

system is transformed to the minimal CIMA system and high-frequency oscillations appear. Then, in a subsequent step, products that are inert or play a secondary role in the high-frequency oscillations initiate the LL oscillations. Note that two of the input reactants in the CIMA-Cl system, IMA and Cl^- , appeared as "inert products" of the minimal CIMA system.

Experiments are in progress in our laboratories to address the following questions:

i. What is the mechanism of the LL oscillations in the CIMA-Cl system? Here, the reversibility of the malonic acid iodination³¹ (dissociation of iodomalonic acid to malonic acid and hypoiodous acid) and the reaction of hypoiodous acid with chlorine ion to form $\text{ICl}^{32,33}$ may play an important role.

ii. Do the reactions and principal components of the LL oscillations play an important role in the Turing experiments? Since the residence times in the gel of a Turing experiment are relatively long (1000 s or more), accumulation of reaction products such as chloride ion and iodomalonic acid is unavoidable. This suggests that these components could contribute to the formation of Turing patterns.

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Gas-Phase Selectivities of Crown Ethers for Alkali Metal Ion Complexation

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Abstract: Gas-phase size selectivities of crown ethers have been investigated by application of the kinetic method. Ion complexes of crown ethers with two different alkali metals were generated by liquid secondary ion mass spectrometry. Upon gas-phase isolation and high-energy dissociation, these complexes predominantly produced crown ether/alkali metal adduct ions. The abundance ratios of product ions were correlated to the alkali metal ion selectivities of the crown ether. The concept of "maximum contact point" best described gas-phase selectivities because binding preferences were for a smaller metal diameter than what is predicted by the "best fit" concept. The following orders of selectivities were observed for alkali metal ions: 15-crown-5, $\text{Li}^+ \gg \text{Na}^+ > \text{K}^+ > \text{Cs}^+$; 18-crown-6, $\text{Na}^+ \geq \text{K}^+ > \text{Li}^+ > \text{Rb}^+ > \text{Cs}^+$; and 21-crown-7, $\text{K}^+ > \text{Na}^+ \geq \text{Rb}^+ > \text{Li}^+ > \text{Cs}^+$. Theoretical studies agree with the present selectivity of 18-crown-6 for sodium ion in the absence of solvation effects. Also, steric and/or pseudo-solvation effects on gas-phase selectivities were evaluated. Complexes of crown ether dimers with two different alkali metal ions were examined, and 18-crown-6 showed a binding preference for potassium over sodium ion.

Introduction

The principles of understanding many biological phenomena, such as enzyme binding and signal transmission across cell membranes, are based on molecular recognition and host-guest binding interactions.¹ The selective binding involved in host-guest complexation requires an optimum or "preorganized" structure for each substrate prior to possible electrostatic or hydrogen-bonding interactions.² These processes are highly influenced by solvation effects.³ Macrocycles such as cage cryptands, which have isolated cavities,⁴ and substituted lipophilic crown ethers⁵ have been designed to study the factors of preorganization and solvation energy in recognition and complexation. However, controversy remains concerning the importance of solvent effects on host-guest selectivities. Gas-phase media provide an optimum environment to study the intrinsic behaviors of host-guest interactions.

Previously, alkali metal/crown ether binding in solution has been investigated by several experimental techniques including calorimetric titration,⁶ potentiometry with ion-selective electrodes,⁷ NMR spectroscopy,⁸ and ultrasonic absorption kinetic methods.⁹ These studies provide a comparison when the solvation energy and ion-pairing effects dominate selectivities. The investigation of

gas-phase encapsulation of alkali metals by crown ethers provides a systematic model for understanding the direct influence of the electronic properties of the enclosing cavity on selective electrostatic interactions. Recent theoretical studies of solvation effects¹⁰ and solvent-induced preorganization¹¹ of ligands have been reported

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Table I. Ion Complexes Observed from Ionization of Crown Ethers (C) and Alkali Metal Halides (MX)

$(C + M)^+$	crown ether/alkali metal
$(C + M + C)^+$	crown ether dimer/alkali metal
$(C + M \cdot M \cdot X)^+$	crown ether/alkali metal dimer
$(C + M \cdot M' \cdot X)^+$	crown ether/mixed-alkali metal dimer
$(C_2 + M \cdot M' \cdot X)^+$	crown ether dimer/mixed-alkali metal dimer

and provide an interesting comparison of selective interactions of crown ethers with alkali metals to present gas-phase results.

