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RESORCINARENES

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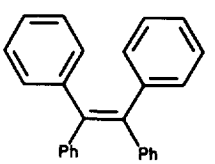
1. INTRODUCTION

In 1872, Adolf von Baeyer[1] reported, in a general study on the synthesis of phenol-based dyes, that the addition of concentrated sulfuric acid to a mixture of benzaldehyde and resorcinol gave a red-coloured product that turned violet in alkaline solution. When the mixture was heated, a crystalline compound was obtained in addition to the reddish resin, that was later found to be isomeric with the resin. Several years later, Michael[2] determined the correct elemental composition of this sparingly soluble, high melting, crystalline product $(C_{13}H_{10}O_2)_n$ and its acetyl derivative $(C_{13}H_8(OCOCH_3)_2)_n$. From these data, he concluded that the product is formed by combination of an equal number of benzaldehyde and resorcinol molecules and loss of an equal number of water molecules. Owing to the physical properties of the product no estimation of the molecular weight could be carried out at that time. Michael suggested the rather improbable structure **1** for the "phenolic" product. This structure was later adopted by Fabre[3] and has been quoted in polymer chemistry.[4] In 1940, Niederl and Vogel[5] studied several condensation products obtained from the reaction between aliphatic aldehydes and resorcinol. From molecular weight determinations they concluded that the ratio between aldehyde and resorcinol in the product should be 4:4. They proposed the cyclic tetrameric structure **2** (R_1=aliphatic, R_2=H) analogous to cyclic tetrameric structures frequently encountered in nature, e.g. porphyrins. This structure was finally proved in 1968 by Erdtman and coworkers by a single crystal X-ray analysis.[6]



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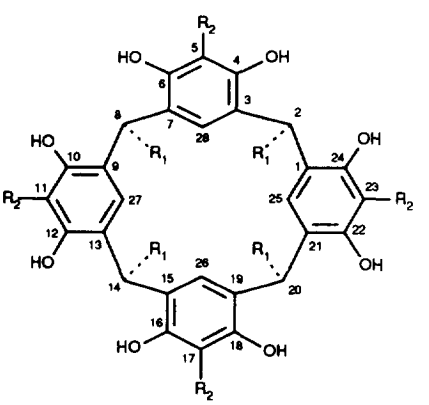


2

Chart 1

The official IUPAC-name for compound **2** (R_1=aliphatic, R_2=H) is 2,8,14,20-tetra-alkylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9, 11,13(27),15,17,19(26),21, 23-dodecaene-4,6,10,12,16,18,22,24-octol. A suitable trivial name for these molecules was never found. Gutsche and Böhmer attempted to classify them as calixarenes by calling them calix[4]resorcinarenes[7] or resorcinol-derived calix[4]arenes,[7,8] but totally different names like Högberg compounds,[9] or simply octols[10,11] also appeared in literature. Very recently, the name resorcinarenes was suggested,[12] which will be used throughout this paper.

In this paper, an overview of the chemistry of resorcinarenes is presented. After discussing the synthesis and conformational properties of these compounds, attention will be focused on their interesting material and complexation properties. Finally, the use of resorcinarenes for the synthesis of cavitands and (hemi)carcerands will be described, together with some applications of this fascinating class of container molecules. The literature cited covers the period to the end of 1994.

2. SYNTHESIS

Resorcinarenes can be prepared in reasonable to high yields via simple, one-step procedures without using templates or high dilution techniques. Most cases involve the acid-catalysed condensation reaction between resorcinol and an aliphatic or aromatic aldehyde.[9,10,13] One example of a Lewis acid-promoted condensation reaction between resorcinol and benzaldehyde has been reported.[14] Recently, two novel procedures for the high-yield synthesis of resorcinarenes were described, involving the Lewis acid-catalysed tetramerisation of 2,4-dimethoxycinnamates[15] and the treatment of 2,4-dimethoxybenzyl alcohol with trifluoroacetic acid.[16]

2.1 RESORCINOL-ALDEHYDE CONDENSATION

The acid-catalysed condensation reaction between resorcinol and an aldehyde is generally carried out by heating the constituents to reflux in a mixture of ethanol and concentrated HCl for several hours, although for every aldehyde different optimal reaction conditions exist.[9,10,13] Usually, the cyclotetramer crystallises from the reaction mixture but, in some cases, water should be added in order to isolate the product.[10,17] The syntheses are generally carried out with unsubstituted resorcinol (1,3-dihydroxybenzene), but in certain cases, for example in the reaction with formaldehyde, the use of 2-methylresorcinol or pyrogallol (1,2,3-trihydroxybenzene) yields isolable amounts of tetrameric products.[18,19] An almost unlimited variation is allowed in the structure of both the aliphatic and aromatic aldehyde. Only the use of very sterically crowded aldehydes, like 2,4,6-trimethylbenzaldehyde[20] or aliphatic aldehydes with functionalities too close to the reaction centre, like $ClCH_2CHO$ or glucose,[10] are an exception to this rule. Resorcinol derivatives carrying electron-withdrawing substituents, like NO_2 or Br,[10] at the 2-position or in which the hydroxyl groups are (partially) alkylated[20] do not give cyclomeric products. Throughout the years, a variety of resorcinarenes has been synthesised. Most of these are listed in Table 1.

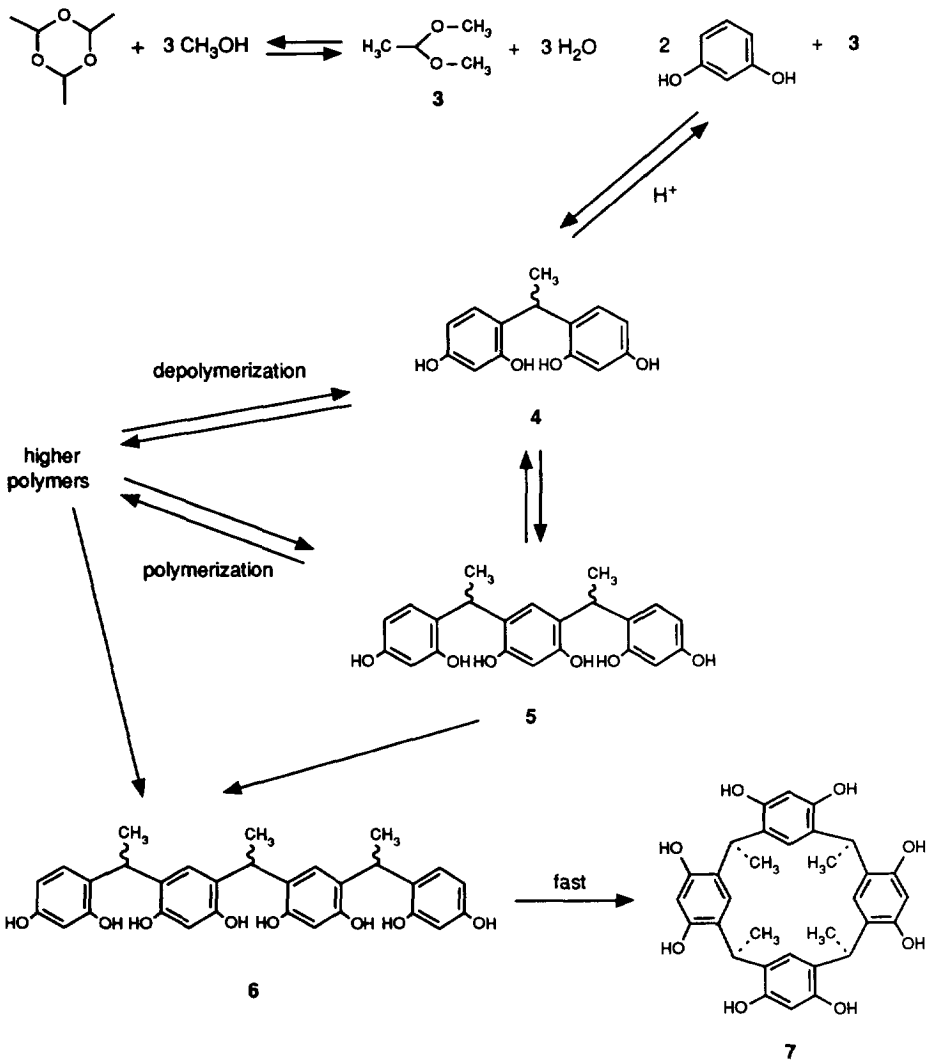
Weinelt and Schneider studied the mechanism of the acid-catalysed condensation reaction between resorcinol and acetaldehyde in methanol/HCl (Scheme 1).[20] Under these conditions, the electrophile stems not directly from the aldehyde, but from its rapidly formed dimethyl acetal **3**. Following quantitatively the formation of all oligomers and cyclic products over time by high field ^1H NMR spectroscopy, they established that formation of cyclotetramer **7** proceeds via sequential coupling of **3** with resorcinol units to form intermediates **4-6** or higher oligomers containing more than four monomers. These higher oligomers are present in concentrations of up to 45% at intermediate reaction times, but largely disappear

Table 1. *Yields of resorcinarenes* **2** *synthesised from (functionalised) aliphatic or (substituted) benzaldehydes and (2-substituted) resorcinols.*

R_1 in **2**	R_2 in **2**	Yield (%)	Reference
CH_3	H	73	11
$CH_3(CH_2)_4$	H	77	10
$CH_3(CH_2)_{10}$	H	70	21
$(CH_3)_2CHCH_2$	H	95	10
$C_6H_5(CH_2)_2$	H	69	10
$NaO_3S(CH_2)_2$	H	40	22
$HO(CH_2)_4$	H	80	10
$Cl(CH_2)_5$	H	67	10
$CH_2{=}CH(CH_2)_8$	H	20	13
C_6H_5	H	83	10
2-HOC_6H_4	H	78	20
3-$O_2NC_6H_4$	H	72	20
3-$H_3CSC_6H_4$	H	77	9
4-BrC_6H_4	H	43	10
4-$(CH_3)_3CC_6H_4$	H	28	10
4-$C_6H_5C_6H_4$	H	99	10
4-NCC_6H_4	H	52	10
4-$HO_2CC_6H_4$	H	79	10
4-$H_2NC_6H_4$	H	a	23
4-$AcHNC_6H_4$	H	52	10
4-$H_3COC_6H_4$	H	93	10
4-$(C_6H_5O)C_6H_4$	H	76	9
4-HOC_6H_4	H	91	20
3,4-$[(OCH_2CH_2)_4O]C_6H_3$	H	43	24
$[(CH)_3S]C$	H	34	9
$(C_5H_5)\cdot Fe\cdot(C_5H_4)$	H	10	25
H	CH_3	90	18
H	OH	53	19
CH_3	OH	72	26

[a] Yield not reported.

towards the end of the reaction since the condensation reaction is reversible under the conditions used. All observed intermediates showed resorcinol and not methoxyethyl units at the terminal positions, which is in accordance with the fast reaction of such species under acidic conditions.[4] The dimers **4** and trimers **5** could be isolated, but the tetramers **6** cyclise too fast to accumulate in observable quantities. This fast cyclisation is related to their conformation, which, according to molecular mechanics calculations, is folded rather than linear as a consequence of the ability to form stronger hydrogen bonds between phenolic hydroxyl groups of adjacent resorcinol units in the folded structure.



Scheme 1

The non-planarity of resorcinarenes means that they can, in principle, exist in many different isomeric forms. The stereochemistry is generally defined as a combination of the following three stereochemical elements:

(i) The conformation of the macrocyclic ring, which can adopt five extreme, symmetrical arrangements: the crown (C_{4v}), boat (C_{2v}), chair (C_{2h}), diamond (C_s), and saddle (D_{2d}) conformation.

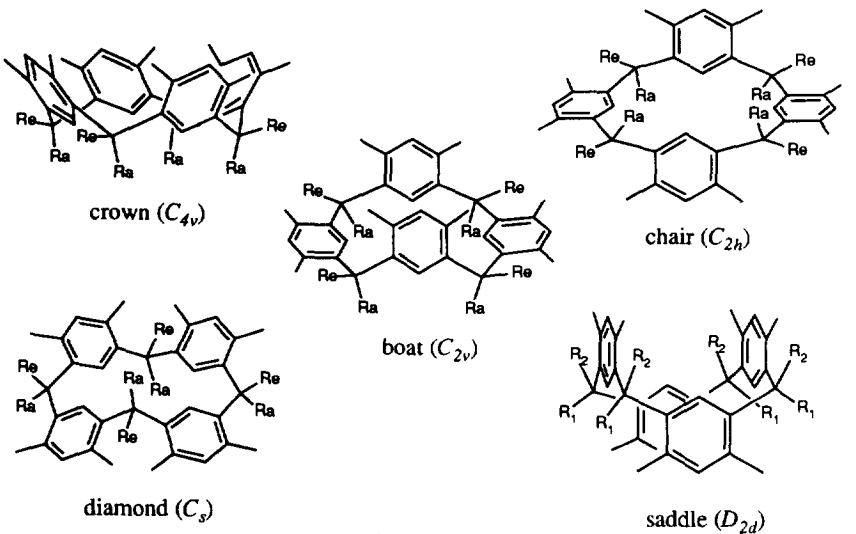


Chart 2

(ii) The *relative* configuration of the substituents at the methylene bridges, giving the all-cis (ccc), cis-cis-trans (cct), cis-trans-trans (ctt), and trans-cis-trans (tct) arrangement.

