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Kinetics of Formation and Dissociation of the 1,4,7-Triazacyclonononane-*N*,*N'*,*N''*-triacetate Complexes of Cerium(III), Gadolinium(III), and Erbium(III) Ions

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The formation rate of the NOTA complexes of lanthanide(III) ions (Ln^{3+}: Ce^{3+}, Gd^{3+}, and Er^{3+}) was found to be slow enough between pH 4.5 and 5.8 to be followed by conventional spectrophotometry. The reactions take place by rapid formation of a monoprotonated intermediate, which deprotonates in a slow, rate-determining step. Rearrangement of the intermediate to form the stable complex is catalyzed by OH^- ions. Exchange reactions occurring between the Ln(NOTA) complexes and Cu^{2+} or Zn^{2+} ions take place by spontaneous as well as proton-assisted dissociation of the complexes. The rates of both the spontaneous and proton-catalyzed dissociation decrease significantly with the smaller radii lanthanide cations while formation rates do not differ appreciably with cation size. Thus, the increase in stability constants of the Ln(NOTA) complexes with increasing atomic number of lanthanides mainly results from a decrease in dissociation rates.

Introduction

Complex formation between lanthanide(III) ions (Ln^{3+}) and monodentate or flexible multidentate ligands is usually very fast, such that the kinetics of complexation can be studied only by relaxation methods.[1] The high rate of complex formation is the consequence of the very fast water exchange reactions taking place between the Ln^{3+}(aq) ions and bulk water.[1,2] Complexation reactions can be significantly slower for protonated, multidentate ligands where ring closure or proton transfer can often be the rate-controlling step. For example, the rate of formation of the $La(CDTA)^-$ complex ($CDTA^{4-}$ = *trans*-1,2-diaminocyclohexane-*N*,*N'*,*N''*,*N'''*-tetraacetate) could be followed by stopped-flow methods since CDTA is rigid and deprotonation of a reaction intermediate was found to be a slow process.[3]

In recent years, there has been increasing interest in the complexes of lanthanides formed with macrocyclic polyazapolycarboxylate ligands such as DOTA, TETA, and NOTA ($DOTA^{4-}$ = 1,4,7,10-tetraazacyclododecane-*N*,*N'*,*N''*,*N'''*-tetraacetate, $TETA^{4-}$ = 1,4,8,11-tetraazacyclotetradecane-*N*,*N'*,*N''*,*N'''*-tetraacetate, $NOTA^{3-}$ = 1,4,7-triazacyclononane-*N*,*N'*,*N''*-triacetate) since their Gd^{3+} complexes have properties that make them potentially useful magnetic resonance imaging (MRI) contrast agents.[4-6] Formation of $Ln(DOTA)^-$, $Ln(TETA)^-$, and Ln(NOTA) complexes was previously found to be so slow that potentiometry could not be used for determination of their stability constants.[7,8] The kinetic behavior of the Ln^{3+} ions with DOTA and TETA differs considerably from that of the alkaline-earth or first-row transition-metal ions, since the DOTA and TETA complexes of Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}, Ni^{2+}, and Cu^{2+} formed relatively fast, as demonstrated by Kasprzyk and Wilkins in a stopped-flow spectrophotometric study.[9] Although the rates of formation and, particularly, dissociation of Gd(III)–macrocyclic polyaza polycarboxylates is important for their use as MRI contrast agents, a detailed study of the kinetic properties of these complexes has not been reported. Earlier work has shown that the rate of dissociation of $Gd(DOTA)^-$ at pH = 7 is much slower than that of $Gd(DTPA)^{2-}$ or $Gd(EDTA)^-$.[10] Also, the reaction of DOTA with Ce^{3+} ion takes place by fast formation and slow deprotonation of a protonated intermediate while dissociation of $Ce(DOTA)^-$ has been shown to occur by a proton-catalyzed process.[11]

Recently, we have begun a systematic study of the kinetics of formation and dissociation of the macrocyclic triaza tricarboxylate complexes of lanthanides. We intend to investigate the effect of the size and rigidity of the macrocycle as well as ring substituent effects on the kinetic properties of these complexes. In this paper, we report results obtained for the reaction of the nine-membered ring chelate $NOTA^{3-}$ with Ce^{3+}, Gd^{3+}, and Er^{3+} ions, which are representative of large, intermediate, and small radii lanthanides, respectively.

