



# Ag<sup>+</sup> Selective Macrocycles Containing Soft Ligating Moieties and Regulation of Ag<sup>+</sup> Binding

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**Abstract.** Strategies are discussed for the design of Ag<sup>+</sup> selective macrocyclic molecules, together with the structures of the Ag<sup>+</sup> complexes. One of the most useful and basic methods is to incorporate heteroatoms, such as nitrogens and sulfurs, and heterocycles into the macrocyclic framework. A side arm containing the heteroatom also enhances Ag<sup>+</sup> selectivity tremendously. A sulfide chain outside or inside the macroring contributes to highly selective Ag<sup>+</sup> binding. Soft alkenyl and alkynyl carbons arranged in a macrocyclic fashion bind Ag<sup>+</sup> preferentially. Regulation of Ag<sup>+</sup> binding by redox reactions and by metal ligation is also described.

**Key words:** silver ion, crown ether, macrocyclic molecule, soft ligand.

## 1. Introduction

Macrocyclic hosts containing oxygen atoms, such as crown ethers, cryptands, etc., strongly bind alkali and alkaline earth metal ions [1, 2]. The binding selectivity is due to the ring size, the number of the oxygen atoms and the heteroatoms, and the spatial arrangement of the ligating groups.

The thermodynamic and kinetic binding properties of the crown ethers are easily modulated by introducing a polyether side chain into the cavity [3–5]. In the modified crown ethers, e.g. lariat ethers, synergistic coordination of the ring oxygen and the additional oxygen atoms of the side chain to metal ions can take place. Consequently, various macrocyclic hosts with diverse affinities toward metal ions and other functions [6, 7] should be readily synthesized by changing the combination of the atoms forming the ring framework and the side chain.

Recently, various macrocyclic hosts have been designed to capture heavy metal ions selectively. The basic strategies of the design are to replace some of the oxygens by other heteroatoms, such as nitrogen and sulfur atoms, and to add one or several side chains to the cyclic framework. Among heavy metal ions, selective Ag<sup>+</sup> binding has attracted significant attention. Strong and specific Ag<sup>+</sup> recognition is important for <sup>111</sup>Ag-based radioimmunotherapy [8–10] and may probably be useful for photographic technology, recovery of Ag<sup>+</sup> from waste water, and development of Ag<sup>+</sup> sensors.

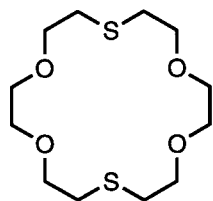
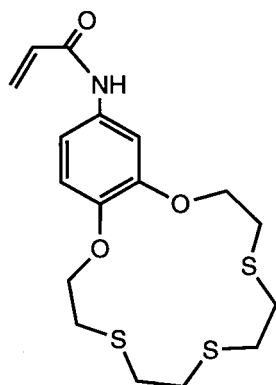
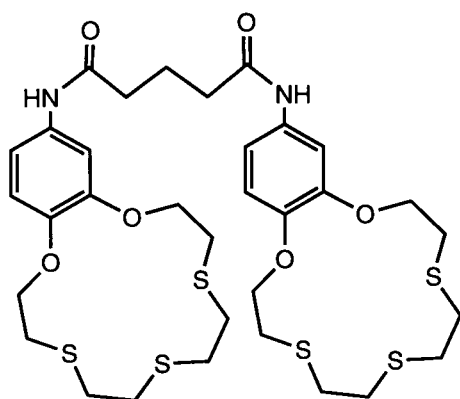
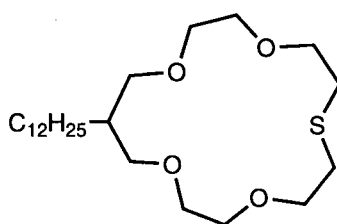
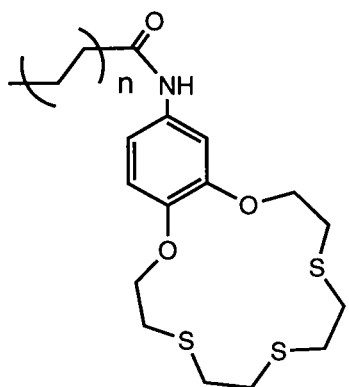
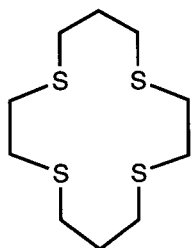
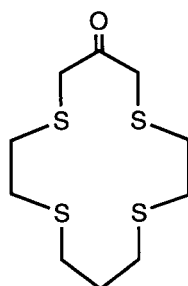
This review discusses research concerning the design of the  $\text{Ag}^+$  ion selective macrocycles which possess soft ligating groups, such as a heteroatom, a heterocyclic ring of the cyclic framework or a side chain, and  $\pi$  bonds. Regulation of  $\text{Ag}^+$  binding by redox reactions and by metal ligation is also described.

