HETEROCYCLES, Vol. 62, 2004, pp. 279 - 296
Received, 20th May, 2003, Accepted, 18th July, 2003, Published online, 16th September, 2003

SYNTHESIS AND ELECTROSPRAY IONIZATION MASS SPECTROMETRIC EVALUATION OF THE METAL CATION COMPLEXATION BEHAVIOR OF CAGE-ANNULATED AZACROWN ETHERS†

Alan P. Marchand,*[a] Zilin Huang,[a] Huiguo Lai,[a] Artie S. McKim,[a] Jennifer S. Brodbelt,*[b] and Sheldon Williams[b]

[a] *Department of Chemistry, University of North Texas, Denton, Texas 76203 U. S. A.* marchand@unt.edu; [b]*Department of Chemistry & Biochemistry, University of Texas at Austin, Austin, Texas 78712-1167 U. S. A.* jbrodbelt@mail.utexas.edu

Abstract - Six new cage-annulated azacrown ethers (**1** - **6**) have been prepared, and their respective abilities to function as alkali metal cation and/or heavy metal cation complexants have been assessed *via* application of electrospray ionization mass spectrometry (ESI-MS) techniques. All of these host systems bind to H^+; however, they also generally display a high degree of selectivity toward complexation with Ag^+.

INTRODUCTION

Macrocyclic crown ethers, first prepared by Pedersen in the 1960s,[1] constitute an important class of host molecules that are used in studies of molecular recognition and inclusion phenomena (i.e., "host-guest chemistry").[2] Crown ethers have received considerable attention in recent years as useful agents for separation and selective transport of both ions and neutral molecules.[3] Recently, as an extension of our past interests in the synthesis and chemistry of novel polycarbocyclic "cage" compounds,[4] our attention has turned to the preparation of macrocyclic polyethers that contain one or more cage moieties within the crown ether framework.[5]

Typically, our cage-annulated crown ethers contain a 3,5-disubstituted 4-oxahexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$]-

† Dedicated to Professor Leo A. Paquette on the occasion of his 70th birthday.

.$0^{5,9}$.$0^{8,11}$]dodecane ("oxahexacyclic") moiety and/or an oxaadamantane moiety as a rigidifying “spacer”. In addition to conferring a measure of rigidity upon crown ethers, incorporation of one or more polycarbocyclic cage moieties serves also to increase the lipophilicity of the resulting crown ether. Also, each cage moiety contributes to overall preorganization and complexation properties of the host by helping to define the shape and size of the cavity within the crown ether.

It should be noted that simple, noncage-annulated monocyclic crown ethers lack facial differentiation, i. e., there is no distinction between approach by a guest ion or molecule *via* the “topside” or “bottom-side” of the approximate plane of the crown ether. However, the presence of a 3,5-disubstituted 4-oxa-hexacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]dodecane cage moiety in a macrocyclic polyether negates this "top/bottom symmetry", thereby rendering the faces of the resulting crown ether diastereotopically nonequivalent.

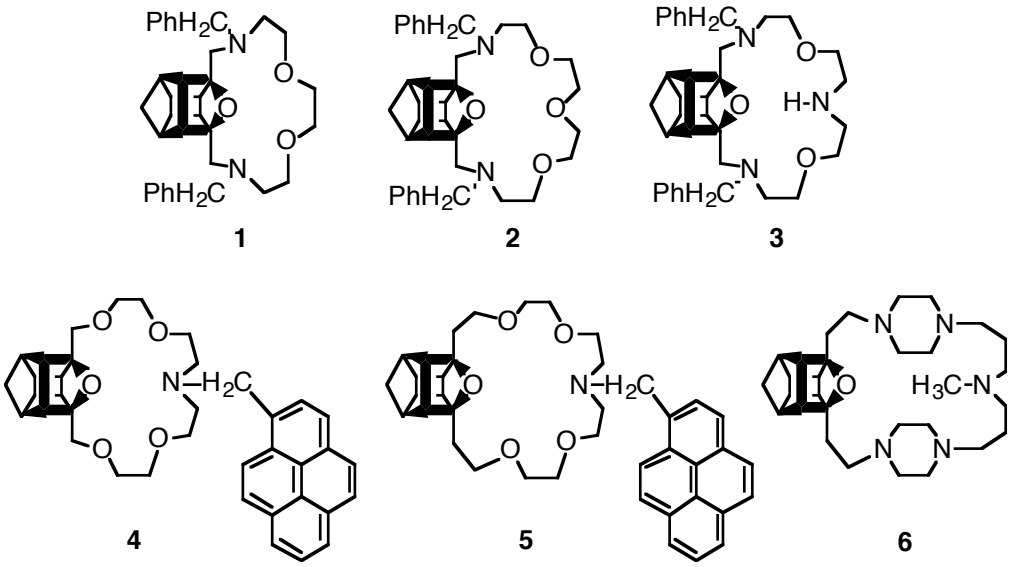
We now report the syntheses of a variety of new cage-annulated azacrown ethers; the alkali metal and divalent heavy metal cation binding properties of these unusual host molecules have been evaluated *via* electrospray ionization-mass spectrometric (ESI-MS) methods. ESI-MS has proved to be a versatile method for analysis of supramolecular complexes formed in solution and transported into the gas phase for detection.[6-21] Based upon the intensities of complexes in the resulting mass spectra, it is possible to estimate the relative binding selectivities of different hosts toward different guests. This general method has been used previously to assess the alkali metal binding properties of crown ethers,[6,10,11,12] lariat ethers,[13,14,20] and caged crown ethers,[17,18,21] and it provides the basis for the results reported herein.

RESULTS AND DISCUSSION

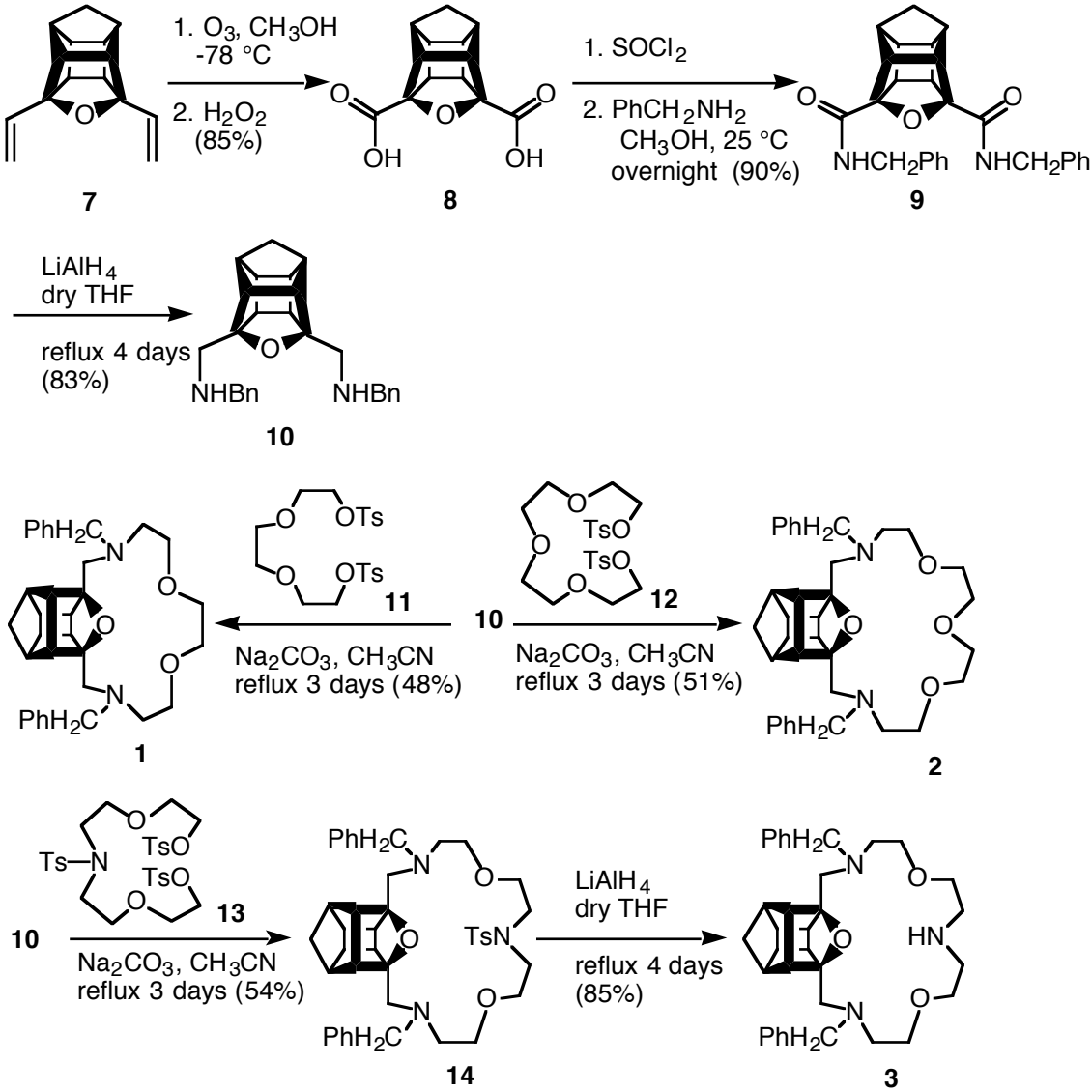
Syntheses of new azacrown ethers. Six azacrown ethers were chosen for study. The structures of these six cage-annulated host molecules are shown in Scheme 1.

