Metal-Assisted Crown Ethers for Evolutionary Design of Metal Hosts

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Abstract. The idea of metal-organization of linear molecules into macrocyclic structures is introduced. This idea has been tested on various oligoether compounds containing two chelate ligands at the terminals. Chelate ligands include β-diketone, salicylic ester, catechol, and salicylic acid. The first two were organized into neutral metallocrown ethers, which showed much better extraction behavior towards alkali and alkaline earth metal cations than conventional monocyclic crown ethers. The last two were organized into 'ate'-type complexes and incorporated metal ions into a newly formed anionic cavity. The stability constants were estimated for salicylate complexes and revealed excellent binding and selectivity. The presence of dipolar O^-—M^{n+} bonds in the metal organization method is concluded to contribute significantly to better interaction with metal ions through enthalpic stabilization.

Key words: crown ether, metal organization, ate complex, NMR titration, dipolar bond, enthalpic interaction.

1. Introduction

Crown ether chemistry, introduced by C.J. Pedersen in 1967, was further developed by J.M. Lehn, D.J. Cram and many other research groups [1]. This is not only related directly to the chemistry of efficient and selective binding of metal ions or ionic species, but created, in a more general sense, a new field of chemistry based on molecular recognition. Therefore, host–guest chemistry and later supramolecular chemistry have their origins in this field.

The leading philosophy has been a so-called 'preorganization' principle. In order to extract metal ions efficiently from aqueous into organic phases, the binding site must be sufficiently attractive for metal ions, which are stabilized by ion-dipolar interaction in the aqueous phase. Desolvation and transfer into the organic phase occur only when the host can provide a stabilizing interaction sufficient to compensate the hydration energy. This becomes possible by assembling several coordinating atoms and creating an appropriate arrangement around the metal ion. This is an entropy-consuming process and is characterized by a negative entropy

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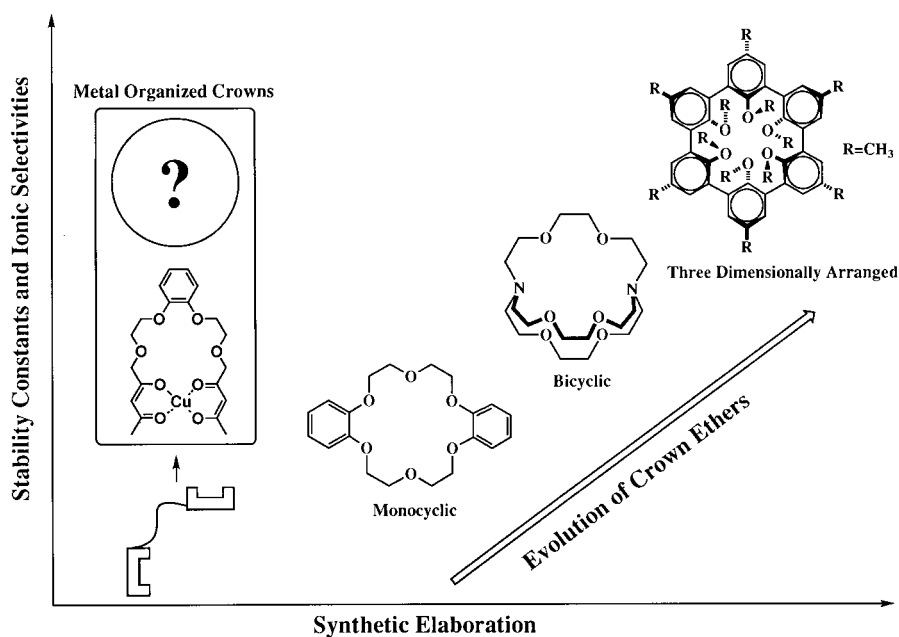
Figure 1. Chemical evolution of crown ethers and introduction of the idea of metal-organized crown.

change. If the binding site is constructed by chemical bond formation, with due consideration for such arrangement, the guest binding process does not need to pay the negative entropy price any longer and is stabilized by the favorable free energy term. Such a guest-binding space was first monocyclic, but bicyclic skeletons soon appeared and ensured more favorable and selective binding of the guests. Further improvement of the guest binding was obtained by restricting the conformational freedom of host molecules to afford rigid cages. This line of reasoning led to great advances in the chemistries of crown ether and other molecular recognition phenomena over the last few decades. Better preorganized, i.e., necessarily more and more sophisticated, hosts have been synthesized primarily via chemical bond formation (Figure 1).

This line, however, must be abandoned at some stage, when the synthetic burden could no longer be compensated by the improved binding characteristics. Alkali and alkaline earth metal ions play important roles in physiology. Their behavior is characterized by rapid association and dissociation kinetics. However, the large stability constants obtained by such rigid hosts do not result from favorable association, but rather extremely slow dissociation kinetics. So-called excellent hosts retain metal ions in their sophisticated cages, for more than even 1000 years, once entrapped [2]. In order to liberate metal ions from the host, the host structure must be destroyed by combustion or other drastic treatment. This may be attractive only
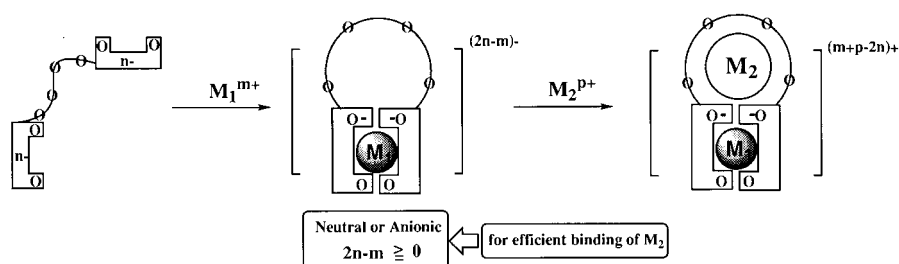
Figure 2. Neutral or 'ate' complexes from intramolecular cyclization of bischelate oligoether.

for the recovery of gold or other precious metal ions, but not for the chemistry of abundant metal ions.

