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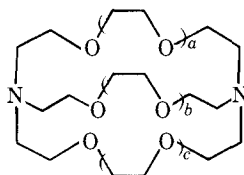# Kinetics of Alkali Metal Complex Formation with Cryptands in Methanol

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Contribution from the Max-Planck-Institut für Biophysikalische Chemie, D-3400 Göttingen, West Germany, and The Chemistry Department, University of Stirling, Stirling FK9 4LA, Scotland. Received September 27, 1977

Abstract: The rates of dissociation of a variety of alkali metal cryptates have been measured in methanol. These have been combined with measured stability constants to give the corresponding formation rates. The pronounced selectivity of the cryptands for alkali metal cations is found to be reflected entirely in the dissociation rates, with the formation rates increasing monotonically with increasing cation size. The specific size-dependent interactions between the metal ions and the cryptands must then occur subsequent to the formation of the transition state (in the formation reaction). For a given metal ion, the formation rates increase with increasing cryptand size, and for 2,2,2 are similar to the rates of solvent exchange in the inner sphere of the cations. This suggests that during complex formation, particularly for the larger cryptands, interactions between the cryptand and the incoming cation can compensate very effectively for the loss of solvation of the cations.

Introduction

The pronounced selectivity of the macrobicyclic cryptands[2] (**1–3**) for alkali metal cations, and the dependence of the se-

1, a = 1; b = c = 0 (2,1,1)
2, a = b = 1; c = 0 (2,2,1)
3, a = b = c = 1   (2,2,2)

lectivity pattern on the ligand size, provide the opportunity for a systematic study of factors influencing the kinetics and thermodynamics of complex formation involving alkali metal cations. Such information is of particular relevance to current studies concerning the mechanism of action of a variety of naturally occurring macrocyclic and open-chain antibiotics.

These species show marked selectivity in the stability constants for complex formation with cations, and in the transport of cations through natural and artificial membranes.[3,4]

Several kinetic studies of complex formation between cryptands and alkali metal ions[5-9] and alkaline earth ions[6,10] in water have been published. Where appropriate comparisons can be made, the results suggest that the dissociation rates vary more from one system to another than the association rates.[2,5,6,10] However, the relatively low stability of the complexes in water (except for complexes corresponding to, or near to, the optimal fit of the cation into the intramolecular cavity of the ligand) makes a study over a wide range of complexes difficult. In methanol, however, the stability constants are several orders of magnitude larger than those in water,[11] permitting a more systematic investigation of complex formation.

In the present paper we present the results of a study of the kinetics and thermodynamics of complex formation in methanol between the cryptands **1–3** and alkali metal cations. The dissociation rates in methanol are slower than the corre-

sponding rates in water, and may be conveniently obtained from the rates of reaction of the metal complexes with acid, as described earlier[6] for reactions in water. The formation rates may then be obtained from the dissociation rates, via the measured stability constants.

Experimental Section

Materials. The cryptands 2,1,1, 2,2,1, and 2,2,2 were commercial samples (Merck) used without further purification. Inorganic salts were of AnalaR or equivalent grade, dried prior to use. Methanol was purified by distillation from magnesium.[12] Anhydrous hydrochloric acid solutions were prepared by bubbling HCl gas into methanol. The resulting solutions were analyzed by titration against standard alkali.

Stability Constant Measurements. The complexes (cryptates) are considerably more stable in methanol than in water and the determination of stability constants (K_s) by standard procedures, involving the use of either selective ion electrodes or pH titrations in the presence and absence of salts, is more difficult.[11] In the former case, the very high stability of many of the complexes results in free ion concentrations too low to be reliably determined by selective ion electrodes, and in the latter, detailed information concerning the protonation of the cryptands in methanol is required. In the present work, we have determined the stability constants indirectly via measurements of the equilibrium constants for the reactions

