# The Ionic Hydrogen Bond. 3. Multiple $NH^+$···O and $CH^{\delta+}$···O Bonds. Complexes of Ammonium Ions with Polyethers and Crown Ethers

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**Abstract:** Complexes of ammonium ions $RNH_3^+$ (R = $CH_3$, $c$-$C_6H_{11}$), $(CH_3)_3NH^+$, and pyridineH⁺ with polyethers and crown ethers are observed in the gas phase in the absence of solvent effects. The dissociation energies, $\Delta H°_D$, of the $RNH_3^+$ polyether complexes range from 29.4 kcal mol⁻¹ (for $RNH_3^+ \cdot CH_3OCH_2CH_2OCH_3$) to 46 kcal mol⁻¹ ($RNH_3^+ \cdot 18$-crown-6). The large $\Delta H°_D$ values for complexes of polydentate ligands indicate multiple –$NH^+$···O– hydrogen bonding. Such multiple bonding can contribute up to 18 kcal mol⁻¹ to the bonding in $RNH_3^+ \cdot CH_3(OCH_2CH_2)_3OCH_3$ and 21 kcal mol⁻¹ in $RNH_3^+ \cdot 18$-crown-6. Multiple interactions are also evident in the $(CH_3)_3NH^+$·polyether complexes where –$CH^{\delta+}$···O– hydrogen bonding seems to occur; and consecutive –$CH^{\delta+}$···O– bonds contribute approximately 6, 4, and 2 kcal/mol⁻¹ respectively for up to three such bonds. Total $\Delta H°_D$ values in the $(CH_3)_3NH^+$·polyether complexes thus range from 26.7 kcal mol⁻¹ in $(CH_3)_3NH^+ \cdot CH_3O(CH_2)_2OCH_3$ to 41 kcal mol⁻¹ in $(CH_3)_3NH^+ \cdot 18$-crown-6. Multiple interaction effects, possibly including van der Waals dispersion forces, are observed also in pyridineH⁺·polyether complexes. Large negative entropies in $RNH_3^+$·acyclic polyether complexes vs. $RNH_3^+$·cyclic crown ethers make the acyclic polyethers less efficient ligands.

Ionic hydrogen bonds lead to stable ion–molecule complexes $BH^+ \cdot B$ in the gas phase[1] and also play a dominant role in ion solvation in the condensed phase.[2] The thermochemistry of the ionic hydrogen bond has been determined in small dimers such as $HCO^+ \cdot CO$, $N_2H^+ \cdot N_2$,[3] $H_3O^+ \cdot H_2O$,[4] and $NH_4^+ \cdot NH_3$,[5] and also in symmetric and mixed dimer ions of numerous monofunctional organic compounds such as alkylamines, alcohols, ethers, and cyanides[2,5] and pyridine.[6]

Empirical trends in the dissociation energies of the dimers $BH^+B'$ can be explained by primary structural effects such as partial proton transfer from $BH^+$ to $B'$ which becomes more efficient as the proton affinity (PA) of $B'$ approaches that of $B$.[7] Theoretical work dealt with primary structural effects such as changes in geometry, electron densities,[8] and molecular orbital energies[9] in the vicinity of the hydrogen bond.

Progressing to more complex organic molecules, we observed higher order structural factors that affect the stabilities of proton-bound dimers. Such higher order effects include steric hindrance in alkylpyridines,[10] substantial attractive van der Waals interactions in dimer ions of polycyclic hydrocarbons,[11] and the mutual weakening of internal and external hydrogen bonds in diamines.[12] Another higher order effect, multiple hydrogen bonding, was seen to contribute up to 10 kcal mol⁻¹ to $\Delta H°_{HB}$ in protonated dimers of nucleic bases, leading to bonding arrangements analogous to those of DNA.[6]

Multiple interactions should be of general significance in interactions of polyfunctional molecules with ions. Indeed, the multiple interactions of a protonated ion with polar functions of an enzyme are seen as the major energy factor in biochemical proton-transfer reactions.[13]

Polyethers and crown ethers are well-known polyfunctional complexing agents for metal, as well as ammonium, ions.[14] The complexing of ammonium ions with crown ethers serves as a model for the interactions of ions with biological membranes, as well as with the interior of enzymes.[14,15] For these reasons, the stabilities of ammonium ion–ether complexes were investigated by several authors. The stabilities are strongly solvent dependent,[15] since the solvations of the free ions, the ligands, and the complex all affect the dissociation constants. To identify the intrinsic thermochemistry of ammonium ion–polyether polydentate complexes, we undertook the present measurements on gas-phase complexation, where complicating solvent effects are absent. The present work is also aimed at the further understanding of higher order structure effects on ion–neutral interactions.

