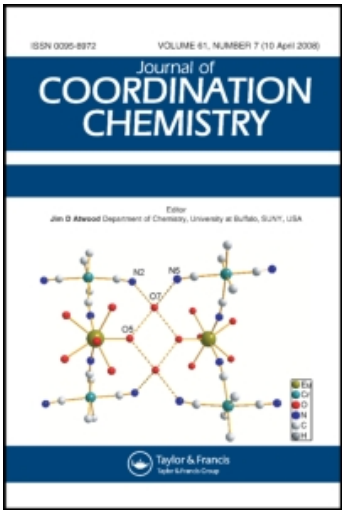

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COMPLEXATION OF NEUTRAL ORGANIC MOLECULES BY (METALLO)MACROCYCLES AND METALLOCLEFTS

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Thermodynamic data of several complexes studied with NMR spectroscopy in solution and X-ray analysis of the solid state showed that hydrogen bond formation between host and guest determines the structures of the complexes, and very likely also their stability. Two methods to enhance the stability of this type of complexes are described. The introduction of intra-annular acidic groups in the cavity offers the ability to transfer (partially) a proton of the host to the guest in a complex, the resultant charge separation gives more stable complexes as can be concluded from X-ray analysis, pK_a-measurements of free and complexed hosts, solid-liquid and liquid-liquid extractions. Co-complexation of electrophilic metal ions in a cavity results in *metallo*macrocycles and *metallo*clefts with excellent complexation properties for neutral organic guests, as is concluded from ^1H NMR- and IR spectroscopy, X-ray analysis and polarographic titrations.

INTRODUCTION

Since the pioneering work of Pedersen[1] on macrocycles most of the complexation studies have concentrated on metal cations[2] or organic cations,[3] but more recently the complexation of neutral guest species has become a rapidly growing field of interest.[4] Although non-cyclic molecular clefts have received much attention recently by Bell *et al.*,[5] Hamilton *et al.*,[6] Kelly *et al.*,[7] Rebek *et al.*,[8] and Zimmerman *et al.*[9] most attention has been focussed on organization in macrocycles.

The interaction(s) of macrocyclic ligands with neutral guests are much weaker than interaction(s) with cations.[2f,10] Therefore we have investigated several ways to increase the stability of the complexes and have developed novel classes of hosts, *viz. metallomacrocycles* and *metalloclefts* for the complexation of neutral organic molecules.

RESULTS AND DISCUSSION

In order to understand the stability of the complexes of simple crown ethers with neutral organic molecules like nitromethane, acetonitrile and malononitrile[10] we have investigated the structure and thermodynamics of the complexes. The X-ray structures of these complexes suggested that the relatively acidic C-H moieties in these guests, if properly positioned relative to the heteroatoms of the host, form hydrogen bonds that may be responsible for complexation (Figure 1). The hydrogen bond formation in the solid state (X-ray analysis) is reflected in a down-field chemical shift of the ^1H NMR signals of these C-H protons in apolar solutions, *e.g.* in benzene.[10] The relatively low association constants calculated from titration data obtained with ^1H NMR spectroscopy showed that complexes between neutral hosts and neutral guests are far less stable than complexes of cations.[2f] This is not unexpected because the

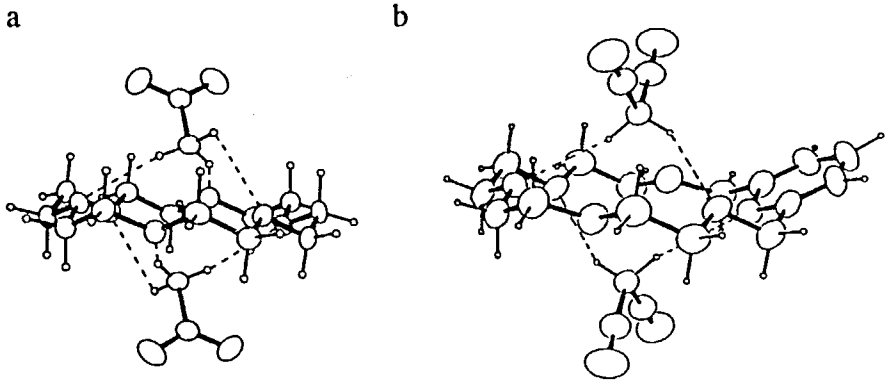
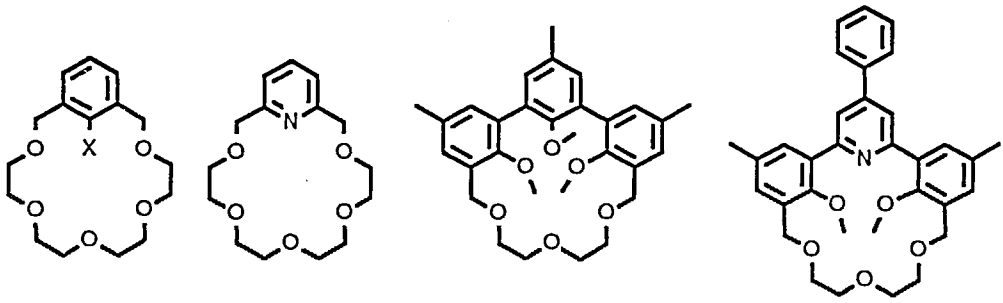


FIGURE 1 X-ray structure of (a) 18-crown-6.CH_3NO_2 (1:2) and (b) 2,6-pyrido-18-crown-5.$CH_2(CN)_2$ (1:2).

electrostatic forces operating in complexes of neutral hosts and neutral guests are much weaker than in complexes with ionic species.

