for HE-DO3A. This observation suggests that coordination of  $\text{Gd}^{3+}$  in the intermediate takes place with a nitrogen atom that has an attached carboxylate. The proton on the most basic nitrogen therefore tends to prevent the coordination process. In the case of DO3MA, all tertiary nitrogens had  $\alpha$  methyl groups. The intermediate,  $\text{Gd}^*(\text{HL})$ , is not a stable protonated form of the chelate, i.e.  $\text{Gd}(\text{HL})$ , in which a proton is presumably on a carboxylate oxygen (vide infra).<sup>10,30</sup> The stability constants for the  $\text{Gd}(\text{HL})$  type species have been calculated (Table 3) from the stability constants of the chelates and the protonation constants of the ligand and the chelate (vide infra).

The value of the pseudo-first-order rate constants ( $k_{\text{obsd}}$ ) and  $k$ , the rate constant of reorganization of the intermediate, increased with increasing pH (Table SI)<sup>28</sup> for HE-DO3A, HP-DO3A,<sup>11</sup> and HIP-DO3A complexes in the  $-\log[\text{H}^+]$  range 3.7–4.7. This observation is consistent with the previously reported work<sup>6,7,11</sup> for the NOTA, DOTA, DO3A, HP-DO3A, and DO3MA complexes of  $\text{Gd}^{3+}$ . The values of  $k$  were calculated from the value of  $K^*$  (Table 2),  $k_{\text{obsd}}$  (Table SI),<sup>28</sup> and using eq 4.<sup>11</sup> The

(27) Wedeking, P.; Kumar, K.; Tweedle, M. F. *Magn. Reson. Imag.* **1992**, *10*, 641.

(28) Two tables of pseudo-first-order rate constants for the formation (Table SI) and dissociation (Table SII) reactions. See paragraph at the end of the paper.

(29) Wilkins R. G. *Kinetics and Mechanisms of Reactions of Transition Metal Complexes*; VCH Publishers, Inc.: New York, 1991.

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

**Table 2.** Parameters  $K^*$ , Equilibrium Constant for the Formation of the Intermediate,  $k$ , Rate Constant of the Reorganization of the Intermediate,  $\log K_{Gd(*HL)}$ , the Stability Constant of  $Gd(*HL)$ , and  $k_{OH}$ , Second-Order Rate Constant for the Base-Assisted Reorganization of the Intermediate, for Macrocylic Polyamino Carboxylate Complexes of  $Gd^{3+}$ <sup>a</sup>

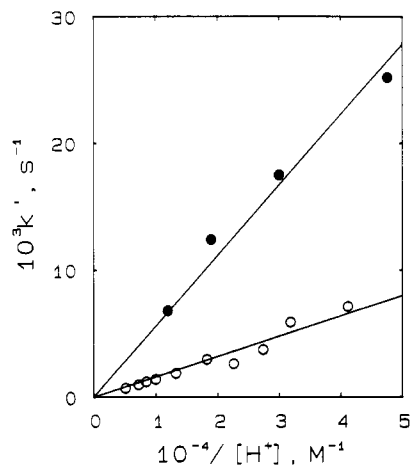
ligand	$-\log [H^+]$	$10^{-3}K^*$ , M <sup>-1</sup>	$10^3k$ , s <sup>-1</sup>	$\log K_{Gd(*HL)}$	$10^7k_{OH}$ , M <sup>-1</sup> s <sup>-1</sup>
1. HE-DO3A	4.07	$1.09 \pm 0.06$	$6.8 \pm 0.1$	8.90	$3.4 \pm 0.1$
	4.27	$0.95 \pm 0.05$	$12.4 \pm 0.2$	8.46	
	4.27	$1.07 \pm 0.08$	$17.5 \pm 0.3$	8.18	
	4.67	$0.98 \pm 0.04$	$25.2 \pm 0.3$	7.83	
		$1.02 \pm 0.07$ (av)		$8.3 \pm 0.4$ (av)	
2. HP-DO3A <sup>b</sup>	4.26	$3.0 \pm 0.6$	$2.6 \pm 0.1$	9.0	$1.23 \pm 0.04$
3. HIP-DO3A	4.26	$0.59 \pm 0.04$	$2.98 \pm 0.08$	8.30	$0.96 \pm 0.04$
	4.38	$1.13 \pm 0.28$	$3.9 \pm 0.2$	8.39	
	4.44	$0.66 \pm 0.14$	$4.0 \pm 0.2$	8.07	
	4.61	$0.78 \pm 0.05$	$7.75 \pm 0.15$	7.89	
		$0.80 \pm 0.24$ (av)		$8.2 \pm 0.2$ (av)	
4. DO3A <sup>b</sup>	4.28	$3.0 \pm 1.0$	$5.6 \pm 0.1$	8.9	$2.1 \pm 0.1$

