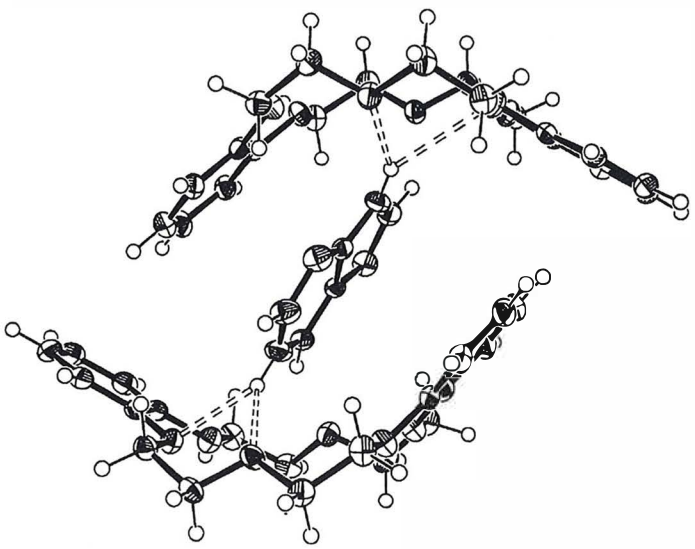
X-RAY STRUCTURAL STUDIES ON WEAK, NON-COVALENT INTERACTIONS IN SUPRAMOLECULAR COMPOUNDS

Maija Nissinen

Academic Dissertation for the Degree of
Doctor of Philosophy



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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals.

I S. Kiviniemi, A. Sillanpää, M. Nissinen, K. Rissanen, M. T. Lämsä and J. Pursiainen, Polar crystals with one-dimensional arrays from achiral components: crystal structures of 2:2 complexes of dibenzo-18-crown-6-imidazolium and pyrazolium perchlorates, *Chem. Commun.*, (1999) 897-898.
https://doi.org/10.1039/A902014D

II S. Kiviniemi, M. Nissinen, M. T. Lämsä, J. Jalonen, K. Rissanen and J. Pursiainen, Complexation of planar, organic, five-membered cations with crown ethers, *New. J. Chem.*, **24** (2000) 47-52; corr. *New. J. Chem.*, **24** (2000) 647.
https://doi.org/10.1039/A907608E

III S. Kiviniemi, M. Nissinen, T. Kolli, J. Jalonen, K. Rissanen and J. Pursiainen, Crown Ether Complexes of Six-Membered *N*-heteroaromatic Cations, *J. Inclusion Phenom. Macrocyclic Chem.*, (2001) in press.
https://doi.org/10.1023/A:1011176602813

IV M. Nissinen, S. Kiviniemi, K. Rissanen and J. Pursiainen, Guest-driven dimer formation of dibenzo-18-crown-6, *CrystEngComm*, **18** (2000) (http://www.rsc.org/ej/ce/2000/B004292G/index.htm).
https://doi.org/10.1039/B004292G

V M. Nissinen, Λ. Dalla Cort, S. Λmabile, L. Mandolini and K. Rissanen, Bis-phenol A Cyclophanes: Synthesis, Crystal Structures and Binding Studies, *J. Inclusion Phenom. Macrocyclic Chem.*, **39** (2001) 229-234.
https://doi.org/10.1023/A:1011174213426

VI A. Dalla Cort, M. Nissinen, D. Mancinetti, E. Nicoletti, L. Mandolini and K. Rissanen, Polyether-bridged Cyclophanes Incorporating Bisphenol A Units as Neutral Receptors for Quats: Synthesis, Molecular Structure and Binding Properties, *J. Phys. Org. Chem.*, (2001) in press.
https://doi.org/10.1002/poc.380

VII O. Mogck, P. Parzuchowski, M. Nissinen, V. Böhmer, G. Rokicki and K. Rissanen, Covalently Linked Multi-Calixarenes, *Tetrahedron*, **54** (1998) 10053-10068.
https://doi.org/10.1016/S0040-4020(98)00594-8

VIII M. Nissinen, P. Parzuchowski, V. Böhmer, G. Rokicki and K. Rissanen, 25,27-Dihydroxyethoxy-26,27-dipropoxy-*tert*-butylcalix[4]arene, *Acta Crystallogr.*, **C55** (1999) 104-106.
https://doi.org/10.1107/S010827019801022

IX M. Nissinen, E. Wegelius, D. Falábu and K. Rissanen, Melamine induced conformational change of ethyl resorcinarene in solid state, *CrystEngComm.*, **28** (2000) (http://www.rsc.org/ej/ce/2000/B006193J/index.htm).
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PREFACE

This work was carried out at the Department of Chemistry, University of Jyväskylä from autumn 1997 to January 2001.

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Jyväskylä, January 2001

Maija Nissinen

ABSTRACT

22 novel crystal structures of organic, supramolecular compounds and their analysis are reported. The structures present examples of a few of the most typical classes of compounds in supramolecular chemistry, *i.e.* crown ethers, cyclophanes, calix[4]arenes and resorcin[4]arenes.

Crown ether structures (original publications I-IV; 14 structures) present an example of host-guest complexes in which hydrogen bonding interactions play a major role but in which other weak interactions also contribute to the complexation. Cyclophane structures incorporating bisphenol A units (publications V and VI; four structures) demonstrate the importance of the preorganisation and the suitable size of the cavity for complexation. The third class of potential, supramolecular macrocyclic host compounds, calix[4]arenes (publications VII and VIII; two structures), showed no molecular or clathrate inclusion of the solvent thus confirming the unsuitability of this type of calix[4]arenes for complexation. However, the crystal structures provided valuable information for the designing of further synthetic steps. The crystal structure of ethyl resorcin[4]arene cocrystallised with melamine (publication IX; two structures) revealed an exceptional guest-induced conformational change of the resorcinarene from crown to boat conformation. Special attention in all these studies has also been paid to the investigation of crystal packing and the weak intermolecular forces affecting it in addition to the sterical effects.

As an introduction to the subject a short review of the literature will present the most typical weak interactions and the classes of macrocyclic, supramolecular hosts discussed in the experimental part.

CONTENTS

ABBREVIATIONS

18C6	18-crown-6
a	axial
ACh	acetylcholine
B18C6	benzo-18-crown-6
B30C10	benzo-30-crown-10
c	*cis*
DB18C6	dibenzo-18-crown-6
DB21C7	dibenzo-21-crown-7
DB24C8	dibenzo-24-crown-8
DB30C10	dibenzo-30-crown-10
DN30C10	dinaphtho-30-crown-10
DNA	deoxyribonucleic acid
e	equatorial
EDA	electron donor-acceptor
m	*meta*
Me	methyl
NMP	*N*-methylpyridinium
NMR	nuclear magnetic resonance
p	*para*
Phe	phenylalanine
t	*trans*
tert	*tertiary*
TMA	tetramethylammonium
Trp	tryptophane
Tyr	tyrosine
VDW	van der Waals
Å	Ångström, 10^{-10} m

1 REVIEW OF THE LITERATURE

1.1 NON-COVALENT INTERMOLECULAR INTERACTIONS

The fastest developing area in modern day chemistry is probably supramolecular chemistry, "chemistry beyond the molecule".[1] Supramolecular chemistry is based on weak, non-covalent interactions that take place between separate molecules - the very same interactions which govern recognition processes in Nature, *e.g.* in enzymes, antibodies, membranes, receptors, carriers and channels.[2] An understanding of these interactions is therefore crucial for a chemist interested in supramolecular chemistry. Supramolecular chemistry provides a convenient and important tool for the detailed investigation of weak interactions, since the direct study of often complex and mobile biological systems with reliable and general results for a specific non-covalent interaction is difficult.[3,4]

The most common non-covalent interactions investigated in organic supramolecular chemistry are hydrogen bonding, interactions involving π-systems (π···π stacking, D-H···π (D = O, N, S or C) and cation···π interactions) and hydrophobic van der Waals interactions.[4] Each of these interactions is an interplay of several different effects, *i.e.* van der Waals (VDW) interactions defining the size and shape specificity of the non-covalent interaction, electrostatic interactions, induction energy between static molecular charge distribution and the proximity-induced change in charge distribution, charge transfer and the desolvation effect.[5]

X-ray crystallography is a very convenient tool for investigating weak interactions, since any organic crystal can be considered an example of a perfect supermolecule built by connecting molecules *via* intermolecular interactions. Weak interactions determining crystal packing can be divided into medium-range isotropic forces (C···C, C···H and H···H interactions), long-range electrostatic, anisotropic forces involving heteroatoms, and very long range ionic forces between metal ions and oxygen or nitrogen atoms.[4] In crystalline state these interactions can be easily and accurately investigated simply by measuring the interatomic distances and angles and investigating the VDW surfaces of the crystal structures. However, it must be emphasised that crystal structures are compromises between interactions of varying strengths, directionalities and distance dependencies. Therefore unambiguous evaluation of the effect of a single interaction is a difficult task.

1.1.1 Hydrogen bonding

Hydrogen bonding is the most important weak interaction affecting all aspects of life, for example by increasing boiling points and solubility of compounds to water and partly determining the structures of large biomolecules, *e.g.* DNA and proteins.[6]

Hydrogen bonding (D-H···A) is defined as a directional, electrostatic attractive force between a partially positive hydrogen atom (D-**H**) and a partially negative atom with unshared valence electrons or polarisable π electrons (A).[6,7] The partial charge of the hydrogen atom arises from the large difference in the electronegativity of hydrogen and the atom to which it is attached (most typically oxygen, nitrogen, sulphur or fluorine), leading to a highly polarised covalent bond. Hydrogen bonding is substantially stronger

than other dipole-dipole interactions but much weaker than typical covalent bonds (bond energies on average 20 - 160 kJ/mol (Table 1) and 300 - 500 kJ/mol, respectively).[7,8] Although a single hydrogen bond is quite weak, several simultaneously acting hydrogen bonds increase the stability of the association significantly. Cooperativity effects, *e.g.* σ and π cooperativity, also strengthen the individual interaction.[7] σ cooperativity refers to the hydrogen bonding of functional groups with both donor and acceptor properties into continuous chains or cycles, while π cooperativity involves hydrogen bonds between molecules with conjugated multiple π bonds (also known as resonance-assisted hydrogen bonding). The formation of hydrogen bonds usually causes a significant decrease in energy compared to non-hydrogen bonding systems. Therefore in solid state as many hydrogen bonds as possible are formed, keeping in mind that geometric restrictions and the demand for the closest packing may create exceptions to this rule.

Table 1 Properties of strong, moderate and weak hydrogen bonds.[7]

	Strong	Moderate	Weak
D-H···A interaction	Mostly covalent	Mostly electrostatic	Electrostatic
Bond length	D-H ≈ H···A	D-H < H···A	D-H << H···A
H···A / Å	~ 1.2 – 1.5	~ 1.5 – 2.2	2.2 – 3.2
D···A / Å	2.2 – 2.5	2.5 – 3.2	3.2 – 4.0
Bond angle (°)	175 – 180	130 – 180	90 – 150
Bond energy / kJmol^{-1}	60 – 170	17 – 63	< 17
Examples	Gas phase dimers with strong acids or bases, acid salts, HF complexes	Acids, alcohols, phenols, hydrates, all biological molecules	Gas phase dimers with weak acids or bases, C-H···O/N and N/O-H···π interactions

The criterion for a weak interaction to be classified as a hydrogen bond is the binding geometry, especially the H···A and D···A hydrogen bond distances and D-H···A hydrogen bond angle.[7] Hydrogen bonds may be subcategorised as strong, moderate (conventional) and weak (Table 1). Strong hydrogen bonds are formed when there is a deficiency of electron density in the donor group or an excess of electron density in the acceptor, which increase the charges in the groups. Strong hydrogen bonds may also form if the configuration or conformation of the molecule force the donor and acceptor groups closer than normally in hydrogen bonding. Moderate (conventional) hydrogen bonds are the most typical cases of hydrogen bonding and are generally formed between neutral donor and acceptor groups.

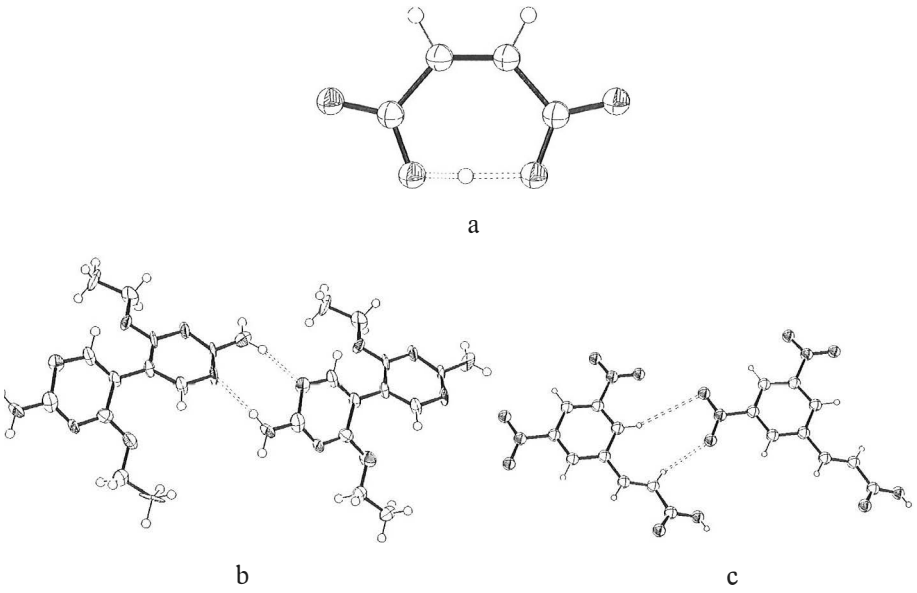
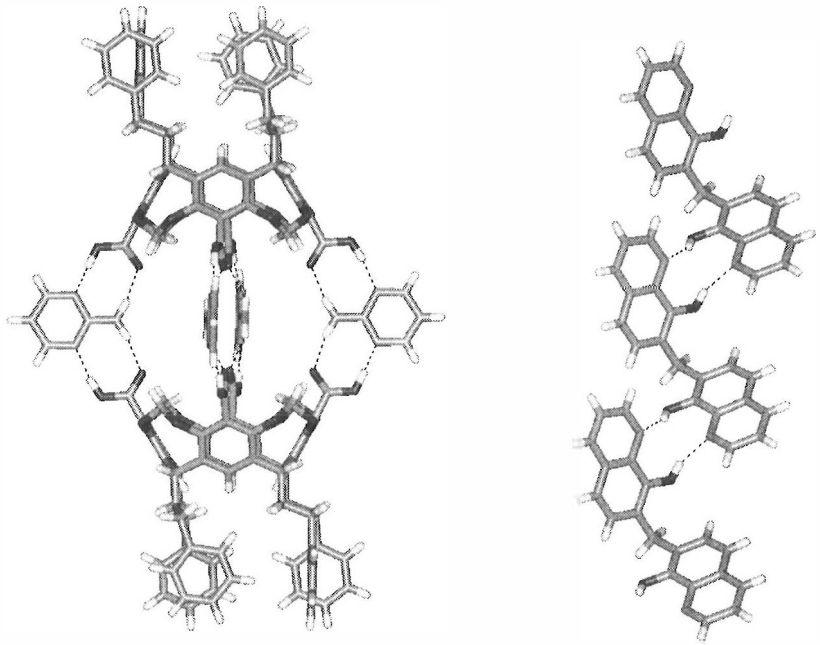


Figure 1 Examples of the crystal structures of the different hydrogen bond categories: "the hesitating proton" is a characteristic of strong hydrogen bond (a);[9] moderate hydrogen bonds form between a neutral donor group and a neutral acceptor with lone-pair electrons (b);[10] weak C-H···O hydrogen bonding (c)[11].

