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Dissociation Kinetics of Macrocyclic EDTA-bis(lactone) Complexes of Cerium(III) and Gadolinium(III)

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Dissociation Kinetics of Macrocyclic EDTA-bis(lactone) Complexes of Cerium(III) and Gadolinium(III)

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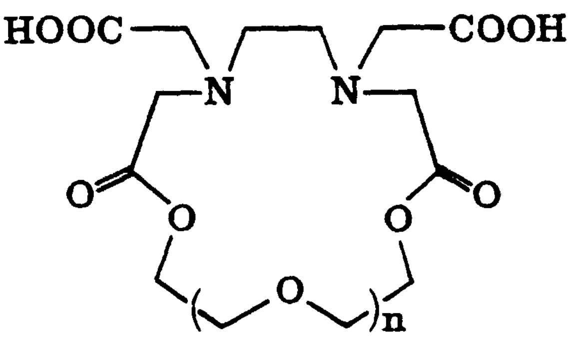
The dissociation kinetics of Ce(III) and Gd(III) complexes of macrocyclic EDTA-bis(lactone) have been studied in an aqueous solution using Cu(II) ions as the scavenger. The measurements were made at 25.0 ± 0.1°C in 0.10 M $NaClO_4$ solution. The rates of dissociation of these complexes have been found to be independent of $[Cu^{2+}]$. Dissociative and associative pathways may present reasonable processes for dissociation of the complexes. The rate decreases in the order $Ln(EDTA\text{-}EG)^- > Ln(EDTA\text{-}DEG)^- > Ln(EDTA\text{-}TEG)^-$. An increase in ring size from 12- to 18-cycle and the number of oxygen atoms between two amide nitrogens of the ligands lead to an enhanced kinetic inertia of the complexes. The results are compared with those of the analogous linear or macrocyclic ligand systems.

INTRODUCTION

The complexation properties of the macrocyclic polyoxa- and polyazapolycarboxylates, DTPA-bis(amide), NOTA (1,4,7-triazacyclononane-N,N′,N″-triacetic acid), DOTRA(1,5,9-triazacyclododecane-N,N′,N″-triacetic acid), DOTA (1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid), and PETA (1,4,8,12-tetraazacyclopentadecane-N,N′,N″,N‴-tetraacetic acid) have attracted considerable interest in recent years, because the structure, equilibrium, and kinetic behavior of their lanthanide complexes differ considerably from those of the analogous linear polyaminopolycarboxylates such as EDTA, TMDTA (triethylenedinitrilotetraacetic acid), and TMEDTA (tetramethylenedinitrilotetraacetic acid). Some of these macrocyclic ligands are also of practical importance, since their Ln^{3+} complexes may be used as contrasting agents in magnetic resonance imaging (MRI)[1,2] and lanthanide ion-selective reagents.[3,4] Several factors influence the rates and mechanisms of the dissociation reaction of Ln^{3+} complexes of macrocyclic polyazapolycarboxylates. The dissociation rates of Ce(DOTRA) and $Ce(PETA)^-$ complexes were found to be much faster than those of Ce(NOTA) and $Ce(DOTA)^-$[5]. The kinetic inertias are significantly affected by the cavity size and the chelate ring size. Kumar *et al.*[6] reported that the dissociation rate of Ln(DO3A) (DO3A = 1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid) is faster than that of Ln $(DOTA)^-$ and Ln(HP-DO3A) (HP-DO3A = 10-(hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic acid). They concluded that these kinetic behaviors resulted as a consequence of the difference in the number and the type of donor atoms and the number of chelate rings formed.[6]

Additionally, a study on the dissociation kinetics of Ce^{3+} and Gd^{3+} complexes of macrocyclic DTPA-bis(amide) ligands was also reported.[7] In this study, it was found that an increase in ring size of the DTPA-bis(amide) ligands led to an increase in kinetic inertia, reflecting the enhanced participation of the amide carbonyl oxygen in Ln^{3+} ion coordination.