Experimental Section

Stock solutions of Ce^{3+}, Gd^{3+}, and Er^{3+} were prepared from lanthanide(III) chlorides (Aldrich, 99.9%) and their concentrations determined by complexometric titration using xylenol orange as indicator. H_3NOTA was synthesized by methods described previously.[12] The concentration of a H_3NOTA stock solution was determined by titration against a standard $CuCl_2$ solution using murexide as indicator.

The ionic strength of the sample solutions was held constant (0.1 M NaCl), and MES (Calbiochem) or potassium formate was used as a buffer where indicated. An Orion Research 701A pH meter with a Cole Parmer combination electrode was used for all pH measurements. The H^+ ion concentration was established from the measured pH value by procedures previously outlined.[13] Kinetic measurements were carried out on a Cary 219 spectrophotometer at 25 °C using thermostated cells (1 cm).

The formation of Gd(NOTA) and Er(NOTA) was studied in weakly buffered solutions by monitoring the pH decrease (0.05–0.1 pH unit) with bromocresol green ($4.6 < pH < 5.2$; 615 nm) or bromocresol purple ($5.2 < pH < 6.2$; 588 nm) as the indicator.[9]

$$Ln^{3+} + H_nL \rightarrow LnL + nH^+ \qquad (1)$$

$$n = 1, 2, \text{ or } 3$$

The concentration of the indicators was 2×10^{-5} M while the concentration of buffers varied between 5×10^{-3} and 2×10^{-2} M, depending upon the pH of the sample (a suitable buffer concentration was determined experimentally). Typically, the concentration of NOTA was 1×10^{-4} M, while the Ce^{3+}, Gd^{3+}, or Er^{3+} concentration was varied between

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Table I. The Parameters K^* and the Stability Constants K_{LnHL^*} of the Reaction Intermediates

Ce			Gd			Er		
pH	K^*, M^{-1}	log K_{CeHL^*}	pH	K^*, M^{-1}	log K_{GdHL^*}	pH	K^*, M^{-1}	log K_{ErHL^*}
5.83	812	3.16	5.39	1187	3.58	5.43	1111	3.53
5.73	599	3.12	5.32	927	3.53	5.28	1226	3.68
5.60	492	3.07	5.25	1229	3.70	4.98	984	3.83
5.48	565	3.20	5.13	833	3.62	4.85	613	3.74
5.30	467	3.25	5.05	708	3.62	4.67	788	4.01
5.05	622	3.56[a]	4.85	521	3.66	4.55	854	4.16
4.85	555	3.69[a]	4.62	568	3.91[a]			
		av 3.2 ± 0.1			av 3.6 ± 0.1			av 3.8 ± 0.2

[a] These data were not used in calculating the average values of log K_{LnHL^*}.

2×10^{-4} and 2×10^{-3} M. The formation and dissociation rates of Ce(NOTA) were studied by following the change in absorbance of Ce(NOTA) at 290 nm, where the absorbance of uncomplexed Ce^{3+} is not significant.

The dissociation rates of Gd(NOTA) and Er(NOTA) were studied in acidic solutions in the presence of a large Cu^{2+} excess. Under these conditions, the exchange reaction

$$Ln(NOTA) + Cu^{2+} \rightarrow Cu(NOTA)^- + Ln^{3+} \qquad (2)$$

takes place, and progress of the exchange may be followed by monitoring the formation of $Cu(NOTA)^-$ at 295 nm. Zn^{2+} was used as the scavenger ion in the corresponding study of Ce(NOTA). The concentration of the Ln(NOTA) was 2×10^{-4} M while that of the exchanging metal ions was either constant at 1×10^{-3} M or it was varied between 5×10^{-4} and 5×10^{-3} M.