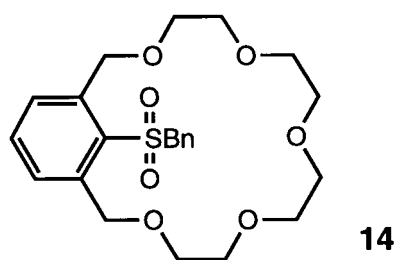
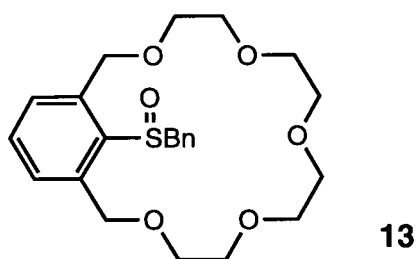
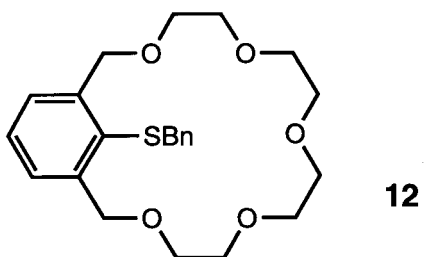
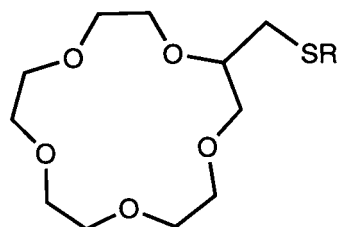
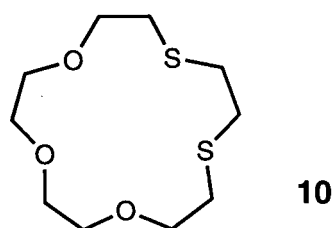
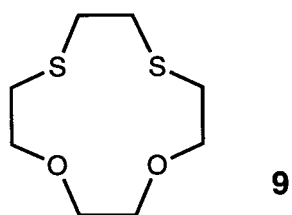
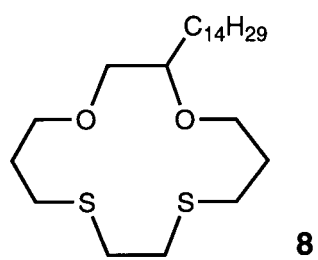
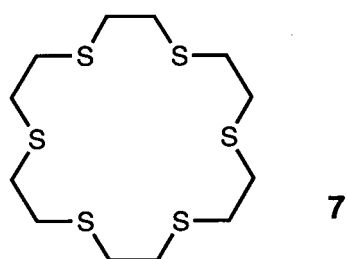
## 2. Thiocrown Ethers

Substitution of sulfur atoms for oxygen atoms of the crown rings increases  $\text{Ag}^+$  binding preference, while the affinity for alkali metal ions decreases tremendously [1, 2]. Thiocrown ethers **1–4** [11–13] containing one or more sulfur atoms show a good  $\text{Ag}^+$  selectivity. Polymer **5** with similar thiocrown ethers binds  $\text{Ag}^+$  and  $\text{Hg}^{2+}$  as well [12]. Thiocrown ethers in which all the oxygen atoms are replaced by sulfurs often show less selectivity than partially substituted ones. For instance, compound **6a** extracts  $\text{Ag}^+$ ,  $\text{Hg}^{2+}$  and  $\text{Pb}^{2+}$ , although the extractability toward  $\text{Ag}^+$  is the highest [12]. In the 1 : 1 complex of  $\text{Ag}^+$  and thiocrown ether **6b** incorporating a propan-2-one unit, the tetrahedrally coordinated  $\text{Ag}^+$  ion is not bound in the cavity, probably because of a tendency to place the sulfurs preferentially exodentate to the crown ring [14]. However, a  $\text{Ag}^+$  inclusion complex which has an octahedral geometry at the metal center is obtained with thiocrown **7** [15]. Applications to a silver ion selective electrode and an optode are accomplished by using **4** [13], and **8** [16], respectively. PVC membrane electrodes based on **9** and **10** provide good sensitivities and selectivities toward both  $\text{Hg}^{2+}$  and  $\text{Ag}^+$  [17].

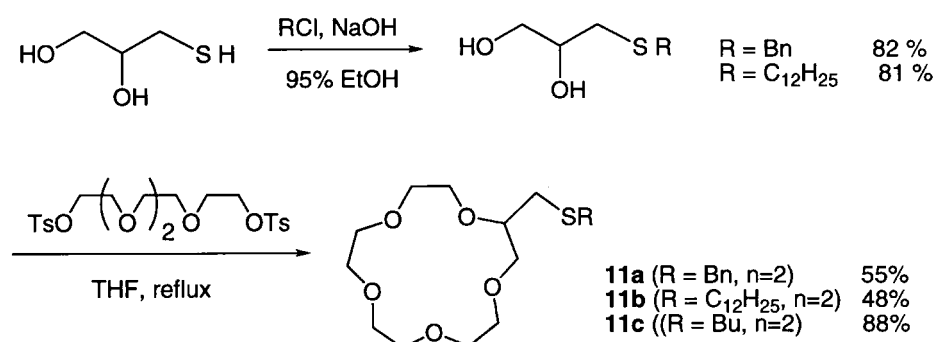
## 3. Macrocycles with a Side Arm Containing a Sulfur Atom

