Ligand Basicity and Rigidity Control Formation of Macrocyclic Polyamino Carboxylate Complexes of Gadolinium(III)

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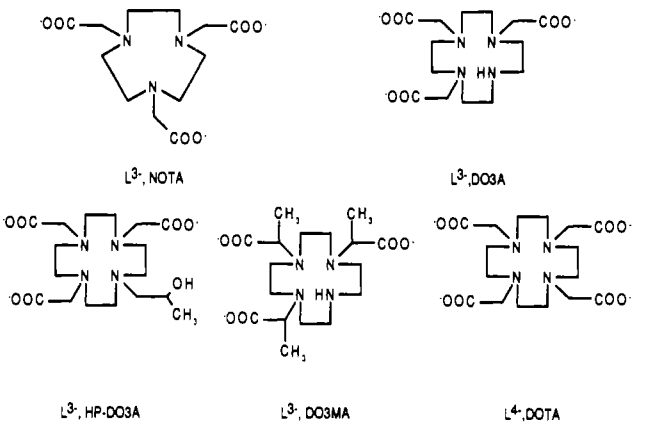
The formation reaction rates of some macrocyclic polyamino carboxylate complexes of gadolinium, GdL (where L is DO3A = 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, H_3L, HP-DO3A = 10-(hydroxypropyl)-1,4,7,-10-tetraazacyclododecane-1,4,7-triacetic acid, H_3L, and DO3MA = (1*R*,4*R*,7*R*)-α,α',α''-trimethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-triacetic acid, H_3L), have been measured at 25.0 ± 0.1 °C and at a constant ionic strength of 1.0 (NaCl) by an indicator method. The formation reactions are first order in the limiting reagent (ligand) and nearly independent of the excess reagent (gadolinium ion). A mechanism of the formation of the gadolinium complexes involves the formation of a precursor (intermediate) complex, Gd(*HL), in an equilibrium step followed by its deprotonation and reorganization to the final product in the rate-determining step. The stability constants (log $K_{Gd(*HL)}$) of the intermediate have been determined from the kinetic data and the values are 8.9 (DO3A), 9.0 (HP-DO3A), and 10.7 (DO3MA). The nature of the intermediate is proposed in which the metal is coordinated to oxygens and at least one nitrogen of the ligand. Deprotonation and reorganization of the intermediate are specific-base assisted. The second-order rate constants (k_{OH}, M^{-1} s^{-1}) for the reorganization of the intermediate, Gd(*HL) (L are given in the parentheses), are (2.1 ± 0.1) × 10^7 (DO3A), (1.23 ± 0.04) × 10^7 (HP-DO3A), and (7.2 ± 0.3) × 10^4 (DO3MA), compared to the literature data (7.1 ± 1) × 10^7 (NOTA) and (5.9 ± 0.2) × 10^6 (DOTA). The specific-base assisted rate of reorganization of the intermediate, Gd(*HL), is correlated with the ligand strain energy and its first protonation constant. These observations lead us to conclude that the rate of reorganization of the intermediate is governed by the basicity and rigidity of the ligand.

Introduction

There has been considerable interest in the coordination chemistry, thermodynamics, and kinetics of lanthanide complexes because of their use as contrast agents in magnetic resonance imaging (MRI).[1-3] The rates of formation of lanthanide complexes with simple ligands such as murexide and oxalate are very fast and can be predicted using the rate of water loss (k^{-H_2O}) and the equilibrium constant for the outer-sphere complex formation (K_{OS}).[4,5] For linear polyamino carboxylates charge density and rigidity influence the rate of complexation and the formation of reaction intermediates.[6-8]

Macrocyclic polyamino carboxylate ligands have some additional features which affect the rate of formation of their complexes including cavity size, steric factors, conformation, and preorganization. Formation kinetics of lanthanide complexes of the hexadentate linear polyamino carboxylate CyDTA (*trans*-1,2-diaminocyclohexane-*N*,*N*,*N*′,*N*′-tetraacetic acid) and the hexa- and octadentate macrocyclic polyamino carboxylates NOTA (1,4,7-triazacyclononane-*N*,*N*′,*N*″-triacetic acid) and DOTA (1,4,7-tetraazacyclododecane-*N*,*N*′,*N*″,*N*‴-tetraacetic acid), respectively, have been reported (Chart I).[6,9,10] Formation of an intermediate, M(*HL), was proposed, followed by reorganization in the rate-determining step to the final product.[6,9] The effect of the size of lanthanide ions (charge density) on the rate of the formation of the lanthanide complexes was not as pronounced as observed for the dissociation reactions of these chelates.[6,9] The effect of pH on the formation reaction rates of Gd^{3+} complexes of NOTA[9] and DOTA[10] was analyzed in terms of hydroxide-assisted reorganization of the intermediate (M(*HL)) and the difference in the reactivity of the monoprotonated (HL^{3-}) and diprotonated (H_2L^{2-}) forms of the ligand, respectively.

Chart I. Structure of the Ligands



We initiated a study with the following goals: (1) to understand how the formation rates and mechanisms of Gd^{3+} complexes are affected by the number of donor atoms, size, basicity, and rigidity of macrocyclic polyamino carboxylate ligands and (2) to compare and understand the reactivity differences between linear and macrocyclic ligands.

In the present work we report a systematic study of kinetics of the formation of Gd^{3+} complexes (forward reaction of eq 1)

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$$M^{3+} + H_nL \rightleftarrows ML^{3-n} + nH^+ \quad (1)$$

of DO3A (1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, H_3L), HP-DO3A (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid, H_3L), and DO3MA ((1*R*,4*R*,7*R*)-α,α',α''-trimethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-triacetic acid, H_3L). The literature data on the formation reactions of Gd^{3+} complexes of NOTA[9] and DOTA[10] are included for comparison.

