ELSEVIER

International Journal of Mass Spectrometry 204 (2001) 133–142

International Journal of Mass Spectrometry

# Determination of alkali metal binding selectivities of caged crown ligands by electrospray ionization quadrupole ion trap mass spectrometry

Michelle L. Reyzer[a], Jennifer S. Brodbelt[a,*], Alan P. Marchand[b], Zhibing Chen[b], Zilin Huang[b], I.N.N. Namboothiri[b]

[a]*Department of Chemistry and Biochemistry,The University of Texas at Austin, Austin, TX 78712, USA*
[b]*Department of Chemistry, The University of North Texas, NT Station Box 305070, Denton, TX 76203-5070, USA*

Received 9 March 2000; accepted 8 June 2000

**Abstract**

The alkali metal ($Li^+$, $Na^+$, $K^+$, $Rb^+$, and $Cs^+$) binding selectivities of caged crown ether compounds are evaluated by way of electrospray ionization mass spectrometry and compared to the binding selectivities of three reference crown ethers, 15-crown-5, 1,7-diaza-15-crown-5, and 18-crown-6. The relative binding selectivities are estimated from the mass spectral intensities of the metal complexes and compared to calculated equilibrium distributions when possible. In general, the selectivities of the caged crown ethers parallel the selectivities for the noncaged reference crowns. However, as the cage moiety imparts a greater degree of rigidity in the polyether ring, the selectivities are shifted slightly toward larger cations. Further understanding of the metal binding preferences is obtained from molecular modeling calculations. (Int J Mass Spectrom 204 (2001) 133–142) © 2001 Elsevier Science B.V.

*Keywords:* Binding selectivity; Host–guest chemistry; Electrospray ionization; Quadrupole ion trap; Crown ether

## 1. Introduction

Synthetic organic chemists have developed elegant strategies for creating complex molecules designed with specific structural features to enhance metal recognition properties. Such strategies must be closely coupled with efficient analytical characterization of binding selectivities and/or avidities to provide feedback for optimization or modification of host structures and allow development of structure/selectivity correlations. Analytical methods that require minimal sample consumption and have wide versatility are particularly appealing when only minute amounts of novel preliminary hosts are available. As the practical applications of molecular recognition continue to expand, particularly in pharmaceutical, biotechnology, and environmental chemistry areas [1–4], more sophisticated analytical tools are required to characterize the host–guest interactions of interest, to determine the structures of host–guest complexes, and to evaluate the selectivities and binding constants of complexation.

Electrospray ionization mass spectrometry (ESI-

* Corresponding author. E-mail: jbrodbelt@mail.utexas.edu


*PII* S1387-3806(00)00332-8

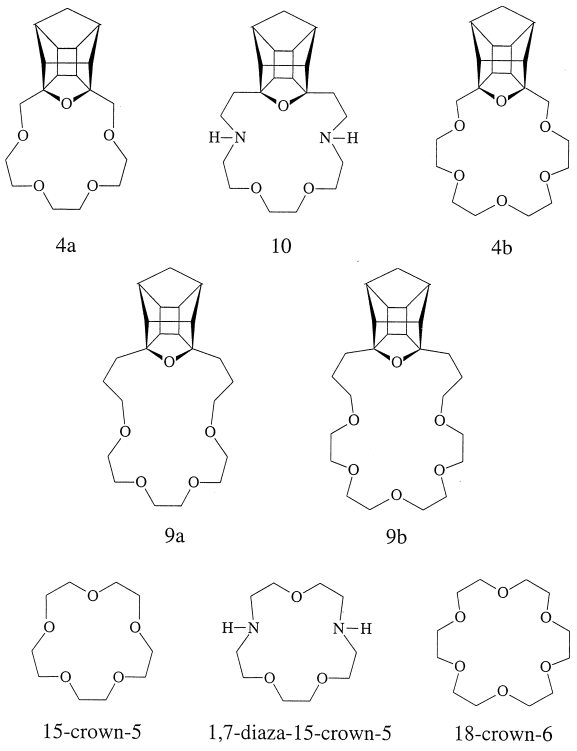



Fig. 1. Compounds studied.

