"KINETICS AND THERMODYNAMICS OF COMPLEX FORMATION BETWEEN IONS AND MACROBICYCLIC LIGANDS IN SEVERAL SOLVENTS"

by

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ABSTRACT

This work deals with the variation of the stability constants and formation and dissociation rate constants with solvent, of complexes (cryptates) formed between macrobicyclic polyether diamines (cryptands) and metal cations, chiefly alkali and alkaline-earth metal cations. Stability and rate constants were determined for complexes of the cryptands (2,1,1), (2,2,1) and (2,2,2) in the following solvents: ethanol, dimethyl sulphoxide, dimethylformamide, N-methylpropionamide, propylene carbonate and acetonitrile (stability constants only). Complexes of monobenzo and dibenzo derivatives of the (2,2,2) cryptand were also studied in propylene carbonate.

The results show a wide range of stability constants (from less than 10 M^{-1} to more than 10^{18} M^{-1}) and dissociation rate constants (from less than 10^{-5} s^{-1} to more than 10^{4} s^{-1}). However, formation rates vary only over few orders of magnitude and, when the cryptand is sufficiently flexible and the metal ion is in a poorly solvating medium, are close to the rates of solvent exchange in the inner coordination shell of the cations. The variations in cryptate stability with metal ion and solvent are almost entirely reflected in the dissociation rather than in the formation rates. This suggests that the transition state lies closer to the reactants (metal ion and cryptand) than to the complex. A quantitative analysis of the results shows a correlation between the free energies of transfer of the reactants and transition state.

A combination of the stability constants and free energies of transfer of the free cations, shows that there is a more favourable transport (in terms of free energy) from water to non-aqueous media of cryptates involving optimum fit of the cation into the ligand cavity.

Finally, results obtained for the acid-catalysed dissociation of cryptates suggest that catalysis is more important for small cations, but also depends upon ligand flexibility and the solvent.

CONTENTS

GENERAL INTRODUCTION

In recent years a number of macrocyclic molecules that are very powerful complexing agents for alkali and alkaline-earth ions have been reported. Such is the case of macrocyclic polyethers or "crown ethers" (Fig.1), first synthesized by Pedersen[1] and macrobicyclic polyether diamines or "cryptands" (Fig.2) first synthesized by Lehn and coworkers[2].

18-Crown-6

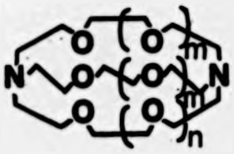
Dibenzo 18-Crown-6

Figure 1. Some examples of macrocyclic polyethers or "crown ethers".

The many chemical and biological applications of the synthetic macrocyclic and macrobicyclic polyethers as complexing and transport agents for metal ions have increased considerably the interest in the solution chemistry of these ligands.

These synthetic ligands exhibit a high selectivity towards metal cations, particularly alkali and alkaline-earth metal cations, with which very stable complexes are formed[3,4]. Both alkali and alkaline-earth metal cations play an important role in living systems. The differences in ionic concentration, especially of Na^+ and K^+, between extracellular and intracelluar fluid allow the transmission of nerve impulses[5]. Changes in Ca^{2+}

concentration occur in contracting tissues and Mg^{2+} is present in many enzymic reactions[6].



m = 0, n = 1 (2,1,1)cryptand: 4,7,13,18-tetraoxa-1,10-diazabicyclo-[8,5,5]-eicosane

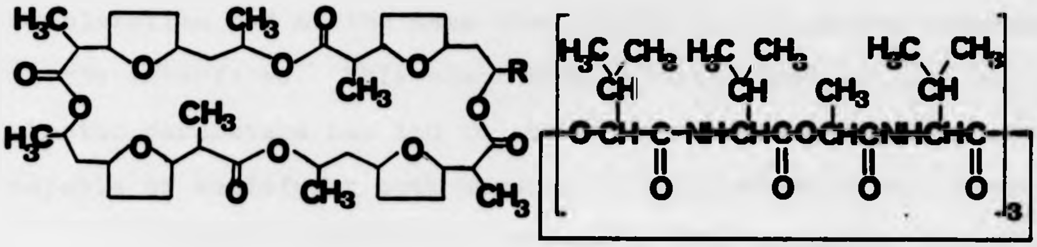
m = 1, n = 0 (2,2,1)cryptand: 4,7,13,16,21-pentaoxa-1,10-diazabicyclo-[8,8,5]-tricosane

m = 1, n = 1 (2,2,2)cryptand: 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo-[8,8,8]-hexacosane

Figure 2. Some examples of macrobicyclic polyether diamines or "cryptands".

The structures and complexing properties of these synthetic ligands are closely related to those of a number of naturally-occurring macrocyclic compounds with considerable biological activity.

The biological activity of these naturally-occurring compounds such as the antibiotics nonactin, monactin and valinomycin (Fig.3) appears to be related to their macrocyclic structure and their ability to assume highly specific conformations in the presence of metal ions[7]. Therefore the study of synthetic macrocyclic and macrobicyclic ligands with various degrees of specificity for cations may have implications in the field of antibiotics. They have also proved to be useful in the removal of radioactive metals, such as ^{85}Sr, from contaminated organisms[8] and their use in pollution control has been envisaged[9,10].



R = CH_3, nonactin

R = CH_3CH_2, monactin

Valinomycin

Figure 3. Some examples of naturally-occurring antibiotics.

The complexing power of the synthetic macropolyethers with various metal ions allows the solubilization of inorganic salts in organic solvents. This has resulted in their application in cationic catalysis[11,12] or catalysis by anions carried into solution with the complexed cations (anionic activation)[10,12]. Alkyl substituted cryptands have been reported to be highly efficient catalysts in two-phase reactions[13,14] and they have been used on a polymer matrix as heterogeneous phase-transfer catalysts in nucleophilic substitutions[15,16]. Their use in anionic polymerization and in the preparation of new initiators of polymeric reactions is described elsewhere[17].

The stabilization of a cation by incorporation into a suitable crown or cryptand complex has made possible the preparation of a series of compounds of alkali metal anions[18].

The high selectivity for cations displayed by macrocyclic and macrobicyclic compounds has aroused interest in the field of transport through membranes. An efficient cation carrier is that which has a high stability and selectivity of complexation and at the same time allows a fast cation exchange at the interfaces. This compromise between thermodynamic and kinetic parameters has led to the design of new carrier molecules capable of satisfying both apparently contradictory requirements[19].

Natural macrocyclic molecules like monactin, nonactin, valinomycin, etc. have been used as cation carriers, and permeability and conductance studies on artificial bilayer membranes indicate that these macrocyclic compounds promote selective transport of alkali metal cations across membranes[20]. Similarly ion transport by crown-ethers has been investigated[21] and extraction experiments have been carried out[22]. Preliminary investigations of carrier properties of the macrobicyclic polyether diamines have also recently been reported[19,23].

Many other applications involving alkali, alkaline-earth or other metal cations may be contemplated, as well as the synthesis of new macropolicyclic molecules designed to suit specific purposes[24,25].

It can be seen from the above that a more detailed understanding of the factors involved in the kinetics and stability of complexes formed between metal ions and macrocyclic ligands, besides being of considerable intrinsic interest, is of relevance to a variety of chemical and biological fields. An advantage of synthetic macrobicyclic ligands of the type shown in figures 2 and 4, is the ease with which the nature and size of the cavity may be systematically varied by altering the bridges linking the nitrogen atoms. All experimental work described in this thesis relates to these ligands.

Of central importance to complex formation involving ions in solution is the involvement of the solvent. This is particularly true of complexes involving both naturally-occurring and synthetic macrocyclic ligands, where in the complex the cation may be isolated from the solvent by the ligand. Thus ion-solvent interactions are expected to influence considerably both the kinetics and thermodynamics of complex formation.

It is known from thermodynamic studies on electrolyte solutions, that alteration of the solvent can lead to quite dramatic variations in the activities of ions, and a considerable amount of quantitative data on such effects is now available[26]. It seemed, therefore, opportune to investigate the influence of solvent variation, and the consequent variations in ion-solvent interactions, on the kinetics and thermodynamics of complex formation between cations and macrobicyclic polyether diamine ligands.

The solvents chosen for the study (Table 1) include representative protogenic solvents* (i.e. a solvent capable of

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* The IUPAC recommends the use of the term "protongenic" instead of the synonym "protic" or the more ambiguous expression "acidic" (Pure Appl.Chem., 51, 1725 (1979).

acting as a proton donor) and dipolar aprotic solvents and cover a wide range of properties such as dielectric constants (from 24 for ethanol to 175 for N-methylpropionamide), donor numbers[27] (from 14.1 for acetonitrile to 29.8 for dimethyl sulphoxide) and acceptor numbers[27] (from 16 for N,N'-dimethylformamide to 54.8 for water).

The thesis consists of three chapters. In the first chapter experimental stability constants of metal complexes involving the macrobicyclic polyether diamine ligands shown in Figure 2 are analysed as a function of the solvent and the nature of the cation. This analysis also provides the opportunity to gain insight into the thermodynamics of transfer of the single and complexed ions.

Chapter II deals with the kinetics of dissociation and formation of these complexes. The formation rate constants are obtained from the measured dissociation rates via the stability constants given in Chapter I. The changes in the magnitudes of the rate constants are discussed in terms of ion-solvent and ligand-solvent interactions.

Alterations in the structure of the ligand itself are reflected in its selectivity and rate constants of complexation. This problem is briefly treated in Chapter III, which studies the change in the stability constants and formation rates of the complexes, due to the introduction of benzo groups into the structure of the (2,2,2) ligand (Figure 2). The resulting monobenzo and dibenzo substituted ligands are shown in Figure 4.

TABLE 1

Physical Properties of Solvents[a]

Solvent[b]	Dielectric const. ε(at 25°C)	Dipole moment μ/D	Refractive index n_D	Viscosity cP (at 25°C)	Donor[c] Number	Acceptor[c] Number
H_2O	78.5	1.84	1.333	0.89	18.0	54.8
MeOH	32.6	1.70	1.3288	0.547	19.0	41.3
EtOH	24.3	1.69	1.3611	1.08	-	37.1
NMP[d]	175.4	3.59	1.4350	5.25	-	-
DMF	36.7	3.82	1.4269	0.796	26.6	16.0
DMSO	48.9	4.3	1.4783	2.000	29.8	19.3
PC	64.9	4.94	1.4212	2.51	15.1	18.3
AN	37.5	3.84	1.3441	0.345	14.1	18.9

a Ref. 26

b Abbreviations are:

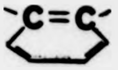
NMP, N-methylpropionamide;
DMF, N,N'-dimethylformamide;
DMSO, dimethyl sulphoxide;
PC, propylene carbonate (1,2-propanediol carbonate);
AN, acetonitrile

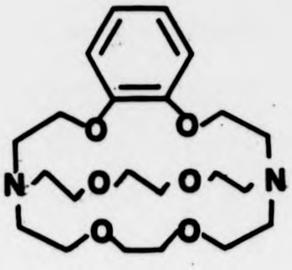
c Ref. 27

d Pure Appl.Chem., 37, 579 (1974)

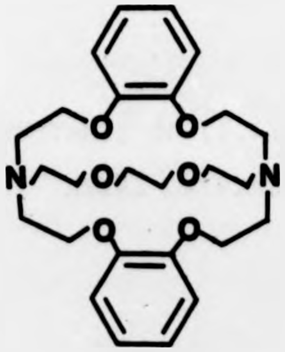
Nomenclature of Macrobicyclic Polyether Diamines

The use of IUPAC nomenclature to designate the macrobicyclic polyether diamine compounds results in very long and cumbersome names. Most of the authors in the literature have favoured the use of the nomenclature introduced by Lehn[2] based on the term "cryptand" to name the ligand and "cryptate" to name the metal complex, since the metal cation is contained in the molecular cavity (or crypt) of the ligand.

Individual ligands may be identified according to the number and types of groups involved in the bridges between the nitrogen atoms. The ligands predominantly used in the present study (2,2,2), (2,2,1) and (2,1,1), where the numbers refer to the number of oxygen atoms in the bridges, are shown in figure 2, together with their IUPAC names. Some work has been carried out with (2,2,2) ligands in which one or two of the central $-CH_2-CH_2-$ groups have been replaced by  . These will be referred to as (2B,2,2) and (2B,2B,2) respectively (Figure 4).



(2B,2,2) : 5,6-benzo-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo-[8,8,8]-hexacosane



(2B,2B,2) : 5,6-14,15-dibenzo-4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo- 8,8,8 -hexacosane

Figure 4. Monobenzo and dibenzo (2,2,2) cryptands.

CHAPTER I

STABILITY CONSTANTS OF (2,1,1), (2,2,1) AND (2,2,2) METAL CRYPTATES

A. INTRODUCTION

One of the most striking properties of the naturally occurring and synthetic macrocyclic ligands is their ability to complex selectively different alkali metal cations. This behaviour contrasts sharply with that of earlier known flexible chelating ligands such as EDTA (ethylendiamine-N,N,N',N'-tetraacetate). For these flexible ligands a simple monotonic variation in stability constant with ion size is observed. Indeed, until the discovery by Moore and Pressman in 1964[28] of the complexing properties of the antibiotic valinomycin and its ability to induce selectively the uptake of potassium ions in the mitochondria, the complexing properties of alkali metal (and alkaline earth metal) cations could be well understood in terms of classical theories for spherical charged particles.

In order to understand the differences in the complexing properties of the two types of ligand, and the origin of the maxima in the stabilities of complexes of the macrocyclic ligands, it is necessary to look more closely at the process of complex formation in solution. This may be represented by equation (1),

$$(M^{n+},mS) + L_{solv} \rightleftharpoons (M^{n+},L)_{solv} + mS \qquad (1)$$

in which L represents the multidentate ligand, M^{n+} the metal ion and S the solvent.

For simplicity, it is assumed that the ligand completely replaces the solvent in the coordination sphere of the ions. The most significant contributions to the overall stability comes from the competition between ligand and solvent molecules for the cation. The interaction of the cation with the solvent can be described by the free energy of solvation ΔG^{o}_{solv}, which is the free energy for the transfer of a cation from the gas phase into the solvated form (equation (2)).

$$(M^{n+})_{gas} + mS \rightarrow (M^{n+},mS) \qquad (2)$$

Similarly, the free energy of ion-ligand interaction ΔG^o_L can be described by the free energy for the transfer of a cation from the gas phase into the solvated ligand with the formation of the solvated complex (equation (3)).

$$(M^{n+})_{gas} + L_{solv} \rightarrow (M^{n+},L)_{solv} \qquad (3)$$

The difference between these two free energies of interaction determines the stability of a complex (equation (4)).

$$\Delta G^o = \Delta G^o_L - \Delta G^o_{solv} \qquad (4)$$

where ΔG^o can be expressed in terms of the stability constant K (equation (5)).

$$\Delta G^o = -RT \ln K \qquad (5)$$

Thus the stability of the complex is a result of the balance between free energies of ion-ligand interaction and solvation.

The free energy of hydration of the alkali metal cations (equation (2) with $S = H_2O$) is known from the work of several authors[29]. By combining these values with ΔG^o from measured stability constants (equation (5)), it is possible to calculate ΔG^o_L for complex formation involving a typical flexible ligand, EDTA,[30] and a typical rigid macrocyclic ligand, (2,2,2) [31,32]. Values for ΔG^o_{solv} and ΔG^o_L are shown in Figure 5, and ΔG^o for complex formation in Figure 6.

The free energy of solvation of the cations increases monotonically with the inverse of cation radius. Thus, in order to compensate for the hydration energy, the process of substitution

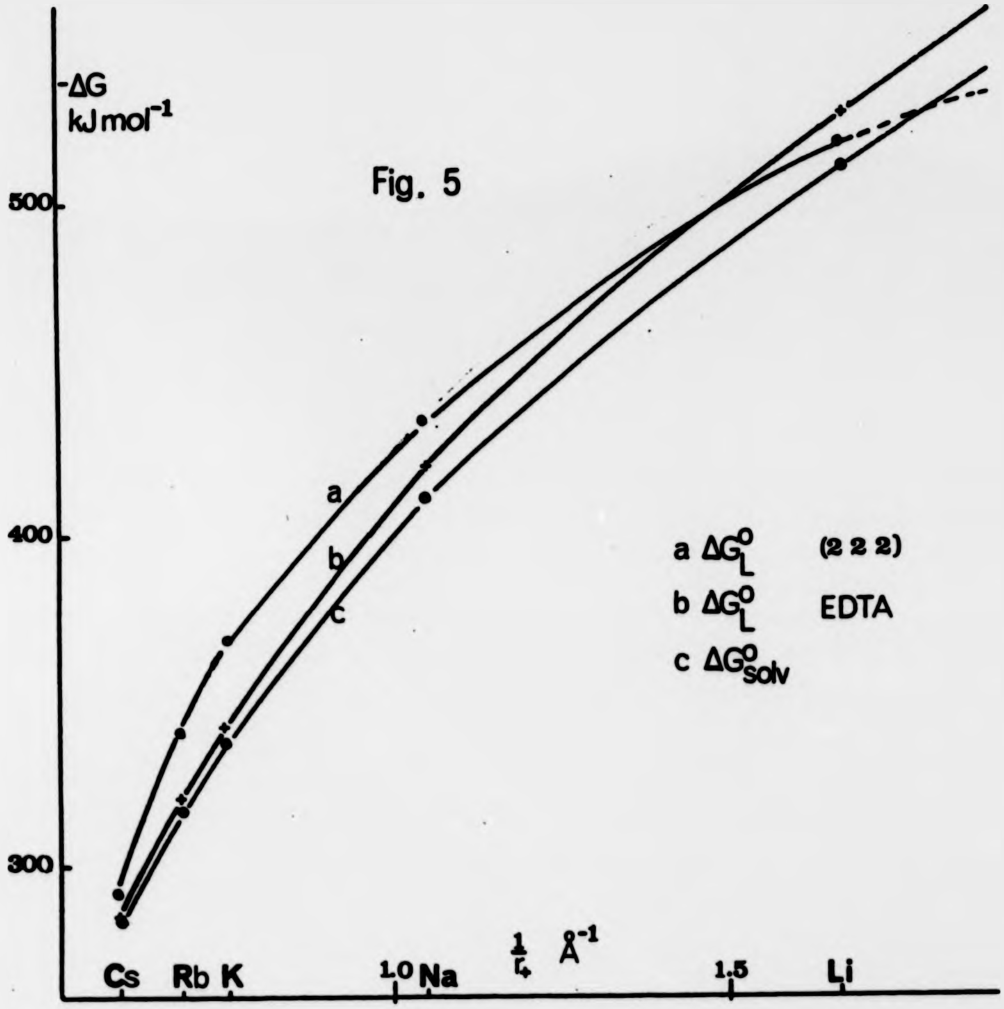


Fig. 5

-ΔG
kJ mol⁻¹
500
400
300
a
b
c
a ΔG°L (2 2 2)
b ΔG°L EDTA
c ΔG°solv
Cs
Rb
K
1.0
Na
1/r₊ Å⁻¹
1.5
Li

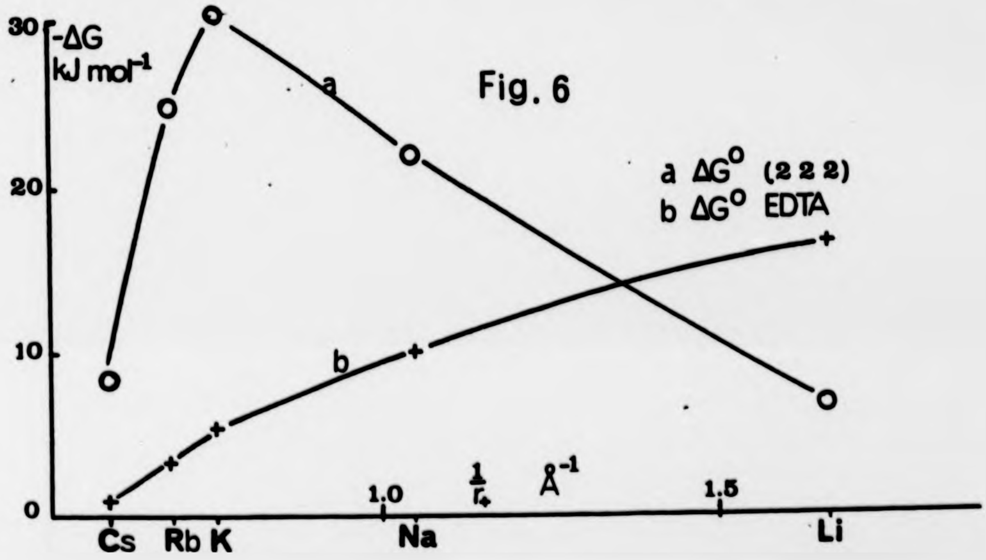


Fig. 6

-ΔG
kJ mol⁻¹
30
20
10
0
a
b
a ΔG° (2 2 2)
b ΔG° EDTA
1.0
1/r₊ Å⁻¹
1.5
Cs
Rb
K
Na
Li

of solvent molecules from the inner coordination shell of the metal ion requires more energy as the size of the cation decreases[33].

The behaviour of ΔG^o_L (Figure 5) and the overall free energy of complex formation, ΔG^o, (Figure 6) for EDTA is typical of that expected for a flexible multidentate ligand, i.e. a ligand in which the various binding sites of the ligand can be arranged as freely around the metal as the mutually unconnected (or weakly connected) solvent molecules. For such a ligand, if it is more strongly bound to the cation than the solvent molecules it replaces, the gain in binding energy for each binding site will be greater the smaller the metal ion. Thus for EDTA, the smaller the cation, the larger the difference between ΔG^o_L and ΔG^o_{solv}, and hence the higher the stability of the complex.

For (2,2,2) as a ligand, although there is still a monotonic increase in ΔG^o_L with inverse cation radius, the overall picture is somewhat different. Macrobicyclic molecules present a three-dimensional cavity where the complexed cation is located[10]. This spheroidal intramolecular cavity favours ligand interactions with spherically-shaped cations, such as alkali and alkaline earth metal ions, provided that the size of the cation is appropriate to fit snuggly into the cavity of the ligand. If the cation is too small, the rigidity of the ligand impedes the cavity contracting sufficiently to maintain optimum binding. This reduces ion-ligand binding energy relative to that of ion-solvent interactions. Conversely, if the cavity is too small to accommodate the cation, the strain created by the distortion of the ligand leads to relatively unfavourable competition with the solvent. There is a correlation between the stability constant and the cation size for a given ligand cavity diameter. The maximum stability is reached when the size of the cation most closely corresponds to that of the cavity of the ligand. Table 2 shows the Pauling ionic radius of various metal cations[34] and the approximate cavity radius of some macrobicyclic ligands as given in reference 3.

TABLE 2

Cation	Ionic Radius (Å)[34]	Ligand	Cavity Radius (Å)[3]
Li^+	0.60	(2,1,1)	0.8
Na^+	0.95	(2,2,1)	1.1
K^+	1.33	(2,2,2)	1.4
Rb^+	1.48		
Cs^+	1.69		
Ag^+	1.26		
Tl^+	1.40		
Ca^{2+}	0.99		

However, as noted above, although the stability constants for a rigid ligand pass through a maximum, the free energy of ion-ligand interaction and the solvation energy increase monotonically with the inverse of the ionic radius, as shown in Figure 5. It is also important to note that even though the cavity radius of the rigid ligand (in this case the (2,2,2) cryptand with a cavity radius of 1.4 Å) is much bigger than the radius of the Li^+ ion (0.6 Å), the ligand-cation interactions are still strong enough to compete with solvent-cation interactions and form a complex. Moreover, although the lithium cryptate is the least stable of the complexes, its free energy of ion-ligand interaction, ΔG^o_L, is larger than that of any of the other cryptates. The lower stability is seen to be a result of the very strong solvation of the lithium cation.

Thus, it can be seen from the above, that the observed maxima in stability constants of rigid ligands cannot be attributed simply to differences in ion-ligand interactions as the relative sizes of the cation and ligand cavities are altered; it is fundamental to consider the influence of the solvent in the process of complex formation.

One further point concerning the influence of the solvent may be mentioned. That is the solvation of the ligand, and particularly of the metal cryptate. Although when considering transfer of ions from the gas phase, ion-solvent and ion-ligand interactions are of major importance (both terms being of the order of several hundreds kJ) the difference between the terms is small. This means that other terms, such as ligand-solvent or complex-solvent interactions, may play an important role in complex formation, and particularly in the solvent dependence of stability constants and the ability of the ligands to extract metal ions into organic solvents or membranes. If there are significant differences in the cryptate-solvent interactions for different metal cryptates, this might be expected to show up in the solvent dependence of stability constants for different ions compared with differences in ion-solvent interactions.

The nature of the metal cation is also important in determining the stability of the complex. Cations such as Ag^+ and Tl^+ capable of increasing the covalent character of the metal-donor atom bond enhance the stability of the complex[3,35].

Previous work on the stabilities of cryptates has been confined almost exclusively to water and methanol as solvents. Several authors report stability constants in water determined by different methods. Lehn and Sauvage used a pH-metric method and a method using cation selective electrodes which allow direct potentiometric measurements of metal cation concentrations[31]. Anderegg[36] as well as Spiess et al.[37] also use acid-base potentiometry. Popov et al. report a few values of the stability constants obtained from NMR studies[38]. Coulombimetric titration is used by Bessiere et al.[39]. Recently Weaver has reported the use of the thallium (I)/thallium amalgam couple in amalgam-forming electroreduction reactions involving cryptates; complexation equilibria were monitored by cyclic voltammetry[40]. Finally, Abraham and Namor used calorimetry[32] and Schneider et al. used an electrochemical method described in this work[41] (see Experimental Section).

Table 3 shows the values of the stability constants of a number of metal cryptates, together with the corresponding stability constants for EDTA[30], 18-Crown-6[42] and valinomycin[43] complexes in water (see also Figure 7).

The values in Table 3 show the higher stability of the cryptates compared with complexes formed with macromonocyclic molecules, because of the more effective chelation of the cation by the cage-like bicyclic molecules (cryptate effect[44]). The selectivity pattern of the cryptands is altered by changing the size of the intramolecular cavity. Thus, if (2,1,1) is the complexing agent the selectivity for alkali metal ions follows the sequence

$$Li^+ > Na^+ > K^+.$$

For (2,2,1), whose intramolecular cavity is bigger than that of (2,1,1) the order is

$$Na^+ > K^+ > Rb^+ \sim Li^+ > Cs^+$$

TABLE 3

Stability Constants of Metal Complexes in H_2O at 25°C (K_s in $mol^{-1}\ dm^3$)

	log Ks					
Cation	(2,1,1)[a]	(2,2,1)[a]	(2,2,2)[a]	18-Crown-6[b]	Valinomycin[c]	EDTA[d]
Li^+	5.5	2.50	1.25[e,f]	ca. 0.11	-	2.85
Na^+	3.2[g]	5.40[h]	3.9[i]	0.80	-	1.79
K^+	<2.0	3.95	5.4[j]	2.03	0.36	0.96
Rb^+	<2.0	2.55	4.35[k]	1.56	0.77	0.59
Cs^+	<2.0	<2.0	1.47[e]	0.99	-0.92	0.15
Ag^+	8.52[ℓ]	11.82[m]	9.6[n]	1.5	-	7.72
Tl^+	-	-	6.3[o]	2.27	-	6.55
Ca^{2+}	2.50	6.95	4.4[p]	<0.5	-	11.0
Sr^{2+}	<2.0	7.35	8.0	2.72	-	8.80

[a] Lehn and Sauvage, ref. 31

[b] ref. 42

[c] ref. 43

[d] ref. 30

[e] Abraham et al., ref. 32

[f] cf. log Ks = 0.99, Popov et al., ref. 38

[g] cf. log Ks = 2.8, Bessiere et al., ref. 39

[h] cf. log Ks = 5.4, idem

[i] cf. log Ks = 3.9, idem and Weaver et al., ref. 40; log Ks = 4.11, Anderegg, ref. 36

[j] cf. log Ks = 5.4, Weaver et al., ref. 40; log Ks = 5.58, Anderegg, ref. 36

[k] cf. log Ks = 4.3, Weaver et al., ref. 40; log Ks = 4.06, Anderegg, ref. 36

[ℓ] Spiess et al., ref. 37; cf. log Ks = 11.13, Schneider et al., ref. 41

[m] Schneider et al. ref. 41; cf. log Ks = 10.6, Lehn and Sauvage, ref. 31

[n] cf. log Ks = 9.6, Schneider et al. ref. 41; log Ks = 9.85, Spiess et al., ref. 37

[o] cf. log Ks = 6.4, Weaver et al., ref. 40; log Ks = 5.5, Anderegg, ref.36

[p] cf. log Ks = 4.57, Anderegg, ref. 36

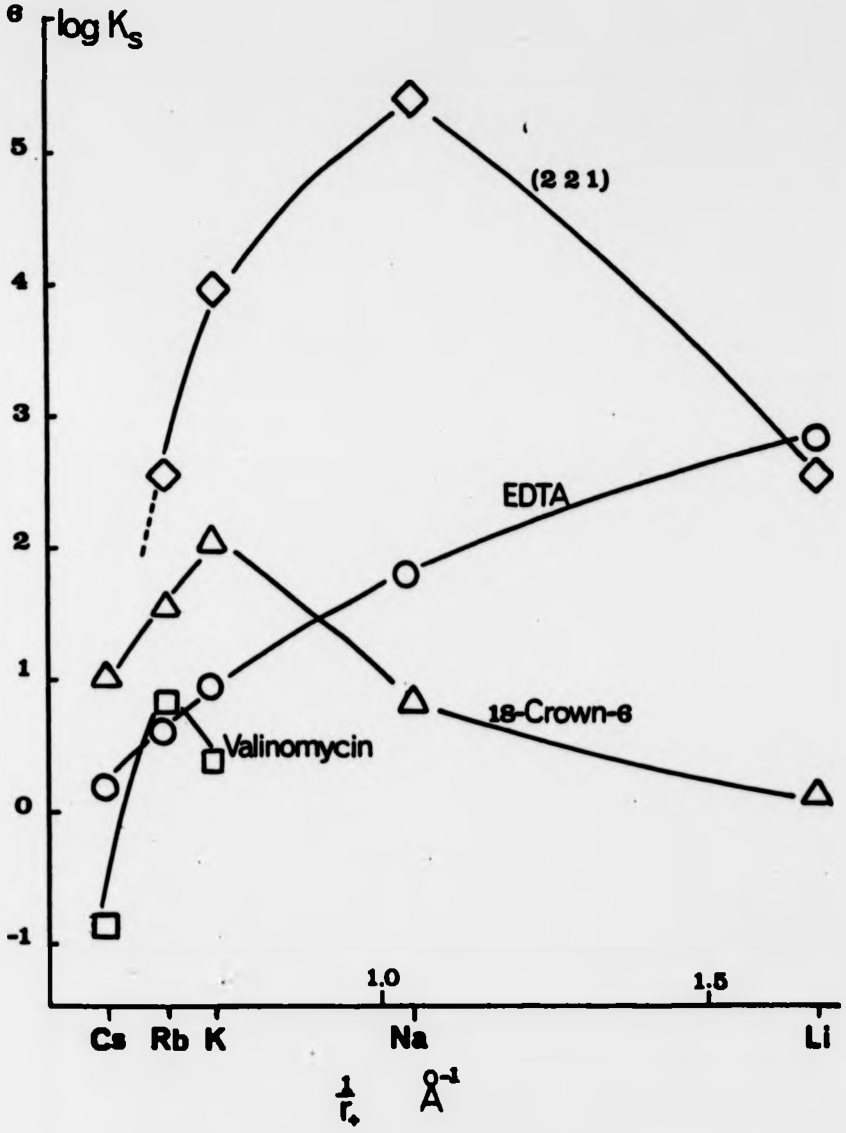


Figure 7 Stability Constants (Ks) of Alkali Metal Complexes in Water

and when (2,2,2), the largest of the three cryptands, is used as the complexing agent the selectivity pattern is altered to

$$K^+ > Rb^+ > Na^+ > Cs^+ \sim Li^+.$$

In each of these sequences the most stable complex corresponds to the cation which most closely fits the cavity of the ligand (cf. Table 2).

Polarizable cations like Ag^+ and Tl^+ undergo distortion of the electron distributions when subject to an electric field. If the distortion is such that there is electron transfer or partial covalence between the ion and the surrounding ligand, an extra stabilization energy, understandable in terms of molecular orbital theory, takes place due to this electron sharing[20]. The electrons of the oxygen and nitrogen atoms of the cryptand may produce an electric field capable of distorting the electron distributions of Ag^+ and Tl^+ and form bonds of partial covalence character with these cations. This results in very stable complexes even when the size of the cation is smaller or larger than the optimum size.

The higher binding force of a double-charge cation with the binding sites of the ligand may lead to a more stable complex when compared with a singly charged cation of the same size; for example Ca^{2+} ($r_+ = 0.99$ Å) and Na^+ ($r_+ = 0.95$ Å) complexes with (2,2,1), (2,2,2) and particularly with the quadruply charged EDTA. In the case of EDTA, ion-ion interactions replace the ion-dipole interactions which occur with the cryptands. The extremely large increase in stability of the EDTA complex with Ca^{2+} over that with Na^+ can be then the result of stronger ion-ion interactions between the ligand and the metal cation. However, the hydration energy of a bivalent cation is higher than that of a monovalent cation; the unfavourable energetics of removing water molecules from the inner solvation shell of the ion is reflected in lower stability constants in the case of the complexes like Ca $(2,1,1)^{2+}$ and Ca $(18\text{-Crown-}6)^{2+}$. In such cases the calcium cation may not be completely enclosed in the ligand and therefore can interact with the surrounding water.

A complete set of stability constants for alkali metal cryptates in methanol is reported by Cox, Schneider and Stroka[45]. They used the method described in this work and their values are in good agreement with those obtained by other authors. Table 4 shows the stability constants for alkali metal, Ag^+ and Tl^+ cryptates alongside with the corresponding stability constants of the valinomycin[46] and 18-Crown-6[4,47] complexes.

The complexes are several orders of magnitude more stable in methanol than in water. Although the cations are less solvated in methanol than in water this, by itself, cannot explain the increase of the stability constants by sometimes up to five orders of magnitude which, in terms of free energy, means a change of up to 29 kJ mol^{-1}. Thus, there must be a significant change in the solvation of the ligand and/or the complex on transfer from water to methanol. A more detailed analysis of the problem will be discussed later in this chapter.

