DESIGN AND SYNTHESIS OF NOVEL CAGE-ANNULATED CROWN ETHERS:

A NEW CLASS OF Ag(I) COMPLEXANTS

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Lai, Huiguo, Design and synthesis of novel cage-functionalized crown ethers: A new class of Ag(I) complexants, Master of Science (Inorganic Chemistry), August 2003, 82 pp., 2 tables, 26 figures, 11 schemes and 126 references.

Three different types of cage crown ethers have been prepared and their complexation properties with Ag(I) have been studied. Atomic absorption, fluorescence quenching, and UV absorption have been used to study the interaction between the hosts (cage crown ethers) and guests (Ag⁺).

For the cage-annulated crown ethers that contain aromatic rings, cation-π and π-π interactions may contribute significantly to the overall complexation ability of the host system. Piperazine groups may cooperate, and the piperazine nitrogen atoms provide unshared electrons, which may form a complex with Ag⁺. In addition, relatively soft donor atoms (e.g., Br) are well-suited for complexation with Ag⁺, which is a softer Lewis acid than alkali metal cations.
ACKNOWLEDGEMENTS

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CHAPTER 1: INTRODUCTION

Supramolecular chemistry is one of the most popular areas of experimental chemistry, and it seems set to remain that way for the foreseeable future. \(^1\) Why is it so popular? Part of the reason for this is its aesthetic appeal. For example, crown ethers resemble a queen’s crown; the oxygen atoms are the beads on the crown. Thus, supramolecular chemistry has developed in many areas; it attracts not only chemists but biochemists, environmental scientists, engineers, physicists, theoreticians, mathematicians, and a host of other researchers. Supramolecular science thus had crossed traditional boundaries, and more and more scientists are likely to become attracted into this field. Crown ethers are one kind of supramolecules.

1.1 History of Crown Ethers

Crown ethers were first prepared in 1967 by Charles Pedersen. \(^2\) However, Pedersen’s initial synthesis of the first crown ether dibenzo-18-crown-6 was accidental. When he attempted to carry out the synthesis of the linear open-chain diol (compound 1), he designed the synthesis route as shown in Figure 1. The starting material was the catechol (1,2-dihydroxybenzene) derivative in which one of the hydroxyl groups is protected by a tetrahydropyran ring. Workup of the reaction mixture afforded some unknown by-products, which Pedersen later identified as macrocyclic crown ether 2. Given the trivial name “dibenzo-18-crown-6” by Pedersen, it was found to be insoluble in methanol by itself, but became readily soluble upon addition of sodium salts. Crown ether 2 was formed in low yield in this reaction. Subsequently, other scientists developed improved methods to synthesize crown ethers. Now, satisfactory yields of macrocycles can be achieved via a "template" approach.
Fig 1. Accidental synthesis of the first crown ether, dibenzo[18]crown-6. [2]


1.2 Definition of Host-Guest Chemistry

“Host-guest chemistry” was defined by Cram in 1974. [8] The host-guest relationship involves the complementary space arrangement of binding sites between the receptor and the ligand. A host is a molecule which can non-covalently interact with a guest to form a host-guest complex. That is, there is a weak attractive interaction between the host and guest. But sometimes, it is very difficult to differentiate the host and guest
because of the close relationship of donor and acceptor. According to Cram’s work, the relationship that distinguish host from guest are delineated in Table 1.

Table 1: The differences between host and guest.

<table>
<thead>
<tr>
<th>Host</th>
<th>Guest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>Small</td>
</tr>
<tr>
<td>Central hole or cavity</td>
<td>Cation, anion or neutral molecule</td>
</tr>
<tr>
<td>Convergent binding sites</td>
<td>Divergent binding sites</td>
</tr>
<tr>
<td>Lewis basic donor atoms</td>
<td>Lewis acid or metal ions</td>
</tr>
<tr>
<td>Donor</td>
<td>Acceptor</td>
</tr>
<tr>
<td>Receptor</td>
<td>Ligand</td>
</tr>
<tr>
<td>Lock</td>
<td>Key</td>
</tr>
</tbody>
</table>

Host-guest chemistry is concerned primarily with the elucidation of the “rules of non-covalency” that are involved in the recognition and binding of a guest by a synthetic receptor. Many cations, anions, and some neutral molecules can serve as guest compounds. Host molecules can be acyclic, macrocyclic, or oligomeric.

1.3 Properties of Host Compounds

The efficiency and selectivity of a host molecule is affected by many factors:

1.3.1 Size-Match Selectivity

An important idea in macrocyclic chemistry is size-match selectivity. That is, in order to make a metal ion form its most stable complex with the member of a series of macrocycles, the size-match between the metal ion and macrocycles must be
complementary. A classic example of size-match selectivity is proved by 18-crown-6, whose cavity (2.60-3.20 Å) can accommodate a guest potassium ion (2.66 Å).

In 1968, Pedersen [13] first suggested the "size-match" principle in his seminal publication. He noted that 14-crown-4 hosts selectively bind to Li⁺, 15-crown-5 hosts selectively bind to Na⁺, and 18-crown-6 systems complex selectively with K⁺. These results reflect the relative size of each cation and the size and shape of the host cavity. In fact, most macrocyclic ligands exhibit significant selectivity toward certain metal ions based on size-match selectivity. When the metal ion radius matches the ligand cavity radius, the complex is usually more stable than similar complexes that involve other metal ions of equal charge. [14] This size-matching effect is very common in systems involving crown ethers; some examples are listed in Table 2. One reason for size-matching selectivity is that when the size of the ligand cavity and the size of the metal ion match, the interaction between the host and guest permits optimal maximal complex stability. Hancock and Martell [15] have reviewed the size-selectivity effect.

This size-match principle has been found to be particularly applicable to relatively rigid, three-dimensional hosts. For example, under comparable experimental conditions, complexes that involve cryptands have larger association constants than do simple crown ethers. Although the cavity of the cryptand is comparable to that of the crown ether, the cryptand possesses a more highly rigid structure, which allows cryptands to bind metal ion guests tightly into their cavities. The thermodynamic stabilities of cryptand complexes are also highly dependent upon the correlation between cation size and cavity size. [16, 17] One crown ether can complex with different metal cations, but the crown’s selectivity will display a large difference among the cations. In fact, the flexible 18-
crown-6 provides a reasonably good size match for all of the guest cations, but it provides an optimal cavity for complex formation with $K^+$.  

Table 2: The size of cations and the crown ethers and cryptands.

<table>
<thead>
<tr>
<th>Cation</th>
<th>Diameter (Å)</th>
<th>Crown ethers</th>
<th>Cavity diameter (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li$^+$</td>
<td>1.36</td>
<td>12-crown-4</td>
<td>1.20-1.50</td>
</tr>
<tr>
<td>Na$^+$</td>
<td>1.90</td>
<td>15-crown-5</td>
<td>1.70-2.20</td>
</tr>
<tr>
<td>K$^+$</td>
<td>2.66</td>
<td>18-crown-6</td>
<td>2.60-3.20</td>
</tr>
<tr>
<td>Rb$^+$</td>
<td>2.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cs$^+$</td>
<td>3.34</td>
<td>21-crown-7</td>
<td>3.40-4.30</td>
</tr>
<tr>
<td>Cu$^+$</td>
<td>1.92</td>
<td>[1.1.1] cryptand</td>
<td>1.0</td>
</tr>
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<td>Ag$^+$</td>
<td>2.52</td>
<td>[2.1.1] cryptand</td>
<td>1.6</td>
</tr>
<tr>
<td>Mg$^{2+}$</td>
<td>1.44</td>
<td>[2.2.1] cryptand</td>
<td>2.2</td>
</tr>
<tr>
<td>Ca$^{2+}$</td>
<td>2.20</td>
<td>[2.2.2] cryptand</td>
<td>2.8</td>
</tr>
<tr>
<td>La$^{3+}$</td>
<td>2.34</td>
<td>[3.2.2] cryptand</td>
<td>4.2</td>
</tr>
<tr>
<td>Lu$^{3+}$</td>
<td>2.00</td>
<td>[3.3.3] cryptand</td>
<td>4.8</td>
</tr>
<tr>
<td>Zr$^{3+}$</td>
<td>1.72</td>
<td></td>
<td></td>
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</tbody>
</table>
1.3.2 The Macrocyclic Effect

The binding ability of macrocyclic hosts generally is greater than that of its acyclic analogue (i.e. podand). This phenomenon called the “macrocyclic effect”, is used primarily to describe the binding strength. \cite{18, 19, 20} The macrocyclic effect varies in magnitude and thermodynamic origin with different systems. The possible reason for this mechanism is: the greater dipole-dipole repulsion in a macrocyclic compound compared with its acyclic analog. When a macrocyclic compound forms a complex with a metal ion, the thermodynamic stability of the resulting system will be increased. \cite{21, 22} When the size of the host cavity is similar to that of the guests, enthalpy rather than entropy plays the major role in determining the magnitude of the macrocyclic effect.

We can compare relative complex stabilities of macrocycles vs. podands according to the change of free energy, (i.e., $\Delta \log K$ or $\Delta(-\Delta G)$ values), Frequently, this difference can amount to a factor of $10^3$-$10^4$. Both enthalpy and entropy can influence the macrocyclic effect; however, when different systems are compared, the enthalpy and entropy effects will vary in a nonlinear fashion value. Which one will dominate the macrocyclic effect? This can only be determined by the experiment. For example, Hinz and Margerum \cite{23} reported that favorable enthalpy changes are the predominant contributor to the observed macrocyclic effect. However, Paoletti et al. \cite{24} and Kodama and Kimura \cite{25} reported that favorable entropy changes are the main contributors to the observed macrocyclic effect in similar systems.

Izatt and co-workers \cite{21} and Hancock and co-workers \cite{26} examined the macrocyclic effect in crown ether-alkali metal ion and crown ether-alkaline earth metal
ion systems. The results indicated that enthalpy changes predominate over entropy changes in these systems.

1.3.3 The Template Effect \textsuperscript{[27, 28, 29]}

When Pedersen synthesized the first crown ether, \textit{i.e.}, dibenzo-18-crown-6, it was obtained in low yield as a reaction by-product. In order to increase the yield, scientists designed new synthetic methods to maximize the yield of the desired macrocyclic compound. Thus, a cation is selected that effectively coordinates to the reactive sites, thereby “guiding” the formation of the macrocycle. Here, one cation functions as a “template”. \textsuperscript{[27]} By using the template, the yield of the desired macrocycle increased; thus 30-93\% yields of macrocycles can be obtained in this fashion. \textsuperscript{[30]}

The “template effect” is illustrated in Figure 2. According to the principle, many substituted \textsuperscript{[31-33]} and unsubstituted \textsuperscript{[34-36]} crown ethers can be synthesized in relatively high yields. The yield is affected by the nature of the template cation, the size of the crown ether cavity, the size of the cation, and the basicity of the template. All four factors play important roles in determining the efficiency of macrocyclization.

Macrocyclic crown ethers are dynamically (rather than thermodynamically) stable products. In Figure 2, complexation with \( K^+ \) arranges the reactants into a structurally defined intermediate, which is preorganized to form a cyclic product. Here, \( K^+ \) serves as a template for the intermolecular reaction that results in macrocycle formation, thereby dramatically increasing the efficiency of the cyclization process. Thus, the product is a kinetic product due to the operation of the template effect. Of course, the template effect also can be used in a single molecule—intramolecular cyclization.
The results of kinetic studies of the template synthesis of benzo-18-crown-6 have been reported.\(^{[29]}\) Not surprisingly, different metal ions display different rates of cyclization.

1.3.4 Gauche Effect

The gauche effect can play a significant role in crown ether syntheses in appropriate situations. In solution and in the solid state, the crown ether may adopt gauche or anti conformations. Which is more stable? Determination of the crystal structure can provide information about the exact conformation of the molecule in the solid state.

Fig 2. The template effect.\(^{[27]}\)
Crown ethers also have at least two conformations; the oxygen atoms may occupy \textit{gauche} or \textit{anti} conformations. In the \textit{anti} conformation (Figure 3b), the oxygen lone pairs are directed away from the center of the cavity while in the \textit{gauche} conformation, they pointed forward the center of the cavity (Figure 3a). Both conformations generally are accessible in solution.

![Diagram](image_url)

\textbf{Fig 3.} Solution behavior of 18-crown-6. (a) in an organic solvent such as dichloromethane, the crown resembles a droplet of water in oil, and (b) in a hydrophilic medium, the macrocycle resembles a droplet of oil in water.

In 18-crown-6, each of the six oxygen atoms possesses a lone electron pair that points inward, toward the cavity. This arrangement recounts the cavity to attract and to solvate cations. If the diameter of the cation matches the size and shape of the cavity, the cation can be bound tightly within the cavity.

The outside of the crown ether consists mostly of nonpolar C-H bonds; this region of the crown ether should associate with other nonpolar molecules and should display larger affinity toward nonpolar solvents. If the lone pairs are directed outward, the inside
of the cavity should be nonpolar; the crown ether cannot complex with the cations in this case.

![Image of gauche and anti conformations of ethylene glycol]

**Fig 4.** The conformation of ethylene glycol.

Information concerning directional binding of a metal cation by most ethylene glycol (-OCH₂CH₂O-) based hosts may be generated via examination of the O-CH₂-CH₂-O torsion angles. For guest binding, all of the torsion angles must be gauche (i.e. < 90°). Generally these fall in the range 65-70°, close to the optimum calculated value 72° for 1,2-dimethoxyethane. In uncomplexed crown ethers, however, at least two anti-torsion angles are usually observed, as illustrated in Figure 4.

