The Modular Approach in Supramolecular Chemistry

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This review describes covalent and non-covalent combinations of building blocks, e.g. calix[4]arenes, resorcin[4]arenes, cyclodextrins, porphyrins, and cyclotriveratrylenes, leading to well-defined large (receptor) molecules.

Introduction

Nature constructs receptor molecules by the combination of a limited number of building blocks. Amino acids are combined to proteins, nucleosides to DNA and RNA, and monosaccharides to carbohydrates. Systematic variation of the monomer sequence gives access to an almost infinite number of different receptors. This is achieved at the expense of a high molecular weight which might be even larger when the biologically active species is composed of several subunits that are organized by non-covalent bonds.

Nowadays a large variety of synthetic receptor molecules for the binding of relatively small guest species e.g. cations, anions, and small neutral molecules has been described in the literature. Most synthetic receptors have been prepared

David N. Reinhoudt (left, front) was born in 1942 in Wolphaartsdijk, The Netherlands. He studied Chemical Technology at the Delft University of Technology and graduated (suma cum laude) in chemistry in 1969 with Professor H. C. Beijerman. In the period 1970−1975 he worked at Shell where he started the crown ether research program. In 1975 he was appointed as a part-time professor (extraordinarius) at the University of Twente followed by the appointment as a full professor in 1978. The major part of his research deals with supramolecular chemistry and technology. Nanotechnology, molecular recognition, and non-covalent synthesis are the major fields. Application of supramolecular chemistry e.g. in membrane transport, in the field of electronic or optical sensor systems, catalysis, and molecular materials. He is the author of more than 550 scientific publications, patents and review articles and books. He has been honored with the Izatt-Christensen award (1995) and the Simon Stevin Mastership (1998). In 1998 he was elected as a member of the Royal Dutch Academy of Sciences.

Peter Timmerman (left, behind) was born in Ommen, The Netherlands in 1966 and obtained his undergraduate degree in chemistry in 1989 with Prof. G. W. Klumpp at the Free University in Amsterdam. Then he moved to the University of Twente to do a PhD with David Reinhoudt on the synthesis of rigid cavities by combination of calix[4]arenes and resorcinarenes, for which he has been awarded the Backer Prize in 1994. After a postdoctoral stay (1994−1995) at the ETH-Zurich in Switzerland with Francois Diederich he moved back to Twente, where he currently holds an assistant professorship position in the group of David Reinhoudt. His research interests are mainly centered on the various aspects of molecular recognition, in particular on noncovalent (combinatorial) synthesis, anion recognition in catalysis, and synthetic oxygen carriers.

Irene Higler (middle) was born in Hilversum, The Netherlands in 1969 and studied chemical technology at the University of Twente where she obtained her PhD with David Reinhoudt in 1998. Since October 1998 she is working with Océ-Technologies B.V. at Venlo.

Willem Verboom (right), born in Goes, The Netherlands in 1954, studied chemistry at Utrecht University (The Netherlands) where he also received his PhD in 1980 with Professor H. J. T. Bos. Subsequently, he joined the group of David Reinhoudt at the University of Twente, where he now is an associate professor in organic chemistry. His present research interests focus on supramolecular chemistry and in particular the application of suitable molecular building blocks for the development of specific receptors and larger (non-)covalent assemblies. He is the author of more than 230 scientific publications.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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using the modern methodologies of classical organic synthesis, which allows an almost unlimited variation. This strategy focuses on the complementarity of functional groups in receptor and guest. This approach is always guest-directed and the drawback is that it requires for each individual guest a new synthetic pathway. With increasing size and structural complexity of the guest species, this approach becomes increasingly demanding in terms of design and the number of steps in the synthesis of a complementary host (i.e. receptor) molecule.

In recent years, we and others have developed an alternative strategy for the synthesis of artificial receptors. This approach is a compromise between the two extremes described above, and is based on the proper combination of (different) molecular *building blocks* to which functional groups can be attached. Coupling of these building blocks via covalent and non-covalent bonds gives rise to molecules with large well-defined cavities and hydrophobic surfaces.

The most important building blocks which are included in this review are calix[4]arenes (**1**, for $n = 4$ see **2**)[1], resorcin[4]arenes (**3** and **4**)[2], cyclodextrins (**5**)[3], cyclotriveratrylenes (**6**)[4], and porphyrins.

Calix[4]arenes have been combined with other functional units e.g. polyethyleneglycols, terphenyls, metallosalophenes, and metallosalenes to give calixcrown ethers[5], calixspherands[6], and anion and ditopic receptors[7], respectively[8].