The same selectivity patterns observed in water are maintained in methanol. The cryptands (2,1,1), (2,2,1) and (2,2,2) form the most stable alkali metal complexes with Li^+, Na^+ and K^+ respectively (Figure 8). One would expect that increasing the size of the cryptand cavity would always lead

TABLE 4

Stability Constants of Metal Complexes in Methanol at 25°C (Ks in $mol^{-1}\ dm^{3}$)

Cation	(2,1,1)[a]	(2,2,1)[a]	(2,2,2)[a]	18-Crown-6[b]	Valinomycin[c]
Li^+	8.0	5.3	2.6[d]	-	< 0.7
Na^+	6.1[d,e]	9.6[f]	7.9[g]	4.3	0.67
K^+	2.3[d]	8.5	10.4[h]	6.1	4.90
Rb^+	1.9[d]	6.7	8.9	5.2[i]	5.26
Cs^+	-	4.3	4.4[d]	4.6	4.41
Ag^+	10.6	14.6	12.2[j]	-	3.90
Tl^+	-	-	10.1	4.7[i]	3.73

[a] Cox, Schneider and Stroka, ref. 45

[b] Ref. 4

[c] Ref. 46

[d] Lehn and Sauvage, ref. 31

[e] cf. log Ks = 6.1, Bessiere et al., ref. 39

[f] cf. log Ks = 9.3, idem

[g] cf. log Ks = 7.8, idem; log Ks = 7.9, Weaver et al., ref.40

[h] cf. log Ks = 10.8, Weaver et al., ref. 40

[i] Calculated values using selectivity data from ref. 47 and ref. 4

[j] cf. log Ks = 12.3, Bessiere et al., ref. 39

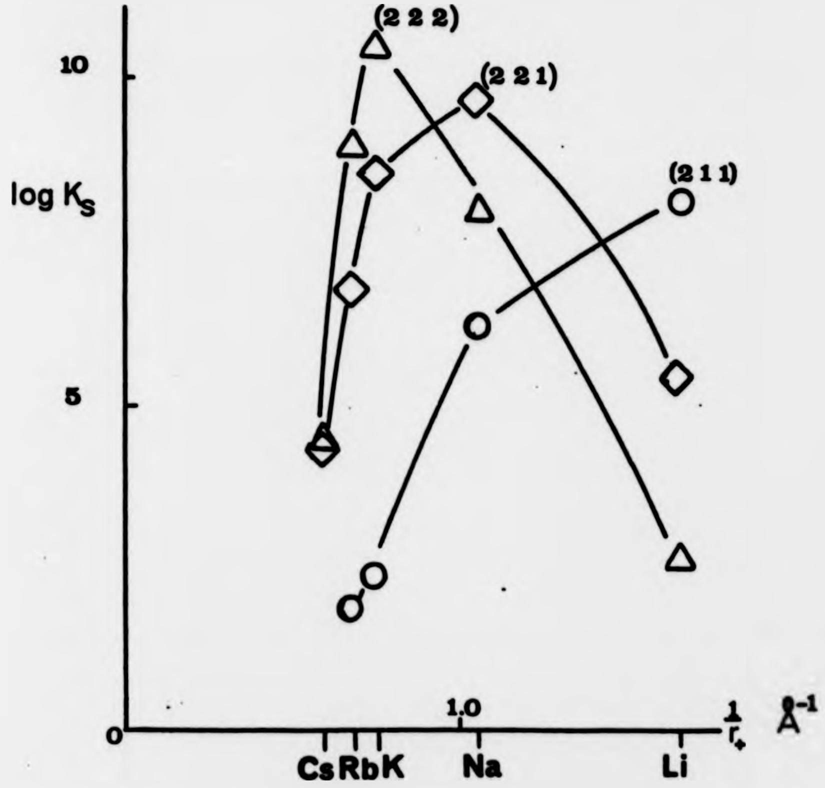


Figure 8 Stability Constants of Alkali Metal Cryptates in Methanol

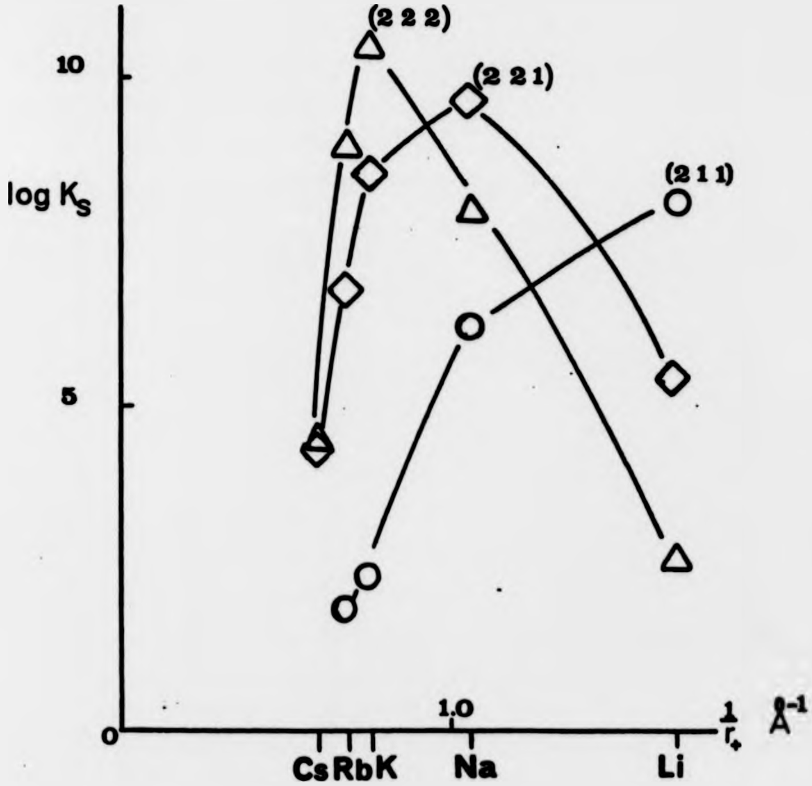


Figure 8 Stability Constants of Alkali Metal Cryptates in Methanol

to preferential complexation with a larger cation. However there is a limit to this, depending on the conformational flexibility of the binding centres in the ligand molecule[48]. For example, if an extra $-CH_2CH_2O-$ group is added to each ring of the (2,2,2) molecule a flexible ligand, the (3,3,3) cryptand, is obtained. Its cavity diameter is 4.8 Å and presents the selectivity pattern $Li^+ < Na^+ < K^+ \sim Rb^+ \sim Cs^+$, i.e. there is little or no recognition among potassium, rubidium and cesium ions by the ligand[3]. Thus, for a sufficiently large ligand, greater conformational flexibility may compensate for the increased cavity size.

In addition to these results in water and methanol, a few isolated stability constants for some metal cryptates in various solvents have been reported. These are mainly stability constants for Cs^+ cryptates obtained from NMR studies[49,50]. Also, during the progress of this research, a preliminary study of some stability constants in DMSO[40] has been reported. These results will be considered along with those here obtained in the Results and Discussion section.

In this work the stability constants of the cryptates formed by alkali metal cations and Ag^+ with the cryptands (2,1,1), (2,2,1) and (2,2,2) have been determined in the following non-aqueous solvents (see Table 1 for physical properties): ethanol (EtOH), dimethyl sulphoxide (DMSO), N,N'-dimethylformamide (DMF), N-methylpropionamide (NMP), propylene carbonate (PC) and acetonitrile (AN).

The stability constants of the calcium cryptates in PC and DMF were also measured.

The influence of the solvent on the stability constants is analysed and discussed in terms of the solvating ability of the different solvents. The free energy of transfer of cryptates in relation to the free energy of transfer of single ions is also discussed.

B. EXPERIMENTAL SECTION

1. Chemicals and Solvents

Cryptands (2,1,1), (2,2,1) and (2,2,2) were commercial samples from Merck and were used without further purification. Tests for the purity of these commercial samples were previously carried out during earlier studies on cryptands, at Stirling University and at the Max-Planck Institut für Biophysikalische Chemie, Göttingen (W. Germany). These have included NMR measurements, pH titrations and conductimetric studies.

The inorganic salts were: $LiClO_4$ (Fluka, purum), $NaClO_4$ (Koch-Light, cryst.Puriss), $KClO_4$ (Fisons, SLR), $RbNO_3$ (Hopkin & Williams, LR), $CsNO_3$ (Hopkin & williams, LR) and $AgClO_4$ (BDH, LR), dried prior to use. In ethanol KF (Hopkin & Williams, purified), RbF (Koch-Light, $\leq$ 99.8%) and CsF (BDH, LR) were used. Solutions of $Ca(NO_3)_2$ were prepared from the corresponding hydrated salt (Fisons, SLR) and dried over molecular sieves.

For electrochemical measurements in DMSO, PC, AN and DMF tetraethylammonium perchlorate (Et_4NClO_4) was used in the salt bridge. Tetraethylammonium picrate (Et_4NPic) was used in EtOH and NMP. These salts were prepared by reacting tetraethylammonium hydroxide (Aldrich 20% solution in water) with the corresponding acid, purified by several recrystallizations and finally dried under vacuum.

The solvents were purified as follows:

EtOH was rectified according to Vogel[51], refluxing with magnesium turnings and iodine and distilling.

DMSO was distilled from CaH_2 under reduced pressure.

PC was dried over $CaSO_4$ and distilled in an N_2 atmosphere several times under reduced pressure in a column packed with Rasching rings. A high purity PC was obtained as confirmed by a background cyclic polarogram[52]. This was particularly important for Ag^+ solutions in PC, as these rapidly turn brown in impure PC.

DMF was dried over molecular sieves and later over Na_2SO_4, and distilled from CaH_2 under vacuum in a pure nitrogen atmosphere[53]. The middle 60% of the distillate was collected. Its conductivity was ca. 10^{-7} Ω^{-1} cm^{-1} at 25°C.

AN was purified according to Coetzee's procedure[54], involving successive distillations from CaH_2 and P_2O_5.

NMP was prepared by the reaction of methylamine and propionic acid[55]. One lot was made using 40% methylamine solution in water (Koch-Light) and propionic acid (Koch-Light, puriss) and another by passing anhydrous methylamine gas (BOC) rapidly into well-stirred propionic acid. The mixture was heated rapidly to 120-140°C and water taken off through a simple distilling head. The crude NMP was fractionally distilled at 5 Torr several times under a N_2 atmosphere. After five distillations, NMP of good quality was obtained, judging by its specific conductance, 2.7×10^{-7} Ω^{-1} cm^{-1} at 25°C. Specific conductance of pure NMP have previously been found to be between 10^{-6} and 10^{-7} Ω^{-1} cm^{-1}.[55] It is one of the most sensitive tests for ionic impurities in a solvent like NMP with a high dielectric constant.

2. Experimental Method for the Determination of Stability Constants

Most of the earlier reported stability constants for cryptate formation have come either from pH titrations of the ligands in the presence and absence of complexing metal ions[31,36,37], or the use of cation selective glass electrodes to determine free metal concentrations in the presence of excess ligand[31]. The latter method is limited to complexes of only moderate stability by the fact that cationic glass electrodes (e.g. K^+, or general cation) only show a simple Nernstian type response to cation concentrations greater than ca. 10^{-5}M. In many of the solvents reported here, stability constants in excess of 10^8 M^{-1} were found, and these could not be studied using these electrodes.

In principle, pH titrations in the presence and absence of metal ions could be used to determine stability constants in non-aqueous solvents. In practice, however, complications arising from the double protonation of the ligand making analysis of results difficult, and the uncertainties associated with the calibration of glass electrodes for pH work over wide ranges of pH in non-aqueous solvents, would make such measurements very difficult.

NMR techniques are also restricted to complexes of only moderate stability, and either symmetrical ligands with simple ^1H spectra (e.g. (2,2,2)), or cations for which appropriate probes are available (e.g. ^{133}Cs).

In view of this, a potentiometric technique previously described by Cox and Schneider[41,45] has been used to measure stability constants. This technique is similar in principle to pH techniques, but is based on equilibrium (6) in which Ag^+ is used as the "indicator" ion.

$$MCry^{n+} + Ag^{+} \overset{Ke(MCry^{n+})}{\rightleftharpoons} AgCry^{+} + M^{n+} \qquad (6)$$

where M^{n+} is the metal cation and Cry is the cryptand.

The equilibrium constant for reaction (6), $Ke(MCry^{n+})$, is defined by equation (7).

$$Ke(MCry^{n+}) = \frac{[AgCry^{+}][M^{n+}]}{[MCry^{n+}][Ag^{+}]} \qquad (7)$$

The free silver ion concentration can be monitored with a silver electrode.

Combining the equilibrium constant $Ke(MCry^{n+})$ for reaction (6) with the equilibrium constant $Ks(AgCry^{+})$ for the reaction (8),

$$Cry + Ag^{+} \overset{Ks(AgCry^{+})}{\rightleftharpoons} AgCry^{+} \qquad (8)$$

$$Ks(AgCry^{+}) = \frac{[AgCry^{+}]}{[Cry][Ag^{+}]} \qquad (9)$$

leads to equation (11) which is the equilibrium constant $Ks(MCry^{n+})$ for the reaction of formation of the cryptate (10)

$$M^{n+} + Cry \overset{Ks(MCry^{n+})}{\rightleftharpoons} MCry^{n+} \qquad (10)$$

$$Ks(MCry^{n+}) = \frac{[MCry^{n+}]}{[M^{n+}][Cry]} \qquad (11)$$

Thus the formation stability constant of the cryptate, $Ks(MCry^{n+})$, can be obtained from measurements of $Ke(MCry^{n+})$ and $Ks(AgCry^{+})$ as shown in equation (12).

$$Ks(MCry^{n+}) = \frac{Ks(AgCry^{+})}{K_e(MCry^{n+})} \qquad (12)$$

It is assumed that Ke($MCry^{n+}$), Ks($AgCry^+$) and Ks($MCry^{n+}$) as defined in equations (7), (9) and (11) are independent of ionic strength and so represent thermodynamic stability constants. This assumption should be reasonable, as in all cases the species on either side of the equilibrium are equally charged, and ionic strengths used are low ($\leqslant 10^{-2}$M).

The electrochemical cell used for determination of Ke($MCry^{n+}$) (equation (7)) and Ks($AgCry^+$) (equation (9)) is shown below.

$$\begin{array}{ccc} & \mathrm{Et_4NClO_4}\ \ 0.1\mathrm{M} & \\ \mathrm{Ag}|\mathrm{Ag^+},\ 0.01\mathrm{M}|| & \mathrm{or} & ||\ \mathrm{xM,Ag^+}|\mathrm{Ag} \\ & \mathrm{Et_4NPic}\ \ 0.1\mathrm{M} & \\ & & \\ \mathrm{SOLVENT\ S} & \mathrm{SOLVENT\ S} & \mathrm{SOLVENT\ S} \end{array}$$

The potential readings were taken with a digital voltmeter (SOLARTRON A210). Et_4NClO_4 (tetraethylammonium perchlorate) or Et_4NPic (tetraethylammonium picrate) was used in the salt bridge joining the two half cells. Both the detecting and the reference electrodes were $Ag|Ag^+$ electrodes.

The detecting electrode is immersed in a solution which originally contained a known concentration of Ag^+,$[Ag^+]i$, giving an initial cell potential reading Ei. Addition of a known quantity of excess cryptand complexes the silver cation according to equation (8). The potential reading is now E_1 and the silver concentration $[Ag^+]_1$ can be calculated from the equation (13)

$$(E_1 - E_i) = 2.303\ RT/F \log \frac{[Ag^+]_i \gamma_i}{[Ag^+]_1 \gamma_1} \qquad (13)$$

where Nernstian behaviour of the electrodes is assumed (as indeed was shown by electrode calibration experiments). γ_i, γ_1 are the corresponding activity coefficients, referred to infinite dilution in the solvents in question.

From the measured $[Ag^+]_1$ and using mass-balance equations (14) and (15), to determine the concentrations of silver cryptate and free cryptand, Ks($AgCry^+$) can be calculated.

$$[Ag^+]_{1,TOTAL} = [Ag^+]_1 + [AgCry^+]_1 \qquad (14)$$

$$[Cry]_{1,TOTAL} = [Cry]_1 + [AgCry^+]_1 \qquad (15)$$

A known concentration of metal ion is then added, and the system is allowed to reach the equilibrium described by reaction (6). The measured potential E corresponds to a silver concentration $[Ag^+]$ which can be determined from the equation

$$(E-E_i) = 2.303\ RT/F \log \frac{[Ag^+]_i \gamma_i}{[Ag^+]\gamma} \qquad (16)$$

From here Ke($MCry^{n+}$) can be calculated since the concentrations of the different species involved in equilibrium (6) can be determined from mass-balance equations (17), (18) and (19).

$$[Ag^+]_{TOTAL} = [Ag^+] + [AgCry^+] \qquad (17)$$

$$[Cry]_{TOTAL} = [AgCry^+] + [MCry^{n+}] \qquad (18)$$

$$[M^{n+}]_{TOTAL} = [M^{n+}] + [MCry^{n+}]\ . \qquad (19)$$

Total metal ion concentrations were ca. 10^{-3} to 10^{-2}M and were always higher than the cryptand concentrations. Under these conditions, the concentrations of uncomplexed cryptand at equilibrium were negligible.

Knowing Ks($AgCry^+$) and Ke($MCry^{n+}$), the formation constant of the metal cryptate is directly obtained from equation (12).

The required activity coefficients were calculated using the Davies equation[56]

$$\log \gamma_i = - \frac{A\, Z_i^2 I^{\frac{1}{2}}}{1 + I^{\frac{1}{2}}} + 0.3A\, Z_i^2 I \qquad (20)$$

where Z_i is the charge of the ionic species; I is the ionic strength

$$I = \tfrac{1}{2} \sum_i c_i Z_i^2$$

(c_i is the concentration)

and A is the Debye-Hückel parameter given by[57]

$$A = \frac{1.823 \times 10^6}{(\varepsilon T)^{3/2}} \qquad (21)$$

ε = dielectric constant

T = temperature in °K

In the Appendix some detailed examples of stability constant calculations are given.

All experiments were carried out at 25 ± 0.1°C.

Values of log Ks were reproducible to at least ± 0.1 log unit.

The values of the stability constants obtained by this method are in good agreement with those few values reported in the literature which have been obtained by different methods such as NMR[49,50], cyclic voltammetry[40,58], coulombimetric titration[39], cation selective electrodes[31] and acid-base potentiometry[36,37].

C. RESULTS AND DISCUSSION

1. Stability Constants in Ethanol

The stability constants of alkali metal and Ag^+ cryptates in EtOH are shown in Table 5. The values of the stability constants were reproducible to ± 0.1 log unit. Potassium, rubidium and cesium fluorides were used instead of the corresponding perchlorates, because of the low solubility of perchlorate salts in EtOH[59].

The large selectivity towards alkali metal cations displayed by the three cryptands shown in Table 5 contrasts with the poor selectivity of the natural occurring macrocyclic valinomycin towards potassium, rubidium and cesium ions[48].

The alkali metal cations are less solvated in EtOH than in MeOH[60]. The reverse is true for the silver cation. This is reflected in the higher stability of alkali metal cryptates and the lower stability of silver cryptates in EtOH compared with those in MeOH.

2. Stability Constants in Dimethyl Sulphoxide

The stability constants of the alkali metal cryptates in this aprotic solvent are shown in Table 6, together with the stability constants for the silver cryptates.

The values of log Ks were reproducible to ± 0.1 log unit.

DMSO solvates cations very strongly[26] compared with solvents like water, MeOH or EtOH. Therefore low stabilities for metal cryptates would be expected. This is true if the values of the stability constants in DMSO are compared with those in MeOH or EtOH. However, the alkali metal cryptates in DMSO are

TABLE 5

Stability Constants of Metal Complexes in EtOH at 25°C (Ks in $mol^{-1}\ dm^{3}$)

	log Ks			
Cation	(2,1,1)	(2,2,1)	(2,2,2)	Valinomycin[a]
Li^{+}	8.47	5.38	$\leq$ 2.3	-
Na^{+}	7.09	10.20	8.57	-
K^{+}	$\leq$ 2.6	8.56	10.50	6.3
Rb^{+}	-	6.88	9.28	6.4
Cs^{+}	-	4.77	4.17	5.8
Ag^{+}	9.70	13.84	11.51	-

[a] Ref. 48

TABLE 6

Stability Constants of Metal Cryptates in DMSO at 25°C (K_s in $mol^{-1}\ dm^3$)

	log Ks		
Cation	(2,1,1)	(2,2,1)	(2,2,2)
Li^+	5.84	2.77	< 2.0[a]
Na^+	4.63[b]	6.98[c]	5.4[d]
K^+	< 2.0	5.97	7.11[e]
Rb^+	-	4.64	5.85[f]
Cs^+	-	3.23	1.45[g]
Ag^+	6.17	9.61	7.30[h]

[a] cf. log Ks < 1.0, ref. 40

[b] cf. log Ks = 4.3, ref. 39

[c] cf. log Ks = 6.9, ref. 39

[d] Refs. 39 and 40; cf. log Ks = 5.32, this work

[e] cf. log Ks = 6.92, ref. 41

[f] cf. log Ks = 5.7, ref. 40

[g] Ref. 41; cf. log Ks = 1.4, ref. 40

[h] cf. log Ks = 7.15, ref. 41; log Ks = 7.2, ref. 39

somewhat more stable than in H_2O. This suggests that either the ligand interacts strongly with water molecules, through binding sites which are capable of being involved in H-bonding with the protons of water molecules, or the cryptate complex is more strongly solvated in DMSO than in H_2O. For the case of Ag^+, however, the stability constants are around two orders of magnitude lower than in water. This suggests that the very strong solvation of Ag^+ is the dominant factor here. Thermodynamic studies[26] indicate that the free energy of transfer of the silver ion from H_2O to DMSO is -33.5 kJ mol^{-1}, this being one of the most negative values of free energy of transfer for Ag^+ from water to any of the common dipolar aprotic solvents[61]. These factors are discussed in more detail later in connection with a more general survey of solvent effects.

The general selectivity pattern in DMSO, however, is similar to that in water and the alcohols. Thus, for example, the most stable complexes for the various ligands are again Li^+ for (2,1,1), Na^+ for (2,2,1) and K^+ for (2,2,2).

3. Stability Constants in N,N'-Dimethylformamide

The stability constants for alkali metal, silver and calcium cryptates in DMF are shown in Table 7. The values of log Ks for the alkali metal and silver cryptates were reproducible to ± 0.05 log unit. Those for the calcium cryptates represent values of log Ks ± 0.1 log unit.

Comparing the stabilities in the two dipolar aprotic solvents DMF and DMSO, one observes a difference in Ks of no more than an order of magnitude. This indeed might be expected,

TABLE 7

Stability Constants of Metal Cryptates in DMF at 25°C (Ks in $mol^{-1}\ dm^3$)

	log Ks		
	(2,1,1)	(2,2,1)	(2,2,2)
Cation			
Li^+	6.99	3.58	< 2.2
Na^+	5.23	7.88	6.17
K^+	< 2.5	6.68	7.98[a]
Rb^+	-	5.35	6.76
Cs^+	-	3.61	2.16[b]
Ag^+	8.60[c]	12.41[d]	10.07[e]
Ca^{2+}	3.08	6.67	3.84

[a] cf. log Ks = 7.89, ref. 41

[b] Ref. 50

[c] cf. log Ks = 8.62, ref. 41

[d] cf. log Ks = 12.43, ref. 41

[e] cf. log Ks = 10.03, ref. 41

as DMSO and DMF are known to interact to a similar extent with ions. The slight differences in the stability constants could readily be accounted for in terms of slight variations in the solvation of the cations[61].

The effect of varying the cation charge upon cryptate stability can be seen when two cations (Na^+ and Ca^{2+}) of similar size but different charge are compared. Although increasing the cationic charge will result in increasing favourable ion-dipole interactions with the binding centres of the cryptate, the highly polar nature of the DMF molecules (see dipole moments in Table I) results in a corresponding increase in ion-solvent dipole interactions. The net effect may be relatively unfavourable energetics for complexation of doubly charged cations. This is reflected in the lower stability of Ca^{2+} cryptates compared with the stability of Na^+ cryptates for all three ligands in DMF. Both metal ions have similar ionic radii (see Table 2).

4. Stability Constants in N-Methylpropionamide

NMP is a solvent with a remarkable high dielectric constant (ε = 175 at 25°C) due to the chainwise hydrogen-bonded association of its molecules[55,62]. Measurements of the stability constants of metal cryptates in this solvent were made in order to compare the results with the corresponding values in a dipolar aprotic solvent containing an amidic group but with a substantially lower dielectric constant (DMF). The values of log Ks (± 0.1 log unit) are shown in Table 8. The value of the stability constant for $K(2,2,2)^+$ given is only approximate because the solvent employed for its measurement did not have the purity reported earlier in the experimental section (its specific conductivity

TABLE 8

Stability Constants of Metal Cryptates in NMP at 25°C (Ks in mol^{-1} dm^3)

	log Ks		
	(2,1,1)	(2,2,1)	(2,2,2)
Cation			
Li^+	6.43	3.48	< 2.9
Na^+	5.06[a]	6.55	5.82
K^+	2.46[b]	6.11	ca. 8
Rb^+	-	5.55	7.28
Cs^+	-	3.87	-
Ag^+	7.64	10.45	9.17

[a] cf. log Ks = 5.05, obtained using a cation selective electrode

[b] Value obtained using a cation selective electrode

was ca. 6 x 10^{-7} Ω^{-1} cm^{-1}). The stability constants for $Na(2,1,1)^+$ and $K(2,1,1)^+$ were measured by direct titration of the cation with the cryptand. The detecting electrode was a Beckman Cation Selective Electrode (No. 39137). The value of Ks for $Na(2,1,1)^+$ was also determined using silver potentiometry, and the agreement between the results for the two methods was excellent (Table 8).

The stability of alkali metal cryptates in NMP and DMF are very similar, in spite of the difference in dielectric constant and the capability of NMP in forming hydrogen bonds. Unfortunately there are no data on the thermodynamics of transfer of ions from DMF to NMP. Values of the free energy of transfer between DMF and other amides with high dielectric constant and similar dipole moments, such as N-methylformamide and formamide[26], suggest that, in general, alkali metal cations are somewhat less solvated in these solvents than in DMF. Assuming that the same happens in NMP, this might be expected to lead to slightly more stable complexes in NMP. It is clear, however, that the very high dielectric constant does not play an important role in complex formation.

5. Stability Constants in 1,2-Propanediol Carbonate (Propylene Carbonate)

Table 9 shows the stability constants for alkali metal, silver and calcium cryptates in PC. Values of log Ks were reproducible to ± 0.1 log unit.

PC has been favoured as a solvent for electrochemical studies. A number of studies on the electrochemical reduction of cryptates of metallic cations in PC have been reported[58,63-65], but only the stability constant of the cryptate $Cs(2,2,2)^+$

TABLE 9

Stability Constants of Metal Cryptates in PC at 25°C (Ks in $mol^{-1}\ dm^{3}$)

	log Ks		
	(2,1,1)	(2,2,1)	(2,2,2)
Cation			
Li^{+}	12.44	9.60	6.94
Na^{+}	8.76	12.09	10.54
K^{+}	3.35	9.88	11.10[a]
Rb^{+}	< 2.2	7.03	9.02
Cs^{+}	-	4.92	4.0[b]
Ag^{+}	14.49	18.50	16.33[c]
Ca^{2+}	8.65	11.48	10.76

a Ref. 41; cf. log Ks = 11.19, this work

b Ref. 49; cf. log Ks = 4.2, ref. 58; log Ks = 4.18, this work

c cf. log Ks = 16.29, ref. 41.

could be quantitatively evaluated, due to the irreversibility of the polarographic reduction of the other metal cryptates. The value of log Ks for $Cs(2,2,2)^+$ (4.2 ± 0.2) obtained from the electrochemical studies[58] agrees with the value obtained by the method described in the present work (4.18 ± 0.1) and with that obtained from NMR measurements[49] (4.0 ± 0.04).

Qualitative support for some of the results in Table 9 also comes from the results of other investigations in PC. For example, preliminary NMR results[50] confirm the somewhat surprising result that the stability of $Cs(2,2,1)^+$ is greater than that of $Cs(2,2,2)^+$ despite the fact that the cavity diameter of the (2,2,2)cryptand is larger than that of (2,2,1). This can also be observed in the other solvents considered so far. It seems likely that Cs^+ is only partially contained within the cavity of these ligands and may be interacting with the solvent. The very high stability of the alkali metal cryptates in general is also in agreement with qualitative conclusions from electrochemical studies[58].

The very high stability of Li^+, Na^+ and Ag^+ cryptates in particular is consistent with the results of thermodynamic studies of ion solvation in PC[66]. Thus free energies of transfer, ΔG_{Tr}, of cations to PC from water and solvents such as DMSO and DMF, are in the order $\Delta G_{Tr}(Ag^+)$, $\Delta G_{Tr}(Li^+) > \Delta G_{Tr}(Na^+) > \Delta G_{Tr}(K^+) > \Delta G_{Tr}(Rb^+) > \Delta G_{Tr}(Cs^+)$[61,66].

The importance of cation solvation is also reflected in the relative stabilities of the most stable alkali metal complexes for the various ligands ($Li(2,1,1)^+$, $Na(2,2,1)^+$ and $K(2,2,2)^+$). The typical order of values of the stability constants in the solvents studied so far is $K(2,2,2)^+ > Na(2,2,1)^+ >$

$Li(2,1,1)^+$, i.e. the stability decreases as the number of donor atoms in the ligands decreases. However, this order is reversed in PC, suggesting that changes in ion solvation may be the predominant factor here.

The high stability of Ag^+ complexes in general, due to the covalent character of the metal-donor atom bond, particularly the Ag^+-N bond, has been commented on earlier. The stability is, however, considerably enhanced when Ag^+ is in a poorly solvating medium such as PC. A spectacular drop, of the order of 10^8-10^9 in Ks, is observed on changing the solvent from PC to DMSO or AN (see next section) where the solvation of Ag^+ is strong (the free energies of transfer of Ag^+ from PC to DMSO and AN have been estimated as -52 kJ mol^{-1} and -40 kJ mol^{-1} respectively).

Values of Ks for Ca^{2+} cryptates in PC are also several orders of magnitude higher than in H_2O or DMF. This also suggests that Ca^{2+} is poorly solvated in PC, in agreement with conclusions drawn from electrochemical studies[67].

Attempts were made to measure the stability constants of Cu^{2+}, Ni^{2+} and Co^{2+} cryptates, but difficulties arose from the preparation of anhydrous solutions of the corresponding perchlorate salts. However, the following conclusions could be drawn from the measurements made:

(a) the stability constants are very high for the complexes of these transition metal ions with all three cryptands, in spite of the small size of the cations, and

(b) there is little or no selectivity between Ni^{2+} and Co^{2+}.

This has also been found in water[37].

The Cu^{2+} cryptates are particularly stable in PC, to the extent that Cu^{2+} displaces Ag^+ from the complexes. Studies on the electrochemical reduction of transition metal cryptates in PC have also indicated a very high stability of these complexes[65]. Spiess et al. have investigated the complexing properties of the cryptands towards Cu^{2+} in H_2O[37] and recently also in MeOH[68]. The existence of a binuclear Cu_2Cry^{4+} species in MeOH, and not in H_2O, is reported. The reported values of Ks in H_2O and preliminary measurements on Cu^{2+} cryptates in DMSO, show a marked decrease ($> 10^8$) in the stability constants in these solvents compared with PC. This reflects a relatively poor solvating ability of PC towards Cu^{2+} which increases the reactivity of the copper ion, thus possibly favouring the formation of binuclear species.

6. Stability Constants in Acetonitrile

The method for measuring the stability constants described in the experimental section of this chapter assumes that the stability of the silver cryptates is sufficiently high so that the equilibrium expressed by equation (6) is displaced to the right and the concentration of free silver is small. Otherwise the sensitivity of the method decreases since the silver electrode has to detect a very small, sometimes practically zero, change in the free silver concentration (a two-fold change in $[Ag^+]$ corresponds to a change in the e.m.f. of the cell of only 18 mV at 25°C).

In the solvents considered so far, the silver cryptates had in all cases been more stable than the corresponding alkali metal cryptates. This does not happen in AN where some of

TABLE 10

Stability Constants of Metal Cryptates in AN at 25°C (K_s in mol^{-1} dm^3)

	log Ks		
	(2,1,1)	(2,2,1)	(2,2,2)
Cation			
Li^+	-	10.33 ± 0.1	6.97 ± 0.1
Na^+	(9.8)[a]	(12.4)[a]	10.9[b]
K^+	2.84[c]	9.5[c]	10.71[d]
Rb^+	-	7.27[c]	9.50[c]
Cs^+	-	5.17[c]	4.57[e]
Ag^+	7.70 ± 0.1	11.29 ± 0.1	8.99 ± 0.1[f]

a Estimated values given by ref. 39

b Ref. 39

c B. G. Cox and H. Schneider, unpublished results

d Ref. 41

e Ref. 50

f cf. log Ks = 8.92, ref. 41;
log Ks = 9.3, ref. 39.

the alkali metal cations form more stable complexes than the silver ion. Therefore, some of the values of the stability constant could not be determined by the method used in most of this work.

Table 10 shows the values of log Ks for the alkali metal and Ag^+ cryptates.

The solvation of alkali metal cations in AN is very similar to that in PC, and this is reflected in the high stability constants, particularly of Li^+ and Na^+ complexes. However, AN interacts very strongly with Ag^+,[61] and a tremendous drop in the value of $Ks(AgCry^+)$ is observed on changing the solvent from PC to AN (ca. seven orders of magnitude). Again, it seems likely that in absolute terms the order of stability is $Li(2,1,1)^+ > Na(2,2,1)^+ > K(2,2,2)^+$, as observed in PC.

7. Stability Constants and Free Energies of Transfer

So far, the stability constants of a number of metal cryptates have been discussed separately for each solvent. It has been seen that the solvation of the cation plays an important part in determining the stability of the complex. However, solvation of the free ligand and the complex should also be taken into account if a more complete analysis of the role of the solvent in the process of complexation is to be carried out. Moreover, it has been seen that sometimes, cation solvation cannot explain by itself the magnitude of the variations of the stability constants with the solvent, but additional factors, such as ligand and complex solvation, have to be invoked. Indeed, the (concentration) stability constant involves three terms (equation (11): the concentrations of the cryptate,

$$Ks = \frac{[MCry^{n+}]}{[M^{n+}][Cry]} \tag{11}$$

the ligand and the metal. The values of log Ks for the complexes formed by the alkali metal, silver and calcium cations with the (2,1,1), (2,2,1) and (2,2,2) cryptands in H_2O and various non-aqueous solvents are summarized in Table 11.

The standard free-energy change for the process of complexation in solution, can be expressed in terms of the stability constant as

$$\Delta G^{o} = -RT \ln K \approx - RT \ln Ks \tag{22}$$

where the thermodynamic stability constant K has been approximated by the concentration stability constant Ks.

The difference in ΔG^{o} between two solvents will reflect the change in the solvation of the different species involved.

If the free energy of complexation in solvent S_1 is ΔG^{o}_{1} and in solvent S_2 is ΔG^{o}_{2}, the difference in ΔG^{o} between solvent S_1 and solvent S_2 is given by equation (23).

$$\begin{aligned} \Delta G^{o}_{2} - \Delta G^{o}_{1} &= -2.303\ RT\ (\log Ks_2 - \log Ks_1) \\ &= \Delta G_{Tr}(MCry^{n+}) - \Delta G_{Tr}(M^{n+}) - \Delta G_{Tr}(Cry) \end{aligned} \tag{23}$$

where Ks_2 and Ks_1 are the stability constants in solvent S_2 and S_1 respectively. ΔG_{Tr} stands for the corresponding free energy of transfer from S_1 to S_2.

The difference between the free energies of transfer

TABLE 11

Stability Constants of Metal Cryptates in Various Solvents

log Ks at 25°C

Cryptand	Cation	H_2O	MeOH	EtOH	DMSO	DMF	NMP	PC	AN
2,1,1	Li^+	5.5	8.0	8.47	5.84	6.99	6.43	12.44	-
	Na^+	3.2	6.1	7.09	4.63	5.23	5.05	8.76	9.8
	K^+	<2.0	2.3	≤2.6	<2.0	<2.5	2.46	3.35	2.84
	Rb^+	<2.0	1.9	-	-	-	-	<2.2	-
	Ca^{2+}	2.50	-	-	-	3.08	-	8.65	-
	Ag^+	8.52	10.60	9.70	6.17	8.60	7.64	14.49	7.70
2,2,1	Li^+	2.50	5.3	5.38	2.77	3.58	3.48	9.60	10.33
	Na^+	5.40	9.6	10.20	6.98	7.88	6.55	12.09	12.4
	K^+	3.95	8.5	8.56	5.97	6.68	6.11	9.88	9.5
	Rb^+	2.55	6.7	6.88	4.64	5.35	5.55	7.03	7.27
	Cs^+	<2.0	4.3	4.77	3.23	3.61	3.87	4.92	5.17
	Ca^{2+}	6.95	-	-	-	6.67	-	11.48	-
	Ag^+	11.82	14.64	13.84	9.61	12.41	10.45	18.50	11.29
2,2,2	Li^+	1.25	2.6	≤2.3	<2.0	<2.2	<2.9	6.94	6.97
	Na^+	3.9	7.9	8.57	5.4	6.17	5.82	10.54	10.9
	K^+	5.4	10.4	10.50	7.11	7.98	ca8.0	11.10	10.71
	Rb^+	4.35	8.9	9.28	5.85	6.76	7.28	9.02	9.50
	Cs^+	1.47	4.4	4.17	1.45	2.16	-	4.0	4.57
	Ag^+	9.6	12.20	11.51	7.30	10.07	9.17	16.33	8.99
	Ca^{2+}	4.4	-	-	-	3.84	-	10.76	-

of the cryptate and the cryptand is given by equation (24).

$$\Delta G_{Tr}(MCry^{n+}) - \Delta G_{Tr}(Cry) = \Delta G_{Tr}(M^{n+}) - 2.303\ RT\ (\log Ks_2 - \log Ks_1) \tag{24}$$

Table 12 shows this difference using water as the reference solvent. The values of the free energies of transfer of the cations were taken from reference 66 for PC, reference 60 for EtOH and references 26 and 61 for all other solvents.

The values of ($\Delta G_{Tr}(MCry^+) - \Delta G_{Tr}(Cry)$) in Table 12 show a tendency to reach minimum values for the cases where the cation most closely fits the cavity of the ligand. This means that, for a given ligand, $\Delta G_{Tr}(MCry^+)$ presents the largest (negative) difference on transfer from H_2O to any of the other solvents, when the cationic diameter and the cavity size of the ligand are of similar magnitude. The case of $\Delta G_{Tr}(M(2,2,2)^+)$ from H_2O to MeOH (Figure 9) and from H_2O to PC (Figure 10) are very good examples of this behaviour. The results in Figure 9 with methanol as solvent, include a value for the free energy of transfer of the ligand of $\Delta G_{Tr}(2,2,2) = 4.6$ kJ mol^{-1} determined by Abraham et al[32]. A similar value of $\Delta G_{Tr}(2,2,2)$ ca. 4.0 kJ mol^{-1} for transfer from water to AN has also been determined[69], and it is safe to assume that ΔG_{Tr} values to other dipolar aprotic solvents are similar. A value of $\Delta G_{Tr}(2,2,2) = 4$ kJ mol^{-1} has been used to calculate the results in Figure 10 for transfer to PC. It is clear, however, that any error in this result will not affect the relative values of $\Delta G_{Tr}(MCry^+)$ for the various cations.

