

Electrospray ionization mass spectrometric study of the metal cation complexation capabilities of a novel, doubly cage-annulated molecular box

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Dedicated to Padmasree A. V. Rama Rao on the occasion of his 70th anniversary
SATAMANAM BHAVATI SATAYU

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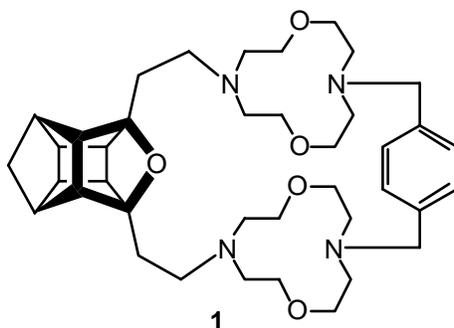
Abstract

An unusual molecular box, **4**, obtained as a mixture of diastereoisomeric, doubly cage-annulated host molecules, i.e., **4a** and **4b**, has been prepared. The metal cation complexation properties of the mixture of **4a** and **4b** thereby obtained have been assessed, with comparison to another bis crown **2**, via application of electrospray ionization mass spectrometric (ESI-MS) methods. Both host systems **2** and **4** bind selectively to Li⁺ and Na⁺, thereby demonstrating preference over the other larger alkali metals. Addition of Ag⁺ to the solutions containing alkali metals does not result in substantial Ag⁺ complexation. Analysis of a solution containing only transition metal, not alkali metal, cations indicates that **4** forms complexes with Zn⁺ and Ag⁺ along with substantial complexation of Na⁺ from residual sodium present in the solvents.

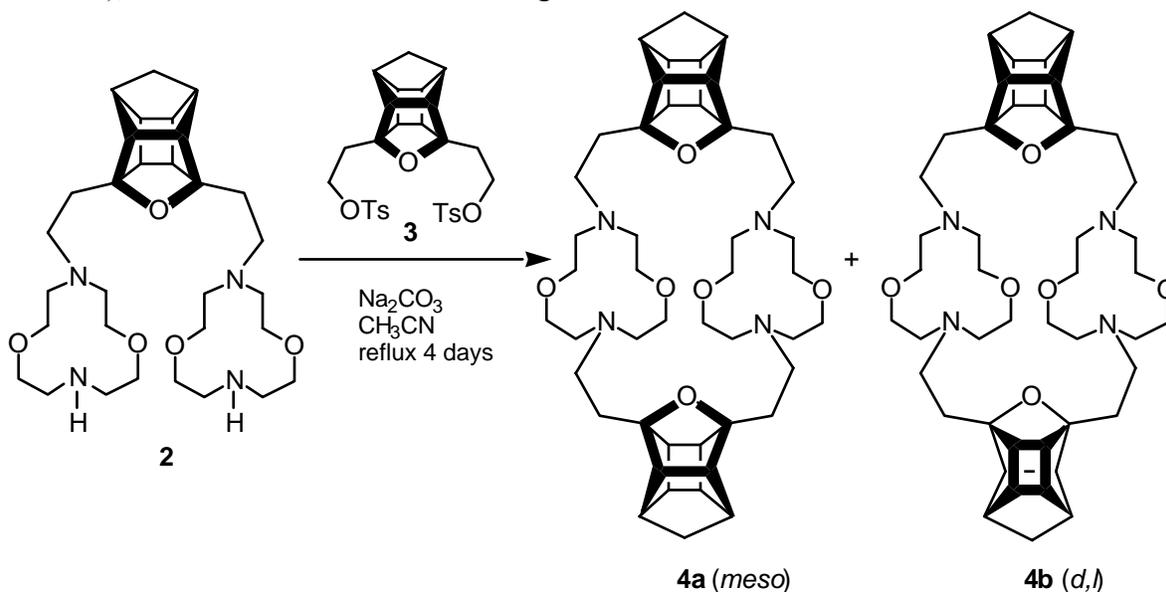
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Introduction

As part of an ongoing research program involved with the synthesis of cage functionalized crown ethers, cryptands, and molecular boxes,¹ we recently reported the synthesis and alkali metal cation complexation characteristics of a series of bis(monoazacrown) ether and bis(diazacrown) ethers.² Incorporation of the two diazacrown ether moieties into a molecular box, as in **1** (Scheme 1), imposes a high level of preorganization upon the resulting host system.

