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New frontiers in host-guest chemistry: The gas phase

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Abstract. Aspects of host-guest complexation are examined in the solvent-free environment of a mass spectrometer. A kinetic dissociation method is used to determine orders of relative ammonium and alkali metal cation binding affinities of an array of model hosts, such as crown ethers and their acyclic analogs. Size-selective effects on binding are observed from these gas-phase experiments. The binding properties of complexes bound by multiple hydrogen-binding interactions are examined by collisionally activated dissociation techniques.

INTRODUCTION

The ability to examine host-guest chemistry without the influence of solvent effects opens up new avenues for understanding some of the fundamental details of molecular recognition. Our recent investigations of host-guest chemistry in the *gas* phase have shown that the intrinsic nature of binding interactions and size-selectivity of complexation can be studied from a solvent-free perspective. Although up to now gas-phase studies have involved relatively simple macrocyclic host models and simple spherical guests, future advances may lead to a novel approach to evaluating biological processes, such as antibiotic interactions with alkali metal ions.

The chemistry of macrocycles has become increasingly important in recent years for understanding principles of host-guest binding in molecular recognition. In particular, crown ethers and their complexes are useful for modeling biologically relevant ion transport processes, enzyme catalysis, and antibody-antigen association. Intermolecular and intramolecular hydrogen-bonds and other electrostatic interactions are arguably the most important interactions in molecular self assembly and molecular recognition in solution chemistry. The phenomena of multiple binding interactions is especially well-modeled by crown ethers which have several identical oxygen donor sites which participate as hydrogen-bond acceptors.

We have undertaken an examination of the bimolecular and dissociation reactions of macrocycles in order to evaluate ligand affinities and the structure of host-guest complexes in the gas phase. In order to examine the intrinsic interactions involved in the host-guest chemistry of these systems, we have undertaken an investigation of crown ether complexation with the proton or ammonium ions in the gas phase. In the present work, a systematic evaluation of the intermolecular binding forces responsible for the association of crown ethers (hosts) with amines (guests) is presented. The relative strengths of hydrogen-bonding interactions of crown ether/amine ion-complexes are examined with respect to macrocyclic size effects, the gas-phase basicities of thirteen different amines and three crown ethers, and the number of possible binding interactions. Table 1 shows the diameters of the guest ions of interest and the cavity sizes of the crown ethers.

EXPERIMENTAL

Measurements were performed in three types of mass spectrometers: a Finnigan triple stage quadrupole mass spectrometer (TSQ-70) equipped with a chemical ionization source, a Finnigan Ion Trap Mass Spectrometer with a laser desorption probe, and a four sector JEOL/HX110/HX110) with a fast atom bombardment source. For the triple quadrupole experiments, the samples were introduced by a direct insertion probe, and typical sample pressure was 1-3 x 10^{-6} torr. Ammonia

was admitted into the source to 2 torr as a chemical ionization agent. For the ion trap experiments, samples were introduced through leak valves or on a probe. The kinetic method was used to determine the orders of relative cation (i.e. ammonium, proton, alkali metal ion) affinities of the various ethers. This method involves forming an ion-bound adduct of two compounds, M_1 and M_2, bound by a cation and designated as $(M_1 + C + M_2)^+$. The adduct is then energized above its dissociation threshold by low energy collisional activation, and the abundances of the resulting fragment ions, such as $(M_1 + C)^+$ and $(M_2 + C)^+$, are measured. Based on the ratio of these abundances, the relative affinities for the C^+ cation by each ether can be estimated.

DISCUSSION

In solution, macrocycles demonstrate size-selective complexation with alkali cations. In fact, there is a *best fit* between any macrocycle and a specific alkali metal ion, and this is termed the hole-size rule. Likewise in the gas phase, there are several important parameters that contribute to relative ligand affinities: cavity diameter, and the nature and number of donor atoms (any heteroatom).

Orders of relative gas-phase proton and ammonium ion affinities

A typical experiment which demonstrates the kinetic method for measurement of proton or ammonium ion affinities is shown in Figure 1. The ammonium ion complex of 15-crown-5 (15-C-5) and tetraethylene glycol dimethyl ether (4-GLYME) is formed by ion-molecule reactions of NH_4^+ with a mixture of the ethers in the ion source. The (tetraethylene glycol dimethyl ether + NH_4 + 15-crown-5)$^+$ ion is collisionally activated to produce the fragment ions shown on the right side of Fig. 1.