A similar relatively low stability was demonstrated for a number of 1:1 complexes of malononitrile with several receptor molecules (Chart 1) in benzene with $\Delta G°$-values ranging from -0.7 to $-2.2\,kcal\,mol^{-1}$. A detailed analysis of the data shows that in these examples a lower enthalpy value is compensated by a lower entropy value. As a first approach to improve the complex stability we have synthesized the macrocycles **3** and **4** in which the binding sites are preorganized.[10c,11] It is clear from X-ray analyses that these compounds do not show "self-complexation"[12] (Figure 2). Comparison of the X-ray structures of the free ligands and complexes with $CH_2(CN)_2$ shows that the receptors **3** and **4** hardly undergo reorganization upon complexation. The values of the free energy of complexation $\Delta G°$ of $-2.0\,kcal\,mol^{-1}$ for both hemispherands **3** and **4** are therefore lower than expected. Evaluation of the data is not simple because the aliphatic oxygens in the compounds **1** and **2** are more basic than the anisole oxygens in hemispherands **3** and **4**.

CHART 1



1 **2** **3** **4**

1,3-Xylyl-18-crown-5 (**1**), 2,6-pyrido-18-crown-5 (**2**), hemispherand (**3**), and pyridohemispherand (**4**).

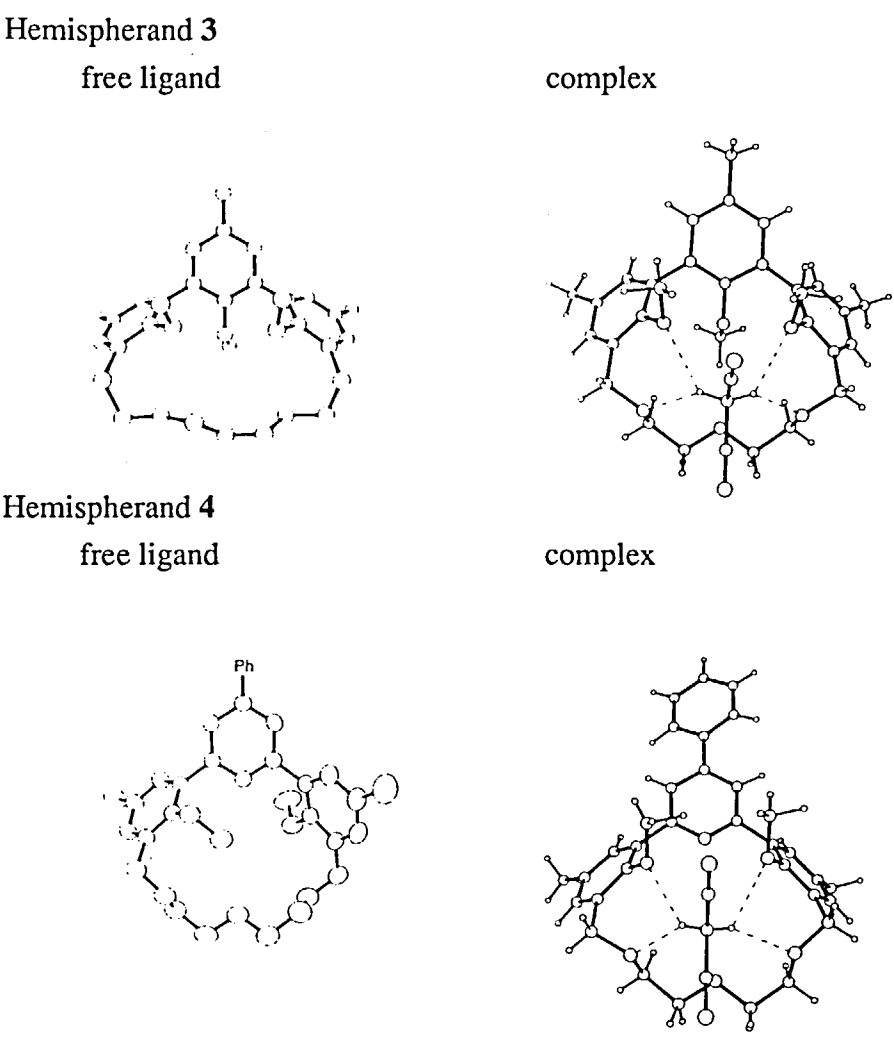


FIGURE 2 X-ray structures of the free ligands 3 and 4 and their 1:1 complexes with malononitrile.

After we had established that well-defined complexes of macrocycles and neutral organic molecules in solution and in the solid state are formed, we concentrated on the complexation of neutral molecules of biological interest, especially urea, and on the complexation of neutral molecules in clefts. Urea, already mentioned in Pedersen's second publication on this subject,[1b] did not give complexes with dibenzo-18-crown-6 but we found that complexes with 18-crown-6 and monoaza-18-crown-6 are formed in a 1:5 stoichiometry (macrocycle: urea).[10d] The X-ray structures of both complexes show that urea is complexed in two different modes. Firstly, urea (three molecules) present in packing layers and secondly, urea (two molecules) hydrogen bond bridged to the macrocycle which is sandwiched between the two packing layers (Figure 3).

