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# Complexation of neutral molecules by synthetic hosts

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Abstract - The interactions of neutral polar molecules with synthetic (macrocyclic) hosts are described. Extraction, NMR spectroscopy, polarography, and membrane transport studies have been carried out in order to understand these interactions. A step-wise process is described in which ultimately a general approach for a rational design of hosts is obtained. This approach has finally led to the first transfer of urea across a membrane by a neutral host (carrier) in which binding sites are placed in such a way that all possible interactions with urea are indeed used.

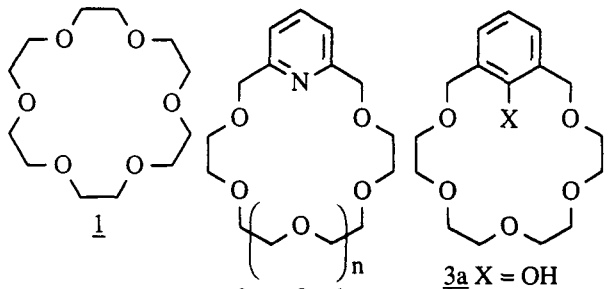
## INTRODUCTION

Since the pioneering work of Pedersen, Cram, and Lehn on macrocyclic hosts, the majority of studies has been devoted to the interaction with cationic species (ref. 1). More recently the interaction of synthetic hosts with neutral molecules and anionic species is also studied. One of the central themes in our group for many years is the interaction of neutral molecules like nitromethane, malononitrile, and urea with synthetic (macrocyclic) hosts. Our concept has developed from the use of hydrogen bonds between donor atoms of the host and weakly acidic protons of the guest, via $H^+$ assisted complexation to a more general approach in which a pH independent electrophilic metal center is immobilized in the host.

## INTERACTION OF CROWN ETHERS WITH NEUTRAL MOLECULES

Our early work dealt with interactions between one of the first synthetic hosts 18-crown-6 (1) and nitromethane or malononitrile. The X-ray analysis of the complexes of 18-crown-6 and nitromethane and malononitrile showed a stoichiometry of host to guest of 1 : 2. On both faces of the 18-crown-6 one guest is bound via three or two hydrogen bonds, respectively (ref. 2). Determination of the association constants by NMR spectroscopy showed a remarkable difference between the two guests. When nitromethane was used as guest both a 1:1 complex and a 1:2 complex were present in $C_6D_6$ at 300 K ($K^{1:1}$ = 1.2 $l \cdot mol^{-1}$; $K^{1:2}$ = 2.5 $l \cdot mol^{-1}$). The complexation of 18-crown-6 and malononitrile gave essentially only a 1:1 complex with a much larger association constant in $C_6D_6$ at 300 K ($K^{1:1}$ = 150 $l \cdot mol^{-1}$) when compared with nitromethane (ref. 3). The complexation of malononitrile and the pyrido-crown ethers 2 and the 1,3-xylyl-crown ethers 3 were studied in more detail by NMR spectroscopy in $C_6D_6$ at 298 K. The results are given in Table 1. As can be seen from Table 1 the standard free energies of complexation $\Delta G^\circ$ do not vary to a large extent. The large differences in the standard enthalpies $\Delta H^\circ$ are in general "compensated" by the entropy contribution $T\Delta S^\circ$. This means that the contribution of the enthalpy by the formation of hydrogen bonds is nearly lost by the decrease in entropy due to a reduced mobility of the two species in the complex.

The idea of increasing the interaction by "preorganizing" (ref. 2c and 4) the host proved not very successful. The standard free energy $\Delta G^\circ$ of the complexation of the hosts 4 with malononitrile are 8.4 $kJ \cdot mol^{-1}$ in $C_6D_6$ at 293 K. X-ray analyses of both 4a·$CH_2(CN)_2$ and 4b·$CH_2(CN)_2$ showed hydrogen bonds to the "outer" methoxy substituents. Comparison of these structures with the structure of the free hosts 4a and 4b showed that only a minor reorganization occurs upon complexation. It was therefore concluded that the less favorable interaction with the less basic anisole oxygens could not be overcome by the preorganization.



