Macrocyclic Chemistry in the Gas Phase: Intrinsic Cation Affinities and Complexation Rates for Alkali Metal Cation Complexes of Crown Ethers and Glymes

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Abstract: Reactions of 12-crown-4, 15-crown-5, 18-crown-6, and 21-crown-7, as well as the acyclic analogs triglyme, tetraglyme, and penta(ethylene glycol), with Li^+, Na^+, K^+, Rb^+, and Cs^+, are observed and characterized using Fourier transform ion cyclotron resonance mass spectrometry (FTICR/MS) and tandem quadrupole mass spectrometry in the gas phase to obtain information on intrinsic host–guest interactions in the absence of the complicating effects of solvation. Radiatively stabilized attachment of the cations to the ligands is a rapid process, with rates in some cases a factor of 2 or more times the Langevin collision rate. The attachment efficiencies increase linearly with cation charge density, suggesting that attachment involves charge-induced rearrangement of the ligands to adopt favorable binding conformations. Attachment is more efficient, and more strongly dependent on charge density, for the cyclic ligands than for their acyclic counterparts. Metal–ligand complexes also undergo reaction with a second ligand to form 1:2 metal–ligand complexes, or "sandwiches". The efficiencies of crown sandwich formation are strongly dependent on the ratio of cation radius to binding cavity radius: when the ratio is less than one, the efficiencies are too low to measure, but they become measurable at a ratio of 1:1 and increase by about 4 orders of magnitude as the ratio increases to about 1.25:1. At higher ratio values, efficiencies fall off slowly, probably due to decreasing cation charge density. The relative cation affinities of the various ligands are compared both using collision-induced dissociation "kinetic" methods, with the tandem quadrupole, and using "bracketing" cation transfer reactions in the FTICR. The tandem quadrupole results are in some cases dependent on the means of producing the 1:2 metal–ligand complexes, and in some cases they do not agree with the FTICR results. The two methods are compared and reasons for the discrepancies are discussed. We favor the FTICR results, which indicate that proton and alkali cation affinities increase with an increase in the number of oxygen donor atoms in the crowns. Equilibria observed in metal exchange reactions between 18-crown-6 and 21-crown-7 were found to always lie on the side of the cation bound to the larger ligand, but K^+ has the smallest equilibrium constant of any of the alkali metals, reflecting the excellent size match between K^+ and 18-crown-6.

Introduction

Since their discovery by Pedersen[1,2] in 1967, crown ethers have generated a tremendous amount of interest because of their ability to selectively bind guests such as alkali metal ions, and because they serve as simple models for selective host–guest binding. The importance of crown chemistry is illustrated by a recent review,[3] which included nearly 1200 references on the chemistry of crowns and related compounds, primarily dealing with work done since 1985. Nearly all of this work has been carried out in condensed media, and thus includes effects arising from solvation and from counterion association.

These complicating effects can obscure the fundamental factors underlying and controlling the binding process. A review of the literature[3] reveals a large spread of values in log *K* for complex formation, even in a given solvent. The diversity of anions used in the different studies and the variety of methods used in making the measurements also undoubtedly contribute to the wide range of values. While general trends are clear from the solution data, details are obscured by the uncertainties imposed by the solvent/counterion environment.

As another example, both quantum[4,5] and molecular mechanical[6] calculations indicate that the Na^+ complex of 18-crown-6 is intrinsically more stable than the K^+ complex. On the other hand, the order of complexation selectivity as determined from the log *K* values[3,7] is generally $K^+ > Rb^+ > Cs^+ > Na^+ > Li^+$, in both polar solvents, such as water or methanol, and nonpolar solvents, such as chloroform or tetrahydrofuran. This apparent contradiction is rationalized by noting that in most solvents the solvation energy for Na^+ is much greater than that for K^+. Because the cation must be at least partially desolvated in order for complex formation to occur, the balance between solvation energies and intrinsic complex stabilities is believed to account for the higher formation constants for the K^+ complex. This widely-accepted explanation has never been directly tested through experiment. Comparisons between polar and nonpolar solvents alone cannot suffice, because of the accompanying variations in the extent of ion pairing.

The correlation between binding affinities and the match of the cation size to the size of the crown binding cavity, noticed[1,2,8] and quantified[9,10] soon after the initial work on crown ethers, has led to a "size match" model for explaining the binding affinities of the crowns for guest cations, which works remarkably well in many cases. However, for simple homologous crown ethers, the model is less successful: in methanol solution, it appears that K^+ has the highest stability constant for all the crowns, regardless of hole size, and that 18-crown-6 has the largest stability constants

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for most cations, regardless of cation size or geometry.[11] As Gokel has noted,[11] in addition to size match, it is necessary to consider the solvation enthalpies and entropies of the cations and ligands, the number of donor atoms participating in the binding, and conformational differences between bound and unbound ligands.

Gas-phase experiments, conducted *in the absence of either solvent or counterion species*, provide a powerful opportunity to probe the intrinsic fundamentals of crown–cation binding. Early proton affinity studies[12,13] established that multiple proton–oxygen interactions contribute to stabilization of the protonated species and correspondingly high gas-phase basicities for crown ethers. Later studies involving molecular guests[14,15] such as H_3O^+ and NH_4^+ also highlighted the importance of multiple hydrogen-bonding interactions between the guests and crown ether ligands.

The fragmentation of crown ethers under electron impact ionization[16] has been shown to occur primarily through losses of the $[C_2H_4O]$ structural unit. Crowns have been shown to undergo bond-insertion reactions with Fe^+ and Co^+, and interestingly, a wider range of products was observed for the crown ethers than for the corresponding acyclic ligands.[17,18] Fast atom bombardment (FAB) and field and plasma desorption mass spectrometry have been successfully used to observe crown complexes of alkali metal cations[19–23] and diazonium ions[24] in the gas phase. The relative intensities of the mass spectrometric peaks for the complex species generally appear to reflect the order of the stability constants observed in solution. This has been exploited in electrohydrodynamic mass spectrometric measurements of the stability constants of various cation/18-crown-6 complexes.[25]

Recently, a number of gas-phase studies of crown complexes have appeared, investigating both the collision-induced dissociation (CID) of the complex species[26–31] and their gas-phase reactions.[32,33] The CID studies demonstrate that under low-energy collision conditions, the most abundant fragment ions are generally those obtained by loss of an intact neutral crown from the complex, strongly suggesting that the ligands retain their structural integrity in the gas-phase complexes. The relative intensities of the CID products have also been related to the relative affinities of different host molecules for ionic guests, using the "kinetic" method[34–36] of determining relative cation affinities.

Part of the recent interest in the mass spectrometry of crown ether complexes probably stems from the development of laser desorption[37] and electrospray[38] ionization techniques, both of which tend to produce high-mass, cation-attached molecular ions. Both of these techniques are particularly valuable for introducing large biomolecules such as peptides into the gas phase, which are often observed as alkali metal cation-attached species. The chemistry of attachment probably involves multidentate bonding of the alkali cation by donor groups in the peptide.[39,40] Crown ethers are useful as small model systems for investigating multidentate binding in the gas phase, which hopefully will shed further light on the cation attachment process.

