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Rates and Mechanisms of Complexation Reactions of Cations
with Crown Ethers and Related Macrocycles

by

Edward M. Eyring and Sergio Petrucci

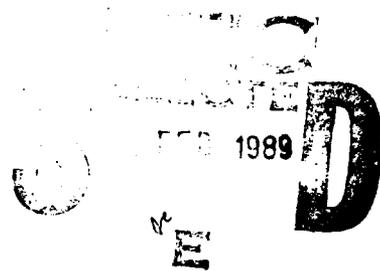
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19 ABSTRACT (Continue on reverse if necessary and identify by block number) Rate studies of complexation reactions of macrocycles reacting with metal cations in nonaqueous solutions are reviewed. Particular attention is given to differing mechanistic pictures arising from ultrasonic absorption and nuclear magnetic resonance studies of crown ethers in a variety of nonaqueous solvents. Future directions of complexation kinetic studies are also considered.			
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Rates and Mechanisms of Complexation Reactions of Cations
with Crown Ethers and Related Macrocycles

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1. Introduction
2. Experimental Methods
3. Possible Mechanisms of Complexation
4. Crown Ether Kinetic Studies
5. Cryptand and Cryptate Kinetic Studies
6. Further Information Obtained by Other Methods
7. Future Directions
8. Acknowledgment
9. References

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1. Introduction

In the eleven years since one of us (Liesegang and Eyring, 1978) last attempted to summarize the published rate studies of complexation reactions involving macrocyclic ligands other reviews of the subject have been published. Lockhart (1982) considered the complexation kinetics of cations from Periodic Groups I-III interacting with a variety of ligands including macrocyclic ligands. Izatt et al. (1985), on the other hand, focused on cation-macrocycle interactions in a comprehensive survey of the thermodynamic and kinetic data including references up through 1984.

The present chapter makes no attempt to include all the literature references since 1984 reporting macrocyclic complexation kinetics. We believe it will be more useful to develop a coherent picture of the present status of the field that may suggest to the reader promising directions that future kinetic studies of macrocyclic complexation of cations should take.

The reader may wonder what the potential technological ramifications are that continue to drive research on crown ethers in general and reaction rate studies of macrocycles in particular. There are many rationales from which to choose, and the sophisticated reader will probably second guess the particular choices made here. For instance, some of the commercially important modern voltaic cells are constructed with lithium anodes, and the desirable high conductivity of the electrolyte in such a cell can be enhanced by the addition of lithium ion selective crown ethers (Kaplan et al., 1987). A lithium ion selective macrocycle capable of carrying this cation across the blood-brain barrier might have important pharmaceutical applications in the treatment of manic-depression (Fieve, Jamison, and

-3-

Goodnick, 1985). The assay of lithium ion present in biological and environmental systems would be facilitated by lithium ion selective electrodes based on crown ethers (Kimura et al., 1987). Turning away from lithium ion, the removal of cesium ions by crown ethers from radioactive wastes is a matter of continuing interest to the nuclear power industry (Blasius and Nilles, 1984).

In each of the above applications it would be reasonable to expect thermodynamic data such as stability constants and entropies of solvation to be of paramount importance. Complexation rate constants alone seldom disclose a great deal more about these systems, but activation parameters and reaction mechanisms deduced from the temperature and solvent dependence of experimental complexation-decomplexation rates can often provide a much clearer picture of the ways by which macrocycles act in chemical processes like those mentioned above.

2. Experimental Methods

What we presently know about the rates and mechanisms of reactions between cations and crown ethers or cryptands has been dictated, of course, by the experimental tools available for their study. We will consider here some of the more important characteristics of the ultrasonic absorption, nuclear magnetic resonance and stopped flow techniques that have been most frequently applied to these systems.

Stuehr (1986) has provided an up-to-date survey of the various ultrasonic absorption relaxation methods of measuring reaction rates in liquids. A change in volume of a liquid solution arising from a change in

the solvation of a solute can absorb energy from a sound wave passing through the liquid. The greatest attenuation of the sound wave will occur when the frequency f of the sound wave and the relaxation time τ of the solvation change bear the following relationship to one another: $\tau^{-1} = 2\pi f$

Elementary reaction steps in liquid solutions have relaxation times ranging from femtoseconds to seconds. X-cut quartz piezoelectric transducers conveniently produce sound waves having frequencies between ~ 0.1 MHz and ~ 500 MHz. Thus ultrasonic absorption techniques can provide a window on elementary reaction steps having relaxation times between approximately 1.6 μ s and 320 ps provided that the reaction involves a detectable volume change as reactants proceed to products. A major advantage of ultrasonic absorption techniques is that no chromophore is needed in the sample equilibrium to assure detectability of the reaction. Disadvantages include 1) the need for high solute concentrations in order to detect small volume changes, 2) a requirement for access to a substantial ultrasonic frequency range in order to resolve the very broad absorption peaks in an ultrasonic spectrum, and 3) the many hours required to determine the ultrasonic absorption spectrum of a sample solution. Thus, for example, there is as much kinetic information in a single stopped-flow spectrophotometry oscillogram obtained in seconds as there is in an ultrasonic absorption spectrum produced in the course of a long day. The reason for bothering with ultrasonic measurements is that they provide a window on a fast time regime that is inaccessible to other more easily used methods.

A representative ultrasonic absorption spectrum is depicted in Figure 1. This spectrum was determined using an ultrasonic resonator technique at frequencies below 10 MHz and an ultrasonic pulse method at higher ultrasonic frequencies. As we will see in the discussion that follows, the various ultrasonic absorption techniques have proven especially useful for exploring the kinetic properties of crown ethers including the second order complex formation step in which a cation and a crown ether molecule come together. At the end of this chapter we will consider what sorts of chemical and physical processes occur in solutions of macrocyclic compounds that are too rapid for study by present ultrasonic techniques.

In principle, the stability constants of macrocycles complexing various cations can be deduced from the amplitudes of the experimental ultrasonic absorptions. In practice, however, those interpreting ultrasonic absorption data on macrocyclic systems prefer to use more reliably determined stability constants obtained from calorimetric titrations or from the variation of the NMR chemical shift of the cation of interest measured as a function of the ligand:cation mole ratio.

Alkali metal cation NMR spectroscopy is also a very effective means of measuring the decomplexation kinetics of a supramolecular system consisting of the macrocycle, the cation, the associated anion and the contiguous solvent molecules (Detellier, 1983). Brevard (1983) has provided a concise, illuminating description of the pulse excitation Fourier transform (FT) NMR spectrometer used in modern multinuclear studies. ^7Li , ^{23}Na , ^{39}K , and ^{133}Cs

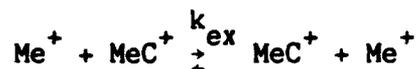
are nuclides that have been used in NMR studies of decomplexation kinetics (Delville, Stover, and Detellier, 1987).