1



2 n = 0 - 6



3a X = OH
3b X = OAlkyl
3c X = COOH
3d X = COOAlkyl
3e X = $SO_3H$

TABLE 1. Thermodynamic parameters for 1 : 1 complexation of the crown ethers 2 and 3 with $CH_2(CN)_2$ at 298 K in $C_6D_6$ in kJ/mol.

| comp. | ΔH° | TΔS° | ΔG° |
|---|---|---|---|
| 2 n = 0 | -26.4 | -19.7 | -6.7 |
| 2 n = 1 | -34.7 | -25.5 | -9.2 |
| 2 n = 2 | -21.8 | -17.6 | -4.2 |
| 2 n = 3 | -18.0 | -15.1 | -2.9 |
| 2 n = 4 | -14.6 | -11.7 | -2.9 |
| 2 n = 5 | -13.4 | -10.5 | -2.9 |
| 2 n = 6 | -16.7 | -13.4 | -3.3 |
| 3a | -18.4 | -14.2 | -4.2 |
| 3b | -19.2 | -13.4 | -5.9 |
| 3c | -7.9 | -2.1 | -5.9 |
| 3d | -50.2 | -41.1 | -8.8 |

The X-ray analysis of the complex between 18-crown-6 (1) and urea shows one urea, bonded via two hydrogen bonds, at both faces of the macrocycle (ref. 2d). However, hosts like 18-crown-6 and the pyrido-crown ethers 2 are unable to transport urea efficiently from neutral aqueous phase into chloroform phase (ref. 5). Less than four percent of the host is occupied when excess urea was offered in the aqueous phase. It was therefore decided to increase the interaction by protonation of the pyrido-crown ethers 2. Transfer of urea from water (pH < 1) into the chloroform layer by the protonated pyrido-crown ethers 2 increased by only a factor of 3 compared to the transfer of the unprotonated hosts (ref. 5).

## HOSTS WITH INTRA-ANNULAR ACIDIC GROUPS

In the approach described above three species have to combine which is in general not favorable in terms of free energy of complexation, so hosts with covalently linked intra-annular acidic groups have been synthesized. Measurements of the $pK_a$ (ref. 6) of the 2-carboxylic-1,3-xylyl-crown ethers 3c showed that the $pK_a$ values of 3c (n = 0; $pK_a$ = 5.31) and 3c (n = 1; $pK_a$ = 5.71) are considerably higher than those of the 3c (n = 2 - 6; $pK_a$ = 4.38 - 3.93). The reason is that the two smaller rings are stabilized by an intra-annular hydrogen bond between the proton and one of the oxygen atoms. The macrocycles 3c (n = 2, 3) have a somewhat larger $pK_a$ than the larger rings due to encapsulation of one water which is bound via three hydrogen bonds to the host. The measurements of the $pK_a$ in the presence of 1.5 % urea showed small, but significant, changes ($\Delta pK_a$ = 0.04, 0.10, and 0.10 for 3c n = 1, 5, and 6, respectively). The explanation that the shifts in $pK_a$ are due to interaction between the host and urea and that the two largest rings are able to encapsulate urea was supported by the X-ray analysis of 3c·urea. The urea is encapsulated by the host having a hydrogen bond between the acidic proton and the carbonyl group of urea and the four hydrogens of urea form bonds with oxygen atoms of the ring. (ref. 6d).

## HOSTS WITH "IMMOBILIZED" ELECTROPHILIC CENTERS

Although the hosts with intra-annular acidic groups were an improvement they will only function properly when the acidic groups are protonated or when the proton is transferred to the guest. The role of a proton as an electrophilic center can be generalized to metal cations as electrophilic center. The first example that this is indeed possible was obtained from the X-ray analysis (Fig. 1) of 2 (n = 4) : urea : $LiClO_4$ (1 : 2 : 1). It showed that the lithium ion and one urea are encapsulated by the ring and the second urea is bound to lithium and to the encapsulated urea (ref. 6a).

After the demonstration that metal cations can assist in the complexation of neutral molecules by synthetic hosts we decided to "immobilize" this electrophilic center in the host. The well-known salen moiety has been selected because of its ability to coordinate to a variety of transition metal cations. The key step in the synthesis of 5 is the macrocyclization using the Schiff-base formation between the appropiate aldehyde and diamine. It proved essential to use $Ba^{2+}$ as template ion that is complexed to the oxygen atoms as has been shown by several X-ray structures (ref. 7). After this macrocyclization the barium complex was reacted with nickel or copper acetate leading to *hetero*-dinuclear complexes. Electrochemical measurements showed that the redox properties are strongly changed by co-complexation of alkali or alkaline-earth metal cations (ref. 7b and 8). Recently it has been shown that electrocatalytic conversion of benzyl chloride and acetic anhydride to phenylacetone can be achieved with the *hetero*-dinuclear complex 5·$Ba^{2+}$ (M = Ni, n = 1) but not with the mononuclear nickel complex 5 (ref. 9). With uranyl acetate the mononuclear uranyl complexes 5 were obtained directly.

The X-ray analysis of 6 (n = 3)·urea showed the validation of this new concept (Fig. 2). The carbonyl group of the encapsulated urea is coordinated to the electrophilic uranyl cation and the four hydrogen atoms of urea form hydrogen bonds to the oxygen atoms of the ring.

