The Kinetics of Complexing of the Alkaline-Earth Ions with Several Cryptands

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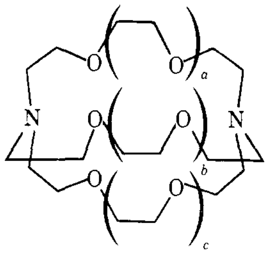
Abstract: The activation parameters for the formation of Ca^{2+} complexes with the cryptands, 2.2.2, 2.2.1, and 2.1.1, Sr^{2+} with 2.2.2 and 2.2.1, and Ba^{2+} with 2.2.2 have been measured using murexide and metalphthalein indicators. The corresponding values for the dissociation of the Ca^{2+} complexes of the three cryptands have been determined using appropriate alkali metal ions as scavengers for dissociated cryptand. The thermodynamic data derived from the kinetic results are in good agreement with independent values obtained potentiometrically and calorimetrically. The pH dependence of formation of Ca^{2+}, Sr^{2+}, and Ba^{2+} complexes of 2.2.2 has been measured. The data are analyzed.

Lehn and his colleagues have described the synthesis of a large number and variety of macrobicyclic and macrotricyclic ligands.[1] These have been termed cryptands and have the ability to combine with alkali and alkaline-earth cations to form metal cryptates of widely varying stability.[1-5] The ligands **1-3** typify the macrobicyclic class, and they completely envelope the metal ion in forming the complexes.



1, $a = b = c = 1$ (2.2.2)
2, $a = b = 1; c = 0$ (2.2.1)
3, $a = 1; b = c = 0$ (2.1.1)

Much more is known about the stability and selectivity of metal complexing with these and other macrocycles than about the dynamic aspects of the cryptation process. Early, temperature-dependent NMR spectra for mixtures of **1** and a number of metal complexes of **1** were described.[6] Exchange rate constants were equated to rate constants (k_d) for the dissociation of the metal cryptates ($M^{n+} = Na^+, K^+, Rb^+, Tl^+, Ca^{2+}, Sr^{2+}$, and Ba^{2+}).

$$M^{n+} + \mathbf{1} \rightleftarrows [M^{n+}\cdot\mathbf{1}] \quad k_f, k_d, K \qquad (1)$$

The combination of k_d and K values gave calculated formation rate constants ($k_f = Kk_d$) many orders of magnitude less than those normally encountered for alkali and alkaline-earth cation reactions, which are near diffusion controlled.[7-9]

These data suggested to us that the rates of formation and dissociation of cryptates, particularly of the alkaline earth metals, should be measurable by flow methods. We report in this paper on the kinetics of formation and dissociation of the cryptates of Ca^{2+} with **1-3**,[10] of Sr^{2+} with **1** and **2**, and of Ba^{2+} with **1**. Additionally, we have studied the effect of pH on the rate of formation of the Ca^{2+}, Sr^{2+}, and Ba^{2+} cryptates of **1**.

Experimental Section

Materials. The cryptands were obtained from E. Merck Laboratories. When the oils **2** and **3** showed signs of decomposition (yellow) they were purified by vacuum distillation. Standard aqueous solutions of the ligand were prepared by weight, and checked by potentiometric titration with standard acid. Piperidine was freshly distilled before use. All solids were reagent or analytical grade, and the metal or ammonium salts used were chlorides except calcium carbonate which was dissolved in HCl. Tetramethylammonium hydroxide was obtained as a 10% aqueous solution (J. T. Baker). Deionized water was boiled and cooled in the absence of air just prior to use.