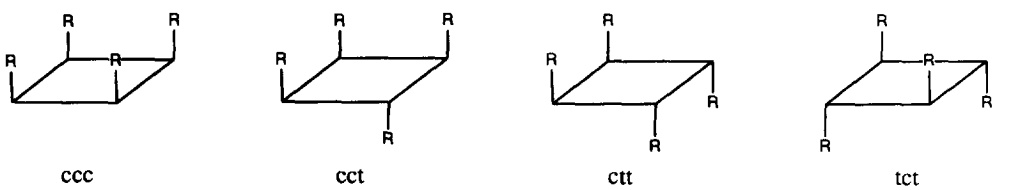
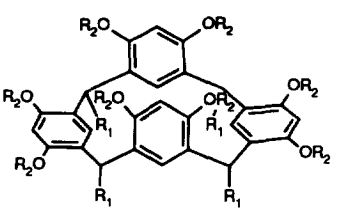


Chart 3

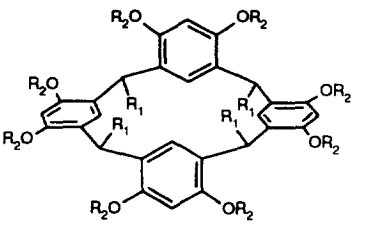
(iii) The *individual* configuration of the substituents at the methylene bridges which, in conformations of the macrocycle with *C* symmetry, may be either axial or equatorial.

Combination of these stereochemical elements gives rise to a vast number of possible stereoisomers. Thus far, only four have been found experimentally.

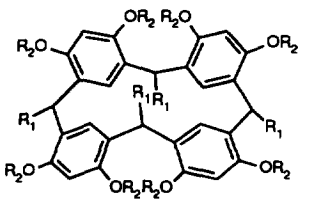
From the acid-catalysed condensation reaction between resorcinol and 4-bromobenzaldehyde, the isomeric products **8a** and **b**, characterised as the corresponding octabutyrates **11a** and **b** by single crystal X-ray analysis, were obtained.[27] Isomer **8a** possesses an all-axial and all-cis configuration of the 4-bromophenyl groups, with the macrocyclic ring in a boat conformation. In isomer **8b**, the macrocyclic ring adopts a chair conformation with the substituents in an all-axial cis-trans-trans (ctt) configuration.



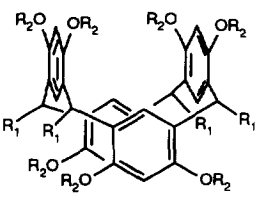
a



b



c



d

7 R_1=CH_3, R_2=H
8 R_1=4-BrC_6H_4, R_2=H
9 R_1=C_6H_{13}, R_2=H
10 R_1=C_6H_5, R_2=H
11 R_1=4-BrC_6H_4, R_2=$C(O)C_3H_7$
12 R_1=C_6H_{13}, R_2=$C(O)CH_3$
15 R_1=$CH_2C(O)OCH_3$, R_2=CH_3
16 R_1=$CH_2C(O)OCH(CH_3)_2$, R_2=CH_3
19 R_1=C_6H_5, R_2=$C(O)C_3H_7$

Chart 4

In addition to boat isomer **9a** and chair isomer **9b**, diamond isomer **9c**, characterised as the corresponding octaacetate **12c**, was isolated from the reaction between resorcinol and heptaldehyde in a 2:2:1 mixture of ethanol, water, and concentrated HCl at 25°C.[28] The diamond isomer **9c** has an all-axial cis-trans-cis (ctc) configuration of the aliphatic chains. A similar isomer (**7c**) was isolated a few years later by Weinelt and Schneider from the reaction between resorcinol and acetaldehyde.[20]

Isomers **a-c** (boat, chair, and diamond) have a *diastereomeric* relationship rather than being *conformationally* isomeric. One would expect them to be interconvertible via rotation through the annulus of one (or more) aromatic ring(s), but this also changes the individual configuration of the adjacent substituents from axial to equatorial or vice versa, giving rise to different isomers. Interconversion of isomers **a-c** takes place only when at least two covalent bonds are broken.

The ratio in which all three diastereomers are formed during the reaction is strongly dependent on the conditions used. There are many factors that can account for the presence or absence of a certain isomer. Under *homogeneous* acidic conditions, the product ratio at equilibrium mainly reflects the thermodynamic stability of the different isomers, since the condensation reaction is reversible under acidic conditions. In order to study the thermodynamic stability of the different isomers, Weinelt and Schneider carried out an isomerisation experiment with boat isomer **7a** (R_1=CH_3, all-cis) in a 5% solution of HCl in methanol at 50°C.[20] The results are shown in **Figure 1**. At equilibrium, reached after approximately 1200s, half of the initial amount of **7a** had isomerised to a 1:4 mixture of **7b** and **7c**, indicating that at this temperature boat isomer **7a** (all-cis) is slightly more stable than diamond isomer **7c** (ctt), leaving chair isomer **7b** (ctt) as the thermodynamically least stable isomer.

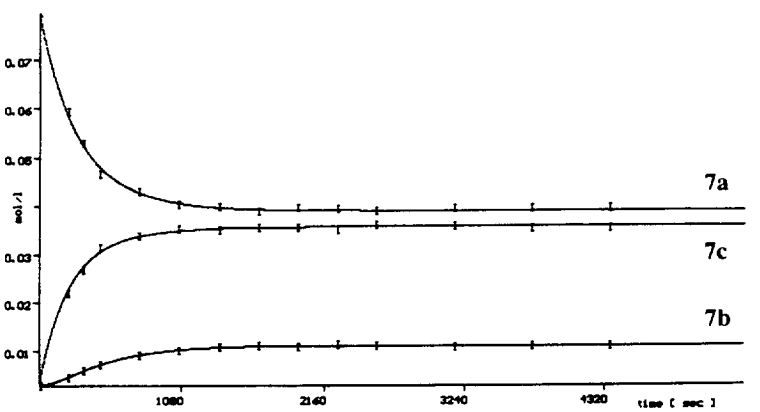


Figure 1. *Time-concentration curve for the isomerisation of 7a in a 5% solution of HCl in methanol at 50°C.*[20] Reproduced with permission of the American Chemical Society, copyright 1991.

When the reaction is carried out under *heterogeneous* conditions, the product ratio at equilibrium is mainly determined by the relative solubilities of the different isomers in the reaction solvent. This is illustrated by the reaction between resorcinol and benzaldehyde in a mixture of ethanol and concentrated HCl (4:1, v/v) at 75°C.[29] Both isomers **10a** and **b** (Chart 4, R_1=C_6H_5) precipitated during the reaction, but isomer **10c** could not be detected. The formation and degradation of boat isomer **10a** (all-cis) and chair isomer **10b** (ctt) were studied as a function of reaction time as is shown in **Figure 2**. While the total yield and the yield of boat isomer **10a** increased during reaction, the yield of the initially formed chair isomer **10b** reached a maximum after 1 hour and then decreased. The final product consisted only of least soluble isomer **10a**, proving once more that formation of products is reversible under acidic reaction conditions. This was confirmed in a separate set of experiments in which a suspension of chair isomer **10b** (ctt) was treated under conditions similar to those used for its synthesis. After 5 hours, 80% of the material recovered was an equimolar mixture

of boat isomer **10a** and chair isomer **10b**. After 10 hours, all recovered material (80%) consisted only of boat isomer **10a**. After a similar treatment of boat isomer **10a** for 20 hours, 87% of unchanged starting material was recovered.

These results show that, under heterogeneous reaction conditions, precipitation of the least soluble isomer serves as a thermodynamic sink, driving the reaction towards formation of one macrocyclic product.

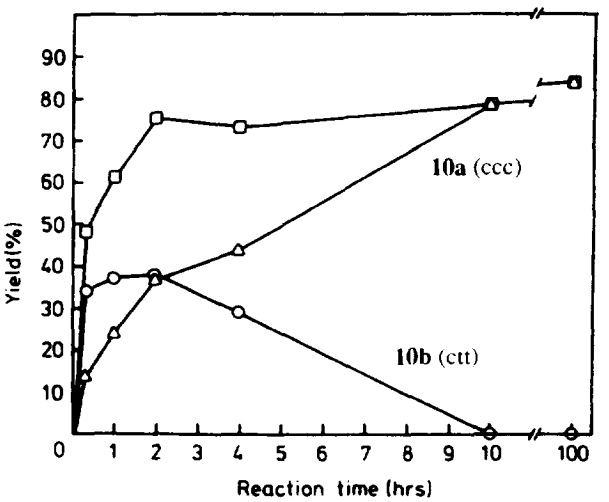
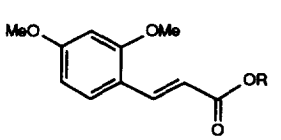


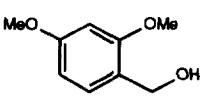
Figure 2. *Yields of all-cis boat isomer **10a** (○) and ctt chair isomer **10b** (△) and total yield (□) as a function of reaction time in the condensation reaction between resorcinol and benzaldehyde in a mixture of ethanol and concentrated HCl (4:1, v/v) at 75°C.*[29] Reproduced with permission of the American Chemical Society, copyright 1980.

2.2 OTHER TYPES OF CONDENSATION REACTIONS

Another high-yield synthesis of resorcinarenes involves the Lewis acid-catalysed tetramerisation of 2,4-dimethoxycinnamates. Treatment of *(E)*-2,4-dimethoxycinnamic acid methyl ester **13** with $BF_3 \cdot Et_2O$ in $CHCl_3$ at room temperature for 15 hours gave the corresponding octamethylated resorcinarene in 75% yield, as a 3:2 mixture of boat isomer **15a** (all-cis) and diamond isomer **15c** (cct) (Chart 4).[15]



13 R=CH_3
14 R=$CH(CH_3)_2$



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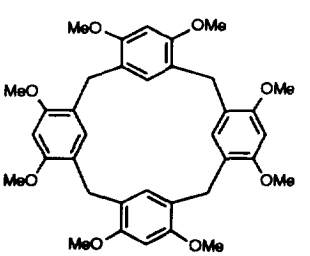


18

Chart 5

A similar treatment of isopropyl ester **14** yielded, in addition to boat isomer **16a** and diamond isomer **16c**, a third isomer **16d** [R_1=$CH_2C(O)OCH(CH_3)_2$], in which the ring adopts a saddle (D_{2d}) conformation with the substituents in an all-cis arrangement. Saddle isomer **16d** seems to be a *conformational* isomer of boat isomer **16a**, but is stable in refluxing xylene (130°C), while it readily converts to the thermodynamically more stable boat isomer **16a** in the presence of 2 equivalents of BF_3•Et_2O, even at room temperature. The conformational change from saddle to boat requires the aliphatic chains to pass between the methoxy groups of neighbouring resorcinol rings, a process which is too unfavourable in case of saddle isomer **16d**. This means that saddle isomer **16d** is conformationally locked by the bulky isopropyl groups and for this reason it can be isolated. In case of methyl ester **13**, saddle isomer **15d** is most probably formed as well, but cannot be isolated because of rapid conversion of this isomer to the thermodynamically more stable boat isomer **15a**.[15]

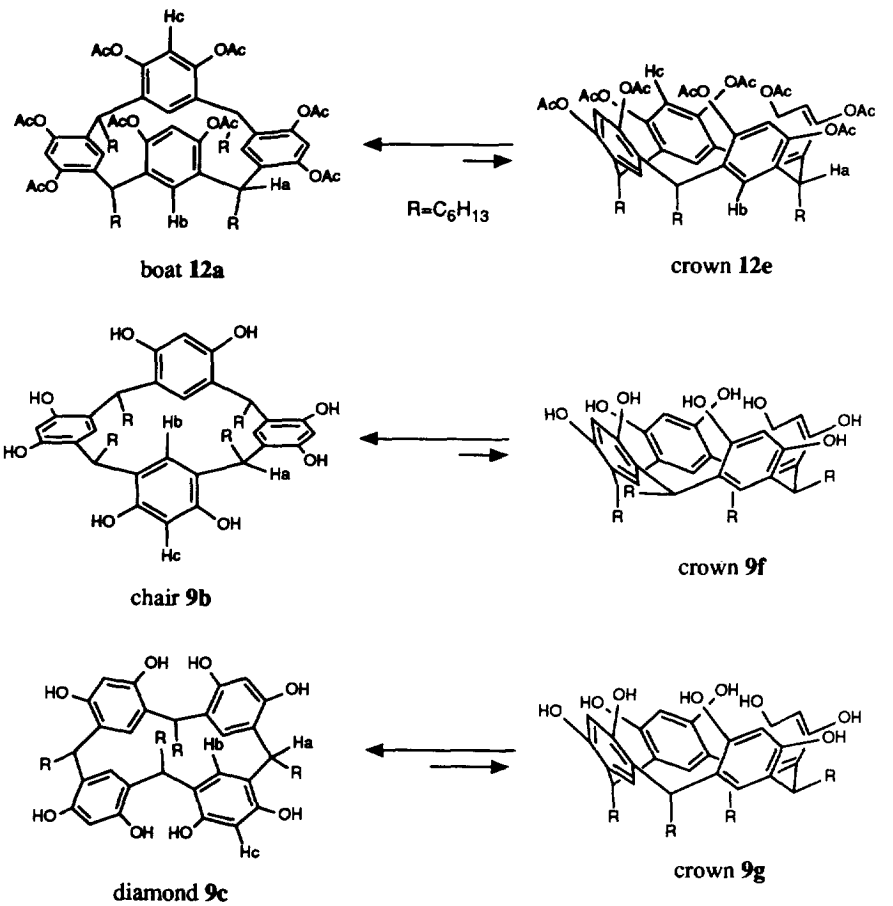
When 2,4-dimethoxybenzyl alcohol (**17**) is treated with trifluoroacetic acid (5% in $CHCl_3$), resorcinarene **18** is obtained in 95% yield.[16] Resorcinarene **18** cannot be synthesised by the acid-catalysed condensation of resorcinol and formaldehyde, since this reaction only gives polymeric products.[7,30] Because of the absence of alkyl chains at the methylene bridges, resorcinarene **18** is conformationally flexible (*vide infra*). Different isomers can therefore not be isolated.