TABLE 12

Values of the difference $\Delta G_{Tr}(MCry^+) - \Delta G_{Tr}(Cry)$ in kJ mol^{-1} (reference solvent: H_2O)

Cryptand	Metal Cation	MeOH	EtOH	DMSO	DMF	PC	AN
2,1,1	Li^+	-10.1	-6.5	-16.6	-18.1	-16.6	-
	Na^+	-8.2	-6.3	-22.0	-22.0	-18.4	-23.9
	Ag^+	-4.4	0.2	-20.1	-17.7	-16.1	-17.1
2,2,1	Li^+	-11.8	-6.0	-16.2	-15.8	-17.5	-15.0
	Na^+	-15.6	-11.5	-22.8	-24.9	-24.8	-26.1
	K^+	-15.9	-10.0	-23.7	-25.1	-28.3	-23.0
	Rb^+	-13.7	-8.8	-22.9	-26.1	-24.0	-20.3
	Ag^+	-8.6	-4.5	-20.9	-20.6	-20.1	-18.8
2,2,2	Li^+	-3.50	-	-	-	- 9.5	- 2.9
	Na^+	-14.50	-10.8	-22.4	-23.4	-24.6	-26.2
	K^+	-18.50	-12.9	-21.9	-24.4	-27.0	-22.3
	Rb^+	-15.9	-12.2	-19.4	-23.8	-24.9	-22.7
	Cs^+	-7.1	-0.5	-12.5	-13.1	-16.1	-12.7
	Ag^+	-7.3	-3.9	-20.3	-19.8	-20.4	-18.3

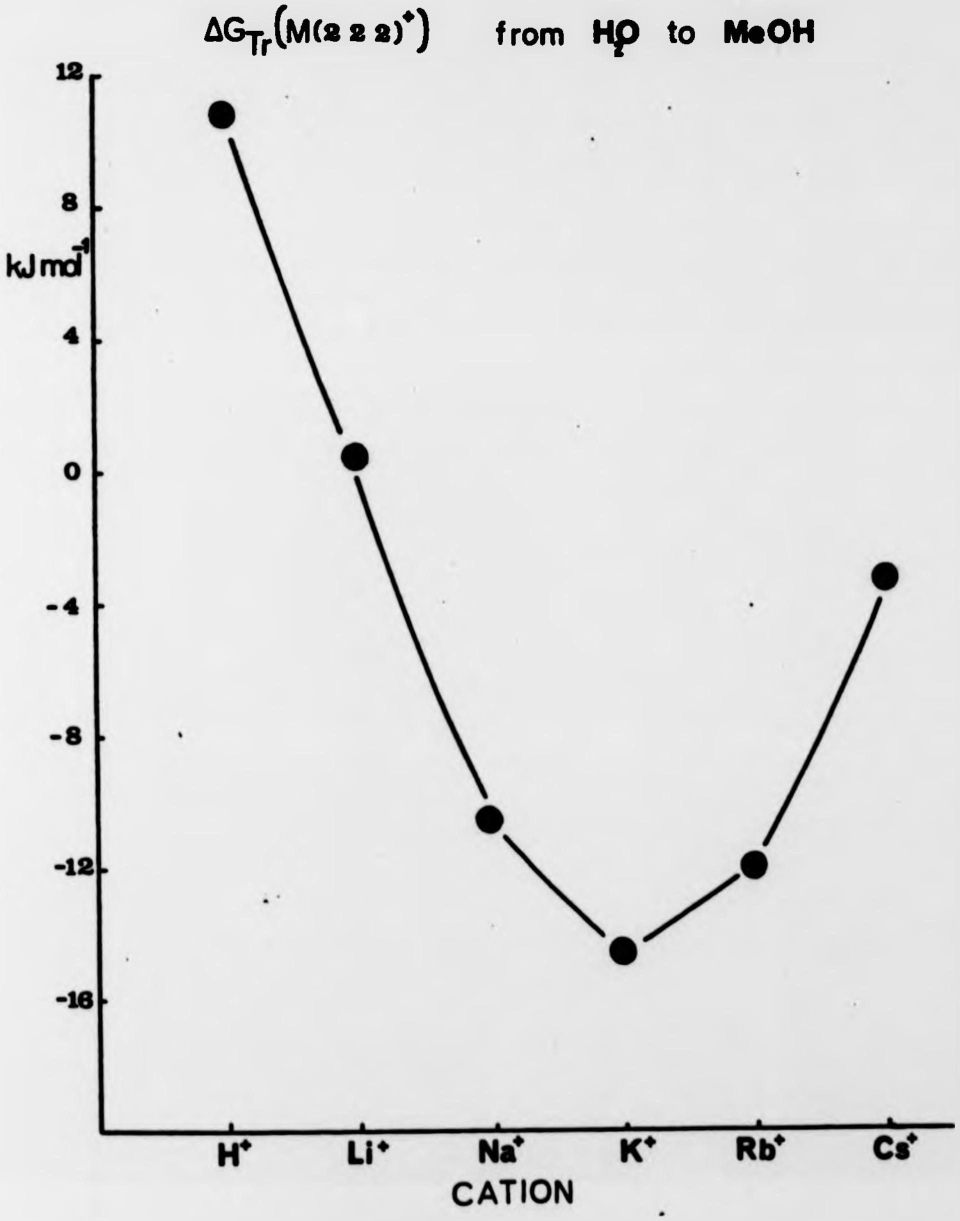

ΔG_Tr(M(2 2 2)^+) from H2O to MeOH
12
8
kJ mol^-1
4
0
-4
-8
-12
-16
H+
Li+
Na+
K+
Rb+
Cs+
CATION

Figure 9

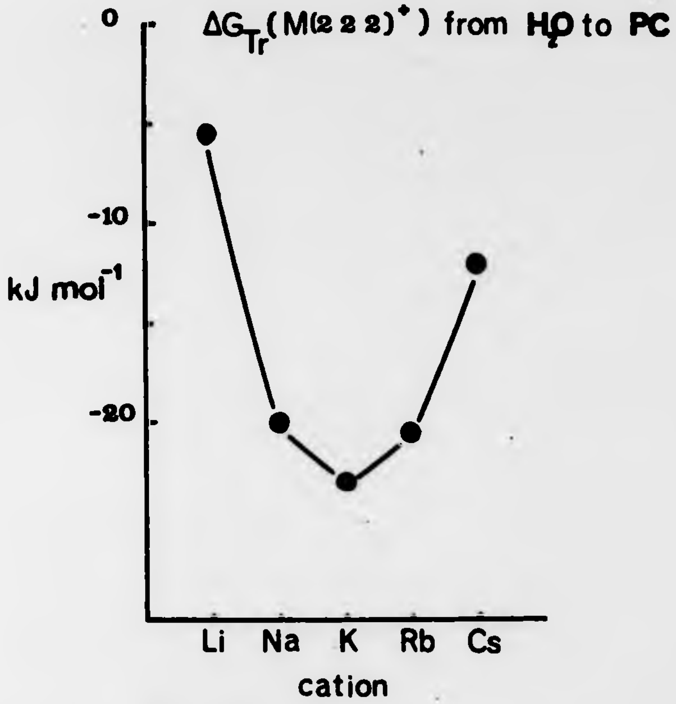


Figure 10

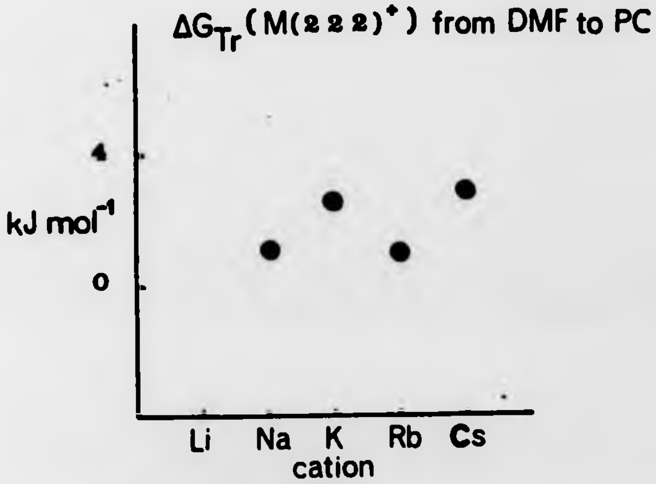


Figure 11

Similarly the transport of an anion X^-, along with the cryptate (as must occur in any real process) will merely result in $\Delta G_{Tr}((MCry)X)$ values that parallel those in figures 9 and 10, with overall values being more positive for small anions of high charge density. Figure 9 also includes values of $\Delta G_{Tr}((2,2,2)H^+)$ from H_2O to MeOH. The values of Ks in H_2O and MeOH are taken from reference 68 (log Ks = 10.0 in H_2O and 10.69 in MeOH) and the value of $\Delta G_{Tr}(H^+)$ from H_2O to MeOH (10.9 kJ mol^{-1}) from reference 26.

The transfer of cryptates between two aprotic solvents (DMF-PC) is illustrated in Figure 11. The values of $\Delta G_{Tr}(M(2,2,2)^+)$ are almost negligible and the trend towards reaching a minimum when the size of the cation is the optimum to fit into the ligand cavity (generally the most stable complex), is not observed.

The thermodynamically favoured transport of the most stable cryptates from H_2O to less solvating media may have implications in the selective extraction by cryptands of metal cations from aqueous solutions. The extracting liquid is normally a organic liquid with poor solvating ability towards metal ions. Thus, apart from the gain in stability of the cryptates predicted by the loss of solvation of the metal cations, there is an extra stabilization due to the change in cryptate-solvent interactions. This increase in stability becomes larger, the better the ligand accommodates the cation in its cavity. In a solvent like H_2O, the oxygen and nitrogen atoms of the complexed cryptand, might participate in hydrogen-bonding with the water molecules. If the cation is too small for the cavity of the ligand or too big to go completely into the cavity, the donor atoms may rotate more freely to come into contact with the solvent, without affecting very much the strength of the metal ion-donor atom bonds. However, if the cation is tightly fixed in the cavity, the solvent will essentially see only the hydrocarbon backbone of the ligand. Thus it should interact more favourably with "organic" solvents than with water, leading to a more negative free energy of transfer from water. For example, the free energy of transfer for K^+ and Cs^+ from H_2O to MeOH are very similar[26]; i.e. the stability constants for the transport reactions $K^+_{aq} \rightleftharpoons K^+_{MeOH}$, and $Cs^+_{aq} \rightleftharpoons Cs^+_{MeOH}$ are practically the same; however, the selectivity of the (2,2,2) cryptand for K^+ over Cs^+ ($Ks(K^+)/Ks(Cs^+)$) changes from 10^4 in H_2O to 10^6 in MeOH. The importance of H-bonded interactions between the ligands and water may be deduced from the fact that the ligands are more soluble in water than in methanol or dipolar aprotic solvents, despite the large hydrocarbon content of the ligands.

If the minimum in $\Delta G_{Tr}(MCry^+)$ found for the transfer of the most stable cryptates from water to organic solvents also holds for other related ligands, particularly the more flexible naturally-occurring ligands, it may have important implications for the selective extraction of metal ions into and through organic media. Thus in the case of the cryptates, not only does the most appropriate cation for a given ligand form the most stable cryptate in water, but the cryptate is also the one most efficiently extracted into organic media (equation (25)).

$$M^+_{aq} + Cry_{aq} \overset{Ks}{\rightleftharpoons} MCry^+_{aq} \overset{extraction}{\rightleftharpoons} MCry^+_{org.solv.} \qquad (25)$$

The limited results available for other macrocyclic ligands, for example valinomycin, make it difficult to present clear evidence of a definite minimum in ΔG_{Tr} values. Values of $\Delta G_{Tr}(ML^+)-\Delta G_{Tr}(L)$ where L = valinomycin and M = K^+, Rb^+, Cs^+ from H_2O to MeOH, are shown in Figure 12. More results, particularly those for Li^+, Na^+ and K^+ in various solvents, including values in aprotic solvents, would be desirable.

Ligands of the crown-ether type, e.g. 18-Crown-6 (Fig.12) hold the metal ion in a bidimensional structure and not in a three-dimensional cavity as cryptands do. Therefore, the solvent can interact with the complexed metal ion. Any change in the free energy of transfer of these complexes would be intimately related to changes in free energy of transfer of the single ions. This is illustrated in Figure 13 for the case of dibenzo 18-Crown-6 on transfer from DMF to PC. The required stability constants were taken from reference 70.

The values given in Table 12 for the difference $\Delta G_{Tr}(MCry^+)-\Delta G_{Tr}(Cry)$ from H_2O to the four dipolar aprotic solvents (DMSO, DMF, PC and AN) are approximately constant (within ± 2.5 kJ mol^{-1}) for a given cryptand and a given metal. This means that the difference between the transfer free energies of the cryptate and the cryptand is nearly zero in the case of the transfer between two aprotic solvents, something that Schneider et al.[41] had found before for the $K(2,2,2)^+$, $Ag(2,2,2)^+$ and $Tl(2,2,2)^+$ cryptates. However, this is not true for the water-methanol or water-ethanol transfer, as already pointed out by Abraham et al.[32], who report a preliminary study on the selective transfer of ions in the water-methanol system. (See also Figures 9 and 10).

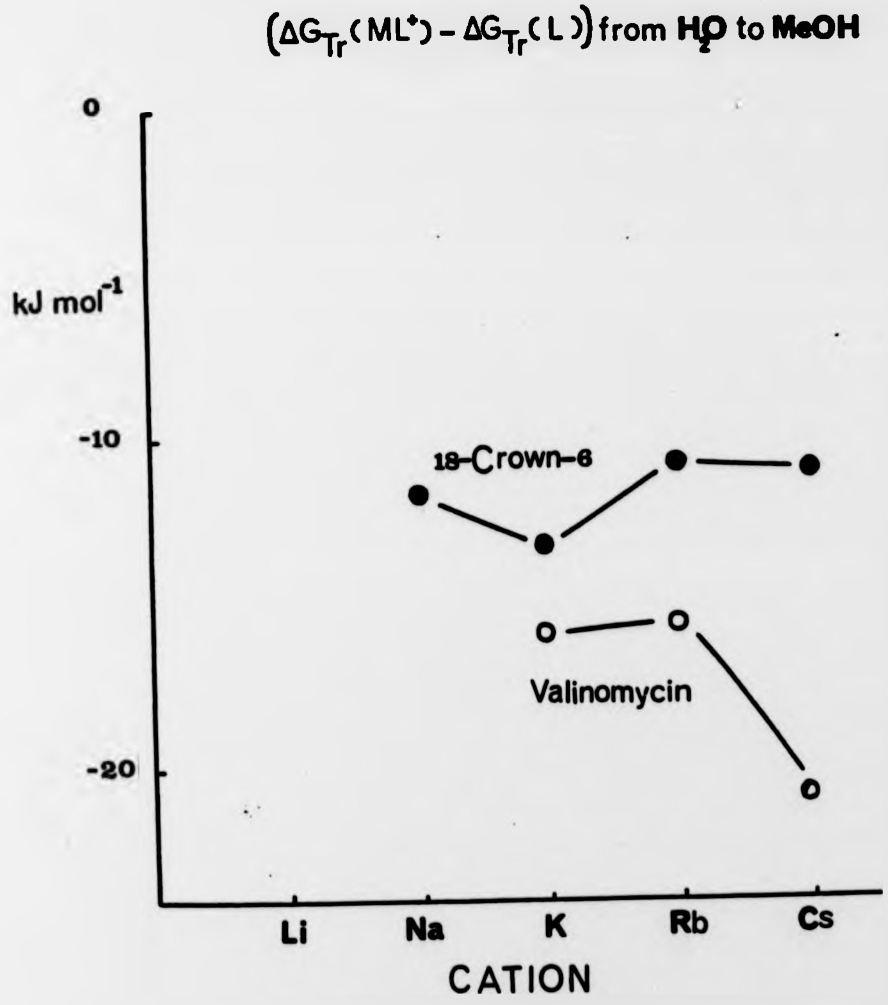

$(\Delta G_{Tr}(ML^+) - \Delta G_{Tr}(L))$ from H_2O to MeOH
0
kJ mol^{-1}
-10
-20
18-Crown-6
Valinomycin
Li
Na
K
Rb
Cs
CATION

Figure 12

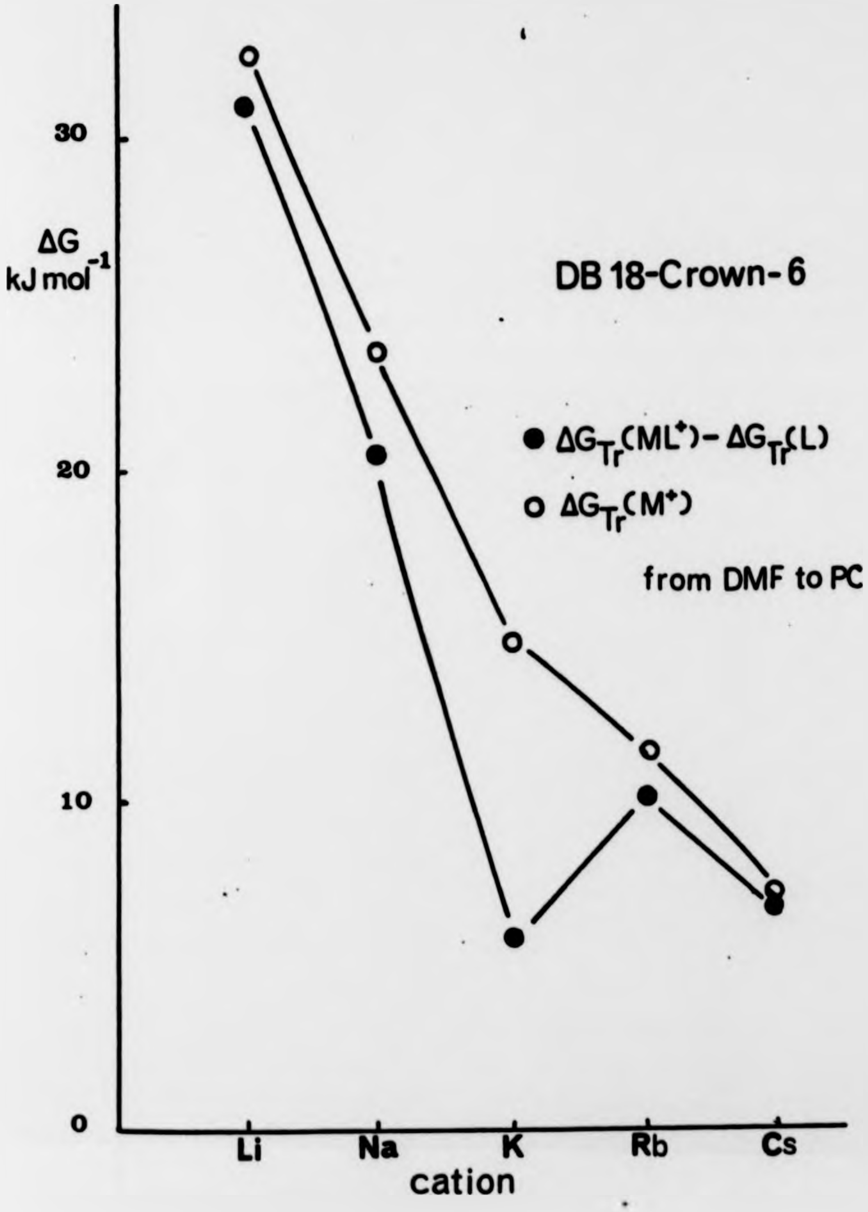

30
20
10
0
ΔG kJ mol^{-1}
DB 18-Crown-6
● $\Delta G_{Tr}(ML^+) - \Delta G_{Tr}(L)$
○ $\Delta G_{Tr}(M^+)$
from DMF to PC
Li
Na
K
Rb
Cs
cation

Figure 13

As has been discussed earlier, the free energy of transfer of the free cryptand does not seem to change appreciably between two non-aqueous solvents. Similarly the results in Table 12 (based on $\Delta G_{Tr}(M^+)$ values estimated from the assumption that $\Delta G_{Tr}(Ph_4As^+) = \Delta G_{Tr}(BPh_4^-)$) suggest that $\Delta G_{Tr}(MCry^+)-\Delta G_{Tr}(Cry)$ values are close to zero for a variety of cations and solvents, i.e. $\Delta G_{Tr}(MCry^+)$ is also close to zero for transfer between aprotic solvents. These observations are not unexpected in view of the fact that acceptor numbers* (see Table 1) for aprotic solvents are similar and small when compared with solvents like H_2O or MeOH. Therefore the interactions between the oxygen and nitrogen atoms of the free or complexed cryptand and the solvent molecules should be small and not very different among aprotic solvents.

Under conditions where $\Delta G_{Tr}(MCry^+)-\Delta G_{Tr}(Cry) = 0$, equation (24) reduces to equation (26), and so measurements

$$\Delta G_{Tr}(M^+) = -2.303\ RT\ (\log Ks_2 - \log Ks_1) \qquad (26)$$

of stability constants provides a means of estimating free energies of transfer of cations between solvents.

---

* The acceptor number (A_N) is taken as a measure of the ability of the solvent to accept electron pairs. It is defined by the equation

$$A_N = \frac{\delta_{corr}}{\delta_{corr}(SbCl_5.Et_3PO)} \times 100$$

where δ_{corr} is the ^{31}P chemical shift of Et_3PO in a given solvent, extrapolated to zero concentration and referred to an infinitely dilute solution of the phosphine oxide in n-hexane ($A_N = 0$); $\delta_{corr}(SbCl_5.Et_3PO)$ is the corresponding chemical shift for an infinitely dilute solution of the $SbCl_5.Et_3PO$ adduct in 1,2-dichloroethane ($A_N = 100$).
(U. Mayer, Pure Appl.Chem., 51, 1697 (1979)).

There is evidence of the existence of a $Cs(2,2,2)^+$ exclusive complex[49] in which the Cs^+ ion is not completely within the cavity of the cryptand and therefore the metal ion may interact with the solvent. However, the results in Table 12 show that $\Delta G_{Tr}(Cs(2,2,2)^+)-\Delta G_{Tr}(2,2,2)$ is also nearly zero on the transference from one aprotic solvent to another, even though $\Delta G_{Tr}(Cs^+)$ can be as large as 17.6 kJ mol^{-1} as in the case of the transfer of the Cs^+ ion from AN to DMSO[26]. The explanation for this could be that the cryptate cation resembles a large cation (low charge density ion) with small free energy of transfer among aprotic solvents, and also that only part of the metal ion is in contact with the solvent.

The case of $Li(2,2,2)^+$ where, in spite of the difference in $\Delta G_{Tr}(Li^+)$ between PC and AN (7 kJ mol^{-1} as reported in ref. 26, although reported $\Delta G_{Tr}(Li^+)$ values often vary remarkably from author to author), the stability does not increase accordingly, suggests that when the cation is very small compared with the cavity size of the ligand there is a certain limit of maximum stability dictated by the large conformational changes that the ligand must undergo to try to isolate the cation from the surrounding solvent and interact most favourably with the cation. Solvation and conformational energies for macromolecules are closely related[71,72]. It may well be that these large conformational changes bring about different solvation energies of the complex among aprotic solvents, so that the equality $\Delta G_{Tr}(MCry^+) = 0$ no longer holds for the case of $Li(2,2,2)^+$.

In spite of its limitations, the resulting expression (eq. (26)) should enable cationic free energies of transfer between two aprotic solvents to be estimated from measurements of the stability constants of metal cryptates in each solvent.

Independent methods to evaluate ionic free energies of transfer are necessary to complement or put into consideration the existing values obtained by the presently used extra thermodynamic assumptions such as the large cation-large anion assumption[61], the negligible liquid junction potential assumption[73] or the ferrocene/ferrocinium[74] or bisbiphenylchromium (I)/ bisbiphenylchromium (O)[75] assumptions.

The effect of the charge of the metal cation in the solvation of the cryptate can be analysed by comparing the cryptates of Na^+ and Ca^{2+}. Both metal ions have similar ionic radii. The variation of the stability constants of $NaCry^+$ and $CaCry^{2+}$ on transfer from H_2O to PC are of similar magnitude. However, the free energy of transfer of a bivalent metal cation (Ca^{2+}) is expected to be much more sensitive to the change of solvent than that of a univalent cation of comparable size (Na^+). This implies that the free energy of transfer of a doubly-charged cryptate is also more sensitive to solvent variation than a singly-charged cryptate, thus suggesting that the cation charge is not precisely "buried" inside the ligand cavity, but it is manifested as the charge of a large size positive ion.

Making use of equation (24), the following expression is obtained for the difference in transfer free energy of calcium and sodium complexes with (2,2,2)

$$\begin{aligned} &\Delta G_{Tr}(Ca(2,2,2)^{2+}) - \Delta G_{Tr}(Na(2,2,2)^{+}) \qquad (27) \\ &= \Delta G_{Tr}(Ca^{2+}) - \Delta G_{Tr}(Na^{+}) - 2.303\ RT[\log Ks_2(Ca^{2+}) - \log Ks_1(Ca^{2+}) \\ &\qquad - \log Ks_2(Na^{+}) + \log Ks_1(Na^{+})] \end{aligned}$$

Studies on the solvation of Na^+ and Ca^{2+} in H_2O and PC[67] indicate that $\Delta G_{Tr}(Ca^{2+})-\Delta G_{Tr}(Na^+)$ from H_2O to PC is quite significant (of the order of 10-30 kJ mol^{-1}). Using the corresponding values of Ks, equation (27) becomes

$$\Delta G_{Tr}(Ca(2,2,2)^{2+})-\Delta G_{Tr}(Na(2,2,2)^+) = \Delta G_{Tr}(Ca^{2+})-\Delta G_{Tr}(Na^+) + 1.6\ \text{kJ mol}^{-1} \tag{28}$$

for the H_2O-PC transfer. Thus, the difference between the free energy of transfer from H_2O to PC of the doubly and single-charged cryptates reflects the difference in free energy of transfer of the bivalent and monovalent metal cations. According to this striking result, it would seem that a much thicker "organic" layer would be needed to shield the charge of a doubly charged cation such as Ca^{2+} from the surrounding medium.

CHAPTER II

FORMATION AND DISSOCIATION RATES OF (2,1,1), (2,2,1) AND (2,2,2) METAL CRYPTATES

A. INTRODUCTION

Most of the applications of the synthetic macrocyclic ligands are based on their ability to form stable metal complexes and their selectivity towards metal cations. These "equilibrium" properties, however, only give information about the initial and final state of a system. From a practical point of view, one would also be interested in knowing the dynamic characteristics of the process of complexation and decomplexation, particularly if these compounds are to be used as cation carriers through membranes. The naturally-occurring antibiotics act as cation carriers in natural membranes. A synthetic macrocyclic compound may well serve as a model to perform this function, thus helping in the understanding of the natural process of transport. If the carrier is contained in a medium (i.e. natural or artificial membrane) such that the transport rate of the cation is determined by the rate of diffusion of the carrier through that medium, then any increase in the stability of the complex should improve the efficiency of the carrier. Indeed, the yield of transported cation should increase without affecting the overall transport rate. However, if the rate at which the carrier uptakes the cation (complexation) from one side of the membrane, or the rate at which the cation is unloaded (decomplexation) on the other side of the membrane are the rate determining steps in the process of transport, any increase in the stability of the complex will alter the overall transport rate[33]. This is because the rate constants of formation and dissociation of the complex are related through the stability constant. Thus, the study of the kinetics of complex formation and dissociation becomes important to the understanding of certain transport processes performed by natural carriers. It is also of some interest to see the way in which the characteristic selectivity displayed by these ligands is reflected in the formation or dissociation rates. It has been pointed out before that many of the characteristics displayed by the natural macrocyclic carriers are present in synthetic ligands such as the cryptands. Therefore, apart from the study of the stability of complexes formed between cryptands and metal cations, a survey on the kinetics of these compounds is necessary. By varying the solvent in which the reactions of complexation and decomplexation take place, one expects that certain aspects of the mechanism of these reactions will become apparent. This may also help as a guide to the design of new ligands capable of performing specific functions, such as that mentioned before, concerned with efficient transport through membranes.

The overall process of complexation between a solvated cation and a solvated ligand can be expressed by equation (1), given in Chapter I. This equation is

$$(L)_{solv} + (M^{n+},mS) \underset{k_d}{\overset{k_f}{\rightleftharpoons}} (L,M^{n+})_{solv} + mS \qquad (1)$$

where k_f and k_d are the overall formation and dissociation rate constants respectively.

If a ligand is to react with a metal cation, it must penetrate into the inner solvation shell of the cation and substitute the solvent molecules by its binding centres. Eigen and Wilkins[76] have proposed two extreme mechanisms for this substitution process. One in which a solvent molecule leaves the inner coordination sphere prior to the entry of the ligand. The intermediate state would have a lower coordination number than both the initial and final states. The other mechanism involves a transition state with a larger coordination number than the initial state due to significant bond formation between the incoming ligand and the metal ion prior to the departure of a solvent molecule. The observed substitution rate constants favour the first mechanism for alkali and alkaline-earth metal cations[48,77].

Simple electrostatic models based on ion-dipole or dipole-dipole interactions are insufficient to explain solvent effects on complex formation. Additional factors such as van der Waals forces, induced polarization, etc. must also be taken into account. Other models have been mainly confined to the calculation of solvation energies and energies of transfer[78,79]. Recent semi-empirical models for the description of solvent effects on chemical reactions are mainly based on the use of reference experimental solvent parameters, such as the donor number[80] and the acceptor number[27].

In the case of macrocyclic polydentate ligands, conformational changes may also occur and play an important role in determining the rates of formation and dissociation of the complex[3,48]. Open chain molecules such as murexide show rates of complexation with alkali metal cations in methanol very near the limit of diffusion controlled reactions. The same can be said of the open chain antibiotic nigericin[77]. The rates of complex formation for macrocyclic compounds are surprisingly high considering that all the solvent molecules of the primary solvation shell must be replaced by the ligand binding centres. This implies that the solvent molecules must be substituted one after another, so that there is a stepwise compensation of the solvation energy by the ligand binding energy. Conformational changes must permit the polar groups of the ligand to be in close contact with the solvent molecules surrounding the cation and also, during complexation, conformation changes must occur in order to enclose the cation in the cavity[48]. Indeed, ultrasonic absorption experiments have shown relaxation times corresponding to conformation changes in macrocyclic polyethers like 18-Crown-6[81,82]. Sometimes this structural change has been the rate limiting step for the complexation reaction as in the case of valinomycin[83], where internal hydrogen bonding stabilizes its conformation.

Macrobicyclic structures of the type depicted in Figure 14 have been useful in understanding conformational-dependent properties based on the atoms or groups at the bridgeheads Z[84],

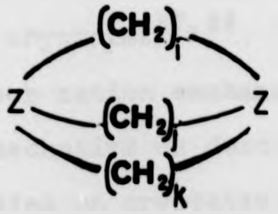


Figure 14 Macrobicyclic Molecule

Macrobicyclic diamines (Z = Nitrogen atom) can exist in three different configurations depending upon whether electron pairs of the bridgehead nitrogen atoms are directed towards the cavity or outwards the cavity defined by the hydrocarbon bridges[85], as shown schematically in Figure 15.

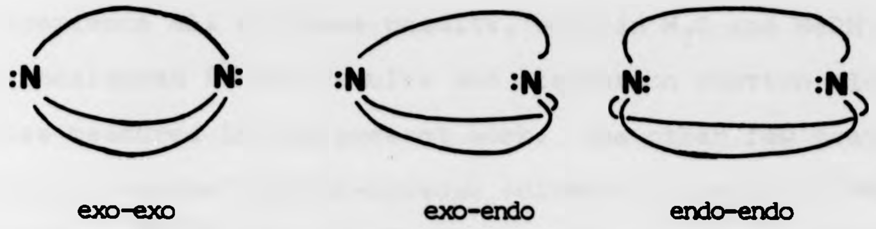


Figure 15 Equilibrium Configurations of Macrocyclic Diamines: exo-exo, exo-endo and endo-endo.

These three configurational isomers are also present in macrobicyclic polyether diamines[86], the endo-endo configuration being the one which stabilizes the complex most effectively since both nitrogen atoms participate in the coordination bonds with the metal. This has been confirmed by crystallographic studies made of several metal cryptates[87,88]. The existence of several conformations may favour cation exchange rates by allowing a stepwise desolvation mechanism as described above.

Kinetic studies on cryptates are very scarce. Only one comprehensive study on the kinetics of alkali metal cryptate formation and dissociation has been reported. This was carried out in MeOH by Cox, Schneider and Stroka[45]. Different authors report some dissociation rates in H_2O obtained by different methods. Dye et al.[89] used ^{23}Na NMR; Lehn et al.[90] used ^{1}H NMR and Popov et al.[91] used ^{7}Li NMR. A conductimetric technique was employed by Cox and Schneider[92] and, using a temperature-jump relaxation procedure, Maass et al.[93] obtained the formation and dissociation rate constants of some sodium and potassium cryptates. Studies on the kinetics of alkaline earth metal cryptates in H_2O have also been reported[92,94]. For convenience all of these results, both in H_2O and MeOH, will be considered in the Results and Discussion section along with those measured in the present work. The other few scattered results obtained in non-aqueous solvents by means of NMR techniques[91,95] will also be included together with the results obtained in this work.

A conductimetric technique was used in this work to measure the dissociation rate constants of a number of alkali metal cryptates involving (2,1,1), (2,2,1) and (2,2,2) cryptands, in the following solvents: EtOH, DMSO, DMF, NMP and PC. The dissociation rate constants of Ca^{2+} cryptates in DMF and PC were also determined. Silver potentiometry was used to monitor dissociation reactions of some alkaline earth metal cryptates in H_2O. The formation rate constants were determined via the stability constants given in Chapter I ($k_f = k_d K_s$).

The variation in the magnitude of the rates with the solvent is analysed in each case in terms of the solvating ability towards the metal ions, the cryptands, and the cryptates of the different solvents involved. A catalysed dissociation of some of the cryptates was also found during the study on the kinetics of cryptate dissociation in the presence of species capable of displacing the metal cation from the ligand. The final part of this chapter deals briefly with this catalytic effect which, not surprisingly, also depends on the solvent.

B. EXPERIMENTAL SECTION

1. Chemicals and Solvents

Cryptands were the same as those used for the stability constant measurements (see Experimental Section, Chapter I). With a few exceptions, the salts used in the kinetic measurements were also the same. In EtOH, LiCl (BDH,LR), KI (M&B Pronalys,AR) and RbCl (JMC,Specpure) were used. KNO_3 (Fisons,AR) was used instead of the corresponding perchloric salt in DMSO.

The acids used were: HCl in EtOH and DMF. HCl gas (HCl,BOC) was bubbled into DMF. In EtOH the acid solutions were prepared from concentrated HCl (Fisons,AR,s.gr. 1.18). Dichloroacetic acid (BDH,LR) was used in the other solvents. The resulting solutions were analysed by titration against standard alkali in all cases.

The solvents were purified as described previously (see Exp.Sec., Chap. I).

2. Dissociation Rate Measurements

Practically no spectral changes associated with alkali or alkaline-earth metal cryptate formation are observed in the visible or ultraviolet region. This makes spectrophotometric techniques unsuitable to monitor reactions involving such complexes. NMR techniques are limited to cases where there exist atoms whose resonance can be readily monitored. They also have the disadvantage that generally the measurements have to be made at temperatures other than room temperature, so that the reaction rates fall within the NMR time scale (e.g. 1-10^3s mean life-time for ^1H NMR)[96]. Thus, values of the rate constants at 25°C are often extrapolated, assuming constant activation energies.

In this work, the measurements of the dissociation rates of metal cryptates were made mainly using a conductimetric technique and, on a few occasions, using silver potentiometry. Both methods are described below.

The formation rate constants are simply calculated as the product of the dissociation rate constant and the stability constant ($k_f = k_dK_s$).

(i) Conductimetric Method

This method has been used by Cox and Schneider[45,92] to measure dissociation rates of metal cryptates in H_2O and MeOH.

The reactions were followed by observing the conductance change on the addition of an excess of acid to an equilibrium metal cryptate/free metal mixture. The overall reaction is

$$MCry^{n+} + 2HA \xrightarrow{k_m} CryH_2^{2+} + M^{n+} + 2A^- \qquad (29)$$

where $MCry^{n+}$ is the metal cryptate, HA is the acid, M^{n+} is the metal ion and $CryH_2^{2+}$ is the diprotonated form of the cryptand. k_m is the measured or observed rate constant.

A conventional conductance cell was used for slower reactions and a stopped-flow apparatus with conductance detection for faster reactions (Durrum Stopped-Flow, Durrum Instrument Corp., Techmation Ltd.).

The following mechanism may be assumed for the overall reaction (29). Firstly, dissociation of the metal cryptate

$$\mathrm{MCry}^{n+} \underset{k_f}{\overset{k_d}{\rightleftharpoons}} \mathrm{M}^{n+} + \mathrm{Cry} \qquad (30)$$

Then, reaction of the free cryptand with the acid

$$\mathrm{Cry} + \mathrm{HA} \xrightarrow{k} \mathrm{CryH}^{+} + \mathrm{A}^{-} \qquad (31)$$

$$\mathrm{CryH}^{+} + \mathrm{HA} \xrightarrow{k'} \mathrm{CryH}_2^{\,2+} + \mathrm{A}^{-} \qquad (32)$$

As long as the second protonation reaction is fast compared with the overall reaction rate, it will only affect the magnitude of the observed conductance change without altering the observed overall rate. This can be checked independently by allowing the monoprotonated cryptand and the acid to react, in the absence of metal ions.

