

# Evaluation of Metal Cation Complexation Properties of Cage-annulated Macrocyclic Hosts via Electrospray Ionization Mass Spectrometry (ESI-MS)

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Electrospray ionization-mass spectrometric (ESI-MS) methods have been used to study metal cation complexation properties of a variety of oxygen-, nitrogen- and/or sulfur-containing cage-annulated macrocyclic host ligands, many of which have potentially important analytical, bio-medical and/or environmental applications.

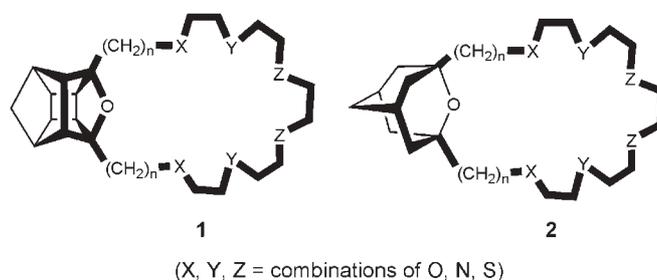
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## Introduction

Macrocyclic polyethers (“crown ethers”), first prepared in the 1960s,<sup>1</sup> constitute an important class of “host” molecules that have found broad application to studies of molecular recognition and inclusion phenomena.<sup>2–7</sup> Thus, compounds of this type have been used extensively for selective complexation and transport of cations, anions and neutral molecules.<sup>2–7</sup> In particular, their unique ability to promote selective complexation and transport of metal cations from aqueous systems into organic media has led to important environmental applications.<sup>8</sup> In addition, synthetic hosts of this type serve as models for biological receptors,<sup>9</sup> and they also have been employed to develop such analytical tools as ion sensors,<sup>10</sup> and chromatographic agents.<sup>11,12</sup>

Our respective research groups at the University of North Texas (UNT) and at the Rudjer Bošković Institute (IRB) have had a long-standing interest in the synthesis and chemistry of novel polycarbocyclic cage compounds<sup>13–18</sup> and, more recently, in their application to the development of novel, cage-annulated macrocyclic host systems.<sup>19–23</sup> Cage-annulated crown ethers and related compounds prepared by the UNT group generally contain a 3,5-disubstituted-4-oxahexacyclo[5.4.1.0<sup>2,6</sup>.0<sup>3,10</sup>.0<sup>5,9</sup>.0<sup>8,11</sup>]dodecane (“oxahexacyclic”) moiety **1** (Scheme 1), while those prepared by the IRB group contain an adamantane or oxaadamantane group **2** (Scheme 1), each of which functions as a “spacer” that serves to rigidify and also to confer a degree of preorganization upon the coronand. Furthermore, the heteroatom that is present in the oxahexacyclic or oxaadamantane cage moiety functions as a donor atom and thereby assists complex formation between the cage-annulated host and a metal cation guest.<sup>20–22</sup> In general, we find that incorporation of a cage moiety affects the shape and size of the cavity in

the resulting crown ether. In addition, the cage moiety increases the lipophilicity of the resulting crown ether relative to noncage-annulated analogs, thereby simplifying recovery of the host from the host-guest complex.



Scheme 1

Initially, we evaluated the metal cation complexation capabilities of our cage-annulated macrocycles by performing a series of alkali metal picrate extraction experiments.<sup>20</sup> Thus, extraction profiles obtained by using freshly prepared alkali metal picrates<sup>24</sup> were generated by using a standard literature procedure.<sup>25,26</sup> In order to gain insight into the effect of cage annulation on the metal cation complexation behavior of crown ethers, the avidity and selectivity of cage-annulated crown ethers were compared directly with the corresponding properties of noncage-annulated model host systems.<sup>20</sup>

Although the picrate extraction technique is useful for assessing both, avidity and selectivity of a specific host molecule toward complex formation with a metal cation guest, extraction methods of this type generally suffer from several drawbacks. In order to minimize systematic errors, it is ne-

cessary to perform several extraction experiments with a given host-guest system and to average the results. Consequently, relatively large amounts of the host, usually ca. 100–300 mg, are required for hosts with molecular mass ca. 500–1000 amu.

The procedure requires extraction of the guest cation from aqueous media into an immiscible organic phase (an equilibrium process). Hence, interpretation of the results of extraction experiments may require explicit consideration of mixing and extraction efficiencies. Finally, at the conclusion of the extraction procedure, the host is recovered and the guest metal cation is isolated from the organic solvent, with consequent production of organic wastes.

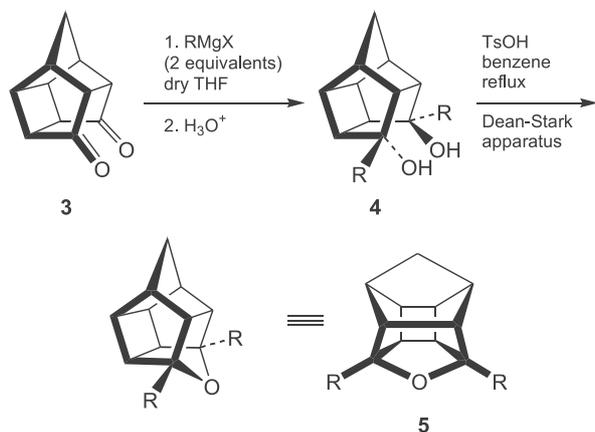
Recently, electrospray ionization mass spectrometry (ESI-MS) has been employed widely to evaluate binding selectivities in host-guest complexes and in related systems that involve noncovalent interactions.<sup>27–41</sup> This highly versatile mass spectrometric technique requires only very small sample quantities, often less than 1 mg, and can be used in conjunction with a wide variety of solvent systems to analyze micromolar quantities of macrocycle-metal cations.

It has been shown, that the relative ESI-MS signal intensities of host-guest complexes of simple crown ethers with different alkali metal cations have been shown to provide an accurate measure of the equilibrium distribution of complexes in solution.<sup>30,32,33</sup> Accordingly, the ESI-MS technique can be used to analyze several complexes simultaneously, thereby permitting competitive complexation experiments to be performed on solutions that contain a single host molecule in the presence of several metal cations.

Herein, we present a brief account of the results of ESI-MS investigations of host-guest complexes of cage-annulated macrocyclic hosts with a variety of metal cations.

## Syntheses of cage-annulated macrocyclic hosts

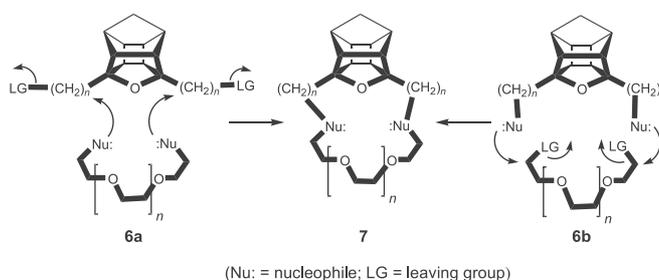
Suitably functionalized podands that possess the general structure **5** (Scheme 2)<sup>42</sup> have been used to prepare oxahexacyclic cage-annulated coronands of the type **1** (Scheme 1). A readily available cage diketone **3**, i. e., pentacyclo[5.4.0.0.2<sup>6</sup>.0.3<sup>10</sup>.0.5<sup>9</sup>]undecan-8,11-dione<sup>43–45</sup> (“PCU-8,11-dione”, Scheme 2) generally is employed as the starting material for this purpose.



