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Proton NMR Study of the Dissociation of the Lanthanum Cryptate of 4,7,13,16,21-Pentaoxa-1,10-diazabicyclo[8.8.5]tricosane

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We have used proton NMR spectroscopy to study the rate of dissociation of La[2.2.1]$(NO_3)_3$ in D_2O solutions with $I = 1.00$ M (NaCl). The dissociation obeys pseudo-first-order kinetics over the pH range from 1 to 13. The dissociation is independent of acid concentration but has a first-power dependence on hydroxide concentration. The variation in the experimental rate constant with hydroxide concentration has the form $k_{obs} = k_1(OH^-) + k_0$, with $k_1 = (1.05 \pm 0.01) \times 10^{-2}$ M^{-1} s^{-1} and $k_0 = (1.49 \pm 0.05) \times 10^{-5}$ s^{-1}. Changes in the NMR spectra that occur when the pH is increased above pH 9 suggest the formation of hydrolyzed La[2.2.1]$(OH)_x$ species at high pH.

Introduction

Cryptands are macropolycyclic amines with polyether linkages connecting the bridgehead nitrogen atoms. Their most noticeable feature is that the electron-donor groups define one or more metal-binding sites within the interior of the molecule. A great deal of experimental work has been done to understand the unusual complexation properties of these ligands.[1] Not only do they form strong aqueous complexes with traditionally weakly complexed cations such as the alkali-metal cations, but they also exhibit a marked selectivity in their complexation properties. For example, logarithms of the aqueous stability constants for alkali-metal cryptates with cryptand [2.2.1][2] show the following trend:[3] Li (2.50), Na (5.40), K (3.95), Rb (2.55), Cs (<2.0). The magnitudes of these complexation constants are unusually large when one considers that the cryptand ligand is electrically neutral. Since the bonding in complexes of hard cations such as the alkali-metal and alkaline-earth-metal cations is primarily electrostatic, few neutral ligands are able to compete with water molecules for the primary-sphere coordination sites. However, cryptands do form strong aqueous complexes because the cation is located inside a 3-dimensional cavity formed by the electron-donor groups (Figure 1).

Lanthanides also form cryptate complexes with primarily electrostatic bonding. However, there is a major difference between the aqueous solution chemistries of a lanthanide–cryptand system and that of an alkali-metal or alkaline-earth-metal system. In any aqueous metal–cryptand system the metal must compete with protons for the electron-donor nitrogen atoms. Since the pK_a values for the two nitrogens in cryptand [2.2.1] are 7.5 (pK_1) and 10.5[3,4] (pK_2), the lower pH limit where metals in general can successfully compete with protons is near pH 7. Unlike alkali-metal or alkaline-earth-metal cations, trivalent lanthanides hydrolyze significantly at this pH. Therefore, lanthanide–cryptate formation proceeds only slightly in aqueous systems. At low pH the diprotonated cryptand dominates the speciation; at high pH, cryptate formation is unable to compete with lanthanide hydrolysis. In addition, other cations that form cryptate complexes (like sodium) also decrease the extent of lanthanide–cryptate formation. For these reasons, nonaqueous syntheses are required to isolate the lanthanide cryptates.

While the evidence for selectivity in the formation of alkali-metal and alkaline-earth-metal cryptates is well-established, conflicting reports have been published concerning trivalent lanthanides. The earliest measurement shows a high selectivity between cryptands [2.2.1] and [2.2.2] for aqueous complexation of trivalent europium (log $K = 5.9$ and 3.4, respectively.)[5] In that study, stability constants for divalent europium cryptates were measured by potentiometry, and the trivalent stability constants were calculated from the formal potential differences between the europium–cryptate$^{3+/2+}$ and free-europium$^{3+/2+}$ couples.