The corresponding kinetic equations for the above reactions (30,31) are given by

$$-\frac{d[\mathrm{MCry}^{n+}]}{dt} = k_d[\mathrm{MCry}^{n+}] - k_f[\mathrm{M}^{n+}][\mathrm{Cry}] \qquad (33)$$

$$-\frac{d[\mathrm{Cry}]}{dt} = k_f[\mathrm{M}^{n+}][\mathrm{Cry}] - k_d[\mathrm{MCry}^{n+}] + k[\mathrm{HA}][\mathrm{Cry}] \qquad (34)$$

The concentration of the free cryptand is kept at a negligible value provided that both metal cation and acid are in excess. The steady state assumption can then be applied to the cryptand species and from equation (34) the concentration of free cryptand at any time will be given by

$$[\mathrm{Cry}] = \frac{k_d[\mathrm{MCry}^{n+}]}{k[\mathrm{HA}] + k_f[\mathrm{M}^{n+}]} \qquad (35)$$

Substitution of equation (35) in (33) leads to

$$-\frac{d[MCry^{n+}]}{dt} = \frac{k_d k[HA]}{k[HA]+k_f[M^{n+}]}[MCry^{n+}] \qquad (36)$$

or

$$-\frac{d[MCry^{n+}]}{dt} = k_m[MCry^{n+}] \qquad (37)$$

where $$k_m = \frac{k_d k[HA]}{k[HA]+k_f[M^{n+}]} \qquad (38)$$

is the "observed" or "measured" first-order rate constant.

If the rate of protonation of the cryptand is significantly faster than the rate of complex formation, i.e.

$$k[HA] >> k_f[M^{n+}]$$

then it can be seen from equation (38) that the observed rate constant is actually the rate constant for the dissociation of the cryptate, i.e.

$$k_m = k_d \qquad (39)$$

However, if there is effective competition between the metal cation and the acid for the free ligand, i.e.

$$k[HA] \approx k_f[M^{n+}]$$

equation (38) can be more conveniently expressed as

$$\frac{1}{k_m} = \frac{1}{k_d} + \frac{k_f}{k_d k}\frac{[M^{n+}]}{[HA]} \qquad (40)$$

Then a plot of $\frac{1}{k_m}$ against $[M^{n+}]$ at constant $[HA]$ should be a straight line whose intercept with the $[M^{n+}] = 0$ axis is $\frac{1}{k_d}$.

For strong acids, reactions (31) and (32) will involve H^+ rather than HA (equations (31') and (32')).

$$Cry + H^+ \xrightarrow{k} CryH^+ \tag{31'}$$

$$CryH^+ + H^+ \xrightarrow{k'} CryH_2^{2+} \tag{32'}$$

It can be easily seen that the same kinetic equations described above apply here just by changing the term [HA] to $[H^+]$. Thus, equation (38) for k_m becomes

$$k_m = \frac{k_d k[H^+]}{k[H^+] + k_f[M^{n+}]} \tag{38'}$$

and equation (40) will read

$$\frac{1}{k_m} = \frac{1}{k_d} + \frac{k_f}{k_d k}\frac{[M^{n+}]}{[H^+]} \tag{40'}$$

In aqueous solutions, methanol and ethanol, the use of strong acids is experimentally quite convenient because of the large decrease in conductance. This is caused by the removal of the highly mobile H^+, which reacts to give $CryH^+$ and $CryH_2^{2+}$ species. In other non-aqueous solvents, the mobility of the proton is no longer significantly different from that of other ions, and it is much more convenient to use a weak acid HA, as in equation (29) because of the large increase in conductance resulting from the production of $CryH_2^{2+}$ and $2A^-$.

For some cryptates, depending on the metal and the solvent, there is an additional acid-catalysed pathway for the dissociation reaction. It has been shown[45,92] that in this case the observed rate constant has the form

$$k_m = k_d + k_{H^+}[H^+] \quad (41)$$

or equivalently

$$k_m = k_d + k_{HA}[HA] \quad (42)$$

A detailed analysis of the reaction mechanisms leading to equations (41) and (42) will be given later in this chapter. There it will be shown that k_{H^+} as given in equation (41) is subject to a positive kinetic salt effect and, in order to obtain a linear relationship between k_m and $[H^+]$, k_m values must be corrected to zero ionic strength.

(ii) Potentiometric Method

As an alternative to the use of acid to displace the metal from the cryptate, and hence determine the dissociation rates, a potentiometric technique based on the use of the Ag/Ag$^+$ electrode was investigated.

If excess silver ion is added to an equilibrium $MCry^{n+}/M^{n+}$ mixture the following overall reaction takes place

$$MCry^{n+} + Ag^+ \xrightarrow{k_m} AgCry^+ + M^{n+} \quad (43)$$

In equation (43) it is assumed that silver forms a much more stable complex with the cryptand so as to displace the metal cation from the complex essentially quantitatively. This holds in most of the solvents (except AN) as can be seen from the stability constant measurements. A silver electrode can be used to monitor the change in silver ion concentration as a function of time. The rate at which Ag$^+$ disappears is the rate at which $AgCry^+$ is formed and from this, a rate constant can be determined. Alternatively, reaction (43) can be followed by measuring the rate at which silver ion has to be added to the system to keep a constant free silver concentration throughout the reaction (cf. the conventional pH-stat technique for following hydrolyses reactions[97]). The automatic equipment set-up (Figure 16) to carry out these measurements consists of a cell similar to that described for stability constant measurements, a voltmeter (Radiometer pH meter, type PHM26), titration unit (Radiometer Titrator, type TTT11), a burette unit (Radiometer Syringe Burette SBU1) and a recorder (Radiometer Titrigraph SBR2)[98].

Before starting the reaction, the potential at which the cell is to be maintained during the reaction is set at the desired value (the so-called "end-point"). This determines the free silver ion concentration at which the reaction is going to take place, although strictly speaking, it is the activity of the free silver ion that is being fixed and not its concentration. However, if the ionic strength does not change appreciably during the course of the reaction, a constant silver concentration can be safely assumed. Furthermore, the rate constants may be independent of the silver concentration under certain conditions as will be seen below.

During the course of the reaction, the volume of the titrating solution used to maintain a given potential, is recorded as a function of time. The concentration of metal cryptate remaining at a given time is proportional to the total volume of Ag^+ solution required to complete the reaction (v_∞) minus the

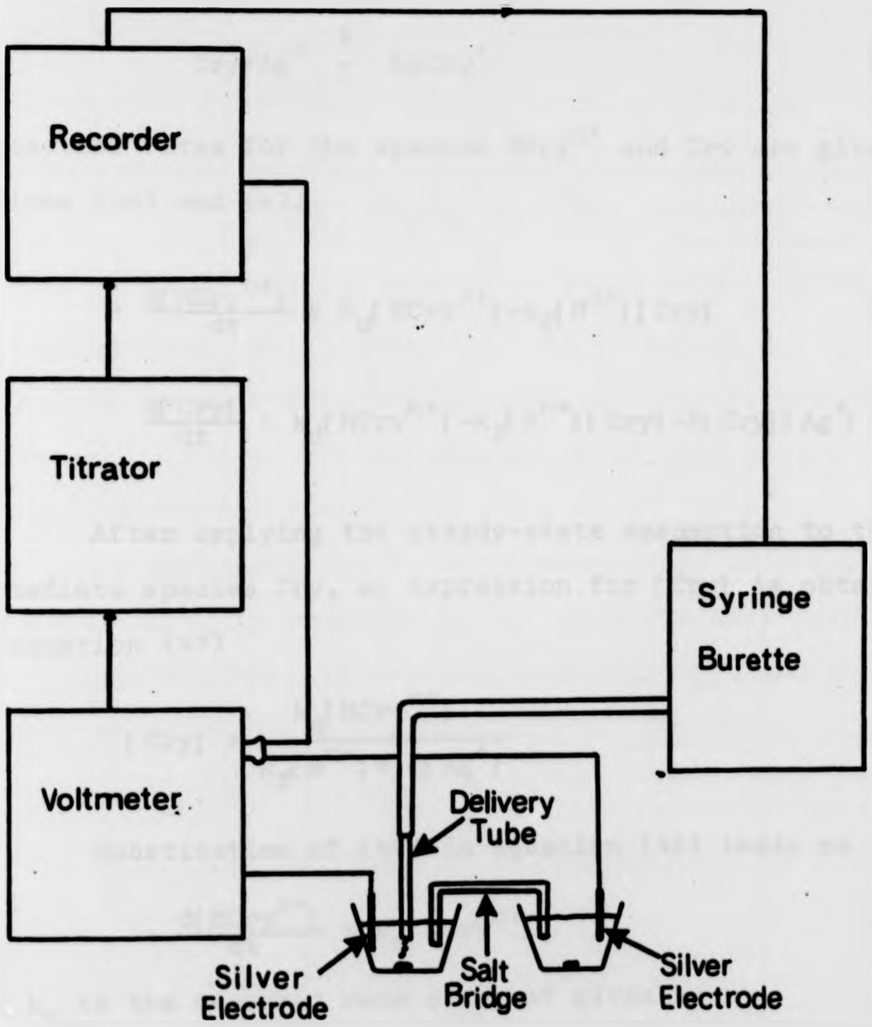


Figure 16 Potentiometric Monitoring of Reactions

volume added at that time (v). A rate constant can thus be measured applying the following kinetic treatment.

If reaction (43) proceeds via the free cryptand

$$MCry^{n+} \underset{k_f}{\overset{k_d}{\rightleftharpoons}} M^{n+} + Cry \qquad (44)$$

$$Cry + Ag^{+} \xrightarrow{k} AgCry^{+} \qquad (45)$$

the reaction rates for the species $MCry^{n+}$ and Cry are given by equations (46) and (47)

$$-\frac{d[MCry^{n+}]}{dt} = k_d[MCry^{n+}] - k_f[M^{n+}][Cry] \qquad (46)$$

$$\frac{d[Cry]}{dt} = k_d[MCry^{n+}] - k_f[M^{n+}][Cry] - k[Cry][Ag^{+}] \qquad (47)$$

After applying the steady-state assumption to the intermediate species Cry, an expression for [Cry] is obtained from equation (47)

$$[Cry] = \frac{k_d[MCry^{n+}]}{k_f[M^{n+}] + k[Ag^{+}]} \qquad (48)$$

Substitution of (48) in equation (46) leads to

$$-\frac{d[MCry^{n+}]}{dt} = k_m[MCry^{n+}] \qquad (49)$$

where k_m is the measured rate constant given by

$$k_m = \frac{k_d k[Ag^{+}]}{k_f[M^{n+}] + k[Ag^{+}]} \qquad (50)$$

As $[Ag^{+}]$ is held constant during a given reaction, it follows that in the presence of excess M^{n+} (so that its concentration is constant), k_m will be a constant and hence the reaction will show first order kinetics. Furthermore, if the reaction between the free cryptand and the silver ion occurs rapidly compared with the formation reaction of the metal cryptate $MCry^{n+}$, that is to say, if

$$k[Ag^+] >> k_f[M^{n+}]$$

then equation (50) becomes

$$k_m = k_d \qquad (51)$$

i.e. the observed kinetics will be of first order, and the observed rate constant is precisely the dissociation rate constant of the cryptate. Under these conditions, the observed or measured rate constant is independent of both silver and metal ion concentrations.

As discussed above, the concentration of metal cryptate is directly proportional to the difference between the total volume of titrating solution employed, ν_{oo}, and the volume of solution spent at any time, ν . Therefore

$$[MCry^{n+}] \propto (\nu_{oo}-\nu)$$

From equation (49), after integration, the following expression is obtained

$$\ln(\nu_{oo}-\nu) = -k_m t + const. \qquad (52)$$

Therefore, a plot of $\ln(\nu_{oo}-\nu)$ vs time should be a straight line whose slope is k_m.

Measurements of the dissociation rates of some alkaline-earth metal cryptates using this method, were carried out in water. The resulting numerical values were in good agreement with values obtained by conductimetric[92] or spectrophotometric (with the aid of an indicator)[94] techniques reported in the literature. However, not much use of this potentiometric technique could be made, because of the relatively slow response of the Radiometer Titrator, which limited measurable rates to $t_{\frac{1}{2}} \geq$ ca. 2 min. Alternative electrochemical techniques for monitoring Ag^+ concentration, however, might enable much faster reactions to be followed (e.g. cyclic voltammetry, etc.).

C. RESULTS AND DISCUSSION

1. Kinetics of Metal Cryptates in Water

A number of studies of the kinetics of cryptates in water have been reported. These studies include cation exchange kinetics, especially by means of NMR techniques[89,90,99]; temperature-jump relaxation kinetics[93] and various stopped-flow studies on the kinetics of dissociation and formation of metal cryptates[92,94,100].

Table 13 shows the dissociation rate constants of some alkali and alkaline earth metal cryptates, as well as those corresponding to the complexes formed with the macrocyclic polyether 18-Crown-6[82,101] and the open chain polydentate ligand EDTA[48]. From these results, the large difference in the dissociation rates between the cryptates and the other two complexes is immediately evident. The dissociation of the cation from tridimensional rigid ligands such as the cryptands, which encapsulate the cation in their intramolecular cavity, is more difficult than from a less rigid two-dimensional ligand like the crown ethers, or from an open chain ligand such as EDTA. The complexes of EDTA with alkali metal cations show dissociation rates that increase as the size of the cation increases, that is to say, the process of dissociation is faster for cations less strongly bound to the ligand. However, this may not be true if the ligand exhibits specific cation selectivity. For example, the $Na(2,2,2)^+$ cryptate has a higher dissociation rate than the $K(2,2,2)^+$ complex, although the ligand-cation interaction free energy is larger for the former than for the latter. The higher

TABLE 13

Dissociation Rate Constants of Metal Complexes in H_2O at 25°C

k_d in s^{-1}

Cation	(2,1,1)	(2,2,1)	(2,2,2)	18-Crown-6[a]	EDTA[b]
Li^+	2.5×10^{-2} [c]	-	-	$\sim6\times10^{7}$	1.4×10^{7}
Na^+	1.4×10^{2} [d]	1.45×10 [c,e]	1.5×10^{2} [f]	3.4×10^{7}	2.3×10^{7}
K^+	-	2×10^{3} [d]	7.5 [c,g]	3.7×10^{6}	3.9×10^{7}
Rb^+	-	-	3.8×10 [h]	1.2×10^{7}	1.3×10^{8}
Cs^+	-	-	-	4.4×10^{7}	2×10^{8}
Ca^{2+}	8.2×10^{-1} [c,i]	6.1×10^{-4} [j]	2.1×10^{-1} [c,k]	-	-
Sr^{2+}	-	1.36×10^{-3} [ℓ]	9.3×10^{-5} [m]	1.5×10^{5} [n]	-
Ba^{2+}	-	6.1×10^{-2} [c]	1.75×10^{-5} [c,o]	-	-

a. Ref. 82

b. Ref. 48

c. Ref. 92

d. Ref. 93

e. cf. $k_d = 1.8 \times 10\ s^{-1}$, ref. 93

f. Ref. 89

g. cf. $k_d = 9$, ref. 93

h. k_d at 9°C, ref. 90

i. cf. $k_d = 6.9 \times 10^{-1}\ s^{-1}$, ref. 94

j. cf. $k_d = 6.6 \times 10^{-4}\ s^{-1}$, ref. 92;
$k_d = 2.2 \times 10^{-3}\ s^{-1}$, ref. 94;
$k_d = 8.4 \times 10^{-4}\ s^{-1}$ at 29.7°C, this work.

k. cf. $k_d = 2.6 \times 10^{-1}\ s^{-1}$, ref. 94

ℓ. cf. $k_d = 1.47 \times 10^{-3}\ s^{-1}$, ref. 92; $k_d = 2.6 \times 10^{-3}\ s^{-1}$, ref. 94

m. cf. $k_d = 7.5 \times 10^{-5}\ s^{-1}$, ref. 92; $k_d = 1 \times 10^{-4}\ s^{-1}$, ref. 94 & ref. 3

n. Ref. 101

o. cf. $k_d = 2.2 \times 10^{-5}\ s^{-1}$, ref. 94; k_d = ca. $10^{-5}\ s^{-1}$, ref. 90.

ion-solvent interaction for a smaller cation (Na^+ in this case) should help to lower the energy barrier for the dissociation process.

The dissociation rates for alkaline earth metal cryptates are especially low. Values of k_d for $Ca(2,2,1)^{2+}$, $Sr(2,2,1)^{2+}$ and $Sr(2,2,2)^{2+}$ were measured using the silver potentiometry method described earlier in the experimental section. These values are compared with those obtained by other methods in the following table (Table 14).

TABLE 14

k_d (s^{-1}) obtained by different methods (25°C)

Cryptate	Silver Potentiometry	Conductimetry[92]	Spectro photometry[94]	Other potentiometric methods[3] *
$Ca(2,2,1)^{2+}$	$6.1x10^{-4}$	$6.6x10^{-4}$	$2.2x10^{-3}$	
$Sr(2,2,1)^{2+}$	$1.36x10^{-3}$	$1.47x10^{-3}$	$2.6x10^{-3}$	
$Sr(2,2,2)^{2+}$	$9.3x10^{-5}$	$7.5x10^{-5}$	1×10^{-4}	1×10^{-4}

* Although ref.3 does not mention it specifically, it is very probable that the method is acid-base potentiometry.

The agreement of k_d values obtained by silver potentiometry with the values resulting from conductimetric measurements is very satisfactory. The four methods quoted in Table 14 give approximately the same value for the dissociation constant of $Sr(2,2,2)^{2+}$. The reported k_d values for $Ca(2,2,1)^{2+}$ and $Sr(2,2,1)^{2+}$ measured by a spectrophotometric technique, with the aid of an indicator (murexide for the calcium complex and metalphthalein for the strontium one), were determined at values of pH at which part of the cryptand is protonated. Therefore a correction should be applied to the values reported by reference 94 (which also do not coincide with some of the values reported by the same authors in a previous paper[100]). This could probably explain the divergency between the results from the spectrophotometric technique and those from the potentiometric and conductimetric techniques.

Comparing the dissociation rates of complexes involving cations with similar size, but different charge (for example, Na^+ and Ca^{2+} or K^+ and Sr^{2+}), one observes a dramatic decrease in k_d values of several orders of magnitude on going from the singly charged cation to the doubly charged one. The formation rates are also considerably lower (ca. 3 orders of magnitude, see Table 15 below). This presumably reflects the considerably higher solvation energies of divalent cations compared to monovalent cations of similar size.

Table 15 shows the formation rate constants for metal complexes of the (2,1,1), (2,2,1) and (2,2,2) cryptands, as well as those formed with 18-Crown-6 and EDTA. The values of k_f, except for EDTA, were calculated as $k_f = k_d K_s$; k_d values were taken from Table 13 and K_s values from Table 3. For EDTA, k_f values are given as reported by reference 48.

The few results in Table 15 show slow formation rates for the cryptates in H_2O, when compared to crown ether complexes like 18-Crown-6 complexes or open-chain polydentate ligand complexes like those formed with EDTA. There is also an increase

TABLE 15

Formation Rate Constants of Metal Complexes in H_2O at 25°C

k_f in $mol^{-1}\ dm^3\ s^{-1}$

Cation	(2,1,1)	(2,2,1)	(2,2,2)	18-Crown-6	EDTA[a]
Li^+	7.9×10^3	-	-	ca. 7.7×10^7	1.0×10^8
Na^+	2.2×10^5	3.6×10^6	1.2×10^6	2.1×10^8	1.7×10^8
K^+	-	1.8×10^7	1.9×10^6	4.0×10^8	8.5×10^7
Rb^+	-	-	-	4.4×10^8	-
Cs^+	-	-	-	4.3×10^8	-
Ca^{2+}	2.6×10^2	5.4×10^3	5.3×10^3	-	-
Sr^{2+}	-	3.1×10^4	9.3×10^3	7.9×10^7	-
Ba^{2+}	-	1.2×10^5 [b]	5.5×10^4 [b]	-	-

a. Ref. 48

b. Ref. 92

in the value of k_f as the size of the cation increases, irrespective of the stability of the complex. This behaviour is also observed in other solvents, as it will be seen later, and it will lead to important conclusions. The fact that the formation rates for cryptates are significantly lower than the rates of solvent exchange in the inner coordination shell of the cation[102], may suggest that the mechanism of dehydration of the cations to enter into the cavity of the ligand is not completely a stepwise mechanism, but involves some solvent molecules leaving the inner solvation shell of the ion simultaneously. This will be discussed later in relation to results in other solvents.

2. Kinetics of Metal Cryptates in Methanol

The rate constants for the dissociation of the cryptates involving the (2,1,1), (2,2,1) and (2,2,2) cryptands and the alkali metal cations in MeOH have been measured by Cox, Schneider and Stroka[45]. These values are shown in Table 16 together with the dissociation rate constants for the complexes of the macrocyclic antibiotic valinomycin[103]. The dissociation rates in all cases follow the same trend as the inverse of the stability constants (dissociation equilibrium constants), the lowest k_d values corresponding to the complexes with the highest stabilities. Table 17 shows the corresponding formation rate constants. The values of k_f increase monotonically with increasing cation size. The fact that the pronounced selectivity is entirely reflected in the dissociation rates rather than in the formation rates, suggests that the transition states more closely resemble the solvated cation and ligand rather than the complex. NMR kinetic studies have led to a similar conclusion[91].

TABLE 16

Dissociation Rate Constants of Alkali Metal Complexes in MeOH at 25°C

		k_d in s^{-1}		
Cation	(2,1,1)[a]	(2,2,1)[a]	(2,2,2)[a]	Valinomycin[b]
Li^+	4.4×10^{-3}	7.5×10	$>3 \times 10^2$	-
Na^+	2.50	2.35×10^{-2}	2.87	1.8×10^6
K^+	-	1.09	1.8×10^{-2}	1.3×10^3
Rb^+	-	7.5×10	8.0×10^{-1}	7.5×10^2
Cs^+	-	ca. 2.3×10^4	4×10^4	2.2×10^3

a. Ref. 45

b. Ref. 103

TABLE 17

Formation Rate Constants of Alkali Metal Complexes in MeOH at 25°C

		k_f in $mol^{-1}\ dm^3\ s^{-1}$		
Cation	(2,1,1)	(2,2,1)	(2,2,2)	Valinomycin[a]
Li^+	4.8×10^5	1.8×10^7	-	-
Na^+	3.1×10^6	1.7×10^8	2.7×10^8	1.3×10^7
K^+	-	3.8×10^8	4.7×10^8	3.5×10^7
Rb^+	-	4.1×10^8	7.6×10^8	5.5×10^7
Cs^+	-	ca. 5×10^8	ca. 9×10^8	2×10^7

a. Ref. 103

It is interesting to note that the dissociation rates of the (2,2,1) and (2,2,2) complexes are, except for Cs^+, much lower than the corresponding dissociation rates of the valinomycin complexes. However, the formation rates of these cryptates are about one order of magnitude higher than those of the valinomycin complexes. Ultrasonic relaxation studies have shown that valinomycin undergoes conformational changes upon complexation[83] and that this conformational change is the rate-determining step in the process of formation of the complex. It is perhaps surprising that the cryptands, which are relatively inflexible ligands compared with valinomycin, are able to form complexes so rapidly. Any conformational changes necessary must occur with little expense in energy. The much greater stability of the cryptates is, however, primarily reflected in the low dissociation rates.

The formation rates for the cryptates in MeOH, particularly those for (2,2,2), are very high and similar to the solvent exchange rates in the inner solvation sphere of the cations. This may suggest effective (stepwise) compensation of the loss of solvation of the cation by ligand-cation interactions.

3. Kinetics of Metal Cryptates in Ethanol

The dissociation rates were determined conductimetrically as explained in the experimental section. The reactions involved a decrease in conductance upon the addition of an excess of hydrochloric acid to an equilibrium $MCry^+/M^+$ mixtures because of the high mobility of the protons relative to the other ions present.

TABLE 18

Kinetics of the Dissociation of Alkali Metal Cryptates in Ethanol at 25°C

Cryptate	k_d s^{-1}	Range of Concentrations M	Equation used to determine k_d (see text)
Li(2,1,1)$^+$	6.0×10^{-4}	[LiCl] : 10^{-3} - 10^{-2} [HCl] : 10^{-3} - 1.2×10^{-2}	(41)
Na(2,1,1)$^+$	7.1×10^{-1}	[NaClO$_4$] : 10^{-3} - 5×10^{-3} [HCl] : 10^{-3} - 1.5×10^{-2}	$k_m = k_d$
Li(2,2,1)$^+$	ca.1.3×10	[LiCl] : 10^{-3} - 10^{-2} [HCl] : 10^{-3} - 2×10^{-2}	$k_m = k_d$
Na(2,2,1)$^+$	2.62×10^{-3}	[NaClO$_4$] : 3×10^{-3} - 8×10^{-3} [HCl] : 10^{-3} - 10^{-2}	(41)
K(2,2,1)$^+$	1.35×10^{-1}	[KI] : 10^{-3} - 10^{-2} [HCl] : 10^{-2} - 10^{-3}	$k_m = k_d$
Rb(2,2,1)$^+$	ca.1.1×10	[RbCl] : 6×10^{-4} - 3×10^{-3} [HCl] : 10^{-3} - 7×10^{-3}	$k_m = k_d$
Na(2,2,2)$^+$	3.0×10^{-1}	[NaClO$_4$] : 3×10^{-4} - 5×10^{-3} [HCl] : 4×10^{-4} - 7×10^{-3}	(41)
K(2,2,2)$^+$	4.08×10^{-3}	[KI] : 10^{-3} - 7×10^{-3} [HCl] : 10^{-3} - 10^{-2}	(40')
Rb(2,2,2)$^+$	9.17×10^{-2}	[RbCl] : 5×10^{-4} - 5×10^{-3} [HCl] : 5×10^{-4} - 10^{-3}	(40')

Table 18 summarizes the measured dissociation rate constants, the ranges of concentrations at which the measurements were carried out and the equations used to evaluate the rate constants.

The observed rate constants for $Na(2,1,1)^+$ and $K(2,2,1)^+$ were independent of both acid and metal ion concentrations, in accordance with equation (39). Rate constants for $Li(2,2,1)^+$ and $Rb(2,2,1)^+$ lie very close to those for the reaction between the acid and the free cryptand; therefore the k_d values reported are only approximate, since their dependence upon the acid and metal ion concentrations could not be properly tested. For $K(2,2,2)^+$ and $Rb(2,2,2)^+$, the observed rate constants showed a significant dependence on the metal ion concentration. Equation (40') was used to determine the actual values of k_d by plotting k_m^{-1} against $[M^+]$ at constant $[H^+]$ ($[HCl] = 10^{-3}M$). These plots are shown in figures 17 and 18.

The dissociation of $Li(2,2,2)^+$ and $Cs(2,2,2)^+$ were too fast to be followed with the stopped-flow apparatus.

Rate constants for $Li(2,1,1)^+$, $Na(2,2,1)^+$ and $Na(2,2,2)^+$ were independent of the metal ion concentration, but were strongly dependent on the acid concentration. This was an indication that an acid catalysed dissociation was taking place. Indeed, Cox and Schneider have reported the existence of an acid-catalysed pathway for the dissociation of a number of metal cryptates in water[92] and in MeOH[45]. The results were analysed according to equation (41). Plots of the measured rate constants (corrected to infinite dilution) against the acid concentration were straight lines whose intercept with the zero-acid axis gave the values of k_d (see Figures 19, 20, 21).

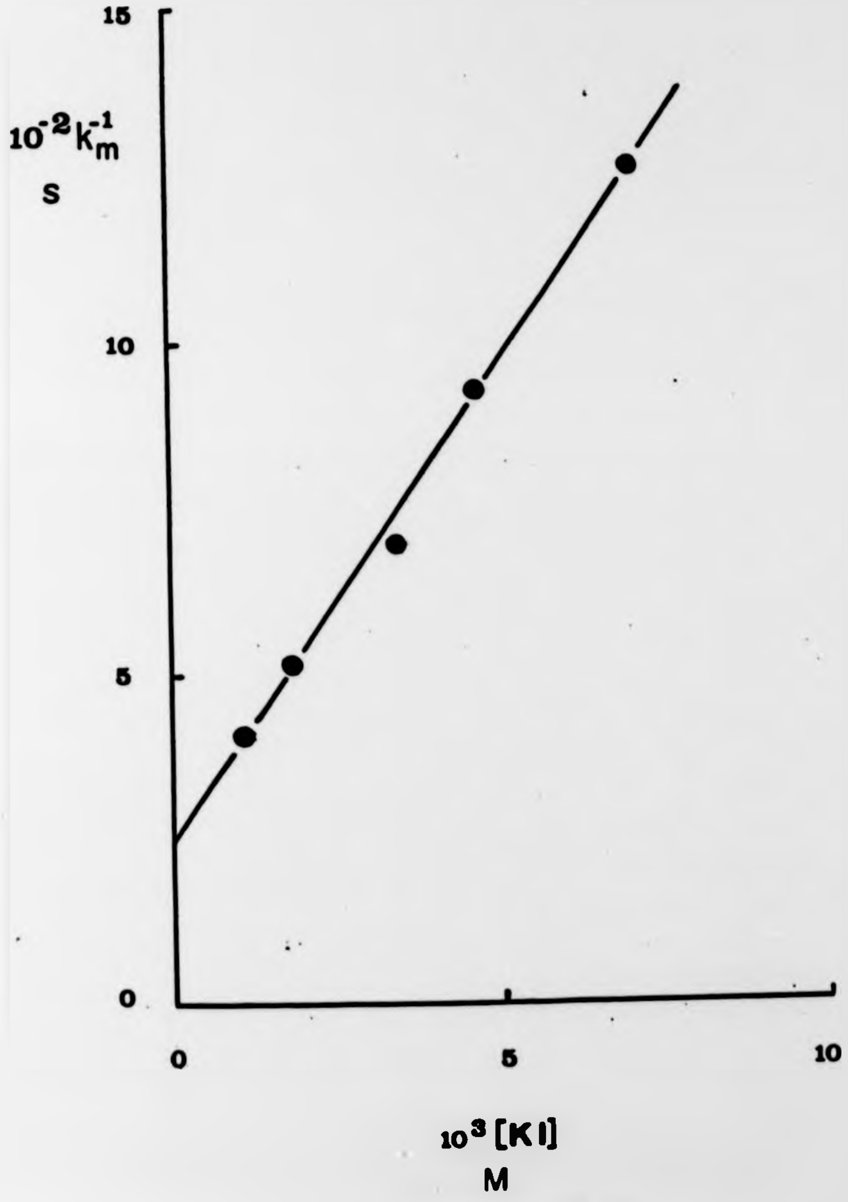
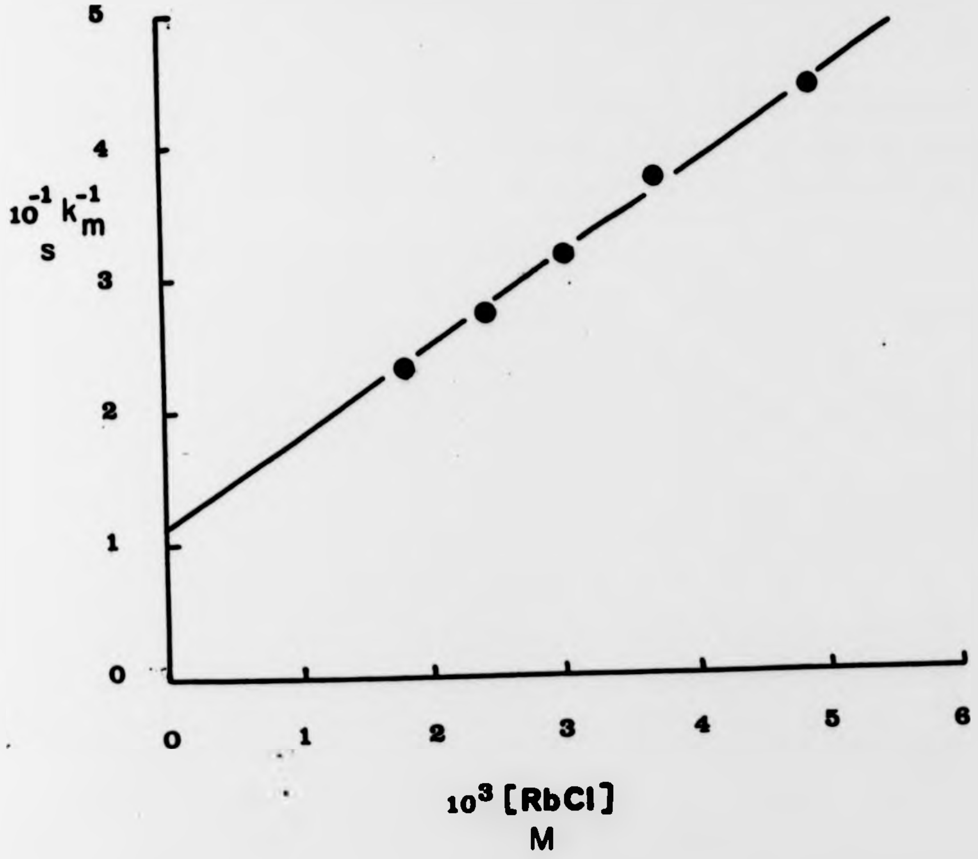


Figure 17 Dependence of k_m^{-1} on [KI] for the dissociation of $K(2,2,2)^+$ in EtOH



<u>Figure 18</u> Dependence of k_m^{-1} on [RbCl] for the dissociation of $Rb(2,2,2)^+$ in EtOH

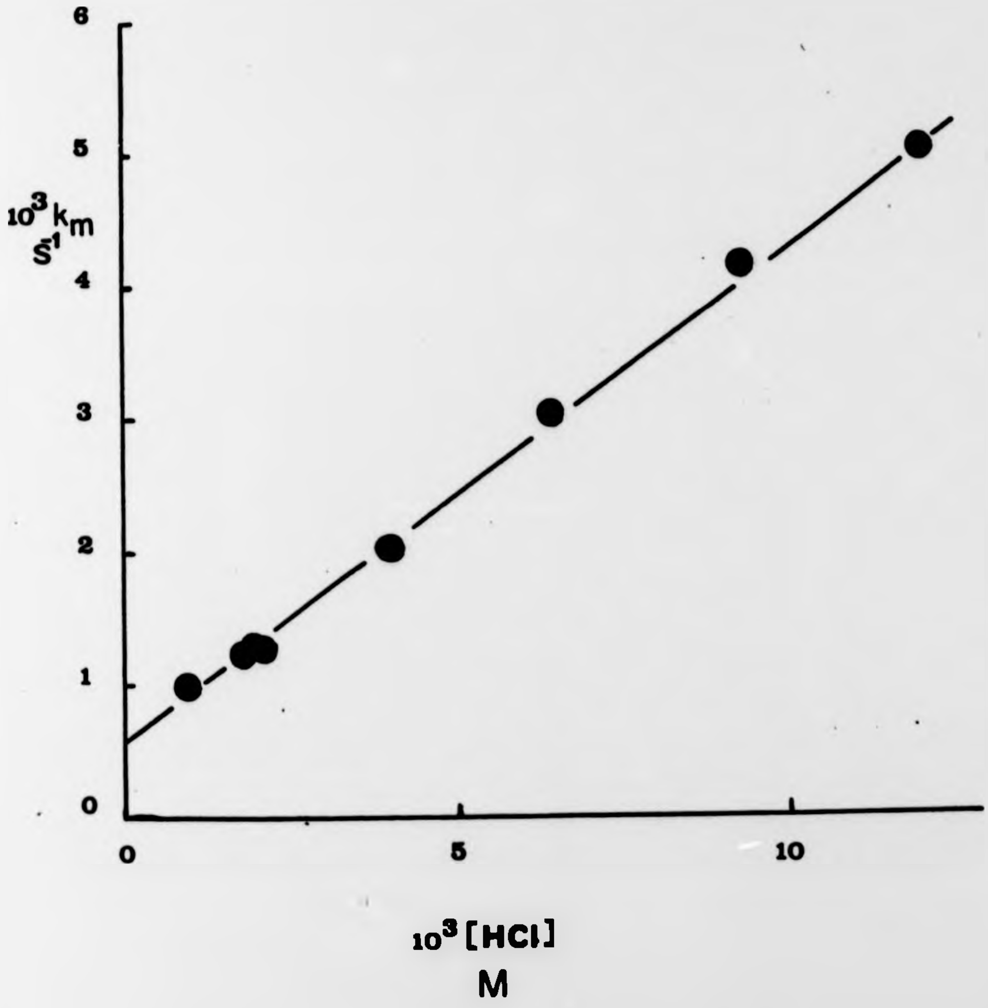


Figure 19   Dependence of k_m on [HCl] for the dissociation of $Li(2,1,1)^+$ in EtOH

