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Influence of Heteroatom Donors on the Orders of Relative Gas-Phase Binding Affinities of Macrocyclic Polyethers

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Abstract. The effects of the heteroatom donor on the complexation of various metal ions by macrocyclic polyethers were qualitatively examined by application of the ligand exchange technique in a quadruple ion trap mass spectrometer. The metal ions, including K^+, Cs^+, Al^+, Mg^+, Cu^+ and Ni^+, were generated by laser desorption and allowed to react with 12-crown-4 and its nitrogen and sulfur analogs, cyclen and 1,4,7,10-tetrathiacyclododecane. The orders of gas-phase basicities were established as a comparison. The relative K^+ and Cs^+ binding affinities of 12-crown-4 are greatest, whereas cyclen has the highest binding affinity for all the other metal ions and also the highest gas-phase basicity.

1. Introduction

The process of complexation in host–guest chemistry plays an important role in many biological and chemical phenomena [1–7], and it has been evaluated from studies of model hosts such as polyethers interacting with model guests such as metal ions or other cations in solution. There are many parameters which influence the ion–polyether interactions, including solvent effects, the number of ligand binding sites, the size of the cation, substitution on the macrocyclic rings, and the nature of the heteroatomic binding sites (donor atoms). These factors have been carefully studied in solution over many years in order to understand their individual effects on the complexation process. Recently, the examination of aspects of host–guest chemistry has been undertaken in the gas phase where the solvent effects can be eliminated and thus the nature of binding interactions can be revealed in a solvent-free environment [8–17]. The primary objective of the present study involves the evaluation of heteroatom donor effects on the gas-phase ion binding affinities of macrocyclic polyethers.

It is well accepted that the model polyether hosts are involved in binding interactions with the guest ions primarily via electron donation through the nonbonding electrons of the heteroatoms. However, the reasons underlying the different selectivities and binding energies demonstrated by hosts containing nitrogen vs. sulfur vs. oxygen donor atoms are less well understood. Several investigations concerning
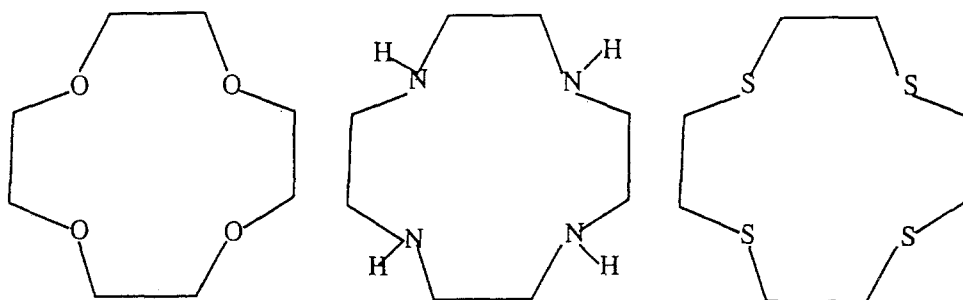
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Fig. 1.   Structures of macrocycles.

the effects of heteroatom substitution of nitrogen or sulfur for oxygen in polyethers have been reported in solution. For example, Milton *et al.* found that 1,4,8,11-tetrathiacyclotetradecane (14-S-4) is likely to change its structure to an 'inside out' conformation upon interacting with a metal ion during the formation of a complex of Cu(14-S-4)(ClO$_4$)$_2$ [18]. In fact, for the log K values (at 25°), cyclen is over seven times larger than 1,4,7,10-tetrathiacyclodecane for reactions with the Cu^{2+} ion [19]. The reason for the large difference may be attributed to the conformations of the polyethers. Tetrathiacyclotetradecane has a quadrangular structure with the sulfur atoms at the corners. This structure is not favorable for chelation which needs an extensive conformational rearrangement to turn the sulfur atoms 'right side in'. Instead, tetrathiacyclotetradecane more often bridges metal ions [20]. Thioethers also can affect the electronic structures of metal ions through delocalization of t_{2g} electron density onto the ligand, thus stabilizing lower oxidation states of metal ions [20]. Frensdorff also reported the effects of nitrogen or sulfur substitution for oxygen in 18-crown-6 [21]. The log K values decreased with the decreasing electronegativity of the binding sites (O > NR > NH > S) for potassium cation complexes. In contrast, the effects of nitrogen or sulfur substitution on Ag$^+$ complexation by the macrocycles are exactly the opposite: nitrogen and sulfur donor atoms favor Ag$^+$ complexation. The differences are attributed to the different types of bonding that are likely involved. The alkali metal ions are held in the cavity of polyethers by ion–dipole forces. For the Ag$^+$ complexes, covalent-type bonding is involved. It has also been shown that oxygen is more favorable for complexation of alkali and alkaline earth ions, while sulfur and nitrogen preferentially bind transition metal ions [22]. These studies are consistent with the knowledge that nitrogen and sulfur, relative to oxygen, favor more covalent-type bonds.