Introduction of a sulfide arm into the crown ethers effectively enhances the  $\text{Ag}^+$  selectivity [18, 19]. Thiolariat ethers **11**, which consist of a 15-crown-5 ring and a sulfide group as a side chain, show a remarkably high  $\text{Ag}^+$  selectivity in solvent extraction and ion transport through a liquid membrane. For metal binding the thiolariat ethers may possess an advantage over the crown ethers containing one or more sulfur atoms in the cyclic framework, because the replacement of the oxygen atoms by the sulfur atoms of a crown ring gives rise to an unfavorable entropic change upon complexation with a metal ion [8, 20]. In addition, the thiolariat ethers are easily prepared from thioglycerol (Scheme 1) [21]. It is strongly suggested that the extraordinarily high selectivity results from the synergistic coordination of the oxygen atoms of the 15-crown-5 ring and the sulfur atom to  $\text{Ag}^+$ . Interestingly, this selectivity of the thiolariat ethers is caused by only one sulfur atom in the vicinity of the cavity, although the atom is located outside the cyclic framework. A sulfide arm located inside the crown ring also results in a high  $\text{Ag}^+$  affinity in solvent extraction. The  $\text{Ag}^+$  selectivity of **12** is much higher than that of **13** and **14** [22]. As seen in **11**, a simultaneous coordination of the sulfur and oxygens of **12** to  $\text{Ag}^+$  is suggested.

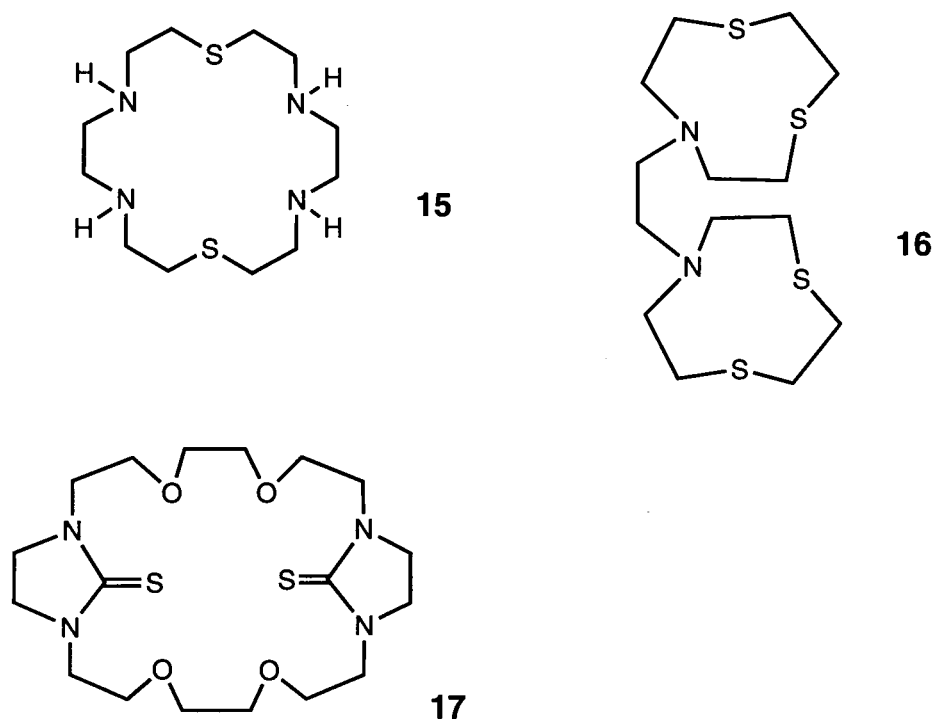
**1****2****3****4****5****6a****6b***Formulae 1–6.*



*Formulae 7–14.*



Scheme 1. Synthesis of thiolariat ethers.