Scheme 2

The target, oxahexacyclic cage-annulated host molecules, then can be prepared by using one of the two convergent synthetic approaches shown in Scheme 3. These procedures involve nucleophilic ( $S_N2$ ) displacement of leaving groups situated in one podand by nucleophiles situated in a second podand. When the nucleophile (Nu:) in **6a** or **6b** is  $O^-$  and the leaving group (LG) is OTs, the resulting coronand, **7** (Scheme 3) will possess Nu: = O.<sup>39,42</sup> If a nitrogen-containing nucleophile, e. g., Nu: = Ts-N<sup>-</sup> or PhCH<sub>2</sub>N<sup>-</sup>, is employed in **6a** or **6b**, then the resulting azacoronand, **7**, will contain Nu: = RN: linkages.<sup>21</sup> Thiacoronands of the type **7** are produced when Nu: = S<sup>-</sup> and LG = OTs are employed in podands **6a** or **6b**.

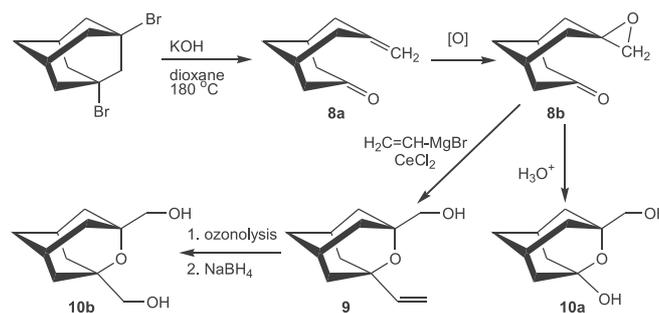
To ensure that cyclization of the two podands occurs (rather than linear polymerization), the displacement reactions are mediated by a metal cation that serves as a “template” for cyclization. This process is aided by the centrally located oxygen atom in the structurally rigid cage moiety, which serves as an anchor-point for coordination to the templating metal cation species.<sup>41</sup>



(Nu: = nucleophile; LG = leaving group)

Scheme 3

Similarly, suitably functionalized podands that possess the general structures **10a** and **10b** (Scheme 4)<sup>23</sup> have been used to prepare oxahexacyclic cage-annulated coronands.



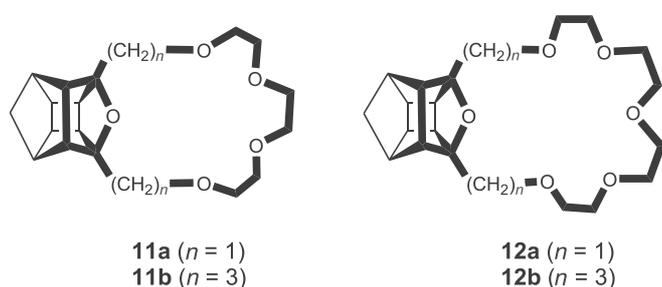
Scheme 4

Thus, the oxadamantane building block was prepared by using the approach shown in Scheme 4. Initially, 1,3-dibromoadamantane was reacted with KOH at high temperature to afford the corresponding ring-opened enone, **8a**. Subsequently, **8a** was converted to the corresponding oxirane, **8b**, which was then subjected to acid catalyzed cyclization to afford **10a**.<sup>42</sup> Alternatively, reaction of **8b** with vinylmagnesium bromide afforded **9**; subsequent ozonolysis of **9** followed by reductive workup ( $NaBH_4$ ) produced **10b**.<sup>23</sup>

## ESI-MS determination of alkali metal binding selectivities

### Cage-annulated crown ethers

ESI-MS binding selectivities toward alkali metal cations ( $\text{Li}^+$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Rb}^+$ ,  $\text{Cs}^+$ ) have been determined for a series of four cage-annulated crown-5 **11a–b** and crown-6 coronands **12a–b** (Scheme 5).<sup>38</sup> The results thereby obtained are compared with the corresponding binding selectivities of 15-crown-5 and 18-crown-6 (model compounds) in Table 1. In each case, the experimental values are expressed as the ratio of  $[\text{M} + \text{alkali metal}^+]$  present in a 1 : 1 : 1 : 1 : 1 : 1 solution, calculated as the peak intensity of  $[\text{M} + \text{alkali metal}^+]$  divided by the sum of the peak intensities of each host-alkali metal cation complex present.<sup>38</sup>



Scheme 5

Inspection of the ESI-MS data in Table 1 reveals that the selectivities of the cage-annulated crown ethers closely parallels the corresponding selectivities displayed by their respective reference compounds (15-crown-5 and 18-crown-6). The experimental selectivities are generally in accord with expectations based upon consideration of the familiar size-fit principle.<sup>46,47</sup> However, incorporation of the cage moiety into crown-5 and crown-6 macrocycles decreases the conformational mobility of the resulting host molecule and also somewhat enlarges the host cavity, thereby resulting in a slight shift in preference toward complexation with larger alkali metal cations by the cage-annulated systems *vis-à-vis* that of the reference host systems.

The results of alkali metal picrate extraction experiments performed by using **11a–b**, **12a–b**, 15-crown-5, and 18-crown-6 also are presented parenthetically in Table 1.<sup>39</sup>

It is instructive to compare the results obtained via ESI-MS methods with the corresponding extraction data obtained by using the conventional alkali metal picrate extraction technique. Such a comparison reveals that both sets of data obtained by using **12a**, 18-crown-6, and, to a lesser extent, **11b**, show a similar selectivity trend, i. e.,  $\text{K}^+ > \text{Rb}^+ > \text{Na}^+ > \text{Cs}^+ > \text{Li}^+$ . This result suggests that the size of the host cavity plays a dominant role in determining the alkali metal cation binding characteristics of these three host systems.<sup>39</sup>

Interestingly, we note an enhanced preference for binding of **12a** and of 18-crown-6 with  $\text{K}^+$  *vis-à-vis*  $\text{Rb}^+$ ,  $\text{Cs}^+$  and  $\text{Na}^+$ , when measured by using ESI-MS methods relative to that observed when the alkali metal picrate extraction method was employed. The selectivity enhancement observed under ESI-MS conditions may be due to the substantial differences in solvation energies of alkali metal cations in met-

Table 1 – ESI-MS Experimental binding selectivities of **11a–b**, **12a–b** compared with binding selectivities of 15-crown-5 and 18-crown-6, respectively (model compounds).<sup>a</sup>