Results and Discussion

Kinetics of Formation of Ln(NOTA) Complexes. The rate of Ln(NOTA) complex formation in the presence of a Ln^{3+} ion excess may be described by

$$\frac{d[LnL]}{dt} = k_f[L]_0 \qquad (3)$$

where $[L]_0$ is the total concentration of the free ligand and k_f is a pseudo-first-order rate constant. The formation reactions were investigated at different pH values and with varying concentrations of Ln^{3+} ions. For all systems at each pH, k_f was found to increase with Ln^{3+} ion concentration, but the curve obtained by plotting the values k_f against the Ln^{3+} concentration is a "saturation curve". This behavior is characteristic of rapid formation of a reaction intermediate that rearranges to the product in a slow, rate-determining process.

The dependence of k_f values on the metal ion concentration can be described[14] by

$$k_f = \frac{kK^*[Ln]}{1 + K^*[Ln]} \qquad (4)$$

where K^* is a parameter characterizing the formation of an intermediate and k is the rate constant for rearrangement of the intermediate to product. The constants k and K^* were obtained by plotting the data according to eq 5.

$$\frac{1}{k_f} = \frac{1}{k} + \frac{1}{kK^*[Ln]} \qquad (5)$$

The raw data are presented in Figures 1–3 and the values of K^* at each pH are summarized in Table I. The rate constants for rearrangement of the intermediate were quite pH dependent (see below) while K^* was found to be only slightly dependent upon pH over the limited range examined (Table I).

We propose that the intermediate is a monoprotonated species, LnHL*, based upon the following observations. After mixing the reactants, we observed a very rapid pH drop followed by a slow decrease in pH. During the slow process, the amount of H^+ ions released was equivalent to the amount of LnL formed. The amount of protons released during the fast process reasonably agreed with that calculated for all H_nNOTA species from the known protonation constants (log K_1 = 11.41, log K_2 = 5.79, log

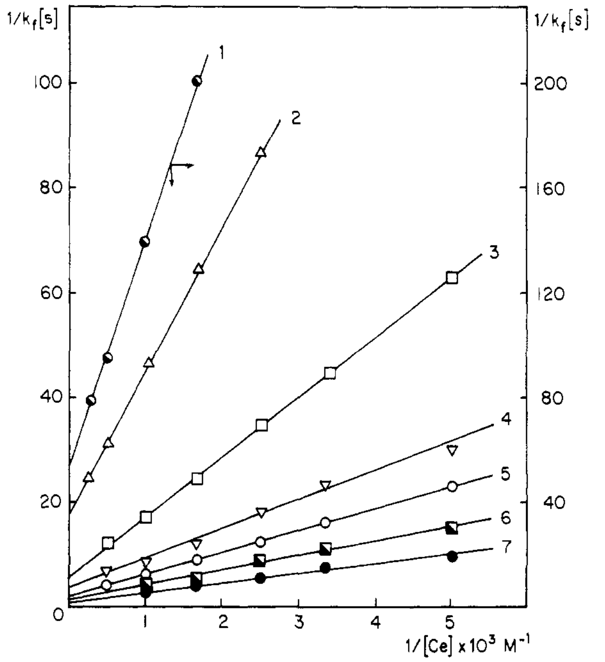

Figure 1. Formation rates (k_f) for Ce(NOTA) as a function of Ce^{3+} concentration. pH = 4.85 (1), 5.05 (2), 5.30 (3), 5.48 (4), 5.60 (5), 5.73 (6), and 5.83 (7).

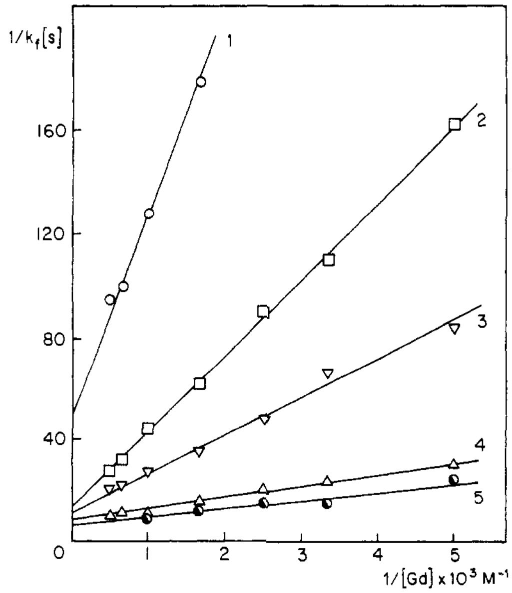

Figure 2. Formation rates (k_f) for Gd(NOTA) as a function of Gd^{3+} concentration. pH = 4.62 (1), 4.85 (2), 5.05 (3), 5.25 (4), and 5.32 (5).

