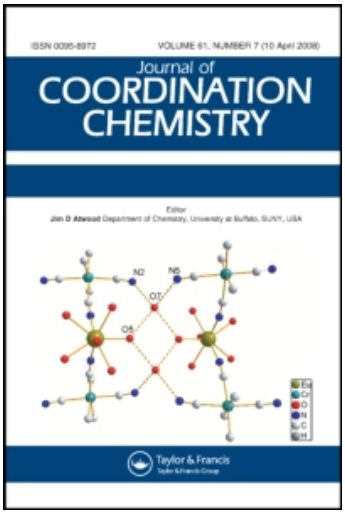

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Novel Strategies for the Complexation of Neutral Guest Molecules by Synthetic Macrocyclic Hosts

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NOVEL STRATEGIES FOR THE COMPLEXATION OF NEUTRAL GUEST MOLECULES BY SYNTHETIC MACROCYCLIC HOSTS

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Abstract Complexes of macrocyclic polyethers with neutral guests have been studied in solution. The first part, a systematic study of complexes of malononitrile with a variety of macrocyclic polyethers, allowed the evaluation of the thermodynamic parameters of complexation. The second part deals with the complexation of urea. Complexes with simple 18-membered macrocycles were prepared. Protonation of urea allowed the phase transfer of urea from aqueous to chloroform solution. Finally the complexation of urea by 2-carboxy-1,3-xylyl crown ethers is described.

Keywords: Macrocyclic polyethers, malononitrile, complexation of urea

INTRODUCTION

Although in his pioneering papers Pedersen already indicated the ability of crown ethers to form complexes with neutral molecules, i.e. thiourea, hithertoo the complexation of centrosymmetrical cations by these host molecules has received most of the attention in crown ether chemistry. However, the large number of uncharged and anionic polyfunctional molecules in both biochemical and industrial processes has stimulated a growing interest in the encapsulation of such species by synthetic receptor molecules. In our research group we have been exploring the complexation of synthetic macrocyclic ligands and neutral molecules. One of the targets is the design and synthesis of receptor molecules for the selective complexation of urea. In this paper we will discuss firstly our fundamental work on the complexation of macrocyclic polyethers

with one simple neutral guest species viz. malononitrile. The second part will deal with novel strategies to improve the stability of complexes with polyfunctional guests in particular urea.

COMPLEXATION OF NEUTRAL MOLECULES BY MACROCYCLIC LIGANDS IN SOLUTION

Host-guest interactions in solution are known from enzyme-substrate reactions between organic molecules in biochemical systems. In 1894 Fischer[1] already stated that the substrate molecule fits the active site of the enzyme in a complementary lock-and-key relationship. Later it was shown that an enzyme is very often relatively flexible, and undergoes a conformational change upon reaction with a substrate.[2] Organic chemists have been successful in imitating such enzyme interactions with cyclodextrins, cyclic basket-like shaped compounds based on α-(1-4)-linked oligo-D-glucose units.[3] These cyclodextrins are water soluble as a result of their hydrophilic exterior and are able to include organic guest molecules as a result of their lipophilic cavity.[4] Van der Waals forces, hydrogen bonding, and hydrophobic interactions can provide the driving force for the host-guest complexation of these systems.[4b] In the absence of guest molecules the cyclodextrin cavity is filled with water molecules. This means that if a guest is added to the aqueous cyclodextrin solution first desolvation must take place before the guest is able to enter the cavity. The advantage of such an exchange is that the host-guest complexation occurs without a large conformational change of the host.[5]

Interactions between cyclodextrins and neutral host molecules have been determined by spectroscopic methods such as NMR,[6] circular dichroism (CD),[4b] and calorimetry.[4b]

A class of synthetic compounds resembling the cyclodextrins, in a sence that they have aromatic rings as hydrophobic "walls", are the cyclophanes. The inclusion of neutral organic guests in

the hydrophilic cavity of water soluble cyclophanes has been shown by fluorescence and NMR spectroscopy, with association constants ranging from 10^2-10^8 L Mol^{-1}.[7] Changing the structure of these cyclophanes, e.g. by the incorporation of more aromatic moieties renders these compounds soluble in organic solvents, but hithertoo only few examples of host-guest interactions in solution have been reported. Whirtlock and Jarvi[8] have reported 'very low' stability constants, measured from Aromatic Solvent Induced Shifts (ASIS), for complexes between aromatic solvents and naphthalenophanes, however without providing thermodynamic parameters. Recently, Bauer and Gutsche have shown the complexation of various amines by calixarenes in organic solvents.[9]

NMR spectroscopy demonstrated that in solution these guests are also included in the cavity of the calixarene. In the presence of the guest ASIS values, decreased relaxation times, and enhanced free energies of activation for conformational inversion of the host were observed.