	15-crown-5	11a	12a	18-crown-6	11b	12b
$[\text{M} + \text{Li}^+]$	6% (1%)	3% (BLD) <sup>b</sup>	2% (BLD) <sup>b</sup>	1% (0.3%)	0% (BLD) <sup>b</sup>	4% (BLD) <sup>b</sup>
$[\text{M} + \text{Na}^+]$	36% (15%)	28% (2%)	11% (BLD) <sup>b</sup>	6% (5%)	6% (11%)	11% (BLD) <sup>b</sup>
$[\text{M} + \text{K}^+]$	34% (7%)	26% (2%)	52% (5%)	60% (64%)	68% (68%)	24% (0.6%)
$[\text{M} + \text{Rb}^+]$	16% (4%)	29% (1%)	28% (1%)	24% (58%)	22% (60%)	30% (0.2%)
$[\text{M} + \text{Cs}^+]$	8% (1%)	13% (0.4%)	6% (BLD) <sup>b</sup>	8% (31%)	3% (40%)	31% (2%)

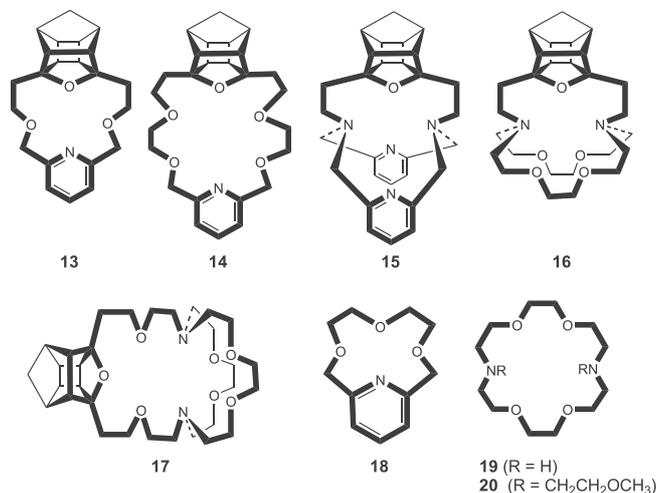
<sup>a</sup> Values in parentheses were obtained via alkali metal picrate extraction experiments

<sup>b</sup> BLD = below limit of detection.

hanol vs. water. Thus, desolvation-complexation of alkali metal cations is expected to be more energetically demanding in aqueous media, thereby tempering differences among alkali metal cations and reducing binding selectivities as measured by alkali metal picrate extraction methods. Since ESI-MS measurements were performed in a less polar medium (methanol), desolvation-complexation energetics are minimized, thereby allowing selectivity to be determined primarily by host-guest size-fit considerations.<sup>39</sup>

### Cage-annulated azacrown ethers

ESI-MS techniques have been used to evaluate the alkali metal binding selectivities of five cage-annulated azacrown ethers **13–17** and three noncage-annulated analogs **18–20** (Scheme 6).<sup>37</sup> An extension of the conventional ESI-MS method, i. e., microelectrospray ionization mass spectrometry (MESI-MS),<sup>48–51</sup> was used for this purpose primarily to permit smaller quantities of materials to be employed and to facilitate handling and analysis of aqueous solutions for the intended host-guest studies.



Scheme 6

Table 2 – Alkali metal cation binding selectivity trends

Compound	Alkali metal picrate extraction trends (extraction percentages) <sup>a</sup>	MESI-MS trends (peak intensities, as % of total complexes formed) <sup>37</sup>
<b>13</b>	Li <sup>+</sup> > Na <sup>+</sup> > K <sup>+</sup> (19.5) (6.3) (5.1) <sup>52</sup>	Li <sup>+</sup> > Na <sup>+</sup> > K <sup>+</sup> (74) (20) (6)
<b>14</b>	Cs <sup>+</sup> > K <sup>+</sup> > Na <sup>+</sup> > Rb <sup>+</sup> > Li <sup>+</sup> (5.2) (3.4) (1.9) (1.8) (1.7) <sup>52</sup>	K <sup>+</sup> > Na <sup>+</sup> > Rb <sup>+</sup> > Cs <sup>+</sup> >>> Li <sup>+</sup> (53) (25) (17) (5) (0)
<b>15</b>	Li <sup>+</sup> > Na <sup>+</sup> > Rb <sup>+</sup> > Cs <sup>+</sup> > K <sup>+</sup> (81.9) (70.7) (46.0) (40.9) (40.3) <sup>52</sup>	Li <sup>+</sup> > H <sup>+</sup> >>> Na <sup>+</sup> , K <sup>+</sup> (79) (21) (0) (0)
<b>16</b>	Na <sup>+</sup> > K <sup>+</sup> > Rb <sup>+</sup> > Li <sup>+</sup> > Cs <sup>+</sup> (95.1) (89.7) (56.1) (39.8) (33.7) <sup>53</sup>	Na <sup>+</sup> > K <sup>+</sup> >>> Rb <sup>+</sup> , Li <sup>+</sup> , Cs <sup>+</sup> (69) (31) (1) (0) (0)
<b>17</b>	K <sup>+</sup> > Rb <sup>+</sup> > Cs <sup>+</sup> > Na <sup>+</sup> > Li <sup>+</sup> (74.4) (68.4) (60.9) (50.0) (36.3) <sup>54</sup>	K <sup>+</sup> > Rb <sup>+</sup> > Cs <sup>+</sup> > Na <sup>+</sup> >>> Li <sup>+</sup> (53) (22) (16) (9) (0)
<b>18</b>	Li <sup>+</sup> > Na <sup>+</sup> > K <sup>+</sup> (3.3) (3.0) (1.3) <sup>52</sup>	Li <sup>+</sup> > Na <sup>+</sup> > K <sup>+</sup> (all 2:1 complexes) <sup>b</sup> (63) (19) (18)
<b>19</b>	Na <sup>+</sup> > K <sup>+</sup> Log K: (1.8) (1.5) <sup>55</sup>	K <sup>+</sup> > Na <sup>+</sup> > Rb <sup>+</sup> ≤ Cs <sup>+</sup> > Li <sup>+</sup> (57) (14) (13) (10) (0)
<b>20</b>	K <sup>+</sup> > Na <sup>+</sup> > Rb <sup>+</sup> > Cs <sup>+</sup> > Li <sup>+</sup> (46.3) (36.0) (34.6) (21.3) (17.5) <sup>55</sup>	K <sup>+</sup> > Na <sup>+</sup> > Rb <sup>+</sup> (72) (16) (12)

<sup>a</sup> Values are for extraction of each alkali metal cation from water into CHCl<sub>3</sub>. Each alkali metal cation was extracted individually.

<sup>b</sup> See text

Initially, MESI-MS evaluation of binding selectivities was performed for the four pyridine-containing host systems, i. e., cage-annulated hosts **13–15** and noncage-annulated analog **18**. The results thereby obtained are compared in Table 2 with previously published results<sup>52–55</sup> that had been garnered by using alkali metal picrate extraction techniques. As might be expected, the smallest cage-annulated coronand **13**, binds selectively to the smallest alkali metal cations in reverse order of their size: Li<sup>+</sup> > Na<sup>+</sup> > K<sup>+</sup>. This same trend was observed to emerge from the results of alkali metal picrate extraction experiments.