Large chemical shifts, large coupling constants, and very broad lines from quadrupolar isotopes can complicate the strategies of NMR kinetic experiments. Thus it is not possible to describe an experimental protocol here that is general and covers all the possible eventualities. A sketch of some of the experimental considerations in a recent ^{23}Na NMR study of decomplexation kinetics of the sodium cation by Dibenzo-2^u-crown-8 (DB24C8) and DB18C6 in nitromethane and acetonitrile (Delville, Stover, and Detellier, 1987) will suggest some of the opportunities and limitations of NMR kinetic methods for studying crown ether complexation mechanisms.

There are two different relaxation times in NMR spectroscopy. The longitudinal relaxation time T_1 arises from the excited nuclei regaining their stable configuration through the dissipation of energy to the "lattice" (surrounding molecules). This energy exchange restores the Boltzmann distribution between the upper and lower nuclear spin states. In liquids T_1 lies between approximately 10^{-2} and 10^2 seconds. (The presence of paramagnetic ions in solution can shorten the T_1 to $\sim 10^{-4}$ seconds.) While T_1 is essentially energy-driven, the transverse or "spin-spin" relaxation time T_2 is entropy-driven and involves a loss of phase coherence through an exchange of spin orientations during the relaxation process. There is no net change in populations of the upper and lower spin states and

no change in the global energy of the system by spin-spin relaxation. T_2 in liquids occurs on approximately the same time scale as T_1 .

When chemical exchange represented by the rate constant k_{ex} in the reaction



is rapid compared to T_2^{-1} and T_1^{-1} , the chemical exchange does not affect the longitudinal relaxation time T_1 . Measurement of T_1 and T_2 yields the exchange contribution to the transverse relaxation rate allowing the calculation of the rate constant for the simple case of a two-site (e.g. solvated and complexed ^{23}Na) uncoupled system. ^{23}Na NMR is well suited to this strategy because the chemical shift difference is large. Relaxation rates for solvated ^{23}Na range between 20 s^{-1} in water to 10^3 s^{-1} in viscous propylene carbonate. Relaxation rates of the complexed ^{23}Na are 200 s^{-1} for Na^+ -DB24C8 and 300 s^{-1} for Na^+ -DB18C6 in nitromethane. The chemical shift difference between the solvated and complexed sites in nitromethane is $3500 \text{ rad sec}^{-1}$ for Na^+ -DB24CC8 and $1500 \text{ rad sec}^{-1}$ for Na^+ -DB18C6.

The great advantage of NMR kinetics experiments is that they permit observation of exchange reactions in which no net chemical or physical change has taken place. In contrast, a net volume change in proceeding from reactants to products must occur if ultrasonic absorption methods are to yield any kinetic information about a chemical equilibrium. Disadvantages

of NMR kinetic experiments would include the need for substantial quantities of the macrocyclic ligands to yield an adequate signal strength and the inaccessibility of picosecond time scale kinetic phenomena.

Stopped-flow kinetic instrumentation is more widely available than either ultrasonic absorption or FT NMR gadgetry. Robinson (1986) has considered some of the recent innovations, e.g. operation at high pressures and low temperatures, and has provided references to previous, more extensive reviews of stopped-flow instrumentation. Reactant mixing times that seldom get under a millisecond and thus preclude the study of very fast chemical reactions constitute a fundamental limitation of this kinetic method. A pulsed-accelerated-flow method (Nemeth et al., 1987) and the collision of two liquid streams to give mixing on a microsecond time scale (Davidovits and Chao, 1980) are among the interesting techniques devised to circumvent this limitation. Since crown ethers and their complexes with alkali metal cations are usually colorless well into the near ultraviolet, conductimetric detection has been more useful than spectrophotometric detection in stopped-flow kinetic studies of systems considered here.

3. Possible Mechanisms of Complexation

Here we will focus on our present understanding of reaction mechanisms of complexation and the nature of current debates over this subject. An attempt at correlating the dynamics of the macrocycle ligand to the mechanism of complexation will be made with the limited data available. A projection of what would be desirable to know, within the next decade,

(either using current technologies or applying novel ones to the field) will also be made.

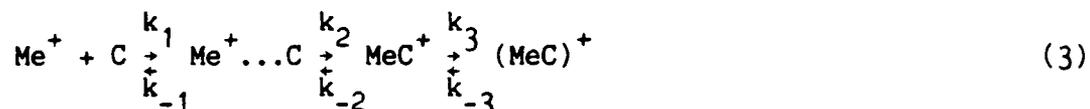
a) historical

The mechanism of complexation that was generally accepted in the seventies is the one attributed to Chock (1972). He suggested that a "fast" isomeric rearrangement process of the macrocyclic ligand C precedes the "slow" complexation of the metal cation Me^+ by one of the configurations of the macrocycle C_2 :



The isomerization process involving the macrocycle alone was thought to be in dynamic equilibrium with the complexation. Years later it was shown (Chen et al., 1984) by determining the rate constants of the isomerization process k_o and k_{-o} for the macrocycle 18C6 in methanol and dimethylformamide, that one of the two rate constants for the isomeric process (the slower one of the two steps, either k_o or k_{-o}) corresponded quite closely to k_2 , the rate constant of formation of the contact species

MeC⁺ as expressed by another mechanism proposed earlier by Eigen (Eigen and Winkler, 1970):



In other words, the misconception of Chock's mechanism was to refer to a "process" rather than to a "step" in comparing the isomerization with complexation reactions. Since relaxation methods relate the relaxation time for a first or pseudo first order process to the rate constants through the equation

$$\tau_0^{-1} = k_0 + k_{-0} \quad (4)$$

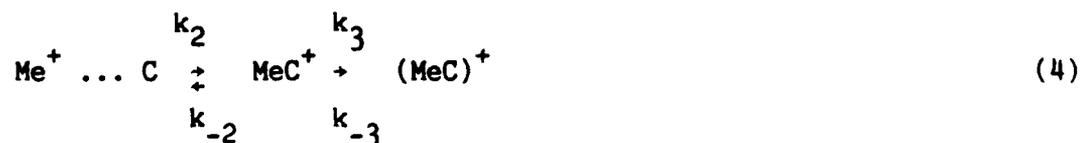
the larger value of the two rate constants k_0 and k_{-0} determined the value of τ_0^{-1} hence creating the misimpression that the isomerization was altogether "fast." Once the slow step was compared to k_2 , it was apparent that the two rate constants were of the same order of magnitude. In fairness to Chock it should be pointed out that the Joule heating temperature-jump relaxation technique he used could not measure the rate of the faster process but only detect that there had to be a faster relaxation than the one attributed to metal ion complexation (by dibenzo-30-crown-10.)