In contrast, two later studies, one by direct potentiometry[4] and the other by spectrophotometry,[6] show little specificity for complexation of a number of trivalent lanthanides by cryptands [2.1.1], [2.2.1], and [2.2.2]. In the former, aqueous log K values of 6.8 and 5.9 were measured for europium complexation by cryptands [2.2.1] and [2.2.2], respectively. In addition, the stability constants for complexes from lanthanum to lutetium with all three ligands varied by only 1 order of magnitude. Since only a very restricted part of the possible titration curve (pH ≤6.4) was used to avoid lanthanide hydrolysis, the accuracy of an individual constant was limited to $\sim\pm 0.3$ log unit. However, the relative variation within the series of lanthanide cryptates should not be affected by this possible bias, and so the conclusion that the data show little specificity is still valid. Since the spectrophotometric measurements were made in the aprotic solvent dimethyl sulfoxide, cryptand protonation and lanthanide hydrolysis reactions are unimportant for this study. Measurements were made for lanthanides from praseodymium through ytterbium with the three ligands, although europium constants were not measured. Variations in stability constants of less than 1 log unit were found for a single cryptand with a series of lanthanides, and variations of less than half of a log unit were found for a single lanthanide with different cryptands.

Kinetic studies have shown that the selectivity of a particular cryptand toward the alkali-metal and alkaline-earth-metal cations is due primarily to variations in the metal-dissociation rates of the cryptates, with the most stable complex having the slowest dissociation rate.[7,8] This suggests that any selectivity trends displayed toward lanthanides might also be due to corresponding large differences in dissociation rates. However, kinetic data are available only for europium and ytterbium cryptates of [2.2.1] and [2.2.2].[5] For example, Eu[2.2.2]$^{3+}$ was shown to dissociate ~3300 times faster than Eu[2.2.1]$^{3+}$. We report here results for the dissociation kinetics of the lanthanum cryptate La[2.2.1].

Experimental Section

Solid La[2.2.1]$(NO_3)_3$ was synthesized according to the procedure developed by Pruett.[9] Lanthanum oxide was dissolved in a minimum of nitric acid, and the solution was heated to dryness to form lanthanum nitrate. The hydrated lanthanum nitrate was dissolved in dry acetonitrile, and the solution was refluxed under dry nitrogen with the dehydrating agent trimethyl orthoformate. Refluxing was continued after adding a slight molar excess (~5%) of cryptand [2.2.1] (Aldrich). After diethyl ether was added to the clear solution and the mixture was cooled to ~0 °C, the resulting solid was filtered, washed successively with ether and hexane, and dried at 110 °C overnight. The product was analyzed for

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(2) The notation used for cryptands and cryptate complexes is that used by Lehn.[1] The numbers in the brackets refer to the number of oxygen atoms in the three polyether strands connecting the nitrogen bridgeheads. The title ligand is therefore abbreviated as cryptand [2.2.1].

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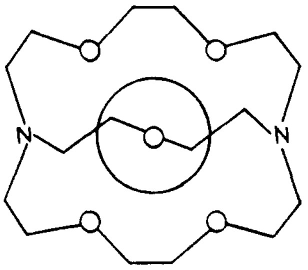

Figure 1. Structure of a $M[2.2.1]^{n+}$ cryptate complex.

lanthanum by EDTA titration with xylenol orange and for nitrate by the standard addition method with a nitrate ion selective electrode (Orion). In addition, the total organic hydrogen was determined by comparing the proton NMR intensities to that of a known concentration of internal chemical shift reference material. Anal. Calcd for $La(C_{16}H_{32}N_2O_5)(NO_3)_3$: La, 21.1; NO_3, 28.3; H, 4.91. Found: La, 20.6; NO_3, 28.7; H, 4.99.