## Experimental Section

The pulsed high-pressure mass spectrometric conditions were as described in the preceding paper.[16] However, while in the proton-transfer systems the pyrolysis of protonated ethers constituted a limiting complication at high temperatures, this is not significant in the association reactions ammoniumH⁺ + ether ⇌ ammoniumH⁺ · ether, since the etherH⁺ ions do not appear in this equilibrium. Therefore, the more strongly bonded systems could be measured up to the highest present instrumental limit, about 420 °C.

Because of its low volatility 18-crown-6 could not be introduced into the ion source at well-defined partial pressures over a useful temperature range. We used a kinetic method to determine the partial pressure,[17] and $\Delta S$ values estimated from other crown ether complexes, to obtain $\Delta H°_D$ from the measurement of association equilibrium at one temperature for this compound.

## Results

Our interest is in amineH⁺·ether complexes, i.e., where the proton is clearly associated with the ammonium ion. Therefore we select $c$-$C_6H_{11}NH_3^+$, $(CH_3)_3NH^+$, and pyridineH⁺ as model ions since the gas-phase basicities of the corresponding bases are higher than those of any of the polyethers. However, we note that the interactions of all primary ammonium ions with a given polyether should be similar, since they all possess three protons on –$NH_3^+$ capable of hydrogen bonding. Indeed, the interactions

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**Table I.** Enthalpy[a] and Entropy[b] Changes for the Complex Dissociation Reactions, $BH^+\cdot$ether $\rightleftarrows BH^+$ + ether

| | c-$C_6H_{11}NH_3^+$ | $(CH_3)_3NH^+$ | pyridineH$^+$ | $CH_3NH_3^+$ | 2-F-pyridineH$^+$ | 1,2-diazineH$^+$ |
|---|---|---|---|---|---|---|
| | | | $\Delta H^\circ{}_D$ | | | |
| $(C_2H_5)_2O$ | 21.9 | 19.5 | 22.5 | 22.0 | | |
| $(n\text{-}C_4H_9)_2O$ | | | | 25.0 | | |
| $CH_3OCH_2CH_2OCH_3$ | 29.4 | 26.7 | 25.4 | 30.1 | | |
| $CH_3OCH_2CH_2CH_2OCH_3$ | 28.4 | 25.5 | 26.5 | 31.2 | 26.2 | |
| $CH_3(OCH_2CH_2)_2OCH_3$ | 39.7 | 32.8 | 31.5 | | 34.7 | 32.4 |
| $CH_3(OCH_2CH_2)_3OCH_3$ | 43.3 | 34.6 | 34.7 | | | 37.0 |
| 12-crown-4 | 37.2 | 35.8 | 36.1 | | | 37.0 |
| 15-crown-5 | 42.3 | 34.9 | 41.0 | | | |
| 18-crown-6 | 46 ± 4[c] | 41 ± 4[d] | 40 ± 4[e] | | | 42 ± 4 |
| | | | $\Delta S^\circ{}_D$ | | | |
| $(C_2H_5)_2O$ | 31.9 | 29.4 | 32.9 | 25.0 | | |
| $(n\text{-}C_4H_9)_2O$ | | | | 28.0 | | |
| $CH_3OCH_2CH_2OCH_3$ | 35.5 | 34.8 | 31.4 | 30.1 | | |
| $CH_3OCH_2CH_2CH_2OCH_3$ | 35.0 | 33.1 | 35.8 | 32.0 | 31.6 | |
| $CH_3(OCH_2CH_2)_2OCH_3$ | 44.6 | 40.0 | 36.5 | | 38.6 | 36.1 |
| $CH_3(OCH_2CH_2)_3OCH_3$ | 43.8 | 40.0 | 38.3 | | | 41.4 |
| 12-crown-4 | 34.8 | 41.5 | 40.0 | | | 40.8 |
| 15-crown-5 | 36.5 | 35.6 | 42.6 | | | |
| 18-crown-6 | (38)[f] | (40)[f] | (44)[f] | | | (44) |

