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Entropy-Controlled Solvolytic Dissociation Kinetics of Lanthanide(III) Complexes with Polyaminocarboxylates in Aqueous Solutions

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The factors involved in the formation of an inert complex in terms of solvolysis reaction have been studied for lanthanide(III)−acyclic polyaminocarboxylate complexes, as the basis for kinetically controlled selectivity used in analytical methodologies such as HPLC and HPCE. The rate constants for solvolysis and acid-assisted dissociation processes of the lanthanide complexes were determined in a batch system through metal- and ligand-exchange reactions. The reagents used were 8-amino-2-[(2-amino-5-methylphenoxy)methyl]-6-methoxyquinoline-*N*,*N*,*N*′,*N*′-tetraacetic acid (Quin2) and *O*,*O*′-bis(2-aminophenyl)ethylene glycol-*N*,*N*,*N*′,*N*′-tetraacetic acid (BAPTA) as octadentate ligands and *trans*-1,2-diaminocyclohexane-*N*,*N*,*N*′,*N*′-tetraacetic acid (CyDTA) as a hexadentate ligand. It has been found that the rate constants for solvolysis vary from 5.7×10^{-3} s^{-1} (La^{3+}) to 1.7×10^{-6} s^{-1} (Lu^{3+}) depending on the ionic radii of Ln(III) ions for the Quin2 complexes, while no such monotonic dependence was observed for the BAPTA complexes. Among the parameters of activation, it is worth noting that there is a considerably large negative entropy of activation, of up to -250 J mol^{-1} K^{-1}, and it is this which is responsible for the inertness of the Ln−polyaminocarboxylate complexes. Our data suggest that multiple ligation of the ligand in favor of the large coordination number of Ln(III) ions is of key importance for formation of the negative entropy of activation, in addition to the basicity of the ligand which also plays a significant role in the slow dissociation kinetics of the Ln(III) complexes.

Introduction

The formation and dissociation kinetics of lanthanide ion (Ln(III))−polyaminocarboxylate complexes have attracted much attention because of their use in magnetic resonance imaging (MRI),[1] radioimmunotherapy,[2] time-resolved fluorescence immunoassay,[3] and ion-exchange chromatography.[4] The rate of the formation reaction for Ln(III)−macrocyclic polyaminocarboxylate complexes is very slow[5−8] because the strain on the ligand at the rate determination step causes a high energy barrier which retards the deprotonation process of the protonated intermediate.[9] For acyclic polyaminocarboxylate complexes, the rate of formation is much faster than the rates of those which are macrocyclic since the acyclic ligands have more flexible molecular frames. In dissociation reactions, the reaction paths are generally bifurcated into solvolysis and proton-assisted decomposition reactions. The latter is of particular interest to the development of MRI contrast reagents under the given physiological conditions.[10] It has been reported that the rigidity and the basicity of macrocyclic ligands govern inertness in the proton-assisted dissociation of the Ln complexes.[11] By contrast, there are few reports dealing with the solvolysis process systematically.

We have developed high-performance liquid chromatography (HPLC) and high-performance capillary electrophoresis (HPCE) methods for the determination of lanthanide ions based on a new separation chemistry, which we called the kinetic differentiation (KD) mode.[12] Since no ligand is added to the eluent in the KD-mode, the injected complex species are exposed to a strong dissociation force. Any metal complex which exhibits its peak in the HPLC/HPCE system is highly likely to be inert. For example, Ln(III)−8-amino-2-[(2-amino-5-methylphenoxy)-methyl]-6-methoxyquinoline-*N*,*N*,*N*′,*N*′-tetraacetacomplexes (Ln-Quin2) were detected by KD-mode HPLC.[12] While Quin2 is an octadentate acyclic polyaminocarboxylate ligand employed as a calcium ion probe, there are no reports as yet concerning the dissociation kinetics of Quin2 complexes with lanthanide ions. Lanthanide(III) complexes are usually classified as kinetically labile on the basis of the large rate constants for water exchange (k_{H_2O}, $\sim 10.6 \times 10^8$ s^{-1})[13−16] and the dissociation