Table 1. Radii of Cations and Cavity Sizes of Crown Ethers

Cation	Radius (Å)	Ether	Radius (Å)
NH_4^+	1.43	12-C-4	0.6-0.75
H^+	< 0.01	15-C-5	0.86-0.92
K^+	1.38	18-C-6	1.34-1.43
Rb^+	1.52	21-C-7	1.68-2.12

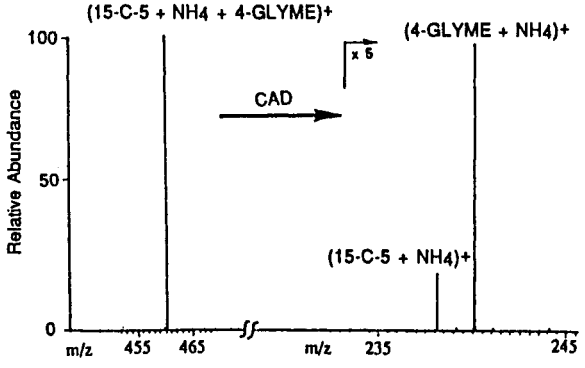

Fig. 1. Selection of (15-crown-5 + NH_4 + tetraethylene glycol dimethyl ether)$^+$ and subsequent CAD of the complex.

Based on the greater peak height of the tetraethylene glycol dimethyl ether fragment ion, it has a higher NH_4^+ affinity than 15-crown-5. On the basis of this type of experiment, orders of the relative proton affinities and ammonium ions affinities were determined and are listed in below.

H^+ AFFINITIES:

12-C-4 < 3-GLYME < 15-C-5 < 3-PROGLYME < 4-GLYME < 18-C-6 < 4-GLYCOL < 21-C-7 < 5-GLYCOL

NH_4^+ AFFINITIES:

15-C-5S < 12-C-4 < 3-PROGLYME < 3-GLYME < 4-GLYCOL < 15-C-5 < 5-GLYCOL < 4-GLYME < 18-C-6 < 21-C-7

Comparison of relative gas-phase proton affinities to ammonium ion affinities

The trends for relative proton affinities and ammonium ion affinities in Table 3 are strikingly different. For the proton affinities, there is a fairly uniform correlation of proton affinity with the number of oxygen atoms in the ether: as the number of oxygen atoms increases, the relative proton affinity increases. Also, the glycols (with hydroxyl end groups) have higher relative proton affinities than the corresponding glymes (with terminal methoxy groups). Moreover, the trend for proton affinity shows that the acyclic ether analogs typically demonstrate greater proton affinities than the corresponding cyclic compounds. The order of relative proton affinities determined herein closely matches the trend derived from Kebarle's report (1) of the relative proton affinities of polyethers obtained from proton-transfer equilibria measurements.

For the trends in ammonium ion affinities, the crown ethers with larger cavity sizes (18-crown-6 and 21-crown-7) demonstrate unusually high affinities relative to the acyclic ethers, and in fact these two crown ethers show the greatest affinities of all the ethers. The ammonium ion is a bulky tetrahedral guest with four hydrogens for possible participation in intramolecular binding to oxygen sites. The pre-organized macrocycles with larger cavity sizes more easily accomodate the configuration necessary for optimum multiple hydrogen-bond interactions to the ammonium ion, whereas the acyclic ethers have greater entropic barriers to arranging to the appropriate geometry needed to multiply bind the same guest.

Interestingly, the scale developed for ammonium ion affinities nearly duplicates those scales already reported for potassium and rubidium ion affinities. The size of the ammonium ion falls between that of the potassium and rubidium ions (see Table 1). The similar trends in cation affinities suggest that a size effect is operative, one that may reflect in part an analogy to the cavity concept that operates in solution host-guest chemistry.