Experimental Section

Chemicals and Reagents. A stock solution of $GdCl_3$ was prepared from a solid sample of $GdCl_3$ purchased from Research Chemicals (Phoenix, AZ) and was used without further purification. The sample solution was standardized by a complexometric titration with xylenol orange as the indicator.[11] Sodium chloride (Alfa) was used for the ionic strength control in all kinetic studies. Distilled deionized water and reagent grade buffer (sodium acetate/acetic acid), acids, and bases were used. The ligands DO3A, HP-DO3A, and DO3MA and their Gd^{3+} complexes were synthesized as given elsewhere.[12,13] The stock solutions of the ligands were prepared and standardized either by the potentiometric or back-titration method.

Methods. The formation reactions were slow and the progress of the reactions was monitored by conventional methods. Since complexed or uncomplexed Gd^{3+} does not have significant absorbance, formation reaction kinetics were studied in weakly buffered medium by monitoring the decrease in pH ($\Delta pH < 0.1$) with the use of indicators.[9,10,14] The rate of the formation of GdL was monitored as an absorbance decrease due to the release of protons in the complexation reaction (eq 2), which in

$$M^{3+} + H_nL \rightleftarrows ML + nH^+ \quad (2)$$

$$In^- + H^+ \rightleftarrows InH \quad (3)$$

turn reacted with the indicator (eq 3) or the base form of the buffer, OAc^-. The amount of protons released and the absorbance change in the formation reaction depended on the pH and the ligand protonation constants. The literature values of the ligand protonation constants and stability constants[15-19] of the Gd^{3+} complexes are given in Table I.

Bromocresol green ($4.6 < pH < 5.2$, 612 nm) and bromophenol blue ($3.6 < pH < 4.6$, 592 nm) were used as the indicators. The concentration of the indicators was kept constant either at 1.0×10^{-5} or at 4.0×10^{-5} M. A small absorbance decrease for the indicator, usually between 0.05 and 0.1 absorbance unit, was seen when lightly buffered ($[OAc]_T = 5.0$ mM) solutions of the ligand (0.1–0.2 mM) and Gd^{3+} (1.16–11.60 mM) at the same pH were mixed.[14] The concentration of the indicators was 2–20-fold lower than $[L]_T$ in these reactions. At higher pHs there was a concern of not having enough indicator to accept the protons released in the reaction, consequently lowering the absorbance change and rate of the reaction. Most of the protons are consumed by the buffer ($[OAc]_T = 5.0$ mM). Only a fraction of the protons are taken up by the indicator ($[In]_T = 0.01$–0.04 mM). At higher pHs, the concentration of the basic form of the buffer and indicator do increase, but the ratio $[In^-]/[B^-]$ remains constant. The size of the absorbance change is reduced at higher pHs due to the reduction in protons released and to the change in the driving force of the reaction. However, the size of the absorbance change would not affect the rate of the reaction. Earlier kinetic measurements[6,9,10,14] with the use of this procedure showed no significant interaction of the indicators with the ligand, the metal, or the buffer, although the base form of the buffer, acetate/acetic acid, forms mono, bis, and tris complexes with Gd^{3+} ($\log \beta_1 = 1.82$, $\log \beta_2 = 3.13$, $\log \beta_3 = 4.0$ at 20 °C and $\mu = 1.0$ (NaCl)).[20] However, the concentration of the buffer was too small ($[OAc]_T = 5.0$ mM) to interfere in the kinetic measurements.

Table I. Protonation Equilibrium Constants of Macrocyclic Polyamino Carboxylates and the Formation Equilibrium Constants of Their Gd(III) Complexes[a]

ligand	$\log K_1$	$\log K_2$	$\log K_3$	$\log K_4$	$\log K_{GdL}$
NOTA[b]	11.61[b]	5.87[b]	3.41[b]		13.7[c]
DO3A[d]	11.59[d]	9.24[d]	4.43[d]	3.48[d]	21.1[d]
HP-DO3A[d]	11.96[d]	9.43[d]	4.30[d]	3.26[d]	23.8[d]
DOTA[e]	12.09[e]	9.68[e]	4.55[e]	4.13[e]	25.3[d]
DO3MA[f]	13.38[f]	9.15[f]	5.30[f]	4.07[f]	25.3[f]

[a] At 25.0 ± 0.1 °C and $\mu = 0.1$ (TMACl) unless otherwise noted. [b] Reference 15. [c] Reference 16. [d] References 17 and 19. A value of 24.6 was reported in ref 19. [e] Reference 18. [f] Reference 13.

All spectrophotometric and kinetic measurements were made with the use of 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 with the use of a Lauda RMS circulatory water bath.

All kinetic studies were carried out at 25.0 ± 0.1 °C, at a constant ionic strength, $\mu = 1.0$ (NaCl), and under pseudo-first-order conditions in the presence of a large excesses of Gd(III). Pseudo-first-order rate constants (k_{obsd}, s^{-1}) were calculated from the absorbance or intensity vs time data and with the use of a first-order model.[21] A SIMPLEX[22] program was used to fit these data.