<sup>a</sup> At  $\mu = 1.0$  (NaCl) and at  $25.0 \pm 0.1$  °C. <sup>b</sup> Data taken from ref 11.

**Table 3.** Summary of Thermodynamic and Kinetic Characteristics of  $Gd^{3+}$  Complexes of Macrocylic Polyamino Carboxylates<sup>a</sup>

chelate	$\log K_{GdL(H)}$	$\log K_{Gd(HL)}^b$	$10^4k_d$ , s <sup>-1</sup>	$K_{GdL(H_2)}$ , M <sup>-1</sup>	$10^3k_2$ , s <sup>-1</sup>
1. HE-DO3A	2.04	13.3	<i>c</i>	$9 \pm 2$	$1.9 \pm 0.2$
2. HP-DO3A	2.38 <sup>d</sup>	14.2	<i>c</i>	$0.35 \pm 0.03^e$	$1.66 \pm 0.09^e$
3. HIP-DO3A	2.23	13.6	$0.2 \pm 0.1$	$0.6 \pm 0.1$	$0.64 \pm 0.05$
4. DO3A	2.06 <sup>d</sup>	11.5	$4.0 \pm 1.5^e$	$1.3 \pm 0.1^e$	$19.3 \pm 1.1^e$

<sup>a</sup> At  $\mu = 1.0$  (NaCl) and at  $25.0 \pm 0.1$  °C. <sup>b</sup> These constants are calculated from the measured stability constant of  $GdL$  and the protonation constants of the ligand and the chelate. Data are used from refs 10 and 11 and this work. <sup>c</sup> Not observed. <sup>d</sup> Reference 10. <sup>e</sup> The recalculated values with the use of eq 22 and data in ref 10.



**Figure 3.** Effect of pH on the formation rates of  $Gd(HE-DO3A)$  and  $Gd(HIP-DO3A)$ . Plots are of  $k$ , the rate of reorganization of the intermediate,  $Gd(*HL)$ , vs  $1/[H^+]$ . The symbols used are as follows: ●, HE-DO3A; ○, HIP-DO3A.

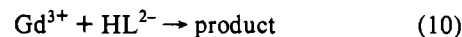
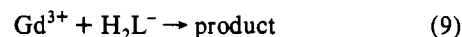
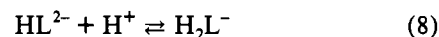
values of  $k$  were found to be inversely proportional to  $[H^+]$  (Figure 3) and followed eq 7. As proposed earlier, this was explained in

$$k = (k_{H_2O} + k_{OH}K_w/[H^+]) \quad (7)$$

terms of an hydroxide-assisted reorganization of the intermediate.<sup>11</sup> According to eq 7, a plot of  $k$  vs  $1/[H^+]$  is expected to be a straight line (Figure 3). Consistent with our previous work<sup>11</sup> and that of others,<sup>6</sup> no significant intercept was observed in the present work and the slope of the plot is the measure of a value of  $k_{OH}$ . The value of  $pK_w$  used was as 13.78 at  $\mu = 0.1$  and 25 °C.<sup>31</sup> Due to the absence of any appreciable concentration of  $Gd(OH)^{2+}$ , the effect of the reactivity of  $Gd(OH)^{2+}$  on the rates of the reactions has been neglected, as described in previous studies.<sup>5,6,7,11</sup>