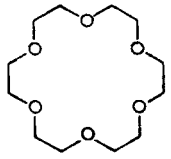
Cram and coworkers[10] have shown that cavitands with cylindrical cavities are able to include linear guest molecules such as CS_2 in an enthalpy favoured and an entropy disfavoured complexation with association constants ranging from 0.8-13.2 L Mol^{-1}.

Recently Collet and coworkers[11] have described cryptophanes, three-dimensional flexible hosts with spherical cavities for neutral guest molecules. The dimension of the cavity of these cryptophanes may be changed by structural modifications of the host. Complexes with $CHCl_3$, CH_2Cl_2, and $CHBr_3$ with association constants ranging from 40-470 L Mol^{-1} have been reported.

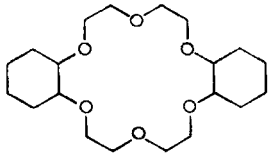
COMPLEXATION OF MALONONITRILE

In this paper the results of a quantitative systematic study of the thermodynamic stabilities of complexes of crown ethers with malononitrile are given. Crown ethers with various functionalities

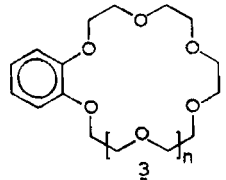
were studied in both C_6D_6 and $CDCl_3$ as solvent, using variable-temperature ^1H NMR spectroscopy. The objective of the work described was to gain a better understanding of host-guest interactions in solution in relation to the crown ether structure. As an interesting result we found that the methodology provides valuable information about the conformation of macrocycles in the uncomplexed state. The observation that when a crown ether is added to a solution of malononitrile in $CDCl_3$ or C_6D_6 the signal of the malononitrile protons in the ^1H NMR spectrum shifts downfield, was used to determine the association constants of malononitrile with a number of crown ethers. In a typical experiment ten samples



1

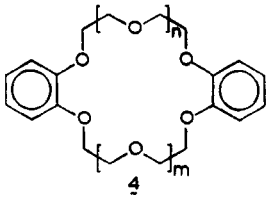


2



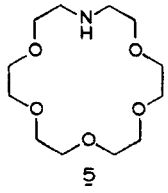
3

a, n=1 d, n=4
b, n=2 e, n=5
c, n=3



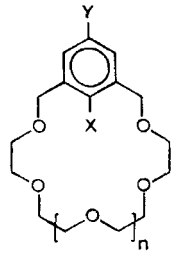
4

a, m=n=1
b, m=n=2
c, m=1, n=5
d, m=2, n=5



5

6 X=Y=H, n=1
7 X=$OCH_2CH=CH_2$, Y=Cl, n=1
8 X=OH, Y=Cl, n=1
10 X=CO_2CH_3, Y=H, n=1



9 X=COOH, Y=H
a, n=0
b, n=1
c, n=2
d, n=3
e, n=4
f, n=5
g, n=6

were prepared in which the crown ether concentration was kept constant (0.04 M) and the malononitrile concentration was varied from 0.01 to 0.20 M. The chemical shift of malononitrile in the samples was measured at four different temperatures for 11 different crown ethers (1-10).

The chemical shift of the protons of $CH_2(CN)_2$ (taking into account only 1:1 complexation) is calculated from eq. 1.

$$\delta_{calcd} = X_M\delta_M + X_{CE.M}\delta_{CE.M} \qquad \text{(eq. 1)}$$

Of these parameters only δ_M, the chemical shift of free $CH_2(CN)_2$ is known, $\delta_{CE.M}$ the chemical shift of $CH_2(CN)_2$ in the complex, X_M and $X_{CE.M}$, the mole fractions of free and complexed $CH_2(CN)_2$, respectively, are unknown. However, X_M and $X_{CE.M}$ can be calculated from a minimum for the function F, given in eq. 2, obtained for a series of samples with an iterative procedure.[12] In this procedure a correction is made for the concentration dependency of δ_M.

$$F = \sum(\delta_{obsd,i} - X_{M,i}\delta_M - X_{CE.M,i}\delta_{CE.M})^2 \qquad \text{(eq. 2)}$$

From the calculated mole fractions the association constants (K) can be calculated from eq. 3.

$$CE + M \rightleftharpoons CE.M \qquad K_{11} = \frac{[CE.M]}{[CE].[M]} \qquad \text{(eq. 3)}$$

$$CE.M + M \rightleftharpoons CE.M_2 \qquad K_{12} = \frac{[CE.M_2]}{[CE.M].[M]} \qquad \text{(eq. 4)}$$