A weak hydrogen bond is formed when a hydrogen atom is bonded to only a slightly more electronegative atom relative to hydrogen (*e.g.* carbon or silicon) or when the acceptor does not have lone-pair electrons but π electrons.[7] During the last thirty years the nature and properties of weak hydrogen bonding, especially C-H···O/N interaction, have attracted increased attention.[11-30] Investigations by spectroscopic,[12,13] computational[14-19] and crystallographic methods[13,20-24] have given clear evidence that such interactions do exist, and owing to their similarity to conventional hydrogen bonds these could indeed be classified as weak hydrogen bonds. However, dissenting opinion labels such similar interactions "anti-H-bonds".[28-30] The basis for this view derives from the only difference between the conventional O-H···O and weak C-H···O interaction, which is observed upon the formation of the hydrogen bond. The conventional hydrogen bond is known to stretch and its vibrational frequency undergoes a red shift whereas C-H···O contracts and undergoes a blue shift.

The geometrical freedom of the weak hydrogen bond is greater than that of the strong hydrogen bond owing to the variation in the nature of the interaction (Table 1).[6,7,25] *Ab initio* molecular orbital studies indicate the that the proton donor capability of carbon and therefore the ability to form weak hydrogen bonds depends on the hybridisation state of the carbon ($sp > sp^2 > sp^3$) as well as the electronegativity of the substituent to which it is attached.[16,18] The hybridisation state and activation effects also correlate with donor-acceptor distances, which are slightly longer than the respective distances in conventional hydrogen bonds.[7,25] However, one must keep in mind that all short contacts are not necessarily hydrogen bonds.[27]

In crystalline state a weak C-H···A hydrogen bond is usually observed interconnected with normal hydrogen bonds or other weak hydrogen bonds, which indicates it to be a cooperative effect, although it has also been suggested that it is additive in nature.[13,24,25] However, the important role of this interaction in determining molecular conformation and crystal packing,[24-26,31] in molecular recognition processes,[31,32] biological molecules[6,19,33] and stabilisation of inclusion compounds[25,34] is obvious.



a b

Figure 2 Examples of crystal structures of hydrogen-bonded supramolecular systems: molecular capsule constructed by multiple hydrogen bonds (a);[35] polymeric strand (b)[36].

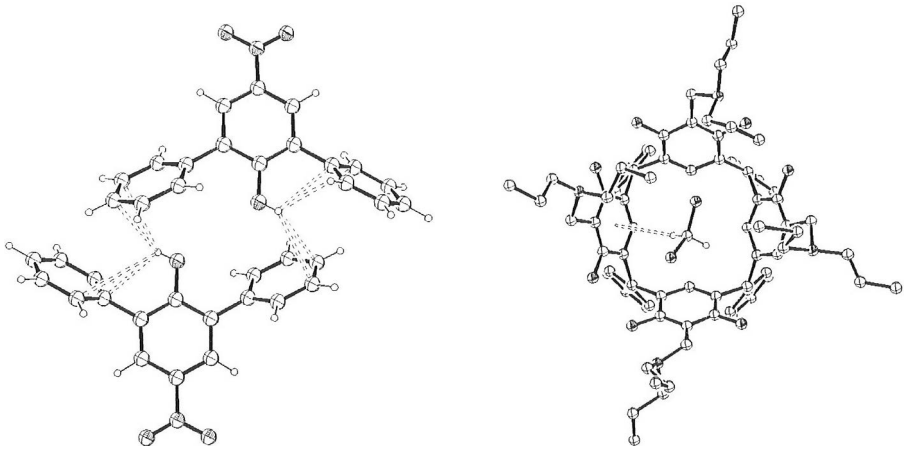
The significance of both conventional and weak hydrogen bonding interactions in biological systems[6,7] and the useful properties of hydrogen bonds (*e.g.* cooperativity, hydrogen bonding directionality and geometry)[25,31] have led to the wide utilisation of these interactions in crystal engineering and supramolecular chemistry. Examples are

self-assembled hydrogen-bonded structural motifs such as capsules,[35,37-44] rosettes,[45-51] spheres,[52] strands[36,54,55] and sheets[10] (Figure 2).

1.1.2 Weak interactions involving π-systems

The interactions involving π-systems, *i.e.* aromatic, double and triple bonded moieties of the molecules, can be roughly divided into three categories; D-H···π (D = C, O, N), π···π (also called π-stacking) and cation···π interactions. D-H···π interactions may also be classified as the weakest type of hydrogen bonding owing to their hydrogen bond-like properties such as directionality (Table 1).[7] The most common as well as the most investigated D-H···π interaction is C-H···π interaction,[56] but examples of O/N-H···π interactions are also known especially in solid state.[57-62] The strength of the C-H···π interaction is quite difficult to evaluate because of its weakness. However, quantum mechanical calculations have succeeded in clarifying the factors affecting this interaction.[56] Electronegative substituents attached to the **C**-H carbon atom as well as the electron-donating substituents on the π-system intensify the C-H···π interaction.

In supramolecular chemistry there are numerous examples of C-H···π-utilising systems, both in clathrates[63,64] and in inclusion complexes[65-77], although some disagreement exists about the significance of the CH···π interactions for inclusion[78]. Especially suitable CH···π-interacting host compounds are aromatic units containing calix- and resorcinarenes[65-72] and their derivatives[73,74], cyclophanes[75-77] and catenanes[79-81].



a b

Figure 3 Examples of O-H···π (a)[57] and C-H···π (b)[65] interactions in crystal structures.

π···π interaction is a non-directional interacting force, which occurs when the attraction between π electrons and a σ framework overcomes the unfavourable π-π repulsions.[5,82] The geometry of the π···π arrangement is determined mainly by electrostatic forces, whilst the VDW and solvophobic interactions contribute to the energy of the interaction. The most typical geometrical arrangements are edge-to-face (herringbone pattern; can also be classified as C-H···π interaction) and offset face-to-face stacking (Figure 4); in both of these the π-σ attraction is the dominating force. Polarisation of π-systems by heteroatoms may lead to direct face-to-face geometry owing to the perturbing of the molecular charge distribution. With highly charged systems the charge-charge interactions instead of π···π interactions become the dominating interacting force. Other suggested models for the mechanism of the π···π interaction are, for example, electron donor-acceptor (EDA) interactions and charge transfer[83,84] and uneven charge distribution across the π-systems[85].

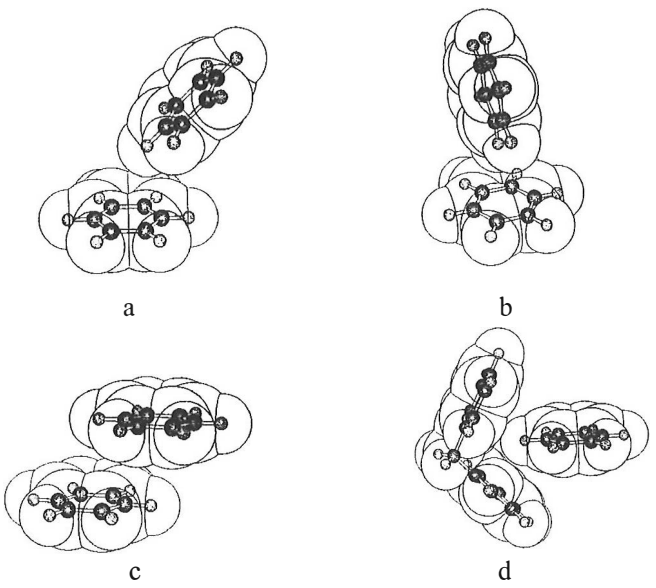


Figure 4 Possible arrangements of π-stacked benzene rings: edge-to-face (a); T-stacking, which is a special case of edge-to-face (b); offset face-to-face (c); and edge-in-angle (d).[86]

π···π interactions have been observed to control diverse natural and artificial phenomena, *e.g.* the double helical structure of DNA *via* base-base interactions, intercalation of drugs to DNA, tertiary structure of proteins, conformational and binding properties of aromatic units containing macrocycles, host-guest complexation, porphyrin aggregation and crystal packing of aromatic molecules.[82]

Cation···π interactions, which are observed between metallic or organic cations and aromatic (or double/triple bonded) regions of a molecule, are widely acknowledged to be among the strongest non-covalent binding forces.[87] In most cases the cation···π interaction is mainly caused by electrostatic interactions. This is confirmed by the binding affinity of benzene to alkali metals, which follows the classical electrostatic sequence, and by experiments with varying aromatic compounds. The other components

of cation···π interaction relate mostly to the polarisability of the aromatics, which are ion-induced dipole, donor-acceptor, charge transfer or dispersion forces by their nature. An evaluation of the strength of the cation···π interaction has been done by Schneider *et al.*[88] in a series of experiments between a selection of aromatic and aliphatic compounds with charged functional groups. When cation···π interactions were possible, an additional binding energy of ~ 2 kJ per phenyl group involved was observed.

Cation···π interactions are widely observed in biological systems such as the side-chain interactions of proteins (interactions of Phe, Trp and Tyr with amino groups), binding of acetylcholine and related ligands, catalysis of some syntheses and in the ion channels.[87] Therefore studies of the supramolecular, artificial systems, *e.g.* cyclophanes, calix- and resorcinarenes, utilising this interaction have been extensive during the last few years.[87,89-91]

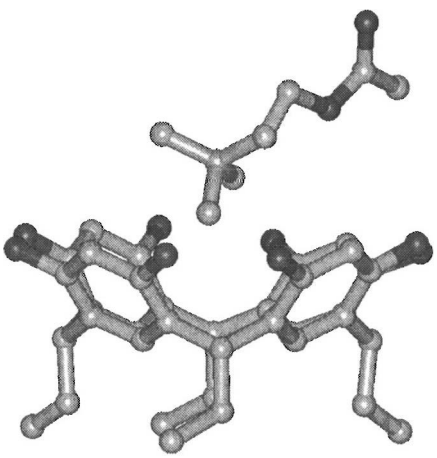


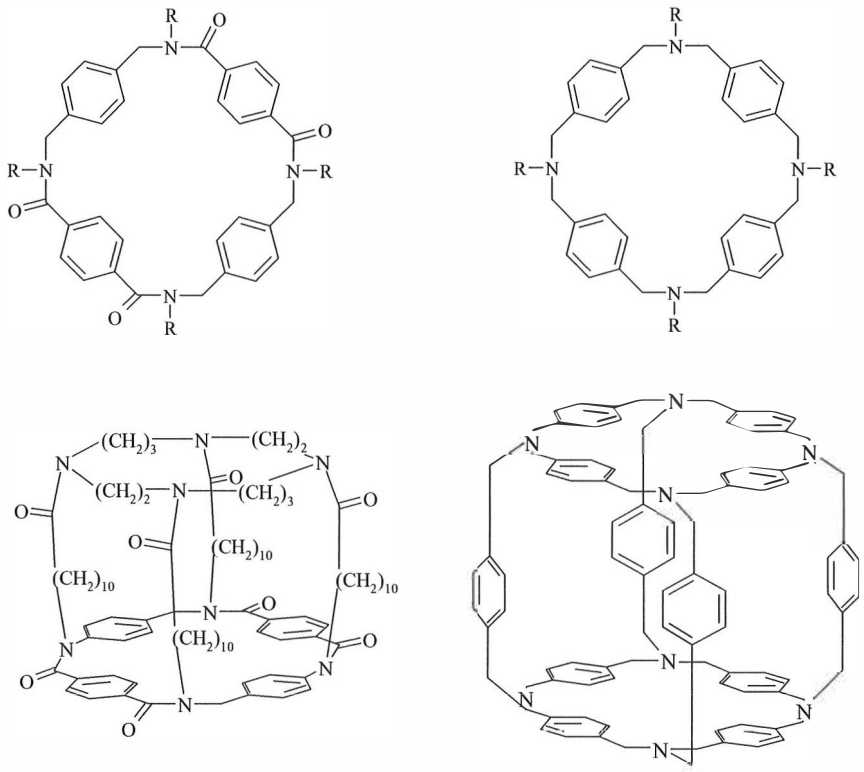
Figure 5 An example of cation···π interaction in molecular recognition of acetylcholine by resorcin[4]arene in solid state.[90]

1.1.3 Van der Waals interactions

Van der Waals (VDW) forces is a collective name for non-directional dispersion forces weakly bonding at long distances and exchange-repulsion forces strongly non-bonding at short distances.[4] The attracting dispersion forces are caused by the fluctuating multipoles of the adjacent molecules and are roughly proportional to the size of the molecule and inversely proportional to the sixth power of distance. Exchange-repulsion forces balance the dispersion forces and define the molecular shape and conformation, and are therefore important in the crystal packing. The strength of the VDW interaction varies from some tenths of a kcal/mol up to the energy of the hydrogen bond. However, these forces constitute a major part of the energy of the crystal because the whole molecule is involved in them.