3. CONFORMATIONAL PROPERTIES

The dynamic behaviour in solution of free resorcinarenes **8-10** and the corresponding octaester derivatives **11**, **12**, and **19** has been studied by several groups.[28,29,31]

The ^{1}H NMR spectrum of octaacetate **12a** (R_1=C_6H_{13}) in acetone-d_6 recorded at ambient temperature shows a single resonance for H_a, H_b, and H_c (Scheme 2).[28] However, at -60°C, H_b is split into two broad peaks. H_c becomes very broad, while H_a remains unchanged. These data are in agreement with two rapidly interconverting boat conformations with C_{2v} symmetry, giving an averaged crown-like structure (**12e**) with C_{4v} symmetry (Scheme 2). For the octabutyrates **11a** (R_1=4-BrC_6H_4) and **19a** (R_1=C_6H_5), which show a similar conformational equilibrium, the barrier for interconversion between the two boat conformers is much higher (T_c = 105°C and 102°C respectively).[29] This is most probably caused by the presence of longer ester chains or more bulky aromatic R_1 groups. Spectral changes corresponding to a rotation through the annulus process were not observed for any of the boat-like octaesters. The ^{1}H NMR spectra of octaester chair isomers **11b** (R_1=4-BrC_6H_4), **12b** (R_1=C_6H_{13}), and **19b** (R_1=C_6H_5), and diamond isomer **12c** (R_1=C_6H_{13}) did not show any changes over a temperature range of -60°C to 120°C, indicating that these structures are very rigid.

The free resorcinarenes **9a-c** were studied both in acetone-d_6 and DMSO-d_6.[31] In both solvents, boat isomer **9a** (all-cis) is exclusively present in the crown conformation and interconversion to other ring conformations was not observed. Even at -60°C, the ^{1}H NMR spectrum is still in accordance with a crown-like structure with C_{4v} symmetry, which indicates that removal of the acetyl groups either dramatically decreases the energy barrier



Scheme 2

for interconversion between identical boat isomers or makes the crown conformer thermodynamically stable.

While in DMSO-d_6 the ^{1}H NMR spectra of **9b** and **c** are similar to those of the corresponding octaester derivatives, the spectra in acetone-d_6 are more complicated. In this solvent, chair conformer **9b** (all-axial, ctt) is in equilibrium with crown conformer **9f** (Scheme 2). This conformer has two adjacent equatorial substituents, which proves that both structures equilibrate exclusively via ring inversion of one of the rings perpendicular to the mean plane of the macrocycle. Diamond isomer **9c** (all-axial, cct) equilibrates in acetone-d_6 with crown conformer **9g**, having one substituent in an equatorial position. This indicates that both isomers equilibrate via ring inversion of the two aromatic rings connected via the methylene bridge carrying the trans substituent. The $\Delta G^{\neq}$ for the inversion process was determined as 80.5 ± 1kJ·mol^{-1} at 55°C. When the acetone-d_6 solution of **9c/9g** was evaporated and the residue dissolved in DMSO-d_6, only diamond conformer **9c** was observed.

These results show that the preference for a certain conformation in case of resorcinarene **9** is governed mainly by two effects. First of all, conformations with the maximum number of hydrogen bonds are preferred. Secondly, axial orientations of substituents are strongly favoured over equatorial orientations. In polar solvents particularly, the axial substituents interact favourably with each other and the alignment of four substituents minimally disrupts a highly ordered solvent structure.[10] Moreover, equatorial substituents may sterically interact with the adjacent pair of phenolic hydroxyl groups.[20] In boat isomer **9a**, both effects contribute to stabilise this conformation. In chair isomer **9b** and diamond isomer **9c**, the effects oppose each other, leading to mixtures of conformations in which crown conformers have the maximum number of hydrogen bonds at the expense of one or two equatorially positioned substituents.

The two effects mentioned above probably also play an important role in determining which isomer is formed preferentially during the acid-catalysed condensation reaction. The exclusive formation of the boat isomer (all-cis) in reactions of simple aliphatic or unsubstituted aromatic aldehydes under heterogeneous conditions seems to endorse this statement, but steric or electronic factors cannot be neglected either as is evident from the reaction of resorcinol with *p-tert*-butyl- and *p*-cyanobenzaldehyde (Table 1), in which the chair isomer (all-axial, ctt) is the only isomer formed.[10]

As was mentioned before, resorcinarenes derived from formaldehyde (see Table 1) are conformationally mobile.[19,32] In apolar solvents, their ^{1}H NMR spectra show an AB quartet for the methylene protons at low temperature, which coalesces at higher temperatures.[33] These spectral features are explained, as reported for calix[4]arenes,[34] by the presence of two rapidly interconverting cone conformers. In polar solvents like pyridine, the saddle conformation seems to be the most stable conformation since hydrogen bond formation between neighbouring phenol rings is disrupted by the solvent.[32]

4. LIQUID CRYSTALLINE BEHAVIOUR

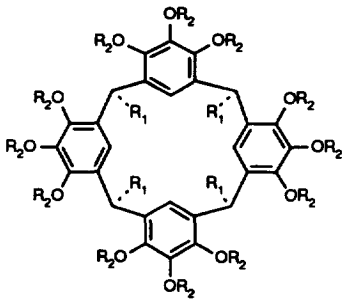
Resorcinarenes that are fixed in the boat conformation have a three dimensional bowl-like shape, which gives them the ability to self-organise in ferroelectric (head-to-tail) or anti ferroelectric (head-to-head, tail-to-tail) columnar arrangements.[35] Their liquid crystalline properties have been studied in detail.[26,36] Particular interest in such columnar mesophases originates from their potential ferroelectricity when all the columns are oriented in the same direction.

Resorcinarenes become liquid crystalline when the following requirements are met:[37]

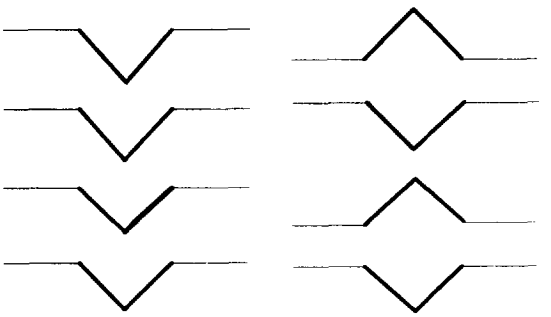
(i) Small R_1 groups (see Chart 6, maximum R_1=CH_3) to allow an optimal core stacking

(ii) The presence of at least twelve linear R_2 side chains, having 12 to 17 carbon atoms each, to cover the periphery of the core in a homogeneous manner

(iii) Ester groups to connect the side chains to the periphery, without bulky substituents close to the macrocyclic core.



20 R_1=CH_3, R_2=$C(O)C_3H_7$
21 R_1=H, R_2=$C(O)C_nH_{2n+1}$



ferroelectric anti-ferroelectric

Chart 6

Single crystal X-ray data of dodecabutyrate **20** reveal that the molecules are oriented in an anti ferroelectric arrangement, most probably as a result of the large dipole moment, which is calculated as 10.3D (based on X-ray data) for the monomer and almost zero for the anti ferroelectric pair.[35] Dodecaesters of type **21**, which have a conformationally mobile macrocyclic core, already exhibit liquid crystalline behaviour with 9-12 carbon atoms in the R_2 side chains.[19] In this case, the presence of a fast ring-inversion process overcomes the constraint for anti ferroelectric coupling of the molecules within the columns. In this way, the mesogens should be able to align their dipoles freely under the influence of an electric field.

5. COMPLEXATION OF CATIONS

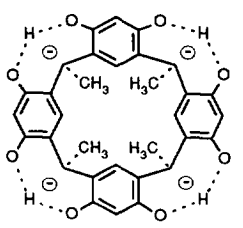
Resorcinarenes are highly soluble in aqueous basic solutions because of deprotonation of the phenolic hydroxyl groups. However, the first four protons are much more acidic than the last four. In NaOD solutions, boat isomer **7a** (R_1=CH_3, all-cis) is exclusively present as tetraphenolate **22**.[38,39] Potentiometric titrations have shown that the pK_a values for the first four protons are lower by two units than the pK_a of resorcinol, while the last four protons cannot even be removed with a strong base like $NaOCH_3$. The stability of tetraphenolate **22** is a result of the ideal geometric disposition of the O-H-O arrangement[40] and the possibility of delocalisation of the negative charges.

Tetraphenolate **22** binds methyl trialkylammonium cations with spectacularly high binding constants ($K \approx 3x10^4M^{-1}$ in 0.5N NaOD),[38,39,41] exceeding the corresponding constants in biological systems.[42] The strength of binding is only moderately affected by changing the ionic strength[38] or solvent polarity,[43] but decreases strongly when the length of the alkyl groups increases (Figure 3), indicating that the interaction is based almost exclusively on electrostatic attraction between the positively charged R_3N^+Me and negatively charged **22**.[44] The small association constant for *tert*-butylphenol ($K = 7M^{-1}$ in 0.5N NaOD) proves that electroneutral molecules are hardly complexed.[45] Recently, it was shown that

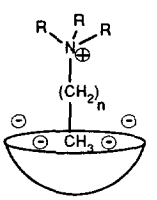
neutral resorcinarenes are also able to complex alkylammonium cations, as was proved by a single X-ray crystal structure.[46]

The affinity of **22** for methyl ammonium cations is especially interesting in the case of acetyl choline (**24**). The binding and hydrolysis of this neurotransmitter in the synapses is an important step in the transmission of nerve signals.[47] The non-enzymatic hydrolysis of acetyl choline is strongly accelerated by the positively-charged ammonium substituent because it is located in close proximity to the reaction centre, in this way stabilising the negative charge developed during hydrolysis.[42] In the presence of **22**, the rate of hydrolysis of acetyl choline is decreased by a factor of 10.[48] This effect can be attributed to the strong affinity of **22** for the positively charged ammonium substituent (K_a for acetyl choline in 0.5N NaOD is 50,000M^{-1}) resulting in an attenuation of the known acceleration effect.

Pyrene-modified *N*-alkylpyridinium cations are also complexed by tetraphenolate **22** with association constants similar to that of acetyl choline. As a result, the orange fluorescence of these pyridinium dyes is strongly quenched. Inouye and co-workers found that such non-fluorescent complexes could be used as optical sensors for the detection of acetyl choline, since fluorescence was regenerated after addition of acetyl choline to a solution of the non-fluorescent complex, something that was not observed for any other neurotransmitter.[49]

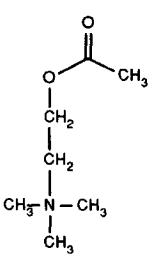


22

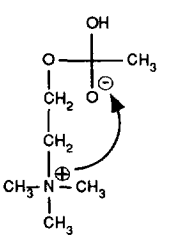


23

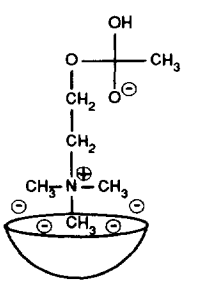
R	K (M^{-1}) for **23** in D_2O (0.5 N NaOD)
CH_3 (n=0)	29 000 ± 6 000
C_2H_5 (n=1)	3 500 ± 400
C_3H_7 (n=2)	32 ± 5
C_4H_9 (n=3)	<2



24



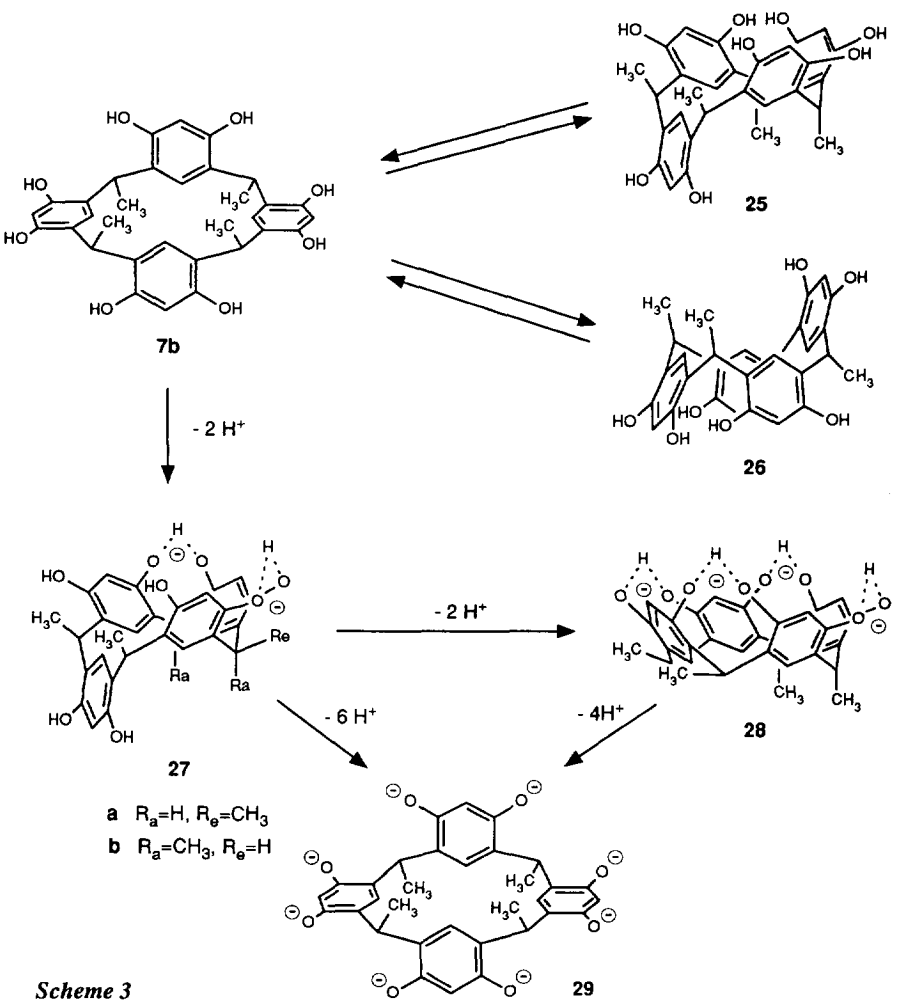
T.S. for hydrolysis of **24** is stabilised by N^+ neighbouring group