[a] kcal mol$^{-1}$. Error estimate based on standard deviation of van't Hoff plots: ±2 kcal mol$^{-1}$. [b] cal mol$^{-1}$ K$^{-1}$. Error estimate: ±4 cal mol$^{-1}$ K$^{-1}$. [c] Obtained from $\Delta G^\circ{}_{670} = -23$ kcal mol$^{-1}$ and estimated $\Delta S^\circ$ (footnote f). [d] Obtained from $\Delta G^\circ{}_{569} = -18$ kcal mol$^{-1}$ and estimated $\Delta S^\circ$ (footnote f). [e] Obtained from $\Delta G^\circ{}_{600} = -16$ kcal mol$^{-1}$ and estimated $\Delta S^\circ$ (footnote f). [f] $\Delta S^\circ$ estimated from $\Delta S^\circ$ for 12-crown-4 and 15-crown-5 complexes.
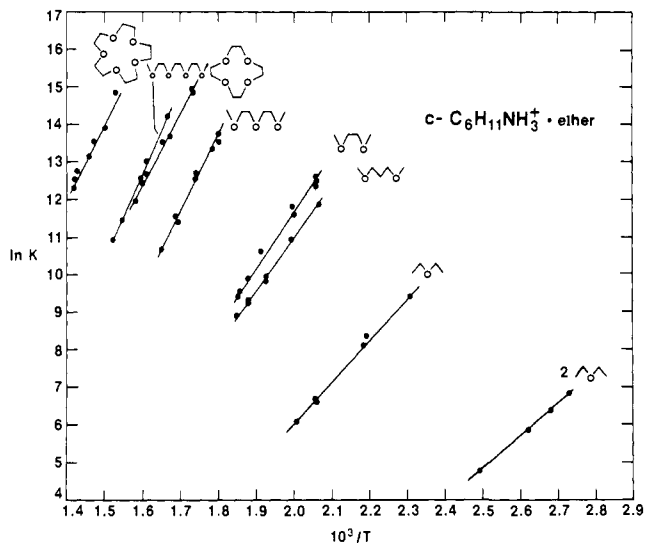


**Figure 1.** van't Hoff plots for the association reactions: c-$C_6H_{11}NH^+$ + ether $\rightleftarrows$ c-$C_6H_{11}NH_3^+\cdot$ether. Ether ligands as indicated.



**Figure 2.** van't Hoff plots for the association reactions: $(CH_3)_3NH^+$ + ether $\rightleftarrows (CH_3)_3NH^+$ + ether.
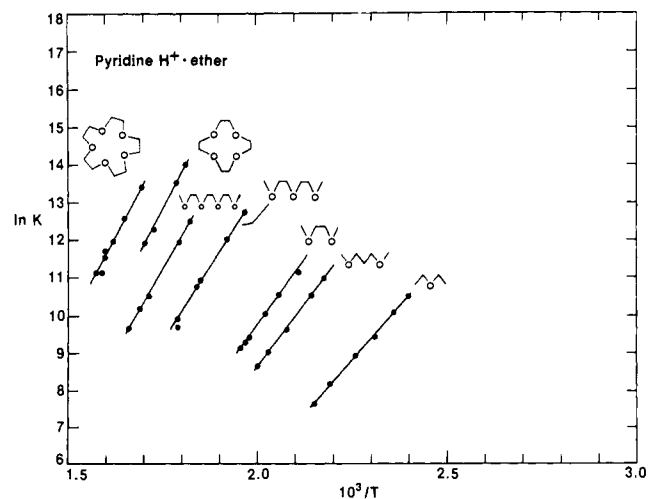


**Figure 3.** van't Hoff plots for the association reactions: pyridineH$^+$ + ether $\rightleftarrows$ pyridineH$^+\cdot$ether.

of c-$C_6H_{11}NH_3^+$ and $CH_3NH_3^+$ with diethers are comparable (Table I).

van't Hoff plots for the association reactions are shown in Figures 1–3, and the thermochemistry and associated error limits are summarized in Table I. The large dissociation energies of the $BH^+\cdot$polyether complexes clearly indicate that multiple ion–neutral interactions occur in the polyether systems. We shall now compare the various complexes to identify the contributions of structural factors to multiple ion–neutral bonding.