Thus his mechanism was a reasonable syllogism in the light of the experimental evidence then available.

b) Present State of Knowledge

In the scheme 3 proposed by Eigen Me^+ and C are the free metal ion and crown ether, $\text{Me}^+ \dots \text{C}$ is a solvent separated species, MeC^+ is a contact species with the metal ion residing outside the cavity, the so-called "exclusive" species, and $(\text{MeC})^+$ is the "inclusive" species with the metal cation imbedded in the ligand "cavity."

The applicability of scheme 3 to the complexation of metal cations by macrocycles was first confirmed by extensive work on Na^+ reacting with valinomycin in methanol (Grell, Funck, and Eggers, 1975), using ultrasonic relaxation techniques. In situations where the molar ratio between metal cation and macrocycles is the order of one, and with larger overall formation constants $K_{\Sigma} = K_1(1+K_2+K_2K_3)$ [where $K_1 = k_1/k_{-1}$, $K_2 = k_2/k_{-2}$, $K_3 = k_3/k_{-3}$], the concentration of Me^+ and C becomes relatively small. Thus at concentrations of the order of 0.1 M and higher, scheme 3 reduces to:



This scheme has proven to apply to the molecular dynamics of alkali metal ions complexed to crown ethers in solvents with relative permittivity less

than that of water such as methanol and dimethylformamide, cited above, and quite recently to acetonitrile (Rodriguez, Eyring, and Petrucci, 1989) and propylene carbonate (Cobranchi *et al.*, 1989).

However, it has been suggested (Shchori *et al.*, 1971; Shamsipur and Popov, 1988) that NMR techniques show for solutions of solvents of low donor number such as acetonitrile and nitromethane that dissociation of the macrocycle complex is not initiated by the solvent S that one would explicitly express for the reverse of process 4 or 3 above as



Rather, the dissociation process is said to be initiated by metal cations in excess



making the reverse dissociation process a bimolecular one (instead of a pseudo first order one, the solvent being in excess).

One ought to mention at this point that in solvents of very low relative permittivity, such as ethers, the electrolyte exists almost exclusively in the form of ion-pairs MeX and/or of higher aggregates $(\text{MeX})_2$, X being the anion. The complexation process occurs between the macrocyclic ligand and the substrate, namely the ion pair, by the reaction



Obviously, since the anion is not present in excess (as in the case of the solvent), process 7 becomes bimolecular (in both the forward and the reverse directions.) The back reaction in 7 may then become bimolecular because it is anion assisted rather than cation assisted as in process 5. In solvents of very low relative permittivity the final product of process 7 is

$(\text{MeC})^+ \text{X}^-$, the anion remaining associated with the metal complex because of electrostatic attraction (at low relative permittivities). The above has been documented in published work for $\text{LiAsF}_6 + 18\text{C}_6$ in 1,2-dimethoxyethane (Richman et al., 1985), for $\text{NaClO}_4 + 18\text{C}_6$ in 1,2-dimethoxyethane (Chen et al., 1984), $\text{LiAsF}_6 + 12\text{C}_4$ in 1,2-dimethoxyethane (Richman et al., 1985), $\text{LiClO}_4 + 18\text{C}_6$ in 1,2-dimethoxyethane (Farber et al., 1981) and for both LiAsF_6 and $\text{LiClO}_4 +$ various macrocycles in 1,3-Dioxolane (Xu et al., 1988).

Returning our attention to solvents of intermediate static permittivity but relatively low donor numbers (Gutmann, 1978) such as acetonitrile ($\epsilon_{25} = 36.0$, $\text{DN} = 14.1$) and nitromethane ($\epsilon_{25} = 35.9$, $\text{DN} = 2.7$), the question is whether or not the findings by NMR are more correctly attributed to anion association and are thus an extension of what occurs in very low relative permittivity solvents such as 1,2-dimethoxyethane ($\epsilon_{25} = 7.20$, $\text{DN} = 20$). In other words, near future research will have to dismiss or confirm the doubt that in solvents of intermediate relative permittivity, but low donor

number, there is competition for the first coordination sphere of the cation. The cation might find itself in two molecular configurations MeX and $(\text{MeC})^+$ (or $(\text{MeC})^+ + \text{MeC}^+ + \text{Me}^+ \dots \text{C}$, when these forms are present). Some recent studies for $\text{Na}^+ + 18\text{C}6$ (Rodriguez et al., 1989) in acetonitrile using NaClO_4 , NaSCN and NaBO_4 have confirmed the Eigen-Winkler mechanism without any indication of anion interference even though IR spectra show specific interaction of the SCN^- anion with Na^+ , even at $c = 0.03 \text{ M}$. Other systems will have to be investigated, especially in cases where the anion can effectively compete with the macrocycle (as expressed by comparable formation constants K_{MeX} and K_{MeC^+}).

c) Futurism

Once the above current problem has been sorted out there will be many other aspects of these reaction mechanisms that will require attention, possibly using new experimental techniques, hence the use of the term futurism. Since every macrocycle is different in some respects from its congeners and since two solvents with nearly identical donor numbers and relative permittivities can have very different reactivities, rate studies of complexation continue to turn up subtle differences that defy generalization like the ones attempted above for high, intermediate and low relative permittivity solvents.

For instance, whether the rearrangement of the ligand to accommodate the cation or desolvation of the latter is the rate limiting step in the complexation process seems to depend heavily on the particular choice of the

solvent rather than simply on the relative permittivity of the medium. Petrucci, Adamic and Eyring (1986) proved that in DMF the ligand rearrangement is the rate determining step of the forward complexation process. However, for the solvent water (presumably because of its larger solvation affinity toward the cation) removal of the solvent is the rate determining step (Rodriguez et al., 1978). Presence of other binding atoms in the ring structure alters dramatically the role of the latter in the complexation process. For the case of nitrogen and the cryptands, rotation of the lone electron pairs of the nitrogen atoms assumes an important role in both ligand isomerization and cation binding processes. This is discussed in detail with literature references in section 5 below.

The effect of chains or tails attached to macrocycle rings upon complexation reactions has been addressed for Na^+ reacting with a monoazo 15C5-tailed macrocycle in methanol (Echegoyen et al., 1987). However, it would be dangerous to generalize regarding the kinetic properties of "lariat ethers" on the basis of this one study and more kinetic studies need to be done with tailed macrocycles.

The role of other binding atoms such as sulfur in the macrocycle in the reaction kinetics of both isomerization of the macrocycle and of complexation has not been studied extensively as yet.

It has been argued that some cations such as Ag^+ may reside outside the ligand ring structure when sulfur is one of the binding atoms of the ring (Izatt et al., 1981). This question also deserves the attention of reaction kineticists.