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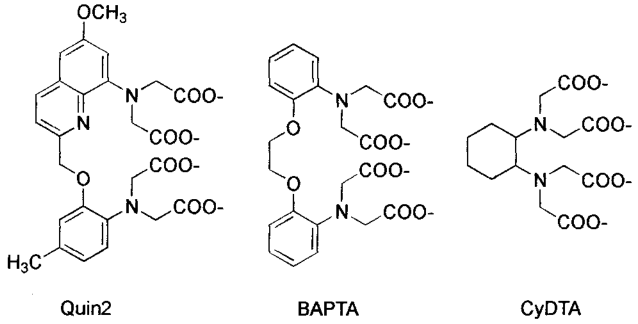

Figure 1. Chemical structures of the polyaminocarboxylate ligands.

processes for monodentate[17−20] or bidentate complexes.[21−26] However, our results have shown that the Ln(III)−quin2 complexes are amenable to the KD-HPLC, which indicates they are sufficiently inert. These findings seem to be in conflict with the current understanding of their labilities. If it were understood why macrocyclic and acyclic complexes are inert in solvolysis, it would be possible to design novel ligands suitable to the KD-mode separations.

In the present work we report a systematic study of the dissociation kinetics on solvolysis and proton-assisted dissociation reactions for Ln(III) complexes with Quin2 and *O*,*O*′-bis-(2-aminophenyl)ethylene glycol-*N*,*N*,*N*′,*N*′-tetraacetic acid (BAPTA) as octadentate ligands and *trans*-1,2-diaminocyclohexane-*N*,*N*,*N*′,*N*′-tetraacetic acid (CyDTA) as a hexadentate ligand. The rate constants were obtained through ligand exchange and metal exchange reactions of these complexes. It is stressed that the large negative entropy of activation is accompanied by the solvolytic dissociation path.

Experimental Section

Chemicals and Reagents. The reagents, Quin2, BAPTA, CyDTA, and ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid (EDTA) were purchased from Dojindo Lab. (Kumamoto, Japan). Figure 1 shows the chemical structures of these ligands. The reagents were dissolved in doubly distilled water and then adjusted to pH 7 with a minimum amount of sodium hydroxide. Standard solutions of Ln^{3+} ions were prepared by dissolving the chloride salts (99.9% purity, Wako Pure Chemical Industries, Japan) in doubly distilled water with a few drops of concentrated hydrochloric acid, except for the Tm ion which was prepared from Tm_2O_3 (99.9% purity, Wako, Japan). The Ln^{3+} solutions were standardized by EDTA titrations to a xylenol orange end-point. The Ln complexes with these ligands were prepared by mixing standard solutions of Ln^{3+} ions and a ligand solution. Potassium chloride (Wako Pure Chemical Industries, Japan) was used for ionic strength control in the kinetics study. The pH buffer solutions of tris(hydroxymethyl)-aminomethane (Tris), bis(2-hydroxyethyl)iminotris(hydroxymethyl)-methane (Bis-Tris), and sodium acetate were prepared from reagents of analytical grade.

Methods. In ligand exchange experiments, to guarantee pseudo-first-order kinetics a large excess of EDTA (50−300-fold for 6×10^{-6} M of Ln^{3+} complex concentration) was added to a solution containing Ln^{3+}−Quin2 or −BAPTA complex at appropriate pHs. The exchange rate processes were followed with the time-course changes in the absorbance of free Quin2 at 262 nm and in the emission of free BAPTA (excitation 290 nm, emission 370 nm).

The metal exchange reactions were initiated by mixing a solution of metal ions (Eu^{3+} for Quin2, Tb^{3+} for BAPTA, and Cu^{2+} for CyDTA) with a solution of the corresponding Ce^{3+} complexes containing a pH buffer (pH 3.8−8.5). The metal concentration was 17∼80 times greater than that of the Ce^{3+} complex (6×10^{-6} M) in the mixture. An absorption spectrophotometric method, which had been reported by D. W. Margerum,[27] was used in the case of the Ce^{3+}−cydta−Cu^{2+} system. The increase of fluorescent intensity and absorbance due to emissive or absorptive complex formation was monitored. The emission is based on ligand to metal energy transfer (excitation 340 nm, emission 610 nm for Eu^{3+}−Quin2 and excitation 270 nm, emission 545 nm for Tb^{3+}−BAPTA).[28−30] The time trace of absorbance was monitored at 240 nm in the metal exchange reaction of Ce^{3+}−cydta. The quantitative dissociation of these lanthanide−polyaminocarboxylate complexes (>99%) under these conditions through either ligand exchange or metal exchange reactions was ensured by the equilibrium calculations. The effect of pH was studied using different Good's buffers of varying pHs: Tris for pHs 6.5−8.5, Bis-Tris for pHs 5.5−7.0, and acetate for pHs 4−5.7. Ionic strength was adjusted to 0.1 with KCl.