Results and Discussion

Formation Kinetics. The formation reaction of Gd^{3+} complexes of DO3A, HP-DO3A, and DO3MA were studied under pseudo-first-order conditions in a lightly buffered medium with Gd^{3+} in large excess. Individual runs gave an excellent fit to the first-order model.[21] However, k_{obsd} values were nearly independent of Gd^{3+} concentration (Table II). The data were fitted to a saturation kinetics model (Figure 1). The observed rate constants follow eq 4, where $[L]_T$ is the concentration of the various

$$d[GdL]/dt = k_{obsd}[L]_T \quad (4)$$

protonated forms of the ligand and k_{obsd} is a pseudo-first-order rate constant. This observation can be rationalized in terms of a precursor (intermediate) complex formation in the equilibrium step, followed by its reorganization in the rate-determining step. As reported before,[9,10] the relationship between k_{obsd} and Gd^{3+} can be generally expressed as (5),[23] where K^* is the equilibrium

$$k_{obsd} = kK^*[Gd^{3+}]/(1+K^*[Gd^{3+}]) \quad (5)$$

constant for the formation of the intermediate complex and k is the rate of its reorganization. From the observed rate constants, k_{obsd}, at a given pH (Table II, Figure 1), the values of k (s^{-1}) and K^* (M^{-1}) were obtained by a weighted linear least-squares analysis of the data according to eq 6. A good fit of the data was obtained

$$1/k_{obsd} = 1/k + 1/kK^*[Gd^{3+}] \quad (6)$$

with correlation coefficients of 0.96 and 0.9 for the HP-DO3A and DO3A reactions, respectively. However, in the case of DO3MA, the pseudo-first-order rate constants, k_{obsd}, were acquired near the end of the saturation kinetics; consequently the fit of eq 6 gave a lower correlation coefficient, 0.58. The values of k and K^* were also obtained from a nonlinear least-squares

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Table II. Pseudo-First-Order Rate Constants for the Formation Reaction of Gd^{3+} Complexes of DO3A, HP-DO3A, and DO3MA at 25.0 ± 0.1 and μ = 1.0 (NaCl)

[Gd(III)], mM	[L], mM	pH	$[buffer]_T$, mM	$10^3 k_{obsd}$, s^{-1}
		Gd(DO3A)		
1.16	0.213	4.28	5.00	4.54 ± 0.09
2.33	0.213	4.27	5.00	5.0 ± 0.1
3.49	0.213	4.27	5.00	5.02 ± 0.02
4.66	0.213	4.29	5.00	5.48 ± 0.03
11.60	0.213	4.29	5.00	5.45 ± 0.02
4.66	0.213	4.31	5.00	6.1 ± 0.1
4.66	0.213	4.35	5.00	6.3 ± 0.2
4.66	0.213	4.49	5.00	9.22 ± 0.02
4.66	0.213	4.63	5.00	14.9 ± 0.4
4.66	0.213	4.70	5.00	15.8 ± 0.3
4.66	0.213	4.73	5.00	16.3 ± 0.4
4.66	0.213	4.83	5.00	24.5 ± 0.4
		Gd(HP-DO3A)		
1.16	0.10	4.26	5.0	1.98 ± 0.08
2.33	0.10	4.26	5.0	2.3 ± 0.1
3.49	0.10	4.26	5.0	2.2 ± 0.2
4.66	0.10	4.27	5.0	2.4 ± 0.2
5.82	0.10	4.25	5.0	2.4 ± 0.2
2.33	0.20	4.09	5.0	1.45 ± 0.05
2.33	0.20	4.15	5.0	1.53 ± 0.06
2.33	0.20	4.23	5.0	1.74 ± 0.08
2.33	0.20	4.60	5.0	7.3 ± 0.3
2.33	0.20	4.69	5.0	10.8 ± 0.3
2.33	0.20	4.79	5.0	11.2 ± 0.2
2.33	0.20	4.86	5.0	12.2 ± 0.4
2.33	0.20	4.96	5.0	17.0 ± 0.4
		Gd(DO3MA)		
0.49	0.10	4.02	5.0	(1.18 ± 0.01) × 10^{-2}
0.98	0.10	4.02	5.0	(1.15 ● 0.01) × 10^{-2}
1.23	0.10	4.01	5.0	(1.37 ± 0.01) × 10^{-2}
1.48	0.10	4.02	5.0	(1.25 ± 0.01) × 10^{-2}
2.46	0.10	4.04	5.0	(1.21 ± 0.01) × 10^{-2}
3.69	0.10	4.04	5.0	(1.41 ± 0.01) × 10^{-2}
1.23	0.10	3.61	5.0	(0.76 ± 0.07) × 10^{-2}
1.23	0.10	3.73	5.0	(0.84 ± 0.08) × 10^{-2}
1.23	0.10	3.86	5.0	(0.99 ± 0.08) × 10^{-2}
1.23	0.10	4.00	5.0	(1.20 ● 0.01) × 10^{-2}
1.23	0.10	4.14	5.0	(1.57 ± 0.02) × 10^{-2}
1.23	0.10	4.30	5.0	(1.96 ± 0.03) × 10^{-2}
1.23	0.10	4.35	5.0	(3.03 ± 0.05) × 10^{-2}
1.23	0.10	4.66	5.0	(6.8 ± 0.1) × 10^{-2}
1.23	0.10	4.83	5.0	(8.9 ± 0.2) × 10^{-2}
1.23	0.10	4.89	5.0	(7.7 ± 0.3) × 10^{-2}
1.23	0.10	5.00	5.0	(10.6 ± 0.3) × 10^{-2}

regression analysis of k_{obsd} vs $[Gd^{3+}]$ data using the "SIMPLEX" procedure (Table III).[22] Both methods gave the same results. The resolved values of K^* (M^{-1}) and k (s^{-1}), at a given pH, are summarized in Table III along with the literature values in the case of NOTA[9] and DOTA[10] reactions with Gd^{3+}. Consistent with the literature, the resolved values of K^* (Table III) had large uncertainties because the k_{obsd} values were acquired near the end of the saturation kinetics. More accurate values could probably be obtained by measuring the rates of the reaction at low reagent concentrations, but the experiments were not possible due to violation of first-order conditions and/or very low absorbance changes under these conditions. For the calculation of solid curve in Figure 1, an upper estimate of the K^* value in Table III was used. Earlier work showed no significant variation in the value of K^* with pH.[9,10] Consequently, the pH dependence of K^* was not determined in the present work.