Mass spectrometric techniques have been used previously to establish facile methods for measurements of thermodynamic stability constants of crown ether complexation with alkali metal ions.¹² Also, selective complex formation has been observed by fast atom bombardment ionization of a solution of crown ethers and alkali metal halides.¹³ However, these studies report selectivities similar to solution results obtained by other techniques, since the measurements were directly based on abundances of desorbed ions from a liquid matrix. The host-guest chemistry of macrocycles formed and evaluated in a purely gas-phase environment was first reported for selective reactions of crown ethers and their perfluorinated analogues with molecular oxygen and fluoride ions.¹⁴ These studies suggested possible size selectivities between different substrates and indicated that both topological and chemical interactions affected the complexation reactions.

More recently, gas-phase reactions of crown ethers and alkali metal ions were examined by ligand exchange experiments.¹⁵ It was reported that alkali metal ions bound to a smaller crown ether exchanged to any crown ether with a larger cavity size. Additionally, crown ether dimers bound by alkali metal ions were generated only when the metal was not completely encapsulated by the ether. The present study applies the kinetic method¹⁶ to the dissociation of complexes of ethers with two different alkali metals. This study qualitatively determines size selectivities of crown ethers in a solvent-free environment and also evaluates pseudo-solvent effects on selectivities.

Experimental Section

Instrumentation. A JEOL HX110/HX110 tandem mass spectrometer¹⁷ was operated at an accelerating voltage of 10 kV in the liquid secondary ionization (LSIMS) mode. A primary Cs⁺ beam generated from a JEOL cesium gun operated at 26 kV and 1.7–2.2 A was used. A postacceleration voltage of -20 kV was used at the detectors. The resolution of both mass spectrometers was 1:1000. For collision induced dissociation (CID) experiments, the collisions occurred at 7 keV with the collision cell floated at 3 kV above ground. The helium collision gas was metered to cause 50% attenuation of the main beam.

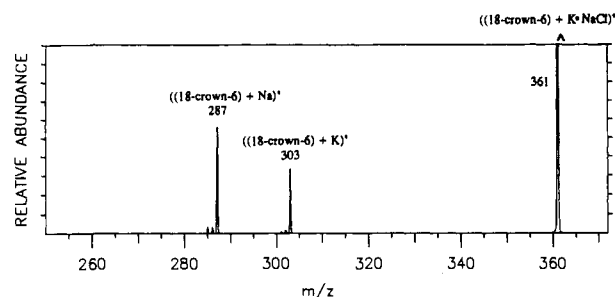
Materials. 12-Crown-4, 15-crown-5, and 18-crown-6 were purchased from Aldrich (Milwaukee, WI), and 21-crown-7 was purchased from Parish Chemical Company (Orem, UT). All alkali metal halides were purchased from Aldrich. The matrix used for LSIMS was *O*-benzylglycerol, purchased from Sigma Chemical Company. All materials were used without further purification.

Alkali Metal/Ether Complex Ion Formation. Solutions of alkali metal halides (1 M) and ethers (1 M) in water were combined with an equal volume of the matrix, and approximately 0.5 μ L was applied to the probe tip for analysis. Alkali metal/ether adduct ions were generated by the LSIMS technique, and ions corresponding to alkali metal adducts of polyethers were also observed. A combination of solution and gas-phase

Table II. Ionic Diameters and Cavity Sizes^a

cation	ionic diameter, Å	polyether ring	cavity size, Å
Li ⁺	1.36	12-crown-4	1.2–1.5
Na ⁺	1.94	15-crown-5	1.7–2.2
K ⁺	2.66	18-crown-6	2.6–3.2
Rb ⁺	2.94	21-crown-7	3.4–4.3
Cs ⁺	3.34		

^a Reference 7a.

**Figure 1.** CID spectrum of $((18\text{-crown-6}) + K \cdot NaCl)^+$ complex.

reactions resulted in metal adduct ion formation in the LSIMS mode.¹⁸ Table I provides a list of the ions observed from ionization of crown ethers (C) and alkali metal halides (MX). Generally, crown ether/alkali metal halide complexes of the $(C + M \cdot M \cdot X)^+$ type were present in 1% abundance relative to the crown ether alkali metal adduct ion $(C + M)^+$. Ionization of 21-crown-7 in an equimolar solution of potassium and rubidium chloride without *O*-benzylglycerol was investigated to establish a basis for relative abundances of possible complex ions generated without the presence of a matrix which competes for alkali metal binding. Complex ions of $(C + M \cdot M \cdot X)^+$ or $(C_2 + M \cdot M \cdot X)^+$ were more abundant than ions of the type $(C + M + C)^+$, especially when metal ion diameters and cavity sizes were compatible. Table II. Gas-phase selectivities of crown ethers for alkali metals were studied by formation of mixed crown ether/alkali metal halide complexes and subsequent CID experiments. The relative ratios of the fragment ions formed by CID of a selected complex are not dependent on the concentrations of the salts, matrix, or crown ethers in the source. This supports the idea that the selectivities measured by the kinetic method are not simply a reflection of concentration-dependent cluster formation, but instead represent actual competitive binding interactions.