Thus, some sort of new concept must be introduced for the design of efficient and readily obtainable host molecules. The simplest class of compounds are linear oligoethers. However, these are certainly not efficient in the binding of metal ions because they must be re-organized into a macrocyclic structure on complexation. This re-organization could be effected by using transition metals, when strong chelate ligands are attached to both terminals of the linear oligoethers. In the synthetic approach, the cyclization is usually conducted under high-dilution conditions, and this process prohibits the efficient preparation of the macrocyclic hosts. Transition metals do the job of this intramolecular cyclization of an α, ω-bis(chelate) even better under dilute conditions, since strong chelate ligands are characterized by large formation constants with appropriate transition metals [3].

It should be critical to use anionic chelates rather than neutral ones to obtain efficient hosts from linear [4] as well as macrocyclic oligoethers [5] by restricting the conformations. Positive charges are carried by transition metals on complexation and must at least be neutralized, because the resulting hosts are designed for metal ions having positive charges. Even if the resulting organized hosts are neutral as a whole, the charge on the metal–chelate bonds never vanishes but remains dipolar, leaving δ- charges on the chelate atom sides. If appropriately designed, chelate atoms carrying δ- charges could be arranged around the newly forming metal binding side. Another smart solution may be the use of an 'ate' complex, which assembles a larger number of anionic charges than that required for the neutralization of the metal charges. These hosts carrying δ- or net negative charges are expected to provide a strong binding force due to enthalpic stabilization arising from charge–charge or charge–dipole interactions. The situation is illustrated in Figure 2.
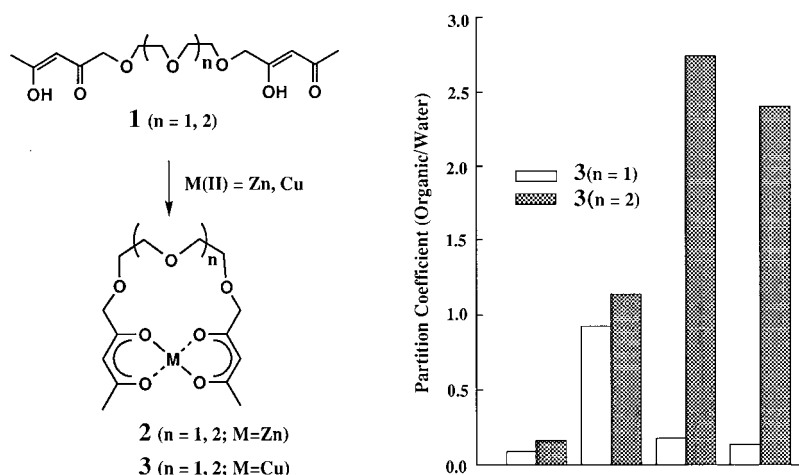
Figure 3. Metal organization of terminal bis(β-diketone) and efficiency in metal picrate extraction.

2. Results and Discussion

2.1. NEUTRAL METAL-ORGANIZED CROWN ETHER

2.1.1. β-Diketone

A β-diketone is an excellent chelating agent for various transition metal ions, and the complexes have been employed in a variety of applications. Therefore, β-diketone units were attached to both terminals of di- and triethylene glycol via an ether linkage to afford **1** ($n = 1$ and 2, respectively) [6]. These linear α, ω-bis(β-diketone)s were subjected to an intramolecular cyclization reaction simply by adding Zn(II) or Cu(II) salt in the presence of two equivalents of KOH in dilute ethanolic solution [7]. Neutral complexes of transition metals and bis(β-diketonate) ligands were isolated in good yields. NMR spectra of the Zn complexes **2** were in complete agreement with the macrocyclic structures, where Zn is coordinated by two β-ketoenolate groupings in an intramolecular fashion. The development of anionic charges was detected by higher field shifts of β-diketonate CH and adjacent CH_3 and CH_2 protons in the NMR spectra. Cu(II) and Zn(II) complexes **3** gave characteristic UV absorptions of the β-ketoenolate at 310 nm and their 1 : 1 stoichiometries were ascertained by FAB mass spectra. Cu(II) complexes **3** ($n = 1$ and 2) were sufficiently hydrophobic to be employed for extracting metal picrates from aqueous into organic phases and the partition coefficients $K_{\mathrm{org/aq}}$ were determined, as shown schematically in Figure 3.