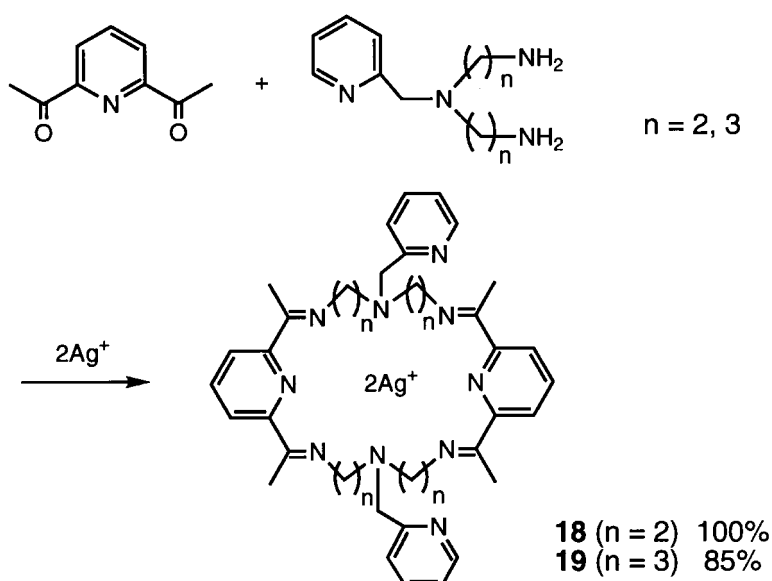


Formulae 15–17.

#### 4. Macrocycles Containing Nitrogen Atoms

Combination of nitrogens and sulfurs is also useful and important in preparing Ag<sup>+</sup> binders. X-ray crystallography clearly reveals that one Ag<sup>+</sup> ion is coordinated by the sulfur and nitrogen atoms of macrocycles **15** and **16** [9]. Macrocyclic thiourea **17** gives the 1 : 1 Ag<sup>+</sup> complex [23].

Template synthesis of macrocycles **18** and **19** containing pyridine and imine moieties is achieved in high yields from the reaction of 2,6-diacetylpyridine with

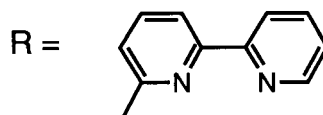
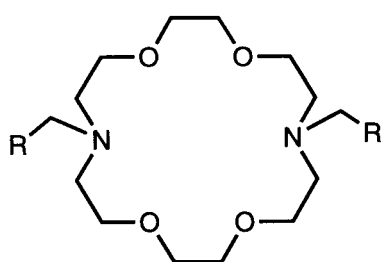
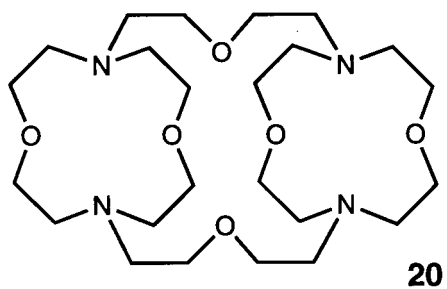
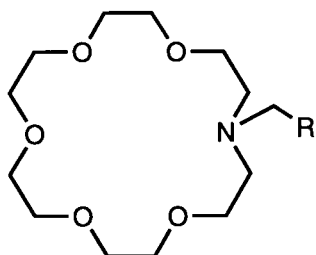
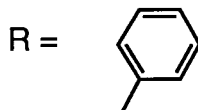
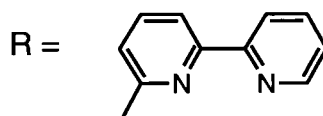
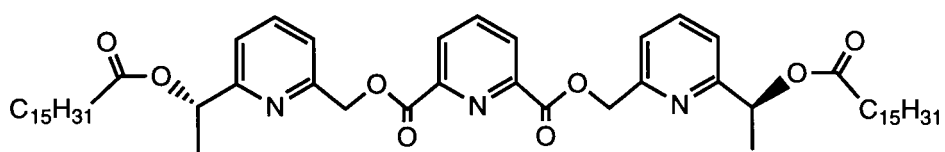
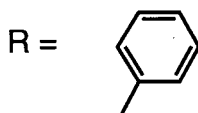


Scheme 2. Template synthesis of **18** and **19**.

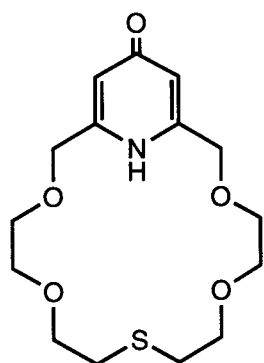
*N,N*-bis-(*n*-aminoalkyl)-2-(aminomethyl)pyridine in the presence of  $\text{Ag}^+$  (Scheme 2) [24]. A molecular cleft is obtained due to the formation of the 1 : 2 complex between **18** (or **19**) and  $\text{Ag}^+$ . In contrast, a  $\text{Ba}^{2+}$  ion affords the 1 : 1 complex related to **18** in 78% yield, probably because of the larger ionic radius than that of  $\text{Ag}^+$  [24]. Complexation with more  $\text{Ag}^+$  ions (1 : 3 complex) is also seen in cryptand **20** [25]. Single and double armed azacrown ethers can be employed for  $\text{Ag}^+$  selective extraction. Hosts **22**, **24** have higher  $\text{Ag}^+$  selectivity than bipyridine hosts **21**, **23** [26]. The host **21** shows a high affinity for  $\text{Ba}^{2+}$  and  $\text{Pb}^{2+}$ . In **23** moderate extraction percentages are observed for  $\text{K}^+$  and  $\text{Ba}^{2+}$ . By contrast, **21**–**24** carry alkali and alkaline earth metal cations more effectively through a liquid membrane than  $\text{Ag}^+$ . However, podand **25**, consisting of three pyridine nuclei, exhibits high  $\text{Ag}^+$  selective transport ability [27].