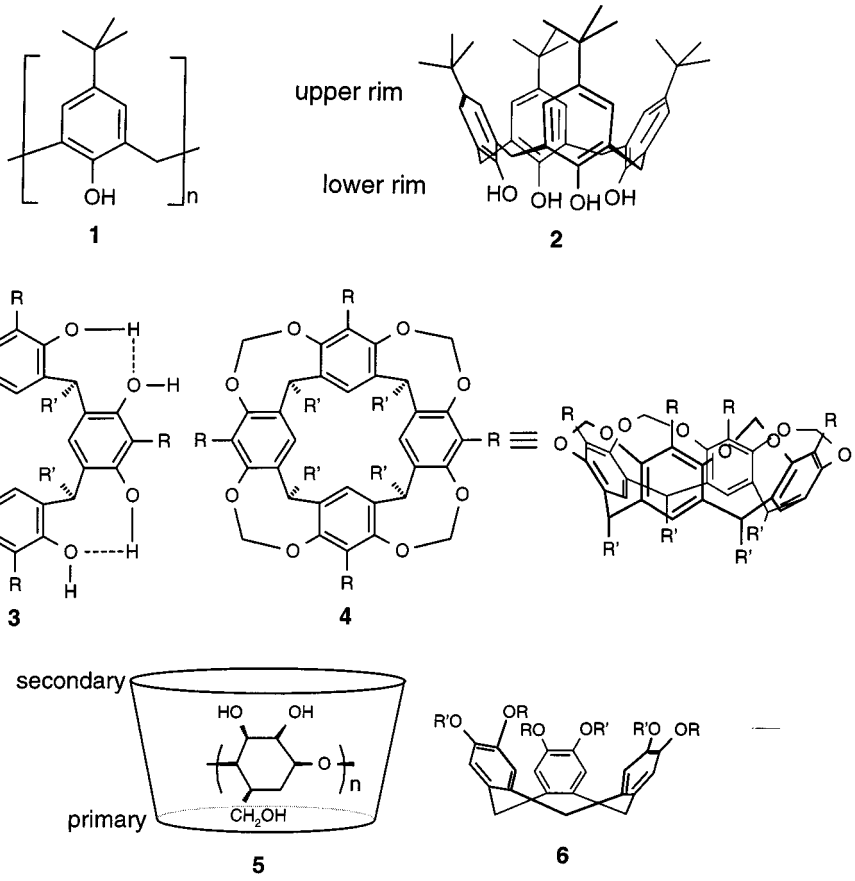
In this review, we will illustrate the modular approach to synthetic receptor molecules with examples of combinations of medium-sized building blocks leading to well-defined structures. Not included are polymeric products, dendrimers[9], metal-coordinated structures[10], and rotaxanes[11]. Special emphasis will be on combinations involving calix[4]arenes and resorcin[4]arenes (and the combination of these two). This review is divided into three parts: (i) covalently linked homocombinations, (ii) covalently linked heterocombinations, and (iii) non-covalently linked combinations.

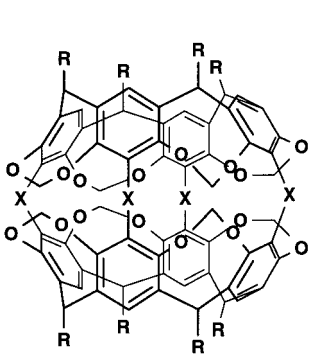
Covalently Linked Homocombinations of Building Blocks

Covalently linked *homocombinations* of building blocks are structures in which two (or more) identical building blocks are connected. This section describes three different possibilities viz. double resorcin[4]arenes (or carcerands), double calix[4]arenes, and combinations of other building blocks.

Carcerands

The pioneer in the area of carcerands and carceplexes is undoubtedly Donald Cram. He combined two cavitands via their broader sides to give closed-surface, globular-shaped molecules with enforced hollow interiors large enough to incarcerate simple organic molecules, inorganic ions, or both. Carcerands (see **7**) were obtained e.g. by reaction of





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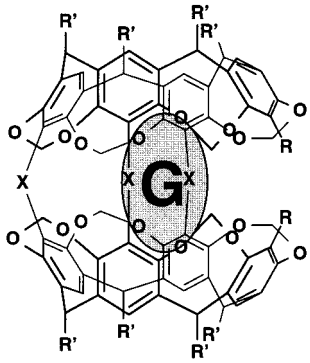

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two tetrahydroxycavitands with four equivalents of bromochloromethane.

In a carceplex the carcerand cavity is occupied by a guest molecule and the guest cannot escape the molecular prison without breaking covalent bonds. Carceplexes with a variety of guests such as 2-butanone, DMF, methanol, acetonitrile, and DMSO have been synthesized. The ^{1}H-NMR spectra show a 1−4 ppm upfield shift for the signals of the hydrogen atoms of incarcerated guests caused by the shielding by the resorcin[4]arene moieties. In hemicarcerands and hemicarceplexes there are only two[12] or three linkages between the two parts or the four linkages are long and flexible enough for prisoner molecules to escape their cages at high temperatures, but to remain incarcerated at temperatures which allow their isolation, purification, and characterization (see **8**)[2c][13].

Shell closures occurring during the synthesis of carcerands show structural recognition for inclusion of polar molecules in the medium. Cram et al.[14] assumed that the shell-closing reactions occur by an S_N2 mechanism and that the more polar components solvate the anion and therefore end up incarcerated.

Recently, in a general study Mecozzi and Rebek[15] demonstrated that molecular recognition through encapsulation processes is largely determined by the volumes of the guest and host. Binding of molecules of suitable dimensions in the cavity of a receptor can be expected when the packing coefficient, the ratio of the guest volume to the host volume, is in the range of 0.55 ± 0.09 (the "55% solution rule"). However, when strong intermolecular forces are involved the packing coefficients are higher.

Sherman et al. investigated the influence of templates (guests) on the carceplex formation; a template effect that ranged one million-fold for good and poor template molecules was found[16]. They demonstrated that the same forces which facilitate the formation of carceplexes drive the formation of hemicarceplexes, despite the presence of a portal in the hemicarceplex, its lower symmetry, and its potential to misalign[17]. The driving forces include favorable van der Waals interactions between the template molecule and the forming cavity with minimum strain being imparted to the complex. Moreover, hydrogen bonding may assist in bringing the different parts together.

