field calculations because this type calculation does not account for any interaction of the vibrational modes.

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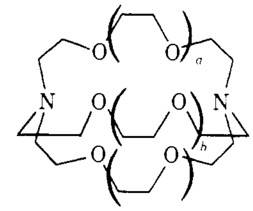
The Kinetics of Complexing of Calcium Ion with Several Cryptands

Sir:

The synthesis of a number of ligands of the type **1**-**3** has been described by Lehn and his colleagues.[1] These macrobicycles, termed cryptands,[2] have an ability to combine with alkali and alkaline-earth cations to form the metal cryptates. Their stability is dependent on the relative sizes of the cation and the cavity of the ligand, in which the cation is located. Much more is known about the stability and selectivity of metal complexing with these and other macrocycles, than about the dynamic aspects.[1,3] Temperature-dependent NMR spectra for mixtures of **1** and a number of metal ion complexes of **1** in D_2O were observed.[4] Exchange rate constants, associated with these spectra, 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+}):



1, $a = b = c = 1$
2, $a = b = 1$; $c = 0$
3, $a = 1$; $b = c = 0$

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

The calculated[1] formation rate constants ($k_f = Kk_d$) for these processes are many orders of magnitude lower than those normally encountered for alkali and alkaline-earth cation reactions, which are near diffusion controlled.[5]

These data suggested to us that the rates of formation and dissociation of these cryptates would be susceptible to measurement by flow methods. Little visible or ultraviolet spectra is associated with the ligand or metal complex, but we have been able to study the complexing of Ca^{2+} with **1**-**3** using murexide as indicator;[6] the Ca^{2+}-murexide equilibrium is very rapidly established in aqueous[7] and methanol[5] solution. The rate of the reaction of Ca^{2+} ion with the cryptands **1**-**3** (Merck Laboratories, N.Y.) was measured from 5 to 40° at pH ~11.5 and $I = 0.1$ *M* using a Gibson-Durrum stopped-flow spectrophotometer. Piperidine-piperidine H^+Cl^- was used as a buffer and for adjustment of ionic strength. At these alkalinities, the cryptands are present as unprotonated bases. The approach to equilibrium was strictly first order, when the ligands were used in large excess. The associated rate constant k_{obsd} was related to the cryptand concentration [C] by (2)

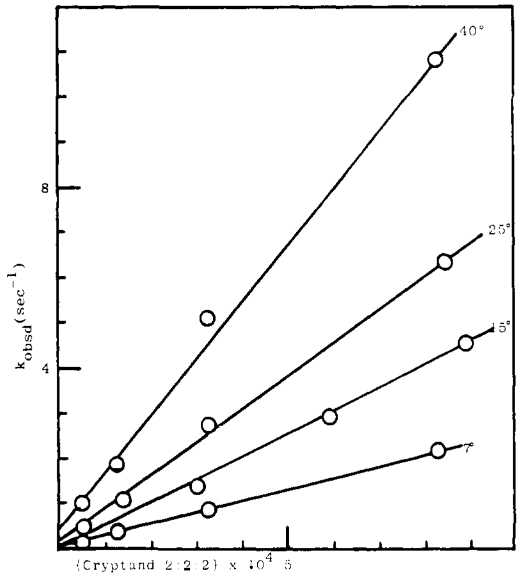


Figure 1. Plot of k_{obsd} vs. concentration of cryptand **1**, at various temperatures, pH 11.3-11.7, $I = 0.1$ *M*.

$$-\frac{1}{[Ca^{2+}]}\cdot\frac{d[Ca^{2+}]}{dt} = k_{obsd} = k_f[C] + k_d \tag{2}$$