Interestingly, only 2 : 1 ligand-M<sup>+</sup> complexes are observed in the MESI mass spectrum of **18**, the noncage-annulated analog of **13**. This result that suggests that the cavity in **18** is too small to provide adequate stabilization of the guest metal cation via encapsulation and/or solvation; hence, the need for the formation of a “sandwich” complex of the type (host)-(M<sup>+</sup>)-(host), wherein the guest metal cation is stabilized via noncovalent association with two host ligands.<sup>37</sup>

Pyridine-containing ligand **14** possesses a considerably larger cavity than either **13** or **18**. The increased cavity size and conformational flexibility associated with **14** vis-à-vis **13** and **18** permits the former host to bind selectively to somewhat larger alkali metal cations, e.g., Na<sup>+</sup> and K<sup>+</sup>. Interestingly, the results of alkali metal picrate extraction studies indicate preferential binding of **14** to Cs<sup>+</sup>. Rather than indicating dimension-fit complementarity between **14** and the largest alkali metal cation, it seems likely that this result may reflect the low solvation energetic requirements of Cs<sup>+</sup> relative to that of the other alkali metal cations. This conceiva-

bly could confer an energetic advantage for extraction of Cs<sup>+</sup> vs. the other, smaller alkali metal cations from aqueous media.<sup>37</sup>

One pyridine-containing, cage-annulated cryptand **15** and two nonpyridine-containing, cage-annulated cryptands **16** and **17**, were also studied. The results obtained via MESI-MS experiments suggest that **15** is strongly basic, preferring to protonate rather than to form complexes with either Na<sup>+</sup> or K<sup>+</sup>. This result is even more remarkable when it is noted that alkali metal hydroxides were employed in the competitive MESI-MS **15**-M<sup>+</sup> complexation experiments. It appears that **15** is sufficiently basic to extract protons from solutions of M<sup>+</sup>OH<sup>-</sup> in methanol!

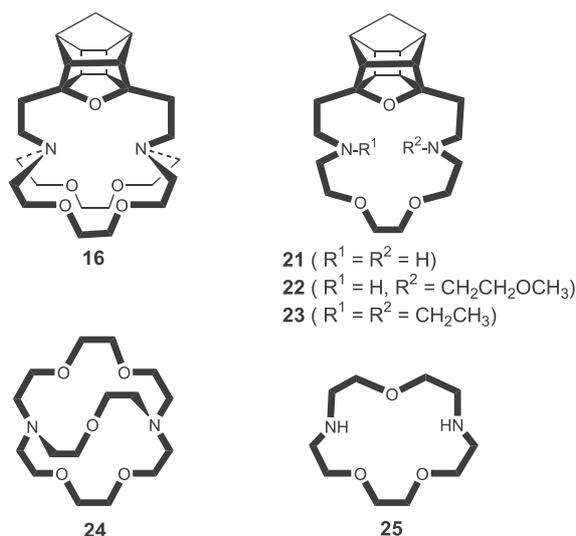
This observation may help us to understand the apparent disparity between the results of alkali metal picrate extraction experiments and MESI-MS experiments that involve **15** as a host. No special precautions were taken to adjust the pH of aqueous solutions (i. e., to render these solutions very strongly basic) when the alkali metal picrate extraction experiments were performed.<sup>52</sup> Thus, it is conceivable that the species being extracted from water into CHCl<sub>3</sub> was, in fact, simply the protonated ligand **15**-H<sup>+</sup>. Here, it should be noted that the counter-ion carried along with **15**-H<sup>+</sup> during the extraction procedure is picrate. Since the extraction profile is determined by measuring picrate anion concentration spectrophotometrically, it follows that the picrate extraction experiments may produce overly optimistic results that do not accurately reflect the true avidity and selectivity of the host ligand toward alkali metal picrate extraction.<sup>56</sup>

## ESI-MS determination of heavy metal binding selectivities

### Cage-annulated azacrown ethers

Binding selectivities of one cage-annulated cryptand **16** and three cage-annulated azacrown ethers **21–23** (Scheme 7) toward  $\text{Hg}^{++}$ ,  $\text{Pb}^{++}$ ,  $\text{Cd}^{++}$  and  $\text{Cu}^{++}$ , were analyzed by comparing ESI mass spectral intensities. The results thereby obtained were compared with corresponding binding selectivities determined for two reference host systems [2.2.1]-cryptand **24** and 1,7-diaza-15-crown-5 (**25**) (Scheme 7).<sup>35</sup> In each case, the host was mixed with heavy metal ( $\text{M}^{++}$ ) chlorides or perchlorates in methanol solution. The sums of the ESI-MS intensities of the resulting ligand-metal cation complexes were compared in order to determine relative binding preferences and trends. Complexes between the host and metal salt complexes as well as those that involve only the host and the free metal cation were considered in order to determine binding preferences.<sup>35</sup>

The results obtained via ESI-MS analysis of solutions that contain one host compound mixed with all four  $\text{M}^{++}$  chloride and  $\text{M}^{++}$  perchlorate salts (molar ratio 1 : 1 : 1 : 1) are summarized in Table 3.

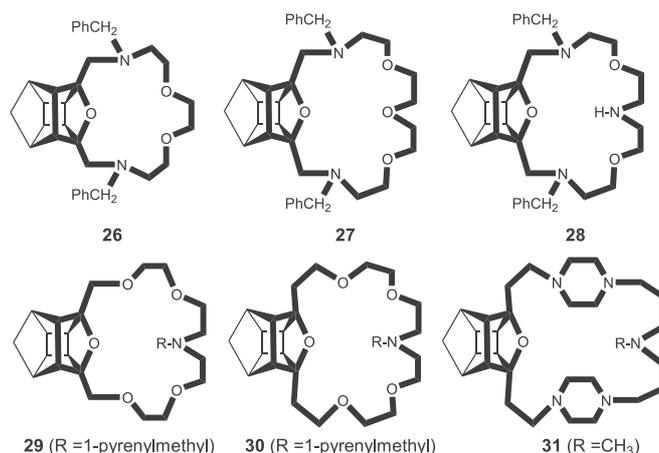


Scheme 7

Interestingly, the results in Table 3 indicate a clear dependence of binding selectivity in the case of cage-annulated azacrown ethers **21** and **22** upon the nature of the counterion (i. e., whether  $\text{Cl}^-$  or  $\text{ClO}_4^-$ ). Other workers have noted that the degree of ion pairing between the counterion and the metal cation in a ligand-metal ion host-guest complex can affect the conformation of the complex.<sup>57,58</sup> Such effects are believed to reflect differences between the strengths of metal-anion bonds, which in turn may affect the ability of the host ligand to compete effectively with the counterion for complexation with the metal cation.<sup>59</sup> A similar dependence of binding selectivity upon the nature of the counterion was also observed for the two reference hosts **24** and **25**.<sup>35</sup>

Six cage-annulated azacrown ethers **26–31** (Scheme 8) have been synthesized, and their  $\text{Ag}^+$  binding selectivities have been evaluated in methanol solution via application of ESI-MS methods.<sup>60–62</sup> During the course of this study, it was noted that all six azacrown ethers bind strongly to  $\text{H}^+$ , which most likely is a reflection of their relatively high basicity.