When 18-crown-6 forms a host-guest complex with K⁺, it forms an inclusion structure as illustrated in Figure 5.

![Image of complexation of K⁺ by 18-crown-6]

**Fig 5.** Complexation of K⁺ by 18-crown-6.
We can model the extent of host-guest interaction by calculating the electric potential surface, which provides a measure of charge distribution in the complex. This has been done by probing the surface of the molecule with a positive charge (a proton) and by calculating the attractive or repulsive forces on the proton.

The operation of the gauche effect will affect the structure of the complex. A considerable body of physical and chemical evidence\textsuperscript{[37-40]} indicates that the C-C bond in -OCH\textsubscript{2}CH\textsubscript{2}O- units prefers to adopt the gauche conformation. As an example, the IR spectrum of 1,2-dimethoxyethane (the simplest model compound) indicates that this compound can occupy a wide range of conformational isomers, including both gauche and anti conformations in the liquid phase at 25 °C. However, it adopts only the gauche conformation in the crystal at -195 °C.

1.3.5 Preorganization Effect

In host-guest chemistry, complementarity can be used to determine structural recognition, but preorganization determines the overall effectiveness of host-guest binding in the complex. Cram’s “Principle of Preorganization” states: “the more highly hosts and guests are organized for binding and low solvation prior to complexation, the more stable will be their complexes. Both host and guest participates in solvent interactions, so that preorganization includes both enthalpic and entropic components.”\textsuperscript{[41]}

Thus, a host is said to be preorganized only if its bound and unbound conformations closely resemble one another. That is, a host molecule should not undergo extensive conformational change upon guest binding. The more highly the hosts are organized for binding and for low solvation during synthesis rather than during complexation, the higher is the resultant binding constant for interaction with a guest.
When the other conditions are the same or the similar, crown ethers have greater binding abilities compared with the acyclic hosts. This phenomenon can be attributed to the operation of preorganization effects.

In addition, host preorganization represents a major (in some cases decisive) factor that determines the overall free energy of guest complexation. If we neglect the effects of solvation, the host-guest binding process may be divided very loosely into two stages: The first stage is called an activation-stage. In this step, the host undergoes conformational readjustment in order to arrange its binding sites in the fashion most complementary to the guest, while at the same time minimizing unfavorable interactions between one binding site and another in the host. This step is energetically unfavorable, because the host must remain in this binding conformation throughout the lifetime of the host-guest complex.

The second stage is called the rearrangement-stage. In this step, binding occurs, that is energetically favorable due to the enthalpically stabilizing attraction between mutually complementary host-guest binding sites. The overall free energy of complexation represents the difference between the unfavorable reorganization energy and the favorable binding energy. If the reorganization energy is large, the overall free energy is reduced and the stability of the resulting host-guest complex will be reduced. If the host is highly preorganized, the expenditure of rearrangement energy is relatively small.

The principle of preorganization tells us that host-guest binding is strongest when only a small change in host conformation is required in order to organize the host, the guest and the solvent in the resulting complex.\textsuperscript{[42]} Alkali metal cations are spherical, and
their binding sites are divergent. Therefore, alkali metal cations prefer a spherical donor atom array in the host to promote respective complex formation.

1.3.6 Solvation of Cation and Ligand.

The solvation free energy increases in the order $K^+ < Na^+ < Ca^{2+}$, hence less energy is required in order to bind to $K^+$. Generally, soft ligands prefer to bind soft metal ions. This theory, first developed by Pearson, is called the “hard-soft acid-base” (HSAB) principle. Hard acids possess small highly charged and nonpolarizable acceptor atoms, and hard bases contain small, highly electronegative donor atoms. Hard acids and hard bases mutually interact via electrostatic interactions. According to the definition, alkali metal cations display these properties: (1) hard, nonpolarizable spheres; (2) little fixed preference for particular coordination geometries; (3) affinity for highly charged, nonpolarizable bases. Oxygen-containing crown ethers are a kind of hard bases; thus, when small metal cations and crown ethers are combined, the binding force should be very strong.

1.3.7 Number of Donor Atoms.

In general, the binding interactions between the host and guest are roughly additive. Thus, we would expect the larger crown ethers to bind more strongly to metal cations, when all of the donor atoms can fit around the guest cation. However, some functional groups in the crown ethers interfere with host-guest binding forces. When the size of the macrocycle is increased, some atoms do not participate in binding. Only those atoms which participate in binding can contribute to the stabilizing interaction between the host and guest. This accounts for the plateau selectivity seen for most cations.
1.3.8 Chelate Ring Size (ligand bite angle). \[^{[44-47]}\]

Generally, there is a two-carbon (ethane) bridge that joins two oxygen atoms in the host molecule; thereby resulting in the formation of a five-membered chelation ring. The bite angle $O-M^+-O$ is close to $72^\circ$ (Figure 6a). When there is a three, or four-carbon bridge that separates two oxygen atoms in the host, a six-membered (Figure 6b) or seven-membered ring will be formed, respectively. The corresponding $O-M^+-O$ bite angle will be smaller than that associated with five-membered rings. For guest binding, all of the torsion angles must be gauche (i.e.< $90^\circ$). Generally, a $65$-$70^\circ$ bite angle of $O-M^+-O$ is optimal.

![Diagram of chelate rings](image)

**Fig 6.** The bite angle relationship of $O-M^+-O$

1.4 Applications of Crown Ethers

1.4.1 Phase Transfer Catalysis (PTC) \[^{[48]}\]

Phase transfer catalysis (PTC) involves the transport of guest species from one phase to another. Generally, the two phases are two immiscible liquids (liquid-liquid phase transport). Crown ethers frequently are employed as phase transfer catalysts to
extract metal ions from the aqueous phase into the organic phase. Several reactions are facilitated when they are carried out in the presence of a phase transfer catalysts.

In practice, this usually means the use of a suitable host to promote the solubility of inorganic salts (e.g., alkaline picrate salts) in organic (nonpolar) media. Thus a reaction between a hydrophilic inorganic salt and a lipophilic organic substrate is catalyzed by the supramolecular host species, since the phase transfer catalyst permits the reactants to mix homogeneously within the organic phase.

When an inorganic cation complexes with a crown ether, a large, lipophilic cationic metal-macrocycle complex is formed. The complex is readily soluble in nonpolar solvents, e.g., benzene and toluene. Meanwhile, in order to maintain charge balance, the cationic complex possesses an associated counter anion. In an immiscible two phase liquid system, e.g. a mixture of chloroform and water, the anion is necessarily pulled into the organic phase as the cationic complex crosses the phase boundary. This mechanism is illustrated in Figure 7.

In the organic phase, reactive anions are able to react chemically with substances in the organic phase in a homogeneous fashion, rather than just at the boundary or interface. This phenomenon results in enormous reaction rate enhancements. This is a true catalytic process because only a small amount of added crown ether or cryptand is required. Once the reaction has taken place, the crown ether may return to the organic-water interface to pick up additional reactant and to release inorganic by-products. Thus, the net equilibrium concentration of the inorganic salt in the organic phase is not necessarily large, but the fact that the anion (e.g., MnO₄⁻) is continually reacting leads to crown ether-mediated diffusion of fresh salt across the interface to ameliorate the
concentration gradient. (the concentration of the inorganic salt in the organic layer is always much lower than in the aqueous phase).

![Diagram showing phase transfer catalysis by a crown ether.](image)

**Fig 7.** Phase Transfer Catalysis by a crown ether. [1]

1.4.2 Crown Ethers as Catalysts and Enzyme Mimics

Crown ethers can catalyze reactions by transporting otherwise insoluble reactants into organic phases to participate in the reaction of interest. Several reactions that are catalyzed by crown ethers via this mechanism have been reported. [49]

Crown ethers also can catalyze reactions in an enzyme-mimicking fashion. Some of the reactions that normally are catalyzed only by natural enzymes now can be catalyzed by crown ethers. [50] In these reactions, molecular recognition by the crown ethers plays a crucial role.
1.4.3 Crown Ethers as Chemical Sensors

Sensors are often used to analyze specific organic analytical mixtures of limited composition, but it is difficult to achieve universal selectivity. Some crown ethers contain special groups, which renders them practically suitable for use as chemical sensors.

Redox-switched crown ethers have both a redox-active group and a crown ether unit within a molecule. This class of crown ethers has two opposing functional facets: that is, the ion-binding ability of the crown ether site can be controlled by the redox state of the redox-active site, whereas the redox potential of the redox-active site can be controlled by the metal binding site. In many cases, we may regard that these two sites “communicate” with each other. Crown ethers that contain a quinone moiety as a redox functional group can be used as redox switches as illustrated in Figure 8. [51-53]

![Redox Switched Crown Ethers](image)

**Fig 8.** "Crowned" quinone-hydroquinone redox system. [52]

1.4.4 Crown Ethers in Medical Applications

In the medical applications field, crown ethers are used in clinical analysis as diagnostic agents and as therapeutic agents. [54] A major application of crown ethers in this area involves the fabrication of ion selective electrodes for medical use. Crown ethers
have been used as diagnostic agents in the human body to help locate a tumor site. Crown ethers also can be useful as administered therapeutic agents to help remove toxins from the human body. Other applications of crown ethers can be found in the literature. \cite{55}
2.1 Introduction

Among the various properties of crown ethers, their unique chemical architecture plays a prominent role and opens the way to practical design of host molecules for selective complexation of various metal ions.\[^{56-59}\]

In order to investigate the complexation properties of crown ethers, host molecules have been modified with different functional groups. For example, when an ester or amide group is added to crown ether, the crown ether displays a different affinity for complexation with alkali metal ions.\[^{60}\]

Aromatic groups also have been used to modify the complexation properties of a host. In general, the benzo substituent reduces the binding strength and selectivity of crown ethers.\[^{61}\] A possible reason on this effect lies in the fact that: the benzene ring is an electron withdrawing group, which can reduce the electron density of the adjacent oxygen atoms inductively with concomitant reduction in their basicity and their complexation ability. Another possible factor is that the relatively rigid benzo group reduces the overall flexibility of the crown ether. Finally, when a benzo substituent is present, the distance between two oxygen atoms is relatively shorter compared with the corresponding O-CH\(_2\)-CH\(_2\)-O in a simple ethylene bridge, thereby reducing the size of the host cavity.

Many examples are known, which indicate that that the complexation ability of a common ether is reduced by incorporation of a benzo group into a host molecule.
However, if two benzo groups are present in the same molecule as in, e.g., dibenzo-18-
crown-6, the benzo groups interact via \( \pi - \pi \) stacking. When the host forms a complex with the metal ion, there is also a cation-\( \pi \) interaction between the guest and host. This kind of cation-\( \pi \) interaction builds novel molecular architectures that permit the introduction of a wide variety of useful electrical and electron-chemical properties. \[^{62-65}\]

The electronic configuration of silver is \( 4d^{10}5s^1 \). That is, silver has a single outer-shell s electron, and a completed d shell, which results in weak crystal fields and directional effects. The diameter of \( Ag^+ \) is intermediate between that of the two alkali cations \( Na^+ \) and \( K^+ \). (The diameter of \( Ag^+ \) is 2.52 Å, \( Na^+ \) is 2.52 Å, \( K^+ \) is 2.66 Å). Thus, the chemical properties of \( Ag^+ \) resemble those of \( Na^+ \) and \( K^+ \). However, \( Ag^+ \) is regarded as a soft acid, while the \( Na^+ \) and \( K^+ \) are hard acids. So if a given macrocycle can complex effectively with \( Na^+ \) or \( K^+ \), it also should complexes with \( Ag^+ \) albeit with smaller binding energy. However, some examples indicate that the \( Ag^+ \) complexes with macrocycles; thus, some other factors may be operative. Silver (I) prefers to coordinate with soft bases. In order to increase host-guest binding to \( Ag^+ \), we must incorporate soft ligands into the host molecule. For example, we can change the binding atoms from oxygen atom to N or S. Complexes with these soft ligands give rise to an interesting array of host-guest stereochemistries and geometrical configurations.

For the purpose of designing new type of silver (I) complexes with macrocycle organic ligands, two new series of host molecules have been designed and synthesized in the present study. In one series, two benzene groups have been incorporated into cage-annulated crown ethers. We wish to obtain cation-\( \pi \) complexes by using these novel hosts and subsequently to study their structures and chemical properties. Of course, \( \pi - \pi \)
stacking interactions may help to increase the binding ability.