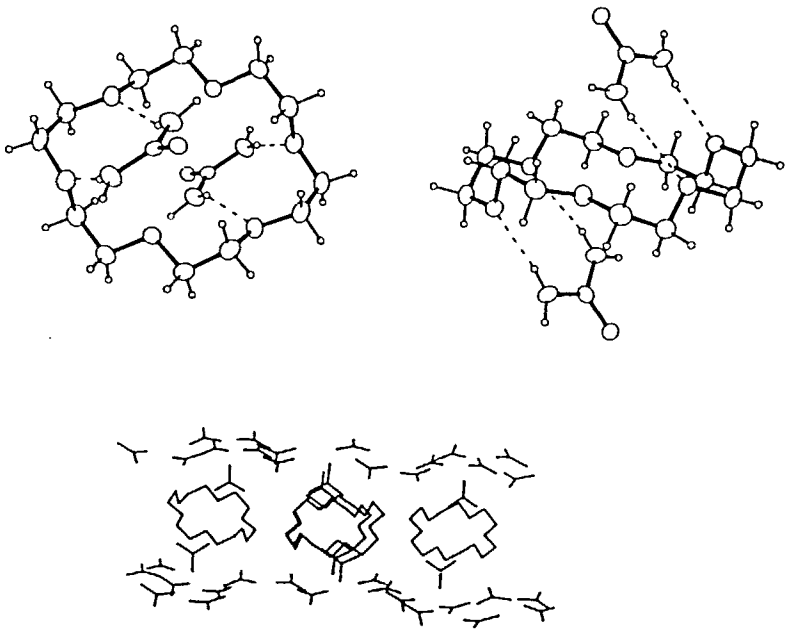


FIGURE 3 X-ray structure of 18-crown-6.urea (1:5).

From potentiometric data it was concluded that if complexes in methanol exist, the association constants are low ($\log K_{ass} < 0.1\ M^{-1}$).[13]

Liquid-liquid extraction in a water (pH=7)/$CHCl_3$ two phase system failed to show any transfer of urea from the neutral aqueous phase to the chloroform phase. However, we demonstrated that at low pH($\leqslant 1$) benzo- and dibenzo crown ethers are able to transfer urea to the $CHCl_3$ layer (Figure 4). Transfer is particularly efficient when the ring size is at least 27. The X-ray structure of benzo-27-crown-9.urea (1:1) showed that the oxygen of urea is protonated and that the uronium cation is completely encapsulated.[14]

The fact that urea is transported in its ionic form and not as a neutral species led us to develop two novel concepts for the complexation of neutral molecules, *viz.* complexation assisted by (partial) proton transfer from the host to the guest and to the co-complexation of electrophiles and neutral guests in the cavity.

The synthesis of macrocycles with an intra-annular acidic group requires, according to literature, multi-step procedures with low overall yields,[15] but we found a new route to this type of compounds (Scheme 1).[16] 2-Bromo-1,3-xylyl crown ether **5** is reacted with *n*-butyllithium at $-78°C$ and under these conditions no ring cleavage is detected. Experiments showed that exchange is complete in 2 hours. Subsequent reaction of the corresponding 2-lithio-1,3-xylyl crown ethers with an electrophile yielded crown ethers with an intra-annular acidic group at the 2-position in good yield. For the synthesis of the 2-sulfo-1,3-xylyl crown ethers we used a modified route[16c] (Scheme 2). After lithiation, compound **6** was reacted with $MgBr_2.Et_2O$ at $-78°C$. Quenching with SO_2Cl_2 and hydrolysis with aqueous HCl yielded the sulfonyl crown ethers **10**. The pK_a values of crown ethers with an intra-annular functional group