T.S. for hydrolysis of **24** is destabilised because of neutralisation of N^+ by **22**

Figure 3. *Association constants of several methyl trialkylammonium complexes **23**. The high affinity of tetraphenolate **22** for the tetramethylammonium cation is used for the inhibition of acetyl choline (**24**) hydrolysis.*

In comparison to boat isomer **7a** (all-cis, Chart 4), chair isomer **7b** (all-axial, ctt) shows an entirely different behaviour upon the addition of NaOD.[39] The ^{1}H NMR spectrum of the electroneutral form, having six signals, is in accordance with structure **7b** or with a rapid equilibrium between the two identical "partial cone" conformers **25** and **26** (see Scheme 3). Addition of up to 3.5 equivalents of NaOD changes the spectrum considerably, now having ten signals, and further addition of NaOD up to 76 equivalents finally gives a spectrum with six signals. Schneider et al.[39] explain the first spectral changes originating from a two-fold deprotonation leading to "partial cone" dianion **27a** having two *equatorial* substituents. This structure does not show further deprotonation upon the addition of NaOD, until finally at 76 equivalents it is fully deprotonated to give **29**. However, studying this conformational change with CPK models showed that, in going from **7b** to **27**, the substituents on the bridges connecting the three upwardly oriented rings do not change their individual orientation from *axial* to *equatorial*. For this reason, formation of dianion **27a** is impossible and it must be concluded that dianion **27b** is formed.



Scheme 3

Compound **27b** can form only two intramolecular hydrogen bonds, whereas isomerisation to **28**, concomitant with loss of another two protons, would lead to formation of four intramolecular hydrogen bonds. This conformation has been observed under neutral conditions (*vide supra*) by Dalcanale et al.[31] and its geometry is in agreement with the ^{1}H NMR spectrum observed at this pH.[39] Although **28** has two equatorially-positioned methyl groups, it is not expected to be energetically unfavourable, especially not in the presence of 3.5 equivalents of NaOD. Moreover, complexation of tetramethylammonium cations by **27**, which was not observed under neutral or strongly basic conditions, is much more likely to occur in crown conformer **28**, bearing in mind the strong affinity of similar conformations for tetramethylammonium cations. Taking all this into account, it must be concluded that in basic solutions isomer **28** is present to a considerable extent.

Very recently, the selective extraction of caesium ions from slightly basic aqueous solutions into benzene solutions containing small amounts of **7a** was reported.[50] Although the structure of the 1:1 complex was not discussed, it seems likely that the caesium ion is located in the hydrophobic cavity[51] and shows a better fit than the other alkali cations, thus explaining the selectivity for complexation.

6. COMPLEXATION OF POLAR ORGANIC MOLECULES

The presence of eight hydroxyl groups at the upper rim of resorcinarenes makes these molecules suitable for complexation of organic molecules that contain polar substituents. Aoyama et al. were the first to recognize this feature half a decade ago and have studied this phenomenon extensively.[52,53]

Resorcinarenes carrying long alkyl chains, like **30**, are readily soluble in apolar, organic media such as CCl_4 and $CHCl_3$. From the large shift for the OH protons in the ^{1}H NMR spectrum (≈4 ppm downfield) and in the IR spectrum (350 cm^{-1} shift to lower wave number) compared to those in 4-undecylresorcinol, it can be concluded that the OH groups are hydrogen bonded.[54] The 1:4 stoichiometry of both the glycerol and the H_2O complex strongly suggests that each pair of hydroxyl groups forms a binding site, and that four such binding sites, occupying a fixed position with respect to each other, independently interact with small polar guests.[21] In complexation studies of molecules that are able to interact with several of such binding sites, remarkable selectivities were observed.

Complexation studies with several cyclohexanediols showed that, of all possible isomers, *cis*-1,4-cyclohexanediol is bound most tightly ($K \approx 10^3 M^{-1}$ in $CDCl_3$ at 25°C), with a *cis/trans* selectivity of 8.[55] The associated free energy of complexation (ΔG_{compl} = -4.11kcal mol^{-1}) is more than two times that of the corresponding mono-ol, cyclohexanol (2 ×-1.42 = -2.84kcal mol^{-1}). Open chain diols are also bound less strongly, emphasising the importance of preorganisation.[56] The *cis/trans* selectivity arises from the perfect geometrical arrangement (one equatorial, one axial) of the two hydroxyl groups in the *cis* isomer. This permits two-point interaction with the host, while in the complex with the *trans* isomer the axial hydrogens of the guest would severely interact with the aryl ring of the host connecting the two binding sites.

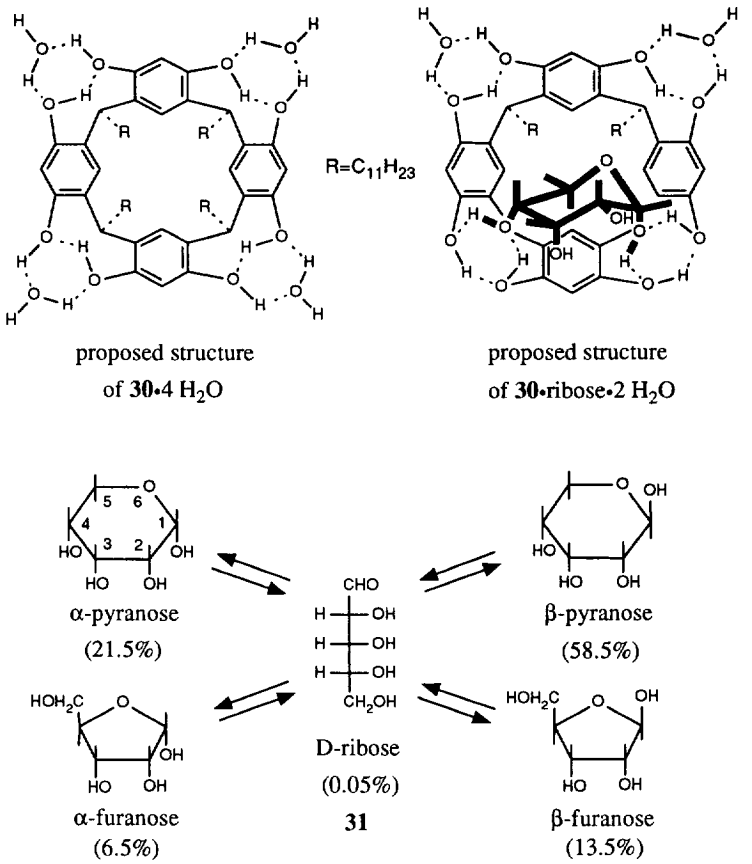


Figure 4. *Proposed structure of the 30•4H_2O complex and the 30•ribose•2H_2O complex in which ribose in complexed selectively in the α-pyranose form.*

The observed 1,4-*cis* selectivity also seems to play an important role in the complexation of sugars.[21] D-Ribose (**31**), a polyhydroxy pentaldehyde (aldopentose) that exists in two cyclic pyranose (six-membered) or two furanose (five-membered) forms (Figure 4) and is virtually insoluble in CCl_4, was readily extracted from a concentrated aqueous solution (5.5M) by a solution of host **30** in CCl_4. This indicates that host-ribose interactions compete favourably with ribose-H_2O and host-H_2O interactions. Extensive NMR investigations showed unambiguously that ribose is complexed *exclusively in the α-pyranose form,*[21b] the only isomer having a *cis* orientation of hydroxyl groups on C-1 and C-4.[57] Extraction experiments with several other related sugars showed that fucose and 2-deoxyribose are even more readily extracted than ribose itself and that xylose is not extracted at all, although it only differs in the configuration at C-3. This reveals the importance of several other structural factors:

(i) A *cis* relation between the C-3 and C-4 OHs is crucial for extraction since a *trans* 3-OH suffers from unfavourable interactions with the aryl ring connecting the two binding sites

(ii) The OH at C-2 is not primarily responsible for binding and should be *cis* to the C-3 and C-4 OHs, as in ribose, or otherwise absent, because it leads only to unfavourable exposure of sugar OH groups to the apolar solvent

(iii) The substituent at C-5, which interacts only with the apolar solvent, should be as hydrophobic as possible, in this way determining the strength of complexation.

From complexation studies of **30** with a variety of different mono-ols, Aoyama et al.[58] found that, in addition to hydrogen bonding as a driving force for complexation, the interaction between an aliphatic moiety in the guest and the electron-rich aromatic rings in the host (CH-π interaction)[59] contributes up to 1.4kcal mol^{-1} to the overall free energy of binding. Evidence for this interaction was found by ^1H NMR spectroscopy which shows upfield shifts for bound guest that are the highest ($\Delta\delta \approx 3$ for borneol) for the terminal methyl group, indicating a deep penetration of this group into the aromatic cavity. The importance of the CH-π interaction gradually increases with increasing chain length or branching of the aliphatic moiety. The carbonyl of an acetyl group considerably increases the acidity of the terminal methyl group, resulting in more favourable CH-π interactions. Guest molecules containing *exclusively* acetyl groups (e.g. borneol acetate) already show complexation with host **30**, although it cannot be ruled out that, in this case, the carbonyl group might be involved in hydrogen bonding with (one of) the hydroxyl groups of the host.

The complexation behaviour of resorcinarenes has also been studied in aqueous systems.[22,60] In the absence of hydrogen bonding as a driving force for complexation, the affinity of tetrasulphonate **32** for polar guests seems to be governed mainly by hydrophobic interactions,[22] resulting in a complete reversal of selectivity in the complexation of sugars. In particular, CH-π interactions[59] play an important role in the binding of hydrophobic molecules. The enhanced affinity of the more hydrophilic resorcinarene **33** for almost all substrates investigated is most probably the result of the increased π-electron basicity of the host.

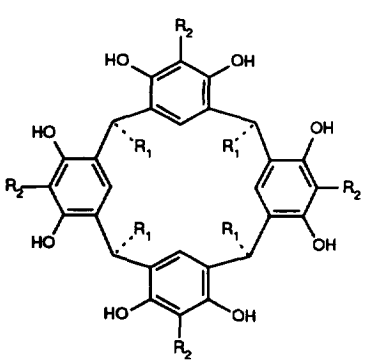


Chart 7

32 $R_1=(CH_2)_2SO_3Na$, $R_2=H$

33 $R_1=(CH_2)_2SO_3Na$, $R_2=OH$

The presence of host **30** can induce remarkable selectivities in the chemical derivatisation of sugars.[61] Glycosidation of ribose, usually carried out by treating a mixture of sugar and methanol with HCl or H_2SO_4,[62] proceeds smoothly in CCl_4 in the absence of additional acid when **30** is present. In this reaction, host **30**, acting as an acid catalyst, plays an important role in the stabilisation of charged intermediates and is responsible for the highly selective formation of the β-anomer. This suggests that the sugar moiety is bound strongly to host **30**, thus preventing methanol from attacking from the α-face.[61a]

Complexes of host **30** with chiral guests exhibit induced Circular Dichroism (CD) with split Cotton effects from which the sign is directly related to the chirality of the guest.[63] Circular Dichroism is specific to chiral molecules that possess two or more chromophoric units, the exciton coupling of which results in split Cotton effects.[64] Since the multi-benzenoid host **30** is achiral but chromophoric and the guest is chiral but non-chromophoric, their complex is (induced) CD active, the exciton coupling arising from an asymmetric interaction of the chiral guest with the aryl rings. This means that host **30** can be used as a supramolecular probe for the stereochemical assignment of a variety of chiral guests, including sugars and steroids.[58,63]

Host **30** complexes methyl and *n*-octyl glucopyranosides via hydrogen bonding in apolar media. In the case of the methyl derivative in $CHCl_3$, a 2:1 (host to guest) sugar-encapsulation complex with a remarkable β/α anomer selectivity was found. On the other hand, the octyl glucoside is bound to host **30** to give a 1:4 (host to guest) complex with only a low anomer selectivity. The four guest molecules are bound at the four unit hydrogen-bonding sites of the host with an exceptionally high cooperativity that arises from intracomplex guest-guest hydrogen bonding involving the 5-CH_2OH and 2-OH groups of the adjacent glucoside molecules.[65] From a series of octyl glycoside derivatives of various monosaccharides, it followed that this cooperative binding involving sugar-sugar interaction is specific for the glucose derivative.[66]

Several detection systems consisting of monolayers of host **30** assembled at the air-water interface or supported on solid supports like SnO_2[67] or Au,[68] make use of the stereoselective complexation of sugars by host **30**. In case of electrochemical detection, a remarkably high sensitivity was reached. Ribose at concentrations as low as 4.2×10^{-5}M in water could be detected.[53b,67a] However, the selectivity for the binding of ribose over other sugars at the air-water interface is considerably different from that observed in CCl_4 solutions. Fucose, which is readily extracted in CCl_4, is only moderately bound at the interface, whereas sugars that are not extracted in CCl_4, like galactose and arabinose, provide significant affinities at the interface.[67a]

The complexation of amino acids by resorcinarenes has only been studied in water.[60] Amino acids with polar side chains exhibit no affinity for **32** or **33**. Only the more hydrophobic amino acids, carrying aliphatic or aromatic side chains, have been complexed with binding constants up to $70M^{-1}$. As in previous cases, complexation is not simply a result of the hydrophobic effect[69] but there is a substantial contribution of CH-π interactions (*vide supra*).