Comparison of gas-phase ammonium ion affinities to solution results

There have been many reports of the determination of stability constants, rate constants, and entropic and enthalpic changes involved in complexation between crown ethers and various guests in solution. Solution studies performed in methanol or water show that the stability constants for crown ether/ammonium ion complexes are most similar to those of alkali metal ion/crown complexes in which the alkali metal ion is of similar size to the ammonium ion. In non-polar solvents, some of the predicted binding affinities are reversed compared to the trends noted in polar solvents, and this indicates that the "best fit" concept is not always strictly valid for rationalizing binding affinities. It was suggested that perhaps in the solution studies the proton involved in complexation was actually a solvated form, and thus its size was effectively much bulkier than that of a single proton.

Alkali metal ion affinities

The comparison of relative alkali cation affinities affords a systematic means of studying size-selective effects of host-guest binding in the gas phase. For example, 15-crown-5 shows the highest Li^+ affinity, whereas 18-crown-6 shows the highest K^+ affinity. The K^+ diameter is larger than the optimum cavity fit for 15-crown-5, and is almost a perfect fit for 18-crown-6.

Li^+ AFFINITIES:

12-C-4 < 3-GLYME < 4-GLYCOL < 18-C-6 ~ 21-C-7 < 5-GLYCOL < 15-C-5

K^+ AFFINITIES:

12-C-4 < 3-GLYME < 4-GLYCOL < 15-C-5 < 4-GLYME ~ 5-GLYCOL < 18-C-6

Mixed alkali metal /crown ether adducts were also formed to evaluate ligand size selectivity for each individual crown ether rather than for comparisons among a series of crowns. For example, in solution the alkali metal affinity of 18-crown-6 follows the trend:

$$K^+ > Rb^+ > Cs^+, Na^+ > Li^+.$$

In the gas phase, the trend is:

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

The difference between the gas and solution scales likely reflects the significance of solvation effects. In fact, if a sandwich complex between two crown ethers and a mixed alkali metal salt is formed in the gas phase instead of a simple crown ether/alkali metal adduct, the trend reverses. Then the affinity order becomes:

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

This suggests that the steric hindrance of the crown-solvated ligand in the gas phase better mimics the solvated ligand effects observed in solution.

Evaluation of multiple hydrogen-bonding interactions

In order to study the effects of hydrogen-bonding interactions in gas-phase host-guest complexes, proton-bound complexes between a crown ether and amine were formed and then collisionally activated to induce dissociation. The formation of only protonated crown ether molecules and/or protonated amine molecules from these types of CAD experiments was presumed to indicate that the overall weakest bonding interactions in the selected ion-complex were the hydrogen-bonds involved in complexation, and the activation barrier to dissociation by decomplexation was lower than the activation barriers for subsequent covalent bond cleavages within the crown ether or amine. Alternatively, the formation of fragment ions corresponding to covalent bond cleavages within either the amine or crown ether portion of the ion-complex was assumed to indicate that the total hydrogen-bonding association energy of the complex was sufficiently large to result in a high activation barrier to dissociation, one which also allowed access to subsequent competitive skeletal cleavages of the amine or crown ether ions.

Examples of the strikingly distinctive types of dissociation behavior obtained for two different crown ether/amine ion-complexes are shown in Fig. 2. As shown, the CAD spectra of hydrogen-bonded complexes formed between 18-crown-6 and pyridine or aminoethanol are compared. Since pyridine and 2-aminoethanol both have similar gas-phase basicities, 213.1 kcal/mole and 213.4 kcal/mole, respectively, they provide an interesting comparison of complex formation with 18-crown-6, whose gas-phase basicity is estimated as 216.0 kcal/mole. Activation of the 18-crown-6/2-aminoethanol ion-complex results in extensive fragmentation of the crown ether ring (Fig. 2B) by losses of ethylene oxide units, even under single collision conditions. In contrast, collisional activation of the 18-crown-6/pyridine ion-complex results in formation of predominantly protonated pyridine and protonated 18-crown-6 (Fig. 2A) with little fragmentation of the crown ether ring, even under multiple collision conditions.