When both 1:1 (eq. 3) and 1:2 (eq. 4) complexes can be formed, eq. 2 can easily be modified, assuming that the chemical shift of malononitrile in both 1:1 and 1:2 complexes is the same.[12] Taking into account both 1:1 and 1:2 complexation we obtained K_{11} values at four temperatures. From a plot of $\ln(K_{11})$ vs. T^{-1} the thermody-

namic constants ΔH^{o} and ΔS^{o} for 1:1 complexation were calculated (Table I). In general 1:2 complexation was negligible. This was demonstrated by a lower minimum for F when only 1:1 complexation is taken into account or even by the absence of a minimum for F. Only in the case of 18-crown-6 1:2 complexation was observed with K_{12} = 11 L Mol^{-1}.

TABLE I Thermodynamic constants[a] for 1:1 complexation of crown ethers (CE) with malononitrile at 298 K.

	C_6C_6				$CDCl_3$			
CE	K_{11}[b]	$-\Delta H^{o}$	$-T\Delta S^{o}$	$-\Delta G^{o}$	K_{11}	$-\Delta H^{o}$	$-T\Delta S^{o}$	$-\Delta G^{o}$
1	159	14.2	11.0	3.2	31	5.3	3.3	2.0
2	63	8.6	6.1	2.5	43	5.6	3.3	2.2
3a	30	8.0	5.9	2.0	50	5.4	3.1	2.3
4a				c	113	4.7	1.9	2.8
5	34	5.7	3.6	2.1				d
6	10	4.7	3.3	1.4	11	5.2	3.8	1.4
7	11	4.6	3.2	1.4				d
8	5	4.4	3.4	1.0	5	4.5	3.6	1.0
9b	11	1.9	0.5	1.4				e
9c	5	3.9	2.9	1.0				e
10	39	12.0	9.9	2.2				e

[a] K in L Mol^{-1}, ΔH^{o}, $T\Delta S^{o}$, and ΔG^{o} in kcal/mol.

[b] Accuracy 10%.

[c] Insoluble in C_6D_6.

[d] Chemical shift difference too small to obtain reliable results.

[e] Not measured.

The results summarized in Table I show that the thermodynamic constants depend on solvent, ring size, the nature of the donor atoms, and the presence of intraannular substituents.

The influence of the solvent on the complexation of malononitrile was studied by comparing the complexation in $CDCl_3$ and in C_6D_6. The smaller enthalpy and entropy changes upon complexation in $CDCl_3$ reflect the greater polarity of $CDCl_3$, which means stronger solvation of both malononitrile and the crown ether. These solvent interactions must be broken before complexation can occur, resulting in a less favourable enthalpy change. Desolvation of both the crown ether and malononitrile prior to complexation will result in a positive entropy change.

To study the influence of decreased flexibility of the crown ether one or two CH_2CH_2 units of 18-crown-6 (1) were replaced by cyclohexyl (2) and benzo (3 and 4) units. A lower association constant is observed for the complexation of malononitrile by dicyclohexyl-18-crown-6 (2) as compared with 18-crown-6 (1) in C_6D_6. This can be attributed to the lower flexibility of the crown ether ring. The complexation of malononitrile by (di)benzo-18-crown-6 is weaker owing to the electron-withdrawing properties of the benzo units, which render the oxygen atoms next to the benzene ring weaker hydrogen bond acceptors. This effect has been found also for the complexation of t-butylammonium salts when a CH_2CH_2 unit in 18-crown-6 was replaced by an aryl unit, resulting in a loss of binding energy of 3.5 kcal/mol.[13]

Compared with the complexation in C_6D_6, benzo-18-crown-6 and dibenzo-18-crown-6 are relatively efficient complexing agents for malononitrile in $CDCl_3$. It might be possible that interaction of the D atom of $CDCl_3$ with the π-electrons of the benzo units[14,15] provides a preorganization of the macrocycle, and upon complexation desolvation then contributes to a favourable entropy change.

The presence of a nitrogen atom in the macrocyclic ligand reduces the enthalpy from -14.2 kcal/mol (18-crown-6) to -5.7

kcal/mol for the complexation by aza-18-crown-6 (5). This observed lower negative enthalpy may be attributed to a stronger intraannular interaction in the uncomplexed aza-18-crown-6.[16] Dibenzo-18-crown-6 (4) is nearly insoluble in C_6D_6. Therefore thermodynamic parameters could not be obtained in C_6D_6.