All atoms in an organic molecule participate in VDW forces, but most typically the term is used to refer to the hydrophobic C···C, C···H and H···H interactions.[4] In aliphatic systems hydrophobic H···H interactions predominate, especially when long alkyl chains (> 5) are involved, while the C···H interactions play a minor role. It is not clear whether the nature of the C···H interaction is same in aliphatic and aromatic compounds;[92] hence in aromatic systems most of these interactions may also be categorised as π interactions (see chapter 1.1.2).[4]

An example of the utilisation of hydrophobic forces in supramolecular chemistry can be found in the work of Murakami and Kikuchi, in which hydrophobic modifications to azacyclophanes have produced a large hydrophobic cavity (Scheme 1).[93]

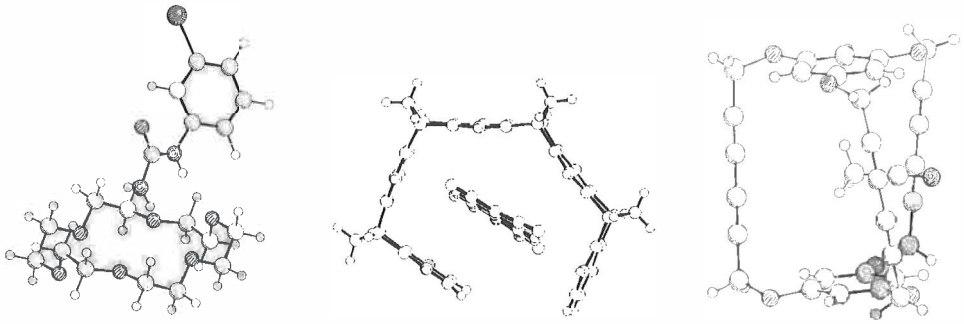


Scheme 1 Azacyclophanes with hydrophobic cavities suitable for utilisation of VDW forces in complexation.[93]

1.2 MACROCYCLIC SUPRAMOLECULAR HOST COMPOUNDS

Supramolecular chemistry has utilised a wide range of open-type, tweezer-type (half-open) and closed-type host compounds with the aim of making suitable receptors for both natural and synthetic chemicals and of studying the interactions involved in receptor binding.[94] The most important features of a host compound are therefore high affinity and selectivity for the desired substrate.[3] In contrast to the diverse nature of biological receptors, the desired functions of an artificial host compound, at least to some extent, can be selected by using suitable functional groups and conformational

properties. However, it must be emphasised that also with artificial systems more than one interaction contributes to the binding, no matter how simple a receptor is used.



a b c

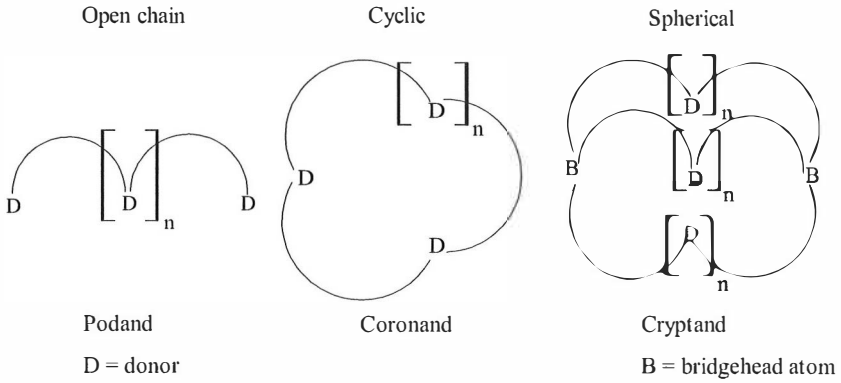
Figure 6 Examples of different receptor structures classified according to Schneider[3,94]: open-type 18C6 binding *N*-*m*-bromophenylurea (a);[95] tweezer-type (half-open) host binding 7,7,8,8-tetracyano-*p*-quinodimethane (b);[96] and closed-type cyclophane host with the inclusion of acetonitrile (c)[97].

Closed or even concave-shaped host molecules are the most common types of receptors both in nature and in synthetic systems.[3] The reason for this is that many interactions can work simultaneously and the loss of entropy is smaller in closed systems, whereas in open shaped receptors, *e.g.* grooves of nucleic acids or antibody surfaces, competitive binding by other ligands, self-association and the access of solvent are more likely.

A simpler way of classifying host compounds without concentrating on their interactions with possible guests is to divide hosts to open chain and cyclic compounds. This thesis focuses briefly on some of the categories of the latter type of compounds, namely crown ethers, cyclophanes and calix- and resorcinarenes, which are among the most common types of cyclic hosts.

1.2.1 Crown ethers

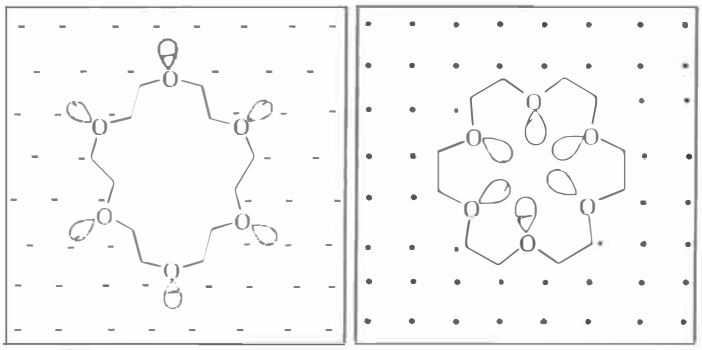
Crown ethers can justifiably be said to form the basis of supramolecular chemistry, given the amount of attention that has been paid to them since Pedersen's discovery of dibenzo-18-crown-6 (DB18C6) in 1967.[98,99] The original definition of crown ethers included compounds with repeating $-OCH_2CH_2-$ units incorporated in a monocyclic backbone.[100] Nowadays the definition has widened to include other donor atoms besides oxygen (*e.g.* azacrowns) and even sometimes multicyclic and open chain systems. Thus there is no general agreement about what kind of compound should or should not be categorised as a crown ether. Other terms such as podand, coronand and cryptand have also been used for crown ether-related compounds (Scheme 2).[101] In this thesis, however, the discussion is limited mainly to the traditional, monocyclic oxygen donor crown ethers.



Scheme 2 Schematic presentation of podand, coronand and cryptand.[101]

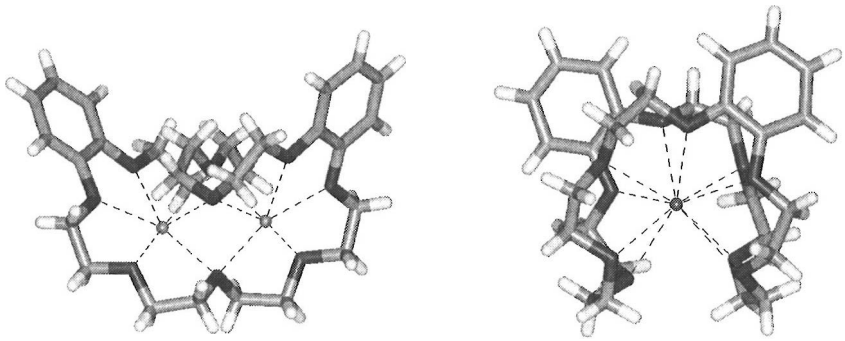
The perfect balance between hydrophilicity and lipophilicity due to hydrophilic oxygen atoms and the lipophilic ethylene moiety gives crown ethers a remarkable solubility in both hydrophilic and lipophilic media.[101] The type of the solvent used affects the

conformation of the crown ether ring, and therefore also affects the complexation properties in solution (Scheme 3).



Scheme 3 Schematic presentation of the behaviour of crown ethers in hydrophilic and lipophilic media.[101]

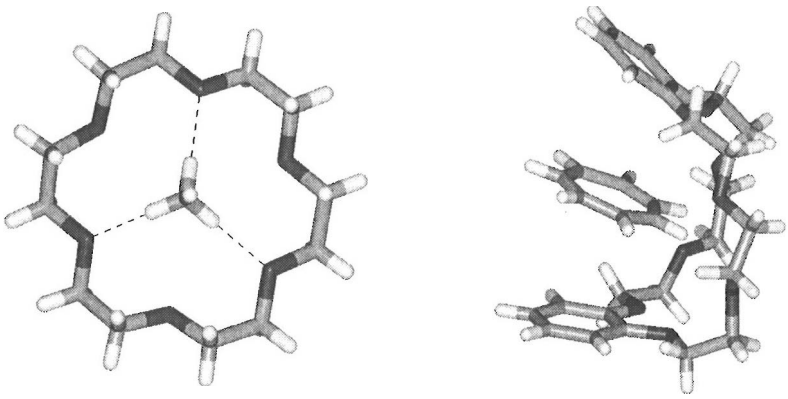
The significant binding and selectivity properties towards alkali and alkaline earth metals made the crown ethers the first synthetic products to mimic the function of natural antibiotics[100] – a goal still pursued by many supramolecular chemists. The features of crown ethers, *e.g.* solubility, coordination and hydrogen bonding ability of donor oxygens and their preorganised macrocyclic cavity also make them suitable hosts for neutral molecules and organic cations and anions.[100-102] Phenyl rings, heteroaromatic moieties and functional groups attached to the macrocyclic backbone as well as the variability of their ring size give crown ethers additional properties such as the possibility for π interactions and selectivity toward different sizes of guests. However, it must be emphasised that with larger ring sizes (> 24 atoms) and increasing flexibility the selectivity of crown ethers suffers owing to the tendency to form complexes with different structures, for example sandwiches and binuclear complexes (Figure 7).[103,104]



a b

Figure 7 Crystal structures of binuclear DB30C10·2 Na^+ complex (a)[103] and sandwich-type DB30C10·K^+ complex (b)[104].

Compared to their open-chain analogues, crown ethers generally have better binding strength and selectivity.[100] The reason for their increasing strength is the so called macrocyclic effect,[105,106] which is specific not only to crown ethers but also to macrocyclic compounds in general. Increasing selectivity, on the other hand, is more specific to crown ethers than to any other macrocyclic compounds.[100] There is no agreement whether the origin of the macrocyclic effect is a favourable entropy or enthalpy change during complexation. However, in the case of crown ethers the enthalpy factors usually dominate. Other factors affecting the macrocyclic effect are preorganisation of the host, relief of dipole-dipole repulsion, differential solvation of the host and increased basicity of the donor atoms of the host. In particular the preorganisation causes the difference in binding compared to the open chain ligands – if the complexation requires only a little adjustment it is enthalpically and entropically cheap. The increase in preorganisation also explains the better stability and selectivity properties of cryptands compared to podands and coronands (*e.g.* crown ethers); however, the rate of complexation shows the opposite trend.[101]



a b

Figure 8 Complexation of ammonium cation with 18C6 is caused by three-point hydrogen bonding (a).[107] The DB24C8·tropylium complex is stabilised by π···π interactions (b).[108,109]

In metal ion-crown ether complexes complexation is caused by ion-dipole interactions between the cation and the free electron pairs of the oxygen atoms of the crown ether.[100] In the complexation of non-metal ions and neutral molecules compared to spherical metal cations, the greater preorganisation of the crown ether becomes more important because of the more complicated structures of guests. The complexation of organic cations, *e.g.* nitrogen containing compounds, is owed mostly to the hydrogen bonding interactions between the hydrogen bond-donating ammonium group and the hydrogen bond-accepting ether oxygens (Figure 8a).[102,107] However, some examples of crown ether complexes with non-hydrogen bonding guests stabilised by other weak interactions are also known. An example of such is the DB24C8·tropylium complex, which is stabilised by π···π interactions (Figure 8b).[108,109]

The binding of neutral guests by crown ethers is due to hydrogen bonding, π···π interactions, hydrophobic interactions and/or molecular inclusion and is usually weaker

than the complexation of charged species.[100] The complexation of anions by neutral crown ethers is negligible, since both the anions and the donor atoms of the ligand are Lewis bases. However, the introduction of positive charge to a ligand by protonation of the nitrogen atoms (azacrowns) or by simultaneous complexation with metal ions facilitates the anion complexation.

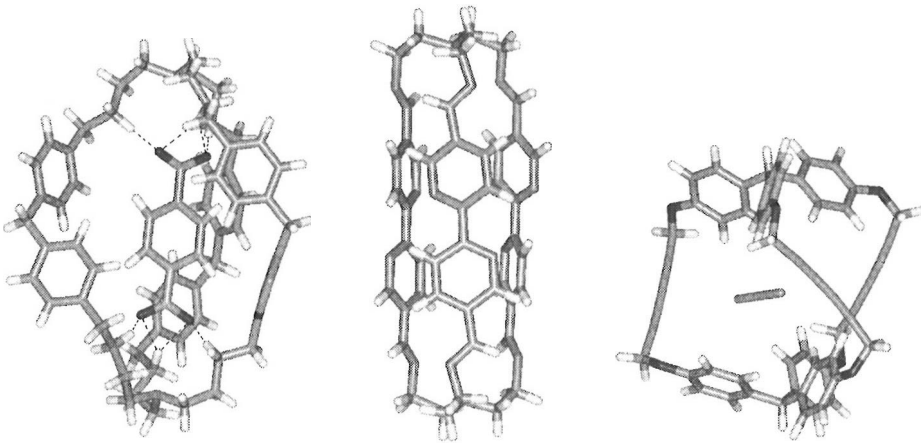
The above characteristics of crown ethers have led to their wide utilisation in analytics, separation and recovery of desired species, transport functions, medical applications and as biological mimics and reaction catalysts.[100,101] Besides these practical functions crown ethers and their derivatives have provided significant information about molecular recognition, intermolecular interactions and other aspects of supramolecular chemistry.

1.2.2 Cyclophanes

The term "cyclophane" is used for a versatile class of artificial, bridged aromatic compounds, which have been investigated since the 1950s and form a central class of synthetic receptors in molecular recognition.[2,110,111] Subcategorising cyclophanes is not unambiguous owing to the versatile nature of these compounds, *e.g.* a majority of crown ethers and all calix- and resorcinarenes can be classified as cyclophanes. However, categorisation according to the functional group responsible for complexation results in endobasic, endoacidic and endohydrophobic cyclophane groups (Figure 9).[86]

The essential features of cyclophanes are their ability to complex *via* π and/or other weak interactions (depending on the functional groups involved), steric suitability and the hydrophobic cavity formed by aromatic parts of the molecule.[2] In addition to their

hydrophobic cavity, the aromatic parts of the cyclophane make the molecule more rigid and therefore improve the preorganisation of the binding site. The other features, such as water-solubility and hydrogen bonding ability, depend on the functional groups used in addition to the aromatic functions. Water-soluble cyclophanes, *e.g.* azacyclophanes, have been a particular focus of interest owing to their contribution to the molecular recognition of organic guests in aqueous media.[112,113]



a b c

Figure 9 Examples of the crystal structures of endoacidic (a);[114] endobasic (b);[115] and endohydrophobic (c)[116] cyclophanes.