Kinetics Procedure. Reaction rates and spectra were measured on a Gibson-Durrum stopped-flow D-130, Cary 14, or Beckman 24 spectrophotometer. Most of the formation rates were measured at pH 11.5 in 0.1 M ionic strength, using piperidine-piperidine H^+Cl^- both as a buffer and for control of ionic strength. A mixture of metal ion (~50 μM) and metal indicator (~5 μM) in one syringe was mixed with cryptand (~0.1-10 mM) and buffer in the other. In the studies of cryptate formation by Sr^{2+} and Ba^{2+}, the rapid complexing was occasionally followed by a slower, much smaller, absorption change which was ascribed to indicator decomposition or precipitation. Reactions with murexide were monitored at 505 nm, and with metalphthalein at 575 nm. The rate was not susceptible to wavelength or indicator concentration changes from 2 to 10 μM. In the pH studies, slightly buffered metal ion (~10^{-4} M buffer, 20 μM metal ion) with pH indicator (5 μM) was mixed with an excess of ligand (~0.5-2 mM) both preset to the desired pH using HCl or $(CH_3)_4NOH$ solutions. A change of about 0.10 pH unit attending complex formation was arranged. The buffer, indicator, and observation wavelength[11] used for the range of pH indicated follow: pH $\geqslant$ 10, piperidine, murexide, 505 nm; pH 9.2-9.6, NH_3, phenolphthalein, 552 nm; pH 8.0-8.6, Tris, phenol red, 560 nm; pH 6.6-7.4, Pipes or Hepes, bromothymol blue, 620 nm. For the studies of the dissociation of the calcium cryptates, calcium ion ($0.4-1.0 \times 10^{-4}$ M) and a small excess of cryptand ($1-3 \times 10^{-4}$ M) were mixed with scavenger metal ion K^+ ($1-3 \times 10^{-3}$ M) or Ba^{2+} ($0.5-1.7 \times 10^{-3}$ M) for **1**, Na^+ (30-90 mM) for **2**, and Li^+ (30-70 mM) for **3** containing murexide (5 μM). The rate constant was independent of the concentrations of calcium cryptand (6-100 μM) and scavenging ion (0.7-2.0 mM). Murexide decomposes in basic solution, particularly when metal complexed.[12] Fresh solutions were used and stored in ice for each set of runs. A series of runs with increasingly aged indicator, but otherwise identical, gave decreasing spectral changes, but identical rate constants, showing that the decomposition product and the concentration of indicator were without effect. In formation runs at pH 11.5 and 9.2 and dissociation runs at pH 11.5, three to five different temperatures were studied. All reactions were first order and oscilloscope traces were treated by standard methods. Exclusion of metal ion from all systems removed flow measurable time-dependent absorption changes.

Results

Monitoring. One of the problems which early arose was the monitoring of these rapid reactions, which are attended by little or no absorption change in the visible and ultraviolet. It was necessary to resort to indicators which would respond to changes in the concentrations of the metal ion as cryptate formation or dissociation occurred. The indicator had to satisfy the criteria of (a) responding rapidly (and preferably linearly) to metal ion concentration and (b) not interacting with cryptand or cryptate. Murexide monitors calcium ion ion concentration but only responds to very high concentrations of strontium and barium ions and could not be used for these.[12]

Table I. Activation and Thermodynamic Parameters for Reaction of Alkaline-Earth Ions with Cryptands in Water at 25 °C, I = 0.1 M