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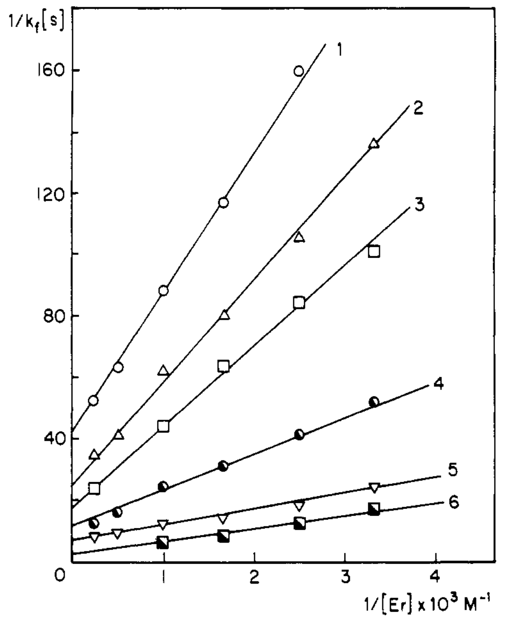

Figure 3. Formation rates (k_f) for Er(NOTA) as a function of Er^{3+} concentration. pH = 4.55 (1), 4.67 (2), 4.85 (3), 4.98 (4), 5.28 (5), and 5.43 (6).

$K_3 = 3.16$[15]), less the one proton equivalent remaining in the form of $LnHL^*$. In the pH interval 4.5–5.8, species H_2L^- and HL^{2-} are present at relatively high concentrations while the amount of H_3L is low. Our proposed monoprotonated intermediate may be similar in structure to that observed directly by spectrophotometry during the formation of $Ce(DOTA)^-$.[11]

On the basis of these results, the following reaction scheme may be written for the formation of the Ln(NOTA) complexes:

$$\begin{tikzcd} Ln^{3+} + & HL^{2-} \arrow[r, shift left, "fast"] \arrow[d, shift left] & LnHL^* \arrow[l, shift left] \arrow[r, "k"] & LnL + H^+ \\ & H_2L^- \arrow[u, shift left] \arrow[d, shift left] & & \\ & H_3L \arrow[u, shift left] & & \end{tikzcd} \qquad (6)$$

Assuming that proton loss from the intermediate and subsequent rearrangement of the complex is the rate-determining step of the reaction, an equation can be derived that relates the measured values of K^* to a "stability constant" for the intermediate species, $LnHL^*$. For a first-order process

$$\frac{d[LnL]}{dt} = k_f[L]_0 = k[LnHL^*] \qquad (7)$$

The total ligand concentration may be expressed as

$$[L]_0 = [LnHL^*] + [L'] \qquad (8)$$

where $[L']$ is the total concentration of all noncomplexed ligand

$$[L'] = [HL^{2-}] + [H_2L^-] + [H_3L] \qquad (9)$$

Note that the fully deprotonated form of the ligand [L] is essentially zero at the pH values used in this experiment (log K_1 = 11.41). Substituting expressions for the protonation constants for the ligand into eq 9 yields

$$[L'] = [HL^{2-}](1 + K_2[H^+] + K_2K_3[H^+]^2)$$

or

$$[L'] = [HL^{2-}]K_H \qquad (10)$$

Substituting eqs 10 and 8 into eq 7 gives

$$k_f([LnHL^*] + K_H[HL^{2-}]) = k[LnHL^*] \qquad (11)$$

Defining a stability constant for $LnHL^*$ as

$$K_{LnHL^*} = \frac{[LnHL^*]}{[Ln][HL^{2-}]}$$

and substituting into eq 11 yields

$$k_f = \frac{k(K_{LnHL^*}/K_H)[Ln]}{1 + (K_{LnHL^*}/K_H)[Ln]} \qquad (12)$$

Comparison of this equation with eq 4 indicates that K_{LnHL^*} may be evaluated from K^* values obtained at each pH, using known protonation constants for NOTA.[15] As shown in Table I, the calculated stability constants for the three intermediate complexes are reasonably pH independent over most of the pH range examined.

