UNIVERSITY OF JYVÄSKYLÄ
DEPARTMENT OF CHEMISTRY
RESEARCH REPORT No. 128

RESORCINARENES AND THEIR DERIVATIVES: SYNTHESIS, CHARACTERIZATION AND COMPLEXATION IN GAS PHASE AND IN SOLUTION

BY

NGONG KODIAH BEYEH

Academic Dissertation
for the Degree of
Doctor of Philosophy

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ABSTRACT

The research described in this thesis focuses on the synthesis, characterization and complexation of unfunctionalized and functionalized resorcinarenes. Resorcinarenes, regarded as a common pillar in supramolecular chemistry, possess a multipurpose scaffold for various applications. The aromatic ring of resorcinarenes is highly activated for electrophilic substitutions by the presence of the hydroxyl groups. The π-basic bowl shaped cavity in the unfunctionalized resorcinarene is mainly responsible for its ability to attract guest species.

This thesis focuses on the synthesis of the core resorcinarenes with several lower rim chains, modifying the upper rim resorcinarene at the 2-position of the resorcinol ring between the two hydroxyl groups. Further functionalization of the 2-position includes the addition of halogens and chiral aminomethylated groups. Sulfonyl esterification of the phenolic hydroxyls of the resorcinarenes is also reported. The guests used in the complexation studies were either synthesized or commercially available. The guests selection ranges from cationic to neutral species. The cationic guests include chiral and non-chiral alkylammonium cations, phosphonium and metalloorganic cations. Encapsulation properties of both the unfunctionalized and functionalized resorcinarenes with the different guests were studied in detail. The size and charge of the encapsulated guests as well as the size and electronic properties of the substituents on the hosts were found to be important. Resorcinarene and pyrogallarene hexameric capsules were shown to exist in the gas phase with $[Ru(2,2'\text{-bipyridine})_3]^{2+}$ acting as the template for hexameric capsule formation by virtue of its size and as it is a dication a lower m/z range was obtained. The conformation, stereochemistry, electronic and inclusion properties of the resorcinarene hosts were studied in the gas phase, liquid and solid state by mass spectrometry, NMR spectroscopy, fluorescence spectroscopy and X-ray crystallography.

A brief review of resorcinarene synthesis, self-assembly and supramolecular chemistry is presented as an introduction to this thesis. The complexation and self-assembling properties of resorcinarenes via mass spectrometry, NMR spectroscopy and X-ray crystallography are reviewed.

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PREFACE

This work was carried out at the Department of Chemistry, University of Jyväskylä from January 2005 to September 2008.

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Jyväskylä, September 2008

Ngong Kodiah Beyeh

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. N. K. Beyeh, M. Kogej, A. Åhman, K. Rissanen and C. A. Schalley, Flying Capsules: Mass Spectrometric Detection of Pyrogallarene and Resorcinarene Hexamers, *Angew. Chem. Int. Ed.* **2006**, 45, 5214–5218.

https://doi.org/10.1002/anie.200600687

II. N. K. Beyeh, D. Fehér, M. Luostarinen, C. A. Schalley and K. Rissanen, Synthesis of Chiral Resorcinarene-based Hosts and a Mass Spectrometric Study of their Chemistry in Solution and the Gas Phase, *J. Incl. Phenom. Macrocyclic Chem.* **2006**, 56, 381–394.

https://doi.org/10.1007/s10847–006–9121–2

III. N. K. Beyeh, J. Aumanen, A. Åhman, M. Luostarinen, H. Mansikkamäki, M. Nissinen, J. Korppi-Tommola and K. Rissanen, Dansylated Resorcinarenes, *New J. Chem.* **2007**, 31, 370–376.

https://doi.org/10.1039/B615772F

IV. N. K. Beyeh, A. Valkonen and K. Rissanen, Encapsulation of Tetramethyl Phosphonium Cations, *Supramol. Chem.* **2008**, *in press*.

https://doi.org/10.1080/10610270802308411

V. N. K. Beyeh, D. Weimann, C. A. Schalley and K. Rissanen, Electronic vs Steric effect: Mass Spectrometric and X-Ray Crystallographic Studies of the Interactions of Resorcinaneres with Neutral and Positively Charged Guests, *Manuscript*.

https://doi.org/10.1002/chem.201103991

VI. E. Kalenius, T. Kekäläinen, R. Neitola, N. K. Beyeh, K. Rissanen and P. Vainiotalo, Size and Structure Selective Noncovalent Recognition of Saccharides by Tetraethyl and Tetraphenyl Resorcinarenes in the Gas Phase, *Chem. Eur. J.* **2008**, 14, 5220–5228.

https://doi.org/10.1002/chem.200800075

To Aka, Margaret and Zacheus

CONTENTS

ABBREVIATIONS

br	broad
CID	collision induced dissociation
d	doublet
dd	pair of doublets
DMF	dimethyl formamide
ESI-MS	electrospray ionization mass spectrometry
e.g.	for example
FRET	fluorescence resonance energy transfer
FTICR	fourier transform ion cyclotron resonance
IRMPD	infrared multiphoton dissociation
m	Multiplet
MS	mass spectrometry
m.p.	melting point
m.w.	molecular weight
NMR	nuclear magnetic resonance
NBS	N-bromosuccinimide
NIS	N-iodosuccinimide
o	overlapping
ppm	part per million
q	quartet
rt	room temperature
s	singlet
sp	splitted
t	triplet
THF	tetrahydrofuran
TLC	thin layer chromatography
TMA	tetramethyl ammonium
TMP	tetramethyl phosphonium
VDW	Van der Waals
Å	Ångström, 10^{-10} m

1 REVIEW OF LITERATURE

1.1 Supramolecular Chemistry

Supramolecular chemistry, commonly described as the chemistry of non-covalent interactions between molecular species or the coalescence of molecules into non-covalent arrays, simply, "chemistry beyond the molecule", is a rapidly growing field in chemistry.[1,2] Since the introduction of the lock and key principle, first postulated in 1894 by Emil Fischer to explain the specific action of an enzyme, where the lock is the enzyme and the key is the substrate,[3] one of the aims of supramolecular chemistry has been to mimic biological recognition processes with synthetic molecules, *i.e.*, host – guest (receptor – substrate) chemistry.[1,4] Supramolecular assemblies are built from more than one molecule and are bound to each other through supramolecular, viz. weak interactions. One of the challenges of supramolecular chemistry is the development of new materials with well-defined properties based on specially designed properties of the molecular constituents for the translation of the intrinsic properties of molecules into material properties. Thus, it is essential to have control over the molecular interactions and orientation in the material.[1,2]

Calixarenes and resorcinarenes are members of the cyclophane family which consists of bridged aromatic compounds.[5] These compounds are readily available and are considered as pillars of supramolecular chemistry. Their most characteristic feature is the hydrophobic cavity formed by the aromatic rings. Additional binding sites such as the hydroxyl functions and restrained flexibility facilitate stronger interactions with guests. The ability of resorcinarenes to be easily functionalized makes them ideal building blocks and their ability to selectively bind specific guest species highlights their role in supramolecular chemistry.[5-8]

1.1.1 Weak interactions

Non-covalent interactions, generally referred to as supramolecular interactions are essential for the formation of molecular assemblies. Weak interactions (excluding electrostatic interactions) can roughly be placed into five different subgroups.[1, 9-22]

- Ion-dipole interactions (bond energy = 50-200 KJ mol^{-1}) which take place when polar molecules coordinate around an ion. This is seen both in the solid state and in solution.[1]

- Dipole-dipole interactions (bond energy = 5-50 KJ mol^{-1}) involving the alignment of polarized molecules. Due to the high energy of the dipole-dipole interactions, molecules can associate with each other.[1]

- Hydrogen bonding (bond energy = 4-120 KJ mol^{-1}) is considered as a particular kind of dipole-dipole interaction in which a hydrogen atom attached to an electronegative atom (or electron withdrawing group) is attracted to a neighboring dipole on an adjacent molecule or functional group. The hydrogen bond is relatively strong and highly directional and is therefore considered to be the most important interaction in supramolecular chemistry. It is operative in determining molecular conformation, molecular aggregation, and the function of a vast number of chemical systems ranging from inorganic to biological.[1,9-13]

- Aromatic interactions (energy = 0-80 KJ mol^{-1}), which could be divided into π···π stacking (overlapping of p-orbitals in π-conjugated systems and becomes stronger as the number of π-electrons increases), C-H···π (a weak hydrogen-bond occurring between soft acids and soft bases) and cation···π (interaction between the face of an electron-rich π system with an adjacent cation).[1]

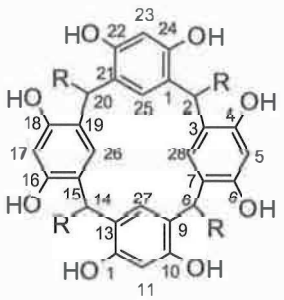
- Van der Waals (< 5 KJ mol^{-1}) interactions, close packing in solids and hydrophobic effects all contributes to the interplay of organic molecules.[1]

The role of these interactions in supramolecular chemistry is discussed in detail in several reviews and text books.[14-22]

1.2 Resorcinarenes

1.2.1 Introduction

In 1872, Adolf Von Baeyer[23,24] reported the synthesis of phenol-based dyes, in which the addition of concentrated sulphuric acid to a mixture of benzaldehyde and resorcinol gave a red coloured product that turned violet in an alkaline solution. Michael[25] determined the correct elemental composition of this high melting crystalline product $(C_{13}H_{10}O_2)_n$ and its acetyl derivatives $(C_{13}H_8(OCOCH_3)_2)_n$ a few years later. From these data, he came to the conclusion that the product is formed by a combination of equal amounts of aldehydes and resorcinol. Neither Baeyer nor Michael was able to determine the correct structure of these compounds. Niederl and Vogel[26] in 1949 studied many condensation products obtained from the reaction between aliphatic aldehydes and resorcinol. Based on the molecular weight determinations they came to the conclusion that the ratio between aldehyde and resorcinol should be 4:4. They proposed the cyclic tetramer structure **1** (Figure 1). Högberg *et al.* [27] proved the structure by single crystal X-ray analysis in 1968.



1

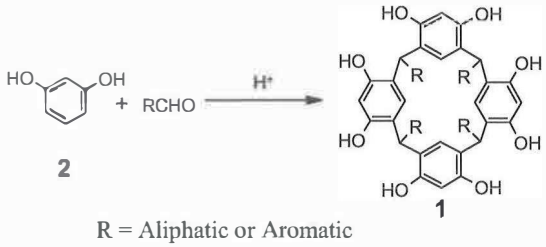
R = Aliphatic or Aromatic

Figure 1: The cyclic tetramer from aldehyde and resorcinol.[27]

Resorcinarenes[6,28,29] can be modified at the 2-position on the aromatic ring and the phenol hydroxyl groups in various ways. Their potential in forming multifunctional compounds makes them important tools in the synthesis of cavitands,[30] dendrimers[31,32] and in the construction of larger supramolecular and tubular assemblies.[33,34]

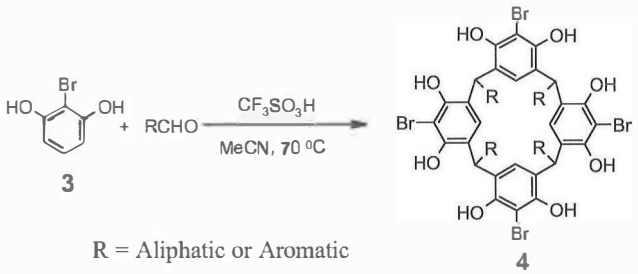
1.2.2 Synthesis

Resorcinarenes **1** can be prepared in reasonably high yields through simple one-step procedures without using templates or high dilution techniques. They are readily available in the form of *rccc* (all cis) isomers by acid catalyzed cyclocondensation of resorcinol with various aliphatic and aromatic aldehydes (Scheme 1).[6,35,36]



Scheme 1: Acid catalyzed condensation of resorcinol and aldehyde.[6,35,36]

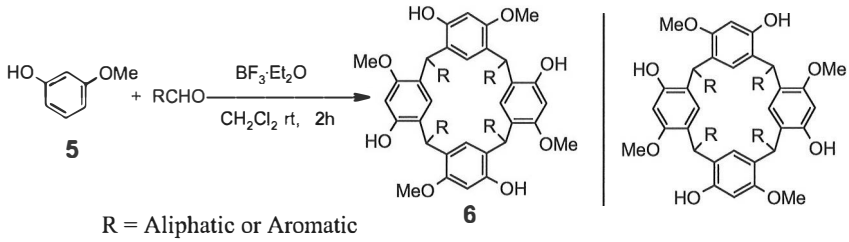
The synthesis is done by refluxing the reactants in a mixture of ethanol, concentrated HCl and water. In some cases the reaction is done in a mixture of ethanol and concentrated HCl only, and water is added to precipitate the product.[6,35,36] There are optimal conditions for different aldehydes. Though the synthesis is usually done with unsubstituted resorcinol, in some cases, 3-methoxyphenol, 2-methylresorcinol or pyrogallol (1,2,3-trihydroxylbenzene) can also be used.[6,37] Tetrabromoresorcinarene **4** catalyzed by trifluoromethane sulfonic acid (CF_3SO_3H) has been synthesized from 2-bromoresorcinol and aldehydes (Scheme 2).[38]



Scheme 2: Acid catalysed condensation of 2-bromoresocinol and aldehyde.[38]

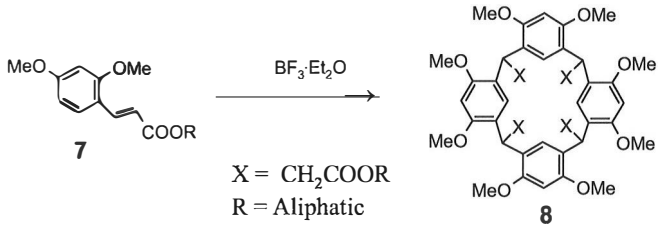
For a selection of aldehydes, both aliphatic and aromatic, there are almost unlimited possibilities. Exceptions to this general condensation reaction are seen with sterically very crowded aldehydes or aliphatic aldehydes with functionalities too close to the reaction center.[35,39]

Condensations of alkylated resorcinol derivatives with aldehydes in the presence of mineral acids in alcoholic solvents do not form cyclic products.[6] However the use of a Lewis acid in the reaction of 3-methoxyphenol with various aldehydes in dichloromethane gives C_4-symmetrical chiral tetra-alkylated resorcinarene **6** (Scheme 3). The ^{1}H NMR spectrum supports the C_4-symmetry, since there is one signal for the methoxy groups, one for the bridging methines, and two signals for the aromatic protons.[40]



Scheme 3: Lewis acid catalyzed synthesis of tetramethoxyresorcinarene.[40]

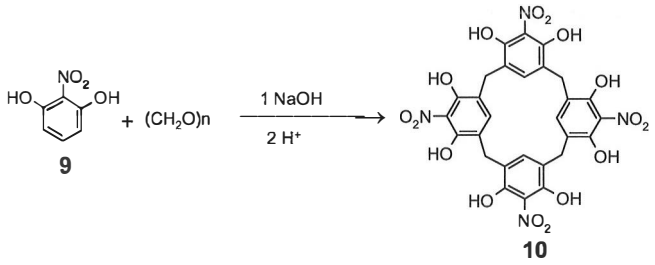
A Lewis acid-catalyzed tetramerization reaction of 2,4-dimethoxycinnamates gives the octamethoxy resorcinarene **8** (Scheme 4).[41-43] The (*E*)-2,4-dimethoxycinnamic acid methyl ester reacts with $BF_3 \cdot Et_2O$ in $CHCl_3$ at room temperature giving the desired resorcinarene derivative.



Scheme 4: Tetramerization reaction of 2,4-dimethoxycinnamates.[40,41]

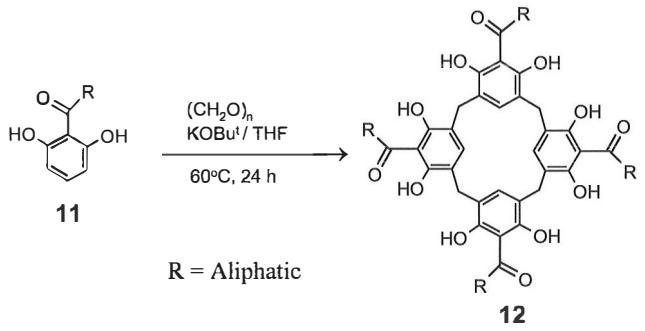
The Lewis acid-catalyzed reaction of 1,3-dimethoxybenzene and isoveraldehyde in chloroform also gives octamethoxyresorcinarene. In the $SnCl_4$ catalyzed reaction, only the *rccc* configurational isomer is formed selectively. Three configurational isomers, *rccc*, *rctt*, *rcct* are formed with other Lewis acids.[43] Resorcinarenes have also been prepared by ytterbium(III) triflate-catalyzed condensation.[44]

Resorcinol derivatives carrying electron withdrawing substituents like nitro[6,35] at the 2-position do not usually give cyclic products. However, in the presence of NaOH and the more reactive paraformaldehyde, 2-nitroresorcinarene **10** has been isolated in relatively high yields (Scheme 5).[45,46]



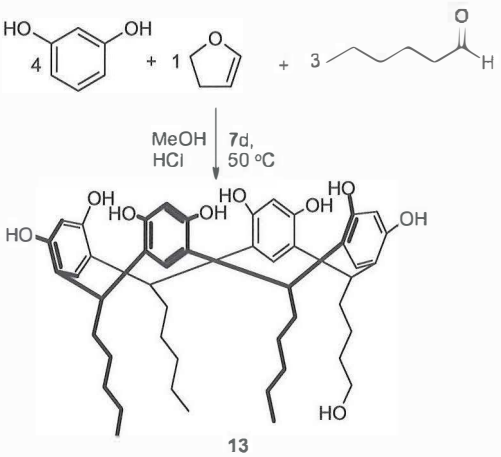
Scheme 5: Base catalysed condensation of 2-nitroresorcinaol and paraformaldehyde.[45,46]

Another base catalyzed method for the synthesis of resorcinarenes is the use of potassium tert-butoxide as a catalyst with deactivated resorcinol and formaldehyde. A mixture of equimolar amounts of 2-butyrylresorcinol and paraformaldehyde in dry THF in the presence of potassium tert-butoxide was heated at 60 °C for 24 hours (Scheme 6).[47]



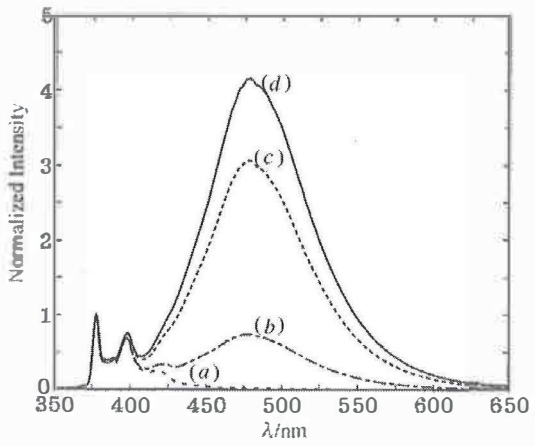
Scheme 6: Base-catalyzed condensation of resorcinol and formaldehyde.[47]

The substituents at the lower rim of resorcinarenes depend on the aldehyde used. Monofunctionalization of resorcinarenes permitting the attachment of particular groups for specific processes have been reported (Scheme 7).[48,49]



Scheme 7: 3:1 mixture of two different aldehydes with resorcinol leads to the formation of mono-functionalized resorcinarene.[48]

Resorcinarenes containing different amounts of pyrenyl groups at the lower rim have been reported.[50] Fluorescence spectroscopy[51-53] was used to analyze the interaction between pyrene moieties which absorb at 345 nm. It was revealed that the absorption maximum and coefficient are not dependent on the number of pyrene substituents. This implies that there is essentially no intramolecular interaction in the electronic ground state between pyrenyl groups (Figure 2).[50]



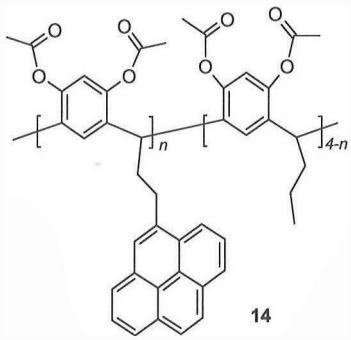


Figure 2: Fluorescence spectra normalized at 377.5 nm of resorcinarene-pyrene in THF; (a) n=1, (*b*) n=2 ,(*c*) n=3, and (*d*) n=4.[50]

1.2.3 Stereochemistry

Due to the flexibility of the macrocycle, several conformations have been observed. Disregarding the substituents of the bridges and aromatic rings, the skeleton of resorcinarenes are the same and they can adopt similar conformations. Högberg[36], in 1980, reported the first conformational analysis of resorcinarenes based on NMR measurements. The reason for the high stereoselectivity of the condensation reaction was described as being the combination of three factors.