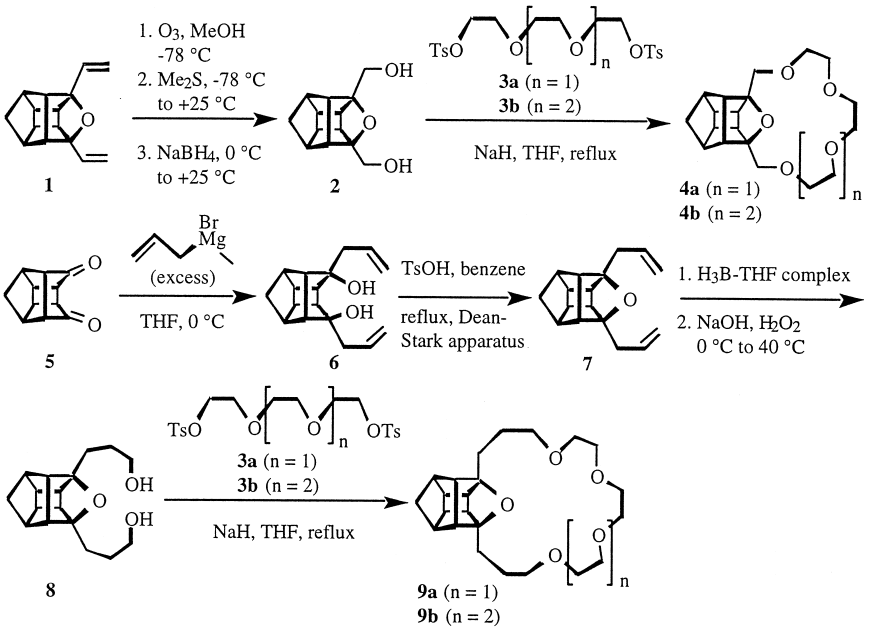
MS) has become a promising tool for the evaluation of binding selectivities of host–guest complexes [5–14]. ESI-MS requires less amounts of sample, is amenable to a wider variety of organic and aqueous solvents, and provides more rapid analysis than many conventional methods, such as potentiometry and NMR, used for such measurements. These advantages make it an attractive choice for screening large numbers of novel synthetic compounds designed to selectively extract metal ions. Several groups have successfully used ESI-MS to determine the binding selectivities of crown ethers and related compounds for alkali metal salts [7–11], and we have also extended the technique to examination of metal complexation of lariat ethers [12], bis-crowned clefts [13], and other caged crown ethers [14].

The goal of the present study is to evaluate the alkali metal binding selectivities of five novel caged crown ethers and three reference crown ethers (Fig. 1) by using ESI-MS, and to understand the structural factors that influence the observed selectivities. These five caged crown ethers are a representative group of related compounds being developed for various environmental remediation purposes, and differences between binding selectivities measured for the caged crown ethers compared to the reference crown ethers can be attributed mainly to the presence of the multicyclic cage substituent. The cage moiety changes the flexibility of the crown ether ring and alters the overall geometry of the binding cavity. The caged ethers are therefore more rigid and exhibit more pre-organization of their binding sites compared to the noncaged compounds. In addition, the cage substituent increases the overall lipophilicity of the host and host–guest system, thus aiding in recovery of the metals from aqueous media. Molecular modeling calculations are utilized in the present study to examine the structures of the host–guest complexes as the size of the metal is varied. As shown in this article, ESI-MS offers an efficient and rapid way to screen new host ligands for metal binding selectivities.

## 2. Experimental

All experiments were performed with a Finnigan quadrupole ion trap mass spectrometer with an electrospray interface modeled after the Oak Ridge National Laboratory design [15]. The ion trap was operated in the mass selective instability mode and the ITD electronics were modified to allow axial modulation using stored waveform inverse Fourier transform. A Harvard syringe pump delivered the solutions at 3.0–5.0 $\mu$L/min to the stainless steel electrospray needle, which was held at 3.4–3.8 kV. Neither a heated capillary nor a sheath gas was used. Although the flow rate and the needle voltage varied from day to day, the values were kept constant as data were collected on a given day for both the caged and reference crown ether solutions. The base pressure of the ion trap was $8 \times 10^{-5}$ Torr in the ESI mode. No helium buffer gas was used.

All solutions were made in methanol and consisted of either one host and one guest or one host and multiple guests. The concentration ratios were either




Scheme 1.

1:1 for the one host–one guest mixture or 1:1:1:1:1:1 for the one host–five guest mixture, and the concentration of each component was $1.5 \times 10^{-4}$ M. The alkali metal guests (Li, Na, K, Rb, and Cs) were added to the solutions as their chloride salts. All reference crown ethers and chloride salts were obtained from Aldrich Chemical Co. (Milwaukee, WI), except for sodium chloride and potassium chloride, which were obtained from EM Science (Gibbstown, NJ). The caged crown ethers were synthesized by means of the general synthetic strategy shown in Scheme 1 [16]. All compounds were used without further purification.

Molecular modeling experiments were undertaken using the commercially available software package PC Spartan Pro (Wavefunction, Inc., Irvine, CA). Conformational searches were performed on a given host with the alkali metal guests that gave the most intense ions in the mass spectra using the molecular mechanics force field MMFF94. The lowest energy conformation that showed an interaction between host and guest was used for further study.

## 3. Results and discussion

### *3.1. ESI-MS methodology*

The method of determining binding selectivities by ESI-MS is straightforward when dealing with individual hosts and multiple guests, as is the case in the present study. Because the ESI-MS signal intensities are dependent on ion desolvation and transmission efficiencies, host–guest complexes which have similar conformations and structural features, such as a simple crown ether binding to two different alkali metal ions, have similar electrospray ionization efficiencies. Thus the resulting ion signal intensities are reflective of the equilibrium distribution of complexes in solution, as shown previously [10–12]. The present study is thus confined to the examination of alkali metal binding selectivities of a series of related hosts, with three well-studied crown ethers serving as reference compounds to provide consistent calibration of the ESI-MS results and to allow comparison of the structural factors that influence selectivity. Due to the large differences in solvation energies that may exist