The microscopic site of protonation of $HNOTA^{2-}$ (the species HL^{2-} reacts with Ln^{3+} to form $LnHL^*$) has been proposed to occur at a ring nitrogen, stabilized by hydrogen bonding with a carboxylate (the second protonation also occurs at a nitrogen while the third takes place at a carboxylate[19]). Electrostatic repulsion between a Ln^{3+} ion and this proton could preclude the Ln^{3+} ion from entering the macrocyclic cavity of the ligand during the initial stages of complex formation. The stability constants of the intermediates $LnHL^*$ obtained here are about 1 order of magnitude

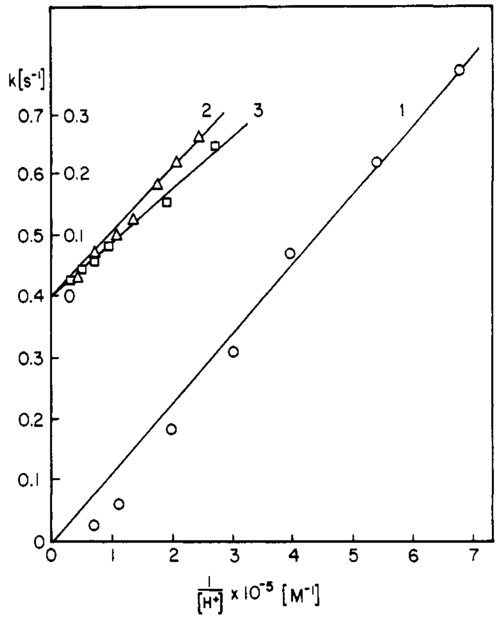

Figure 4. Formation rate constants (k) for Ce(NOTA) (1), Gd(NOTA) (2), and Er(NOTA) (3) as a function of $1/[H^+]$.

Table II. Formation (k_{OH}) and Dissociation (k_d^0, k_d^1) Rate Constants of the Complexes

	Ce(NOTA)	Gd(NOTA)	Er(NOTA)
k_{OH}, M^{-1} s^{-1}	$(6.3 \pm 1) \times 10^7$	$(7.1 \pm 1) \times 10^7$	$(5.5 \pm 0.7) \times 10^7$
k_d^0, s^{-1}	$(2.5 \pm 0.3) \times 10^{-5}$	$(8.3 \pm 1) \times 10^{-6}$	$(2.7 \pm 0.5) \times 10^{-6}$
k_d^1, M^{-1} s^{-1}	$(4.3 \pm 0.5) \times 10^{-2}$	$(2.3 \pm 0.3) \times 10^{-2}$	$(1.6 \pm 0.3) \times 10^{-3}$

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higher than those for the corresponding monoacetate complexes.[20] This suggests the Ln^{3+} ion is coordinated to more than just a single carboxylate group in the intermediate. Stability constants for lanthanide complexes formed with long-chain dicarboxylic acids are not known, but log K values for La^{3+}– and Y^{3+}–glutarate complexes are 3.02 and 3.25, respectively.[20] These are similar in magnitude to the K_{LnHL^*} values obtained for the LnHL* intermediates in this study. This suggests that at least two carboxylate groups are coordinated to the Ln^{3+} ion in the protonated intermediates LnHL*.

The values of k for the rate-determining step in the formation of LnL are plotted versus $[H^+]^{-1}$ in Figure 4. This relationship indicates that formation of LnL from LnHL* is more complex than that indicated in the reaction scheme in (6). We propose that OH^- catalyzes the deprotonation and rearrangement of LnHL*.

$$\mathrm{LnHL^*} + \mathrm{OH^-} \xrightarrow{k_{OH}} \mathrm{LnL} + \mathrm{H_2O} \tag{13}$$

Spontaneous transformation of LnHL* (as represented by k) must be very slow, since the straight lines in Figure 4 nearly intersect at the origin. The experimental data deviate slightly from the lines at high $[H^+]$ (especially apparent for the Ce^{3+} and Gd^{3+} data in Figure 4), indicating that a second pathway may contribute to dissociation of LnL* when the $[OH^-]$ is low. Nevertheless, the dominant pathway over a wide range of pH is the OH^--catalyzed pathway represented by eq 13. The rate constants, k_{OH}, characterizing the OH^- ion catalyzed transformation of the intermediate LnHL* were calculated from the slopes of the straight lines in Figure 4. A comparison of the values obtained for the three lanthanides (Table II) shows that formation rates of the complexes do not differ appreciably.