The effect of pH on the rates of the formation of  $GdL$  (where  $L = HE-DO3A, HP-DO3A, \text{ and } HIP-DO3A$ ) can be expressed

in terms of the reactivity difference of the mono- and diprotonated forms of the ligand (eqs 8–10).<sup>7,32</sup> The formation of the



$$d[GdL]/dt = k[Gd][L]_T = k_{H_2L}\alpha_{H_2L}[Gd] + k_{HL}\alpha_{HL}[Gd] \quad (11)$$

$$\alpha_{H_nL} = \beta_n[H^+]^n / 1 + \beta_1[H^+] + \beta_2[H^+]^2 + \dots + \beta_n[H^+]^n \quad (12)$$

$\beta_n$  = overall formation constant for  $H_nL$  species

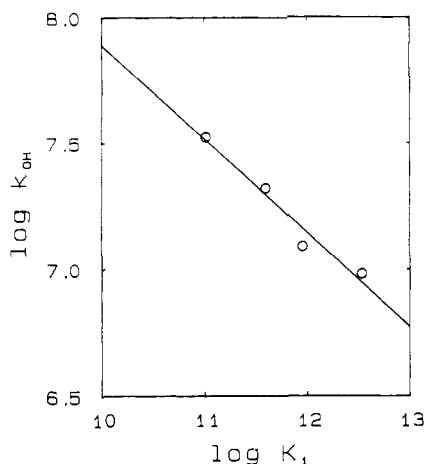
$$\log k = \log k_{HL} + \alpha_{HL} \quad (13)$$

$$k = k_{HL}/K_2[H^+] \quad (14)$$

intermediate, presumable  $Gd(*HL)$ , was proposed from the reactions of the  $HL^{2-}$  and  $H_2L^-$  forms of the ligand. Such a situation can be accommodated by a rate law of the form given by eq 11. As reported earlier,<sup>7</sup>  $HL$  is the only reactive species; this equation transforms into eqs 13 and 14 in the narrow pH range in which the measurements were made. In eq 14,  $K_2$  is the equilibrium constant for the formation of the diprotonated form of the ligand,  $H_2L$ . A plot of eq 14 predicts a straight line (Figure 3), with the slope being a measure of  $k_{HL}/K_2$  and a zero intercept. In terms of eq 7, the slope and the intercept are the measure of  $k_{H_2O}$  and  $k_{OH}K_w$ , respectively, the  $k_{H_2O}$  term being negligible in the present work. Consequently, the data given in the present work can be analyzed by both approaches. However, evidence of the formation of the intermediate,<sup>11</sup>  $Gd(*HL)$ , and a good correlation between  $\log k_{OH}$  and  $\log K_1$  (vide infra) led us to express our results in terms of a hydroxide-assisted pathway.

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(32) Kasprzyk, S. P.; Wilkins, R. G. *Inorg. Chem.* **1982**, *21*, 3349.



**Figure 4.** Correlation of  $\log k_{\text{OH}}$  vs the first protonation constant ( $\log K_1$ ) of the deprotonated macrocyclic polyamino carboxylates.

The relative rates of the hydroxide-assisted reorganization of the intermediate,  $\text{Gd}^*(\text{HL})$  ( $\text{L} = \text{HE-DO3A, HP-DO3A, HIP-DO3A, and DO3A}$ ), are inversely proportional to the first protonation constant ( $\log K_1$ ) of the deprotonated ligand. Figure 4 shows a good linear correlation ( $r^2 = 0.98$ ) between the second-order base-assisted rate constant of reorganization of the intermediate ( $\log k_{\text{OH}}$ ) and  $\log K_1$  (eq 15). An expected value of

$$\log k_{\text{OH}} = -(0.37 \pm 0.05) \log K_1 + (11.6 \pm 0.6) \quad (15)$$

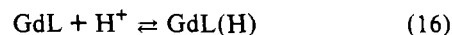
the slope is  $-1.0$  or more positive if the rate is controlled only by proton transfer. In our previous work,<sup>11</sup> the slope of such a correlation was found to be more negative than  $-1.0$ , which was explained in terms of the difference in the nitrogen atom basicity and the rigidity of the ligands. In the present work, however, the value is more positive than  $-1.0$ , suggesting that the relative rates of the reactions are due to the difference in the basicity of nitrogen atoms. Since no variation in the rigidity is expected in the ligands, this seems to be the case.