Table 1
Binding selectivities of 15-crown-5, **4a**, and **9a** for alkali metal ions[a]

| | 15-crown-5 | | **4a** | **9a** |
|---|---|---|---|---|
| | Theoretical[b] | Experimental | Experimental | Experimental |
| [M + $Li^+$] | 0% | 6% | 3% | 2% |
| [M + $Na^+$] | 34% | 36% | 28% | 11% |
| [M + $K^+$] | 40% | 34% | 26% | 52% |
| [M + $Rb^+$] | 14% | 16% | 29% | 28% |
| [M + $Cs^+$] | 12% | 8% | 13% | 6% |

[a] Experimental values expressed as percent of [M + alkali $metal^+$] present in a 1:1:1:1:1:1 solution, calculated as the peak intensity of [M + alkali $metal^+$] divided by the sum of the peak intensities of each complex present (average of 2–5 trials). The total percentages include the contribution from the isotopic peaks. All values ±5% for data sets collected on different days. The initial concentrations of 15-crown-5, **4a**, **9a**, and the five metal salts are each $1.5 \times 10^{-4}$ M.

[b] Theoretical values obtained using MINEQL+ solution equilibria software, version 4.01 (Environmental Research Software, Hallowell, ME), and the following log *K* values reported in the literature [17]: Li = 1.21, Na = 3.31, K = 3.38, Rb = 2.88, Cs = 2.8. The initial concentrations of 15-crown-5 and the five metal salts are each $1.5 \times 10^{-4}$ M.

for complexes of different sizes and structures, the ESI-MS method is not well suited to examining equilibrium behavior for solutions involving multiple hosts with one guest. Previous attempts to examine multiple hosts binding the same guest using the ESI-MS method required the use of large correction factors to account for these differences [10], and therefore these types of experiments (i.e. ESI-MS of solutions containing multiple hosts competing for a single guest) were not undertaken for the present study.

The alkali metal complexation behavior of reference compound 15-crown-5 was examined to ensure the ESI-MS signal intensities scaled with the expected theoretical solution composition calculated using known stability constants (log *K*) found in the literature [17]. The theoretical solution composition was obtained using MINEQL+ solution equilibria software (version 4.01, Environmental Research Software, Hallowell, ME) and the following log *K* values for formation of 15-crown-5 complexes with Li, Na, K, Rb, and Cs ions in methanol [17]: Li = 1.21, Na = 3.31, K = 3.38, Rb = 2.88, Cs = 2.8. The resulting percentages of each 15-crown-5/alkali metal complex expected in a 1:1:1:1:1:1 solution are reported in Table 1. Fig. 2(A) shows the electrospray ionization mass spectrum obtained from spraying a 1:1:1:1:1:1 solution of 15-crown-5 : LiCl:NaCl:KCl:RbCl:CsCl in methanol. Peak heights were used to determine the amount of each complex present in the mass spectrum, including isotope peaks, and the results expressed as percentages are shown in the second column of Table 1 (average of three trials). As shown, there is very good agreement between the predicted percentages of 15-crown-5/alkali metal complexes in solution and those determined experimentally by means of the ESI-MS method. Based on the excellent correlation seen in the first two columns of Table 1, correction of the ESI-MS ion intensities due to non-equivalent ESI efficiencies is unwarranted.

It is worth noting that the theoretical solution

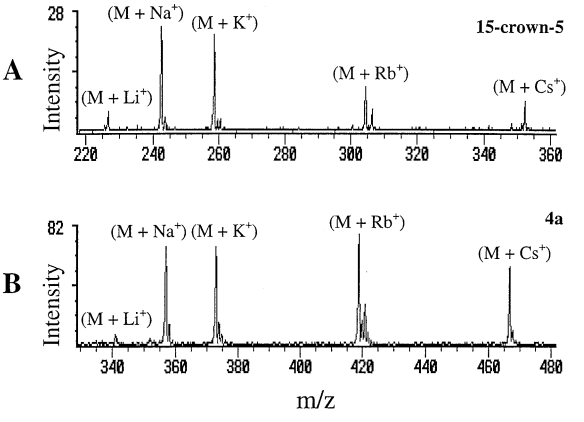



Fig. 2. ESI mass spectra of (A) 15-crown-5 and (B) **4a** with LiCl, NaCl, KCl, RbCl, and CsCl, 1:1:1:1:1:1 in methanol. Each ligand and alkali metal chloride is $1.5 \times 10^{-4}$ M initially.