The less negative enthalpy of complexation of malononitrile with 1,3-xylyl-18-crown-5 (6) compared with 18-crown-6 is due to the reduction of the number of oxygen atoms in the macroring. A similar difference in the free energy of complexation has been reported for the corresponding t-butylammonium hexafluorophosphate complexes of these crown ethers.[17] For the complexation of t-butylammonium salts Cram and coworkers[17] have found, that the replacement of a $CH_2CH_2OCH_2CH_2$ unit in 18-crown-6 by an aromatic unit results in a loss of binding energy, which is larger for a benzo unit than for a 1,3-xylyl unit.

Intraannular substituents can have a strong influence on complexation. Weak binding results from the introduction of a carboxylic acid group as in 2-carboxyl-1,3-xylyl-18-crown-9 (9b). From the X-ray crystal structure[18] and pK_a measurements[19] of this 18-membered macrocycle, we know that a strong intraannular hydrogen bond is formed between the carboxylic acid group and an oxygen atom of the crown ether ring. Before complexation can take place this hydrogen bond must be broken. When compared with the acid, the methyl ester of 2-carboxyl-1,3-xylyl-18-crown-5 (10) clearly shows the effect of an intraannular H-bond. The binding enthalpy of malononitrile with the ester is much stronger than with the acid because no hydrogen bonds to the crown ether have to be broken. The additional binding site of the ester group can be used to form a hydrogen bond with the guest. In the larger 2-carboxyl-1,3-xylyl-21-crown-6 (9c), the intraannular hydrogen bond is much weaker,[19] and consequently a more negative ΔH° of complexation is observed even though the ring lacks the optimum size of 18 atoms. Lower association constants for crown ether complexes with

intramolecular transannular hydrogen bonds were also found for metal ions.[20]

In 2-hydroxy-5-chloro-1,3-xylyl-18-crown-5 (8) there is also a hydrogen bond between the hydroxyl group and one of the benzylic oxygen atoms of the crown ether ring.[21] This interaction is probably not very strong as can be seen from the small influence of the ring size on the acidity of 2-hydroxy-1,3-xylyl crown ethers.[21] Moreover, a phenolic hydroxyl group is not a very good hydrogen bond acceptor. Therefore, binding of malononitrile to 2-hydroxy-5-chloro-1,3-xylyl-18-crown-5 resembles the complexation to 1,3-xylyl-18-crown-5. In 2-allyloxy-5-chloro-1,3-xylyl-18-crown-5 (7), the situation is not much different. Although this macrocycle has one additional oxygen atom which might serve as an additional binding site,[22] the allyl group uses much space and causes steric interaction with the guest molecule. Therefore malononitrile is believed to bind to the crown ether only from the least hindered side, possibly using the allyl oxygen.

When all crown ethers are compared, both in $CDCl_3$ and C_6D_6 as the solvent, the large individual differences in ΔH^o and ΔS^o along the series are apparent. From a plot of ΔH^o vs. $T\Delta S^o$ (Fig. 1) it is obvious that there is an overall relationship between enthalpy and entropy of complexation.

Such a compensating effect of $T\Delta S^o$ on ΔH^o was previously reported by Izatt et al.[23] for the complexation of metal ions with 15-crown-5 and 18-crown-6, and by Michaux and Reisse[24] for the complexation of alkali cations with 12-crown-4, 15-crown-5, and 18-crown-6. Recently Inoue and Hakushi have studied the universal validity of the relationship between ΔH^o and $T\Delta S^o$ for the complexation of cations by a large number of different macrocyclic polyethers.[25] It can, at least in part, be attributed to the rigidity of a complex. If the host-guest binding is strong, the flexibility of the macroring in the complex will be limited, and consequently the loss of entropy upon complexation will be large. Desolvation