### RNH$_3^+\cdot$Polyether Complexes. Multiple –NH$^+\cdots$O– Hydrogen Bonds

To evaluate the effects of multiple bonding in the ammonium complexes of polyethers, we shall compare the thermochemistry with analogous complexes of model monoethers. We use $(C_2H_5)_2O$ as a model for the diethers $CH_3O(CH_2)_2OCH_3$ and $CH_3O(CH_2)_3OCH_3$. We shall use the larger, more polarizable di-$n$-butyl ether for comparisons with the higher ethers.

We have measured $\Delta H^\circ{}_D$ for the $BH^+\cdot(C_2H_5)_2O$ complexes. We also observe that $\Delta H^\circ{}_D$ of $CH_3NH_3^+\cdot(n\text{-}C_4H_9)_2O$ is higher by 3.0 kcal mol$^{-1}$ than that of $CH_3NH_3^+\cdot(C_2H_5)_2O$ due to the higher polarizability of dibutyl ether. A similar difference is expected between the other $BH^+\cdot(C_2H_5)_2O$ and $BH^+\cdot(n\text{-}C_4H_9)_2O$

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**Table II.** Multiple Bonding Contributions[a] to Ammonium Ion-Polyether Interactions

| | c-$C_6H_{11}$-$NH_3^+$ | $(CH_3)_3$-$NH^+$ | pyri-dineH$^+$ |
|---|---|---|---|
| $CH_3O(CH_2)_2OCH_3$ | 8 | 7 | 6 |
| $CH_3O(CH_2)_3OCH_3$ | 7 | 6 | 4 |
| $CH_3(OCH_2CH_2)_2OCH_3$ | 15 | 10 | 6 |
| $CH_3(OCH_2CH_2)_3OCH_3$ | 18 | 12 | 9 |
| 12-crown-4 | 12 | 13 | 11 |
| 15-crown-5 | 17 | 12 | 15 |
| 18-crown-6 | 21 | 19 | 15 |

[a] $\Delta H°_{multiple\ bonding}$ in kcal mol$^{-1}$. Derived from Table I and eq 1 and 2.

complexes. We therefore use eq 1 and 2 to estimate the magnitude of the multiple bonding effects in the BH$^+$·diethers and BH$^+$·polyether complexes, respectively. The values observed from eq

$$\Delta H°_{multiple\ bonding} =$$
$$\Delta H°_D(BH^+·ether) - \Delta H°_D(BH^+·(C_2H_5)_2O) \quad (1)$$

$$\Delta H°_{multiple\ bonding} =$$
$$\Delta H°_D(BH^+·ether) - (\Delta H°_D(BH^+·(C_2H_5)_2O + 3\ kcal\ mol)) \quad (2)$$

1 and 2 are summarized in Table II.

Inspecting the complexes of the primary ammonium ion c-$C_6H_{11}NH_3^+$ we find that bidentate bonding with the diethers increases the interaction energy by about 7 kcal mol$^{-1}$ compared with that of the monoethers. The interaction of c-$C_6H_{11}NH_3^+$ with the two diethers $CH_3O(CH_2)_2OCH_3$ and $CH_3O(CH_2)_3OCH_3$ is similar in magnitude. This is in contrast to the interactions of the two ethers with H$^+$, where bidentate bonding (or intramolecular hydrogen bonding) is much diminished in the smaller species due to the constrained geometry. Molecular models show that a bidentate geometry (a) allows optimal bond lengths, even



a
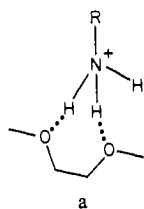
in RNH$_3^+$·$CH_3O(CH_2)_2OCH_3$. The bond angles in both RNH$_3^+$·diether complexes are about 140°, less than the optimum 180°.

Proceeding to the triether $CH_3(OCH_2CH_2)_2OCH_3$ allows the addition of a third hydrogen bond (b) and the increase of the



b
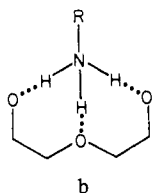
-NH$^+$···O- angles of the terminal methoxy functions to about 160°. The combined effect increases the interaction energy by an additional 10 kcal mol$^{-1}$. Interestingly, proceeding to the tetraether $CH_3(OCH_2CH_2)_3OCH_3$ further increases $\Delta H°_D$, although the three H atoms on -NH$_3^+$ are already hydrogen bonded in the triether complex. Therefore, the increased interaction energy with the tetraether must be due to further geometry optimization, or possibly due to a -CH$^{\delta+}$···O- hydrogen bond, as we shall see below. The dissociation energy of c-$C_6H_{11}NH_3^+$·$CH_3$-$(CH_2OCH_2)_3OCH_3$ is the largest observed so far for a hydrogen-bonded ion-molecule complex.

