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Dissociation Kinetics of 1,5,9-Triazacyclododecane-1,5,9-triacetate and 1,4,8,12-Tetraazacyclopentadecane-1,4,8,12-tetraacetate Complexes of Cerium(III)

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Synopsis. The dissociation kinetics of DOTRA$=$H$_3$dotra (1,5,9-triazacyclododecane-1,5,9-triacetic acid) and PETA$=$H$_4$peta (1,4,8,12-tetraazacyclopentadecane-1,4,8,12-tetraacetic acid) complexes of Ce(III) ion have been studied in an aqueous solution of 0.1 M (NaClO$_4$) at 25.0±0.1°C using Cu(II) ions as a scavenger. The dissociation rate constant for the acid-catalyzed pathway decreases in the order, $[\mathrm{Ce(peta)}]^- > [\mathrm{Ce(dotra)}] > [\mathrm{Ce(teta)}]^- > [\mathrm{Ce(nota)}] > [\mathrm{Ce(dota)}]^-$ according to the present and literature data. The rate constant is significantly affected by internal cavity and chelate ring sizes.

Recently, there has been growing interest in the lanthanide complexes with macrocyclic polyaza polycarboxylates, NOTA$=$H$_3$nota (1,4,7-triazacyclononane-1,4,7-triacetic acid), DOTA$=$H$_4$dota (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), and TETA$=$H$_4$teta (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid) because of their special use as aqueous NMR shift reagents,[1,2] lanthanide ion selective reagents,[3,4] and magnetic resonance imaging (MRI) contrast agents.[5,6] Kinetic behavior of these macrocyclic complexes differs considerably from that of analogous linear polyamine polycarboxylates such as EDTA$=$H$_4$edta, TMDTA$=$H$_4$tmdta (trimethylenedinitriloteraacetic acid), and TTHA$=$H$_6$ttha (triethylenetetraminehexaacetic acid) because of remarkable rigidity of macrocyclic aza rings compared with their flexible linear analogues. Brucher et al.[7,8] reported that the dissociation rate of $[\mathrm{Ce(dota)}]^-$ is much slower than that of [Ce(nota)]. This probably reflects the thermodynamic stability conferred by the rigidity of the tetraaza (dota) vs. the triaza ring (nota) cycle. Additional study on the dissociation kinetics of the lanthanide complexes with teta were also reported.[9] In this study, although the difference in thermodynamic stability between [Ln(nota)] and $[\mathrm{Ln(teta)}]^-$ is not very significant, [Ln(nota)] dissociates more slowly than $[\mathrm{Ln(teta)}]^-$. This is likely a consequence of the destabilizing effect of the 6-membered N–Ln–N chelate ring by the trimethylenediamine group of the teta ligand.

Since the kinetic properties of the lanthanide complexes have been shown to be dependent upon the ligand topology such as the cavity and chelate ring sizes of the macrocyclic ligands, we have studied the dissociation kinetics of Ce(III) complexes with DOTRA$=$H$_3$dotra (1,5,9-triazacyclododecane-1,5,9-triacetic acid) (**1**) and PETA$=$H$_4$peta (1,4,8,12-tetraazacyclopentadecane-1,4,8,12-tetraacetic acid) (**2**) (Chart 1).

Experimental

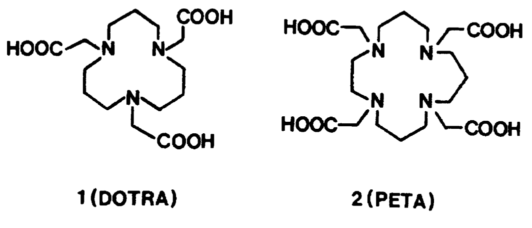
Reagents and Solutions. **1** and **2** ligands were synthesized and characterized by published method.[10,11] The concentrations of **1** and **2** stock solutions were determined by titration against a standard Cu(ClO$_4$)$_2$ solution using murexide as an indicator. Stock solution of Ce^{3+} was prepared from CeCl$_3$ (Aldrich, 99.9%) and its concentration was determined by titration with EDTA using Xylenol Orange as an indicator. The stock solutions of complexes were prepared by mixing equimolar amounts of Ce(ClO$_4$)$_3$ and ligands. The complex concentration in the reaction mixtures was 5.0×10^{-5} M (M$=$mol dm^{-3}). The buffer solutions were made by using 0.01 M [OAc$^-$] and varying the amount of [HOAc] necessary for attainment of the desired pH. The ionic strength was adjusted to 0.1 M with NaClO$_4$. All chemicals used were of analytical grade and were used without further purification. Distilled water was used for all solutions.