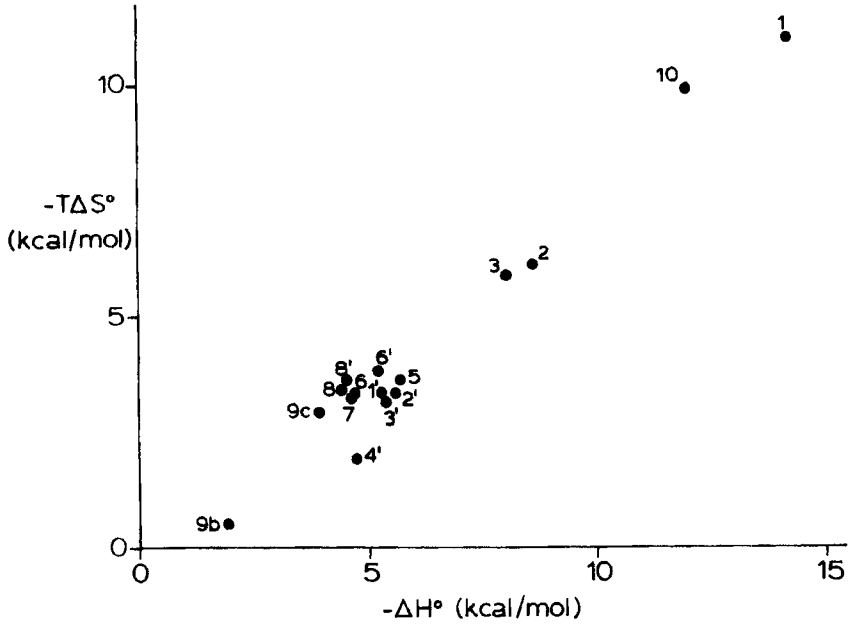


FIGURE 1 ΔH^{O} vs. $T\Delta S^{O}$ for 1:1 complexation of malononitrile by crown ethers in C_6D_6 and $CDCl_3$.

of both host and ligand is another important factor. The extent of replacing guest solvation by ligand donors is reflected in the intrinsic entropy change. For complexation of cations the parameters A and B of the linear relation $T\Delta S^{O} = A(\Delta H^{O}) + B$ have been determined, A = 0.76 and B = 2.4 kcal/mol.[25] For complexation of malononitrile by the macrocycles 1-10 in C_6D_6 and $CHCl_3$ we find A = 0.86 and B = 1.0 kcal/mol (n = 16, r = 0.99). The parameter B represents the intrinsic entropy change upon complexation and reflects mainly desolvation. Because neutral molecules are less strongly solvated than cations, B will be smaller for the complexation of malononitrile. The difference in the values of A for the complexation of neutral molecules (A = 0.86) and cations (A = 0.76) may be due to the contribution of hydrogen bonds in the complexation of neutral molecules. This type of interaction re-

quires a more defined relative orientation of the binding sites compared with the ion-dipole interactions in cation complexes.

Recently in our laboratory we also found an enthalpy-entropy compensation effect for the complexation of malononitrile by hemispherands.[26] Besides it was shown that complexation with a solvated host results in an entropically favoured process.

COMPLEXATION OF UREA

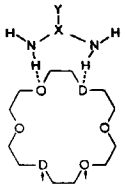
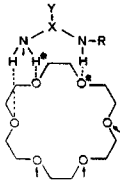
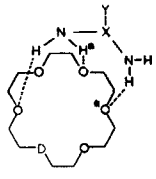
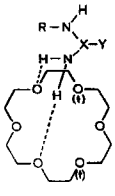
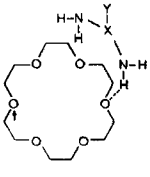
In one of the first papers on macrocyclic polyethers Pedersen[27] already reported that urea and thiourea increase the solubility of dibenzo-18-crown-6 in methanol, suggesting that there is some kind of interaction between these compounds. Although crystalline complexes of urea with different polyethers could not be obtained, with thiourea and related compounds several crystalline complexes have been isolated by Pedersen.

These complexes, prepared by dissolving the host and guest in hot methanol, crystallized upon cooling and were characterized by elemental analysis. Melting points of all the complexes were different from the uncomplexed macrocycles. Pedersen isolated crystalline complexes of thiourea with benzo-15-crown-5 (4:1), dibenzo-15-crown-5 (1:10), dibenzo-16-crown-5 (1:3), dibenzo-18-crown-6 (1:1), bis(butyl)benzo-18-crown-6 (6:1), benzocyclohexyl-18-crown-6 (6:1 and 5:1), dicyclohexyl-18-crown-6 (6:1), and dibenzo-24-crown-8 (7:2).

In the literature a few crystal structures of complexes between 18-membered macrocyclic ligands and urea analogues have been reported.[28-37] By comparing the NH-hydrogen bonding schemes of these complexes they can be arranged in five classes, types A-E,[28-37] as reflected in Table II.

When we added diethyl ether to a solution of 18-crown-6 and urea in methanol/chloroform, colourless crystals precipitated that

TABLE II Hydrogen bonding schemes of complexes between urea analogues (G) and 18-membered macrocyclic ligands (H).