- Resorcinarenes can in principle exist in four different configurations at the methine bridges, giving the cis-cis-cis (*rccc*), cis-cis-trans (*rcct*), cis-trans-trans (*rctt*) and cis-trans-cis (*rtct*) (Figure 3).[35,54]

- The conformations of the macrocycle can adopt five extreme arrangements: The crown (C_{4v}), boat (C_{2v}), chair (C_{2h}), diamond (C_s), and saddle (D_{2d}) conformations as seen in Figure 4.[54]

- At the methine bridges, the configuration of the substituents which in conformations of the macrocycle with *C*-symmetry, could be either equatorial or axial (Figure 4).

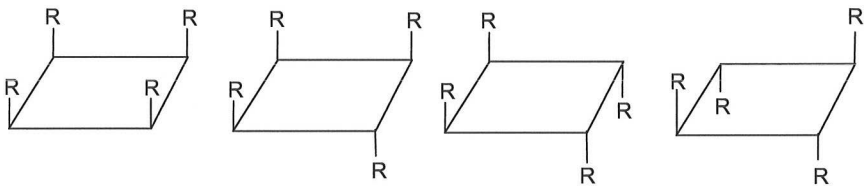


Figure 3: Orientations of the substituents of the methine bridge of resorcinarenes.[35]

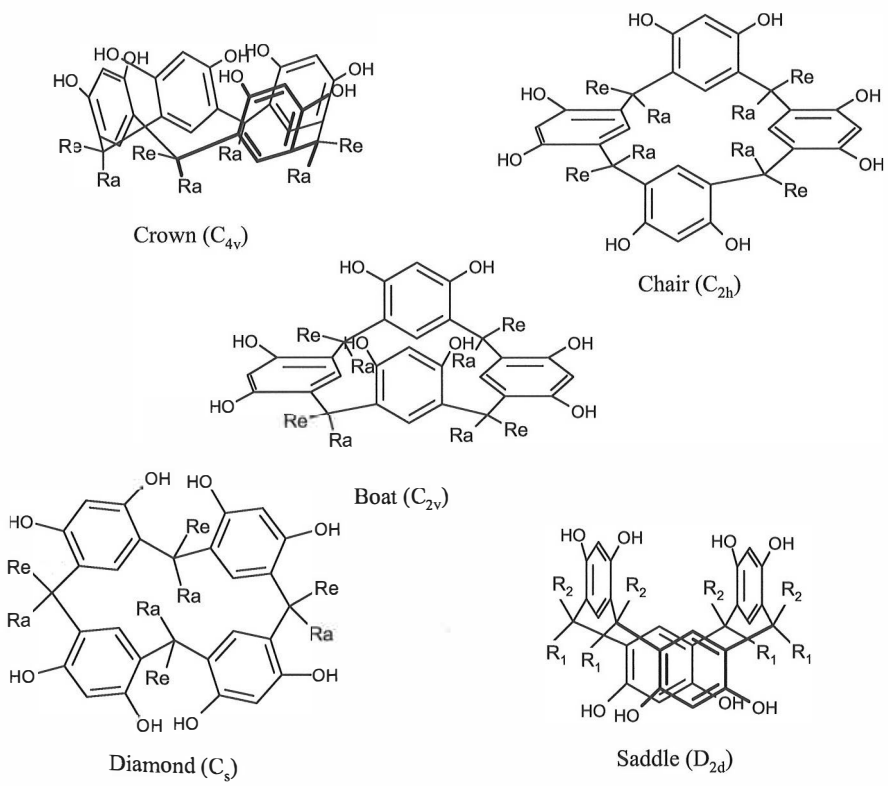


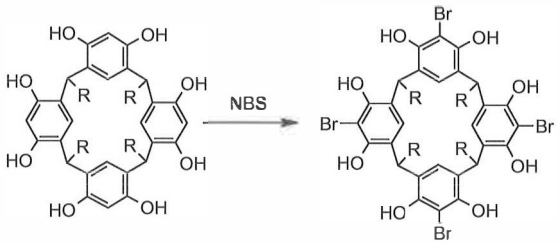
Figure 4: The conformations of resorcinarenes (e = equatorial, a = axial).[54]

Taking into account all possible conformers, the number of diastereoisomers that can be obtained increases substantially. Solvents strongly affect the conformational properties of the resorcinarenes with free hydroxyl groups which influence the formation of the intra- and intermolecular hydrogen bonds.[54] Studies on the conformational properties of resorcinarenes with unsubstituted phenolic hydroxyl groups reveal the crown both in solution[36,55,56] and in the solid state.[57-60] There are however examples where the unsubstituted resorcinarene adopts the boat[61,62] and chair[63-66] comformations.

1.2.4. Reactions of resorcinarenes

1.2.4.1. Reaction of the aromatic ring

The aromatic ring of resorcinarenes is highly activated for electrophilic substitutions by the presence of the hydroxyl groups. Tetrabromoresorcinarenes **4** are synthesized in high yields through the bromination of resorcinarenes with N-bromosuccinimide at room temperature (Scheme 8).[35,67]



1 **4**

R = Aliphatic or Aromatic

Scheme 8: Synthesis of Tetrabromoresorcinarene.[35]

Tertiary amines or tetrakis-aminoalkylated resorcinarenes **15** are synthesized from secondary amines and formaldehyde through a Mannich condensation reaction. When primary amines are used, the resulting secondary amine reacts intramolecularly with one of the phenolic hydroxyl groups and a second equivalent of formaldehyde, forming tetrabenzoxazenes **16** (Figure 5).[68-70] The NMR spectra and X-ray structures of these compounds reveal the C_{4v}-symmetry, which is stabilized by four intramolecular hydrogen bonds and is axially chiral.[69] The importance of the four intramolecular O-H···O hydrogen bonds could be seen from the fact that only one isomer is formed out of a possible seven. In the presence of traces of acids in solution, the compound undergoes rapid diastereoisomerization.[71]

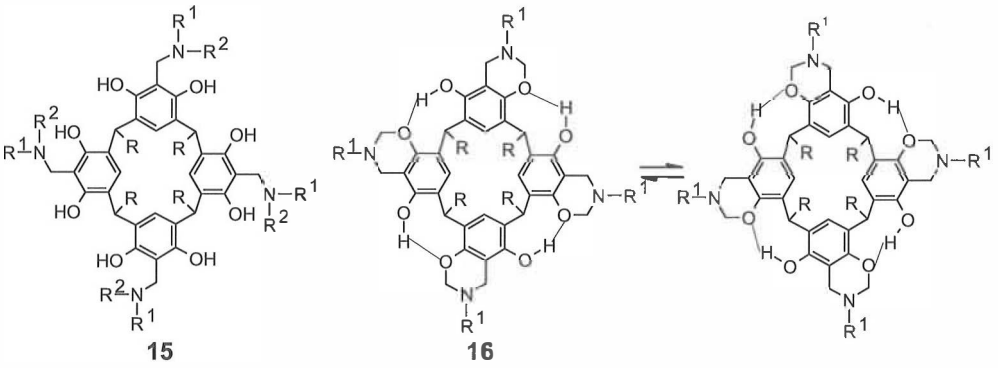
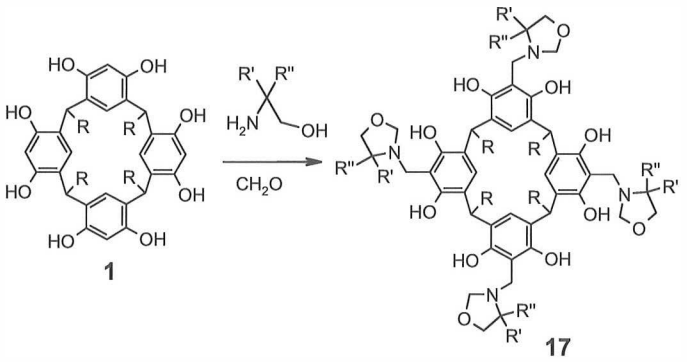


Figure 5: (a) Tetrakis-aminoalkylated resorcinarene, (b) tetrabenzoxazene.[68-70]

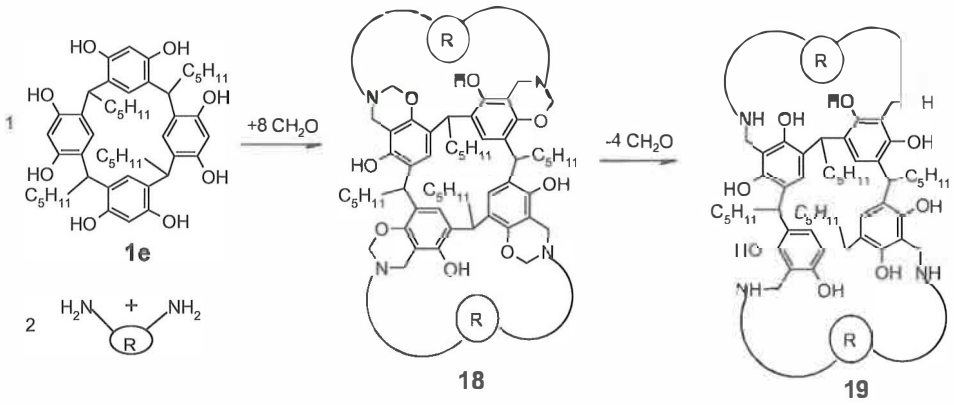
The application of aminoethanols in the Mannich condensation is a special case of these reactions. The 2-substituted derivatives of 2-aminoethanol showed differences compared to the formation of benzodihydro-1,3-oxazines. Under the same reaction conditions these reactions yielded 1,3-oxazolidines **17** in which the second formaldehyde molecule reacts with the hydroxyl group of aminoethanol instead of the phenolic hydroxyl group (Scheme 9).[72]



R = Aliphatic or Aromatic, R',R" = H, or Aliphatic

Scheme 9: Reaction of Resorcinarene and aminoethanol.[72]

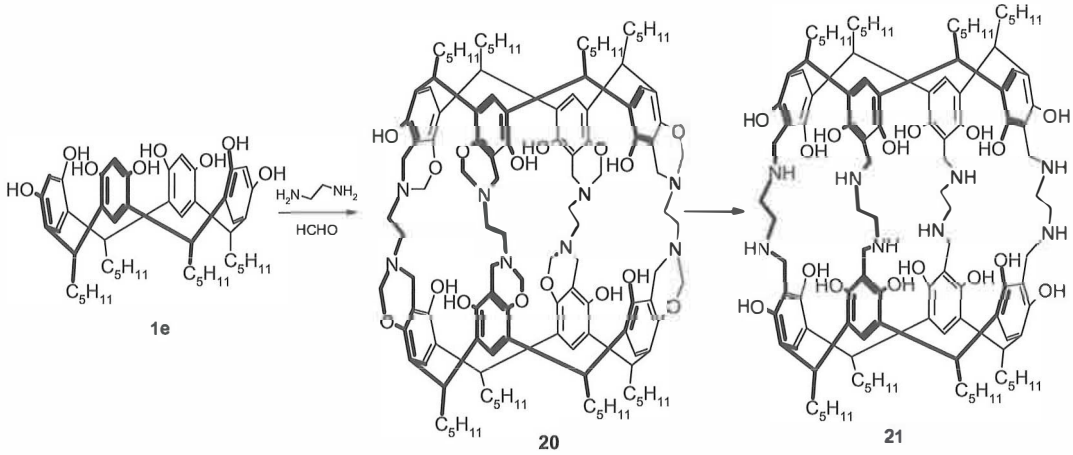
The condensation of resorcinarenes with certain long chain aliphatic diamines and an excess of formaldehyde under high dilution leads to tetrabenzoxazene derivatives **18** in which pairs of adjacent oxazine rings are linked (Scheme 10).[73]



18,19 a R= -$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$- **18,19 c** R= -$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-O-$(CH_2)_2$-
18,19 b R= -$(CH_2)_3$-O-$(CH_2)_4$-O-$(CH_2)_3$- **18,19 d** R= -$(CH_2)_8$-

Scheme 10: Bridged tetrabenzoxazenes.[73]

Similarly, covalently linked resorcinarene dimers were synthesized from resorcinarene and ethylenediamine and an excess of formaldehyde in a moderate 15% yield under high dilution conditions (Scheme 11).[74]



Scheme 11: Covalently linked resorcinarene dimer.[74]

A Diazo coupling of *C*-methylresorcinarene with four equivalents of *p*-sulfonate benzene-diazonium salt gave a water soluble tetrasubstituted product which has a large, extended cavity **22** (Figure 6).[75] Thiomethylated resorcinarenes **23** can be obtained with thiols and formaldehyde (Figure 6).[76]

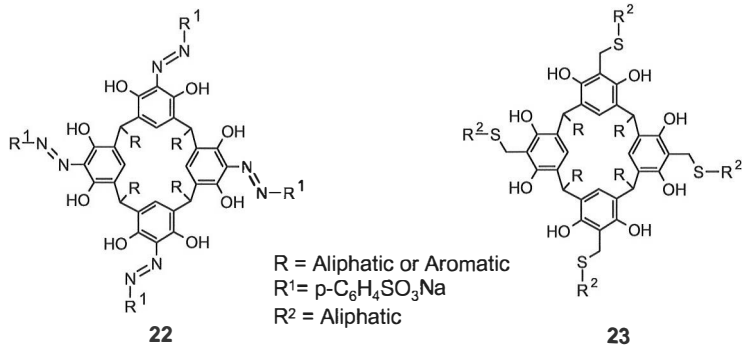


Figure 6: Diazo coupling of C-methylresorcinarene **22** and thiomethylated resorcinarene **23**.[75,76]

Resorcinarenes bearing Kemp's triacid (Figure 7) have been reported starting from tetrabromooctahydroxy-resorcinarene via a 6-step synthetic procedure.77 These hosts are shown to strongly bind various 2-aminopyridines in chloroform showing the influence of electron donating and withdrawing effect of the substituents over a large scale of guest molecules.77

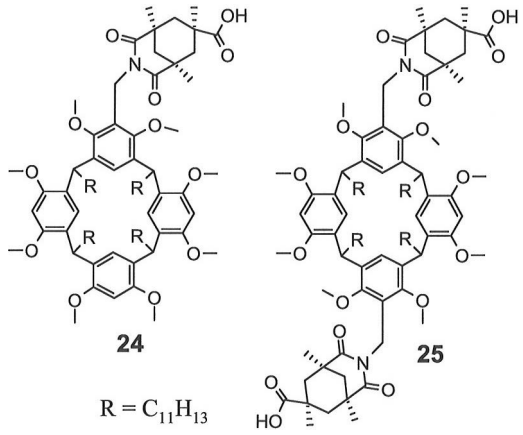


Figure 7: Functionalized resorcinarenes bearing Kemp's triacid. [77]

1.2.4.2 Reaction of the phenolic hydroxyl groups

The phenolic hydroxyl groups of resorcinarenes react in a similar manner as phenol or resorcinol. They can be completely (Figure 8) and partially (Scheme 12) alkylated and acylated to ethers and esters.[26,35] The cyclic array of hydrogen bonds does not exist in resorcinarenes having substituted hydroxyl groups. The molecules undergo a conformational change from crown to boat.[27]

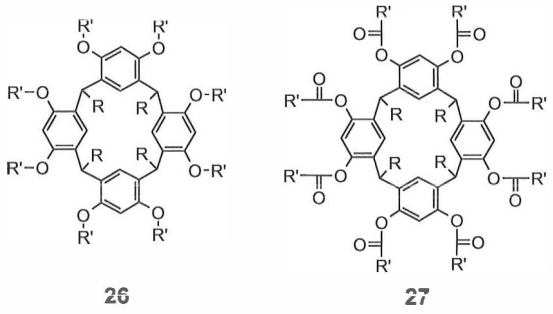


Figure 8: Octaacylated resorcinarene derivatives.[26,35]

It is reported that the regioselective phosphorylation of resorcinarenes affords tetraphosphates **28** with the C_{2v}-symmetry (Figure 9).[78] Regioselective tetraacylation and tetraalkylation of resorcinarenes have also been reported.[79] The reaction between resorcinarene and acid chloride or sulfonyl chloride in the presence of a base such as triethyl amine acting as the catalyst in acetonitrile in a 1:4:4 molar ratio gives tetraacylated products. The conformational change from C_{4v} to C_{2v} could be seen from the ^{1}H NMR spectra.[79]

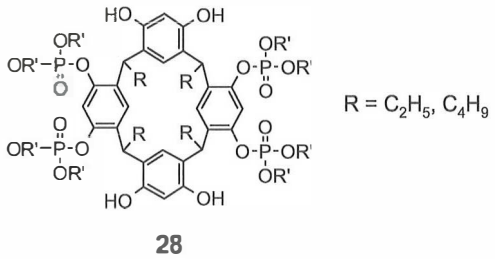
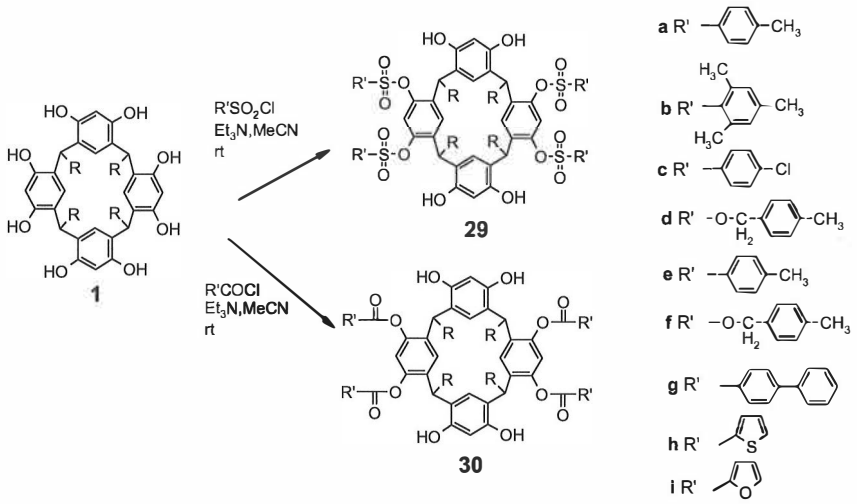