The result clearly indicates that **3** ($n = 1$) is selective for the extraction of Na^+ ion, as is **3** ($n = 2$) for K^+, exhibiting a typical selectivity match between ionic diameters and the hole size. In a metal assisted macrocyclic conformation of these complexes, contributions from two anionic oxygen atoms each from two
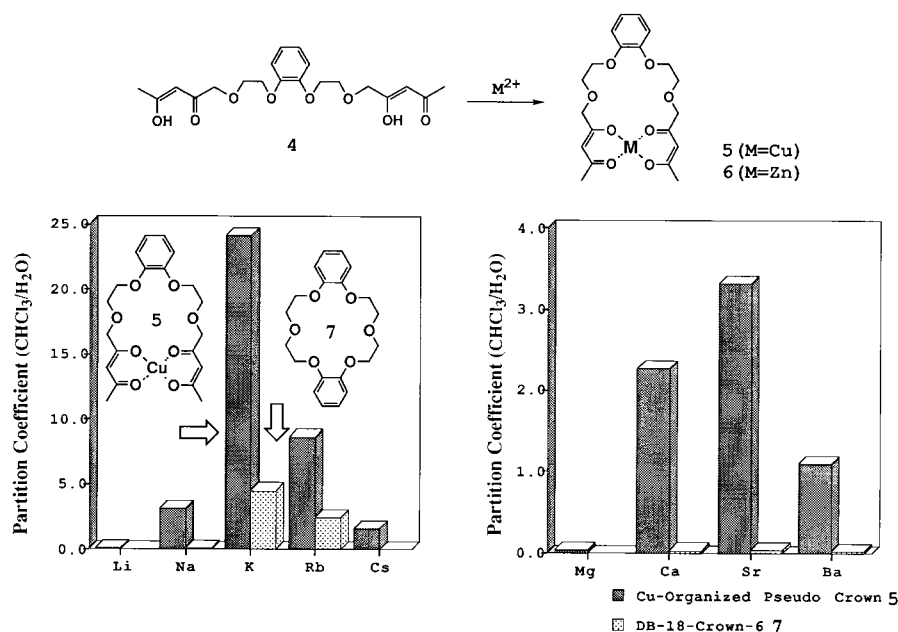
Figure 4. Metal picrate extraction by intramolecular complex of bis(β-diketonyl)oligoether having an *o*-phenylenedioxyether unit.

β-ketoenolate units and three or four neutral oxygens of the oligoether linkages afford the assembly of 5 or 6 oxygen atoms of neutral and partially anionic charges, respectively. These arrangements should provide the most appropriate and selective binding site to alkali metal ions of appropriate size. By contrast, the partition coefficients of Na^+ and K^+ picrates were negligibly small when **1** was used in the free or K^+ salt form. In the sense that the extraction of metal ions takes place only with the assistance of another metal ion binding, the cooperativity of metal ion binding is absolute.

As a structural modification of oligo(ethyleneoxy) unit, an *ortho*-dioxyphenylene unit was then introduced to make **4** [7]. Here, favorable geometric as well as electronic environments towards metal coordination were expected, considering the structure of the *cis*-dioxyethylene configuration. In addition, the increase of hydrophobicity seemed to favor the distribution equilibria into the organic phase for extraction experiments. Intramolecular cyclization of **4** was undertaken in a similar way by using Cu(II) and Zn(II) metal ions in a dilute ethanol solution to yield transition metal-organized macrocycles **5** and **6**, respectively, in a chloroform soluble form.

Picrate extraction experiments have been undertaken using these metal-organized hosts. The partition coefficients of metal picrates by Cu-organized host **5** are shown schematically for alkali and alkaline earth metal cations in Figure 4, along with data obtained using dibenzo-18-crown-6, **7**, as the reference host.

The metal-organized host **5** shows a typical characteristic of host–guest molecular recognition, i.e., the complementarity of the self-organized cavity (ca. 1.3 Å in its radius) and cation sizes determined the extraction efficiency, since sharp maximum extractions were observed for K^+ (1.33 Å) and Sr^{2+} (1.27 Å) in a series of alkali and alkaline earth metal cations, respectively.

The most important behavior in this extraction experiment is that the metal-organized host **5** is greatly superior to **7** for all of the alkali and alkaline earth metal cations. Under the extraction conditions where **5** extracted alkali metal ions efficiently with high metal ion selectivities, **7** showed much less extractability with similar metal ion selectivities. The difference is more obvious for alkaline earth metal cations. The metal-organized host **5** extracted appreciable amounts of alkaline earth metal ions with a maximum at Sr^{2+}. The same extraction condition was totally ineffective for the case of **7**. Although the metal-organized host is electrically neutral as a whole, the enolate oxygen atoms still retain their partial anionic charges and can afford coordination to another metal cation with stronger stabilization interaction than neutral ether oxygens. Such charge interaction seems more important for alkaline earth metal cations carrying more positive charges and this should find reflection in the difference of extraction behavior between alkali and alkaline earth metal ions.