The same principles of complex formation also apply to cyclophanes as to crown ethers: in complexation of organic guests the requirements of steric and functional complementarity and preorganisation of the host are relatively high.[86] In aqueous solution the principal factor affecting the binding of lipophilic guests by endohydrophobic cyclophanes is the hydrophobic effect[117], *i.e.* the fact that lipophilic guests prefer the lipophilic cavity to water. Therefore the binding constants have been observed to correlate with the water solubility of the guest and hydrophobicity of the cyclophane.[113] The effect of the solvent for complexation can not be underestimated

either.[86,110] Complexation in nonpolar solvents is weaker owing to the competitive binding of suitably sized solvent molecules and unfavourable polarisation and cohesion effects.

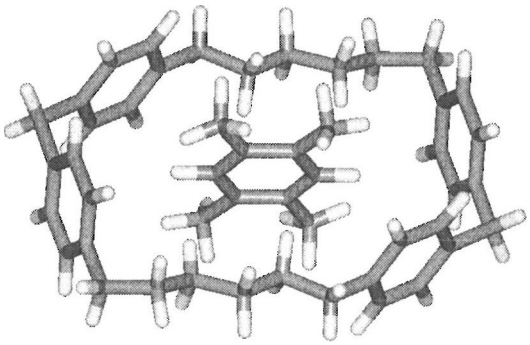


Figure 10 The first example of the solid state inclusion complex of water-soluble azacyclophane with durene by Koga *et al*.[118]

In general, the binding of aliphatic guests is weaker than the binding of aromatic compounds, thus indicating the importance of π interactions for complexation.[113] The importance of π interactions is also emphasised by the ability of cyclophanes to bind aromatics in nonpolar solvents as well.[86] While cations are successfully bound by cyclophanes owing to stabilising cation···π interactions, the complexation of anions is quite ineffective due to their repulsive interactions with the negative regions of the aromatic rings.[113] However, with functional groups the features of the cyclophane cavity can be changed to favour different types of guests with different interaction possibilities such as anions (Figure 9a).[114]

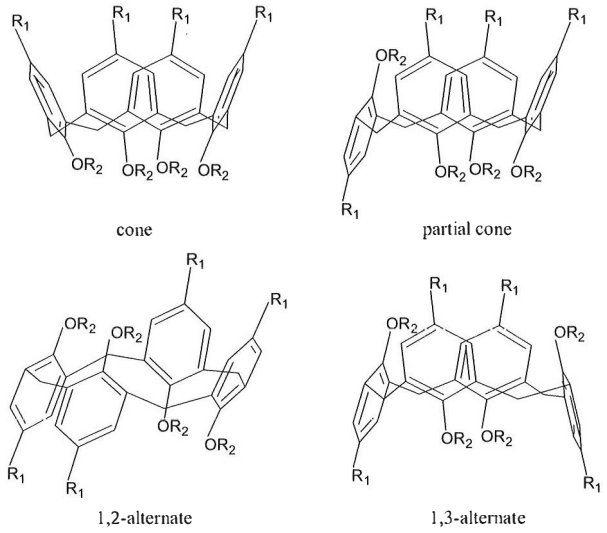
1.2.3 Calix- and resorcinarenes

Calix- and resorcinarenes are a vastly expanding and studied group of [1_n] metacyclophanes synthesised by a simple condensation reaction of an aldehyde with phenol or resorcinol, respectively.[119-123] In this context the terms "calixarene" and "resorcinarene" refer to calix[4]- and resorcin[4]arenes, excluding larger macrocyclic products as well as other related compounds such as cavitands, carcerands and hemicarcerands.

The reason for the popularity of this class of compounds is their easy availability and their potential for further functionalisation, which makes them an ideal building block for supramolecular chemistry.[119-123] In addition favourable features for the selective complexation of various guests, such as the basket-shaped hydrophobic cavity in cone (crown) conformation, the ability to interact *via* π interactions and the hydrogen bond-forming phenolic oxygens, make calix- and resorcinarenes a popular subject of supramolecular investigation.

The non-planarity of conformations of calix- and resorcinarenes means that they can exist in many different isomeric forms. Calixarenes have four possible conformations (cone, partial cone, 1,2-alternate and 1,3-alternate; Scheme 4), which depend on the solvent used, the temperature and the additional functionalisation.[119,120,122] The conformation of the calixarene has crucial importance in supramolecular chemistry, *e.g.* in complexation, therefore several molecular modelling studies have been performed to illuminate their conformational properties.[123-126] In solution native calixarenes are conformationally mobile, *i.e.* interconversion between two mirror-image cone

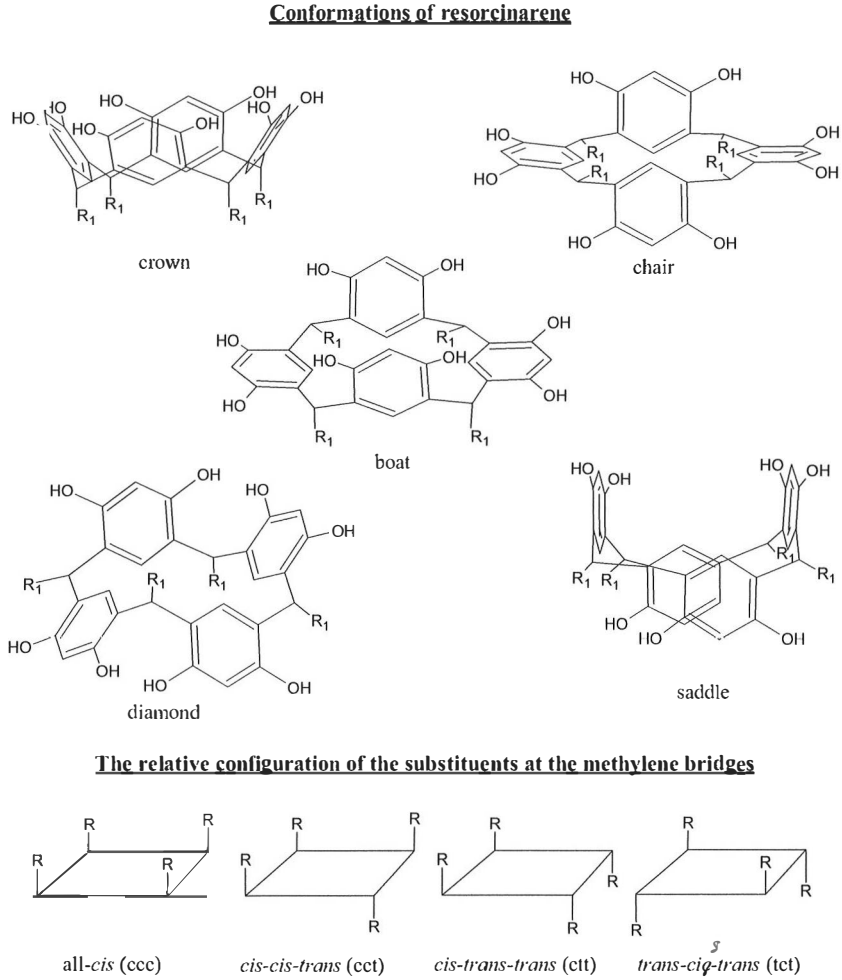
conformations is observed.[119,120] The rate of interconversion depends on the solvent and the substituents of the hydroxyl groups and *para*-positions of the calix, which can, for example, if the opposite aromatic nuclei are connected, prohibit conversion. In solid state, however, calixarenes exist exclusively in cone conformation as long as at least one of the hydroxyl groups is unsubstituted, owing to the strong intramolecular hydrogen bonds between the adjacent hydroxyl groups of the calixarene.



Scheme 4 Conformers of calix[4]arene.

Stereochemistry of the resorcinarenes is generally defined as a combination of the conformation of the macrocyclic ring, the relative configuration of the substituents at the methylene bridges and the individual configuration of the methylene bridge substituents.[121] The macrocyclic ring of the resorcinarene may adopt five different conformations: crown (cone), boat (flattened cone), chair, diamond (1,2-alternate) and saddle (1,3-alternate) (Scheme 5), which depend strongly on the nature of the methylene bridge substituent and the maximal hydrogen bonding possibilities. The relative configuration of the methylene bridge substituents may adopt an all-*cis* (*ccc*), *cis*-*cis*-

trans (*cct*), *cis-trans-trans* (*ctt*) or *trans-cis-trans* (*tct*) arrangement (Scheme 5), while the individual configuration of the substituents may be either axial (*a*) or equatorial (*e*). The combination of these stereochemical elements might be expected to yield a vast number of different stereoisomers: however, only a limited number have so far been found experimentally. The stereochemistry of resorcinarenes also depends, apart from the methylene bridge substituents, on the reaction conditions and solvents, which affect both intra- and intermolecular hydrogen bonding.



Scheme 5 The conformations of the macrocyclic ring of resorcinarene and relative configurations of the substituents at the methylene bridges.

The complexation properties of calix- and resorcinarenes and their derivatives have been widely investigated during the last two decades.[35,40,42-44,65-74,90,91,119-123,127,128] Both compound classes have been proved to be suitable for the complexation of neutral and cationic compounds *via* conventional and weak hydrogen bonding, CH···π and cation···π interactions. The role of the CH···π interaction is somewhat controversial – studies of the *p-tert*-butylcalix[4]arene·toluene complex indicate that the toluene methyl group rotates inside the cavity, and therefore instead of directional CH···π interactions, steric interactions seem to govern the complexation.[78,120] Easy deprotonation of the hydroxyl groups of resorcinarenes by bases results in the complexation of ammonium cations *via* electrostatic forces with very high affinity.[121] Examples of anion complexation by calixarenes are also known, but here complexation requires additional functional groups such as electron-deficient or Lewis acid centres, positively charged ammonium groups or metal centers.[119,123,129]

Besides the wide use of calix- and resorcinarenes in the field of supramolecular chemistry (investigation of weak and multipoint interactions, formation of new architectures such as capsules etc.), their good complexation affinity and selectivity have led also to practical applications. Examples of such are the use of these compounds as catalysts, ion and molecular separators, chemical sensors and in medicinal diagnostics.[122,130]

2 EXPERIMENTAL

2.1 AIMS OF THE STUDY

Weak interactions affecting recognition and complexation phenomena have been widely investigated over the last few decades. The increased interest in these interactions is due in part the refinement and development of computational methods and equipment as well as the rise of a whole new branch of chemistry, *i.e.* supramolecular chemistry. However, there is still a great deal of work to be done in this particular field, including the area of weak interactions.

The aim of this study was to investigate supramolecular host compounds and the weak interactions affecting their complex formation and crystal packing by means of single crystal X-ray crystallography. Weak interactions can also be studied in solution and in gaseous state, but solid state crystal structures offer more unambiguous and detailed information about conformational aspects, inclusion or lack of inclusion and the nature of interactions affecting the structure and recognition processes. In addition, when studied in solution, many weak interactions are destroyed or affected by the solvent and can therefore be investigated only *via* solid state structural studies.

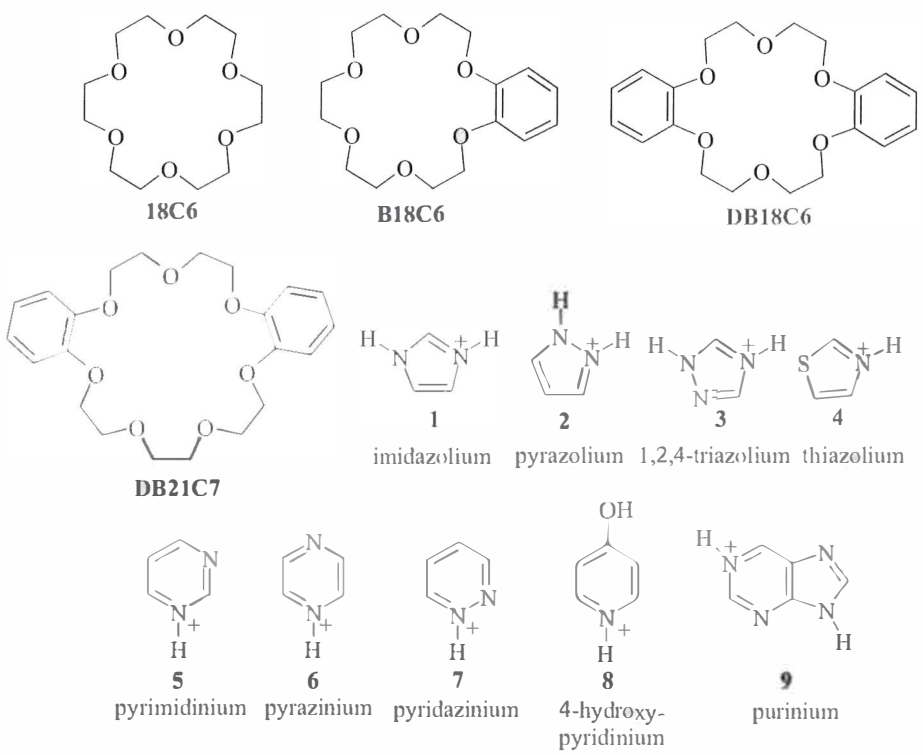
The problem with using crystallographic methods to investigate weak interactions, however, is the fact that a crystal structure is always a compromise between several interactions of different strength, length and direction. Thus drawing a conclusion regarding the correlation between a structure and a single interaction is difficult and one might add, even unnecessary. Other problems with crystallography are of a more practical nature. The crystallisation of compounds into the crystals of suitable quality is

a challenging task, and even after obtaining good quality crystals and a reasonable crystallographic data from them, there remains a considerable amount of work to do in solving the structure, refinement, and, finally, in the detailed analysis of the results.

2.2 CROWN ETHER STRUCTURES[I-IV]

Crown ethers are excellent starting materials for the investigation of weak interactions because of their electron donating and hydrogen bonding oxygen atoms and their easy availability. Additional functional groups, such as aromatic rings, add the possibilities for preorganisation and interaction. A majority of the complexation studies of crown ethers have involved the binding of metal ions,[100] but binding of neutral or cationic organic molecules, especially biologically significant compounds such as guanidine and imidazole, also form an essential part of complexation studies.[100,102,108,109,131-142]

The investigation of various small crown ether complexes with biologically important five[I,II] and six-membered[III] aromatic cations and a bicyclic purinium cation[IV] (Scheme 6) has resulted in detailed information about the weak interactions contributing to complexation. The significance of hydrogen bonding for the strength of the association was clearly observed when the stability constants of hydrogen bonding guests were compared to those of non-hydrogen bonding guests (Table 2).[I-III]



Scheme 6 The crown ethers and heteroaromatic guests used in the study.