The procedure employed to prepare host systems (**1**, **2**, and **3**) is shown in Scheme 2. The starting material needed to initiate this reaction sequence, i.e., **7**, can be prepared conveniently from readily available starting materials, i.e., cyclopentadiene and *p*-benzoquinone.[5] Subsequently, **7** was elaborated into the corresponding bis(benzylamine) functionalized podand (**10**) by using the method outlined in Scheme 2. Finally, **10** was converted into host systems (**1**, **2**, and **3**) by reacting it in turn with nitrogen-containing podands (**11**, **12**, and **13**), respectively (Scheme 2).

The method used to synthesize host systems (**4**) and (**5**) is shown in Scheme 3. Thus, reaction of **15**[19] and **16**[5] with podand (**13**) afforded **17**[22] and **18**, respectively. Reductive deprotection of the nitrogen atom in

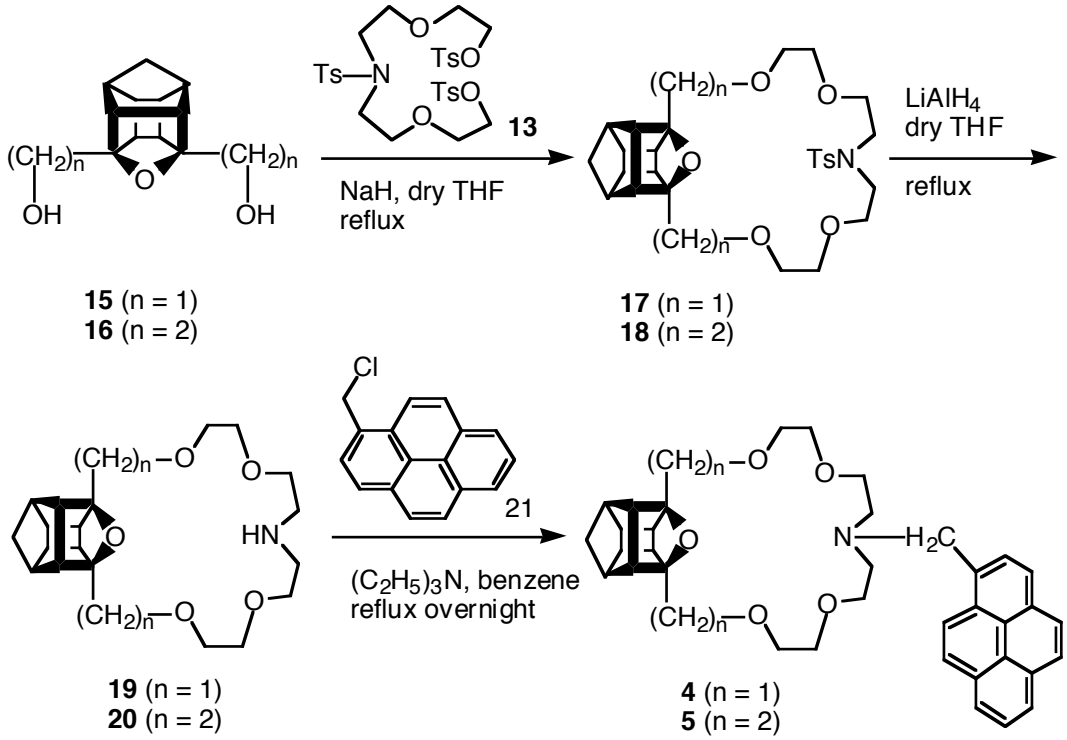


Scheme 1.



Scheme 2.

17 and **18** afforded **19**[22] and **20**, respectively. Subsequent reaction of **19** and **20** with 2-chloromethylpyrene (**21**) produced **4** and **5**, respectively (Scheme 3).

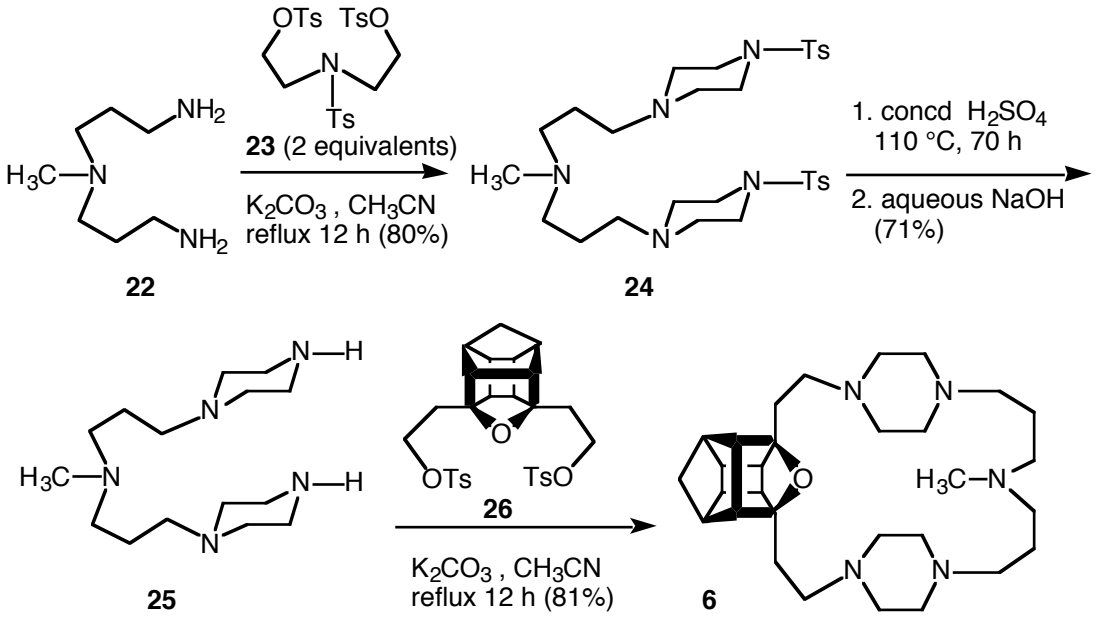


Scheme 3.

Finally, host system (**6**) was prepared by following the procedure outlined in Scheme 4. Thus, **24** was prepared *via* base promoted reaction of **22** with **23** (2 equivalents, Scheme 4).[23] Acid promoted hydrolysis of the *N*-tosyl groups in **24** led to the formation of the corresponding amine (**24**). Subsequent base promoted reaction of **24** with **25**[24] produced the desired host system (**6**) in moderate yield.

Results of electrospray ionization mass spectroscopic (ESI-MS) studies. ESI-MS has developed into a useful tool for the evaluation of binding selectivities of host-guest complexes.[8-21] This technique requires only very small sample quantities (50 □g to 1 mg depending on the extent of the study), can be used to assess complexation in a wide range of aqueous and organic solvent systems, and gives a rapid method of screening the binding properties of new ligands so that more detailed studies can be focused on a few key ligands that show the desired binding properties. These advantages render ESI-MS attractive for screening large numbers of novel compound that are destined for applications involving the selective complexation, extraction, or transport of metal cations. We have employed ESI-MS to examine the metal complexation properties of lariat ethers,[13,20] bis-crowned clefts,[14] and other cage-annulated crown

ethers.[15,17-19,21]



Scheme 4.

