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Comparison of Gas-Phase Proton and Ammonium Ion Affinities of Crown Ethers and Related Acyclic Analogs

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Abstract: In order to evaluate the intrinsic binding interactions involved in host–guest complexation of crown ethers with ammonium ions or protons, the relative orders of gas-phase ammonium ion and proton affinities of crown ethers and acyclic analogs have been measured by the kinetic method. The polyether/cation complexes were generated by ion–molecule reactions between ammonium ions and neutral ether substrates in the chemical ionization source of a triple quadrupole mass spectrometer. The proton or ammonium ion complexes of interest, $(M_1 + H + M_2)^+$ or $(M_1 + NH_4 + M_2)^+$, were selectively activated, and the abundances of the resulting fragment ions (i.e. single polyethers attached to a proton or ammonium ion) were measured and used to establish a relative order of affinities. The order of ammonium ion affinities of the polyethers was determined to follow the trend 12-crown-4 < triethylene glycol dimethyl ether < tetraethylene glycol < 15-crown-5 < pentaethylene glycol < tetraethylene glycol dimethyl ether < 18-crown-6 < 21-crown-7. Compared to the affinities of the acyclic ethers, the crown ethers with large cavity sizes demonstrate dramatically higher relative affinities for the ammonium ion than for the proton. This preference is attributed to the favorable ability of the crown ethers to form multiple hydrogen-bonding interactions to the bulky tetrahedral ammonium ion with an overall lower entropy of complexation. The order of relative ammonium ion affinities is similar to the orders of relative affinities for rubidium or potassium ions, both of which are cations of similar size to the ammonium ion. The structures of the crown ether/ammonium ion complexes were characterized by collisionally activated dissociation techniques, and evidence was found to suggest that the crown ethers maintain their cyclic nature upon complexation.

Introduction

The ability to examine host–guest chemistry[1-3] without the influence of solvent effects opens up new avenues for understanding some of the fundamental details of molecular recognition. Recent investigations of host–guest chemistry in the *gas* phase[4-7] have shown that the intrinsic nature of binding interactions and size-selectivity of complexation can be studied from a solvent-free perspective. In the first study, perfluorinated crown ether anions selectively reacted with O_2, but not with CO or CO_2 in the chemical ionization source of a mass spectrometer.[4] The selectivity of these reactions was attributed to both chemical and topological differences in the various substrates. In another gas-phase study, size-dependent ligand–metal ion sandwich formation was observed for a variety of crown ethers.[5] More recently, the relative alkali metal ion affinities and selectivities of an array of crown ethers and their open chain analogs were measured[6,7] by application of the kinetic method. It was found that the trends observed in the gas phase most closely paralleled those solution trends obtained for nonpolar solvent environments and that the relative differences in alkali metal ion affinities of the ethers were most dramatic for the smallest, most densely charged metal ions. 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.[2]

Many key studies of host–guest chemistry in solution have focussed on the complexation of two noteworthy guests, the proton[8,9] and the ammonium ion,[10-16] with a variety of macrocycles. The proton is an important guest for two reasons. First, it is the smallest and most charge-dense cationic guest. Second, proton-transfer reactions are among the most ubiquitous processes in all biological systems. In contrast, the ammonium ion is a bulkier guest which has the ability to promote coordination through multiple N···H···O hydrogen bonds. The ammonium ion is also commonly involved in many types of biochemical processes. The stability constants of crown ether complexation with protons or ammonium ions in solution have been extensively measured[8-17] by using such methods as conductometry,[9] potentiometry,[11-14] ultrasonic absorption,[16] and titration calorimetry.[17] Many different solvents have been used for these measurements, ranging in polarity from water[14,15] and methanol[11] to acetonitrile.[9] Additionally, the stability constants of crown ether/NH_4^+ complexes were compared to those of crown ether/alkali metal ion complexes in order to evaluate guest size effects.[11,14,15] However, in many cases, there were differences in the results obtained with different solvents, and this has made extraction of intrinsic properties impossible.