$\Delta H°_D$ values for the complexes of c-$C_6H_{11}NH_3^+$ with the cyclic crown ethers are similar to those associated with the complexes with the acyclic tri- and tetraethers. This may be expected since in all complexes three hydrogen bonds are possible. We also note

the increasing stabilities of the complexes with increasing size of the cyclic crown ethers. Molecular models show that the -NH$^+$···O- angles can be increasingly optimized with the larger ethers, and in c-$C_6H_{11}NH_3^+$·18-crown-6 additional -CH$^{\delta+}$···O- or dispersive interactions may be possible.

We also note the large negative entropies of complexation that result from the transition of the large flexible chains of the free acylic tri- and tetraethers to the highly constrained structures in their complexes. In comparison, entropies of complexation with the cyclic crown ethers are less negative since the structure of the crown ethers is already constrained before complexation.

**$(CH_3)_3NH^+$·Polyether Complexes. -CH$^{\delta+}$···O- Hydrogen Bonds**

Proceeding to the tertiary ammonium ion $(CH_3)_3NH^+$, $\Delta H°_{multiple\ bonding}$ should be negligible or at least substantially reduced, since here only one NH$^+$···O- hydrogen bond can form. Indeed, in solution the dissociation constants of crown ether complexes of tertiary ammonium ions are orders of magnitude larger than those of primary ions.[15] It is therefore surprising that



c
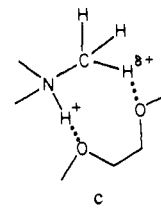
$\Delta H°_{multiple\ bonding}$ of the complexes of $(CH_3)_3NH^+$ are comparable to those of the primary ions. More substantial differences between RNH$_3^+$ and R$_3$NH$^+$ complexes are observed in the triply bonded systems of the higher ethers. However, the absolute values of $\Delta H°_{multiple\ bonding}$ in all the $(CH_3)_3NH^+$·polyether complexes are significant, and these multiple interactions, beyond the first NH$^+$···O- bond, must be provided by -CH$^{\delta+}$···O- hydrogen bonds (c). Specifically, the term "CH$^{\delta+}$···O- bonds" suggests here interactions between the partial positive charges on the methyl hydrogens in $(CH_3)_3NH^+$ and the dipoles and/or lone pairs of the ether functions. The gas-phase data for the diethers show that the first -CH$^{\delta+}$···O- bond strength is 6 ± 1 kcal mol$^{-1}$. It must be remembered however that this is the second hydrogen bond in the system, the first one being the -NH$^+$···O- bond. The next -CH$^{\delta+}$···O- bond then contributes a further 4 kcal mol$^{-1}$ in the triether complex, and a further -CH$^{\delta+}$···O- bond yet another 3 kcal mol$^{-1}$ in the tetraether and crown ether complexes where a total of one -NH$^+$···O- and three -CH$^{\delta+}$···O- is possible.

While the indicated strength of -C-H$^{\delta+}$···O- hydrogen bonds may seem unexpected, there exists previous evidence for similar bonds. Kebarle[18] observed the addition of a third $(CH_3)_2O$ molecule to the $(CH_3)_2OH^+$···$O(CH_3)_2$ dimer. Since in this case the only -O-H$^+$ proton is already H bonded, the third molecule should be H bonded to a methyl hydrogen.[20] The strength of this -C-H$^{\delta+}$···O- bond is 11 kcal mol$^{-1}$. Also, we have observed HCN···HCN···H$^+$···NCH···NCH clusters.[6] Here the addition of the third to fifth HCN molecules involve -CH···N- hydrogen bonds with strength 13.8, 11.8, and 9.2 kcal mol$^{-1}$, respectively. This structure was confirmed by theoretical calculations.[21] -CH$^{\delta+}$···N- bonding must also exist in $CH_3CN$···$CH_3CN$···H$^+$···NCCH$_3$, where $\Delta H°_D$ for this bond is 9.3 kcal mol$^{-1}$.[6]