It is very difficult to achieve  $\text{Ag}^+$  selectivity over  $\text{Hg}^{2+}$  by using macrocyclic hosts containing heteroatoms. This is due to the fact that  $\text{Hg}^{2+}$  usually has a much larger affinity for soft and hard donors than  $\text{Ag}^+$ , and the ionic radius is similar to that of  $\text{Ag}^+$ . However, pyridonothia-18-crown-6 (**26**) binds  $\text{Ag}^+$  preferably to  $\text{Hg}^{2+}$  with the interactions of the pyridone portion [28]. Pyridine-diamide-diester ionophores **27** and **28** show a high  $\text{Ag}^+$  selectivity in extraction and transport [29, 30]. The substituents of the amide groups play an important role in binding  $\text{Ag}^+$ . The amide carbonyl groups are positioned toward the cavity by the substituents to provide a suitable arrangement of the heteroatoms in the cavity for  $\text{Ag}^+$  selectivity.

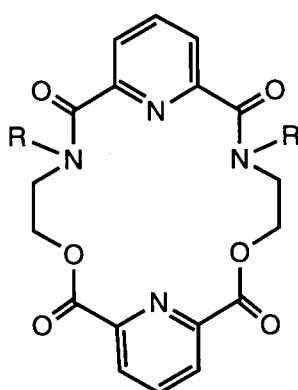
Unique and highly cooperative  $\text{Ag}^+$  binding was reported. The cyclic marine peptide **29** forms the  $\text{Ag}^+$ –**29** complex with a 4 : 2 stoichiometry in the crystalline

**22****24****24**

Formulae 20–25.

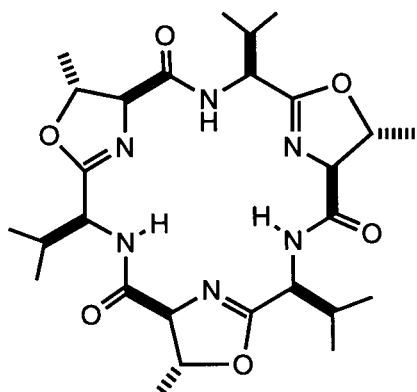


26



27 R = Me

28 R = Bn



29

Formulae 26–29.

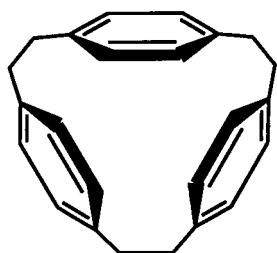
state and in solution [31]. In  $^1\text{H}$  NMR titration, signals assigned only to free **29** and the 4 : 2 complex are evident.

### 5. Macrocycles Without Heteroatoms

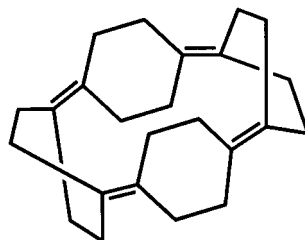
Soft alkenyl and alkynyl carbons interact weakly with a  $\text{Ag}^+$  ion. However, efficient coordination can be attained when several  $\pi$ -bonds are arranged appropriately. The stability constant of [2,2,2]paracyclophane **30** and  $\text{Ag}^+$  is ca. 100-fold larger than those of the usual complexes of arenes such as benzene and toluene [32–34]. Tetraene **31** gives a 1 : 1  $\text{Ag}^+$  complex which is considerably stable to air, heat, light, and hydrolytic solvents [35]. Deltaphane **32** also produces a highly stable  $\text{Ag}^+$  complex where the  $\text{Ag}^+$  ion is exterior to the cyclophane moiety [36]. A light-sensitive sandwich complex is given by the reaction of macrocyclic triyne **33** with  $\text{Ag}^+$  in THF in low yields [37]. The complex is dissociated in toluene, probably due to complexation between toluene and the  $\text{Ag}^+$ .

Kinetically stable 1 : 1  $\text{Ag}^+$  complexes of calixspherands **34** have been obtained, although **34a,b** do not possess a soft ligand [10]. The half lives of the