We initiated the kinetic study to observe the ligand effects of the number of donor atoms and the cavity size of the macrocycle. We report herein the systematic dissociation kinetics of Ce^{3+} and Gd^{3+} complexes of EDTA-EG (1,4-bis(carboxymethyl)-6,11-dioxo-7,10-dioxa-1,4-diazacyclododecane), EDTA-DEG (1,4-bis(carboxymethyl)-6,14-dioxo-7,10,13-trioxa-1,4-diazacyclopentadecane) and EDTA-TEG (1,4-bis(carboxymethyl)-6,17-dioxo-7,10,13,16-tetraoxa-1,4-diazacyclooctadecane) (Figure 1).



n	Macrocycle
0	EDTA-EG
1	EDTA-DEG
2	EDTA-TEG

FIGURE 1 Structures of the macrocyclic EDTA-bis(lactone) ligands.

EXPERIMENTAL

Reagents and Solutions

The ligands EDTA-EG, EDTA-DEG and EDTA-TEG were synthesized and characterized by the published method.[8] The concentrations of the stock solution of the ligands were determined by titration against a standard $Cu(ClO_4)_2$ solution using murexide as an indicator. The stock solutions of Ce^{3+} and Gd^{3+} were prepared from $CeCl_3$ and Gd_2O_3 (Aldrich, 99.99%) and their concentrations were determined by titration with EDTA using xylenol orange as an indicator. All solutions were made in deionized water. Complex solutions were made by mixing appropriate amounts of lanthanide perchlorate with a slight excess of ligand. The concentration of the complex in the reaction mixtures was 5.0×10^{-5} M, while that of Cu^{2+} ion was constant at 5.0×10^{-4} M, or it was varied between 1.0×10^{-4} and 1.0×10^{-3} M. The buffer solutions were made by fixing the concentration of acetate ion and varying the concentration of acetic acid for the attainment of the desired pH values. The concentrations of sodium acetate buffer solution were varied between 5.0×10^{-3} and 7.5×10^{-2} M. The ionic strength was adjusted to 0.10 M with $NaClO_4$. All other chemicals used were of analytical grade and were used without further purification.

Measurements

The pH measurements of the solution were made by a Beckman Model Φ71 pH meter fitted with a combination electrode. The concentrations of hydrogen ion were calculated from the measured pH value by previously reported procedures.[9] The pH range studied was 4.09–5.22. Kinetic measurements were made with the use of a Hi-Tech stopped-flow spectrophotometer interfaced with a Scientific data acquisition system. The temperature of the reaction mixture was maintained at 25.0 ± 0.1°C using a Lauda RM 6 circulatory water bath. Since the lanthanide complexes did not show appreciable absorption in the UV or visible region, Cu^{2+} was used as the scavenger of free ligand. The progress of the dissociation reactions of LnL^+ was monitored by following the absorbance increase at 290 nm for CuL. Pseudo-first-order rate constants (k_{obs}, s^{-1}) were calculated by using a first-order kinetic model referring the absorbance *versus* time data.[10]

RESULTS AND DISCUSSION

Since the stability constants of copper(II) EDTA-bis(lactone) complexes are much greater than those of lanthanide complexes,[8] the exchange reaction is complete in the presence of a tenfold excess of Cu^{2+} ions:

$$LnL^+ + Cu^{2+} \rightarrow CuL + Ln^{3+} \qquad (1)$$

where L is H_2EDTA-EG, H_2EDTA-DEG and H_2EDTA-TEG ligands, respectively. The experimental data show excellent pseudo-first-order reaction rates. The concentrations of Cu^{2+} ion were varied by a factor of 10, and the observed rate constant (k_{obs}) values were within 5% of the average value of k_{obs} at a given pH. The similar independence of Cu^{2+} concentration in the dissociation kinetics of lanthanide complexes has been observed by other workers.[11–13] The dependence of k_{obs} on the concentration of acetate ion is given in Table I at different concentrations of hydrogen ion. The standard deviations were in the range of 1–5%. In each case, the data fit the straight lines with measurable non-zero intercepts. This confirms that the exchange reaction proceeded *via* both acetate-independent and acetate-dependent pathways. Thus, the observed rate constants can be expressed as:

$$k_{obs} = k_d + k_{OAc}[OAc^-] \qquad (2)$$

where k_d represents spontaneous dissociation of the complexes and k_{OAc} reflects the acetate-assisted pathway. Both k_d and k_{OAc} are also functions of acidity, $[H^+]$. The dependences of k_d and k_{OAc} on the concentration of H^+ ion are a quadratic expression for the Gd^{3+} complex and so a quadratic and linear expression for the Ce^{3+}