In this brief report, the influence of the heteroatom donor sites on the binding affinities of model hosts was qualitatively evaluated by examining the metal ion complexes of 12-crown-4 and its nitrogen and sulfur analogs, cyclen and 1,4,7,10-tetrathiacyclododecane, respectively (see Figure 1). These effects were examined by application of the ligand exchange method [23] in a quadruple ion trap. The

metal ions including Al^+, K^+, Cs^+, Ni^+, Mg^+ and Cu^+ were generated by a laser desorption method and then allowed to react with a pair of ligands (either 12-crown-4 or cyclen or 1,4,7,10-tetrathiacyclododecane). The ligand exchange technique was employed to determine the relative order of binding affinities. The order of binding strength may reflect both the electronic nature and size of the cations, while the polarizability and cavity size of the ligands may also have dramatic effects. The relative gas-phase basicities were also measured as a comparison to the orders of metal ion affinities. The 12-crown-4 skeletal structure was chosen specifically because its cavity size is small enough to prevent the various metal ions from being completely encapsulated by the polyether ligand, which would sterically inhibit metal ion transfer from one ligand to another; however, the polyether is still large enough to promote multi-site coordination to the metal ions.

2. Experimental

The experiments were carried out in a Finnigan quadruple ion trap mass spectrometer (ITMS) [24] equipped with a probe-mounted fiber optic laser desorption assembly [25]. A Nd:YAG laser was operated in the Q-switch mode at 1064 nm, generating a power density from $2 \times 10^7 - 2 \times 10^8$ W/cm^2. The metal ions used for this study, including Al^+, K^+, Cs^+, Ni^+, Mg^+ and Cu^+, were produced from metal foils (Al, Ni, Mg, and Cu) or salts (KBr and CsI). The metal ions were stored in the ion trap and then allowed to react with the macrocyclic polyethers. Because the laser desorption process is fairly energetic, the metal ions may be formed in a range of electronic states. Despite the possible existence of metal ions in excited electronic states, the reactions with the polyether ligands yield similar product distributions on a day-to-day basis. Likewise, altering the laser power density causes a slight increase in the abundance of fragment-type ions of the polyether/metal complexes. When the helium buffer gas pressure is raised, and when the delay time between the periods for formation/isolation of the metal ions and for the reaction with the polyether ligands is increased, there are no changes noted in the ligand exchange experiments. We feel that these results indicate that any metal ions in excited states react in nearly identical ways with the polyether ligands as the ground state metal ions, thus making the existence of excited states unproblematic.

Cyclen and 1,4,7,10-tetrathiacyclododecane were admitted through a heated solids probe. The 12-crown-4 was introduced through a leak valve to 2×10^{-6} torr. The metal/macrocyclic polyether complexes were mass-analyzed in the mass selective instability mode. The helium buffer gas pressure was typically maintained at 1.5–2.0 mtorr to assist in cooling down the energies of the complexes formed.