Type	Structure[a]	X-Y		R	H:G	ref.
A		C=S		-	1:4[b]	29
		C=S		-	1:4[b]	30
B		C=S[c]	-	H	1:2	31
		C=O	-	C_6H_5	1:1	32
		C=N-R'[c,d]	-	H	1:2	33
C		C-S-t-Bu[c]		-	1:1	34
D		C=S	-	CH_3	1:2[e]	35
		C-S-t-Bu	-	H	1:2	36
E		$C=NH_2$	-	-	1:2	37

[a]Indicates hydrogen bond acceptor for the second guest molecule. [b]Only two guest molecules have a direct interaction with the host. [c]Between N^* and O^* a bifurcated hydrogen bond is formed. [d]R'=benzimidazoyl. [e]The RNH_2 interacts in a different way with a second host molecule.

were recrystallized from methanol/ethyl acetate. The material had a well-defined melting range of 146-148 °C and analyzed correctly for an adduct of urea and 18-crown-6 in a ratio of 5:1.[38]

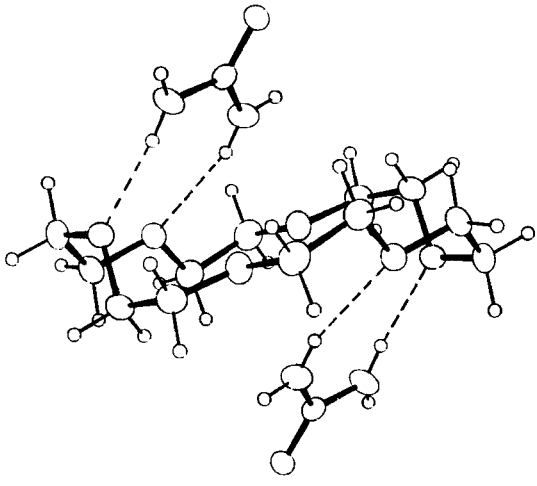


FIGURE 2 X-ray structure of the 18-crown-6.urea (1:5) complex; only two guest molecules are shown.

The crystal structure of this complex (Fig. 2) is best explained as consisting of 18-crown-6.urea (1:2) complexes linked by the remaining three urea molecules. The complex thus exists of layers of 18-crown-6 molecules, and layers of urea molecules, hydrogen bonded to each other. In the 1:2 crown ether.urea complex the urea molecules are situated each at one face of the macroring and are hydrogen bonded to the ring both via two hydrogen bonds to two adjacent oxygen atoms. The urea molecule is probably small enough to interact with both its functional groups with the crown ether. As the urea molecule is planar and the urea oxygen atom is directed away from the crown ether, only two hydrogen atoms are well-directed for hydrogen bonding with the host. Compared with the complexes given in Table II this complex can be classified as type A.

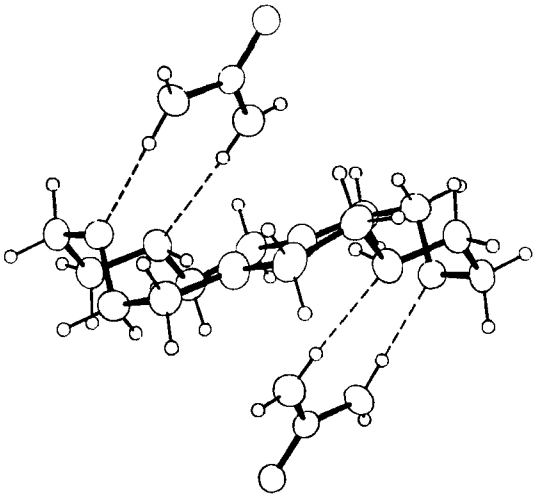


FIGURE 3 X-ray structure of the aza-18-crown-6.urea (1:5) complex.

In a similar way as used for the preparation of the urea complex of 18-crown-6 a 1:5 complex of aza-18-crown-6.urea was synthesized. Upon the addition of petroleum ether (bp 60-80 °C) to an equimolar solution of urea and aza-18-crown-6 in a mixture of methanol/chloroform white crystals precipitated which had a melting range of 127-130 °C. The crystal structure of this complex (Fig. 3) shows that no intraannular hydrogen bond is formed as reported for the diaza-18-crown-6.thiourea complex.[30] The structure of the complex is similar to the structure of the 18-crown-6.urea complex (type A).

Diaza-18-crown-6, (di)benzo-18-crown-6, dicyclohexano-18-crown-6, and crown ethers with less than 18 ring atoms, on the contrary, gave no solid adducts with urea using similar procedures.

In order to increase the stability of complexes of macrocyclic polyethers with urea we have investigated the effect of protonation of this neutral guest. Since urea is a very weak base and the amount of protonated urea (UrH^+) in a neutral aqueous solution

will be low [pK_a(urea, H_2O, 25 °C) = 0.10], we have studied previously the complexation of protonated guanidine (GuH^+) [pK_a(guanidine, H_2O, 25 °C) = 13.6]. This cation was regarded as a good model for protonated urea because these compounds are isoelectronic and have a comparable size and shape.