Cryptate	k_f, M^{-1} s^{-1}	$\Delta H_f^{\ddagger}$, kcal mol^{-1}	$\Delta S_f^{\ddagger}$, cal mol^{-1} deg^{-1}	k_d, s^{-1}	$\Delta H_d^{\ddagger}$, kcal mol^{-1}	$\Delta S_d^{\ddagger}$, cal mol^{-1} deg^{-1}
Ca^{2+}, **1**	$7.3 \times 10^{3\,a}$	7.9	−14	0.26^{a} (0.21^{i})	8.4	−33
Ca^{2+}, **2**	$1.6 \times 10^{4\,g}$	13.8	+7	2.2 $(0.2,^{h}$ $0.66^{i}) \times 10^{-3}$	15.1	−20
Ca^{2+}, **3**	$1.1 \times 10^{2\,g}$	13.7	−3	0.69 (0.82^{i})	13.4	−14
Sr^{2+}, **1**	1.0×10^{4}	7.4	−15	1.0^{c} $(0.6,^{h}$ $0.75^{i}) \times 10^{-4}$	17.7^{c}	-17^{c}
Sr^{2+}, **2**	$5.7 \times 10^{4\,g}$	12.7	+5	2.6^{c} $(0.8,^{h}$ $1.5^{i}) \times 10^{-3}$	18.8^{c}	-8^{c}
Ba^{2+}, **1**	7.0×10^{4}	6.8	−13	2.2^{c} $(1.0,^{h}$ $1.8^{i}) \times 10^{-5}$	20.9^{c}	-9^{c}
Ca^{2+}, **1**[b]	1.4×10^{3}	16.9	+13			
Sr^{2+}, **1**[b]	2.2×10^{3}	16.2	+11			
Ba^{2+}, **1**[b]	1.3×10^{4}	19.5	+26			

Cryptate	K,[d] M^{-1}	ΔH,[d] kcal mol^{-1}	ΔS,[d] cal mol^{-1} deg^{-1}	K,[e] M^{-1}	ΔH,[e] kcal mol^{-1}	ΔS,[e] cal mol^{-1} deg^{-1}
Ca^{2+}, **1**	2.8×10^{4}	−0.5	+19	2.5×10^{4}	−0.2	+20
				$3.7 \times 10^{4\,f}$	-0.2^{f}	$+20^{f}$
Ca^{2+}, **2**	7.3×10^{6}	−1.3	+27	8.9×10^{6}	−2.9	+22
Ca^{2+}, **3**	2.0×10^{2}	−0.3	+11	3.2×10^{2}	−0.1	+11
Sr^{2+}, **1**				1.0×10^{8}	−10.3	+2
				$1.8 \times 10^{8\,f}$	-10.6^{f}	$+2^{f}$
Sr^{2+}, **2**				2.2×10^{7}	−6.1	+13
Ba^{2+}, **1**				3.2×10^{9}	−14.1	−4
				$5.0 \times 10^{9\,f}$	-14.3^{f}	-4^{f}

[a] Reference 1 cites values for $k_f \geqslant 10^3$ and $k_d \approx 0.1$ at 25 °C by a potentiometric method. [b] Data obtained at pH 9.2. [c] Combining formation rate data with thermodynamic data (ref 3–5). [d] From kinetic data, $K = k_f/k_d$; $\Delta H = \Delta H_f^{\ddagger} - \Delta H_d^{\ddagger}$; $\Delta S = \Delta S_f^{\ddagger} - \Delta S_d^{\ddagger}$. [e] From potentiometric and calorimetric studies, I = 0.05 M (ref 3, 5). [f] Reference 4, I = 0.1 M. [g] At pH 11.5, only ~90% of ligand is present as unprotonated base. A small adjustment of k_f (10% higher than stated) should be made. [h] Reference 19. [i] Reference 18.

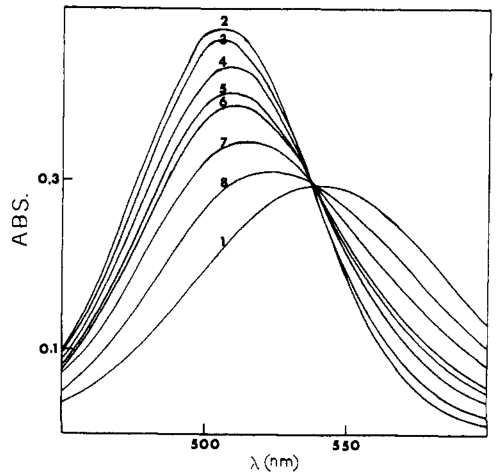


Figure 1. Spectra of mixtures of murexide (m), 28 μM, cryptand (C), and calcium ion at pH 11.5, I = 0.1 M and 25 °C. 1, m alone; 2, m + Ca^{2+} = 0.32 mM; 3, m + Ca^{2+} = 0.16 mM; 4, m + Ca^{2+} = 81 μM; 5, m + Ca^{2+} = 49 μM; 6, m + Ca^{2+} = 81 μM + C = 68 μM; 7, m + Ca^{2+} = 81 μM + C = 0.14 mM; 8, m + Ca^{2+} = 81 μM + C = 0.23 mM.