The cavity of carcerands was called by Cram et al.[18] a "*new phase of matter*". Since the inner phases are not bulk-phase-dependent, they are one discrete molecular inner phase and molecules behave differently inside a carcerand. Striking examples are cyclobutadiene and *ortho*-benzyne which can normally only be isolated at very low temperatures but are stabilized by incarceration inside a carcerand. Also the photophysical properties of molecules imprisoned in a (hemi)carcerand are different from those in the bulk; e.g. the electron and energy transfer of biacetyl inside a cage[19].

Cram et al. showed that guest hydroquinones are oxidized to their corresponding incarcerated quinones, and these hemicarcerand quinones are again reduced to their original hemicarcerand hydroquinones[20].

Covalently Linked Double Calix[*n*]arenes

Calix[4]arenes are able to complex neutral molecules although the association constants are moderate[21]. To obtain receptor molecules with better complexation properties, several groups synthesized double calix[4]arenes with enforced cavities[1b][22]. There are three possibilities, viz., connected via both upper rims, *head-to-head* (**9**)[23], via both lower rims, *tail-to-tail* (**10**)[24], or via connecting the upper rim of one with the lower rim of another, *head-to-tail* (**11**)[25].

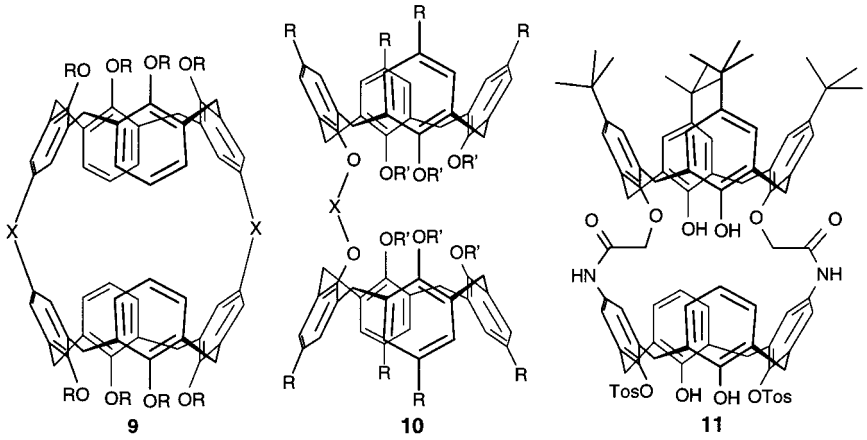
We found that a very short head-to-head linkage can be achieved by reaction of 1,3-diaminocalix[4]arenes with 1,3-diformylcalix[4]arenes to give the Schiff base based double calix[4]arenes (**9**, X = −NCH−) in high yields (74−92%)[26]. They show a high affinity for silver(I) ions (K_{ass} = 9.5·10^5 M^{-1} in $CDCl_3/CD_3OD$, 4:1, v/v).

For energy-transfer studies between two different lanthanide ions, we prepared double calix[4]arenes (**10**) linked tail-to-tail via one linkage using different spacers. These biscalix[4]arenes contain carboxylic ester and/or amido functions at their remaining phenolic oxygen atoms (OR′) to complex the lanthanide ions[27].

Reactions between lower-rim 1,3-difunctionalized calix[4]arenes and difunctional reagents such as diacid dichlorides gave double and triple calix[4]arenes, the ratio depending on the reaction conditions[28]. Three to eight calix[4]arenes were combined by Shinkai et al.[29] in a cyclic array[30].

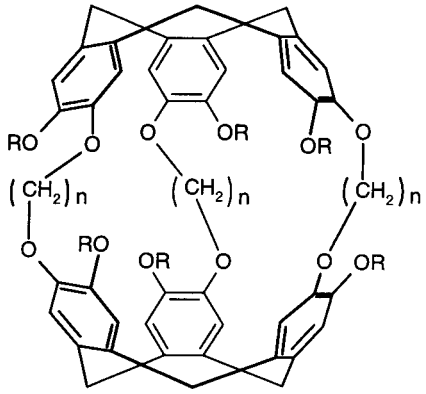
Covalently Linked Homocombinations of Other Building Blocks

Several groups have prepared cyclodextrin dimers for the complexation of guest molecules. Comparable to the calix[4]arenes, these can be divided into three types: dimers connected via (i) two spacers linked at the primary side, (ii) two at the secondary side, or (iii) one at the primary and one at the secondary side[31]. Primary-side-linked dimers complex neutral guest molecules in aqueous solutions[32]. To bind porphyrinoid derivatives in water cyclodextrins were coupled via the broader secondary side[33].



9 **10** **11**

Cryptophanes (**12**)[34], dimers of two CTV subunits linked via the wider side, complex methane, small halocarbons, and noble gases[35]. Water-soluble cryptophanes, obtained by introduction of acid derivatives at the R positions (see **12**; $n = 3$ or 5; R = $-CH_2CO_2H$) complex acetylcholine and ammonium ions[36].