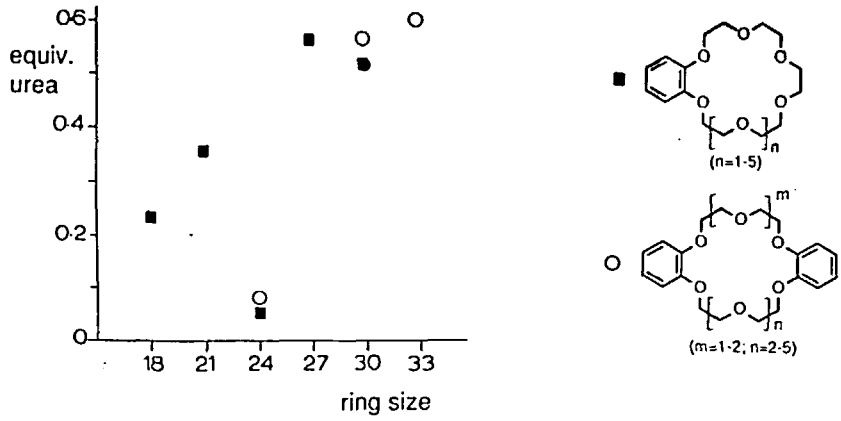
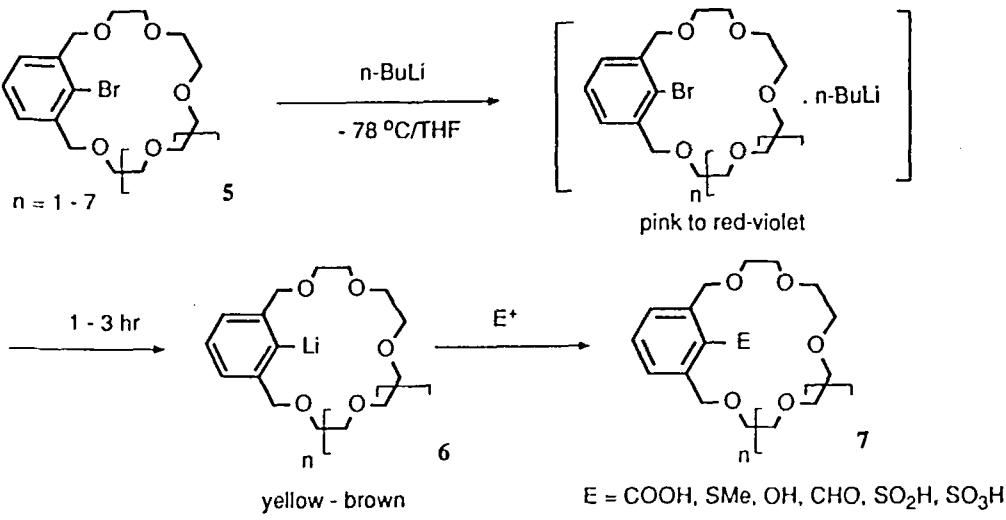


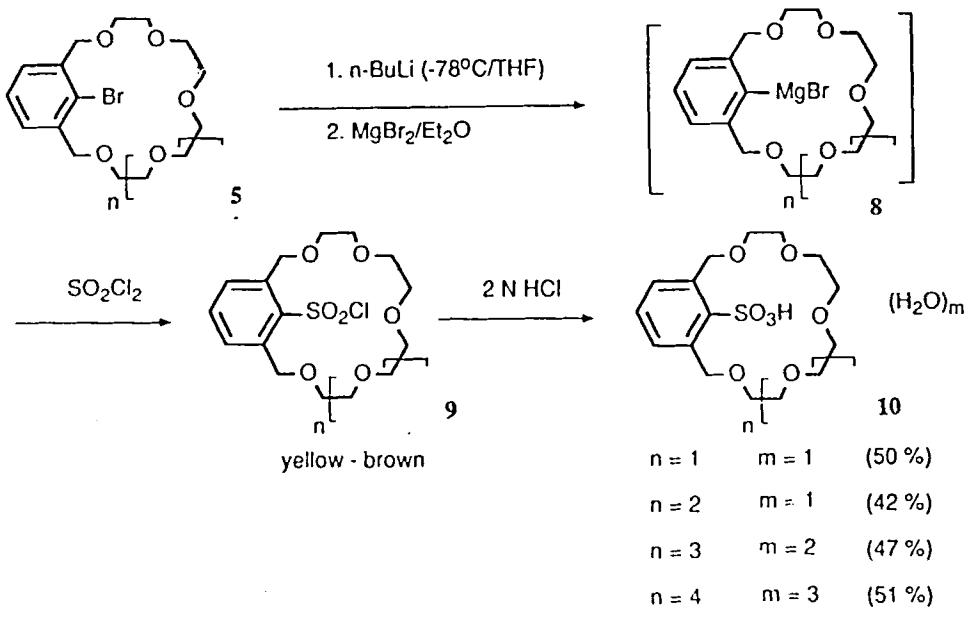
FIGURE 4 Liquid-liquid phase transfer of urea.



Scheme 1

may serve as a sensitive probe for the systematic study of (weak) host-guest interactions. Accurate potentiometric titrations[17] showed a ring size dependent acidity for both the 2-carboxy-1,3-xylyl- and the 2-sulfo-1,3-xylyl crown ethers (Figure 5).[16c,18]

The enhanced pK_a values of the 15- and 18-membered 2-carboxy crown ethers 7 may be attributed mainly to stabilization of the acid by intra-annular hydrogen bonding to ring oxygens. Cram *et al.* showed that in 2-carboxy-1,3-xylyl-18-crown-5 such a hydrogen bond is present in the solid state.[15b] The enhanced pK_a's of the 21- and 24-membered rings could be explained by complexation of a water molecule



Scheme 2

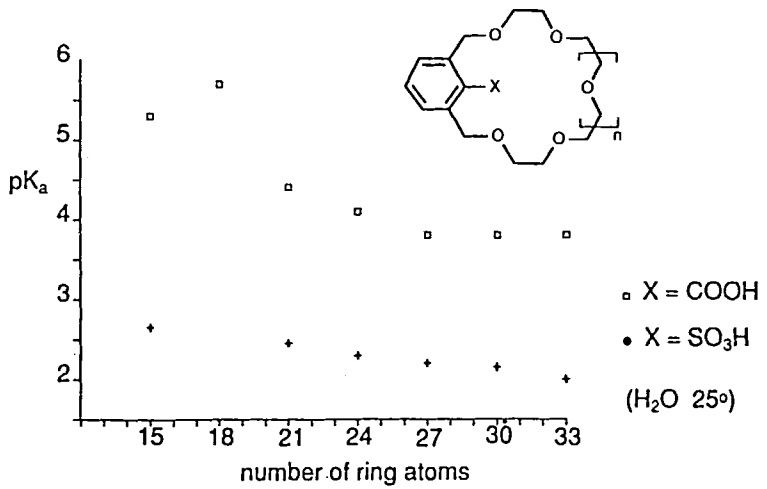


FIGURE 5 Ring size dependent acidity.