Similarly, the dynamic behavior of the solvent adjacent to or solvating the macrocycle has not been fully addressed. For studies of non-macrocyclics such as proteins in aqueous solutions microwave and UHF dielectric relaxation spectra have been reported with the claim that two types of water molecules, surface and bulk, exist with definitely different behavior, bulk water showing a decay time of the polarization at about 9 picoseconds, whereas the surface bound water shows a band at about 1 nanosecond (Grant et al., 1978). No similar work has been done on macrocycles except for a pilot study of liquid 15C5 reporting a Cole-Davidson dielectric distribution with an average relaxation time of ~ 100 picoseconds for the crown ether containing traces of water (Delsignore et al., 1983). More work, involving also nonaqueous solvents, appears necessary, focusing on the relaxation dynamics of the solvent. Novel technologies such as pulsed-laser time resolved spectrophotometry, overlapping microwave dielectric relaxation down to the picosecond time scale but able to break through into the femtosecond range, appears to be the developing new technology for this application.

4. Crown Ether Kinetic Studies

In the many cation-crown ether systems we have examined so far by ultrasonic absorption methods in aqueous and nonaqueous media the Eigen-Winkler reaction mechanism, eq. 3, adequately describes the kinetic data. In the first step an outer-sphere complex is formed involving some rearrangement of the macrocyclic ligand and partial cation desolvation. The third step may be rate limiting either by desolvation (as in aqueous

solution) or ligand rearrangement (as in dimethylformamide). When the more rigid dibenzo-18-crown-6 ligand is substituted for 18-crown-6 with K^+ in DMF, rate limiting ligand rearrangement becomes particularly apparent (Wallace et al., 1985).

The rate determining step for the complexation of Ag^+ by 18-crown-6 (18C6) in dimethylformamide (DMF) is the final ligand rearrangement around the cation (Petrucci, Adamic, and Eyring, 1986). This was proven for silver by reacting Ag^+ with dibenzo-18C6, a more rigid ligand than 18C6. The anion is at times competitive with the macrocyclic ligand for a site in the first coordination sphere of the cation. Dramatic differences in both relaxation frequencies and maxima in the excess sound absorption per wavelength were found by reacting $AgNO_3$ instead of $AgClO_4$ and $TlNO_3$ instead of $TlClO_4$ with 18C6 in DMF. $AgNO_3$ in DMF with no crown ether present produced an ultrasonic relaxation indicating interaction between Ag^+ and NO_3^- ions.

Dimethylformamide has a relative permittivity of 36.71 at 25°C and a Gutmann donor number of 26.6 and acceptor number of 16.0. Tetrahydrofuran (THF), on the other hand, has a relative permittivity of only 7.39 and donor and acceptor numbers of 20.0 and 8.0, respectively.

Microwave dielectric relaxation spectra of NaNCS in THF in the frequency range ~ 1 GHz to 90 GHz (1 GHz = 1 kHz = 10^9 Hz) showed large differences when 18C6 in the molar ratio ($[18C6]/[Na^+] = 1$) was added to NaNCS in THF (Xu, Eyring, and Petrucci, 1986). Previous infrared work (Saar

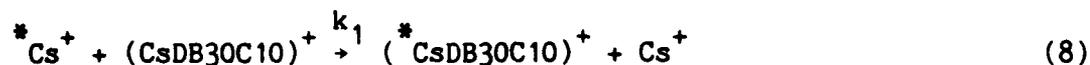
and Petrucci, 1986) had shown that the IR spectra of the "CN stretch" of the NCS^- ion is composed of three bands, one centered at 2057 cm^{-1} , another at 2043 cm^{-1} , and the third comparatively small band at 2074 cm^{-1} . These bands were attributed to NaNCS ion pairs, $(\text{NaNCS})_2$ dimers, and probably triple ions at the respective frequencies of 2057, 2043, and 2074 cm^{-1} . The addition of 18C6 in molar ratio ($[\text{18C6}]/[\text{Na}^+] \approx 1$) alters dramatically the IR spectral envelope which then can be interpreted by only one Gaussian-Lorentzian band centered at 2060 cm^{-1} . Both the microwave dielectric spectra and the IR spectra were attributed to a residual complex ion-pair Na^+C , NCS^- , wherein the Na^+ , imbedded in the cavity of the 18C6, still is paired to the NCS^- ion.

The contrast between 18C6 complexing Ag^+ in DMF and Na^+ in THF is striking because in the latter solvent there is so much evidence of macrocycle, anion, and solvent all competing for the first coordination sphere sites of the cation. The notion of a rate limiting dissociation of a solvent molecule from the first coordination sphere of a cation that so many kineticists acquired from aqueous solution studies becomes quite irrelevant in low relative permittivity, low donor number solvents. A specific example of the breakdown of the high charge density explanation for rate limiting desolvation is the speedier complexation of Ba^{2+} than of K^+ by 18C6 in DMF (Wallace, Eyring, and Petrucci, 1984). In contrast, in aqueous solution Ba^{2+} reacts slower with 18C6 than does K^+ .

If the cation undergoing complexation has a nonspherical shape, complexation by a crown ether can be very slow, and solvation forces can become irrelevant. For instance, Fux and coworkers (1985) found that the reaction of UO_2^{2+} with 18C6 in propylene carbonate is so sluggish that it can be studied conveniently by stopped-flow spectrophotometry. In a similar vein, Rebek and coworkers (1986) found that elongated species such as $\text{Hg}(\text{CN})_2$ and $\text{Hg}(\text{CF}_3)_2$ are also very slowly complexed by 18C6 in nonaqueous solutions. The macrocycle slowly assumes a high energy conformation that permits the substrate to enter the ring.

Dibenzo-30-crown-10, the crown with which Chock (1972) first started crown ether complexation kinetic studies, is still one of the most interesting ligands of this class. It is large enough and also flexible enough to twist around a metal ion of the appropriate size like the seam on a baseball as evidenced by X-ray crystallographic studies of potassium (Bush and Truter, 1972) and rubidium ion (Haskek, Huml, and Hlavata, 1979) complexes of DB30C10. Shamispur and Popov (1988) have used cesium-133 NMR to study the exchange kinetics of the Cs^+ complex with DB30C10 in nitromethane, acetonitrile, propylene carbonate and methanol solutions. Their NMR data showed that the complexed Cs^+ ion is largely isolated from the surrounding solvent molecules thus indicating the same "wrap around" conformation of the complex exists in the liquid phase as had been reported in crystal studies.

As we noted earlier, NMR kinetic data for these systems indicate that the transition of cations from a solvated to a complexed condition occurs by two possible mechanisms



and



The relative importance of the two processes can be deduced from a plot of $[\tau[\text{Cs}^+]_{\text{tot}}]^{-1}$ versus $[\text{Cs}^+]_{\text{free}}^{-1}$ that follows from the equation

$$\tau^{-1} = [\text{Cs}^+]_{\text{tot}} (k_1 + k_{-2}[\text{Cs}^+]_{\text{free}}^{-1}) \quad (10)$$

where τ is the mean lifetime of the cesium ion. A full cesium-133 NMR line shape analysis of solutions with [crown]/[Cs⁺] mole ratios of less than unity yields the mean lifetime, τ , for the exchange processes.