Table 2
Binding selectivities of 15-crown-5 and 18-crown-6[a]

| | 15-crown-5 + LiCl + NaCl + KCl + RbCl + CsCl | | | |
|---|---|---|---|---|
| | 1:1:1:1:1:1, each $1.5 \times 10^{-4}$ M | | 1:1:1:1:1:1, each $1.5 \times 10^{-5}$ M | |
| | Theoretical[b] | Experimental | Theoretical[b] | Experimental |
| [M + $Li^+$] | 0% | 6% | 0% | 4% |
| [M + $Na^+$] | 34% | 36% | 39% | 42% |
| [M + $K^+$] | 40% | 34% | 46% | 36% |
| [M + $Rb^+$] | 14% | 16% | 14% | 12% |
| [M + $Cs^+$] | 12% | 8% | 0% | 6% |
| | 18-crown-6 + NaCl + KCl | | | |
| | 1:1:1, each $1.5 \times 10^{-4}$ M | | 5:1:1, $7.5 \times 10^{-4}$ M: $1.5 \times 10^{-4}$ M | |
| | Theoretical[b] | Experimental | Theoretical[b] | Experimental |
| [M + $Na^+$] | 11% | 12% | 48% | 48% |
| [M + $K^+$] | 89% | 88% | 52% | 52% |

[a] Experimental values expressed as percent of [M + alkali $metal^+$] present in solution, calculated as the peak intensity of [M + alkali $metal^+$] divided by the sum of the peak intensities of each complex present (average of 2–5 trials). The total percentages include the contribution from the isotopic peaks. All values ± 5% for data sets collected on different days.

[b] Theoretical values obtained using MINEQL+ solution equilibria software, version 4.01 (Environmental Research Software, Hallowell, ME), and the following log *K* values reported in the literature [17]: for 15-crown-5: Li = 1.21, Na = 3.31, K = 3.38, Rb = 2.88, Cs = 2.8 and for 18-crown-6: Na = 4.46, K = 6.20.

results indicate that 15-crown-5 should exhibit a slight preference for potassium over sodium, whereas the ESI-MS spectra consistently show a slight preference for sodium over potassium. This may be due to a slight transmission difference for the sodium versus potassium complexes in the ESI interface. However, it also may be due to errors associated with the log *K* values reported in the literature. The review by Izatt et al. reports eight different log *K* values for 15-crown-5 binding with $Na^+$ in methanol, ranging in value from 3.23 to 3.42 [17]. Similarly, thirteen values are reported for 15-crown-5 binding with $K^+$ in methanol, ranging from 3.3 to 3.86 [17]. These values were obtained by several research groups using a variety of methods, including potentiometry, ion-selective electrodes, and polarography. Thus there may be considerable error associated with selecting log *K* values from the literature, in addition to the error associated with each individual log *K* value from the experimental method used in its determination.

The versatility of the ESI-MS method is illustrated as the concentrations and ratios of hosts and guests are changed. For example, the selectivities of 15-crown-5 in both an equimolar $1.5 \times 10^{-4}$ M solution and an equimolar $1.5 \times 10^{-5}$ M solution with the five alkali metal guests are shown in Table 2. The calculated equilibrium percentages of each complex in solution do not change greatly between the more concentrated and dilute solutions, although slight increases in both sodium and potassium complexes are predicted in the more dilute solution. This shift in the distribution of complexes is seen in the ESI-MS results shown in Table 2. For a tenfold change in solution concentration, there is only a five percent or less change expected in the equilibrium distribution of complexes, with the exception of (M + $Cs^+$), which is calculated to go from 12% in the more concentrated solution to 0% in the dilute solution. Although the ESI-MS trend for (M + $Cs^+$) decreases on going from more concentrated to more dilute solution, there is still a measurable amount of the cesium complex present in the $1.5 \times 10^{-5}$ M solution, which may be due to contamination in the electrospray source. In general however, the ESI-MS results still follow closely the results expected based on known log *K* values over at least a tenfold change in solution concentration, and indicate that the ESI-MS method can be used to reliably screen alkali metal selectivities over a range

of concentrations, a feature that may be important when examining mixtures or when sample quantities are limited.

A more dramatic change is observed for the selectivity of 18-crown-6 binding $Na^+$ and $K^+$ when the ratio of host to guests is changed from 1:1:1 to 5:1:1, as shown in Table 2. In an equimolar solution containing 18-crown-6 and both sodium and potassium, 18-crown-6 shows a pronounced selectivity for potassium, with the equilibrium distribution calculated to be 89% ($M + K^+$) and 11% ($M + Na^+$). The ESI-MS results reflect the expected trend to within 1% based on duplicate trials. When the amount of 18-crown-6 is increased fivefold relative to the amount of sodium and potassium salts present, the selectivity drops such that the expected distribution is 48% ($M + Na^+$) and 52% ($M + K^+$). This decrease in selectivity is mirrored in the electrospray results. Thus the ESI-MS method is capable of reflecting the solution equilibrium distributions of host–guest complexes over a range of host–guest ratios, giving great flexibility in the design of experiments to screen selectivities by ESI-MS. For simplicity, the experiments with the caged crown ethers were all performed in equimolar solutions with each compound and metal salt initially present at $1.5 \times 10^{-4}$ M in methanol.