Previously reported kinetic results for $La(CDTA)^-$, $Ca(DOTA)^{2-}$, $Cu(DOTA)^{2-}$, $Ni(DOTA)^{2-}$, and $Ce(DOTA)^-$ shows that the rate determining step of each complexation reaction is also deprotonation of an intermediate formed in a fast preequilibrium step.[3,9,11] The reactions of these same metal ions with more flexible amino polycarboxylate ligands, such as EDTA, take place faster, and a protonated intermediate cannot be detected. This indicates that the rigidity of the cyclic polyaza polycarboxylate macrocycles is likely an important factor in the formation of the protonated intermediate, which in turn contributes to their lower reactivity. The increase in complex formation rate with increasing $[OH^-]$ is also observed in the formation reactions of complexes of the cyclic amines.[16,17]

The catalytic effect of OH^- ions is likely a specific base catalysis, since a 5- or 10-fold increase in the buffer concentration did not affect the rate of complexation. Acetate ions and, to a much lesser extent, formate ions slow the rates of formation of these complexes, probably as a result of a decrease in concentration of the intermediate LnHL* due to competition between $HNOTA^{2-}$ and acetate or formate ions for binding to a Ln^{3+} cation.

Kinetics of Dissociation of Ln(NOTA) Complexes. The displacement of Ln^{3+} ions from the Ln(NOTA) complexes is complete in the presence of excess Cu^{2+} or Zn^{2+} ions (eq 2), since the stability constants of Ce(NOTA), Gd(NOTA), and Er(NOTA) are 4–5 orders of magnitude lower than those of $Cu(NOTA)^-$ or $Zn(NOTA)^-$.[8,18] The rates of these exchange reactions have been measured between pH 2 and 4. In the presence of excess Cu^{2+} or Zn^{2+} ion (M^{2+}), the rate of exchange may be expressed as

$$-\frac{d[\mathrm{LnL}]}{dt} = \frac{d[\mathrm{ML}]}{dt} = k_d[\mathrm{LnL}] \tag{14}$$

where k_d is a pseudo-first-order rate constant. The rate of exchange (k_d) was found to be independent of $[Cu^{2+}]$ or $[Zn^{2+}]$ but dependent upon $[H^+]$. Thus, rate-determining dissociation of the Ln(NOTA) complex is followed by rapid formation of $Cu(NOTA)^-$ or $Zn(NOTA)^-$. The experimental results are shown in Figure 5.

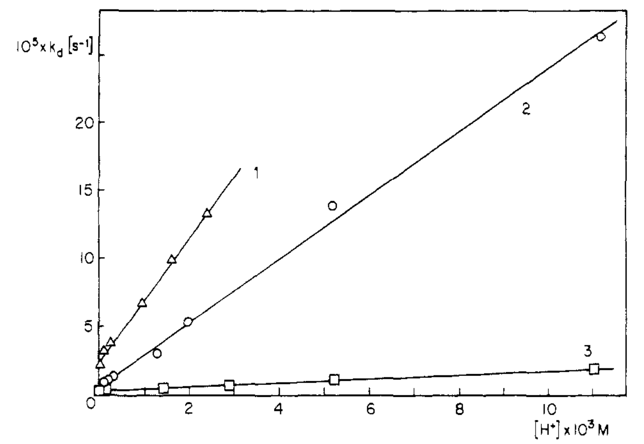


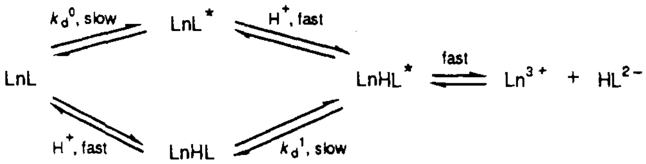
Figure 5. *Dissociation rates* (k_d) *for* Ce(NOTA) (1), Gd(NOTA) (2), and Er(NOTA) (3) as a function of H^+ concentration.