Shamsipur and Popov (1988) found that in nitromethane the associative-dissociative exchange mechanism, eq. 9, dominates for Cs⁺ and DB3OC10. In the other three solvents the bimolecular exchange mechanism, eq. 8, dominates at temperatures below -10°C. Above -10°C the dissociative pathway takes over as the more important one in propylene carbonate and methanol solutions. (Exchange is so rapid in acetonitrile above -10°C that mean lifetime measurements are precluded.)

Replacement of two of the oxygen atoms in the 18C6 ring to give 1,10-diaza-18C6 (denoted C22) produces a ligand that binds Cs^+ weakly in nitromethane. An NMR study of this system (Shamsipur and Popov, 1987) showed that a bimolecular exchange mechanism predominates in contrast to the associative-dissociative mechanism found above for Cs^+ and DB30C10 in nitromethane. One cannot predict from the solvent donor number alone or from the identity of the cation whether the mechanism of exchange between solvated and complexed Cs^+ sites will be dissociative or bimolecular. Properties of the crown ether such as ring size and the comparative hardness or softness of all the interacting species must also be important factors in determining which mechanism predominates.

Continuing our focus on the kinetics of Cs^+ complexation by crown ethers, Strasser, Shamsipur, and Popov (1985) found that the mechanism of exchange between solvated and complexed sites for Cs^+ reacting with DB21C7 and DB24C8 in both acetone and methanol is predominantly bimolecular rather than dissociative. Comparing these results with their kinetic studies of Na^+ and K^+ complexation by crown ethers (Strasser and Popov, 1985a; Strasser and Popov, 1985b; Strasser, Hallenga, and Popov, 1985; Schmidt and Popov, 1983), they speculated that the greater tendency for complexation of Cs^+ to proceed by a bimolecular mechanism than in the case of Na^+ and K^+ may be because the larger Cs^+ ion has a lower charge density and a consequent

smaller electrostatic repulsion of cations in the transition state of the bimolecular exchange process.

The competition between exchange mechanisms is complicated by the choice of solvent just as much for sodium ion as it is for cesium. In at least one case the dominance of one mechanism over the other is dictated by the sodium salt concentration: When sodium tetrphenylborate is complexed by DB24C8 in nitromethane, the exchange mechanism is primarily bimolecular for high sodium concentrations and predominantly associative-dissociative for lower sodium concentrations (Delville, Stover, and Detellier, 1985). The bimolecular cation interchange mechanism is predominant for monobenzocrown-15-crown-5 (B15C5) complexing sodium tetrphenylborate in nitromethane with evidence for a slow unimolecular process developing at low sodium concentrations (Brière and Detellier, 1987). For Na^+ complexing with 18C6 in methanol the exchange mechanism is unimolecular (dissociative) whereas in propylene carbonate it is bimolecular (Strasser and Popov, 1985).

Strasser, Hallenga, and Popov (1985) generalized that large organic counterions slow the exchange between solvated and complexed sites for Na^+ ions reacting with 18C6 in tetrahydrofuran. Workers in this same laboratory later showed that sodium pentamethylcyclopentadienide undergoes fast exchange in the presence of 18C6, either diastereoisomer of dicyclohexano-18-crown-6 (DC18C6), DB18C6, diaza-18-crown-6 (DA18C6), and dithia-18-crown-6 (DT18C6) in tetrahydrofuran (Szczygiel et al., 1987).

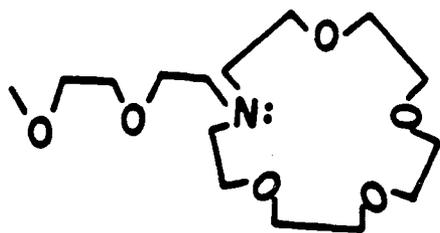
In the case of the DA18C6-NaSCN system in THF Szczygiel et al. found both exchange mechanisms: The dissociative mechanism dominates above $\sim -20^\circ\text{C}$

while the bimolecular mechanism holds sway below $\sim -35^{\circ}\text{C}$. They commented that the temperature dependence of the mechanism could be due to a temperature dependence of complexation constants, to the temperature dependence of the solvent relative permittivity that could affect ion-pair formation, to a temperature dependence of ligand conformation, or a combination of two or more of these factors.

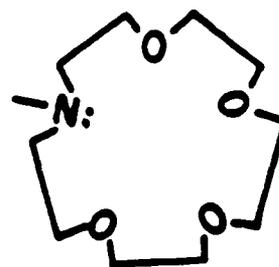
In a similar NMR study of the kinetics of site exchange for Na^+ complexing with 18C6 in propylene carbonate, acetonitrile, pyridine, and acetone Graves and Detellier (1988) found the two exchange mechanisms to be in competition in the first three solvents, but almost exclusively unimolecular (dissociative) exchange occurs in acetone. No simple relationship between Gutmann (1978) donor numbers of the solvents and activation parameters ΔG^{\ddagger} or ΔH^{\ddagger} could be demonstrated suggesting that "several factors, including conformational rearrangement of the ligand and reorganization of the solvent cage, contribute to the barrier of exchange."

Inconsistencies in conclusions drawn from NMR and ultrasonic absorption data about the mechanism of decomplexation of alkali metal cations by crown ethers should encourage further ultrasonic absorption studies in which the low temperature conditions that yield NMR evidence for bimolecular exchange mechanisms are matched. Then if the new ultrasonic data require no different mechanistic interpretation than the Eigen-Winkler mechanism that works so well near room temperature, it will be time to look for new explanations for the discrepancy.

Because of the limited availability of the compounds very few rate studies have been conducted of complexation reactions involving macrocycles with tails. Consider, for example, the tailed or "lariat" crown ethers containing a nitrogen atom in the ring as in (a) and (b) depicted below.



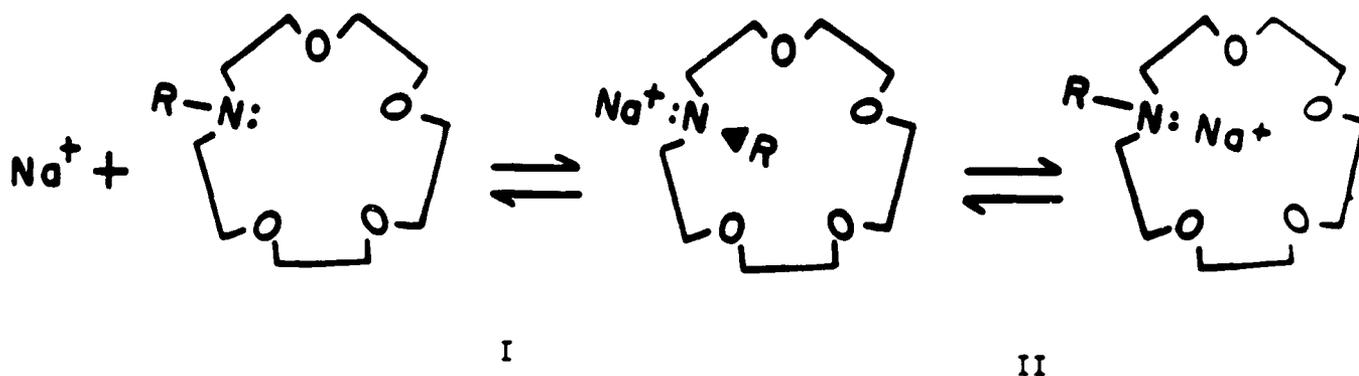
(a)