### *3.2. 15-crown-5 and caged analogs* **4a** *and* **9a**

The caged crown ether analogs have been designed to enhance binding selectivity and/or avidity over nonsubstituted crown ether ligands and with analytical remediation properties in mind (i.e. solubility and ability to anchor to polymeric resins). **4a** is simply 15-crown-5 with the cage moiety built into the macrocycle, while **9a** has an additional ethylene bridge on each side of the cage moiety separating the cage oxygen from the rest of the macrocycle (Fig. 1). These additional structural features are expected to alter the binding selectivities of the caged ligands. Fig. 2 shows an example of spectra recorded for a 1:1:1:1:1:1 mixture of the alkali metal chlorides and either 15-crown-5 [Fig. 2(A)] or **4a** [Fig. 2(B)]. This comparison shows that **4a** has enhanced selectivity for the larger alkali metal ions $Rb^+$ and $Cs^+$ relative to that

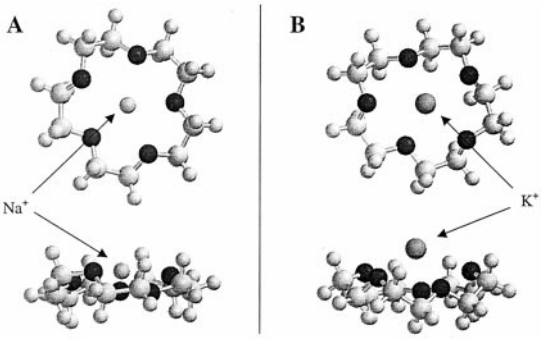



Fig. 3. Low energy conformer of 15-crown-5 binding (A) $Na^+$ and (B) $K^+$. Atom key: small gray = hydrogen, medium gray = carbon, black = oxygen.

observed for 15-crown-5. The experimental alkali metal binding selectivity results for 15-crown-5, **4a**, and **9a** are shown in Table 1. 15-crown-5 is most selective for $Na^+$ and $K^+$, with lower affinities for $Cs^+$ and $Li^+$. The binding interactions of 15-crown-5 with $Na^+$ and $K^+$ were examined by molecular mechanics and are shown in Fig. 3(A) and (B), respectively. Both cations are centered in or slightly above the binding cavity and are equidistant from the oxygen atoms of 15-crown-5. 15-crown-5 adopts a flatter conformation when binding the smaller sodium cation, as it rests inside the relatively flat ring. However, the larger potassium cation perches slightly above the 15-crown-5 ring which adopts a more bent conformation.

The cage moiety of **4a** makes the ligand somewhat more rigid and open than the flexible 15-crown-5 ring and thus more amenable to larger cations. This is evident in the ESI-MS results shown in Table 1 and the spectra shown in Fig. 2. The binding of **4a** to $K^+$ was examined by molecular mechanics and the results are shown in Fig. 4. The potassium ion sits further down in the cavity compared to its position when bound by 15-crown-5 [Fig. 3(B)], as a result of the restrictions in movement imposed by the cage substituent. **4a** has nearly equal affinities for $Na^+$, $K^+$, and $Rb^+$, compared to 15-crown-5, which is almost twice as selective for $Na^+$ and $K^+$ compared to $Rb^+$. The rigidity imposed by the cage substituent of **4a** forces the oxygen atoms to remain further apart and in

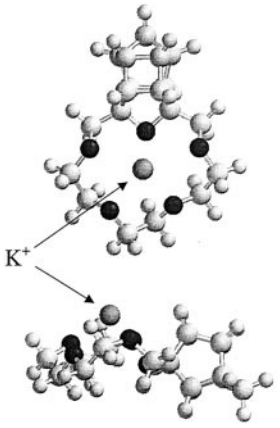



Fig. 4. Low energy conformer of **4a** binding $K^+$. Atom key: small gray = hydrogen, medium gray = carbon, black = oxygen.

a more favorable position for binding larger cations such as $Rb^+$. In addition, **4a** shows a ~30% increase in the binding selectivity for $Cs^+$ compared to 15-crown-5, again due to the more favorable positions of the oxygen atoms.

For the larger 15-crown-5 analog, **9a**, the cage group adds rigidity as for **4a**, but the additional carbon atoms add extra flexibility and at the same time enlarging the binding cavity as well. The ESI-MS binding trend shows a high selectivity for $K^+$ in this case, with the overall trend $K^+ > Rb^+ > Na^+ > Cs^+$, and very low lithium binding (Table 1). In fact, the percentages recorded for **9a** more closely parallel the results for 18-crown-6 (Table 4) than 15-crown-5. The 19-atom ring of **9a** is closer in size to the 18-atom ring of 18-crown-6 than the 15-atom ring of 15-crown-5, and thus the size of the binding cavity appears to be a dominant feature affecting the binding selectivity of this host compound. The low energy conformer calculated for **9a** binding with $K^+$ is shown in Fig. 5. The larger ring size allows the potassium ion to fit into the center of the binding cavity and allows the ring to lay much flatter than 15-crown-5 when binding to potassium [Fig. 3(B)]. Interestingly, the oxygen associated with the cage moiety is not in the plane of the ring, but rather it is at almost a 90° angle. This allows the cage oxygen to be closer to the potassium ion and thus assist in binding.

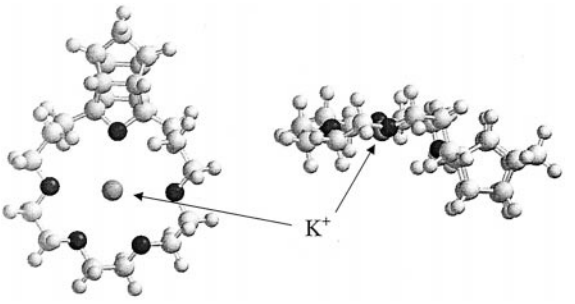



Fig. 5. Low energy conformer of **9a** binding $K^+$. Atom key: small gray = hydrogen, medium gray = carbon, black = oxygen.