In the present study, we report the results of our evaluation of the alkali metal and transition metal binding selectivities of host systems (**1-6**) (Scheme 1) by using ESI-MS. The method by which binding selectivities are determined *via* ESI-MS relies upon comparison of signal intensities obtained upon spraying solutions containing a single host molecule and multiple metal ions. A competitive equilibrium is established in solution, thus leading to a distribution of macrocycle-metal complexes that reflect the relative binding constants of the macrocycle-metal complexes or the selectivity of the macrocyclic host. Upon electrospraying the solutions, the complexes generated in solution are transported to the gas phase, and the intensities of the complexes observed in the resulting mass spectra reflect the distribution in the solution. The intensities of the complexes depend upon ion desolvation, and thus host-guest complexes that have similar conformations and solvation energies generally possess similar ESI efficiencies. For the most confident interpretation of ESI-MS results, calibration experiments are undertaken involving the ESI-MS analysis of solutions containing a single host and a single guest in excess, thus giving a non-competitive binding environment and allowing evaluation of the signal intensities obtained for each different host-guest complex. These latter signal intensities can be used to calibrate or normalize the ESI-MS responses obtained for different host-guest complexes, thus allowing the most accurate quantitative comparisons.

In the present study, two general types of selectivity experiments were pursued, i.e., those that involve a single host (**1**-**6**) competing for complexation with (i) alkali metals with and without added Ag^{+} and (ii) heavy metal salts, e.g., Cd^{+2}, Ni^{+2}, Pb^{+2}, and Zn^{+2} nitrates, in the presence of Ag^{+}.

Alkali metal binding selectivities with and without added Ag^+. Selectivities were determined by integrating the areas under the ESI-MS peaks for the various macrocycle-metal complexes, and then by correcting the peak areas based on the ESI-MS response factors. Although the macrocyclic ligands described herein were not designed specifically for alkali metal selectivity, the evaluation of alkali metal selectivity provides benchmark data for assessing the general size selectivity of the macrocyclic cavities. Examples of competition experiments that involve only alkali metal hydroxides as guest ions are shown in Figure 1. The ligands do not show large selectivities for any of the alkali metal ions, although the two

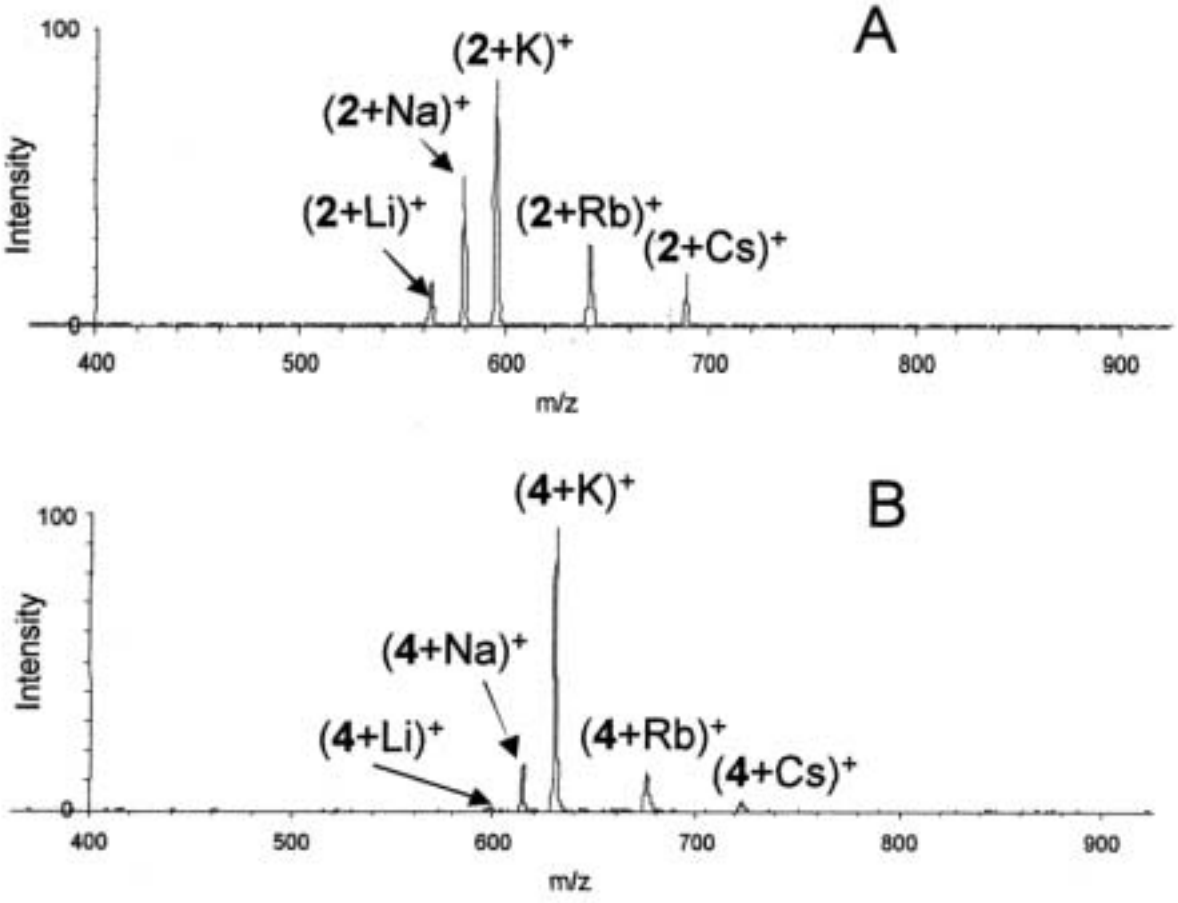


Figure 1. ESI-MS spectra of solutions containing 1:3:3:3:3:3 macrocycle:alkali metal ions in methanol where the concentration of the macrocycle is 2.5 x 10^{-5} M for (A) macrocycle (**2**) and (B) macrocycle (**4**).

shown in Figure 1 display a moderate preference for K^+ over the other metals. Note that if alkali metal chlorides are used as the source of alkali metals instead of alkali metal hydroxides, then the macrocycles prefer to protonate rather than bind the alkali metals, a result attributed to the relatively high basicities of the nitrogen-containing macrocycles.

Competition experiments that involve Ag(I) as one of the potential host cations along with other transition metal ions have also been performed. The results obtained for host systems (**2**) and (**3**) in the presence of Ni^{+2}, Cd^{+2}, Pb^{+2}, Zn^{+2} and Ag^+ nitrates in methanol solution are shown in Figure 2. Once again, some