Silver is of great commercial importance in the photographic industry, and reliable sensing methods are needed for solutions that contain Ag$^+$ in low concentrations. Polythiamacrocycles display excellent selectivity in ion selective electrode membrane transport of Ag$^+$.\textsuperscript{[66]} Originally, it was thought that two sulfur atoms situated near an aromatic ring might coordinate axially to silver ions (Fig 9).\textsuperscript{[67]} These simple structures display good selectivity toward complex formation with Ag$^+$. 

\begin{center}
\includegraphics[width=\textwidth]{fig9.png}
\end{center}

\textbf{Fig 9.} Simple host system for Ag$^+$.\textsuperscript{[67]}

\begin{center}
\includegraphics[width=\textwidth]{fig10.png}
\end{center}

\textbf{Fig 10.} Anthracenophanes is good host for Ag$^+$.\textsuperscript{[68]}
Anthracenophanes, with a cryptand as receptor, were found suitable for the study of heavy metal ions $\text{Ag}^+$ and $\text{Tl}^+$, which proved to effectively alter the fluorescent behavior of the anthracenyl moieties.\cite{68} This potentially produces a basis for fluorescent sensing of these heavy cations. (Figure 10)

Munakata reported that silver (I) complexes with the dibenzo-18-crown-6 via cation-$\pi$ and $\pi-\pi$ interactions (Figure 11).\cite{69}

![Silver (I) and dibenzo-18-crown-6 dinuclear unit.][69]

Fuji\cite{70} reported that the presence of a hetero atom in the chain that connects two piperazine rings is required for metal binding, especially in the case of complex with $\text{Ag}^+$. 

![Crown ethers containing two piperazine groups.][70]
Sevdić [71-72] and Sekido [73] and co-workers studied silver (I) binding ability toward saturated thioethers. Subsequently, Kamigata [74] reported the synthesis, crystal structures and redox properties of silver (I) complexes with 18- and 21- membered unsaturated thiocrown ethers. The cavity dimension of the ligands is always an important factor in determining metal ion discrimination. The number of donor atoms and the geometry of the ligand are crucial for the formation of stable transition metal complexes, because most transition metal ions have pronounced geometric preferences. For example, Ni^{2+}, Co^{2+}, and Cu^{2+} prefer square planar or octahedral geometry, while Ag^{+}, Hg^{2+}, and Cd^{2+} generally prefer linear geometry. [75]

![Fig 13. Sulfur-containing crown ethers for Ag^{+}. [73, 74]](image)

In addition to the functional groups, the spacers that separate Lewis base centers in crown ethers also exert an important influence upon binding ability. Also, conformational flexibility affects the complexation ability. The ethylene bridge is lipophilic group; it is soluble in organic solvent. When an alkyl group is appended onto the spacer, the solubility behavior of the resulting crown ether will be changed. For example, dicyclohexyl-18-crown-6 displays a greater solubility than 18-crown-6. When dicyclohexyl-18-crown-6 is placed in contact with water, most of the crown ether remains in the organic phase, although the guest cation and it’s counter anions are
transported rapidly into the aqueous phase. Moriarty and coworker [76] added two 1,4-bridged cubyl groups as rigid lipophilic components, which serve to anchor the ionophore in the organic membrane during the extraction.

Fig 14. A rigid spacer crown ether. [76]

The anthraquinone subunit has been introduced into the crown ethers as a rigid bridge, [77-79] thereby affording a series of interesting and novel ligands whose properties have been characterized by electrochemical and ESR studies. Adamantane [80] also can be added into crown ethers as a rigid bridge.

Fig 15. Rigid spacer crown ethers. [78, 80]
Pyridine, bipyridine, or phenanthroline groups can be introduced into crown ethers, \cite{81} thereby inferring increased rigidity upon the ligand structure and providing additional soft ligating atoms that may interact constructively with a cationic guest.

![Pyridine, bipyridine or phenanthroline as a spacer or crown ether. \cite{81}](image)

**Fig 16.** Pyridine, bipyridine or phenanthroline as a spacer or crown ether. \cite{81}

Lactone groups also can be introduced in order to render spacer more rigid. \cite{82-85}

![Crown ethers containing lactone groups. \cite{82-85}](image)

**Fig 17.** Crown ethers containing lactone groups. \cite{82-85}

In addition, \textit{p-tert}-butylcalix[4]arene can be introduced into crown ethers as a rigid spacer. The resulting calyx-crown ethers often display high selectivity and strong binding ability toward alkali metal cation guests. \cite{86}
Spherands or semi-spherands also can be introduced into crown ethers. The term “sphereand” originated from the word “sphere”, because the shape of its macrocyclic cavity is suitable for occupation by spherical guests. Spherands and calixene are both rigid groups. When the calix[4]arene unit and spherand unit are introduced into the crown ether, the rigidity of the crown ether will be increased greatly.

In summary, incorporation of benzene, cyclohexane or pyridine rings and/or other similar constituents into macrocyclic skeletons leads to a more highly rigid hosts and may alter the strength and selectivity of ligand interaction with a cationic guest. Many factors are known to affect the complexation behavior of crown ethers. The number, kind, and arrangement of donor atoms also play important roles in macrocyclic selectivity. Oxygen donor atoms in classical crown ethers have the largest affinities for alkali metal, alkaline-earth and lanthanide cations. Nitrogen donor atoms favor complex formation with transition metal cation, whereas sulfur donor atoms interact preferentially with Ag$^+$, Pb$^{2+}$, and Hg$^{2+}$. So, one should make judicious use of functional groups and/or rigid spacer to increase the rigidity of the crown ether and concomitantly to improve the binding ability of the crown ether.

When a polycyclic cage moiety is introduced into the crown ether, the selectivity of the crown ether toward cationic guests is often altered dramatically. Oxahexacyclic cage employed in our study (Fig 18) possesses left-right but not front-back symmetry. In addition, since the cage is highly rigid, the adjacent C-C bonds can not rotate freely. The cage consists of only saturated carbons, (similar to a bulky alkyl group); thus, its presence in the host serves to increase the solubility in organic solvents. In addition, the oxygen atom in the oxahexacyclic cage moiety can serve as a donor site.
in the resulting host system. The results of alkali metal cation extraction experiments indicated that cage-annulated crown ethers display higher avidity toward all alkali metal picrates when compared with the corresponding model compound that lacks a cage moiety.

![Crown ethers containing rigid spacer.](image)

Based upon literature precedents, it seems clear that the nature of functional groups and spacers affects the complexation properties. In order to increase the binding ability with \( \text{Ag}^+ \), we designed several novel cage-annulated crown ethers. Two aromatic rings have been incorporated into the crown ethers in an effort to take advantage of \( \pi-\pi \) stacking interactions and cation-\( \pi \) interactions to increase the stability of the resulting host-guest complex. In addition, two piperazine groups have been introduced into the host to increase its avidity and selectivity toward \( \text{Ag}^+ \). Finally, since \( \text{Ag}^+ \) is a soft acid, a Br atom has been introduced into the host system in order to increase the effectiveness of the resulting crown ether as a \( \text{Ag}^+ \) complex.
2.2 Results and Discussions

2.2.1 Designing and Synthesis of Cage-Annulated Crown Ethers

The strategy begins with the synthesis of the oxahexacyclic cage compound. Reaction of cyclopentadiene with \( \rho \)-benzoquinone at 0-5 °C afforded the corresponding Diels-Alder cycloadduct, i.e., 1. Subsequent, intramolecular \([2+2]\) photocyclization of 1 provided the corresponding cage dione, 2, i.e., pentacyclo\([5.4.0.0^2,6.0^3,10.0^5,9]\)undecan-8,11-dione (PCU-8,11-dione). \(^{[93, 94]}\) This cage is employed as a key starting material for synthesis of our cage-annulated crown ethers.

Reaction of 2 with excess allylmagnesium bromide afforded the corresponding endo-8, endo-11 cage diol 3. \(^{[95, 96]}\) Compound 3 can be dehydrated by refluxing a benzene solution of 3 in the presence of a catalytic amount of TsOH. During the reaction, water is removed via azeotropic distillation in a Dean-Stark apparatus, thereby affording the corresponding diallyl functionalized cage compound, 4 (Scheme 1).

![Reactions diagram](image-url)
Ozonolysis of 4 in MeOH at -78 °C, followed by reductive workup with Me$_2$S and subsequent NaBH$_4$ reduction of the reaction mixture afforded the corresponding reduction cage-diol 5 (Scheme 1). Cage diol 5 could be converted to the corresponding cage ditosylate, 6, by using the method shown in Scheme 2.

In order to produce a larger crown ether, it is necessary extend podand 5. The synthetic route employed to prepare the extended cage-annulated podand, i.e., 10 is illustrated in Scheme 3. Thus, reaction of 2-benzyloxyethyl tosylate (8) with cage diol 5 afforded podand 9. This compound was debenzylated via hydrogenolysis of the O-Bn bond, thereby affording extended diol 10, which subsequently was converted to the corresponding ditosylate, 11 (Scheme 3).
An alternative synthesis of 10 is illustrated in Scheme 4. Thus, base-promoted reaction of 5 with allyl bromide (2 equivalents) afforded 12; subsequent ozonolysis of 12 followed by reductive workup produced 10. This synthetic route consists of only two steps; both of which proceed in high yield without the necessity of intervening protection and deprotection steps.

Scheme 4. The second method used to prepare 10.

Scheme 5. Synthesis of cage-annulated crown ether 16.
Cage annulated crown ether 17 was prepared via the method shown in Scheme 5. Thus, tetraethylene glycol was converted into podand 14 in three synthetic steps. Subsequent reaction of 14 with cage-annulated podand ditosylate 11 afforded 16 in moderate yield (Scheme 5). A somewhat smaller cage-annulated crown ether, i.e., 17, was prepared in analogous fashion (Scheme 6).


A somewhat different aromatic substitution arrangement was employed to make another kind of cage-annulated crown ether, i.e., 18 (Scheme 8). Once again, π-π stacking interactions and/or cation-π interactions may be involved in complexes of 18 with metal cation guests.

An analogous crown ether, 19, which containing a somewhat smaller cavity has been prepared by using the procedure shown in Scheme 8.


As part of this study, a nitrogen-containing cage annulated crown ethers, i.e., 25 (Scheme 9), has been prepared that contains two piperazine moieties. We anticipate that
the two piperazine moieties can interact cooperatively with a guest Ag\(^{+}\) cation to form a stable host-guest complex. Fuji\(^{[70]}\) reported that two cooperative piperazine moieties provide an especially effective arrangement for host-guest complexation with Ag\(^{+}\). The route used to prepare 25 is illustrated in Scheme 9.


According to hard and soft acids and bases theory,\(^{[43]}\) the Ag\(^{+}\) is a soft acid and therefore prefers to interact with soft bases. Bromine has been incorporated into a cage-annulated crown ether, 27, in an effort to provide a soft ligand site for bonding to an Ag(I) guest cation. The synthesis of 27 is illustrated in Scheme 10 and Scheme 11.
Scheme 10. Synthesis of cage-annulated crown ether 27.

2.2.2 Atomic Absorption Experiments

The general procedures employed herein are similar to those reported previously. Solutions of Ag₂O (125 mM) in 5% aqueous HNO₃ solution were prepared. In the experiment, no pH adjustment was required. A 5.0 mM solution of the Ag(I) picrate in 5% aqueous HNO₃ was prepared as follows: Picric acid (28.6 mg, 0.125 mmol) and 5% aqueous HNO₃ (5 mL) along with an aliquot (1 mL) of a 125 mM solution of Ag₂O in 5% aqueous HNO₃ was placed into a 25 mL volumetric flask. The resulting mixture was shaken to effect complete dissolution, at which time the resulting solution was diluted to volume (25.00 mL) via addition of 5% aqueous HNO₃. Chloroform was washed with water to remove EtOH and then was used to prepare 5 mM solutions of each of the hosts to be tested. Aliquots (0.5 mL) of the CHCl₃ solution that contained host compound and the aqueous solution (0.5 mL) that contained the Ag(I) picrate were introduced into a screw-topped vial and then were shaken mechanically at ambient temperature during 30 minutes. The resulting mixture was allowed to stand at least 2 hours at ambient temperature in order to effect complete phase separation. A 50 µL aliquot was transferred from the aqueous phase of each vial into a 25 mL volumetric flask and was diluted to volume by addition of 5% aqueous HNO₃.

The atomic absorption measurements of silver ion (ppm) were obtained by using the Buck Scientific Atomic Absorption Spectrophotometer model 200A. The light source is a hollow-cathode Ag lamp. Initially, the instrument was calibrated with 5.0 ppm Cu²⁺ solution by using a Cu lamp, and then standard Ag⁺ solutions were used to complete instrument calibration. The concentrations of Ag⁺ employed were 0.25 ppm, 0.50 ppm, 0.75 ppm, 1.00 ppm, 1.25 ppm, 1.50 ppm, respectively. Plots of absorbance vs.
concentration, afforded a straight line. The slope and intercept were derived from the linear equation: \( Y = mX + b \), where \( Y \) is absorbance, \( X \) is the sample concentration, \( m \) is the slope of the straight line, \( b \) is the \( y \) axis intercept. The correlation coefficient of the straight line is thereby obtained \( r = 0.999 \).

Experimental measurements were made in terms of transmittance (\( T \)), which is defined as: \( T = \frac{I}{I_0} \), where \( I \) is the light intensity after it passes through the sample and \( I_0 \) is the initial light intensity. The relationship between \( A \) and \( T \) is:

\[
A = -\log T = -\log \frac{I}{I_0}
\]

A control experiment (blank) was performed for the Ag(I) picrate wherein no host was present in the CHCl\(_3\) layer. For each host-Ag(I) picrate combination, three separate experiments were performed in three separate vials. The percentage of silver picrate that had been extracted into the organic phase by a particular host was calculated by using the following equation:

\[
\text{% extracted} = \frac{(\text{absorbance of blank}) - (\text{absorbance of sample})}{(\text{absorbance of blank})} \times 100
\]
The cage-annulated crown ethers 16-19 that contain aromatic rings were chosen as hosts for the atomic absorbance studies. The extraction efficiency toward Ag$^+$ picrate was found to be 46.5%, 63.2%, 73.1%, and 86.3%, respectively. Accordingly, the following conclusions can be drawn:

1. The longer the chain, the lower is the observed extraction efficiency. The extraction efficiency of 16 is less than that of 17; similarly, the extraction efficiency of 18 is less than that of 19. This behavior may be due to the fact that the cavity size of 16 and 18 is larger than the diameter of Ag$^+$. When the cavity size become larger and larger, the macrocyclic molecule conformation becomes more and more flexible. It then becomes more difficult to form a stable complex with the guest (metal cation), and the extraction efficiency decreases accordingly.