Methanol solutions that contained a single host ( $2.5 \times 10^{-5}$  mol  $\text{dm}^{-3}$ ) with multiple heavy metal cations, introduced as 1 : 2 : 2 : 2 : 2 : 2 mixtures of host :  $\text{AgNO}_3$  :  $\text{Cd}(\text{NO}_3)_2$  :  $\text{Ni}(\text{NO}_3)_2$  :  $\text{Pb}(\text{NO}_3)_2$  :  $\text{Zn}(\text{NO}_3)_2$ , were subjected to ESI-MS



Scheme 8

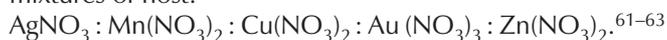
Table 3 – Heavy metal cation binding selectivity trends for **16**, **21**, **22** and **23**<sup>35</sup>

Compound	Heavy metal chloride binding selectivity trends <sup>a</sup> (percentages) <sup>b</sup>	Heavy metal perchlorate binding selectivity trends <sup>a</sup> (percentages) <sup>b</sup>
<b>16</b>	$\text{Pb}^{++} \gg \text{Cd}^{++}, \text{Hg}^{++}, \text{Cu}^{++}$ (100) (*) (*) (*)	$\text{Pb}^{++} \gg \text{Cd}^{++}, \text{Hg}^{++}, \text{Cu}^{++}$ (100) (*) (*) (*)
<b>21</b>	$\text{Cu}^{++} > \text{Cd}^{++} \gg \text{Hg}^{++}, \text{Pb}^{++}$ (100) (77) (*) (*)	$\text{Hg}^{++} \gg \text{Cd}^{++}, \text{Pb}^{++}, \text{Cu}^{++}$ (100) (*) (*) (*)
<b>22</b>	$\text{Cu}^{++} \geq \text{Cd}^{++} \gg \text{Hg}^{++}, \text{Pb}^{++}$ (100) (83) (*) (*)	$\text{Hg}^{++} \gg \text{Cd}^{++}, \text{Pb}^{++}, \text{Cu}^{++}$ (100) (*) (*) (*)
<b>23</b>	(no complexes observed)	(no complexes observed)

<sup>a</sup> Trends shown were obtained by summing the intensities of all metal cation-containing complexes observed in the ESI mass spectra

<sup>b</sup> Percentages listed below trends are scaled relative to the most abundant metal ion-containing complexes within each set. An asterisk indicates that no significant amount of complex formation could be detected.

analysis. Interestingly, when  $\text{Ag}^+$  was present, hosts **27** and **28** were observed to bind virtually exclusively to  $\text{Ag}^+$ , thereby excluding the other heavy metal cations present in solution.<sup>61</sup> Similar results were obtained via ESI-MS analysis of methanol solutions that contained host systems **27** and **29** ( $2.5 \times 10^{-5}$  mol dm<sup>-3</sup> in each case) with another mixture of multiple heavy metal cations, introduced as 1 : 2 : 2 : 2 : 2 mixtures of host:



In addition, binding selectivities of azamacrocycles **26–31** toward complexation of alkali metal cations *vis-à-vis*  $\text{Ag}^+$  have been studied.<sup>62</sup> Thus, methanol solutions of a single host macrocycle with equimolar  $\text{AgNO}_3$ ,  $\text{LiClO}_4$ ,  $\text{NaClO}_4$ ,  $\text{KClO}_4$  and  $\text{RbClO}_4$  (macrocycle : metal cation molar ratio = 1 : 3 : 3 : 3 : 3) were analyzed by using ESI-MS methods. Under these conditions, azamacrocycles **26–31** displayed nearly exclusive  $\text{Ag}^+$  selectivity. Indeed, no signals that correspond to host-alkali metal cation complexes were observed in these experiments for macrocycles **26–29**.<sup>62</sup>

Finally, extraction experiments were performed by using azamacrocycle **28** as host. For comparison, 1,10-diaza-18-crown-6 was chosen as a reference macrocycle. Metal cations were extracted by the host azamacrocycle from an aqueous phase into chloroform. The organic layer was then separated and was subjected to ESI-MS analysis. In one such experiment, extractions were performed on an aqueous mixture of  $\text{Ag}^+$ ,  $\text{Cu}^{2+}$ ,  $\text{Zn}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Fe}^{3+}$ ,  $\text{Ni}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Mg}^{2+}$  and  $\text{Ca}^{2+}$  nitrates. The transition metal cations were present in fivefold molar excess, whereas the alkali metal cations were present in 25-fold molar excess *vis-à-vis* **28**; a  $2 \times 10^{-4}$  mol dm<sup>-3</sup> solution of **28** in chloroform was employed in these experiments.<sup>62</sup> Under these conditions, **28** proved to be capable of *nearly exclusive extraction* of  $\text{Ag}^+$  in the presence of several other potentially competing transition metal, alkali metal, and alkaline earth metal cations.<sup>62</sup>

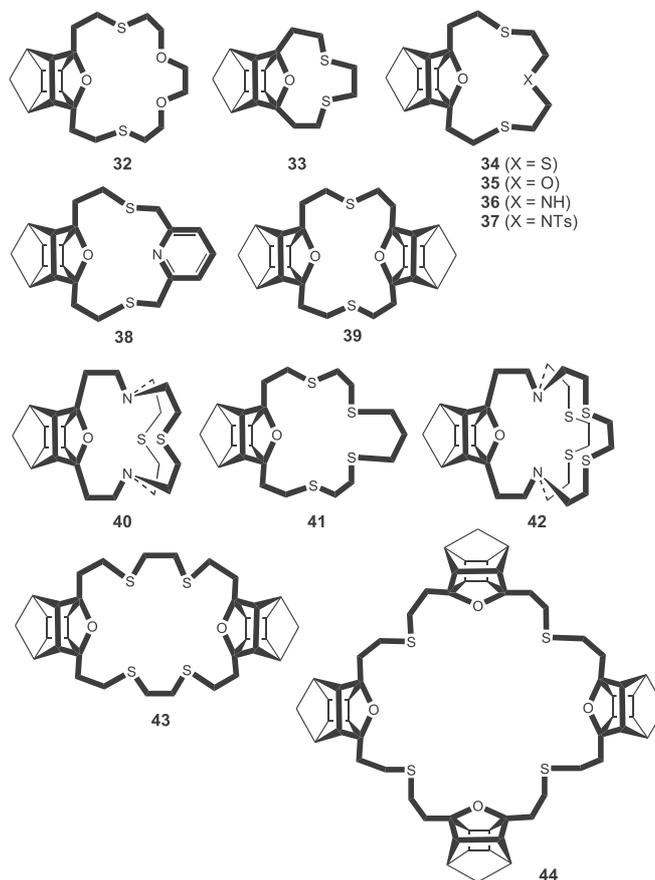
Several important conclusions emerge from this study. First, the comparison of the binding selectivities of azamacrocycles **26–31** vs 18-crown-6 (a non-nitrogen containing model macrocycle) suggest that the presence of nitrogen atoms in the macrocyclic host is essential for selective  $\text{Ag}^+$  binding.<sup>62</sup>