The structure of this metal-organized host was successfully analyzed by X-ray crystallography, fortunately in the form of K^+ picrate adduct (Figure 5). Therefore, this elucidated not only the mode of organization by Cu(II), but the nature of binding of the guest ion. Cu(II) ion organized the prehost into a quasi-crown structure, by intramolecular coordination from two β-diketonate ligands in a planar tetradentate structure. The O—Cu bonds on the side close to K^+ ion are a little stretched compared with O—Cu bonds on the other side. This suggests the active participation of the former diketonate oxygen anions to the coordination to K^+ ion. K^+ ion sits almost in the center of the cavity provided by four neutral ether and two β-diketonate oxygen atoms. However, the mean of the coordinating bonds of K^+-diketonate oxygens, i.e., 2.822 and 2.887 Å, is shorter by 0.075 Å than those of phenylenedioxy, 2.893 and 2.966 Å. The coordination from dipolar $O(\delta-)$ $\cdots Cu(\delta+)$ is therefore suggested to be stronger than that from the neutral ether oxygens.

2.1.2. *Salicylic ester*

A similar prehost **8**, having salicylic ester at two terminals of triethylene glycol, was prepared and subjected to complexation with Cu(II), affording metal organized host **9**. The extraction efficiencies using **9** are illustrated in Figure 6. Again, the efficiencies are much better than dibenzo-18-crown-6, **7**, as the reference compound. It is interesting to note that this host shows higher partition towards alkaline earth than alkali metal ions.
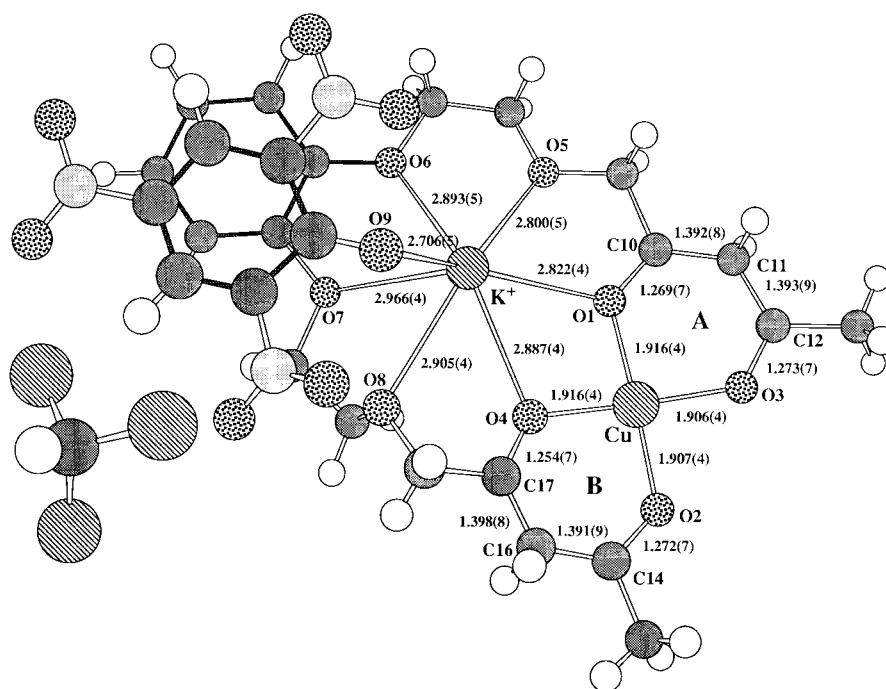
Figure 5. X-ray crystallographic structure of [Cu(II)-bis(β-diketonate)]-K$^+$ picrate complex.
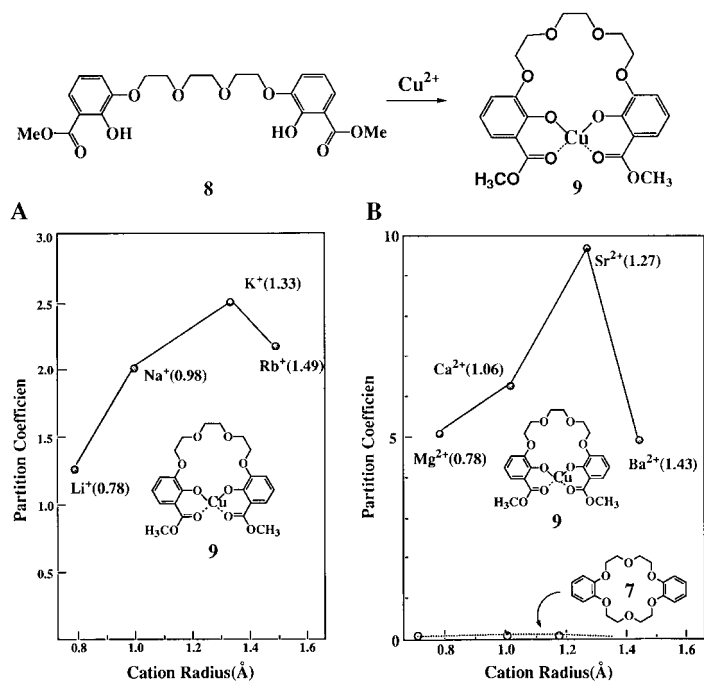

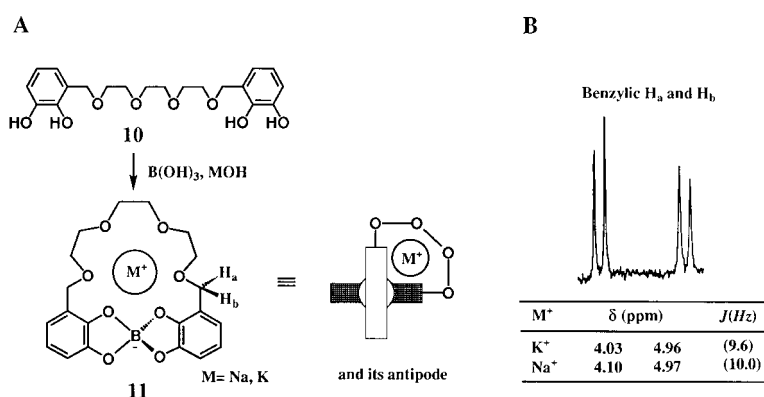*Figure 6.* Metal picrate extraction by Cu-bis(salicylic acid ester) complex.