2. The aromatic ring will affect the extraction efficiency, too. For example, compound 16 and 18 have the same chain length between the cage and aromatic rings (5
oxygen atoms). Compound 16 is \textit{para} disubstituted benzene crown ether, while compound 18 is \textit{ortho} disubstituted benzene crown ether. According to the experimental data, the \textit{ortho} disubstituted benzene is better than the \textit{para} disubstituted benzene ring. The extraction efficiency of 16 is less than that of 18; similarly, the extraction efficiency of 17 is less than that of 19. It may be possible for the two benzene rings in 16 to “stack”, i.e., may line up in a parallel (face to face) conformation. Complex formation between between the cation and the two benzene rings in crown ether 16 might involve an intramolecular interaction. However, in 18, the two benzene rings may lie in the same plane. One of the Ag\textsuperscript{+} can enter the cavity, and then another crown ether can help to stabilize the Ag\textsuperscript{+} via intermolecular cation-\pi interactions. The stabilizing effect of intermolecular interactions is likely to be more significant in 18 than corresponding 16. The “sandwich” structure is likely to be more stable than corresponding “stacking” structure.

2.2.3 Fluorescence and UV-Titration Electronic Absorption Experiments

Fluorescence Experiments. A 5 mM solution of host in CH\textsubscript{2}Cl\textsubscript{2} was prepared and then was diluted to 1.0 \times 10^{-3} mole\cdot L^{-1} and 1.0 \times 10^{-4} mole\cdot L^{-1} solutions, respectively. A solution of the guest (aqueous AgNO\textsubscript{3}) in deionized water then was prepared; the concentration of guest was 1.0 \times 10^{-3} mole\cdot L^{-1} and 1.0 \times 10^{-4} mole\cdot L^{-1}, respectively. A mixture of 5.0 mL of 1.0 \times 10^{-3} mole\cdot L^{-1} host solution and 5.0 mL 1.0 \times 10^{-3} mole\cdot L^{-1} of aqueous AgNO\textsubscript{3} solution was mixed in a screw-top vial and then was shaken during 30 minutes. In another vial, a mixture of 5.0 mL of 1.0 \times 10^{-4} mole\cdot L^{-1} host solution and 5.0 mL 1.0 \times 10^{-4} mole\cdot L^{-1} AgNO\textsubscript{3} solution was shaken for 30 minutes.
Compound 19 was chosen as an example for luminescence studies. Generally, at room temperature, the luminescence is very weak and the fluorescence quenching effect of the host due to the complexation of Ag\(^+\) was undetectable. Compound 19 indeed displays weak luminescence, since it contains only two benzene groups that are not strongly fluorescent groups. It is known that luminescence is usually much stronger at 77 K than at room temperature.\[^{100}\]\(^\text{[100]}\) Thus, the weak luminescence in compound 19 was detected at low temperature (77 K).

The host luminescence properties were examined first. Then the guest (aqueous AgNO\(_3\)) was added, whereupon luminescence quenching could be observed. The fluorescence effects could qualitatively explain the interaction between the host and the guest. The organic phase was studied subsequently for luminescence experiments. The data thereby obtained are shown in Figures 20 and 21.
**Fig 20.** Luminescence emission and excitation spectra of host 19 and AgNO$_3$ at $1.0 \times 10^{-3}$ mole·L$^{-1}$
Fig 21. Luminescence emission and excitation spectra of host 19 and AgNO₃ at $1.0 \times 10^{-4}$ mole·L⁻¹.
Host-guest interactions detected by luminescence techniques have been observed in the literature and they usually have the following features:

(1) The host emission spectrum changes and new bands appear after interaction with the guest. When guest (e.g., metal cation) is added to the host system, the metal ion can modulate the fluorescence properties by inducing a strong conformation change.

The spectrum could also change from excimer structureless emission from a host that has π-π stacking to a short wavelength monomer emission after interaction with a guest. Obviously, the host-guest interactions prevent π-π stacking due to the cation-π interaction. In order to strongly increase the complexing ability of the anthracenophanes, the macrotricyclic bisanthracene dubbed “tonnelet” (small barrel), because of its shape was fixed. The anthracene groups can increase the rigidity of the crown ether. This fluorescent ditopic receptor is comprised of two hydrophilic diazacrown subunits and two anthracenes which delineate a large hydrophobic cavity (Figure 10). The fluorescence emission in methanol is dual (with a locally excited emission and excited complex band peaking at 450 nm and 530 nm, respectively) but relatively weak in intensity; the low intensity emission is attribute to the existence of several possible exciplexes between the guest and the aromatic rings, which are prone to collapse to non fluorescing ion-pairs in a polar solvent such as methanol. Addition of rubidium perchlorate induces in the spectrum a new and strong red-shifted band. These large spectral changes are specific to Rb⁺. When Rb⁺ was added, no cooperative effect was observed. The fluorescence emission with Rb⁺ is characteristic of a quasi-sandwich excimer whose formation results from the complexation of two Rb⁺ which forces the two aromatic planes to adopt a superimposed configuration. It is illustrated in Figure 22.
When $\pi-\pi$ interactions exist between the two aromatic rings, the two aromatic rings are very close. This leads to an excimer emission in the fluorescence spectrum (an excimer is in excited state dimmer). When the metal cation was added to this system, the distance between the two aromatic rings are larger. It decreased the chance of $\pi-\pi$ interactions. So there is no excimer emission (only monomer emission).\textsuperscript{[68]}

If the metal was a light one (e.g., Na$^+$ or K$^+$), the monomer emission is fluorescence from a singlet excite state. If the metal is a heavy one (e.g., Ag$^+$, Tl$^+$, Hg$^+$ or Hg$^{2+}$), the monomer emission could be either fluorescence from a singlet excite state or phosphorescence from a triplet excited state. An example of phosphorescent monomer emissions enhanced by a heavy atom effect has been reported recently by Omary et al.,\textsuperscript{[103]} in which interaction of aromatic hydrocarbons with a mercury Lewis acid leads to spin-orbit coupling and results in room temperature monomer phosphorescence.

When the guest is an inorganic salt (e.g., $M^+X^-$), the anion of the salt can be chosen as a strongly-fluorescent species, where $X^-$ is a counter ion.\textsuperscript{[104]} For example,
Blanzo et al. used extractive fluorimetric determination of ultratraces of Pb$^{2+}$ with cryptand 2.2.2 and eosin. The host is not fluorescent sensitive while the counter ions (eosin) are fluorescent. The method was very sensitive to detect µg/L (that is, ppb) levels of Pb$^{2+}$. Another similar method was also reported to determine cryptand 2.2.1.\cite{105}

(2) The host emission intensity increases upon interaction with the guest. Inoue et al. reported\cite{109} the inclusion complexation behavior with amino acids by using fluorescence spectrometry. The fluorescence effect was increased by addition of amino acids. This is because the chromophore originally attached on the edge of β-cyclodextrin must suffer substantial conformational change upon guest inclusion and therefore functions as a fluorescent probe to determine complex stability constants in differential fluorescence spectrometry. Because of the formation of inclusion, fluorescence effect increased.

(3) The host emission intensity decreases upon interaction with the guest. This is because of a conformational change. The interaction with a heavy metal may also lead to a decrease in the emission intensity of the host without change the spectrum. (i.e., without new phosphorescence bands).\cite{102, 106} This takes place if the heavy metal enhances the singlet-triplet intersystem crossing without enhancing the phosphorescent emission from the triplet. The triplet decays by non-radiative decays. So the fluorescence were not detectable.\cite{68} That is, with the addition of Ag$^+$, the chance of intersystem crossing ($S_1 \rightarrow T_1$) is enhanced. But the triplet excite state can quench by non-radiative decay. So the phosphorescence effect was not detectable. The energy enters the solvent. Because the energy is too less, the temperature change was not detectable. This mechanism is illustrated in Figure 23.
In our host system, there is two aromatic rings which is very similar with these literature results. Every factor can be the possibility to affect the luminescence. According to luminescence study, some conclusion can be drawn:

(1) The observation of fluorescence applies to benzene-functionalized crown ether where Ag$^+$ cation entered the cavity by inducing a strong conformational change in the host.\textsuperscript{[101]} Fluorescence effect decreased when the guest (Ag$^+$) was added to the host (crown ether) solution. The fluorescence properties of 19 are determined primarily by the degree of mutual overlap between the two aromatic nuclei, which is sensitive to conformation changes of the complexing unit and the strain energy of the ethano bridge. Similar results have been reported previously for fluorescence quenching via addition of Na$^+$.\textsuperscript{[68, 101]}

Fig 23. Mechanism of luminescence.
(2) Fluorescence quenching is observable in similar systems. The mechanism of fluorescence quenching has been reviewed; \textsuperscript{102} fluorescence quenching can occur via either energy or electron transfer. In compound \textbf{19}, fluorescence quenching is made possible because of $\pi$-$\pi^*$ electron transfer between the two benzene rings.

(3) The guest (Ag$^+$) might form a sandwich-type adduct with the flat-shaped crown ether \textbf{19}. $\pi$-$\pi$ interactions between the aromatic rings can occur during complexation with the metal cation guest. The insertion of Ag$^+$ between the two aromatic rings accounts for the mutual inhibition of the photoreactivity and luminescence of both host and guest. \textsuperscript{68}

(4) According to our experimental data, no new bands formed during addition of Ag$^+$. Because of the existence of Ag$^+$, it decreases the chance of $\pi$-$\pi$ interaction. So only the host spectrum is detectable. Besides, Ag$^+$ enhanced intersystem crossing possibilities, and then the triplet excite state quench via a non-radiative decay. So the luminescence are not detectable.

In a word, conformation change and $\pi$-$\pi$ stacking interaction are main reasons for the luminescence spectrum decrease.

In the corresponding absorbance experiment, when the guest was added to the host, the absorbance was observed to increase as illustrated in figure 24. It indicates that guest enters the cavity of the host. So the absorbance changed. Because the host and the complex should have different absorbance spectrum.
According to the fluorescence experiments, the Ag⁺ enters the cavity of crown ether. The fluorescence effect decreased. In order to further prove that Ag⁺ enters the cavity of crown ether, anhydrous silver perchlorate (AgClO₄) was chosen for UV-titration. Similar results were obtained.

**Fig 24.** The UV absorbance of compound 19. (host and 1:1 complex with Ag⁺ at 1.0 × 10⁻⁴ mole·L⁻¹)
Methods for UV-titration have been reported in literature.\textsuperscript{[107-110]} Thus, $1.0 \times 10^{-5}$ mole \cdot L\textsuperscript{-1} solution of compound 19 in HPLC grade acetonitrile was prepared as a stock solution. Anhydrous AgClO\textsubscript{4} was dissolved in HPLC grade acetonitrile to afford a solution in which guest concentration was $1.0 \times 10^{-2}$ mole \cdot L\textsuperscript{-1}. Aliquots (5.0 µL) of this solution were added to the host solution. The absorbance was observed to increase with increasing guest ion concentration; the resulting titration plot appears in Figure 25.

**UV titration data in acetonitrile with the host:guest ratio as shown**

Fig 25. Plot of UV-titration of compound 19 in HPLC grade MeCN.