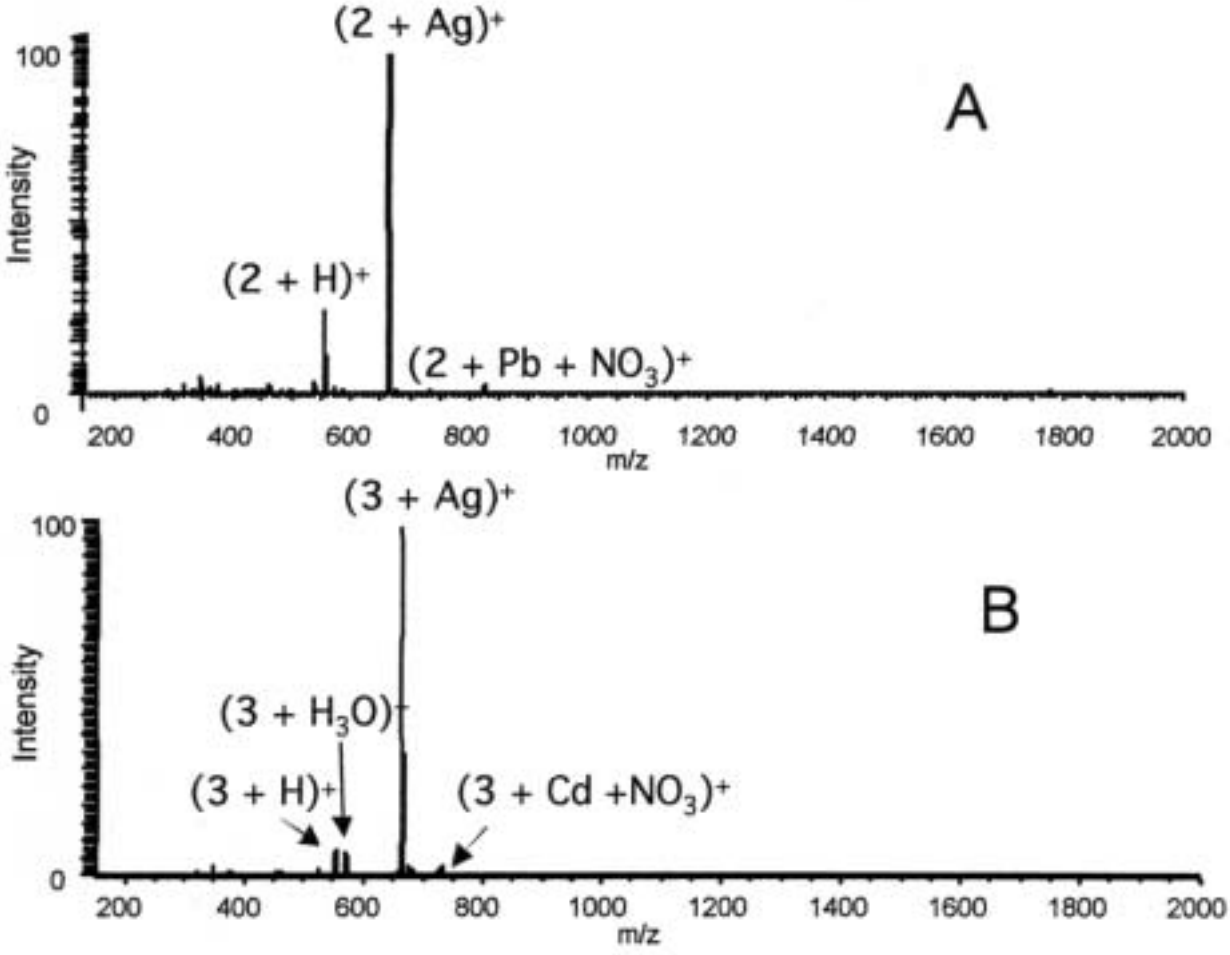


Figure 2. ESI-MS spectra of solutions containing 1:2:2:2:2:2 macrocycle: $AgNO_3$:$Cd(NO_3)_2$:$Ni(NO_3)_2$:$Pb(NO_3)_2$:$Zn(NO_3)_2$ in methanol where the concentration of the macrocycle is 2.5 x 10^{-5} M for (A) macrocycle (**2**) and (B) macrocycle (**3**).

binding of **2** and **3** to H^+ is observed. However, in the presence of Ag^+, both of these host molecules bind selectively to Ag^+ with virtually complete exclusion of the other metal ions which also are present in solution. Comparable results were obtained by using the other host systems, i.e., **4**-**6**, as well.

We have also investigated binding of host systems (**1** - **6**) to other metal cations, i.e., Ag^+, Au^{+3}, Mn^{+2}, Cu^{+2}, and Zn^{+2} nitrates in methanol solution. The results obtained by using **2** and **4** as hosts are shown in Figure 3. The affinity for the proton is observed by the detection of protonated **2** and **4**, and once again, a high degree of selectivity toward Ag^+ is evidenced by the ESI MS spectral results.

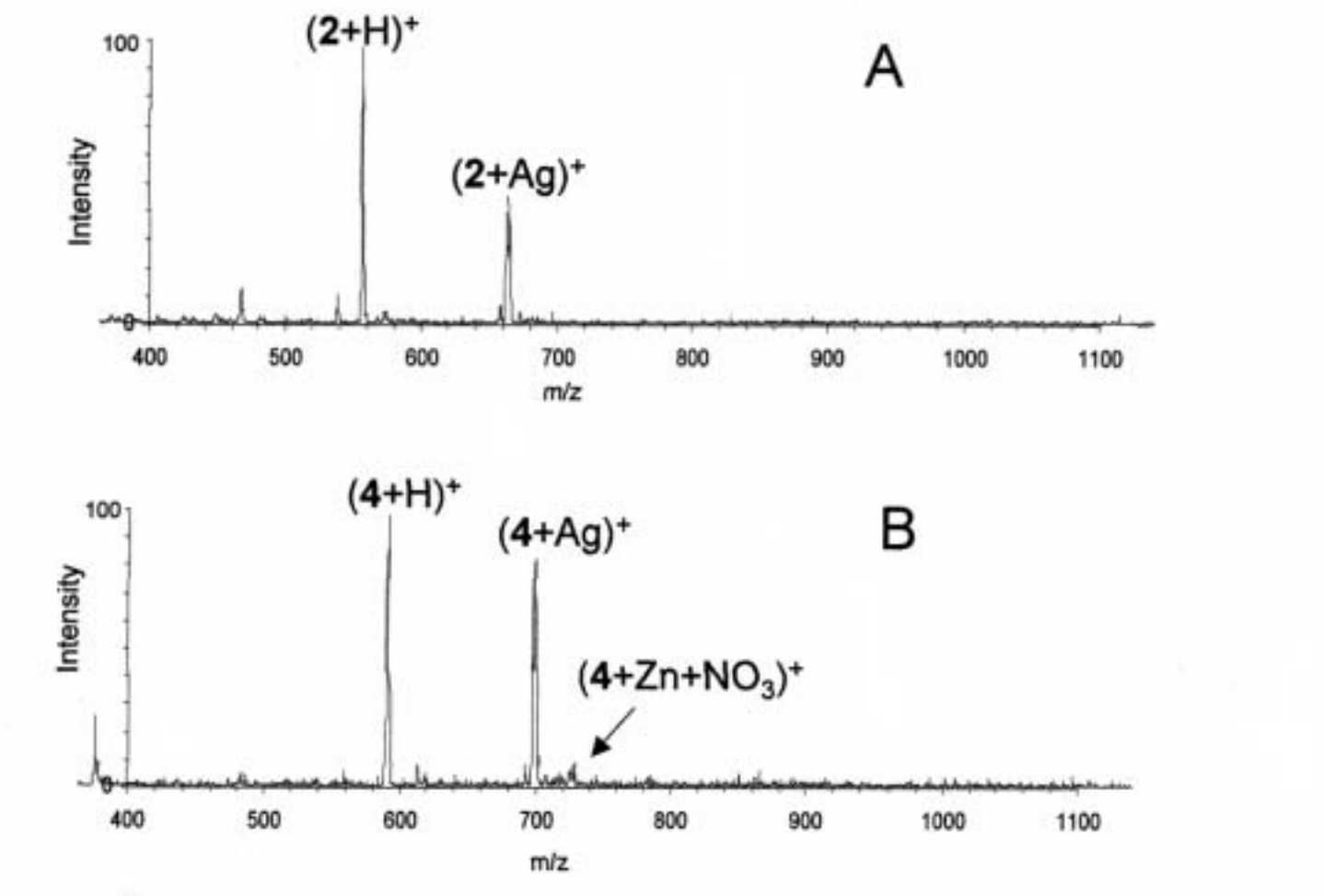


Figure 3. ESI-MS spectra of solutions containing 1:2:2:2:2:2 macrocycle: $AgNO_3$:$Mn(NO_3)_2$:$Cu(NO_3)_2$:$Au(NO_3)_2$:$Zn(NO_3)_2$ in methanol where the concentration of the macrocycle is 2.5 x 10^{-5} M for (A) macrocycle (**2**) and (B) macrocycle (**4**).

These initial studies suggest that macrocycles (**1-6**) exhibit large Ag^+ selectivities, and a more comprehensive evaluation of the degree of selectivity and the structural factors that influence the selectivity will be presented in a separate report.

SUMMARY AND CONCLUSIONS

Several new cage-annulated azacrown ethers (**1**-**6**) have been prepared, and their respective abilities to function as alkali metal cation and/or transition metal cation complexants have been assessed via application of electrospray ionization mass spectrometry techniques. All of these host systems are quite basic and thus exhibit protonation upon electrospray ionization; in addition, they also generally display a high degree of selectivity toward complexation with Ag^+ relative to alkali metals or other transition metals.