### *3.3. Diaza-15-crown-5 and caged analog* **10**

Diaza-15-crown-5 is itself an analog of 15-crown-5, incorporating two nitrogen atoms in place of two oxygen atoms on opposite sides of the ring. This changes the alkali metal binding selectivities in several ways. The nitrogen heteroatoms are softer donor atoms than oxygen, and they may participate in hydrogen bonding with electron-donating solvent molecules, unlike the oxygen heteroatoms which only engage in hydrogen bonding interactions with hydrogen-donor solvents.

The ESI-MS alkali metal binding selectivities are shown in Table 3. No reliable log *K* values have been reported for diaza-15-crown-5 and alkali metals in

Table 3
Binding selectivities of diaza-15-crown-5 and **10** for alkali metal ions[a]

| | Diaza-15-crown-5 Experimental | **10** Experimental |
|---|---|---|
| $[M + Li^+]$ | 22% | 14% |
| $[M + Na^+]$ | 52% | 58% |
| $[M + K^+]$ | 12% | 10% |
| $[M + Rb^+]$ | 8% | 12% |
| $[M + Cs^+]$ | 6% | 6% |

[a] Experimental values expressed as percent of [M + alkali metal$^+$] present in a 1:1:1:1:1:1 solution, calculated as the peak intensity of [M + alkali metal$^+$] divided by the sum of the peak intensities of each complex present (average of 2 trials). The total percentages include the contribution from the isotopic peaks. All values ±5% for data sets collected on different days. No theoretical values are shown as log *K* values were only available for diaza-15-crown-5 with sodium and potassium. The initial concentrations of diaza-15-crown-5, **10**, and the five metal salts are each $1.5 \times 10^{-4}$ M.

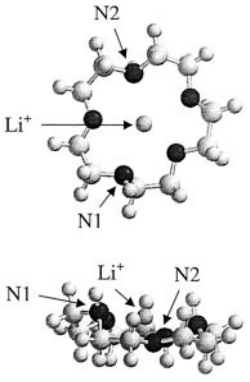



Fig. 6. Low energy conformer of diaza-15-crown-5 binding $Li^+$. Atom key: small gray=hydrogen, medium gray=carbon, black=oxygen or nitrogen, nitrogen atoms are labeled.

methanol, so there are no theoretical equilibrium distributions for comparison. Diaza-15-crown-5 shows a pronounced binding selectivity for $Na^+$, with the overall trend $Na^+ > Li^+ > K^+ > Rb^+ \geq Cs^+$. As shown in Table 1, 15-crown-5 exhibits selectivity for both $Na^+$ and $K^+$, whereas the diaza analog shows a preference for $Na^+$ and $Li^+$. The low energy conformer calculated for diaza-15-crown-5 binding with the lithium cation is shown in Fig. 6. The ring has a small kink in it, presumably enabling both nitrogen atoms to align their dipoles optimally with the cation. The resulting structure appears similar to the structure calculated for 15-crown-5 binding to the larger sodium cation [Fig. 3(A)]. Thus the presence of the two nitrogen atoms shifts the binding selectivities for the diaza ether toward smaller cations.

The alkali metal binding selectivities of the caged analog, **10**, are shown in Table 3. The overall binding trend for **10** is $Na^+ > Li^+ > Rb^+ \approx K^+ > Cs^+$, and this parallels that seen for diaza-15-crown-5. **10** appears to be more selective for $Na^+$ and less selective for $Li^+$ than diaza-15-crown-5, due to the greater cavity size and decreased flexibility of the caged crown ligand imparted by the cage moiety and discussed earlier for **4a**.

### *3.4. 18-crown-6 and caged analogs* **4b** *and* **9b**

The binding cavities of 18-crown-6 and its caged analogs, **4b** and **9b**, are larger than those of the 15-crown-5 ethers and as such are more suited for binding larger cations. The equilibrium distribution predicted for the 18-crown-6/alkali metal complexes are shown in Table 4 and indicate a pronounced selectivity for $K^+$. No reported log *K* value is available for the complexation of 18-crown-6 with lithium; however, binding is not expected to be significant. Thus, the theoretical percentages were calculated based on an equimolar solution of 18-crown-6 with the four alkali metal cations, $Na^+$, $K^+$, $Rb^+$, and $Cs^+$. As the predicted percentages for (18-crown-6 + $Na^+$) and (18-crown-6 + $Cs^+$) are only 3%, neglecting lithium is a reasonable approximation. The binding

Table 4
Binding selectivities of 18-crown-6, **4b**, and **9b** for alkali metal ions[a]

| | 18-crown-6 | | **4b** | **9b** |
|---|---|---|---|---|
| | Theoretical[b] | Experimental | Experimental | Experimental |
| [M + $Li^+$] | N/A | 1% | 0% | 4% |
| [M + $Na^+$] | 3% | 6% | 6% | 11% |
| [M + $K^+$] | 61% | 60% | 68% | 24% |
| [M + $Rb^+$] | 32% | 24% | 22% | 30% |
| [M + $Cs^+$] | 4% | 8% | 3% | 31% |