The kinetic method has been applied to other complex systems in which multiple binding interactions are operative.^{16c,d} These systems include deoxynucleosides^{16c} and amino acids.^{16d} For these other studies and the present one, it is assumed that the frequency factors for cleavages of the multiple binding interactions are similar, and the multiple collision environment for adduct formation (i.e., in the ion source) approaches thermal equilibrium. Thus, we emphasize that the values reported in this study are estimates and are derived from a method which involves several substantial approximations. However, on the basis of the reproducibility of the dissociation spectra under a variety of conditions, we feel that relative binding selectivities can be extracted from the data.

Results and Discussion

Selectivities of cyclic ethers for alkali metal complexation in the gas phase have been examined by the application of the kinetic method. This method has been employed to quantitate relative gas-phase basicities using reactions that have similar frequency factors and negligible reverse activation barriers.¹⁶ These assumptions are not clearly delineated for crown ether/alkali metal ion complexes. However, under the experimental conditions of this study, the relative peak intensities of the product ions from collisional activation still give a qualitative measure of the relative affinities of crown ethers for alkali metal ions. Complexes of crown ethers with two different alkali metals were formed by the LSIMS technique. These complexes were isolated in the gas phase and activated by high-energy collisions. Upon dissociation, mostly fragment ions such as crown ether/alkali metal adducts, i.e., $(C + M)^+$, were observed. This dissociation pattern suggests that

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Table III. Ratios of Percent Abundances of Bis(alkali metal) Halide Product Ions to Crown Ether/Alkali Metal Complex Ions^a

$$(C + M \cdot M \cdot X)^+ \xrightarrow{\text{CID}} (C + M)^+ + (M + MX)^+$$

alkali metal	12-crown-4 (M + MX) ⁺ :(C + M) ⁺	15-crown-5 (M + MX) ⁺ :(C + M) ⁺	18-crown-6 (M + MX) ⁺ :(C + M) ⁺
Li	5:95	1:99	1:99
K	84:16	36:64	21:79
Cs	94:6	66:34	53:47

^aThe ratios were calculated from CID spectra that contained an average of three to five accumulated scans.

Table IV. Selectivities of Crown Ethers for Alkali Metal Ion Complexation Based on Product Ion Ratios of (C + M)⁺ to (C + M')⁺^a

$$(C + M \cdot M' \cdot X)^+ \xrightarrow{\text{CID}} (C + M)^+ + (C + M')^+ + (M + M'X)^+$$

15-crown-5	Li > Na	Li > K	Li > Cs	Na > K	Na > Cs	K > Cs
	100:10	100:2	100:1	100:10	100:3	100:15
18-crown-6	Na > Li	K > Li	Li > Rb	Li > Cs	Na > K	Na > Cs
	100:40	100:40	100:40	100:10	100:60	100:3
21-crown-7		Rb > Li	Li > Cs	K > Na	Na > Rb	Na > Cs
		100:50	100:60	100:85	100:80	100:85
						K > Rb
						100:60

^aThe numbers were calculated from CID spectra that contained an average of three to five accumulated scans. Alkali metal halides of chlorides and iodides were examined in several cases, and the general selectivity trend remained the same.

complexes held only by electrostatic or van der Waals forces are formed and was the basis for application of the kinetic method. Clearly, the two alkali metals in a complex such as ((18-crown-6) + K·Na·Cl)⁺ may qualitatively experience different interactions with the crown ether; however, alkali metal solvation effects are completely absent in these experiments, and most importantly, the dissociation patterns are independent of the initial metal salt concentrations used to form the complexes. Figure 1 illustrates the selectivity pattern for 18-crown-6 from dissociation of the ((18-crown-6) + K·Na·Cl)⁺ complex.