in the cavity of the macrocycle. This interpretation is supported by the X-ray structure of the water complex of the 24-membered ring.[18] The water molecule is bound *via* three hydrogen bonds. Two are donating to two different crown ether oxygens and one is accepted from the carboxylic OH-group. No proton transfer from the carboxylic acid to water is observed. Titration experiments with urea gave different ΔpK_a's

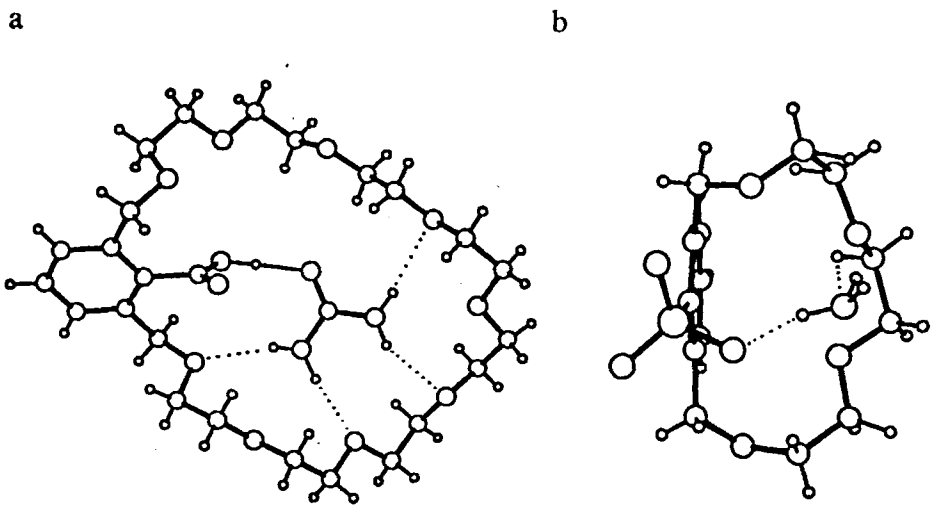


FIGURE 6 X-ray structure of 2-carboxy-1,3-xylyl-30-crown-9.urea (a) and 2-sulfo-1,3-xylyl-15-crown-4.H_3O^+ (b).

varying from 0.03 (for the 15–21 membered rings) to 0.15 (for the 27–33 membered rings). The ΔpK_a indicates assistance of the intra-annular carboxylic acid in complexation. The X-ray structure of 2-carboxy-1,3-xylyl-30-crown-9.urea (1:1) confirmed the assistance because the hydrogen of the carboxylic OH-group is coordinated to the oxygen of urea (Figure 6a).[18] Further evidence for the assistance came from liquid-liquid and solid-liquid extraction experiments, especially for the 27-membered and larger rings and the fact that open analogues are less efficient at transferring urea from the water to the chloroform layer.[18]

The 2-sulfo-1,3-xylyl crown ethers give different results. The acidity of the crown compounds is strikingly different from benzenesulfonic acid ($pK_a = -2.8$).[19] The ring size dependent acidity is not so pronounced as in the case of the 2-carboxy-1,3-xylyl crown ethers (Figure 5). X-ray structures of the 15-, 24-, and 27-membered 2-sulfo-1,3-xylyl crown ethers revealed that 1, 2, or 3 water molecules, respectively, were encapsulated in the cavity (Figure 6b) and the structure also indicates that the sulfonic acid proton of **10** is transferred to (one of the) water (molecules) present in the cavity.[16c] The difference with benzenesulfonic acid is that these acids form strong tight-ion pairs. The difference between the water complexes, where a proton of sulfonic acid is completely transferred, and the water complex of 2-carboxy-1,3-xylyl-24-crown-7 where no proton is transferred is mainly due to a different acidity. Complexation studies with other neutral guests *via* proton transfer are under investigation.

Inherent to the use of acids is that complexation can only be achieved at low pH. Realizing that a proton is only one example of an electrophile, the possibility to generalize the concept was studied.

Initially, we studied the co-complexation of a small cation and urea in the 2,6-pyrido crown ethers. From previous studies we know that 2,6-pyrido crown ethers give complexes with Li^+ [20] and from the literature it is known that urea forms complexes