Table I. Radii of Cations[29,30] and Cavity Sizes of Crown Ethers[30]

cation	radius (Å)	crown 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

Gas-phase proton affinities of some polyethers, including the simple crown ethers, have been measured by equilibium methods in a pulsed high-pressure mass spectrometer,[18,19] and the relative order of proton affinities derived from the most recent study is NH_3 (204 kcal/mol) ≪ 12-crown-4 (221 kcal/mol) < 15-crown-5 (223 kcal/mol) < triethylene glycol dimethyl ether (224 kcal/mol)

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Table II. Ethers and Number of Oxygen Donor Atoms

ether	abbreviation	structure	no. of donor atoms[b]
12-crown-4[a]	12-C-4	$[CH_2CH_2O]_4$	4
15-crown-5	15-C-5	$[CH_2CH_2O]_5$	5
18-crown-6	18-C-6	$[CH_2CH_2O]_6$	6
21-crown-7	21-C-7	$[CH_2CH_2O]_7$	7
triethylene glycol dimethyl ether	3-glyme	$CH_3O[CH_2CH_2O]_3CH_3$	4
tetraethylene glycol dimethyl ether	4-glyme	$CH_3O[CH_2CH_2O]_4CH_3$	5
tripropylene glycol dimethyl ether	3-proglyme	$CH_3O[CH_2CH_2CH_2O]_3CH_3$	4
tetraethylene glycol	4-glycol	$HO[CH_2CH_2O]_4H$	5
pentaethylene glycol	5-glycol	$HO[CH_2CH_2O]_5H$	6

[a] The crown ether designation, *n*-crown-*m*, indicates (*n*) the total number of carbon and oxygen atoms in the ring and (*m*) the number of oxygen atoms in the ring. [b] Except in the case of 4-glycol and 5-glycol, which each have two terminal hydroxyl groups, all hydrogen-bond donors are ether oxygen atoms.

< tetraethylene glycol dimethyl ether (227 kcal/mol) < 18-crown-6 (230 kcal/mol).[18] Additionally, the strengths of hydrogen-bonding interactions involved in formation of the gas-phase complexes between alkylammonium ions[20] or protons[19] and polyethers were evaluated by application of variable-temperature equilibrium techniques. For example, it was found that the interaction energy of an alkylammonium ion with a polyether could be as much as 45 kcal/mol.[20]

In order to examine the intrinsic interactions involved in the host–guest chemistry of macrocycles, we have undertaken an investigation of crown ether complexation with a proton or ammonium ion in the gas phase, a truly solvent-free environment. The complexes of interest are formed by NH_3 chemical ionization of crown ether neutrals in the source of a mass spectrometer. Collisionally activated dissociation (CAD) techniques were used to probe the structures of the resulting complexes, and the kinetic method[21–26] was applied to measure orders of relative proton affinities and ammonium ion affinities of the crown ethers. The trends obtained in the gas phase were compared to those observed in solution, and the concept of optimum cavity fit was evaluated as a valid means to rationalize these gas-phase results. Additionally, the orders of relative affinities were compared to the orders derived for alkali metal ion affinities because alkali metal cations represent spherical guests of variable size.[7] Finally, the binding properties of acyclic ethers were also examined to assess the importance of the cyclic structure in determining host–guest chemistry (i.e. the macrocyclic effect). Table I shows the diameters of the guest ions of interest and the cavity sizes of the crown ethers, and Table II gives an overview of the polyether structures and name abbreviations.

Experimental Section

All measurements were performed in a Finnigan triple stage quadrupole mass spectrometer (TSQ-70) equipped with a chemical ionization source. The samples were introduced by a direct insertion probe, and typical sample pressure was $1-3 \times 10^{-6}$ Torr. Ammonia was admitted into the source to 2 Torr as a chemical ionization agent. Positive ions were formed by using a 70 eV electron beam at 200 μA. The source temperature was 80 °C. Under these conditions, the typical relative abundances of product ions formed was $(M_1 + NH_4 + M_2)^+$:$(M + H)^+$:$(M + NH_4)^+$ = 1:2:4, where M_1 and M_2 represent any two ethers introduced into the source. The relatively high pressure of the chemical ionization source ensures that the complexes experience hundreds of collisions, and thus equilibrium conditions are approached. Additionally, the complexes are necessarily formed by gas-phase processes because there is no operative mechanism for condensed-phase reactions.

Table III. Orders of Relative Affinities of Polyethers[a]

H^+	NH_4^+
12-C-4 (1)	12-C-4 (1)
3-glyme (2)	3-proglyme (4)
15-C-5 (20)	3-glyme (25)
3-proglyme (40)	4-glycol (350)
4-glyme (160)	15-C-5 (3500)
18-C-6 (600)	5-glycol (15000)
4-glycol (1000)	4-glyme (17500)
21-C-7 (1500)	18-C-6 (400000)
5-glycol (5000)	21-C-7 (4000000)

[a] Order of increasing affinity down the column. Given in parentheses under each compound (M) is the probability of dissociation of the proton-bound or ammonium-bound complex to form $(M + H)^+$ or $(M + NH_4)^+$ ions, respectively, relative to dissociation to form $(12\text{-crown-4} + H)^+$ or $(12\text{-crown-4} + NH_4)^+$ ions, respectively (based on a ladder of peak height measurements as shown in Figure 1). Uncertainties in all values are estimated as ±25%.