Figure 9: Phosphorylated tetraacylation of resorcinarenes.[68,78]

There are four singlets for the aromatic protons of the resorcinarene, one for the methine and hydroxyl protons and one set for the for the acyl fragments. The four free hydroxyl groups of tetraacylated resorcinarenes can undergo intra- and intermolecular hydrogen bonds. There are two kinds of intra-molecular S=O···H-

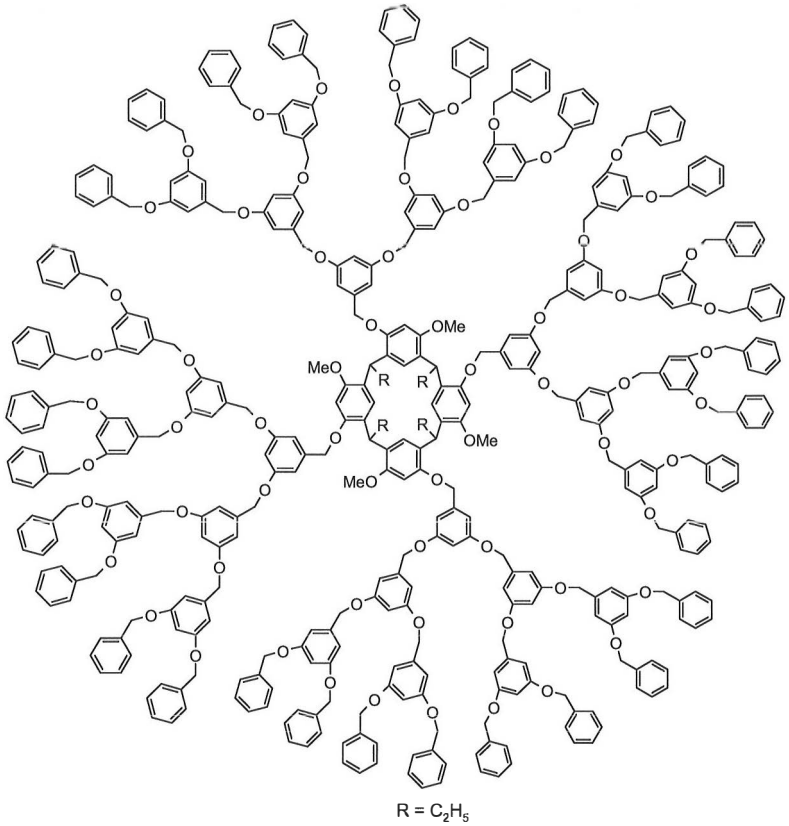
O hydrogen bonds of slightly different strength that are formed in tetrasulfonated resorcinarene compounds.[79]



Scheme 12: Tetraacylation of resorcinarenes with sulfonic acid and acetyl acid chlorides.[68,79]

Several acid chlorides have been reported as applicable for tetraacylation. The benzylchloroformate is applicable as well. It is frequently used as a protective group which can be removed under mild conditions.[78,79]

Under phase-transfer conditions, Fréchet-type dendron bromides were easily attached with high yields to the tetramethyl resorcinarene core in acetone solution in the presence of potassium carbonate and [18]crown-6 mediating the solid-liquid phase transfer of the potassium carbonate into the organic solvent. Up to a four generation resorcinarene dendrimers **31** was isolated in high yields (Figure 10).[32]



31

Figure 10: Tetramethylated resorcinarene dendrimer.[32]

1.2.5 Complexation of resorcinarenes

The host-guest chemistry of macrocyclic compounds has attracted much attention in recent years and it now impinges on wide areas of both chemistry and biochemistry.[80-84] Resorcinarenes have the ability to form host-guest complexes with cations, neutral groups and anions via conventional and weak hydrogen bonding, cation···π, C-H···π, and C-H···anion interactions.[85-88] Open 1:1 inclusion complexes of resorcinarenes with alkylammionium cations are known in the solid state (Figure 11).[89]

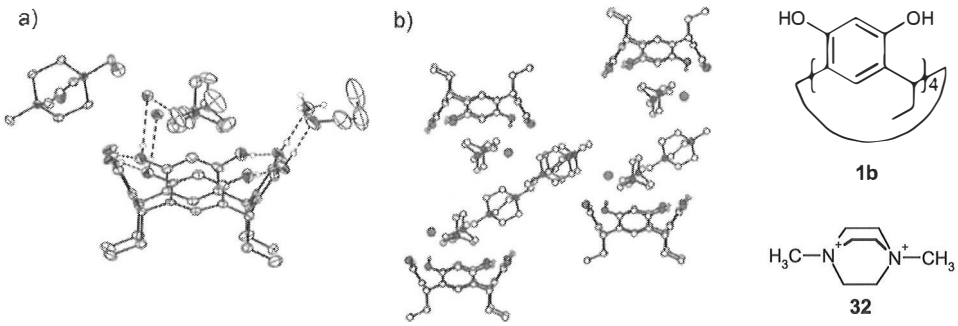


Figure 11: X-ray crystal structure of complex between host **1b** and guest **32**, in propanol water mixture. a) The asymmetric unit. One of the two bromide anions and one n-propanol are H-bonded to hydroxyl groups. Hydrogen bonds are shown by dashed lines. b) Side view of the packing with guest ions. Non-hydrogen bonding hydrogen atoms and solvent molecules are omitted for clarity.[89]

Open inclusion and dimeric complexes in solution by unsubstituted resorcinarenes or pyrogallarenes have been shown by ^{1}H NMR spectroscopy. An intense red colour suggesting a charge-transfer interaction of the topylium ion with the electron-rich pyrogallol rings[90] was seen when topylium tetrafluoroborate was added to a methanol-d_4 solution of pyrogallarene.[91] The complexation equilibrium was fast on the NMR timescale at 295 K but becomes slow at 233 K. Figure 12 shows host-guest complexes corresponding to 3:1 (a), 2:1 dimer (b) and 1:1 open inclusion complex (c) in methanol-d_4 at 233 K. A Kinetically stable (*i.e.* slow exchange on the NMR timescale) 1+2 dimeric complex between **34** and **57c** at 233 K was seen. The NMR signals of the guest's methyl groups are shifted up field by 3.8 ppm, typical for an encapsulation complex.[91]

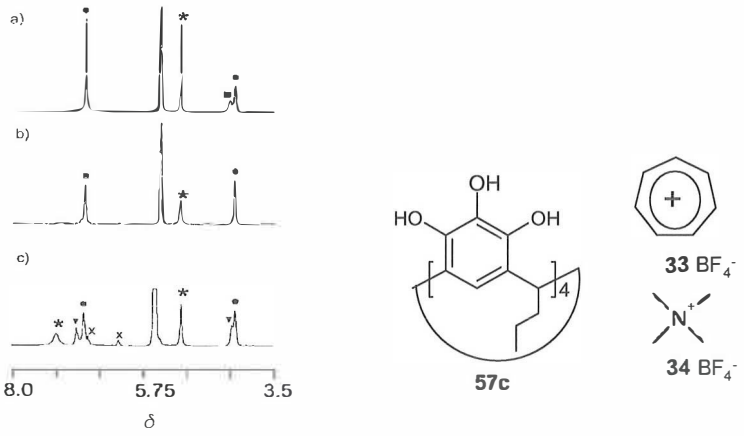


Figure 12: ^{1}H NMR spectra at 233 K (methanol-d_4, 600 MHz, [**H1**]total = 10 mM): a) 3(**57c**) + **33** BF_4^-; b) 2(**57c**) + **33** BF_4^-; c) **57c** + **33** BF_4^-; (*) tropylium cation; (■) free **57c**; (•) **57c** in a 2:1 complex; (▼) **57c** in an open complex; (x) products of methanolysis of the tropylium cation (established by control experiments with **33** BF_4^- in methanol-d_4).[91]

One interesting feature of unsubstituted resorcinarenes is their capability to form dimeric[60,92-97] and hexameric[98-105] molecular capsules encapsulating neutral and/or charged guests inside the cavity. The tetramethylammonium cation is known to form dimeric capsules with unsubstituted resorcinarenes (Figure 13). Hydrogen bonding and cation···π interaction appear to be the most important interactions in the capsule formation process. The alkyl chain length of the resorcinarenes affects the crystal packing of the complex significantly.[94-96]

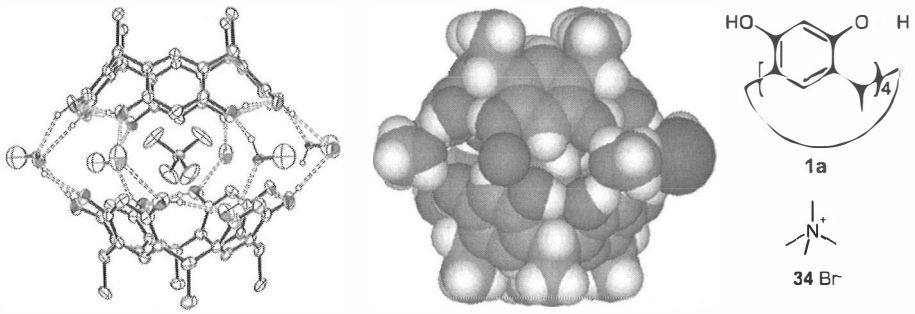


Figure 13: Ortep and CPK plots of the X-ray structure of hydrogen bonded solvent–anion mediated Resorcinarene **1a** capsule with TMA^+ **34** ion (**34**@**1a**$_2$·Br^-·4MeOH·3H_2O). Non-hydrogen bonding molecules have been omitted for clarity from the Ortep plot.[93]

Atwood *et al.*[98] discovered the capacity of *C*-methyl resorcinarene to form hexameric solvent-mediated capsular assembly in the solid state where the hexamer is held together by 60 intermolecular hydrogen bonds and the disordered solvent molecules are fully encapsulated in its cavity of ~1500 Å^3 (Figure 14).[98]

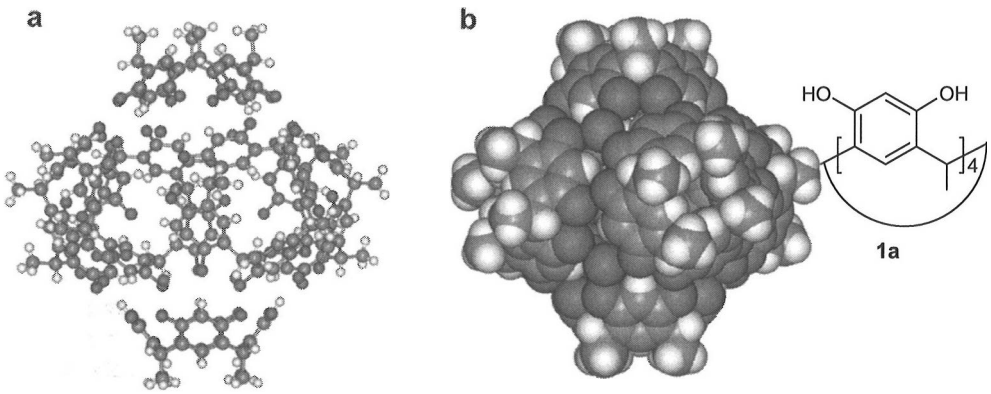


Figure 14: (a) A ball and stick (b) a space-filling representation of a hexameric *C*-methyl resorcinarene **1a** capsule held together by an H-bond network mediated by eight water molecules.[98]

Mattay *et al.*[99] later reported a crystal structure of directly hydrogen bonded hexameric capsule of C-isopropyl pyrogallarene that fully encapsulates ten acetonitrile molecules (Figure 15).[99]

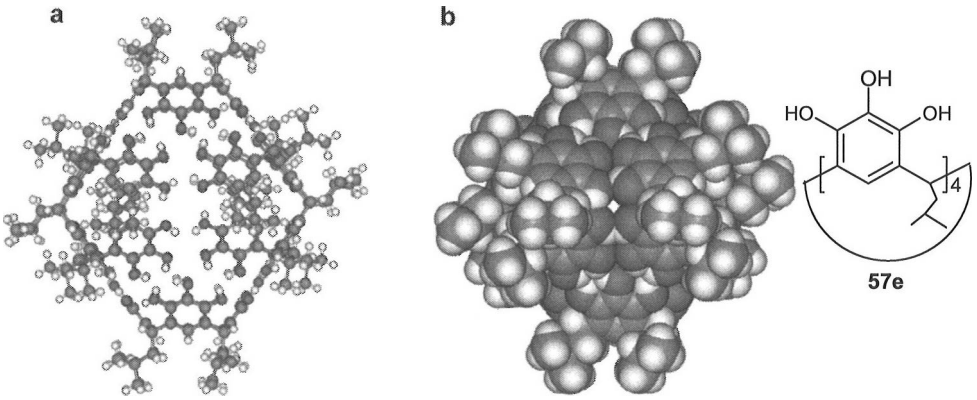


Figure 15: (a) A ball and stick (b) a space-filling representation of a hexameric C-isopropyl pyrogallarene **57e** capsule held together by 72 intermolecular hydrogen bonds.[99]

These results have been supported by several studies on hexameric assemblies of resorcinarenes and pyrogallarenes by the research groups of Atwood[106-108], Rebek[109-112] and Cohen.[101,113-120] Pan *et al.*[121] recently showed that a highly fluorinated or "Teflon footed" resorcinarene dissolves in wet fluorous solvents as a result of the formation of hexameric capsules. Cohen *et al.* showed by means of diffusion NMR that the capsule formation takes place in solution in water saturated $CDCl_3$ without the need for an additional guest[113] and that some chloroform molecules are encapsulated instead.[114] Through the addition of other guest molecules that are more easily complexed with resorcinarenes, the encapsulated chloroforms are released (Figure 16).[102,117] Water molecules are usually involved to complete the network of the resorcinarenes[98,102,113] while pyrogallarenes assemble without the need for water incorporation.[99,114,116]

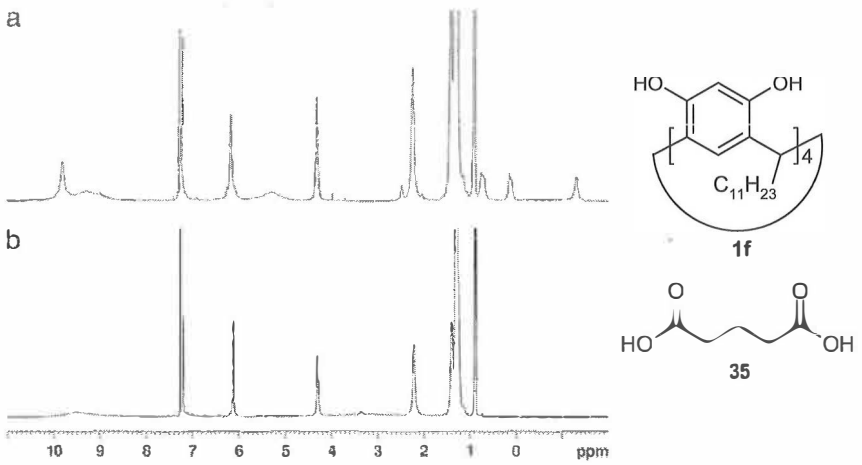


Figure 16: ^1H NMR spectra of resorcinarene **1f** (30mM) with glutaric acid **35** (90mM) (a) and without it in $CDCl_3$ (b). Peaks for encapsulated glutaric acid can be seen far upfield. Based on integration, stoichiometry is ~1:1, that is, a hexamer with five to six encapsulated glutaric acid molecules.[117]

The encapsulation of the glutaric acid depends on both the concentration of the glutaric acid and the time elapsed before acquiring the spectra. It also occurs at the expense of the encapsulated chloroform molecules, as indicated by the disappearance of the two smaller peaks in the range of 4.9-5.1 ppm attributed to encapsulated chloroform molecules (figure 17).[117] Diffusion NMR showed the same diffusion coefficients for resorcinarene **1f** and glutaric acid **35**. In addition, a 6:6 encapsulation complex diffuses as a single supramolecular entity.[117]

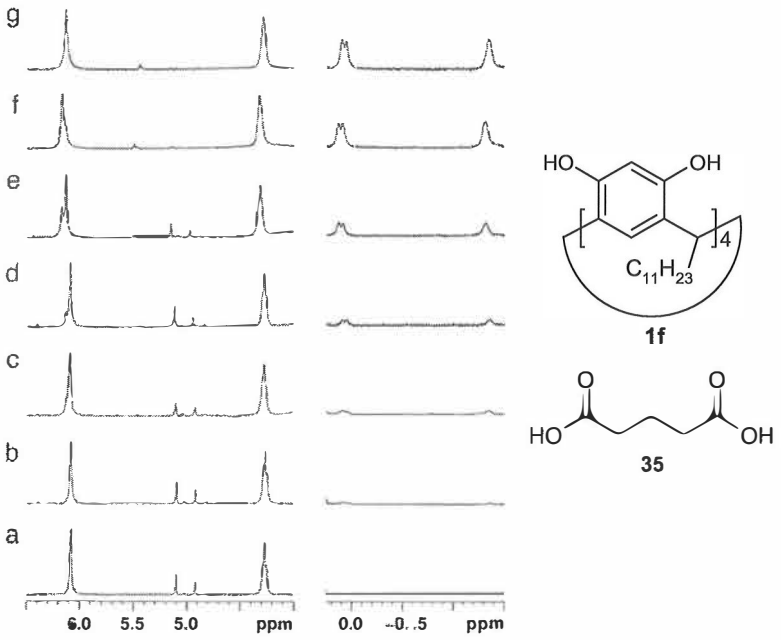


Figure 17: Sections of the ^{1}H NMR spectra (400MHz, 298 K) of **1f** (30mM) in $CHCl_3$ titrated with varying amounts of **35** and collected at different times after sample preparation. The sections of the spectra are of C_{11}Resorcinarene, **1f** (a); **1f** and 15mM of glutaric acid **35**, 1h (b); **1f** and 25mM of **35**, 1h (c); **1f** and 25mM of **35**, 4 days (d); **1f** and 30mM of **35**, 4 days (e); **1f** and 60 mM of **35**, 4 days (f); and **1f** and 25 mM of **35**, 3months (g).[117]