with metal salts, with the metal ion coordinating to the carbonyl oxygen of urea.[21] Our aim was to complex both urea and a metal cation in the macrocyclic cavity in such a way that the metal ion is coordinating to the oxygen of urea and to the macrocycle. The electrophilic metal ion should induce charge separations in the complexed guest, resulting in more stable hydrogen bonds between host and guest in the ternary complex. The X-ray structure of 2,6-pyrido-27-crown-7.$LiClO_4$.urea (1:1:2 complex)[22] proved the validity of this concept (Figure 7). One urea molecule is complexed in the cavity and the other urea molecule is only present to complete the four-coordination of the complexed lithium cation. With these results in mind we investigated the possibility of *immobilizing* electrophilic cations in the cavity and this requires very high association constants. The Schiff bases (salen units) of aromatic and aliphatic diamines with salicylaldehyde are reported to give very stable complexes with transition metals.[23] Therefore we incorporated the salen moiety in macrocycles (Chart 2).[22,24] Essential for macrocyclization of **11** is the presence of $Ba(ClO_4)_2$ or $Ba(CF_3SO_3)_2$. The resulting barium complexes **12** were reacted with the appropriate metal acetate to give the hetero-dinuclear compounds **13** except for uranyl acetate which gave a mononuclear macrocycle **14**. The barium salt could be removed easily in a chloroform/aqueous guanidinium sulfate two phase system by precipitating $BaSO_4$.

Several X-ray structures of the hetero-dinuclear compounds **13**,[24b–c] of which one is given in Figure 8, showed that the Ba^{2+} cation is encapsulated by crown ether oxygens and the two phenolic oxygens. The metal-barium distances are 3.6–3.7 Å, the metals are close enough to influence each other. We have shown that there is a fundamental difference between the hetero-dinuclear compounds **13** and the mononuclear compounds **14** with respect to the interaction in their reduced state with *neutral* organic substrates.[25]

Treatment of the uranyl macrocycles **14** with several neutral guests resulted in a number of solid complexes which were characterized by mass spectrometry, melting points, elemental analyses and infrared data.[24a] The shifts of the C=O stretching

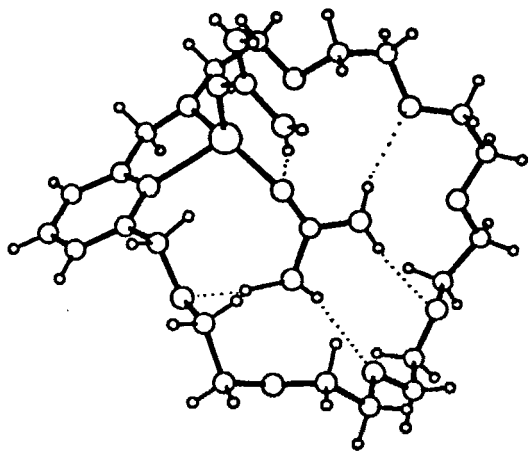
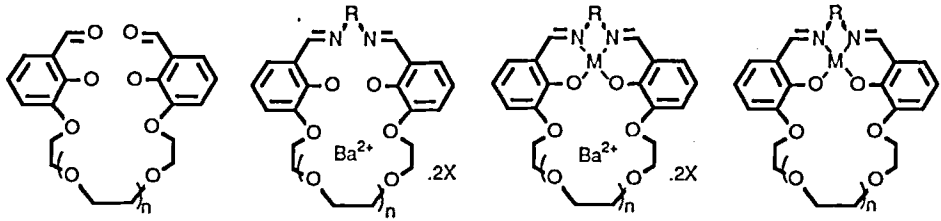


FIGURE 7 X-ray structure of the 2,6-pyrido-27-crown.$LiClO_4$.urea complex (1:1:2).

Chart 2



11 12 13 14

R = o-C_6H_4, $CH_2CH(CH_3)$, OCH_2CH_2O
X = ClO_4^-, $CF_3SO_3^-$
M = Ni^{2+}, Cu^{2+}, Zn^{2+}, UO_2^{2+}
n = 1 - 5

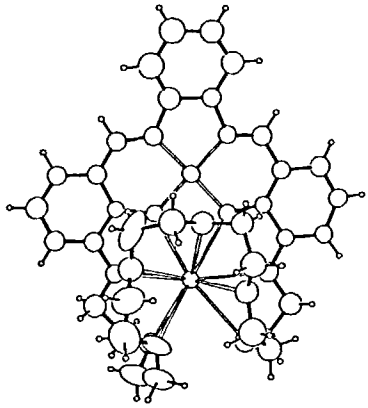


FIGURE 8 X-ray structure of Ni-Ba complex **13**.

frequency to lower values indicate coordination to the uranyl as is found in the crystal structure of the uranyl.urea complex (n = 5), where the urea oxygen coordinates to the uranyl and the NH_2 groups form hydrogen bonds with oxygens in the cavity (Figure 9). From the complexation studies described we concluded that generalization of the concept from electrophilic protons to electrophilic metal cations is allowed for the complexation of neutral molecules.