The ligand exchange experiments between macrocyclic complexes were performed in both forward and reverse directions. Each pair of macrocyclic polyether was introduced into the ion trap chamber at approximately the same concentration in order to ensure almost the same number of collisions during the exchange reactions. Relative concentrations of each ligand were correlated with the initial total

TABLE I. Orders of relative ion affinities[a]

H^+	cyclen > 12-crown-4 > 1,4,7,10-tetrathiadodecane
K^+	12-crown-4 > cyclen[a] > 1,4,7,10-tetrathiadodecane
Cs^+	12-crown-4 > cyclen > 1,4,7,10-tetrathiadodecane
$(Mg^{2+}OH^-)^+$	cyclen $\geq$ 12-crown-4[a] > 1,4,7,10-tetrathiadodecane
Al^+	cyclen > 12-crown-4 > 1,4,7,10-tetrathiadodecane
Ni^+	cyclen > 1,4,7,10-tetrathiadodecane > 12-crown-4
Cu^+	cyclen > 1,4,7,10-tetrathiadodecane > 12-crown-4

[a] In most cases, the cation transfer occured exclusively in one direction. However, the potassium cation transfer between 12-crown-4 and cyclen, and the transfer of $(Mg^{2+}OH^-)^+$ between cyclen and 12-crown-4 were observed to some degree in both directions.

ion intensity attributed to each compound, based on efficient protonation reactions [16]. One macrocyclic polyether complex was isolated by a combination of DC and RF voltages, and then allowed to react with another neutral macrocyclic polyether for a period of 0–500 ms. The occurrence or non-occurrence of the cation transfer reaction was correlated with the relative cation affinities of the two competing ligands.

All compounds used in this study were purchased from Aldrich Chemical Company (Milwaukee, MN).

3. Results and Discussion

After laser desorption of the metal, the metal ions (M^+) were allowed to react with the polyether ligands (L), resulting predominantly in generation of the $(L + M)^+$ complexes and $(2L + M)^+$ dimer ions. Other products, such as fragments of $(L + M)^+$ complexes, usually accounted for less than 5% of the total ion signal observed. The observation of fragments of $(L + M)^+$ complexes appeared to be partly influenced by the laser power density, so the power was kept low to minimize the production of these ions. An example of a typical ligand exchange experiment is shown in Figure 2. The metal complex (1,4,7,10-tetrathiacyclododecane + Cs^+) is isolated, then allowed to react with neutral 12-crown-4 for 100 ms. The Cs^+ ion is transferred to 12-crown-4. In the reverse direction, the Cs^+ ion is not efficiently transferred from 12-crown-4 back to 1,4,7,10-tetrathiacyclododecane. In fact, in most cases the cation transfer reaction *only* proceeds in one direction. This result is evidence that the cation transfer reaction is exothermic in one direction, but substantially endothermic in the other direction and thus not observable in the ion trap environment. This type of experiment was repeated for every combination of metal ion and macrocyclic polyether. The complete set of orders of relative metal ion affinities is shown in Table I. Also listed is the order of gas-phase basicities as a comparative result.
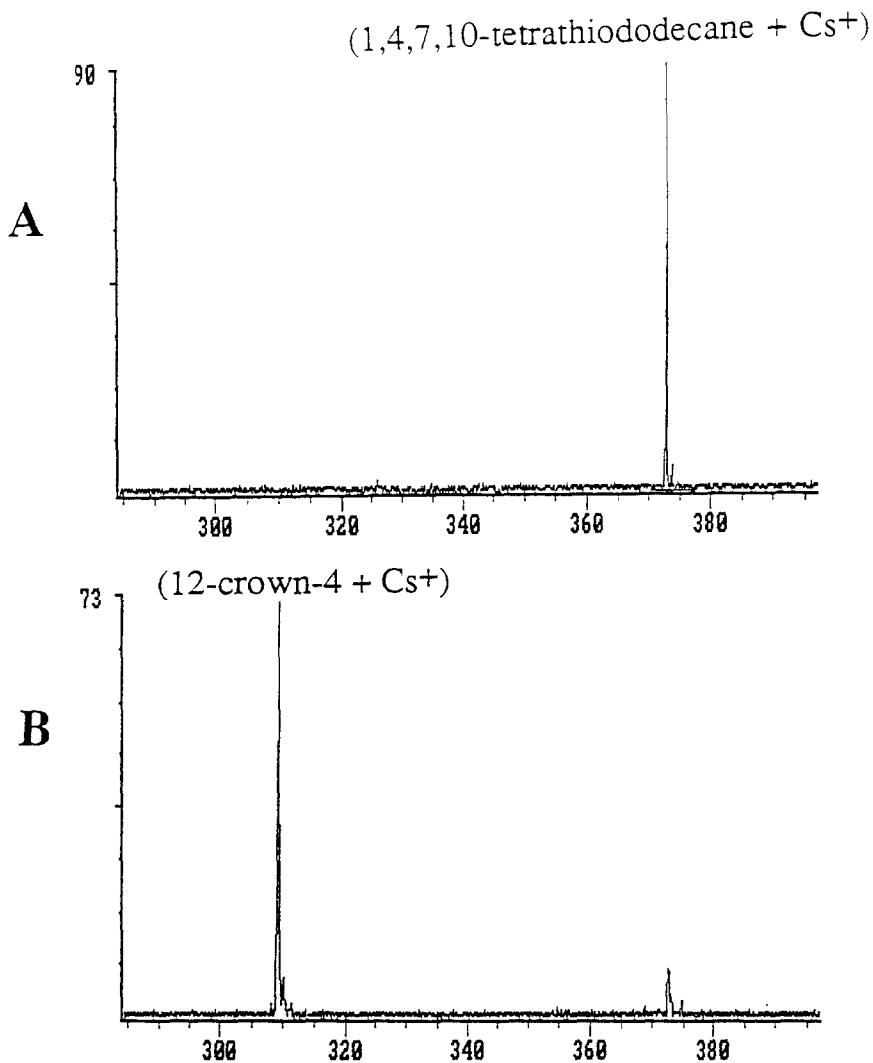
Fig. 2. Ligand exchange experiment showing (A) the isolation of (1,4,7,10-tetrathiadodecane + Cs)$^+$ and (B) transfer of the Cs$^+$ ion to 12-crown-4 during a 100 ms reaction period.