Measurements. The pH measurements were made using a Beckman Model ϕ71 pH meter fitted with a combination electrode. The hydrogen ion concentrations were established from the measured pH value by procedures previously reported.[12] Kinetic measurements were carried out using a UVIDEC-610 spectrophotometer at 25.0±0.1°C with the use of a Lauda RM 6 circulatory water bath. Since the [Ce(dotra)] and $[\mathrm{Ce(peta)}]^-$ complexes do not show appreciable absorption in the UV or visible region, Cu^{2+} was used as a scavenger of free ligand and the reaction kinetics was followed by monitoring the growth in absorbance due to the formation of copper complex at 260 nm.

Results

Since the thermodynamic stabilities of $[\mathrm{Cu(dotra)}]^-$ ($\log K=18.7$) and $[\mathrm{Cu(peta)}]^{2-}$ ($\log K=21.1$) are significantly higher than those of corresponding Ce(III) complexes ($\log K=11.9$ and 12.8),[10,13] the displacement of Ce^{3+} ion from the Ce(III) complexes is complete in the presence of excess Cu^{2+} ions

$$\mathrm{CeL} + \mathrm{Cu}^{2+} \longrightarrow \mathrm{CuL} + \mathrm{Ce}^{3+} \tag{1}$$



1 (DOTRA) **2 (PETA)**

Chart 1.

where L is H_2dota^- and H_3peta^- ligands. In the pH range 4.1—5.2, $[Ce(H_2dotra)]^{2+}$ and $[Ce(H_3peta)]^{2+}$ are the predominant complex species in solution. The experimental data show excellent pseudo-first-order reaction rates. The reactions were followed up to 3—5 half-lives. The observed rate constants (k_{obsd}) were obtained from the absorbance vs. time data using a first-order kinetic model.[14]

Ligand 1. The observed rate constant, k_{obsd} was found to be independent of acetate ion concentration. The dependence of k_{obsd} on the $[Cu^{2+}]$ is plotted in Fig. 1 at different pH values. The standard deviations were in the range 1—5%. In each case, the data fit straight lines with measurable non-zero intercepts, which confirm the exchange reaction as proceeding via both $[Cu^{2+}]$-independent and $[Cu^{2+}]$-dependent pathways. The observed rate constants can therefore be expressed as

$$k_{obsd} = k_d + k_{Cu}[Cu^{2+}] \tag{2}$$

where k_d and k_{Cu} are functions of the acidity, $[H^+]$. Figure 2 shows that k_d is proportional to $[H^+]$ while k_{Cu} is proportional to $[H^+]^{-1}$. Based on these results, the overall rate of reaction can be expressed as

$$\begin{aligned}-d[CeL]/dt &= k_1[CeL] + k_2[CeL][H^+] \\ &+k_3[CeL][Cu^{2+}] + k_4[CeL][Cu^{2+}][H^+]^{-1}\end{aligned} \tag{3}$$

Values of the specific rate constants, k_n ($n = 1$—4), calculated from a weighted least-squares program, are listed in Table 1.

Ligand 2 The observed rate constant, k_{obsd} was found to be independent of Cu^{2+} and acetate ion concentrations. The dependence of k_{obsd} on the $[H^+]$ is shown in Fig. 3. A linear least-squares fit to this plot had a non-zero intercept which is consistent with the exchange reaction proceeding via both acid-independent and acid-catalyzed pathways. Thus, the observed rate constants can be expressed as

$$k_{obsd} = k_d + k_H[H^+] \tag{4}$$

The rate constants, k_d and k_H, calculated from a weighted least-squares program, are listed in Table 1.

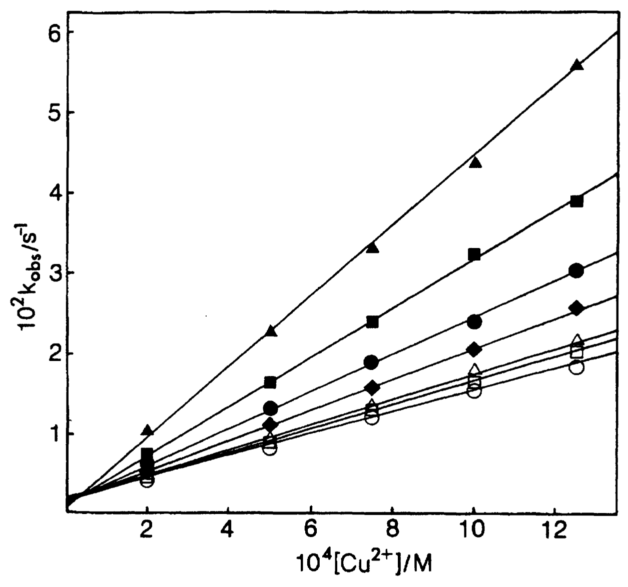


Fig. 1. Plots of k_{obsd} vs. $[Cu^{2+}]$ for the dissociation kinetics of [Ce(dotra)] at different pH values ([Ce(dotra)] = 5.0×10^{-5} M, $[OAc^-]$ = 0.01 M, I = 0.1 M ($NaClO_4$), T = 25.0±0.1°C; pH: ○, 4.06; □, 4.16; △, 4.25; ◆, 4.45; ●, 4.63; ■, 4.82; ▲, 5.04).