Temperature: 25 °C. The host concentration is $1.0 \times 10^{-5}$ mole\cdotL\textsuperscript{-1}. The concentrations of AgClO\textsubscript{4} (mole\cdotL\textsuperscript{-1}) are 0, $4.0 \times 10^{-5}$, $6.0 \times 10^{-5}$, $1.4 \times 10^{-4}$, $1.6 \times 10^{-4}$, $1.8 \times 10^{-4}$, and $2.0 \times 10^{-4}$ reading from bottom to top.
In the titration experiments using UV spectroscopy, as can be seen from Figure 25., the absorption maximum of the aromatic group gradually increased upon the addition of Ag$^{+}$ (1.0 ~ 24 × 10$^{-5}$ mole·L$^{-1}$). There were two characteristic absorptions at 228 and 276 nm, indicating that the host must suffer substantial conformational change upon guest inclusion, and form inclusion complex with Ag$^{+}$. This substantial conformational change is used to determine complex stability constants. With assumption of a 1 : 1 stoichiometry, the inclusion complexation of Ag$^{+}$ (G) with crown ether (H) is expressed by equation 1.

$$H + G \leftrightarrow K \cdot HG$$  \hspace{1cm} (1)

Under the conditions employed, the concentration of host is much less than that of host, i.e., $[H_0] << [G_0]$. Therefore, the stability constants can be calculated according to the modified Hildbrand and Benesi equation. It is illustrated in equation 2.

$$\frac{1}{\Delta A} = \frac{1}{K_a \Delta \varepsilon [H]_0 [G]_0} + \frac{1}{\Delta \varepsilon[H]_0}$$  \hspace{1cm} (2)

Where, $[G]_0$ denotes the total concentration of Guest; $[H]_0$ refers to the total concentration of Host; $\Delta \varepsilon$ is the difference of molar extinction coefficients for free and complexed Host; $\Delta A$ denotes the changes in the absorption intensity of Host upon addition of Guest.
Fig 26. Typical plot of \([G]_0[H]_0/\Delta A\) vs. \([G]_0\) for the inclusion complexation of compound 19 with AgClO₄ in HPLC grade MeCN at 25 °C. (Absorbance was obtained at \(\lambda_{\text{max}} = 227.0\) nm)

The free energy change can be obtained by equation 3:

\[
\Delta G_0 = -RT \ln K_a
\]

(3)

Where R is constant (R = 8.314); T stands for the experiment temperature (T = 298.15 K); \(K_a\) donates the stability constatin which is obtained from the experimental data.
For the guest compound examined the plot of calculated \([G]_0[H]_0/\Delta A\) values as a function of \([G]_0\) give a good straight line. A typical plot is shown in figure 26 for the inclusion complexation of compound 19 with AgClO₄, where the calculated \([G]_0[H]_0/\Delta A\) are plotted against \([G]_0\) to give an excellent linear relationship \((r^2 = 0.955\) or \(r = 0.977\)\) with a slope of \(3.562 \times 10^{-4}\) mole·L⁻¹ and an intercept of \(5.014 \times 10^{-8}\) mole²·L⁻². The stability constant \((K_a)\) and the free energy change \((-\Delta G^0)\) calculated from the slope and the intercept are \(7.104 \times 10^{3}\) M⁻¹ and \(21.98\) kJ·mole⁻¹, respectively. The results obtained verified the 1:1 stoichiometry of complexation as assumed above.

In a word, according to the experiment data, the following conclusions can be drawn: the interactions between host (crown ether) and guest (Ag⁺) can change the conformation of host.

2.3 Conclusions

Hosts 19 and 25 proved to be the most efficient Ag (I) complexants. Pi-pi stacking interactions and cation-π interactions can operate in these host systems to increase their Ag(I) binding ability. The cage unit and two piperazine groups also help to increase binding ability toward Ag(I).

2.4 Experimental Sections

Melting points are uncorrected. Absorption intensities of alkali metal picrate solutions were measured at \(\lambda = 374\) nm by using a Hewlett-Packard Model 24524 Diode Array UV-visible spectrophotometer. UV-titation experiments were obtaind by using a Perkin-Elmer lambda 900 double-beam UV/VIS/NIR spectrophotmeter. High-resolution mass spectral data reported herein were obtained by Professor Jennifer S. Brodbelt 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 chemical ionization mode. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ. Atomic absorption experiments were performed at UNT by using a model 200A Buck Scientific Atomic Absorption Spectrophotometer. Steady-state luminescence spectra were acquired with a PTI QuantaMaster Model QM-4 scanning spectrofluorometer equipped with a 75-watt xenon lamp, emission and excitation monochromators, excitation correction unit, and a PMT detector. The emission spectra were corrected for the detector wavelength-dependent response while the excitation spectra are presented uncorrected due to the unreliability of correction methods at short wavelengths below 250 nm, at which the samples here absorb and the xenon lamp output is rather low.

Synthesis of 1,4,4a,8a-Tetrahydro-endo-1,4-methanonaphthalene-5,8-dione (1)

To a solution of \( p \)-benzoquinone (110.3 g, 1.0 mol) in MeOH (750 mL) was added a solution of freshly cracked cyclopentadiene (66.0 g, 1.0 mol) at -78 ºC in MeOH (90 mL) during 1 h. After the addition had been completed, the reaction mixture was allowed to warm gradually to ambient temperature. Temperature was maintained at that temperature during additional 24 h. The precipitate was collected by suction filtration, and the residue was washed with cold MeOH (3 × 50 mL). The filtrate was concentrated in vacuo, and the solid residue was purified via fractional recrystallization from hexane. Pure 1 (106 g, 61%) was thereby obtained as a yellow microcrystalline solid: mp 67-68 ºC (lit.\[93\] 76-78.5 ºC); IR (KBr) 2953 (s), 3320 (w), 1660 (s), 1601 (s), 1295 (m), 1280 (m), 1060 (m), 875 (m), 720 cm\(^{-1}\) (m); \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 1.34-1.50 (m, 2 H), 3.14-3.16 (m, 2 H), 3.44-
3.48 (m, 2 H), 5.98-5.99 (m, 2 H), 6.52 (s, 2 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 48.2 (d), 48.5 (t), 48.6 (d), 135.2 (d), 141.9 (d), 199.3 (s).

Synthesis of Pentacyclo[5.4.0.0$^2$.6.0$^3$.10.0$^5$.9]undecane-8,11-dione (2). A solution of 1 (34.8 g, 0.2 mol) in acetone (400 mL) was irradiated under argon with a Hanovia medium-pressure Hg lamp for 12 h. The solvent was removed in vacuo. The residue was recrystallized in ethyl acetate, thereby affording a pale yellow solid (33.0 g). This material was dissolved in MeOH (500 mL), charcoal (10 g) was added, and the resulting mixture was refluxed during 30 minutes. The hot solution was filtered, and the filtrate was concentrated in vacuo. Pure 2 (29.0 g, 83%) was thereby obtained a colorless microcrystalline solid: mp 238-239 °C (lit. $^{[93]}$ 242-243 °C); IR (KBr) 2950 (m), 2860 (s), 1460-1430 (w), 2.65 (s, 2 H), 2.74-2.77 (m, 2 H), 2.88-2.89 (m, 2 H), 3.11-3.13 (m, 2 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 38.6 (d), 40.4 (t), 43.7 (d), 44.6 (d), 54.6 (d), 212.1 (s).

exo-8-exo-11-Diallylpentacyclo[5.4.0.0$^2$.6.0$^3$.10.0$^5$.9]undecane-endo-8-endo-11-diol (3). $^{[95,96]}$ To a slurry of Mg (15.0 g, 0.617 mol) in dry Et$_2$O (125 mL) under argon was added dropwise with stirring a solution of freshly distilled allyl bromide (25mL, 35.8 g, 0.296 mol) in dry Et$_2$O (175 mL) during 4 h. At such a rate, the internal reaction temperature did not rise above 5 °C. After the addition of allyl bromide had been completed, the reaction mixture was allowed to stir at ambient temperature during 17 h and then was refluxed during 2 h. The resulting solution was transferred under argon to another 500 mL flask. The reaction mixture was concentrated in vacuo, and dry THF (200 mL) was added. The resulting solution was cooled to 0 °C via application of an
external ice-water bath. To this cooled solution was added slowly with stirring a solution of 2 \[^{93, 94}\] (8.5 g, 49 mmol) in dry THF (50 mL). After the addition had been completed, the ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring under argon during 20 h. The reaction mixture was cooled once again to 0 °C (ice-water bath), and the reaction was quenched via careful addition of saturated aqueous NH\(_4\)Cl (50 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 70 mL). The combined organic layers were dried (MgSO\(_4\)) and filtered, and the filtrate was concentrated \textit{in vacuo}. The residue was recrystallized from hexane, thereby affording 3 (9.2 g, 73%) as a colorless microcrystalline solid: mp 82-83 °C; IR (KBr) 3169 (s), 2976 (s), 1639 (m), 756 cm\(^{-1}\) (m); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.03 (AB, \(J_{AB} = 10.6\) Hz, 1 H), 1.49 (AB, \(J_{AB} = 10.6\) Hz, 1 H), 1.98-2.20 (m, 6 H), 2.35-2.50 (m, 6 H), 4.99-5.09 (m, 4 H), 5.80-6.01 (m, 2 H), 6.43 (br s, peak disappears when sample is shaken with D\(_2\)O, 2 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 33.9 (t), 39.9 (d), 42.8 (d), 444.0 (d), 44.1 (t), 49.1 (d), 77.2 (s), 117.6 (t), 133.8 (d); Anal. Calcd for C\(_{17}\)H\(_{22}\)O\(_2\): C, 79.03; H, 8.58. Found: C, 79.14; H, 8.42.

3,5-Diallyl-4-oxahexacyclo[5.4.1.0\(^2,6\).0\(^3,10\).0\(^5,9\).0\(^8,11\)]dodecane (4). \[^{94, 111}\] To a solution of 3 (6.0 g, 232 mmol) in benzene (120 mL) was added TsOH (350 mg, 1.8 mmol, catalytic amount), and the resulting mixture was refluxed in a Dean-Stark apparatus during 36 h. Additional TsOH (350 mg) was added at 12 h intervals. The reaction mixture was allowed to cool gradually to ambient temperature and then was washed sequentially with 10% aqueous NaHCO\(_3\) (3 × 50 mL), water (3 × 50 mL) and brine (3 × 50 mL). The layers were separated; the organic layer was dried (MgSO\(_4\)) and filtered, and the filtrate was concentrated \textit{in vacuo}. The residue was purified via column
chromatography on silica gel by eluting with 5% EtOAc-hexane. Pure 4 (3.3 g, 60%) was thereby obtained as a colorless oil; IR (film) 3075 (m), 2965 (s), 1640 (m), 997 (s), 910 cm⁻¹ (s); ¹H NMR (CDCl₃) δ 1.41 (AB, JₐB = 10.3 Hz, 1 H), 1.77 (AB, JₐB = 10.3 Hz, 1 H), 2.30 (br s, peak disappears when sample is shaken with D₂O, 2 H), 2.43-2.50 (m, 10 H), 4.94-5.07 (m, 4 H), 5.63-5.83 (m, 2 H); ¹³C NMR (CDCl₃) δ 37.4 (t), 41.6 (d), 43.2 (t), 44.4 (d), 47.6 (d), 58.4 (d), 94.9 (s), 116.8 (t), 134.2 (d); Exact mass (Cl-HRMS) Calcd for C₁₇H₂₀O: [Mr + H]+ m/z 241.1592. Found: [Mr + H]+ m/z 241.1601.

3,5-[2,2′-Bis(hydroxyethyl)]-4-oxahexacyclo[5.4.1.0²,6.0³,10.0⁵,9.0⁸,11]-dodecane (5). [¹¹²] A two-neck round bottom flask equipped with a bubbler and a magnetic stirrer was charged with a solution of 4 (5.95 g, 24.8 mmol) in freshly dried MeOH (200 mL), and the reaction vessel was cooled to -78 ºC via immersion in an external dry ice-acetone cold bath. Ozone was bubbled through this solution until a blue color persisted (ca. 1 h), at which time the ozone source was disconnected from the reaction flask. Argon was bubbled through the cold reaction mixture to purge excess ozone, and this was followed by dropwise addition of Me₂S (5 mL, 68 mmol) with stirring to the cold (-78 ºC) reaction mixture. After the addition of Me₂S had been completed, the external cold bath was removed, and the resulting mixture was allowed to warm gradually to ambient temperature while stirring during 2 h. The reaction mixture was cooled to 0 ºC via application of an external ice-water bath, and NaBH₄ (2.0 g, 53 mmol, excess) was added portionwise to the reaction mixture at such a rate that the internal temperature did not exceed 5 ºC. After all the NaBH₄ had been added, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 4 h. Concentrated aqueous HCl was added dropwise to
adjust the pH to ca. 5.0; then, solid NaHCO₃ (2.0 g, 24 mmol) and solid NaCl (5.0 g, 86 mmol) were added sequentially to the reaction mixture. The resulting mixture was filtered, and the filtrate was concentrated in vacuo. The residue was extracted sequentially with CHCl₃ (3 × 75 mL) and EtOAc (3 × 75 mL). The combined organic layers were washed sequentially with water (3 × 75 mL), and brine (3 × 75 mL), dried (MgSO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 30% EtOAc-hexane. Pure 5 (4.86 g, 79%) was thereby obtained as a colorless microcrystalline solid: mp 153.0-153.5 ºC; IR (film) 3320 (m), 2980 (s), 1365 (m), 1130 (s), 1052 (s), 742 cm⁻¹ (s); ¹H NMR (CDCl₃) δ 1.49 (AB, J_AB = 10.5 Hz, 1 H), 1.85 (AB, J_AB = 10.5 Hz, 1 H), 1.94-2.00 (m, 4 H), 2.37 (s, 4 H), 2.52-2.55 (m, 6 H), 2.86 (s, peak disappears when sample is shaken with D₂O, 2 H); 3.67-3.76 (m, 4 H); ¹³C NMR (CDCl₃) δ 34.2 (t), 41.3 (d), 43.4 (t), 44.0 (d), 47.6 (d), 58.1 (d), 59.9 (t), 96.4 (s); Anal. Calcd for C₁₅H₂₀O₃: C, 72.55; H, 8.12. Found: C, 72.65; H, 8.06.