Fourier transform proton NMR measurements in D_2O were made at 200 MHz with sodium 4,4-dimethyl-4-silapentane-1-sulfonate, DSS (Cambridge Isotope Laboratories), or acetonitrile as the internal reference [δ(acetonitrile)= δ(DSS) + 2.071 ppm]. Except for studies to measure the activation parameters for La[2.2.1] cryptate dissociation, all NMR measurements were made at ambient probe temperature (~24 °C). To measure the dissociation rate, a 7- to 15-mg sample of La[2.2.1] was placed in a centrifuge cone, and at zero time the sample was dissolved in 0.75 mL of the selected pH buffer. After brief centrifugation at ~15 000 rpm, the supernate was transferred to an NMR tube. Twenty to thirty spectra covering 4–5 half-lives were acquired for each experiment. The appropriate delay between spectra was obtained by selecting the number of pulses to be "discarded" before data acquisition in the programmable pulse sequencer of the spectrometer.

Solutions of various pH were prepared by using noncoordinating, deuterated buffers with the ionic strength adjusted to I = 1.00 M with NaCl. One experiment at pH 7 had ammonium chloride as the supporting electrolyte to measure the possible effect of sodium on the dissociation rate. Deuterium oxide and solutions of DCl, NaOD, and ND_3 were purchased from Cambridge Isotope Laboratories. Methylamine-d_5 hydrochloride-d was purchased from Aldrich Chemical Co. Hydroxylamine hydrochloride and hydrazine dihydrochloride were deuterated by repeated evaporation with D_2O. We used NaCl as the supporting electrolyte rather than $NaClO_4$ because of the formation of an insoluble La[2.2.1] species at pH 8 in perchlorate media. No solubility problems were encountered when chloride ion was used.

The pH quoted for an experiment is the average of the initial buffer pH and the sample pH at the end of the kinetics run. The pH electrode was calibrated operationally with standard phthalate, phosphate, and borate buffers. The pH measurements were made only to verify that the buffer capacity was not exceeded in the experiment. For this reason we did not convert hydrogen ion "activities" to concentrations, nor did a differentiate between normal hydrogen and deuterium.

For the activation energy measurements the diluent was preheated to the desired temperature, and the NMR probe temperature for each experiment was measured with a methanol (≤45 °C) or an ethylene glycol (>45 °C) thermometer.[10]

To calculate the rate constants, integration data from the NMR spectra were fit to the appropriate integral rate equation by using a compiled BASIC version of the Marquardt algorithm for nonlinear least-squares ffitting, rigorously weighted by the estimated uncertainties in the integrals.[11]

Results and Discussion

The La[2.2.1] complex dissociates very slowly (Table I) compared to the NMR time scale, which is on the order of microseconds. Consequently, the "free" and lanthanum-complexed ligands give rise to separate NMR signals. As the La[2.2.1] complex dissociates, the La[2.2.1] signals decrease, and the "free" [2.2.1] signals increase in intensity. The intensities as determined from the integrals provide a convenient measure of the relative amounts of each that exist as the complex dissociates.

The actual "free" cryptand species, which occur as La[2.2.1] dissociates, depend on the particular experimental conditions, namely the pH and the sodium concentration. Since each of the two nitrogens in [2.2.1] can be protonated, $H_2[2.2.1]^{2+}$, $H[2.2.1]^+$, and neutral [2.2.1] are possible components, while $La[2.2.1]^{3+}$ and $Na[2.2.1]^+$ are possible metal cryptate species. With I = 1.00

Table I. Dissociation Rates for La[2.2.1] in D_2O with I = 1.00 M (NaCl)

molarity and medium	pH	$t_{1/2}$, h[a]
0.596 DCl		11.73 ± 0.04
0.202 DCl		12.69 ± 0.05
0.4 ND_2OD	6.0 ± 0.1	11.8 ± 0.1
0.2 ND_2OD, 0.2 ND_2ND_2	6.98 ± 0.02	14.24 ± 0.09
0.2 ND_2OD, 0.2 ND_2ND_2[b]	7.2 ± 0.2	13.96 ± 0.08
0.333 ND_2ND_2	8.28 ± 0.07	13.2 ± 0.2
0.334 ND_3	9.4 ± 0.1	13.9 ± 0.2
0.432 CD_3ND_2	11.2 ± 0.1	4.4 ± 0.1
0.101 NaOD		0.182 ± 0.003
0.113 NaOD		0.155 ± 0.005
0.198 NaOD		0.090 ± 0.002
0.398 NaOD		0.046 ± 0.002

[a] Uncertainties in half-lives are 1σ errors from least-squares fits. [b] I = 1.00 M (ND_4Cl); no NaCl.