Figure 7. (A) Intramolecular cyclization of bis(catecholate) by boric acid and entrapment of alkali metal in the cavity. (B) NMR spectrum of benzylic protons of B(catecholate)-Na^+ or K^+ complex.

2.2. METAL-ORGANIZED CROWN ETHER OF 'ATE'-COMPLEX TYPE

2.2.1. *Catecholate*

Two catechol ligands were attached to both terminals of triethylene glycol to make **10** [8]. This was treated with boric acid in the presence of four equivalents of KOH to afford an intramolecular complex **11**. Since two catecholate dianions provide four anionic charges to trivalent boron, the resulting complex has one anionic charge. This monoanionic cavity entrapped alkali metal ion. The FAB mass spectrum gave a parent peak corresponding to the sum of the mass of prehost, boron, and potassium. Later the same methodology was repeated and kinetic investigation has been undertaken [10]. Since boron complexes are known to have a tetrahedral structure, two catecholate ligands are orthogonal to each other. Therefore, the benzylic protons were split into an AB quartet, where chemical shifts and coupling constants were different between Na^+ and K^+ ions. According to this stereochemical arrangement, the host having a C_2 symmetry should be a mixture of *R* and *S* isomers. When a chiral europium reagent was added, the AB quartet was now deshielded with a separation into two sets of AB quartets. Furthermore, two components having an identical UV absorption spectrum were isolated when the host was subjected to liquid chromatographic separation with a chiral adsorbent. Therefore the structure of the complex is illustrated as **11** and its chiral antipode (Figure 7).
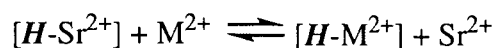
2.2.2. *Salicylate*

Bis(salicylate) oligoether **12** was obtained by hydrolyzing **8** in an almost quantitative yield. This was organized into an intramolecular complex by using UO_2^{2+} ion, which is known to have a high tendency to give planar, multi (i.e., tetra to

hexa)dentate 'ate' complexes. The organized host from bis(salicylate) is then expected to be appropriate for the binding of 2+ ions.
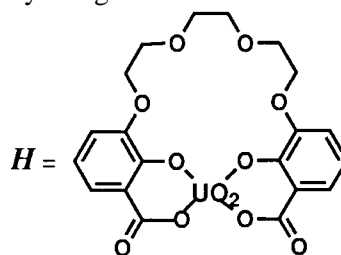
Bis(salicylate) **12** was treated with two equivalents of Sr(OH)$_2$ and one equiv. of UO$_2$(OAc)$_2$ and complex **13** was obtained in methanol-soluble form. The FAB mass spectrum gave a molecular ion peak at 777, which was compatible with the expected structure containing UO$_2^{2+}$ and Sr^{2+} ions. The UV spectrum suggested uranyl complexation by a shift of the absorption maximum of salicylic acid and appearance of a broad peak near 380 nm characteristic of uranyl absorption. The NMR spectrum (Figure 8) finally confirmed the proposed structure. *para*-H in the aromatic portion was shifted to a higher field, suggesting the development of anionic charge on the salicylate ring on complexation. On the contrary, all the methylene signals, α, β and γ, were shifted to lower fields. This suggests entrapment of metal cation into the central cavity, since signals of a vacant cavity should shift to higher fields, as was generally observed for the case of β-diketonate [4, 5].

A similar organization by UO$_2^{2+}$ was successful when NaOH was employed as the external base. However, the employment of other alkali and alkaline earth metal ions as the external base gave erroneous results, as the yields varied for repeated trials and a complex product mixture was obtained in some cases. Extensive research revealed that the uranyl organized host accommodated another uranyl ion itself most favorably in the cavity and the complex tends to contain two uranyls, the metal ion of the external base source did not fit the size of the cavity. The host organization was then successfully conducted in the presence of excess external cation, usually as a halide form. Various uranyl organized hosts containing Ca^{2+}, Ba^{2+}, and K$^+$ ions in the central cavity were then synthesized in pure forms. This finding implies an important suggestion, that the metal organization proceeds through a template effect of the external cation. When the size of the external cation fits the size of the newly generating cavity, the pseudo crown ring is formed in a good yield, but the employment of a non-fitting ion tends to pick up uranyl even if the amount is just an equivalent amount, and the blockage of the other route simply means sacrifice of the yield of organized host. If such a process occurs, the yield of uranyl-organized host decreases, with contamination by other forms. The suggested scheme is illustrated in Figure 9.