Apparatus. A HITACHI Model U-3210 spectrophotometer (HITACHI, Japan) and an Aminco-Bowman Series 2 luminescence spectrometer (SLM-AMINCO, New York) were used for time-course measurements of absorbance and fluorescence intensity, respectively. The temperature of the cells was kept constant (280−320 K) in the thermostat (EX-300, NESLAB INSTRUMENTS INC., USA). Solution pH was measured with a HORIBA M-13 pH meter.

Results and Discussion

Ligand Exchange Kinetics of Ln^{3+}−Quin2 and −BAPTA Complexes with EDTA. The rate of the ligand exchange reaction was measured under pseudo-first-order conditions in the presence of a large excess of EDTA at 298 K. The rate of exchange can be given as

$$-d[LnL]_T/dt = k_{obs}[LnL]_T \qquad (1)$$

where k_{obs} is a pseudo-first-order rate constant and $[LnL]_T$ is the total concentration of Ln^{3+}−Quin2 or −BAPTA. The observed rate constants are proportional to the EDTA concentration with significant positive intercepts which represent the solvolytic dissociation pathway independent of the EDTA concentration (Figure 2). The relationship between k_{obs} and the EDTA concentration can be expressed as

$$k_{obs} = k_{EDTA}[EDTA] + k_d \qquad (2)$$

where k_{EDTA} is the rate constant for a ligand exchange path with EDTA and k_d is the rate constant for spontaneous dissociation, i.e., solvolysis. The complex formation reaction ($Ln^{3+} + L \rightarrow LnL$) is negligible, because the observed rate constants were independent of the LnL concentrations. The rate constants (k_{EDTA} and k_d) obtained for Ln^{3+}−Quin2 and −BAPTA are listed in Table 1.

In the ligand exchange reactions with EDTA for La^{3+}− and Eu^{3+}−Quin2 and Ce^{3+}−BAPTA complexes, no pH dependence

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Table 1. Dissociation Rate Constants of Ln^{3+}−Quin2 and −BAPTA Chelates[a]

	quin2			BAPTA		
Ln^{3+}	$k_{EDTA}/M^{-1}\,s^{-1}$	k_d/s^{-1}	$\log K_{M-Quin2}$[b]	$k_{EDTA}/M^{-1}s^{-1}$	k_d/s^{-1}	$\log K_{M-BAPTA}$[b]
La	2.2 ± 0.7	$(5.7 \pm 0.7) \times 10^{-3}$	11.89	91 ± 4	$(8.5 \pm 2) \times 10^{-2}$	10.7
Ce	1.6 ± 0.3	$(4.0 \pm 0.5) \times 10^{-3}$	12.26	41 ± 8	$(5.9 \pm 0.4) \times 10^{-2}$	11.1
Pr	1.2 ± 0.2	$(2.5 \pm 0.4) \times 10^{-3}$	12.53	53 ± 4	$(5.3 \pm 0.2) \times 10^{-2}$	11.23
Nd	0.82 ± 0.05	$(9.9 \pm 0.6) \times 10^{-4}$	12.69	99 ± 5	$(7.7 \pm 0.2) \times 10^{-2}$	11.01
Sm	0.42 ± 0.04	$(3.5 \pm 0.8) \times 10^{-4}$	13.28	161 ± 20	0.13 ± 0.01	10.87
Eu	0.22 ± 0.01	$(1.4 \pm 0.1) \times 10^{-4}$	13.60	282 ± 84	0.16 ± 0.04	10.6
Gd	0.20 ± 0.01	$(1.4 \pm 0.2) \times 10^{-4}$	13.54	500 ± 32	0.25 ± 0.02	10.78
Tb	0.098 ± 0.002	$(7.7 \pm 0.5) \times 10^{-5}$	14.04	159 ± 67	0.25 ± 0.03	10.73
Dy	0.061 ± 0.014	$(3.4 \pm 2.5) \times 10^{-5}$	14.2	134 ± 26	0.20 ± 0.01	10.49
Ho	$(6.1 \pm 0.6) \times 10^{-2}$	$(2.0 \pm 1.3) \times 10^{-5}$	14.13	171 ± 10	0.21 ± 0.004	10.54
Er	$(2.5 \pm 0.4) \times 10^{-2}$	$(2.0 \pm 1.2) \times 10^{-5}$	14.23	164 ± 24	0.18 ± 0.01	10.51
Tm	$(2.3 \pm 0.3) \times 10^{-2}$	$(1.0 \pm 0.8) \times 10^{-5}$	14.35	113 ± 25	0.16 ± 0.001	10.51
Yb	$(8.7 \pm 0.4) \times 10^{-3}$	$(4.0 \pm 0.5) \times 10^{-6}$	14.68	81 ± 1	0.14 ± 0.006	10.61
Lu	$(5.0 \pm 0.7) \times 10^{-3}$	$(1.7 \pm 2.8) \times 10^{-6}$	14.69	103 ± 23	0.14 ± 0.01	10.42