EXPERIMENTAL

Melting points are uncorrected. HRMS reported herein were obtained at the Mass Spectrometry Facility at the Department of Chemistry and Biochemistry, University of Texas at Austin by using a ZAB-E double sector high-resolution mass spectrometer (Micromass, Manchester, England) that was operated in the chemical ionization mode. Elemental micoanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

4-Oxapentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$.$0^{8,11}$]hexacyclododecane-3,5-dicarboxylic Acid (8). Into an oven dried two-neck round bottom flask that contained a magnetic stirring bar was placed a solution of **1** (5.20 g, 24.5 mmol) in dry MeOH (150 mL), and the contents of the flask were cooled to -78 °C *via* application of an external dry ice-acetone bath. Ozone was bubbled through the stirred reaction mixture until a blue color persisted (*ca*. 4 h), at which time the flow of ozone was halted, and the reaction mixture was stirred at -78 °C during an additional 0.5 h. Excess ozone was purged by bubbling argon through the reaction mixture during 10 min. The external cold bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 0.5 h. The reaction mixture was concentrated *in vacuo* (rotary evaporator, bath temperature 50 °C). The residue was cooled *via* application of an external ice-water bath, and a solution of 90% aqueous HCO_2H (40 mL) and 30% aqueous H_2O_2 (15 mL) was added during 10 min. After the addition of oxidant had been completed, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature during 20 min and then was stirred at that temperature during 2 h. The resulting mixture was refluxed gently until the reaction mixture gave a negative KI-starch paper test. The reaction mixture was concentrated *in vacuo*; the residue was washed with a small quantity of ice-cold CH_3OH (*ca*. 5 mL) and

then was recrystallized from CH_3OH. Pure **8** (5.93 g, 98%) was thereby obtained as a colorless microcrystalline solid: mp 236-237 °C; IR (KBr) 3489 (s), 3128 (s), 2976 (s), 1732 (s), 1011 cm^{-1} (s); ^1H NMR (CD_3OD) □ 1.61 (*A*B, J_{AB} = 10.8 Hz, 1 H), 2.04 (A*B*, J_{AB} = 10.8 Hz, 1 H), 2.55-3.10 (m, 8 H), 4.80-5.10 (br s, 2 H); ^{13}C NMR (CD_3OD) □ 42.2 (d), 43.0 (t), 45.2 (d), 49.3 (d), 58.6 (d), 94.4 (s), 172.8 (s). Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 62.83; H, 5.05.

4-Oxapentacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]hexacyclododecane-3,5-dibenzamide (9). Into an oven dried 100 mL flask was placed **8** (9.40 g, 37.9 mmol). To this flask was added dropwise thionyl chloride (10 mL, 137 mmol), and the resulting mixture was stirred at ambient temperature during 1 h and then was refluxed gently with stirring during an additional 1 h. The reaction mixture was concentrated *in vacuo* to remove excess $SOCl_2$. Meanwhile, a solution of $PhCH_2NH_2$ (20 g, 186 mmol, 4.9 equivalents) in dry THF (100 mL) was cooled to -40 °C *via* application of an external dry ice-acetonitrile cold bath. The oily residue that remained after excess $SOCl_2$ had been removed *in vacuo* was added dropwise with stirring to the cold solution of $PhCH_2NH_2$ (20 g, 186 mmol) in dry THF (100 mL) during 10 min. After the addition of the amine had been completed, the resulting mixture was stirred during 2 h, at which time the external cold bath was removed, and the reaction mixture was allowed to warm gradually with stirring to ambient temperature. The reaction mixture then was concentrated *in vacuo*, and the residue was partitioned between EtOAc (100 mL) and water (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 □ 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* recrystallization from EtOAc, thereby affording pure **9** (15.0 g, 93%) as a colorless microcrystalline solid: mp 182.5-183.5 °C; IR (KBr) 3329 (s), 2975 (s), 2868 (m), 1674 (s), 1643 (s), 1542 (s), 1453 (m), 1121 (m), 700 cm^{-1} (s); ^1H NMR ($CDCl_3$) □ 1.61 (*A*B, J_{AB} = 10.9 Hz, 1 H), 1.99 (A*B*, J_{AB} = 10.7 Hz, 1 H), 2.76-3.02 (m, 8 H), 4.46 (d, *J* = 6.2 Hz, 4 H), 6.50 (t, *J* = 6.2 Hz, 2 H), 7.24-7.40 (m, 10 H); ^{13}C NMR ($CDCl_3$) □ 42.4 (d), 42.6 (t), 43.2 (t), 45.8 (d), 49.3 (d), 58.8 (d), 96.0 (s), 127.4 (d), 127.7 (d), 128.6 (d), 138.0 (s), 170.6 (s). Anal. Calcd for $C_{27}H_{26}N_2O_3$: C, 76.02; H, 6.15. Found: C, 76.15; H, 6.04.

3,5-Dibenzylaminomethyl-4-oxapentacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{5,9}.0^{8,11}]hexacyclododecane (10). Into an oven dried 250 mL flask under argon was placed $LiAlH_4$ (5.00 g, 131.6 mmol) and dry THF (15 mL). To this mixture was added dropwise with stirring a solution of **9** (15.0 g, 35.2 mmol) in dry THF (30 mL), and the resulting mixture was refluxed with stirring under argon during 9 days. The reaction mixture then

was cooled to 0 °C *via* application of an external ice-water bath, and the reaction was quenched *via* careful, dropwise addition with stirring of saturated aqueous Na_2SO_4 (5 mL, excess). The resulting mixture was filtered, and the residue was washed with THF (50 mL). The combined filtrates were washed with brine (100 mL), dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was recrystallized from EtOAc, thereby affording pure **10** (13.5 g, 96%) as a colorless microcrystalline solid: mp 109-110 °C; IR (KBr) 3427 (m), 2976 (m), 2956 (m), 2854 (m), 2823 (s), 1493 (m), 1451 (s), 1120 (m), 795 (s), 743 cm^{-1} (s); ^1H NMR ($CDCl_3$) □ 1.51 (*A*B, J_{AB} = 10.5 Hz, 1 H), 1.88 (A*B*, J_{AB} = 10.5 Hz, 1 H), 2.31-2.44 (m, 2 H), 2.53-2.72 (m, 6 H), 2.83-3.02 (m, 4 H), 3.83 (s, 4 H), 7.16-7.39 (m, 10 H); ^{13}C NMR ($CDCl_3$) □ 41.5 (d), 43.5 (t), 44.0 (d), 46.6 (d), 50.5 (t), 54.3 (t), 56.8 (t), 96.4 (s), 126.7 (d), 128.0 (d), 128.2 (d), 140.5 (s). Exact MS (CI-HRMS) Calcd for $C_{27}H_{30}N_2O$: $[M_r + H]^+$ *m/z* 399.2436. Found: $[M_r + H]^+$ *m/z* 399.2429.

Synthesis of 1. An oven dried 250 mL flask was charged with a mixture of **10** (796 mg, 2.00 mmol), **11** (1.10 g, 2.40 mmol, 1.2 equivalents), and Na_2CO_3 (2.12 g, 20.0 mmol, 10 equivalents) in dry CH_3CN (50 mL) under argon, and the resulting mixture was refluxed under argon during 3 days. Subsequently, the reaction mixture was allowed to cool gradually to ambient temperature and then was concentrated *in vacuo*. The residue was partitioned between EtOAc (75 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 □ 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on basic alumina by eluting with 10% EtOAc-hexane. Pure **1** (431 mg, 42%) was thereby obtained as a colorless microcrystalline solid: mp 94-95 °C; IR (KBr) 2963 (s), 2861 (s), 2789 (s), 1449 (m), 1369 (m), 1300 (m), 1101 (s), 1050 (s), 742 (m), 697 cm^{-1} (m); ^1H NMR ($CDCl_3$) □ 1.39 (*A*B, J_{AB} = 10.3 Hz, 1 H), 1.84 (A*B*, J_{AB} = 10.3 Hz, 1 H), 1.96-2.06 (m, 2 H), 2.36-2.48 (m, 4 H), 2.64-2.72 (m, 4 H), 2.74-2.92 (m, 4 H), 3.15-3.32 (m, 2 H), 3.43-3.54 (m, 2 H), 3.66-3.82 (m, 10 H), 7.20-7.43 (m, 10 H); ^{13}C NMR ($CDCl_3$) □ 41.0 (d), 43.5 (t), 43.7 (d), 46.6 (d), 54.4 (t), 54.7 (t), 55.3 (d), 60.8 (t), 69.1 (t), 70.5 (t), 97.5 (s), 126.8 (d), 128.01 (d), 128.06 (d), 140.0 (s). Exact MS (CI-HRMS) Calcd for $C_{33}H_{40}N_2O_3$: $[M_r + H]^+$ *m/z* 513.31171. Found: $[M_r + H]^+$ *m/z* 513.31169.