Plots of k_{obsd} vs. [C] are shown in Figure 1 for reaction of **1** at various temperatures. Only approximate values for the intercepts can be obtained, and accurate values for k_d were obtained directly by treating the calcium cryptate with an appropriate scavenger ion. For example, dissociation of $[Ca^{2+}\cdot\mathbf{1}]$ could be effected by Ba^{2+} or K^+ ions.[1] The first-order rate constant, using murexide indicator, was independent of the concentration and the nature of the scavenger and could thus be equated with k_d. *Thus no associative path in the metal interchange was important.* Activation parameters determined in these ways are collected in Table I. The independence of rate constants observed from pH ~10 to 11.5 shows that there is no participation of basic form of calcium(II) in the complexing. A small dependence on ionic strength of both the forward and reverse rate constants was noted. The agreement between formation constants from our kinetic data and potentiometric studies is good (Table I). Except for the cryptand **1**, agreement between enthalpies and entropies of reaction from kinetics and calorimetry is very poor. We have no explanation for these discrepancies.

Since the earlier work of Lehn, Sauvage, and Dietrich,[4] there have been several reported NMR studies of exchange reactions of metal cryptates.[2,8-11] It appears that the most stable complex of the triad of cryptands with a common metal ion is a result generally of having the slowest dissociation rate. Our results for the Ca^{2+} complexes show also that the most stable cryptate (with **2**) dissociates by far the slowest. It is attended by a large activation energy, although this is offset by a more positive entropy of activation (compared with cryptates of **1** and **3**). The 10^4 faster dissociation rate for Li^+-**2** than Li^+-**3** in pyridine resides also in a lower $\Delta H^{\ddagger}$ (by 6 kcal mol^{-1}).[11]

It has been suggested that the mechanism of complexation is intricate because of conformational equilibrium in the ligands.[1,4] A number of cryptate complexes and the solid cryptand **1** have an endo-endo configuration in which the lone pairs of the bridgehead nitrogens are directed inside the cavity.[1] In the exo-exo form the lone pairs are directed away from the cavity and this would not be expected to complex appreciably with metal ions. If therefore this is

Table I. Activation and Thermodynamic Parameters for Reaction of Ca^{2+} Ion with Cryptands in Water at 25°, $I = 0.1\ M$

Cryptand	k_f, $M^{-1}\ sec^{-1}$	$\Delta H_f^\ddagger$, kcal mol^{-1}	$\Delta S_f^\ddagger$, cal $mol^{-1}\ deg^{-1}$	k_d, sec^{-1}	$\Delta H_d^\ddagger$, kcal mol^{-1}	$\Delta S_d^\ddagger$, cal $mol^{-1}\ deg^{-1}$
1	6.6×10^{3a}	7.5	−15	0.26^a	8.2	−33
2	1.2×10^4	10.6	−4	1.9×10^{-3}	17.8	−11
3	1.6×10^2	7.8	−22	0.10	2.7	−54

Cryptand	K,[b] M^{-1}	ΔH,[b] kcal mol^{-1}	ΔS,[b] cal $mol^{-1}\ deg^{-1}$	K,[c] M^{-1}	ΔH,[c] kcal mol^{-1}	ΔS,[c] cal $mol^{-1}\ deg^{-1}$
1	2.5×10^4	−0.7	+18	2.5×10^4 $(3.7 \times 10^4)^d$	−0.2 $(-0.2)^d$	+20 $(+20)^d$
2	6.2×10^6	−7.1	+7	9.0×10^6	−2.7	+23
3	1.6×10^3	+5.1	+32	6.3×10^2	0	+13

[a] Reference 1 cites values for $k_f \geqslant 10^3$ and $k_r \approx 0.1$ at 25° by a potentiometric method. [b] From kinetic data, $K = k_f/k_d$; $\Delta H = \Delta H_f^\ddagger - \Delta H_d^\ddagger$; $\Delta S = \Delta S_f^\ddagger - \Delta S_d^\ddagger$. [c] From potentiometric and calorimetric studies in 0.04–0.08 M NMe_4Br solutions ref 3 and 18. [d] Reference 19.