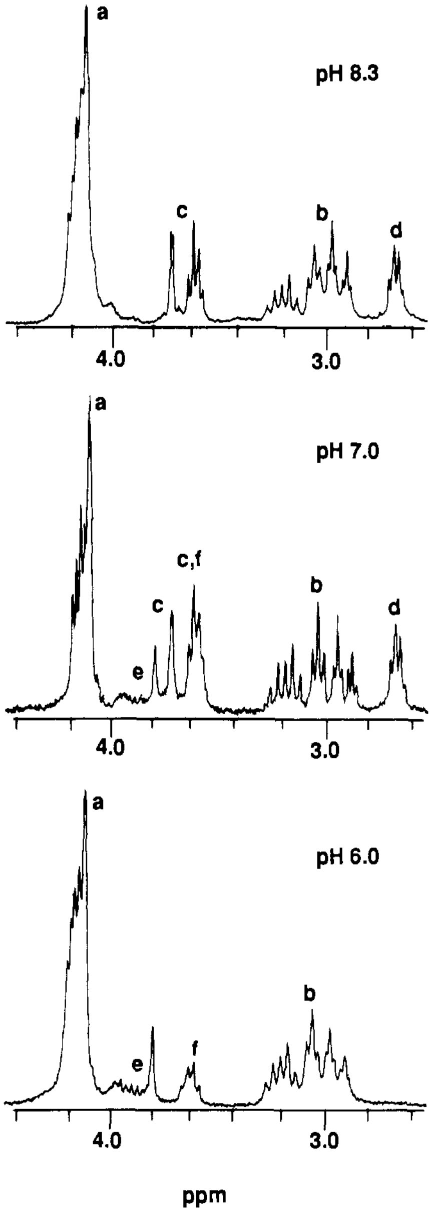

Figure 2. Proton NMR spectra for $La[2.2.1]^{3+}$ dissociation with I = 1.00 M (NaCl) at pH 6.0, 7.0, and 8.3. Assignments are as follows. La[2.2.1]: (a) O–CH_2; (b) N–CH_2. Na[2.2.1]: (c) O–CH_2; (d) N–CH_2. $H_2[2.2.1]$: (e) O–CH_2; (f) N–CH_2.

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Table II. Temperature Variation of Dissociation Rate Constants for La[2.2.1] in 0.202 M DCl with I = 1.00 M (NaCl)

T, K[a]	10^4k_0, s^{-1} [b]	T, K[a]	10^4k_0, s^{-1} [b]
298.4	0.1518 ± 0.0006	317.9	1.076 ± 0.027
309.6	0.503 ± 0.009	327.0	2.117 ± 0.056

[a] Uncertainties in the measured temperatures based on the calibration curves given in ref 10 are ±0.7 K (1σ). [b] Uncertainties in the rate constants are 1σ errors from least-squares fits.

M (NaCl), any neutral or monoprotonated cryptand that would exist if no sodium were present is totally converted to the sodium complex, so only La$[2.2.1]^{3+}$, Na$[2.2.1]^{+}$, and $H_2[2.2.1]^{2+}$ are observable in the NMR spectrum (Figure 2). At pH 6 the "free" cryptand is predominantly the diprotonated cryptand; at pH 8, it is entirely the sodium complex. In the intermediate pH region, separate signals from both species are observed, indicating that exchange between the two is also very slow. A detailed interpretation of the proton NMR spectra of lanthanide [2.2.1] complexes is given in ref 12.