Nature of the Intermediate. The formation reactions of GdL (where L = DO3A, HP-DO3A, and DO3MA) were studied in the limited pH range of 3.6–5.0. At lower pH the rates of the reactions were slow, and at higher pH Gd^{3+} hydrolyzes to insoluble hydroxides. The concentrations of HL^{2-}, H_2L^-, and H_3L were computed with the use of the ligand protonation constants (Table I) and the program SPE.[24] In this pH range the species H_2L^- and H_3L are in high concentration while HL^{2-} is in low concentration (7 × 10^{-6} to 0.01%). Kasprzyk and Wilkins[14] demonstrated in the case of the reaction of Cu^{2+} with DOTA that the monoprotonated form, HL^{2-}, was 5–6 orders of magnitude more reactive than the diprotonated form, H_2L^-. The triprotonated form, H_3L, is highly unreactive due to the formation of neutral zwitterionic form of the ligand (structure I). In the present work we have considered HL^{2-} and H_2L^- as reactive species. These reactive species form an intermediate, Gd(*HL), in the equilibrium step (see below).

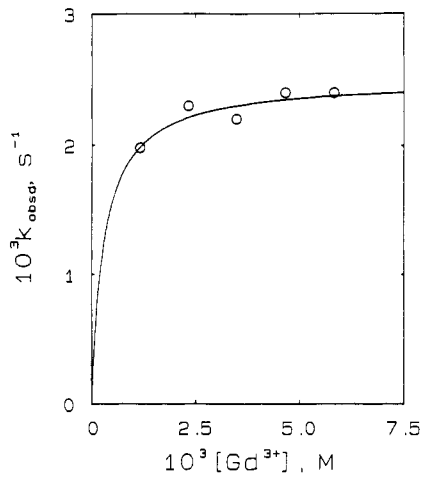
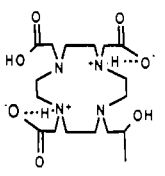


Figure 1. Dependence of pseudo-first-order rate constants on the concentration of excess reagent for the reaction of Gd^{3+} with HP-DO3A. The conditions used are [HP-DO3A] = 1.0 × 10^{-4} M and pH = 4.26. The solid curve is the calculated curve from the resolved values of the equilibrium (upper estimate) and rate constants and with the use of eq 5.

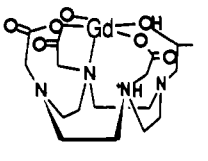
Table III. Parameters K^* (M^{-1}), Equilibrium Constant for the Formation of the Intermediate, k, Rate of the Reorganization of the Intermediate, and log $K_{Gd(^*HL)}$, the Stability Constant of Gd(*HL), for Macrocyclic Polyamino Carboxylate Complexes of Gd^{3+} [a]

ligand	pH	K^*, M^{-1}	k, s^{-1}	log$K_{Gd(^*HL)}$
NOTA[b]	4.85	521	0.0655	3.7
DO3A	4.28	(3.0 ± 1.0) × 10^3	(5.6 ± 0.1) × 10^{-3}	8.9
HP-DO3A	4.26	(3.0 ± 0.6) × 10^3	(2.6 ± 0.1) × 10^{-3}	9.0
DOTA[c]	4.48	(9.2 ± 0.9) × 10^3	(3.52 ± 0.02) × 10^{-3}	9.6
DO3MA	4.02	(1.2 ± 1.0) × 10^4	(1.4 ± 0.1) × 10^{-5}	10.7

[a] This work at 25.0 ± 0.1 °C and μ = 1.0 (NaCl). The values of K^* and k are calculated from a weighted nonlinear least-squares analysis of eq 5. A weighted linear least-squares analysis of the data with the use of eq 6 gave the same values of K^* and k. [b] Reference 9. The average of the data in the pH range 4.62–5.39 (N = 7) gave K^* = (850 ± 280) M^{-1} and log $K_{Gd(^*HL)}$ = 3.6 ± 0.1. [c] Reference 10. The average of the data in the pH range 4.48–5.67 (N = 6) gave K^* = (6860 ± 1390) M^{-1} and log $K_{Gd(^*HL)}$ = 8.7 ± 0.6.



structure I



structure II

The nature of this intermediate was confirmed by mixing equimolar unbuffered solutions of $GdCl_3$ and DO3A or HP-DO3A at a constant pH of 4.0. An instantaneous pH drop (~20%) was observed on mixing (eq 7) followed by a slow decrease (eq 8). The amount of protons released during the equilibrium step quali-

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$$Gd^{3+} + H_2L^- \rightleftarrows Gd(*HL) + H^+ \quad (7)$$

$$Gd(*HL) \rightarrow GdL + H^+ \quad (8)$$

tatively corresponded to the amount of H_2L^- and HL^{2-} (~20%). At this low pH, the calculated concentration of the H_2L^- form of the ligands DO3A and HP-DO3A is ~25%, thereby suggesting the nature of the intermediate. The concentration of HL^{2-} is very low. Consequently, it has not been included in eqs 7 and 8. In the intermediate, Gd(*HL), the proton is proposed to be on the ring nitrogen (structure **II**, where L = HP-DO3A) and the metal is coordinated with a nitrogen and oxygens.

The overall stability constant of the intermediate, Gd(*HL), defined by eq 9 can be calculated from the value of K^* at a pH, the ligand protonation constants, and with the use of eq 10. The

$$K_{Gd(*HL)} = [Gd(*HL)]/[Gd^{3+}][HL^{2-}] \quad (9)$$

$$K_{Gd(*HL)} = K^*(1 + K_2[H^+] + K_2K_3[H^+]^2 + K_2K_3K_4[H^+]^3) \quad (10)$$

calculated values of log $K_{Gd(*HL)}$ for the complexes of DO3A, HP-DO3A, and DO3MA are summarized in Table III along with the value of the constant of NOTA.[9] We have utilized the data of Desreux and co-workers[10] to calculate the constant of DOTA (Table III). In eq 10, K_2, K_3, and K_4 are the ligand protonation constants for the formation of the H_2L^-, H_3L, and H_4L^+ forms of the ligand.