**Scheme 1**

“Forced cooperativity” occurs between the diazacrown ether moieties in **1** as they form a sandwich-type complex³⁻⁷ with a metal cation guest. Host systems of this type generally display high avidity and high selectivity toward complexation of specific metal cation guests.² We now report the synthesis of two diastereoisomeric host systems, **4**, obtained as a mixture of **4a** and **4b** (Scheme 2), which are close structural analogs of **1**.

**Scheme 2**

Results and Discussion

Synthesis of 4a and 4b. The method employed to prepare **4a** and **4b** is outlined in Scheme 2. Base promoted, Na⁺ templated reaction of **2**² with podand ditosylate **3**⁸ produced a mixture of diastereoisomeric products, i.e., **4a** and **4b**, in 80% yield. These two diastereoisomeric products display virtually identical NMR spectral properties and solubilities in common organic solvents; as a result, we were unable to separate this mixture into its components. Since our intent was to study the host-guest behavior of these molecules toward metal cations, and due to the fact that

their structures are so similar, we decided to utilize the mixture of diastereoisomeric products, **4**, as obtained in the subsequent metal cation complexation studies (*vide infra*).

Electrospray ionization mass spectral studies. Electrospray ionization mass spectrometry (ESI-MS) was the analytical method of choice for study of metal cation complexation properties of **2** and **4**. In the past, ESI-MS has proved invaluable for qualitative and quantitative evaluation of host binding selectivities in weakly bound, noncovalent host-guest complexes in the gas phase.⁹⁻²¹ ESI-MS is quite useful for obtaining an initial assessment of the metal binding affinities of new ligands, particularly when followed by more detailed quantitative studies performed by using conventional methods to obtain binding constants of specific complexes of interest.

For screening of the metal cation selectivities of **2** and **4**, solutions containing **2** or **4** with multiple metal ions were analyzed. Throughout the study, the concentration of each metal and **2** or **4** in the solution was 2.0×10^{-5} M. Piperidine (1 mM) was added to each solution containing **2** or **4** to minimize protonation of the macrocycle. Figure 1 shows the ESI-mass spectrometric results for a solution containing **4** with five alkali metals. In addition to protonated **4**, the observation of Na^+ and Li^+ complexes indicates that **4** binds these metals preferentially over the other larger alkali metals.