In order to make a quantitative assessment of the ion selectivity towards various alkali and alkaline earth metal ions, exchange reactions of Sr^{2+} in the central cavity by other metal cations M^{2+} were undertaken by using the NMR titration method.

$$[\boldsymbol{H}\text{-}Sr^{2+}] + M^{2+} \rightleftharpoons [\boldsymbol{H}\text{-}M^{2+}] + Sr^{2+}$$

$$K(M^{2+}/Sr^{2+}) = \frac{[Sr^{2+}][\boldsymbol{H}\text{-}M^{2+}]}{[\boldsymbol{H}\text{-}Sr^{2+}][M^{2+}]}$$
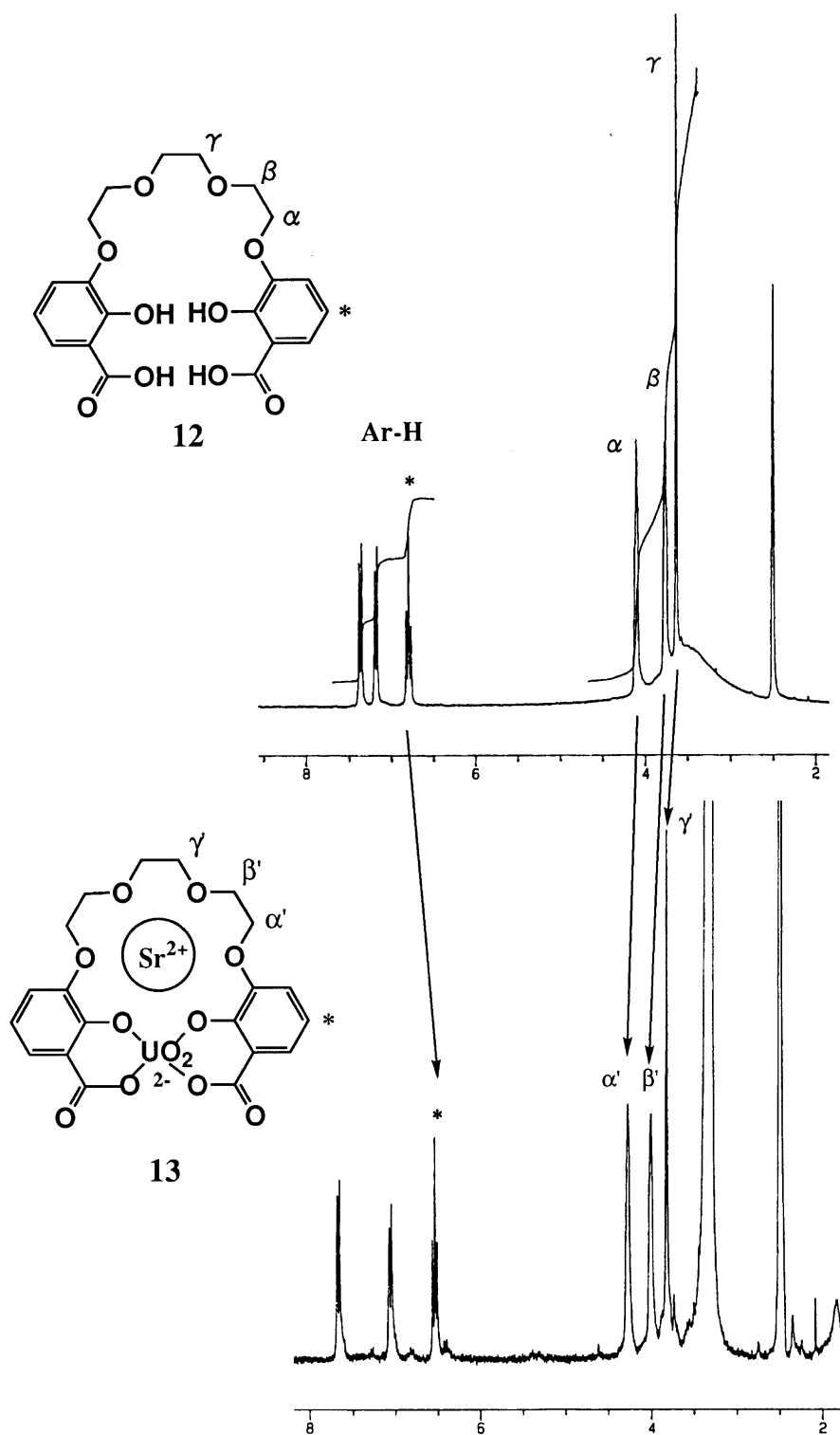
$\boldsymbol{H} =$