$$MCry^+ + Ag^+ \xrightleftharpoons{K_e} AgCry^+ + M^+ \tag{1a}$$

where

$$K_e = \frac{[AgCry^+][M^+]}{[MCry^+][Ag^+]} \tag{1b}$$

The measured equilibrium constants, $K_e = K_s(AgCry^+)/K_s(MCry^+)$, can be readily determined from potentiometric titrations involving the addition of excess $M^+/MCry^+$ to standard $Ag^+(NO_3^-, ClO_4^-)$ solutions, the titrations being monitored with an Ag/Ag^+ electrode. Thus, if the initial concentrations of $MCry^+$, Ag^+, and M^+ (eq 1a) are known, and the equilibrium concentration of Ag^+ is determined from the potential of the Ag/Ag^+ electrode when the system has reached equilibrium, the equilibrium concentrations of the species required to evaluate K_e (eq 1b) may be directly determined from the stoichiometry of the equilibrium. Total metal ion concentrations were ca. 10^{-3}–10^{-2} M and were always higher than the cryptand concentrations. Under these conditions, the concentrations of uncomplexed cryptand at equilibrium were negligible. The required $K_s(AgCry^+)$ were determined from direct potentiometric measurements of silver ion concentrations in solutions of the cryptands, using an Ag/Ag^+ electrode. For a given determination, K_e was evaluated at a variety of different concentrations of $MCry^+$, Ag^+Cry, and M^+ and showed no trends with the concentrations of any of the species. During a typical titration, for example, with total metal ion concentration of 5×10^{-3} M and total cryptand concentration of 10^{-3} M, the total silver ion concentration was varied between 10^{-4} and 8×10^{-4} M. Titrations could be carried out either with silver ion concentrations increasing or decreasing during the titration. The reactions were carried out in the presence of 5×10^{-2} M Et_4NClO_4 so that the activity coefficient of the silver ion remained constant. As there is no change in charge in equilibrium 1a, however, K_e as defined in eq 1b refers to the value at infinite dilution. To avoid the possibility of systematic errors resulting from incorrect potential measurements, the system was calibrated using standard solutions of known Ag^+ concentrations. Values of K_e, and hence K_s, determined by the above method in water, showed excellent agreement with values earlier reported.[5] The wider use of equilibrium 1a in studying the thermodynamic properties of cryptates is discussed elsewhere.[13] The results are summarized in Table I. Values of log K_s were reproducible to ±0.1 log unit.

Kinetic Measurements. The reactions were followed conductimetrically (see below) using a stopped-flow apparatus with conductance detection for faster reactions, or a conventional conductance cell monitored with a Wayne-Kerr conductance bridge (B221A).
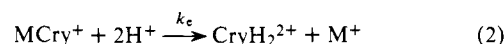
The reactions were initiated by the addition of an excess of acid to an equilibrium $MCry^+/M^+$ mixture such that the final pH values of the solutions were in the range pH ca. 2–4.[6] Under these conditions, the cryptands are quantitatively converted to their doubly protonated

Table I. Stability Constants (Log K_s) of Alkali Metal Cryptates in Methanol at 25 °C (K_s in mol^{-1} dm^3)

Ligand	Li^{+}	Na^{+}	Log K_s with cation K^{+}	Rb^{+}	Cs^{+}
2,1,1[a]	8 0₄	6.1[b]	2.3[b]	1.9[b]	
2,2,1[a]	5.3₈	9.6₅	8.5₄	6.7₄	4.3₃[c]
2,2,2[a]	2.6[b]	7.9₈	10.4₁	8.9₈	4.4[b]

[a] Log K_s for Ag^+: 2,1,1, log K_s = 10.6; 2,2,1, log K_s = 14.6₄; 2,2,2, log K_s = 12.2₀. [b] Reference 11. [c] Reference 11 reports log K_s ca. 5.

derivatives:

$$MCry^+ + 2H^+ \xrightarrow{k_e} CryH_2^{2+} + M^+ \tag{2}$$
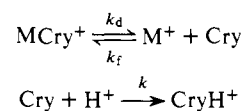
The reaction is accompanied by a significant decrease in conductance, even in the presence of a tenfold excess of acid, primarily because of the high mobility of H^+ relative to the other ions present.