3,5-Bis[2,2’-(p-toluenesulfonyloxy)ethyl]-4-oxahexacyclo[5.4.1.0²,6.0³,10.0⁵,9]dodecane (6). To a solution of 5 (8.81 g, 35.5 mmol) and NaOH (4.0 g, 100 mmol) in dry CH₂Cl₂ (120 mL) at 0 ºC (ice-water bath) was added TsCl (16.93 g, 88.8 mmol) portionwise during 30 minutes. After the addition of TsCl had been completed, the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 24 h. The reaction mixture was diluted with CH₂Cl₂ (120 mL) and then was extracted sequentially with water (3 × 75 mL) and brine (3 × 75 mL). The organic layer was dried (MgSO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 50% EtOAc-
hexane. Pure 6 (16.2 g, 82%) was thereby obtained as a pale yellow oil, which slowly solidified upon standing at ambient temperature; the resulting solid displayed mp 73-74 °C; IR (KBr) 2957 (m), 2858 (m), 1596 (s), 1493 (m), 1459 (s), 1352 (s), 1291 (m), 1174 (s), 1094 (s), 961 (s), 854 (m), 770 cm⁻¹ (m); ¹H NMR (CDCl₃) δ 1.48 (AB, J₆₋₇ = 10.5 Hz, 1 H), 1.79 (AB, J₆₋₇ = 10.5 Hz, 1 H), 2.07 (t, J = 7.0 Hz, 4 H), 2.33-2.54 (m, 14 H), 4.07 (t, J = 7.0 Hz, 4 H), 7.31 (AB, J₆₋₇ = 8.2 Hz, 4 H), 7.73 (AB, J₆₋₇ = 8.2 Hz, 4 H); ¹³C NMR (CDCl₃) δ 21.6 (q), 31.7 (t), 41.5 (d), 43.5 (t), 44.2 (d), 48.2 (d), 58.7 (d), 67.6 (t), 93.6 (s), 127.9 (d), 129.8 (d), 133.1 (s), 144.8 (s).

Synthesis of Benzyloxyethanol (7).¹¹⁴ A 100 mL round-bottom flask equipped with a thermometer and magnetic stirring bar was charged with KOH (85% pure, 13.3 g, 0.2 mol) and ethylene glycol (28 mL, 0.502 mol). After a small amount of water had been removed by distillation, benzyl chloride 13.3 mL (0.20 mol) was added dropwise with stirring during 30 minutes, while the temperature of the reaction mixture was maintained at 85-95 °C. After the addition of benzyl chloride had been completed, the temperature of the reaction mixture was increased to 130 °C and was maintained at this temperature during 2 h. The mixture then was allowed to cool to ambient temperature and then was diluted by addition of water (50 mL). The insoluble oily product was extracted with ether (3 × 100 mL). The organic phase was washed with brine (3 × 100 mL), dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. Pure 7 (18.8 g, 62%) was thereby obtained as a colorless viscous oil. ¹H NMR (CDCl₃) δ 2.10 (s, peak disappears when sample is shaken with D₂O, 1 H), 3.50-3.61 (m, 2 H), 3.69-3.78 (m, 2 H), 4.55 (s, 2 H), 7.31-7.39 (m, 5 H); ¹³C NMR (CDCl₃) δ 62.6 (t), 72.1 (t), 73.9 (t), 128.5 (d), 129.1 (d), 138.7 (s).
Synthesis of Benzyloxyethyl-\(p\)-toluenesulfonate (8) To a stirred solution of 2-benzyloxyethanol (4.56 g, 30 mmol) and triethylamine (20 mL, 143 mmol) was added a solution of \(p\)-toluenesulfonyl chloride (6.86 g, 36 mmol) in 40 mL of CH\(_2\)Cl\(_2\) at ambient temperature, and the resulting mixture was stirred overnight. Water (100 mL) was added to the mixture, the layers were separated, and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (3 × 100 mL). The combined organic layers were washed sequentially with water (3 × 50 mL), and brine (3 × 50 mL) and dried over Na\(_2\)SO\(_4\) and filtered and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 70% EtOAc-hexane. Pure 8 (7.8 g, 85%) was thereby obtained as a colorless oil product. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 2.41 (s, 3 H), 3.61-3.67 (m, 2 H), 4.115-4.21 (m, 2 H), 4.46 (s, 2 H), 7.26-7.30 (m, 7 H), 7.78 (AB, \(J_{AB} = 8.3\) Hz, 2 H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 22.3 (q), 67.4 (t), 69.2 (t), 73.1 (t), 127.5 (d), 127.7 (t), 127.8 (d), 128.3 (d), 129.7 (d), 132.9 (s), 137.5 (s), 144.7 (s).

3,5-Bis[2-(2’-benzyloxyethoxy)ethyl]-4-oxahexacyclo[5.4.1.0\(^2\).6\(^3\).10\(^5\).9\(^8\).11\(^1\)]dodecane (9). A suspension of NaH (60% dispersion in mineral oil, 660 mg, 16.4 mmol) in dry THF (10 mL) under argon was cooled to 0 °C via application of an external ice-water bath. To this solution was added dropwise with stirring a solution of 8 (1.85 g, 7.45 mmol) in DMF (10.0 mL). The resulting white suspension was stirred at 0 °C for 10 minutes, at which time the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring during 2 h. The reaction mixture again was cooled to 0 °C via application of an external ice-water bath. To the cooled reaction mixture was added dropwise stirring a solution of 1-(benzyoxy)-2-(\(p\)-toluenesulfonyloxy)ethane (5.02 g, 16.4 mmol) in DMF (10 mL). The resulting
suspension was stirred at 0 ºC for 10 minutes, at which time the external cold bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature and was stirred at the temperature during 2 days. The reaction mixture was concentrated in vacuo, and ice-water (50 mL) was added to the residue. The resulting aqueous suspension was extracted with CH₂Cl₂ (3 × 40 mL). The combined organic layers were dried over MgSO₄ and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 20% EtOAc-hexane. Pure 9 (3.28 g, 85%) was thereby obtained as a colorless viscous oil; IR (film) 2951 (s), 2870 (s), 1450 (m), 736 cm⁻¹ (s); ¹H NMR (CDCl₃) δ 1.45 (AB, J₆₇ = 10.3 Hz, 1 H), 1.82 (AB, J₆₇ = 10.3 Hz, 1 H), 2.10 (t, J = 7.14 Hz, 4 H), 2.36 (br s, 2 H), 2.48-2.54 (m, 6 H), 3.51-3.59 (m, 12 H), 4.55 (s, 4 H), 7.27-7.34 (m, 10 H); ¹³C NMR (CDCl₃) δ 32.8 (t), 41.8 (d), 43.4 (t), 44.5 (d), 48.4 (d), 58.8 (d), 68.4 (t), 69.5 (t), 70.2 (t) 73.2 (t), 94.4 (s); Anal. Calcd for C₃₃H₄₀O₅: C, 76.71; H, 7.80. Found: C, 76.48; H, 7.70.

3,5-Bis[2-(2’-hydroxyethoxy)ethyl]-4-oxahexacyclo[5.4.1.0².6.0⁵.9.0⁸.11]dodecane (10). To a solution of 9 (1.70 g, 3.29 mmol) in EtOH (50 mL) was added 10% Pd-C (180 mg), and the resulting mixture was hydrogenated by using H₂ (g) (55 psi) on a Parr shaker apparatus during 24 h. The reaction mixture was filtered through a bed of Celite® to remove the catalyst. The filtrate was concentrated in vacuo, thereby affording 10 (1.0 g, yield 90%) as a colorless viscous oil. IR (film) 3416 (s), 2945 (s), 1367 (w), 1128 (s), 1066 cm⁻¹ (s); ¹H NMR (CDCl₃) δ 1.47 (AB, J₆₇ = 10.3 Hz, 1 H), 1.83 (AB, J₆₇ = 10.3 Hz, 1 H), 2.04 (t, J = 6.6 Hz, 4 H), 2.35 (br s, 2 H), 2.50-2.56 (m, 6 H), 2.94 (s, peak disappears when sample is shaken with D₂O, 2 H), 3.47-3.67 (m, 12 H); ¹³C NMR
(CDCl$_3$) δ 32.3 (t), 41.6 (d), 43.4 (t), 44.2 (d), 48.1 (d), 58.5 (d), 61.5 (t), 67.9 (t), 71.7 (t), 94.9 (s); Anal. Calcd for C$_{19}$H$_{28}$O$_5$: C, 67.83; H, 8.39. Found: C, 67.60; H, 8.23.

3,5-Bis[2-(2’-p-toluenesulfonyloxyethoxy)ethyl]-4-oxahexacyclo [5.4.1.0$^{2,6}$.0$^{3,10}$.0$^{5,9}$.0$^{8,11}$]dodecane (11). A solution of p-TsCl (697 mg, 3.66 mmol) in dry pyridine (6 mL) was placed in a 100 mL round bottom flask that previously had been thoroughly flushed with argon. This solution was cooled to 0 °C via application of an external ice-water bath. To this cooled solution was added dropwise with stirring a solution of 10 (410 mg, 1.22 mmol) in dry CH$_2$Cl$_2$ (10 mL) during 15 minutes. After the addition of 10 had been completed, the external ice-water bath was removed, and the reaction mixture was allowed to warm gradually to ambient temperature while stirring overnight. The reaction mixture was poured into ice-water (150 mL), and the resulting aqueous suspension was extracted with CH$_2$Cl$_2$ (2 × 200 mL). The organic layer was washed with ice-cold 5.0 M HCl (2 × 50 mL), dried (MgSO$_4$), and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 50% EtOAc-hexane. Compound 11 (590 mg, 75%) was thereby obtained as a colorless viscous oil. IR (film) 2858 (s), 1356 (s), 1178 (s), 1024 (m), 927 (s), 665 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) δ 1.44 (AB, $J_{AB} = 10.3$ Hz, 1 H), 1.80 (AB, $J_{AB} = 10.3$ Hz, 1 H), 1.99 (t, $J = 7.0$ Hz, 4 H), 2.30 (br s, 2 H), 2.42 (s, 10 H), 2.49-2.58 (m, 2 H), 3.45 (t, $J = 7.0$ Hz, 4 H), 3.56 (t, $J = 4.6$ Hz, 4 H), 4.11 (t, $J = 4.6$ Hz, 4 H), 7.31 (AB $J_{AB} = 8.6$ Hz, 2 H), 7.77 (AB, $J_{AB} = 8.6$ Hz, 2 H); $^{13}$C NMR (CDCl$_3$) δ 21.6 (q), 32.5 (t), 41.7 (d), 43.4 (t), 44.4 (d), 48.3 (d), 58.7 (d), 68.1 (t), 68.3 (t), 69.2 (t), 94.2 (s), 127.9 (d), 129.8 (d), 132.9 (s), 144.7 (s); Anal. Calcd for C$_{33}$H$_{40}$O$_9$S$_2$: C, 61.47; H, 6.25; Found: C, 61.62; H, 6.08.
Synthesis of 12. A solution of diol 5 (4.96 g, 20.0 mmol) in dioxane THF (50.0 mL) was cooled to 0 °C via application of an external ice-water bath. Sodium hydride (1.00 g, 60% dispersion in mineral oil) was added portionwise with stirring to the reaction mixture during 30 minutes. After the addition of NaH had been completed, the reaction mixture was stirred for an additional 30 minutes. A solution of allyl bromide (4.0 g, 33.0 mmol) in THF (10.0 mL) was added dropwise with stirring to the reaction mixture during 30 minutes. After the addition of allyl bromide had been completed, the reaction mixture was stirred during an additional 8 h. The reaction mixture then was concentrated in vacuo, and EtOAc (40 mL) was added to the residue. The resulting solution was washed sequentially with water (3 × 150 mL) and brine (3 × 150 mL). The aqueous layer was dried over MgSO₄ and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 10% EtOAc-hexane. Pure 12 (6.0 g, 92%) was thereby obtained as a colorless viscous oil. ¹H NMR (CDCl₃) δ 1.46 (AB, J_AB = 10.2 Hz, 1 H), 1.82 (AB, J_AB = 10.2 Hz, 1 H), 2.06-2.16 (m, 4 H), 2.35 (br s, 2 H), 2.50-2.66 (m, 6 H), 3.51-3.59 (m, 4 H), 3.94-3.99 (m, 4 H), 5.13-5.32 (m, 4 H), 5.81-6.02 (m, 2 H); ¹³C NMR (CDCl₃) δ 32.7 (t), 41.7 (d), 43.3 (t), 44.4 (d), 48.3 (d), 58.8 (d), 67.3 (t), 71.7 (t), 94.3 (s), 116.5 (t), 134.8 (d).

Synthesis of Tetraethylene glycol ditoluenesulfonates (13) To a stirred solution of NaOH (1.6 g, 40 mmol) in water (6 mL) was added a solution of tetraethylene glycol (1.942 g, 10 mmol) in 80% aqueous THF (10 mL). The resulting reaction mixture was cooled to −20 °C via application of an external ice–salt bath. A solution of TsCl (4.28 g, 22 mmol) in THF (8 mL) was added dropwise in such a way that the temperature did not exceed 5 °C. After the addition of TsCl had been completed, the resulting mixture was...
stirred for an additional 6.5 h. The mixture was allowed to stand for a few minutes to allow the layers to separate. The aqueous layer was extracted with EtOAc (4 × 15 mL) and then was washed sequentially with water (4 × 30 mL), and brine (4 × 30 mL). The organic extract was dried (MgSO₄) and filtered and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 30% EtOAc-hexane. Pure 13 (4.27 g, 85%) was thereby obtained as a colorless viscous oil. IR (film) 3320 (m), 2980 cm⁻¹ (s); ¹H NMR (CDCl₃) δ 2.40 (s, 6 H), 3.52 (s, 8 H), 3.63 (t, J = 4.48 Hz, 4 H), 4.11 (t, J = 4.48 Hz, 4H), 7.30 (AB, JₐB = 8.32 Hz, 4 H), 7.75 (AB, JₐB = 8.32 Hz, 4 H); ¹³C NMR (CDCl₃) δ 21.6 (q), 68.6 (t), 69.2 (t), 70.4 (t), 70.6 (t), 127.9 (d), 129.7 (d), 132.8 (s), 144.7 (s).