The presence of aromatic rings in the macrocyclic host, as in **26–30** and also in dibenzo-18-crown-6, a model non-nitrogen containing macrocycle, appears to enhance  $\text{Ag}^+$  complexation capability. It seems likely that host-guest cation- $\pi$  interactions may contribute to the enhanced ability of **26–30** and of dibenzo-18-crown-6 to function, as selective  $\text{Ag}^+$  complexants.<sup>64–66</sup>

It was also noted that the pH of the aqueous phase can have a dramatic effect upon the  $\text{Ag}^+$  extraction capabilities of **26–31**. Thus, decreasing the pH of the aqueous medium results in concomitant decrease in the extraction capability of the azamacrocyclic host in the organic (chloroform) layer. This observation reflects the relatively high basicity of azamacrocycles **26–31** and their increasing tendency to suffer competing protonation at lower pH, which compromises their ability to function effectively as  $\text{Ag}^+$  complexants and extractants.<sup>62</sup>

### Cage-annulated thiocrown ethers

Several new cage-annulated, sulfur-containing macrocycles, i. e., **32**<sup>35</sup> and **33–44**<sup>35,41</sup> (Scheme 9), have been prepared,<sup>22,67</sup> and their metal cation complexation properties have been investigated by application of ESI-MS methods. Thus, equimolar mixtures of host **32** with  $\text{Hg}^{2+}$ ,  $\text{Pb}^{2+}$ ,  $\text{Cd}^{2+}$  and  $\text{Cu}^{2+}$  chlorides and perchlorates were subjected to ESI-MS analysis. Host **32**,



Scheme 9

which possesses a small cavity and thus is expected to bind selectively to small transition metal cations, was observed to function as a selective  $\text{Hg}^{2+}$  complexant in these experiments.<sup>35</sup> This host also displayed some ability to bind to  $\text{Cu}^{2+}$ , but **32** showed no tendency to form complexes with  $\text{Cd}^{2+}$  or  $\text{Pb}^{2+}$ .<sup>35</sup>

Divalent mercury forms strong bonds to sulfur and prefers linear  $\text{S}\cdots\text{Hg}^{2+}\cdots\text{S}$  geometry in the resulting complexes.<sup>68</sup> Thus, the observed binding preference that **32** displays toward  $\text{Hg}^{2+}$  complexation most likely results from the favorable positioning of the two sulfur atoms in the macrocycle, which permits linear  $\text{S}\cdots\text{Hg}^{2+}\cdots\text{S}$  association in the resulting complex.

The corresponding metal cation binding efficiencies of hosts **33–44** also have been studied by using ESI-MS techniques.<sup>41</sup> These experiments employed mixtures of a single thiamacrocycle with multiple transition metal cations, i. e.,  $\text{Cd}^{2+}$ ,  $\text{Pb}^{2+}$  and  $\text{Zn}^{2+}$  perchlorates, with and without added  $\text{Hg}^{2+}$  perchlorate, in 1 : 1 methanol-chloroform solution. Identical concentrations ( $2.5 \times 10^{-5}$  mol dm<sup>-3</sup>) of the

macrocyclic host and of each metal perchlorate salt were employed in these experiments.

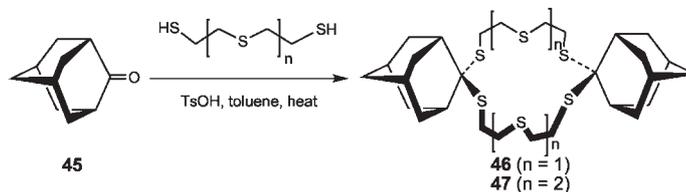
A qualitative summary of the results thereby obtained appears in Table 4. In the absence of added  $\text{Hg}^{++}$ , thiamacrocycles **35**, **37**, **43** and **44**, displayed similar binding capabilities toward  $\text{Cd}^{++}$ ,  $\text{Pb}^{++}$  and  $\text{Zn}^{++}$ , while **34**, **39** and **41** showed small differences among their binding capabilities toward these same three transition metal cations.<sup>41</sup>

When the foregoing experiment was repeated in the presence of added  $\text{Hg}^{++}$  perchlorate, the corresponding host- $\text{Hg}^{++}$  host-guest complexes were dominant. Not surprisingly, thiamacrocycles **36**, **38**, **40** and **42**, all of which contain one or more basic nitrogen atoms, displayed some tendency to bond to a proton in solution. For these four thiamacrocycles, binding to  $\text{Hg}^{++}$  is generally preferred *vis-à-vis* binding to a proton, with the exception of hosts **36** and **40**, each of which bind exclusively to  $\text{H}^+$ .<sup>41</sup>

Finally, extraction experiments were performed by using several thiamacrocycles as hosts in chloroform solution to extract a mixture of  $\text{Cd}^{++}$ ,  $\text{Pb}^{++}$ ,  $\text{Zn}^{++}$  and  $\text{Hg}^{++}$ , chlorides, from aqueous solution into chloroform. The molar ratio of macrocycle to metal chlorides employed in these experiments was 1 : 125 : 125 : 125 : 125.<sup>41</sup>

In all cases studied, the species that was detected via ESI-MS methods proved to be the corresponding [macrocycle +  $\text{Hg} + \text{Cl}$ ]<sup>+</sup> complex. Thiamacrocycle **43** proved to be the most efficient  $\text{Hg}^{++}$  extractant among the host systems employed in this study. The superior performance of **43** appears to be due to a combination of factors, including, e. g., (i) stabilizing interactions between  $\text{Hg}^{++}$  and the four S atoms, two O atoms, and one Cl atom in the host-guest complex and (ii) the favorable nature of size-fit complementarity between host **43** and the  $\text{HgCl}^+$  guest cation in the resulting complex.<sup>41</sup>

Two unusual bis-spiroadamantyl-annulated thiacycrown ethers, **46** and **47** (Scheme 10) have been prepared via acid catalyzed condensation of adamantan-2-one (**45**) with 2,2'-thiadiethanethiol and 3,6-dithiaoctane-1,8-dithiol, respectively.<sup>69,70</sup> Subsequently, ESI-MS techniques were used to evaluate the metal cation binding abilities of **46** and **47** toward  $\text{Hg}^{++}$ ,  $\text{Pb}^{++}$ ,  $\text{Cd}^{++}$  and  $\text{Zn}^{++}$  ions.