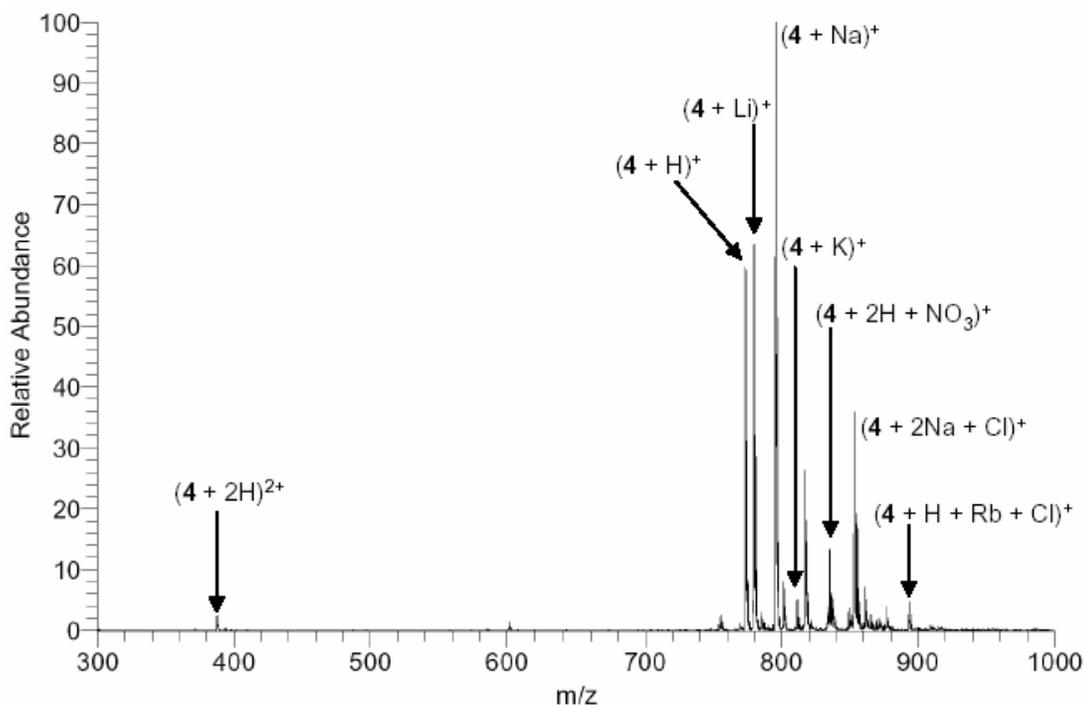


Figure 1. Mass spectrum of **4** with LiCl, NaCl, KCl, RbCl, and CsCl (all 2×10^{-5} M in MeOH) with 1 mM piperidine to raise the pH.

A similar result (i. e. preference for Li^+ and Na^+) is obtained upon ESI-MS analysis of a solution containing **2** with the alkali metals. Interestingly, complexes that contain **2** and two metal ions are not observed despite the greater conformational flexibility of **2**, which potentially could allow one metal ion to be solvated by each of the diazacrown ethers. The lack of complexes containing two metals suggests that the relatively small cavity size of the diazacrown ether may not allow complete encapsulation of a metal ion, along with sufficient interaction between the two diaza crown ethers that results in some cooperative metal coordination, thus restricting **2** to complexation of a single metal ion.

Addition of silver to the solution containing **4** and the alkali metals does not result in substantial silver complexation (Figure 2).