Synthesis of 1,11-Bis[4-(benzyloxy)phenoxy]-3,6,9-trioxaundecane (14). A solution of 4-(benzyloxy)phenol (4.0 g, 20 mmol) in CH₃CN (200 mL) was added during 20 minutes to a suspension of K₂CO₃ (19.4 g, 140 mol) in CH₃CN (200 mL) at ambient temperature. After the addition of 4-(benzyloxy)phenol had been completed, the temperature of the reaction mixture was increased to 70 °C, and the temperature was maintained at this temperature during additional 30 minutes. A solution of tetraethylene glycol ditosylate (5.2 g, 10 mmol) in CH₃CN (100 mL) then was added dropwise with stirring to the reaction mixture during 30 minutes. After the addition had been finished, the resulting mixture was refluxed during 2 days. The reaction mixture was allowed to cool to ambient temperature, and then was filtered, and the residue was washed with CH₃CN (2 × 50 mL). The combined filtrates were concentrated in vacuo, and CH₂Cl₂ (150 mL) was added to the residue. The resulting solution was extracted with 1 M NaOH solution (150 mL). The organic layer was sequentially washed with water (3 × 50 mL)
and brine (3 × 50 mL), and dried (NaSO₄) and filtered, and the filtrate was concentrated \textit{in vacuo}. The residue was purified via column chromatography on silica gel by eluting with 30% EtOAc-hexane. Pure 14 (3.35 g, 60\%) was thereby obtained as a colorless microcrystalline solid: mp 77-78 °C (lit.\textsuperscript{[7, 8]} 78-80 °C ); IR (KBr) 3032 (w), 2930 (w), 2876 (s), 1591 (w), 1505 (s), 1453 (s), 1382 (m), 1290 (m), 1227 (s), 1135 (s), 1108 (s), 960 (m), 924 (m), 836 (s), 766 (m), 737 cm\(^{-1}\) (s); \textsuperscript{1}H NMR (CDCl\(_3\)) \(\delta\) 3.69 (s, 8 H), 3.80 (t, 4 H), 4.05 (t, 4 H), 4.98 (s, 4 H), 6.84 (m, 8 H), 7.28-7.40 (m, 10 H); \textsuperscript{13}C NMR (CDCl\(_3\)) \(\delta\) 68.1 (t), 69.8 (t), 70.7 (t), 70.8 (t), 115.6 (d), 117.8 (d), 127.5 (d), 127.9 (d), 128.5 (d), 137.3 (s), 153.1 (s), 153.1 (s).

Synthesis of 1,11-Bis(4-(hydroxyphenoxy)-3,6,9-trioxaundecane (15).\textsuperscript{[115]} A solution of 14 (2.6 g, 466 mmol) in 50% CHCl\(_3\)-MeOH (40 mL) was subjected to hydrogenation on 10% Pd/C (260 mg, catalytic amount) by using H\(_2\) (g) (55 psi) on a Parr Shaker apparatus during 24 h. The reaction mixture was filtered through a bed of Celite\textsuperscript{®} to remove spent catalyst. The solid residue in the funnel was washed with CHCl\(_3\) (3 × 50 mL), and the filtrate was concentrated \textit{in vacuo}. Compound 15 (1.74 g, 99\%) was thereby obtained as a viscous pale yellow oil (1.74 g, 99\%), which was employed immediately in the next step without further purification; IR (film) 3352 (br, s), 2921 (s), 1603 (w), 1511 (s), 1454 (s), 1351 (m), 1296 (m), 1234 (s), 1126 (s), 1064 (s), 949 (m), 829 (s), 756 cm\(^{-1}\) (s); \textsuperscript{1}H NMR (CDCl\(_3\)) \(\delta\) 3.67 (s, 8 H), 3.72-3.76 (m, 4 H), 4.10 (br s, peaks disappears when sample is shaken with D\(_2\)O, 2 H), 6.61-6.72 (m, 8 H); \textsuperscript{13}C NMR (CDCl\(_3\)) \(\delta\) 67.9 (t), 69.8 (t), 70.5 (t), 115.6 (d), 116.0 (d), 150.2 (s), 152.3 (s).
Synthesis of a Cage-annulated Crown Ether 16. A suspension of 11 (1.12 g, 1.74 mmol), 15 (658 mg, 1.74 mmol), KI (664 mg, 4.0 mmol), and K$_2$CO$_3$ (2.76 g, 20 mmol) in CH$_3$CN (40 mL) was refluxed during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The residue was washed with CH$_3$CN (2 × 50 mL). The combined filtrates were concentrated in vacuo, and CH$_2$Cl$_2$ (150 mL) was added to the residue. The resulting solution was washed sequentially with water (3 × 50 mL) and brine (3 × 50 mL), dried (MgSO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 50% EtOAc-hexane. Pure 16 (604 mg, 52%) was thereby obtained as a colorless viscous oil; IR (film) 2932 (s), 2870 (s), 1509 (s), 1545 (s), 1539 (m), 1229 (s), 1129 (s), 1065 (s), 929 (s), 896 (m), 828 (s), 755 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.44 (AB, $J_{AB}$ = 10.3 Hz, 1 H), 1.78 (AB, $J_{AB}$ = 10.3 Hz, 1 H), 2.01-2.52 (m, 8 H), 3.58-3.81 (m, 22 H), 3.98-4.04 (m, 10 H), 6.77-6.80 (m, 8 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 32.6 (t), 42.8 (d), 43.4 (t), 44.4 (d), 48.4 (d), 58.8 (d), 68.1 (t), 68.2 (t), 69.1 (t), 69.7 (t), 69.8 (t), 70.8 (t), 94.5 (s), 115.5 (d), 115.6 (d), 153.0 (s), 153.1 (s). Exact mass (CI-HRMS) Calcd for C$_{39}$H$_{50}$O$_{10}$: [M$^+ + H]^+$ m/z 679.3404. Found: [M$^+ + H]^+$ m/z 679.3484.

Synthesis of a Cage-annulated Crown Ether 17. A suspension of 6 (726 mg, 1.3 mmol), 15 (493 mg, 1.3 mmol), and K$_2$CO$_3$ (3.64 g, 37.3 mmol) in CH$_3$CN (80 mL) was refluxed during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The residue was washed with CH$_3$CN (2 × 50 mL). The combined filtrates were concentrated in vacuo, and CH$_2$Cl$_2$ (150 mL) was added to the residue. The resulting solution was washed sequentially with water (3 × 50 mL) and brine (3 × 50 mL), dried (MgSO$_4$) and filtered, and the filtrate was concentrated in vacuo.
The residue was purified via column chromatography on silica gel by eluting with 50% EtOAc-hexane. Pure 17 (446 mg, 58%) was thereby obtained as a colorless viscous oil; IR (film) 2953 (s), 2870 (s), 1596 (w), 1508 (s), 1470 (m), 1360 (s), 1234 (s), 1132 (s), 1067 (s), 824 (s), 751 cm\(^{-1}\) (m); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.50 (AB, \(J_{AB} = 9.6\) Hz, 1 H), 1.85 (AB, \(J_{AB} = 9.6\) Hz, 1 H), 2.12-2.20 (m, 4 H), 2.40 (s, 2 H), 2.59 (s, 6 H), 3.87 (s, 8 H), 3.81 (t, \(J = 4.5\) Hz, 4 H), 3.96-4.07 (m, 8 H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 32.5 (t), 41.2 (d), 43.4 (t), 43.7 (d), 48.1 (d), 58.9 (d), 66.2 (t), 67.9 (t), 69.5 (t), 70.4 (t), 70.6 (t), 94.1 (s), 115.2 (d), 115.7 (d), 152.7 (s), 153.3 (s). Exact mass (CI-HRMS) Calcd for C\(_{35}\)H\(_{42}\)O\(_8\): \([M_r + H]^+\) \(m/z\) 591.2958. Found: \([M_r + H]^+\) \(m/z\) 591.2950.

Synthesis of a Cage-annulated Crown Ether 18. A suspension of 11 (849 mg, 1.32 mmol), 20 \(^{[117]}\) (440 mg, 1.32 mmol), and K\(_2\)CO\(_3\) (3.20 g, 23.5 mmol) in CH\(_3\)CN (60.0 mL) was refluxed during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The residue was washed with CH\(_3\)CN (2 \(\times\) 50 mL). The combined filtrates were concentrated in vacuo, and CH\(_2\)Cl\(_2\) (150 mL) was added to the residue. The resulting solution was washed sequentially with water (3 \(\times\) 50 mL) and brine (3 \(\times\) 50 mL), dried (MgSO\(_4\)) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 50% EtOAc-hexane. Pure 18 (568 mg, 68%) was thereby obtained as a colorless viscous oil; IR (film) 2939 (s), 2862 (s), 1591 (s), 1500 (s), 1453 (s), 1362 (m), 1328 (m), 1255 (m), 1117 (m), 1053 (s), 925 (m), 740 cm\(^{-1}\) (m); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.44 (AB, \(J_{AB} = 10.3\) Hz, 1 H), 1.80 (AB, \(J_{AB} = 10.3\) Hz, 1 H), 2.01-2.11 (m, 4 H), 2.35 (s, 2 H), 2.47-2.54 (m, 6 H), 3.64-3.67 (t, \(J = 7.26\) Hz, 4 H), 3.77-3.90 (m, 12 H), 4.09-4.18 (m, 8 H), 6.83-6.90 (m, 8 H); \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 32.7 (t), 41.7 (d), 43.4 (t), 44.3 (d), 48.2 (d),
58.9 (d), 68.6 (t), 69.1 (t), 69.4 (t), 69.7 (t), 70.9 (t), 94.2 (s), 114.0 (d), 114.8 (d), 121.3 (d), 121.5 (d), 148.9 (s), 149.2 (s). Exact mass (CI-HRMS) Calcd for C$_{37}$H$_{46}$O$_{9}$: [M$\,\,+$ H]$^+$ m/z 635.32201. Found: [M$\,\,+$ H]$^+$ m/z 635.32210.

Synthesis of a Cage-annulated Crown Ether 19. A suspension of 6 (556 mg, 1.0 mmol), 20 (334 mg, 1.0 mmol), and K$_2$CO$_3$ (2.72 g, 20.0 mmol) in CH$_3$CN (50.0 mL) was refluxed during 4 days. The reaction mixture was allowed to cool gradually to ambient temperature and then was filtered. The residue was washed with CH$_3$CN (2 $\times$ 50 mL). The combined filtrates were concentrated in vacuo, and CH$_2$Cl$_2$ (150 mL) was added to the residue. The resulting solution was washed sequentially with water (3 $\times$ 50 mL) and brine (3 $\times$ 50 mL), dried (MgSO$_4$) and filtered, and the filtrate was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 50% EtOAc-hexane. Pure 19 (284 mg, 52%) was thereby obtained as a colorless microcrystalline solid: mp 49-50 °C; IR (KBr) 2933 (s), 2871 (s), 1592 (s), 1499 (s), 1469 (s), 1389 (m), 1329 (m), 1113 (m), 1068 (m), 748 cm$^{-1}$ (m); $^1$H NMR (CDCl$_3$) $\delta$ 1.32 ($AB$, $J_{AB}$ = 10.3 Hz, 1 H), 1.75 ($AB$, $J_{AB}$ = 10.3 Hz, 1 H), 2.17 (s, 2 H), 2.29-2.41 (m, 4 H), 2.56 (s, 4 H), 2.99 (t, $J$ = 3.6 Hz, 2 H), 3.81 (s, 4 H), 3.93 (t, $J$ = 3.6 Hz, 4 H), 4.08-4.13 (m, 8 H), 6.84 (m, 8 H); $^{13}$C NMR (CDCl$_3$) $\delta$ 32.6 (t), 42.3 (d), 43.4 (t), 44.9 (d), 49.0 (d), 59.5 (d), 65.2 (t), 68.7 (t), 70.3 (t), 71.1 (t), 94.7 (s), 112.1 (d), 112.7 (d), 120.5 (d), 121.0 (d), 148.5 (s), 148.7 (s). Anal. Calcd for C$_{33}$H$_{38}$O$_7$: C, 72.51; H, 7.01. Found: C, 72.36; H, 6.85.