Scheme 10

Thus, homogeneous  $2.5 \times 10^{-5}$  mol  $\text{dm}^{-3}$  solutions of **46** and of **47** with each of the various metal perchlorate salts in 50 % MeOH- $\text{CHCl}_3$ , were prepared. Each of the metal perchlorates was mixed individually with the host in the molar ratio 1 : 1, 1 : 2 and 2 : 1. Selectivity studies were performed by mixing the host and all four metal salts in a molar ratio 1 : 1 : 1 : 1 : 1, 1 : 2 : 2 : 2 : 2 and 4 : 1 : 1 : 1 : 1.

Interestingly, ESI-MS analysis of the various mixtures of **46** and of **47** with these mixtures of metal ion perchlorates indicated that both macrocyclic hosts are capable of forming 1 : 1 host-guest complexes with  $\text{Pb}(\text{ClO}_4)^+$ ,  $\text{Cd}(\text{ClO}_4)^+$ , and  $\text{Zn}(\text{ClO}_4)^+$  ions. Host **46** forms complexes selectively with  $\text{Cd}(\text{ClO}_4)^+$  [i.e.,  $\text{Cd}(\text{ClO}_4)^+ > \text{Zn}(\text{ClO}_4)^+ = \text{Pb}(\text{ClO}_4)^+$ ], whereas **47** displays relatively minor differences in its ability to form complexes with each of these cationic species [ $\text{Cd}(\text{ClO}_4)^+ > \text{Pb}(\text{ClO}_4)^+ > \text{Zn}(\text{ClO}_4)^+$ ]. However, neither **46** nor **47** appear to function effectively as  $\text{Hg}^{++}$  complexants.<sup>70</sup> This result stands in striking contrast with the results of competitive complexation experiments performed for other thiacycrown ethers [see Scheme 9 and related dis-

Table 4 – Heavy metal cation binding selectivity trends for **33–44** in 1 : 1 methanol-chloroform<sup>41</sup>

Compound	Complexes observed when $\text{Cd}^{++}$ , $\text{Pb}^{++}$ and $\text{Zn}^{++}$ perchlorates were added to solution of macrocycle. <sup>a</sup>	Complexes observed when $\text{Cd}^{++}$ , $\text{Pb}^{++}$ , $\text{Hg}^{++}$ and $\text{Zn}^{++}$ perchlorates were added to solution of macrocycle. <sup>a</sup>
<b>33</b>	$\text{Na}^+ \gg \text{Cd}^{++}, \text{Pb}^{++}, \text{Zn}^{++}, \text{Cu}^{++} \gg \text{H}^+ (*)$	$\text{Hg}^{++} \gg \text{Cd}^{++}, \text{Zn}^{++}, \text{Cu}^{++} \gg \text{Na}^+ (*), \text{H}^+ (*)$
<b>34</b>	$\text{Zn}^{++} > \text{Cd}^{++} > \text{Pb}^{++} > \text{Cu}^{++} > \text{H}^+ \gg \text{Na}^+ (*)$	$\text{Hg}^{++} > \text{Cd}^{++}, \text{Zn}^{++} > \text{Cu}^{++} > \text{H}^+ \gg \text{Na}^+ (*)$
<b>35</b>	$\text{Cd}^{++}, \text{Pb}^{++}, \text{Zn}^{++} \gg \text{Na}^+ > \text{Cu}^{++}, \text{H}^+$	$\text{Hg}^{++} \gg \text{all others} (*)$
<b>36</b>	$\text{H}^+ \gg \text{all others}$	$\text{H}^+ > \text{Hg}^{++} \gg \text{Cd}^{++} (*), \text{Zn}^{++} (*), \text{Cu}^{++} (*), \text{Na}^+ (*)$
<b>37</b>	$\text{Cd}^{++}, \text{Pb}^{++}, \text{Zn}^{++} \gg \text{Na}^+, \text{H}^+ > \text{Cu}^{++}$	$\text{Hg}^{++} > \text{Cd}^{++}, \text{Zn}^{++} > \text{Cu}^{++}, \text{H}^+ \gg \text{Na}^+ (*)$
<b>38</b>	$\text{H}^+ > \text{Cd}^{++}, \text{Pb}^{++}, \text{Cu}^{++} \gg \text{Zn}^{++} (*), \text{Na}^+ (*)$	$\text{Hg}^{++} \gg \text{Cd}^{++} (*), \text{Zn}^{++} (*), \text{Cu}^{++} (*), \text{Na}^+ (*), \text{H}^+ (*)$
<b>39</b>	$\text{Cd}^{++}, \text{Zn}^{++} > \text{Pb}^{++}, \text{H}^+ > \text{Cu}^{++}, \text{Na}^+$	$\text{Hg}^{++} \gg \text{Cd}^{++}, \text{Zn}^{++}, \text{H}^+ \gg \text{Cu}^{++} (*), \text{Na}^+ (*)$
<b>40</b>	$\text{H}^+ \gg \text{all others} (*)$	$\text{H}^+ \gg \text{all others} (*)$
<b>41</b>	$\text{Pb}^{++} > \text{Cd}^{++} > \text{Zn}^{++} > \text{Cu}^{++}, \text{H}^+ \gg \text{Na}^+ (*)$	$\text{Hg}^{++} > \text{Cd}^{++}, \text{Cu}^{++} > \text{Zn}^{++} (*), \text{Na}^+ (*), \text{H}^+ (*)$
<b>42</b>	$\text{H}^+ > \text{Cd}^{++} \gg \text{Cu}^{++} > \text{Pb}^{++} \gg \text{Zn}^{++} (*), \text{Na}^+ (*)$	$\text{Hg}^{++} > \text{Cu}^{++} \gg \text{Cd}^{++} (*), \text{Zn}^{++} (*), \text{Na}^+ (*), \text{H}^+ (*)$
<b>43</b>	$\text{Pb}^{++}, \text{Cd}^{++}, \text{Zn}^{++} > \text{Cu}^{++} \gg \text{Na}^+ (*), \text{H}^+ (*)$	$\text{Hg}^{++} \gg \text{Cd}^{++}, \text{Cu}^{++} > \text{Zn}^{++} (*), \text{Na}^+ (*), \text{H}^+ (*)$
<b>44</b>	$\text{Cd}^{++}, \text{Pb}^{++}, \text{Zn}^{++} > \text{H}^+ > \text{Cu}^{++} \gg \text{Na}^+ (*)$	$\text{Hg}^{++} > \text{Zn}^{++} \gg \text{Cd}^{++}, \text{Cu}^{++}, \text{Na}^+ (*), \text{H}^+ (*)$