The mechanism of the formation of  $\text{Gd}^{3+}$  complexes is consistent with the previously proposed mechanism.<sup>11</sup> In this mechanism the metal first coordinates with carboxylate oxygens and one nitrogen in the equilibrium step, which is favored by electrostatic attraction between  $\text{Gd}^{3+}$  and the carboxylate oxygens. The reorganization of the intermediate to the final product is water- or hydroxide-assisted, and the rate is limited by proton transfer.

In the transition state it is proposed that as  $\text{Gd}^{3+}$  moves into the vicinity of the nitrogen the proton departs. There is no actual bond formation between  $\text{Gd}^{3+}$  and the protonated nitrogen, but the metal moves into the first coordination sphere of the nitrogen while the base-assisted proton removal is the rate-determining step. The crystal structure studies of  $\text{H}_3\text{DO3A}^{2+}$  demonstrated<sup>20</sup> that the two protons are attached to ring nitrogens trans to each other and three carboxylates are protonated. The lone pairs on nitrogen or attached protons are directed into the cavity of the macrocycle. For a metal coordination with nitrogen and its deprotonation, nitrogen inversion probably occurs. This process requires a significant energy and a rearrangement of the macrocyclic ring that slows down the rate of the complexation reaction. In our previous work,<sup>11</sup> the rate-determining step of the reaction, the rearrangement of the intermediate, appeared to be proportional to the ligand strain energy which we explained in terms of nitrogen inversion in the process. However, in the present work the energy of nitrogen inversion and of reorganization of the intermediate is presumably the same; consequently the difference in rates is proton-transfer controlled. The role of coordinated water or hydroxide was also considered and was found unacceptable on the basis of previous discussions.<sup>11</sup>

**Dissociation Kinetics and Mechanisms.** The protonation constants of the chelates,  $\text{Gd}(\text{HE-DO3A}), \text{Gd}(\text{HP-DO3A}),$ <sup>10</sup> and

$\text{Gd}(\text{HIP-DO3A}),$  eq 16, were determined by a fluorimetric



method.<sup>10</sup> The instantaneous fluorescence intensity ( $\Delta I$ ) as a function of  $[\text{H}^+]$  for  $\text{GdL}$  (where  $\text{L} = \text{HE-DO3A, HP-DO3A, and HIP-DO3A}$ ) was measured and used to plot eq 17.<sup>10</sup> The

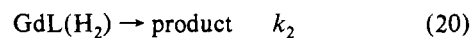
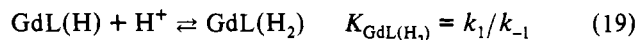
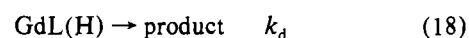
$$[\text{GdL}]_{\text{T}}/\Delta I = \{1/b(\Delta\epsilon)K_{\text{H}}[\text{H}^+]\} + \{1/b(\Delta\epsilon)\} \quad (17)$$

ratio of the intercept and the slope gave the protonation equilibrium constant,  $K_{\text{GdL}(\text{H})}$  ( $\text{M}^{-1}$ ), for  $\text{GdL}$  (Table 3). In eq 17,  $[\text{GdL}]_{\text{T}}$  is the sum of the concentrations of protonated and unprotonated complex and  $\Delta I$  and  $\Delta\epsilon$  are the differences in the fluorescence intensity and emission coefficients of the protonated and unprotonated forms of the complex, respectively.