For cases in which the metal ion transfer reaction goes to completion in one direction and no metal ion transfer is observed in the reverse direction, then it is apparent that the difference in binding affinities of the two ligands may be greater than 2.5 kcal/mole. This estimate is based on previous evaluation of the equilibrium method for measurement of gas-phase basicities in a quadruple ion trap [26,27]. For the gas-phase equilibrium method, two ligands are admitted to the ion trap, typically at similar concentrations. In a gas-phase basicity experiment, the two ligands are protonated and allowed to undergo numerous collisions with other

neutral ligands in which subsequent proton transfer may occur until an equilibrium population of the protonated ligands is established. From the relative intensities of the two protonated ligands, one can estimate the difference in gas-phase basicities of the two ligands, a value that actually represents the free energy change for the reaction. This type of experiment can also be applied toward the determination of metal cation affinities. The boundary value of 2.5 kcal/mole is established by the dynamic range limitations of the mass spectrometer. In a gas-phase ion equilibrium or ligand exchange experiment, the transfer of a labile cation (such as a metal ion or proton) between two substrates (i.e. two polyether ligands) ultimately results in the formation of two cationized products of different intensities. For cases in which the cation affinities of the two substrates vary substantially, one must be able to accurately measure the ratio of an ion with a large intensity relative to an ion with a small intensity, and it is experimentally difficult to make such quantitative estimates when the ratio exceeds 100 : 1. For example, when the cation exchange reaction occurs nearly to completion in an equilibrium or ligand-exchange experiment, the resulting depletion of the initial metal ion complex prevents the establishment of the measurable equilibrium ratio. For the environment of a quadruple ion trap, the experimental conditions set the limit for the differences in relative cation affinities at 2.5 kcal/mole.