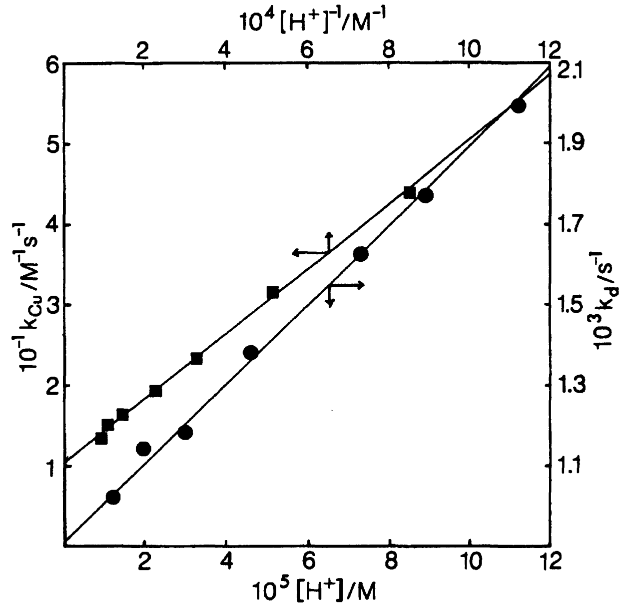


Fig. 2. Plots of k_d vs. $[H^+]$ and k_{Cu} vs. $[H^+]^{-1}$ for the dissociation kinetics of [Ce(dotra)] ([Ce(dotra)] = 5.0×10^{-5} M, $[Cu^{2+}]$ = 2.0—12.5×10^{-4} M, $[OAc^-]$ = 0.01 M, I = 0.1 M ($NaClO_4$), T = 25.0±0.1°C).

Discussion

The reaction between [Ce(dotra)] complex and Cu^{2+} ions proceeds by reaction pathway that are similar to those reported for the exchange of lanthanide ions in their $[Ln(teta)]^-$ complexes.[9] Both dissociative pathway, which obviously shows an acid-independent and an acid-catalyzed contribution, and associative pathways take place. The first and the second terms in Eq. 3 are responsible for the dissociative pathway of the $[Cu^{2+}]$-independent mode. The rate-determining step involves the loss of Ce^{3+} ion from the complex and the free ligand released reacts rapidly with Cu^{2+}. Equation 3 also represents the associative pathway of the $[Cu^{2+}]$-dependent mode which is composed of the direct attack route of Cu^{2+} on [Ce(dotra)] and the $[H^+]^{-1}$ dependence and also of the direct attack route of Cu^{2+} on CeL with no $[H^+]$ dependence. The $[H^+]^{-1}$ behavior could be explained by the existence of the attack of hydrolyzed copper species ($CuOH^+$) on [Ce(dotra)], even though investigated pH is not higher. Thus, k_{CuOH^+} is obtained by the expression $k_4 = k_{CuOH^+}\beta_{CuOH^+}$ where β_{CuOH^+}

Table 1. Rate Constants for Dissociation Reactions of Ce(III) Complexes of Polyaza Polycarboxylates at 25.0±0.1°C and $I=0.1$ M ($NaClO_4$)

Complexes	k_1/s^{-1}	$k_2/M^{-1}s^{-1}$	$k_3/M^{-1}s^{-1}$	$k_{CuOH^+}/M^{-1}s^{-1}$
[Ce(nota)]$^{b)}$	$(2.5\pm0.3)\times10^{-5}$	$(4.3\pm0.5)\times10^{-2}$	a)	a)
[Ce(dotra)]	$(9.16\pm0.17)\times10^{-4}$	9.56 ± 0.26	$(1.05\pm0.06)\times10^{1}$	$(1.94\pm0.07)\times10^{4}$
[Ce(dota)]$^{-}$ $^{c)}$	a)	$(8.0\pm2.0)\times10^{-4}$	a)	a)
[Ce(teta)]$^{-}$ $^{d)}$	$(9.13\pm0.12)\times10^{-4}$	2.29 ± 0.19	3.19 ± 0.10	$(1.36\pm0.14)\times10^{4}$
[Ce(peta)]$^{-}$	$(1.74\pm0.10)\times10^{-2}$	$(4.35\pm0.14)\times10^{1}$	a)	a)

a) Not observed. b) Ref. 8. c) Ref. 7; a second-order dependence in [H^+] with a third-order rate constant $(2.0\pm0.5)\times10^{-3}$ $M^{-2}s^{-1}$ was also observed. d) Ref. 9.