The Ca^{2+}-murexide equilibrium is very rapidly established in aqueous[13] and methanol[7] solution. An isosbestic point at 538 nm for the Ca^{2+}-murexide complex in mixtures with murexide is maintained when **1** is added to the system (Figure 1). Formation constants for the Ca^{2+}-murexide and Ca^{2+}-**1** complexes from analysis of these spectra (7.6 ± 2.0 × 10^4 and 8.5 ± 2.0 × 10^4 M^{-1}) are in fair agreement with the more accurate literature[3,12] values (6 × 10^4 and 3.7 × 10^4 M^{-1}). Metalphthalein was used as an indicator for Sr^{2+} and Ba^{2+} ions.[14] The equilibrium between Ca^{2+} and metalphthalein is rapidly established[15] and a similar rapidity would be anticipated for Sr^{2+} and Ba^{2+} and was indeed found in separate stopped-flow experiments. At pH 10–11.5, the pale pink indicator was transformed into the deep violet of the complex.[14] The indicator–metal ion interactions were not modified spectrally by addition of **1**. Thus, small concentrations of metal ion (< 50 μM) react rapidly and in a linear fashion (optical absorbance vs. metal ion concentration) with these indicators.

Formation Rates at High pH. Since the experiments were carried out at pH ~11.5, the reactions involve predominantly the unprotonated ligand (vide infra). The cryptand concentration [C] was used in excess over metal ion, so that (a) there would be a more sensitive metal indicator spectral change and (b) reaction 1 would reduce to a pseudo-first-order reaction in the forward direction and a first-order reaction in the reverse. For this situation, a first-order rate constant, k_{obsd}, describes the approach to equilibrium, and is the sum of the first-order rate constants for the forward and reverse directions,[16] i.e.,

$$-\frac{1}{[M^{n+}] - [M^{n+}]_e}\frac{d[M^{n+}]}{dt} = k_{obsd} = k_f[C] + k_d \quad (2)$$

A typical plot (for k_{obsd} vs. concentration of cryptand **1** in Ca^{2+} complexing) has been recorded previously.[10] The slope of the appropriate plot gives an accurate value for the second-order formation rate constant k_f. These are collected in Table I, together with activation parameters for a number of systems (see also Figure 2). The Ca^{2+}-**1** system was most carefully studied to examine various effects. The formation rate constant doubled and the dissociation rate constant decreased by 30% when the ionic strength was raised from 0.05 to 0.3 M. The rate constant was the same whether the ionic strength of 0.1 M was provided by piperidine or $(CH_3)_4N^+$ medium. Only approximate values for the intercept of the k_{obsd} vs. [C] plot are obtained and accurate values for k_d, particularly when required in temperature variation studies, are best obtained directly.

Dissociation Rates. These were studied only for the Ca^{2+} complexes of the three cryptands. The rates were measured by reacting the cryptate $[Ca^{2+} \cdot C]$ with an appropriate metal ion M^{2+}:

$$[Ca^{2+} \cdot C] \rightleftarrows Ca^{2+} + C \quad k_1, k_{-1} \quad (3)$$

$$C + M^{n+} \rightleftarrows [M^{n+} \cdot C] \quad k_2, k_{-2} \quad (4)$$

$$Ca^{2+} + \text{murexide} \rightleftarrows \text{Ca(murexide) fast} \quad (5)$$