Obtaining crystals from complexes with non-hydrogen bonding guests proved to be difficult: because of the poor ability of the guest to associate with the host, co-crystallisation does not take place but the crown ether and the cation salt crystallise out separately. However, on the basis of the crystal structures of DB18C6·imidazolium (**1**) and DB18C6·pyrazolium (**2**), it can be reasoned that hydrogen bonding is also important in solid state.[I,II] Imidazolium (**1**) has two hydrogen bonding sites separated by one carbon while in pyrazolium (**2**) the hydrogen bonding sites are adjacent. The separated hydrogen bonding sites of imidazolium cause that the cation can interact with two different hosts, so that some hydrogen bonds are intracomplex and some intercomplex

(Figure 11). With pyrazolium only intracomplex hydrogen bonding interactions are possible owing to the proximity of the binding sites. Thus "doubled" hydrogen bonding adds significantly the stability of the 1:1 complex.

Table 2 Stability constants (K) for the crown ether complexes determined by ^{1}H NMR titration in CD_3CN solution at 30 °C.[I-IV,109,131]

Complex	K / dm mol$^-$	Complex	K / dm mol$^-$
Guests with two hydrogen bond donating sites		*Guests with one hydrogen bond donating site*	
18C6 · imidazolium (**1**)	81 ± 1	DB18C6 · 1-Meimidazolium	35 ± 3
B18C6 · imidazolium (**1**)	59 ± 1	DB18C6 · 1-Pheimidazolium	32 ± 1
DB18C6 · imidazolium (**1**)	54 ± 2	DB18C6 · thiazolium (**4**)	65 ± 2
DB21C7 · imidazolium (**1**)	24 ± 2	18C6 · pyrimidinium (**5**)	349 ± 35
DB24C8 · imidazolium (**1**)	22 ± 2	B18C6 · pyrimidinium (**5**)	224 ± 7
DB18C6 · pyrazolium (**2**)	130 ± 3	DB18C6 · pyrimidinium (**5**)	103 ± 5
DB18C6 · 1,2,4-triazolium (**3**)	37 ± 3	DB24C8 · pyrimidinium (**5**)	60 ± 4
DB18C6 · 4-OH-pyridinium (**8**)	38 ± 5	DB18C6 · pyridazinium (**7**)	162 ± 3
DB18C6 · purinium (**9**)	154 ± 8	DB18C6 · pyrazinium (**6**)	39 ± 2
DB24C8 · purinium (**9**)	107 ± 8	18C6 · pyridinium[131]	113 ± 10[a]
		B18C6 · pyridinium[131]	96 ± 6[a]
Non-hydrogen bonding guests		DB18C6 · pyridinium[131]	33 ± 4[a]
DB18C6 · 1-Mepyrimidinium	10 ± 3	DB21C7 · pyridinium[131]	22 ± 4[a]
DB18C6 · tropylium[109]	5.6 ± 2.8[a]	DB24C8 · pyridinium[131]	19.2 ± 0.3[a]
DB24C8 · tropylium[109]	10.2 ± 0.3[a]	B18C6 · 1-aminopyridinium[131]	33 ± 1[a]
DB18C6 · 1-Mepyridinium[131]	9 ± 1[a]	DB18C6 · 1-aminopyridinium[131]	13 ± 2[a]
DB21C7 · 1-Mepyridinium[131]	10 ± 5[a]	DB21C7 · 1-aminopyridinium[131]	5.7 ± 0.3[a]

[a] Determined at 25°C.

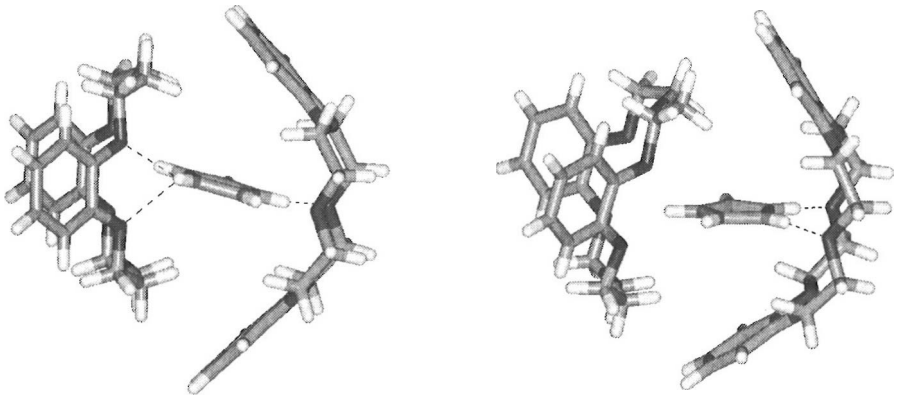


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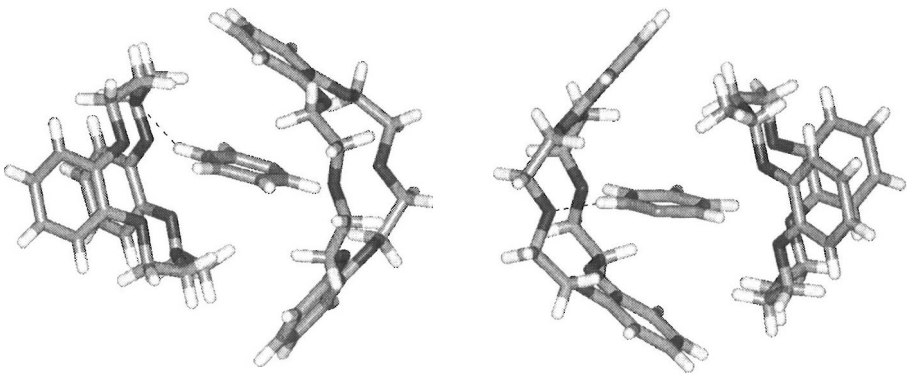
Figure 11 DB18C6·imidazolium (**1**) complex has intracomplex and intercomplex hydrogen bonds (a). In the DB18C6·pyrazolium (**2**) complex the close proximity of the hydrogen bonding sites facilitates the formation of two intracomplex hydrogen bonds (b).

The effect of the other weak interaction becomes evident when the stability constants and the crystal structures of the DB18C6 complexes of the *N*-heteroaromatic five-membered cations[I,II] are compared to those of the thiazolium (**4**)[II] and the six-membered cation complexes[III]. Thiazolium and six-membered cations are bigger than five-membered cations, thus giving better sterical fit in complexes. The bigger size of the cation also allows better opportunity for π and charge transfer interactions. This is proved by the closest distances between the centroids of the cation and phenyl rings of the host, which with five-membered cations are on average 4.1 Å and with six-membered cations between 3.7 and 4.0 Å. The same applies for the B18C6·imidazolium (**1**)[II] and B18C6·pyrimidinium (**2**)[III] complexes, in which the respective centroid distances are ~ 4.7 and ~ 3.8 Å. Thus, even if thiazolium (**4**) and six-membered cations only have one hydrogen bonding site, they generally form more stable complexes than five-membered cations with two hydrogen bonding sites (Table 2). Stabilising weak C-

H···O hydrogen bonds (C···O distances of 3.17 – 3.67 Å) are also observed with six-membered cations.

It is possible to observe the additive nature of the different interactions, especially when the DB18C6 complexes of pyrimidinium (**5**), pyrazinium (**6**) and pyridazinium (**7**) are compared.[III] The hydrogen bonds of pyrimidinium (**5**) and pyrazinium (**6**) orient to a different host than the one in the cavity of which they are located and with which they π interact, thus being intercomplex type of hydrogen bonds (Figure 12). In pyridazinium (**7**), however, the hydrogen bonds orient to the same host in the cavity of which the cation is located, and are thus intracomplex by nature. This observation confirms the greater stability of the pyridazinium (**7**) complex in solution compared to the other structural isomers (Table 2).



a b

Figure 12 The hydrogen bonds and π interactions of DB18C6·pyrimidinium (**5**) complex orient to different hosts (a), while in DB18C6·pyridazinium (**7**) the hydrogen bonds and π-interactions are to the same host (b).

The substituents, either to nitrogen or other positions of the heteroaromatic ring, have an unfavourable effect on complexation, which is natural when a hydrogen bonding site is replaced by a non-hydrogen bonding group such as methyl or phenyl.[II,131] However, in the case of the DB18C6·4-hydroxypyridinium (**8**) complex no hydrogen bonding site is lost, but one is gained and yet no significant change in complexation affinity is observed.[III] The reason for this is the relative position of the hydrogen bonding sites to each other. Hydrogen bonding to a single host is virtually impossible and thus no reinforcement of the 1:1 complex by an additional hydrogen bond occurs. Instead, the hydrogen bonds of the nitrogen and the hydroxyl group can orient more easily to two different hosts, thus favouring 2:1 host-to-guest stoichiometry or columnar packing of 1:1 complexes, the latter of which is indeed observed in the crystalline state (Figure 13).

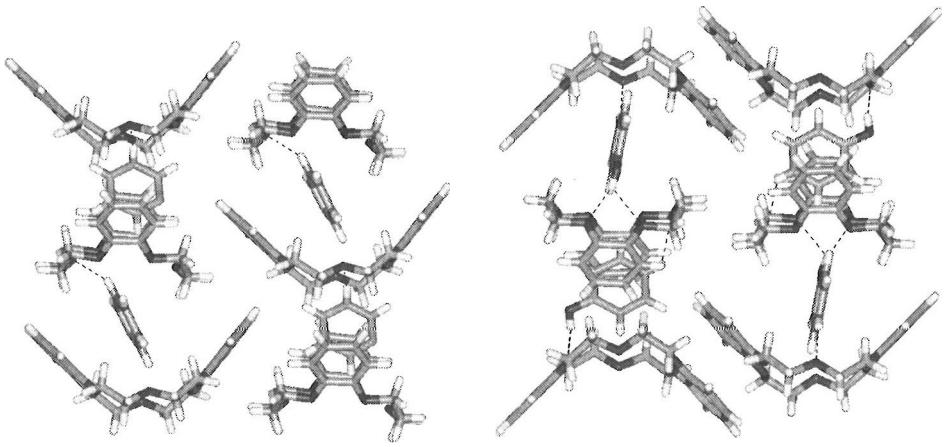


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Figure 13 All DB18C6 complexes pack into unidirectional, 1-D columns (a) except for the DB18C6·4-hydroxypyridinium (**8**) complex, which packs into centrocymmetrical columns (b).

All DB18C6 complexes have a close structural resemblance regardless of whether the cation is five- or six-membered, *i.e.* they all crystallise in an acentric monoclinic space group, C*c*, with very similar unit cell dimensions and almost isomorphous structures.[I-III] The 1:1 complexes pack into one-dimensional arrays of host-guest complexes turned at 90° in relation to the adjacent DB18C6 molecules (Figure 13). Owing to the weak interactions between the neighbouring arrays, all arrays pack in same direction and the polar axis is created in the crystal lattice.

The only exception to the DB18C6 complexes is DB18C6·4-hydroxypyridinium (**8**), which crystallises in a centric space group $P2_1/n$.[III] However, the packing of this complex is also columnar and therefore similar to that of other DB18C6 complexes. In contrast to the other DB18C6 complexes the columnar arrays pack centrosymmetrically, *i.e.* the adjacent columns orient in opposite directions (Figure 13). The reason for this may be determined by investigating the asymmetric unit of the crystal structure. Whilst the other DB18C6 complexes are formally 1:1 complexes, the DB18C6·4-hydroxypyridinium (**8**) is formally 2:2 complex. This means that the asymmetric unit contains two hosts in slightly different conformations, two differently orienting guests and two BF_4^- anions, one of which is hydrogen-bonded to one of the cations. Such interaction between anion and cation is not observed in any other DB18C6 complex, indicating this to be the probable reason for difference in packing of the arrays.

The complexation studies of DB18C6 with a larger, bicyclic purinium cation (**9**) resulted in a very interesting and totally different type of packing in solid state.[IV] Purinium, as a larger guest with two hydrogen bonding sites, forms in the crystalline state a 2:1 dimeric, capsule-like complex stabilised by several simultaneous weak

interactions (Figure 14). The hydrogen bonding sites of the purinium cation are located at opposite sides of the molecule, presenting an excellent possibility for hydrogen bonding interaction with two different hosts at the same time. Although simultaneous hydrogen bonding to two different hosts was also observed with the imidazolium (**1**) and triazolium (**3**) cations,[I,II] the larger size of the purinium cation (**9**) and thus the greater distance between the hydrogen bond donating sites (2.11 vs. 3.92 Å, respectively) mean that sterically the most efficient packing is not head-to-tail but head-to-head. Also, the significantly stronger π···π interactions between the cation and the crown ether as well as the capsule stabilising C-H···π interactions between the facing hosts affect dimer formation. The dimeric packages are self-complementary and therefore they pack into continuous chains stabilised by intercapsular C-H···N interactions (Figure 14).

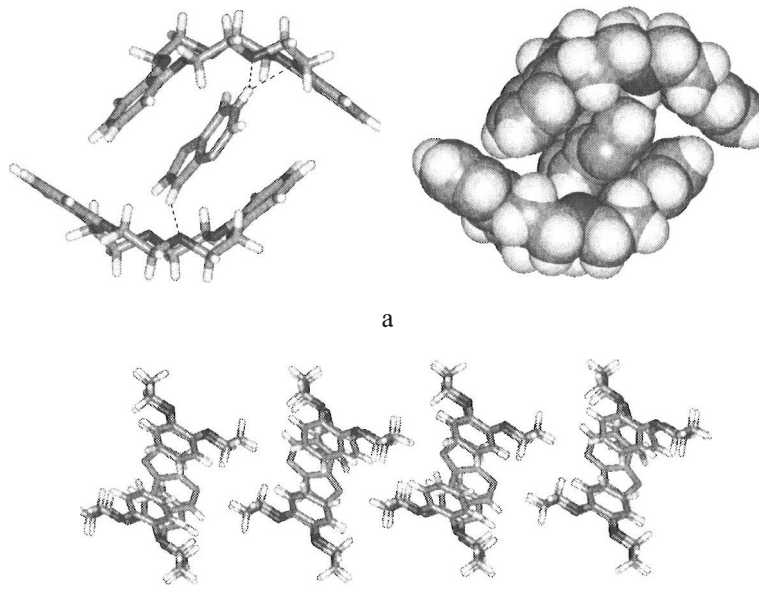

Figure 14 Molecular structure of $(DB18C6)_2$·purinium (**9**) capsules, stick and VDW presentations (a). Self-complementary packing of the capsules into continuous chains (b).