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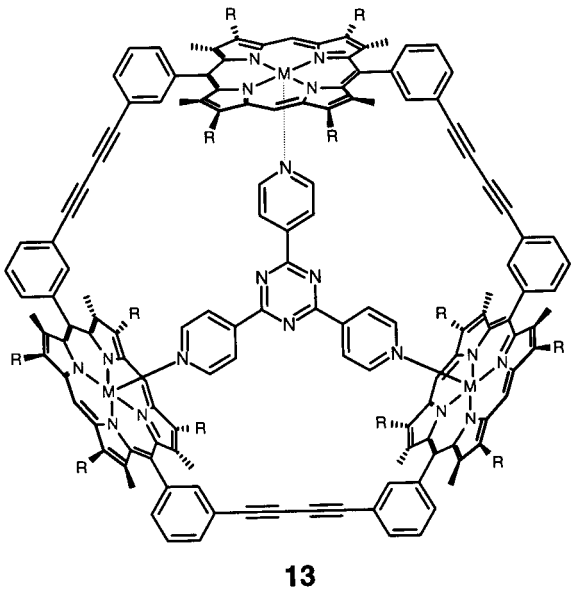

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Sanders et al.[37] prepared rigid porphyrin dimers and trimers by Glaser–Hay coupling of preformed monomers (for an example of a trimer complex see **13**). Inside the cavity of a porphyrin trimer a stereoselective acceleration of a Diels–Alder reaction was achieved by proper positioning of the reactants by perpendicular coordination to the zinc porphyrins[38].

Covalently Linked Heterocombinations of Building Blocks

Covalently linked *heterocombinations*, structures in which two (or more) different building blocks are connected, are described in three parts: combinations of (i) calix[4]arenes and resorcin[4]arenes, (ii) calix[4]arenes and other building blocks, and (iii) heterocombinations of other building blocks.

Combinations of Calix[4]arenes and Resorcin[4]arenes

We synthesized calix[4]arene-based carceplexes by combining one calix[4]arene and one resorcin[4]arene (see **14** in Figure 1). These container molecules are different from carcerands described above because the cavity of calix[4]arene-based carcerands have a different upper and lower halve and consequently, different orientations of incarcerated non-symmetrical guest molecules give different diastereoisomers. The incarcerated guest molecules show considerable upfield shifts in the ^{1}H-NMR spectrum with respect to the neat guests as is illustrated in Figure 1 for the carceplex of **14** (R = $-C_3H_7$, R′ = $-C_{11}H_{23}$) with DMF.

The energy barriers for interconversion between the various orientations of the guest molecules inside the carcerands were determined with 2D EXSY NMR. The activation energies calculated with molecular modeling using the TRAVEL module in CHARMM, showed good quantitative agreement with the experimental results. Although the differences between the calculated and the experimental values range from 3.5 to 0.3 kcal mol^{-1} for NMP and DMA, respectively, the trend in the calculated energy barriers follows the experimental values. For instance in the case of calix[4]arene-based carcerand **14** (R = $-C_3H_7$,

Figure 1. ^{1}H-NMR spectrum of calix[4]arene-based carceplex **14** in $CDCl_3$ at room temperature; the positions of proton signals for neat DMF are indicated with dashed arrows, the signals corresponding to incarcerated DMF are indicated with solid arrows

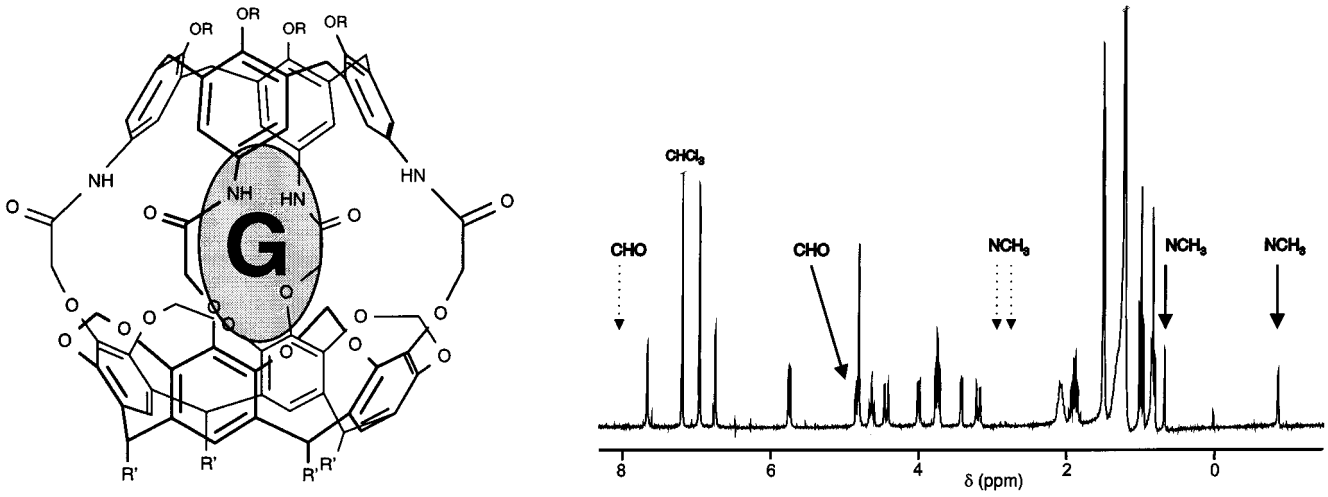

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Table 1. Templating ability of potential guests during the synthesis of calix[4]arene-based carceplexes by doped inclusion

Guest	Templating ability[a]	Yield (%)[b]
DMA	100	27
DMSO	63	16[c]
DMF	27	13[c]
2-Butanone	27	16

[a] DMA is set at 100. – [b] Isolated carceplex when only one guest is used during doped inclusion. – [c] Yield of deuterated guests.

