Synthetic Metallomacrocycles; Complexes with Neutral Guests and \textit{Hetero-di-} \textit{and \textit{Hetero-Trinuclear Complexes}}

\textit{Frank C. J. M. van Veggel and David N. Reinhoudt}

Introduction

Complexation of Neutral Guests

The organization of binding sites in \textit{synthetic} (macrocyclic) molecular receptors for \textit{electrophilic} guests (often cations) is relatively simple. “Hard” and “soft” \textit{Lewis bases} like oxygen, sulfur, nitrogen, etc., can be incorporated by stable covalent bonds. By systematic variation of ring size, type, and number of binding sites remarkable stabilities have been achieved for complexes with cationic species, as well as a high degree of shape and size selectivity \cite{1}. Concepts of hole-size relationship \cite{2} and preorganization \cite{3} can be used to optimize selectivity and stability of binding.

The field of molecular recognition of \textit{neutral} guests by synthetic (macrocyclic) hosts has only more recently received the attention it definitely deserves.

One important difference between molecular complexes of electrophilic cationic guests and neutral guests is the lack of formal charge, which reduces the interaction forces to the much weaker hydrophobic, dipole-dipole and H-bonding contributions. Nevertheless in recent years substantial progress has been made toward utilizing these weaker interactions for the design of molecular receptors for neutral guests. This requires not only the organization of Lewis bases as binding sites in the receptor molecule but also of \textit{(Lewis) acids} as binding sites. Recently, OH, NH, and COOH groups have been organized properly in non-cyclic molecular clefts, for example by Rebek \cite{4}, Bell \cite{5}, and Hamilton \cite{6}.

We have investigated the possible contribution of acidic groups that are covalently incorporated into \textit{macrocyclic cavities}, and more recently of “immobilized” electrophilic metal cations that can act as Lewis acids in the molecular recognition process.
In metallo-enzymes the metal is essential for binding, and it often activates the complexed guest for subsequent chemical transformation. Therefore, we felt that the use of immobilized cations as Lewis acids might represent an important tool for the synthetic chemist in designing receptor molecules for neutral guests. Moreover, such Lewis acids can activate the guest for further chemical transformation in a manner similar to reactions catalyzed by metallo-enzymes.

In this chapter we will first review briefly our earlier work on synthetic receptors for neutral guests and the role of intra-annular acidic groups in the complexation. The second part will outline our recent work on macrocycles that contain immobilized cations as Lewis-acidic binding sites.

Complexes of Crown Ether and Neutral Molecules

During our work on the recovery of crown ethers from industrial waste-streams and non-destructive purification methods [7] we found that 18-membered crown ethers form stable crystalline complexes with a variety of organic guests that have relatively acidic CH₂ or CH₃ groups [e.g., CH₂NO₂, CH₂(CN)₂]. When we determined the thermodynamic stability of these complexes it became clear that the free energy of complexation (25°C) was small (ΔG° ≤ 2.2 kcal/mol) [8]. Attempts to increase the stability by designing more rigid receptor molecules met with limited success [9].

Similar results were obtained with urea as the guest, although we isolated complexes of urea and crown ethers with a well-defined stoichiometry in the solid state. We concluded that the interaction between the oxygen (or nitrogen) Lewis base of the macrocycle and the NH₂-groups of urea was insufficient for the formation of a stable complex.

Macroycles with Intra-annular Acidic Groups

Therefore, we subsequently synthesized series of macrocycles (15- to 33-membered rings) that have one acidic binding site in a position suitable for formation of a H-bond with the urea carbonyl group. In the extreme case, transfer of the proton of the acidic group to the urea oxygen in the complex would be possible.

We have found that 2-carboxy-1,3-xylyl-30-crown-9 forms a complex of the predicted structure in which the urea guest is completely encapsulated (Figure 1a) [10]. This receptor is capable of extracting urea from an aqueous to a non-aqueous
phase with reasonable efficiency. Moreover, 2-carboxy-1,3-xylyl-30-crown-9 permits dissolution of urea in chloroform.

When the acidity of the intra-annular group is increased, as in 2-sulfo-1,3-xylyl crown ethers, the acidic proton is transferred to a neutral guest like \((H_2O)_n\) \((n = 1, 2, 3; \text{Figure 1b})\) and also urea [11].

**Metallomacrocycles**

**Synthesis**

In the approach described above the proton is used in the complexation process as an electrophilic center. A disadvantage of the assistance of intra-annular acidic groups is the pH dependence of the complexation. In principle there are many other electrophiles that can assist complexation, including metal cations. We therefore decided to test a novel and probably more general concept by using a lithium cation as the electrophile in the complexation of urea. From our previous
work it was known that 2,6-pyrido-crown ethers (e.g., 1) form complexes with LiClO$_4$ and urea even when the ring size is large [12].

Upon reaction of 2,6-pyrido-27-crown-9 (1) with 1 eq. of LiClO$_4$ and 2 eq. of urea, a crystalline 1:1:2 complex (2) was formed (Scheme 1).

![Scheme 1](image)

The lithium cation is coordinated to the pyridyl nitrogen, to one of the benzylic oxygens, and to both oxygens of the two urea molecules (Figure 2).

The encapsulated urea is coordinated to lithium via the oxygen, and it forms four hydrogen bonds to the polyether oxygens. The second urea, which is not encapsulated by the crown ether, simply completes the tetrahedral coordination of the lithium cation in the solid state. Formation of this complex proved that not only a proton but also an electrophilic metal cation can be used to assist in the complexation of a neutral molecule, providing a Lewis-basic site is present in the guest.

However, in the 2,6-pyrido-27-crown-9·LiClO$_4$·(urea) complex 2 at least three species must combine in solution to form a complex. This requires either a high association constant for the metallomacrocycle or a high salt concentration.