Synthesis of 2. An oven dried 250 mL flask was charged with a mixture of **10** (796 mg, 2.00 mmol), **12** (1.21 g, 2.41 mmol, 1.2 equivalents), Na_2CO_3 (2.12 g, 20.0 mmol, 10 equivalents), and K_2CO_3 (2.76 g, 20.0 mmol, 10 equivalents) in dry CH_3CN (50 mL) under argon, and the resulting mixture was refluxed

under argon during 3 days. Subsequently, the reaction mixture was allowed to cool gradually to ambient temperature and then was concentrated *in vacuo*. The residue was partitioned between EtOAc (75 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on basic alumina by eluting with 15% EtOAc-hexane. Pure **2** (523 mg, 47%) was thereby obtained as a colorless oil; IR (KBr) 2948 (s), 2861 (s), 2816 (m), 1451 (m), 1297 (m), 1126 (s), 1048 (m), 737 (m), 698 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.41 (*A*B, J_{AB} = 10.4 Hz, 1 H), 1.86 (A*B*, J_{AB} = 10.4 Hz, 1 H), 2.04-2.15 (m, 2 H), 2.38-2.55 (m, 4 H), 3.00-3.16 (m, 2 H), 3.53-3.85 (m, 16 H), 7.17-7.43 (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 41.2 (d), 43.4 (t), 43.9 (d), 46.6 (d), 54.9 (t), 54.4 (t), 55.8 (d), 60.6 (t), 69.8 (t), 70.1 (t), 70.9 (t), 97.3 (s), 126.6 (d), 128.0 (d), 128.6 (d), 140.2 (s). Exact MS (CI-HRMS) Calcd for $C_{35}H_{44}N_2O_4$: $[M_r + H]^+$ *m/z* 557.3379. Found: $[M_r + H]^+$ *m/z* 557.3383.

Synthesis of 14. An oven dried 250 mL flask was charged with a mixture of **10** (1.19 g, 3.00 mmol), **13** (2.36 g, 3.60 mmol, 1.2 equivalents), Na_2CO_3 (3.18 g, 30.0 mmol, 10 equivalents), and K_2CO_3 (4.14 g, 30.0 mmol, 10 equivalents) in dry CH_3CN (100 mL) under argon, and the resulting mixture was refluxed under argon during 3 days. Subsequently, the reaction mixture was allowed to cool gradually to ambient temperature and then was concentrated *in vacuo*. The residue was partitioned between EtOAc (100 mL) and water (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on basic alumina by eluting with 5% EtOAc-hexane. Pure **14** (1.16 g, 54%) was thereby obtained as a colorless, viscous oil; IR (KBr) 2956 (s), 2861 (s), 2817 (m), 1605 (w), 1493 (w), 1451 (m), 1341 (s), 1161 (s), 1113 (s), 1044 (s), 739 (s), 699 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.38 (*A*B, J_{AB} = 10.7 Hz, 1 H), 1.84 (A*B*, J_{AB} = 10.7 Hz, 1 H), 1.96-2.04 (m, 2 H), 2.34-2.50 (m, 7 H), 2.65-2.90 (m, 8 H), 2.96-3.16 (m, 2 H), 3.29-3.40 (m, 4 H), 3.50-3.80 (m, 4 H), 7.16-7.40 (m, 12 H). 7.30 (A*B*, J_{AB} = 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (q), 41.0 (d), 43.3 (t), 43.6 (d), 46.3 (d), 49.8 (t), 53.6 (t), 54.2 (t), 55.4 (d), 60.4 (t), 69.0 (t), 70.5 (t), 97.5 (s), 126.6 (d), 127.0 (d), 127.9 (d), 128.5 (d), 129.5 (d), 136.3 (s), 139.9 (s), 142.9 (s). Exact MS (CI-HRMS) Calcd for $C_{42}H_{51}N_3O_5S$: $[M_r + H]^+$ *m/z* 710.3628. Found: $[M_r + H]^+$ *m/z* 710.3632.

Synthesis of 3. Into an oven dried 100 mL flask under argon was placed $LiAlH_4$ (196 mg, 5.16 mmol) and dry THF (15 mL). To this mixture was added dropwise with stirring a solution of **9** (1.16 g, 1.63

mmol) in dry THF (10 mL), and the resulting mixture was refluxed with stirring under argon during 4 days. The reaction mixture then was cooled to 0 °C *via* application of an external ice-water bath, and the reaction was quenched *via* careful, dropwise addition with stirring of saturated aqueous Na_2SO_4 (1.0 mL, excess). The resulting mixture was filtered, and the residue was washed with THF (50 mL). The combined filtrates were washed with brine (40 mL), dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on basic alumina by eluting with 50% EtOAc-CH_2Cl_2. Recrystallization of the eluate from EtOAc afforded pure **3** (771 mg, 85%) as a colorless microcrystalline solid: mp 92.5-93.5 °C; IR (KBr) 3650 (m), 3440 (m), 2943 (s), 2861 (s), 2805 (s), 1450 (m), 1366 (m), 1303 (m), 1118 (s), 1050 (s), 736 (s), 697 cm^{-1} (s); ^1H NMR ($CDCl_3$) □ 1.42 (*A*B, J_{AB} = 10.5 Hz, 1 H), 1.86 (A*B*, J_{AB} = 10.5 Hz, 1 H), 2.10-2.20 (m, 2 H), 2.26-2.60 (m, 6 H), 2.67-2.88 (m, 11 H), 2.96-3.12 (s, 2 H), 3.44-3.80 (m, 12 H), 7.17-7.42 (m, 10 H); ^{13}C NMR ($CDCl_3$) □ 30.3 (t), 41.3 (d), 43.5 (t), 44.0 (d), 46.6 (d), 49.0 (t), 54.2 (t), 54.9 (t), 55.9 (d), 60.1 (t), 69.3 (t), 69.7 (t), 97.4 (s), 126.5 (d), 128.0 (d), 128.7 (d), 142.1 (s). Exact MS (CI-HRMS) Calcd for $C_{35}H_{45}N_3O_3$: $[M_r + H]^+$ *m/z* 556.35392. Found: $[M_r + H]^+$ *m/z* 556.35395.

Synthesis of 4. A mixture of **19**[25] (189 mg, 0.50 mmol), **21**[26] (138 mg, 0.55 mmol) and Et_3N (2 mL) in dry benzene (15 mL) under argon was refluxed with stirring overnight. The reaction mixture then was allowed to cool gradually to ambient temperature and was concentrated *in vacuo*. The residue was partitioned between EtOAc (50 mL) and water (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 □ 30 mL). The combined organic layers were washed sequentially with water (10 mL) and with brine (30 mL), dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on basic alumina by eluting with a 1:40:100 MeOH-EtOAc-CH_2Cl_2 solvent mixture. Pure **4** (169 mg, 57%) was thereby obtained as a pale yellow oil; IR (KBr) 3037 (w), 2948 (s), 2861 (s), 1453 (w), 1293 (w), 1123 (s), 847 (s), 753 (s), 710 cm^{-1} (m); ^1H NMR ($CDCl_3$) □ 1.32 (*A*B, J_{AB} = 10.3 Hz, 1 H), 1.69 (A*B*, J_{AB} = 10.3 Hz, 1 H), 2.13 (s, 2 H), 2.36 (s, 2 H), 2.60-2.68 (m, 4 H), 2.86-2.97 (m, 4 H), 3.46-3.75 (m, 15 H), 4.25 (s, 2 H), 7.72-8.05 (m, 8 H), 8.66-8.75 (m, 1 H); ^{13}C NMR ($CDCl_3$) □ 41.7 (d), 43.9 (t), 44.0 (d), 45.6 (d), 55.0 (t), 55.5 (d), 59.5 (t), 69.7 (t), 70.6 (t), 70.7 (t), 71.4 (t), 97.4 (s), 124.8 (d), 125.1 (d), 125.1 (d), 125.2 (s), 125.5 (s), 125.61 (s), 126.0 (d), 127.20 (d), 127.24 (d), 127.9 (d), 128.4 (d), 130.4 (s), 131.1 (s), 131.5 (s), 131.8 (s), 134.3 (s), Exact MS (CI-HRMS) Calcd for $C_{38}H_{41}NO_5$: $[M_r + H]^+$ *m/z* 592.30623. Found: $[M_r + H]^+$ *m/z* 592.3053.