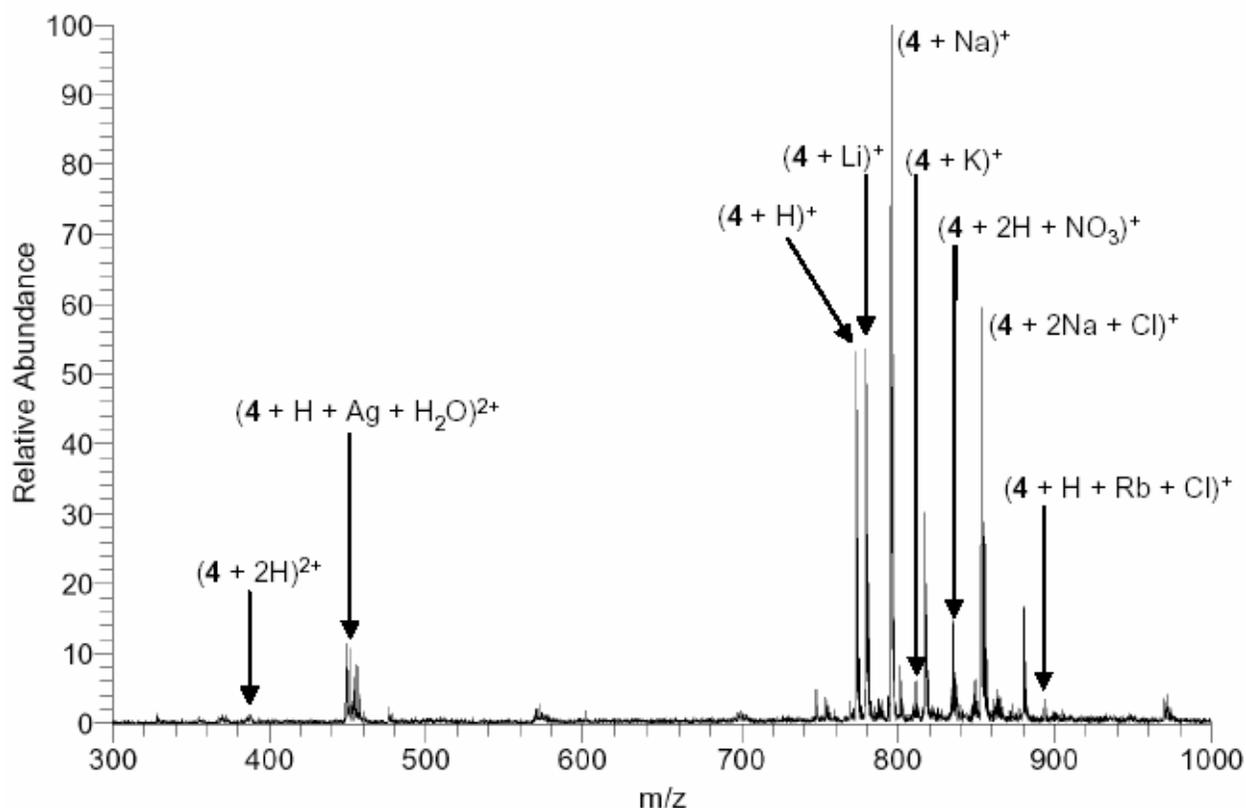


Figure 2. Mass spectrum of **4** with LiCl , NaCl , KCl , RbCl , CsCl , and AgNO_3 (all 2×10^{-5} M in MeOH) with 1 mM piperidine to raise the pH.

Analysis of solutions that contain only transition metals (Figure 3), not alkali metals, indicates that **4** forms complexes with zinc and silver, along with substantial complexation of Na^+ from residual sodium in the solvent. By way of contrast, host **2** is very non-selective and forms complexes with all the metal ions: cadmium, silver, sodium, zinc, lead and manganese. These preliminary results involving the transition metals suggest that **4** may be somewhat more selective than **2**, but neither shows great avidities toward the transition metal ions, as both

protonation and alkali metal complexation are favored over coordination with the transition metals.

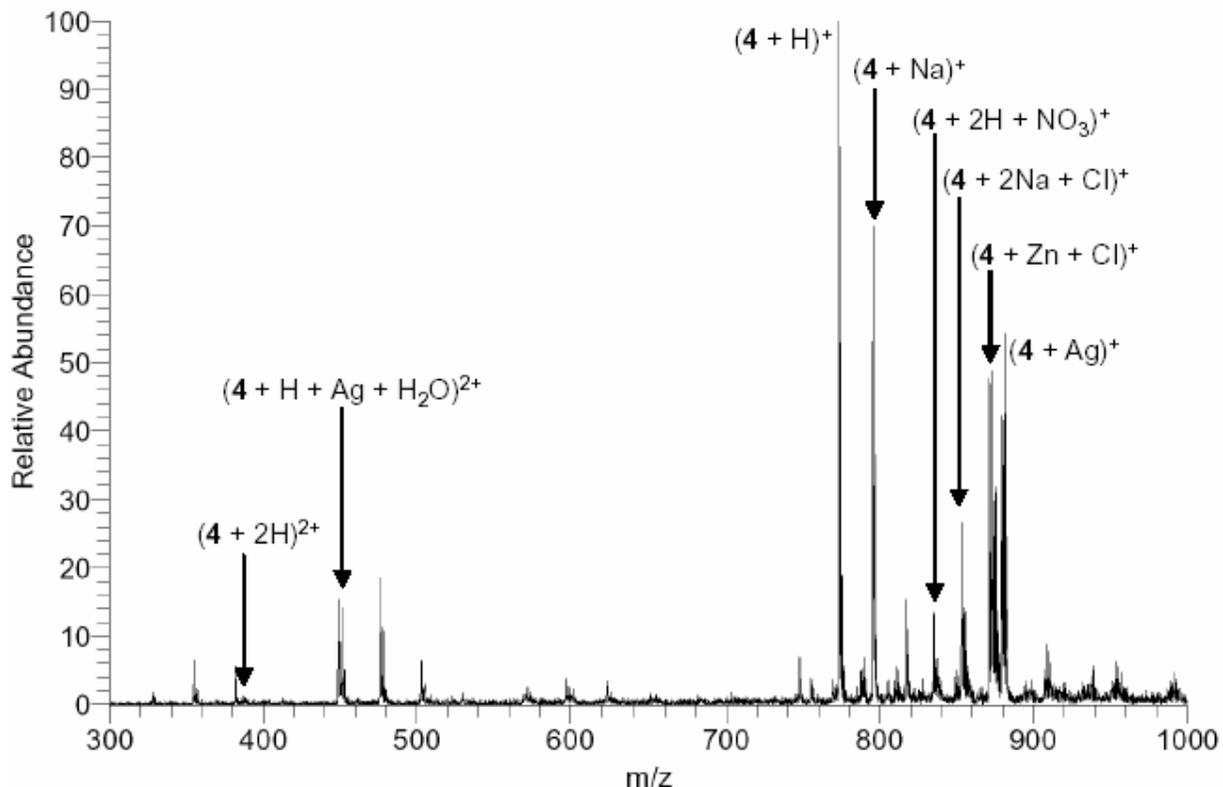


Figure 3. Mass spectrum of **4** with AgNO_3 , MnCl_2 , ZnCl_2 , CdCl_2 , and $\text{Pb}(\text{NO}_3)_2$ (all 2×10^{-5} M in MeOH) with 1 mM piperidine to raise the pH.