![Figure 2. View of the structure of 2. The perchlorate anion is not shown. Reproduced with permission from the Am. Chem. Soc.](image)
Therefore, we have investigated the possibility of "immobilizing" an electrophilic cation in a macrocyclic cavity. The advantage of this approach is that only two species are required to combine to form a complex: the neutral guest and the metallomacrocycle, in which the electrophile is now incorporated [13]. "Immobilization" in the concentration range of interest requires a very high association constant for the complex between metal cation and macrocycle. For this reason we selected as building blocks the (Schiff base) condensation products of salicylaldehyde and aromatic or aliphatic diamines, the so called "salen ligands". Because these salen ligands form very stable complexes with transition-metal cations we decided to incorporate salen moieties in a new type of macrocyclic ligand (Chart 1).

The proper starting dialdehydes can be prepared in one step from 2,3-dihydroxybenzaldehyde and glycol ditosylates in DMSO with NaH [13].

The crucial macrocyclization of the dialdehyde and the diamine in refluxing methanol requires a barium salt such as Ba(ClO₄)₂ or Ba(CF₃SO₃)₂ as template salt (Scheme 2). When 1,2-benzenediamine was used as diamine the corresponding barium complexes 3 (Chart 2) could be isolated. In the subsequent reaction of
these barium complexes 3 with nickel, copper, or zinc acetate the "immobilized" electrophilic centres were introduced; surprisingly, this always led to the heterodinuclear complexes 4 (MX$_2$=BaX$_2$). However, the barium salt can be removed with guanidinium sulfate in a two-phase water/chloroform system. The barium simply precipitates as BaSO$_4$. With this procedure a number of complexes has been synthesized with a ring size ranging from "crown-6" to "crown-10" (Chart 2).

Complexation of Urea and other Neutral Ligands

The literature suggests that the enzyme urease, which catalyzes the hydrolysis of urea, employs at least one nickel cation to bind and activate urea during the hydrolysis (Fig. 3) [14].

Because there are several examples of planar coordination of nickel cations in complexes of cyclic ligands we felt it might be possible to induce such a pentagonal planar coordination in the nickel complexes 4 (M$_1$=Ni; MX$_2$=--) with urea. A complex of this type should be further stabilized by hydrogen bonding in the macrocyclic polyether cavity. The complexation experiment was carried out by recrystallizing the nickel complexes 4 (n=3–5) from a 0.1 M solution (excess) of urea in MeOH. In the case of the largest macrocycle (4, n=5) the IR spectrum reveals the urea carbonyl group at 1670 cm$^{-1}$, and an elemental analysis was in agreement with a 1:1 complex. An X-ray crystal structure determination showed that a 1:1 complex of urea and the nickel complex 4 (n=5) had indeed been formed. However, as shown in Figure 4, urea in this complex is not encapsulated in the polyether cavity.
Figure 3. Intermediate in the mechanism of the urease reaction.

Figure 4. View of the structure of the nickel complex $4 \ (M_1 = \text{Ni}; \ MX_2 = \text{---}; \ n = 5)$ urea. The three urea molecules are symmetry-related. Reproduced with permission from the *Am. Chem. Soc.*
Instead, three crystallographically equivalent urea molecules are hydrogen bonded to each macrocycle and vice versa. Obviously the preferred square-planar coordination of the nickel cation prevents cooperative interaction with a urea carbonyl group. Consequently, the planar pentagonal coordination required for co-complexation of urea with assistance from the polyether moiety is not energetically favorable for the nickel cation.

We therefore concluded that a cation with a preferentially planar pentagonal coordination should be used for further complexation studies [13]. The X-ray structure of the complex of the uranyl cation (UO$_2^{2+}$) with salen shows that the uranyl cation prefers a pentagonal bipyrimidal coordination (with the oxygen atoms at the axial positions) and also that a molecule of water is coordinated at the fifth equatorial position. Therefore, we decided to use the uranyl cation as the electrophilic center in the salen moiety. The synthesis follows the same route as depicted for the other metallomacrocycles (Scheme 2). The barium complex 3 obtained after cyclization was reacted with uranyl acetate in MeOH. In all cases, a barium-free mononuclear uranyl complex 4 (MX$_2$̅=̅-) was obtained.

When a solution of the uranyl complex 4 (M$_1$=UO$_2$, MX$_2$=̅-, n=5) in MeOH was treated with 1 eq of urea in MeOH, the 1:1 complex precipitated immediately as a red powder. The $^1$H-NMR spectrum (DMSO-$d_6$) shows a broad singlet at 5.4 ppm, indicating the presence of urea. An elemental analysis was consistent with a 1:1 complex. In the IR spectrum, strong absorptions are present at 1640 cm$^{-1}$ (C=O) and 1602 cm$^{-1}$ (C=N). The signal at 1640 cm$^{-1}$ is in agreement with the C=O stretching frequencies of complexes of urea and uranyl salts reported in the literature. This indicates that the urea molecule is bound via the carbonyl oxygen atom, and that a strong interaction is present. Finally, an X-ray crystal structure determination proved that urea is indeed coordinated within the macrocyclic cavity (Figure 5).

Because of its size, the uranyl cation opens up the salen moiety, thus allowing coordination of the urea carbonyl oxygen and resulting in pentagonal planar coordination of the cation. Urea is also coordinated to one of the phenolate oxygens and to five oxygen atoms of the polyether ring via hydrogen bonds donated by the NH$_2$ groups. The result is a highly structured complex with a large number of host–guest interactions. The structure of this complex 4 (M$_1$=UO$_2$, MX$_2$=urea, n=5) confirms that it is possible to complex a neutral molecule within a macrocyclic ligand that possesses an immobilized electrophilic cation, provided the geometry for coordination of the cation is consistent with the geometry necessary for complexation of the neutral guest.