In our preliminary communications describing the gas-phase ion chemistry of crown ether/alkali metal cation complexes,[32,33] we have noted that the formation of 1:1 ligand–metal species can occur as a gas-phase ion–molecule reaction and have described the subsequent reaction of the 1:1 complexes with a second ligand to form 1:2 metal–ligand species. The reactivity patterns strongly suggest that size relationships are important in the formation of 1:2 complexes. Comparison of the formation rates for 1:2 complexes involving crown ether ligands with rates involving the corresponding acyclic glymes[33] also demonstrated a strong macrocyclic effect[41] in the gas phase, with the cyclic ligands forming 1:2 complexes more rapidly and more selectively than their acyclic analogs.

Herein we report rate data for both 1:1 and 1:2 metal–ligand complexation between crown ethers and alkali metal cations, as well as relative cation affinity measurements for the crown ethers made using both CID methods and gas-phase bracketing/equilibrium studies. Our goals include the identification and characterization of size-dependent effects in ion–molecule reactions and clarification of the intrinsic factors that govern molecular recognition, in the absence of solvent effects. The rate measurements quantify our earlier reports and provide strong evidence for both size-selective chemistry and macrocyclic effects in gas-phase cation attachment processes. The cation affinity experiments enable a comparison of the kinetic and bracketing techniques for multidentate systems and make possible, for the first time, measurement of the intrinsic affinities of different ligands for a given cation in a solvent- and anion-free environment.

Experimental Section

Experiments were conducted using two instruments, a Fourier transform ion cyclotron resonance mass spectrometer (FTICR/MS) and a tandem quadrupole mass spectrometer. The discussion of experimental techniques is organized around the instruments.

Alkali metal chlorides and 12-crown-4 (12C4), 15-crown-5 (15C5), 18-crown-6 (18C6) and the glymes and glycols were obtained from Aldrich, while 21-crown-7 (21C7) was purchased from Parish Chemical Co. (Orem, UT). All compounds were used directly without further purification.

FTICR/MS Experiments. This work employed a Nicolet (now Extrel) FTMS-1000 instrument equipped with a 3 T superconducting solenoid magnet and modified as noted below. A base vacuum of 10^{-9} Torr was maintained by two 300 L s^{-1} diffusion pumps. The system was equipped with two vacuum locks to facilitate the insertion of two independent temperature-regulated probes for solid samples. One probe, inserted

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along the solenoid axis to within about 10 cm of the trapping cell, was used for laser desorption. In addition, solid samples placed in a capillary tube on the face of the probe were thermally vaporized. The second probe was inserted perpendicular to the solenoid axis, to a point approximately 80 cm from the trapping cell. This transverse probe was used for thermal vaporization of solids. The less-volatile crowns 18C6 and 21C7 were typically inserted on the two solid probes, while 12C4, 15C5, the glymes, and the glycols were introduced using precision variable leak valves. Ambient temperatures, estimated at 350 K, were sufficient to vaporize all of the ligands studied (i.e., the solid probes were not warmed). Typically, ligand pressures were approximately $1-5 \times 10^{-7}$ Torr.

The trapping cell used for most experiments has an open design based on that of Laude[42] and is constructed from type 304 stainless steel. Radio frequency excitation is capacitively coupled to the trapping plates to decrease axial ion ejection during excitation events.[43] A pulse from an excimer-pumped dye laser (Lambda Physik LPX205i/FL3002) was used to generate alkali metal cations that were captured in the trapping cell, typically with a 1 V trap potential. Pulse energies of 1-10 mJ at 360 nm were normally employed. For experiments comparing reaction kinetics or equilibria as a function of metal cation, two to four metal salts were simultaneously desorbed from the probe to guarantee that the metals under comparison experienced identical ligand pressures.

Ligand–metal complexes generated in the trapping cell through ion–molecule reactions were isolated using swept-RF and/or SWIFT[44,45] techniques. No special efforts were made to thermalize the complexes, other than allowing long reaction delays (several hundred milliseconds to several seconds) prior to beginning the kinetics experiments. There is some curvature at short reaction times (a few hundred milliseconds or less) in the kinetic plots, but with longer delays the plots are linear, suggesting that insufficient cooling did not complicate the kinetic results. Recent studies of ion thermalization also indicate that these conditions should be sufficient to thermalize the ions.[46]

For volatile ligands, pressure measurements were made with a Bayard-Alpert ionization gauge, calibrated against the rate of self-chemical ionization of acetone[47] to obtain pressures in the trapping cell. Because many of the ligands we examined are relatively involatile and condense before reaching the pressure transducer, relatively high pressures can exist in the trapping cell without registering on the ionization gauge. Fortunately, several means exist for circumventing these pressure measurement problems.

Ridge[48] has pointed out that the FTICR itself can be used as a pressure measurement device that samples pressures in the trapping cell. The technique involves 70 eV electron impact ionization of the neutrals present in the cell. The total signal intensity observed, corrected for relative ionization cross sections,[49] is proportional to the neutral pressure, as long as conditions are chosen so that the space charge limit of the trapping cell is not approached. We have tested this method by plotting total FTICR signal versus ionization gauge pressure for 12C4, a volatile crown ether, and find the plots to be linear in the 10^{-9}-10^{-7} Torr range. This method was used in cases where the ligands being measured gave distinct fragmentation patterns.

Alternatively, ion–molecule reaction kinetics can be used to determine ligand pressures. Exothermic proton transfer reactions are generally highly efficient, occurring at 90% or more of the collision rate.[50] Since all of the ligands in this study have relatively high proton affinities, if it is assumed that the efficiency of proton transfer to each of the ligands under comparison is the same, relative pressures can be measured by comparing relative proton transfer rates. Because all the ligands being compared are structurally very similar, we believe this is a reasonable assumption. The pressure measurements can be put on an absolute basis by assuming the transfer reaction is 100% efficient and comparing the measured rate with the collision rate calculated using LGS[51] collision theory. While LGS theory will underestimate the collision rates, and therefore yield pressures that are too large, it is much simpler to apply than more sophisticated treatments such as ADO theory[52] and avoids ambiguities arising from conformation-dependent dipole moments. This method was used in cases (such as the simple homologous crowns) in which the different ligands give common fragment ions.

Table I. Homogeneous Ligand–Cation Species Observed Using Triple Quadrupole Mass Spectrometry[a]

	12C4	15C5	18C6	21C7
(crown)Cat$^+$	H$^+$, M$^+$	H$^+$, M$^+$	H$^+$, M$^+$	H$^+$, M$^+$
(crown)$_2$Cat$^+$	H$^+$, M$^+$	H$^+$, M$^+$	H$^+$, M$^+$	H$^+$, M$^+$ (except Li$^+$)
(crown)$_3$Cat$^+$	H$^+$, Cs$^+$	H$^+$	H$^+$	*
(crown)$_4$Cat$^+$	H$^+$	*	*	*

[a] "H$^+$" indicates a protonated complex of the indicated stoichiometry, "M$^+$" indicates Li$^+$–, Na$^+$–, K$^+$–, Rb$^+$–, and Cs$^+$–ligand complexes, and an asterisk indicates no species of the indicated stoichiometry were observed.