Comparison of the crystal structures and stabilities of the imidazolium (**1**)[II] and pyrimidinium (**5**)[III] complexes with crown ethers containing different numbers of aromatic units shows that aromatic moieties decrease the stability of the complex (18C6 > B18C6 > DB18C6) (Table 2). The aromatic rings decrease the electron density of the adjacent oxygen atoms, thus decreasing the ability to form hydrogen bonds. The stability of the complexes may also be affected for sterical reasons: the oxygen atoms are more shielded from the side of the cavity and thus not so easily accessible by the cation.

Owing to the more flexible nature of the B18C6 and 18C6 hosts there is no close resemblance in their crystal packing. The B18C6·imidazolium (**1**) complex packs into centrosymmetrical columns *via* hydrogen bonding of imidazolium (**1**) to the adjacent hosts,[II] whilst B18C6·pyrimidinium (**5**) forms π-stacked layers (Figure 15).[III]

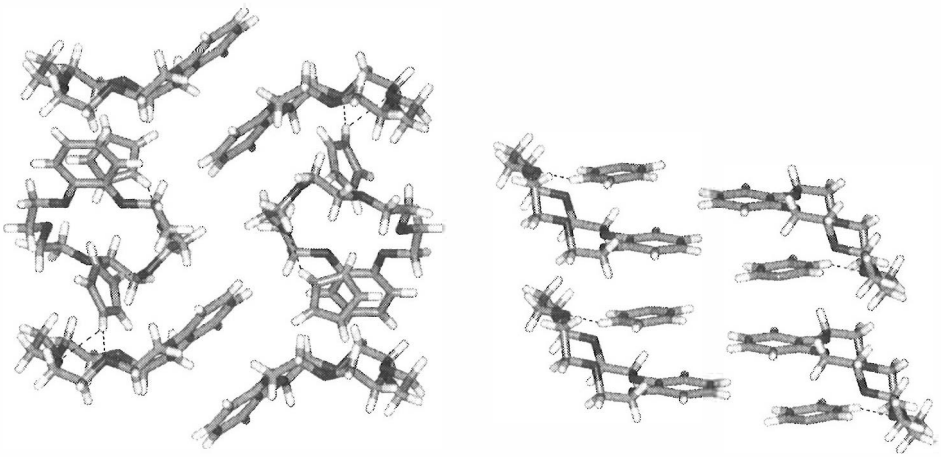

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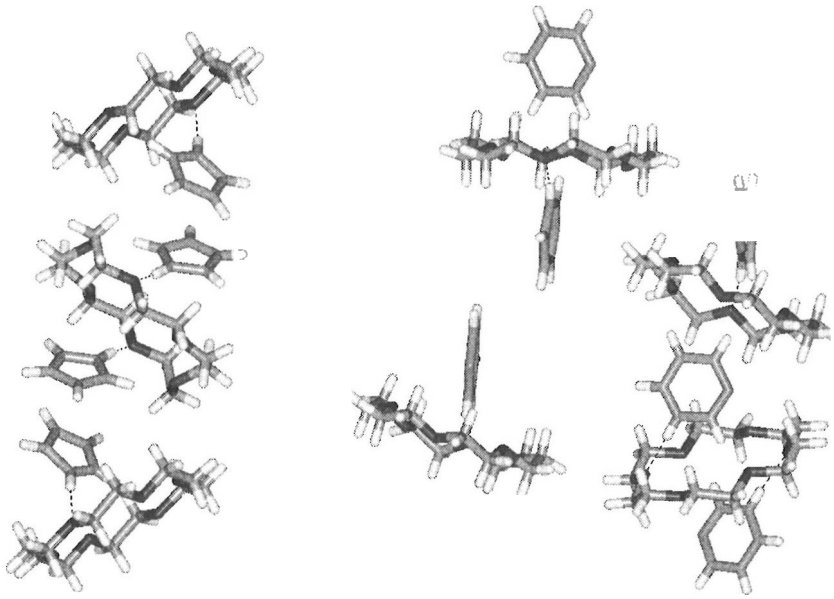
Figure 15 B18C6·imidazolium (**1**) complexes pack into hydrogen-bonded centrocymmetrical columns (a); while B18C6·pyrimidinium (**5**) forms π-stacked layers (b).



a b

Figure 16 Crystal packing of 18C6·imidazolium (**1**) (a) and 18C6·pyrimidinium (**5**) (b) complexes.

Both the 18C6·imidazolium (**1**)[II] and 18C6·pyrimidinium (**5**)[III] complexes have in solid state a host-guest ratio different from the 1:1 observed in the respective DB18C6 and B18C6 complexes. The 18C6 complex of imidazolium (**1**) has a 1:2 ratio with two guests hydrogen-bonded to opposite sides of the host (Figure 16). The 1:2 units pack into loose centrocymmetrical columns with an open space for hydrogen bonding between the cations and the intercolumnar anions. The 18C6 complex of pyrimidinium (**5**) also pack into centrocymmetrical arrays, which are basically similar to those of the other columnar complexes. However, the uneven host-to-guest ratio of 3:4 causes an exception to the symmetry in some columns, *i.e.* instead of the usual "host-guest-host-guest" order a part of the column is in the order "host-guest-guest-host" (Figure 16).

The effect of the ring size of the crown ether on the stability of the complex relates to the best sterical fit of the guest. For five-membered cations a ring with fewer than 18 members might provide a better fit, while bigger crown ethers (DB21C7 and DB24C8) are clearly too big for the perfect complexation (Table 2).[II] The effective complexation of the cation by bigger crown ethers (ring size 18 – 30 atoms) would require a conformational change, *i.e.* folding of the host over the guest to the sandwich-like structure earlier observed with the DB24C8·tropylium[108,109] (Figure 8b) and DN30C10·diquat[137] complexes. The only larger crown ether complex which it proved possible to crystallise in this study was DB21C7·imidazolium (**1**), the structure of which showed that imidazolium (**1**) is not located in the cavity of the crown ether but "backside" of the crown *via* moderately long hydrogen bonds.[II] The cavity of the crown is filled by the longer $-CH_2CH_2O-$ chain, *i.e.* competitive self-inclusion occurs (Figure 17). Competitive self-inclusion and the more flexible nature of the larger crowns also provide a reasonable explanation for the difficult crystallisation and poor affinity of other bigger crown ethers for the cations studied (Table 2).[II,III]

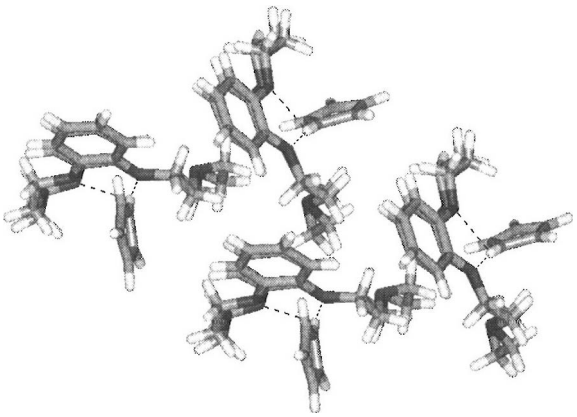


Figure 17 A packing diagram of the DB21C7·imidazolium (**1**) complex. The hosts are self-included and the cations are hydrogen-bonded to backside of the crown.

On the other hand, the earlier study by Reinhoudt *et al.* shows that if even larger crown ether rings (more than 30 ring atoms) are used, the complexation of imidazolium (**1**) is again facilitated.[142] The reason for this is clearly seen from the crystal structure of the B30C10·imidazolium (**1**) complex: the cation is of just the right size to fit in the middle of the crown ether ring *via* multiple N-H···O and C-H···O hydrogen bonds (Figure 18).

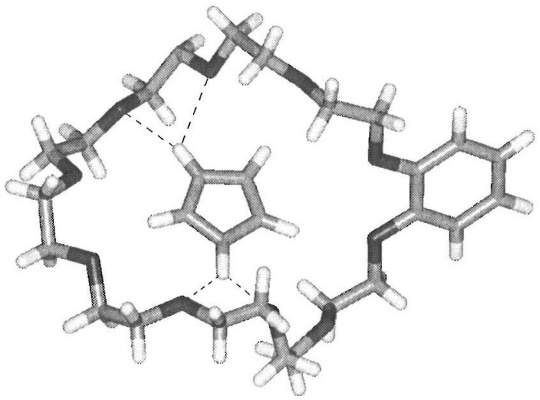
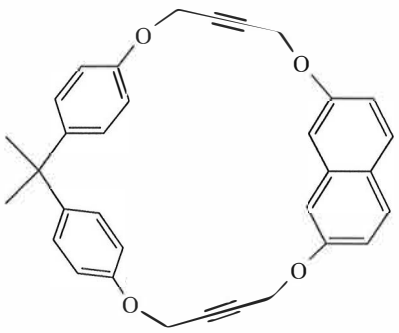


Figure 18 B30C10·imidazolium (**1**) complex by Reinhoudt *et al.* The cation is located in the middle of the crown ether ring *via* multiple hydrogen bonds.[142]

The effect of the solvent and the anions for the complexation and packing of the complexes in solid state are quite difficult to estimate. In some cases interaction between the cation and the anion probably affects packing (*e.g.* in the DB18C6·4-hydroxypyridinium (**8**)^{III} and 18C6·imidazolium (**1**)^{II} complexes), but the inclusion of the solvent in the interstices in the crystal lattice, which is observed in some structures ((DB18C6)$_2$·purinium (**9**)^{IV} and 18C6·pyrimidinium (**5**)^{III}), has no other obvious effect on complexation or packing beyond creating the most efficient packing.

2.3 CYCLOPHANE STRUCTURES[V,VI]



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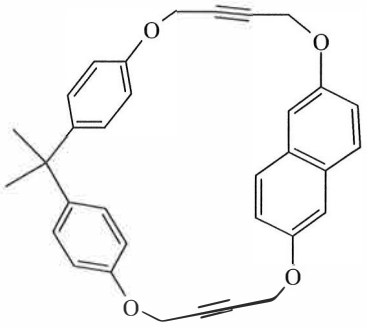

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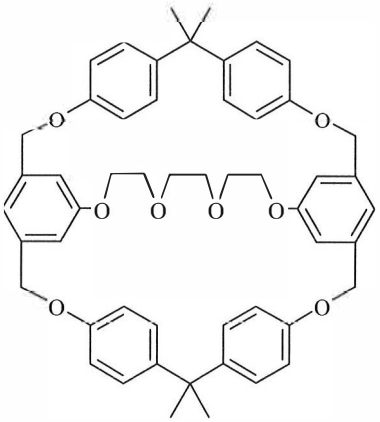

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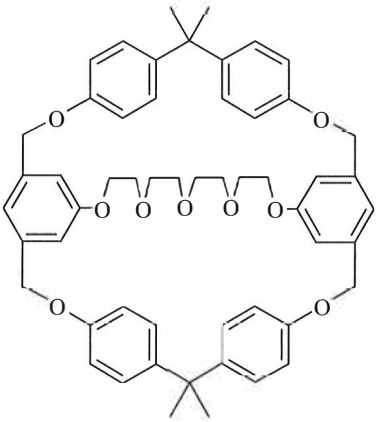


13

Scheme 7

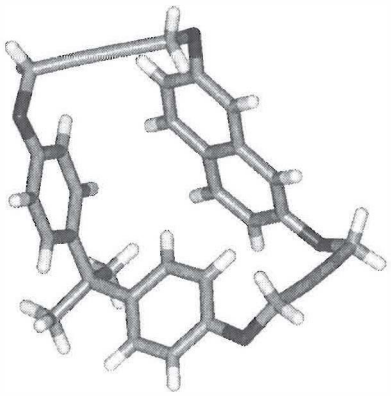
Bisphenol A cyclophanes **10** and **11** were synthesised in order to obtain new macrocyclic hosts for the binding of quats *via* cation···π interaction.[V] The NMR binding studies showed weak but yet detectable interaction between the host and the guest (Table 3) and X-ray crystallographic studies yielded a probable reason why complexation is not as strong as could be expected.

Table 3 Stability constants (K) for cyclophanes **10** - **13** with tetramethylammonium (TMA), *N*-methylpyridinium (NMP) and acetylcholine (ACh) salts determined by ^{1}H NMR titration in $CDCl_3$ solution at 30 °C.[V,VI]

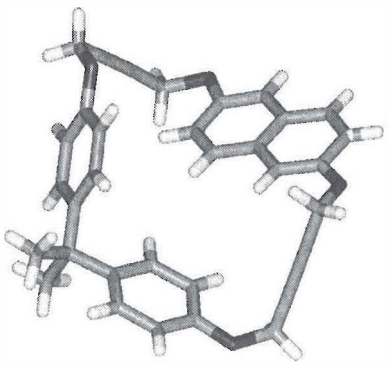
Cyclophane	TMA K / dm^3mol^{-1}	NMP K / dm^3mol^{-1}	ACh K / dm^3mol^{-1}
10	< 10	< 10	< 10
11	< 10	< 10	< 10
12	41	45 / 410[a]	40
13	25	42 / 65[a]	35

[a] In $(CDCl_2)_2$

Owing to the small available amount of cyclophanes it was not possible to cocrystallise the cyclophanes with quats, instead only the hosts were crystallised.[V] Both cyclophanes adopt distorted conformations in the crystalline state. However, the conformation of **10** is more nest-like while cyclophane **11** is completely twisted (Figure 19). The distortion of the conformations is owed to the weak intramolecular C-H···π interactions between the phenyl and naphthalene units and the bending of the phenyl rings to an almost 90° angle in respect to each other.