Dicarboxylic acids also form complexes with resorcinarene **30** in $CDCl_3$ via a two-point hydrogen bonding interaction.[70] Interestingly, the free energy of binding is strongly dependent on the length of the carbon spacer separating the two carboxylic end groups, once more emphasising the rigid structure of the host. Glutaric acid (C_3-spacer, $K = 1.2x10^{-5}M^{-1}$) is most strongly bound, exhibiting a high selectivity over pimelic acid (C_5-spacer, $K_{glut}/K_{pim} = 105$).

Recently, the complex formation of **30** with triethylamine and [2.2.2] cryptand was detected using conductometry.[71] The stoichiometry was established to be 1:3, but further details were not disclosed. Resorcinarenes **2** (R_1=CH_3, C_2H_5, *n*-C_3H_7, *n*-C_9H_{19}; R_2=H) form 1:1 complexes with caffeine in methanol containing 1% of water via hydrogen bond formation with the O(6) carbonyl oxygen of caffeine.[72]

7. FUNCTIONALISATION OF RESORCINARENES

The presence of two electron-releasing hydroxyl groups on the aromatic rings of resorcinarenes makes them highly activated for electrophilic aromatic substitution reactions. Several examples of substitution reactions at the four positions in between the hydroxyl groups have been reported.

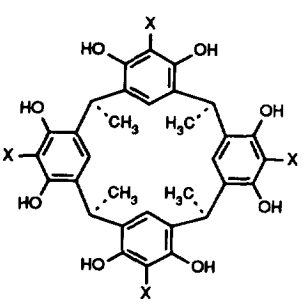
Bromination[11,73] with *N*-bromosuccinimide (NBS) at room temperature gives tetrabromide **34** (Chart 8) in 80% yield. The reaction takes place *exclusively* at the four positions in between the hydroxyl groups without affecting other positions in the molecule, even when excess NBS is used.

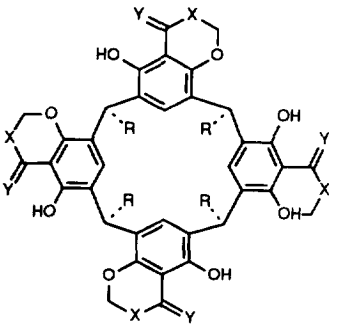
Diazo coupling of octol **7** (R_1=CH_3) with 4 equivalents of p-sulfonatebenzenediazonium affords tetradiazonium salt **35** in 29% yield. The product is water-soluble and has a large, extended cavity able to complex hydrophobic molecules like pyrene and coronene.[74]

Several aminomethylated resorcinarenes have been synthesised in high yields (59-83%) by a Mannich reaction of **7** with formaldehyde and a secondary amine.[12,75,76] This reaction can also be performed with amines carrying functional groups in their side chains to give **36** and **37**. In case of **37**, the product is chiral ($[\alpha]_D^{20} = -33.7°$) and water soluble, even in neutral aqueous solutions. Recently, Aoyama et al. showed that this type of optically active compound can be used as an alternative for lanthanide chiral NMR shift reagents.[77]

When the reaction is carried out with primary amines, the resulting secondary amine reacts intramolecularly with one of the phenolic hydroxyl groups at the *ortho* positions, and a second equivalent of formaldehyde gives rise to the formation of four 1,3-oxazine rings, as in **38**. As the macrocycle is conformationally rigid, this compound should be chiral, but this was not explicitly mentioned in the paper.

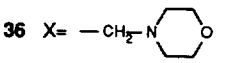
Tetralactone **39**, a closely related macrocycle, was obtained from a base-catalysed saponification reaction with tetraester **48** (Chart 10) and subsequent acidification in 18% yield.[78c] The reason for this unusual rearrangement is presumably the ideal positioning of the carboxyl groups to assist in acid-catalysed ring opening of four eight-membered rings and formation of four six-membered rings.

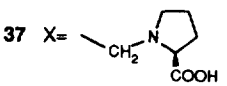




34 X=Br

35 X=p-$N_2C_6H_4SO_3Na$





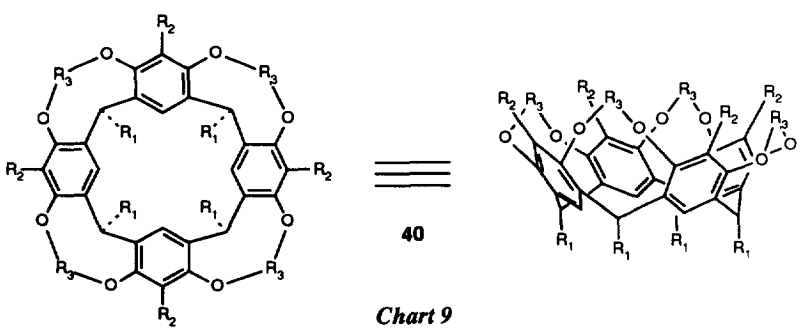
38 R=CH_3, X=NPh, Y=H_2

39 R=CH_2CH_2Ph, X=Y=O

Chart 8

8. CAVITANDS

A great deal of literature has been devoted to the use of resorcinarenes as starting materials in the synthesis of a new family of *cavitands* (**40**).[79] The name *cavitands* was given in 1982 by Cram[73] to the class of synthetic organic compounds that contain an enforced concave cavity sufficiently large to accommodate other molecules or ions. The concave surface permits the positioning of different functional groups that converge on the substrate-binding site that is usually located inside the cavity.[80] As an excellent book by Cram appeared very recently reviewing cavitands and (hemi)carcerands,[79] in this section only the highlights of the work of Cram and coworkers will be described.



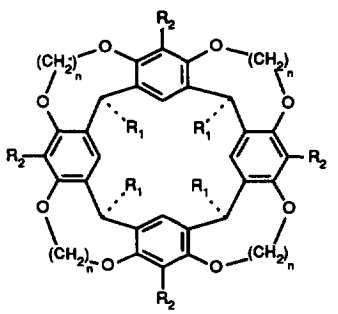
40

Chart 9

Cavitands of type **40** are generally synthesised by covalent linkage of neighbouring phenolic hydroxyl groups in the corresponding octols. They are particularly attractive because the rims of the bowls can be varied by different R_2 substituents and bridging groups R_3 for shaping the bowl cavity and for manipulating the solubilities of the cavitands, or for introducing potentially cooperating functional groups to act as catalysts.

8.1 ALKYLENEDIOXY-BRIDGED CAVITANDS

The first synthesis of a cavitand was reported in 1982.[73] Treatment of boat isomer **7a** (all-cis) with excess CH_2BrCl and base in a mixture of DMSO and DMF gave cavitand **41** in 23% yield.[11] However, the use of resorcinarenes with bromine atoms or methyl groups at the 5,11,17 and 23-positions (see Chart 1) gave much higher yields (**42** in 55%, **43** in 63% respectively), most probably because of the increased stability of the phenoxy anions under the reaction conditions used. Generally, DMSO-Cs_2CO_3 gave the best results in the reactions described.[81] In our hands, DMF gave the highest yields of cavitands (up to 73%), whereas reactions in DMSO mostly stopped at the stage of the tri-bridged resorcinarene (**44**, 52% yield).[82] A remarkably high selectivity for formation of A,C-di-bridged resorcinarene **45**[83] was observed in these reactions. Interestingly, only A,B-di-bridged resorcinarene **46** was formed in reactions with resorcinarenes lacking the bromo substituents at the 5,11,17 and 23-positions.[84] Partially-bridged resorcinarenes have been used for the synthesis of C- and Z-shaped cavitands,[84] as monodentate ligands for transition metals,[85] and in combination with upper rim functionalised calix[4]arenes.[86]



R_1=CH_3, n=1

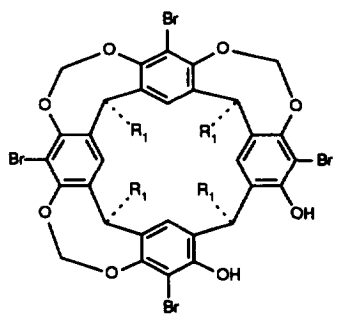
41 R_2=H
42 R_2=Br
43 R_2=CH_3
47 R_2=I
48 R_2=C(O)OCH_3
51 R_2=CH_2OH
52 R_2=CH_2Cl
53 R_2=CH_2SH
54 R_2=CH_2Br

R_1=CH_2CH_2Ph, n=1

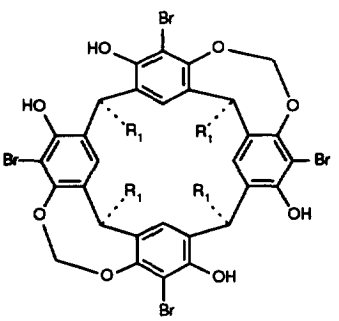
49 R_2=OH
50 R_2=CHO

n=2,3

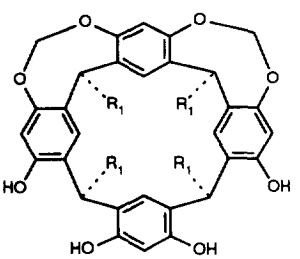
62 R_1=CH_3, R_2=Br



44 R_1=CH_2CH_2Ph



45 R_1=CH_2CH_2Ph



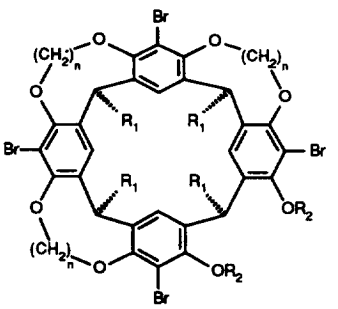
46 R_1=C_5H_{11}

Chart 10

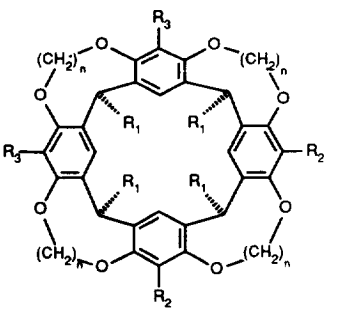
An advantage of cavitands carrying bromo substituents at the 5,11,17 and 23-positions is the possibility of substituting these atoms with other functional groups. Treatment of tetrabromocavitands, like **42**, with *n*-BuLi at -70°C followed by quenching the lithiated

product with an appropriate electrophile, gives access to cavitands with functional groups that are not compatible with the reaction conditions for resorcinarene or cavitand formation.[10] Cavitands carrying iodo (**47**),[11] carboxylic ester (**48**),[87] hydroxyl (**49**)[88] or aldehyde (**50**)[78a] groups were synthesised in this way. These cavitands give easy access to other functionalised cavitands, e.g. by reduction of tetraester **48** to give tetrol **51**, which can be chlorinated with NCS to give tetrachloride **52** and subsequently thiolated to give tetrathiol **53**.[87] Recently, a different route for the synthesis of functionalised cavitands was described by Sorrell et al.[89] Treatment of cavitand **43** with NBS and a catalytic amount of benzoyl peroxide gave tetrakis(bromomethyl) derivative **54** in 67% yield. The novelty of the reaction lies in the selective functionalisation of the methyl groups, while the theoretically more reactive isopropyl substituents are unaffected.[89]

Two routes for the selective functionalisation of cavitands were developed, both using a tri-bridged resorcinarene as a key intermediate. Sorrell et al. reported the Claisen-rearrangement of diallyl ether **55** to give cavitand **56**, bearing two 1-propenyl groups and two bromine atoms, in 75% yield over two steps.[90] A different route exploring the selective debromination of tri-bridged resorcinarene **57** was developed in the Reinhoudt group. The remaining two bromine atoms could be substituted by a variety of other functional groups after incorporation of the last bridge. In this way, cavitands **58-61** were synthesised in 60-95% yield.[82,91]



55 R_1=CH_3, R_2=$CH_2CH{=}CH_2$, n=2
57 R_1=$C_{11}H_{23}$, R_2=H, n=1



56 R_1=CH_3, R_2=$CH{=}CHCH_3$, R_3=Br, n=2
58 R_1=$C_{11}H_{23}$, R_2=Br, R_3=H, n=1
59 R_1=$C_{11}H_{23}$, R_2=$C(O)OCH_3$, R_3=H, n=1
60 R_1=$C_{11}H_{23}$, R_2=CN, R_3=H, n=1
61 R_1=$C_{11}H_{23}$, R_2=OH, R_3=H, n=1

Chart 11

Compared to the parent resorcinarenes, cavitands are extremely rigid molecules. They adopt a crown-like conformation with C_{4v} symmetry in the solid state and only slightly deviate from this structure in solution.[11] Compared to methylene-bridged cavitands, ethylene-(**62**, n=2) and propylene-bridged cavitands (**62**, n=3) (see Chart 10) are somewhat more flexible and adopt a boat-like conformation in the solid state.[11]

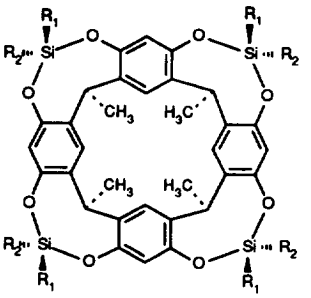
The complexation properties of cavitands have been studied both in the solid state[11,92] and in solution.[92] Most cavitands crystallise as thermally stable solvates (caviplexes) from a variety of solvents. Complementarity is high with guests like CH_3CN, $C_6H_5CH_3$, CH_2Cl_2 and $CHCl_3$, but low with C_6H_6 or cyclohexane. All of these are inclusion complexes, but some contain solvent molecules packed between the inclusion complexes. Most caviplexes could be freed from solvent by heating under vacuum. In case of **42**•EtOAc, the solvent molecule was not removed even after 24h at 180°C and 10^{-5}Torr. Only sublimation of the caviplex at 450°C and 10^{-5}Torr did provide cavitand **42** free of solvent. In the crystal structure of **43**•$(CH_2)_6$•C_6H_5, the cyclohexane molecule is complexed specifically in a *boat* conformation. Boat cyclohexanes are rarely encountered in organic chemistry without additional bridges or substituents. Apparently, the host plays the role usually played by bulky substituents that force cyclohexane into the boat conformation.