R′ = $-C_{11}H_{23}$) for the interconversion between different orientations of encarcerated DMA and NMP energy barriers ($\Delta G^{\neq}_{273}$) of 12.7 and 15.7 kcal mol^{-1} were experimentally obtained, while the corresponding calculated values $\Delta E_{calcd.}$ are 9.8 and 13.0 kcal mol^{-1}, respectively[39].

The most straighforward method for the synthesis of calix[4]arene-based carceplexes comprises the closure of the final two bridges in solvents such as amides, e.g. *N*,*N*-dimethylacetamide and *N*-methylpyrrolidin-2-one, and sulfoxides, e.g. ethyl methyl sulfoxide (so-called solvent inclusion). In these cases the yield of the carceplex decreases with increasing guest size. However, the disadvantage of this method is that carceplexes can only be formed in highly polar solvents with a hydrogen-bond-accepting group. Therefore, a method, called doped inclusion, was developed which allows the use of a large variety of guests, such as 2-butanone and 3-sulfolene. In this case 1,5-dimethyl-2-pyrrolidinone, which itself is a poor template for incarceration, is used as a solvent and potential guests are added in 5–15 vol-%. In several doped inclusion competition experiments the templating ability of different guests was studied. From Table 1 it is clear that DMA is the best template for the carceplex synthesis.

Since the carceplexes can only be formed when the guest occupies the calix[4]- and resorcin[4]arene cavity, the templating ability is comparable to the association strength between host and guest. Furthermore, the observed yields are a rough indication for the rate of carceplex formation. The results as a whole indicate that DMA provides the best solvation of the transition state during the closure of the final two bridges. This might be due to the guest polarity as well as the size and shape of guest[39].

Solid-state NMR indicated that the behavior of incarcerated guests in the solid state differs from that in solution[40]. ^{13}C-CP/MAS dipolar dephasing experiments revealed that the cavity of the calix[4]arene-based carcerands is probably not as flexible as in solution. This will increase the energy barriers for rotation between different stereoisomers with respect to the values determined in solution.

When the amide bridges of the calix[4]arene-based carceplexes were converted into thioamide bridges, the energy barriers for interconversion between the various orientations of the guest molecule inside these thiacarcerands, are higher than for the corresponding carcerands with amide bridges (for DMA and NMP carceplexes 2.5 and 1.8 kcal mol^{-1}, respectively, at 273 K). This may be due to the stronger hydrogen-bond-donating character of the thioamide group. Furthermore, molecular-modeling simulations indicated that the thiacarcerand cavity is smaller[39].

The combination of calix[4]arenes and resorcin[4]arenes with the largest cavity synthesized by our group[41] is the so-called *holand* **15** (Figure 2). This molecule is formed by the cyclic combination of two calix[4]arenes and two resorcin[4]arenes via highly organized amido spacers. This molecule has a shielded cavity of nanosize dimensions (1000 Å^3). A systematic search for suitable guest molecules using the computer simulation program DOCK[42] revealed among others a good fit for different steroids, aromatic compounds, and sugar derivatives. However, no complexation of such molecules in $CDCl_3$ could be detected. Molecular modeling (Figure 2) revealed that probably four solvent molecules (chloroform or tetrahydrofuran) are located in the cavity, and the interaction energy of the four solvent molecules has to be overcome by the binding energy of a guest molecule. Furthermore, the extreme rigidity of

holand **15** might prevent the structural deformations that are necessary for complexation.

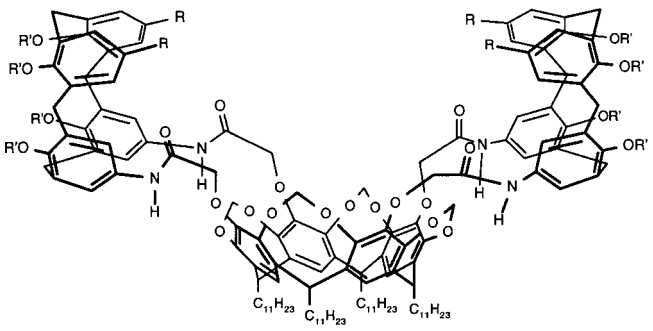
U-shaped receptor molecules **16** and **17**, composed of either two calix[4]arenes and one resorcin[4]arene[43] or of one calix[4]arene and two resorcin[4]arenes[44], have a cavity similar to that of holand **15**, but are more flexible than holand **15**. This allows them to accommodate the structural deformations probably necessary for complexation.

Receptor molecules **16**, **18**, and **19** were obtained by reaction of 1,2-bis(chloroacetamido)calix[4]arenes with tetrahydroxycavitand. Polar substituents at the remaining 3- and 4-positions of the calix[4]arenes such as nitro, acetamido, and phthalimido groups, favor the exclusive *endo* orientation of the first coupled calix[4]arene. A favorable intramolecular interaction during the formation of the second bond between the building blocks leads to an orientation of the calix[4]arene which enables only the formation of *endo*-coupled combinations. The 2:1 diastereoisomers are formed according to a statistical distribution.