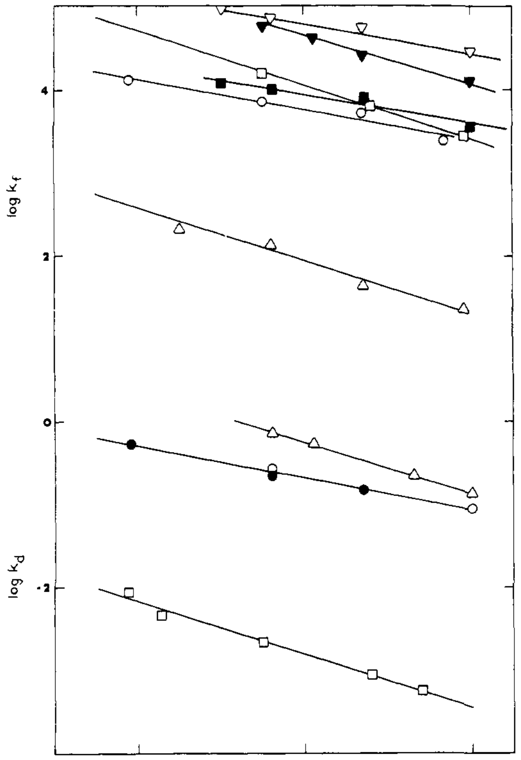


Figure 2. Arrhenius plots for formation and dissociation of cryptates at pH 11.5 and $I = 0.1$ M. ○, Ca^{2+} – 1, K^+ scavenger; ●, Ca^{2+} – 1, Ba^{2+} scavenger; □, Ca^{2+} – 2; △, Ca^{2+} – 3; ■, Sr^{2+} – 1; ▼, Sr^{2+} – 2; ▽, Ba^{2+} – 1.

The scavenger ion was chosen so that (a) $k_2[M^{n+}][C] \gg k_{-1}[Ca^{2+}][C]$ and (b) the stability of the M^{n+} complex was greater than that of Ca^{2+} so that the reaction was irreversible (k_{-2} could be ignored). With these conditions,

$$-\mathrm{d} \ln [Ca^{2+} \cdot C]/\mathrm{d}t = k_{obsd} = k_1 \qquad (6)$$

Certain of the alkali metal ions or (high concentrations of) Ba^{2+} ion are effective scavengers for the three systems studied since they react more rapidly and quantitatively with the cryptands than does Ca^{2+} ion.[1] This was shown by the value of k_{obsd} being independent of the concentration (and in certain cases the nature) of the scavenger (Figure 2). All studies were carried out in the same conditions as the formation experiments. Figure 2 shows temperature variation plots for the three dissociations studied.

The slow dissociation of the Sr and Ba cryptates and the instability of the metalphthalein indicator over long periods of time precluded a monitoring of the dissociation in situ. Using a batch method led to erratic results, which were traced to indicator instability and precipitation in the high concentrations of scavenger ions, which were necessary to promote dissociation. We therefore combined our formation rate data with the thermodynamic values of Lehn et al.,[3,5] to calculate dissociative rate data. These are included in Table I.

Effect of pH on the Formation of Ca^{2+}, Sr^{2+}, and Ba^{2+} Complexes with 1. We have determined the ionization constants K_1 and K_2 (eq 7, 8) of mono- and diprotonated cryptand **1** in the conditions of our kinetic experiments. The values, $pK_1 = 7.4$ and $pK_2 = 9.8$ at 25 °C and $I = 0.1$ *M*, compare well with literature values ($pK_1 = 7.3$[3,4] and $pK_2 = 9.6$[3], 9.7[4]).