The calculated value of log $K_{Gd(*HL)}$ for Gd(NOTA) (Table III) was 3.66, and the coordination of at least two carboxylate oxygens was suggested on the basis of comparison of the stability constant of the intermediate and the stability constant of glutarate complex of Gd^{3+}.[9] Similarly, Nyssen and Margerum[6] suggested the coordination of at least three carboxylate oxygens in the intermediate, La(*HCyDTA), on the basis of the calculated values of the equilibrium constant, i.e. $(0.8–1.0) \times 10^6$ M^{-1}. However, in the present work, the values of the constant (log $K_{Gd(*HL)}$) are in the range 8.9–10.7 (Table III). This suggests that the intermediate is coordinated to more than just three carboxylate oxygens of the ligand.

The stability constants of the protonated complexes of Eu^{3+}, Sm^{3+}, and Gd^{3+} with EDTA are 8.18, 8.18, and 9.81, respectively.[25] EDTA in Ln(HEDTA) was proposed as pentadentate.[25] With this knowledge, we propose that macrocyclic polyamino carboxylates (DO3A, HP-DO3A, DOTA, DO3MA) are coordinated to at least one nitrogen in addition to the carboxylate and alcoholic oxygens. The stability constant of the intermediate of the DO3MA reaction with Gd^{3+} is 63 times higher than the stability constant of the DO3A reaction intermediate. The enhanced stability of the DO3MA intermediate may be due to the increased basicity of the DO3MA nitrogens and the reduced conformational freedom of the DO3MA ligand due to methyl substitution. Due to electrostatic repulsion between Gd^{3+} and protonated nitrogen, the coordination of Gd^{3+} with the protonated nitrogen and other nitrogens in its close proximity is not possible. Hence, in structure **II** of the intermediate, Gd(*HL), Gd^{3+} is coordinated to the nitrogen which is trans to the protonated nitrogen.

The intermediate, Gd(*HL), is not a stable protonated form of the chelate, i.e. GdL(H), in which a proton is presumably on a carboxylate oxygen.[25,26] The stability constants of GdL(H) type species have been calculated from the stability constants of the chelates and the ligand and chelate protonation constants.[13,26]

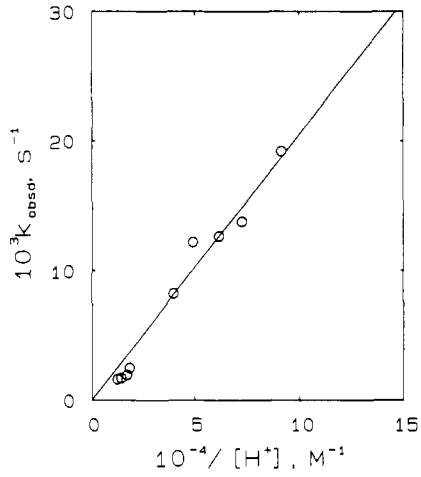

Figure 2. Effect of pH on the formation rates of Gd(HP-DO3A): Plot of k, the rate of reorganization of the intermediate, Gd(*HL), vs $1/[H^+]$.

The stability constant of GdL(H) (L is given in parentheses) complexes are 11.4 (DO3A), 14.2 (HP-DO3A), 16.0 (DOTA), and 14.2 (DO3MA). These values are 2–7 orders of magnitude higher than the stability constants of Gd(*HL) intermediates.

The information on solution-state structure and conformational analysis of the free ligands, DO3A, HP-DO3A, and DO3MA, is not available. However, the crystal structure studies of Gd(HP-DO3A)[17] showed that Gd^{3+} in the chelate is sandwiched between two planes, viz. the oxygen plane and the nitrogen plane. This is consistent with previous studies.[27,28] In the chelate Gd(HP-DO3A), the ligand is preorganized[29] and the metal lies 1.61 Å above the nitrogen plane and 0.75 Å below the oxygen plane. Preorganized structures in X-ray crystal structure studies of H_5DO3A^{2+} and H_2DOTA^{2-} were observed by us[17] and Reibenspies,[30] respectively. In these X-ray crystal structure studies it was demonstrated that the ligands are preorganized in the [3,3,3,3] conformation,[31] with all carboxylate oxygens on one side of the nitrogen plane and $-CH_2$ groups alternating regularly around the ring above and below the nitrogen plane. It is proposed that the metal ion, Gd^{3+}, in the intermediate is coordinated to oxygens and is in the oxygen plane of the preorganized ligand. Probably the nitrogen plane in the ligand is distorted so that at least one nitrogen is also coordinated to Gd^{3+}. In contrast Gd^{3+} was proposed to be outside of the cavity of the ligand CyDTA in the formation reactions of Ln(CyDTA).[6]

Specific Base-Assisted Formation of GdL. The value of the pseudo-first-order rate constants (k_{obsd}) and k, the rate of reorganization of the intermediate, increased with increasing pH (Table II) for DO3A, HP-DO3A, and DO3MA complexes in the pH range 3.6–5.0. This observation is consistent with the previously reported work in the case of NOTA[9] and DOTA[10] complexes of Gd^{3+}. A plot of log k_{obsd} as a function of pH was linear with a slope of 1.0 ($r^2 = 0.99$). The values of k were calculated from the values of K^* (Table III) and k_{obsd} (Table II) and with eq 5. The values of k were found to be inversely proportional to $[H^+]$ (Figure 2). An expression consistent with this functional dependence is given by eq 11, where $[L]_T$ is a sum of bound and various protonated forms of the ligand and k_{H_2O} and k_{OH} are water and hydroxide-assisted rates of reorganization of the intermediate, Gd(*HL).