We have extended the concept of co-complexation of electrophilic metal ions, *e.g.* the uranyl cation, to *metallo*clefts by attaching aromatic rings to salophene-uranyl complexes (Chart 3).[26] Two types of interactions may stabilize the complex formed, *viz.* coordination to the uranyl cation and π-π stacking of the aromatic rings of host and guest. The distance between the nearly parallel, aromatic cleft walls of ~5.7–8.1 Å is approximately the same as the regarded optimal (6.8 Å) for π-π stacking.[27] Aldehyde **15** was prepared from 2,3-dihydroxybenzaldehyde and benzyl bromide in

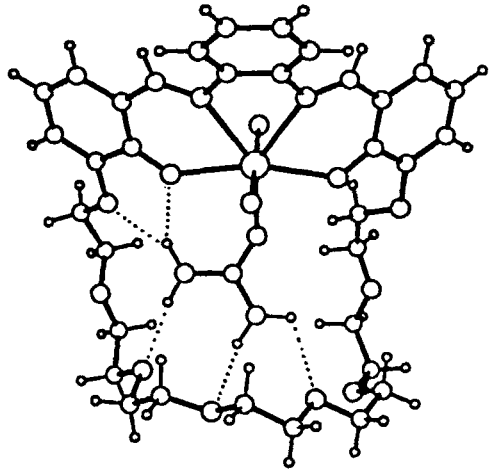
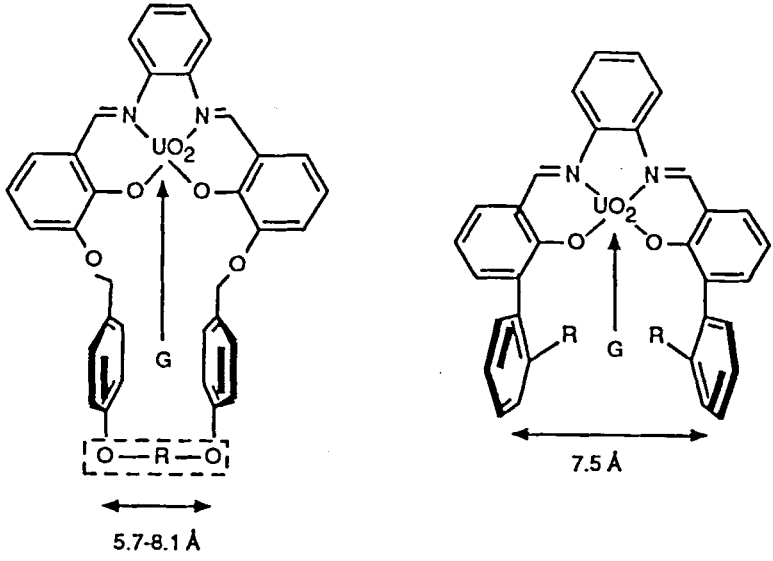


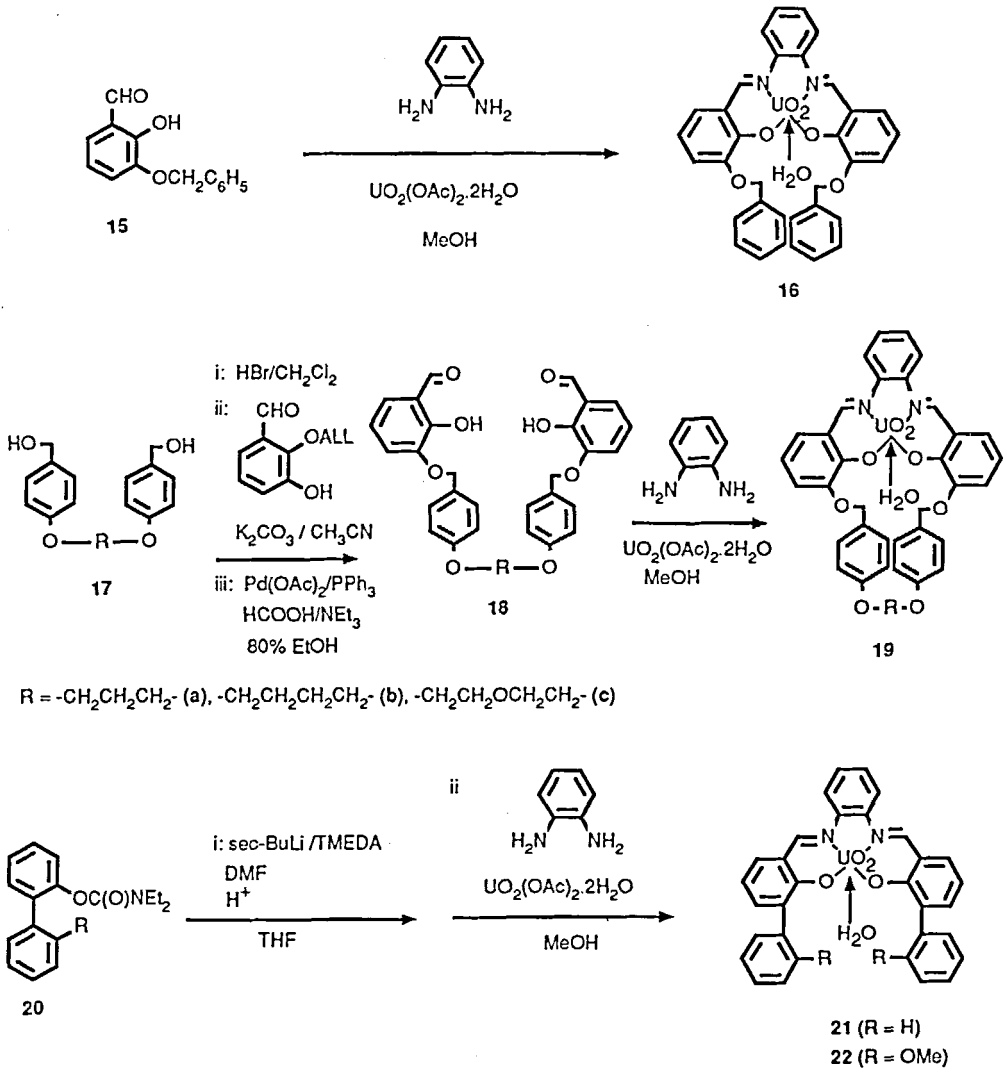
FIGURE 9 X-ray structure of **14**.urea ($M=UO_2^{2+}$).