At very low concentrations (e.g. nanomolar), the encapsulation process and dynamic behavior of the monomers can be observed. FRET has been used to show the real-time exchange of monomer sub-units between hexameric capsules (Figure 18). This method has also been used to observe the encapsulation of a fluorophore within a resorcinarene hexamer. It was revealed that pyrogallarenes are very sensitive to the concentration of the mixing, with an increase in the equilibrium half-life from 36 minutes at 250nM to 156 minutes at 10μM while the resorcinarenes show little difference in exchange rates over the same concentration range. The temperature of mixing was found to be important for both systems. The stability of the capsules to polar additives such as methanol was probed and it revealed that the pyrogallarenes required a higher percentage of methanol to disassemble the capsule as compared to resorcinarenes.[122,123]

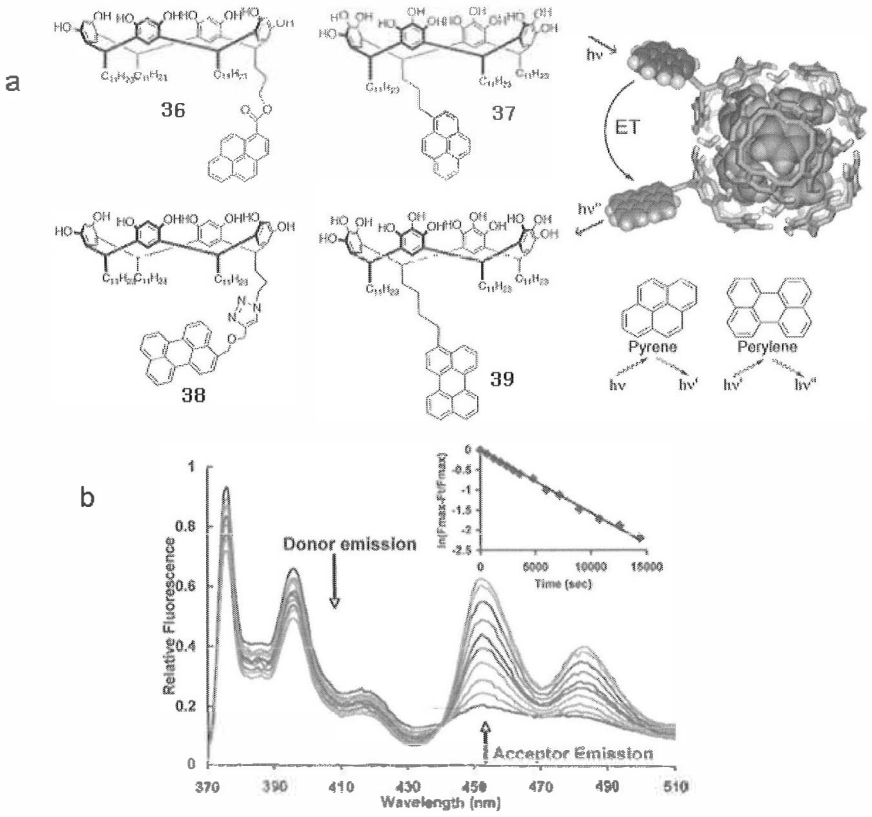


Figure 18: a) Pyrene donor and perylene acceptor labeled resorcinarenes **36** and **38** and pyrene donor and perylene acceptor labeled pyrogallarenes **37** and **39**. b) Development of FRET with time upon mixing of **37** and **39** solutions at 1 μM in CH_2Cl_2 (times from 0 to 6.5 h): λ_{exc}=346 nm. The inset shows first-order kinetic treatment of the data.[123]

A suitable environment for anion inclusion by resorcinarenes can be created when electrophilic metal clusters are incorporated into the upper rim. Anion inclusion is selective and the geometry imposed by the host can stabilize an unusual μ_4-face bridging binding mode of the guest halide.[124] A deep cavity phosphoresorcinarene derivative forms a stable copper (I) and silver derivative in which the guest anion is weakly bonded to three of the four metal centers (Figure 19).[124]

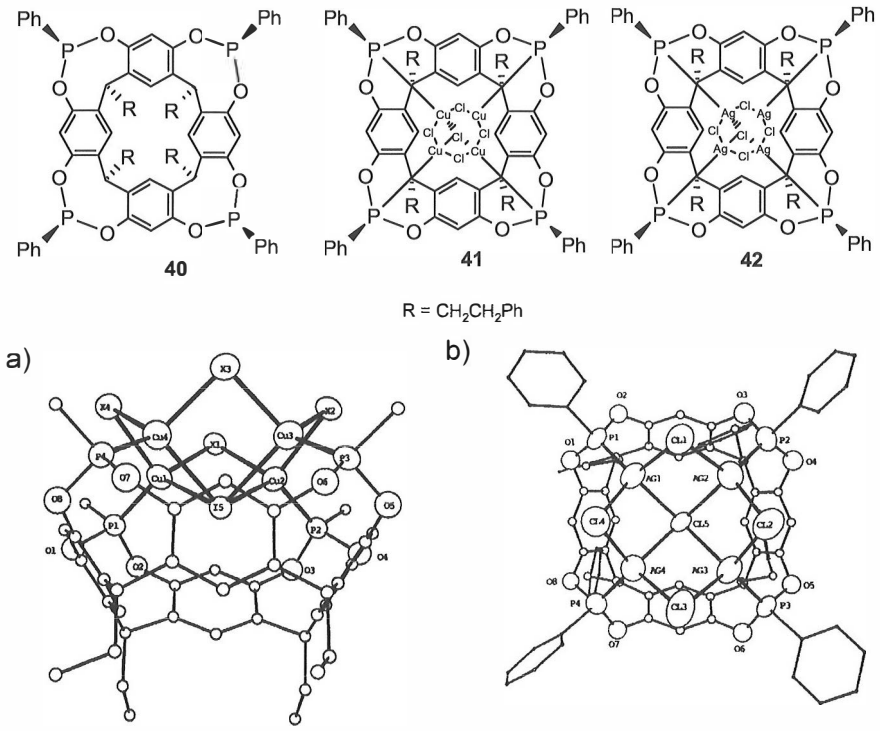


Figure 19. Anion complexation of resorcinarenes. a) Side view of molecular structure of the iodide analog of **41**. The phenyl rings on both PhP- and $-CH_2CH_2Ph$ groups have been omitted for clarity and carbon atoms are assigned arbitrary radii. The central iodide is I(5). b) A top view of the molecular structure of **42**.[124]

Specific functionalization of the upper rim could lead to compounds with very interesting complexation abilities. Atwood *et al.*[125,126] showed a new approach, where anion recognition utilizing hydrogen bonding and electrostatic interactions was demonstrated by the placement of the whole ion-pair in a molecular capsule. The anion confinement was verified by X-ray structural analysis. Figure 20 shows the X-ray crystal structure of a complex where the anion remains in the proximity to the TMA cation and is symmetrically bound by all four NH_{amide} hydrogen bonds. Additionally, from the top, four aromatic hydrogens (from *ortho*- positions) are in close proximity to the chloride that also adds to the overall binding efficiency and selectivity.

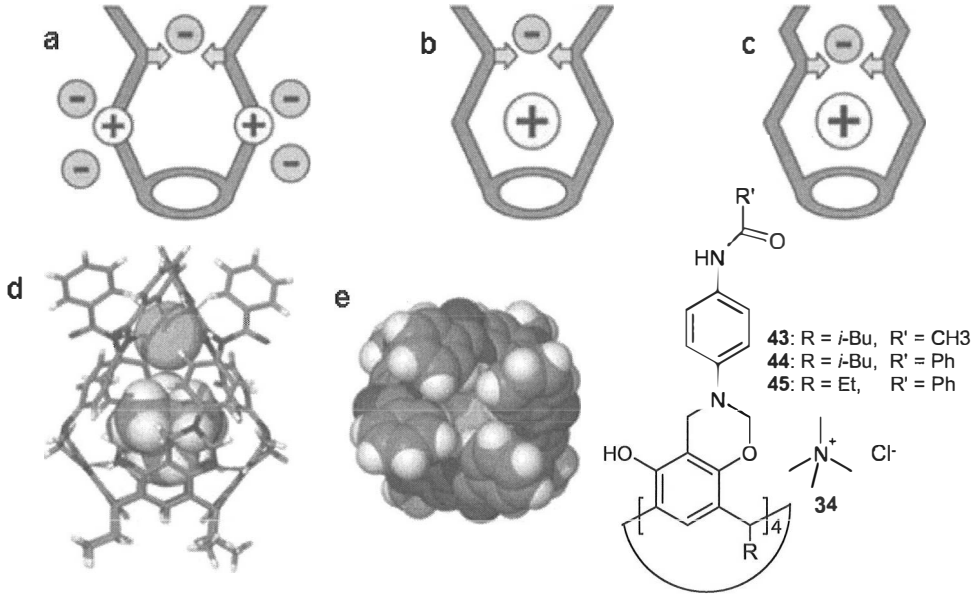


Figure 20: Receptors based on electrostatic and hydrogen bonding interactions: (a-c) shows possible positions for anions. Crystal structure of **45**·**34**: d) side view, e) top view.[126]

From the development of soft ionization methods in the 1980s, in particular electrospray ionization, mass spectrometry[127-131] has proven to be an important tool to examine binding interactions of cations in the gas phase. It has the advantage of proving the complexation without solvent interference. Dimeric[89,93] capsules of resorcinarenes, pyrogallarenes and related compounds encapsulating small and large cations have been shown to prevail in the gas phase without solvent mediation and have been predicted to be directly hydrogen bonded.[132-137] Prior to this work, resorcinarene and pyrogallarene hexameric capsules in the gas phase were not known (see page 58-61).

Mass spectrometry has been used to support the formation of resorcinarene capsules with tetraalkylammonium cations in the gas phase whereby size selectivity, heterodimer formation and fragmentation behavior are analyzed (Figure 21).[93] Doubly charged ammonium cations have also been shown to form dimeric capsules with resorcinarenes in the gas phase despite the difference in the size of the guest and the selectivity preference towards singly charged cationic guests shown by the resorcinarenes.[93,94] The assumption is that the dication allows tighter binding due to its dication nature. Since each side of the dication may bind one resorcinarene with one charge, cation···π interactions will be stronger than those operative in the monocations.[92]

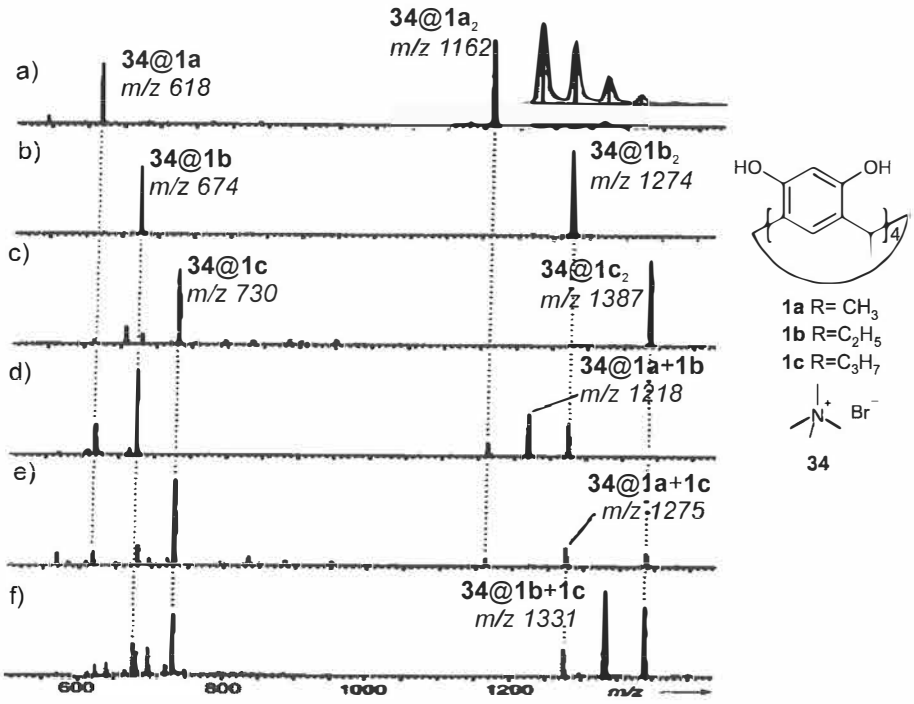


Figure 21: ESI mass spectra of 50μM acetonitrile solutions of a) **1a**, b) **1b**, and c) **1c** with equimolar amounts of tetramethylammonium bromide **34**$^+$Br$^-$. Spectra d to f were obtained from mixtures of d) **1a** and **1b**, e) **1a** and **1c**, and f) **1b** and **1c**, with **34**Br$^-$. The inset in a) shows the experimental (curve) in comparison to the one calculated on the basis of natural isotope abundances (vertical lines) of **34@1b**$_2$.[93]

The importance of C-H···anion interactions has been shown in the gas phase between resorcinarene cavitands and selected anions.[87] Suitably positioned C-H bonds can complex anions, if they are polarized by neighboring electronegative heteroatoms. ESI-FTICR-MS experiments were used to assess the anion binding behaviour of the easy-to-access methylene-bridged resorcinarene cavitands. The cavitands provide the right geometric arrangement of such groups to support anion binding through multiple interactions with up to four converging C-H groups. Interestingly, one cavitand was able to solvate a sulfate dianion well enough to prevent electron autodetachment (Figure 22).[87]

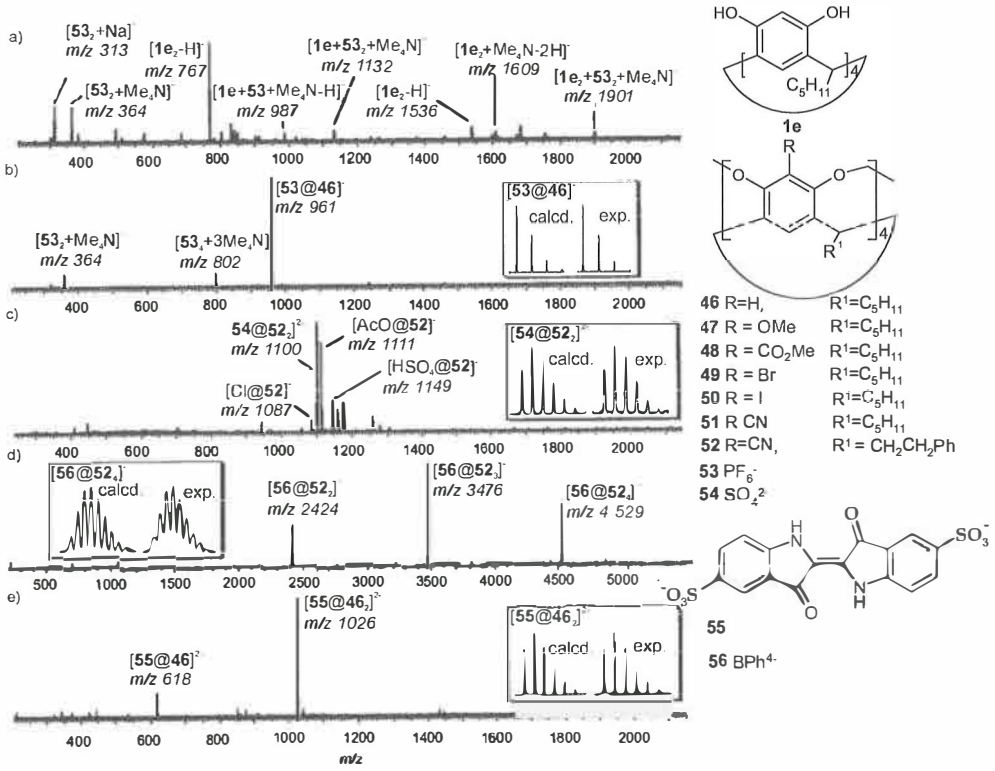


Figure 22: ESI-FTICR mass spectra of solutions of a) **1e** + 1 equiv. Me_4N^+**53** (200 μM), b) **46** + 1 equiv. Me_4N^+**53** (200 μM), c) **52** + 10 equiv. $(Me_4N^+)_2$**54** (680 μM), d) **52** + 10 equiv. Na^+**56** (250 μM), e) **46** + 0.5 equiv. Na^+_2**55** (780 μM) in acetone (a-b,d) or acetone/MeOH (40:7 (c) and 40:1 (e)). AcO=acetate.[87]

To study the stability of capsules in the gas phase, tandem MS experiments were conducted with the mass selected peak. The whole isotope pattern of the capsule was isolated in the analyzer cell of the FTICR mass spectrometer and then irradiated in an IRMPD experiment with IR radiation from a CO_2 laser for different time intervals. Fragmentation was induced after a short induction period by an increase in the internal energies of the ions through photon absorption.

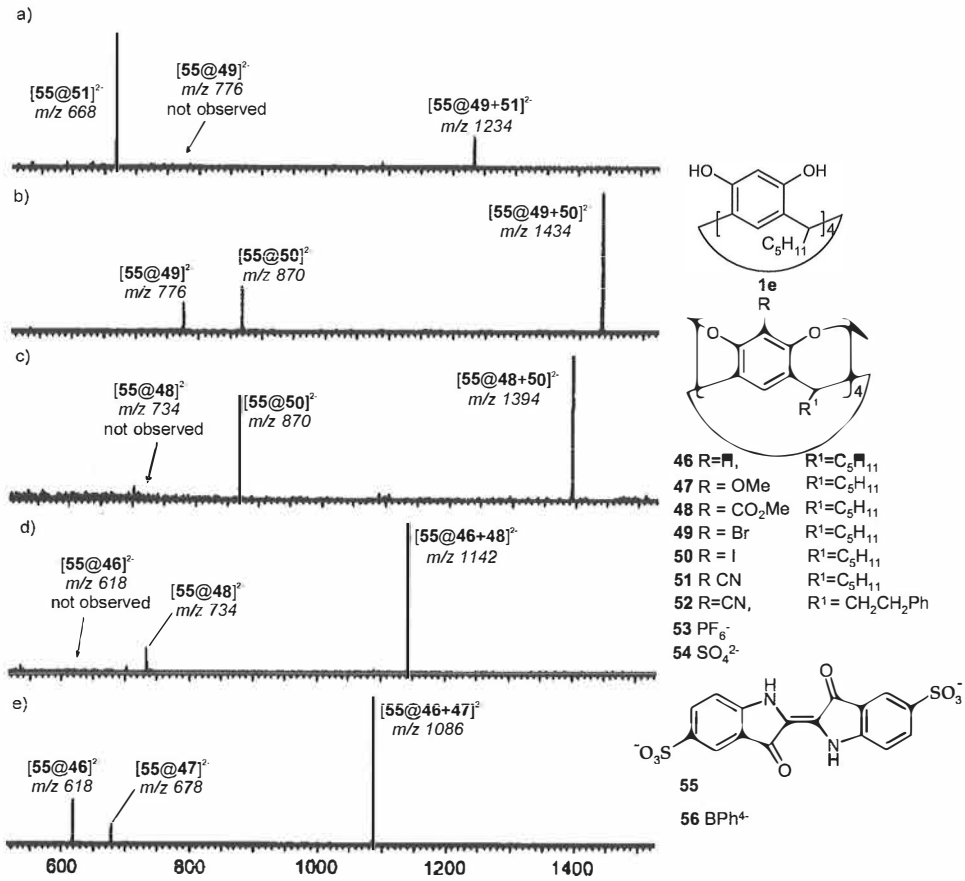


Figure 23: CID Experiments with mass selected, doubly charged heterodimer indigo carmine complexes: a) **[55@49+51]**$^{2-}$, b) **[55@49+50]**$^{2-}$, c) **[55@48+50]**$^{2-}$, d) **[55@46+48]**$^{2-}$, e) **[55@46+47]**$^{2-}$.[87]

The electronic nature of electron-withdrawing or electron donating substituents on the cavitands' upper rims influences the complex stabilities. CID experiments were conducted with mass selected peaks of heterodimers. The CID spectra show that the strength of the cavitands' sulfonate interactions increase as follows: **47** ≤ **46** << **48** << **49** << **50** << **51**. In terms of substituents' electronic nature, the order is OMe ≤ H << CO_2Me << Br ≈ I <<CN, which is in agreement with the electron withdrawing or donating ability of the aromatic substituents (Figure 23).[87]

2 AIMS OF THE STUDY

The first goal of this study was to synthesize novel resorcinarenes and resorcinarene derivatives and characterize them using NMR spectroscopy, X-Ray crystallography, mass spectrometry, elemental analysis and fluorescence spectroscopy. The synthetic aim was to use known procedures to develop known and new interesting resorcinarene derivatives. The second goal was to use both the core resorcinarenes and the newly synthesized resorcinarene derivatives as host compounds for complexation purposes. A variety of compounds were used as guests ranging from alkyl ammonium cations, alkyl phosphonium cations, neutral species and metalloorganic complexes. The commercially unavailable guests were synthesized.