Recently, crystallographic evidence was obtained for the 18-crown-6···$CH_3NO_2CH^{\delta+}$···O- hydrogen bond.[19] A crystallography survey showed that CH$^{\delta+}$···O and CH$^{\delta+}$···N bonds are common in organic crystals, being especially prominent when the CH group is adjacent to N$^+$ functions.[22]

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## PyridineH$^+$·Polyether Complexes. Attractive van der Waals Interactions

$\Delta H^\circ_{\text{mutiple bonding}}$ in the pyridineH$^+$ complexes of the acyclic ethers is lower than that in the respective (CH$_3$)$_3$NH$^+$ complexes. Molecular models show that the geometry constraints for the pyridine −C−H$^+$···O− hydrogen bonds are more severe than those in the (CH$_3$)$_3$NH$^+$ complexes due to the inflexible planar geometry of pyridine. Indeed, it is possible that the multiple bonding in the pyridine system results from electrostatic attraction between the polar ether groups and the partial positive charge on the pyridine moiety, including the carbon as well as hydrogen atoms.

The geometry constraints on −CH$^{\delta+}$···O− hydrogen bonding in the pyridineH$^+$·cyclic crown ether complexes are even more severe than those in the acyclic ether complexes. Despite that, $\Delta H^\circ_D$ for the pyridineH$^+$·cyclic crown ether complexes is comparable to that for the respective (CH$_3$)$_3$NH$^+$. Molecular models show that with the −NH$^+$···O− bond formed, the plane of cyclic crown ether complexes the pyridine ion, and the principal plane of the crown ethers can align to a nearly parallel 150°.

In a previous study on dimer ions of protonated polycyclic hydrocarbons,[11] we observed that dispersive van der Waals forces contributed significantly to $\Delta H^\circ_D$. The magnitude of this factor is 3.5 kcal mol$^{-1}$ in (benzene)$_2$H$^+$· and becomes the dominant bonding force, 13.1 kcal mol$^{-1}$, in (anthracene)$_2$H$^+$·, as shown by electrostatic Lennard-Jones type calculations. The interaction energy is on the average approximately 0.8 kcal mol$^{-1}$ per interacting carbon atom centers in the two interacting molecules.
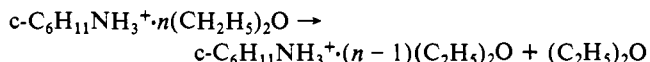
Judging from molecular models, the geometry of the pyridineH$^+$·crown ether dimers is not planar, and the molecular planes are not exactly parallel. Nonetheless, from molecular models, up to four interactive −C···C− centers can be aligned in the dimer, leading to an estimated 3 kcal mol$^{-1}$ contribution by dispersive van der Waals attraction to the dissociation energy.

The thermochemistry of the 2-F-pyridineH$^+$ and 1,2-diazineH$^+$ complexes is similar to the pyridineH$^+$ complexes (Table I). Evidently, small structural changes of the ion do not affect significantly the stabilities of the complexes.

## Polydentate vs. Multiligand Solvation

In the preceding paper[16] we compared the solvation of a protonated ion by an intramolecular group and an external solvent molecule in order to evaluate the bond weakening factors in the bidentate solvation of H$^+$. By analogy, we can compare the polydentate solvation of RNH$_3$$^+$ by several functional groups of one ligand to inner-sphere solvation of RNH$_3$$^+$ by several monoether molecules.

We shall use (C$_2$H$_5$)$_2$OH$^+$ as a model monoether. We measured $\Delta H^\circ_D$ for the reactions

c-C$_6$H$_{11}$NH$_3$$^+$·$n$(CH$_2$H$_5$)$_2$O →

$\qquad$ c-C$_6$H$_{11}$NH$_3$$^+$·($n$ − 1)(C$_2$H$_5$)$_2$O + (C$_2$H$_5$)$_2$O

as 21.9 kcal mol$^{-1}$ for the first ligand ($n$ = 1) and 17.6 kcal mol$^{-1}$ for the second ligand ($n$ = 2). From trends in other cluster ions such as NH$_3$$^+$·2H$_2$O, we can estimate $\Delta H^\circ_D$ for the third ligand as ≈14 kcal mol$^{-1}$.