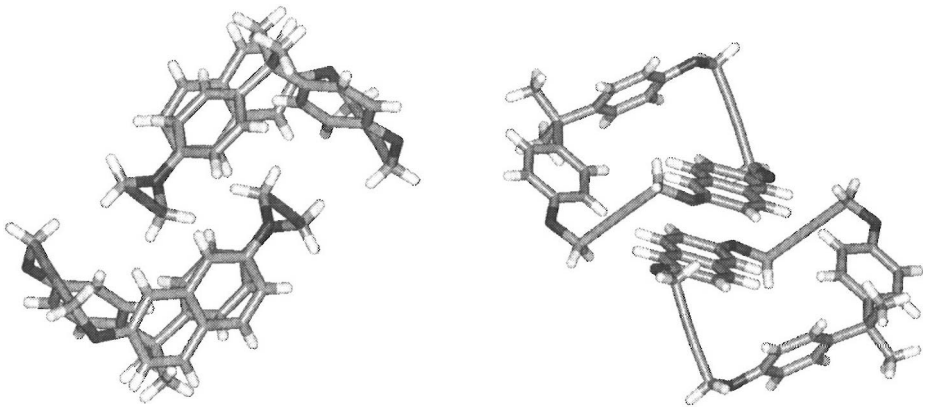
10



11

Figure 19 Distorted molecular conformations of cyclophanes **10** and **11**.

The distortion of the conformations also explains the poor affinity towards the quats.[V] Another reason for weak complexation is revealed when the molecular packing of the cyclophanes is investigated. Both cyclophanes self-assemble into dimeric pairs (Figure 20), indicating that if the affinity for self-assembly is greater than the affinity for the guest, then complexation is prohibited. The dimeric pairs are held together *via* π···π or C-H···π interactions between the aromatic units and the triple bond or methylene carbon.



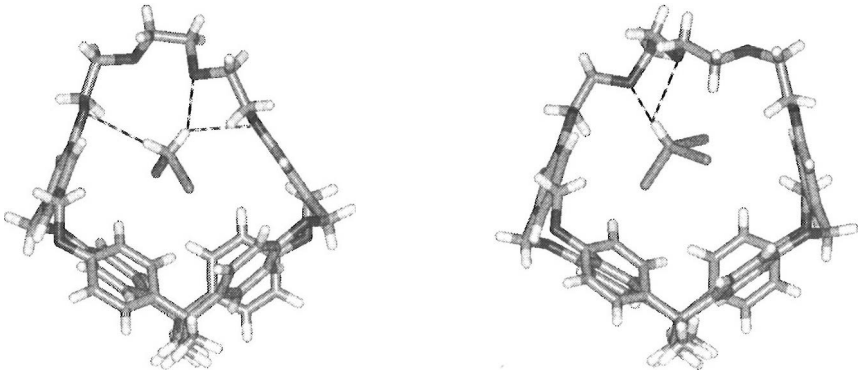
a b

Figure 20 Cyclophanes **10** (a) and **11** (b) self-assemble into dimeric pairs.

Cyclophanes **12** and **13** are bicyclic cyclophanes, which are also based on bisphenyl A units.[VI] The bisphenyl A units form the basis for the hydrophobic part of the molecule while the crown ether bridge adds hydrophilicity and enhances the preorganisation and the rigidity of the cavity. Cyclophanes **12** and **13** proved to have better complexation properties in solution than monocyclic cyclophanes **10** and **11** owing to the bigger size of the cavity and a more favourable and preorganised conformation (Table 3). Also the crystal structures support the better complexation affinity toward small molecules, since both cyclophanes **12** and **13** crystallised with an included solvent molecule (dichloromethane and chloroform, respectively). It was not possible to cocrystallise the

cyclophanes with quats or from 1,1,2,2-tetrachloroethane as a comparison and support for the complexation studies in solution because of the small available amount of the cyclophanes.

Both bicyclic cyclophanes **12** and **13** have a basket-shaped conformation with biphenyl A units forming the hydrophobic bottom and the crown ether bridge the hydrophilic handle of the basket (Figure 21).[VI] The bottom of the basket is almost totally closed since the aromatic rings of the biphenyl A units are bent to the angles of 84 and 65° in **12**, and 87 and 82° in **13** with respect to each other. Thus the guest can enter the cavity only through the space between the handle and the bottom of the basket. The inclusion of the solvent molecules is facilitated by the weak hydrogen bonding interactions between the crown ether oxygens and the solvent hydrogens (Figure 21).



a b

Figure 21 Molecular structures of **12** (a) and **13** (b) showing the included solvent molecules.

In 1,1,2,2-tetrachloroethane solution enhanced stabilities for the complexation of NMP by cyclophanes **12** and **13** were observed (Table 3).[VI] However, the enhancement of stability for **12** was much greater than for **13**. The reason for this could be explained by

the competitive binding of the solvent into the cavity of the larger cyclophane **13**, while the cavity of the **12** is obviously too small to include a bulky tetrachloroethane molecule. The crystal structure studies support the observation in solution, since visual observation of VDW surfaces and comparison of the sizes of the cavities indicate the too small size of **12** (Figure 22). In addition the longer crown ether chain of **13** is more flexible and can thus also adjust itself for the inclusion of a bigger guest than chloroform. The shape of the cavity with two open sides and a closed bottom might also be suitable for rotaxane-like inclusion, *i.e.* the guest extends through the cavity, only a small part being really inside.

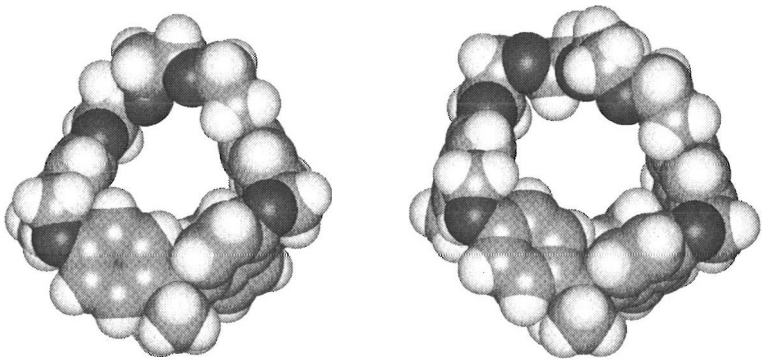


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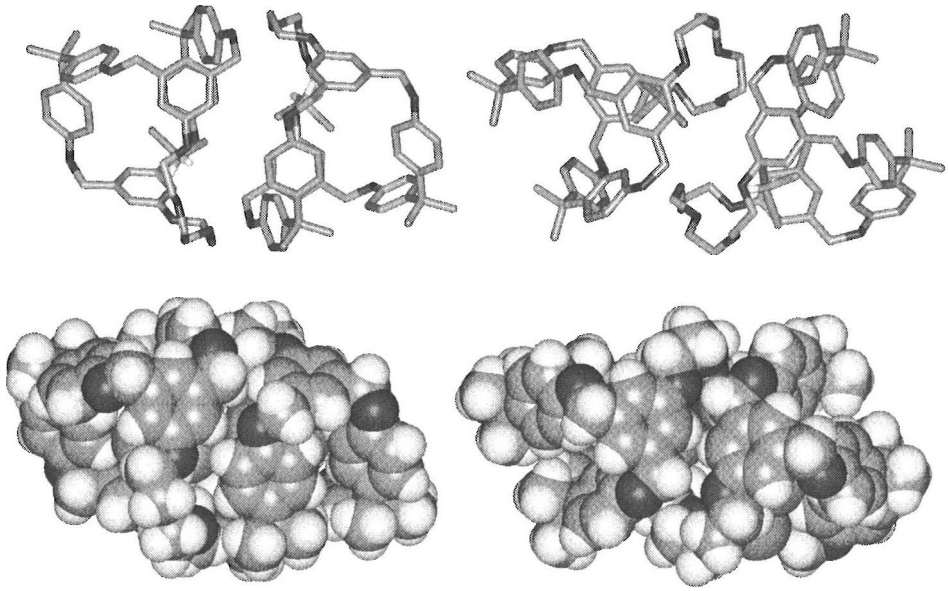
Figure 22 VDW presentation of the empty cavities of **12** (a) and **13** (b). The cavity of the latter is clearly larger, thus indicating the greater affinity for inclusion of bulky tetrachloroethane.

The dimer formation is also observed with bicyclic cyclophanes **12** and **13**.[VI] Cyclophane **13** with a longer crown ether chain forms a tennis ball-like dimer with the crown ether loop located between the bottom and the handle of the adjacent molecule (Figure 23). The dimeric packing is caused both by the best possible sterical fit and the weak C-H···O hydrogen bonds between methylene carbons and ether oxygens. In

cyclophane **12** the shorter crown ether loop is not located between the bottom and the handle but closer to the bottom, forming a tube-like structure.

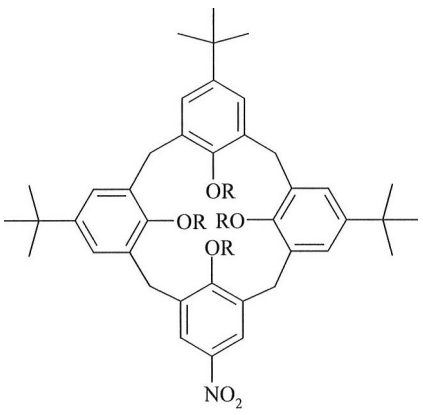


a b

Figure 23 Stick and VDW presentations of the dimeric packing of **12** (a) and **13** (b). In **12** the cavities face each other exactly while the dimerisation of **13** is tennis ball-like. Hydrogen atoms of the cyclophane are excluded from the stick presentation for clarity.

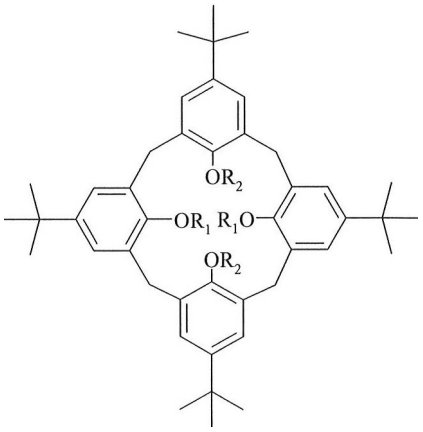
2.4 CALIXARENE STRUCTURES[VII,VIII]

The crystal structures of *p-tert*-butylcalix[4]arene tetraethers **14** and **15** were as expected with regard to their conformational and inclusion properties.[VII,VIII] In contrast to the almost perfect cone conformation of *p-tert*-butylcalix[4]arene with free hydroxyl groups the tetraether derivatives usually adopt a pinched (also called flattened) cone conformation in solid state.[122] This was also the case with calixarenes **14** and **15**, in which the two opposite aryl groups are almost parallel, while the other two are nearly perpendicular (Figure 24).



R = $CH_2COOCH_2CH_3$

14

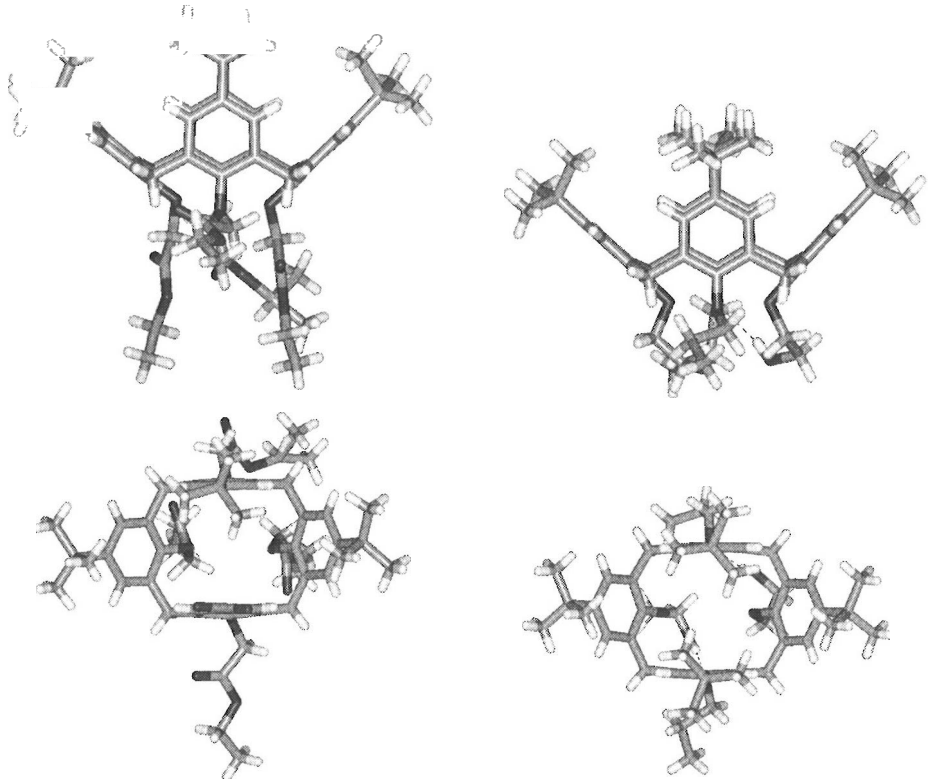


$R_1 = CH_2CH_2OH$
$R_2 = CH_2CH_2CH_3$

15

Scheme 8

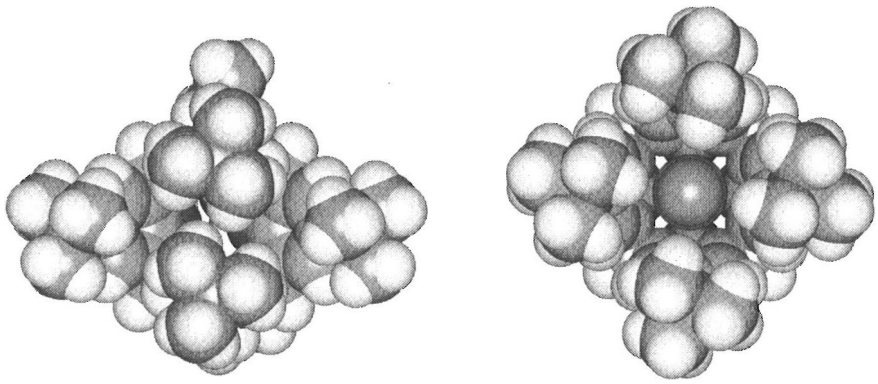
The reason for the flattening of the cone is the absence of conformation-stabilising hydrogen bonds between the adjacent phenolic oxygens, while the bulkiness of the *tert*-butyl groups and the lower rim substituents prohibits conversion to any other conformation. The conformation of nitro derivative **14** is slightly more pinched than the conformation of either **15** or tetra-*tert*-butylcalix[4]arene tetraether determined earlier[143,144] (interplanar angles between the opposite aromatic rings are –7 and 96° for **14**, 1 and 90° for **15** and 2 and 94° for the tetra-*tert*-butylcalix[4]arene tetraether[143,144]), owing to the weak attractive forces between the nitro group and the opposite *tert*-butyl group. Since the *tert*-butyl group is severely disordered, it is difficult say whether these forces are in fact C-H···O/N hydrogen bonds or simply weak electrostatic attractions.



a b

Figure 24 X-ray crystal structures of calixarenes **14** (a) and **15** (b). Side view and top view.