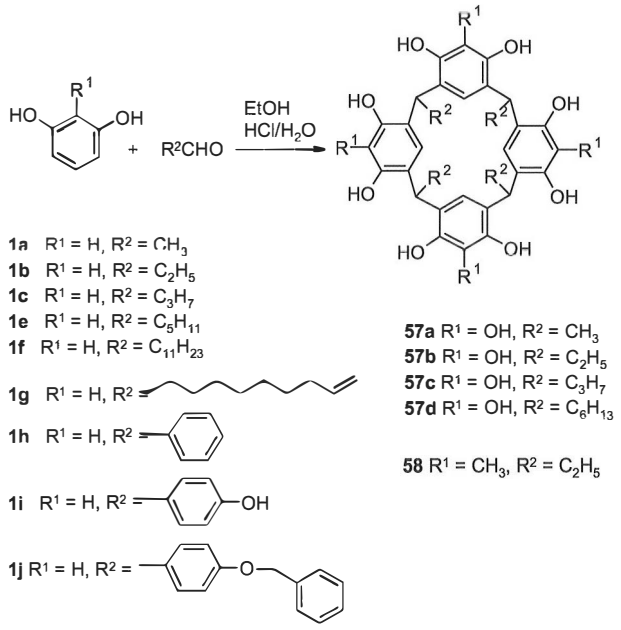
The complexations of the resorcinarenes and the differents guests was studied in the gas phase by electrospray ionization mass spectrometry, which has the advantage of proving the complexation without solvent interference. Electrospray ionization methods were used to study the fragmentations and complexations in the gas phase. The studies of the hosts-guest complexes were complemented in solution by ^{1}H NMR and fluorescence spectroscopy and in the solid state by single crystal X-ray crystallography. Complexes ranging from open inclusion to dimeric and hexameric capsules were detected and analyzed.

3 RESULTS AND DISCUSSION

3.1 Synthesis

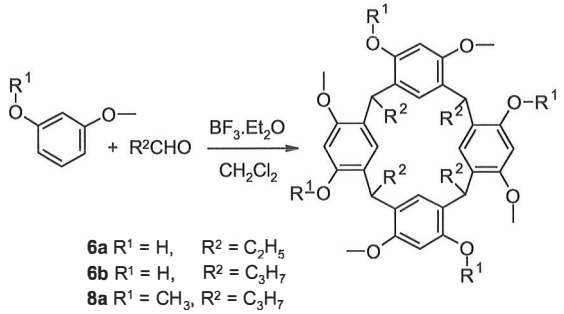
3.1.1 Core resorcinarenes

The core resorcinarenses were synthesized to obtain starting compounds for further modifications and for use as hosts in the complexation studies. The *rccc* isomers were synthesized by acid-catalysed one-pot synthesis from resorcinol, 2-methyl resorcinol or pyrogallol with the corresponding aldehydes (Scheme 13).[6,28,29] The choice of aldehydes depended on the length of the alkyl chain which determines the solubility of the compounds. Conformational properties of resorcinarenes **1** reported show that, with unsubstituted phenolic hydroxyl groups, they are exclusively in the crown conformation in solution[36,55,56] and in the solid state.[57 60]. There are however examples where the resorcinarenes adopt the boat[61,62] or chair[63-66] conformation.



Scheme 13: The core resorcinarenes.[I,II,III,IV,V,VI]

The NMR-spectra of the resorcinarenes were easy to interpret due to their high symmetry and independence of temperature within the range of 233 to 373 K. The most characteristic signal belongs to the methine bridge between 4 and 5 ppm. The signals of the aromatic protons and the phenolic hydroxyl groups vary from 6 to 9 ppm. The signals for alkyl chain are usually between 0.5 to 3.5 ppm.



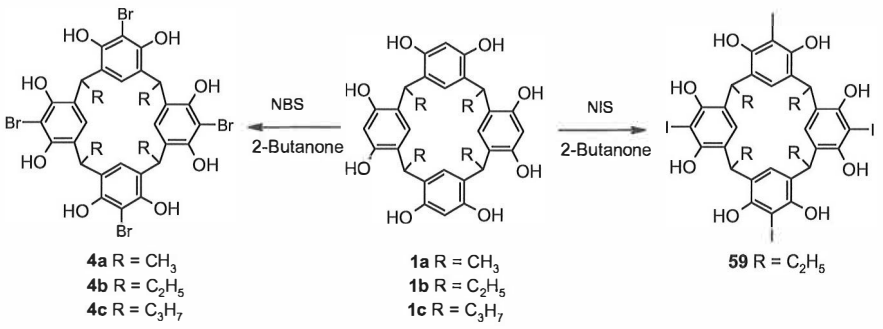
Scheme 14: Methoxy resorcinarenes.[I]

3-methoxyphenol with various aldehydes in CH_2Cl_2 gives C_{4v}-symmetrical chiral tetra-alkylated resorcinarenes **6** in the presence of a Lewis acid (Scheme 14). The

^{1}H NMR spectrum supports the C_{4v}-symmetry, since there is one signal for the methoxy groups, one for the bridging methines and two signals for the aromatic protons.[I]

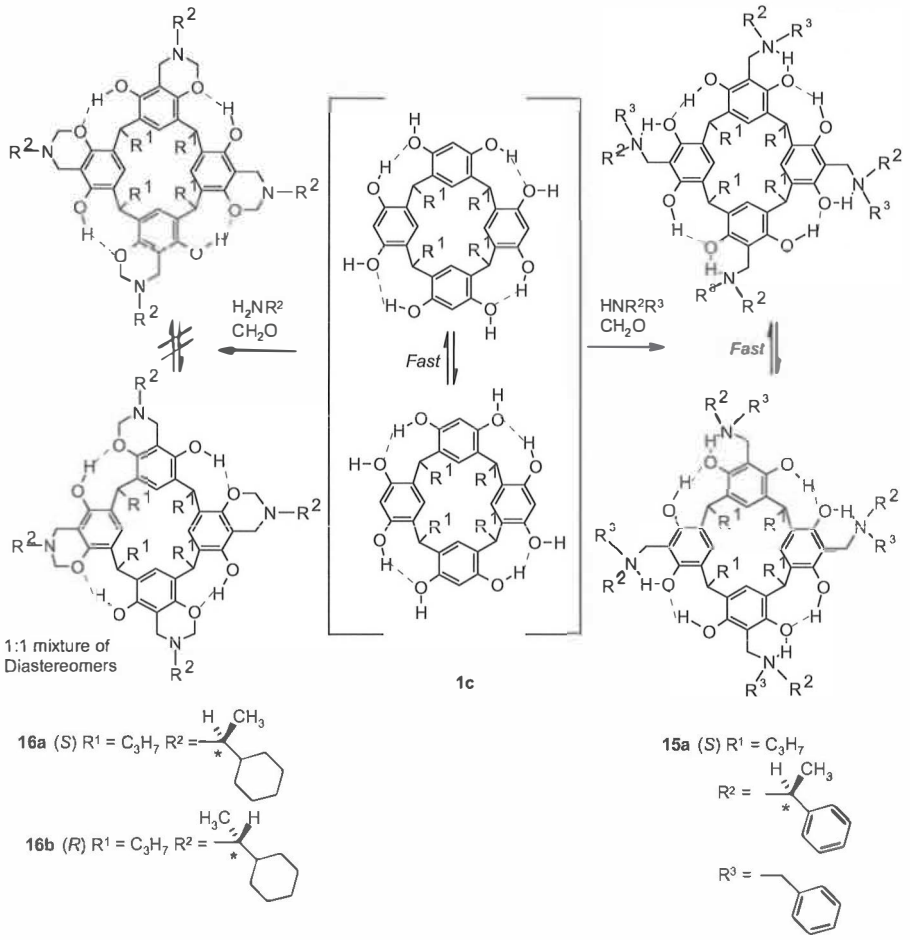
3.1.2 Aromatic substitutions of resorcinarenes

Further functionalization of the bowl shape *rccc*-isomers of the resorcinarenes has been used for the synthesis of cavitands, carcerands, hemicarcerands,[138-140] and molecular capsules.[60,80,94,141] Electrophilic aromatic substitution is one way of modifying the resorcinarene core. Halogens can be easily attached to the 2-position of the resorcinarene in a one step synthesis (Scheme 15).



Scheme 15: Tetrabromo- and tetraiodoresorcinarenes.[V]

Mannich condensation has arguably been the most important of these electrophilic aromatic substitution reactions on resorcinarenes. Several chiral aminomethylated resorcinarenes were synthesized in order to investigate their complexation and fragmentation properties. The Mannich condensation reaction with formaldehyde and primary amines provides intermediate secondary amines, which further react with one of the phenolic hydroxyl groups and a second equivalent of formaldehyde, forming four benzoxazine rings.[79,142,143] The resorcinarene cavities are stabilized by four hydrogen bonds and are modified by the substituent amines (Scheme 16). The product is usually a precipitate from ethanol solution. They are more soluble in apolar solvents such as chloroform but the solubility is also dependent on the pendant alkyl chains as well. Mannich condensation with secondary amines provides tetrakis-aminomethyl resorcinarenes. The position of the nitrogen is organised previously for hydrogen bonding with the neighboring hydroxyl groups. They build an array of eight intramolecular hydrogen bonds (Scheme 16).[II]



Scheme 16: Synthesis of chiral resorcinarene tetrabenzoxazines **16a** and **16b** and tetrakis-aminomethylated resorcinarene **15a**.[II]

The ^{1}H NMR spectra of the tetrabenzoxazines **16** contain two characteristic signals of the benzoxazine methylene groups with the disappearance of the substituted aromatic proton close to 6.2 ppm. The protons of the benzoxazine rings are diastereotopic due to the chiral methine bridges and emerge between 4.8 and 5.2 ppm for the ON-acetal, while the other methylene is usually overlapping or shifted up field relative to the methine bridge (Figure 24a). The NMR spectrum of **15a** shows only one set of signals in line with the quick interconversion of hydrogen-bonding patterns of opposite directionality. Some broadening of the signals that may indicate that this exchange process occurs is observed. Four doublets (a-d in Figure 24b) are observed between 3 and 4 ppm, which correspond to the resorcinarene-CH_2-N and N-CH_2-phenyl methylene groups. The fact that two doublets are found for each indicates that these protons

are diastereotopic and thus prove the presence of the chiral information within the amine substituent.

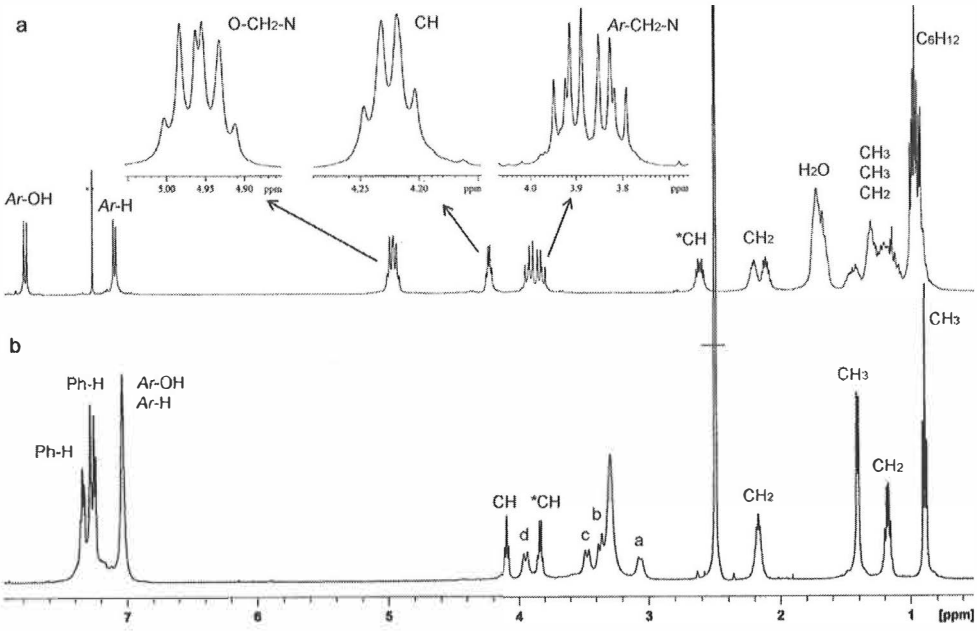


Figure 24: ^{1}H NMR of **16a** (a) and **15a** (b) at 303 K in DMSO-D_6.[II]

For an examination of the gas-phase fragmentation process, the ions of interest are mass-selected (monoisotopic ions only) in the analyzer cell of the Fourier transform ion-cyclotron-resonance mass spectrometer. Subsequent collisions with argon as the collision gas induce fragmentation (CID = collision-induced dissociation). The results for both the protonated molecule and its TMA adduct are shown in Figure 25. Product signals appear at repetitive distances of Dm = 211 Da which corresponds to the loss of the amine shown in the inset of Figure 25a. (*S*)-**16a** and (*R*)-**16b** can be ionized analogously by protonation or TMA adduct formation. Instead of a 1,4-elimination, another reaction proceeds here upon collisional activation (Figure 25b): The loss of Dm = 139 Da indicates that cyclohexyl-ethyl-substituted imines are liberated in a retro-Diels–Alder reaction. The CID mass spectrum nicely shows that both reactions, 1,4-amine elimination and retro-Diels–Alder reactions, can occur in any sequence.[II]

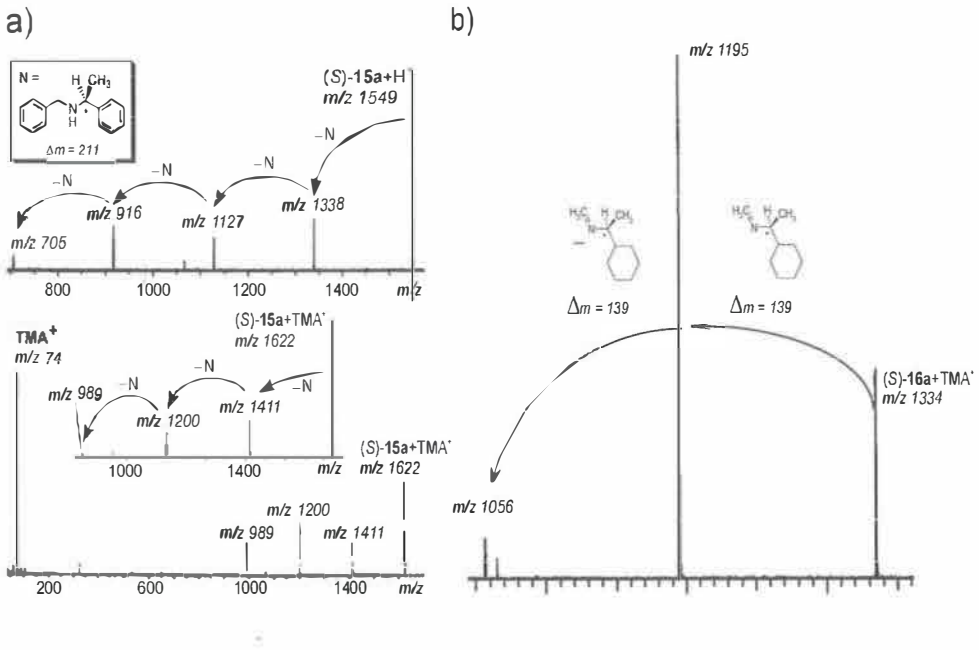
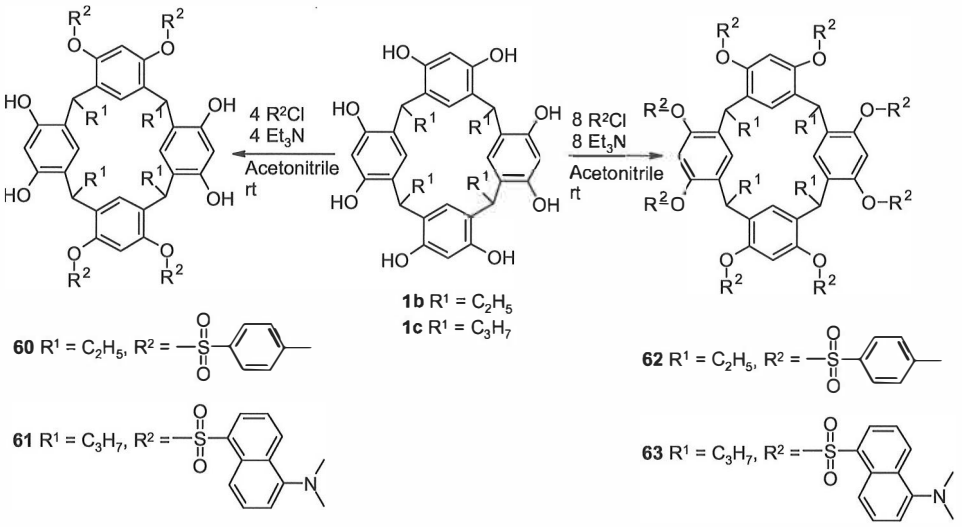


Figure 25: a) Collision-induced fragmentation (CID) of protonated (*S*)-**15a** (top) and its TMA adduct (bottom). b) CID mass spectrum of the mass selected TMA adduct of (*S*)-**16a**.[II]

3.1.3 Reactions of the hydroxyl groups

Intramolecular and intermolecular bonds play a vital role in the rigidity and pre-organization of resorcinarenes.[54] Intramolecular hydrogen bonds stabilize the crown conformation of the resorcinarenes and some of their derivatives[54] while intermolecular bonds are partly responsible for the dimeric[60,92-97] and hexameric[98-105] capsules as well as resorcinarene based nanotubes.[33,34] The hydroxyl groups on the resorcinarenes behave similarly to the hydroxyl groups on phenol or resorcinol. When the resorcinarenes hydroxyl groups are substituted, the array of hydrogen bonds disappears. The bowl-like conformation changes through the flattened crown to the boat or in some cases, can even adopt the saddle conformation. In solution, resorcinarenes perform a boat-boat transition at room temperature while at low temperatures, the molecules freeze in the C_{2v}-symmetry.[78,79]