Caviplexes **41**•CH_2Cl_2, **42**•$CHCl_3$ and **62**(n=2)•CH_2Cl_2 provide interesting comparisons. In case of tetrabromocaviplexes **42**•$CHCl_3$ and **62**(n=2)•CH_2Cl_2, one chloro substituent penetrates deeply into the cavity in such a way that the C-Cl dipole of the guest is aligned to complement the C-Br dipoles of the host. The absence of the C-Br dipoles in caviplex **41**•CH_2Cl_2 correlates with the absence of a chloro substituent in the cavity of **41**.

A remarkable selectivity for perchloroethylene (C_2Cl_4) over other chlorinated guest molecules was observed for a monolayer of dialkylsulfide-substituted cavitands self-assembled on a gold surface.[93]

8.2 DIALKYLSILICON-BRIDGED CAVITANDS

Treatment of a resorcinarene with the appropriate dialkyldichlorosilanes in THF/NEt_3 at high dilution gave the tetrasilyl derivatives **63-65** in 37%, 9% and 7% yields respectively.[94] The silyl bridges are highly base-sensitive and moderately acid-sensitive. The inner alkyl substituents of the silicon bridges considerably narrow the cavities of **63-65** which therefore can only accommodate slim linear guests. Their complexation behaviour was studied both in the solid state[95] and in solution.[94] From the X-ray crystal structure of the **63**•CS_2 complex (Figure 5) it is evident that the guest molecule is almost entirely encapsulated within the cavitand. In solution, the complexation of linear guests like CS_2, $CH_3C{\equiv}CH$ and even O_2 was observed from ^1H NMR chemical shift changes.[94] The stability of the complexes with CS_2 increases going from **63** to **65**. Determination of the dissociation constants at different temperatures revealed that complexation is enthalpy-favoured and entropy-disfavoured. The existence of a totally organised organic complex with O_2, observed from the broadening of the ^1H NMR spectrum upon saturation of the $CDCl_3$ solution with O_2, is striking considering the importance of the storage and transport of O_2 in biological systems.[96]



63 $R_1=R_2=CH_3$

64 $R_1=R_2=C_2H_5$

65 $R_1,R_2= -(CH_2)_5-$

Chart 12

SIDE VIEW

TOP VIEW

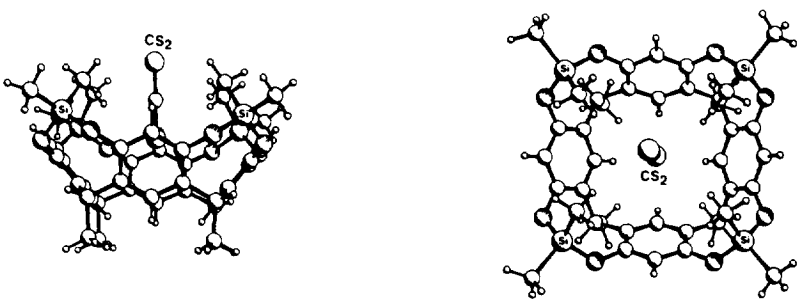
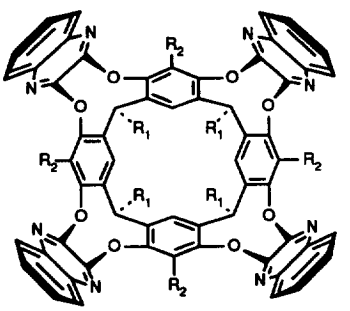


Figure 5. *X-ray crystal structure of complex* ***63***$\cdot CS_2$. Reproduced by permission of Kluwer Academic Publishers, copyright 1986.

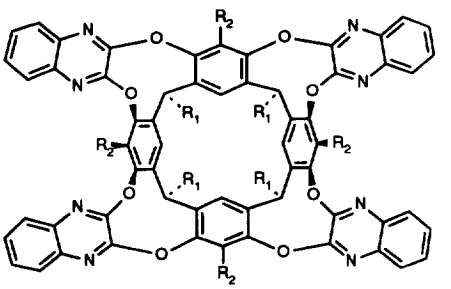
8.3 HETEROPHENYLENE-BRIDGED CAVITANDS

The cavity of resorcinarenes can be largely extended by bridging the phenolic hydroxyl groups with aromatic spacers.[73,97] Using 2,3-dichloroquinoxaline, **66** was synthesised in 37% yield.[98] The quinoxaline spacers can occupy either axial (*a*) or equatorial (*e*) positions. In the vase (*aaaa*) conformer (**66a**), the spacers touch each other via their α-hydrogens while forming a box-like cavity with C_{4v} symmetry which is approximately 7Å wide and 8Å deep.[99a] The cavity is open at the top and closed at the bottom by the cavitand itself. In the kite (*eeee*) conformer (**66b**), the spacers are more or less in the same plane. In order to minimise steric strain with the methyl groups, the spacers rotate slightly and the cavity deforms to a boat-like conformation with C_{2v} symmetry by elongation in one dimension and narrowing in the other. Variable temperature ^{1}H NMR studies with **66** have shown that, at temperatures above 45°C, **66** is exclusively present in the vase (*aaaa*) conformation. On lowering the temperature, the equilibrium starts to shift in the direction of the kite conformer (*eeee*), and at temperatures below -62°C the vase conformer can no longer be detected.[98b] This quite unique conformational behaviour is attributed to the fact that in the kite-to-vase conversion (**66b**→**66a**) several solvent molecules are liberated because the kite conformer is

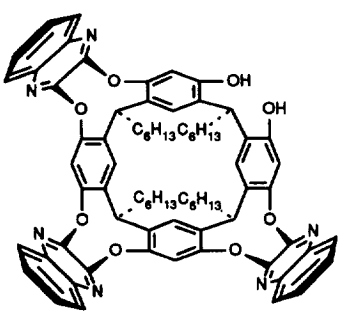
expected to contact more solvent molecules than the vase conformer on account of its more extended surface. This higher degree of solvation in the kite conformation is enthalpy-stabilising but entropy-destabilising.[96] At sufficiently low temperatures, this favourable enthalpy of solvation overrides both the unfavourable entropy of solvation and the greater strain energy in the kite conformation. When the temperature rises, the unfavourable entropy term becomes more important, and at sufficiently high temperature the equilibrium is shifted towards the vase conformer.



a (vase)



b (kite)



72

66 R_1=CH_3, R_2=H
67 R_1=CH_3, R_2=CH_3
68 R_1=CH_3, R_2=C_2H_5
69 R_1=C_5H_{11}, R_2=CH_3
70 R_1=C_5H_{11}, R_2=C_2H_5
71 R_1=C_6H_{13}, R_2=H

Chart 13

Substitution of a methyl or an ethyl group at the 2-resorcinyl positions, as in compounds **67-70**, makes the vase conformation sterically very unlikely, and therefore the molecule exists exclusively in the kite conformation.[98] The ^{1}H NMR spectrum of **68**, in which dimerisation (*vide infra*) is inhibited, is consistent with the kite conformation with C_{2v} symmetry at low temperatures, but shows coalescence at higher temperatures. This behaviour can be explained by an equilibrium between two identical kite conformations which is slow on the ^{1}H NMR timescale at low temperatures, but at higher temperatures gives an averaged spectrum with C_{4v} symmetry.

Both in solution and in the solid state, **69** is present as a *dimer*.[97,98a] From the X-ray crystal structure, it can be seen that in the dimer one molecule is turned upside down and rotated over 90° with respect to the other (see Figure 6). In this way, both molecules,

containing two guest-like protruding methyl groups at 3 and 9 o'clock and two host-like methyl-sized cavities at 6 and 12 o'clock, are perfectly preorganized[100] for dimerisation, enabling the four aryls of one partner to interact face-to-face with the four aryls of the second partner. Compound **70**, in which the methyl groups have been replaced by ethyl groups, exists only as a monomer. The ethyl groups are too large for the small cavities, thus destroying the complementarity required for the observed dimerisation. The high structural recognition for monomers of **69** resembles that frequently observed in evolutionary systems in nature, but is unique in the fact that it takes place in the absence of hydrogen-bonding, metal-ligation, ion-pairing or hydrophobic effects.

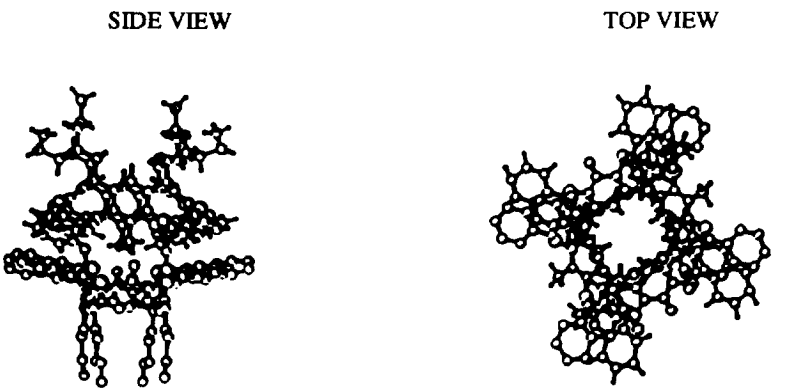


Figure 6. *X-Ray crystal structure of velcraplex **69**, showing the dimeric structure of this compound.* Reproduced with permission of the American Chemical Society, copyright 1992.

Dimerisation in solution is a close interplay between several energy-consuming and energy-delivering processes. In order to dimerise, a molecule must first desolvate. This process involves the loss of attractive interactions with the solvent, which is enthalpy-destabilising, but liberates many solvent molecules which are more or less oriented, which is entropy-stabilising. When the desolvated molecules dimerise, they will share a large common surface, which is generally enthalpy stabilising, but this process involves the well-defined orientation of two molecules, which is entropy destabilising. Whether dimerisation will occur or not and, if so, which energy contribution is the driving force, is mainly dependent on the size and nature of the contacting areas.

A variety of cavitands, named *velcrands* when monomeric and *velcraplexes* when they exhibit dimer formation, differing in the size of the aromatic spacer (pyrazine and benzene versus quinoxaline) and the substitution pattern at the periphery, were subjected to homodimerisation (association with themselves) or heterodimerisation (association with another velcrand) studies, in order to analyse which energy contribution dominates in the overall energy of binding. The enthalpies and entropies of complexation showed a large spread of values with changes in structures of the complexing partners. In all cases, the "solvophobic" monomer-to-monomer attraction is present and sometimes dominates, making

enthalpy driven, entropically-neutral processes the most commonly encountered.[97] First of all, the quinoxaline-based velcraplexes show generally higher energies of binding than the pyrazine- or benzene-based velcraplexes, which can be attributed to the larger number of attractive contacts between the surfaces. Secondly, the heterodimers show, with one exception, higher binding constants than the homodimers, which is an indication of the presence of four aligned pairs of proximate and identical dipoles in the homodimers. In the heterodimers, these aligned dipoles differ enough to make binding more favourable. Finally, it was found that the activation energies for association and dissociation are remarkably high for dimers held together only by dipole-dipole, van der Waals and solvophobic forces. The slow dissociation can be easily understood because the four methyl-into-cavity locks prevent the dimers from dissociating by sliding or rotating with respect to the second partner. Insertion of one solvent molecule between the rigid dimer faces destroys the attractive interactions completely.