Tandem Quadrupole Experiments. Gas-phase clustering and complexation reactions were studied using a triple-stage quadrupole mass spectrometer (Finnigan MAT TSQ-70). Proton-bound clusters were generated by placing 2–5 μL of ligand into a capillary tube on the temperature-programmable direct insertion solid probe (DIP). The probe was inserted into the mass spectrometer source with a chemical ionization (CI) ion source in place and was heated to volatilize the ligands. The source pressure, measured using a Pirani gauge, varied with probe temperature and with the volatility of the crown samples, but it was typically between 0.2 and 0.5 Torr, ensuring collisional thermalization. Electron impact (EI) was used to ionize the samples, after which reactions occurred in the source before extraction into the first quadrupole. In a few cases, crown–cation complexes were also generated using Ar fast atom bombardment (FAB). The FAB gun (Ion Tech) was typically operated at 8 kV. In collision-induced dissociation (CID) experiments, Ar was used as the collision gas, with pressures around 0.8 mTorr in the collision region. Pressures in the collision cell were measured using a Baratron capacitance manometer (MKS Instruments). The collision energy, determined by the potential difference between the ion source and second quadrupole, was set at 5 eV (lab frame) for most studies, corresponding to center-of-mass energies of about 0.4-0.9 eV.

For relative cation affinity studies using the kinetic method, alkali metal cations were introduced by heating their salts (between 600 and 800 °C) on the temperature-programmable direct exposure solid probe (DEP), with the EI filament on. The ligands were painted on the CI ion source and thermally vaporized by heat from the DEP. Typically about 8 μL of ligand is required for each experiment. The collision energy was held between 3 and 5 eV (lab frame) and Ar was used as the collision gas (0.2–0.9 eV in the center-of-mass frame). The Ar pressure in the collision cell was held below 6×10^{-4} Torr and the source pressure was about 0.7 Torr.

Molecular Mechanics Calculations. Minimum energy geometries for 1:2 cation–crown "sandwich" complexes were estimated using the AMBER force field implemented in the HyperChem program, supplemented by alkali metal cation size parameters obtained from the literature.[6,53]

Results

The results of tandem quadrupole and FTICR/MS experiments are discussed separately below.

Tandem Quadrupole Results. (a) Observed Species. The homogeneous ligand complexes seen using the triple quadrupole instrument are listed in Table I. The relatively high pressures present in the ion source of this instrument resulted in the production of a very wide range of cluster ions from ion–molecule reactions in the source, including many that were not observed in the low-pressure FTICR experiments.[32]

Under CI conditions, proton-bound clusters were found to form readily in the ion source. Proton-bound dimers of all the crowns studied, trimers of 12C4, 15C5, and 18C6, and the tetramer of 12C4 were seen. Heterogeneous clusters, such as (12C4)(15C5)H$^+$, (12C4)(18C6)H$^+$, (15C5)(18C6)H$^+$, (18C6)(21C7)H$^+$, and

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Table II. Collision-Induced Dissociation of Heterogeneous (crown 1)(crown 2)M$^+$ Species Generated by Ion–Molecule Reactions and by Fast Atom Bombardment (FAB) in the Source of the Triple Quadrupole Instrument

(crown 1)(crown 2)M$^+$ precursor ion	fragments from ion–molecule generated precursors[a]	fragments from FAB generated precursors[b]
(12C4)(15C5)H$^+$	(12C4)H$^+$, (15C5)H$^+$ (1:6.2)	
(12C4)(18C6)H$^+$	(18C6)H$^+$	
(15C5)(18C6)H$^+$	(18C6)H$^+$	
(18C6)(21C7)H$^+$	(18C6)H$^+$, (21C7)H$^+$ (1:5.8)	
(12C4)(15C5)Li$^+$	(15C5)Li$^+$	
(15C5)(18C6)Li$^+$	(15C5)Li$^+$, (18C6)Li$^+$ (1:3.5)	
(15C5)(21C7)Li$^+$	(21C7)Li$^+$	(15C5)Li$^+$, (21C7)Li$^+$ (6:1)
(18C6)(21C7)Li$^+$	(18C6)Li$^+$, (21C7)Li$^+$ (2.4:1)	(18C6)Li$^+$, (21C7)Li$^+$ (1:1)
(12C4)(15C5)Na$^+$	(15C5)Na$^+$	
(15C5)(18C6)Na$^+$	(18C6)Na$^+$	(15C5)Na$^+$, (18C6)Na$^+$ (4:3)
(18C6)(21C7)Na$^+$	(18C6)Na$^+$, (21C7)Na$^+$ (1:10.2)	
(12C4)(15C5)K$^+$	(15C5)K$^+$	
(15C5)(18C6)K$^+$	(18C6)K$^+$	
(18C6)(21C7)K$^+$	(18C6)K$^+$, (21C7)K$^+$ (1:2.3)	
(12C4)(15C5)Rb$^+$	(15C5)Rb$^+$	
(15C5)(18C6)Rb$^+$	(18C6)Rb$^+$	
(18C6)(21C7)Rb$^+$	(21C7)Rb$^+$	
(12C4)(15C5)Cs$^+$	(15C5)Cs$^+$	
(15C5)(18C6)Cs$^+$	(18C6)Cs$^+$	
(18C6)(21C7)Cs$^+$	(21C7)Cs$^+$	

[a] This work. [b] Reference 29.

(12C4)$_2$(15C5)H$^+$, were also observed. Under the pressure conditions typically employed, the protonated molecular ions were the base peaks in the spectra, followed by dimers (20–50%), with much weaker trimer (a few percent) and tetramer (<1%) signals.

Introduction of an alkali metal cation into the source along with the ligand resulted in the formation of metal–ligand complexes by ion–molecule reactions. Complexes of 12C4, 15C5, 18C6, and 21C7 with all of the alkali metals were observed in reactions similar to those seen under low-pressure ion cyclotron resonance conditions.[32] In addition, the alkali cation-bound crown ether dimers (sandwiches) were also observed (Table I). The relatively high pressures in the ion source of the triple quadrupole instrument made possible formation of a number of species, such as (18C6)$_2$Li$^+$, which were not observed under low-pressure FTICR conditions. The sandwiches were typically 20% or less as intense as the 1:1 complexes. In one case, a peak corresponding to a metal-bound crown trimer, (12C4)$_3$Cs$^+$, was observed, approximately 0.2% as intense as the (12C4)Cs$^+$ signal.

(b) CID Experiments. The CID products from various precursor species, as well as the relative product ion abundances, are listed in Table II. The relative product ion abundances were reproducible from day to day with a standard deviation of about 25%.

When CID was performed on homogeneous proton-bound clusters, the only product ions were the protonated crowns. Likewise, neutral loss scans revealed that the only important neutral loss processes were losses of intact neutral crowns. In the MS/MS spectra of the mixed clusters (12C4)(18C6)H$^+$ and (15C5)(18C6)H$^+$, the only product was the proton bound to the larger crown. For (12C4)(15C5)H$^+$ and (18C6)(21C7)H$^+$, both protonated crown fragments were seen. In each case, the abundance of the larger protonated crown is about six times greater than that of the smaller protonated crown.