Synthesis of $N,O,O'$-Tritosyldiethanolamine (22). To a solution of diethanolamine (10.5 g, 0.10 mol) was dissolved in CH$_2$Cl$_2$ (50 mL) and triethylamine
(45 mL) at ambient temperature was added TsCl (58.2 g, 0.31 mol) in small portions with stirring. After the addition had been completed, the resulting mixture was stirred at ambient temperature during an additional 24 h. The white precipitate generated during the reaction was removed via vacuum filtration. The solid residue was washed sequentially with water (2 × 100 mL), 5% HCl solution (2 × 100 mL), saturated NaHCO₃ solution (3 × 100 mL), and brine (3 × 100 mL). The solid was air dried and then was purified via fractional recrystallization from EtOH. Pure 22 (51.0 g, 90%) was thereby obtained as a colorless microcrystalline solid: mp 93-94 °C; (lit. [120] 78-79 °C); ¹H NMR (CDCl₃) δ 2.40 (s, 3 H), 2.43 (s, 6 H), 3.34 (t, J = 6.0 Hz, 4 H), 4.08 (t, J = 6.0 Hz, 4 H), 7.31 (t, J = 8.3 Hz, 6 H), 7.58 (4AB, J_AB = 8. 3 Hz, 2 H), 7.73 (AB, J_AB = 8.3 Hz, 4 H); ¹³C NMR (CDCl₃) δ 21.5 (q), 21.6 (q), 48.4 (t), 68.2 (t), 127.2 (d), 127.9 (d), 129.9 (d), 130.0 (d), 132.4 (s), 135.2 (s), 144.1 (s), 145.2 (s).

Synthesis of 4′,4′′-Ditosylbis(3-piperazinylpropyl)methylamine (23). To a refluxing mixture of 3,3'-diaminodipropyl-N-methylamine (21, 2.90 g, 20.0 mmol) and K₂CO₃ (27.6 g, 20.0 mmol) in CH₃CN (200 mL) was added dropwise with stirring a solution of N-tosyl-2.2'-ditosyloxydiethyl-N-tosylamine [104-108] (22, 23.4 g, 40.0 mmol) during 7 h. After the addition of 22 had been completed, the resulting suspension was refluxed during an additional 12 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was gravity-filtered. The filtrate was concentrated in vacuo, and the residue was purified via fractional recrystallization from EtOH. Pure 23 (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), 68
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 (AB, $J_{AB}$ = 8.1 Hz, 4 H), 7.56 (AB, $J_{AB}$ = 8.1 Hz, 4 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$_5$O$_4$S$_2$: C, 58.85; H, 7.66. Found: C, 58.70; H, 7.47. Exact mass (CI-HRMS) Calcd for C$_{29}$H$_{45}$N$_5$O$_4$S$_2$: [M$+\text{H}^+$]$^+$ m/z 592.29912. Found: [M$+\text{H}^+$]$^+$ m/z 592.29907.

Synthesis of Bis(3-piperazinylpropyl)methylamine (24). A solution of 23 (1.77 g, 3.0 mmol) in 96% H$_2$SO$_4$ (15 mL) was heated at 110 °C during 70 h. The resulting mixture was allowed to cool gradually to ambient temperature and then was added dropwise with stirring to 200 mL diethyl ether. During this addition, a viscous oil gradually separated from the reaction mixture. The supernatant liquid was decanted, and the residue was washed with Et$_2$O (3 × 50 mL). The residue was dissolved in a minimum quantity of water (10 mL), and the resulting solution was rendered alkaline via careful addition of saturated aqueous NaOH (ca. 20 mL). The resulting aqueous suspension was extracted with CHCl$_3$ (3 × 100 mL). The combined organic layers were dried (Na$_2$SO$_4$) and filtered, and the filtrate was concentrated in vacuo. Compound 24 (600 mg, 71%) was thereby obtained as a colorless oil. This material was used as obtained without further purification; IR (KBr) 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); $^1$H 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\(_2\)O, 2 H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 24.4 (t), 42.3 (q), 45.9 (t), 54.4 (t), 55.7 (t), 57.2(t). Exact mass (CI-HRMS) Calcd for C\(_{15}\)H\(_{33}\)N\(_5\): [\( M_f + H \)]\(^+ \) m/z 284.2814. Found: [\( M_f + H \)]\(^+ \) m/z 284.2807.

Synthesis of 25. To a suspension of 24 (493 mg, 1.74 mmol) and K\(_2\)CO\(_3\) (2.70 g, 19.8 mmol) in refluxing CH\(_3\)CN (100 mL) was added dropwise with stirring a solution 6 (968 mg, 1.74 mmol) in CH\(_3\)CN (80 mL) during 7 h. After the addition of 6 had been completed, the resulting mixture was refluxed during 12 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was gravity-filtered. The residue was washed with CH\(_3\)CN (3 \( \times \) 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\(_2\)Cl\(_2\). Pure 25 (698 mg, 81%) was thereby obtained as a colorless microcrystalline solid: mp 113-114 °C; IR (KBr) 2 943 (m), 2807 (m), 1458 (s), 1373 (m), 1297 (s), 1204 (w), 1159 (s), 1091 (w), 1003 (m), 918 (m), 870 (m), 749 cm\(^{-1}\) (m); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 1.50 (AB, \( J_{AB} = 10.5 \) Hz, 1 H), 1.58-1.72 (m, 4 H), 1.91-1.98 (m, 4 H), 2.23 (s, 3 H), 2.34-2.58 (m, 36 H); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 23.6 (t), 28.6 (t), 41.3 (d), 43.0 (q), 43.5 (d), 43.8 (d), 47.7 (d), 52.2 (t), 3.4 (t), 53.9 (t), 54.5 (t), 54.8 (t), 58.3 (t), 94.9 (s). Exact mass (CI-HRMS) Calcd for C\(_{30}\)H\(_{49}\)N\(_5\)O: [\( M_f + H \)]\(^+ \) m/z 496.4015. Found: [\( M_f + H \)]\(^+ \) m/z 496.4008.
Synthesis of 2-Bromo-1,3-Bisbromomethylbenzene (26). To a solution of 2-bromo-
m-xylene (9.25 g, 0.05 mol) in CCl₄ (100 mL) was added N-bromosuccinimide (17.8 g, 0.1 mol) and benzoyl peroxide (605 mg, 2.5 mmol). Nitrogen gas was bubbled through the reaction mixture during 30 minutes to purge dissolved oxygen. The resulting solution was refluxed during 24 h, and then was allowed to cool gradually to ambient temperature. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel by eluting with 10% EtOAc-hexane. Pure 26 (7.7 g, 45%) was thereby obtained as a colorless microcrystalline solid: mp 98-99 ºC; ¹H NMR (CDCl₃) δ 4.62 (s, 4 H), 7.26-7.32 (m, 1 H), 7.38-7.41 (m, 2 H); ¹³C NMR (CDCl₃) δ 3.8 (t), 126.6 (s), 128.0 (d), 131.4 (d), 138.4 (s).

Synthesis of a Cage-annulated Crown Ether 27. To a solution of 10 (336 mg, 1.0 mmol) in dry THF (100 mL) was added NaH (400 mg, 60% dispersion in mineral oil, 10 mmol), and the resulting solution was refluxed under N₂ during 3 h. The reaction mixture then was allowed to cool gradually to ambient temperature. To the reaction mixture was added dropwise with stirring a solution of 26 (343 mg, 1.0 mmol) in THF (20 mL) during 30 minutes, and the resulting mixture was refluxed during 12 h. The reaction mixture was allowed to cool gradually to ambient temperature and water (2.0 mL) was added dropwise with stirring to quench the reaction. After the mixture had become clear, an additional quantity of water (30 mL) was added. The resulting mixture was extracted with EtOAc (4 × 50 mL). The combined extracts were washed sequentially with water (2 × 30 mL), and brine (3 × 30 mL), dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel by eluting with 30% EtOAc-hexane. Pure 27 (134 mg, 26%) was thereby
obtained as a colorless microcrystalline solid: mp 90-91 °C; IR (KBr) 2865 (s), 1455 (w), 1422 (w), 1357 (m), 1292 (s), 1129 (s), 1109 (s), 1018 (m), 796 (m), 770 cm\(^{-1}\) (m); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 1.33 (AB, \(J_{AB} = 10.3 \text{ Hz, } 1 \text{ H}\)), 3.21 (AB, \(J_{AB} = 10.3 \text{ Hz, } 1 \text{ H}\)), 1.92 (t, \(J = 6.2 \text{ Hz, } 4 \text{ H}\)), 2.20 (s, 2 H), 2.30 (s, 6 H), 3.47 (t, \(J = 6.2 \text{ Hz, } 4 \text{ H}\)), 3.56-3.60 (m, 4 H), 3.69-3.73 (m, 4 H), 7.28-7.42 (m, 3 H); \(^{13}\)C NMR (CDCl\(_3\)) \(\delta\) 32.6 (t), 41.6 (d), 43.3 (t), 44.2 (d), 48.0 (d), 58.9 (d), 67.8 (t), 69.5 (t), 69.6 (t), 72.7 (t), 94.2 (s), 124.8 (s), 126.8 (d), 129.3 (d), 138.3 (s). Exact mass (CI-HRMS) Calcd for C\(_{27}\)H\(_{33}\)BrO\(_5\): \([M + H]^+\) \(m/z\) 517.1590. Found: \([M + H]^+\) \(m/z\) 517.1573. Anal. Calcd for C\(_{27}\)H\(_{33}\)BrO\(_5\): C, 62.70; H, 6.50. Found: C, 62.52; H, 6.53.

Synthesis of a podand 28. To a solution of 2-(2-chloroethoxy)ethanol (630 mg, 5.0 mmol) in dry THF (100 mL) was added NaH (1.20 g, 60% dispersion in mineral oil, 30 mmol), and the resulting solution was refluxed under N\(_2\) during 3 h. The reaction mixture then was allowed to cool gradually to ambient temperature. To the reaction mixture was added dropwise with stirring a solution of 26 (1.72 g, 5.0 mmol) in THF (20 mL) during 30 minutes, and the resulting mixture was refluxed during 3 days. The reaction mixture was allowed to cool gradually to ambient temperature and saturated aqueous NH\(_4\)Cl solution (40 mL) was added dropwise with stirring to quench the reaction. The resulting mixture was allowed to stand 10 minutes. Two layers were separated; the water layer (bottom layer) was washed with EtOAc (2 \(\times\) 50 mL). The organic layer (upper layer) solvent was dried (MgSO\(_4\)) and filtered. The solvent was concentred in vacuo, and the residue was dissolved in EtOAc (100 mL). The combined extracts were washed sequentially with water (2 \(\times\) 100 mL) and brine (2 \(\times\) 100 mL), dried (Na\(_2\)SO\(_4\)) and filtered, and the filtrate was concentred in vacuo. The residue was
purified by column chromatography on silica gel by eluting with 40% EtOAc-hexane.

Pure 28 (1.81 g, 84%) was thereby obtained as a colorless viscous oil. IR (neat) 2871 (s), 1459 (m), 1450 (m), 1428 (m), 1351 (s), 1298 (s), 1250 (m), 1143 (s), 1104 (s), 1024 (m), 788 cm⁻¹ (m); ¹H NMR (CDCl₃) δ 3.62 (t, J = 5.6 Hz, 4 H), 3.72-3.79 (m, 12 H), 4.63 (s, 4 H), 7.29-7.40 (m, 3 H); ¹³C NMR (CDCl₃) δ 42.7 (t), 70.1 (t), 70.6 (t), 71.4 (t), 72.8 (t), 122.8 (s), 127.2 (d), 128.0 (d), 137.9 (s). Exact mass (CI-HRMS) Calcd for C₁₆H₂₃BrCl₂O₄: [M⁺ + H]+ m/z 428.0152. Found: [M⁺ + H]+ m/z 428.0157.

Synthesis of a Cage-annulated Crown Ether 29. To a solution of 5 (496 mg, 2.0 mmol) in dry THF (100 mL) was added NaH (obtained as a 60% dispersion in mineral oil, 480 mg, 12 mmol), and the resulting solution was refluxed under N₂ during 3 h. The reaction mixture then was allowed to cool gradually to ambient temperature. To the reaction mixture was added dropwise with stirring a solution of 28 (1.72 g, 5.0 mmol) in THF (20 mL) during 30 minutes, and the resulting mixture was refluxed during 3 days. The reaction mixture was allowed to cool gradually to ambient temperature; subsequently, the stirred reaction mixture was quenched via dropping addition of saturated NH₄Cl solution (40 mL). The resulting mixture was allowed to stand 10 minutes, during which time two layers were separated. The water layer (bottom layer) was washed with EtOAc (2 × 50 mL). The organic layer (upper layer) solvent was removed in vacuo. The residue was dissolved EtOAc (100 mL). The combined EtOAc solutions were washed sequentially with water (2 × 100 mL) and brine (2 × 100 mL), dried (Na₂SO₄) and filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel by eluting with 30% EtOAc-hexane.

Pure 29 (800 mg, 66%) was thereby obtained as a colorless viscous oil. IR (neat) 2952
NMR (CDCl₃) δ 1.32 (AB, JAB = 10.3 Hz, 1 H), 1.67 (AB, JAB = 10.3 Hz, 1 H), 1.98-2.09 (m, 8 H), 3.49-3.79 (m, 20 H), 4.63 (s, 4 H), 7.32-7.49 (m, 3 H); ¹³C NMR (CDCl₃) δ 32.9 (t), 41.8 (d), 43.2 (t), 44.4 (d), 48.2 (d), 58.8 (d), 68.4 (t), 70.1 (t), 70.2 (t), 70.7 (t), 71.1 (t), 72.5 (t), 94.3 (s), 122.3 (s), 127.3 (d), 127.7 (d), 137.9 (s). Exact mass (CI-HRMS) Calcd for C₃₁H₄₁BO₇: [Mᵋ + H]⁺ m/z 605.2114. Found: [Mᵋ + H]⁺ m/z 605.2113.

2.5 References