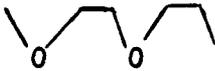


(b)

Macrocycles such as valinomycin at the surface of biological cells are thought to interact selectively with sodium ion, binding to Na^+ after stripping away the ion's water of solvation. The cation then, imbedded in the cavity of the macrocycle and "dressed" with a hydrophobic shell (the polar groups pointing inward, toward Na^+), can be transported through the hydrophobic membrane, to be subsequently released into the aqueous medium of the biological cell where the cation is rehydrated. What this model fails to consider is the possibility of a competition for the Na^+ cation between the macrocycle and a neighboring polar group, attached perhaps to a protein of the cell membrane. Crown (a) is a primitive model suitable for a study of this possible competitive interaction. Crown ether (b), on the other hand, is nearly the same model ligand lacking only the competing tail.

These compounds were synthesized and studied with sodium ion in methanol by NMR techniques (Echegoyen *et al.*, 1984). Subsequently, an ultrasonic absorption study was carried out of sodium ion reacting with (a) and (b) in methanol that produced some rather surprising conclusions (Echegoyen *et al.*, 1987). Each of these compounds when dissolved in methanol with NaClO_4 also present gives rise to excess ultrasonic absorption at two well separated frequencies in the 0.5 to 500 MHz frequency range. Both relaxations for each compound are concentration dependent and may be interpreted in terms of the Eigen-Winkler scheme (referred to as processes I and II below):



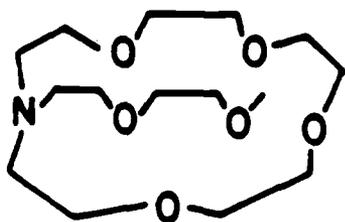
where for (a) R denotes  and for (b) R denotes a methyl group. The rate determining step for process (I) is the rotation of the nitrogen lone electron pair to an exo-configuration. The isomeric relaxation of (a) [i.e., a concentration independent relaxation with no NaClO_4 present] in methanol occurs at ~100 MHz which corresponds closely in frequency to process (I) above (although the isomerization is concentration independent whereas (I) is concentration dependent). The rate determining step of the

overall complexation process corresponds to the entrance of Na^+ into the cavity, depicted above by process (II). The surprising finding is that (b) dissolved in methanol with NaClO_4 also gives rise to two detectable relaxation processes that can be described by the above Eigen-Winkler mechanism. The higher frequency relaxation occurs, however, at ~ 40 MHz (instead of the ~ 100 MHz found for (a)). Again there is a concentration dependence in the two relaxations involving (b) plus NaClO_4 , and again one notes a rough correspondence in frequencies between the ~ 40 MHz relaxation of (b) plus NaClO_4 and the isomeric relaxation of (b) dissolved alone in methanol. In other words, the presence or absence of the lariat ether side chain has no detectable impact on the mechanism of Na^+ complexation by these crown ethers even though the stability of the complex with Na^+ is greater in the case of (a) than of (b). Thus it appears that the lariat side chain enhances the first forward specific rate of complexation with the rotation of the nitrogen atom in (a) being faster than in (b). (The stability constant for (a) reacting with Na^+ is about three times as large as that for (b) plus Na^+ in methanol.)

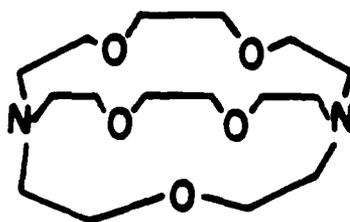
The isomerization of (a) and (b) in methanol mentioned above has been more thoroughly characterized by ultrasonic absorption measurements covering a 0.05 to 0.5 M concentration range, a 0.5 to ~ 400 MHz frequency range, and a -7 to 25°C temperature range (Gokel *et al.*, 1987). This additional information permits an interesting comparison of thermodynamic and activation parameters for the isomerization of these two crown ethers in

methanol and generally confirms the conclusions drawn by Echegoyen et al., 1987.

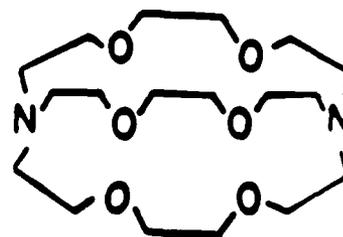
When the molecule (a) is redrawn in the fashion shown below it is seen to bear an interesting similarity to cryptand 221 (c) and cryptand 222 (d).



(a)

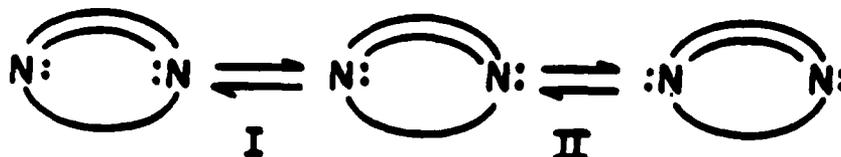


(c)



(d)

Ultrasonic relaxation spectra of (d) in methanol, methylcellosolve, 1,2-dimethoxyethane (1,2-DME) and propylene carbonate (PC) had been interpreted (Eggers et al., 1987) in terms of the endo-endo ⇌ endo-exo ⇌ exo-exo sequence:

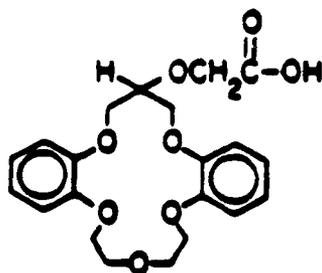


where the term "endo" refers to the two lone electron pairs facing the interior of the ring.

In protic solvents such as methanol and methylcellosolve, HO-CH₂-CH₂-OCH₃, both processes are observable whereas in the aprotic solvents propylene carbonate and 1,2-DME, CH₃O-CH₂-CH₂-OCH₃, only one of the two processes above is detectable. This difference may be related to the

interaction of the proton of the protic solvent with the nitrogen causing enough exo-exo configuration to be present that both processes (I) and (II) are observable. It was this work on the conformational change in a cryptand that led to the idea that the rate determining step for process (I) in the complexation of Na^+ by the lariat ether is the rotation of the bridgehead nitrogen atom.