These 2:1 receptor molecules selectively complex certain corticosteroids with association constants of $(0.9-9.5) \times 10^2$ M^{-1} in $CDCl_3$. Complexation studies with structurally related corticosteroids revealed that the acetate group at C^{21} and the two hydroxy groups at C^{11} and C^{17} are crucial functionalities for complexation of the steroids by this group of receptor molecules in $CDCl_3$[43].

By combining 1:1 calix-resorcin[4]arenes with a second cavitand, 1:2-coupled products (**17**) were obtained. The stereochemistry of these 1:2-calix-resorcin[4]arenes is perhaps influenced by intramolecular interactions leading exclusively to *endo-endo* isomers. The tetrahydroxy *endo-endo* isomer (**17**, R = −H) forms a spherical dimeric assembly, which may be held together by eight hydrogen bonds between the hydroxy groups and the amido bridges. From a dilution experiment a dimerization constant of K_{dimer} of 11 ± 2 M^{-1} in $CDCl_3$ was determined. Molecular-dynamics simulations showed that this dimer is stable in chloroform and the cavity is large enough to accommodate eight molecules of chloroform (Figure 3).

According to ^{1}H-NMR spectroscopy, these 1:2-calix-resorcin[4]arene receptor molecules selectively complex certain corticosteroids, sugar derivatives, and alkaloids with association constants of $(1.0-6.0) \times 10^2$ M^{-1} in $CDCl_3$. For the complexation of corticosteroids it is necessary that the guest has the acetate moiety and hydroxy groups as mentioned above. Receptor molecule **17** (R = −H) is selective for acylated five-membered sugars and quinine derivatives[44].



16 (endo-endo)
18 (endo-exo, not shown)
19 (exo-exo, not shown)

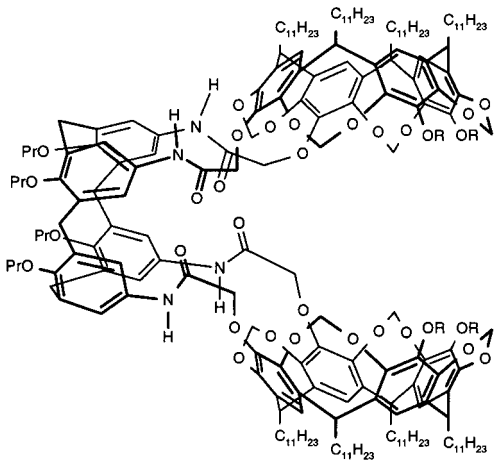


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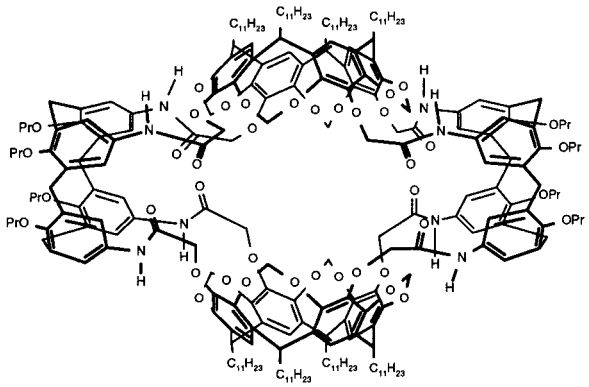
Figure 2. Time-averaged structure of holand **15** (hydrogen atoms not shown for clarity) and snapshot of typical $CHCl_3$ positions in a MD simulation



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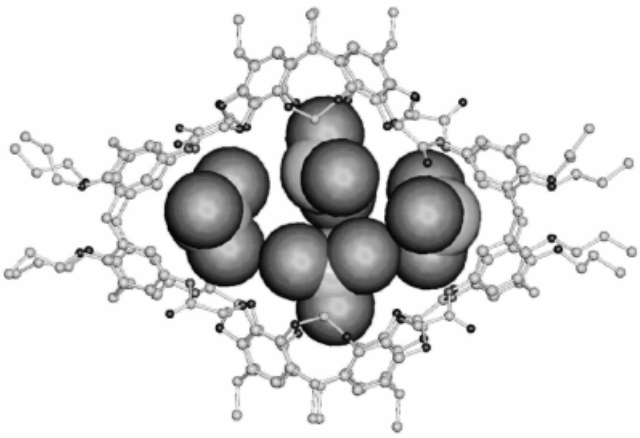
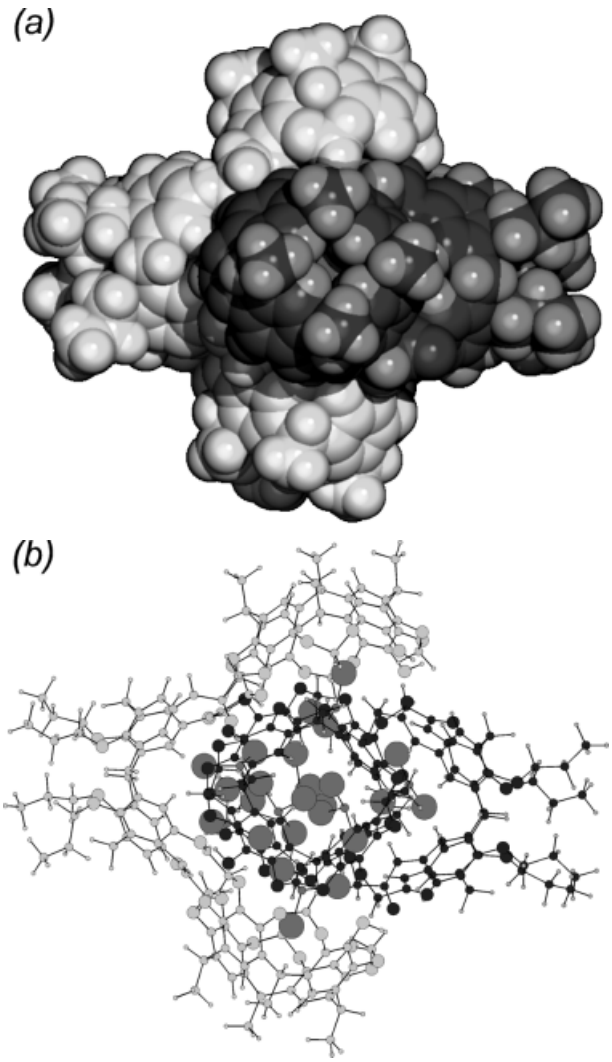