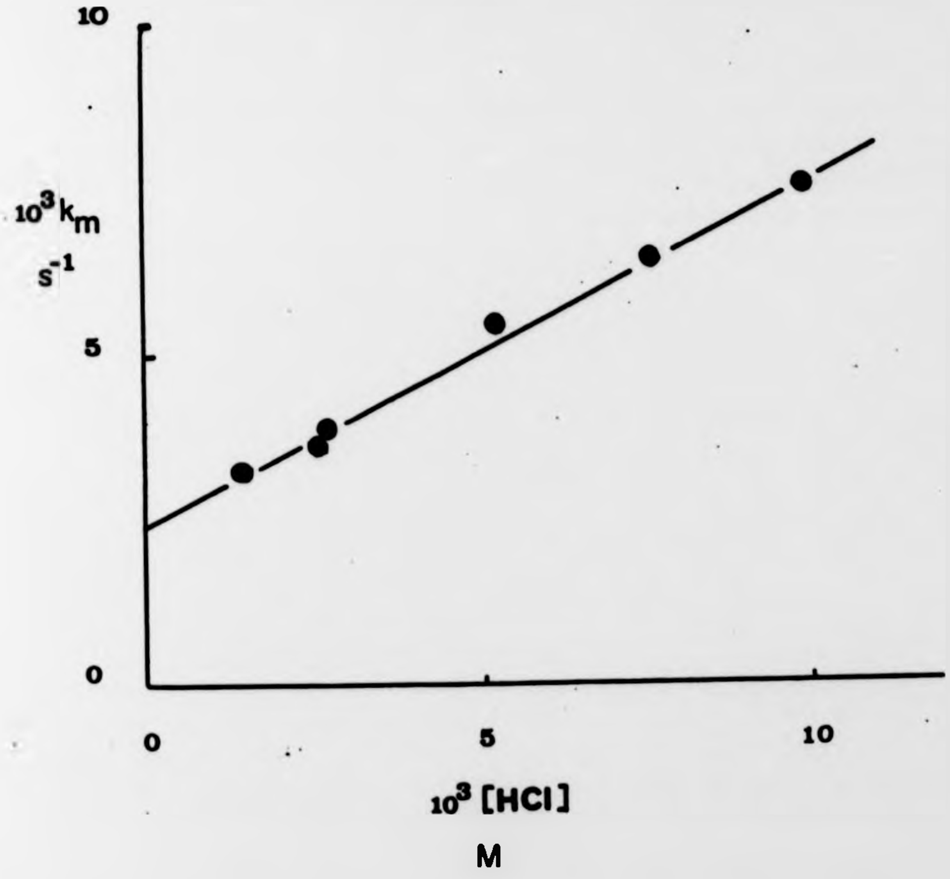
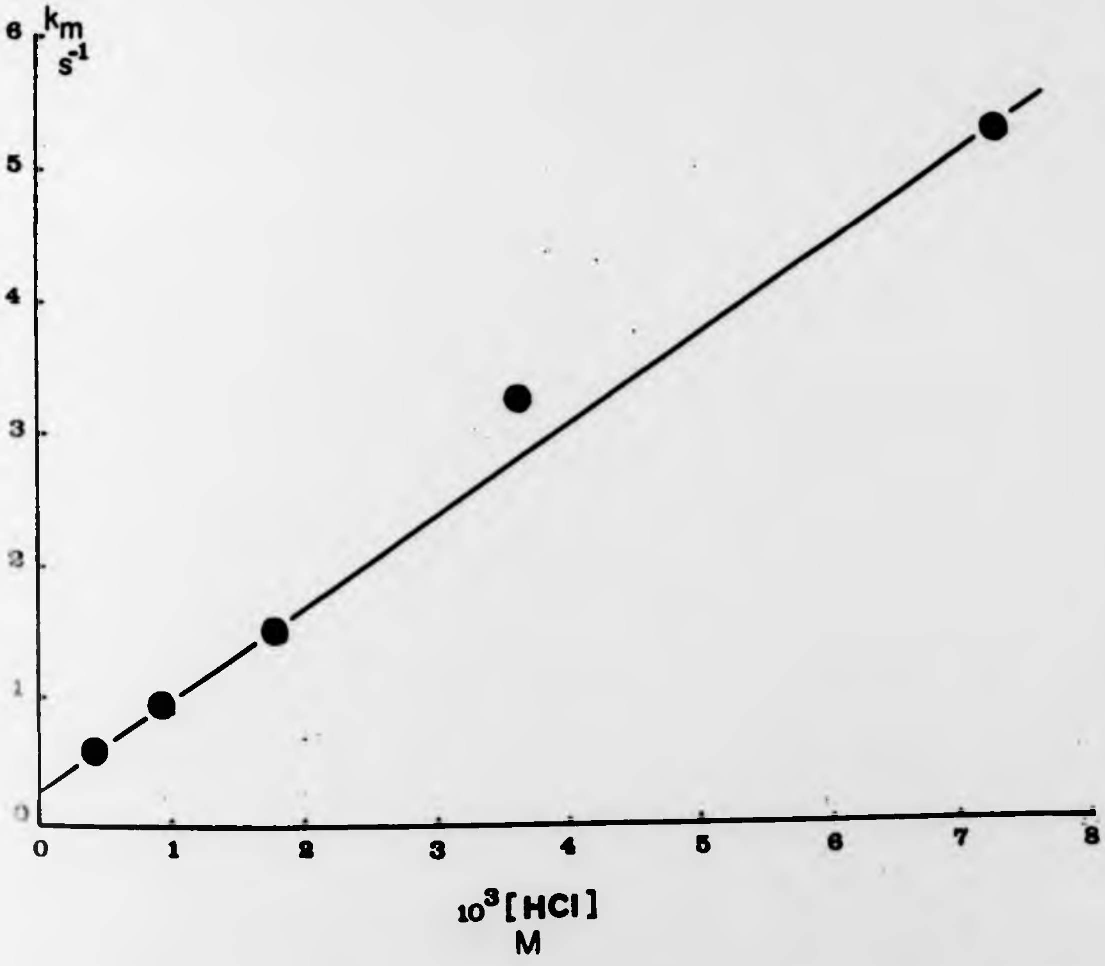


Figure 20 Dependence of k_m on [HCl] for the dissociation of $Na(2,2,1)^+$ in EtOH



<u>Figure 21</u> Dependence of k_m on [HCl] for the dissociation of $Na(2,2,2)^+$ in EtOH

The values of k_d given in Table 18 show again that the pronounced selectivity of the ligands is reflected in the dissociation rates. In contrast, the formation rate constants (Table 19) increase monotonically with the size of the cation. These two features are illustrated in Figure 22, where log k_d and log K_s^{-1} for the (2,2,1) complexes are plotted against the inverse of the ionic radii of the cations; and in Figure 23, where log k_f is plotted also against $1/r_+$. It is clearly observed, from Figure 22, that the pattern displayed by the dissociation equilibrium constants (K_s^{-1}) is exactly reproduced by the dissociation rate constants. These results seem to confirm that the transition state for the formation reaction lies very close to the reactants.

Since the stability of the cryptates is reflected in the dissociation rates and the cryptates are (except for $Cs(2,2,2)^+$) more stable in EtOH than in MeOH, it is not surprising that the dissociation rate constants in the former are lower than in the latter.

The formation rates in both MeOH and EtOH are relatively high compared, say, with H_2O and in the case of (2,2,2), they are close to the rate of solvent exchange in the inner coordination shell of the cations[102]. This suggests an effective compensation for the loss of solvation energy, by the ion-ligand interaction energy during the process of complexation.

4. Kinetics of Metal Cryptates in Dimethyl Sulphoxide

Table 20 shows the dissociation rate constants for $Li(2,1,1)^+$, $Na(2,1,1)^+$, $Na(2,2,1)^+$ and $K(2,2,2)^+$ in DMSO. The

TABLE 19

Formation Rate Constants of Alkali Metal Cryptates in EtOH at 25°C

Cation	k_f in $mol^{-1}\ dm^3\ s^{-1}$ (2,1,1)	(2,2,1)	(2,2,2)
Li^+	1.8×10^5	ca. 3×10^6	-
Na^+	8.8×10^6	4.2×10^7	1.1×10^8
K^+	-	4.9×10^7	1.3×10^8
Rb^+	-	ca. 8×10^7	1.7×10^8
Cs^+	-	ca. 10^8 [a]	-

[a] Estimated value from the plot of log k_f against $1/r^+$

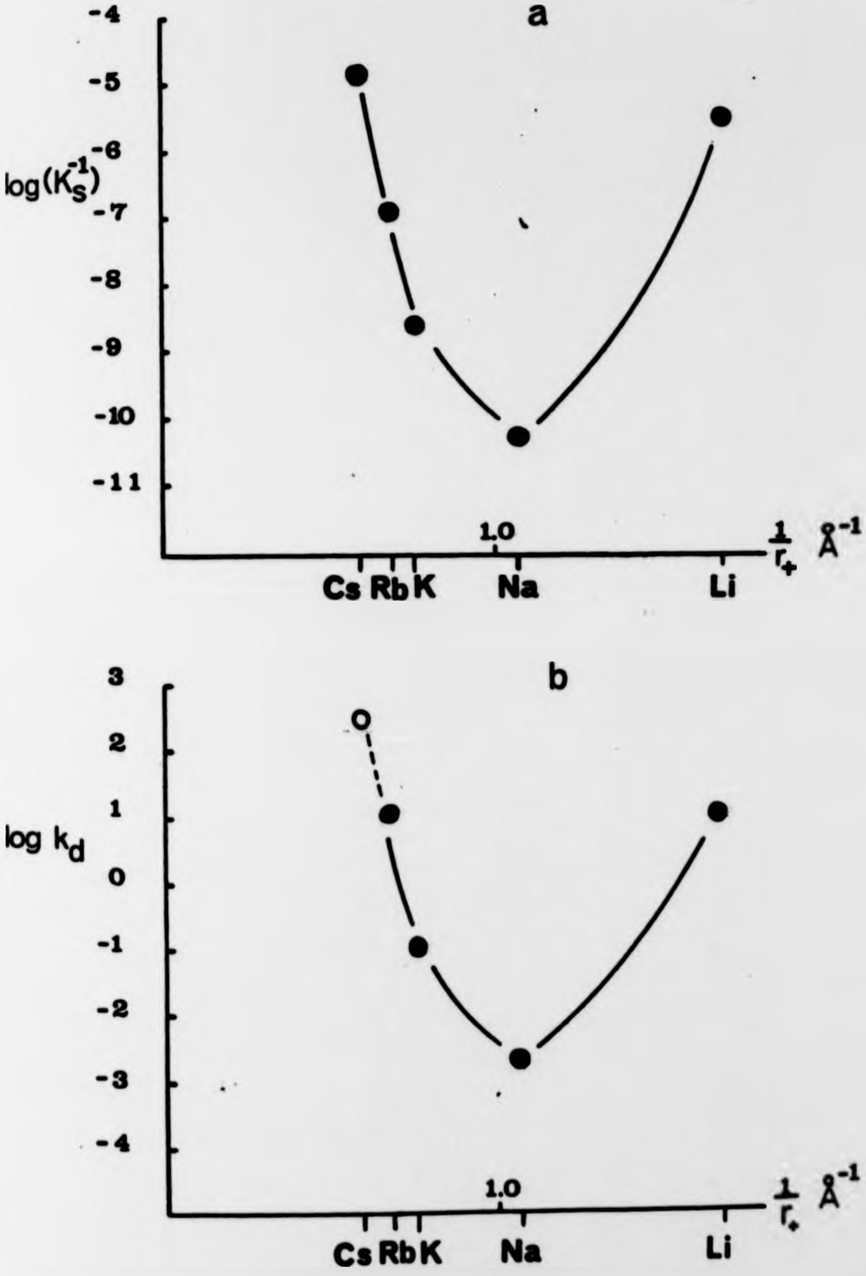


Figure 22 (a) Stability Constants and (b) Dissociation Rate Constants for Alkali Metal (2,2,1) Cryptates in EtOH

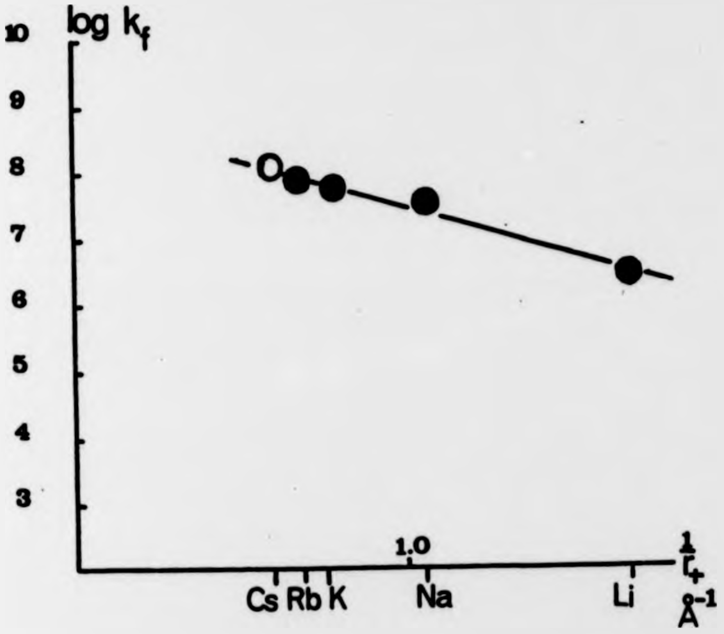


Figure 23 Formation Rate Constants for Alkali Metal (2,2,1) Cryptates in EtOH

range of concentrations at which the experiments were carried out and the kinetic equations used for the evaluation of k_d are also indicated in Table 20.

The acid used in the conductimetric measurements was dichloroacetic acid (DCA) which is a weak acid in DMSO ($pK_a = 5.9$)[104]. The reactions were accompanied by an increase in conductance due to generation of ionic species (protonated cryptands and dichloroacetate ions) according to equation (29).

The reaction rates were independent of both metal ion and acid concentrations within the range of concentrations indicated. This suggested that the observed rate constants were in fact the dissociation rate constants of the cryptates. The reported values were obtained by averaging all the measured experimental values.

Cahen, Dye and Popov[91] measured k_d for $Li(2,1,1)^+$ using Lithium-7 Nuclear Magnetic Resonance. The value $(2.32 \pm 0.54) \times 10^{-2}\ s^{-1}$ is in excellent agreement with the value obtained in this work, $(2.12 \pm 0.1) \times 10^{-2}\ s^{-1}$.

The dissociation rates for other cryptates could not be determined due to the interference of the second protonation reaction of the cryptand. The reactions between DCA and the monoprotonated (2,1,1), (2,2,1) and (2,2,2) cryptands in DMSO were found to be quite slow, and in fact slower than the dissociation rates of the cryptates in most cases. However, the reaction between monochloroacetic acid and (2,1,1) was surprisingly about an order of magnitude faster than that with DCA. Therefore, monochloroacetic acid (MCA) was used to determine k_d for $Na(2,1,1)^+$. The value obtained was only

TABLE 20

Dissociation Rate Constants of Alkali Metal Cryptates in DMSO at 25°C

Cryptate	k_d s^{-1}	Range of concentrations M	Equation used to determine k_d
$Li(2,1,1)^+$	2.12×10^{-2}	$[LiClO_4]: 5x10^{-4}-3x10^{-3}M$ $[DCA]: 10^{-3} - 10^{-2}M$	$k_d = k_d$
$Na(2,1,1)^+$	ca. 5	$[NaClO_4]: 5 \times 10^{-4}$ $[MCA]: 10^{-3} - 5 \times 10^{-3}$	$k_d = k_m$
$Na(2,2,1)^+$	7.5×10^{-1}	$[NaClO_4]: 10^{-3}-2x10^{-3}M$ $[DCA]: 10^{-3} - 4x10^{-2}M$	$k_d = k_m$
$K(2,2,2)^+$	2.68	$[KNO_3]: 10^{-3} - 2x10^{-3}M$ $[DCA]: 3x10^{-3}-3x10^{-2}M$	$k_d = k_m$

TABLE 21

Formation Rate Constants of Alkali Metal Cryptates in DMSO at 25°C

Cryptate	k_f in mol^{-1} dm^3 s^{-1}
$Li(2,1,1)^+$	1.5×10^4
$Na(2,1,1)^+$	ca. 2×10^5
$Na(2,2,1)^+$	7.2×10^6
$K(2,2,2)^+$	3.5×10^7

approximate since, even for this acid, there was still some interference coming from the conductance change involved in the second protonation reaction of the cryptand.

5. Kinetics of Metal Cryptates in Dimethylformamide

The values of the dissociation rate constants for a number of alkali metal and Ca^{2+} cryptates were obtained in DMF. These values are shown in Table 22, which also gives the range of concentrations of the acid and salt, and indicates the expression used for the treatment of the experimental results in order to determine k_d.

For the most stable complexes, $Li(2,1,1)^+$, $Na(2,2,1)^+$ and $K(2,2,2)^+$, two acids were used in the measurements; dichloroacetic acid, whose pKa in DMF is 7.2[105] and HCl with a pKa of 3.4[106]. At the concentrations used, DCA is essentially undissociated, whereas HCl is significantly dissociated. When DCA was used to displace the metal from these cryptates, it was found that (a) the observed rates decreased with increasing acid concentration, with the rate constants levelling off to a constant value at higher DCA concentrations, and (b) the observed increase in conductance during the reaction was smaller at lower DCA concentrations. Both of these observations suggest that at lower DCA concentrations, the protonation reaction (equation (29)) is not going to completion, and that the observed rate represented the rate of approach to equilibrium. As DCA increases then, reaction (29) is displaced to the right, and the measured rate should correspond to the true dissociation rate. Thus values reported for these cryptates in Table 22 represent rates extrapolated to high DCA concentration (ca. 6×10^{-2}M). This extrapolation was more difficult in the case of $Na(2,2,1)^+$ and

TABLE 22

Dissociation Rate Constants of Metal Cryptates in DMF at 25°C

Cryptate	k_d s^{-1}	Range of concentrations M	Equation used to determine k_d (see text)
$Li(2,1,1)^+$	1.4×10^{-2}	[LiCl] : 10^{-3}-$3x10^{-3}$ [DCA] : 10^{-3}-$6x10^{-2}$	$k_d = k_m$ at [DCA] > 6×10^{-2}
	$(1.56 \pm 0.06)x10^{-2}$	[$LiClO_4$] : $6x10^{-4}$-$3x10^{-3}$ [HCl] : 10^{-3} - 10^{-2}	(40)
$Ca(2,1,1)^{2+}$	ca. 2×10^{-1}	[$Ca(NO_3)_2$] : 10^{-3}-10^{-2} [HCl] : 10^{-3}-10^{-2}	$k_d = k_m$
$Na(2,2,1)^+$	ca. 3×10^{-1}	[$NaClO_4$] : 10^{-3}-$3x10^{-3}$ [DCA] : 10^{-3}-$6x10^{-2}$	$k_d = k_m$ at [DCA] > $6x10^{-2}$
	2.5×10^{-1}	[$NaClO_4$] : 10^{-3}-$4x10^{-3}$ [HCl] : 10^{-3}-10^{-2}	(40)
$K(2,2,1)^+$	ca. $2.6^{24°C}$	[$KClO_4$] : 10^{-3} - 10^{-2} [HCl] : 10^{-3}-10^{-2}	(40)
$Ca(2,2,1)^{2+}$	8×10^{-4}	[$Ca(NO_3)_2$] : $7x10^{-4}$-$3x10^{-3}$ [HCl] : 10^{-3} - 10^{-2}	(40)
$K(2,2,2)^+$	ca. 5×10^{-1}	[$KClO_4$] : 10^{-3}-$2x10^{-3}$ [DCA] : 10^{-3}-$6x10^{-2}$	$k_d = k_m$ at [DCA] > $6x10^{-2}$
	4.0×10^{-1}	[$KClO_4$] : 10^{-3}-$4x10^{-3}$ [HCl] : 10^{-3}-$2x10^{-2}$	(40)
$Ca(2,2,2)^{2+}$	4.4×10^{-2}	[$Ca(NO_3)_2$] : $5x10^{-4}$-$3x10^{-3}$ [HCl] : 10^{-3} - 10^{-2}	$k_d = k_m$

K(2,2,2)$^+$; therefore the values of the dissociation rates are only approximate.

In order to check these values, the reactions were also carried out using the much stronger acid HCl. For each of Li(2,1,1)$^+$, Na(2,2,1)$^+$ and K(2,2,2)$^+$, the observed rates were dependent upon both metal ion concentration and acid concentration, but the dependence could be quantitatively accounted for using equation (40) as described earlier, and k_d values were obtained by plotting k_m^{-1} vs [M$^+$] at constant acid concentration (generally 3 x 10^{-3}M). As an example, the results for Na(2,2,1)$^+$ are shown in Figure 24. It can be seen from Table 22 that the results obtained using the two acids are in quite good agreement. Furthermore, it is possible to compare the results for Li(2,1,1)$^+$ with those obtained by Popov et al.[91] from ^{7}Li NMR studies and Gutknecht[107] using methanesulphonic acid and a relaxation technique (pressure-jump). The results from the different sources are as follows.

k_d (in s^{-1}) of Li(2,1,1)$^+$ in DMF at 25°C

<u>This work</u> Using DCA	Using HCl	Reference 91	Reference 107
1.4×10^{-2}	$(1.56 \pm 0.06) \times 10^{-2}$	$(1.30 \pm 0.33) \times 10^{-2}$	$(1.53 \pm 0.08) \times 10^{-2}$

It can be seen that the agreement is very satisfactory.

The other cryptates listed in Table 22 were all studied using HCl as the scavenging acid. For Ca(2,1,1)$^{2+}$ and Ca(2,2,2)$^{2+}$ the rates were independent of both acid concentration

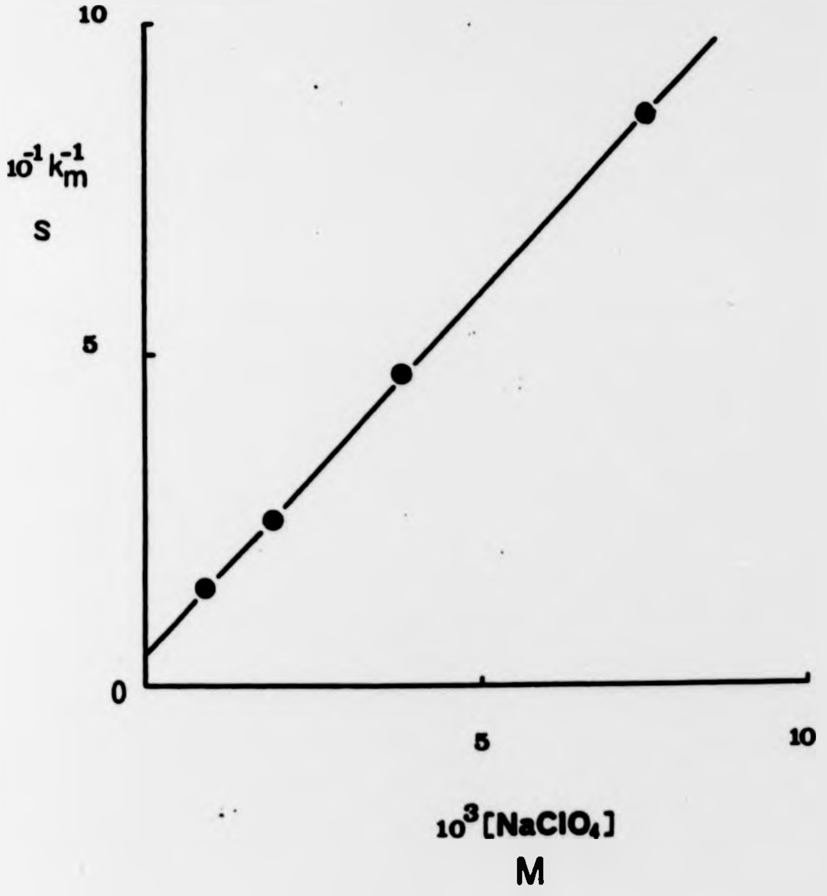


Figure 24 Observed Rate Constant as a function of $NaClO_4$ concentration for the dissociation of $Na(2,2,1)^+$ in DMF

TABLE 23

Formation Rate Constants of Metal Cryptates in DMF at 25°C

Cryptate	k_f in mol^{-1} dm^3 s^{-1}
$Li(2,1,1)^+$	1.4×10^5
$Ca(2,1,1)^{2+}$	ca. 2.4×10^2
$Na(2,2,1)^+$	1.8×10^7
$K(2,2,1)^+$	ca. 1.3×10^7
$Ca(2,2,1)^{2+}$	3.7×10^3
$K(2,2,2)^+$	3.8×10^7
$Ca(2,2,2)^{2+}$	3.1×10^2

and metal ion concentration. The reactions of $K(2,2,1)^+$ and $Ca(2,2,1)^{2+}$ were both studied over a range of acid and metal ion concentrations, and the results analysed according to equation (40). The quoted results for $Ca(2,1,1)^{2+}$ and $K(2,2,1)^+$ are, however, uncertain as the measured rates were close to those observed on reaction of the ligands with the acid in the absence of metal ions, so that some interference of the second protonation reaction may have occurred.

Table 23 gives the corresponding formation rates. It is difficult to draw many conclusions from the scattered results within this solvent by itself. It is noticeable, however, that the formation rates for the Ca^{2+} cryptates are again several orders of magnitude lower than those for the monovalent cations.

Dye et al.[95] report a value of 9.0×10^6 s^{-1} for the rate constant for the exchange of Cs^+ from $Cs(2,2,2)^+$, determined from Cesium-133 NMR studies. Taking this result as the value for k_d, and combining it with the corresponding stability constant, gives a value of 1.3×10^9 mol^{-1} dm^3 s^{-1} for k_f. This value seems rather large compared with the result for $K(2,2,2)^+$ in Table 23. However, if Cs^+ is not held completely within the ligand cavity because of its large size, a more rapid rate of exchange is not unreasonable.

6. Kinetics of Metal Cryptates in N-Methylpropionamide

The dissociation rate constants of a number of alkali metal cryptates in NMP have been measured. The results are shown in Table 24. Again, only the slowest dissociation reactions could be monitored due to the interference of the protonation reactions of the cryptands.

TABLE 24

Kinetics of the Dissociation of Alkali Metal Cryptates in NMF at 25°C

Cryptate	k_d s^{-1}	Range of concentrations M	Equation used to determine k_d (see text)
$Li(2,1,1)^+$	4.81×10^{-3}	$[LiClO_4]$: $3x10^{-3}-7x10^{-3}$ $[DCA]$: $10^{-3} - 10^{-2}$	$k_d = k_m$
$Na(2,1,1)^+$	4.7×10^{-1}	$[NaClO_4]$: $2x10^{-3}-8x10^{-3}$ $[DCA]$: $3x10^{-3}-2x10^{-2}$	$k_d = k_m$
$Na(2,2,1)^+$	1.67×10^{-1}	$[NaClO_4]$: $10^{-3} - 2x10^{-2}$ $[DCA]$: $3x10^{-3}-2x10^{-2}$	(40)
$K(2,2,1)^+$	1.35	$[KClO_4]$: $10^{-3} - 10^{-2}$ $[DCA]$: $3x10^{-3}-6x10^{-3}$	(40)
$Na(2,2,2)^+$	5.68	$[NaClO_4]$: $10^{-3} - 10^{-2}$ $[DCA]$: $4x10^{-3}-2x10^{-2}$	$k_d = k_m$
$K(2,2,2)^+$	1.33×10^{-1}	$[KClO_4]$: $10^{-3}-7x10^{-3}$ $[DCA]$: $10^{-3} - 2x10^{-2}$	(40)
$Rb(2,2,2)^+$	5.0×10^{-1}	$[RbNO_3]$: $10^{-3} - 10^{-2}$ $[DCA]$: $10^{-3} - 10^{-2}$	(40)

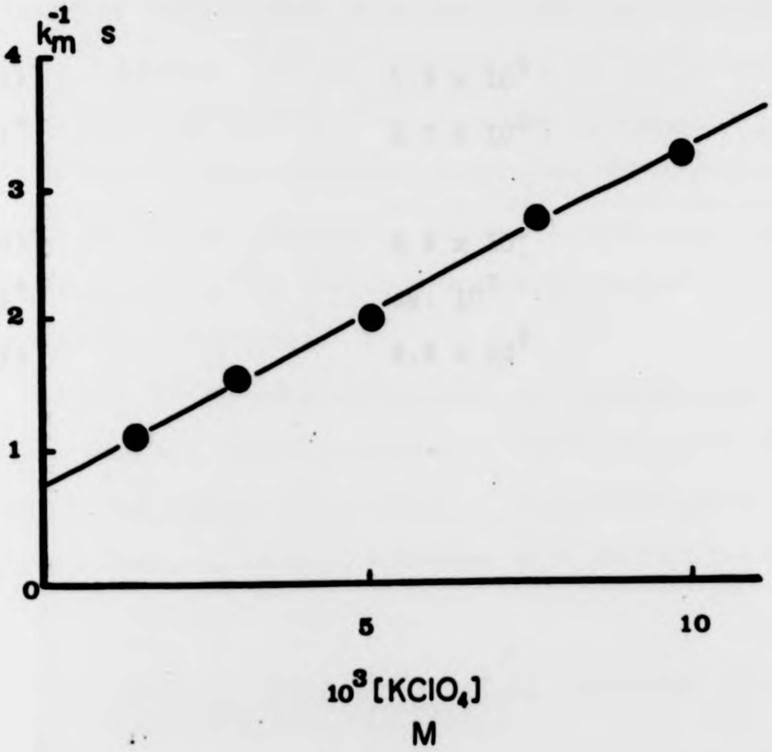


Figure 25 Rate Constant as a function of $KClO_4$ concentration for the dissociation of $K(2,2,1)^+$ in NMP

TABLE 25

Formation Rate Constants of Alkali Metal Cryptates in NMP at 25°C

Cryptate	k_f in mol^{-1} dm^3 s^{-1}
$Li(2,1,1)^+$	1.3×10^4
$Na(2,1,1)^+$	5.4×10^4
$Na(2,2,1)^+$	5.9×10^5
$K(2,2,1)^+$	1.7×10^6
$Na(2,2,2)^+$	3.8×10^6
$K(2,2,2)^+$	ca. 10^7
$Rb(2,2,2)^+$	9.5×10^6

The observed rate constants for $Li(2,1,1)^+$, $Na(2,1,1)^+$ and $Na(2,2,2)^+$ were practically independent of both metal cation and acid concentrations in the range of concentrations indicated in Table 24. For all other cryptates: $Na(2,2,1)^+$, $K(2,2,1)^+$, $K(2,2,2)^+$ and $Rb(2,2,2)^+$, the measured rate constants showed dependence upon $[M^+]$ and [DCA]. The results were quantitatively consistent with equation (40). Plots of k_m^{-1} against $[M^+]$ at constant [DCA] were straight lines which, extrapolated to $[M^+] = 0$, gave the values of k_d. The case of $K(2,2,1)^+$ is given as an example in Figure 25. Here, $[DCA] = 6 \times 10^{-3}M$ and $[KClO_4]$ is varied in the range 10^{-3}-$10^{-2}M$.

Table 25 gives the corresponding formation rate constants of the cryptates.

Again it is noticeable that the selectivity of the ligands for cations in this solvent results primarily from the variation of the dissociation rates. The formation rates show a relatively small monotonic increase with increasing cation size.

7. Kinetics of Metal Cryptates in Propylene Carbonate (1,2-propanediol carbonate)

The dissociation rate constants of alkali metal and Ca^{2+} cryptates have been measured in PC. The results are shown in Table 26.

In contrast to the behaviour in DMSO and DMF, the observed dissociation rates of some of the cryptates in PC showed catalysis by DCA. DCA is a very weak acid in PC, with a pK_a that is probably similar to that of salicylic acid ($pK_a = 15.2$)[108], so that the concentration of free protons

TABLE 26

Kinetics of the Dissociation of Metal Cryptates in PC at 25°C

Cryptate	k_d s^{-1}	Range of Concentrations	Equation used to determine k_d (see text)
$Li(2,1,1)^+$	$<10^{-5}$	$[LiClO_4]: 2 \times 10^{-3}$ $[DCA]: 2 \times 10^{-3} - 2 \times 10^{-2}$	(42)
$Na(2,1,1)^+$	3.6×10^{-2}	$[NaClO_4]: 10^{-3} - 8 \times 10^{-3}$ $[DCA]: 10^{-3} - 1.5 \times 10^{-2}$	(40),(42)
$Ca(2,1,1)^{2+}$	3.4×10^{-2}	$[Ca(NO_3)_2]: 10^{-3} - 5 \times 10^{-3}$ $[DCA]: 10^{-3} - 7 \times 10^{-3}$	$k_d = k_m$
$Na(2,2,1)^+$	$<10^{-2}$	$[NaClO_4]: 10^{-4} - 4 \times 10^{-4}$ $[DCA]: 4 \times 10^{-4} - 2.1 \times 10^{-3}$	(42)
$K(2,2,1)^+$	3.7×10^{-2}	$[KClO_4]: 10^{-4} - 5 \times 10^{-4}$ $[DCA]: 4 \times 10^{-4} - 2.1 \times 10^{-3}$	(42)
$Rb(2,2,1)^+$	7.5	$[RbNO_3]: 10^{-4} - 1.5 \times 10^{-3}$ $[DCA]: 4 \times 10^{-4} - 1.5 \times 10^{-2}$	(40)
$Cs(2,2,1)^+$	ca. 4×10^2	$[CsNO_3]: 10^{-3}$ $[DCA]: 10^{-3}$	$k_d = k_m$
$K(2,2,2)^+$	3×10^{-3}	$[KClO_4]: 10^{-4} - 8 \times 10^{-4}$ $[DCA]: 7 \times 10^{-4} - 2.5 \times 10^{-2}$	(42)
$Rb(2,2,2)^+$	1.7×10^{-1}	$[RbNO_3]: 10^{-4} - 8 \times 10^{-4}$ $[DCA]: 4 \times 10^{-4} - 4.1 \times 10^{-3}$	(40),(42)
$Cs(2,2,2)^+$	ca. 3×10^2	$[CsNO_3]: 10^{-3}$ $[DCA]: 4 \times 10^{-4}$	$k_d = k_m$
$Ca(2,2,2)^{2+}$	$<10^{-4}$	$[Ca(NO_3)_2]: 10^{-3} - 5 \times 10^{-3}$ $[DCA]: 10^{-3} - 10^{-2}$	(42)

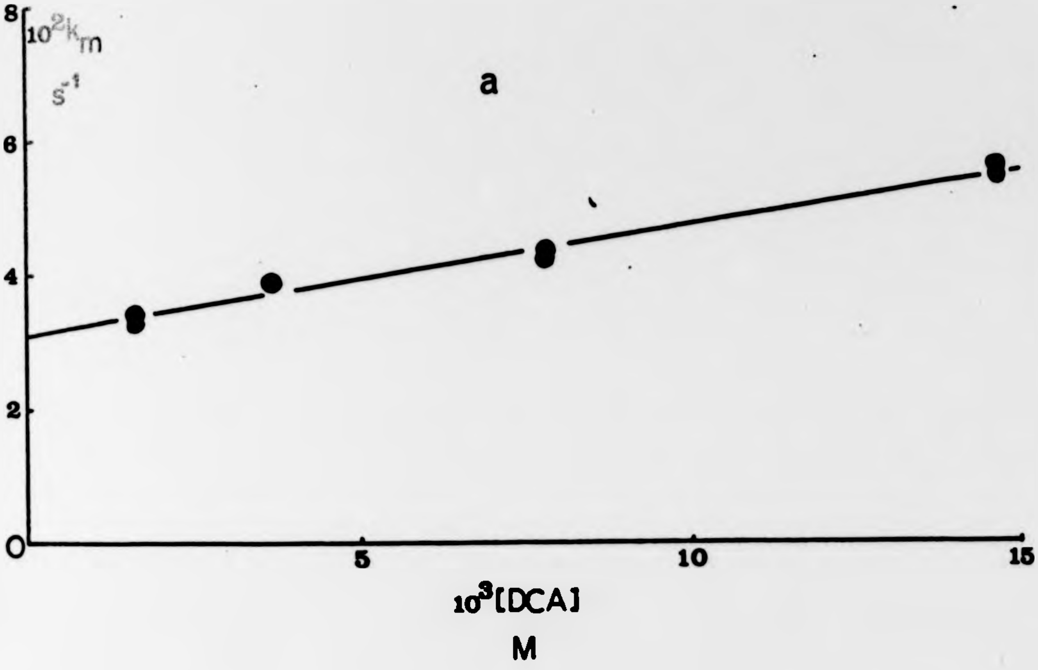
should be negligibly small in the solutions studied. Therefore, it is most likely that this represents a case of general acid catalysis involving the undissociated acid molecules, rather than the free protons. The acid catalysed dissociation of cryptates will be discussed later in this chapter.

The particular conditions under which the measurements were carried out are discussed below for each of the three cryptands.

<u>(2,1,1)</u>.

The observed dissociation rate constants for $Li(2,1,1)^+$ showed a very strong dependence on acid concentration. Only an upper limit for the value of k_d ($< 10^{-5}$ s^{-1}) can be given due to the uncertainties in the extrapolation of the curve k_m vs [DCA] to zero acid concentration. At the lowest acid concentrations, the reactions were extremely slow (with half-lives of about 10 hours); the Guggenheim method[109] was used in these cases to find the rate constant of the reaction.