[a] At 298 K, and $I = 0.1$ (KCl). [b] Reference 30.

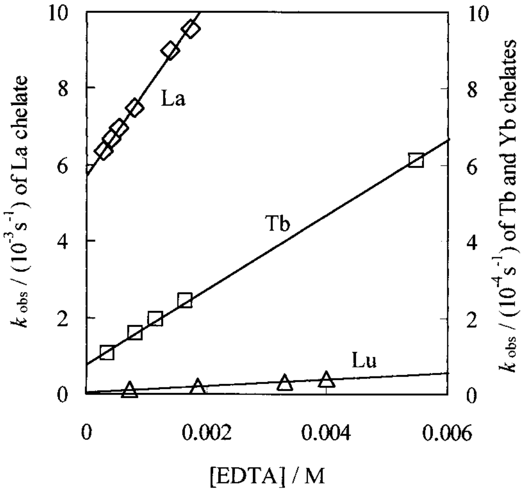

Figure 2. The dependence of observed rate constants on EDTA concentration for La^{3+}−, Tb^{3+}−, and Lu^{3+}−Quin2 complexes. [Ln^{3+}−Quin2] = 6.0×10^{-6} M; $I = 0.1$ (KCl); pH 7.0; 25 °C.

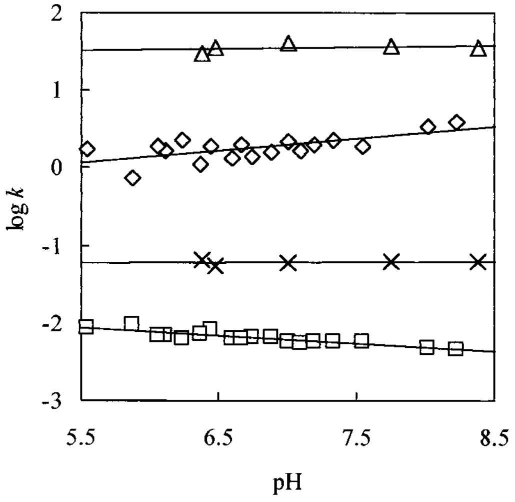

Figure 3. pH effect on dissociation rate constants of La^{3+}−Quin2 and Ce^{3+}−BAPTA complex on ligand exchange reaction. △, for log $k_{edta,Ce-bapta}$; ◇, for log $k_{edta,La-quin2}$; ×, log $k_{d,Ce-bapta}$; □, log $k_{d,La-quin2}$. Experimental conditions are the same as those in Figure 2.

of the solvolysis rate constants (k_d) was observed over a pH range of 6−8 (Figure 3), indicating that the proton-assisted dissociation plays a minor role under such conditions, whereas the k_{EDTA} values slightly increase with increasing pH because of the changing distribution of different protonated EDTA species in the solutions.