TABLE I Pseudo-first-order rate constants (10^2 k_{obs}, S^{-1}) for the dissociation of Gd(III)EDTA-bis(lactone) complexes[a]

Ligand	10^2[OAc] (M)	10^5 [H^+] (M)						
		0.780	1.675	2.795	5.129	7.456	8.912	10.498
EDTA-EG	0.5	0.40	0.68	1.17	2.60	4.30	5.60	7.40
	1.0	0.45	0.79	1.35	2.90	4.80	6.30	8.40
	2.5	0.60	1.12	1.87	4.00	6.50	8.20	10.9
	5.0	0.85	1.68	2.82	5.70	9.20	11.5	15.6
	7.5	1.10	2.24	3.72	7.40	12.1	15.3	20.0
EDTA-DEG	0.5	0.39	0.62	1.08	2.20	3.95	5.20	6.60
	1.0	0.44	0.74	1.20	2.60	4.40	5.90	7.60
	2.5	0.56	1.05	1.74	3.50	6.10	7.90	10.1
	5.0	0.79	1.50	2.46	5.20	8.70	11.3	14.4
	7.5	1.05	1.95	3.24	6.80	11.1	14.4	18.5
EDTA-TEG	0.5	0.21	0.42	0.77	1.79	3.22	4.31	5.68
	1.0	0.23	0.50	0.92	2.01	3.65	4.80	6.40
	2.5	0.32	0.72	1.34	2.80	4.97	6.50	8.50
	5.0	0.48	1.09	2.02	4.10	7.10	9.30	12.0
	7.5	0.63	1.45	2.68	5.33	9.20	12.0	15.5

[a] At 25.0 ± 0.1°C, I = 0.10M ($NaClO_4$), [complex] = 5.0×10^{-5}M and [Cu^{2+}] = 5.0×10^{-4}M.

complex, as shown in Table I and Figure 2. Based on these results, the overall rate of the exchange reactions can be expressed as:

$$\text{Rate} = k_1[\text{LnL}^+] + k_2[\text{LnL}^+][\text{H}^+] + k_3[\text{LnL}^+][\text{H}^+]^2 + k_4[\text{LnL}^+][\text{OAc}^-] + k_5[\text{LnL}^+][\text{OAc}^-][\text{H}^+] + k_6[\text{LnL}^+][\text{OAc}^-][\text{H}^+]^2 \quad (3)$$

where k_4 values of Ce^{3+} complexes are slightly negative, which indicates that the acid-independent mode of the acetate-assisted pathway makes practically no contribution to the exchange reaction. Values of the specific rate constants, k_n ($n = 1 - 6$), calculated from a least square polynomial fitting program, are listed in Table II. The reaction between Ln^{3+} complexes and Cu^{2+} ion proceeds by reaction pathways that are similar to those reported in the displacement of Ln^{3+} ions in their polyoxa- and polyaminopolycarboxylate complexes.[7,14] The increase in the dissociation rate of the macrocyclic EDTA-bis(lactone) complexes for the H^+ ion at the dissociative pathway was interpreted by the formation of small amounts of the mono- and diprotonated complexes. In the pH range of 4.09–5.22 the diprotonated species of three ligands represents 2.3–41.6%. It seems that the diprotonated intermediate, LnH_2L, involves coordination with both one of the amine groups and one of the carboxylate groups of the EDTA-bis(lactone) ligand to the Ln^{3+} ion. The rate-determining step may involve the rupture of the Ln-N bond followed by the formation of the intermediate. The EDTA-bis(lactone) ligands liberated on the comparatively slow dissociation of the complexes interact immediately with the excess Cu^{2+} ion to yield Cu(EDTA)-bis(lactone). The enhanced rates in the presence of higher acetate buffer concentration for the associative pathway may be attributed to the acetate ion complexation. If an acetate complex, LnLOAc is present, it is more sensitive than a binary LnL^+ complex to attack by the hydrogen ions.