In another type of crown ether the sidearm has the possibility of being titrated from the neutral to the charged state. An example is the molecule (e) whose kinetics of the complexation of Na^+ in 99% (w/w) methanol-water

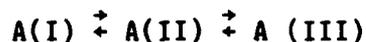


(e)

were examined with the electric field jump relaxation technique (Adamic et al., 1986). The specific rate of complex ion formation is nearly diffusion controlled and indicates significant interaction between the sidearm and Na^+ prior to the desolvation of the cation by the polyether ring.

5. Cryptand and Cryptate Kinetic Studies

As we have noted above, the 222 cryptand undergoes isomeric relaxations on the ultrasonic time scale in solvents such as methanol, methylcellosolve and propylene carbonate (Eggers et al., 1987). Cryptand 222 is also well known to form cryptates with metal cations on a stopped-flow [millisecond] time scale (Loyola, Pizer, and Wilkins, 1977; Bemtgen et al., 1984; Cox, Garcia-Rosas, and Schneider, 1980, 1982; Cox et al., 1984; Cox et al., 1986; Kitano et al., 1986). The molecular dynamics of the alkali metal ion 222 cryptates in propylene carbonate have also been explored by ultrasonic measurements on a much faster time scale (Schneider et al., 1988). A high frequency relaxation is detected at around 130 MHz at 25°C. A lower frequency relaxation (2 MHz to 25 MHz at 25°C) decreases in frequency in the order $\text{Na}^+ > \text{K}^+ > \text{Rb}^+ \gg \text{Cs}^+$. The relaxations are interpreted by a scheme of the form

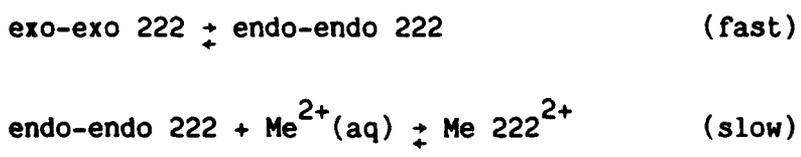


probably involving a rotation of the two nitrogen atoms of the cryptand which coordinate the metal cation (with the cation always bound to the cryptand). When the cation diameter exceeds the ligand cavity size in the case of Cs^+ the rotational process becomes more difficult and the lower relaxation frequency declines steeply.

It is interesting to compare three recent kinetic studies of cryptate formation kinetics that were all published in the same year, 1986. Cox et

al. (1986) used a conductometric stopped-flow technique to explore the kinetics of Ag^+ and Pb^{2+} reacting with several different cryptands in dimethyl sulfoxide. These ions exhibit covalency in their bonding to cryptands that makes their complexes more stable than those formed by alkali and alkaline earth ions of similar ionic radii. They observed the usual strong correlation of variations in stability constants with dissociation rate constants. There was also evidence for the complexed Pb^{2+} ion being outside the ligand cavity. This confirms "the ability of Pb^{2+} to form quite stable complexes without the stabilization conferred by complexation within a cavity containing appropriately oriented donor atoms." However, no experimental evidence was presented for multiple steps in the formation-dissociation complexation equilibrium.

Kitano et al. (1986) also used the conductometric stopped-flow method to study the rate of complexation of Ca^{2+} , Sr^{2+} and Ba^{2+} by cryptand 222 in water. These concentration-jump relaxation method (small perturbation) experiments permitted the observation of two distinct relaxation steps. Assuming that the $exo-exo \rightleftharpoons endo-endo$ equilibrium of the cryptand 222 was too fast for their observation, the authors interpreted their results in terms of the mechanism





The last two reaction steps were those presumed to be detected by the concentration jump experiment. The slowest or rate limiting step the authors described as "the capture of a metal ion into the cavity followed by a strong binding of the metal ion with reaction sites of the cavity."

Shamsipur and Popov (1986) used lithium-7 NMR to examine the kinetics of Li^+ ion complexation by cryptands 222 and 221 in acetonitrile, propylene carbonate and acetone solutions. As in the NMR studies of crown ethers considered above, these authors described the complexation process as a competition between the dissociative-associative mechanism, eq. 5, and the bimolecular exchange mechanism, eq. 6. They found that the Li^+ -cryptand 222 combination undergoes decomplexation by the dissociative mechanism in all three solvents whereas the exchange mechanism prevails for the Li^+ -cryptand 221 system in acetonitrile and propylene carbonate. The authors speculated that the greater rigidity of the 221 structure more easily accommodates the simultaneous arrival of a free cation and departure of the complexed cation as is required for the transition state of the bimolecular mechanism. The more flexible 222 cryptand could wrap itself around the Li^+ ion so well that the only avenue to exchange between solvated and complexed sites would be the dissociative mechanism.

In these three 1986 papers each picture of cation-cryptand complexation is greatly influenced by the different experimental technique used in that

particular laboratory. One of these sample systems ought to be reexamined in a collaboration by these three (and possibly other) laboratories with a view to developing a coherent kinetic picture of one cryptate system in which the disharmonies of these three pictures are eliminated.

6. Further Information Obtained by Other Methods

It is clearly an advantage, in any kinetic study, to have collateral information acquired with structural tools indicating the structure and possibly the amount of the species present in equilibrium. Vibrational spectrometry, both Raman and infrared, is one of the most useful methods for such a parallel study. Because of the time range (approximately 10^{-13} to 10^{-12} secs) involved in vibrational spectra, no species can escape detection if present in a given system provided that its relative concentration is sizeable compared to concentrations of other species (1% and larger), and provided all the species have stable configurations in dynamic equilibrium with each other.

In parallel Raman and ultrasonic studies (Maynard et al., 1984) the relative stabilities of Na^+NCS^- and K^+NCS^- and of NaC^+ and KC^+ (where C denotes 18C6) in DMF were determined. It was found that the crown ether could exclude the thiocyanate ion from the first coordination sphere of the cations. This result was important since it accounted for the indifference of the molecular relaxation phenomena determined by ultrasonic techniques to the nature of the anion present in the sample system.

Another illustration of the fruitfulness of combining structural and kinetic techniques in the study of macrocycle systems was a microwave dielectric relaxation-infrared spectroscopic study of NaSCN in THF and of NaSCN + 18C6 in THF (Xu et al., 1986). It was shown that the crown ether could prevent the thiocyanate anion from contacting the cation although the rotating, relaxing entity studied by microwave techniques was NaC^+ , NCS^- , namely an ion pair with the cation imbedded in the cavity of the macrocycle. The interpretation of the microwave data without access to the infrared spectroscopic data would have necessitated some hazardous speculation.

Mosier-Boss and Popov (1985) were able to provide detailed quantitative information on the self-association of acetonitrile and its two stages of interaction with 18C6 in the inert solvent CCl_4 . Although they relied heavily on NMR techniques, the foundation of their work lay in the study of the alteration of the IR bands at $2100\text{-}2300\text{ cm}^{-1}$ related to the CN stretch of CH_3CN when this compound was complexed to 18C6. A model of the mode of association through the $-\text{CH}_3$, interacting with the oxygens of the macrocycle was proposed. The same study, deprived of the infrared background, would not have achieved the same level of insight.