Regarding k_d and k_{EDTA} for the Quin2 complexes at pH 7 (Table 1), as the ionic radii increase, larger rate constants are observed. This is probably due to the fact that the higher charge density of the central metal ions gives rise to stronger binding with the ligand, Quin2. Such a charge effect on solvolysis rate constants is generally observed for macrocyclic[7,31,32] and acyclic polyaminocarboxylate complexes.[27,33] The marked difference between the solvolysis rate constants for La^{3+}− and Lu^{3+}−Quin2 complexes is as large as nearly 4 orders of magnitude, which is translated into half-lives for the solvolysis path of 3 min to 112 h. These values prove that lanthanid−-Quin2 complexes are kinetically inert. In sharp contrast, with Ln−Quin2 complexes, it is somewhat surprising that no ionic radius dependence of the rate constants is observed for the BAPTA complexes (Table 1). This tendency of the dissociation rate constants seems to be similar to those of diaza and triaza crown ether carboxylate complexes.[34,35] Even the longest half-life for solvolysis is only 15 s, which shows that BAPTA complexes are relatively labile.

The activation enthalpies ($\Delta H^{\ddagger}$) and the activation entropies ($\Delta S^{\ddagger}$) were determined according to the Eyring equation:

$$\ln(\chi k_d/T) = \ln(k_B/h) + \Delta S^{\ddagger}/R - \Delta H^{\ddagger}/RT \qquad (3)$$

where χ is a transmission factor (in this case, $\chi = 1$), k_B is the Boltzmann constant, h is Planck's constant, and R is the gas constant. The activation parameters for the solvolysis path of Ce^{3+}−Quin2 and −BAPTA complexes were determined in accordance with eq 3 using the rate data obtained by repeated runs at different temperatures. The activation parameters derived are given in Table 3. The activation entropies obtained are negative, and the absolute values are remarkably large.

Metal Exchange Kinetics for Ce^{3+}−Quin2, −BAPTA, and −cydta Complexes. A slight dependence of the rate constant on the metal concentration in the solutions was observed for the Ce^{3+}−Quin2-Eu^{3+} and Ce^{3+}−BAPTA-Tb^{3+} systems, whereas no such dependence was found in Ce^{3+}−cydta−Cu^{2+} system.

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Table 2. Proton Assisted Rate Constants of Ce^{3+}- Polyaminocarboxylate Complexes[a]

	EDTA	CyDTA	EGTA[d]	BAPTA	quin2
k_H s^{-1} M^{-1}	2.9×10^3 [b]	91 ± 3 (60 ± 3)[c]	$(3.6 \pm 0.2) \times 10^3$ [d]	$(1.5 \pm 0.2) \times 10^4$	$(1.4 \pm 0.1) \times 10^3$
k_d s^{-1}	2×10^{-4} [b]	$(5.5 \pm 2.7) \times 10^{-4}$ $((2.0 \pm 0.5) \times 10^{-4})$[c]	$(8.7 \pm 4.5) \times 10^{-5}$ [d]	$(5.9 \pm 0.4) \times 10^{-2}$	$(4.0 \pm 0.5) \times 10^{-3}$

[a] At 298 K, $I = 0.1$ (KCl). [b] Reference 41. [c] Refference 27. [d] Refernce 36.

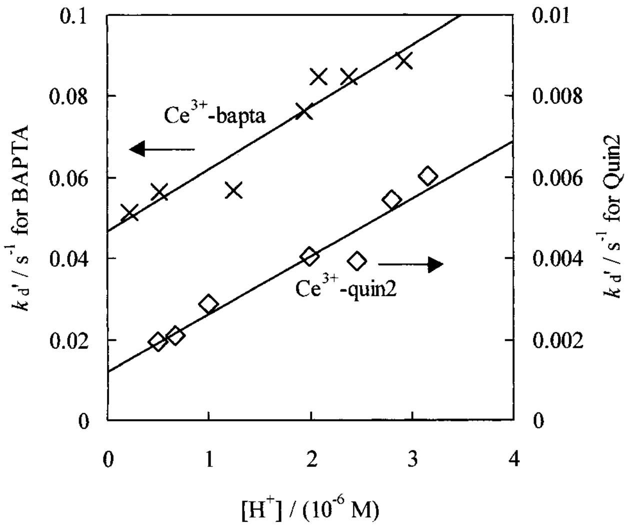

Figure 4. The dependence of solvolysis rate constants on proton concentrations for Ce^{3+}−Quin2 and −BAPTA complexes on metal exchange reaction. [ML] = 6×10^{-6} M; $I = 0.1$ (KCl); 25 °C.