Conclusions

The results of an ESI-MS study of the metal cation complexation properties of an unusual molecular box, **4**, are reported along with the corresponding results obtained for another bis(diazacrown) host, **2**, that serves as a model compound for comparison. Both host systems bind selectively to Li^+ and Na^+ . Addition of Ag^+ to the solutions containing alkali metals does not result in substantial Ag^+ complexation. Analysis of a solution containing only transition metal cations indicates that **4** forms complexes with Zn^+ and Ag^+ along with substantial complexation of Na^+ from residual sodium present in the solvents. Although the preliminary ESI-MS results involving the transition metals suggest that **4** may be somewhat more selective than **2**, neither of these host systems displays marked avidities toward complexation with the transition metal ions. Instead, both protonation and alkali metal complexation are favored in each case *vis-à-vis* coordination with the transition metals.

Experimental Section

Synthesis of 4a and 4b. To a mixture of **2**² (560 mg, 1.00 mmol) and **3**⁸ (557 mg, 2.00 mmol) in CH₃CN (150 mL) was added Na₂CO₃ (1.50 g, 15.0 mmol), and the resulting mixture was refluxed with stirring during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The precipitate was washed with CH₂Cl₂ (2 × 30 mL), and the combined filtrates were concentrated *in vacuo*. The residue was purified via column chromatography on basic alumina by using a 7-10% MeOH-EtOAc gradient elution scheme. A mixture of **4a** and **4b** (650 mg, 80%) was thereby obtained as a viscous brown oil; IR (KBr) 2951 (s), 2860 (s), 1737 (m), 1671 (m), 1451.(s), 1358 (s), 1295 (s), 1126 (s), 916 (m), 735 cm⁻¹ (s); ¹H NMR (CDCl₃) δ 1.43 (AB, *J*_{AB} = 10.0 Hz, 2 H), 1.75-1.97 (m, 6 H), 2.25-2.84 (m, 44 H), 3.48-3.67 (m, 16 H); ¹³C NMR (CDCl₃) δ 29.4 (t), 41.5 (d), 43.18 (t), 43.3 (t), 44.1 (d), 47.8 (d), 51.5 (t), 54.2 (t), 58.7 (d), 94.5 (s), 95.8 (s). Exact MS: [*M*_r + 1]⁺ calc'd for C₄₆H₆₈N₄O₆, *m/z* 773.5217. Found (high-resolution chemical ionization mass spectrometry): *m/z* 773.5225.

ESI-MS Studies. Mass spectrometric analyses of **2** and **4** were performed on an LCQ Duo quadrupole ion trap mass spectrometer equipped with an electrospray ionization (ESI) source (ThermoFinnigan, San Jose, CA). The ESI needle voltage was 4.5 kV, and the heated capillary was held at 200°C. Source conditions were optimized for the detection of host-metal complexes in the positive mode. Presented spectra are averages of one hundred scans. Solutions analyzed contained **2** or **4** along with indicated mixtures of the following metal salts: LiCl (Aldrich Chemical Co., Milwaukee, WI), NaCl (EM Science, Gibbstown, NJ), KCl (EM Science), RbCl (Aldrich), CsCl (Aldrich), MnCl₂ (Aldrich), ZnCl₂ (Sigma Chemical Co., St. Louis, MO), AgNO₃ (Alfa Aesar, Ward Hill, MA), CdCl₂ (Aldrich), and PbNO₃ (EM Science). Purities of purchased reagents were at least 98%. All reagents had concentrations of 20 μM, and solutions were prepared in methanol (Spectranalyzed[®], Fisher Scientific, Fair Lawn, NJ). All solutions also contained piperidine (Sigma) at concentrations of 1 mM to suppress protonation of **4**.

Acknowledgments

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