Synthesis of 5. A mixture of **20**[27] (190 mg, 0.47 mmol), **21** (137 mg, 0.55 mmol) and Et_3N (2 mL) in dry benzene (15 mL) under argon was refluxed with stirring overnight. The reaction mixture then was allowed to cool gradually to ambient temperature and was concentrated *in vacuo*. The residue was partitioned between EtOAc (50 mL) and water (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were washed sequentially with water (10 mL) and with brine (30 mL), dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* column chromatography on basic alumina by eluting with a 1:40:100 MeOH-EtOAc-CH_2Cl_2 solvent mixture. Pure **5** (107 mg, 37%) was thereby obtained as a pale yellow oil; IR (KBr) 3037 (w), 2949 (s), 2859 (s), 1478 (w), 1453 (w), 1352 (w), 1291 (w), 1115 (s), 846 (s), 710 cm^{-1} (m); ^{1}H NMR (benzene-d_6) δ 1.36 (*A*B, J_{AB} = 10.3 Hz, 1 H), 1.72 (A*B*, J_{AB} = 10.3 Hz, 1 H), 2.09 (t, J = 6.3 Hz, 2 H), 2.10 (t, J = 6.3 Hz, 2 H), 2.16-2.24 (m, 2 H), 2.36-2.43 (m, 2 H), 2.56-2.68 (m, 4 H), 2.94 (t, J = 5.9 Hz, 4 H), 3.33-3.56 (m, 10 H), 3.77 (t, J = 6.3 Hz, 2 H), 4.27 (s, 2 H), 7.72-8.07 (m, 8 H), 8.67-8.73 (m, 1 H); ^{13}C NMR (benzene-d_6) δ 33.2 (t), 41.8 (d), 43.8 (t), 44.4 (d), 48.7 (d), 55.0 (t), 58.3 (t), 59.4 (d), 68.6 (t), 70.4 (t), 70.5 (t), 71.5 (t), 94.6 (s), 124.8 (d), 124.9 (d), 125.16 (d), 125.2 (d), 125.5 (s), 125.6 (s), 126.0 (d), 127.27 (d), 127.30 (d), 128.4 (d), 130.4 (s), 131.1 (s), 131.5 (s), 131.8 (s), 134.1 (s), 143.9 (t). Exact MS (CI-HRMS) Calcd for $C_{40}H_{45}NO_5$: $[M_r + H]^+$ *m/z* 620.3376. Found: $[M_r + H]^+$ *m/z* 620.3366.

Synthesis of 4',4''-Ditosyl*bis*(3-piperazinylpropyl)methylamine (24). To a refluxing mixture of *N*-methyl-*N*,*N*-bis(3'-aminopropyl)amine (**22**, 2.90 g, 20.0 mmol) and K_2CO_3 (27.6 g, 200 mmol) in CH_3CN (200 mL) was added dropwise with stirring a solution of **23**[28] (23.4 g, 40.0 mmol) during 7 h. After the addition of **23** had been completed, the resulting suspension was refluxed during 12 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was gravity-filtered, and the filtrate was concentrated *in vacuo*. The residue was purified *via* fractional recrystallization from EtOH. Pure **24** (4.71 g, 80%) was thereby obtained as a colorless microcrystalline solid: mp 140-141 °C; IR (KBr) 2952 (s), 2815 (s), 1450 (s), 1345 (s), 1324 (s), 1164 (s), 1091 (m), 946 (m), 813 (m), 737 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.46-1.52 (m, 4 H), 2.07(s, 3 H), 2.16-2.28 (m, 8 H), 2.36 (s, 3 H), 2.42 (t, J = 4.6 Hz, 8 H), 2.94 (t, J = 4.6 Hz, 8 H), 7.26 (*A*B, J_{AB} = 8.1 Hz, 4 H), 7.56 (A*B*, J_{AB} = 8.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.3 (q), 24.5 (t), 42.0 (q), 45.9 (t), 52.1 (t), 55.4 (t), 56.0 (t), 127.7 (d), 129.5 (d), 132.2 (s), 143.5 (s). Anal. Calcd for $C_{29}H_{45}N_5O_4S_2$: C, 58.85; H, 7.66. Found: C, 58.70; H, 7.47. Exact MS (CI-HRMS) Calcd for $C_{29}H_{45}N_5O_4S_2$: $[M_r + H]^+$ *m/z* 591.29912. Found: $[M_r + H]^+$ *m/z* 592.29907.

Synthesis of *Bis*(3-piperazinylpropyl)methylamine (25). A solution of **24** (1.77 g, 3.0 mmol) in 96% H_2SO_4 (15 mL) was heated with stirring at 110 °C during 70 h. The reaction mixture was allowed to cool gradually to ambient temperature. The supernatant liquid was decanted, and the residual viscous oil was washed with Et_2O (3 × 50 mL). The residue was dissolved in a minimum volume of water (10 mL) and then was rendered basic *via* addition of saturated aqueous NaOH (*ca*. 20 mL). The resulting aqueous suspension was extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue, **25** (600 mg, 71%) was used as obtained, without additional purification; IR (film) 3314(br, s), 2943 (s), 2799 (s), 1667 (m), 1470 (m), 1321 (m), 1264 (m), 1136 (m), 1063 (w), 998 (m), 846 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.58-1.68 (m, 4 H), 2.16 (s, 3 H), 2.24-2.37 (m, 16 H), 2.83-2.88 (t, J = 4.6 Hz, 8 H), 3.22 (br s, peak disappears when sample is shaken with D_2O, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.4 (t), 42.3 (q), 45.9 (t), 54.4 (t), 55.7 (t), 57.2(t). Exact MS (CI-HRMS) Calcd for $C_{15}H_{33}N_5$: $[M_r + H]^+$ *m/z* 284.2814. Found: $[M_r + H]^+$ *m/z* 284.2807.

Synthesis of 6. To a suspension of **25** (493 mg, 1.74 mmol) and K_2CO_3 (2.70 g, 19.8 mmol) in refluxing CH_3CN (100 mL) was added dropwise with stirring a solution of **26**[29] (968 mg, 1.74 mmol) in CH_3CN (80 mL) during 7 h. After the addition of **26** had been completed, the resulting mixture was refluxed during 2 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was gravity-filtered. The residue was washed with CH_3CN (3 × 20 mL), and the combined filtrates were concentrated *in vacuo*. The residue was purified *via* column chromatography on alumina by eluting with 4% MeOH-CH_2Cl_2. The eluate was recrystallized from EtOAc-hexane, thereby affording pure **6** (698 mg, 81%) as a colorless microcrystalline solid: mp 113-114 °C; IR (KBr): 2943 (m), 2807 (m), 1458 (s), 1373 (m), 1297 (s), 1204 (w), 1159 (s), 1091 (w), 1003 (m), 918 (m), 870 (m), 749 (m) cm^{-1} (m);^1H NMR ($CDCl_3$) δ 1.50 (*A*B, J_{AB} = 10.5 Hz, 1 H), 1.58-1.72 (m, 4 H), 1.83 (A*B*, J_{AB} = 10.5 Hz, 1 H), 1.91-1.98 (m, 4 H), 2.23 (s, 3 H), 2.34-2.58 (m, 36 H); ^{13}C NMR ($CDCl_3$) δ 23.6 (t), 28.6 (t), 41.3 (d), 43.0 (q), 43.5 (d), 43.8 (d), 47.7 (d), 52.2 (t), 53.4 (t), 53.9 (t), 54.5 (t), 54.8 (t), 58.3 (t), 94.9 (s). Exact MS (CI-HRMS) Calcd for $C_{30}H_{49}N_5O$: $[M_r + H]^+$ *m/z* 495.40154. Found: $[M_r + H]^+$ *m/z* 495.40082.