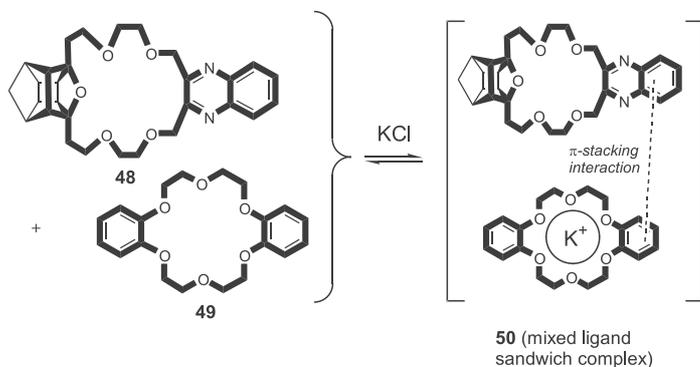
<sup>a</sup> Observation of copper complexes is due to copper sources in the mass spectrometer; copper was not added to the solution. Observation of sodium complexes is due to residual sodium impurities in chemicals, solvents, glassware, instrumentation, etc.; sodium was not added to the solution. An asterisk (\*) indicates that no significant amount of complex formation could be detected.

cussion, wherein it was noted that  $\text{Hg}^{++}$  complexes usually are the dominant species (or, occasionally, the *only* species) observed in the ESI mass spectra obtained from mixtures cage-annulated thiocrown hosts with  $\text{Hg}^{++}$ ,  $\text{Pb}^{++}$ ,  $\text{Cd}^{++}$  and  $\text{Zn}^{++}$  perchlorates].<sup>41</sup>

### ESI-MS detection of self-assembly in a cage-annulated crown ether complex

We conclude our discussion with a brief account of a recent ESI-MS study of the unusual metal cation binding properties observed for a mixture of a cage-annulated, quinoxaline-containing macrocycle **48** (Scheme 11) with dibenzo-18-crown-6 (**49**).<sup>71</sup> Here, evidence was sought that might support (or refute) the concept that the operation of  $\pi$ -stacking interactions, between the relatively electron-poor quinoxaline ring in **48** and the electron-rich aromatic rings in **49**, could lead to the formation of a 1 : 1 : 1 host-guest sandwich complex<sup>72</sup> with a metal cation guest.

Thus, solutions that contained equimolar quantities of **48**, **49**, and a metal cation were examined by using ESI-MS methods. The distribution of (i) 1 : 1 macrocycle-metal cation complexes, (ii) 2 : 1 (homo ligand)-metal cation sandwich complexes, and (iii) 2 : 1 (mixed ligand)-metal cation sandwich complexes was monitored. The results thereby obtained were compared subsequently with the corresponding results obtained when dibenzo-18-crown-6 was replaced by dicyclohexano-18-crown-6 (chosen due to its lack of aromatic substituents and the similar size and shape of its cavity *vis-à-vis* that of 18-crown-6).<sup>71</sup>



In order to analyze the ESI-MS data, a new quantity, “enhancement ratio”, was defined as the ratio of the abundance of the 1 : 1 : 1 (mixed ligand)-metal cation complex to the average of the abundances of the two corresponding 2 : 1 (homo ligand)-metal cation complexes. Subsequently, the enhancement ratio thus defined was used to provide a semi-quantitative measure of the effectiveness of mixed ligand – vs. homo ligand-metal cation sandwich complexes.<sup>71</sup>

ESI-MS analysis of methanol solutions of **48** with various alkali metal cations indicated the formation of 2 : 1 (homo ligand)-metal cation sandwich complexes  $[\mathbf{48}] \cdot \text{M}^+$ , with  $\text{M}^+ = \text{K}^+$ ,  $\text{Rb}^+$  and  $\text{Cs}^+$ , but not with  $\text{Li}^+$  or  $\text{Na}^+$ . Next, solutions of **48** and **49**, that contained various other macrocycles, including **49**, were examined *via* ESI-MS techniques. The results thereby obtained are presented in Table 5.<sup>71</sup>

Table 5 – Enhancement molar ratios for formation of 1 : 1 : 1  $[\mathbf{48}] \cdot \text{K}^+$  (mixed ligand)- $\text{K}^+$  sandwich complexes<sup>71</sup>

Macrocycle	Enhancement ratio <sup>a</sup>
18-crown-6	0.044
aza-18-crown-6	0.032
dicyclohexano-18-crown-6	0.050
benzo-18-crown-6	1.4
dibenzo-18-crown-6	4.4

<sup>a</sup> See text. Enhancement ratio values greater than 1.0 signify enhancement of formation of 1 : 1 : 1 (mixed ligand)- $\text{K}^+$  complexes *vis-à-vis* formation of 2 : 1 (homo ligand)- $\text{K}^+$  complexes.

The results shown in Table 5 indicate that addition of either benzo- or dibenzo-18-crown-6 to solutions that contain **48** and  $\text{KCl}$  results in enhanced formation of 1 : 1 : 1 (mixed ligand)- $\text{K}^+$  complexes (i.e., enhancement ratios greater than 1.0 are observed in both cases).<sup>71</sup> The fact that the other macrocycles studied, i.e., 18-crown-6, aza-18-crown-6 and dicyclohexano-18-crown-6 fail to display this enhancement suggests strongly that donor-acceptor  $\pi$ -stacking interactions contribute to stabilization of (mixed ligand)- $\text{M}^+$  complexes that involve **48**,  $\text{K}^+$  and either of the two benzo-containing ligands that were studied.

The foregoing observations attest to the potential utility of  $\pi$ -stacking interactions as a means to promote the design of self-assembled supramolecular host-guest complexes. Importantly, they also demonstrate that ESI-MS methods can be used profitably to monitor the formation of these supramolecular complexes.

### Conclusions

The results presented herein serve to demonstrate the utility of electrospray ionization-mass spectrometric methods for the study of metal cation complexation properties of cage-annulated macrocycles. In general, ESI-MS methods require minute samples for analysis and permit rapid screening of binding selectivities of the various ligands studied. This technique has been applied successfully to study the metal cation binding selectivities of a wide variety of oxygen-, nitrogen- and/or sulfur-containing, cage-annulated macrocyclic host ligands, many of which have potentially important analytical, biomedical and/or environmental applications.

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### SAŽETAK

#### Sinteza makrocikličkih liganada s ugrađenim kavezastim molekulama te ispitivanje njihovih kompleksirajućih svojstava s metalnim kationima pomoću ESI-spektrometrije masa (ESI-MS)

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Rezultati prikazani u ovom radu pokazuju korisnost metode ESI-MS za ispitivanje kompleksirajućih svojstava različitih makrocikličkih molekula s metalnim kationima. Općenito, metoda ESI-MS zahtijeva minimalne količine uzoraka za analizu te omogućava vrlo brzi uvid u selektivnost liganda prema različitim kationima. Ta je tehnika vrlo uspješno primijenjena za studij selektivnosti vezivanja metalnih kationa s brojnim okso-, aza-, i tita-makrocikličkim ligandima s ugrađenim kavezastim molekulama od kojih mnogi imaju potencijalnu važnost u analitici, biomedicini ili pak primjenu u zaštiti okoliša.

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