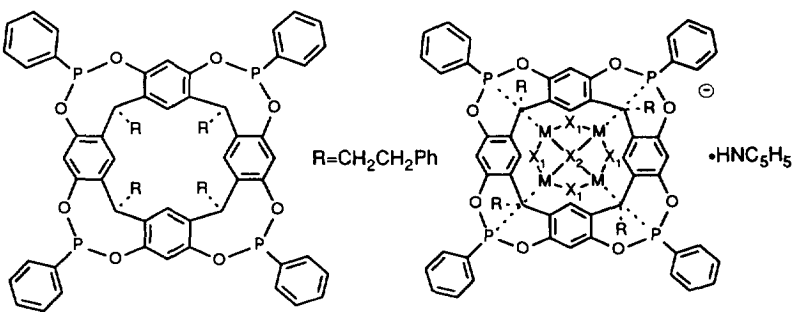
Velcrand **71**, which exists exclusively in the vase conformation above 5°C, forms inclusion complexes in the solid state with neutral molecules like acetone[99] and dichloromethane,[98b] but preferentially binds aromatic guests, with binding constants up to $200M^{-1}$ for 4-(dimethylamino)nitrobenzene in acetone.[99a] This value is considerably higher than those observed for other aromatic guests, like benzene and toluene, because of the strong dipole-dipole interaction between host and opposite-directed guest in addition to π-π interaction.[99]

The complexation behaviour of velcrands has also been studied extensively in the gas phase.[101] Using Desorption Chemical Ionisation mass spectrometry,[102] the velcrands are evaporated in an atmosphere of pure guest[101a] or methane containing small amounts (~0.5%) of guest.[101b] After complexation has taken place between the *neutral* species, the complexes are ionised.[101] Remarkable differences in selectivity were observed between velcrands **71** and **72**, in which a binding site for hydrogen bonding is present since only three quinoxaline spacers have been introduced. Whereas **71** shows high affinity for aromatic guests similar to the situation in solution, **72** complexes preferentially acetic acid, *n*-butanol, *n*-butylamine, and ethyl acetate, probably via hydrogen bonding. Moreover, selectivities of ethyl acetate over methyl acetate and *n*-butanol over ethanol exceeding 250 were observed. A possible explanation for these high selectivities may be an additional CH-π interaction between the methyl groups of the guests with longer alkyl chains, like *n*-butanol and ethyl acetate, and the electron-rich quinoxaline spacers which is not possible in the smaller guests like ethanol and methyl acetate.[101b]

8.4 PHOSPHORYL-BRIDGED CAVITANDS

Markovsky et al. were the first to report the phosphorylation of resorcinarenes.[103] Using a variety of different reaction conditions, they showed that resorcinarenes can be selectively tetraphosphorylated as well as octaphosphorylated, both in moderate to high yields. A temperature and solvent-dependent equilibrium between an open and a closed cavitand structure was observed in one case. Several others have reported on the synthesis of phosporyl-bridged resorcinarenes, sometimes leading to mixtures of up to six different isomers.[104]

An interesting example comprises the reaction of resorcinarene **2** (Chart 1, R_1=CH_2CH_2Ph) with phenyldichlorophosphine and pyridine as a base to give phosphoryl-bridged cavitand **73**,[105] bearing four coordinatively unsaturated phosphorus ligands. The four phenyl rings bound to the phosphorus atoms can occupy either axial or equatorial positions, but the single resonance in the ^{31}P NMR spectrum is consistent with a similar orientation for all four phenyl rings and the X-ray crystal structure indicates that this is the equatorial position.



73

74 M=Cu, X_1=X_2=Cl
75 M=Cu, X_1=Cl, X_2=I
76 M=Ag, X_1=X_2=Cl

Chart 14

Treatment of tetradentate **73** with $[(CuC{\equiv}CPh)_n]$ in the presence of pyridinium chloride afforded complex **74**, in which a crown-like $Cu_4(\mu\text{-}Cl)_4$ unit is positioned on top of the cavitand, in this way including a chloride anion in the cavity. The chloride anion is weakly bound to three of the four copper(I) centers, which all form stronger bonds to a phosphorus atom and to two of the four remaining chlorides.[105] In an attempt to synthesise the iodide analogue of **74** by treating this compound with excess *n*-Bu_4NI, Puddephatt et al.[106] found that not all chlorides could be substituted by iodides. The X-ray structure revealed that the iodide anion is selectively included in the middle of the cavity (position X_2) by the formation of weak bonds to all four copper atoms, while the other positions (X_1) are occupied by chlorides and iodides in a disordered way in a ratio of approximately 1:1. The selective inclusion of iodide in the cavity should be attributed to its larger size better filling the cavity to bind to all four copper atoms. In the analogous complex **76**, the central chloride is able to bind to the somewhat larger silver atoms. In this complex, the chlorides could be easily substituted by bromides and iodides.

The anion complexes **75** and **76** show a high affinity for alkali metal cations, as evidenced by their ability to extract such cations from aqueous solutions into organic solvents containing **75** and **76**. Interestingly, **76** has a strong affinity for Li^+.[106]

9. CARCERANDS AND HEMICARCERANDS

When two cavitands are covalently linked via their upper rims, a molecule with a closed surface, named a *carcerand*, is formed.[79] Such a molecule contains an enforced cavity

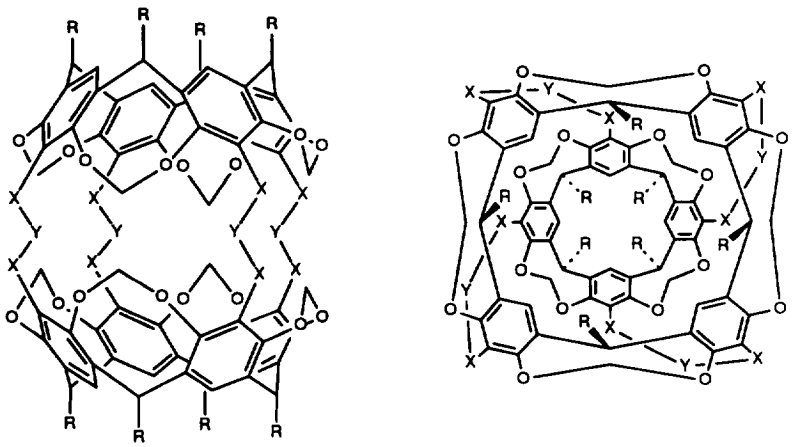
with the shape of an American football, sufficiently large to accommodate small organic molecules. During their synthesis, carcerands capture molecules from the medium which, when incarcerated, cannot leave the cavity without breaking covalent bonds in the host molecule.

Carcerand **77**, reported in 1985, was the first example of a synthetic molecule that imprisons another molecule.[107] In this compound, the two cavitand parts are held together by four CH_2SCH_2-spacers, leaving no portals in this part of the molecule. Two small openings are present at the top and the bottom of the shell which only permit entrance and exit of small molecules, like water and acetonitrile.[108] Compound **77** proved to be essentially insoluble in most organic solvents. From the elemental analysis and FAB mass spectrum, it was found that, in addition to the inclusion of solvent molecules (DMF and THF), considerable amounts of Cs^+ were included. Prolonged heating in CF_3CO_2H, which slowly digests the host molecule, liberated the guests, thus proving their incarceration unambiguously.[87] Compounds **78** and **79**, bearing eight ethylphenyl groups at their periphery, are sufficiently soluble in non-polar organic solvents to permit their characterisation. The syntheses, comprising a fourfold S_N2 reaction, were studied in many different solvents and solvent mixtures.[88,108] This revealed that carcerand formation is templated by the solvent and no empty carcerands are formed. Moreover, the cavity shows molecular recognition, since reactions carried out in 1:1 mixtures of solvents produce one of the possible carcerands in preference to the other.[88] For a long time it was believed that the molecule incarcerated stabilises the transition state for the formation of the last bridge, and that for this reason only solvent molecules that are able to stabilise an S_N2 transition state will be incarcerated. However, Sherman et al.[109] recently showed that many other guest molecules can be incarcerated, e.g. benzene and tetrahydrofuran, when the carcerand synthesis is carried out in a solvent too large to enter the carcerand containing small amounts of these guest molecules.

The inner surface of (hemi)carcerands provides a new phase of matter, which is essentially different from both the solid state, liquid or gas phase.[88a] Therefore, it is expected that incarcerated guests behave in a totally different way to the same molecules in bulk solution. An example of such different behaviour in the interior phase is the rotation around the C-N bond in amides, which is markedly different from that in vacuum and in solution.[88]

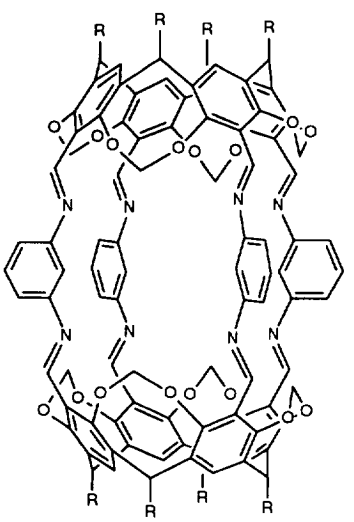
One of the drawbacks of the carcerands mentioned above is the inability to exchange their incarcerated guest molecules. Therefore the synthesis of carcerands that permit guest exchange after shell closure would be more general. This idea has been realised in the synthesis of the so-called *hemicarcerands*, of which two types have been reported, *viz.* molecules in which *four* portals are created by the choice of much larger spacers between the two cavitand parts and molecules in which *one* or *two* portals are created by the elimination of spacers in **79**. These two types of hemicarcerands will be discussed together with a few applications.

SIDE VIEW TOP VIEW

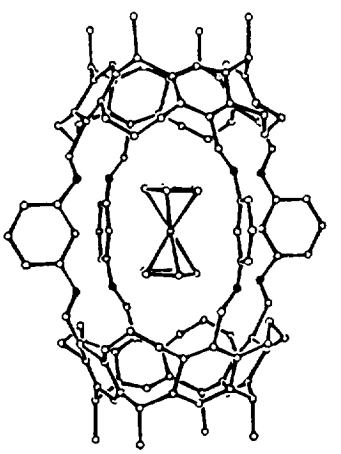


77 R=CH_3, X=CH_2, Y=S
78 R=$CH_2CH_2C_6H_5$, X=CH_2, Y=S
79 R=$CH_2CH_2C_6H_5$, X=O, Y=CH_2

Chart 15



80 R=CH_2CH_2Ph



X-ray crystal structure
of **80**•ferrocene

Figure 7. *Structure of hemicarcerand* ***80*** *together with the X-ray crystal structure of hemicarceplex* ***80****•ferrocene.* Reproduced with permission of the American Chemical Society, copyright 1992.

The first type of hemicarcerand is generally synthesised via the four-fold coupling of cavitands like **50** and **51** (Chart 10) with 1,2- or 1,3-disubstituted aromatic spacers.[78] Such hemicarcerands, usually isolated as stable complexes (hemicarceplexes) with solvent molecules, can be liberated of solvent by extended heating in solvents too large to enter the cavity. Subsequent addition of excess of an appropriate guest to the solution gives access to almost every desired carceplex.[110,111] Most of these complexations exhibit large positive entropy effects because the liberation of solvent molecules as a result of guest desolvation more than compensates for the negative entropy associated with organising two molecules.[110] Carceplexes possessing guests sufficiently large to inhibit their dissociation can be conveniently isolated and characterised. The term "constrictive binding", which is defined as the activation energy for dissociation,[78a,d] was introduced for this phenomenon. An example of such a hemicarceplex is **80**•ferrocene (Figure 7),[78a,112] which has a half-life for decomplexation in $C_2D_2Cl_4$ of approximately 20 hours at 112°C. Such kinetically stable complexes have potential application in the medical field, e.g. in organ imaging or radiation delivery systems that keep heavy metals from being deposited in the bone.[112,113] Recently, Balzani and coworkers succeeded in the preparation of hemicarceplex **80**•9-cyanoanthracene and showed that the absorption and excited state properties of the guest are strongly modified upon inclusion.[114]

Reaction of cavitand **51** (Chart 10) with two equivalents of either (*R*)- or (*S*)-2,2'-bis-(bromomethyl)binaphthylene affords the corresponding enantiomerically pure $(R)_4$- or $(S)_4$-hemicarcerands in 13% yield.[115] These hemicarcerands show chiral recognition between enantiomers with differences in activation energy for decomplexation ($\Delta\Delta G^{\neq}$) of up to 1.3kcal mol^{-1}.

The type of hemicarcerand described here can also be used to carry out chemical reactions inside the cavity. A hemicarcerand containing four aliphatic bridges, obtained from the reaction of **51** with two equivalents of $TsO(CH_2)_4OTs$, proved to form stable complexes with several hydroquinones which could be fully characterised.[116] Essentially quantitative oxidation reactions, which turned out to be reversible as well, were carried out on these hydroquinones to convert them into the corresponding quinones, which could not be introduced directly into the hemicarcerand because of extensive decomposition. The resulting complexes were stable to chromatography and in solution up to 100°C.

The second type of hemicarcerand is prepared in a similar way to that described for **79** (Chart 15), with the exception that the starting compounds are cavitands that lack one of their functional groups at the upper rim. Hemicarcerand **81** was synthesised in this way from a side product (23%) in the synthesis of cavitand **49**, missing one hydroxyl group.[117] Like in **80**, hemicarcerand **81** was isolated as a hemicarceplex, but the solvent molecule could be easily removed by extended heating in mesitylene, leaving empty **81**.[117a]

Hemicarcerand **81** is able to protect small reactive molecules from reactions with all kind of species because of its small entrance. This has been most beautifully exemplified by the trapping of cyclobutadiene, which proves to be stable *at room temperature* inside the interior of **81**.[118,119] When α-pyrone (**82**) is complexed inside **81** and subsequently irradiated with a 75W Xe lamp, it rearranges photochemically to photopyrone (**83**), which decomposes

upon extended irradiation into cyclobutadiene and carbon dioxide. On account of the small size of the cavity, molecules other than O_2 cannot enter, and when the experiment is performed under oxygen-free conditions (reaction with oxygen gives dialdehyde **84**), the presence of cyclobutadiene could be determined even with ^1H NMR spectroscopy.