Collisionally activated dissociation spectra were obtained by using the constant precursor transmission mode. The desired precursor ion was selected with the first quadrupole and passed into the collision quadrupole at an average collision energy of 2 eV. Typical collision gas pressure was 0.6 mTorr of argon. The argon pressure and collision energy were kept low to maintain gentle activation conditions. The experiments are reproducible from day to day and show little dependence on collisional activation conditions. The signal-to-noise ratio for all spectra was at least 100:1. Absolute conversion of the selected adduct ion to the two representative fragment ions was 10–25%. All compounds except 21-crown-7 were obtained from Aldrich Chemical Co. (Milwaukee, WI) and used without further purification. The 21-crown-7 was obtained from Parish Chemical Co. (Orem, UT). Purities were >97%.

The kinetic method[21–26] was used to determine the orders of relative proton affinities and ammonium ion affinities of the various ethers. This method involves forming an adduct of two compounds, M_1 and M_2, bound by an ammonium ion or proton and designated as $(M_1 + NH_4 + M_2)^+$ or $(M_1 + H + M_2)^+$. The adduct is then energized above its dissociation threshold by low-energy collisional activation, and the abundances of the resulting fragment ions, such as $(M_1 + NH_4)^+$ and $(M_2 + NH_4)^+$, are measured. On the basis of the ratio of these abundances, the relative affinities for the NH_4^+ ion by each ether can be estimated. This sequence is repeated for many combinations of ethers to ultimately derive a complete order of affinities. For a valid measurement of affinities, the adducts should dissociate by cleavage of only the weakest binding interactions (such as the hydrogen bonds which bind the ammonium ion to the ethers), the types of binding interactions must be similar for the different compounds involved, and the structures of the compounds studied must be similar. In the context of this study, these conditions are reasonably presumed to be satisfied. Quantitative values of proton affinities are not estimated in this study because a single consistent "calibration" factor to convert ratios of ion abundances to differences in proton affinities could not be derived. For example, as shown in Table III, the relative abundance of the $(15\text{-crown-5} + H)^+$ ions is 20 times greater than the measured abundance of $(12\text{-crown-4} + H)^+$ upon dissociation of the $(12\text{-crown-4} + H + 15\text{-crown-5})^+$ complex, and the difference in their proton affinities (as reported by Kebarle[18]) is 2 kcal/mol. However, the relative abundance of the (tetraethylene glycol dimethyl ether + H)$^+$ ion is only eight times greater than that of $(15\text{-crown-5} + H)^+$ ion after dissociation of the sandwich complex, yet the difference in their proton affinities (again as reported by Kebarle[18]) is greater: 4 kcal/mol. It is not surprising that small differences in proton affinities and structures can cause reasonably large differences in the dissociation behavior of these multiply-bound sandwich complexes.

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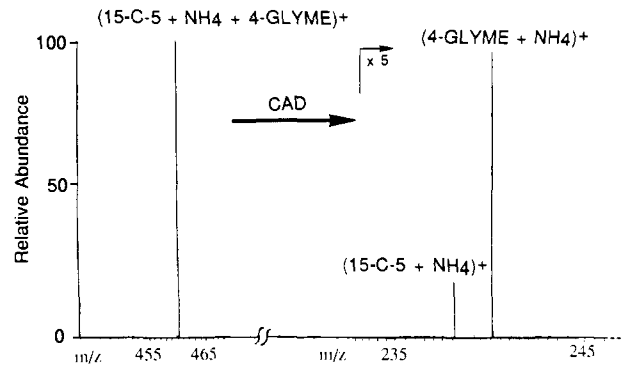

Figure 1. Mass selection of (15-crown-5 + NH_4 + tetraethylene glycol dimethyl ether)$^+$ and subsequent collisionally activated dissociation of the complex.

The kinetic method was originally derived as a means of measuring proton affinities of related compounds. On the basis of our previous use of the kinetic method for determination of alkali metal ion affinities of crown ethers,[6,7] we have shown that the method may be used to estimate other types of ligand affinities of polyethers. Additionally, the dissociation experiments discussed herein demonstrate no dependence on the concentration of the polyethers in the ionization source which suggests that the dissociation of the complexes truly reflects the intrinsic binding interactions and not simply the nature or sequence of the ion formation processes. However, it should be emphasized that the values described herein are estimates obtained by a method that has known limitations.