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$$d[GdL]/dt = k_{obsd}[L]_T = (k_{H_2O} + k_{OH}[OH^-])[Gd(*HL)] \quad (11)$$

Equation 11 can be expressed as follows:

$$k_{obsd}([Gd(*HL)] + [HL^{2-}] + [H_2L^-] + [H_3L] + [H_4L^+]) = (k_{H_2O} + k_{OH}[OH^-])[Gd(*HL)] \quad (12)$$

Equation 12 can be converted in terms of Gd^{3+} and HL^{2-} by considering an equilibrium relation (eq 9) and various protonation constants of the ligand:

$$k_{obsd}\{(K_{Gd(*HL)}[Gd^{3+}][HL^{2-}]) + [HL^{2-}](1 + K_2[H^+] + K_2K_3[H^+]^2 + K_2K_3K_4[H^+]^3)\} = (k_{H_2O} + k_{OH}[OH^-])K_{Gd(*HL)}[Gd^{3+}][HL^{2-}]$$

$$k_{obsd}\{(K_{Gd(*HL)}[Gd^{3+}]) + (1 + K_2[H^+] + K_2K_3[H^+]^2 + K_2K_3K_4[H^+]^3)\} = (k_{H_2O} + k_{OH}[OH^-])K_{Gd(*HL)}[Gd^{3+}] \quad (13)$$

Rearranging eq 13, and substituting eq 10 into 13, leads to eq 14. The use of eq 5 leads to a simple equation for the rate of

$$k_{obsd}\{(1 + K^*[Gd^{3+}])/(K^*[Gd^{3+}])\} = k_{H_2O} + k_{OH}[OH^-] \quad (14)$$

reorganization, k, in terms of the concentration of $[OH^-]$ or $[H^+]$ and the dissociation constant of water, K_W.

$$k = k_{H_2O} + k_{OH}[OH^-] \quad (15)$$

$$k = k_{H_2O} + k_{OH}K_W/[H^+] \quad (16)$$

According to eq 16, a plot of k vs $1/[H^+]$ is expected to be a straight line (Figure 2). Consistent with the work of Brucher and Sherry,[9] no significant intercept was observed in the present work and the slope of the plot is the measure of the value of k_{OH}. We reanalyzed the kinetic data of Desreux and co-workers, and the calculated value of k_{OH} is given in Table IV. The hydrolysis equilibrium constant[32] of Gd^{3+} is −8.20. The percentage of $Gd(OH)^{2+}$ is very low in our working conditions. Consequently, the effect of the reactivity of $Gd(OH)^{2+}$ on the rates of the reactions has been neglected previously[6,9,10] and in this work.

Since the formation reactions are assisted by the specific base, hydroxide, it is expected that these reactions are general-base assisted. In the present work, the concentration of buffer is very low. No significant contribution from the base form of the buffer is expected. Larger concentrations of the buffer to study this effect are not possible due to a limitation of the measurement technique, which requires low buffer concentration. However, work in progress on the formation kinetics of Ce^{3+} complexes will demonstrate this effect.[33]

The effect of pH on the rate of the formation of GdL (where L is a macrocyclic polyamino carboxylate) can be expressed in terms of the reactivity difference of the mono- and diprotonated forms of the ligand. However, evidence of the formation of the intermediate, 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.

Correlation of k_{OH} with the First Protonation Constant of the Ligand. The relative rates of the hydroxide-assisted reorganization of the intermediate, Gd(*HL) (L = NOTA, DO3A, HP-DO3A, DOTA, and DO3MA), are inversely proportional to the basicity of nitrogen expressed as the first protonation constant of the ligand (log K_1). Figure 3 shows a good linear correlation (r^2 = 0.97) between the second-order rate of reorganization of the intermediate (log k_{OH}) and log K_1 (eq 17). An expected value

$$\log k_{OH} = -(1.53 \pm 0.16) \log K_1 + (25.3 \pm 2.0) \quad (17)$$

of the slope is −1.0 or more positive if the rate is controlled only by proton transfer. However, in the present work a more negative slope suggests the involvement of rigidity of the macrocyclic polyamino carboxylate in the rate of the reorganization of the intermediate.

Table IV. First Ligand Protonation Constant (log K_1) and Ligand Strain Energy ($E_{d,l}$, kcal/mol) of the Free Ligand, Specific-Base Assisted Rate Constants (k_{OH}, M^{-1} s^{-1}), and Activation Free Energy (ΔG^*, kcal/mol) for Reorganization of Intermediate Gd(*HL)[a]

ligand	log K_1	$E_{d,l}$, kcal/mol[b]	k_{OH}, M^{-1} s^{-1}	ΔG^*, kcal/mol
NOTA	11.61	41.1	$(7.1 \pm 1) \times 10^7$ [c]	6.71
DO3A	11.59	66.2	$(2.1 \pm 0.1) \times 10^7$	7.43
HP-DO3A	11.96		$(1.23 \pm 0.04) \times 10^7$	7.74
DOTA	12.06	93.8	$(0.59 \pm 0.02) \times 10^7$ [d]	8.18
DO3MA	13.38		$(7.2 \pm 0.3) \times 10^6$	10.77

[a] At 25 °C and μ = 1.0 (NaCl). [b] References 34 and 35. [c] Reference 9. [d] Reference 10.

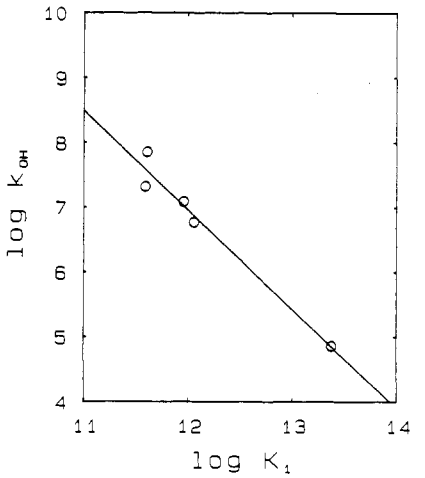

Figure 3. Correlation of log k_{OH} vs the first protonation constant (log K_1) of the deprotonated macrocyclic polyamino carboxylates.