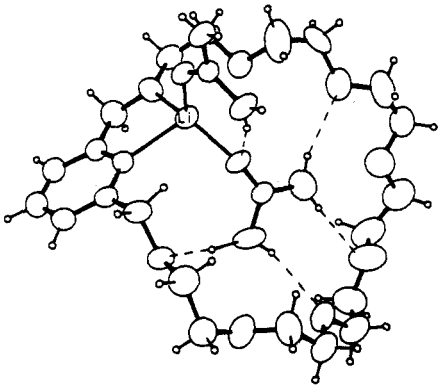


Fig. 1 X-ray structure of
2(n = 4) : urea : $Li^+$ (1 : 2: 1)

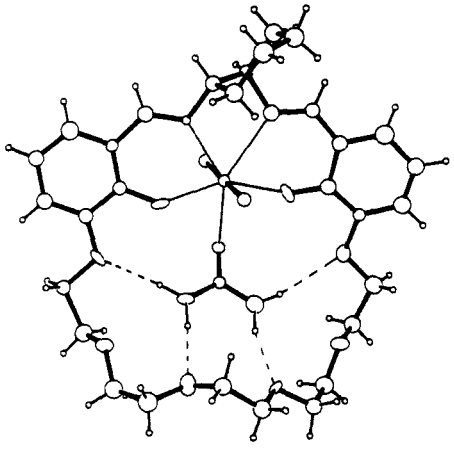
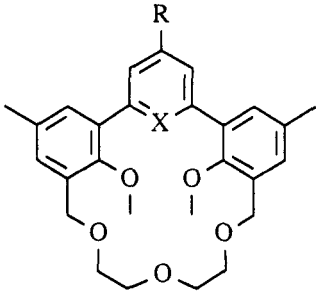
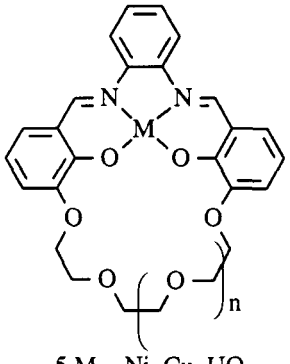


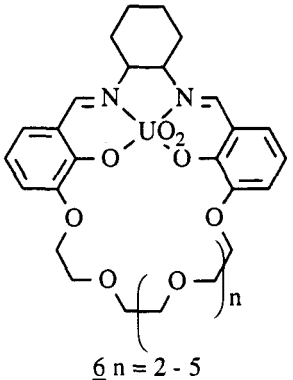
Fig. 2 X-ray structure of
6 (n = 3) : urea (1 : 1)



4a R = Me, X = C-OMe
4b R = Ph, X = N



5 M = Ni, Cu, $UO_2$
n = 1 - 5



6 n = 2 - 5

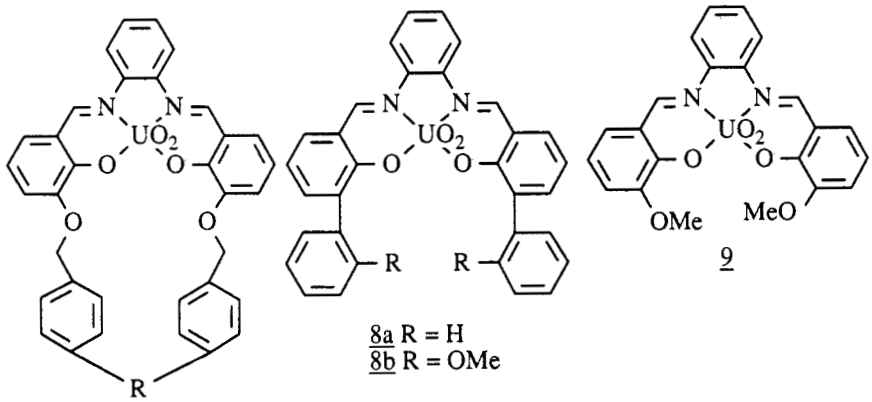
Because of the rather low solubility of the uranyl complexes 5 it was decided to replace the aromatic diamine by an aliphatic diamine. The synthesis of 6 follows essentially the same route as has been applied for 5 and as expected the solubility of the uranyl complexes 6 is much higher (ref. 10). Extraction of urea from an aqeous phase into the organic phase ($CDCl_3$) showed that 6 (n = 2) is not able to transfer urea, whereas 6 (n = 3-5) have an efficiency of more than 95 %. The association constants of the 6·urea complex in $CDCl_3$ at 298 K are < 100, > 1.0 $10^8$, > 2.5 $10^8$, and > 1.0 $10^6$ $l \cdot mol^{-1}$, respectively (ref. 10).

Polarography has been used to determine the association constants with several neutral polar guests in $CH_3CN$ and they are given in Table 2. It can be seen that 6 (n = 2) showes only very weak, if any, interactions with these polar guests. Also the larger macrocyles show moderate interactions with acetone, formamide, and acetamide. The data for N-methylurea show a ring-size selectivity. The association constants for 6·urea (n = 3 - 5) were too high to be determined by this technique but are at least > $10^5$ $l \cdot mol^{-1}$. The fact that urea is bound more strongly than N-methylurea is due to steric hindrance of the methyl group and due to the "loss" of one hydrogen bond in the latter complex.