The process of alkali metal complexation by crown ethers in solution has been described by concepts of "preorganization",² "macrocyclic effect",¹⁹ and "best fit".^{6,20} The results of collision induced dissociation experiments are partly described with these concepts in mind. The "macrocyclic effect", which accounts for the disparity of complexation selectivities and binding affinities between cyclic and acyclic ether analogues, has been investigated in a parallel study by application of the kinetic method to ether dimer/alkali metal ion complexes, (C₁ + M + C₂)⁺. The present study focuses on the selectivities of the cyclic ethers for different alkali metal ions from dissociation of crown ether/mixed-alkali metal dimer complexes, (C + M·M'·X)⁺. Alternatively, dissociation of the crown ether/alkali metal dimer complexes (C + M·M·X)⁺, provides information about relative metal ion affinities vs cavity sizes.

Collision-induced dissociation of (C + M·M·X)⁺ complexes generated two types of product ions, (C + M)⁺ and (M + MX)⁺, and the results are summarized in Table III. The abundance ratio (M + MX)⁺:(C + M)⁺ decreases as the size of the crown ether increases. When the metal ion and cavity sizes are not compatible on the basis of a simple encapsulation model, such as cesium binding to any of the crown ethers studied, the ratio (M + MX)⁺:(C + M)⁺ is largest. These results indicate that the metal ion affinities of the crown ethers increase with cavity size, but give no qualitative description of selectivities. The increase in metal ion affinities as the crown cavity size increases can be attributed to the increasing number of oxygen donor sites, which facilitates multiple electrostatic bonding interactions to the positively charged metal ion. Alternatively, a change in the metal:cavity size ratio

could also lead to a change in the frequency factor for the metal-ether dissociation reaction.

For evaluation of selectivities, the crown ether/mixed-alkali metal dimers (C + M·M'·X)⁺ were examined. Collision-induced dissociation of these complexes resulted predominantly in the formation of two fragments: (C + M)⁺ and (C + M')⁺. The results of this dimer study are shown in Table IV. Under the present experimental conditions, it is assumed that the crown ether/metal ion complex of greater abundance represents the preferred host-guest binding. Selectivities or preferences of crown ethers for alkali metals in the gas phase is perhaps best described by a "maximum contact point" (MCP) concept rather than the "best fit"^{6,20} concept. The "best fit" is defined so that the predicted preference in solution will be for the cation whose ionic radius best matches the cavity sizes determined from atomic models and crystal structures. However, "maximum contact point" predicts that, in the absence of solvation effects, the preferences of the ethers will be for a slightly smaller cation because this achieves a higher electric field-dipole interaction within the cavity for a given conformation of the ether. The MCP concept emphasizes the importance of the structural flexibility of the crown ether and its ability to maximize crown-cation interactions, and this serves as a basis for derivation of energy-optimized structures of complexes in molecular mechanics studies.¹⁰ For example, in the present gas-phase studies the selectivity of 15-crown-5 for alkali metal ions is Li⁺ >> Na⁺ > K⁺ > Cs⁺. The trend for 18-crown-6 follows Na⁺ > K⁺ > Li⁺ > Rb⁺ > Cs⁺, and the selectivity of 21-crown-7 is K⁺ > Na⁺ > Rb⁺ > Li⁺ > Cs⁺. Although the cavity size of 15-crown-5 fits optimally with the Na⁺ ion, the preference of 15-crown-5 is for the Li⁺ ion. The preferences of 15-crown-5 for Li⁺, 18-crown-6 for Na⁺, and 21-crown-7 for K⁺ suggest that the selectivity of each cyclic ether is for the next smaller metal diameter than what is predicted by the concept "best fit".

In all cases, the formation of Cs⁺/crown ether ions is disfavored following collisional activation of the crown ether/mixed-alkali metal adducts. This is presumably because it is difficult for the macrocycle to maximize the Cs⁺/crown interaction while also minimizing Cs⁺/crown van der Waals repulsion.¹⁰ Even though the cesium ion has a relatively good fit in the 21-crown-7 cavity, the repulsive terms remain significant. Moreover, crystal structures of crown ethers with various alkali metal ions have shown that the out-of-plane distance from the metal ion to the crown ether molecule increases as the size of the alkali metal ion increases.²²

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On the other hand, the retention of the lithium ion is favored only in the case of 15-crown-5, whereby lithium ion can simultaneously interact with all cavity oxygens. Lithium ion appears to be bound only relatively loosely to 18-crown-6 and 21-crown-7. For these latter two macrocycles, only the cesium ion interactions are even more strongly disfavored. Steric effects or electronic properties of the enclosing cavity also influence structural preferences for complexation. Comparison of the binding of lithium and rubidium ions to 18-crown-6 and 21-crown-7 provides a unique example of molecular size recognition; whereas 18-crown-6 selects lithium ion by a factor of 2, the 21-crown-7 prefers rubidium ion.