In order to demonstrate the scope and selectivity of the uranyl complexes 4 (M$_1$=UO$_2$, MX$_2$=̅-, n=3–5), complexation of the uranyl complexes with other neutral guests was investigated. In addition to urea derivatives and amides, acetone and DMSO were also tested for their ability to form a complex with the uranyl complexes. In some cases a complex crystallized immediately. In all cases the melting points of the complexes with a neutral guest were higher than those of
the corresponding uranyl complexes 4. This probably reflects increased rigidity of the complex. All elemental analyses were in agreement with the formation of 1:1 complexes. Infrared spectra (KBr pellets) of the complexes reveal absorptions for the guest molecules. The complexes of formamide, urea, N-methylurea, and (2-pyridylmethyl)urea exhibit C=O stretching frequencies at lower values relative to the uncomplexed guest species (Table 1). This indicates strong interaction between the guest molecule and the electrophilic uranyl cation. Similarly, a shift was observed in the S=O stretching frequency for the DMSO complex (Table 1).
Table 1. Infrared spectral data (cm⁻¹) for the uranyl complexes 4 (Mᵢ = UO₂; MXᵢ₋ = ⋯; n = 3–5) with neutral guests.

<table>
<thead>
<tr>
<th>Guest</th>
<th>none</th>
<th>n = 3</th>
<th>n = 4</th>
<th>n = 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>formumide</td>
<td>1680</td>
<td>-a-</td>
<td>1670</td>
<td>1671</td>
</tr>
<tr>
<td>acetamide</td>
<td>1685</td>
<td>-a-</td>
<td>-a-</td>
<td>-a-</td>
</tr>
<tr>
<td>urea</td>
<td>1683</td>
<td>1630</td>
<td>1630</td>
<td>1640</td>
</tr>
<tr>
<td>N-methyurea</td>
<td>1650</td>
<td>-a-</td>
<td>-a-</td>
<td>1639</td>
</tr>
<tr>
<td>(Q-pyrid/methyl)urea</td>
<td>1664</td>
<td>-b-</td>
<td>-b-</td>
<td>1642</td>
</tr>
<tr>
<td>acetone</td>
<td>1700</td>
<td>-b-</td>
<td>-a-</td>
<td>-a-</td>
</tr>
<tr>
<td>DMSO</td>
<td>1050</td>
<td>-a-</td>
<td>-a-</td>
<td>1005</td>
</tr>
</tbody>
</table>

a) no crystalline product isolated. b) not attempted.

**Hetero-Dinuclear Complexes**

One of the surprising results in the synthesis of the metallomacrocycles was formation of hetero-dinuclear complexes upon reaction of the barium complexes with metal acetates, except in reactions with uranyl acetate. This sequence of reactions thus provides a simple method of obtaining hetero-dinuclear complexes in which two different metal cations are present.

For a variety of reasons, dinucleating ligands able to form homo- and hetero-dinuclear complexes are of great interest. First, such species may serve as models for metallo-proteins such as superoxide dismutase, oxidases, and peptidases. Dinuclear copper-containing complexes attract a great deal of attention because of the two copper centers in the active site of copper proteins like hemocyanin, which transport O₂, and the mono-oxygenases tyrosinase and dopamine β-hydroxylase, which incorporate oxygen (from O₂) into organic substrates [15]. Very recently, Karlín and co-workers [16] have reported that symmetrical dicopper complexes are able to bind molecular oxygen reversibly at low temperature.

Second, such dinuclear complexes may bind and activate other small molecules. Floriani and co-workers have shown this beautifully for CO₂ and CO₂-like molecules [17]. They prepared non-cyclic [L²⁻·Co¹⁺]⁻·M⁺ (M = Na, K, Cs) complexes in which the Co¹-center acts as a Lewis base and the M⁺-center as a Lewis acid.

Third, dinuclear complexes can be applied as bifunctional catalysts, as was shown by McKenzie and Robson [18] for a dipalladium complex in the hydration
of acetonitrile. They observed a pathway involving concerted action of the two metal centers. Collman et al. [19] and Leznoff et al. [20] have reported the electrocatalytic reduction of oxygen with cofacial diporphyrins and cofacial diphthalocyanins, respectively.

In principle, the behavior of dimetallic complexes can be quite different from that of monometallic analogues when the distance between the two metal centers is quite small. Ciampolini et al. [21] have demonstrated the interaction of two cations in dinickel and dicopper complexes of \( N,N \)-linked bis(cyclam) ligands, where the interaction is dependent on the nature of the bridge between the two rings. Mandal et al. [22] observed two one-electron reductions, two one-electron oxidations, and mixed oxidation states in a symmetrical dicopper(II)-complex, an unusual result in such a system.

Hitherto, the majority of hetero-dinuclear complexes have contained only combinations of two transition metal ions, and virtually nothing is known about cyclic ligands with two different types of cavities: one "hard" cavity that can bind alkaline or alkaline-earth cations and a "soft" cavity capable of binding cations like \( \text{Ni}^{2+}, \text{Cu}^{2+}, \text{Co}^{2+}, \text{and Zn}^{2+} \). A few hetero-dinucleating cyclic ligands have been reported, but these all have identical cavities. To the best of our knowledge, Carroy and Lehn [23] very recently designed the only dinuclear complexes of cyclic ligands containing both a transition metal ion and a non-transition metal ion (\( \text{Li}^+, \text{Ba}^{2+}, \text{Al}^{3+} \)).