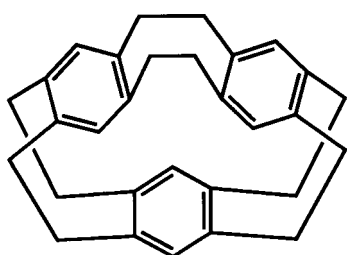




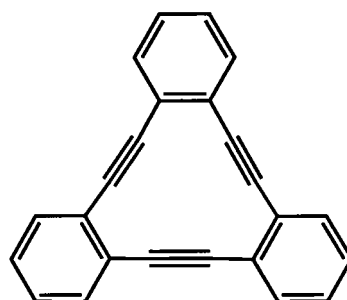
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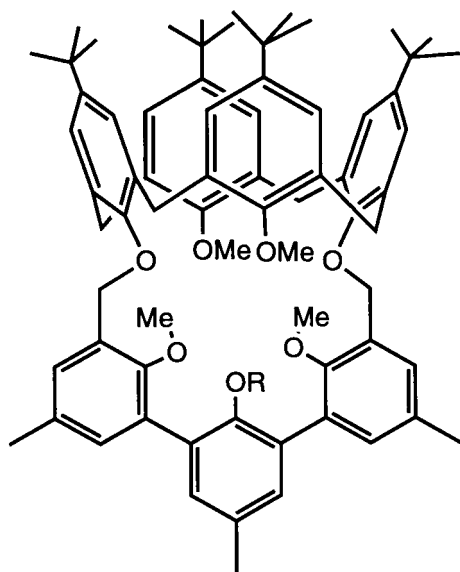
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32



33

**34a** R = Et**34b** R = <sup>i</sup>Pr*Formulae 30–34.*

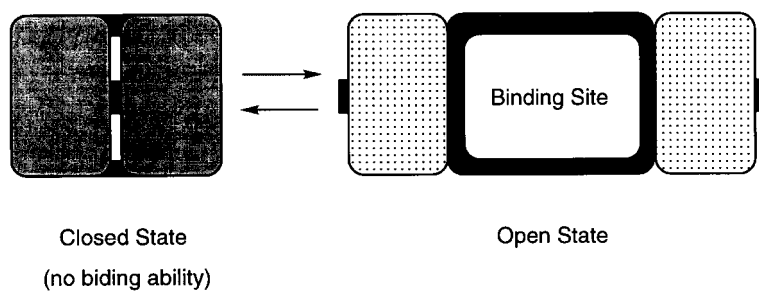


Figure 1. Interconversion between closed and open states by gating.

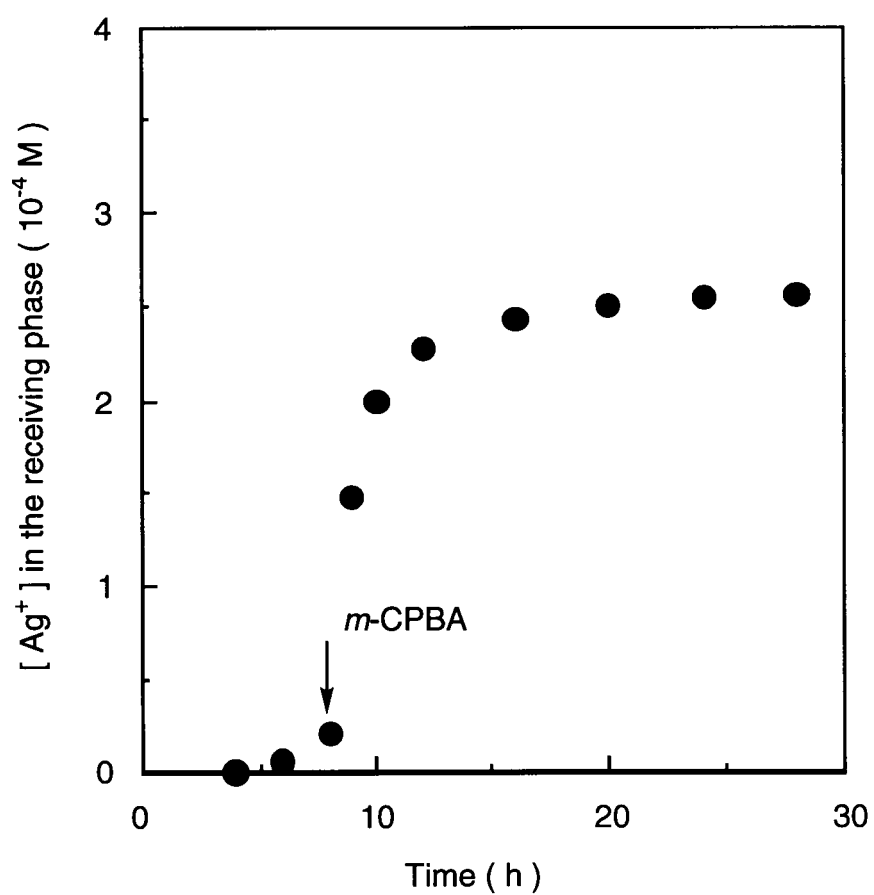
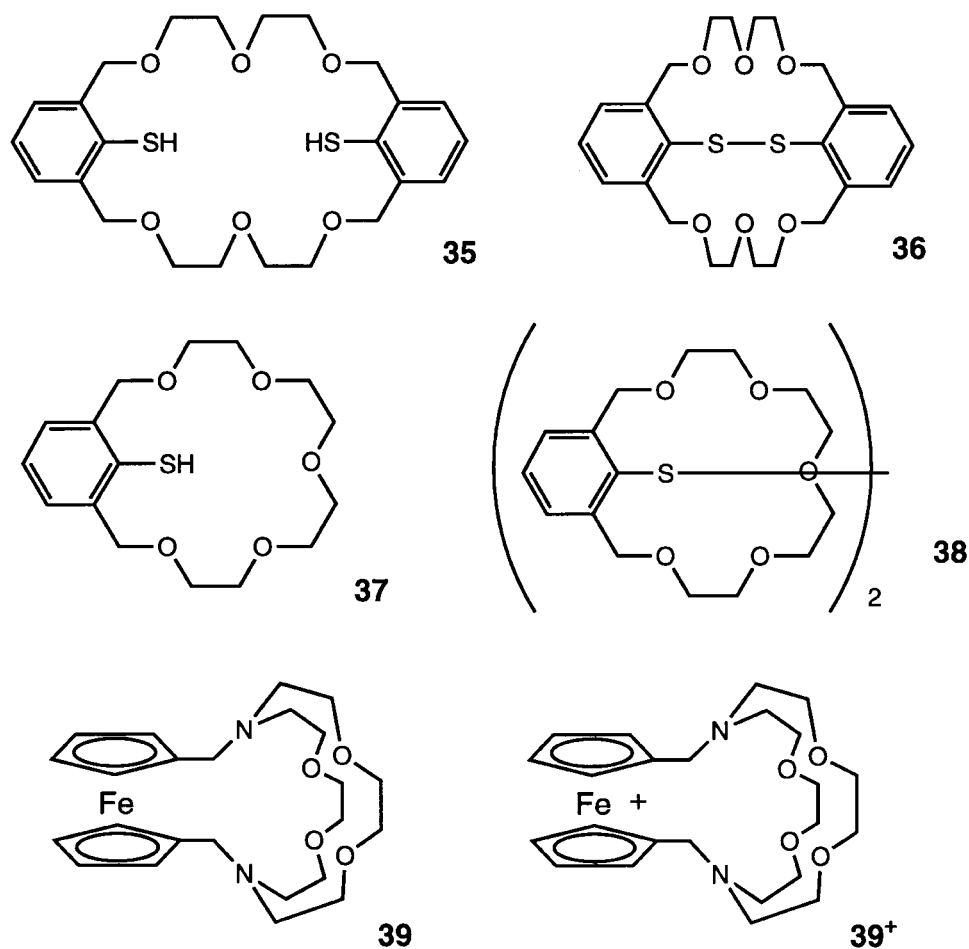