Scheme 17: Octaacylation and tetraacylation of resorcinarenes.[III]

Tetradansylated resorcinarenes **61** was prepared in moderate 45% yield by regioselective acylation in the presence of triethylamine as base (Scheme 17). The compound **61** exists in the boat conformation in both the solid and liquid state. The ^{1}H NMR reveals four singlets for the aromatic protons of the resorcinol rings indicating the boat conformation. The X-ray structure reveals the two substituted resorcinols are approximately on the same plane while the unsubstituted rings face each other. Two intramolecular hydrogen bonds are formed to sulfonyl oxygens (S=O··O distances 2.781(9) and 2.798(8) Å). All four dansyl groups are in a propeller-like orientation beside the core resorcinarene, leaving enough space for intermolecular hydrogen bonds. Two molecules of **61** form directly hydrogen bonded dimeric assemblies where two out of four intermolecular hydrogen bonds form between opposing hydroxyl groups (O··O distance 2.802(9) Å) and the other two are between opposing sulfonyl oxygen and hydroxyl group (S=O··O distance 2.874(8) Å, Figure 26).[III]

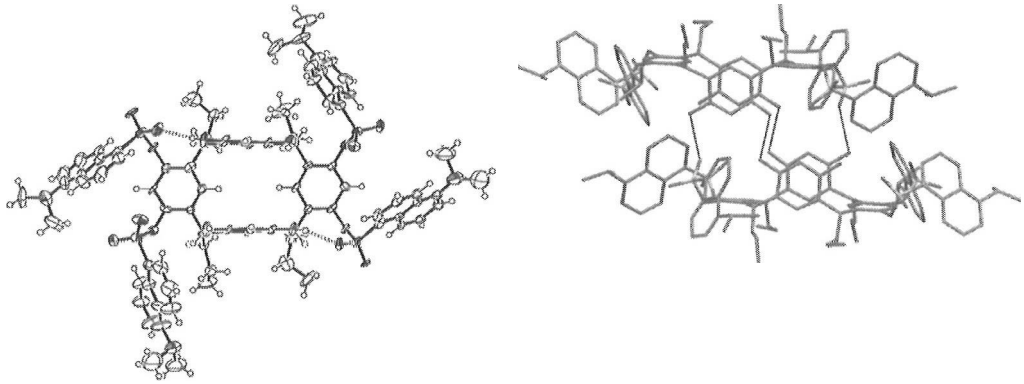


Figure 26: (a) Ortep-plot presentation of X-ray crystal structure of tetra-substituted resorcinarene **61**. (b) Dimeric assembly of **61**. Intermolecular hydrogen bonds are shown as dotted lines and hydrogen atoms are omitted for clarity. Solvent molecules are omitted for clarity.[III]

Complete acylation of the phenolic hydroxyl groups with dansyl chloride provided the octadansylated resorcinarene (Scheme 17). The ^{1}H NMR spectrum of the persubstituted octadansyl **63** in $CDCl_3$ at 323 K shows one sharp and one broad (at 6.5 ppm) overlapping signal for the aromatic protons of the resorcinarene skeleton. This is due to fast dynamics of the resorcinarene skeleton resulting in a spectrum consistent with time averaged C_{4v}-symmetry. The dynamics is verified at 243 K where this signal splits into four separate peaks indicating the formation of the rigid C_{2v} boat conformation (Figure 27). In the solid state, **63** adopts the boat conformation (Figure 28).[III]

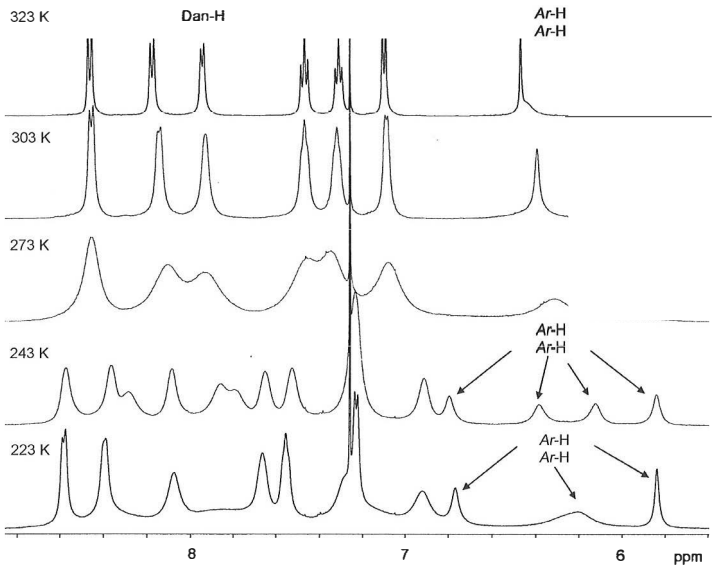


Figure 27: ^{1}H NMR spectrum of resorcinarene **63** in $CDCl_3$ at different temperatures. At 323 K the compound shows two overlapping signals for the aromatic protons, which broaden as the temperature is reduced and finally splits into four singlets at 243 K to confirm a C_{2v}-symmetry conformation. The single peak at higher temperatures can be explained as a result of the fast dynamics resulting in time averaged C_{4v}-symmetry.[III]

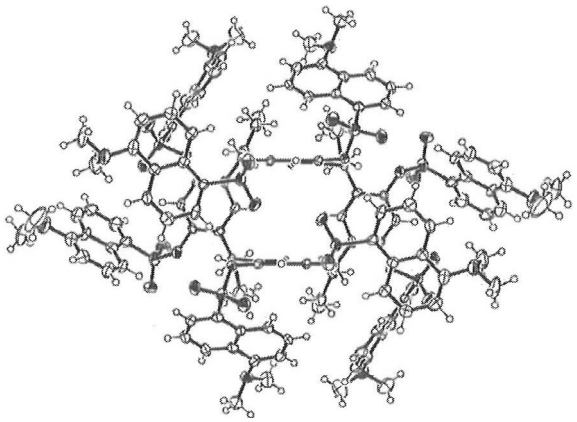
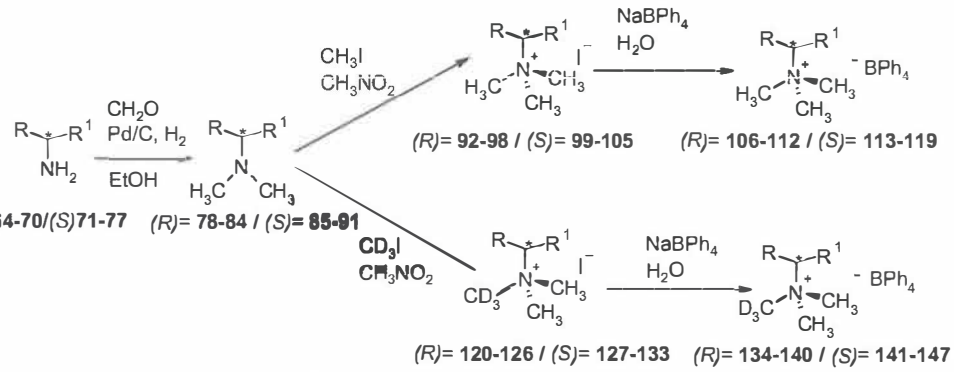


Figure 28. Ortep-plot of the X-ray crystal structure of completely dansylated resorcinarene **63**. All solvent molecules are omitted for clarity.[III]

3.1.4 Synthesis of the chiral guests

Several small ammonium compounds were synthesized, with the aim of utilizing them in different complexation experiments. The chiral ammonium salts were synthesized according to a known procedure by Undheim *et al.*[144] (Scheme 18). Since direct permethylation usually leads to a product mixture and because the use of base racemizes the amino acid derivatives, a two-step synthesis involving reductive methylation with formaldehyde followed by methylation of the tertiary amine with methyl iodide (CH_3I or CD_3I, respectively) was applied. The synthesis terminates with an anion exchange of iodide against tetraphenyl borate in order to avoid interference of the iodide with the hydrogen bonding at the upper rim of the host molecules and to increase the solubility of the salts in organic solvents. CD spectra confirmed that racemization did not occur during the synthesis (Figure 29).



(R) (S) (R) (S) (R) (S) (R) (S) (R) (S) (R) (S) (R) (S)

64, **71**, **78**, **85**, **92**, **99**, **106**, **113**, **120**, **127**, **134**, **141** R = Ph, $R^1 = CH_3$

65, **72**, **79**, **86**, **93**, **100**, **107**, **114**, **121**, **128**, **135**, **142** R = CH_2OH, $R^1 = CH_2Ph$

66, **73**, **80**, **87**, **94**, **101**, **108**, **115**, **122**, **129**, **136**, **143** R = CH_2OH, $R^1 = CH_2CH(CH_3)_2$

67, **74**, **81**, **88**, **95**, **102**, **109**, **116**, **123**, **130**, **137**, **144** R = $COOCH_3$, $R^1 = CH_3$

68, **75**, **82**, **89**, **96**, **103**, **110**, **117**, **124**, **131**, **138**, **145** R = $COOCH_3$, $R^1 = CH(CH_3)_2$

69, **76**, **83**, **90**, **97**, **104**, **111**, **118**, **125**, **132**, **139**, **146** R = $COOCH_3$, $R^1 = CH_2CH(CH_3)_2$

70, **77**, **84**, **91**, **98**, **105**, **112**, **119**, **126**, **133**, **140**, **147** R = $COOCH_3$, $R^1 = CH_2Ph$

Scheme 18: Synthesis of chiral, quaternary ammonium ions suitably labeled for their use in mass spectrometric studies. The (S)-series was prepared through the same synthetic steps just starting from the corresponding (S)-enantiomer of the precursors.[II]

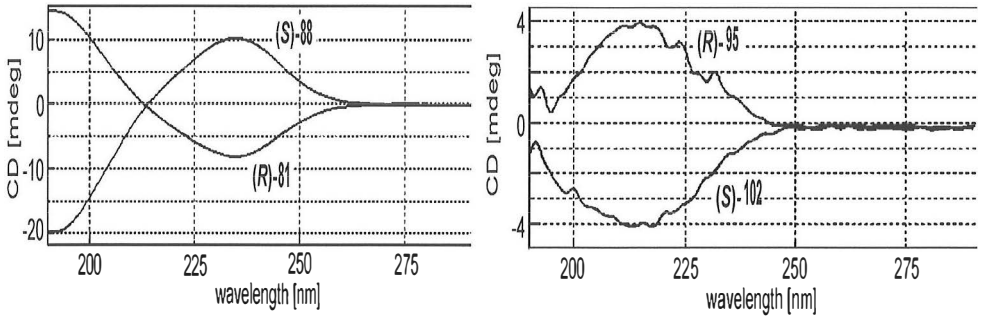
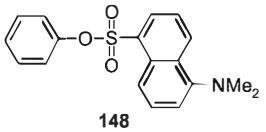


Figure 29: CD spectra of intermediate (*S*)-**88** and (*R*)-**81** and iodides (*S*)-**102** and (*R*)-**95** as representative examples.[II]

As a reference for the fluorescence spectroscopic studies of compound **61** and **63**, a model compound was prepared by the base catalyzed acylation of phenol with dansyl chloride in CH_2Cl_2 giving dansyl phenolate **148**. The X-ray structure shows that π-π interactions affect the crystal packing. Two CH···O=S hydrogen bonds are detected between methyl hydrogens of the amine and the oxygens of the sulfonyl group (Figure 30).



148

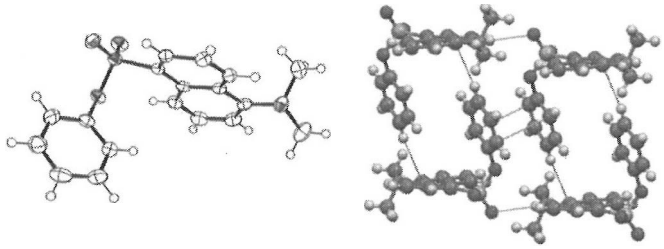


Figure 30: Reference compound **148** and its X-ray structure.[III]

In this section, the syntheses of unfunctionalized resorcinarenes, methyl resorcinarene, tetramethoxyresorcinarenes, octamethoxyresorcinarene and pyrogallarenes are described. The unfunctionalized resorcinarenes were further functionlized at the 2-position of the benzene ring to bromo- and iodoresorcinarenes. Mannich procedure was used to attach chiral amino groups to the core resorcinarenes giving tetrabenzoxazenes and tetrakis-aminomethylated resorcinarene. The hydroxyl groups were tetraacylated and

octaacylated by tosyl and dansyls groups with the aim of studying the fluorescence properties of the dyes.

Chiral tetraalkylammonium, amino alcohol and amino ester cations were synthesized and used as guests in the complexation studies. The synthesized dansylphenolate was used as the reference compound in fluorescence studies.

3.2 Complexation studies

3.2.1 Gas phase complexation

The investigation of supramolecular, i.e. weakly bound, non-covalent complexes in the gas phase by mass spectrometric means[127-131] is rapidly growing and has profited much from the development of soft ionization methods in the 1980s, electrospray ionization in particular. A variety of inclusion complexes with crown ethers as chiral hosts have been studied in the gas phase and the effects of the guest configuration have been investigated[145-147]. Figure 31 and 32 show the guests used in this study.

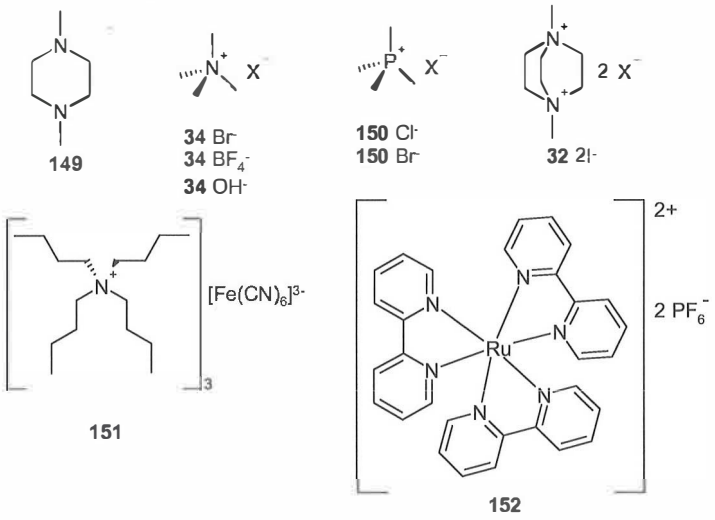


Figure 31: Neutral and cationic guest species.

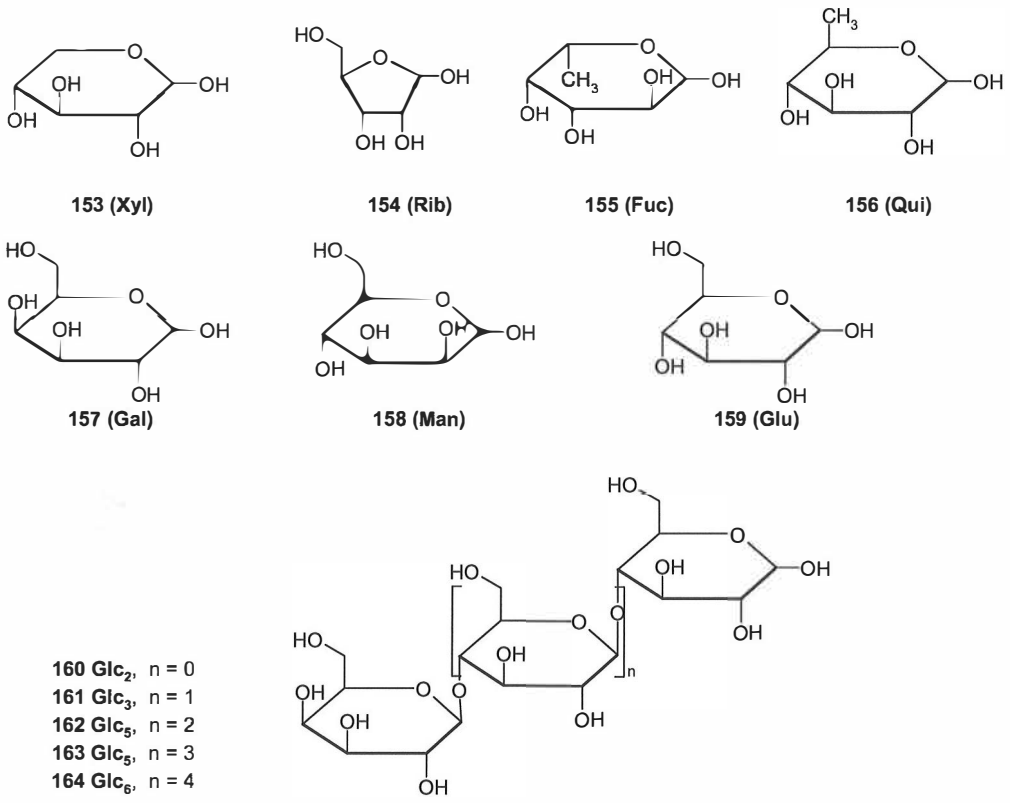


Figure 32: The saccharide guests

An investigation of model systems by mass spectrometry, consisting of a chiral resorcinarene serving as host and chiral quaternary ammonium salts serving as guests, can give information about non-covalent interactions between these components. The complexation ability with ammonium ions extends to chiral ammonium ions. Utilizing Sawada's enantiomer-labeled guest method,[148] the possibility to analyze the hosts' capability to bind chiral guests with selectivity[151] was studied.