For the reaction path, represented in Scheme I,[22]

Scheme I

$$MCry^+ \xrightleftharpoons[k_f]{k_d} M^+ + Cry$$

$$Cry + H^+ \xrightarrow{k} CryH^+$$

involving protonation of the free ligand, application of the steady-state approximation to [Cry] gives rise to the equations

$$\frac{-d[MCry^+]}{dt} = k_e[MCry^+] \tag{3}$$

where

$$k_e = \frac{k_d k[H^+]}{k_f[M^+] + k[H^+]} \tag{4}$$

If the rate of protonation is considerably faster than that of complex formation (i.e., $k[H^+] \gg k_f[M^+]$) then eq 4 simplifies to

$$k_e = k_d \tag{5}$$

Values of k_d, obtained from eq 4 or 5, may then be combined with the measured stability constants K_s ($= k_f/k_d$) to give the rate constants for the formation reactions.

In addition to the mechanism represented in Scheme I, we have previously shown that there is an acid-catalyzed pathway for the dissociation of a number of alkaline and alkaline-earth metal cryptates.[6] Evidence for similar acid-dependent pathways for the dissociation of Eu^{III} and Eu^{II} cryptates has also recently been presented.[14] Where this is the case, k_e has the form shown in the equation

$$k_e = k_d + k_{H^+}[H^+] \tag{6}$$

and values of k_d may be determined by extrapolating k_e values to zero acid concentration. The particular conditions under which the measurements were carried out are discussed separately below for each of the three cryptands.

2,1,1. Reaction rates for Li^+ and Na^+ complex dissociation were measured. For $NaCry^+$, the observed rate constants were independent of acid concentration and sodium ion concentrations over the range [HCl] ca. 10^{-2} to 5×10^{-2} M, [NaCl] ca. 10^{-3}–10^{-2} M, with [2,1,1] ca. 0.05–0.1[HCl], in accordance with eq 5. Rate constants for $LiCry^+$ were independent of [Li^+] in the range ca. 2×10^{-3} to 10^{-2} M, but were dependent upon the acid concentration (cf. Li^+ 2,1,1 complexes in H_2O).[6] Values of k_d and k_{H^+} (eq 6) were obtained from the intercept and slope, respectively, of plots of k_e against [H^+]. k_{H^+} has been corrected to zero ionic strength $k_e(I = 0)$ according to eq 7, the required activity coefficients γ, being calculated from the Davies equation (8)[15] in which A is the Debye–Hückel function and I the ionic strength.

$$\log [k_{H^+}/k_{H^+}(I = 0)] = \log (\gamma_{H^+}\gamma_{MCry^+}/\gamma_{(\neq)^{2+}}) \tag{7}$$

$$-\log \gamma_\pm = \frac{AZ^2I^{1/2}}{1 + I^{1/2}} - \frac{AZ^2I}{3} \tag{8}$$

The results are listed in Table II.

Table II. Kinetics of Complex Formation between Alkali Metal Cations and Cryptands in Methanol at 25 °C

Ligand	Cation	k_d, s^{-1}	k_f,[a] M^{-1} s^{-1}	k_{H^+},[b] M^{-1} s^{-1}
2,1,1	Li$^+$	4.4×10^{-3}	4.8×10^5	4.9×10^{-1}
2,1,1	Na$^+$	2.50	3.1×10^6	0[c]
2,2,1	Li$^+$	7.5×10	1.8×10^7	2.1×10^3
2,2,1	Na$^+$	2.35×10^{-2}	1.7×10^8	3.7×10^{-1}
2,2,1	K$^+$	1.09	3.8×10^8	d
2,2,1	Rb$^+$	7.5×10	4.1×10^8	d
2,2,1	Cs$^+$	$\sim 2.3 \times 10^4$ [e]	$\sim 5 \times 10^8$ [e]	
2,2,2	Li$^+$	$> 3 \times 10^2$		
2,2,2	Na$^+$	2.87	2.7×10^8	4.2×10^2
2,2,2	K$^+$	1.8×10^{-2}	4.7×10^8	0[f]
2,2,2	Rb$^+$	8.0×10^{-1}	7.6×10^8	0[f]
2,2,2	Cs$^+$	$\sim 4 \times 10^4$ [e]	$\sim 9 \times 10^8$ [e]	