For the alkali metal ion complexation, 12-crown-4 shows the largest binding affinity, and the thio analog has the lowest binding affinity (see Table I). This result reflects the superior ability of oxygen atoms to participate in electrostatic binding interactions. The trend reverses for aluminum and magnesium ion complexation. Both of these metals have s electrons and clearly promote different types of bonding interactions relative to alkali metal ions. For these two cases, cyclen demonstrates the greatest metal ion affinity and the thio analog continues to have the lowest binding affinity. As discussed in a recent report [28], production of magnesium ions in the gas phase leads to a series of unusual reactions with polyether ligands. The initially monopositive Mg^+ ions bind a hydroxyl unit when associating with oxygenated polyethers in order to achieve their favored oxidation state in the gas phase [28]. The Mg^+ ion donates its s electron to form a strong ionic bond with the oxygen atom of a water molecule, with concomitant elimination of $H^·$ from the water molecule [28]. It is believed that the water molecule is hydrogen bonded to a polyether molecule. In effect, the magnesium atom is incorporated into $Mg^{2+}OH^-$, a species that is subsequently solvated by a polyether ligand in the gas phase, resulting in the net product $[L + (Mg^{2+}OH^-)]^+$. This characteristic addition/solvation reaction also occurs with the nitrogen and sulfur polyether analogs and is attributed to the special nature of the electronic configuration of the initial Mg^+ ion. In all cases, the magnesium ion is transferred in conjunction with the hydroxide unit.

The relative orders of cation affinities undergo another reversal when monopositive transition metal ions are evaluated. For Cu^+ and Ni^+ ions, cyclen shows the highest affinity, followed by the sulfur analog, then the oxygenated 12-crown-4 macrocycle (Table I).

Finally, the order of gas-phase basicities of the polyether ligands agrees with the well-established polarizability and electronegativity guidelines for predicting gas-phase basicities [29]. The nitrogen macrocycle has the highest gas-phase basicity, whereas the sulfur analog has the lowest gas-phase basicity. Incidentally, this trend is qualitatively the same as the orders observed for Mg^+ and Al^+ complexation in the gas phase. As previously tabulated, cyclen is substantially more basic than 12-crown-4 in solution [30], and this trend agrees with the gas-phase order reported herein. The basicity of 1,4,7,10-tetrathiacyclododecane has not been reported.

Several correlations can be drawn with the results previously reported for solution studies. For example, the oxygenated 12-crown-4 polyether has the highest alkali metal ion affinity in both solution and in the gas phase. In one of the earlier studies [21], stability constants were measured for the complexation of 18-crown-6 and partially sulfur- or nitrogen-substituted 18-crown-6 with K^+ in methanol. The partially sulfur-substituted polyether had the lowest binding affinity, and the fully oxygenated 18-crown-6 ether had the greatest affinity [21]. The similarity between the gas-phase and solution results suggests that the same type of binding interactions (electrostatic) are operative in both environments and that the electronegativity of the donor atom plays a large role in determining the strength of the binding interactions between the alkali metal ions and the donor atoms. In the same study, the stability constants for complexes formed between the 18-crown-6 ligands and Ag^+ ion in water were also measured [21]. In this case, the nitrogen-substituted ligand had a greater binding affinity than the sulfur analog, which had a greater affinity than the fully oxygenated polyether. This trend parallels the one observed in the present gas-phase investigation of monopositive Cu^+ and Ni^+ ions and also correlates with reports of stability constants involving complexation of polyethers with divalent transition metal ions in solution [18–20]. The trends suggest a similar rationalization: nitrogen and sulfur atoms participate more effectively in covalent-type bonds in conjunction with the d orbitals of the transition metals. Although the metal ions in the gas-phase experiment are monopositive, whereas the ones in solution are typically divalent, the electronic interactions involve d-orbital components for the most part in both situations. Thus, the correlation between gas-phase and solution results is still relevant and stems from a similar foundation.

In summary, the nature of the heteroatom donor has a strong influence on the complexation of different types of metal ions by the macrocyclic polyethers in the gas phase. The nitrogen and sulfur donors favor binding to transition metal ions, whereas the oxygenated macrocycle prefers complexation to the alkali metal ions. Moreover, based on the completeness of the metal ion transfer at long reaction times, it appears that the relative binding energies of the three polyethers to each metal ion may differ by more than 3 kcal/mole. This latter result affirms that there may be substantial variations in the nature and magnitude of the effective binding interactions in the gas phase for ligands possessing nitrogen vs. sulfur vs. oxygen donors, just as previously reported in solution.

Acknowledgements

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