Figure 8. Intramolecular cyclization of bis(salicylic acid) by UO_2^{2+} and Sr^{2+} ions.
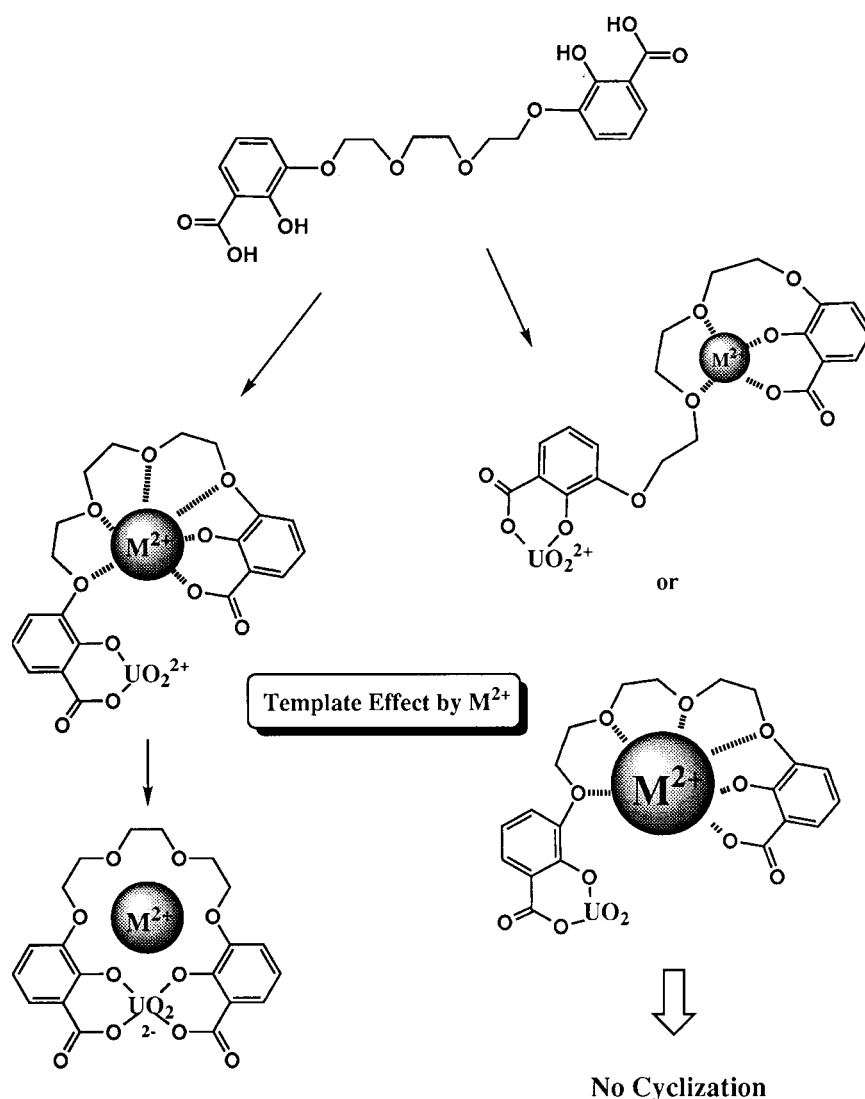
Figure 9. Template effect on intramolecular cyclization of bis(salicylate).

The NMR spectrum of the Ba^{2+} complex superimposed that of the Sr^{2+} complex and the relative equilibrium constant was analyzed by exchange with Ca^{2+} complex. Titration curves for Ca^{2+}/Sr^{2+} and Ca^{2+}/Ba^{2+} are illustrated in Figures 10A and B, respectively.

Data points are shown by ♦ and ▲ for % Ca^{2+} and Ba^{2+} complexes, respectively. The curves were calculated by using the exchange equilibrium constants, $K(Ca^{2+}/Sr^{2+}) = 0.2$ and $K(Ca^{2+}/Ba^{2+}) = 3$. The largest constant in an alkaline earth series was obtained for Sr^{2+} ion, in agreement with the expected cavity size of the hexaoxa pseudo crown from a CPK model. This hole size effect is compatible
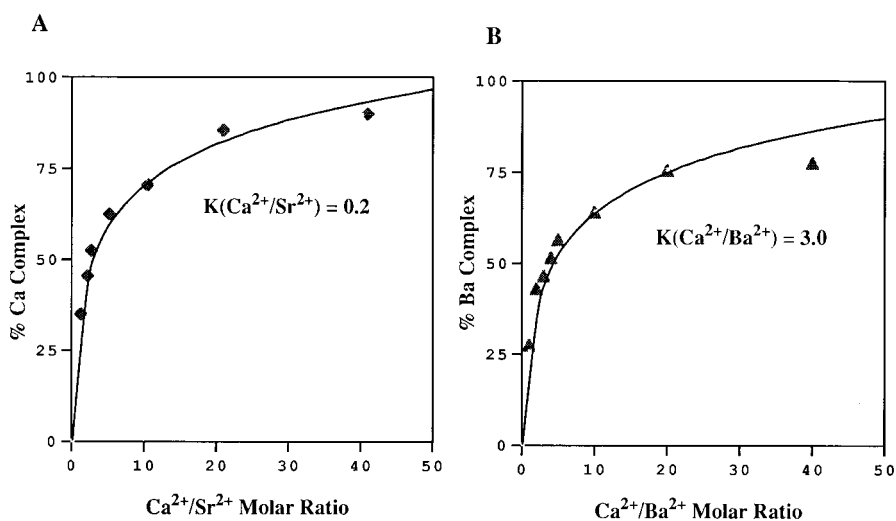
Figure 10. Exchange equilibrium of metal ions in uranyl-organized bis(salicylate) host. (A) Ca^{2+}/Sr^{2+}, (B) Ca^{2+}/Ba^{2+}.

with the maximum partition of Sr^{2+} for uranyl-organized β-diketonate and salicylic acid described in the above section.