For all experiments with I = 1.00 M (NaCl), the dissociation is a pseudo-first-order process that proceeds to completion. However, the rates of dissociation for pH ≥11 are much faster than those at pH ≤9.4. In addition, the proton NMR spectra of La[2.2.1] in strong base are extensively broadened and shifted, while the spectra are unchanged for pH <9.4. Therefore, these two pH regions are discussed separately.

Although the dissociation rates in the range pH 1–9 vary considerably compared to the errors determined form the individual fits (1–2%), the variation is more likely due to temperature variations from experiment to experiment rather than a true change in the dissociation mechanism. While the temperature of the NMR probe can be considered constant over the 2–3 days required for an individual experiment, several weeks to months might separate one measurement from another. The average probe temperature from two measurements separated by a 6-month interval was 24 ± 1 °C. To estimate the possible effect of temperature changes of this magnitude, we measured the dissociation rates over the range of 25–55 °C (Table II). From these data, temperature changes of ~1 °C correspond to an uncertainty of ±10% in the measured rate constant. Therefore, to this degree of precision the dissociation rate for pH ≤9.4 is constant, with an average half-life for dissociation of 12.9 ± 0.4 h.

Previous studies have shown that the dissociation of aqueous [2.2.1] cryptates of Na^+, Ag^+, Ca^{2+},[7] and Eu^{3+} [5] is acid-catalyzed at pH ≤2. However, our results indicate that protons (and by inference protonated buffer species) do not accelerate the dissociation of La[2.2.1]. Furthermore, since the rates at pH 7 in NaCl and NH_4Cl are identical, the presence of a cation such as sodium, which forms a [2.2.1] complex, also has no direct effect on the dissociation rate. This agrees with other studies that show the dissociation rates of metal cryptates are not affected by increases in the concentration of competing metal cations.[5,7,8] However, the competing cation can shift the final equilibrium composition. At pH 7 and I = 1.00 M (NH_4Cl) the dissociation reaches an equilibrium consisting of ~16% La$[2.2.1]^{3+}$ and ~84% "free" [2.2.1], while the dissociation when I = 1.00 M (NaCl) is complete. Since [2.2.1] does not form a complex with ammonium, the "free" [2.2.1] is predominantly $H_2[2.2.1]^{2+}$ with some H-$[2.2.1]^{+}$ in ammonium chloride media, while in sodium chloride it is predominantly Na$[2.2.1]^{+}$. Therefore, the presence of sodium is necessary to cause complete dissociation, since lanthanide hydrolysis and ligand protonation alone are not sufficient at pH 7.

Thus, the decomplexation of La$[2.2.1]^{3+}$ in the pH range 1–9 appears to be a true dissociative process:

$$\mathrm{La}[2.2.1]^{3+} \rightarrow \mathrm{La}^{3+} + [2.2.1]$$

with $k_0 = (1.49 \pm 0.05) \times 10^{-5}\ s^{-1}$, and scavenger cations such as protons or sodium ions only react with the neutral cryptand