Chart 3



DMSO with 2 equiv of NaH to achieve selective introduction of the benzyl group in the 3-position (Scheme 3). Condensation of aldehyde **15** and 1,2-benzenediamine gave, after the addition of uranyl acetate, the metallocleft **16**.

In order to study the effect of rigidifying and varying the spacer length on the complexation behaviour of this type of metalloclefts, macrocycles **19** were prepared. Starting from 4-hydroxybenzyl alcohol the diols **17** were synthesized by selective

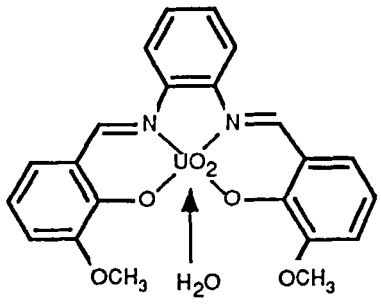


Scheme 3

alkylation of the phenolic oxygens. Diols **17** were converted to the corresponding dibromides followed by reaction of the dibromides with 3-hydroxy-2-(2-propenoxy)-benzaldehyde to afford the diallyl compounds. Deallylation could be achieved with $Pd(OAc)_2$, PPh_3 and $HCOOH/NEt_3$ to give aldehydes **18**. Macrocyclization of dialdehydes **18** with 1,2-benzenediamine was carried out by a slow simultaneous addition to a refluxing solution of $UO_2(OAc)_2.2H_2O$ in methanol to afford macrocycles **19** in 50% yield.

Another type of metallocleft is based on biphenyls. The carbamates **20** could be obtained by reaction of 1,1′-biphenyl-2-ol or the monomethyl ether of 1,1′-biphenyl-2,2′-diol with diethylcarbamoyl chloride. Treatment of carbamates **30** with *sec*-BuLi,

Chart 4



23

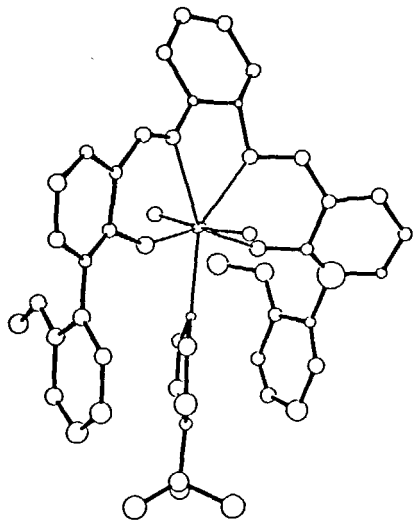


FIGURE 10 X-ray structure of **22**.4-*tert*-butylpyridine.

TMEDA and DMF in THF afforded the biphenyl aldehydes. Addition of uranyl acetate to a refluxing solution of the aldehyde and 1,2-benzenediamine in methanol gave the metalloclefts **21** and **22**. In order to study the influence of the cleft on the complexation properties we synthesized also non-cleft compound **23** (Chart 4).

From ^{1}H NMR spectroscopy experiments it was clear that the neutral guests coordinate with their Lewis basic site to the Lewis acidic uranyl and consequently we concluded that the neutral molecule is in the metallocleft. The X-ray structure of one complex is depicted in Figure 10. Polarography proved to be an excellent technique for determining the stability of our complexes of *metallo*clefts/*metallo*macrocycles and *neutral* molecules in solution. From shifts of the half-wave potentials and the limiting currents in titration experiments the free energies of complexation were calculated.

A range of *neutral* molecules, *e.g.* pyridine (-derivatives), pyridine-N-oxide, isoquinoline, benzylamine and benzamide, afforded stable complexes with free energies of complexation up to more than 6.3 kcal mol^{-1}.

The introduction of an extended cleft results in more stable complexes, compared to non-cleft compound **23**. For the flexible metallocleft **16**, increases of stability of the complexes up to 1.7 kcal mol^{-1} were found. Rigidifying the cleft **16** gives even more stable complexes with a maximum stability for complexes of **19b** in most cases. The maximum stability increase is 2.2 kcal mol^{-1} for the **19b**.benzylamine complex. In the case of **19b**.4-aminopyridine, **19b**.pyridine-N-oxide, and **19c**.pyridine-N-oxide the complex stabilities were too high to be measured. In nearly all cases **19b** forms the most stable complexes. Molecular modelling shows a distance of 6.8–6.9 Å for the benzyl groups of cleft **19b**, which is the regarded optimal for π-π stacking.[27] The biphenyl based hosts show stability-increases of the complexes up to 1.6 kcal mol^{-1} compared to **23**. The distance between the aromatic rings of the biphenyl clefts of 8.25 Å may be the reason that the stability-increase is less as for the hosts **19** with distances closer to the optimal of 6.8 Å.

Studies to explore the concept of co-complexation of electrophilic metal ions are in progress.

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