The data in Figure 5 indicate that the rate of complex dissociation is linearly proportional to $[H^+]$. The small positive intercepts along the ordinate of these plots indicates that a $[H^+]$-independent dissociation also occurs. Thus, the data may be described by

$$k_d = k_d^0 + k_d^1[H^+] \tag{15}$$

The rate constants, k_d^0 and k_d^1, calculated from the data are presented in Table II.

These data indicate that dissociation of Ln(NOTA) can take place by spontaneous decay of the complex or through a proton-assisted reaction pathway. Spontaneous dissociation of the complex is slow, but at higher pH values (pH > 6), the average lifetime of the complex is largely determined by the rate constant k_d^0. The data are consistent with the following reaction scheme:



In the spontaneous dissociation pathway, the Ln^{3+} ion first steps out of the macrocyclic cavity of the ligand to form LnL* in a slow, rate-determining step (k_d^0). This model would require the Ln^{3+} to be bound to less than three nitrogens in LnL* and perhaps bound to only carboxyl groups. This is followed by rapid protonation of LnL* to form LnHL*, which dissociates along a H^+ ion assisted pathway. The formation of the reaction intermediate, LnHL*, may also be initiated by protonation of a carboxylate group, which are known to be quite labile in the complex.[12] The species, LnHL, formed by carboxylate protonation may then transfer its proton to a ring nitrogen, which subsequently, as a result of electrostatic repulsion, assists in removal of the Ln^{3+} from the macrocyclic cavity to form LnHL*. In this pathway the slowest, rate-determining step is probably the proton-assisted rearrangement of the complex, resulting in the intermediate LnHL*. Another possible mechanism could involve direct protonation of one of the macrocyclic nitrogens, after spontaneous dissociation and inversion. Such a direct mechanism has been proposed for dissociation of Ni^{2+}–ethylenediamine.[21] The rates of dissociation of Ce(NOTA), Gd(NOTA), and Er(NOTA) differ considerably (Figure 5), with k_d^0 and k_d^1 decreasing with decreasing ionic size of the Ln^{3+} ions (Table II). Since the rates of formation of the Ln(NOTA) complexes were found not to differ significantly, the increase in stability of these complexes with decreasing ionic size[8] largely results from differences in their rates of dissociation. These results are important when considering the use of such complexes as magnetic resonance imaging agents. The

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half-lives for spontaneous dissociation of Ce(NOTA), Gd(NOTA), and Er(NOTA) at a physiological pH of 7.4 are 7.7, 23.2, and 71.3 h, respectively.

Dissociation of the Ln(NOTA) complexes is catalyzed only by H^+ ions. NH_4^+ ions or other protonated amines that might act as Brønsted acids have no effect upon the rate of dissociation. Spontaneous dissociation of $Ce(DOTA)^-$ was not observed in a similar kinetic study.[11] This likely reflects the differing sizes and rigidities of the tetraaza (DOTA) versus the triaza (NOTA) macrocycles. The coordination cage of NOTA is too small for a Ln^{3+} cation, and as a result, less energy is required for the cation to leave the coordination cage and form the reactive LnL* species.

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Non-Metal Redox Kinetics: Reactions of Iodine and Triiodide with Sulfite and Hydrogen Sulfite and the Hydrolysis of Iodosulfate