[a] k_f obtained from $k_f = k_d K_s$, K_s values coming from Table I. These values have an uncertainty of ±25% because of uncertainty in K_s. [b] Catalytic constants for acid-catalyzed dissociation of complexes, corrected to $I = 0$ (see text). [c] Independent of [HCl] up to ca. 2×10^{-2} M. [d] Acid catalysis observed when [HCl] > ca. 10^{-2} M. [e] Estimated values (see text). [f] Independent of [HCl] up to ca. 5×10^{-3} M.
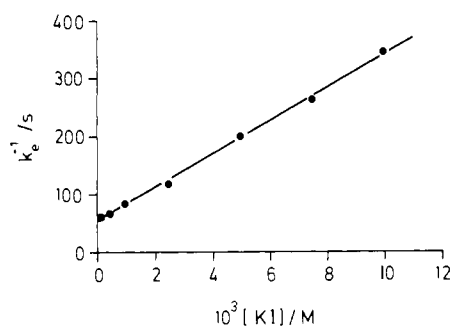

Figure 1. Effect of added KI on the rate of reaction of K(2,2,2)$^+$ with HCl (5×10^{-4} M) in MeOH at 25 °C.
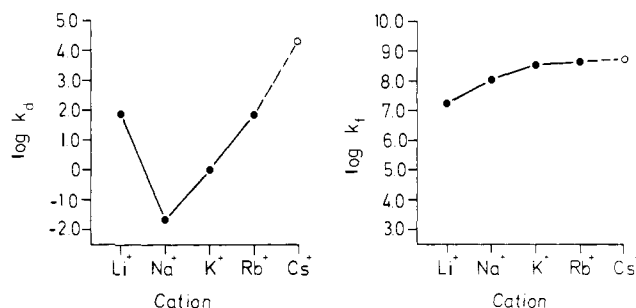

Figure 2. Rates of dissociation (k_d) and formation (k_f) of 2,2,1 cryptates in MeOH at 25 °C.

2,2,1. Reaction rates were measured for Li$^+$, Na$^+$, K$^+$, and Rb$^+$ complexes. Metal ion concentrations were in the range ca. 5×10^{-4} to 3×10^{-2} M, acid concentrations ca. 10^{-3} to 5×10^{-2} M, and cryptand concentrations (0.1[HCl]) ca. 10^{-4} to 2×10^{-3} M. The rate constants were again independent of M$^+$ (normally 0.2[HCl]). For Li$^+$ and Na$^+$ complexes, k_e was strongly acid dependent, and the results were analyzed according to eq 6, as described above for cryptand 2,1,1. For K$^+$ and Rb$^+$ complexes, there was some increase in rate at acid concentrations above 10^{-2} M, but the effects were not sufficiently large to enable accurate determination of k_{H^+} values. The results are listed in Table II.

2,2,2. Na$^+$, K$^+$, and Rb$^+$ complexes were studied, those of Li$^+$ and Cs$^+$ reacting too rapidly to be followed with the stopped-flow apparatus. For each of these systems, there was a significant dependence of the rate upon M$^+$ at higher [M$^+$]/[H$^+$] ratios, the effect being largest for Rb$^+$. Such behavior is to be expected (Scheme I, eq 3, 4) when there is effective competition between M$^+$ and H$^+$ for the free ligand (i.e., k_f[M$^+$] $\sim k$[H$^+$]). The results were shown to be quantitatively consistent with eq 4, via its reciprocal form

$$\frac{1}{k_e} = \frac{1}{k_d} + \frac{k_f[M^+]}{k_d k[H^+]} \qquad (9)$$

by plotting k_e^{-1} against [M$^+$] at constant [H$^+$]. An example of such a plot, using the results for $K(2,2,2)^+$, is shown in Figure 1. From the slopes and intercepts of such plots, values of k/k_f and k_d, respectively, may be obtained. k/k_f values for Na$^+$, K$^+$, and Rb$^+$ complexes were found to be 9.8, 3.8, and 1.2, respectively. These correspond to values of k (the rate constant for protonation of 2,2,2) of 2.6×10^9, 1.9×10^9, and 1.0×10^9 mol^{-1} dm^3 s^{-1}, using values of k_f for the respective cations listed in Table II, i.e., $k = 1.8 \pm 1 \times 10^9$ mol^{-1} dm^3 s^{-1}.