Our preliminary results have shown that hard cations can be co-complexed in the metallo-macrocycles 4. This offers a unique opportunity to study systematically the properties of hetero-dinuclear complexes of cyclic ligands, including the dinuclear complexes 4. These ligands have a unique combination of two very different cavities, a hard polyether and a soft site of the salen type. Because of their structure, these dinucleating ligands are able to bring the two different cations into close proximity. We therefore decided to investigate this novel type of hetero-dinucleating cyclic ligand in detail, with the ultimate objective of applying such hetero-dimetallic complexes as catalysts.

Synthesis

One disadvantage of the monotransition metal complexes 4 (\( M_1 = \text{Ni, Cu, Zn}; \ MX_2 = \cdot; n = 1, 2 \)) is their low solubility in common organic solvents, which renders comparison with the dinuclear analogues very difficult. The planarity of the salen moiety could be one cause of this behavior, so we have utilized 2-methyl-1,2-propanediamine as the diamine component. Cyclizations of the dialdehyde and diamine were carried out under high dilution conditions and with
Ba(CF$_3$SO$_3$)$_2$ as template salt (Scheme 2). The resulting barium complex 5 was not isolated, because we expected the imine bonds here to be less stable than in the case of an aromatic diamine. After the cyclization, 1 eq. of nickel or copper acetate was added, and the resulting hetero-dinuclear complexes 6 (Chart 3) were isolated in excellent yields (71–82%).

![Diagram](image1)

The mononuclear complexes 6 (MX$_2$ = –) were readily obtained by stirring for a few hours a suspension of a dinuclear complex in chloroform with a solution of excess guanidinium sulfate in water.

So far, all the dinucleating ligands described have a salen type “soft” cavity for complexation of transition metals and a crown type “hard” cavity of alkali and alkaline-earth cations, but both cavities in this structure are subject to systematic variation.
The "soft" cavity was modified with alkylated oxime bonds (8 and 9, Chart 3) [25]. The synthesis of the dinuclear complexes 8 is analogous to that of 6 starting from 1,2-bis(aminooxy)ethane and the proper dialdehyde. The barium complex 7a could be isolated after cyclization (74%), and it was characterized by X-ray analysis [25]. The dinuclear complexes 8 were obtained in 78–81% yield.

The synthesis of the non-cyclic dinuclear complexes 9 is slightly different. The dialdehyde is first converted to the O-methylated dioxime 7b, which is subsequently reacted with nickel, copper, or zinc acetate in MeOH using barium as template cation and high dilution conditions, affording dinuclear complexes in 55–82% yield. The formation of 9 can be regarded as the first example of self-organization of a polyether cavity in which alkali or alkaline-earth cations can be complexed [26].

Besides polyether chains we have also incorporated in the dialdehydes the much more rigid terphenyl unit, developed by Cram et al. [27] for the construction of preorganized (hemi)spherands. Reaction of the corresponding dialdehyde [24] with 1,2-benzenediol or 2-methyl-1,2-propanediol and subsequent reaction with an acetate salt gave the dinuclear complexes 11 and 13. Barium was eliminated from the complexes by the procedure mentioned previously.

Crystal Structure

The most important feature of these hetero-dinuclear complexes is the relative positions of the two metal centers, because this is what determines the extent to which one metal center influences the properties (e.g., redox properties) of the other. We will discuss five representative structures.

The structure of the nickel/barium complex 6 (n = 1) is shown in Figure 6a. The nickel cation has a square planar coordination. The barium cation is ninefold coordinated by the six oxygen atoms of the ligand (Ba²⁺…O 2.71–2.87 Å), two triflate (CF₃SO₂⁻) anions (Ba²⁺…O 2.77–2.82 Å), and one water molecule (Ba²⁺…O 2.78 Å). Barium is displaced by 0.84 Å out of the mean plane of the crown ether oxygens towards the two triflate anions. At the other face, one water molecule occupies the apical position. The distance between the two metal ions in this dinuclear complex is 3.69 Å.

In order to study the effect of the valency of the hard cation we have also determined the solid state structure of the nickel/sodium picrate complex 6 (MX₂ = Na Pic; n = 1) (Figure 6b).

In this nickel/sodium complex the nickel cation again has a square planar coordination. The six macrocyclic oxygens all fall within 0.04 Å of their mean plane. The sodium cation is displaced only 0.13 Å out of this plane, giving an encapsulated complex. The two apical positions are occupied by two picrate anions, one
Figure 6a. Space filling representation of the solid state structure and X-ray structure of the nickel/barium complex \(6 (M_1 = \text{Ni}; M_2 = \text{Ba(CF}_3\text{SO}_3); n = 1) \cdot \text{H}_2\text{O}\). The two triflate anions and the water molecule have been omitted for clarity.

Figure 6b. View of the structure of the nickel/sodium complex \(6 (M_1 = \text{Ni}; M_2 = \text{Na}^+ \text{Pic}^-; n = 1)\). Only the coordinated oxygens of the two picrate anions are shown for clarity. Reproduced with permission from the \textit{Am. Chem. Soc.}
**Figure 6c.** View of the structure of the zinc/barium complex 11 (M₁ = Zn; MX₂ = Ba(CF₃SO₂)₂)·3DMF. Only the coordinated oxygens of the three DMF molecules and the coordinated anion are shown for clarity. Reproduced with permission from the *Am. Chem. Soc.*

**Figure 6d.** View of the structure of the copper/barium complex 8 (M₁ = Cu; MX₂ = Ba(CF₃SO₂)₂)·2H₂O. Only the oxygens of the coordinated anion are shown for clarity. Reproduced with permission from the *Am. Chem. Soc.*

**Figure 6e.** View of the structure of the zinc/barium complex 9 (M₁ = Zn; MX₂ = Ba(CF₃SO₂)₂). The atoms labeled with asterisks are the equatorial ligands of the complexed zinc cation. The oxygens marked with "a" are from the anion that is coordinated to both zinc and barium. The oxygens marked with "b" are from the anion that is coordinated only to the barium. Reproduced with permission from the *Am. Chem. Soc.*
coordinating with the phenolic oxygen ($Na^+\cdots O$ 2.40 Å) and the other with an oxygen of a para-nitro group ($Na^+\cdots O$ 2.60 Å). The distance between the two metal ions is 3.63 Å.