On the basis of solid-state IR,<sup>30</sup> crystal structure,<sup>33</sup> NMR,<sup>34</sup> thermodynamic, and kinetic studies,<sup>4,5,7,10,35</sup> it is proposed that the protonation of  $\text{Gd}^{3+}$  chelates takes place on a carboxylate oxygen.<sup>4,5,7,10,30,33-35</sup> The values of the protonation constants determined in this work are similar to the values reported in our previous work.<sup>10</sup>

The rates of the dissociation reactions of  $\text{Gd}^{3+}$  complexes of  $\text{HE-DO3A, HP-DO3A,}$ <sup>10</sup> and  $\text{HIP-DO3A}$  were measured in  $0.0125\text{--}1.0\text{ M HCl}$  solutions under pseudo-first-order conditions ( $\text{GdL}$  was the limiting reagent) (Table SII)<sup>28</sup> at a constant ionic strength ( $\mu = 1.0$ ) and at  $25.0 \pm 0.1$  °C. In the present work,  $\text{GdL}(\text{H})$  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. (2) Under the experimental conditions, a large percentage of the complex is in the protonated forms ( $>55\%$ ). (3) The protonated species probably has one less coordinated group and consequently will be less stable and more reactive.

The reactions were first-order in the limiting reagent,  $\text{GdL}$ , and the value of  $k_{\text{obsd}}$  increased linearly with increasing acid concentration; however, at high acid concentration  $k_{\text{obsd}}$  values were independent of acid concentration (Table SII).<sup>28</sup> This behavior suggests a rapid preequilibrium step (i.e. the formation of the diprotonated species,  $\text{GdL}(\text{H}_2)$ ) prior to its dissociation in the rate-determining step. The observed results are expressed by eqs 16 and 18–20, where  $k_{\text{d}}$  is the rate constant of direct



dissociation,  $k_1$  is the acid-assisted dissociation rate constant and  $k_{-1}$  is the reverse rate constant for eq 19,  $K_{\text{GdL}(\text{H}_2)}$  is the equilibrium constant for the formation of the diprotonated species,  $\text{GdL}(\text{H}_2)$ , and  $k_2$  is its rate of dissociation. Saturation kinetics behavior suggests the formation of  $\text{GdL}(\text{H}_2)$  in appreciable concentrations, and this is expressed by eq 5. A rate expression consistent with these observations is given in eqs 21 and 22. The  $k'_{\text{obsd}}$  values for

$$-\text{d}[\text{GdL}]_{\text{T}}/\text{d}t = k_{\text{obsd}}([\text{GdL}] + [\text{GdL}(\text{H})] + [\text{GdL}(\text{H}_2)]) = [k_{\text{d}} + \{k_2 K_{\text{GdL}(\text{H}_2)}[\text{H}^+]/(1 + K_{\text{GdL}(\text{H}_2)}[\text{H}^+])\}][\text{GdL}(\text{H})] \quad (21)$$

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

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

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

$$k'_{\text{obsd}} = k_{\text{obsd}} \left\{ (1/K_{\text{GdL(H)}}[H^+] + 1 + (K_{\text{GdL(H}_2)}[H^+])) \right\} = [k_d + \{k_2 K_{\text{GdL(H}_2)}[H^+]/(1 + K_{\text{GdL(H}_2)}[H^+])\}] \quad (22)$$

dissociation of GdL were fitted to eq 22 by a SIMPLEX procedure,<sup>23</sup> and the resolved values of the equilibrium,  $K_{\text{GdL(H}_2)}$ , and the rate constants,  $k_d$  and  $k_2$ , are given in Table 3. The data on Gd(HE-DO3A) did not show any appreciable direct dissociation of the chelate. However, a  $k_d$  value was calculated as  $(2 \pm 1) \times 10^{-5} \text{ s}^{-1}$  for Gd(HIP-DO3A). This value of  $k_d$  has a large error; however, it seems to be real as it was required to calculate the solid curve in Figure 5, a plot of eq 22 ( $k'_{\text{obsd}}$  vs  $[H^+]$ ) for the dissociation of protonated Gd(HIP-DO3A). The calculated values of  $K_{\text{GdL(H}_2)}$ ,  $9 \pm 2 \text{ M}^{-1}$ , from the kinetic data and fluorimetrically determined value of  $K_{\text{GdL(H)}}$ ,  $110 \text{ M}^{-1}$ , for Gd(HE-DO3A) are close to each other. Consequently, the value of  $K_{\text{GdL(H)}}$  may have some contribution from the formation of GdL(H<sub>2</sub>). In our previous report,<sup>10</sup> we failed to take the GdL(H<sub>2</sub>) formation into account<sup>36</sup> in the left-hand side of eq 21; consequently, the data on Gd(HP-DO3A) and Gd(DO3A) are reanalyzed and listed in Table 3.