The reactions were also tested for the presence of an acid-dependent pathway, by varying the acid concentration at constant (and large, ca. 5) ratios of [H$^+$]/[M$^+$]. For K$^+$ and Rb$^+$, rates were independent of acid concentration up to [HCl] = 5×10^{-3} M. The dissociation reaction for Na(2,2,2)$^+$ was found to be acid catalyzed, and the results were analyzed according to eq 6, as described for 2,1,1 above. The

combined results are listed in Table II. The rate constants for the dissociation reaction, k_d, were reproducible to better than ±5%.

Discussion

The typical selectivity patterns displayed by cryptands for alkali metal cations are readily apparent from the results in Table I. As in water,[15] the cations forming the most stable complexes with the cryptands 2,1,1, 2,2,1, and 2,2,2, respectively, are Li$^+$, Na$^+$, and K$^+$. It is noticeable, however, that the complexes are 10^3–10^5 times more stable in methanol than in water. Such a difference seems much too large to be attributable solely to a decrease in the solvation of the cations in methanol relative to water.[16-18] A recent study of the effects of solvent variation on the stabilities of cryptates suggests that the free cryptands are considerably more strongly solvated in aqueous solution than in nonaqueous solvents.[19] This could readily account for the large increase in the stability of the cryptates on transfer from water to methanol.

The most striking feature of the kinetic results presented in Table II is the contrast between the dependence (for a given cryptand) of the formation and dissociation rates on the nature of the cation. This is illustrated in Figure 2 for complex formation with 2,2,1. It can be seen that the very high selectivity of the ligand is reflected entirely in the dissociation rates, with the formation rates showing a monotonic increase with increasing cation size. The formation rate for Cs$^+$ (and hence k_d, via the stability constant) has been estimated from a plot of log k_f against $(r_{m^+})^{-1}$ where r_{m^+} is the crystal radius of M$^+$. Such a plot is linear within experimental error.

The results strongly suggest that the transition state for the formation reaction lies very close to the reactants. The relatively high formation rates, particularly for 2,2,1 and 2,2,2, suggest that the required desolvation of the metal ions is largely

compensated for by interaction with the ligand in the transition state, the energy required decreasing as the solvation energy of the ions decreases. It is clear, however, that at this stage there is no specific interaction between the cryptands and the cations that strongly differentiates between the various cations. Molecular models show that the oxygen atoms in the bridges can rotate outward from the cavity, and these may form the basis of the initial interaction between the cations and ligands. The subsequent steps in which the metal ion enters the cavity of the ligand, where the more specific size-dependent interactions occur, must then proceed rapidly from this stage.

A comparison of the rates of complex formation for a given cation with the different cryptands shows that the rates increase with increasing ligand size. In the case of 2,2,2, the formation rates are approaching values expected for the rate of exchange of solvent in the inner sphere of the cations,[3] while those for 2,1,1 are some three orders of magnitude slower. This presumably reflects the fact that the larger ligands are more flexible, and so can more readily interact with the incoming cation, leading to more effective compensation for the loss of solvation energy.

In recent years, the kinetics and mechanism of complex formation between monovalent cations and a variety of biofunctional ligands have been investigated.[3] This has led to the concept of the stepwise replacement of coordinated solvent molecules, together with appropriate changes in the conformation of the ligands, in order to explain the very high recombination rates frequently observed.[20] In a number of cases, such as for the macrotetralides (nonactin and analogues)[4] and the synthetic crown ethers,[21] direct evidence of conformational changes in the ligands, occurring prior to complex formation, has come from ultrasonic relaxation studies. No such studies have been reported for the cryptands, although the possibility of conformational changes associated with inversion of the nitrogen atoms clearly exists.[11] Indirect evidence suggesting that conformational changes may occur during the dissociation of the cryptates comes from the observation that the reactions are subject to acid catalysis.[6] This suggests that during the

dissociation process, at least one of the nitrogen lone pairs is directed outward (exo conformation) where it may interact with a proton. The stable equilibrium conformation of the cryptates, however, is almost certainly endo–endo, in which both lone pairs can interact with the included metal ion. It is not unreasonable that such a conformational change may be a necessary prerequisite to the solvation of the metal ion during the dissociation step.

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