The solid state structure of the zinc/barium complex $11\cdot 3$DMF was determined in order to study the effect of a non-transition metal cation in the soft cavity and a rigid polyether cavity (Figure 6c).

In contrast to the square planar coordination of nickel and copper observed in the salen moiety, the zinc cation has a square pyramidal coordination formed by the two nitrogen atoms ($Zn^{2+}\cdots N$ 2.07–2.08 Å), the two phenolate oxygens ($Zn^{2+}\cdots O$ 1.96–1.97 Å) of the macrocycle, and an oxygen atom from dimethylformamide at the axial position ($Zn^{2+}\cdots O= C$ 2.04 Å). The zinc cation is displaced by 0.39 Å out of the mean plane of the four coordinating atoms of the macrocycle and towards the coordinated carbonyl of DMF. The barium cation is complexed in the polyether cavity by all seven oxygens ($Ba^{2+}\cdots O$ 2.74–3.26 Å). In addition to these seven oxygens of the macrocycle, two molecules of DMF are coordinated to the barium on the same side as the DMF that is coordinated to the zinc ($Ba^{2+}\cdots O= C$ 2.70–2.72 Å). The tenth coordination site is occupied by a triflate anion ($Ba^{2+}\cdots O$ 2.59 Å). The distance between the two metal ions is 3.63 Å. It can thus be concluded that when nickel (or copper) is coordinated by a salen moiety, hardly any residual electrophilicity remains at the axial position. This means that further coordination of a substrate does not occur easily. In the case of zinc some electrophilicity is retained.

The solid state structure of the copper/barium complex $8\cdot 2$H$_2$O was determined to study the effect of a different “soft” cavity (Figure 6d).

The copper cation is complexed in the soft cavity in a distorted square planar coordination. The barium is complexed in a perching fashion by the macrocycle ($Ba^{2+}\cdots O$ 2.68–2.91 Å). In addition, two oxygens of one anion ($Ba^{2+}\cdots O$ 2.76–2.86 Å) and one water molecule ($Ba^{2+}\cdots O$ 2.82 Å) are coordinated at one side of the ligand. The extent of displacement of the barium out of the mean plane of the six macrocyclic oxygen is 0.90 Å, which is larger than in the case of the barium complex 7a (0.50 Å). This is due to a contraction of the macrocycle upon complexation of the copper cation. The distance between the two metal ions in $8\cdot 2$H$_2$O is 3.73 Å.

The solid state structure of the zinc/barium complex 9 was determined to see the effect of a much more flexible non-cyclic dinucleating ligand (Figure 6e).

The zinc cation has a trigonal bipyramidal coordination sphere. The groundplane is formed by one phenolate oxygen and one nitrogen of the macrocycle and an oxygen of an anion (these atoms are labeled with asterisks). The zinc cation is displaced 0.10 Å out of this plane towards the axial nitrogen atom. The barium cation is complexed in the hard polyether cavity in a perching fashion ($Ba^{2+}\cdots O$ 2.65–2.85 Å). At one side of the ring, two anions are coordinated, one with two oxygens ($Ba^{2+}\cdots O$ 2.90–3.15 Å) and the other with one oxygen ($Ba^{2+}\cdots O$ 2.74 Å). The latter anion is bridged via another oxygen to the zinc cation. At the
other side of the macrocycle the apical position is occupied by an oxygen of an anion (Ba$^{2+}$ → O 2.72 Å). The barium cation is displaced 0.70 Å out of the mean plane of the six oxygens of the ring towards the two coordinating anions. The distance between the two metal ions is 3.69 Å.

In the five structures discussed we were surprised to observe very little effect of the ligand on the distance between the two metal cations (3.63–3.73 Å). We believe this to be due to the phenolate oxygens, which are partially negatively charged and hence capable of interacting more strongly with the hard cations than the other coordinating oxygens.

Electrochemistry

As mentioned in the introduction, a major objective of the work described in this paper was to study the effect of a hard cation in the polyether cavity on the (redox) properties of the coordinated soft transition metal cation. In order to evaluate this effect, a number of hetero-dinuclear complexes and mono-transition metal complexes were investigated by sampled DC-polarography and cyclic voltammetry in DMSO with Et$_4$N$^+$ClO$_4^-$ as the supporting electrolyte [24, 25]. A representative selection of data is presented in Tables 2a and 2b. These data will be discussed in the section that follows.

When alkali or alkaline earth cations are complexed in the copper complexes 6 (MX$_2$ = –, n = I, 2) an anodic shift is observed in the half-wave potential varying from 9 mV for 6 (n = 2) with K$^+$ up to 213 mV for 6 (n = 1) with Ba$^{2+}$ (Figure 7; Table 2a data for 6: M$_1$ = Cu, n = 1) [24].

For the cations Ba$^{2+}$, K$^+$, and Na$^+$ the results indicate reversible one-electron reduction, but for Li$^+$ the reduction is far from reversible. In all cases the bivalent Ba$^{2+}$ gave the largest shift in half-wave potential. It is known from the literature

![Figure 7. Polarograms of the copper/barium and copper complex 6 (M$_1$ = Cu; MX$_2$ = Ba(CF$_3$SO$_2$)$_2$ –; n = 1) in DMSO at 20°C.](image-url)
Table 2a. Polarographic data for reduction of the copper complex 6 (M₄ = Cu; n = 1) at a dropping mercury electrode at 20°C, 0.1 M Et₄N⁺ClO₄⁻ in DMSO vs. Ag/AgCl.