The complex formation of benzo and dibenzo crown ethers with uronium perchlorate was studied by means of two-phase liquid-liquid extraction experiments. An aqueous solution of urea and perchloric acid was equilibrated with a solution of a (di)benzo crown ether in $CDCl_3$. The amount of the uronium salt transferred to the organic phase was determined by enzymatic degradation with urease, after separation of the two liquid layers with an overall accuracy of 10%. The amount of urea transferred to the organic phase is expressed as the extraction efficiency, which is the ratio of the uronium ion concentration and the crown ether concentration in the organic phase. Obviously the urea is extracted as the corresponding uronium perchlorate complex. With an uronium perchlorate concentration of 1.7 M, present in an aqueous solution of 2.0 M urea in 28% perchloric acid, a reasonable extraction efficiency was obtained, and was chosen as the standard aqueous phase used in the two phase extraction experiments. The crown ether concentration in the organic phase has less influence on the extraction efficiency, and a crown ether concentration of 0.2 M in chloroform was chosen for the experiments. The urea determinations were carried out after 17 h of equilibration, since after this period the equilibrium is reached.

The results of the extraction experiments with benzo and dibenzo crown ethers with 18- to 33-membered rings are summarized in Table III. They show a striking analogy with the results of extraction experiments and membrane transport experiments with benzo[39] and pyrido[40] crown ethers and guanidinium salts.[39-41] The amount of uronium perchlorate extracted into the organic phase is considerably larger with crown ethers that have 27 or more ring

atoms than with the smaller crown ethers. These larger crown ethers are able to encapsulate the polar guest and this gives a complex with an apolar exterior and a polar interior. Such complexes will preferably be transferred to the organic phase.

TABLE III Extraction efficiency[a] of (di)benzo crown ethers in the complexation with uronium perchlorate.

Crown ether	Ring size	Extraction efficiency
3a	18	0.23
3b	21	0.36
3c	24	0.06
4b	24	0.08
3d	27	0.57
3e	30	0.52
4c	30	0.57
4d	33	0.68

[a] The ratio of the uronium ion concentration and the crown ether concentration in the organic phase.

The X ray structure analysis of the benzo-21-crown-7.uronium picrate (1:1) complex revealed that this complex has a nesting conformation, and not as assumed a perching one. The crystal structure (Fig. 4) shows that a complex is formed in which the uronium salt is hydrogen bonded with three NH_2 hydrogen atoms to crown ether ring oxygen atoms. The fourth hydrogen atom is involved in an intramolecular hydrogen bond to the anion.

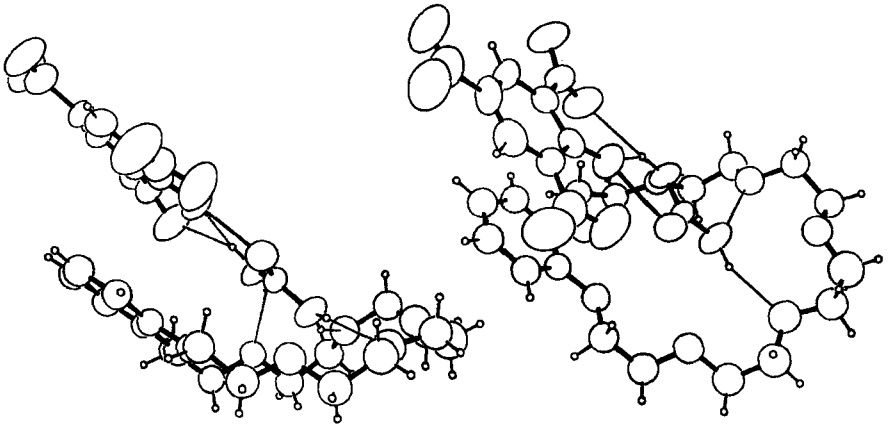


FIGURE 4 Crystral structure of the benzo-21-crown-7.uronium picrate (1:1) complex

The hydrogen bonding scheme is similar to the hydrogen bonding scheme in the related 18-crown-6.uronium perchlorate complex,[38] which means that one hydrogen atom of one NH_2 group is hydrogen bonded to a crown ether oxygen atom adjacent to the crown ether oxygen atom that accepts a hydrogen bond of the second NH_2 group. The third hydrogen atom is hydrogen bonded to the crown ether in such a way that one oxygen atom is passed over. In addition the aromatic ring of the guest is located parallel to the aromatic ring of the host, probably due to π-electron interaction.