In the case of the metal-dependent system, the rate law can be represented as

$$-d[Ce\text{-}L]/dt = (k_M[M] + k_d + k_H[H])[Ce\text{-}L] \quad (5)$$

$$= k_{obs}[Ce\text{-}L] \quad (5)$$

where k_M, k_H, k_d, and k_{obs} are the metal-dependent, the proton-assisted dissociation, the solvolysis, and observed rate constants, respectively, and M is the scavenger metal ion. The pseudo-first-order rate constants were determined as a function of scavenger metal ions and proton concentrations. In the Ce^{3+}−CyDTA−Cu^{2+} system, the first term in the right-hand side of eq 4 can be omitted. Figure 4 shows the dependence of the observed rate constant on proton concentration. The calculated rate constants are presented in Table 2. The values of k_H and k_d for the Ce^{3+}−egta system (EGTA; *O*,*O*′-bis(2-aminoethyl)-ethylene glycol-*N*,*N*,*N*′,*N*′-tetraacetic acid) were determined by a capillary electrophoresis method.[36] Although the value of k_H for Ce^{3+}−cydta has an order of magnitude similar to that reported by Margerum,[27] k_d is about 2 times larger than that reported. The activation parameters determined using eq 3 for Ce^{3+}−cydta on repeated runs at different temperatures are given in Table 3.

Acid-Assisted Dissociation Rate Constants of Different Ligands. Since all of the ligands studied in this report form five-membered rings, the chelate ring size effect found by Choppin et al.[33,37,38] can be ruled out. It was also reported that the rigidity of the ligand controls kinetic stability of acyclic, macrocyclic,[7,8,39] polyaminocarboxylate, and aza crown carboxylate[34,40] complexes. In the case of octadentate acyclic polyaminocarboxylate complexes with Ce^{3+} ions, the order of k_H as BAPTA > EGTA > Quin2 (Table 2) does not seem to be reconciled with those of the ligand rigidity, Quin2 > BAPTA > EGTA, nor the basicity of the donor atoms in terms of the pK_a values, EGTA > Quin2 > BAPTA. By contrast, for the hexadentate ligand complexes the difference of the k_H values is more drastic; the fact that the k_H for the Ce^{3+}−edta complex is 2.9×10^3 M^{-1} s^{-1} [41] (30 times larger than that for CyDTA complex (Table 2)) seems to be attributable to the flexibility of the EDTA ligand. Kumar and Tweedle found that the rates of the hydroxide-assisted reorganization of the intermediate for Gd^{3+}-macrocyclic polyaminocarboxylate complexes are inversely proportional to the basicity of nitrogen, that is, the first protonation constant (amino nitrogen) of the ligands.[9] At this stage, the k_H order of the octadentate ligand complexes in relation to the reaction mechanism remains unclear in terms of the nitrogen basicity and the structure rigidity, which is now under investigation.

Table 3. Activation Parameters of Ce(III)−Acyclic Polyaminocarboxylate Complexes[a]

	$\Delta H^‡$/(kJ mol^{-1})	$\Delta S^‡$/(J mol^{-1} K^{-1})
solvolysis		
BAPTA	5 ± 9	-252 ± 32
quin2	13 ± 3	-249 ± 11
CyDTA	43 ± 4	-162 ± 14
proton-assisted dissociation		
CyDTA	53 ± 5	-28 ± 19
La−cydta[b]	54.34	−21

[a] $I = 0.1$ (KCl). [b] Reference 27.

Solvolysis Rate Constants of Different Ligands. The order of the solvolytic dissociation rate constant, k_d, is BAPTA > Quin2 > CyDTA > EDTA > EGTA for Ce^{3+} complexes. In contrast to the tendency of k_H, the ligand rigidity does not seem to make a contribution to the order of k_d, as observed for both octadentate and hexadentate ligands, and the order of k_d is almost compatible with that of the basicity of the ligand. Since the rupture of Ln−L bonds probably occurs at the rate-determining step, the activation enthalpy, $\Delta H^‡$, may be related to the Ln−L bonding strength, depending upon the basicity of the ligand.