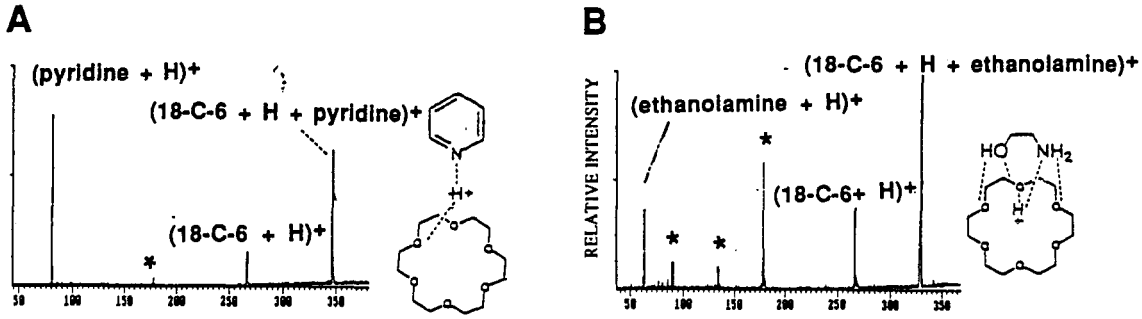

Fig. 2. CAD spectra of 18-crown-6 complex with (A) pyridine, and (B) 2-aminoethanol.

Fig. 2B shows the dissociation spectra of the 18-crown-6/2-aminoethanol complex, one in which multiple hydrogen-bonding interactions between the two organic substrates are an important factor. For example, the binding interactions may include: coordination of two of the crown ether oxygens to two of the amine hydrogens, proton-bridge formation between one of the crown ether oxygens and the nitrogen atom, and one final hydrogen bond between an ether oxygen and the hydroxyl hydrogen of the aminoalcohol. Ions due to cleavages and rearrangements of covalent bonds in the crown ether skeleton are predominant. This behavior suggests that the interaction energy of the complex is so high that the internal energy necessary to surpass the dissociation threshold is also sufficient to cause subsequent skeletal cleavages in conjunction with decomplexation reactions.

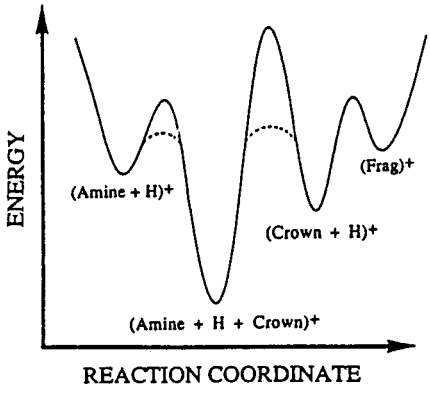

Figure 3. Proposed energy diagram for the dissociation of an amine/crown ether ion-complex. Dotted line represents a loosely-bound complex, solid line represents a strongly-bound complex.

A potential energy diagram which may used to rationalize how these complexes dissociate is shown in Figure 3. As shown by the solid line, for strongly-bound complexes both the activation barrier to decomplexation and the reverse activation energy for formation of the intact protonated crown ether are large. Under these circumstances, the protonated crown ether resulting from decomplexation is internally hot and may undergo spontaneous dissociation by cleavages of the macrocyclic skeleton, especially when the barriers to subsequent dissociation are relatively low (as is the case for protonated crown ethers). As shown by the dashed line, weakly-bound complexes have low activation barriers to dissociation, and thus subsequent skeletal fragmentation is not promoted after decomplexation.

Finally, the thermochemistry of the dissociation reactions of protonated crown ethers was estimated to obtain an understanding of the energetics of fragmentation of protonated macrocycles. The energy required for formation of each possible protonated cyclic ether and neutral cyclic ether counterpart from cleavage of the selected protonated crown ether was calculated from known heats of formation of the products and reactants (2). Each of the dissociation reactions examined are 14 - 35 kcal/mole endothermic, and these values set the lower bounds on the extra energy required by any protonated crown ether to promote dissociation. Additional energy may be required to surmount other activation or entropic barriers. However, as a first-order estimation of the energetics involved in dissociation of the crown ether/amine complexes, these numbers suggest that some of the complexes must be bound by at least 14 - 35 kcal/mole in order for the subsequent crown ether cleavages to occur.