Rate constants for $Na(2,1,1)^+$ were slightly dependent on acid and metal concentrations at low acid concentrations. The results were consistent with equation (40); therefore a plot of k_m^{-1} vs [$NaClO_4$] at [DCA] = constant = 2 x 10^{-3}M, gave the value for k_d (Figure 26b). At higher acid concentrations (4 x 10^{-3} - 1.5 x 10^{-2}M) k_m became practically independent of metal ion concentration, but still acid dependent. A plot of k_m against [DCA] gave a straight line (according to equation (42)) from which a value for k_d was obtained by extrapolation to [DCA] = 0 (Figure 26a). The value of k_d thus obtained agreed with that determined using equation (40). In the case of



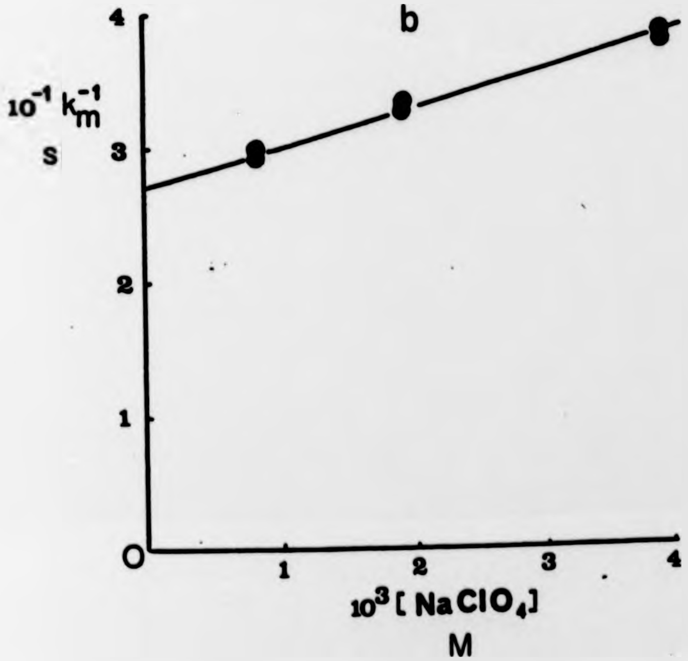


Figure 26 Dependence of k_m on (a) [DCA] and (b) [$NaClO_4$] for the dissociation of $Na(2,1,1)^+$ in PC

$Ca(2,1,1)^{2+}$, the observed dissociation rates were practically independent of $[Ca(NO_3)_2]$ and [DCA] when the concentration of acid approached the upper limit ($7 \times 10^{-3}M$) of the range of concentrations at which the experiments were carried out. That is to say, k_m was approaching the value of k_d when $k[DCA] >> k_f[Ca(NO_3)_2]$, in accordance with equation (39).

(2,2,1).

The dissociation reactions of Li^+ and Na^+ complexes were very strongly acid catalysed. This made k_m difficult to extrapolate to zero acid concentration. In the case of $Li(2,2,1)^+$ no reliable value of k_d could be obtained. For $Na(2,2,1)^+$ only an upper limit to the value of k_d could be estimated, based on the measured rate constants at very low acid concentrations (ca. $4 \times 10^{-4}M$).

Reaction rates for $K(2,2,1)^+$ were independent of metal ion concentration, but acid dependent. A straight line was obtained when k_m was plotted against [DCA] according to equation (42). k_d was determined from the extrapolation to [DCA] = 0 (Figure 27).

The observed dissociation rates for $Rb(2,2,1)^+$ were slightly dependent on $[RbNO_3]$ and [DCA]; however, when rubidium ion concentration was low (e.g. $10^{-4}M$) and the acid concentration sufficiently high (e.g. $> 2 \times 10^{-3}M$), the measured value k_m tended to the actual dissociation rate constant k_d, according to equations (38) and (39). A more accurate value of k_d was determined using equation (40); k_m^{-1} was plotted against $[RbNO_3]$ at [DCA] = constant = $2 \times 10^{-3}M$ (Figure 28).

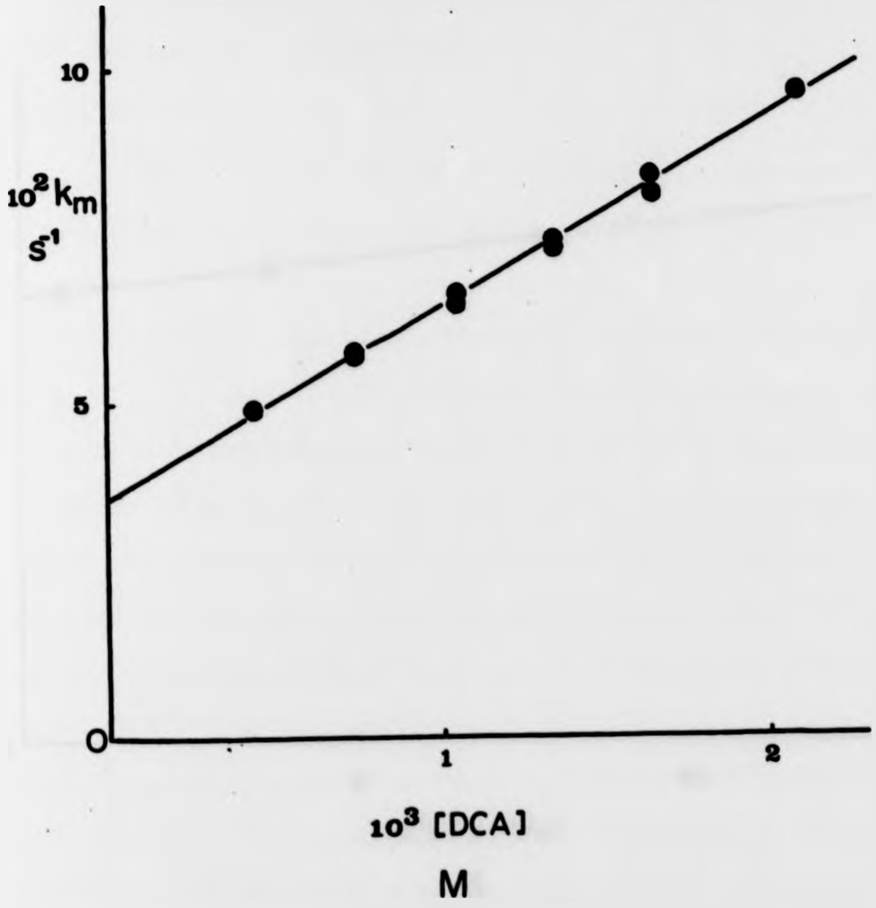


Figure 27 Dependence of k_m on [DCA] for the dissociation of $K(2,2,1)^+$ in PC

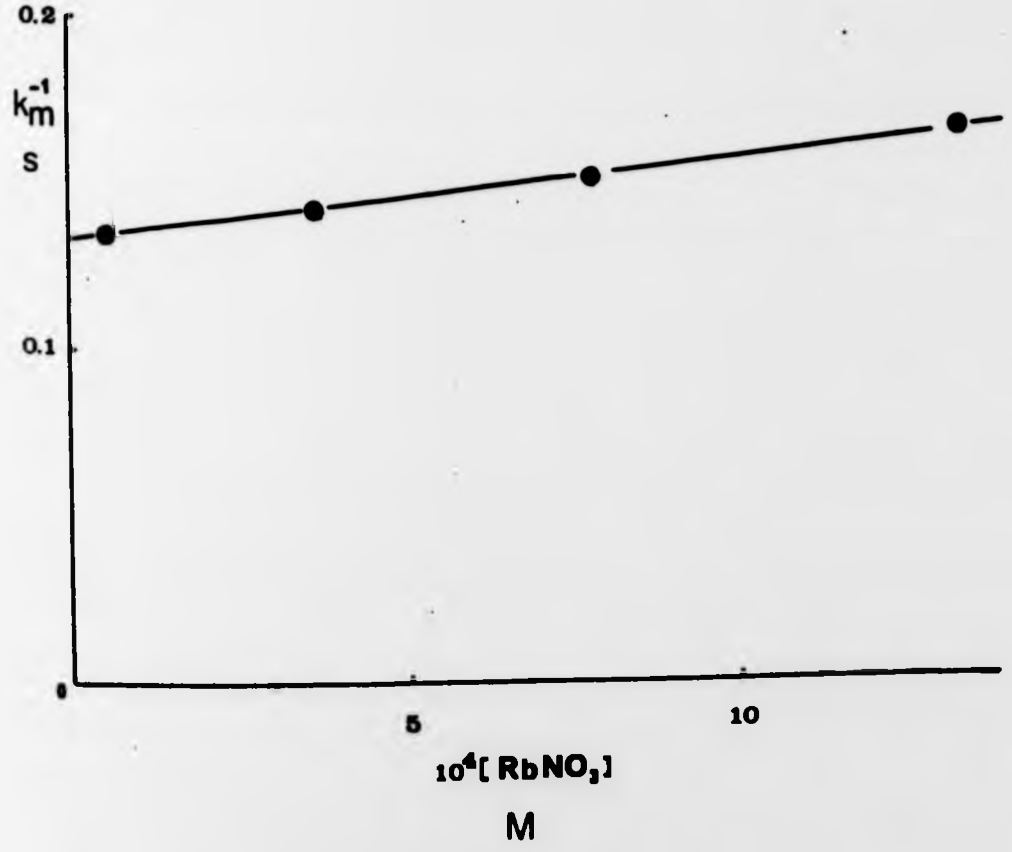


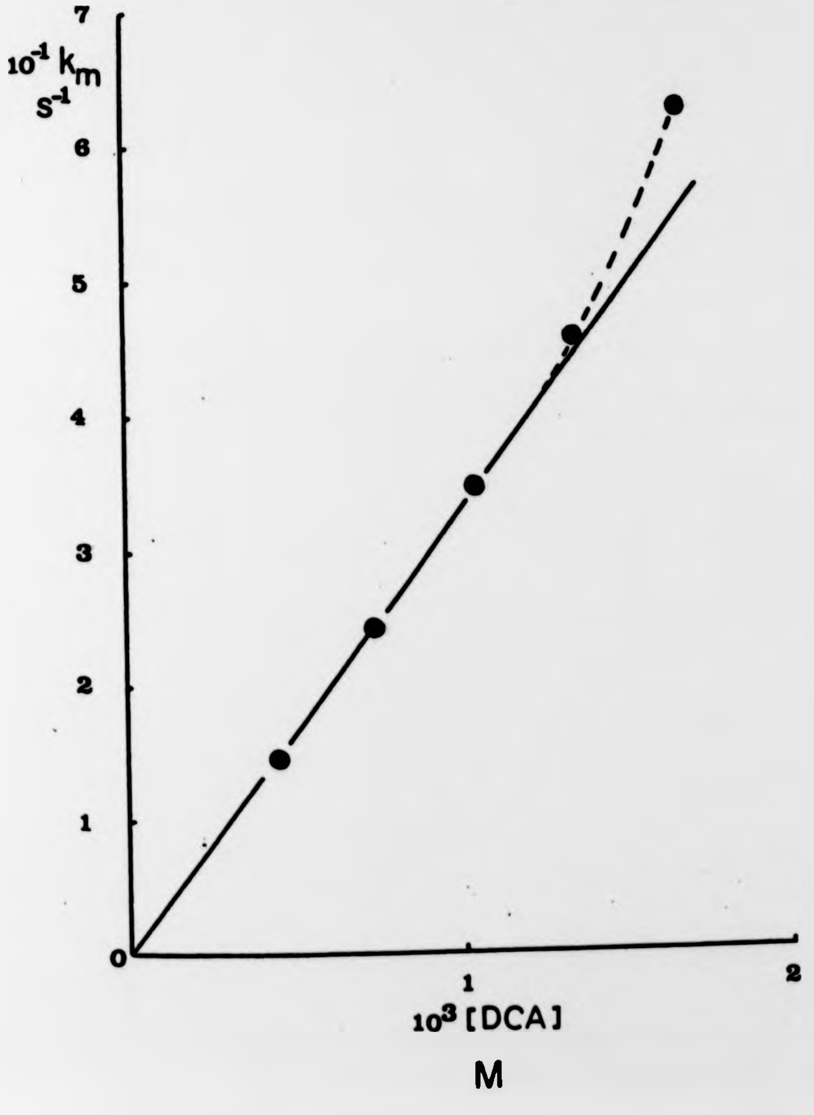
Figure 28 Dependence of k_m on [RbNO$_3$] for the dissociation of Rb(2,2,1)$^+$ in PC

The value of k_d given for $Cs(2,2,1)^+$ is based on measurements made at only one acid concentration and one metal concentration. The observed rates were on the limit of the stopped-flow measuring capability. Small signals with high noise perturbations were obtained when other concentrations were tried. However, it is expected that, as in the case of Rb^+, the reaction rates are practically independent of free metal ion and acid concentrations.

(2,2,2).

Na^+, K^+, Rb^+ and Cs^+ complexes were studied, that of Li^+ reacting too rapidly to be followed with the stopped-flow apparatus.

Strong acid catalysis was observed in K^+ and Na^+ cryptates. In the latter case, extrapolation to zero acid concentration was impossible and therefore k_d could not be determined (Figure 29). For $K(2,2,2)^+$, the experimental results were described by equation (42) which predicts a linear relationship between k_m and the acid concentration (Figure 30). This was true for $[DCA] < ca.\ 1.5 \times 10^{-3}M$; nevertheless at higher [DCA], the dissociation reaction became remarkably faster than predicted by a simple linear function on the acid concentration. This acceleration of the reaction was also observed in the other cryptates where strong acid catalysis was detected. The explanation of this acceleration at higher acid concentrations is uncertain. However, it may result from the presence of equilibria $2HA \rightleftharpoons HA_2^- + H^+$, involving the homoconjugate species HA_2^-. It is known that weak acids (e.g. methanesulphonic or p-toluenesulphonic acid) are particularly prone to this type of behaviour in PC[110] and



<u>Figure 29</u> Dependence of k_m on [DCA] for the dissociation of $Na(2,2,2)^+$ in PC

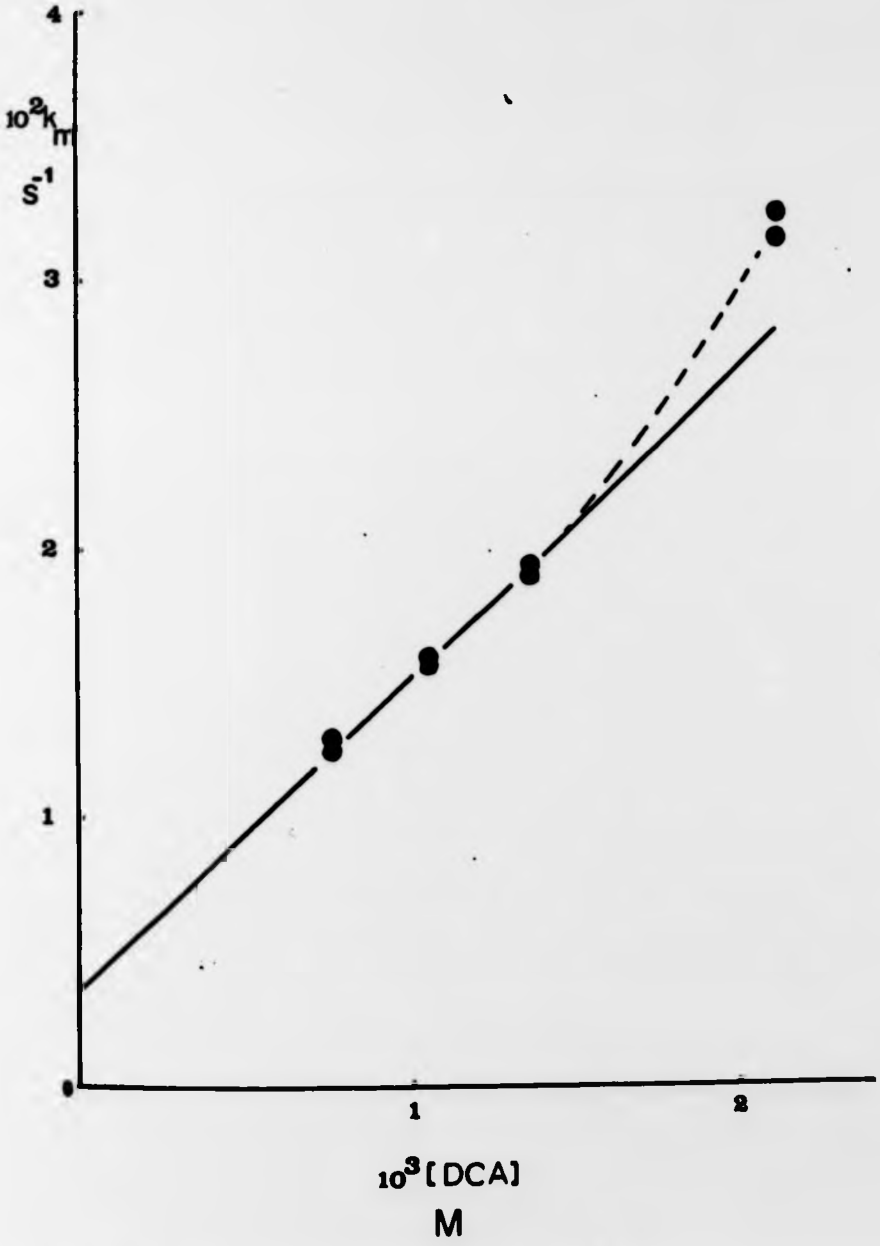


Figure 30 Dependence of k_m on [DCA] for the dissociation of $K(2,2,2)^+$ in PC

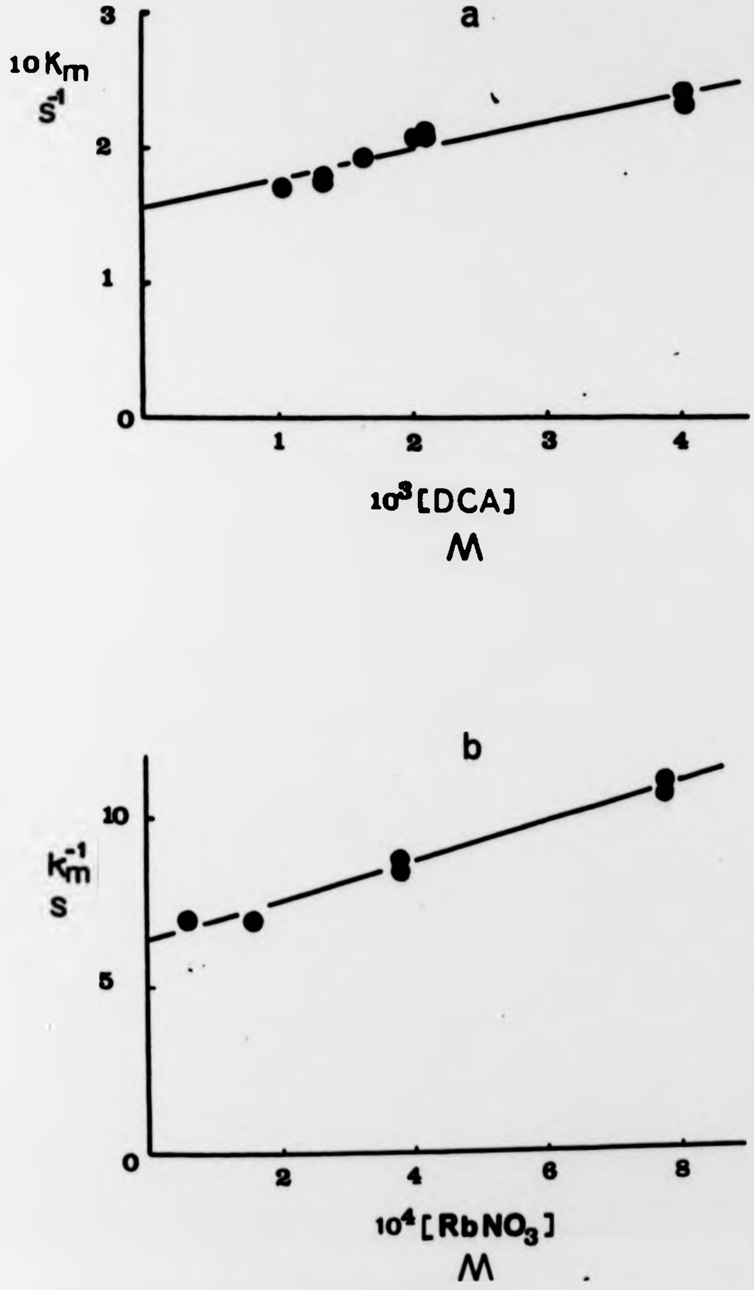


Figure 31 Dependence of k_m on (a) [DCA] and (b) [$RbNO_3$] for the dissociation of $Rb(2,2,2)^+$ in PC

other dipolar aprotic solvents[111]. This could explain a non-linear dependence upon acid concentration, as the $[H^+]$ and $[HA_2^-]$ produced would increase initially as the square of $[HA]$.

For $Rb(2,2,2)^+$ the dissociation rate constant was calculated using equation (40). Thus, at $[DCA] = 4.5 \times 10^{-4}M$, the values of k_m^{-1} were plotted against $[RbNO_3]$. At this acid concentration, there is effective competition between Rb^+ and DCA for the free ligand ($k_f[Rb^+] \approx k[HA]$). This results in a dependence of the rate upon the metal cation concentration, as it has been mentioned before. However, at concentrations of DCA > ca. $10^{-3}M$, some acid catalysis was observed and the observed rates became practically independent of free metal ion concentration. A plot of k_m vs $[DCA]$ was a straight line, according to equation (42). The value of k_d determined from the intercept of this straight line with the zero-acid axis was in good agreement with that obtained using equation (40) (Figure 31).

The case of $Cs(2,2,2)^+$ is similar to that of $Cs(2,2,1)^+$. The rates were measured at $[CsNO_3] = 10^{-3}M$ and $[DCA] = 5 \times 10^{-4}M$. Assuming that the rate constant is independent of both acid and metal ion concentrations, the value of k_d is estimated to lie near the value of the measured rate constant k_m. The exchange rate constant of Cs^+ between two (2,2,2) ligands in PC has been measured by Koryta and Gross[112]. The reported value is ca. 397 s^{-1} and is close to the value of the dissociation rate constant (ca. 300 s^{-1}) obtained in this work.

Finally, an attempt was made to measure the dissociation rate constant for $Ca(2,2,2)^{2+}$. Strong acid

TABLE 27

Formation Rate Constants of Metal Cryptates in PC at 25°C

Cryptate	k_f, $mol^{-1}\ dm^3\ s^{-1}$
$Li(2,1,1)^+$	$< 3 \times 10^7$
$Na(2,1,1)^+$	2.1×10^7
$Ca(2,1,1)^{2+}$	1.5×10^7
$Na(2,2,1)^+$	$< 10^{10}$
$K(2,2,1)^+$	2.8×10^8
$Rb(2,2,1)^+$	8.0×10^7
$Cs(2,2,1)^+$	ca. 3.3×10^7
$K(2,2,2)^+$	4.5×10^8
$Rb(2,2,2)^+$	1.8×10^8
$Cs(2,2,2)^+$	ca. 4×10^6
$Ca(2,2,2)^{2+}$	$< 7.5 \times 10^6$

catalysis was observed and the rates were independent of $[Ca(NO_3)_2]$. Only an upper limit of k_d ($< 10^{-4}$ s^{-1}) was obtained.

The formation rate constants can now be calculated from the values of the dissociation rate constants (Table 26) and the stability constants (Table 9). The values of k_f are listed in Table 27.

The dissociation rate constants in PC, as in all the other solvents studied, reflect the pronounced selectivity of the cryptands. Higher stability and lower dissociation rates of the alkali metal cryptates are observed in PC. However, the formation rates do not follow the same pattern as in other solvents. Although the k_f values do not vary nearly as much as k_d values as the metal ion is altered, the k_f values seem to be higher, the more stable the complex is. This suggests that in this solvent the transition state lies further along the reaction path towards the product cryptates than in the other solvents considered, and the ligand is thus able to at least partially "recognise" the incoming cation. However, the very large variations of k_d for different cations with a given ligand (ca. 7 orders of magnitude) compared with the relatively smaller variations in k_f (ca. 2 orders of magnitude) suggests that even in this solvent, the transition state more closely resembles the reactants. Changes in the nature of the transition state with solvent have been reported for a number of reactions[79].

8. Solvent Effects on the Kinetics of Cryptates

Any complexation reaction involving solvated metal ions requires partial or total desolvation of the ion so that the binding centres of the ligand substitute the solvent molecules in the inner coordination shell of the ion. Whether this is a more or less rapid process, depends on how efficiently the ligand binding energy compensates for the loss of solvation of the ion. In the Eigen-Wilkins model[76], a stepwise substitution of the solvent molecules is less demanding in terms of activation energy and henceforth the process of complexation occurs rapidly. With the development of fast-reaction techniques, a number of rate constants for the complexation reactions of the alkali metal ions have been able to be measured. These have been found to be extremely fast and very near the limit of diffusion-controlled reactions. Table 28 lists some examples of these reactions.

TABLE 28

Formation and Dissociation Rate Constants of some Na^+ Complexes in MeOH (ref. 77)

Ligand	k_f, M^{-1} s^{-1}	k_d, s^{-1}
Murexide	1.5×10^{10}	5.9×10^{6}
Nigericine	$\sim 2 \times 10^{10}$	$\sim 2 \times 10^{6}$
Monactin	$\sim 2 \times 10^{8}$	$\sim 4 \times 10^{5}$

The typical reaction scheme for the complexation of a metal ion by a unidentate ligand (equation (53)), involves the rapid formation of an "outer-sphere complex", followed by the loss of a solvent molecule from the inner solvation sphere of the cation.

$$(M^{n+},mS) + L \overset{K_o}{\rightleftharpoons} (M^{n+},mS)L \xrightarrow{k_{ex}} (M^{n+}L,(m-1)S) + S \qquad (53)$$

The overall formation rate constant k_f is related to k_{ex}, the rate constant of exchange of a solvent molecule between the inner solvation shell and the bulk solvent, by the expression

$$k_f = K_o k_{ex} \tag{54}$$

where K_o is the equilibrium constant for the formation of the outer-sphere complex.

If the ligand is polydentate, the process indicated in reaction (53) has to be repeated for each ligand binding centre that substitutes a solvent molecule.

The general applicability of equation (54) has been proved in many cases although, in some others, it still remains unconvincing (see for example Bennetto and Caldin[113,114]).

For macrocyclic ligands, the attaining of a stepwise substitution process depends to a large extent on the flexibility of the ligand. The case of valinomycin and crown-ethers undergoing conformational changes during complexation has been mentioned before, in the Introduction to this chapter. When only kinetic data in water existed for the cryptates, the relatively low formation rates of the alkali metal cryptates ($\sim 10^6\ M^{-1}\ s^{-1}$) were attributed to the rigidity of the cryptands. However, results in MeOH and EtOH show that the formation rate constants, particularly for the (2,2,2) complexes ($\sim 10^8\ M^{-1}\ s^{-1}$), are near the rate of exchange of solvent molecules in the inner sphere of the cations. It is often asserted that water is a non-typical solvent[115] and as such, reaction rates in this solvent sometimes do not correlate with those in other solvents. Never-the-less, there is a certain tendency towards lower values of the formation rate constants for solvents with stronger solvating properties. Table 29 lists the formation rate constants for the alkali metal and Ca^{2+} complexes with (2,1,1), (2,2,1) and (2,2,2)

TABLE 29

Formation Rates of Alkali Metal Cryptates in several Solvents at 25°C

Metal Cryptate	H_2O	MeOH	EtOH	DMSO	DMF	NMP	PC
				k_f, $mol^{-1}\ dm^3\ s^{-1}$			
$Li(2,1,1)^+$	8×10^3	4.8×10^5	1.8×10^5	1.5×10^4	1.4×10^5	1.3×10^4	$<3 \times 10^7$
$Na(2,1,1)^+$	2.2×10^5	3.1×10^6	8.8×10^6	ca. 2×10^5	-	5.4×10^4	2.1×10^7
$Ca(2,1,1)^{2+}$	2.6×10^2	-	-	-	ca.2.4×10^2	-	-
$Li(2,2,1)^+$	-	1.8×10^7	ca. 3×10^6	-	-	-	-
$Na(2,2,1)^+$	3.6×10^6	1.7×10^8	4.2×10^7	7.2×10^6	1.8×10^7	5.9×10^5	$<10^{10}$
$K(2,2,1)^+$	1.8×10^7	3.8×10^8	4.9×10^7	-	ca.1.3×10^7	1.7×10^6	2.8×10^8
$Rb(2,2,1)^+$	-	4.1×10^8	ca.8.3×10^7	-	-	-	8.0×10^7
$Cs(2,2,1)^+$	-	ca.5×10^8	-	-	-	-	ca.3.3×10^7
$Ca(2,2,1)^{2+}$	5.4×10^3	-	-	-	3.7×10^3	-	-
$Na(2,2,2)^+$	1.2×10^6	2.7×10^8	1.1×10^8	-	-	3.8×10^6	-
$K(2,2,2)^+$	2.0×10^6	4.7×10^8	1.3×10^8	3.5×10^7	3.8×10^7	ca. 10^7	6×10^8
$Rb(2,2,2)^+$	-	7.6×10^8	1.7×10^8	-	-	9.5×10^6	1.8×10^8
$Cs(2,2,2)^+$	-	ca.9×10^8	-	-	-	-	ca.5×10^6
$Ca(2,2,2)^{2+}$	5.3×10^3	-	-	-	3.1×10^2	-	-

TABLE 30

Dissociation Rates of Alkali Metal Cryptates in several Solvents at 25°C

				k_d, s^{-1}			
Metal Cryptate	H_2O	MeOH	EtOH	DMSO	DMF	NMP	PC
$Li(2,1,1)^+$	2.5×10^{-2}	4.4×10^{-3}	6.0×10^{-4}	2.12×10^{-2}	1.40×10^{-2}	4.81×10^{-3}	$<10^{-5}$
$Na(2,1,1)^+$	1.4×10^2	2.50	7.1×10^{-1}	ca. 5	-	0.47	3.6×10^{-2}
$Ca(2,1,1)^{2+}$	8.2×10^{-1}	-	-	-	ca.2×10^{-1}	-	-
$Li(2,2,1)^+$	-	7.5×10	ca.1.3x10	-	-	-	-
$Na(2,2,1)^+$	1.45×10	2.35×10^{-2}	2.62×10^{-3}	7.5×10^{-1}	2.5×10^{-1}	1.67×10^{-1}	$<10^{-2}$
$K(2,2,1)^+$	2×10^3	1.09	1.35×10^{-1}	-	ca. 2.6	1.35	3.7×10^{-2}
$Rb(2,2,1)^+$	-	7.5×10	ca.1.1x10	-	-	-	7.5
$Cs(2,2,1)^+$	-	ca.2.3×10^4	-	-	-	-	ca.4×10^2
$Ca(2,2,1)^{2+}$	6.1×10^{-4}	-	-	-	8×10^{-4}	-	-
$Li(2,2,2)^+$	-	$>3 \times 10^2$	-	-	-	-	-
$Na(2,2,2)^+$	1.47×10^2	2.87	3.0×10^{-1}	-	-	5.68	<1
$K(2,2,2)^+$	7.5	1.8×10^{-2}	4.08×10^{-3}	2.68	4.0×10^{-1}	1.33×10^{-1}	4×10^{-3}
$Rb(2,2,2)^+$	-	8.0×10^{-1}	9.17×10^{-2}	-	-	5.0×10^{-1}	1.7×10^{-1}
$Cs(2,2,2)^+$	-	ca.4×10^4	-	-	-	-	ca.3×10^2
$Ca(2,2,2)^{2+}$	2.1×10^{-1}	-	-	-	4.4×10^{-2}	-	-

cryptands in the different solvents. The corresponding dissociation rate constants are summarized in Table 30.

A more detailed survey of solvent effects on the kinetics of complex formation would involve analysing changes of solvation during reaction. Free energies of transfer for the transition state (ΔG_{Tr}^{T}) can be calculated from the free energy of transfer of the reactants (ΔG_{Tr}^{R}) and the free energies of activation for the formation reaction in the solvent in question ($\Delta G_{S}^{\ddagger R}$) and in the reference solvent ($\Delta G_{O}^{\ddagger R}$). This can be visualised in the following diagram (Figure 32).

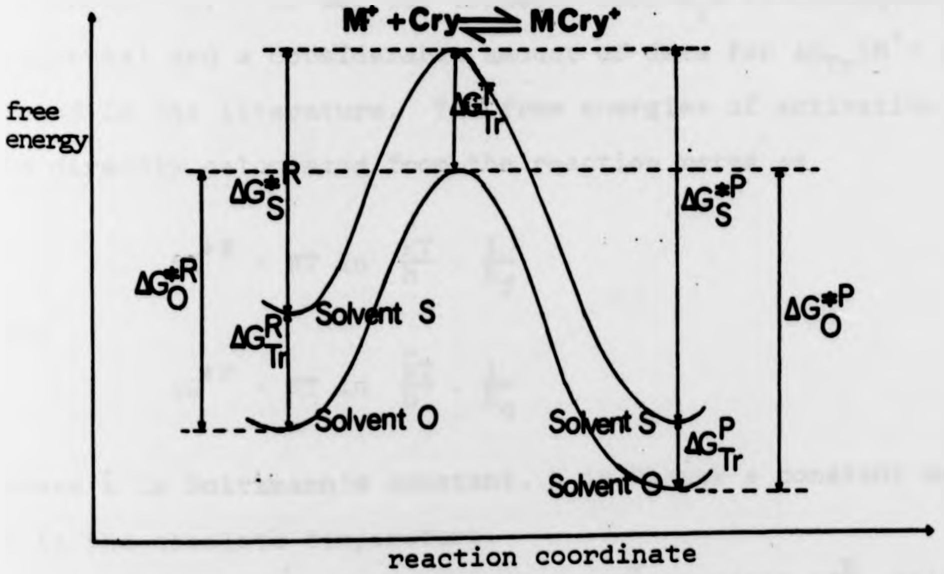


Figure 32 Relation between Free Energies of Activation and Free Energies of Transfer

From the above diagram it can be easily seen that ΔG_{Tr}^{T} is given by

$$\Delta G_{Tr}^{T} = \Delta G_{Tr}^{R} + \Delta G_{S}^{\ddagger R} - \Delta G_{O}^{\ddagger R} \tag{55}$$

or equivalently, ΔG_{Tr}^{T} can be expressed in terms of free energy parameters of the products

$$\Delta G^{T}_{Tr} = \Delta G^{P}_{Tr} + \Delta G^{\ddagger P}_{S} - \Delta G^{\ddagger P}_{0} \qquad (55')$$

where ΔG^{P}_{Tr} is the free energy of transfer of the product (the cryptate) and $\Delta G^{\ddagger P}_{S}$, $\Delta G^{\ddagger P}_{0}$ are the free energies of activation for the dissociation reaction in solvent S and in the reference solvent respectively.

Determination of $\Delta G^{R}_{Tr} = \Delta G_{Tr}(M^{+}) + \Delta G_{Tr}(Cry)$ and $\Delta G^{P}_{Tr} = \Delta G_{Tr}(MCry^{+})$ was discussed in the first chapter, concerning the thermodynamics of complex formation. Actual values of ΔG^{R}_{Tr} and ΔG^{P}_{Tr} can be obtained for (2,2,2) complexes since $\Delta G_{Tr}(2,2,2)$ is known (ca. 4 kJ mol for transfer from H_2O to non-aqueous solvents) and a considerable amount of data for $\Delta G_{Tr}(M^{+})$ is found in the literature. The free energies of activation can be directly calculated from the reaction rates as

$$\Delta G^{\ddagger R} = RT \ln \frac{\bar{k}T}{h} \cdot \frac{1}{k_f} \qquad (56)$$

and

$$\Delta G^{\ddagger P} = RT \ln \frac{\bar{k}T}{h} \cdot \frac{1}{k_d} \qquad (56')$$

where $\bar{k}$ is Boltzmann's constant, h is Planck's constant and T is the absolute temperature.