Dissociation of Gd<sup>3+</sup> chelates studied in the present work follows the mechanism discussed in our previous work<sup>10</sup> and in the work of Brucher and Sherry.<sup>7</sup> In this mechanism GdL(H) and H<sup>+</sup> react to form GdL(H<sub>2</sub>) in the equilibrium step. This intermediate converts to GdL(H<sub>2</sub>)\* in the rate-determining step, which dissociates rapidly to Gd<sup>3+</sup> and the protonated ligand. Presumably, a second proton associates to a carboxylate oxygen in GdL(H<sub>2</sub>). But in GdL(H<sub>2</sub>)\* the proton shifts to a nitrogen in a rate-determining step. Consistent with the formation reaction mechanism, dissociation of the Gd-N bond and proton transfer to nitrogen are rate limiting. As proposed in the case of the formation reactions, the metal-nitrogen bond breaks first, while the nitrogen is still in the first coordination sphere of the metal, followed by proton transfer to nitrogen, which is rate determining.<sup>37,38</sup>

A comparison of the kinetic inertia of GdL (L = HE-DO3A, HP-DO3A, and HIP-DO3A) is in order. It is very difficult to compare in detail the equilibrium and rate constants for the dissociation of the gadolinium complexes of the various macrocyclic polyamino carboxylates given in Table 3. Instead we have compared the  $10^5 k_{\text{obsd}}$  values in 0.1 M HCl for dissociation of Gd(III). The values are 46.6 (HE-DO3A), 6.4 (HP-DO3A),

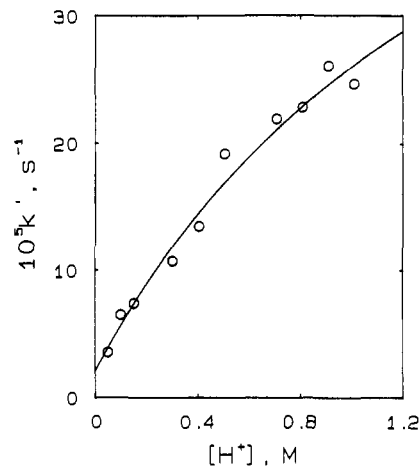


Figure 5. Acid dependence of pseudo-first-order rate constants,  $k'_{\text{obsd}}$  (corrected for the fraction of GdL(H)) on  $[H^+]$  for dissociation of Gd(HIP-DO3A). The solid curve is calculated from the resolved values of equilibrium and rate constants.

and 5.8 (HIP-DO3A), suggesting that the rate of dissociation of GdL(H) depends on the basicity of nitrogen ( $\log K_1$ ) and the stability constant of GdL (Table 1). This observation is in agreement with the previous study of Moore and Wilkins<sup>39</sup> in the case of dissociation of transition metal complexes.

### Conclusions

For 12-membered octadentate macrocyclic polyamino carboxylate ligands, containing four nitrogens, three carboxylate oxygens, and one alcoholic oxygen, it appears that an  $\alpha$ -methyl group increases the stability of Gd<sup>3+</sup> complexes and the basicity of nitrogen atoms<sup>40</sup> substituted by an alcohol arm. The formation of GdL involves the formation of an intermediate in which the metal is coordinated to all oxygens and at least one nitrogen, to which a carboxylate arm is attached. The base-assisted rate constant of reorganization of the intermediate,  $k_{\text{OH}}$ , and the acid-assisted rate of dissociation of GdL,  $10^5 k_{\text{obsd}}$ , correlate well with the basicity of nitrogen.

**Supplementary Material Available:** Tables of  $k_{\text{obsd}}$ ,  $\text{s}^{-1}$ , values for the formation and dissociation reactions (3 pages). Ordering information is given on any current masthead page.

(36) The authors wish to thank one of the reviewers for pointing this out.

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