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The reactions of I_3^- and I_2 with SO_3H^- and SO_3^{2-} (in the p[H^+] range 4.1–6.6) are studied by the pulsed-accelerated-flow technique. Pseudo-first-order rate constants (excess $[SO_3^{2-}]_T$ and $[I^-]$) are measured in the range from 6300 to 74000 s^{-1} (25.0 °C, $\mu = 0.50$). The proposed mechanism is

$$I_3^- + SO_3H^- \xrightarrow{k_1} ISO_3^- + 2I^- + H^+$$

$$I_2 + SO_3H^- \xrightarrow{k_2} ISO_3^- + I^- + H^+$$

$$I_3^- + SO_3^{2-} \xrightarrow{k_3} ISO_3^- + 2I^-$$

$$I_2 + SO_3^{2-} \xrightarrow{k_4} ISO_3^- + I^-$$

where the second-order rate constants ($M^{-1}\ s^{-1}$) are $k_1 = 1.5 \times 10^7$, $k_2 = 1.7 \times 10^9$, $k_3 = 2.9 \times 10^8$, and $k_4 = 3.1 \times 10^9$. The iodosulfate that is formed hydrolyzes with a first-order rate constant of 298 s^{-1} at 25.0 °C.

$$ISO_3^- + H_2O \xrightarrow{k_h} I^- + SO_4^{2-} + 2H^+$$

A temperature-dependent stopped-flow study gives $\Delta H^{\ddagger} = 65$ kJ mol^{-1} and $\Delta S^{\ddagger} = 21$ J $mol^{-1}\ K^{-1}$ for the hydrolysis reaction. The positive $\Delta S^{\ddagger}$ value indicates a dissociative mechanism without the addition of H_2O in the transition state for ISO_3^- hydrolysis.

Introduction

The reaction between iodine and sulfite is a component of the Landolt[1] system (a mixture of acidic KIO_3 and Na_2SO_3 that is well-known as a clock reaction). The iodine reaction with sulfite is extremely rapid, but Bünau and Eigen[2] were able to measure the kinetics in acidic solution in the presence of excess iodide. The disappearance of I_3^- was followed by a continuous-flow method with dilute, equimolar reactants. They proposed reactions 1 and 2, where k_1' was 2.2×10^7 $M^{-1}\ s^{-1}$ and k_2' was 2.3×10^9 $M^{-1}\ s^{-1}$

$$I_3^- + HSO_3^- \xrightarrow{k_1'} HSO_3I + 2I^- \qquad (1)$$

$$I_2 + HSO_3^- \xrightarrow{k_2'} HSO_3I + I^- \qquad (2)$$

(22 °C, ionic strength $\mu = 1.0$). Unfortunately, the abstract of their paper gave an incorrect exponent for k_1' (10^9 rather than the 10^7 value reported in their tables of data) and the incorrect k_1' value was also given in *Chem. Abstr.* **1962**, *57*, 2891f. The proposed HSO_3I intermediate was treated as a steady-state species that hydrolyzed rapidly (eq 3). Inoue and Sudo[3] studied the

$$HSO_3I + H_2O \xrightarrow{k_h} HSO_4^- + I^- + 2H^+ \qquad (3)$$

reaction of I_2 and Na_2SO_3 by measurement of the temperature increase due to the heat of reaction under adiabatic conditions in a continuous-flow apparatus. They found that the initial reaction was too fast to be measured and that the rate obtained was due to the first-order hydrolysis of HSO_3I (eq 3). They reported a rate constant (k_h) of 130 s^{-1} at 17 °C for this hydrolysis.

A mixed Landolt chemical oscillator was demonstrated with hexacyanoferrate(II) as an additional reactant.[4] Edblom et al.[5] proposed a set of 13 elementary reactions and rate constants to fix the oscillatory behavior. The rate constant used for eq 4 was

$$I_2 + HSO_3^- + H_2O \rightarrow 2I^- + SO_4^{2-} + 3H^+ \qquad (4)$$

1.0×10^6 $M^{-1}\ s^{-1}$, which is 3 orders of magnitude lower than the value measured by Bünau and Eigen.[2] Luo and Epstein[6] proposed an alternative feedback pathway for the mixed Landolt reaction and gave a set of 10 elementary reactions to simulate the oscillatory behavior. They used 2.2×10^7 $M^{-1}\ s^{-1}$ as the value of the rate constant for eq 4 but suggested that most of the iodine was present as I_3^- to justify use of the rate constant for eq 1. Both oscillator studies[5,6] neglected the proposed HSO_3I intermediate.

The reaction of HOCl and SO_3^{2-} to give chlorosulfate (eq 5) proceeds by a very rapid Cl^+-transfer process with a rate constant

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