<table>
<thead>
<tr>
<th>MX₂</th>
<th>E₁/₂ (V)</th>
<th>Slope (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>—1.332</td>
<td>68</td>
</tr>
<tr>
<td>1 eq Ba(CF₃SO₂)₂</td>
<td>—1.119</td>
<td>51</td>
</tr>
<tr>
<td>1 eq KClO₄</td>
<td>—1.278</td>
<td>58</td>
</tr>
<tr>
<td>2 eq KClO₄</td>
<td>—1.277</td>
<td>58</td>
</tr>
<tr>
<td>1 eq NaClO₄</td>
<td>—1.280</td>
<td>59</td>
</tr>
<tr>
<td>2 eq NaClO₄</td>
<td>—1.279</td>
<td>59</td>
</tr>
<tr>
<td>1 eq LiClO₄</td>
<td>—1.219</td>
<td>74</td>
</tr>
<tr>
<td>2 eq LiClO₄</td>
<td>—1.204</td>
<td>75</td>
</tr>
<tr>
<td>3 eq LiClO₄</td>
<td>—1.295</td>
<td>77</td>
</tr>
<tr>
<td>4 eq LiClO₄</td>
<td>—1.291</td>
<td>82</td>
</tr>
<tr>
<td>5 eq LiClO₄</td>
<td>—1.286</td>
<td>81</td>
</tr>
</tbody>
</table>

Table 2b. Polarographic data for reduction of mono- and dinuclear complexes at a dropping mercury electrode at 20°C, 0.1 M Et₄N⁺ClO₄⁻ in DMSO vs. Ag/AgCl.

<table>
<thead>
<tr>
<th>Complex</th>
<th>M₁</th>
<th>n</th>
<th>MX₂</th>
<th>E₁/₂ (V)</th>
<th>Slope (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Ni</td>
<td>1</td>
<td>—</td>
<td>—1.669</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>Ni</td>
<td>1</td>
<td>Ba(CF₃SO₂)₂</td>
<td>—1.338</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>Ni</td>
<td>2</td>
<td>—</td>
<td>—1.621</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>Ni</td>
<td>2</td>
<td>Ba(CF₃SO₂)₂</td>
<td>—1.359</td>
<td>104</td>
</tr>
<tr>
<td>6</td>
<td>Cu</td>
<td>1</td>
<td>—</td>
<td>—1.332</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>Cu</td>
<td>1</td>
<td>Ba(CF₃SO₂)₂</td>
<td>—1.119</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>Cu</td>
<td>2</td>
<td>—</td>
<td>—1.265</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>Cu</td>
<td>2</td>
<td>Ba(CF₃SO₂)₂</td>
<td>—1.108</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>Ni</td>
<td>—</td>
<td>Ba(CF₃SO₂)₂</td>
<td>—0.931</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>Cu</td>
<td>—</td>
<td>Ba(CF₃SO₂)₂</td>
<td>—0.438</td>
<td>61</td>
</tr>
<tr>
<td>9</td>
<td>Ni</td>
<td>—</td>
<td>Ba(CF₃SO₂)₂</td>
<td>—0.959</td>
<td>58</td>
</tr>
<tr>
<td>9</td>
<td>Cu</td>
<td>—</td>
<td>Ba(CF₃SO₂)₂</td>
<td>—0.284</td>
<td>51</td>
</tr>
<tr>
<td>11</td>
<td>Ni</td>
<td>—</td>
<td>—</td>
<td>—1.247</td>
<td>55</td>
</tr>
<tr>
<td>11</td>
<td>Ni</td>
<td>—</td>
<td>Ba(CF₃SO₂)₂</td>
<td>—1.018</td>
<td>55</td>
</tr>
<tr>
<td>11</td>
<td>Cu</td>
<td>—</td>
<td>—</td>
<td>—1.008</td>
<td>54</td>
</tr>
<tr>
<td>11</td>
<td>Cu</td>
<td>—</td>
<td>Ba(CF₃SO₂)₂</td>
<td>—0.821</td>
<td>53</td>
</tr>
<tr>
<td>13</td>
<td>Ni</td>
<td>—</td>
<td>—</td>
<td>—1.552</td>
<td>40</td>
</tr>
<tr>
<td>13</td>
<td>Ni</td>
<td>—</td>
<td>Ba(CF₃SO₂)₂</td>
<td>—1.237</td>
<td>68</td>
</tr>
</tbody>
</table>

that reduction can be shifted in the anodic or cathodic direction by introducing substituents into (copper) complexing ligands [28]. Kanda et al. [29] have reported cathodic shifts (up to 690 mV) together with deprotonation of two carboxylic groups upon complexation of cations (Ba²⁺, Ca²⁺, Mg²⁺, Zn²⁺) in mono-copper
complexes of a non-cyclic dinucleating ligand. Anodic shifts of molybdenum compounds containing crown ether moieties and complexed hard cations have been reported by Beer et al. [30]. We found that upon addition of 1 eq. of Ba(ClO$_4$)$_2$ to the mono-copper complexes 6 (n = 1, 2) the characteristics of hetero-dinuclear complexes were observed, and that addition of more Ba(ClO$_4$)$_2$ did not affect the observed values. This indicates a stoichiometric 1:1 reaction between Ba$^{2+}$ and the ligands, as well as large association constants for these complexes (K$_\text{ass}$ $\geq$ 10$^6$ l/mol).