The values of activation entropy for the solvolysis rate constants of the Ce^{3+} complexes of Quin2, BAPTA, and CyDTA are negative and considerably larger (Table 3), implying an associative mechanism which results from the attack of the water molecules. Both the entropy and enthalpy terms remarkably contribute to the inertness of Ln−polyaminocarboxylate complexes at 298 K. To our knowledge, so far such large negative activation entropies for lanthanide complex dissociation in aqueous solution have only been reported for a diaza crown ether carboxylate system by V. Chandra and C. A. Chang,[42] who presumed that large negative entropies ($\Delta S^‡ = -207$ J

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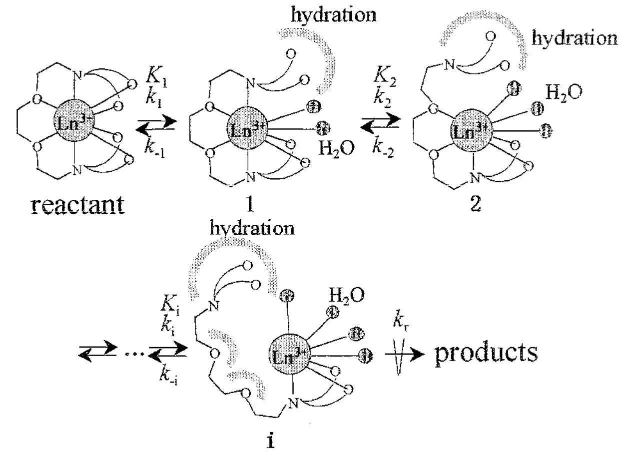
mol^{-1} K^{-1} for the La^{3+} complex) arise from the slow distortion of the chelate in the rate-determining step. Shinkai et al. found unusual inertness and a large negative change of entropy ($\Delta S^{\ddagger} = -200$ J mol^{-1} K^{-1}) through the dissociation reaction of a Cs^{+}-capsule-like calix[*n*]arene system in tetrahydrofuran.[43] In our case, the large entropy change probably originates from solvation of the complexes during the approach to the transition state. Interestingly, the values for each of the octadentate ligand complexes are almost the same ($\Delta S^{\ddagger} = -252$ J mol^{-1} K^{-1} for BAPTA, -249 J mol^{-1} K^{-1} for Quin2 complex) and are more negative than that of the hexadentate complex ($\Delta S^{\ddagger} = -162$ J mol^{-1} K^{-1} for CyDTA). This difference in the $\Delta S^{\ddagger}$ values is likely due to the degree of envelopment of the center metal ion with the ligand in the transition state.

The rate constants and the activation parameters of the solvolytic dissociation process obtained in this study possibly result from the overall dissociation reaction consisting of successive elementary reactions as shown in Scheme 1 as a speculative mechanism. The Ln−L bond breakage in each step probably gives rise to a large negative $\Delta S^{\ddagger}$ owing to the immobilization of several water molecules solvating the central metal ion and the free carboxylate oxygen atoms (species 1and and 2 in Scheme 1). As a result of some preequilibria having small energy barriers in this model, the concentration of the final reactant (species i) is kept very low at the rate-determining step. Therefore, the dissociation rate is slow (rate $= K_1K_2 \ldots K_ik_r[\mathrm{Ln{-}L}]$), even when the rate constants are comparably large at each preequilibrium step as well as at the rate-determining step. This proposed reaction mechanism is entirely different from that generally found in which only one elementary reaction, having the largest energy barrier, actually determines the dissociation rate.

In this work, we found that Ln^{3+}−Quin2 and −cydta complexes are kinetically inert in solvolysis, while the BAPTA complexes are relatively labile. While the basicity of coordinating atoms plays a certain role in the inertness on a $\Delta H^{\ddagger}$ basis, the entropic barrier is likely dependent upon the ability of the multidentate ligand to envelope Ln ions by removing water molecules from its first coordination sphere. Dissociation reactions in which activation entropy governs the rate are uncommon. The multistage dissociation process of the Ln complexes gives rise to the enormous negative entropy. It should be stressed that the new "chelate effect" on the dissociation process stems from this entropic force, and this is considerably different from the conventional model in terms of thermodynamics.[44]

Scheme 1



For simplicity, aromatic rings are omitted from BAPTA in this Scheme.

The design of novel reagents for KD-mode and the development of more powerful detection systems are now underway, on the basis of the valuable information obtained in this work.

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