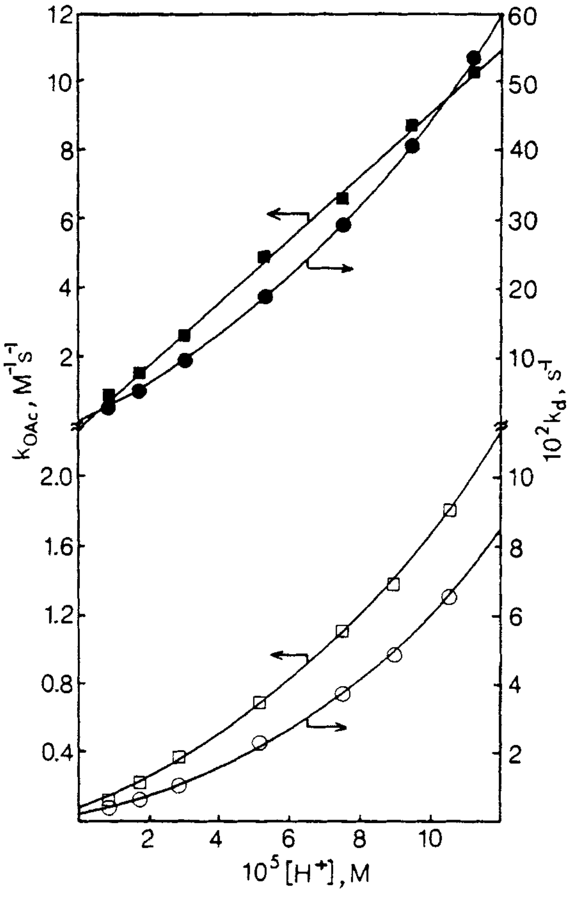


FIGURE 2 Plots of k_d and k_{OAc} *versus* $[H^+]$ for the dissociation kinetics of $Ce(EDTA\text{-}EG)^+$ (■,●) and $Gd(EDTA\text{-}EG)^+$ (□,○) ([complex] = 5.0×10^{-5}M, $[Cu^{2+}] = 5.0 \times 10^{-4}$ M, I = 0.10 M ($NaClO_4$), T = 25 ± 0.1°C).

The ligand effect on the rate constants for the dissociation reactions of Ln(III) EDTA-bis(lactone) complexes can be observed by comparing the values in Table II with other linear and macrocyclic polyaminopolycarboxylates. The observed kinetic trends in the series of macrocyclic EDTA-bis(lactone) ligands by changing from Ce^{3+} to Gd^{3+} can be explained in terms of the thermodynamic stability of these complexes with decreasing ionic size or increasing charge density of the Ln^{3+} ions. The comparisons of the dissociation rate constants of Ln(III) EDTA-bis(lactone) complexes indicate that the rates of the

TABLE II Rate constants for dissociation reactions of lanthanide complexes of linear and macrocyclic polyaminopolycarboxylates at 25.0 ± 0.1°C and I = 0.10M ($NaClO_4$)

Complex	k_1 (s^{-1})	k_2 ($M^{-1}s^{-1}$)	k_3 ($M^{-2}s^{-1}$)	k_4 ($M^{-1}s^{-1}$)	k_5 ($M^{-2}s^{-1}$)	k_6 ($M^{-3}s^{-1}$)	Ref.
$Ce(EDTA\text{-}EG)^+$	1.60×10^{-2}	1.94×10^{3}	2.38×10^{7}	a	9.30×10^{4}	a	
$Ce(EDTA\text{-}DEG)^+$	1.41×10^{-2}	1.78×10^{3}	1.95×10^{7}	a	8.95×10^{4}	a	
$Ce(EDTA\text{-}TEG)^+$	5.98×10^{-3}	1.54×10^{3}	1.50×10^{7}	a	8.66×10^{4}	a	
$Gd(EDTA\text{-}EG)^+$	1.83×10^{-3}	1.78×10^{2}	3.98×10^{6}	4.62×10^{-2}	8.73×10^{3}	7.42×10^{7}	
$Gd(EDTA\text{-}DEG)^+$	1.68×10^{-3}	1.69×10^{2}	3.57×10^{6}	2.95×10^{-2}	8.12×10^{3}	7.30×10^{7}	
$Gd(EDTA\text{-}TEG)^+$	7.13×10^{-4}	1.10×10^{2}	3.41×10^{6}	1.51×10^{-2}	6.73×10^{3}	6.15×10^{7}	
$Ce(EDTA)^-$	a	1.38×10^{3}	a	a	a	a	17
Ce(DO3A)	1.80×10^{-3}	1.12×10^{-1}	a	a	a	a	6
$Ce(DOTA)^-$	a	8.0×10^{-4}	2.0×10^{-3}	a	a	a	18
Gd(DTPA-EAM)	3.04×10^{-5}	1.24×10^{-1}	1.31×10^{5}	a	a	a	7
Gd(DTPA-PenAM)	1.91×10^{-5}	1.50×10^{-2}	1.17×10^{5}	a	a	a	7
$Eu(K21DA)^+$	1.76×10^{-3}	3.11×10^{1}	a	8.09×10^{-2}	a	a	11
$Eu(K22DA)^+$	4.31×10^{-4}	5.70×10^{-1}	a	a	a	a	12