Figure 33 shows a plot of ΔG^{T}_{Tr} against ΔG^{R}_{Tr} using DMSO as the reference solvent, for the reaction $K^{+} + (2,2,2) \rightleftharpoons K(2,2,2)^{+}$. The value of ΔG^{T}_{Tr} becomes larger as ΔG^{R}_{Tr} increases. No clear correlation, however, was observed between ΔG^{T}_{Tr} and ΔG^{P}_{Tr}. This was expected to be so since, as it has been noted before, the transition state lies closer to the reactants than to the products. Thus, any change in the solvation energy of

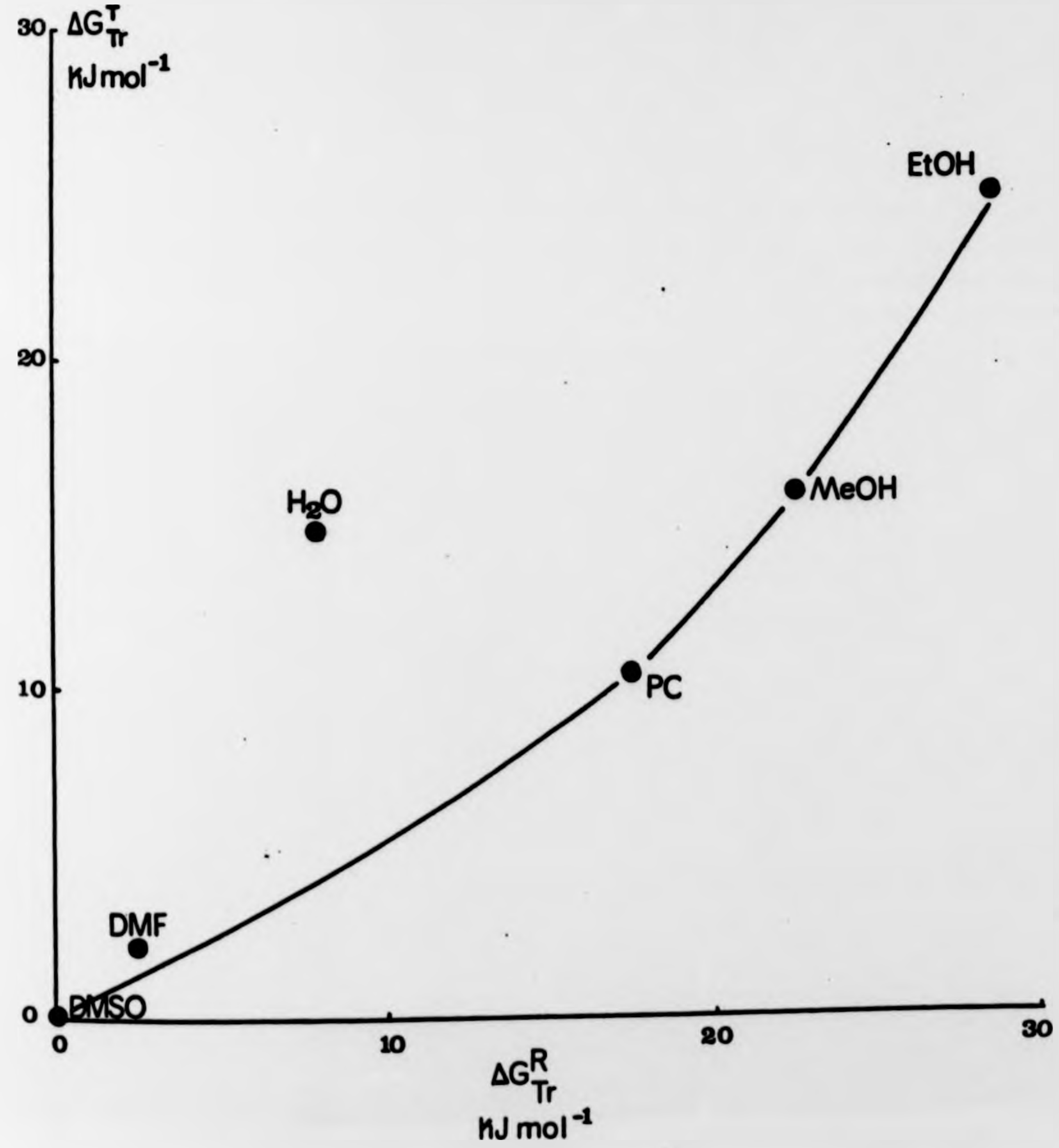


Figure 33 Free Energy of Transfer of the Transition State as a function of the Free Energy of Transfer of the Reactants for the Formation Reaction of $K(2,2,2)^+$

the reactants, chiefly of the metal ion, on transfer from one solvent to another, will result in a change in the energy required to partially desolvate the reactants in order to reach the transition state. The very good correlation between ΔG^{R}_{Tr} and ΔG^{T}_{Tr} values shown in Figure 33, suggests that only a very small amount of desolvation of the metal ion has occurred in the transition state. Thus the transition state behaves very much like the free metal ion on transfer between solvents.

The importance of the ligand-metal ion interactions in compensating for the loss of solvation that does occur on formation of the transition state may be seen more clearly by comparing the free energies of formation of the transition states for two different cations in the same solvent. Indeed, changes in the free energies of solvation of two different alkali metal ions in the same solvent are generally larger than the free energies of transfer of the individual ions between solvents; however, the formation rate constants seem to vary more from solvent to solvent than from one ion to another within a single solvent. For example, the value of k_f for $K(2,2,2)^+$ increases by slightly more than an order of magnitude on transfer from DMSO to MeOH, but it is not even twice as large as k_f for $Na(2,2,2)^+$ in MeOH. However, $\Delta G_{Tr}(K^+)$ from DMSO to MeOH is only 22 kJ mol^{-1} compared with the difference in the free energy of solvation between Na^+ and K^+ in MeOH which is 75 kJ mol^{-1}. This suggests that for smaller cations, the ligand-cation interactions compensate more effectively for the loss of solvation, than larger cations. Formation rates of $Li(2,1,1)^+$ and $Li(2,2,1)^+$ are comparatively low; it seems that Li^+ is so strongly solvated that even a relatively small amount of desolvation requires quite a lot of energy. Alternatively, it may be that these smaller ligands are not sufficiently flexible to allow an effective stepwise substitution process. The same argument may be applied to explain the decrease in formation rates on passing from the more flexible (2,2,2) cryptand to a less flexible (2,2,1) and particularly to the most rigid of all three, the (2,1,1) cryptand.

There is a wide range of $\Delta G_{Tr}(M^+)$ for the alkali metal cations on transfer from any common solvent to PC[26]. This is observed, for example, on transfer from H_2O to PC, where the spectrum of values for $\Delta G_{Tr}(M^+)$ ranges from highly positive for Li^+ to a negative value for Cs^+. Thus, the poorly solvated ions Li^+ and Na^+ present very high complexation rates; K^+ and Rb^+ show rates comparable to those in MeOH or EtOH, and Cs^+ presents values of k_f not far from those in DMF or DMSO. Additional factors may be contemplated in attempting to give a satisfactory explanation to the results in PC. The decreasing value of k_f with increasing cation size, as opposed to that observed in other solvents, may be originated by a slight change in the nature of the transition state, involving detectable participation of the cryptate. This, as mentioned before, would cause the stability of the cryptate to be manifested in the formation rates, with the most stable complexes displaying the highest rates.

The values of the dissociation rate constants (Table 30) for all the cryptates (except for $Li(2,1,1)^+$) in all solvents considered here vary proportionally with the stability constant, i.e. the most stable cryptates show the lowest dissociation rates. This was not unexpected since larger (free) energies of activation are necessary to overcome larger (free) energies of complexation (ΔG^{o} = -RT ln K, equation (22)) in order to reach the transition states which, as it has already been seen, are closer to the solvated cation and cryptand than to the cryptate. A plot of log k_d vs. log K_s (Figure 34) shows that these two parameters are roughly linearly correlated with each other. However, the values of log k_d for $Li(2,1,1)^+$ fall well below the drawn straight line. This may be due to the high rigidity of the ligand which, combined with the high stability of the complex, presents a large energetic barrier to the process of dissociation.

It has been tried, so far, to use transfer parameters of the species involved to explain changes in the reaction rates from solvent to solvent. However, it is always desirable to relate these rate variations to some solvent property. Throughout the years, considerable effort has been aimed to find suitable solvent parameters that may be used to predict the extent to which reaction rates are altered on transfer among solvents.

Dielectric constants in general have shown to be inappropriate to explain these rate differences[48]. In the case of the cryptates, it is clearly seen that neither the formation rate constants nor the dissociation ones, are ranked in the same sequence as the dielectric constant of the solvents.

Various empirical parameters, such as the Gutmann donor number[116] (Table 1), have been proposed. These empirical parameters are based on the behaviour of a particular system towards a change of solvent. The donor number (DN) is taken as a measure of solvent basicity. It is defined as the negative

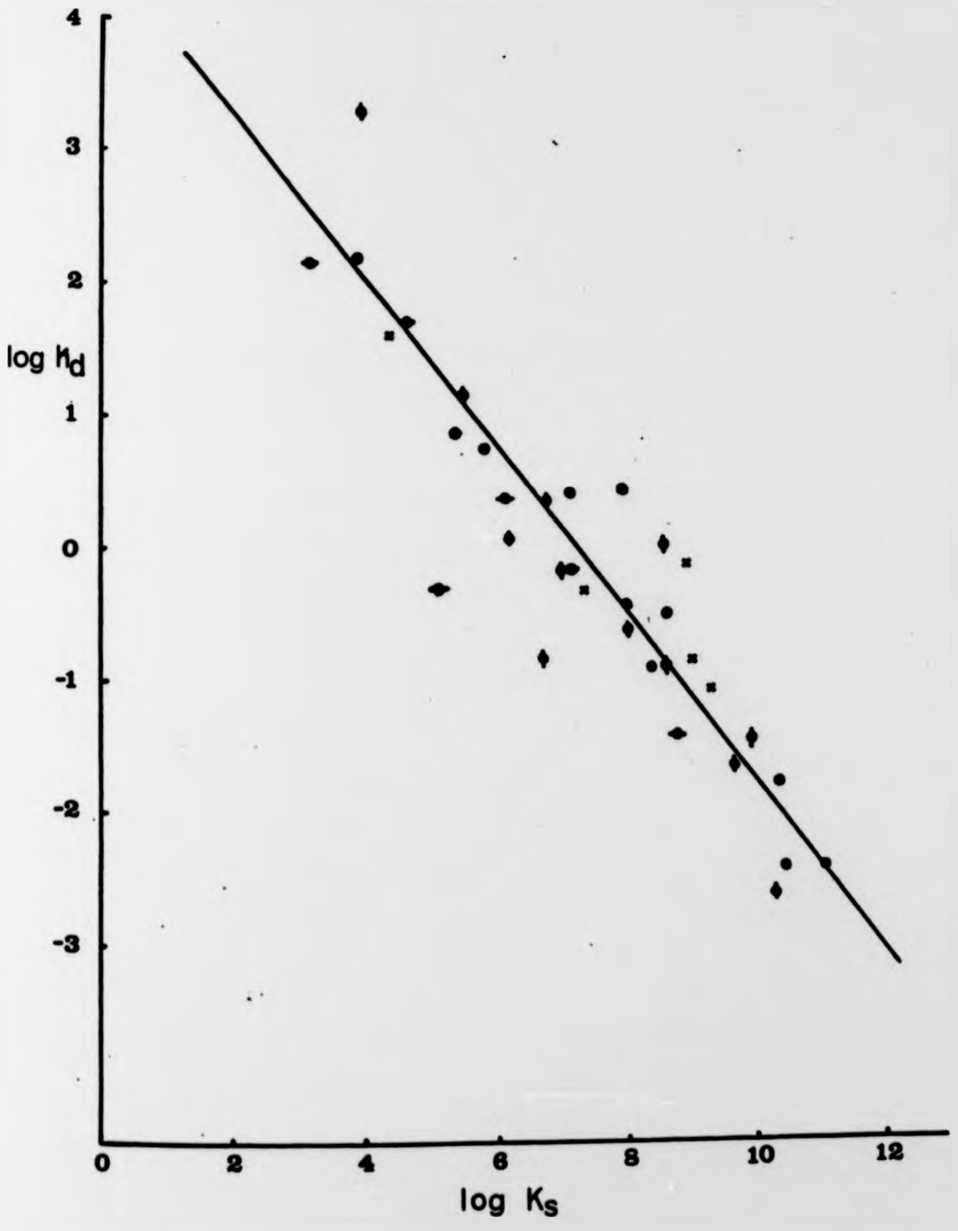


Figure 34 Variation of the dissociation rate constant with the stability of the cryptate

H-value for the 1:1 adduct formation between solvent molecules and the reference base $SbCl_5$ in 1,2-dichloroethane solution. The dissociation rate constants (log k_d) for $Li(2,1,1)^+$, $Na(2,2,1)^+$ and $K(2,2,2)^+$ were found to correlate linearly with DN; only in water, the dissociation rates were higher than predicted (Figures 35 and 36). It was also observed (Figure 33) that for water, ΔG_{Tr}^{T} was larger than could be expected from estimations based on ΔG_{Tr}^{R}. It seems that the strong hydrogen-bonding nature of water makes it a unique solvent, difficult to be compared with other solvents. Indeed, the fast dissociation rates and low formation rates of cryptates in water should be related to the strong interactions between H_2O and the ligands. Thus, formation would require removal of H_2O which could be H-bonded to the ligand electronegative groups, and dissociation would be assisted by this interaction.

A linear correlation between the values of k_f and DN (Figure 37) is less clear. However, more results would be needed to confirm that the proposed correlations with DN are valid over a wide range of solvents.

Rates in DMF and NMP

When comparing the values of k_f in these two amidic solvents, it is observed that the rate constants in NMP are about an order of magnitude lower than in DMF. It is improbable that the difference in dielectric constants (37 for DMF and 175 for NMP) is responsible for the lower k_f values in NMP, since dielectric properties basically do not alter the nature of the inner coordination shell of the cation; moreover, it has been pointed out that k_f does not follow the same order as ϵ. It

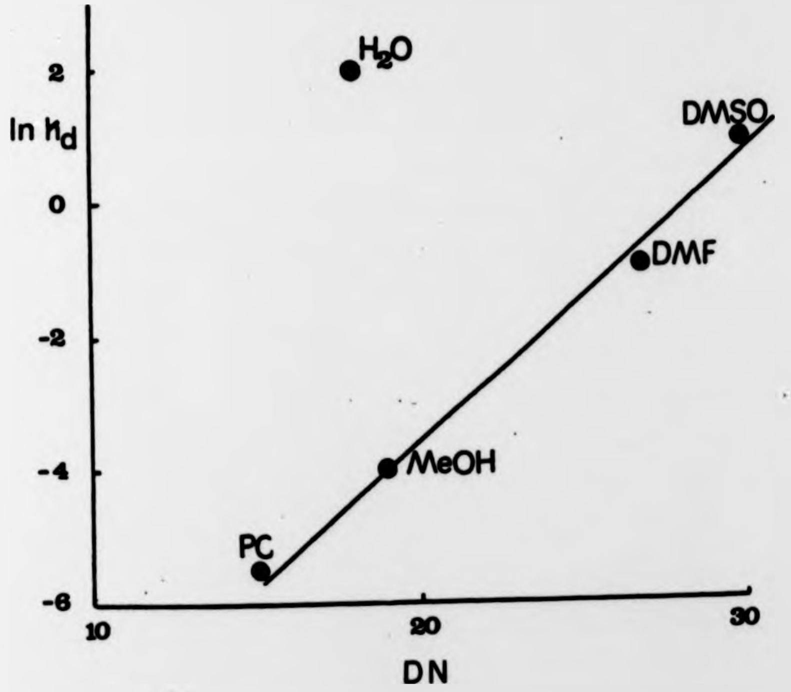


Figure 35 Dissociation Rate Constant for $K(2,2,2)^+$ as a function of Gutmann's Donor Number of the Solvent

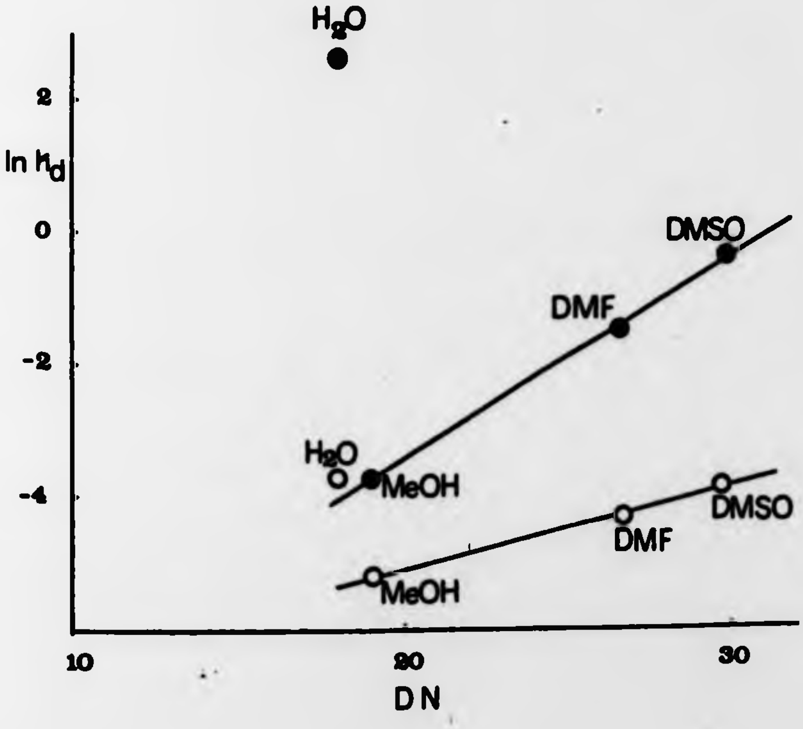


Figure 36 Dissociation Rate Constants for $Na(2,2,1)^+$ (●) and $Li(2,1,1)^+$ (O) as a function of Gutmann's Donor Number of the Solvent

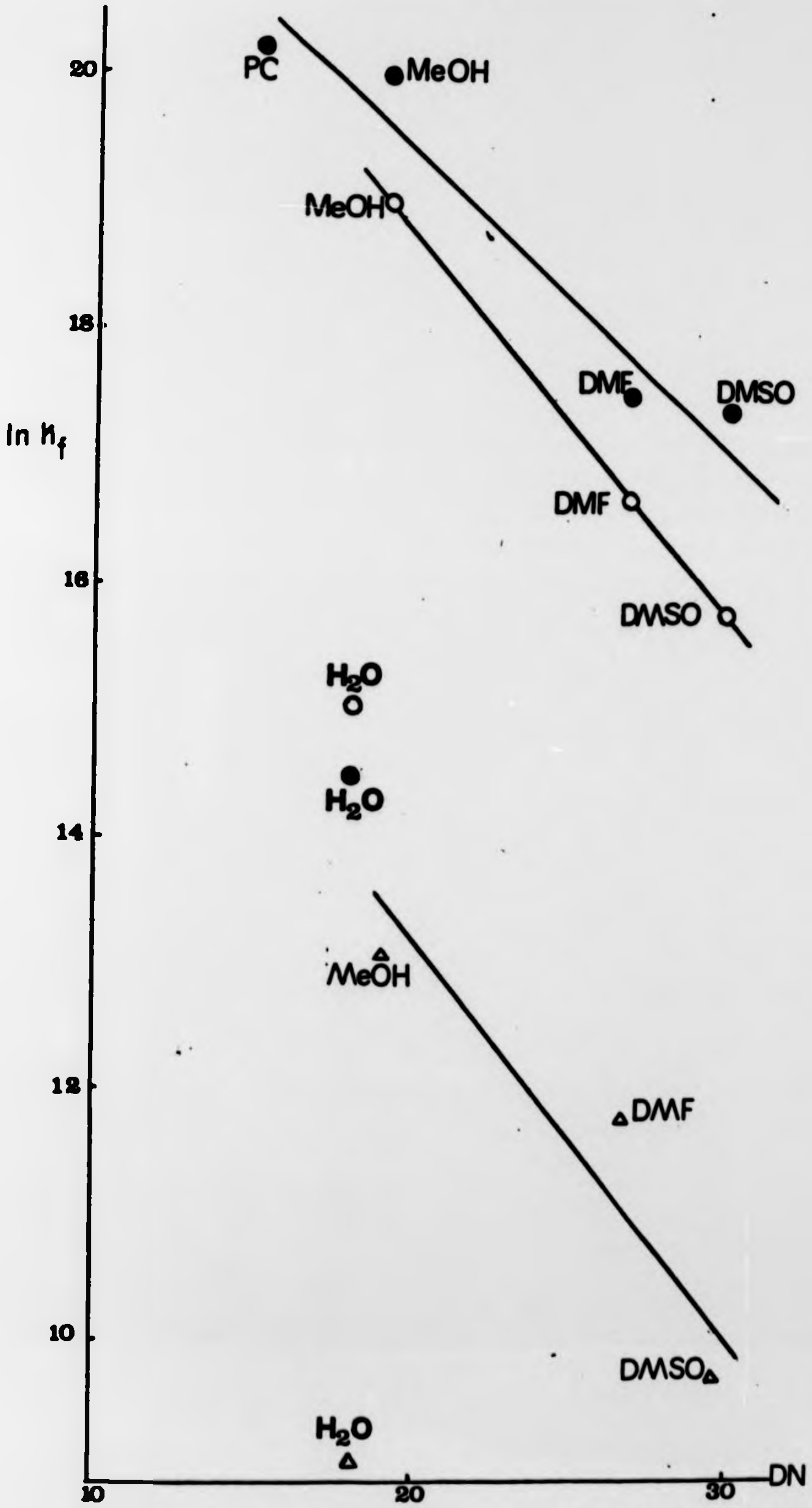


Figure 37 Formation Rate Constants for $K(2,2,2)^+$ (●), $Na(2,2,1)^+$ (O) and $Li(2,1,1)^+$ (Δ) as a function of Solvent Donor Number

as been suggested[117] that solvent structure can be an mportant factor influencing the rates of reactions involving ons. So it might be that the higher formation rates observed in DMF, compared with NMP, are related to the fact that NMP is a much more structured solvent than DMF.

Charge Effects upon Cryptate Kinetics

Results in H_2O and DMF show a slowing effect of doubly-charged cations on the reactions of dissociation and, particularly, of formation of the cryptates. The formation rate constants for Ca^{2+} complexes are about three orders of magnitude lower than those for Na^+. Studies on the kinetics of solvent substitution from the inner coordination sphere of the cations in H_2O[76], show that the characteristic substitution rate constants of the alkali metal and alkaline-earth metal cations (except for Mg^{2+}) are extremely high (ca. 10^8-10^9 s^{-1}) and not very different from each other. Therefore, the process of formation of a cryptate of the type $MCry^{2+}$ may involve substantial non-stepwise substitution of the solvent molecules surrounding the cation by the binding groups of the ligand. This increases the energy required to achieve complexation because there is no immediate compensation for the loss of solvation of the cation by the formation of cation-ligand bonds. Furthermore, any partial desolvation required to reach the transition state, should demand more energy if the cation is a strongly solvated M^{2+} ($\Delta G^o_{HYDR.}(Ca^{2+}) = -1593$ kJ mol^{-1})[29] than if it is a less solvated M^+ ($\Delta G^o_{HYDR.}(Na^+) = -411$ kJ mol^{-1})[29], particularly if, as mentioned before, ligand-cation interactions are not going to compensate effectively for the loss of solvation.

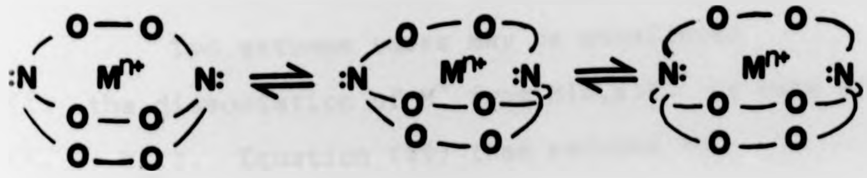
The case of valinomycin and other macrocyclic antibiotics

One of the conclusions that can be drawn from the present study is that cryptands, although apparently sufficiently flexible to allow relatively fast complex formation rates in most cases, only form complexes at rates close to the diffusion controlled limit when cations are poorly solvated. So, for example, remarkably high formation rate constants ($> 10^8$ M^{-1} s^{-1}) can be achieved by the (2,2,2) cryptand in MeOH, EtOH or PC. Many of the results obtained for valinomycin and other macrocyclic antibiotics have been in MeOH[48]. Studies of these compounds in H_2O are often hampered by solubility problems, low stabilities, protonation, etc. It is quite possible then that the high formation rates in MeOH for complexes of these naturally-occurring macrocycles, are only due to the poor solvating ability in this medium, and that significant lower rates could be expected in other solvents, including water. In this latter solvent, as discussed before, not only solvation of the cation but also solvation of the ligand and the hydrogen-bonding structure of the solvent, seem to be responsible for the low formation rates observed in the case of the cryptands. Measurements of the formation rate constants for some valinomycin complexes with alkali metal ions in water-methanol mixtures[118] seem to confirm the prediction for low complexation rates in H_2O. Indeed, the value of k_f for the K^+ complex of valinomycin in 90% MeOH-10% H_2O is 1.3×10^7 M^{-1} s^{-1}, in 80% MeOH-20% H_2O is 5.5×10^6 M^{-1} s^{-1} and in 70% MeOH-30% H_2O is 1.3×10^6 M^{-1} s^{-1}. This indicates a clear tendency of k_f towards lower values as the proportion of water in the water-methanol mixtures is increased.

9. The Catalysed Dissociation of Cryptates

The observed dissociation rate constants of a number of metal cryptates in EtOH and PC were strongly dependent on the acid concentration. The results could not simply be explained by a competition between acid and metal ion to complex the free cryptand, according to equation (40) or (40'). The acid was acting as a catalyst in the dissociation reaction. Indeed, Cox and Schneider have reported the existence of an acid-catalysed pathway for the dissociation of a number of metal cryptates in water[92] and methanol[45]. Eu(II) and Eu(III) cryptates have also been found to exhibit acid-dependent dissociation rates in water[119].

The most basic centres in the ligands, and hence the most likely to be involved in acid catalysed pathways, are the nitrogen atoms. Possible mechanisms for these reactions almost certainly have to take into account the fact that there are three possible conformations for cryptates in solution involving different configurations of the nitrogen atoms[90]. Figure 38 shows these three equilibrium conformations for a $M(2,2,2)^{n+}$ cryptate.



exo-exo $M(x,x)^{n+}$ exo-endo $M(x,n)^{n+}$ endo-endo $M(n,n)^{n+}$

Figure 38 Conformations of Metal Cryptates

As explained in the Introduction to this chapter, the endo-endo conformation is the one which stabilizes the complex. It is likely then that the catalysed pathway involves a conformational change from the rather unreactive endo-endo species to the more reactive exo-endo or exo-exo (where the nitrogen lone pair is free to interact with an acid)^{120}, preceding the dissociation reaction. A similar conformational change may also be involved in the uncatalysed pathway, although there is no direct evidence for this.

A possible kinetic scheme (for H^+ catalysis) involving an exo-endo conformation is shown below.

$$\begin{array}{c} M(n,n)^+ + H^+ \overset{K_{conf}}{\rightleftharpoons} M(n,x)^+ + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} M(n,x)H^{2+} \\ \hphantom{M(n,n)^+ + H^+ \rightleftharpoons M(n,x)^+ + H^+ \rightleftharpoons} \downarrow k_2 \\ \hphantom{M(n,n)^+ + H^+ \rightleftharpoons M(n,x)^+ + H^+ \rightleftharpoons} M^+ + H(n,x)^+ \end{array} \qquad (57)$$

Assuming a steady-state concentration of the intermediate species, i.e.

$$[M(n,x)^+], [M(n,x)H^{2+}] << [M(n,n)^+], [M^+] \qquad (58)$$

it readily follows that

$$-\frac{d[M(n,n)^+]}{dt} = K_{conf}\frac{k_1 k_2}{k_{-1} + k_2}[H^+][M(n,n)^+] \qquad (59)$$

Two extreme cases may be considered

(i) the dissociation of M^+ from $M(n,x)H^{2+}$ is rate determining ($k_2 << k_{-1}$). Equation (59) then reduces to

$$-\frac{d[M(n,n)^+]}{dt} = K_{conf}\ K_H k_2[H^+][M(n,n)^+] \qquad (60)$$

where $K_H = k_1/k_{-1}$.

(ii) the protonation of $M(n,x)^+$ is rate determining ($k_2 >> k_{-1}$). Equation (59) then reduces to

$$-\frac{d[M(n,n)^+]}{dt} = K_{conf}\,k_1[H^+][M(n,n)^+] \qquad (61)$$

In all cases the overall rate law has the form

$$-\frac{d[M(n,n)^+]}{dt} = k_{H^+}[H^+][M(n,n)^+] \qquad (62)$$

It is difficult to distinguish between the different possibilities for the rate-determining steps without additional information, such as may come from studies of deuterium isotope effects[121,122], etc. Similar schemes involving exo-exo conformations may be considered, and it may be readily shown that they also lead to a rate law of the form shown in equation (62).

Thus the observed rate constant (including the uncatalysed dissociation rate constant, k_d) will be given by

$$k_m = k_d + k_{H^+}[H^+] \qquad (41)$$

Therefore a plot of k_m vs $[H^+]$ should give a straight line whose intercept is k_d, the dissociation rate constant. Strictly speaking, however, k_m should be corrected to zero ionic strength. This is particularly true if the solvent has a relatively low dielectric constant, like EtOH (ε = 24.3), where the effect of the ionic strength on the rates of reactions involving ionic species becomes important. According to transition-state theory[109], two species A^+ and B^+ react to give the activated complex $(\neq)^{2+}$ from which the products will be formed (equation (63)).

$$A^+ + B^+ \rightleftharpoons (\neq)^{2+} \rightarrow \text{products} \qquad (63)$$

The theory assumes that the reaction rate is proportional to the concentration of the activated complex (equation (64)).

$$\text{rate} = \frac{\bar{k}T}{h}[(\neq)^{2+}] \qquad (64)$$

where $\bar{k}$ is Boltzmann's constant, T is the absolute temperature and h is Planck's constant.

The equilibrium constant for the formation of the activated complex, $K_{\neq}$, is given by

$$K_{\neq} = \frac{[(\neq)^{2+}]}{[A^+][B^+]} \cdot \frac{\gamma_{\neq}}{\gamma_A \gamma_B} \qquad (65)$$

from where the concentration of the activated complex can be obtained in terms of the concentrations of the reactants and the activity coefficients ($\gamma_{\neq}$, γ_A and γ_B) for the different species involved (equation (66)).

$$[(\neq)^{2+}] = K_{\neq}[A^+][B^+]\frac{\gamma_A \gamma_B}{\gamma_{\neq}} \qquad (66)$$

Substitution of (66) in (64) leads to equation (67)

$$\text{rate} = \frac{\bar{k}T}{h} K_{\neq} \frac{\gamma_A \gamma_B}{\gamma_{\neq}} [A^+][B^+] \qquad (67)$$

Thus, the reaction rate constant at any given ionic strength, k', is given by

$$k' = \frac{\bar{k}T}{h} K_{\neq} \frac{\gamma_A \gamma_B}{\gamma_{\neq}} \qquad (68)$$

At infinite dilution (or zero-ionic strength), $\gamma_A = \gamma_B = \gamma_{\neq} = 1$; therefore the rate constant at zero-ionic strength, k^o, becomes

$$k^o = \frac{\bar{k}T}{h} K_{\neq} \tag{69}$$

The ratio k'/k^o is then only a function of the activity coefficients (equation (70)).

$$\frac{k'}{k^o} = \frac{\gamma_A \gamma_B}{\gamma_{\neq}} \tag{70}$$

The activity coefficients can be calculated from the Davies equation (equation (20), Chapter I) with $Z_A = Z_B = 1$ and $Z_{\neq} = (Z_A + Z_B) = 2$. Upon substitution of the corresponding expressions for γ_A, γ_B and $\gamma_{\neq}$, equation (70) is transformed to

$$k^o = k' \, 10^{-2A\left(\frac{I^{\frac{1}{2}}}{1+I^{\frac{1}{2}}} - 0.3I\right)} \tag{71}$$

Equation (71) gives the rate constant corrected to zero-ionic strength. This correction only applies to the acid-catalysed pathway reaction (equation (57)) since the uncatalysed reaction involves an activated complex with the same (univalent) charge as the cryptate.

Equation (41) can now be written in a more precise form, as follows

$$k_m^o = k_d + (k_m' - k_d)\gamma_{\pm}^2 \tag{72}$$

where k_m' is the observed rate constant at ionic strength I,

k_m^o is the observed rate constant corrected to zero ionic strength and $\gamma_{\pm}^2$ is the square of the mean ionic activity coefficient, as given by the Davies equation with $Z_i = 1$, i.e.

$$\gamma_{\pm} = 10^{-2A\left(\frac{I^{\frac{1}{2}}}{1+I^{\frac{1}{2}}} - 0.3I\right)} \qquad (73)$$

A plot of k_m^o vs $[H^+]$ should be a straight line whose intercept with the $[H^+] = 0$ axis is the dissociation rate constant k_d (see Kinetics in EtOH section, Figures 19, 20 and 21). Since it is necessary to know the value of k_d to determine the value of k_m^o (equation (72)), an iterative method of calculation must be used. An alternative method which avoids the problem of iteration is to plot k'_m vs $[H^+]/\gamma_{\pm}^2$. Indeed, k_m^o can be defined in terms of the catalytic rate constant corrected to zero-ionic strength, $k_{H^+}^o$, as

$$k_m^o = k_d + k_{H^+}^o[H^+] \qquad (74)$$

Combining equations (72) and (74), it can be easily seen that k'_m is also given by

$$k'_m = k_d + k_{H^+}^o \frac{[H^+]}{\gamma_{\pm}^2} \qquad (75)$$

and therefore a plot of k'_m vs $[H^+]/\gamma_{\pm}^2$ should be a straight line whose interception with the $[H^+]/\gamma_{\pm}^2 = 0$ axis is k_d.

Whichever method is used, the value of $k_{H^+}^o$ can be obtained from the slope of the plotted lines (k_m^o vs $[H^+]$ or k'_m vs $[H^+]/\gamma_{\pm}^2$). Tables 31 and 32 list the values of $k_{H^+}^o$ and

TABLE 31

Catalytic Constants for the Dissociation of Cryptates

	k^{o}_{H+}, M^{-1} s^{-1}		
	H_2O	MeOH	EtOH
Li(2,1,1)$^+$	2.1×10	4.9×10^{-1}	3.7×10^{-1}
Na(2,1,1)$^+$	-	0	0
Li(2,2,1)$^+$	-	2.1×10^3	-
Na(2,2,1)$^+$	1.8×10^2	3.7×10^{-1}	5.0×10^{-1}
K(2,2,1)$^+$	-	0	0
Rb(2,2,1)$^+$	-	0	-
Na(2,2,2)$^+$	-	4.2×10^2	6.8×10^2
K(2,2,2)$^+$	0	0	0
Rb(2,2,2)$^+$	-	0	0

TABLE 32

Acid Catalysed Dissociation of Cryptates

	$k^{o}_{H^+}/k_d$, M^{-1}		
	H_2O	MeOH	EtOH
$Li(2,1,1)^+$	850	111	622
$Na(2,1,1)^+$	-	0	0
$Li(2,2,1)^+$	-	28	-
$Na(2,2,1)^+$	12.4	15.7	192
$K(2,2,1)^+$	-	0	0
$Rb(2,2,1)^+$	-	0	-
$Na(2,2,2)^+$	-	146	2267
$K(2,2,2)^+$	0	0	0
$Rb(2,2,2)^+$	-	0	0

$k^{o}_{H^+}/k_d$ for EtOH, MeOH[45] and H_2O[92]. In all three solvents, HCl was used in the kinetic measurements.

If the acid is weak, like DCA in PC, a mechanism for the acid catalysed dissociation of the cryptates would involve acid molecules HA and free protons H^+. The expression for the rate constant of a reaction exhibiting general acid catalysis has the form[121]

$$k = k_d + k_{H^+}[H^+] + k_{HA}[HA] \qquad (76)$$

However, if the concentration of H^+ is negligible, equation (76) becomes

$$k = k_d + k_{HA}[HA] \qquad (77)$$

The observed rate constants in PC were consistent with equation (77) at low acid concentrations. A kinetic scheme similar to the scheme (57) can be proposed. There and in the successive rate equations ((59) to (62)) HA substitutes H^+. Equation (70) predicts no correction for ionic strength if the reaction involves a molecule (the acid) and an ion (the cryptate).

At high acid concentrations ($> 5 \times 10^{-3}$M), the measured rates in PC became larger than predicted by equation (77). This acceleration of the rates may be related to homoconjugation, a process frequently observed in dipolar aprotic solvents[111]. In this process, the following equilibrium involving the acid molecule HA and the anion A^- takes place

$$HA_2^- \overset{K_2}{\rightleftharpoons} HA + A^- \qquad (78)$$

Methanesulphonic and p-toluenesulphonic acids, which are weak acids in PC, are reported to form homoconjugate species HA_2^- in this solvent[110]. Reaction (78) combined with the dissociation of the acid HA, equation (79), gives the overall

$$HA \overset{K_1}{\rightleftharpoons} H^+ + A^- \qquad (79)$$

equilibrium reaction (80) involving two acid molecules

$$2HA \rightleftharpoons HA_2^- + H^+ \qquad (80)$$

Values of pK_1 and pK_2 in PC for methanesulphonic acid are reported to be 7.2 and 3.4, and for p-toluenesulphonic acid 6.4 and 3.2, respectively[110]. It is probable then that a weak acid like DCA ($pK_a > 10$) is also involved in homoconjugation equilibria in PC. This could account for the non-linear dependence on acid concentration, which becomes evident at high DCA concentrations, as the H^+ and HA_2^- produced would increase as the square of [HA].

Table 33 contains the values of k_{HA} and k_{HA}/k_d for several metal cryptates in PC. The acid catalysis is very strong for lithium and sodium complexes, and decreases or even disappears for the other cryptates. A similar trend is observed in MeOH and EtOH (see Tables 31 and 32). It is also observed that the (2,2,2) complexes are the most highly catalysed. This could be related with the higher flexibility of the (2,2,2) cryptand which permits different conformations to be attained more easily.

From this and from the fact that no acid catalysis was manifested in strong solvating media (e.g. DMSO, DMF, NMP),

TABLE 33

Acid Catalysed Dissociation of Cryptates in PC

Cryptate	k_{HA}, M^{-1} s^{-1}	k_{HA}/k_d M^{-1}
$Li(2,1,1)^+$	a	a
$Na(2,1,1)^+$	1.6	44
$Ca(2,1,1)^{2+}$	0	0
$Li(2,2,1)^+$	a	a
$Na(2,2,1)^+$	$\sim 9 \times 10$	>9000
$K(2,2,1)^+$	2.8×10	757
$Rb(2,2,1)^+$	~ 0	0
$Na(2,2,2)^+$	$\sim 3 \times 10^4$	>30000
$K(2,2,2)^+$	1.2×10	3000
$Rb(2,2,2)^+$	3×10	176
$Ca(2,2,2)^{2+}$	a	a

a Strongly acid-catalysed dissociation.

the following conclusions may be drawn about the conditions leading to an acid-catalysed pathway in the dissociation of cryptates (see reaction scheme (57)).