$\Delta H^\circ_{\text{multiple bonding}}$ for the second hydrogen bond in the diether complexes is about 7 kcal mol$^{-1}$. The solvation of −NH$_3$$^+$ by the second ether group in the bidentate ligand is therefore weakened by about 10 kcal mol$^{-1}$ compared with that of a second free ligand. As in the protonated ions, polarization, unoptimized H bond angles, and ring strain are the probable bond weakening factors. Although all of these factors should be more severe in the protonated ion than in the ammonium complex, the bond weakening effects in CH$_3$O(CH$_2$)$_3$OCH$_3$H$^+$ and c-C$_6$H$_{11}$NH$_3$$^+$·CH$_3$O-(CH$_2$)$_3$OCH$_3$ are comparable in magnitude.

With the tridentate ligand CH$_3$(OCH$_2$CH$_2$)$_2$OCH$_3$, $\Delta H^\circ_{\text{multiple bonding}}$ = 15 kcal mol$^{-1}$. This effect, contributed by the addition of the second plus third oxygen groups, is significantly less than the total of 21 kcal mol$^{-1}$ for the addition of the second plus third ether molecules to the inner solvent sphere of RNH$_3$$^+$. However, the multiple bonding effect with the largest ligand,

CH$_3$(COH$_2$CH$_2$)$_3$OCH$_3$, 18 kcal mol$^{-1}$, approaches the bonding with the second plus third free solvent molecules.

Interestingly, the trends in the efficiency of interactions of the polyethers with ammonium ions and with a proton[16] as given by $\Delta H^\circ_{\text{multiple bonding}}$ and $\Delta H^\circ_{\text{internal bonding}}$, respectively, are closely parallel, despite the great difference between the nature of the ionic species.

In the complexes of RNH$_3$$^+$ with cyclic crown ethers, the multiple solvent effect becomes increasingly efficient with increasing size. In the complex with 18-crown-6 the bonding energy is comparable with that from complete inner-sphere solvation by three free ether molecules.

## Conclusions

Multiple interactions between ammonium ions and polyether or crown ether ligands contribute significantly to the bonding energy. Multiple −N−H$^+$···O− hydrogen bonding between primary ammonium ions and large polyethers can approach the effects of complete inner-sphere solvation. With tertiary ammonium ions, the multiple interactions are probably due to −CH$^{\delta+}$···O− hydrogen bonds. In the pyridineH$^+$·crown ether complexes, dispersive inter-ring van der Waals attraction may play a role. Our results indicate that the total interaction of any ammonium-type ion with multiple functional groups of a single macromolecule can approach up to 45 kcal mol$^{-1}$.

Warshel[13] proposed that the determinant factor in the energetics of enzyme-catalyzed proton transfer may be the solvation of an ionic intermediate in the interior of an enzyme. Interactions with polar functional groups would stabilize the same intermediate even more than solvation by water, thereby lowering the activation energy in the enzyme interior. An ion−enzyme interaction energy of over 70 kcal mol$^{-1}$ would be necessary for the mechanism.[13] Our results suggest, however, that the multiple interactions between a protonated ion and multiple functional group of the enzyme would not significantly surpass about 45 kcal mol$^{-1}$. This discrepancy may be resolved by additional ion stabilization in the enzyme by factors that do not appear in our complexes, such as interactions with −COO$^-$ groups. Additional stabilization of the ionic intermediate should also result from the interactions of the negative pole of the intermediate with the enzyme dipoles. An additional possibility is an unfavorable *entropy* effect that would appear in water but not in the enzyme. Thus, in water the ionic intermediate will orient surrounding free H$_2$O molecules by hydrogen bonding and/or electrostatic interactions, resulting in a negative term in the entropy of activation. Such a term would not contribute in interactions with the already constrained enzyme dipoles.

Another aspect of entropy effects is observed in the complexation of the c-C$_6$H$_{11}$NH$_3$$^+$ ion by the polyether (Table I). The entropy change upon complexation by the tri- and tetraethers is more negative by about 10 cal mol$^{-1}$ K$^{-1}$ than complexation by 12-crown-4 and 15-crown-5. The entropy factor makes the open ethers less efficient ligands. Similar differences between open-chain vs. cyclic ligands are observed in solution.[14]

Gas-phase measurements of the present type can be extended to RCOO$^-$·crown ether complexes, as models of RCOO$^-$−dipole interactions in enzyme interiors. Further, $\Delta H^\circ_D$ of gas-phase metal ion−crown ether complexes, combined with solution data in Born cycles, can yield the thermochemistry of solvation of the crown ether complexes by bulk solvent.