Results and Discussion

A typical experiment which demonstrates the kinetic method is shown in Figure 1. The ammonium ion complex of 15-crown-5 and tetraethylene glycol dimethyl ether 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 mass-selected, and then it is collisionally activated to produce the fragment ions shown on the right side of Figure 1. 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, scales of the relative proton affinities and ammonium ion affinities were determined and are listed in Table III.

Comparison of Orders of Relative Gas-Phase Proton Affinities to Ammonium Ion Affinities. The trends for relative proton affinities and ammonium ion affinities in Table III 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 earlier report[18] of the relative proton affinities of polyethers obtained from proton-transfer equilibria measurements. The similarity between the present results and the previous results serves as a validation of the kinetic method for establishing orders of binding strengths for these multiply-bound polyether complexes and offers support that the kinetic method may be used to qualitatively evaluate trends of ammonium ion affinities, ones for which there are no established gas-phase values.

It has been shown that the optimal hydrogen bonding geometry for proton attachment to polyethers involves an $O\cdots H^+\cdots O$ bond angle of 180°.[19] Such a geometry of proton coordination can be adopted for most of the polyethers assuming that the oxygen atoms involved in the bridge are located at non-adjacent ether positions. The lower proton affinity of the crown ethers is therefore attributed to their increased rigidity relative to the acyclic ethers which reduces the favorability of proton coordination via linear hydrogen bonds. Despite the fact that the glymes have polarizable methyl end groups which should enhance the basicity of the terminal oxygen atoms and thus assist in stabilization of an attached proton relative to attachment of a proton to the glycols, it is the glycols which demonstrate greater relative gas-phase proton affinities than the glymes and crown ethers. This unexpected trend in the gas phase may be related to the concept of "double action" host,[2,26] to draw an analogy to solution host–guest chemistry concepts. In solution, "double action" refers to those hosts which can stabilize an anion and cation simultaneously. For example, the oxygen atoms in glycols are electron-donating hydrogen-bond acceptors, thus able to stabilize a cation, whereas the terminal hydroxyl groups are also hydrogen-bond donors, thus able to stabilize a negatively polarized ligand. Because glycols have terminal hydroxyl groups, these end groups may also participate in intramolecular cyclization by hydrogen-bond formation between the hydrogen atom of one hydroxyl group and the oxygen atom of the other end group. In the gas-phase protonation experiments, glycols promote internal hydrogen bonding to stabilize the attached proton and may potentially further stabilize the pseudocyclized structure by interaction of the terminal groups as described for the double action hosts.

Alternatively, a less well-understood competitive binding phenomenon may cause the glycols to demonstrate greater affinities than the glymes. For example, in solution it has been shown that pentaethylene glycol and pentaethylene glycol dimethyl ether show different trends in their stability constants for complexation of Ba^{2+} vs K^+, two guests of similar size that apparently enhance different types of binding interactions.[27] The glycol shows a larger stability constant for Ba^{2+}, but the glyme shows a larger stability constant for K^+. Therefore, it is not without precedent that the glycols may demonstrate higher relative affinities than the corresponding glymes and crown ethers.

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 special ammonium ion affinities of the crown ethers are best rationalized by consideration of the favorability of the hydrogen-bonding interactions[19] possible for binding of an ammonium ion vs a proton to the polyethers. A proton is a miniscule, densely charged cation which is bound most favorably through a near linear hydrogen bridge to two oxygens in any polyether.[19] The more flexible acyclic ethers are better able to adopt the optimum geometry for hydrogen bonding, and this is reflected by their relatively higher proton affinities compared to the more rigid crown ethers. By contrast, 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 accommodate 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.[8] This explains why the cyclic ethers demonstrate particularly high ammonium ion affinities.

Interestingly, the scale developed for ammonium ion affinities nearly duplicates those scales already reported for potassium and rubidium ion affinities.[7] The size of the ammonium ion falls between that of the potassium and rubidium ions (see Table I). 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.[1-3] The proton is a far smaller cation than any of the alkali metal ion models, and thus any similarities in the relative affinity scales based on size effects are not expected.