1. The ligand. The cryptand molecule should be sufficiently flexible so that any conformational alteration necessary for the acid to interact with the cryptate, occurs with a minimum of energy.

2. The metal ion. Smaller cations are enclosed in the cavity of the ligand but still allow the nitrogen atoms at the bridgeheads a certain degree of freedom to rotate, so that the cryptate molecule can more easily attain exo configurations, capable of reacting with the acid molecules. Large cations, on the other hand, may introduce considerable strain, making the cryptate molecule more rigid and less able to attain reactive configurations.

3. The solvent. The surrounding medium should not solvate the reactants (cryptate and acid) very strongly, thus hindering the reaction between them. This is particularly true for the acid, whose reactivity may vary remarkably from one solvent to another.

Further support for the first point (flexibility of the ligand) will be given in Chapter III, where it will be seen that the acid catalysed dissociation becomes less important as the rigidity of the (2,2,2) cryptand molecule is increased by modifications in its structure to give the monobenzo and dibenzo (2,2,2) cryptands.

In a preliminary study on the dissociation of a number of cryptates in PC by means of displacing the metal cation of the complex by Ag^+, as described in the Experimental section, a marked accelerating effect upon the dissociation rates was observed. The substitution of Ag^+ from silver cryptates by Cu^{2+} also showed to be a fast reaction. A simple mechanism having the dissociation of the cryptate as the rate determining step (equations (44), (45)) would not explain these high observed rates. Therefore, other dissociative pathways should be considered. Such is the case of a mechanism involving the release of the complex cation from a species $MCry^{n+}...M'^{n+}$ formed by the interaction between the substituting cation and the electron pair of one of the nitrogen atoms of cryptand, probably in an exo-conformation. Further investigations are, however, necessary to elucidate these mechanisms.

The catalysed dissociation of cryptates may have implications in their use as cation carriers through membranes. It has been mentioned before that a good carrier molecule displays high selectivity and a rapid loading and unloading of the cation. Cryptands exhibit this high selectivity and reasonably high formation rates. Therefore, if there is an effective catalyst for the dissociation process of the cryptates, cryptand molecules may become as well efficient cation carriers.

CHAPTER III

STABILITY CONSTANTS AND FORMATION AND DISSOCIATION RATE CONSTANTS OF (2B,2,2) AND (2B,2B,2) METAL CRYPTATES

A. INTRODUCTION

In previous chapters, it has been mentioned that the study of the complexation properties of the existing macrocyclic ligands may serve as a guide for the design of new ligands suitable for specific purposes. Sometimes, it may be desirable to add organic groups to the ligand molecule in order to increase its solubility in low-polar organic media[14,123], or simply in order to change the structure of the ligand so that it displays a different selectivity pattern or different complexation and decomplexation rates[19]. Recently, the term "lateral discrimination" has been used to describe specific interactions between side groups of a macrocyclic ligand and the substrate[25]. This property has been applied to the resolution of racemic mixtures, e.g. resolution of racemic ammonium salts by crown-ethers containing the binaphtyl group[124]. Therefore, it is of interest to investigate the way in which the properties (stability, reaction rates, etc.) of ligands may be altered by certain structural changes in the ligands.

Substitution of a -CH_2-CH_2- group of the cryptand (2,2,2) by a benzo group leads to the monobenzo (2,2,2) cryptand or (2B,2,2). Further replacement of a -CH_2-CH_2- group by another benzo group gives as a result the dibenzo (2,2,2) cryptand or (2B,2B,2). These substitutions have the effect of increasing the rigidity of the ligand and reducing the cavity size[50]. The addition of the benzo rings will also increase the general size of the "organic" part of the ligand and complexes, and should help to isolate the cation in the complex from the solvent. These structural alterations of the cryptand molecule are expected to be reflected in the stability and kinetics of its cryptates. Studies on the stability of alkali metal complexes with (2B,2,2) and (2B,2B,2) in water and methanol[3,125,126] have shown that Ks decreases in the order (2,2,2) > (2B,2,2) > (2B,2B,2). A study on the kinetics of $M(2B,2,2)^+$ ($M=Na^+,K^+,Rb^+$) in MeOH[125] has shown that the rates of dissociation of these cryptates are somewhat higher than the corresponding rates for $M(2,2,2)^+$ complexes.

In this work, stability constants and dissociation rate constants have been measured for the alkali metal complexes with the cryptands (2B,2,2) and (2B,2B,2) in PC. These results are compared with those for the (2,2,2) complexes given in Chapters I and II. The reported results in water and methanol, and the results in PC obtained here, are also compared and discussed in terms of solvating abilities of the solvents. This analysis is similar to that made in the previous chapters.

B. EXPERIMENTAL SECTION

1. Chemicals and Solvents

Cryptands (2B,2,2) and (2B,2B,2) were purchased from Merck and used without further purification. Tests of purity, similar to those mentioned for the other cryptands (Chapter I), had been previously carried out.

The salts used were the same as for the case of (2,2,2) measurements (see Chapter I).

DCA was used in the kinetic measurements.

PC was purified as described before. (See Experimental Section, Chapter I).

2. Stability Constant and Kinetic Measurements

The experimental method used to measure the stability constants was the same Ag^+-potentiometry technique described in Chapter I.

The dissociation rate constants were determined by the conductimetric method described in Chapter II. The formation rate constants were simply calculated as $k_f = k_d Ks$.

C. RESULTS AND DISCUSSION

1. Stability Constants

The stability constants of the alkali metal and Ag^+ complexes with the (2B,2,2) and (2B,2B,2) cryptands in PC are shown in Table 34, together with the corresponding values of log Ks for the (2,2,2) cryptates. From these results, it is observed that in all cases the stability of the cryptates follow the sequence $M(2,2,2)^+ > M(2B,2,2)^+ > M(2B,2B,2)^+$. However, potassium and rubidium complexes are the most strongly affected by the reduction of the cavity size of the cryptands. The stability constant of the $K(2B,2B,2)^+$ complex drops by 10^2 when compared with $K(2,2,2)^+$, and that of $Rb(2B,2B,2)^+$ drops by more than 10^2 compared with $Rb(2,2,2)^+$. Li^+ and Na^+ complexes, although on a smaller scale, also experience a decrease in stability on going from (2,2,2) to the monobenzo ligand, and from this to the dibenzo cryptand. In the case of Li^+ and Na^+, the decrease is most likely to be a result of the greater rigidity of the ligands. Another noteable feature of the results is the change in the selectivity pattern of the ligands. While (2,2,2) exhibits the selectivity sequence $K^+ > Na^+ > Rb^+$, the (2B,2,2) and (2B,2B,2) cryptands present the pattern $Na^+ > K^+ > Rb^+$. Thus Na^+ becomes the "preferred" cation, in contrast to what has been observed in H_2O[3] or MeOH[125,127] (Tables 35 and 36), where K^+ forms the most stable complex with all three cryptands. This fact comes to emphasize, once again, that the stability of a complex not only depends on ligand-ion interactions, but is a result of the competition between solvent and ligand molecules for the cation. The free energy of

TABLE 34

Stability Constants of Alkali Metal and Ag^+ Cryptates in PC at 25°C

	log Ks		
Cation	(2,2,2)[a]	(2B,2,2)[b]	(2B,2B,2)[b]
Li^+	6.94	6.36	5.59
Na^+	10.54	10.24	9.72
K^+	11.10	10.00	9.15
Rb^+	9.02	7.59	6.63
Cs^+	4.18	3.31[c]	ca. 3.0
Ag^+	16.33	15.74	15.46

a (log Ks) ± 0.1

b (log Ks) ± 0.05

c cf. log Ks = 3.17, ref. 50

TABLE 35

Stability Constants of Alkali Metal and Ag^+ (2B,2,2) Cryptates in H_2O, MeOH and PC

	log Ks at 25°C		
Cation	H_2O[a]	MeOH[b]	PC
Li^+	-	2.19	6.36
Na^+	4.0	7.50	10.24
K^+	4.9	9.21	10.00
Rb^+	3.4	7.19	7.59
Cs^+	-	2.99	3.31
Ag^+	-	11.9	15.74

a Ref. 3

b Ref. 125

TABLE 36

Stability Constants of Alkali Metal and Ag^+ (2B,2B,2) Cryptates in MeOH and PC

	log Ks at 25°C	
Cation	MeOH[a]	PC
Li^+	2.3 (0.97)	5.59
Na^+	6.3 (7.60)	9.72
K^+	>8.0 (8.74)	9.15
Rb^+	4.8 (5.93)	6.63
Cs^+	2.8 (2.60)	ca. 3.0
Ag^+	>8.0	15.46

a Ref. 3; ref. 127 in parenthesis

TABLE 37

Stability Constants of some Alkali Metal Complexes with 18-Crown-6, Benzo-18-Crown-6 and Dibenzo-18-Crown-6 in MeOH

	log Ks at 25°C		
Cation	18-Crown-6[a]	Benzo-18-Crown-6[b]	Dibenzo-18-Crown-6[c]
Na^+	4.3	4.5	4.36
K^+	6.1	5.05	5.0
Rb^+	5.2	-	4.1[d]
Cs^+	4.6	-	3.55

a Values from Table 4

b Ref. 128

c Ref. 4

d Estimated value using selectivity data from ref. 56 and ref. 4

transfer[26] of Na^+ from water or methanol to PC is relatively larger than that of K^+ and this should result in an increase of the stabilities of Na^+ complexes in PC relative to those of K^+. This, combined with the effect of the reduction in ligand cavity size, is sufficient to shift the peak selectivity to Na^+.

Measurements of the stability of crown-ether complexes also seem to indicate a larger effect on the biggest cations when introducing a benzo unit in the macrocyclic molecule. Table 37 contains the values of log Ks for some alkali metal complexes of the macrocyclic polyethers 18-Crown-6, Benzo-18-Crown-6 and Dibenzo-18-Crown-6 in MeOH. The stability constants of Na^+ complexes with all these three ligands remain practically unaltered, while those of K^+, Rb^+ and Cs^+ complexes are reduced by more than a factor of ten. This suggests that the ligand (18-Crown-6) suffers a decrease in its cavity size, but still retains its flexibility.

2. Dissociation and Formation Rate Constants

The dissociation rate constants for the alkali metal complexes of the (2B,2,2) and (2B,2B,2) cryptands in PC were measured using the conductimetric technique described in Chapter II. The results are shown in Table 38, which also includes those for (2,2,2) complexes for comparison.

The experimental conditions under which the measurements were carried out are discussed below for each case.

(2B,2,2)

The dissociation rates for Cs^+ and Li^+ complexes were beyond the measuring capability of the stopped-flow. The dissociation of the Na^+ complex was so strongly acid catalysed

TABLE 38

Dissociation Rate Constants for Alkali Metal Cryptates in PC at 25°C

	k_d in s^{-1}		
Metal	(2,2,2)	(2B,2,2)	(2B,2B,2)
Na^+	-	ca. 10^{-1}	2×10^{-1}
K^+	3×10^{-3}	5.7×10^{-3}	2.0×10^{-2}
Rb^+	1.7×10^{-1}	3.32	1.88×10
Cs^+	ca. 3×10^{2}	-	-

TABLE 39

Formation Rate Constants for Alkali Metal Cryptates in PC at 25°C

	k_f in $mol^{-1}\ dm^3\ s^{-1}$		
Metal	(2,2,2)	(2B,2,2)	(2B,2B,2)
Na^+	-	ca. 10^{9}	10^{9}
K^+	4.5×10^{8}	5.7×10^{7}	2.9×10^{7}
Rb^+	1.8×10^{8}	1.3×10^{8}	8.0×10^{7}
Cs^+	ca. 4×10^{6}	-	-

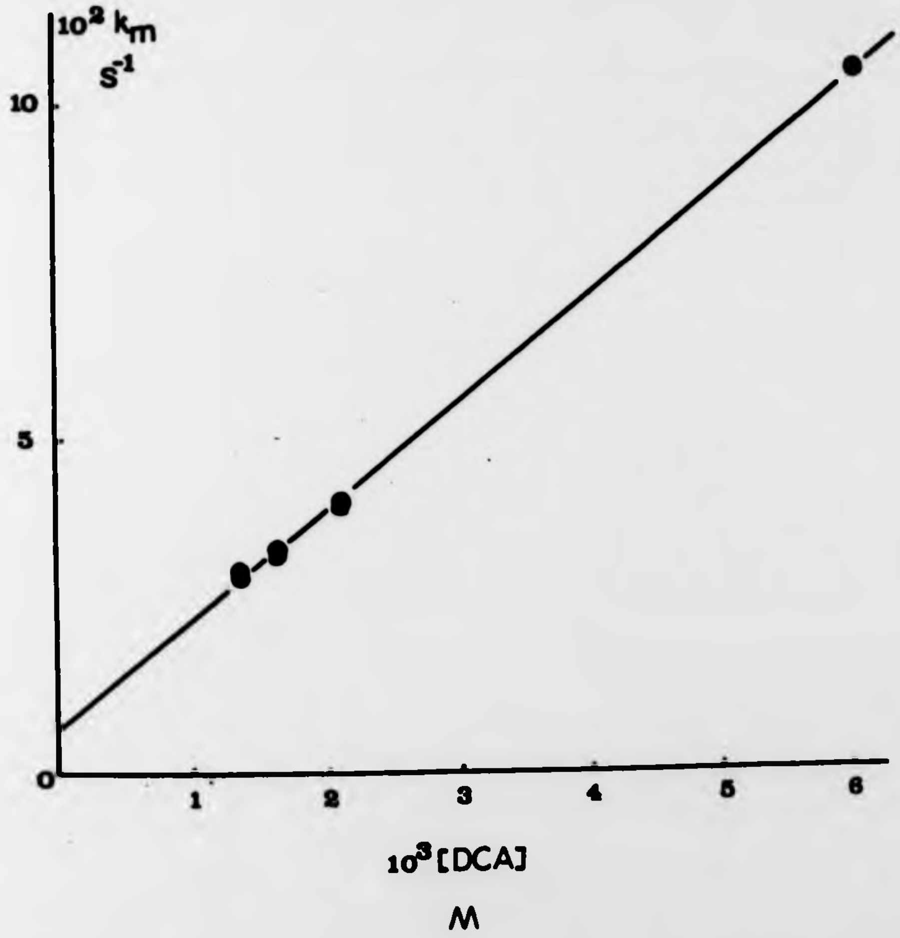


Figure 39 Dependence of k_m on acid concentration for the dissociation of $K(2B,2,2)^+$ in PC

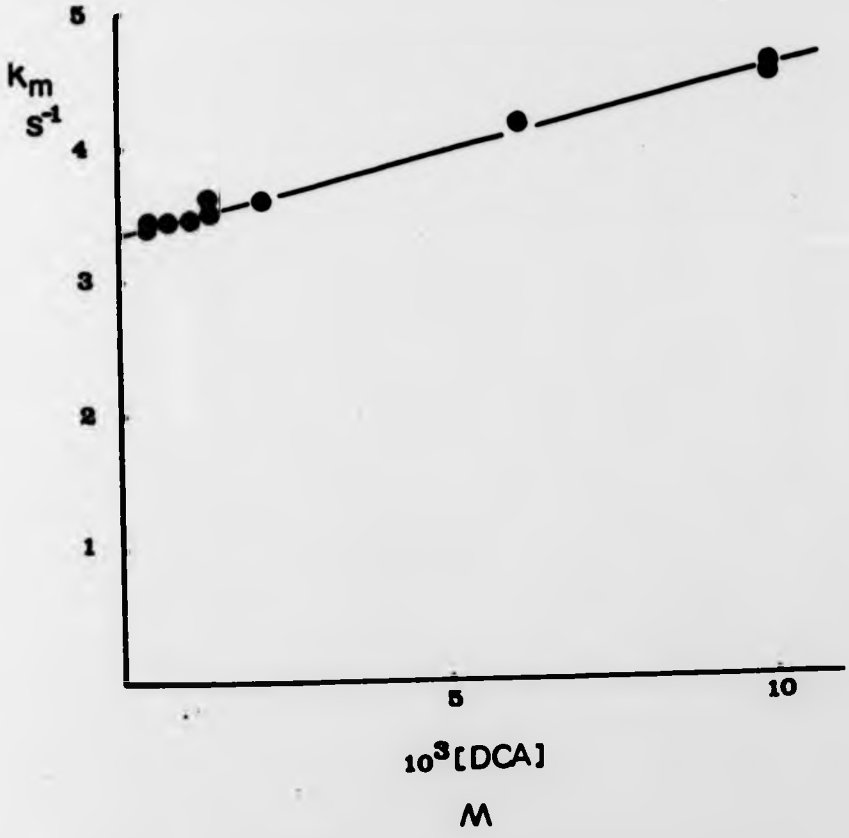


Figure 40 Dependence of k_m on acid concentration for the dissociation of $Rb(2B,2,2)^+$ in PC

that extrapolation to zero-acid concentration was very difficult. Therefore only an approximate value of k_d ($\sim 10^{-1}$ s^{-1}) could be obtained. In the case of $K(2B,2,2)^+$, the dissociation reaction was also catalysed by DCA; the observed rates varied linearly with [DCA] (1.3×10^{-3} M $\leq$ [DCA] $\leq 6 \times 10^{-3}$M) and were independent of [$KClO_4$] (10^{-4}M $\leq$ [$KClO_4$] $\leq 4 \times 10^{-4}$M). k_d was calculated using equation (42), i.e. extrapolation to [DCA] = 0 of a plot k_m vs [DCA] (Figure 39). For $Rb(2B,2,2)^+$ the observed dissociation rates were practically independent of [$RbNO_3$] (range: 10^{-4} - 4×10^{-4}M) and slightly dependent on [DCA] (range: 5×10^{-4} - 10^{-2}M). The plot of k_m against [DCA] was a straight line whose intercept with the [DCA] = o-axis gave the value of k_d (Figure 40).

(2B,2B,2)

Li^+ and Cs^+ complexes presented dissociation rates that were too high to be measured by the stopped-flow.

The dissociation of $Na(2B,2B,2)^+$ was very strongly acid catalysed (10^{-3}M $\leq$ [DCA] $\leq 8 \times 10^{-3}$M). The observed rates were, however, independent of [$NaClO_4$] (range: 10^{-4} - 5×10^{-4}M). Equation (42) was used to determine k_d from a plot of k_m against [DCA] (Figure 41). However, at concentrations of acid > ca.3×10^{-3}M, the observed rate constants became larger than predicted by a linear relationship between k_m and [DCA], equation (42). This, as it was explained in the case of the (2,2,2) complexes (see Chapter II), could be related to the production of homoconjugate species of the acid.

Rates for $K(2B,2B,2)^+$ were practically independent of

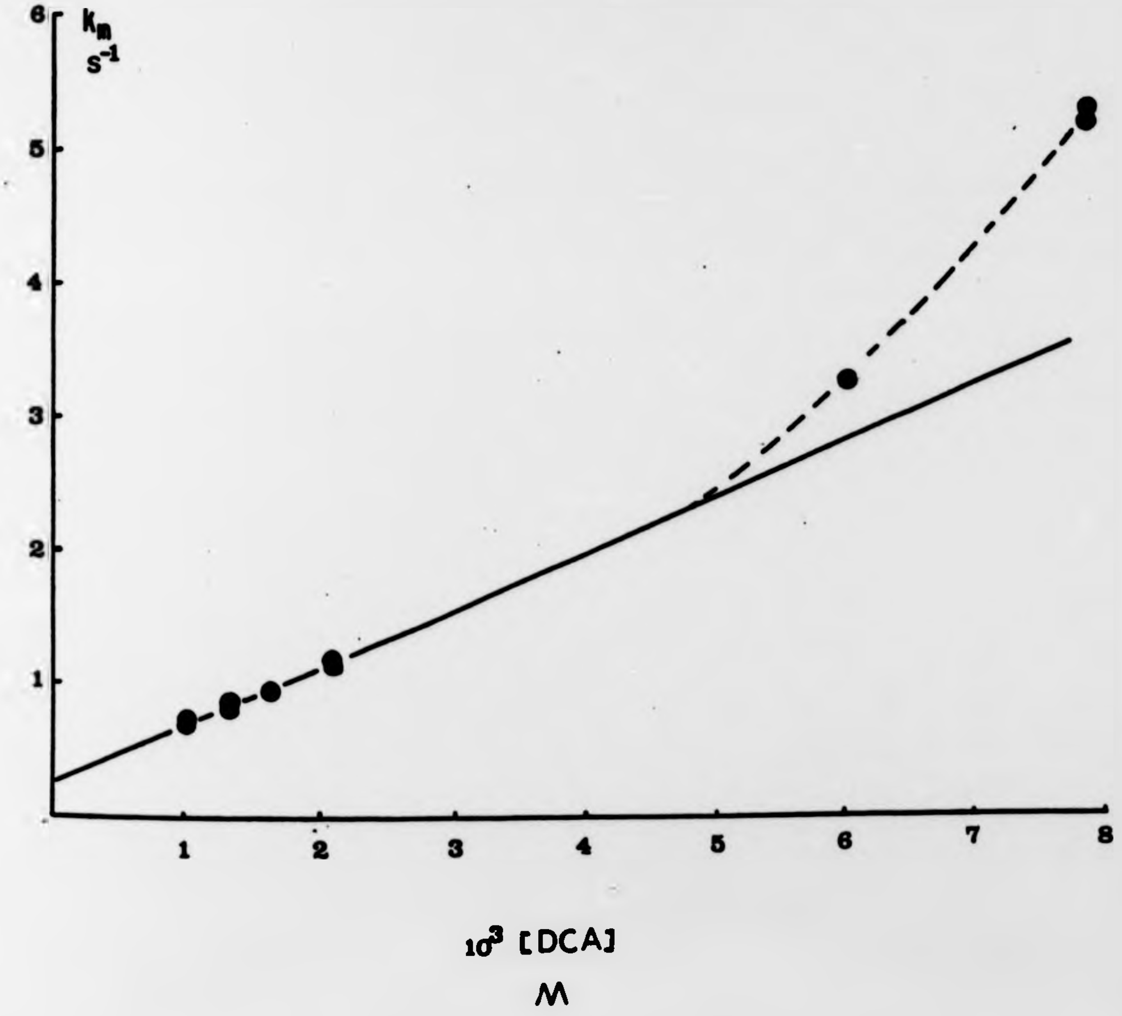


Figure 41 Dependence of k_m on acid concentration for the dissociation of $Na(2B,2B,2)^+$ in PC

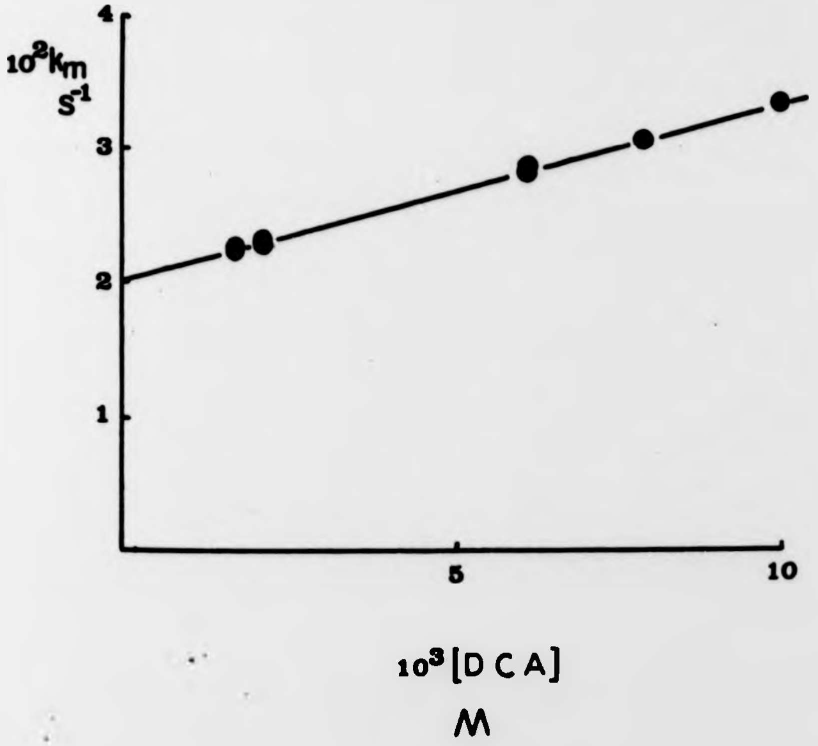


Figure 42 Dependence of k_m on acid concentration for the dissociation of $K(2B,2B,2)^+$ in PC

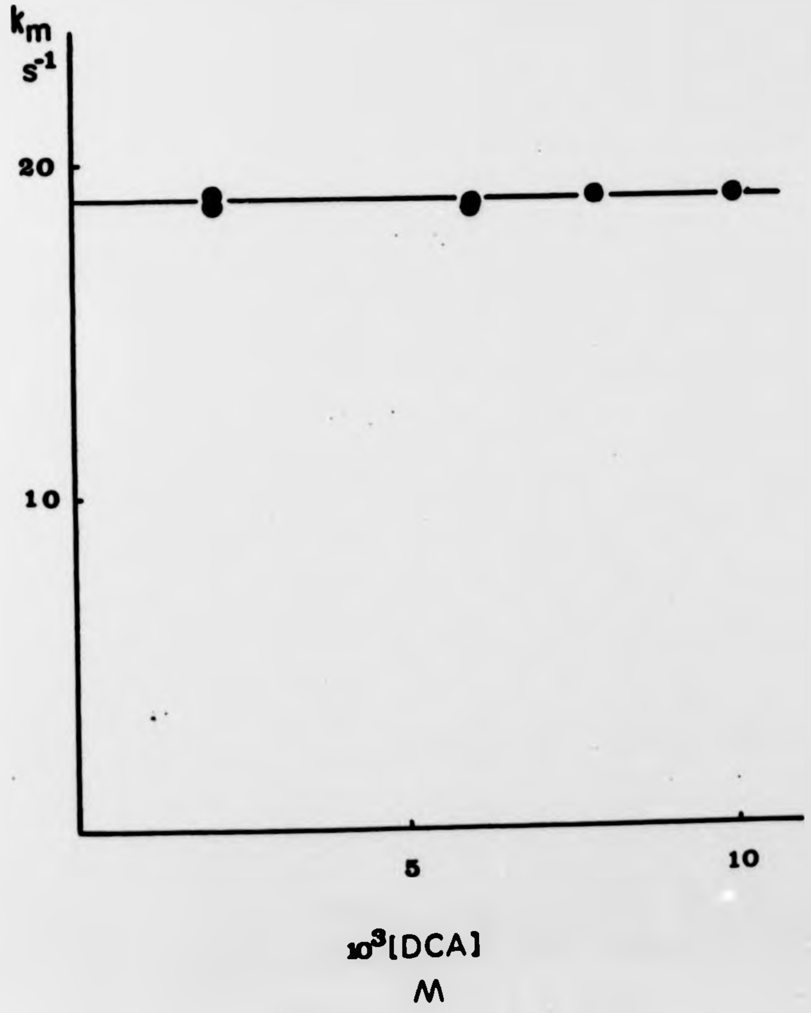


Figure 43 Dependence of k_m on acid concentration for the dissociation of $Rb(2B,2B,2)^+$ in PC

$[KClO_4]$ (range: 10^{-4} - 4×10^{-4}M), but showed some dependence on [DCA] (range: 1.5×10^{-3} - 10^{-2}M). A plot of k_m against [DCA] was a straight line, according to equation (42); from this, k_d was calculated (Figure 42).

The observed dissociation rates for Rb^+ complex were independent of both acid ($10^{-3}M \leq [DCA] \leq 10^{-2}M$) and metal ion ($10^{-4}M \leq [RbNO_3] \leq 4 \times 10^{-4}M$) concentrations. The value of k_d was determined by averaging all the values of k_m obtained ($k_d = k_m$, equation (39)) (Figure 43).

Using the values of k_d (Table 38) and Ks (Table 34) obtained for the different cryptates, k_f was calculated as $k_f = k_dKs$. The values of k_f are listed in Table 39.

From the results in Table 38, it is observed that the dissociation rate constants increase in the order (2,2,2) < (2B,2,2) < (2B,2B,2), thus reflecting the order in which the stability constants decrease: (2,2,2) > (2B,2,2) > (2B,2B,2) (see discussion in Chapter II). The formation rate constants (Table 39) drop in the sequence (2,2,2) > (2B,2,2) > (2B,2B,2). This may be attributed to an increase in the rigidity of the ligand, as benzo groups are added to the ligand molecule, thus making it more difficult for the ligand to form the complex. A study on the kinetics of (2,2,2) and (2B,2,2) complexes in MeOH[125] also showed lower formation rates for these latter. In the same study, higher dissociation rates for K^+, Rb^+ and Cs^+ complexes of the monobenzo cryptand in MeOH are reported. All this is consistent with the observed results in PC.

Dye et al.[95] have determined, by means of ^{133}Cs-NMR, the exchange rate constant for $Cs(2B,2,2)^+$ in PC (3.4×10^5 s^{-1}).

If the exchange process proceeds via a rate-determining dissociation of the cryptate, then this exchange rate constant reported can be taken as k_d. From this, a value of $k_f = 6 \times 10^8$ mol^{-1} dm^3 s^{-1} is obtained via the stability constant. This value of k_f seems to be consistent with the values of the formation rate constants for the other (2B,2,2) complexes in PC (Table 39). However, it represents an increase of about two orders of magnitude with respect to the formation rate constant of the $Cs(2,2,2)^+$ complex. It has been found[49] that the complex of Cs^+ with (2,2,2) can be of two types: one inclusive, in which the cation is enclosed in the ligand cavity, and the other exclusive, in which the metal ion is only partially within the cavity and therefore it can interact with the solvent. NMR studies[49] report that the $Cs(2,2,2)^+$ exclusion complex presents binding energy, activation energy and chemical shift that are similar to those of the complex between Cs^+ ion and the monobenzo (2,2,2) cryptand. This strongly suggests that $Cs(2B,2,2)^+$ is chiefly an exclusion complex and, as such, has a high formation rate.

As in the case of (2,2,2), some of the (2B,2,2) and (2B,2B,2) complexes show an acid-catalysed dissociation by DCA. Table 40 contains the values of k_{HA} and Table 41 those of k_{HA}/k_d for the complexes of these three cryptands. Although the values of k_{HA} by themselves do not provide much information, those for k_{HA}/k_d indicate that (a) for a given metal, the dissociation reaction is more strongly accelerated the more flexible the ligand, i.e. the values of k_{HA}/k_d follow the order

TABLE 40

Acid-Catalysed Dissociation Constants of Metal Cryptates in PC (25°C)

	k_{HA} in mol^{-1} dm^{3} s^{-1}		
Cation	(2,2,2)	(2B,2,2)	(2B,2B,2)
Na^+	-	ca. 6.6×10^3	4.7×10^2
K^+	1.5×10	1.6×10	1.35
Rb^+	2.5×10	1.3×10^2	0

TABLE 41

Values of k_{HA}/k_d for some Alkali Metal Cryptates in PC (25°C)

	k_{HA}/k_d in mol^{-1} dm^{3}		
Cation	(2,2,2)	(2B,2,2)	(2B,2B,2)
Na^+	-	ca. 6.6×10^4	2.4×10^3
K^+	5×10^3	2.8×10^3	6.8×10
Rb^+	1.5×10^2	3.9×10	0

(2,2,2) > (2B,2,2) > (2B,2B,2); and (b) for a given cryptand, k_{HA}/k_d decreases with decreasing cation size ($Na^+ > K^+ > Rb^+$). Similar results were found for other cryptates in PC as well as in other solvents where acid catalysis was observed, eg. EtOH, MeOH, H_2O (see the section on the acid-catalysed dissociation of cryptates, Chapter II).

APPENDIX

EXAMPLES OF DETERMINATION OF STABILITY CONSTANTS

Solvent: N-methylpropionamide (NMP)

(a) Determination of the stability constant Ks for $Ag(2,2,2)^+$

Reference electrode: silver electrode immersed in a 0.01M $AgClO_4$ solution in NMP

Salt bridge: 0.1M Tetraethylammonium picrate in NMP

Detecting electrode: silver electrode.

The silver detecting electrode was originally immersed in 5.1 ml of a solution 1.961×10^{-4}M $AgClO_4$. Initial potential reading E_i = 106.5 mV. Addition of different volumes of a 0.02M (2,2,2) solution gave the potential readings (E_1) shown in the table A1, together with the calculated silver concentrations $[Ag^+]_1$, (equation (13))*, silver cryptate concentrations $[AgCry^+]_1$ (equation (14)), free cryptand concentrations $[Cry]_1$ (equation (15)), and the corresponding value of Ks for $Ag(2,2,2)^+$ (equation (9)). The average value of Ks obtained was 1.5×10^9 M^{-1}.

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* It was assumed that the activity coefficients γ_i and γ_1 were approximately the same since no ionic species were added to the original solution and the effect by dilution was negligible.

TABLE A1

Determination of the Stability Constant Ks for $Ag(2,2,2)^+$ in NMP

Total Volume of 0.02M(2,2,2) Solution added	E_1	$[Ag^+]_1$	$[AgCry^+]_1$	$[Cry]_1$	Ks
ml	mV	M	M	M	M^{-1}
0.2	456	$2.45x10^{-10}$	$1.89x10^{-4}$	$5.66x10^{-4}$	$1.4x10^9$
0.3	470	$1.42x10^{-10}$	$1.85x10^{-4}$	$9.26x10^{-4}$	$1.4x10^9$
0.4	480	$9.62x10^{-11}$	$1.82x10^{-4}$	$1.27x10^{-3}$	$1.5x10^9$
0.5	488	$7.05x10^{-11}$	$1.79x10^{-4}$	$1.61x10^{-3}$	$1.6x10^9$
0.6	493.5	$5.69x10^{-11}$	$1.75x10^{-4}$	$1.93x10^{-3}$	$1.6x10^9$

Average Ks : $1.5x10^9$

(b) Determination of the equilibrium constant Ke for the system

$$Na(2,2,2)^+ + Ag^+ \rightleftharpoons Ag(2,2,2)^+ + Na^+$$

Detecting and reference electrodes and salt bridge were the same as in part (a).

The detecting electrode was initially immersed in 5.1 ml of a 1.961×10^{-4}M $AgClO_4$ solution. Initial potential reading E_i = 106 mV. After the addition of 0.2 ml of a 0.02M solution of (2,2,2) cryptand, the potential reached the value E_1 = 458 mV, which is in good agreement with the value obtained in part (a) and gives a value of Ks for $Ag(2,2,2)^+$ of 1.5×10^9 M^{-1}. Successive amounts of a 0.1M $NaClO_4$ solution were added and each time the system was allowed to reach equilibrium (approximately within 20-30 min.). The potential readings (E) were recorded and the silver concentrations were calculated according to equation (16), using an activity coefficient for the initial solution γ_i = 0.995. From here, the values of $[AgCry^+]$ (equation (17)), $[NaCry^+]$ (equation (18)) and $[Na^+]$ (equation (19)) were determined, and a series of values for Ke (equation (7)) was obtained. Table A2 summarizes all these values and gives the activity coefficients γ (Davies equation, Chapter I) for each case. The average value for Ke obtained is 2.2×10^3.

TABLE A2

Determination of the equilibrium constant Ke for the system $Na(2,2,2)^+ + Ag^+ \rightleftharpoons Ag(2,2,2)^+ + Na^+$

Total Volume of 0.1M $NaClO_4$ Solution added	E	γ	$[Ag^+]$	$[AgCry^+]$	$[NaCry^+]$	$[Na^+]$	Ke
ml	mV		M	M	M	M	
(0.0)	(106)	(0.995)	(1.96×10^{-4})				
0.2	261	0.980	4.80×10^{-7}	1.81×10^{-4}	5.46×10^{-4}	3.09×10^{-3}	2.1×10^{3}
0.3	251	0.976	7.11×10^{-7}	1.78×10^{-4}	5.36×10^{-4}	4.82×10^{-3}	2.3×10^{3}
0.4	243	0.973	9.73×10^{-7}	1.75×10^{-4}	5.27×10^{-4}	6.49×10^{-3}	2.2×10^{3}
0.5	238	0.971	1.19×10^{-6}	1.71×10^{-4}	5.18×10^{-4}	8.10×10^{-3}	2.3×10^{3}
					Average Ke :		2.2×10^{3}

(c) Determination of the stability constant Ks for $Na(2,2,2)^+$.

From the values obtained in parts (a) and (b), Ks for $Na(2,2,2)^+$ can be immediately obtained (equation (12)).

$$Ks(Na(2,2,2)^+) = \frac{Ks(Ag(2,2,2)^+)}{Ke(Na(2,2,2)^+)} = \frac{1.5 \times 10^9 M^{-1}}{2.2 \times 10^3} = 6.8 \times 10^5\ M^{-1}$$

$$\log Ks(Na(2,2,2)^+) = 5.82$$

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