the predominant form in solution, and the equilibrium is established rapidly,[12] the rate of reaction could be substantially reduced, e.g.

$$\text{exo–exo} \overset{K_c}{\rightleftharpoons} \text{endo–endo} \xrightarrow[Ca^{2+}]{k_{Ca^{2+}}} Ca \cdot (\text{endo–endo})^{2+} \quad (3)$$

from which $k_f \sim K_c k_{Ca^{2+}}$. If $k_{Ca^{2+}}$ is a "normal" rate constant[5,13] $\sim 10^9\ M^{-1}\ sec^{-1}$, K_c would need to be $\sim 10^{-5}$ to produce the observed formation rate constants. The values of K_c might be expected to vary for the three cryptands leading to some variation in k_f. For a particular cryptand, and a series of reactions with different metal ions M^{n+}, k_f might parallel the substitution lability of M^{n+}.[5,13] Preliminary data[1,4] support this for the reaction of **1**, $Ca^{2+} \sim Sr^{2+} < Ba^{2+}$; $Na^+ < K^+ < Rb^+$. This reactivity pattern does not support the idea of a rate-limiting conformational change associated with complexation (as proposed in the Ca^{2+}, antamanide case).[14]

It has been suggested[1,8] that the transition state involves little loss of water bound to metal ion. The activation entropies support this idea. While ΔS is positive in all three cases, reflecting the fact that most,[15] if not all,[16] of the water coordinated to the metal is lost on complex formation,[17] $\Delta S_f^\ddagger$ is negative and $\Delta S_d^\ddagger$ is more negative. While some water may be lost on going to the transition state, this could be balanced by a considerable decrease in ligand internal entropy resulting in $\Delta S_f^\ddagger$ being negative. The remaining water molecules are then stripped off as rapid insertion into the bicyclics occurs. In the reverse direction, the water molecules are again coordinated to Ca^{2+}, giving a large negative $\Delta S_d^\ddagger$.

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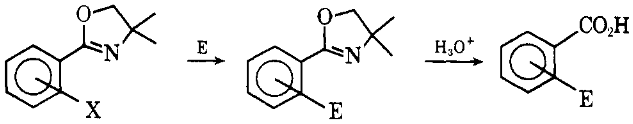
Oxazolines. XXII. Nucleophilic Aromatic Substitution on Aryl Oxazolines. An Efficient Approach to Unsymmetrically Substituted Biphenyls and *o*-Alkyl Benzoic Acids

Sir:

In previous reports, we[1a,b] and others[1c] have demonstrated that aryl oxazolines **1a, 1b** may be transformed into their metalated derivatives **1c, 1d** which are capable of elaboration with a variety of electrophiles, E, to substituted aryl oxazolines **2**. Hydrolysis in aqueous acid provides a



1a, X = *o*-, *m*-, *p*-Br
1b, X = H
1c, X = MgBr
1d, X = Li

2
(E = alkyl, allyl, D, acyl, thioalkyl)

3

route to ortho-, meta-, and para-substituted benzoic acids. We now report that aryl and alkyl substitution may be readily accomplished via a nucleophilic mode by displacement of an *o*-methoxy group with organometallics in 2-(*o*-methoxyphenyl)oxazolines **4**. Treatment of **4a**[2] or **4b** with either Grignard reagents (Et_2O–THF, 25°) or organolithium reagents (THF, −45°) gave good-to-excellent yields of the 2-substituted phenyl oxazolines **5** which were hydrolyzed to the corresponding biphenic acids **6** (R = aryl) or alkyl benzoic acids **6** (R = alkyl). The results of various organometallic reactions with **4a** and **4b** are tabulated in Table I. It is interesting to note that in those instances where the aryl lithium reagents gave poor yields of **5**, the corresponding Grignard reagent proved to be much more effective (compare entries 6 and 7, 8 and 9). For alkyl metallics, there appears to be little difference in the yield of aromatic substitution (entries 10 and 11) although the alkyl