[a] Experimental values expressed as percent of [M + alkali metal$^+$] present in a 1:1:1:1:1:1 solution, calculated as the peak intensity of [M + alkali metal$^+$] divided by the sum of the peak intensities of each complex present (average of 2 trials). The total percentages include the contribution from the isotopic peaks. All values ±5% for data sets collected on different days. The initial concentrations of 18-crown-6, **4b**, **9b**, and the five metal salts are each $1.5 \times 10^{-4}$ M.

[b] Theoretical values obtained using MINEQL+ solution equilibria software, version 4.01 (Environmental Research Software, Hallowell, ME), and the following log *K* values reported in the literature [17]: Li = none available, Na = 4.46, K = 6.20, Rb = 5.73, Cs = 4.49. The initial concentrations of 18-crown-6 and the four metal salts are each $1.5 \times 10^{-4}$ M.

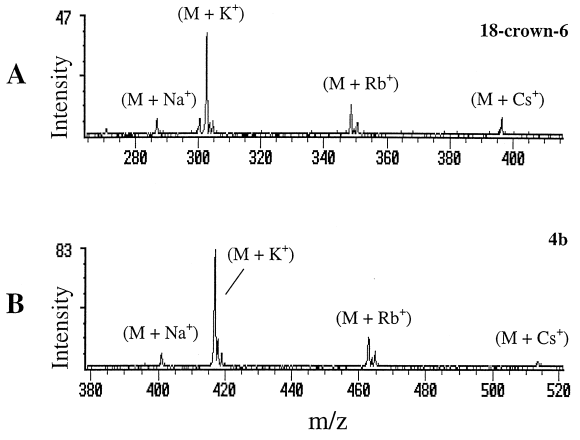



Fig. 7. ESI mass spectra of (A) 18-crown-6 and (B) **4b** with LiCl, NaCl, KCl, RbCl, and CsCl, 1:1:1:1:1:1 in methanol. Each ligand and alkali metal chloride is $1.5 \times 10^{-4}$ M initially.

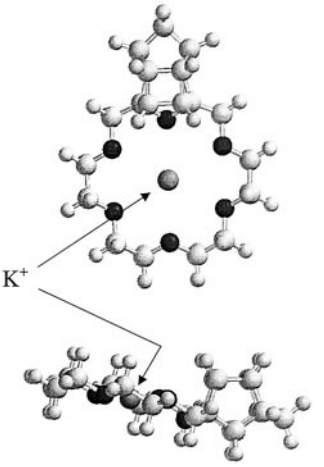



Fig. 8. Low energy conformer of **4b** binding $K^+$. Atom key: small gray = hydrogen, medium gray = carbon, black = oxygen.

trend observed for 18-crown-6 via the ESI-MS method is $K^+ > Rb^+ > Na^+ \approx Cs^+ > Li^+$, and it agrees well with the predicted trend. An example of the spectra taken for the alkali metal binding of 18-crown-6 with alkali metals is shown in Fig. 7(A). As shown, a tiny amount of lithium complexation occurs, but it is barely above the baseline and not quantifiable.

**4b** is a caged analog of 18-crown-6 consisting of the same 18-membered ring but with the cage group attached around one ring oxygen (Fig. 1). The ESI-MS selectivities of **4b** are similar to those of 18-crown-6 [see Fig. 7(B)] and are reported in Table 4. The selectivity for potassium is enhanced for **4b**, with ~70% (**4b** + $K^+$) versus ~60% (18-crown-6 + $K^+$) in the mixed alkali metal solutions. This enhanced selectivity towards $K^+$ is presumably due to the pre-organization of the macrocyclic ring which is held more rigid and open due to the presence of the cage, and thus is more optimally organized for complexation of $K^+$. The low energy conformer of **4b** binding $K^+$ is shown in Fig. 8. As shown, the potassium ion fits in the center of the cavity and the ring is almost completely flat, allowing optimal access to each oxygen binding site. The larger macrocyclic ring allows larger cations to fit better inside the binding cavity, compared to the smaller 15-crown-5 hosts, which cannot fully encompass larger cations such as $K^+$ [see Fig. 3(B) for example].

In contrast, **9b** has a 22-membered ring along with the cage moiety, resulting in a larger binding cavity and a pronounced shift in selectivities toward the larger cations, $Rb^+$ and $Cs^+$. The binding selectivities for **9b** are shown in Table 4 and reflect the following binding trend: $Rb^+ \approx Cs^+ > K^+ > Na^+ > Li^+$. This shift stems both from the greater size of the binding cavity as well as from the greater flexibility available from the 22-membered ring which enables optimal interactions between the ether oxygen atoms and the cation guest. The increase in $Cs^+$ complexation for this caged compound is quite dramatic compared to the low $Cs^+$ affinities of the other ligands in this study.