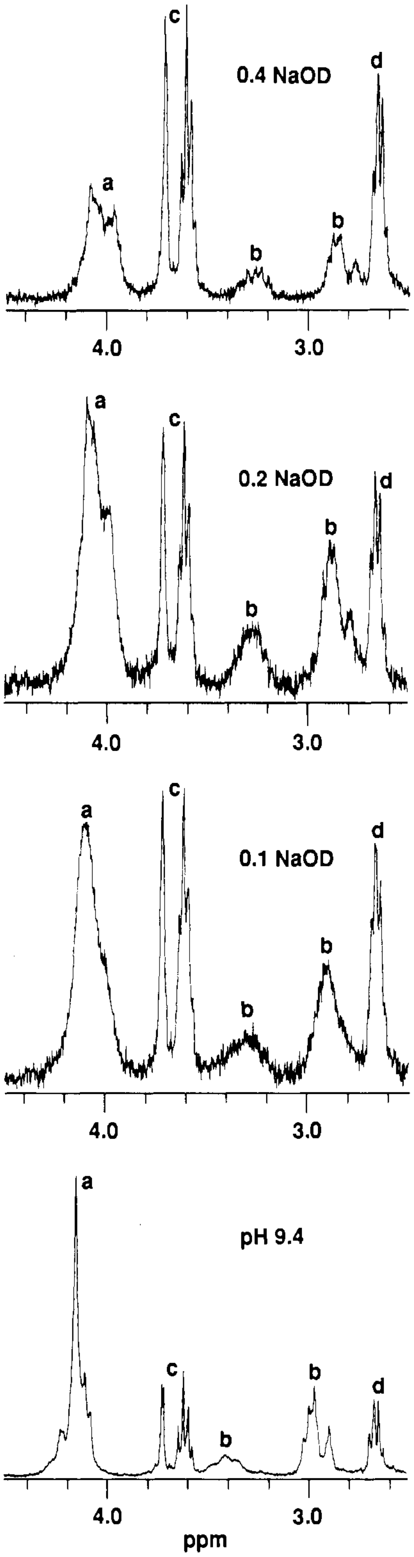

Figure 3. Proton NMR spectra for La[2.2.1] with I = 1.00 M (NaCl) at pH 9.4 and in 0.10, 0.20, and 0.40 M NaOD. Assignments are as follows. La[2.2.1]: (a) O–CH_2; (b) N–CH_2. Na[2.2.1]: (c) O–CH_2; (d) N–CH_2.

after the lanthanum has left the cryptand cavity. It is likely that this "unimolecular" path involves a change in hydration (i.e., involves water as a reactant), although we cannot observe the participation of water with our experimental conditions. Comparing this dissociation constant to those of noncryptate lanthanide complexes provides a clear demonstration of the restraints imposed by the unique geometry in these complexes. The La[2.2.1] dissociation rate is orders of magnitude slower than the millisecond or faster rates which are typical of other lanthanide complexes

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in aqueous solution. Even the very stable La–EDTA complex dissociates with a half-life of only a few seconds.[13] Since the metal cation is inside a central cavity in a cryptate complex, it is much more isolated from the solvent water molecules by the hydrophobic connecting strands than in simple macrocyclic and acyclic complexes. With this structure, the slow dissociation reaction can be understood if the mechanism is really an aquation reaction of the metal cation.

At pH ≥9.4 (Figure 3), changes in the proton NMR spectra strongly suggest the formation of hydrolyzed $La[2.2.1](OH)_x$ species. Since hydrolytic lanthanide reactions in the absence of solid/solution phase equilibria are much faster than the NMR time scale, the pH 9.4 spectrum is probably a weighted average of the component spectra, rather than the superposition of individual spectra observed in a slow-exchange process. The La[2.2.1] hydrolysis constants are necessary for estimating this composition. It has been reported that the first hydrolysis constant of $Eu[2.2.1]^{3+}$ is comparable to that of free Eu^{3+}.[5] A similar case for the La[2.2.1] complex would imply a first-hydrolysis constant of log $K \sim 5$,[14] and at pH 9.4 macroscopic amounts of $La[2.2.1](OH)^{2+}$ and $La[2.2.1]^{3+}$ would coexist in a ratio of ~2:1. Since the dissociation rate at pH 9.4 is unchanged from that observed at lower pH, the dissociation rate constants of the hydrolyzed species present must be nearly equal (within 10–20%) to that of the unhydrolyzed cryptate.