[a] Not observed.

dissociative and associative pathways decrease in the other $Ln(EDTA\text{-}EG)^+ > Ln(EDTA\text{-}DEG)^+ > Ln(EDTA\text{-}TEG)^+$. Both rate constants are significantly affected by the ring cavity size and the number of oxygen atoms between two amide nitrogens. An increase in ring cavity size from 12 (EDTA-EG) to 18 (EDTA-TEG) leads to an increase in kinetic inertia, because the 15- and 18-membered ring macrocycles (EDTA-DEG and EDTA-TEG) form relatively more stable complexes than does the 12-membered one (EDTA-EG). It indicates that the larger macrocycles are normally more flexible for a suitable match of cavity ring size of the ligand with the Ln^{3+} ion. The acid-catalyzed rate constant of the dissociative pathway for $Ce(EDTA\text{-}EG)^+$ is either similar to or only twice larger in magnitude than that of $Ce(EDTA)^-$, even though the stability constant of $Ce(EDTA\text{-}EG)^+$ ($\log\beta = 5.58$) is much smaller than that of $Ce(EDTA)^-$ ($\log\beta = 15.94$).[8,15] This fact may be attributed to the remarkable rigidity of cyclic dioxadiaza ring of EDTA-EG compared to flexibility of linear EDTA. Meanwhile, the acid-catalyzed rate constant of $Ce(EDTA\text{-}EG)^+$ is about four or six orders of magnitude larger than those of Ce(DO3A) and $Ce(DOTA)^-$, although EDTA-EG has the same ring cavity size (12 cycle) as DO3A and DOTA. This is presumably due to the decrease of thermodynamic stability by the decrease in nitrogen donor basicity, the difference in the type of cyclic ring donor atoms (dioxadiaza- *versus* tetraaza-ring) and the number of carboxylic acid pendent arms of ligands. The acid-catalyzed rates of $Gd(EDTA\text{-}DEG)^+$ and $Gd(EDTA\text{-}TEG)^+$ dissociate about three to four orders of magnitude faster than those of DTPA-EAM (1,4,7-tris(carboxymethyl)-9,14-dioxo-1,4,7,10,13-pentaazacyclopentadecane) and DTPA-PenAM (1,4,7-tris(carboxymethyl)-9,17-dioxo-1,4,7,10,16-pentaazacyclooctadecane) complexes of Gd^{3+}, despite the same ring cavity size (15 and 18 cycles). This may be explained by the decrease of the number of nitrogen donor atoms and carboxylic acid pendent arms compared to DTPA-DEG and DTPA-TEG complexes, in which the amide carboxyl oxygen of the DTPA-bis(amide) ligands are coordinated to Gd^{3+} ion, resulting in the increase of the thermodynamic stability ($\log\beta = 11.15$ and 15.94).[16] On the other hand, the acid-catalyzed rate constants of $Gd(EDTA\text{-}DEG)^+$ and $Gd(EDTA\text{-}TEG)^+$ are faster than those of $Eu(K21DA)^+$ and $Eu(K22DA)^+$ (K21DA = 1,7-diaza-4,10,13-trioxacyclopentadecane-N,N'-diacetic acid and K22DA = 1,10-diaza-4,7,13,16-tetraoxacyclooctadecane-N,N'-diacetic acid). This indicates that, at least for 15- and 18-membered macrocycles, the decrease in kinetic inertias of EDTA-DEG and EDTA-TEG complexes is not probably caused by the position of the nitrogen atoms and the corresponding carboxylic acid pendent arms, but by the decrease of the basicity of the nitrogen donor by the strong electron-withdrawing ability of the carbonyl group of EDTA-bis(lactone) ligands.

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