The electrochemical behavior of the copper/barium complex 6 (n = 1) was also studied by cyclic voltammetry. At scan rates from 1 to 6 V/s the cyclic voltammograms showed one reduction and one oxidation between -0.2 and -2 V. At these scan rates the peak surfaces of the cathodic and anodic sweep were equal to within 10%, which suggests a chemically reversible reduction. Therefore, we conclude that the Cu$^+$/species generated are stable in DMSO solution in the absence of oxygen.

The dinuclear nickel/barium complexes 6 (n = 1, 2), 11, and 13 all exhibited one polarographic wave, and the reductions proceed via a reversible one-electron transfer. The nickel complexes 6 (n = 1, 2), 11 and 13 show the same anodic shifts upon complexation of hard cations in the polyether cavity. Here again, the largest shifts are observed for the bivalent Ba$^{2+}$ and the weakest association constants for Li$^+$. The nickel/barium complex 6 (n = 1) was also investigated in more detail by cyclic voltammetry. At scan rates of 0.5 to 6 V/s the dinuclear complex 6 showed one reduction and one oxidation between -0.2 and -2 V (Figure 8a).

![Cyclic voltamogram of the nickel/barium complex 6 (M$_1$ = Ni; MX$_2$ = Ba(ClO$_4$)$_2$; n = 1) in DMSO at a scan rate of 0.5 V/s.](image1.png)

![Cyclic voltamogram of the copper/barium complexes 9 (M$_1$ = Cu; MX$_2$ = Ba(ClO$_4$)$_2$) in DMSO at a scan rate of 6 V/s. Reproduced with permission from the Am. Chem. Soc.](image2.png)
At these scan rates the peak surfaces of the reduction and oxidation sweeps are equal. When we applied five subsequent scans at scan rates of 0.5 and 6 V/s the cyclic voltammograms were identical. The Ni$^1$-species generated is thus chemically stable in DMSO in the absence of oxygen.

When we compare the nickel/barium complexes 6 (n = 1, 2) with 13, which has a much more rigid terphenyl-containing cavity, we found a relatively large effect on the half-wave potential going from the flexible crown ether cavity in 6 (−1.338 and −1.359 V, respectively) to the much more rigid cavity in 13 (−1.237 V).

The stabilizing effect of the Ni$^1$-complex by an aromatic vs. an aliphatic salen moiety is obvious from a comparison of the reductions of the nickel/barium complexes 11 and 13 (−1.018 vs. −1.237 V).

The nickel/barium and copper/barium complexes 8 and 9 were also investigated by polarography and cyclic voltammetry, and the resulting data are included in Table 2b [25]. Except for the copper/barium complex 9, which shows two one-electron reductions, one-electron reduction is observed. The two-electron reduction of copper/barium complex 9 was verified by coulometry. Cyclic voltammetry revealed that reduction occurs in two distinct steps, whereas oxidation occurs in one step (Figure 8b).

Comparison of these complexes containing alkylated oxime bonds with the dinuclear complexes 6 (n = 1) showed that the latter are reduced at a more cathodic potential. This is interpreted in terms of less donation of the nitrogen lone-pair in the oxime bond due to the presence of electron-withdrawing oxygen. Greater deviation from planarity in the complexes with oxime bonds may also play a role.

The effect of the hard cations Ba$^{2+}$, K$^+$, Na$^+$, and Li$^+$ complexed in the polyehter cavity is to reduce the electron density at the phenolic oxygen atoms, which in turn reduces their electron-donating ability towards the transition metal ion. Consequently, the transition metal ion becomes more positive, making the reduction easier. Our results indicate that the association constants of Li$^+$-complexes are smaller than those of complexes of the other hard cations.

**Hetero-Trinuclear Complexes**

A logical extension of the work on hetero-dinuclear complexes would be the synthesis of ligands that can complex two soft cations and one hard cation. In such ligands the two soft centers are relatively isolated from each other, but coordination of a hard metal cation can in principle be used to organize the two soft binding sites. Moreover, hard cations may affect redox properties in the resulting trinuclear complexes.
This type of positioning of two soft metal centers differs in an essential way from that in the more common dicopper complexes that have been designed as mimics of the active site in dicopper metalloproteins like hemocyanin, tyrosinase, and dopamine β-hydroxylase [15, 16]. Almost all the model compounds that have been described in the literature are dinucleating ligands in which the two copper sites are bridged in the plane by a hydroxide, a phenolate, or an alkanolate anion. In our complexes the two “soft” metal centers would not have such an “in-plane” bridging ligand, and consequently should exhibit different binding properties.

The Ba(CF₃SO₃)₂ complex of 14 was prepared by simultaneous slow addition of a solution of 1,2-benzenediamine and a solution of the proper dialdehyde to a refluxing solution of Ba(CF₃SO₃)₂ in MeOH [31]. Barium complex 14 was obtained as a red crystalline material in 63% yield. The FAB mass spectrum of this complex shows a parent peak at m/e 1123, which corresponds to [M—CF₃SO₃]⁺.

The conversion of barium complex 14 into the trinuclear complexes 15 was carried out by reaction with 2 eq. of copper and nickel acetates, respectively. The FAB mass spectrum of 15 (M₁ = Cu) exhibits a parent peak at m/e 1245, which corresponds to [M—CF₃SO₃]⁺. The FAB mass spectrum of 15 (M₁ = Ni) shows a parent peak at m/e 1234, which is in agreement with the calculated value for [M—CF₃SO₃ + H]⁺.