A similar exchange reaction was undertaken for alkali metal ions. The equilibrium constants for Na^+ and K^+ relative to that of Sr^{2+} were obtained as 1/14 and 1/30, respectively. All the exchange equilibrium constants were calculated as values relative to the stability constant of Sr^{2+} and are summarized in Table I. Compared to the equilibrium constants of alkaline earth metal cations of comparable ionic diameters, alkali metal cations gave smaller equilibrium constants. This suggests the important contribution of polar interactions to the host–guest complexation. In the same way, the presence of anionic charges on the host enhances the interaction with positive metal ions due to enthalpic stabilization and this is the reason why the metal organized pseudo crown gives better extractability towards metal ions for alkali metals and far better for alkaline earth metal ions having more positive charges.

As described above, UO_2^{2+} ion was favorably included in the central cavity of the metal organized crown. In order to assess the strength quantitatively, the exchange equilibrium constant of the UO_2^{2+} vs. the Sr^{2+} complex was evaluated by NMR titration and the $K(UO_2^{2+}/Sr^{2+})$ value obtained was more than 30. This is an extremely large value, if one considers the same formal charge of two and the small ionic diameter of UO_2^{2+}, around 1.1 Å, which is close to that of Ca^{2+}. This is reasonably explained by considering the characteristics of the coordination chemistry of the uranyl ion. Planar hexacoordination is the most stable form for uranyl complexes and the structure may be illustrated as **14**, where six coordinating oxygen atoms locate in the same plane containing the uranium atom. Although the formal charge of uranyl ion is two, uranium itself is formally hexavalent and may

Table I. Relative stability constants of metal ions with uranyl organized host **16**.

| M^{2+}	r (Å)	K_{rel}	M^+	r (Å)	K_{rel}
Mg^{2+}	0.78	1/900			
Ca^{2+}	1.06	1/5	Na^+	0.98	1/14
Sr^{2+}	1.27	1	K^+	1.33	1/30
Ba^{2+}	1.43	1/15			
UO_2^{2+}	1.1	30			

14
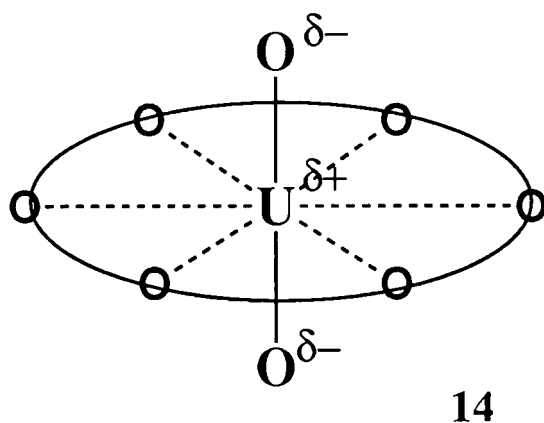
Compound 14

retain more than two positive charges. This may contribute to a larger stabilization in terms of enthalpy with a macrocycle composed of four neutral and two anionic oxygen atoms.

Combined evidence supports the importance of charge interaction for stabilizing metal ions in crown ether moieties. There are good reasons to believe that polar bonds and 'ate' complexes provided by metal-assisted organization of prehost are good ways to provide enthalpic stabilization towards incorporation of second metal ions in the central cavity. These ion-stabilizing cavities are certainly stronger than the conventional neutral crowns.

In order to find more convincing evidence for the above idea, it must be demonstrated by direct comparison of metal-organized hosts and crown ethers. Metal ion extraction experiments have already been compared under identical conditions, and the idea has been shown to be true in a series of monocyclic crown-type compounds. Cryptands are difficult to characterize by such an experiment and no test has been undertaken so far. It is reported that [2.2.1]cryptand **15** has maximum stability with Sr^{2+} in a series of cryptands [11]. Therefore, Sr^{2+} ion was tried to exchange into the cavity of [2.2.1]cryptand from uranyl-organized host–Sr^{2+}
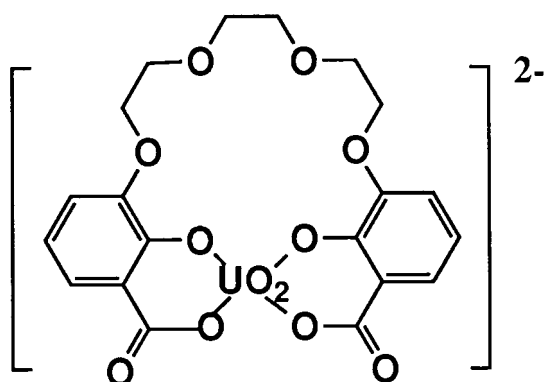
16

Compound 16

complex **13** by the addition of **15**. An equimolar amount of **15** did not induce any change in the NMR spectrum of **13**. The addition of ten molar equivalents of **15** generated a small number of new peaks in addition to those of **13**. Titration was continued up to 50 equivalents of **15** where half of the peaks of **13** have been exchanged. The stability of Sr^{2+} complex **13** is then larger than the [2.2.1]cryptand–Sr^{2+} complex by a factor of approximately 50. Then the question mark in Figure 1 may safely be substituted by **16**.

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6. The critical step for introducing chelate groupings into the oligoethyleneglycol unit was performed in 60% yields. Good yields were obtained similarly for all the other linear prehost syntheses: **4** (83%), **8** (82%), and **10** (60%).

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