It is difficult to acquire high-resolution NMR spectra of La[2.2.1] in very basic solution, both because the dissociation rates are so fast and because the formation of insoluble $La(OH)_3$ as the cryptate dissociates might distort the spectra. Nevertheless, the spectral changes and increased dissociation rates that occur suggest the formation of more highly hydrolyzed species than those at pH 9.4. The last five data points in Table I show that the variation of the experimental first-order dissociation constant with hydroxide concentration is described by

$$k_{obs} = k_1(OH^-) + k_0$$

with $k_1 = (1.05 \pm 0.01) \times 10^{-2}\ M^{-1}\ s^{-1}$ and $k_0 = (1.7 \pm 0.2) \times 10^{-5}\ s^{-1}$. The intrinsic (uncatalyzed) dissociation rate constant determined from the analysis of the high-pH data agrees very well with that determined by averaging all of the data at pH ≤9.4 ($k_0 = (1.49 \pm 0.05) \times 10^{-5}\ s^{-1}$.) In order to include the data at pH 11.2 with those of the concentrated NaOD solutions, we calculated the hydroxide ion concentration in the methylamine buffer from the total analytical concentrations of methylamine hydrochloride and sodium hydroxide that were used to prepare the buffer and from the appropriate equilibrium constants at $I = 1.0$ M.[15] Thus, for total methylamine hydrochloride and sodium hydroxide concentrations of 0.432 and 0.325 M, $pK_a = 10.73$, and $pK_w = 13.79$, we calculate a free hydroxide concentration of 2.56×10^{-3} M in the buffer solution.

Although the likely mechanistic explanation for this hydroxide dependence is unclear, two general cases are possible:

$$(1)\ La[2.2.1](OH)_{x-1} + OH \xrightarrow{k_1} La[2.2.1](OH)_x \xrightarrow{\text{fast}} LaOH + [2.2.1]$$

$$\text{rate} = k_1\{La[2.2.1](OH)_{x-1}\}\ (OH)$$

and

$$(2)\ La[2.2.1](OH)_{x-1} + OH \overset{K}{\rightleftarrows} La[2.2.1](OH)_x \xrightarrow{k_2} LaOH + [2.2.1]$$

$$\text{rate} = k_2\{La[2.2.1](OH)_x\} = K\ k_2\{La[2.2.1](OH)_{x-1}\}\ (OH)$$

The first case involves the rate-determining reaction between a hydroxide ion and some less hydrolyzed lanthanum cryptate species. This would be very unusual, since lanthanide hydrolysis reactions are typically very fast. The second case involves a preequilibrium between successive hydrolyzed species, followed by the rate-determining dissociation of the second species. The first mechanism predicts that the rate should increase linearly with each increase in hydroxide concentration; the second predicts the change in rate with increasing hydroxide concentration should deviate from linearity as the concentration of the second species becomes appreciable and should become constant when the hydroxide concentration is high enough to completely form the second species. The expression for the fraction of the metal existing as the second species, $K(OH)/(1 + K(OH))$, varies linearly with hydroxide concentration only when $K(OH) \ll 1$, or $K \ll 1/(OH)$. Since the rate continues to increase linearly up to 0.4 M hydroxide (the highest concentration used), the stepwise equilibrium constant would have to be less than $K \sim 2$ if the preequilibrium model is valid. We cannot choose between these two possibilities with our current understanding of the data and interpretation of the spectra.

Table II summarizes the data we obtained for the temperature dependence of the rate constant, k_0, of the La[2.2.1] dissociation. The corresponding activation parameters for dissociation are $\Delta H^* = 73 \pm 3$ kJ mol^{-1} and $\Delta S^* = -93 \pm 9$ J mol^{-1} K^{-1}. These data are reasonably consistent with the only other activation data available for trivalent lanthanides: Eu[2.2.1] ($\Delta H^* = 80$ kJ mol^{-1}; $\Delta S^* = -103$ J mol^{-1} K^{-1}) and Yb[2.2.1] ($\Delta H^* = 93$ kJ mol^{-1}; $\Delta S^* = -44$ J mol^{-1} K^{-1}), corresponding to dissociation half-lives of 640 and 150 h, respectively.[5] Although the Yb entropy data appear anomalous, further considerations are not justified until more data for other lanthanides are available.

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