The structure of one of the two independent molecules in the asymmetric unit of the barium complex 14 is shown in Figure 9a.
Figure 9a. View of the structure of the barium complex 14 (M₁ = 2H; MX₂ = Ba(CF₃SO₂)₂). Only the coordinating oxygen of the triflate anion is shown. Reproduced with permission from *Angew. Chem.*

Figure 9b. Space-filling representation (top view) of the solid state structure and X-ray structure of the dicopper/barium complex 15 (M₁ = Cu; MX₂ = Ba(CF₃SO₂)₂ - 2 H₂O. The two anions and the two water molecules have been omitted for clarity.

The macrocycle is folded around the barium cation, which allows coordination by all ten oxygen atoms of the macrocycle (Ba²⁺ ⋯ O 2.69-3.14 Å). The eleventh position around barium is occupied by an oxygen from a triflate anion (Ba²⁺ ⋯ O 2.82 Å). The mean planes through the four heteroatoms of the salen units are approximately parallel, with an angle of 12.6°.
The structure of the dicopper/barium complex 15 (Figures 9b and 9c) is similar to that of 14.

The two copper cations are complexed in the "soft" salophen cavities, and barium is complexed in the large polye ther cavity. Both copper cations are complexed in an almost square planar coordination. The mean planes through the coordinating atoms of the copper cations are approximately parallel, with an angle of 5.8°. The barium cation is coordinated by all ten oxygens of the macrocycle (Ba$^{2+}$...O 2.76-3.63 Å), one water molecule (Ba$^{2+}$...O 3.01 Å), and one triflate anion (Ba$^{2+}$...O 2.89 Å). Distances in this cation cluster are: Ba$^{2+}$...Cu$^{2+}$ 3.70 and 3.85 Å and Cu$^{2+}$...Cu$^{2+}$ 3.50 Å, with an angle Cu$^{2+}$-Ba$^{2+}$-Cu$^{2+}$ of 55.1°.

The structure of the dinickel/barium complex 15 resembles the structure of the dicopper/barium complex 15. Distances in this cation cluster are: Ba$^{2+}$...Ni$^{2+}$ 3.66 and 3.73 Å and Ni$^{2+}$...Ni$^{2+}$ 3.42 Å. The angle Ni$^{2+}$-Ba$^{2+}$-Ni$^{2+}$ is 55.1°.

The electrochemical properties of the trinuclear complexes 15 were investigated by polarography and cyclic voltammetry at a mercury drop electrode in DMSO with 0.1 M Et$_4$N$^+$ClO$_4$ as supporting electrolyte. The polarogram of the dicopper/barium complex 15 shows two waves between -0.2 and -1.4 [E$_{1/2}$ = -1.065 and -1.110 V (slope 52 and 50 mV, respectively)]. The ratio of the limiting currents is one, which indicates two one-electron reductions. Cyclic voltammograms at scan rates of 0.5 to 6 V/s of 15 (M$_1$ = Cu) were also recorded. At these scan rates the two-step process is reflected as a shoulder on a peak in the reductive sweep as well as on one in the oxidative sweep (Figure 10a).

This two-electron reduction/oxidation is chemically reversible. The reduction can be regarded as following a simple EE-mechanism; i.e., two one-electron transfers, via a (formally) M$_1^+/M_1^0$ oxidation state to a (formally) M$_1^0$/M$_1^-1$ oxidation state.

The polarogram of the dinickel/barium complex 15 shows two waves between -0.2 and -1.4 V [E$_{1/2}$ = -1.036 and -1.137 V (slope 50 and 46 mV, respective-
ly)). The ratio of the limiting currents is about one. The cyclic voltammograms of 15 (M₁ = Ni) at scan rates of 0.5 to 6 V/s between -0.2 and -1.4 V are shown in Figure 10b.

Cyclic voltammetry showed that the reduction/oxidation of 15 is chemically reversible. However, this reduction/oxidation can not be regarded as two simple

---

**Figure 10a.** Cyclic voltammograms of the dicopper/barium complex 15 (M₁ = Cu; MX₂ = Ba(CF₃SO₂)₂) in DMSO at scan rates of 0.5 to 6 V/s (shown on the curves); vs. Ag/AgCl.

**Figure 10b.** Cyclic voltammograms of the dinickel/barium complex 15 (M₁ = Ni; MX₂ = Ba(CF₃SO₂)₂) in DMSO at scan rates of 0.5 to 6 V/s (shown on the curves); vs. Ag/AgCl. Reproduced with permission from Angew. Chem.
one-electron transfers; instead it is complicated by reversible intra- and intermo-
lecular C-C coupling of two (reduced) imine bonds. A similar reductive C-C cou-
pling of two imine bonds in Ni(salophen) units has also been observed in the solid
state by Floriani et al. upon reduction of Ni(salophen) with 1 eq. of lithium on
sodium metal [32].

Conclusions

In this review we have shown that not only a proton but also a cation can assist
in the complexation of neutral guests in macromolecular receptor molecules. The syn-
thesis of these receptors was easily extended to hetero-di- and hetero-trinuclear
complexes, complexes that combine hard and soft cations in one ligand. From
electrochemical studies we have learned that hard cations like Ba$^{2+}$, K$^+$, Na$^+$,
and Li$^+$ affect the redox potential of the complexed transition metal cations. We
have also demonstrated a new approach to bringing two soft cations into close
proximity.

Acknowledgements

These investigations were supported in part by the Netherlands Technology
Foundation (STW), the Future Technical Science Branch of the Netherlands Or-
ganization for Advanced and Pure Research (ZWO), and AKZO International Re-
search BV.

References

[1] (a) de Jong, F., Reinhoudt, D. N., Stability and Reactivity of Crown Ether Complexes, New York:
Chem. 1988, 100, 91].
Reinhoudt, D. N., Dijkstra, P. J., in 't Veld, P. J. A., Bugge, K. E., Harkema, S., Ungaro, R., Ghid-
van Veggei and Reinhoudt