Figure 3. Typical structures from the MD simulations of the dimer of 1:2-*endo-endo*-**17** (R = −H) with eight chloroform molecules inside the cavity, (a) van-der-Waals representation and (b) ball-and-stick representation; for a color view, see ref.[44]

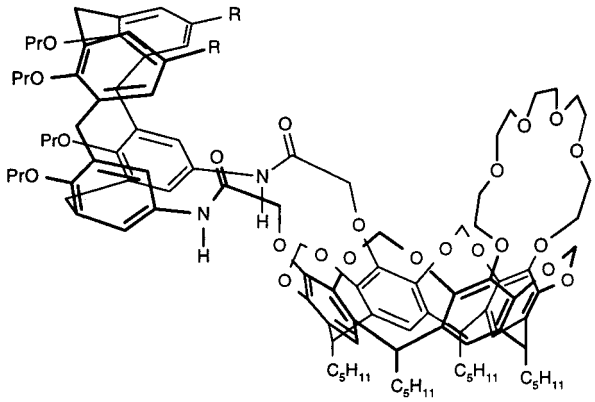


A new class of building blocks, crown[*n*]cavitands, was obtained by alkylation of tetrahydroxycavitands with polyethyleneglycol ditosylates. The combination of 1,2-crown-[6]cavitands with calix[4]arenes (**20**) and resorcin[4]arenes (**21**; x = $-CH_2-m-C_6H_4-CH_2-$ and $-[CH_2]_4-$) resulted in molecules with large hydrophobic surfaces[45].

We[46] also combined two 1,3-bis(isothiocyanato)calix[4]-arenes with two 1,3-bis(aminomethyl)resorcin[4]arenes in a cyclic array in 35−42% yield.

Combination of upper-rim 1,3-difunctionalized calix[4]-arenes with tetrahydroxycavitands resulted in 2:1-coupled products **23** in yields up to 47%. The flexibility of calix[4]-arenes and their rapid interconversion between two pinched-cone conformations prevents the formation of a 1:1-coupled product in which the calix[4]arene reacts with two hydroxy groups at opposite aromatic rings of the resorcin[4]arene[41a].

Upper-rim 1,3-difunctionalized calix[4]arenes were also combined with tribridged and A,C-dibridged resorcin[4]-



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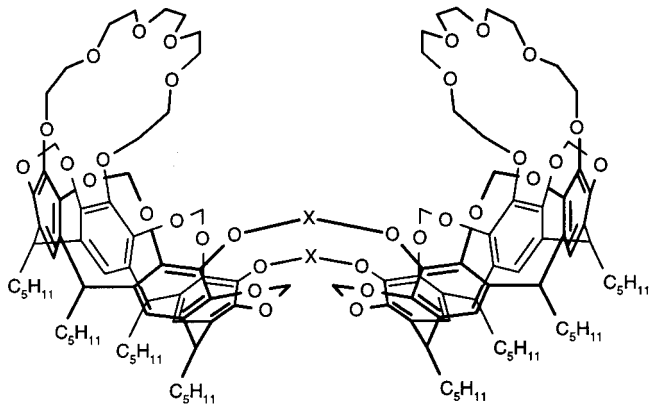

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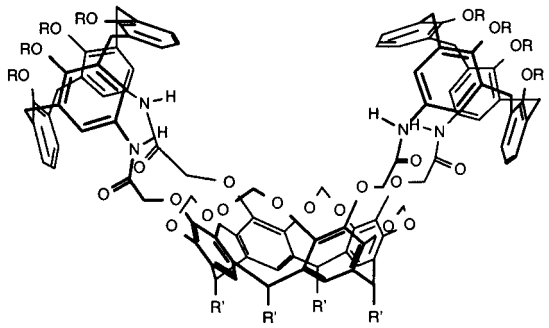
arenes which led to 1:1- and 2:1-coupled products, respectively (for the 2:1 combination see **24**)[47].

Combinations of Calix[*n*]arenes with Other Building Blocks

Chemo- and regioselective monofunctionalization of the secondary hydroxy face of β-cyclodextrins makes it possible to couple β-cyclodextrins with at the *upper-rim* monofunctionalized calix[4]arenes. The hydrophobic cavities of the β-cyclodextrins of the resulting water-soluble host molecules are shielded by flexible calix[4]arene moieties (**25**). We[48] found that these molecules show enhanced binding of fluorescent guests compared with non-derivatized β-cyclodextrin (K_{ass} value up to $1.5 \cdot 10^5$ M^{-1} in pH = 7.0 buffered aqueous solution). Pappalardo et al.[49] linked a monofunctionalized β-cyclodextrin with a calix[4]arene via the *lower rim* of a tetrafunctionalized calix[4]arene.