$$CH_2^{2+} \rightleftarrows CH^+ + H^+ \quad K_1 \qquad (7)$$

$$CH^+ \rightleftarrows C + H^+ \quad K_2 \qquad (8)$$

Since the alkaline earth ions form stable complexes with **1** it was possible to investigate the effect of pH to as low a value as 6.5 on the rates of complexing. There is a release of protons which attends cryptate formation (eq 10 and 11)

$$C + M^{2+} \rightarrow [M^{2+} \cdot C] \quad k_1 \qquad (9)$$

$$CH^+ + M^{2+} \rightarrow [M^{2+} \cdot C] + H^+ \quad k_2 \qquad (10)$$

$$CH_2^{2+} + M^{2+} \rightarrow [M^{2+} \cdot C] + 2H^+ \quad k_3 \qquad (11)$$

when pH $\lesssim pK_2$, since the cryptate complex is not protonated.[3] The decrease in pH can be monitored by acid-base indicators. Since the equilibria eq 7 and 8 are rapidly established, the temporal spectral change associated with a pH change reflects accurately the rate of complex formation. For this system the rate of loss of total cryptand, $[C]_{total}$, is given as[16a]

$$-\mathrm{d}[C]_{total}/\mathrm{d}t = k_f[C]_{total}[M^{2+}] \qquad (12)$$

and

$$k_f = \frac{k_3[H^+]^2 + k_2K_1 + k_1K_1K_2}{[H^+]^2 + K_1[H^+] + K_1K_2} \qquad (13)$$

The decrease in rate as the pH is lowered below pK_2 suggests that CH^+ (and CH_2^{2+}) is unreactive. If $k_2 = k_3 \sim 0$, eq 13 then simplifies to

$$k_f = \frac{k_1K_1K_2}{[H^+]^2 + K_1[H^+] + K_1K_2} \qquad (14)$$

The experimental values of k_f vs. pH for complexing of **1** by Ca^{2+}, Sr^{2+}, and Ba^{2+} are shown in Figure 3. The single solid curve is based on eq 14, using $K_1 = 4 \times 10^{-8}$ M, $K_2 = 1.6 \times 10^{-10}$ M, and $k_1 = 7.3 \times 10^3$ (Ca^{2+}), 1.1×10^4 (Sr^{2+}), and 6.5×10^4 M^{-1} s^{-1} (Ba^{2+}), the rate constants being obtained at pH 11.5 using metal indicators. The agreement between experimental points and the theoretical equation is very good. This result supports the assumption of unreactivity of the protonated cryptands, and indicates that any (small amount of) hydroxy form of the metal ion present at pH 11.5 has a similar reactivity to that of the aquated species. Finally, the metal- and pH-indicator monitoring give consistent results. The plots of k_{obsd} vs. $[C]_{total}$ used to calculate k_f gave zero or near-zero intercepts over the pH range examined, indicating

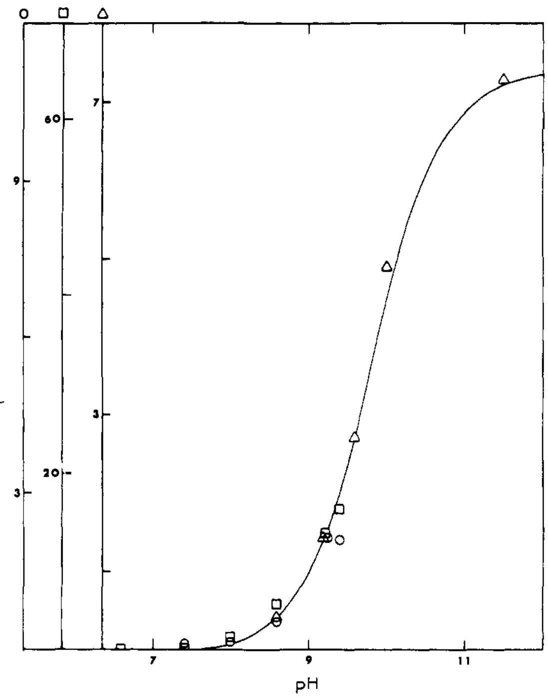


Figure 3. Rate constant-pH profile for formation of Ca^{2+} (△), Sr^{2+} (○), and Ba^{2+} (□) complexes of **1** at $I = 0.1$ M and 25 °C.