In order to evaluate the extent by which chiral recognition can be achieved, pseudo-racemates were prepared from one unlabeled guest enantiomer and the other deuterium-labeled enantiomer. ESI mass spectra of the pseudo-racemates yield intense signals for anion bridged dimers. Homo- and heterodimers of the ammonium ions appear with a statistical 1:2:1 ratio when an exact 1:1 mixture is used. Thus, these mass spectra can be used to make sure that both cations are present in exactly equal amounts. Then, part of this stock solution was mixed with one of the resorcinarenes.[II]

Since one of the host–guest complexes is labeled with a -CD_3 group, the two diastereomeric host–guest complexes overlap with their isotope patterns. Nevertheless, the relative ratio of both complexes can be analyzed by isotope pattern analysis. Significant differences between the intensities of the two complexes were not observed in any of the cases studied. This lack of chiral recognition is confirmed by the control experiment in which the other guest enantiomer was deuterium labeled (Figure 33).[I]

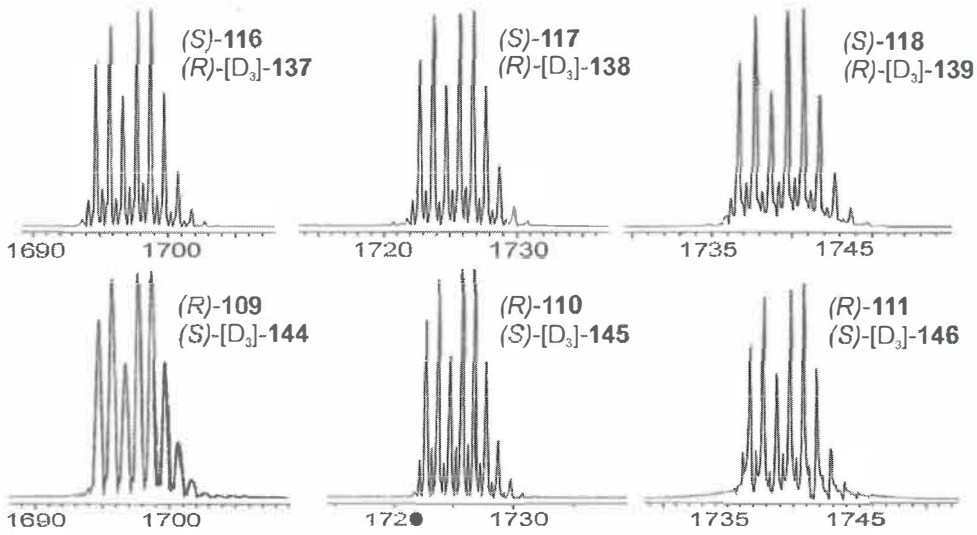


Figure 33: Isotope pattern regions of the ESI-FTICR mass spectra of (S)-**15a** with pseudo-racemates of the two guests. The bottom row represents control experiments with a reversed labeling of the two guest enantiomers as compared to the top row.[II]

While the ESI-FTICR mass spectrum of a freshly prepared sample of (S)-**15a** in methanol was almost perfectly clean, additional signals raised over time with a repetitive peak spacing of Dm = 179 Da. This mass difference corresponds to the replacement of an amine substituent (Dm = 211 Da) by a methoxy group (Dm = 32 Da, thus 211-32 = 179 Da) originating from the solvent. Three such replacements are possible and give rise to ions at m/z 1371, m/z 1192, and m/z 1013. The replacement of the last amine was however not observed. Instead, a signal rose at m/z 1045 which formally corresponds to a methanol adduct of the product of three amine/methanol exchanges. Upon replacement of the last amine, no site that could easily be protonated is left. Instead, many free amines are present in the solution. This is the reason why the final product is visible in the mass spectrum as a complex with the ammonium ion generated from the liberated amine. As long as an amine incorporated in the resorcinarene is protonated, complex formation with another ammonium ion is unlikely due to

charge repulsion. All four amines can be exchanged with no assistance from any other group in the molecule (figure 34).

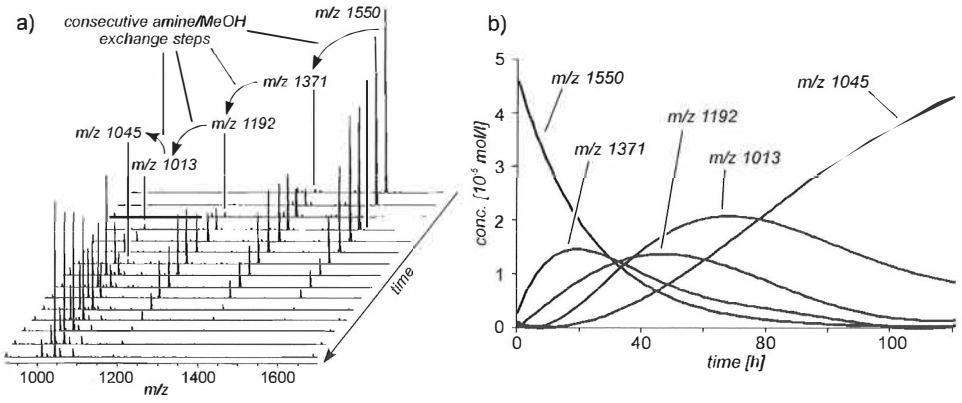


Figure 34: a) Change of the ESI-FTICR mass spectrum of a methanol solution of (S)-**15a** over time. b) Kinetics plot for the reactions monitored assuming that - as a first approximation - intensities can be translated into concentrations in solution.[II]

The complexation of tetramethylphosphonium cation with resorcinarenes and pyrogallarenes behaves very similarly to the corresponding tetramethylammonium cation. Gas phase studies confirm the structures of the 1:1 open complexes and 1:2 dimeric capsules. Heterodimeric capsules encapsulating the guest are formed when equimolar mixtures of two different resorcinarenes or two different pyrogallarenes are mixed with the guest, showing intensity distribution close to the statistically 1:2:1 ratio as expected (Figure 35). This trend is, however, different when a heterodimeric capsule encapsulating the guest is formed from mixing two equimolar mixtures of a resorcinarene and a pyrogallarene with the guest. The intensity distribution clearly shows that the pyrogallarene monomer is more favoured (Figure 35).[IV]

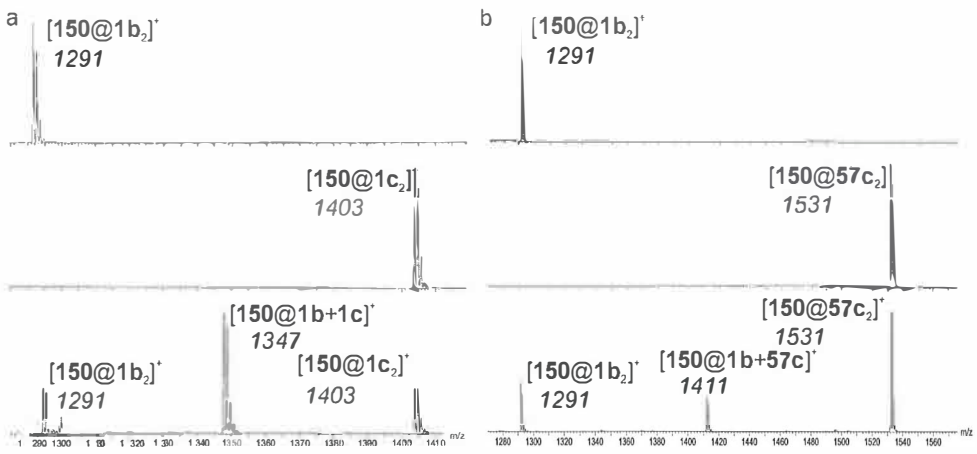


Figure 35: Partial ESI mass spectra of (a) **150@1b**$_2$, **150**$^+$**@1c**$_2$, **150@1b+1c** showing a statistical 1:2:1 intensity distribution. (b) **150@1b**$_2$, **150@57c**$_2$, **150**$^+$**@1b+57c** showing a more favored pyrogallarene homodimeric capsule formation.[IV]

Substituents on the upper rim of resorcinarenes can affect their complexation ability. Several substituted resorcinarene hosts were used to study the influence of the substituents towards binding with cationic guests **34** and **32**. A solution of each two of the hosts and one of the guests in equimolar concentrations in acetonitrile with 1-5 % MeOH was electrosprayed and the corresponding heterodimeric complex encapsulating the guest cation was isolated and fragmented by irradiation with an IRMPD laser. With this methodology, it is possible to determine even small differences in binding strength since the peak intensity for the monomeric complexes is directly related to it. Experiments were performed accordingly with different equimolar mixtures of each two of the resorcinarenes and **34** and a clear ranking of binding strength evolved. The capability to bind the guest **34** decreases in the following order of upper-rim substituents R: CH_3 (**58**) > OH (**57b**) ≈ H (**1b**) > I (**59**) >> Br (**4b**). This behavior can be explained by the electronic effects of the substituents (Figure 36).[V]

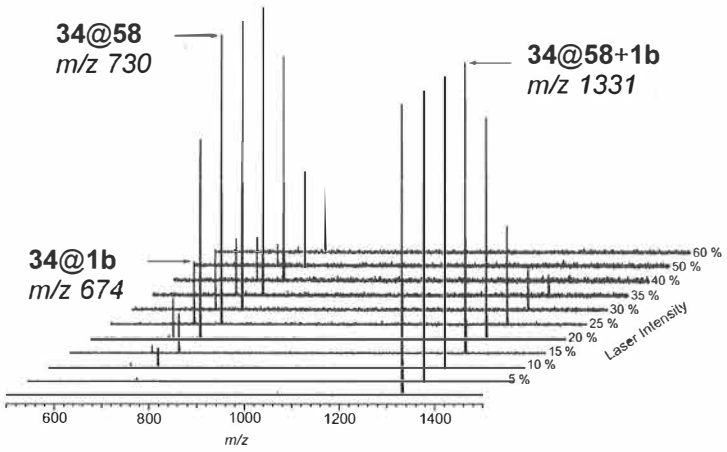


Figure 36: Gas phase isolation and laser induced fragmentation spectra of heterodimeric complex **[34@58+1b]**$^{+}$.[v]

This trend was however slightly different when doubly charged N,N′-dimethyl-1,4-diazoniabicyclo[2.2.2]octane **32** was used (I(**59**) ≈ OH (**57b**) > CH_3 (**58**) > H (**1b**) >> Br (**4b**)). Surprisingly, iodosubstituted resorcinerene turned out to be the most strongly bound species (Figure 37). This is in stark contrast to the trend seen with guest **34**. The orientation of the guest, the size and hydrogen bonding ability of the iodide could be used to explain this behaviour. Varga *et al.*[150] in the review article reported that in some host-guest systems, the stronger bonding of haloderivatives was attributed to the formation of weak C-H···X-C hydrogen bonds. The strength of the bonding increases with the halogen size from X = Cl to I.[132] Estimated hydrogen bond energies from the association constants taking into account the entropy change of adduct formation gave a trend of I > Br > Cl. The rigidity of the host results in less favorable H···X distances in case of X = Cl or Br.[132,151,152] Intramolecular hydrogen bonding involving the phenolic hydroxyl groups with the halogen also help to stabilize the complex. Reports in the literature show cases where the phenolic hydroxyl groups form hydrogen bonds with the neighboring halogen and stabilize the complex where, in contrast to the expectations based on the general hydrogen bond strength of the halogens[153,154], the strength of the hydrogen bond increases in the order F < Cl < Br < I.[132,155-159] This trend was dubbed an 'anomalous' order in the strength of the intramolecular hydrogen bond.[v]

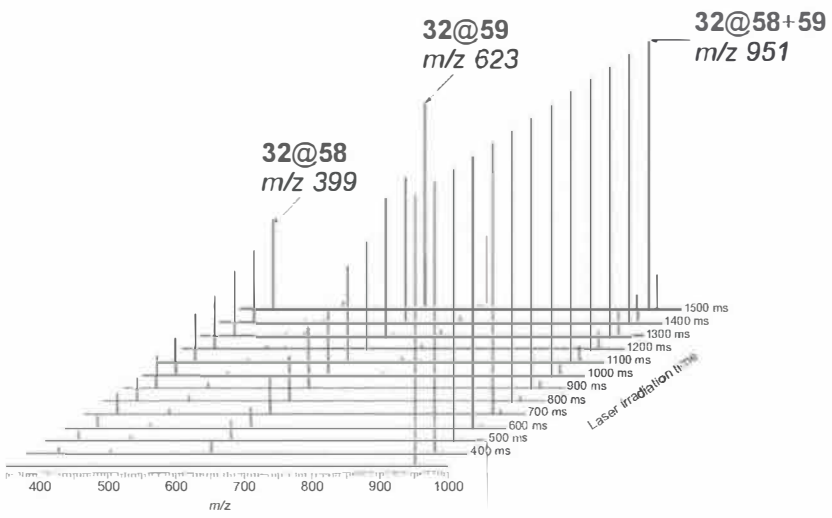


Figure 37: Gas phase isolation and laser induced fragmentation spectra of heterodimeric complex **[32@59+58]**$^{2+}$.[V]

A selection of several guests with a systematic increase in size and shape and providing the charge needed for the ionization process to act as a template could lead to the isolation of higher complexes in the gas phase. $[Ru^{II}(bpy)_3]^{2+}$ (**152**; bpy=2,2′-bipyridine) proved to be the best template for hexameric capsule formation, not only because it is a pseudooctahedral metal complex with a shape more congruent to the interior of the hexamer, but also because it is a dication and thus a lower m/z range is needed (Figure 38). When the ionization conditions are optimized, unspecific binding can almost completely be avoided with fragmentation minimized to only a small extent.[I]

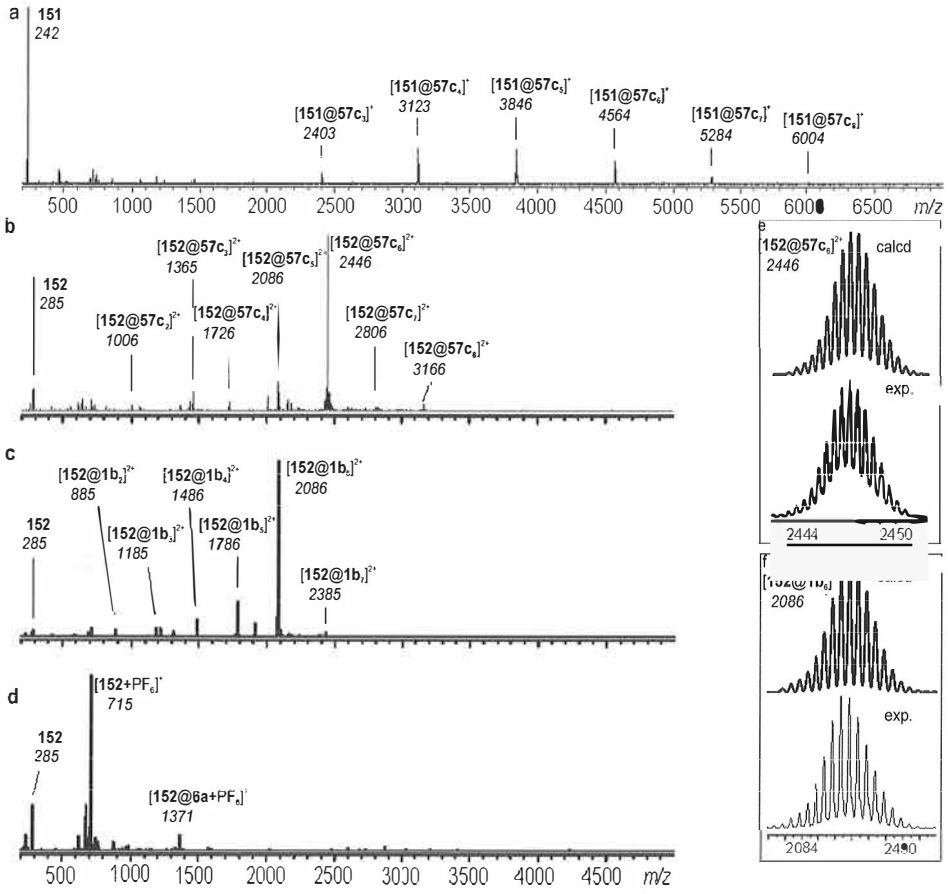


Figure 38: Mass spectra of a 200 mM solution of **57c** in $CHCl_3$/acetone (2:1) after addition of: a) $(\mathbf{151})_3[Fe(CN)_6]$. b, c) ESI-FTICR mass spectra of the same solution of **57c** and **1b**, respectively, with $\mathbf{152}(PF_6)_2$, each optimized for hexamer intensity. d) Control experiment with tetramethylresorcinarene **6a**. e,f) Experimental and calculated isotope patterns of the hexamer ions $[\mathbf{152@57c_6}]^{2+}$ and $[\mathbf{152@1b_6}]^{2+}$.[1]

The whole isotope pattern of the hexamer ion was isolated in the analyzer cell of the FTICR mass spectrometer. These ions were irradiated in an IRMPD experiment with IR radiation from a CO_2 laser for different time intervals. Fragmentation is induced after a short induction period by an increase in the internal energies of the ions through photon absorption. Fragmentation commences by three consecutive losses of pyrogallarene monomers, with signals corresponding to $[\mathbf{152@57c_5}]^{2+}$ and $[\mathbf{152@57c_4}]^{2+}$ becoming visible after 0.02 s and a signal corresponding to $[\mathbf{152@57c_3}]^{2+}$ becoming visible after 0.03 s irradiation. At laser pulse lengths below 0.03 s, no signal corresponding to the free

$[Ru(bpy)_3]^{2+}$ ion **152** is observed, while up to three monomers are already missing in the structure. Only at longer irradiation periods does the signal for bare **152** arise together with those of $[\mathbf{152@57c}_2]^{2+}$ and $[\mathbf{152@57c}]^{2+}$ (Figure 39).[I]

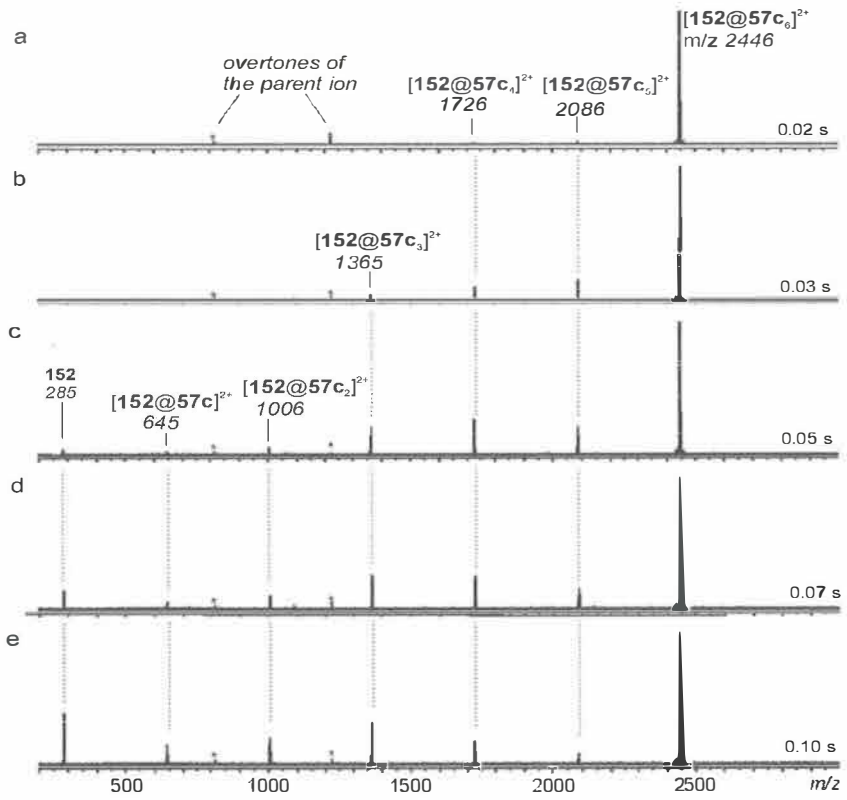


Figure 39: IRMPD experiment with mass-selected $[\mathbf{152@57c}_6]^{2+}$: Longer irradiation times lead to consecutive monomer losses. The formation of free **152** starts to compete with the loss of additional monomers from the trimer $[\mathbf{152@57c}_3]^{2+}$.[I]

If either **57c** and **1c** or **1b** and **1c** are mixed in 1:1 ratios, the mass spectra reveal the formation of heterohexameric capsules. An intensity distribution close to the statistically expected one is obtained from a mixture of the two resorcinarenes **1b** and **1c**, while there is some bias towards resorcinarene hexamers in mixtures of resorcinarene **1b** and pyrogallarene **57c**. The exchange of monomers is too fast to be monitored by mass spectrometry. The equilibrium is reached before the first spectrum can be recorded (ca. 30 s after mixing the two solutions of the homohexamers). Recently, Rebek *et al.*[123] showed evidence by FRET that

resorcinarenes and pyrogallarene hexamers self-sort in solution in contrast to the gas phase.