The inclusion properties of calix[4]arenes in pinched cone conformation are negligible since the closest opposite upper rim substituents completely block the path to the cavity. This was also the case in **14** and **15**, both of which showed no inclusion of the solvent in the cavity or in the crystal lattice (Figure 25).[VII,VIII] Interesting examples of closely related *tert*-butylcalix[4]arene tetraesters and -ethers, which include a molecule of acetonitrile in their almost perfect cone-like cavity, however, indicate that with a suitable, in this case rod-like guest, the conformation may change for inclusion.[145-147]



a b

Figure 25 VDW presentations of top view of **15**, showing the steric hindrance which prohibits the inclusion of the solvent (a)[VII] and of the situation where a suitable guest changes the conformation of a similar calixarene to allow inclusion (b).[145]

The packing of calixarenes **14** and **15** is affected by the sterical efficiency and weak VDW interactions, since the compounds do not have any suitable functional groups to enable significant intermolecular interactions. Free hydroxyl groups in **15** form intramolecular hydrogen bonds and are thus not available for intermolecular hydrogen bonding.[VIII] In calixarene **14** there are no hydrogen bond acceptor groups, which makes only weak C-H···O hydrogen bonds possible.[VII] Indeed, some interactions of this type are observed between the methyl carbons of a *tert*-butyl or an ester group and the nitro groups of the adjacent calix[4]arenes as well as between the ester groups of the adjacent molecules (distance between the hydrogen bond donor and acceptor varies from 3.1 to 3.4 Å).

The molecules of **14** pack in head-to-tail fashion into adjacent arrays, which orient in opposite directions (Figure 26). From the packing of **15** it is difficult to observe any clear pattern; instead the adjacent molecules orient themselves in various directions.

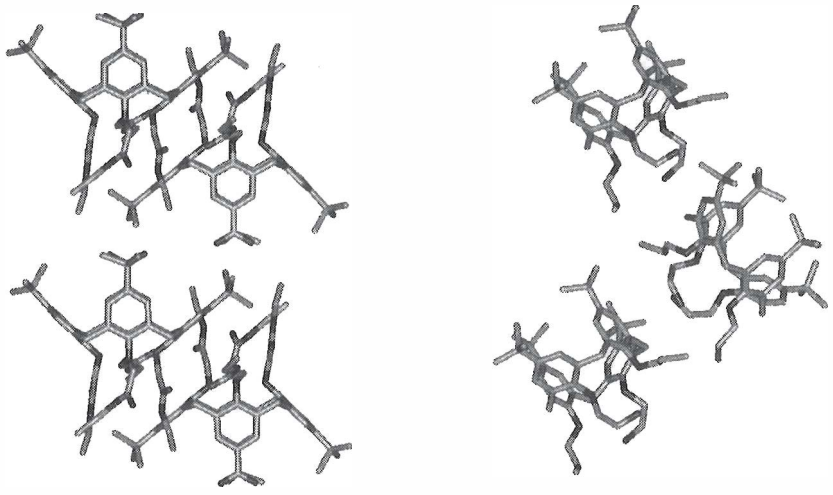


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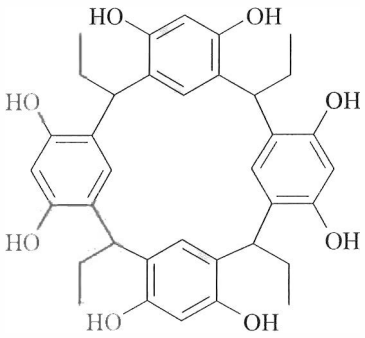
Figure 26 Packing diagrams for calixarenes **14** (a) and **15** (b).

2.5 RESORCINARENE STRUCTURES[IX]



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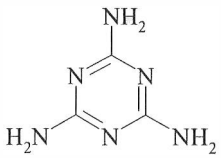
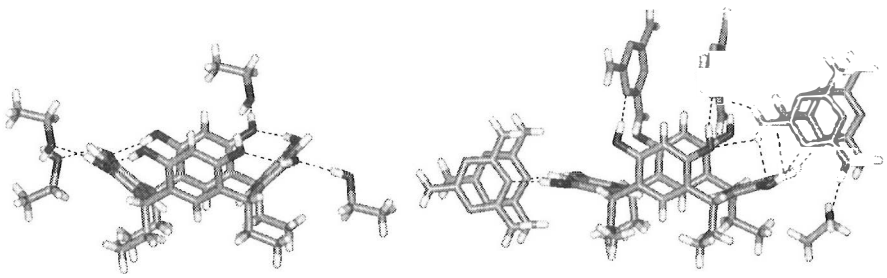


17

Resorcinarenes[35,38,40,42,43,52] as well as melamine (**17**)[45-51,53-55] are both widely used as precursors for supramolecular assemblies. Therefore the co-crystallisation of two such versatile components in order to obtain highly organised supramolecular structures

produces an interesting hydrogen-bonded network as well as a rare solid state conformational change of the ethyl resorcin[4]arene (**16**) from crown to boat.[IX]

Earlier studies of the conformational properties of the resorcin[4]arenes with unsubstituted hydroxyl groups and methylene bridge substituents in all-*cis* arrangement have shown exclusive crown conformation both in solid state[38,43,52,65,90,91,148-150] and in solution[151-154]. The only exception is the silver complex of Munakata *et al.* in which the coordination of silver to resorcinarene oxygens induces the conformational change from crown to boat.[155]



a b

Figure 27 The crystal structures of ethyl resorcinarene (**16**) crystallised from ethanol (a) and cocrystallised with melamine (**17**) (b).

The conformational change of ethyl resorcinarene (**16**) is due to the ability of melamine (**17**) to act simultaneously as a hydrogen bond donor and an acceptor.[IX] Therefore the intramolecular hydrogen bonds, which usually keep resorcinarene in a crown conformation, are replaced by the maximal amount of intermolecular hydrogen bonds. Investigation of the hydrogen bonds shows two types of interaction: primary hydrogen bonding between the aromatic nitrogens of melamine and the hydroxyl groups of resorcinarene and secondary hydrogen bonding between the melamine amino groups and resorcinarene hydroxyl groups. The primary hydrogen bonds are shorter (2.64 -

2.77 Å) and approximately the same length as the intramolecular hydrogen bonds in the reference structure of ethyl resorcinarene (**16**), which was crystallised without a guest in ethanol solution (Figure 27). The primary hydrogen bonds connect three resorcinarenes around a pair of melamine molecules into wheel-like clusters (Figure 28). The secondary hydrogen bonds of length 2.94 - 3.38 Å reinforce the complexation and cause the asymmetry of the conformation.

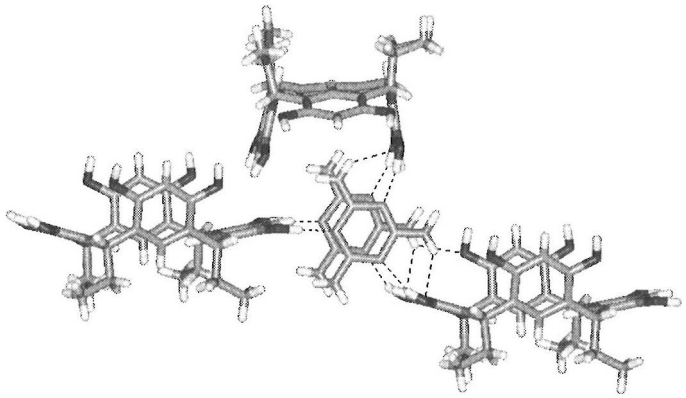


Figure 28 Primary hydrogen bonds connect three resorcinarene (**16**) molecules around a pair of melamine (**17**) molecules into wheel-like clusters.

The conformational properties of melamine cocrystallised resorcinarene can be compared to those of the reference crystallisation,[IX] the Ag-complex[155] and the almost perfect crown conformation of ethyl resorcin[4]arene·$N(CH_3)_4^+Br^-$[156] (Figure 29). In the reference crystallisation the conformation is a slightly pinched crown stabilised by intramolecular hydrogen bonds, while in the silver complex the conformation is totally flipped into the boat conformation.[155] The conformation of the melamine complex lies in between these two owing both to the lack of crown-stabilising intramolecular hydrogen bonds and to the weakness of melamine-resorcinarene hydrogen bonding compared to the metal coordination. The almost perfect crown conformation of ethyl resorcinarene·$N(CH_3)_4^+Br^-$ is induced by the inclusion of the guest in the cavity of the

resorcinarene as well as the inclusion of the bromide in the lower rim.[156] The results emphasise the significance of the guest for the conformation of the resorcinarene and yield new perspectives from the crystal engineering point of view.

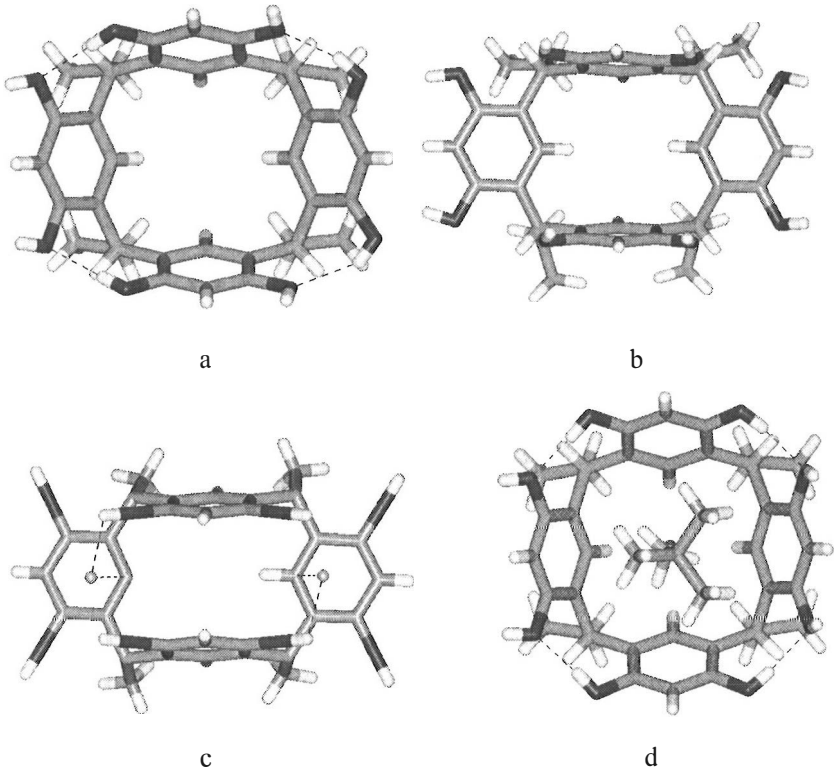


Figure 29 The conformations of ethyl resorcinarene (**16**) crystallised from ethanol (a); ethyl resorcinarene cocrystallised with melamine (b); complex of methyl resorcinarene with silver (c);[155] and ethyl resorcinarene·$N(CH_3)_4^+Br^-$ complex (d)[156].

The superstructure of the melamine complex is described as a pile of hydrophobic layers formed by the criss-crossing melamine-resorcinarene chains, in which the hydrophilic parts are buried in the middle of the chains leaving no possibility for direct hydrogen bonding contacts between the resorcinarenes. In the reference crystallisation, however, the adjacent hosts are connected *via* intermolecular hydrogen bonds.[IX]

3 SUMMARY AND CONCLUSIONS

This study reports the crystal structures of 22 supramolecular compounds. 14 of these are the host-guest complexes of various crown ethers with small *N*-heteroaromatic cations, for which a detailed analysis of the weak interactions affecting their complexation and crystal packing in solid state was carried out. Hydrogen bonding was observed to be the most important weak interaction between hosts and guests but π interactions also contributed to complexation. Interesting polar, columnar packing was observed in all the DB18C6 complexes regardless of weather the guest was five- or six-membered. The complexes of the more flexible B18C6 and 18C6 crown ethers did not share such a close resemblance. Guest-facilitated dimer formation of DB18C6 was observed when bicyclic purinium (**9**) cation was used as the guest.

Cyclophane structures **10 - 13** proved the importance of preorganisation for complexation. The smaller monocyclic cyclophanes **10** and **11** did not form inclusion complexes with the solvent but adopted distorted conformations and organised themselves into dimers held together *via* weak π interactions. The bigger, bicyclic cyclophanes **12** and **13** have a more preorganised structure and a larger cavity suitable for guest inclusion. Thus both crystallised with the inclusion of a solvent molecule, which together with NMR spectrometric studies indicates the suitability for complexation of other small compounds such as quats. Again, the packing into dimeric units was observed.

The crystal structures of calix[4]arene tetraethers **14** and **15** are typical examples of solid state structures of compounds of this type. Thus the crystal structures confirm the

information obtained in solution and yield detailed information about the conformational aspects, crystal packing and the interactions affecting them. This information can be used to consider the suitability of these compounds as starting materials for further synthetic steps, for complexation studies and in designing variations of the molecules studied.

Ethyl resorcin[4]arene (**16**) was crystallised successfully with melamine (**17**), when a rare conformational change from crown to boat occurred. Comparison of the crystal structure with the reference crystallisation from ethanol and the crystal structure of **16**·$N(CH_3)_4^+Br^-$[156] showed the importance of the guest for the conformation of resorcin[4]arene in solid state. An additional point of interest was the formation of a hydrogen-bonded network, in which the hydrophilic parts of the melamine and resorcin[4]arene molecules face each other, thus forming hydrophobic layers.

To summarise, X-ray crystallography has been used as a tool to investigate weak intermolecular interactions in host-guest complexes and in crystal packing. In addition, the estimation of the suitability of the given compounds for complexation studies, the confirmation and detailed investigation of the compounds as well as the conformational studies of the macrocyclic hosts were performed with the help of the X-ray structure analysis. The results can be utilised in crystal engineering, designing syntheses and programmed functions for molecules as well as in theoretical studies of the nature of weak interactions. X-ray crystallography has proved to be a fruitful and convenient tool for the detailed study of the weak, intermolecular interactions.

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PAPER I

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PAPER II

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