The CID results for the "sandwich" complexes generated using ion–molecule reactions are also listed in Table II. The only products, in most of the complexes studied, are the cation-attached 1:1 complexes. For sandwich complexes generated using ion–molecule reactions, in every case except dissociation of (18C6)-(21C7)Li$^+$, the product representing cation attachment to the larger crown is more abundant than that arising from attachment to the smaller crown. Signal due to bare alkali metal cation products was always very weak or absent, suggesting that secondary dissociation of the initially-formed products was not significant. This is as expected under predominantly single-collision CID conditions. Our FAB-CID results (not shown) agree closely with the results published previously.[29]

CID of the Cs$^+$-bound trimer of 12C4 gave similar results. Two major peaks, of m/z 485 ((12C4)$_2$Cs$^+$) and m/z 309 ((12C4)-Cs$^+$), were seen in the product ion spectra of (12C4)$_3$Cs$^+$, representing consecutive losses of neutral 12C4 from (12C4)$_3$-Cs$^+$.

In several instances, the relative product ion abundances from the FAB-generated 1:2 complexes were dramatically different from those obtained when the 1:2 complexes were produced by ion–molecule reactions in the ion source. For example, CID of FAB-generated (18C6)(21C7)Li$^+$ gave (18C6)Li$^+$ and (21C7)-Li$^+$ in roughly equal abundances,[29] but the precursor of the same mass generated using ion–molecule reactions gave a ratio of (18C6)Li$^+$:(21C7)Li$^+$ of 2.4:1. Likewise, dissociation of FAB-generated (15C5)(21C7)Li$^+$ yielded (15C5)Li$^+$ and (21C7)Li$^+$ in an approximately 6:1 ratio,[29] although CID of the precursor of the same mass made by ion–molecule reactions gave only (21C7)Li$^+$. Differences were also observed in the CID of Na$^+$ sandwiches: (15C5)(18C6)Na$^+$ from FAB gave (15C5)Na$^+$ and (18C6)Na$^+$ in a 4:3 ratio,[29] while the same precursor from ion–molecule reactions gave only (18C6)Na$^+$. These differences are probably too large to be accounted for by experimental error.

FTICR/MS Results. Three general reaction types were observed in the FTICR/MS instrument: 1:1 metal–ligand complex formation, subsequent reaction of the 1:1 complexes with an additional ligand to form 1:2 complexes, and transfer of the cation from one 1:1 complex to another ligand to form a different 1:1 complex.

As we have noted previously,[32,33] 1:1 alkali metal–crown complexes form in the gas phase when alkali metal cations trapped in the electromagnetic well of the instrument are exposed to neutral crown ethers. Rate constants measured for the complexation reactions of Na$^+$, K$^+$, Rb$^+$, and Cs$^+$ with 12C4, 15C5, triglyme, and tetraglyme are given in Table III. The rates, which were reproducible from day to day with the precisions indicated, are very fast, and they decrease monotonically as the mass of the alkali metal increases.

The rate constants for 1:2 cation–ligand complexation, given in Table IV, exhibit a more complex pattern of reactivity, which follows the general rule we noted in our earlier report:[32] when the cation is small relative to the ligand cavity, reaction is very slow, but when the cation is comparable in size to the ligand cavity, reaction is facile. The 1:2 reaction was not observed for any of

Table III. Rate Constants, k ($\times 10^{-10}$ cm^3 mol^{-1} s^{-1}), and Reaction Efficiencies for Formation of 1:1 Alkali Cation–Crown Complexes in the Gas Phase

	triglyme		12C4		tetraglyme		15C5	
	k	k/k_{Langevin}	k	k/k_{Langevin}	k	k/k_{Langevin}	k	k/k_{Langevin}
Na^+	6.2 ± 0.4	0.3 ± 0.02	22.5 ± 13.5	2.2 ± 1.3	33.1 ± 16.5	1.6 ± 0.8	109.1 ± 29.4	4.6 ± 1.2
K^+	5.0 ± 0.6	0.3 ± 0.04	9.3 ± 2.8	0.9 ± 0.3	16.2 ± 10.8	1.0 ± 0.6	52.5 ± 37.9	2.8 ± 2.0
Rb^+	3.3 ± 0.8	0.3 ± 0.07	3.7 ± 1.5	0.4 ± 0.2	5.3 ± 3.0	0.4 ± 0.2	14.4 ± 2.6	1.0 ± 0.2
Cs^+	1.6 ± 0.5	0.1 ± 0.04	4.7 ± 6.2	0.5 ± 0.7	2.8 ± 1.2	0.3 ± 0.1	11.0 ± 1.9	0.9 ± 0.2

Table IV. Rate Constants, k ($\times 10^{-10}$ cm^3 mol^{-1} s^{-1}), and Reaction Efficiencies for Formation of 1:2 Alkali Cation–Crown Complexes in the Gas Phase[a]

	triglyme		12C4		tetraglyme		15C5		18C6	
	k	k/k_{Langevin}	k	k/k_{Langevin}	k	k/k_{Langevin}	k	k/k_{Langevin}	k	k/k_{Langevin}
Li^+	0.09 ± 0.02	0.01 ± 0.002	3.6 ± 1.4	0.35 ± 0.13	n.o.	n.o.	n.o.	n.o.	n.o.	n.o.
Na^+	0.5 ± 0.2	0.05 ± 0.02	12.4 ± 4.2	1.23 ± 0.41	0.06 ± 0.05	0.007 ± 0.005	0.67 ± 0.18	0.06 ± 0.02	n.o.	n.o.
K^+	0.6 ± 0.3	0.07 ± 0.03	2.2 ± 1.1	0.23 ± 0.11	0.4 ± 0.1	0.05 ± 0.01	4.51 ± 1.90	0.45 ± 0.19	0.006 ± 0.001	0.0006 ± 0.0001
Rb^+	0.4 ± 0.08	0.04 ± 0.01	1.2 ± 1.4	0.13 ± 0.15	0.6 ± 0.4	0.07 ± 0.04	2.95 ± 1.01	0.31 ± 0.10	0.15 ± 0.02	0.015 ± 0.002
Cs^+	0.07 ± 0.01	0.01 ± 0.001	0.6 ± 0.2	0.07 ± 0.02	0.4 ± 0.1	0.05 ± 0.01	1.34 ± 0.37	0.14 ± 0.04	0.89 ± 0.23	0.096 ± 0.024

[a] "n.o." indicates 1:2 complexation was too slow to observe.

Table V. Direction of Cation Transfer between Gas-Phase Polyethers[a]

	12C4 → 15C5	15C5 → 18C6	18C6 → 21C7	G3 → 12C4	G4 → 15C5	PEG → 18C6
H^+	fwd	fwd	fwd	rev	rev	rev
Li^+	fwd	fwd	fwd	1:2	fwd	fwd
Na^+	fwd	fwd	fwd	1:2	1:2	fwd
K^+	fwd	fwd	fwd	1:2	1:2	fwd
Rb^+	fwd	fwd	fwd	1:2	1:2	fwd
Cs^+	fwd	fwd	fwd	1:2	1:2	fwd

[a] "fwd" implies transfer is in the direction indicated, "rev" indicates transfer is in the reverse direction to that indicated, and "1:2" means clustering was too rapid to allow clear determination of the direction of transfer. G3 = triglyme, G4 = tetraglyme, PEG = penta(ethylene glycol).

the alkali metal cations reacting with 21C7, which has a cavity large enough to accommodate any of these metals.