Figure 2. Effect of *m*-CPBA as an oxidant on Ag<sup>+</sup> transport with **35** [36].



Formulae 35–39.

decomplexation of Ag<sup>+</sup>-**34a** and Ag<sup>+</sup>-**34b** in CDCl<sub>3</sub> saturated with D<sub>2</sub>O are 51 and 131 h, respectively. This stability probably results from the fact that the cavity is complementary to Ag<sup>+</sup> and highly shielded from solvent.

## 6. Regulation of Ag<sup>+</sup> Binding

A new and general concept, gating of a cavity to regulate ion and molecular recognition, has been proposed. The open state binds a guest effectively in the cavity, whereas the closed state does not capture the guest at all (Figure 1). Hence, all-or-none-type switching of the recognition can be achieved by the use of this principle. This strategy was applied to highly selective Ag<sup>+</sup> binding [38]. The host **35** containing two thiol groups (an open state) extracts and transports Ag<sup>+</sup> very selectively. Alkali metal ions are not captured by **35**. In contrast, the corresponding

closed host **36** shows no affinity for metal ions, because the cavity is closed by the disulfide linkage. It is noteworthy that the hosts **35** and **36** are interchanged quantitatively by the suitable redox reactions. When *m*-chloroperbenzoic acid (*m*-CPBA) is added as an oxidant to a solution of **35** as an organic phase of the transport experiment, an abrupt increase of  $\text{Ag}^+$  in the receiving phase is observed followed by termination of the transport (Figure 2). This is rationalized by the fact that  $\text{Ag}^+$  bound by **35** is released by the conversion to **36**, which has no transport ability. Intermolecular interconversion is also useful and effective to control  $\text{Ag}^+$  transport. Compounds **37** and **38** are interconvertible [39]. A similar response to the oxidant during the transport is performed, but the response is slightly less sensitive than the intramolecular system (**35–36**) described above.