the small value of k_d even at lowered pH. There is evidence that at higher acid pH, an acid-catalyzed path may contribute to dissociation.[18]

At pH 9.2, the cryptand **1** is mainly present as the monoprotonated form. The enthalpy of activation for reaction of the cryptand at this pH will therefore be the sum of the heat of reaction 8 and the enthalpy of activation of reaction 9. The former value has been measured as 10.8 kcal mol^{-1} (ref 4), and therefore from Table I, the calculated values of $\Delta H_f^{\ddagger}$ for eq 9 are 6.1 (Ca^{2+}), 5.4 (Sr^{2+}), and 8.7 (Ba^{2+}). These compare quite well with those determined directly at pH 11.5, namely, 7.9 (Ca^{2+}), 7.4 (Sr^{2+}), and 6.8 (Ba^{2+}), all units in kcal mol^{-1} at 25 °C. The data show, however, that small differences or trends in $\Delta H^{\ddagger}$ values should be deemphasized.

Discussion

Cox and Schneider[18] have recently reported the rate constants for dissociation of a number of cryptates, by adding excess acid and monitoring attendant pH changes by a conductance-stopped flow method. The acid-independent dissociation rate constants are included in Table I. By following the slow pH changes which occur during titration experiments, approximate dissociation rate constants for a number of cryptates have also been reported.[6,19] All these values are in reasonable agreement with the present work. The agreement of values for K, ΔH, and ΔS calculated from kinetic data with the values obtained potentiometrically[3] and calorimetrically[5] for Ca^{2+} with **1-3** is very good (Table I).[10]

Cryptate formation and dissociation are straightforward second-order and first-order processes, respectively. These characteristics do not differ then from complex formation by many other ligands with metal ions. However, the formation rate constants are several orders of magnitude lower than for complexing of alkali or alkaline-earth ions with simple ligands[7,9] or biological carriers (often in methanol solution).[8,20] This may reside in a very low concentration of the reactive endo, endo form (in which lone pairs of the bridgehead nitrogens are directed inside the cavity) of the cryptand in solution.[10] Alternatively, or additionally, the reaction may be strongly sterically controlled[21] in that first bond formation is not very effective with this rigid ligand. The reaction order $Ca^{2+} < Sr^{2+} < Ba^{2+}$ toward **1** and $Ca < Sr^{2+}$ toward **2** parallels the expected lability of the metal ion[7,9] and indicates that desolvation of the metal ion is important before or at the rate-determining stage of cryptate formation.

It appears that the most stable complex of a pair or trio of cryptands with a common ion is generally a result of its having the slowest dissociation rate,[22] and an attendant large $\Delta H_d^{\ddagger}$.[22] However, our data also indicate that values of k_f vary substantially and the situation is more complex than with simple octahedral complex formation.[17b]

The activation entropies support the idea[1,23] that the transition state lies nearer to reactants than cryptate product. Some water may be lost on going to the transition state but this is offset by a considerable decrease in ligand internal and translational entropies. The result is a negative $\Delta S_f^{\ddagger}$. In the reverse direction, a number of water molecules becomes coordinated to metal ion, which still binds to cryptand (although probably outside the ligand cavity). This gives a large negative $\Delta S_d^{\ddagger}$. The dissociation therefore involves substantial opening up of the cryptate and the relatively large values of $\Delta H_d^{\ddagger}$ arise from a number of contributions—disruption of the solvation of the cryptate, opening the cryptate, and rupturing metal ion-ligand bonds. The data for dissociation of the alkaline-earth cryptates contrast with those for dissociation of potassium[18] and sodium[24] cryptates with **1**. Enthalpies of activation are high (20.7 and 16.1 kcal mol^{-1}, respectively) but positive entropies of activation (+16 and +5 eu) lead to much larger k_d values than for the Ca, Sr, and Ba cryptates with **1**. Further data in this area promise to be very interesting.

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