The above three studies illustrate the necessity of a multimethod attack to decipher solution phase dynamic data in a nonspeculative fashion. Ultrasonic absorption can tell us that a rapid equilibrium exists between species present in a sample liquid, but it cannot tell us the identity of the chemical species present in the equilibrium.

7. Future Directions

Many more ultrasonic absorption, NMR, and stopped-flow kinetic studies of macrocyclic-cation systems in nonaqueous solvents will certainly be carried out with larger and larger macrocycles and more exotic cations in a variety of nonaqueous solvents. It is even reasonable to expect some surprises when this work lurches into the more unusual solvents such as polymeric solids typified by poly(ethylene oxide) and the various room temperature "molten salts" (Rhinebarger, Rovang, and Popov, 1984).

There are at least two other exciting ways in which the present story is likely to change in the next decade. The wider availability of supercomputers and of ultra short light pulses from lasers will be the instruments of these changes.

The idea of using big computers to simulate reaction dynamics in liquid solutions is certainly not a new one (see, for example, Adelman, 1985). Because they have dealt with lithium ion that is likely to be of interest to readers of the present chapter, we will consider the recent theoretical work of Banerjee, Simons and coworkers (Banerjee, Shepard and Simons 1980; Banerjee and Simons, 1981; and Banerjee et al., 1987) that previews the likely future impact of big computers on macrocycle rate studies. These workers have probed the equilibrium properties of ions and ion-pair hydration using quantum electronic structure and Monte-Carlo methods. They examined (a) the structure of hydration shells of the individual ions $\text{NO}_2^+(\text{H}_2\text{O})_n$ and $\text{Li}^+(\text{H}_2\text{O})_n$ as well as of the complex $\text{NO}_2^-:\text{Li}^+(\text{H}_2\text{O})_n$, (b) the changes in hydration shells during complex formation, and (c) changes in

potential energy and mapping of potential barriers for chemically important pathways toward complex formation.

They found the first hydration shell of $\text{NO}_2^-(\text{H}_2\text{O})_n$ to be highly anisotropic with the second and third hydration shells forming even before the first shell is completely closed. Thus inner hydration shells may have "weak spots" susceptible to attack by an approaching reactant.

Water molecules between the ions in the solvent separated ion-pair $\text{NO}_2^-\text{Li}^+(\text{H}_2\text{O})_n[\overset{\circ}{\text{R}}\text{5}\overset{\circ}{\text{A}}]$ achieve orientations favorable to both ions whereas for the intimate ion-pair $[\overset{\circ}{\text{R}}\text{3}\overset{\circ}{\text{A}}]$ the hydration shells are very anisotropic. Again the second and third hydration shells form before the first is completely closed. The solvent separated and intimate ion pairs both have a potential minimum. The solvent separated ion-pair is more stable than the intimate ion-pair by $\sim 20 \text{ kcal mol}^{-1}$ with a $\sim 25 \text{ kcal mol}^{-1}$ potential energy barrier above the solvent separated ion-pair cluster. This potential barrier may slow the rearrangement of the solvent separated ion-pair to an intimate ion-pair.

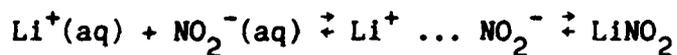
Since particular inner sphere water molecules are more weakly bound to the NO_2^- anion than certain other second hydration shell water molecules, these authors postulate that a spherical cation such as Li^+ bearing down on the nonspherical $\text{NO}_2^-(\text{aq})$ will experience more favorable energetics by approaching $\text{NO}_2^-(\text{aq})$ at its more negative oxygen end. As soon as the outer

sphere ion pair forms, a reorientation permits the cation to penetrate the "weak spot" in the NO_2^- hydration shell on the nitrogen end. Subsequent reorientation of the resulting intimate ion pair will produce the

energetically more favorable $[\text{N} \begin{array}{l} \text{O}^- \\ \text{O} \end{array} \text{Li}^+]$ conformation. Conceivably, these

successive stages could show up as measurable volume changes using ultrasonic absorption techniques.

Practical limitations such as computer memory size and the high cost of lengthy calculations encourage theoreticians to investigate low molecular weight solute species with comparatively few electrons in their molecular dynamics computations on liquid systems. Experimentalists, on the other hand, have customarily selected liquid systems for their thermodynamic and kinetic investigations either on the basis of technological ramifications or to enhance fundamental scientific understanding but certainly with little if any prejudice in favor of low molecular weight (i.e. low number of electrons) solute species. Thus, for example, there are no stability constants in the literature for the complexation of aqueous lithium ion by the nitrite ion nor are there any reports of kinetic studies of this complexation reaction



- 5 -

Kineticists interested in macrocycles who wish to have synergistic interactions with theoreticians in the near future should focus more effort on lithium ion complexation by the simplest acyclic and cyclic ligands (resembling 12-crown-4) that have comparatively few total electrons and are thus more propitious for concurrent theoretical investigation.

Another major opportunity for applying new methods to the study of solution macrocycle kinetics involves the use of picosecond, visible wavelength laser pulses to investigate solvation dynamics. Maroncelli and Fleming (1987) and Simon and Xie (1987) have published pulse laser studies of nonmacrocylic liquid solutions. Their studies nevertheless suggest the direction that this sort of work will take. After a short (picosecond) laser pulse excitation of a solute species from its ground to its first excited singlet electronic state, the fluorescence spectrum of the solute probe species red shifts with time as the surrounding solvent molecules reequilibrate to the new, excited state charge distribution of the solute probe. Theories based on a dielectric continuum model of the solvent turn out to explain inadequately the experimental nonexponential time dependence of the solvent reequilibration. Molecular aspects of the solvation dynamics will emerge from this type of study. The time scale examined is that between a few tenths of a picosecond and ~ 1.5 ns. Simon and Xie (1987) have shown, for instance, that solvent coordination around a chromium carbonyl solute probe can occur in under 0.5 ps. Coumarin dyes resembling the fluorescent probe employed by Maroncelli and Fleming (1987) have already (Stinson, 1987) been incorporated into cryptands. Thus the time is ripe for an extension of these solvation dynamics studies into macrocyclic solutions.

8. Acknowledgment

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Figure 1. Debye plot of the ultrasonic absorption spectrum of 0.125 mol dm^{-3} LiClO_4 and 0.125 mol dm^{-3} 18-crown-6 dissolved in dry propylene carbonate at 298 K. Data points below 10 MHz were obtained with an ultrasonic resonator. The rest of the data points were obtained by the laser Debye-Sears and the pulse methods. The relaxation amplitudes, A, relaxation frequencies, f, and background, B, deduced from these data are: $A_I = 281$, $f_I = 1.21$ MHz, $A_{II} = 166.4$, $f_{II} = 2.14$ MHz, and $B = 56.8$.