Deprotonated resorcinarenes **2** and **8** readily form noncovalent 1:1 complexes in the gas phase with neutral saccharides. In addition, these resorcinarenes exhibit a clear structure and size selectivity towards the saccharides. Both the thermodynamic and kinetic stabilities seem to increase with hexoses. This behavior results most likely from a maximum of three hydrogen bonds formed between the hexose and resorcinarene (Figure 40).[VI]

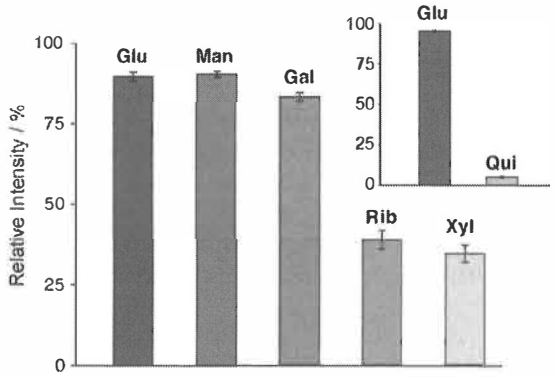


Figure 40: Relative intensities (%) of monosaccharide complexes ([**1b**+saccharide-H]$^-$/[**1b**+saccharide-H]$^-$+[**1b**+**Fuc**-H]$^-$) and the relative intensities (%) of **Glu** and **Qui** (inset).[VI]

Comparison studies of the di- and oligosaccharides (Figure 41) show that the complexation of biose and triose is the most beneficial and is even more favorable than the binding of a monosaccharide as a result of a maximum of four hydrogen bonds between the host and saccharide. As the length of the sugar chain is increased, the resorcinarene affinity towards saccharides decreases, although complexation still occurs. Surprisingly, complexation of such large sugars (i.e., cellohexaose) was observed, but this behavior was rationalized by theoretical calculations that showed the formation of a curved conformation of the larger sugars suitable for interaction with resorcinarenes.[VI]

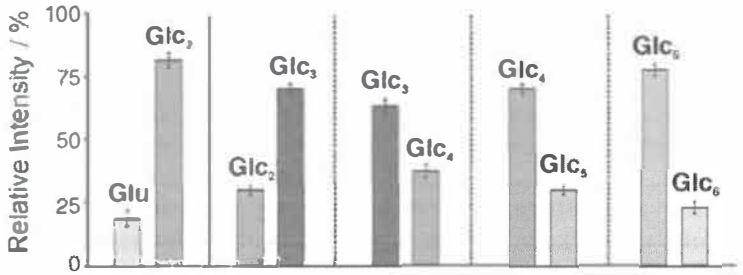


Figure 41: Di- and oligosaccharide competitions in the presence of **1h**. The relative intensities (%) are presented.[VI]

The highlight of the complexation studies is the observation of the first example of a hexameric capsule in the gas phase via mass spectrometry. It was revealed that with a suitable template, it is possible to see higher resorcinarene and pyrogallarene complexes with cationic species. Resorcinarene and pyrogallarene hexameric capsules containing $[RuII(bpy)_3]^{2+}$; (bpy=2,2′-bipyridine) as the guest exist in the gas phase with the guests acting as the template, not only because it is a pseudooctahedral metal complex with a shape more congruent with the interior of the hexamer, but also because it is a dication and thus a lower m/z range is obtained. The stability of the hexameric capsules was studied using IRMPD with IR radiation from a CO_2 laser for different time intervals. The experimental results are in good agreement with simple molecular modeling calculations. These results not only indicate the stabilizing influence of suitable templating cations, they also point to the remarkable intrinsic softness of electrospray ionization mass spectrometry, which permits their characterization in the gas phase as isolated molecules without the influence of solvents and counterions

In the gas phase, both 2:1 and 1:1 resorcinarene and pyrogallarene complexes with tetramethylphosphonium cations were observed. Comparison studies show that the pyrogallarenes complexes are far more stable than the corresponding resorcinarene complexes. The effect of substituents on the resorcinarene hosts towards their binding ability with TMA and DABCO was studied and results reveal that the size and electronic nature of the substituents have an important influence on the binding ability of the hosts. It was also seen that resorcinarenes can nicely bind to saccharides.

3.2.2 Complexation in solution

NMR spectroscopy is an excellent tool for the investigation of host-guest complexation in solution. Significant complexation-induced upfield shifts of guest signals were observed when resorcinarene **1c** and pyrogallarene **57c** were mixed with **150**Cl^- or **150**Br^- in methanol-d_4, which is in agreement with the effect of shielding of the methyl protons of the cation by the aromatic rings of the bowl-shaped host cavity. Pyrogallarenes showed larger upfield shifts of the guests as compared to the respective resorcinarenes. The extra hydroxyl groups of the pyrogallarenes make the cavity more π-basic and thus enhance the shielding effect of the aromatic rings. The titration data clearly support a fast guest exchange compared to the NMR timescale at 303 K. The stoichiometry of the complexes was determined by Job plot[160,161] experiments and revealed in all cases a clear 1:1 complexation model in methanol-d_4. The association constants for **150** at 303K for hosts **1c** and **57c** were determined to be 130±10 and 390±37 M^{-1}, respectively, by a non-linear least-squares fitting of the titration curve.[162,163] As expected, the association constants of the pyrogallarene were much higher than with the respective resorcinarene due to the more π-basic character of the pyrogallarenes.[IV]

It is known that the absorption and fluorescence properties of the dansyl group are very sensitive to acid because of the protonation of the nitrogen in the dansyl unit at low pH.[164-169] Upon addition of trifluoroacetic acid, the absorption of compounds **61**, **63** and **148** (at 260 and 350 nm) decreases continuously. A new absorption peak appears at 288 nm with a shoulder at 323 nm, which gains intensity with the addition of the acid. These new absorption peaks correspond to the protonated dansyl unit. Two isosbestic points observed at 270 and 313 nm indicate an A to B transformation of dansyls to protonated dansyls. Valeur *et al.*[164,166] observed the same phenomenon with dansylated calixarenes and Vögtle *et al.*[165] with dansylated dendrimers.

Different fluorescence measurements of the acid titration of these compounds with excitation at the isosbestic point were performed. The fluorescence intensity decreases with increase in trifluoroacetic acid. The decrease in the fluorescence emission of the compounds with excitation at the isosbestic point is proof that the protonation of the dansyl group is responsible for this behaviour (Figure 42). The addition of TMA^+Br^- had no influence on the absorption behavior of these compounds but the fluorescence intensity shows a concentration dependent decrease with increasing TMA^+Br^- concentration (Figure 42).[III]

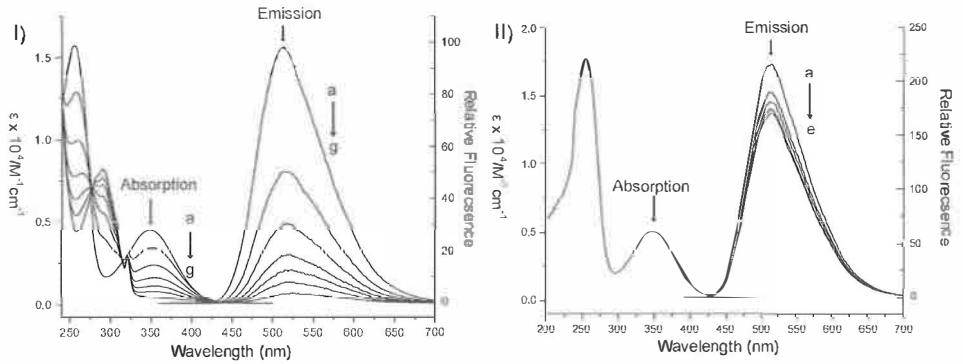


Figure 42: (I) Absorption and fluorescent titration of resorcinarene **63** with trifluoroacetic (TFA) acid in chloroform, **[63]** = 1.25×10^{-5}molL^{-1}, [TFA] = 1.0×10^{-3}molL^{-1}, λ_{exc} = 313 nm (isosbestic point). From a-g: 0, 0.8, 1.6, 2.4, 3.2, 4.0, 6.0, 8.0 equiv. (II) Absorption and fluorescent titration of octadansylated resorcinarene **63** in chloroform with TMA^+Br^- in H_2O, **[63]** = 1.25×10^{-5}molL^{-1}, $[TMA^+Br^-] = 1.0 \times 10^{-3}$molL^{-1}, λ_{exc} = 350 nm (λ_{max}). From a-e: 0, 0.8, 1.6, 3.2, 4.0 equiv.[III]

^{1}H NMR spectrometroscopy of 1:1 complexes in solution showed the encapsulation of the TMP cation by resorcinarenes and pyrogallarenes with the pyrogallarenes showing more intense up field shifts and higher binding constants than resorcinarenes. The dansyls groups attached to the resorcinarenes showed intense absorbance and fluorescence. Fluorescence quenching occurred when the dansyl groups were either protonated or were interacting with TMA^+.

3.2.3 Solid state complexations

In crystal structure **I**, resorcinarene **58** forms a dimeric capsule with neutral guests **149**. In the structure, one hydroxyl of the resorcinarene is deprotonated while the nitrogen atoms of **149** are protonated. There is a hydrogen bond interaction between one protonated nitrogen of **149** and the deprotonated hydroxyl group of **58** while the second protonated nitrogen of **149** is hydrogen bonded with the deprotonated hydroxyl of a second resorcinarene unit constituting the dimeric capsule (Figure 43).[V]

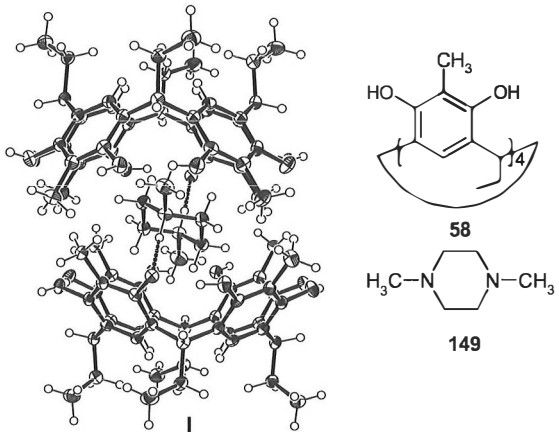


Figure 43: X-ray crystal structures of complex I. Plot of a thermal ellipsoid drawn with 50% probability level of **I**: **149@58**$_2$ (Intermolecular hydrogen bonds are shown as dotted lines).[V]

Crystal structure **II** reveals an open complex of resorcinarene **1b** and chiral tetraalkyl ammonium guest **92** in which the cation is complexed within the cavity of **1b** (Figure 44). The crown conformation of **1b** is maintained by four intramolecular hydrogen bonds between adjacent hydroxyl groups. The tetraphenyl borate was not seen at all and instead one hydroxyl group of **1b** is deprotonated providing the counter anion in the system.[V]

In crystal structure **III**, the capsule, **150@1b**$_2$·Br$^-$·16H_2O, two molecules of **1b** are linked via water molecules and, as expected, the cation **150** is encapsulated inside the cavity formed by the two resorcinarene hosts (Figure 45a). However, the disorder of the TMP is so severe that definite conclusions about its orientation and possible interactions with the host could not be made. As with other C_2resorcinarene capsules[93] the bromide anion is found to reside in the small pocket between the ethyl groups of the host via weak C-H···anion interactions. As in crystal stucture **III**, the methanol molecules in the capsule **IV** (**150@1c**$_2$·Br$^-$·4MeOH) mediate the capsule formation. The encapsulated TMP cation inside the cavity is also severely disordered. In addition to solvent molecules, the capsule is also mediated by Br$^-$ anions (Figure 45b).[IV]

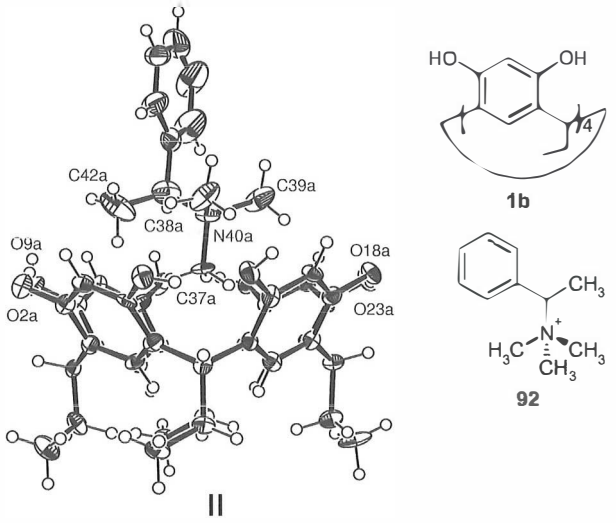


Figure 44: X-ray crystal structures of complex **II**. Plot of a thermal ellipsoid drawn with 50% probability level of **II**: **92@1b**.[v]

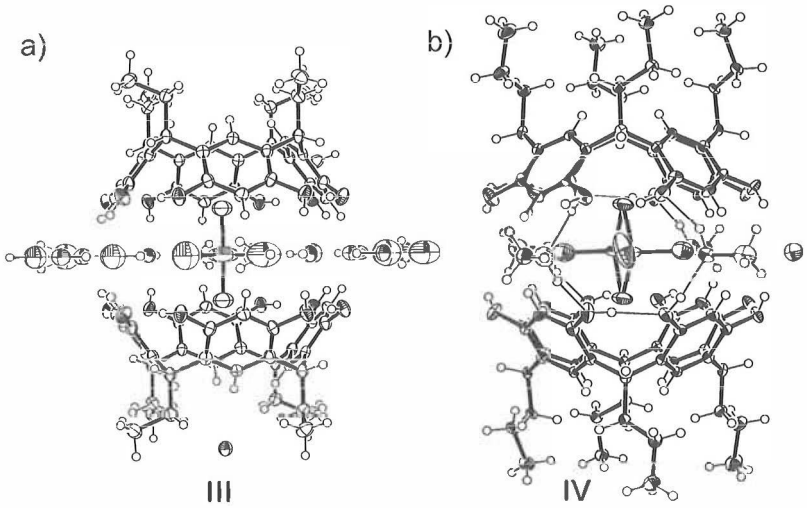


Figure 45: Ortep and CPK plots of the X-ray structure of hydrogen bonded solvent–anion mediated resorcinarene: a) Complex **III**: **150@1b**$_2$·Br$^-$ ·16H_2O, (b) Complex **IV**: **150@1c**$_2$·Br$^-$·4MeOH.[iv]

Two dimeric resorcinarene capsules were formed around the TMP cation. A third dimeric capsule was formed with one neutral guest in which the two nitrogens of the guest were protonated and one of the hydroxyl groups of each

resorcinarene was deprotonated. One open 1:1 inclusion complex was formed between resorcinarene **1b** and guest **92** which is slightly larger compared to the other guests. Capsule formation is induced by cation···π and π···π interactions between the host and guest species bound together by solvent and also by anion-mediated hydrogen bonds.

4 SUMMARY AND CONCLUSIONS

In this study, the syntheses of various unfunctionalized and functionalized resorcinarenes and pyrogallarenes are described. The basic resorcinarenes were further functionalized at the 2-position of the benzene ring to halogenated and chiral aminosubstituted derivatives. The hydroxyl groups were acylated by tosyl and dansyls groups with the aim of studying the fluorescence acitivities of the dyes. Reported synthetic procedures were used to synthesize the resorcinarenes and resorcinarene derivatives. Most of the synthesized resorcinarenes were used as hosts in the complexation studies.

Several guests were synthesized. Extensive work was done in synthesizing the chiral tetraalkylammonium amino alcohols and amino esters cations. Dansylphenolate, used as the reference compound in fluorescence studies, was also synthesized. Other guests were commercially available.

Mass spectrometry, NMR spectroscopy, fluorescence spectroscopy and X-ray crystallography were used to study the complexation of the resorcinarene hosts with the guests. The chiral tetrabenzoxazines and the tetrakis-aminomethylated resorcinarenes showed 1,4-elimination and retro-Diels-Alder fragmentation in the gas phase. While not showing any chiral discrimination in complexing the chiral guests, methanol was found to slowly replace up to four of the amine substituents in the gas phase. In the gas phase, both 2:1 and 1:1 resorcinarene and pyrogallarene complexes with tetramethylphosphonium cation were observed. Comparison studies showed that pyrogallarene complexes are far more stable then the corresponding resorcinarene complexes. The effect of substituents on the resorcinarene hosts towards their binding ability with TMA and N,N′-dimethyl-1,4-diazoniabicyclo[2.2.2]octane were studied and results reveal that the size and electronic nature of the substituents have an important influence on the binding ability of the hosts.

Gas phase experiments showed that with a suitable template, it is possible to see higher resorcinarene and pyrogallarene complexes with cationic species. Resorcinarene and pyrogallarene hexameric capsules containing $[RuII(bpy)_3]^{2+}$;

(bpy=2,2′-bipyridine) as the guest were shown to exist in the gas phase with the guest cation acting as the template, not only because it is a pseudooctahedral metal complex with a shape more congruent to the interior of the hexamer, but also because it is a dication and thus a lower m/z range is needed. The stability of the hexameric capsules was studied using IRMPD experiments with IR radiation from a CO_2 laser for different time intervals. The formation of hexameric capsules in the gas phase turned out to be the highlight of the work.

UV-Vis experiments showed fluorescence quenching when the dansyl group is either acid protonated or interacting with a tetramethylammonium cation. 1:1 complexes were observed in the encapsulation of TMP cations by resorcinarenes and pyrogallarenes in solution by ^1H NMR spectrometroscopy, with the pyrogallarenes showing more intense up field shifts and higher binding constants than resorcinarenes.

Crystal structures of four complexes of resorcinarenes with neutral guests, chiral alkyl ammonium salts and alkyl phosphonium salts were studied. Of the resulting solid-state structures, three were dimeric resorcinarene capsules that were formed around the guest species. Capsule formation was induced by cation···π and π···π interactions between the host and guest species bound together by solvent and also by anion-mediated hydrogen bonds.

The results of this thesis contribute to the general knowledge of various non-covalent interactions and capsule formation properties of resorcinarenes and pyrogallarenes in the gas phase, in solution and in the solid state. It shows that by tuning known synthetic routes, new interesting compounds could be obtained. This work also highlights the strength of mass spectrometry in studying the non-covalent interactions in supramolecular chemistry as seen with resorcinarenes and pyrogallarenes. By carefully chosing the substituents on the resorcinarenes and guests, new and interesting resorcinarene complexes can be achieved.

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