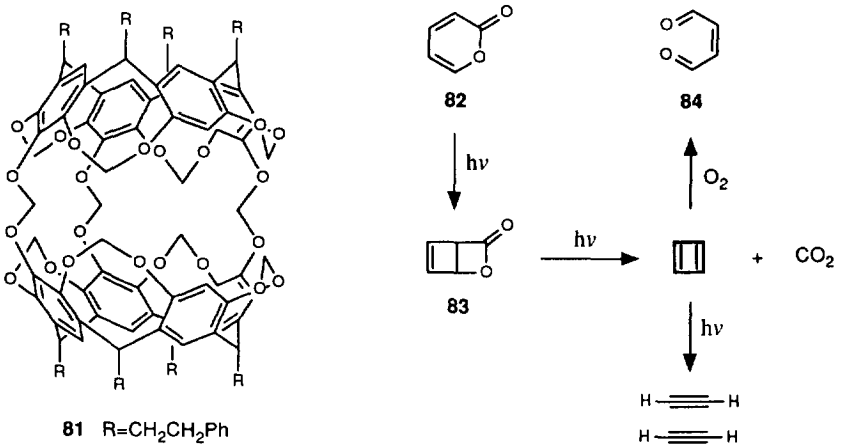


Figure 8. *Inhibition of the dimerisation of cyclobutadiene by complexation inside the cavity of hemicarcerand **81**.*

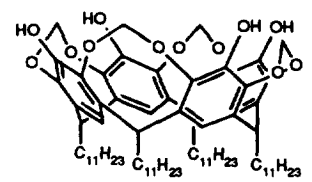
The few examples shown here demonstrate that hemicarcerands are an extraordinary class of molecules that certainly claim interest outside the field of pure chemistry, e.g. as potential slow-release drug-delivery systems in medical or agricultural applications. However, the largest guest molecule incarcerated in a hemicarcerand up to now has a mass of 208, whereas most medicines, antibiotics and pesticides have molecular masses in the range of 300 to 400. This clearly underlines the need for hemicarcerands with larger cavities.

10. COMBINATION OF CAVITANDS WITH CALIX[4]ARENES

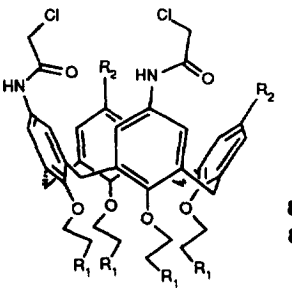
As part of a general study on the combination of medium-sized building blocks[120] Reinhoudt and co-workers have studied the possibilities of coupling cavitands to upper-rim functionalised calix[4]arenes. Reaction of cavitand **85** with upper rim 1,2-functionalised calix[4]arene **86** gave, depending on the ratio used, either *endo* 1:1 **87a** (20%) and *exo* 1:1 **87b** (32%) or the three isomeric 2:1 products **88a-c** in an almost statistical yield of 64%.[121,122] 2:1 Products **88a-c** possess a preorganised cavity that selectively binds corticosteroid prednisolone-21-acetate by a combination of CH-π interactions and hydrogen bonding with association constants up to $8.3 \times 10^2 M^{-1}$ for *endo-exo* isomer **88b**.[123]

A remarkable selectivity for an *endo* orientation was observed in the reaction of cavitand **85** with 1,2-functionalised calix[4]arene **89**, carrying two nitro groups at the remaining aromatic rings. Exclusively *endo* 1:1 **90** (42%) was formed in this reaction together with small amounts of *endo-endo* and *endo-exo* 2:1 isomers **91a** and **b**, respectively.

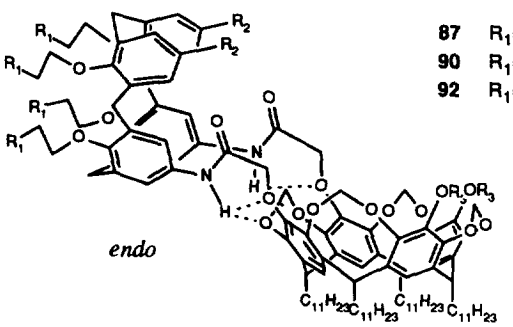
Neither the *exo* 1:1 nor the *exo-exo* 2:1 product was formed, which should be attributed to a favourable interaction of the nitro groups with the cavitand in the transition state leading to *endo* 1:1 **90**.[122]



85

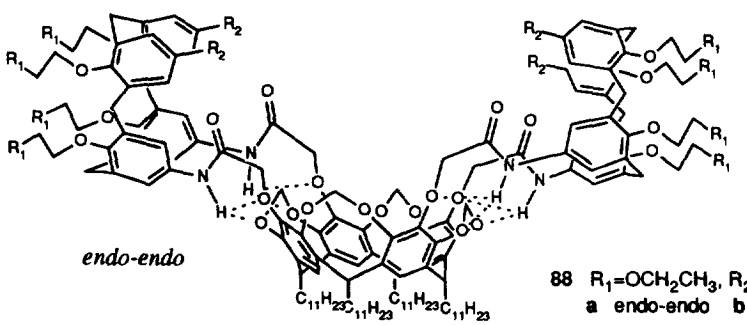


86 R_1=OCH_2CH_3, R_2=H
89 R_1=CH_3, R_2=NO_2



endo

87 R_1=OCH_2CH_3, R_2=R_3=H **a** endo **b** exo
90 R_1=CH_3, R_2=NO_2, R_3=H endo
92 R_1=CH_3, R_2=NHC(O)CH_2Cl, R_3=$Si(CH_3)_2C(CH_3)_3$ endo



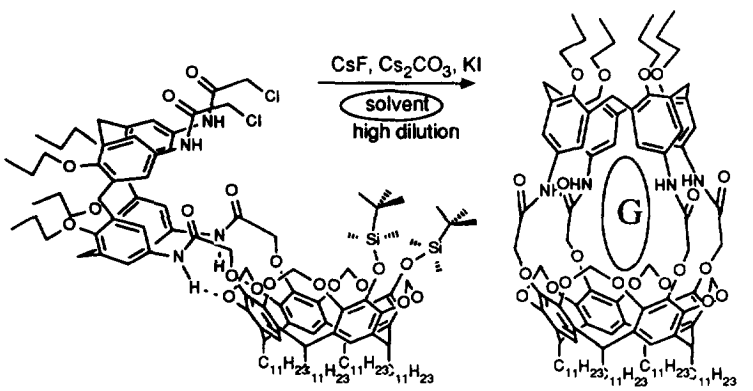
endo-endo

88 R_1=OCH_2CH_3, R_2=H
a endo-endo **b** endo-exo **c** exo-exo
91 R_1=CH_3, R_2=NO_2
a endo-endo **b** endo-exo
97 R_1=CH_3, R_2=NHC(O)CH_2Cl endo-endo

Chart 16

Endo 1:1 products of type **90** provide access to the calix[4]arene-based carcerands, a novel type of carcerand in which one cavitand is replaced by a calix[4]arene. These compounds are not available via one-step procedures analogous to those described for symmetrical carcerands (see section 9) because of the enhanced flexibility of calix[4]arenes compared to cavitands.[124] Treatment of *endo* 1:1 **92** with CsF, Cs_2CO_3 and KI under high

dilution conditions in either *N,N*-dimethylformamide (DMF), *N,N*-dimethylacetamide, or 1-methyl-2-pyrrolidinone provides the corresponding carceplexes **93-95**, carrying one molecule of solvent inside the cavity, in almost quantitative yields.[125] As a result of different orientations of the guest molecule inside the cavity, these carceplexes exhibit a novel type of stereoisomerism, called *carceroisomerism*. For carceplex **94**, the isomerisation process is fast on the ^{1}H NMR timescale above room temperature, but at temperatures below -30°C both isomers can be observed separately (see Figure 9). This type of carceplex provides a novel type of molecular switch with potential application in the field of molecular electronics and data storage.



92

93 G = DMF
94 G = DMA
95 G = NMP

Chart 17

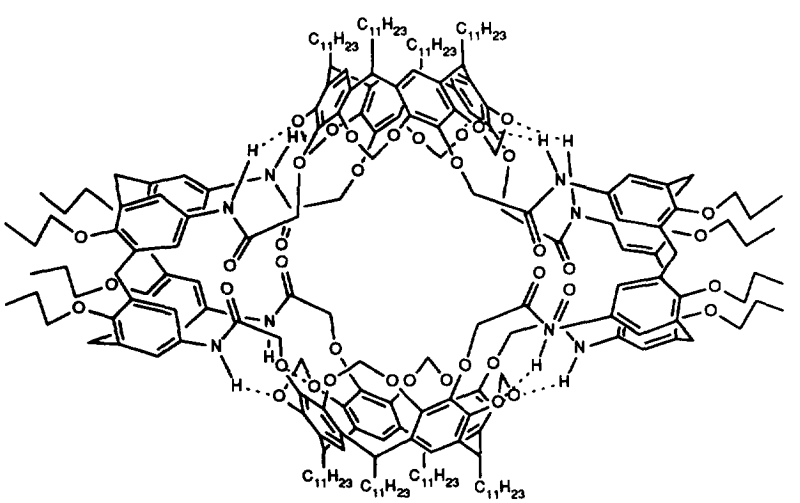


Chart 18

96

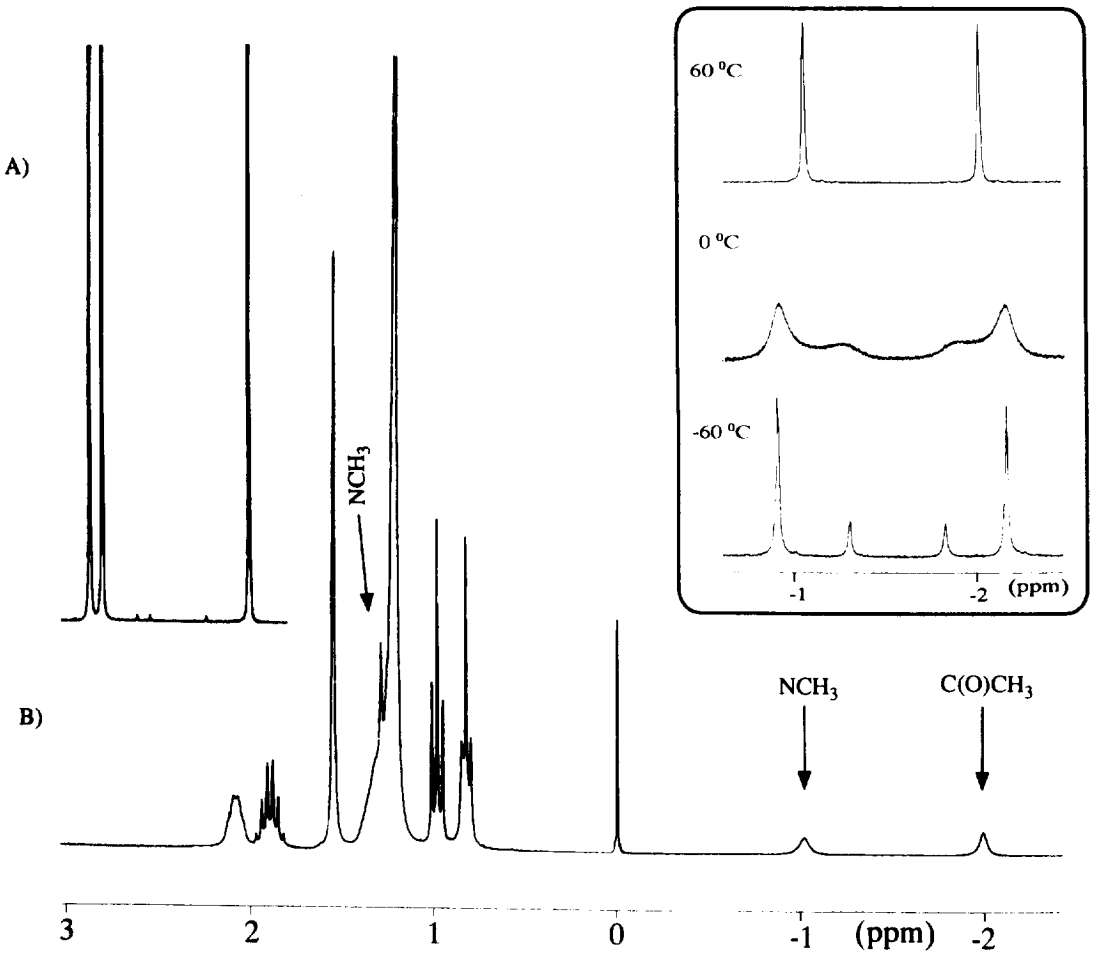


Figure 9. *^1H NMR spectra (250 MHz) of (A)* N,N-*dimethylacetamide (DMA) and (B) carceplex **94** in $CDCl_3$ at room temperature; the framed inset shows sections of the ^1H NMR spectra (400 MHz) of carceplex **94** at different temperatures.* Reproduced with permission of VCH Verlagsgesellschaft, copyright 1994.

When *endo* 1:1 **92** was fully desilylated with CsF in DMF (5mM) prior to treatment with Cs_2CO_3/KI, beside carceplex **92**, isolated in 27% yield, compound **96** was formed in 26% yield.[121,122] Compound **96** can also be synthesised via reaction of *endo-endo* 2:1 **97** with cavitand **85** under high dilution conditions in 30% yield. For its size compound **96** is extremely rigid; it contains a cavity of nanosize dimensions with a calculated internal volume of approximately 1.0nm^3. Compound **96** should be able to accommodate large organic guest molecules.

11. CONCLUSIONS

The chemistry of resorcinarenes is well established nowadays. Their synthesis, conformational behaviour and complexation properties have been studied in detail, showing that resorcinarenes can be useful building blocks in supramolecular chemistry. Bridging of the phenolic hydroxyl groups in resorcinarenes gives cavitands, a family of very rigid host molecules. Covalent coupling of two such cavitands via the upper rim gives access to (hemi)carcerands, a whole family of container molecules with very special complexation properties. Combination of cavitands with calix[4]arenes has led to the synthesis of carcerands with nanometer-sized cavities and has opened the way to a new type of molecular switches based on hindered mobility of the guest molecule.

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