Correlation of k_{OH} with the Ligand Strain Energy. Molecular mechanical calculations and molecular dynamic simulations have been used to explain differences in the stability constants of Gd^{3+} complexes of linear and macrocyclic polyamino carboxylates.[34,35] Total energy of the formation of the lanthanide complexes of polyamino carboxylates in vacuo ($E_{r,g}$) was described as a sum of ligand strain energy ($E_{d,l}$) and cation–ligand interaction energy (E_i). The ligand strain energy ($E_{d,l}$), a measure of the rigidity of ligand, was defined as the difference between the energy of the ligand in the complex ($E_{l,c}$) and the energy of the free ligand in its lowest energy conformer (E_l). A preorganized form of the ligand will be the most preferred form for complexation of lanthanides. Presumably the conformations of the ligand most useful for complexation are [3,3,3] for NOTA and [3,3,3,3] for DO3A, HP-DO3A, DOTA, and DO3MA. These conformations of the ligand are not necessarily the lowest-energy conformations. Energy differences between hydration of free and bound carboxylates and Gd^{3+} and the water–water interaction energy were

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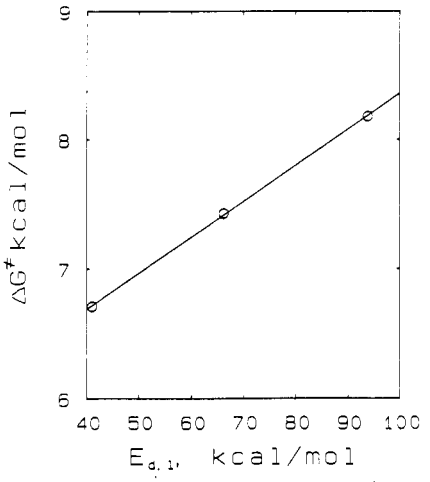

Figure 4. Correlation of activation free energy ($\Delta G^{\ddagger}$) for the reorganization of Gd(*HL) with the ligand strain energy, $E_{d,l}$.

also added to compute the energy of formation of the complex in aqueous solution. While the ligand-strain energy, cation–ligand interaction energy, and hydration energy describe the thermodynamics of complexation, it is proposed that the rate of reorganization of the intermediate, Gd(*HL), is controlled by the ligand-strain energy or the rigidity of the ligand. While these energy data are available for NOTA, DO3A, and DOTA, data for HP-DO3A and DO3MA are lacking. We have calculated the activation energy ($\Delta G^{\ddagger}$) for the reorganization of Gd(*HL) from the second-order rate of base-assisted reorganization of the intermediate by using the relationship of eq 18.[21] These are

$$k = (k_B T/h) \exp(-\Delta G^{\ddagger}/RT) \qquad (18)$$

compiled with the literature values of the ligand-strain energies, $E_{d,l}$, in Table IV. An excellent linear correlation ($r^2 = 0.999$) between $\Delta G^{\ddagger}$ and $E_{d,l}$ is shown in Figure 4. This linear correlation gives $\Delta G^{\ddagger} = 5.6$ kcal/mol for $E_{d,l} = 0.0$, which translates to a calculated second-order rate constant of 4.7×10^8 M^{-1} s^{-1}. This constant is in good agreement with the second-order rate constant (3×10^8 M^{-1} s^{-1}) for the formation of Gd(EDTA)$^-$.[7] EDTA is a linear and flexible ligand with minimum ligand strain energy. The plot in Figure 4 predicts a value of $E_{d,l}$ for DO3MA as >180 kcal/mol. This seems to be a "bit extreme"; however, further work is needed to demonstrate the fact.[38] This correlation suggests that the rate of the reorganization of the intermediate is controlled by the rigidity of the ligand also.

Comparison of the Rate of Formation of Macrocylic Polyamino Carboxylate Complexes of Gd^{3+} with Linear Polyamino Carboxylates. Formation of macrocyclic polyamino carboxylate complexes differs in two ways from the linear polyamino carboxylates such as EDTA:[7] (1) The rate of the reaction of lanthanides is faster for linear than for macrocyclic polyamino carboxylate ligands. Even the rigid linear polyamino carboxylate ligand, CyDTA,[6] reacts faster with lanthanides than with macrocyclic polyamino carboxylates, NOTA, DO3A, HP-DO3A, and DO3MA. (2) This work, together with previously reported work on the formation kinetics of Ln(CyDTA)$^-$, M(DOTA) (where M = transition, alkali, and alkaline earth metal ion), and Ln(NOTA) complexes, is consistent with the formation of monoprotonated chelates as intermediates.[6,7,14,33] The reactions of lanthanides with more flexible polyamino carboxylates such as EDTA did not show any evidence of the formation of such species, probably due to their fast reorganizational rates. Therefore, the rigidity of the polyamino carboxylate is an important factor which retards the deprotonation pathway enough to expose the formation of the protonated intermediates.