Electronic nature of the guest ion

Not only the size of the guest ion has a significant effect on both the capability for complexation with a selected host and the structure of the resulting complex, but also the electronic nature of the guest ion plays an important role in influencing the chemistry of the host-guest association. The types of structures of the complexes formed between macrocycles and alkali metal ions or transition metal ions were evaluated by application of collisionally activated dissociation techniques. The metal ions were generated by laser desorption of metal substrates in a quadrupole ion trap, then the metal ions were allowed to attach to a macrocyclic host. The CAD spectra are shown in Fig. 4 for the complexes of

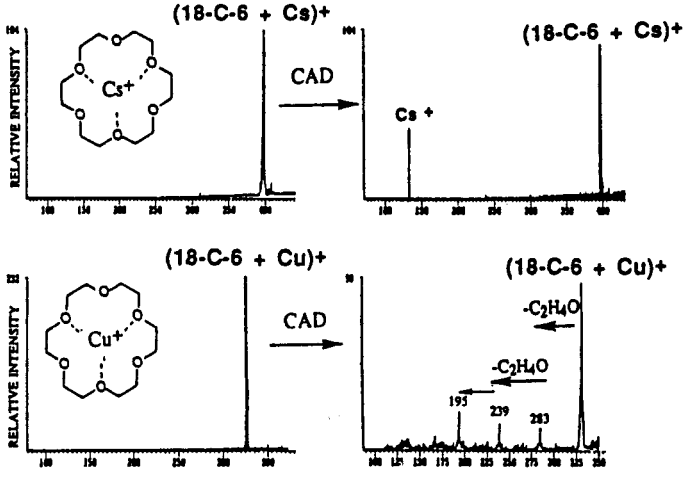

Fig. 4. Formation and activation of (A) (18-C-6 + Cs^+) and (B) (18-C-6 + Cu^+) complexes.

18-crown-6 with Cs^+ or Cu^+ ions. The (18-C-6 + Cs^+) complex dissociates exclusively to form Cs^+ ion, demonstrating that this is a loosely-bound complex held by weak electrostatic bonds. In contrast, the (18-C-6 + Cu^+) complex dissociates by consecutive losses of C_2H_4O units, indicating systematic covalent bond cleavages of the macrocyclic skeleton with retention of the Cu^+ion. The latter complex is strongly bonded with much covalent character in the metal-oxygen bonds. In fact, the Cu^+ ion may undergo insertion into C-C or C-O bonds of the polyether structure. These dramatically different CAD spectra highlight the importance of electronic factors in determining the nature of host-guest complexation.

CONCLUSIONS

The kinetic method is a versatile way to measure many types of ligand affinities of macrocycles, and size-selective binding affinities are observed in gas-phase measurements of crown ether complexes. In general, gas-phase ligand affinities do not always follow the same relative trends as solution results, however, the solution and gas phase affinities follow parallel trends when the complexity and steric effects of the gas-phase adducts is increased. The relative order determined for ammonium ion affinities of polyethers is different from that determined for proton affinities, and this is rationalized in part because of the different sizes of the cations which promote selective hydrogen-bonding interactions. The bulky ammonium ion may bind via several N···H···O bonds, whereas the proton is most favorably bound by a single near-linear proton bridge. The latter type of binding is more easily achieved by the flexible acyclic ethers rather than the crown ethers, and this is reflected in the generally higher relative proton affinities of the acyclic polyethers. Apparently the "cavity size" concept plays a role in influencing the favorability of multiple binding interactions involved in the ammonium ion/crown ether complexes. The order of relative ammonium ion affinities of crown ethers and acyclic analogs closely parallels the orders of affinities obtained for alkali metal ions of similar size (i.e. K^+, Rb^+).

The formation of multiple hydrogen-bonds can have striking effects on the dissociation behavior of amine/crown ether ion-complexes because the multiple hydrogen-bonding interactions allow formation of strongly-bound complexes, in contrast to the loosely-bound proton-bridged complexes that are typically formed by ion-molecule association reactions. Both the number of possible interactions and the difference in gas-phase basicity affect the capability of any crown ether and amine for forming a strongly-bound complex. The ability to form multiple bonds can compensate for a relatively large difference in proton binding affinity, but ultimately a very large difference in gas-phase basicity causes one substrate to be much more strongly coordinated to the proton, resulting in a less stable complex. These studies have provided insight into some of the requirements for multiple binding interactions of simple model host-guest systems in the gas phase.

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