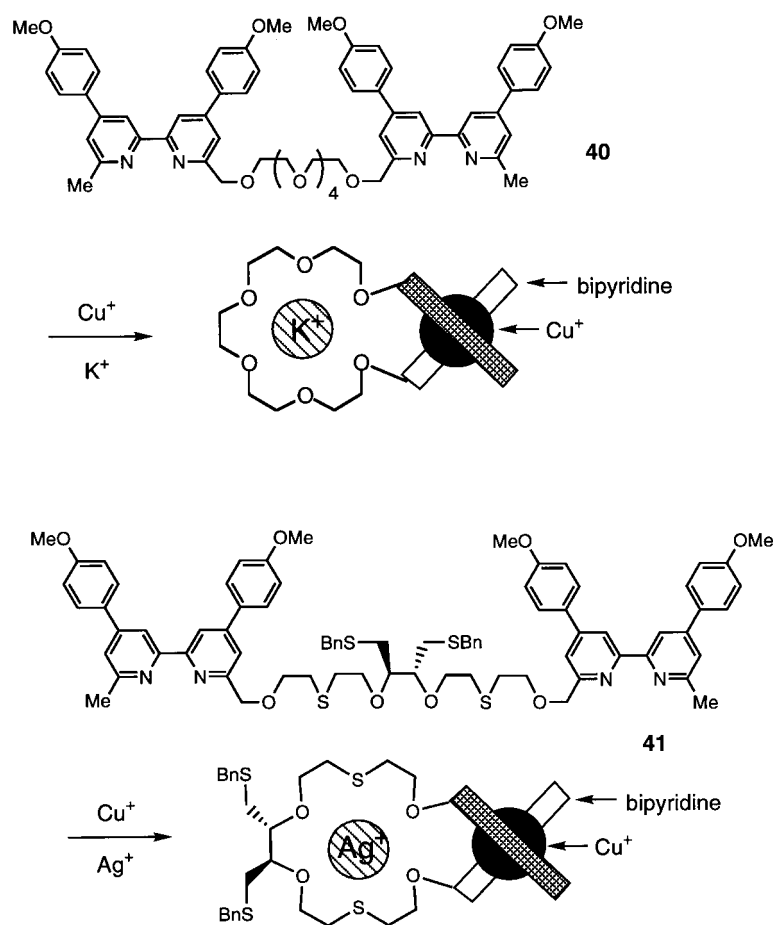
Gokel reported that ferrocenyldimethyl[2.2]cryptand (**39**) is a redox-switched receptor for  $\text{Ag}^+$  [40]. The binding constant of **39** for  $\text{Ag}^+$  is much higher ( $2 \times 10^5$ -fold) than that of the oxidized form **39**<sup>+</sup>. A direct, stabilizing Ag-Fe interaction is confirmed by the large  $\text{Ag}^+$  binding constant and electrochemistry.

We reported the first example of pseudocrown ether **40**- $\text{Cu}^+$  which shows high  $\text{K}^+$  selectivity in ion transport (Scheme 3) [41–44]. Upon formation of the  $\text{Cu}^+$  complex the linear compound **40** is changed quantitatively into the cyclic polyether (pseudocrown ether) and the  $\text{K}^+$  selectivity is enhanced dramatically. This is a nice example of an artificial allosteric system. When some of the oxygens are replaced by sulfurs, pseudothiacrown ethers are generated by the complexation with  $\text{Cu}^+$  [45]. In the absence of  $\text{Cu}^+$  the bipyridine moieties of host **41** bind  $\text{Ag}^+$ . 2,2'-Bipyridine and 1,10-phenanthroline derivatives are well known to complex with  $\text{Ag}^+$  [46–48]. However, in the presence of both  $\text{Ag}^+$  and  $\text{Cu}^+$  the pseudothiacrown is produced to give the cavity where  $\text{Ag}^+$  is bound. Enhancement (*positive allostery*) of the transport ability toward  $\text{Ag}^+$  is successfully accomplished by the formation of the pseudothiacrown ether.

## 7. Conclusions and Future Directions

High  $\text{Ag}^+$  selectivity has been achieved by using the various compounds described above, although a much more specific and strong  $\text{Ag}^+$  binder is still required for radioimmunotherapy. Importantly, a  $\text{Ag}^+$  ion can be differentiated from other metal ions, whose ionic radii are similar to that of  $\text{Ag}^+$ , by appropriate combination of heteroatoms of the hosts and the spatial arrangement of the ligating moieties. It is interesting and noticeable that the ring size of the host is not the only critical factor for  $\text{Ag}^+$  selectivity. Certain macrocyclic hosts bearing a small cavity, and even a linear host, can bind one or more  $\text{Ag}^+$  ions with the one host molecule. These results will open a new way to construct specific hosts for other heavy metal ions.

Apparently, the concept of regulating  $\text{Ag}^+$  recognition by redox reactions can be applied to other regulating systems for ions, and even for molecular recognition. On the basis of this concept, it may probably be possible to synthesize a heavy-metal-ion-mediated-catalysis system with a recognition site whose catalytic activities are



Scheme 3. Formation of pseudocrown and pseudothiacrown ethers.

controlled by redox reactions. Hence, although this review deals with designing Ag<sup>+</sup> binders and regulation of Ag<sup>+</sup> recognition, the strategies shown here contain enormous potentialities for other novel host–guest chemistry.

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