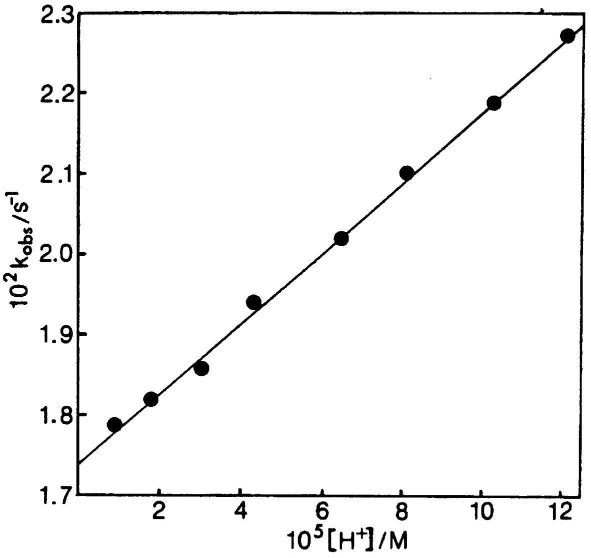


Fig. 3. Plots of k_{obsd} vs. [H^+] for the dissociation kinetics of [Ce(peta)]$^-$ ([Ce(peta)]$^-=5.0\times10^{-5}$ M, [Cu^{2+}]$=1.0\times10^{-3}$ M, [OAc^-]$=0.01$ M, $I=0.1$ M ($NaClO_4$), $T=25.0\pm0.1$°C).

($=K_{CuOH^+}K_w$) is a stability constant (i.e., 2.0×10^{-8}).[9]

Turning now to ligand **2** with more donor atoms, the dissociation of [Ce(peta)]$^-$ complex follows a mechanism similar to that of the dissociation of other lanthanide polyaza and polyamine polycarboxylate complexes.[15,16] The contribution of the Cu^{2+}-dependent pathway in [Ce(peta)]$^-$ is not shown in contrast to [Ce(dotra)] complex. In these mechanisms, the Ce-carboxylate bonds are rapidly formed and broken, allowing attachment of H^+ or Cu^{2+} to dissociated carboxylate. Presumably, the slow step involves the rupture of a Ce–N bond subsequent to the formation of a protonated CeLH or a ternary CeLCu intermediate.

A comparison of the dissociation rate constants of Ce(III) polyaza polycarboxylate complexes in Table 1 indicates that the acid-catalyzed dissociation rates decrease in the order [Ce(peta)]$^-$ > [Ce(dotra)] > [Ce(teta)]$^-$ > [Ce(nota)] > [Ce(dota)]$^-$. Both rate constants are significantly affected by internal cavity and chelate ring sizes. The acid-catalyzed rate constant of [Ce(nota)] was found to be about fifty times larger than that for the [Ce(dota)]$^-$ complex. An increase in ring size from 9 (nota) to 12 (dota) leads to an increase in kinetic inertness because of remarkable rigidity of the tetraaza (dota) compared with the triaza (nota) macrocycles. However, [Ce(dotra)] dissociates about 10^2 times much faster then [Ce(nota)], even though **1** has an increased internal cavity ring size (12-membered cycle) compared with nota. This fact may be attributed to the destabilizing effect of the six-membered N–Ce–N chelate rings involving the three triethylenediamine groups of **1**. This conformation may allow easier dissociation of one of the macrocyclic nitrogens from the Ce^{3+} ion. A similar argument has been used to explain the dissociation rate of [Ce(teta)]$^-$ being much faster than [Ce(dota)]$^-$.[9] Meanwhile, although **1** has the same ring size as dota, the acid-catalyzed rate constant of [Ce(dotra)] is about four orders of magnitude larger than that of [Ce(dota)]$^-$. This may be interpreted as reflecting the thermodynamic stability by the decrease of donor atoms (N and O) and rigidity of the triaza ring (**1**) vs. the tetraaza ring (dota) cycle. On the other hand, the acid-catalyzed rate constant for [Ce(peta)]$^-$ is about twenty times larger than that of [Ce(teta)]$^-$, even though **2** has an increased internal cavity ring size (15-membered cycle) compared with teta (14-membered cycle). This probably reflects the thermodynamic stability by destabilizing effect of two trimethylene (teta) vs. three trimethylene chelate rings (**2**).

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