As noted in Table V, cations were observed to transfer from smaller to larger ligands when both were present (reaction 1). Proton transfer was also observed from 12-crown-4 to triglyme, from 15-crown-5 to tetraglyme, and from 18-crown-6 to penta(ethylene glycol). Alkali cation transfer, however, in cases where the competing formation of 1:2 complexes was not so fast as to obscure its observation, was in the opposite direction: Li^+ transfers from tetraglyme to 15-crown-5, and all the alkali metals were transferred from penta(ethylene glycol) to 18-crown-6.

$$\text{(crown 1)M}^+ + \text{crown 2} \rightleftharpoons \text{crown 1} + \text{(crown 2)M}^+ \qquad (1)$$

When the reaction exothermicity is less than about 3 kcal mol^{-1}, it is possible to observe equilibrium for the cation transfer reactions. The reactions were checked in both the forward and the reverse direction by isolating each of the metal-attached crowns and monitoring for the appearance of the other. This procedure helped ensure that the results reflected true equilibria.

Equilibrium for reaction 1 was observed in the case of crown 1 = 18C6 and crown 2 = 21C7 for M = Li, Na, K, and Rb. For M = Cs, some (18C6)M^+ remained after several seconds of allowing isolated (18C6)M^+ to react with 21C7, but no (18C6)M^+ was observed after up to 60 s of reaction with 18C6, indicating that true equilibrium is not reached. The measured equilibrium constants are listed in Table VI. The same values were obtained regardless of the direction of approach to equilibrium. Equilibrium studies were not performed for the smaller crowns because of complications due to the rapid competing reactions arising from formation of 1:2 complexes.

Table VI. Equilibrium Constants Observed for Transfer of Alkali Metal Cations from 18-Crown-6 to 21-Crown-7 in the Gas Phase, at Instrument Ambient Temperature[a]

	K	ΔG_{350} (kJ mol^{-1})
Li^+	13.3 ± 0.9	−7.5 ± 0.2
Na^+	24.5 ± 2.0	−9.3 ± 0.2
K^+	3.8 ± 0.3	−3.9 ± 0.2
Rb^+	50.6 ± 3.7	−11.4 ± 0.2
Cs^+	>200	<−16

[a] ΔG values derived assuming T = 350 K.

Discussion

Comparison of Kinetic and Bracketing Methods for Determining Relative Cation Affinities. Gas-phase experiments enable cation affinities to be compared without complications arising from solvent or counterion effects, and thus they can serve as a unique approach for studing the *intrinsic* factors that govern the binding properties of the ligands as cation size and charge density are systematically varied. Several reports have recently appeared[27,29,30] that interpret CID data to estimate the relative cation affinities of gas-phase crowns, using the kinetic method. Alternatively, ligand exchange "bracketing" methods such as we present in this work can be used. In several cases, the two methods do not agree, prompting us to consider the differences between the two approaches.

The kinetic method involves synthesis, in a mass spectrometer ion source, of heterogeneous 1:2 cation–ligand complexes, LM^+L'. The 1:2 complexes are mass selected and then induced to dissociate, usually by collision with an inert species such as Ar or Xe. The product ions are mass analyzed, and the relative abundances of the products are measured. A fundamental assumption of the kinetic method is that the relative abundances of the products, which arise from the relative rates of the unimolecular dissociation processes leading to LM^+ and $L'M^+$, reflect the relative metal–ligand bond strengths. Weaker bonds are assumed to break faster and thus give rise to larger corresponding product peaks.

When the kinetic method is successful, it should reflect the relative strengths of the metal interactions with the two ligands *in the 1:2 complex*, but these may not be the same as the relative strengths of the metal–ligand interactions in the two isolated LM^+ 1:1 complexes. Preliminary molecular modeling calculations we have carried out using the AMBER force field to describe both 1:1 and 1:2 complexes indicate that in low-energy conformations of 1:1 and sandwich complexes, the average metal–oxygen distances in the former are much shorter (by about 0.3 Å) than in the corresponding sandwiches. Bond strengths in the sandwich complexes therefore may not be related to the strengths of the interactions in the isolated 1:1 complexes.

Several additional assumptions implicit in the kinetic method suggest the need for corroboration of the results of this type of experiment when determining the relative cation affinities of multidentate ligands. First, the kinetic method assumes that the frequency factors for the two dissociation pathways under comparison are similar. In other words, the transition states for the two pathways are assumed to be similar. Second, the fragmentation is assumed to be a simple cleavage process with little or no reverse activation barrier. In other words, extensive, thermodynamically costly rearrangements are assumed not to be operative. For the kinetic method to be valid at all internal energies E, the $k(E)$ vs. E curves for the processes being compared must be parallel.

These assumptions may be reasonable for proton affinity measurements involving bases with single proton attachment sites, but they require further scrutiny for more complex metal–ligand systems, where multidentate binding occurs and there may be substantial thermodynamic barriers associated with achieving ligand conformations optimal for binding. Fundamentally, with the kinetic method some assurance is required that the intensities of the fragment peaks reflect equilibrium ion populations.

The fact that FAB-generated and ion–molecule reaction-generated sandwich species give different relative CID product abundances also indicates the kinetic method should be used with caution, and that it may not be reliable for systems involving multidentate metal binding. Our experiments give no indication as to why the two methods of sandwich making should lead to such different results, but we speculate that the two ionization techniques lead to species that are structurally and/or energetically distinct. Cation-bound crown ether dimers are structurally complex enough that it is difficult to estimate how their fragmentation patterns will vary with energy. In light of the uncertainties involved, we believe FTICR/MS bracketing experiments to be a much more reliable approach.

Ion–molecule bracketing methods were developed and originally used extensively for the measurement of gas-phase proton affinities.[54] The FTICR/MS techniques compare the cation affinities of the 1:1 complexes, rather than bond strengths in 1:2 complexes. Further, these methods are often quantitative in that they enable the measurement of equilibrium constants[50] in cases where the difference *in* cation affinities is not too large. This is accomplished either by measuring equilibrium concentrations directly or by measuring the rates of the forward and reverse reactions.[55]

Intrinsic Cation Affinities of Crown Ethers. Although little is known about the gas-phase cation affinities of crown ethers, considerable work has been done with smaller molecules, particularly in determining alkali cation affinities, and in comparing proton and alkali cation affinities. Absolute Li^+ affinities have been measured experimentally for a number of small n- and π-donor bases, and they fall approximately in the 35–45 kcal mol^{-1} range for N- or O-donors.[56–58] Studies of the bond energies in $M(NH_3)_n^+$ (M = alkali metal) cluster species[59,60] show that bond energies decrease as the size of the metal ion increases and drop significantly when more than four ligands are added to Li^+ or Na^+, but not for the larger cations. This suggests that steric crowding around the cation center may play a significant role in influencing the thermochemistry.