## 4. Conclusions

Electrospray ionization mass spectrometry was used to screen the alkali metal binding selectivities of a group of reference crown ethers and caged crown ether analogs. The results obtained for the reference compounds show good agreement with theoretical equilibrium distributions calculated using stability constants from the literature, notwithstanding the errors associated with the existing log *K* values from

the experimental methods employed to obtain them and the selection of one of a number of log *K* values available for the complexes of interest. The caged crown ethers in general show an increased selectivity for larger cations compared to the noncaged analogs due to the rigidity in the ring imposed by the cage moiety, which enforces a more open cavity. Only for the 15-crown-5 analog, **4a**, does the addition of the caged substituent reduce the selectivity for any specific metal ion relative to the noncaged reference (15-crown-5). In the other cases (i.e. **10** relative to diaza-15-crown-5 and **4b** relative to 18-crown-6), the degree of selectivity is slightly enhanced for the caged analogs, confirming that the inclusion of the cage substituent affords a convenient, nonintrusive way to change the solubility properties of the novel extraction agents while also providing an anchor point for future attachment of the ligands to polymeric resins. In the case of **9a** and **9b** which have additional carbon units in the macrocyclic ring, an increase in the size of the binding cavity also contributes to the increased preference for binding larger cations. For these two ligands, the addition of two more carbons (i.e. **4b**) in the macrocyclic ring significantly enhances the selectivity for a specific metal ($K^+$) relative to that observed for 15-crown-5, but the addition of four more carbons (i.e. **9a**) diminishes the gain in selectivity. In addition, the presence of nitrogen atoms in the crown ether ring alters the binding selectivities compared to the all oxygen ethers. Diaza-15-crown-5 shows an increased preference for binding lithium compared to 15-crown-5, due to the softer nature of the nitrogen donor atoms and the changes in conformation incurred while optimizing the binding interactions to both the oxygen and nitrogen atoms in the ring.

## Acknowledgements

Funding from the National Science Foundation (CHE-9820755), the Welch Foundation (F-1155), and the Texas Advanced Technology Program (003659-0206) are gratefully acknowledged. One author (M.L.R.) acknowledges an ACS Analytical Division Fellowship sponsored by Dow Chemical Company. Another author (A.P.M.) thanks the Robert A. Welch Foundation (grant no. B-0963) and the U. S. Department of Energy (grant no. DE-FG07-98ER14936) for partial financial support of this study. A.P.M. also gratefully acknowledges the kind assistance of Dr. Kasireddy Krishnudu with the synthesis and characterization of **8**.

## References

[1] S. Rudra, A.V. Eliseev, J. Am. Chem. Soc.120 (1998) 11543.
[2] R.E. Babine, S.L. Bender, Chem. Rev. 97 (1997) 1359.
[3] V.H. Perez-Luna, M.J. O'Brien, K.A. Opperman, P.D. Hampton, G.P. Lopez, L.A. Klumb, P.S. Stayton, J. Am. Chem. Soc. 121 (1999) 6469.
[4] B. Swanson, S. Johnson, J. Shi, X. Yang, in Polymers in Sensors: Theory and Practice, N. Akmal, A.M. Usmani (Eds.), ACS Symposium Series 690, Oxford University Press, Oxford, 1997, pp. 130–138.
[5] T.J.D. Jorgensen, P. Roepstorff, A.J.R. Heck, Anal. Chem. 70 (1998) 4427.
[6] T.J.D. Jorgensen, T. Staroske, P. Roepstorff, D.H. Williams, A.J.R. Heck, J. Chem. Soc., Perkin Trans. 2 (1999) 1859.
[7] E. Leize, A. Jaffrezic, A. Van Dorsselaer, J. Mass Spectrom. 31 (1996) 537.
[8] K. Wang, G.W. Gokel, J. Org. Chem. 61 (1996) 4693.
[9] D.-S. Young, H.-Y. Hung, L.K. Liu, J. Mass Spectrom. 32 (1997) 432.
[10] S.M. Blair, E.C. Kempen, J.S. Brodbelt, J. Am. Soc. Mass Spectrom. 9 (1998) 1049.
[11] J.S. Brodbelt, E. Kempen, M. Reyzer, Struct. Chem.10 (1999) 213.
[12] E.C. Kempen, J.S. Brodbelt, R.A. Bartsch, Y. Jang, J.S. Kim Anal. Chem. 71 (1999) 5493.
[13] Blair, S. M., Brodbelt, J. S., Reddy, G. M., and Marchand, A. P., *J. Mass Spectrom*., **1998**, *33*, 721-728.
[14] S.M. Blair, J.S. Brodbelt, A.P. Marchand, K.A. Kumar, H.-S. Chong, Anal. Chem., 72 (2000) 2433.
[15] G.J. Van Berkel, G.L. Glish, S.A. McLuckey, Anal. Chem. 62 (1990) 1284.
[16] A.P. Marchand, Z. Chen, Z. Huang, I.N.N. Namboothiri, unpublished.
[17] R.M. Izatt, K. Pawlak, J.S. Bradshaw, R.L. Bruening, Chem. Rev. 91 (1991) 1721. Synthesis of caged crown ethers