From a comparison of the present gas-phase results to solution studies, the gas-phase selectivity trend of 15-crown-5 is most similar to the trend observed in less polar solvents where solvation effects are minimum.^{23a} It has been pointed out that metal ion solvation effects are a dominant contribution to observed equilibria in solution. For example, in propylene carbonate,^{23a} the log equilibrium constants measured by conductivity methods for complexation of 15-crown-5 were 4.26 for Li⁺, 3.7 for Na⁺, 3.41 for K⁺, 3.04 for Rb⁺, and 2.69 for Cs⁺. In an aprotic solvent such as acetonitrile, the values^{23b} measured were 3.60 for Li⁺, 5.28 for Na⁺, and 2.98 for K⁺, and all of the latter values adhered to the "best fit" concept. In fact, in one comprehensive study^{23c} of solvation effects on the interactions of Na⁺ with 15-crown-5, the log equilibrium constants ranged from 1.49 in 20% methanol to 2.97 in 90% methanol. Numerous other solution studies report equilibrium constants that vary with the nature of the solvent, but few report results for the entire array of alkali metal ions. Moreover, theoretical treatment of 18-crown-6 predicts that the sodium ion complex is thermodynamically more stable than the potassium ion complex in the absence of solvation effects.^{10a,c} More comprehensive theoretical treatments of macrocyclic binding are not yet available; however, this first-case agreement with the present gas-phase results suggests that the intrinsic selectivities of macrocycles can be evaluated *experimentally* by application of mass spectrometric techniques.

It was suggested earlier that structural factors such as "preorganization" of the precursor dimer ion may influence selectivities. For investigation of this hypothesis and to evaluate steric and/or pseudo-solvation effects on selectivities, complexes of (C₂ + M·M'·X)⁺ were examined. In this context, "pseudo-solvation" refers to increased complexity of or increased steric/structural constraints within the selected adduct undergoing unimolecular dissociation. In solution, solvation effects result from equilibrium intermolecular processes; in the gas-phase, the observed changes in cation binding selectivity result from the intramolecular interaction within the different combinations of cations, ethers, and associated anions. Because gas-phase selectivities from Table IV did not follow the best fit concept, dimer complexes of 15-

crown-5 with sodium and lithium ions, 18-crown-6 with sodium and potassium ions, and 21-crown-7 with potassium and rubidium ions were generated as pseudo-solvated clusters and reexamined for this additional study. The complexes were produced from the same LSIMS mode described earlier, but this time the adducts formed with incorporation of two (rather than one) crown ether molecules were selected for CID experiments. The second crown ether molecule serves as a simple model of a competitive binding force, such as might be derived from a solvent shell. In all three cases, selectivities of the crown ethers were shifted more toward the larger metal ion. For example, dissociation of ((18-crown-6)₂ + K·Na·Cl)⁺ results in a fragment ion, (18-crown-6 + K)⁺, that is more abundant than (18-crown-6 + Na)⁺. Presumably the additional crown molecule effectively shields or solvates the salt molecule, and the resulting alterations in selectivity more closely mimic trends observed in solution. Likewise, these effects increase the selectivity of 15-crown-5 for sodium ions from 10% to 70% relative to lithium ions. The effects of the additional ether molecule also resulted in an equal preference for potassium and rubidium ions by 21-crown-7, as compared to the preferred selectivity for potassium ions by 21-crown-7 in the nonsolvated case.

Conclusion

The selectivities of crown ethers for alkali metal ion complexation have been studied in a solvent-free condition. The kinetic method was used to estimate relative affinities of crown ethers for alkali metal ions, and the resulting gas-phase selectivities followed the concept of "maximum contact point" for alkali metal ion complexation. The observed selectivities provide experimental evidence to support predictions of selectivities determined from theoretical studies carried out to account for solvent effects. Pseudo-solvation effects were examined by evaluating the selectivities of crown ether/alkali metal clusters. Dissociation of complexes of (C₂ + M·M'·X)⁺ indicated that these pseudo-solvent effects shifted the selectivities in the direction of those observed in solution.

The structures of the complexes before dissociation may influence the product ion distribution, since it is possible that a crown ether molecule binds preferably to a metal where minimum conformational changes are required from the "preorganized" precursor ion. Currently, experiments are being designed to form these complexes from spatially separated targets by a divided-probe LSIMS experiment and also by laser desorption techniques. A comparison of CID results for complexes formed by different techniques may prove useful in understanding the effect of preorganization in CID results. Also, the structures of these complexes are presently being evaluated by application of molecular mechanics calculations.

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