The correlation of Li^+ affinities with proton affinities is relatively poor, because "bonding to Li^+ is largely ionic while bonding to H^+ may also reflect strong covalent interactions."[56] Experimental K^+ affinities, measured for small ligands with single O- and N-donors using high-pressure equilibrium mass spectrometric methods,[61] are consistent with primarily electrostatic bonding in these complexes. Recent high-energy CID experiments on proton[62,63] and alkali metal cation complexes[28] of crown ethers also indicate considerable differences in bonding between protonated and alkali cation-attached ligands.

Ab initio calculations have also been used to show that the bonding of small molecules to Li^+ is primarily electrostatic.[64–68] It is reasonable to expect that bonding in the crown complexes is similarly electrostatic. Alkali cation attachment in general is still an active area of theoretical investigation. For example, gas-phase Na^+ affinities were recently calculated for glycine and related molecules.[69]

Crown ethers present an additional dimension, because they are *multidentate* ligands. Very few investigations of multidentate binding in the gas phase have been carried out, most involving proton affinity determinations, but the results so far are quite interesting. The proton affinities of crown ethers and glymes,[12,13] for example, increase as the number of oxygen donor atoms is increased, suggesting that multiple oxygen–proton interactions contribute to the bonding. Both the CID results and the proton transfer bracketing experiments of this study are consistent with these earlier findings. However, even for small molecules, it has been found through a set of *ab initio* calculations at the 6-31G*//3-21G level that alkali cation affinities correlate poorly with proton affinities,[70] highlighting the need for direct alkali cation affinity measurements.

From the results of the cation transfer experiments, it is evident that the *intrinsic* alkali cation affinities of the crown ethers are strongly affected by the number of oxygen donors in the ligand, in contrast to what is observed in solution. In every case we have examined, the gas-phase proton and alkali cation affinities increase with the number of donor atoms. On the other hand, in polar solvents with high donor numbers such as methanol, the relative magnitudes of the stability constants show only a rough correlation with cation size (Table VII); 12C4 has the smallest stability constants for all the alkali cations, while 18C6 has the largest for Na^+, K^+, and Rb^+, and 21C7 has the largest for Cs^+.

One might expect the situation to be somewhat simpler in propylene carbonate, where a high dielectric constant and a low donor number combine to produce conditions where cations and

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Table VII. log K Values for Crown Ether–Alkali Metal Cation Complex Formation in Methanol and Propylene Carbonate (Values from Ref 3 Unless Otherwise Noted)

	methanol				propylene carbonate		
	12C4	15C5	18C6	21C7	12C4	15C5	18C6
Li$^+$	–0.57[a]	1.21[c]	0.00[d]		2.23[f]	4.03[h]	2.70[h]
Na$^+$	1.67[b]	3.32	4.28	2.12[b]	3.55	4.87[h]	4.55[h]
K$^+$	1.60[b]	3.50	5.67	4.30[b]	2.09[b]	3.78[h]	6.08[h]
Rb$^+$	1.65[c]	3.22	5.53	4.86[e]	1.69[g]	3.74[h]	5.30[h]
Cs$^+$	1.63	2.74	4.50	5.01[b]	1.43[g]	3.39[h]	4.47[h]

[a] In MeOD, from ref 86. [b] Average of values from refs 3 and 7. [c] Reference 87. [d] Reference 88. [e] Reference 89. [f] Reference 90. [g] Reference 91. [h] Reference 92.

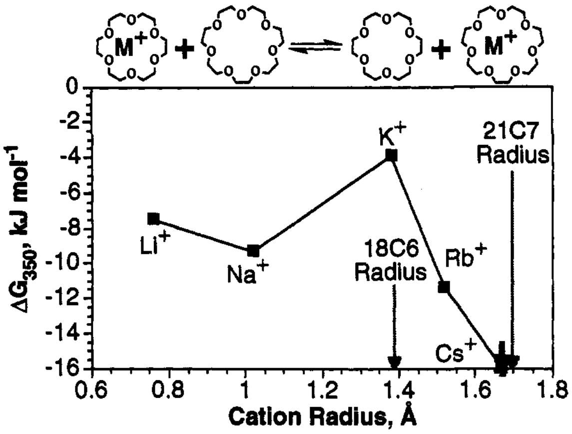

Figure 1. ΔG_{350} values derived from equilibrium constants for transfer of alkali metal cations from 18-crown-6 to 21-crown-7 in the gas phase, assuming a temperature of 350 K. Equilibrium was not observed in the case of Cs$^+$; the plotted value is an upper limit for ΔG_{350}. Cation radii from ref 84.

ligands are weakly solvated while ion pairing also remains weak. However, stability constants for Li$^+$ complexes in propylene carbonate show the same ligand ordering as those in methanol: the order for Na$^+$ is 12C4 < 18C6 < 15C5, and K$^+$, Rb$^+$, and Cs$^+$ all have increasing stability constants as ligand size incrases. As has been noted,[11] these trends probably originate from a complex interplay between intrinsic cation affinities and solvation effects. Only in the gas phase is the intrinsic simplicity of the crown–cation interactions revealed.

At first glance, these findings appear to imply that the size match model has little merit for predicting the strengths of the intrinsic interactions between crown ethers and alkali cation guests. However, consideration of the ΔG values for cation transfer between 18C6 and 21C7, determined from the gas-phase equilibrium constants assuming a temperature of 350 K (Table VI and Figure 1), indicates that size match does play a role. Although equilibrium lies on the side of the (21C7)M$^+$ complex for all the cations examined, the magnitude of ΔG is smallest for K$^+$, which has an ionic radius[71] nearly exactly matching the cavity radius[7] of 18C6. The most negative value, on the other hand, is for Cs$^+$, which has a good size match with the 21C7 cavity.

All the ΔG values except that for Li$^+$ seem to correlate well with expectations based on size match. It is surprising that the equilibrium constant for Li$^+$ is smaller than that for Na$^+$. Conjecturing on the reasons for this apparent disparity, we note that at some point the rule of increasing cation affinity with increasing number of ligand donor atoms must break down as the ligands become too large to allow all the donor groups to interact effectively with the cation guest. Perhaps that point is approached in the case of Li$^+$, the smallest alkali cation for which an equilibrium constant involving these large crowns was measured. In this view, Li$^+$ is too small to interact optimally with all the oxygens of 21-crown-7, and thus it is not bound as tightly as the larger Na$^+$ cation. Further experimentation with larger ligands may shed light on this hypothesis.

Our current experiments yield relative rather than absolute cation affinities, but we can make at least rough estimates of the absolute values. On the low side, we expect the metal cation binding strengths of the multidentate crowns to be at least as great as the 35–45 kcal mol^{-1} values observed for unidentate, single-donor-atom ligands.[56,57] The presence of multiple donors will certainly lead to higher bond energies than are seen in the single donor cases. An upper limit can be estimated from the cumulative bond strengths measured for clusters.[59,60] The existence of a covalent backbone in a multidentate ligand restricts the placement of the donor atoms with respect to the cation center and should make the interaction less favorable than in cases such as the clusters where the ligands can move freely to adopt an optimal arrangement around the cation. Upper limits to the strengths of the interactions can also be estimated from low-energy collision-induced dissociation data,[29] which generally show that loss of the intact ligand, rather than fragmentation of the ligand covalent structure, is the lowest-energy dissociation pathway. These conditions suggest the absolute bond strengths multidentate binding of alkali metal cations by crown ethers must lie somewhere in the range 35–85 kcal mol^{-1}.