COMPLEXATION OF UREA ASSISTED BY INTRAANNULAR PROTON DONATING GROUPS

Participation of an intraannular proton donating group in the encapsulation of an uncharged guest was first reported by Cram and

coworkers for the complexation of a water molecule by 3,3'-(1,1'-bi-2-naphthol)-21-crown-5.[42] Although in this complex the acidic hydrogen atom is not transferred to the water molecule, one of the two phenolic hydrogen atoms is involved in the hydrogen bonding of the guest. Another example of an encapsulated water molecule hydrogen bonded to an acidic proton of the host has been reported by Bradshaw et al. for a macrocyclic polyether-diester ligand containing a triazole subunit.[43] The acidic NH-hydrogen atom of the triazole moiety is involved in hydrogen bonding of the water molecule, while the two H_2O hydrogen atoms are hydrogen bonded with two crown ether oxygen atoms. For a similar complex with uncharged urea as the encapsulated guest molecule, macrocyclic ligands with acidic groups such as OH or COOH and ring sizes of 27 or more atoms were expected to be of interest.

Previously a series of 2-hydroxy-5-chloro-1,3-xylyl crown ethers 8 was synthesized in our laboratories.[44] Hitherto only a water complex with the 27-membered ring could be obtained in this series, but no urea complex. Consequently the possible participation of an intraannular carboxylic acid hydrogen atom in the complexation of urea was investigated. In the literature the synthesis of the methyl ester of a 2-carboxyl-1,3-xylyl-18-crown-5 with two sulphur atoms as donor sites in the macrocyclic ring has been reported by Weber and Vögtle.[45] Cram and coworkers reported the synthesis of a number of 2-carboxyl-1,3-xylyl crown ethers with only oxygen atoms as the donating sites and we have extended this method to a series of 2-carboxyl-1,3-xylyl crown ethers having ring sizes of 15 to 33 (9a-g).

The pK_a values of these crown ethers 9, show a strong ring size dependency.[46] The extremely high pK_a values for the 15- and 18-membered rings can be attributed to stabilization of the acid by a transannular hydrogen bond.

Such an intraannular hydrogen bond was shown by Cram and coworkers[47] in the crystal structure of the 18-membered ring. The

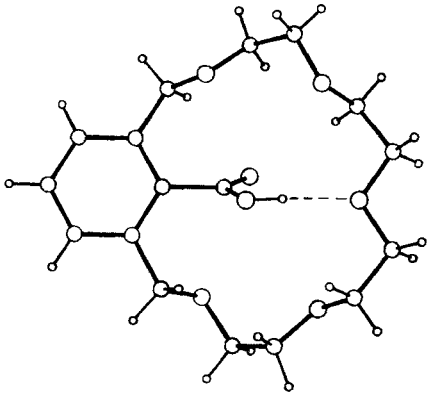


FIGURE 5 Crystal structure of 2-carboxyl-1,3-xylyl-18-crown-5, showing intraanular hydrogen bonding.[47]

relatively high pK_a values of the 21- and 24-membered rings can be due to specific coordination of a water molecule in the cavity, stabilizing the carboxylic acid group. For the larger rings (≥ 27) the pK_a values are the same as for the corresponding acyclic compounds.[46]

In order to study the participation of the intraannular carboxyl group in the complexation of urea two-phase extraction experiments were carried out. These clearly demonstrated that the larger ($n \geq 30$) macrocyclic rings extracted urea much more efficiently than the smaller rings. The highly enhanced extraction efficiencies for the 30- and 33-membered cycles are obviously due to assistance of the intraannularly located acidic proton of carboxylic acid crown ethers. From CPK model studies it is obvious that the cavity of 2-carboxyl-1,3-xylyl-27-crown-8 is too small to encapsulate both the carboxylic acid group and a urea molecule in a planar conformation in the cavity. This observation is reflected in the relatively low extraction efficiency found for the urea

solubilization by the 27-membered macrocycle. However, CPK model studies also show that the cavity of a 30-membered macrocycle is able to include both a carboxylic acid group and a urea molecule in a planar conformation. The existence of such a stable complex was supported by the isolation of the urea complex of 2-carboxyl-1,3-xylyl-30-crown-9 (9f).[19]

CONCLUSIONS

Our work described in this paper has confirmed that simple macrocyclic polyethers form complexes with neutral guests such as malononitrile and urea. The stability of the urea complexes can be enhanced by the assistance of a proton-donating carboxyl group. Although there is no proton-transfer in the complex, the strong hydrogen bond between the oxygen atom of urea and the carboxyl group plays an important role.

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