Comparison of Gas-Phase Ammonium Ion Affinities to Solution Results. As mentioned earlier, 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.[1-3,8-17] Although the

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results of condensed-phase experiments are solvent dependent, comparison of the trends reported to those observed in this gas-phase study provides qualitative insight into differences in complexation behavior. 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.[10,13,14] Specifically, potentiometric determinations of stability constants in methanol indicate that 12-crown-4 complexes either sodium or potassium ion more favorably than the bulky ammonium ion,[10] whereas 21-crown-7 binds the ammonium ion more strongly than the sodium ion.[10] In water, 18-crown-6 binds the ammonium ion less favorably than the potassium ion,[13] presumably because the ammonium ion is too large to fit optimally in the 18-crown-6 cavity and the ammonium ion itself is better solvated by water. In nonpolar 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.[10,12,14] Despite the occurrence of such solvation effects, it is interesting that certain parallels between trends for selective alkali metal ion binding and ammonium ion binding in solution and the present gas-phase studies can be drawn: clearly some size effects are operative in both the gas phase and solution.

The trend measured for proton complexation constants of polyethers in acetonitrile was 12-crown-4 < 15-crown-5 < 21-crown-7 < 18-crown-6.[8] This trend differs from the one determined in the present gas-phase study in which the proton affinity increases with the number of oxygen donors of the polyether. 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 larger than that of a single proton.[8] This solvation of the proton would result in a bulkier guest, one which could demonstrate very different cavity size effects upon complexation with the crown ethers than expected for a nonsolvated proton. To our knowledge no study has reported proton and ammonium ion complexation equilibria of macrocycles in the same solvent, so this comparison to gas-phase results cannot be made.

Structures of Ammonium Ion Complexes. The structures of the $(M_1 + NH_4 + M_2)^+$ and $(M_1 + H + M_2)^+$ complexes are presumed to be sandwich-type structures in which the ammonium ion or proton serves as a bridge between the two polyethers, with the oxygen atoms from each ether competing for hydrogen-bond coordination to the shared guest. Since the explanation for some of the unusual ammonium ion affinities observed in this study is based on the proposal that a macrocyclic effect[1-3] is operative in the gas phase just as it is operative in solution, additional CAD studies were done to offer support that the polyether hosts retain their skeletal integrity upon complexation. First, the $(M + NH_4)^+$ complexes formed directly from ion–molecule reactions of NH_4^+ and a crown ether were examined by collisionally activated dissociation. At the lowest collision energies, loss of NH_3 is observed. Upon 20-eV (higher energy) collisional activation, each $(M + NH_4)^+$ ion dissociates by competing losses of $[n(C_2H_4O) + NH_3]$ where $n = 0, 1, 2, \ldots$, resulting in a series of fragment ions at $[n(C_2H_4O) + H]^+$ (i.e. forming m/z 45, 89, 133, 177, ...). The NH_3 molecule is never retained by the ionic portion of the dissociating complex. This helps to validate our prediction that the N···H···O hydrogen bonds which bind the ammonium ion to the crown ether are the weakest binding interactions in the complex and are thus the first to cleave, leaving a strongly bound proton attached to the oxygen atoms of the crown ether. In fact, the CAD spectrum observed for each crown ether $(M + NH_4)^+$ complex virtually duplicates the CAD spectra obtained for the simple protonated crown ethers.[28] These observations offer some evidence, albeit incomplete, that the crown ethers maintain their cyclic structure upon complexation, and the covalent bonds of the macrocyclic skeleton are only broken after much higher energy activation.

Additionally, the structures of the ammonium bound *dimers*, $(M_1 + NH_4 + M_1)^+$, of each crown ether were characterized by 2-eV CAD. These complexes dissociate predominantly to $(M_1 + NH_4)^+$ (97% TIC) and $(M_1 + H)^+$ (<3% TIC). Formation of $(M_1 + NH_4)^+$ ions results from disruption of the N···H···O bridge (specifically at the H···O bond) for one of the crown ether units. The $(M_1 + H)^+$ ion likely results by subsequent elimination of neutral NH_3 from the aforementioned $(M_1 + NH_4)^+$ product ion. Direct elimination of neutral NH_3 from the $(M_1 + NH_4 + M_1)^+$ complex, resulting in the $(M_1 + H + M_1)^+$ ion, is not observed. This absence suggests that the NH_4^+ ligand is indeed multiply coordinated between the two crown ether molecules, and thus NH_3 cannot be readily eliminated while still maintaining an intact proton-bound sandwich complex. Moreover, cleavages of the macrocyclic ring are not indicated on the basis of the fragmentation pattern described, again supporting the notion that the crown ethers maintain skeletal integrity upon complexation.

Conclusions

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.[19,20] 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^+). Finally, collisional activated dissociation of the complexes suggests that the complexes are loosely-bound adducts, perhaps sandwich structures. No evidence for disruption of the skeletal structures of the ethers was observed.

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