Radiative Stabilization. The gas-phase environment lacks a thermal solvent bath capable of removing excess energy from exothermic processes and thereby stabilizing the products of exothermic bimolecular encounters such as the 1:1 and 1:2 complexation reactions. Collision complexes tend to dissociate back to reactants unless they are stabilized by some means. The reactions may be stabilized collisionally, where excess energy is carried off through encounters with third bodies, and/or radiatively,[72,73] where emission of (usually) infrared photons provides the necessary cooling.

Both the 1:1 and 1:2 complexation reactions are probably examples of radiative association. Although collisional stabilization may account for some of the cooling, collision rates at the 10^{-8} Torr pressures used in the experiments are too slow (generally only a few collisions per second) to account for all of the observed stabilization. Radiative association has been postulated to account for the stability of adducts of Li$^+$ with small organic carbonyl compounds,[74] and has been invoked to explain the observation of stable 1:1 and 1:2 complexes of transition metal cations with tribenzocyclotriyne.[75] Further, on the basis of work with small organic molecules, it has been suggested that molecules with C–O bonds probably have exceptionally fast radiative association rates.[76] If this is so, polyethers should be very amenable to radiative cooling.

Although we have not observed the infrared emission that would prove radiative association is occurring, radiative cooling would seem the most likely important stabilization mechanism. RRKM calculations indicate that for any reasonable metal–ligand bond strength, the crowns have enough internal degrees of freedom that the lifetimes of the collision complexes are quite long. For instance, assuming a bond strength of only 30 kcal mol^{-1} for an (18C6)Li$^+$ complex and an orbiting transition state for dissociation, the calculations predict complex lifetimes of greater than 1 s for energies as great as 6 kcal mol^{-1} above the dissociation threshold. Higher bond strengths and tighter transition states both give even longer lifetimes. Finally, the slight curvature in the early portion of the log (product abundance) vs. time plots

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for the formation of the 1:2 complexes indicates that the nascent 1:1 complexes are internally hot and cool with time.

Complexation Reaction Efficiencies. Rate constants measured for the formation of 1:1 complexes of alkali metal cations with triglyme, 12-crown-4, tetraglyme, and 15-crown-5 in the gas phase are listed in Table III. The rate constants can be converted to reaction efficiencies by dividing them by collision rates calculated using theory. One of the simplest and most widely-used approaches for determining collision rate constants, k_c, was developed originally by Langevin and applied to ion–molecule reactions by Gioumousis and Stevensen[51] (eq 2). Here, q is the

$$k_c = 2\pi q\sqrt{\alpha/\mu} \qquad (2)$$

ionic charge, α is the polarizability of the neutral, and μ is the reduced mass of the collision complex. Polarizabilities suitable for use in this expression are easily estimated using the method of atomic hybrid components.[77,78] More complex, more accurate means of calculating collision rates have been developed, but virtually all incorporate the same dependence on $\alpha^{1/2}$. For simplicity, we will use collision rates calculated using LGS theory.

Comparison of the experimental rate constants with collision rate constants calculated using LGS theory shows the experimental values to be very fast, in many cases *exceeding* the LGS constants. Because the reaction rates cannot exceed the collision rates, either the rate constants are too large or the calculated collision rate constants are too small. The rate constants might be too large if there is a systematic error in the pressure measurements, which, given the uncertainties involved, is not unlikely. (However, because all measurements are subject to the same systematic error, the *relative* magnitudes of the rate constants would still be correct. All of the effects noted below depend on *relative* reaction efficiencies, not on the absolute values.) None of the measured constants exceeds the LGS rate constants by more than the factor required to correct the ionization gauge readings to trapping cell pressures.

On the other hand, LGS theory is known to underestimate collision rates for polar molecules,[79] although probably not by enough to account fully for the fast reactions observed here. More sophisticated theoretical approaches that predict faster collision rates arising from dipole "locking", such as ADO theory,[52] are difficult to apply in the case of the crowns since the overall dipole moment of the molecule depends on conformation, which is not known in these experiments. Finally, it is possible that these polarization-based collision theories, which assume point charges and do not account for conformational changes during a collision, may be inadequate to calculate collision rates for large ligands with multiple dipoles.

Significantly, for all four ligands, the reaction efficiency is not constant as the metal cation is varied. The most obvious way in which the alkali metal cations differ from each other is in size, and, therefore, in charge density. This is examined in Figure 2, where reaction efficiencies are plotted as a function of $1/R^3$ (R = alkali metal ionic radius). Although the precision of the data is relatively poor, several interesting trends are evident. The efficiencies are not controlled by the efficiency of radiative cooling, because in that case the *less* exothermic reactions involving the less charge-dense cations would be expected to be the *most* efficient. Linear least-squares fitting of the results for each ligand yields functions that extrapolate to approximately zero reaction efficiency as $1/R^3$ approaches zero. This is physically reasonable, because one would expect no reaction for an infinitely diffuse cation. The slopes also appear to correlate with ligand size, with larger slopes for the larger ligands. We speculate that this effect arises from the fact that the larger ligands are more polarizable and contain more permanent dipoles, and therefore are more susceptible to the polarizing influence of the cation. Thus, the data can be accounted for by cation-induced conformational changes that promote complex formation. Examination of additional systems, particularly as the flexibility of the ligand is systematically varied, should shed further light on this issue.

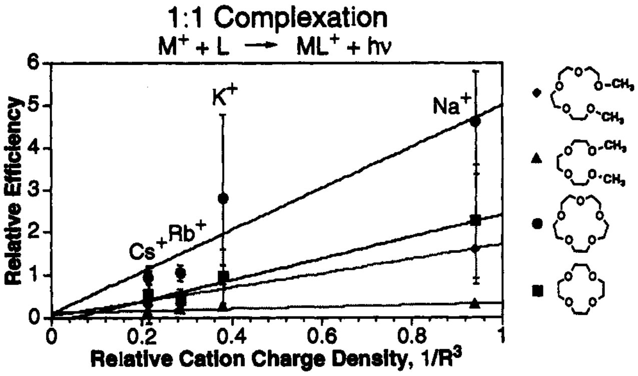

Figure 2. Relative efficiencies for attachment of alkali metal cations to triglyme, 12-crown-4, tetraglyme, and 15-crown-5 as a function of the cube of the cation radius,[84] which is a measure of relative charge density. Lines are linear least-squares fits to the data for each ligand, and error bars represent standard deviations for repeated measurements.

Size–Reactivity Relationships. (a) 1:1 Complexation. The results can be analyzed for size effects in at least two ways. *Cation* size effects are apparent when reactivity is examined as the cation is varied for a given ligand, while *ligand* size effects can be explored by examining variations in reactivity as the ligand is varied for a given cation. Cation size effects on the rates of 1:1 complexation were discussed above.

The effects of varying ligand size are also of interest. For each metal, the values increase with ligand size. It is not surprising that the reactions are faster for the larger homologs. The larger species have greater polarizabilities, and therefore greater collision cross sections. Further, the density of states at a given energy is larger for the larger molecules, increasing the lifetimes of the collision complexes and the probability that stabilization of the complexes to form products will occur.