Electrospray ionization mass spectrometry experiments: All mass spectrometry experiments were performed with a Finnigan ITMS quadrupole ion trap mass spectrometer (ThermoFinnigan, San Jose, CA) operated in the ESI mode. The Harvard syringe pump system (Harvard Apparatus Inc., Holliston, MA) was operated at a flow rate between 2 and 5 μL/min for all experiments, and the ESI needle voltage

was 3.4 kV. A heated desolvation capillary was not used for the experiments. A nitrogen sheath-flow gas of 5 psi was used for experiments involving multiple transition metal binding and no sheath gas was used for the experiments involving solutions containing alkali metals ions with or without silver ion. Each spectrum was an average of 150 scans. For screening of the alkali and transition metal ion selectivities of macrocycles (**1** - **6**), solutions containing a single host with multiple metal ions were analyzed. Solutions containing one part of host and three parts of each metal ion were analyzed for each ligand in pure methanol. The excess of metal ions relative to the ligands creates a more competitive binding environment for complexation with the host compound. Throughout the study, the concentration of each host was 5.0 x 10^{-5} M and concentrations of the metal ions were 1.0 x 10^{-4} M. These concentrations were used to ensure solubility of all salts in the solvent medium while maintaining conditions for increased selectivity versus solutions containing one part host and one part of each guest metal ion. Metal salts used for these experiments were purchased from Aldrich Chemical Co. (Milwaukee, Wisconsin), except the hydrogen tetranitratoaurate(III) which was purchased from J and J Materials Incorporated (Neptune City, New Jersey). All chemicals were used as received.

ACKNOWLEDGEMENTS

We thank the Robert A. Welch Foundation [Grants B-0963 (A. P. M.) and F-1155 (J. S. B.)], the Texas Advanced Technology Program (Grant 003659-0206-1999), and the U. S. Department of Energy (Grant DE-FG07-98ER14936, to A. P. M.) for financial support of this study.

REFERENCES

1. C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **78,** 2495, 7017.
2. G. R. Newkome, J. D. Sauer, J. M. Roper, and D. C. Hager, *Chem. Rev.*, 1977, **77,** 513.
3. G. W. Gokel and S. J. Korzeniowski, 'Macrocyclic Polyether Synthesis', Springer-Verlag, Berlin, 1982; E. Blasius and K.-P. Janzen, 'Host-Guest Complex Chemistry: Macrocycles', ed. by F. Vögtle and E. Weber, Springer-Verlag, Berlin, 1985, pp. 189-216; J.-M. Lehn, 'Supramolecular Chemistry', VCH, Weinheim, 1995.
4. A. P. Marchand, 'Advances in Theoretically Interesting Molecules', Vol. 1, ed. by R. P. Thummel, JAI: Greenwich, CT, 1989, pp. 357-397; A. P. Marchand, *Synlett*, 1991, 73; A. P. Marchand, *Aldrichimica Acta*, 1995, **28**, 95; K. Mlinaric-Majerski and G. Kragol, *Kem. Ind.,* 2001, **50**, 129.
5. A. P. Marchand, K. A. Kumar, A. S. McKim, K. Mlinaric-Majerski, and G. Kragol, *Tetrahedron*, 1997, **53**, 3467; A. P. Marchand, A. S. McKim, and K. A. Kumar, *Tetrahedron*, 1998, **54**, 13421; A. P. Marchand, H.-S. Chong, S. Alihodzic, W. H. Watson, and S. G. Bodige, *Tetrahedron*, 1999, **55,** 9687; A. P. Marchand and H.- S. Chong, *Tetrahedron*, 1999, **55**, 9697.

6. T. J. D. Jorgensen, P. Roepstorff, and A. J. R. Heck, *Anal. Chem.*, 1998, **70**, 4427.
7. T. J. D. Jorgensen, T. Staroske, P. Roepstorff, D. H. Williams, and A. J. R. Heck, *J. Chem. Soc., Perkin Trans. 2*, 1999,1859.
8. E. Leize, A. Jaffrezic, and A. Van Dorsselaer, *J. Mass Spectrom.*, 1996, **31**, 537.
9. K. Wang and G. W. Gokel, *J. Org. Chem.*, 1996, **61**, 4693.
10. D. S.Young, H.-Y. Hung, and L. K. Liu, *J. Mass Spectrom.*, 1997, **32**, 432.
11. S. M. Blair, E. C. Kempen, and J. S. Brodbelt, *J. Am. Soc. Mass Spectrom.*, 1998, **9**, 1049.
12. J. S. Brodbelt, E. Kempen, and M. Reyzer, *Struct. Chem.*, 1999, **10**, 213.
13. E. C. Kempen, J. S. Brodbelt, R. A. Bartsch, Y. Jang, and J. S. Kim, *Anal. Chem.*, 1999, **71**, 5493.
14. S. M. Blair, J. S. Brodbelt, G. M. Reddy, and A. P. Marchand, *J. Mass Spectrom.*, 1998, **33**, 721.
15. S. M. Blair, J. S. Brodbelt, A. P. Marchand, K. A. Kumar, and H.-S. Chong, *Anal. Chem.*, 2000, **72**, 2433.
16. E. Kempen and J. S. Brodbelt, *Anal. Chem.*, 2000, **72,** 5411.
17. S. Blair, J. S. Brodbelt, A. P. Marchand, H.-S. Chong, and S. Alihodzic, *J. Am. Soc. Mass Spectrom.*, 2000, **11**, 884.
18. M. L. Reyzer, J. S. Brodbelt, A. P. Marchand, Z. Chen, Z. Huang, and I. N. N. Namboothiri, *Int. J. Mass Spectrom.,* 2001, **204**, 133.
19. A. P. Marchand, Z. Huang, Z. Chen, H. K. Hariprakasha, I. N. N. Namboothiri, J. S. Brodbelt, and M. L. Reyzer, *J. Heterocycl. Chem.*, 2001, **38**, 1361.
20. S. Williams, S. M. Blair, J. S. Brodbelt, X. Huang, and R. A. Bartsch, *Int. J. Mass Spectrom.,* 2001, **212**, 389.
21. S. M. Williams, J. S. Brodbelt, D. Cal, and A. P. Marchand, *Anal. Chem.*, 2002, **74**, 4423.
22. The procedure used to prepare **17** and **19** has been reported previously; see: J. C. Bryan, T. G. Levitskaia, C. Giacovazzo, G. Cascarano, A. P. Marchand, Z. Huang, V. S. Kumar, and T. D. Power, *Struct. Chem.*, 2001, **12**, 275.
23. C. Bazzicalupi, A. Bencini, V. Fusi, M. Micheloni, P. Paoletti, and B. Valtancoli, *J. Org. Chem.*, 1994, **59**, 7508.
24. A. P. Marchand, S. Alihodzic, A. S. McKim, and K. A. Kumar, *Tetrahedron Lett.*, 1998, **39**, 1861.
25. J. C. Bryan, T. G. Levitskaia, C. Giacovazzo, G. Cascarano, A. P. Marchand, Z. Huang, V. S. Kumar, and T. D. Power, *Struct. Chem.*, 2001, **12**, 275.
26. K. Yamana, Y. Ohashi, K. Nunota, M. Kitamura, H. Nakano, and O. Sangen, *Tetrahedron Lett.*, 1991, **32**, 6347.
27. A. P. Marchand, K. A. Kumar, A. S. McKim, S. Alihodzic, H.-S. Chong, K. Krishnudu, M. Takhi, K. Mlinaric-Majerski, G. Kragol, and T. Sumanovac, *Kem. Ind.*, 2001, **50**, 129; T. G. Levitskaia, B. A.

Moyer, P. V. Pnnesen, A. P. Marchand, K. Krishnudu, Z. Chen, Z. Huang, H. G. Kruger, and A. S. McKim, *J. Am. Chem. Soc.*, 2001, **123**, 12099.

28. L. G. Qian, Z. Sun, M. P. Mertes, and K. B. Mertes, *J. Org. Chem.,* 1991, **56**, 4904; I. Yoon, K. M. Park, and S. S. Lee, *Acta. Crystallogr., Sect. C: Cryst. Struct. Commun.,* 2001, **C57**, 321.
29. A. P. Marchand, K. A. Kumar, A. S. McKim, K. Mlinaric-Majerski, and G. Kragol, *Tetrahedron,* 1997, **53**, 3467.