TABLE 2. Association constants (l/mol) of the uranyl complexes 6 in $CH_3CN$ determined by polarography at 293 K.

| | n = 2 | n = 3 | n = 4 | n = 5 |
|---|---|---|---|---|
| acetone | <10 | <10 | <10 | <10 |
| formamide | <10 | 170 | 80 | <25 |
| acetamide | <10 | <25 | 90 | <25 |
| N-methylurea | <10 | 900 | 2100 | 17000 |
| urea | <10 | $>10^5$ | $>10^5$ | $>10^5$ |

The hosts 7 and 8 contain, besides the electrophilic uranyl, aromatic rings instead of oxygen atoms as coordination sites for π-π-inteactions with aromatic guests. Polarography has been used to determine the free energy of complexation with a variety of aromatic guests in $CH_3CN$ at 293 K. The results are presented in Table 3 (ref. 11).




8a R = H
8b R = OMe

9

7a R = $O(CH_2)_3O$
7b R = $O(CH_2)_4O$
7c R = $O(CH_2)_2O(CH_2)_2O$
7d R = HH

The introduction of a cleft in the hosts leads to a stabilization up to 7.1 kJ·mol$^{-1}$ due to π-π-stacking, as compared to host 9. Macrocyclic hosts give a somewhat larger stabilization (up to 9.2 kJ·mol$^{-1}$).

TABLE 3. Free energies of complexation -ΔG (kJ/mol) in $CH_3CN$ determined by polarography at 293 K.

| | 7a | 7b | 7c | 7d | 8a | 8b | 9 |
|---|---|---|---|---|---|---|---|
| pyridine | 15.31 | 16.28 | <10.5 | 14.64 | 11.00 | 7.87 | 10.67 |
| 4-methylpyridine | 18.12 | 16.78 | 15.69 | 16.19 | 14.77 | 9.58 | 12.09 |
| 4-t-butylpyridine | 17.49 | 14.39 | <10.5 | 13.35 | 14.69 | 9.83 | 11.72 |
| 2,6-dimethylpyridine | <10.5 | 11.92 | <10.5 | <8.4 | <10.5 | <6.3 | <6.3 |
| 4-aminopyridine | 21.80 | >23.4 | 23.22 | >16.7 | 19.20 | 19.25 | >16.7 |
| pyridine N-oxide | 26.36 | >26.4 | >26.4 | >16.7 | 19.62 | 20.04 | >16.7 |
| aniline | <10.5 | <10.5 | <10.5 | <8.4 | <10.5 | <6.4 | <6.3 |
| isoquinoline | 15.15 | 15.10 | <10.5 | 13.26 | <10.5 | 11.25 | <6.3 |
| benzylamine | 19.25 | 19.92 | 19.50 | 12.84 | 17.28 | 14.35 | 10.54 |
| benzonitrile | 12.09 | 14.73 | <10.5 | 12.55 | <10.5 | <6.3 | <6.3 |
| benzamide | 15.73 | 18.87 | <10.5 | 13.68 | <10.5 | <6.3 | 17.87 |
| N-phenylurea | <10.5 | 14.31 | <10.5 | <10.5 | 16.19 | 12.09 | 15.86 |
| methyl phenyl sulfoxide | 15.44 | 14.10 | <10.5 | 11.88 | <10.5 | 12.64 | 13.01 |

Although determination of the free energy of complexation provides much information on which interactions are important free energies give only qualitative information for the selective separation across liquid membranes. The selectivity across a membrane is mainly determined by the product of the association constant and the partition coefficient ($K_{ex} = K_{ass} \cdot K_p$) and the diffusion constant ($D_m$) (ref. 12). Measurements of the flux of urea by these uranyl containing hosts through supported liquid membranes have been performed (ref. 12) and showed that 6 (n = 2) is hardly able to transport urea, whereas 6 (n = 3 -5) show a flux up to thirteen times the blank transport at a host concentration of 6.0 mmol·l$^{-1}$. The fact that the host 6 (n = 2) is not a good carrier for urea is consistent with the very low association constant. The host 6 (n = 3) is the most efficient carrier, which was anticipated from CPK modelling showing the best fit of urea in this host and the X-ray analysis of 6 (n = 3)·urea (ref. 12b).

## CONCLUSIONS

It has been shown that the concept of proton assisted complexation of neutral polar guest in synthetic hosts can be generalized to "immobilized" electrophilic metal centers. This has led, to the best of our knowledge, for the first time to transfer of urea across a membrane by a synthetic host (carrier) in which all possible sites for interaction with urea are indeed used.

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