(b) 1:2 Complexation. The kientics of 1:2 metal–ligand complex formation ("sandwiching") are extremely interesting in that both size effects and macrocyclic effects are readily apparent. As we have noted,[32] the rate constants for these reactions are very small when the ionic radius of the metal is smaller than the cavity radius of the crown. This is dramatically evident when the reaction efficiencies for 1:2 complexation involving the various crowns are plotted against the ratio of ionic radius to cavity radius (Figure 3). Data for 12C4, 15C5, and 18C6 all fall on approximately the same curve. The "sandwiching" reaction was not observed for 21C7, which has a cavity larger than that of any of the alkali cations. For the smaller crowns, when the ratios are less than one, the reaction efficiencies are too small to measure using our technique. When the cation size matches the cavity size (as in the instance of 18C6 and K^+), the efficiency is barely measurable (relatively high ligand pressures, on the order of 10^{-6} Torr or higher, must be used), and as the ratio increases reaction efficiency increases precipitously. Optimum reaction efficiency occurs at a cation:cavity ratio of about 1.25:1, then appears to fall. The decrease may have the same origin as the observed decrease in 1:1 complexation efficiency with decreasing ion charge density.

It is interesting to note that some degree of size dependence is evident in the 1:2 kinetics even for the acyclic glymes. The reaction efficiencies (Table IV) for L = triglyme are very small for M = Li and Cs, peaking for M = K. For tetraglyme, the same sort of pattern is evident: the reaction for M = Li was too slow to measure, and efficiencies increase with metal size and peak for M = Rb and then decrease again for M = Cs. This indicates that

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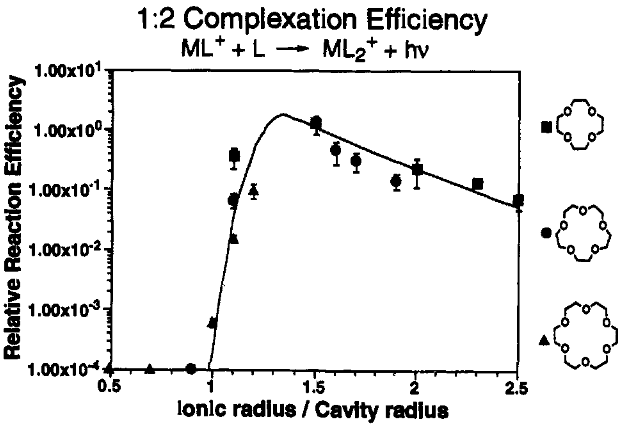

Figure 3. Reaction efficiencies for formation of 1:2 alkali metal–ligand "sandwich" complexes of 12-crown-4, 15-crown-5, and 18-crown-6, as a function of the ratio of ionic radius[84] to crown cavity radius.[85]

a preorganized binding cavity in the ligand is not a necessary condition for guest size-dependent kinetics.

Macrocyclic Effects. The comparison between 1:1 complexation reaction efficiencies for the cyclic and acyclic ligands provides another example of a gas-phase macrocyclic effect,[33] which has heretofore been noted primarily in solution. The term "macrocyclic effect"[41] refers to the ability of cyclic ligands to form complexes more selectively, and with higher stability constants, than the corresponding acyclic ligands. The differences arising from the macroring are even more apparent when reaction efficiencies are considered. The glymes and corresponding crowns have nearly equal polarizabilities, yet the relative reaction efficiencies for the crowns are greater by approximately a factor of 4. This is most likely due to more favorable configurational entropy in the case of the crowns. We have not yet undertaken variable temperature experiments that would shed further light on the entropic origins of this effect.

The slopes of the plots of reaction efficiency vs. relative charge density are in the order triglyme < tetraglyme < 12C4 < 15C5. It is curious that the cyclic ligands appear to be more strongly influenced by charge density than the acyclic ones, especially in view of the fact that the difference in polarizabilities between the glymes and the corresponding crowns is small (the polarizabilities of the glymes are slightly higher than those of the crowns). This again may arise from more favorable configurational entropy in the case of the crowns, which have binding cavities with at least some degree of preorganization such that all the dipoles in the crown can act in concert more easily than in the case of the acyclic ligands.

Macrocyclic effects for these systems in the gas phase were first noted when the 1:2 complexation kinetics for crowns and the corresponding acyclic glymes were compared.[33] The cyclic ligands react significantly more rapidly and with greater kinetic selectivity than their acyclic counterparts. In solution, such effects are often attributed to the greater degree of "preorganization"[80] of the crowns in conformations favorable for binding cation guests. The crowns undoubtedly enjoy a large advantage in configurational entropy, but in solution the macrocyclic effect can also be attributed to a higher degree of solvation for the open-chain molecules.[81–83] Entropic effects are expected to be more important in the gas phase, where solvation is absent.

An additional, simple rationalization for the observed differences in the rate constants of the cyclic and acyclic ligands deals with the degree to which the first ligand is able to sterically block the cation center and impede the approach of a second ligand. The acyclic polyethers are less restricted than the more rigid crowns in their ability to surround the cation center. The 1:2 complexation kinetics data probably reflect the degree to which the cation is encapsulated by the first ligand. Steric interactions prevent the approach of a second ligand close enough to electrostatically bind the cation in cases where the ion is "buried" in the ligand binding cavity.

Conclusions

The gas phase provides an important new perspective on crown ether chemistry and on molecular recognition in general, because gas-phase studies allow intrinsic host–guest interactions to be examined directly, without solvent perturbations. We believe fundamental new insights can be gained using this approach. For example, the intrinsic affinities of small crown ethers for alkali metal cations increase as the number of donor groups increases. This is a much simpler picture than is seen in solution where binding constants depend on trade-offs between intrinsic cation affinities and the solvation energies of the cations and the ligands. Macrocyclic effects are also clearly evident in the gas phase, where they must arise from configurational, rather than solvent, effects. The differences between the proton and cation affinities of corresponding cyclic and acyclic ligands also have general implications. The proton affinities of triglyme, tetraglyme, and penta(ethylene glycol) are greater than those of 12-crown-4, 15-crown-5, and 18-crown-6, respectively, in agreement with earlier equilibrium mass spectrometric studies. The Li^+ affinity of 15-crown-5, however, is greater than that of tetraglyme, and 18-crown-6 has higher affinities for all the alkali cations studied than those of penta(ethylene glycol). This suggests that ligand flexibility is important for proton binding, while a preorganized cavity is more important for alkali cation binding.

The study of multidentate ligands also has important implications for gas-phase ion–molecule chemistry. Experiments based on collisional methods yield different relative cation affinities than do equilibrium "bracketing" measurements. The former are difficult to interpret, while the latter are easily rationalized, suggesting that caution should be used when interpreting fragmentation data to estimate the relative cation affinities of multidentate ligands. It is clear that binding cavity–ionic guest size relationships can have profound effects on both the kinetics and thermodynamics of the host–guest interactions. Cations residing *within* the binding cavity of a ligand behave very differently from those attached *outside* the cavity. It is our hope that this chemistry will develop into a powerful new probe of ion binding sites and of the conformations of cation-attached species in the gas phase.

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