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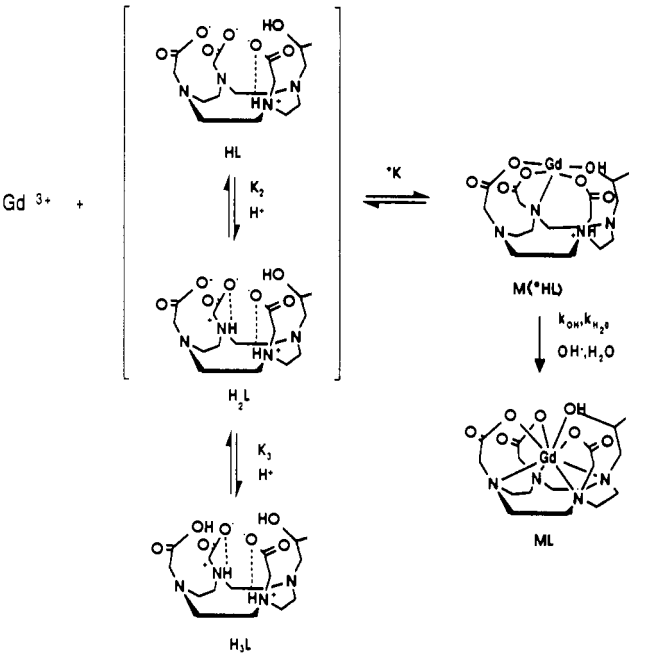
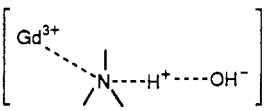
Scheme I



Proposed Mechanisms. The formation of the intermediate, Gd(*HL), its specific-base assisted reorganization, the linear dependence of k_{OH} on log K_1, and the ligand strain energy are consistent with the proposed mechanism (Scheme I). In this mechanism the metal first coordinates with carboxylate oxygens and one nitrogen in the equilibrium step. Electrostatic attraction favors coordination of Gd^{3+} with carboxylate oxygens. The reorganization of the intermediate to the final product is water- or hydroxide-assisted and rate is limited by proton transfer. The proton transfer from R_3–$^+$NH (where R = CH_2 from the ring and the arm of the ligand) to solvent has large unfavorable ΔpK_a and is not observed.[36,37] However the reaction between OH^- and R_3–$^+$NH should be favorable and relatively fast. We propose a transition state (structure **III**) in which transfer of a proton from



structure III

R_3–$^+$NH to hydroxide and Gd^{3+}–N bond formation are concerted. In the transition state it is proposed that as Gd^{3+} moves into the vicinity of the nitrogen, the proton departs. The crystal structure studies of $H_2(DOTA)^{2-}$ demonstrated[30] that the free ligand exists in a preorganized conformation for metal complexation which implies that the nitrogen lone pairs or attached protons should be directed into the cavity of the macrocycle. For a metal coordination with nitrogen and its deprotonation, nitrogen inversion probably occurs. This process requires significant rearrangement of the macrocyclic ring and energy and slows down the rate of the complexation reaction. The rate-determining step of the reaction, the rearrangement of the intermediate, appears to be proportional to the ligand strain energy, which we think indicates nitrogen inversion in the process. Nitrogen inversion has been proposed in the dissociation reactions of lanthanide complexes of linear and macrocyclic polyamino carboxylates,[8-10,16] including complexed NOTA and DOTA type ligands, in the deutrium-exchange reactions of NH_4^+ and base-catalyzed conversion of Cu(Tet a) (blue) to Cu(Tet a) (red).[39-41] Nuclear

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magnetic resonance studies of some EDTA, PDTA, BDTA, and CyDTA complexes have suggested nitrogen inversion on the NMR time scale.[42,43]

In the structure of the intermediate, Gd(*HL), we proposed the coordination of oxygens and at least one nitrogen. The formation of a second Gd–N chelate ring, assisted by proton transfer, appears to be the rate-determining step. A rate-determining proton transfer followed by a *fast* Gd–N chelate ring formation cannot account for the correlation between log k_{OH} vs log K_1; such a scenario would require a more positive slope than −1.0. The possibility of Gd–N bond formation in the rate-determining step, followed by the fast proton transfer, is a more remote possibility involving a "true intermediate" with penta-coordinated nitrogen. Although such intermediates and compounds with five-coordinated nitrogen *do* exist.[39,41,44,45] they have been extremely rare.

An alternate mechanism which does not invoke nitrogen inversion in the intermediate is the involvement of coordinated water or hydroxide, which assists the deprotonation and reorganization of the intermediate. The coordinated water or hydroxide is presumably more acidic than free water or hydroxide. In the present work no evidence was observed for a water-assisted reorganization of the intermediate (no intercept in Figure 2); consequently, there is no reasonable possibility of a coordinated water-assisted process. The possible role of coordinated hydroxide was considered but does not seem to be possible on the basis of the following: (1) The precursor (intermediate), Gd(*HL), is very similar to Gd(H.EDTA), the proton being on nitrogen, and somewhat similar to Gd(NTA). Formation of a hydroxo species was not observed in the case of Gd(H.EDTA),[25] and a hydrolysis constant (K_h) for Gd(NTA) was reported as −6.58.[20] (2) At pH 5.0, the concentration of Gd(NTA)(OH) is 100 times more than [OH^-]; however, the proton transfer to the coordinated hydroxide is 6.5 orders of magnitude less favorable than to free hydroxide. (3) Coordinated hydroxide is easily accessible to $R_3{-}^+NH$ in each of the reaction intermediates. On the basis of the difference in the first protonation constants of the ligands, the rates of the reactions should vary by a factor of 60 as it does not require any significant reorganization. Contrary to this, 3 orders of magnitude variation in the rates was observed (Table III).

Conclusions

(1) The rate of the formation of the gadolinium complexes of macrocyclic polyamino carboxylates is much slower than the rate of the formation of linear polyamino carboxylate complexes of Gd^{3+}. (2) Due to the greater rigidity and basicity of these macrocyclic polyamino carboxylate ligands, the formation of their lanthanide complexes is characterized by saturation kinetics caused by the formation and slow reorganization of a precursor complex (intermediate), Gd(*HL). (3) The dependence of log k_{OH} on log K_1 and the ligand-strain energy are suggestive of a concerted mechanism involving the proton transfer to OH^- and Gd–N bond formation.

Acknowledgment. We thank Professors Dale Margerum, A. Dean Sherry, and David Rorabacher for helpful discussions during this work.

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