The flexibility of calix[6]arene can be restricted by capping to give conformationally more defined structures. 1,3,5-Trimethoxy-*para-tert*-butylcalix[6]arenes with bulky substituents in the 2-, 4-, and 6-positions exist in a flattened-cone conformation[50]. Starting from this conformation a three-point capping leads to symmetric, bowl-shaped molecules. We[51] synthesized in situ a cyclotriveratrylene unit at the lower rim of the calix[6]arene. First three



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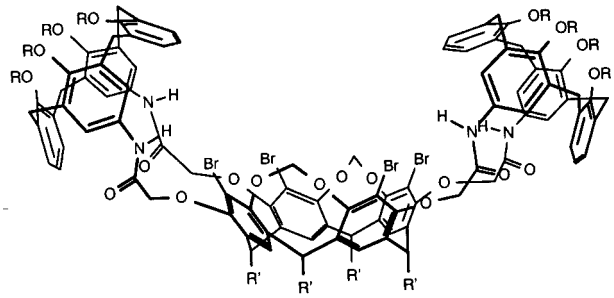

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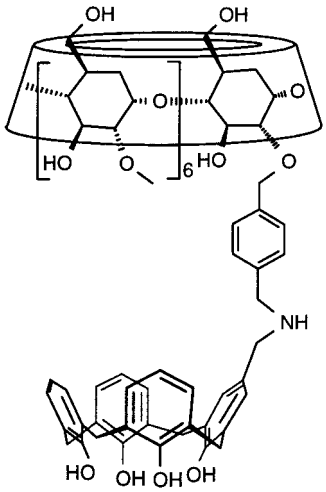

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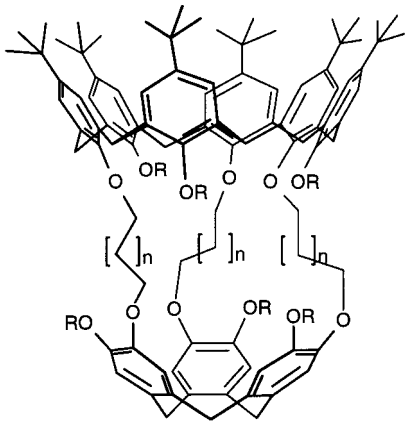

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veratryl units were coupled to a 1,3,5-trimethoxycalix[6]arene and subsequently these were intramolecularly cyclized giving cryptocalix[6]arenes **26** with an increased rigidity which mainly have C_3 symmetry.

Several groups combined calix[4]arenes with porphyrins[52]. We[53] used in situ synthesis of the porphyrin skeleton by attaching two benzaldehyde groups at the upper rim as well as at the lower rim of calix[4]arenes. Condensation with pyrrole led to porphyrins substituted with two calix[4]arenes, both attached via two linkages.

Capped biscalix[4]arene-Zn-porphyrin **27** (Figure 4) was prepared in two steps[54]. One calix[4]arene with two benzaldehyde groups was treated with pyrrole to give a bis(dipyrromethane), followed by reaction with another calix[4]arene with two benzaldehyde groups leading to the biscapped porphyrin. This receptor binds N-heterocycles circa 10-10^3 times stronger than unsubstituted porphyrins, reflecting the shielding effect of the calix[4]arene moieties.

Covalently Linked Heterocombinations of Other Building Blocks

Resorcinarenes were relatively recently introduced in supramolecular chemistry and they are not widely used in combination with other building blocks. Okazaki et al.[55] combined a cavitand, functionalized with four phenol groups, with tetrabromoterphenyl to obtain lantern-shaped molecules, which are very effective for the stabilization of highly reactive species such as monosubstituted simple enols. Sherman et al.[56] used a cavitand as a platform to organize peptides. Alkylation of tetrathiol cavitand with amino acid derivatives afforded a fixed four-helix bundle (a so-called cavitein).

Recently, Collet reviewed a number of heterocombinations of cyclotriveratrylenes with other building blocks, which he called hemicryptophanes[4].

Several groups incorporated porphyrins into supramolecular structures because they mimick biochemical functions. Mostly, only the synthesis of these systems is described; porphyrins were combined with steroid building blocks[57], with bicyclo[2.2.2]octane units[58], with azacrown moieties[59], with peptide fragments[60], and with cyclodextrins[61].

Non-Covalently Linked Combinations of Building Blocks

Non-covalently linked combinations of building blocks can be divided into three classes: (i) double calix[4]arenes, (ii) double resorcin[4]arenes, and (iii) non-covalently linked combinations of other building blocks.

Recently, Conn and Rebek[62] published a review on self-assembling capsules, including systems based on hydrogen bonding of cyclodextrins, calix[4]arenes, and cavitands. A few of these structures are also included in this review. Coordination chemistry has also been used to assemble *cage compounds*[63] but this is not within the scope of this article.

Figure 4. Complexation of N-heterocycles by biscalix[4]arene-Zn-porphyrin **27** in $CDCl_3$; (*) binding is very strong, $-\Delta G > 33.0$ kJ м$^{-1}$

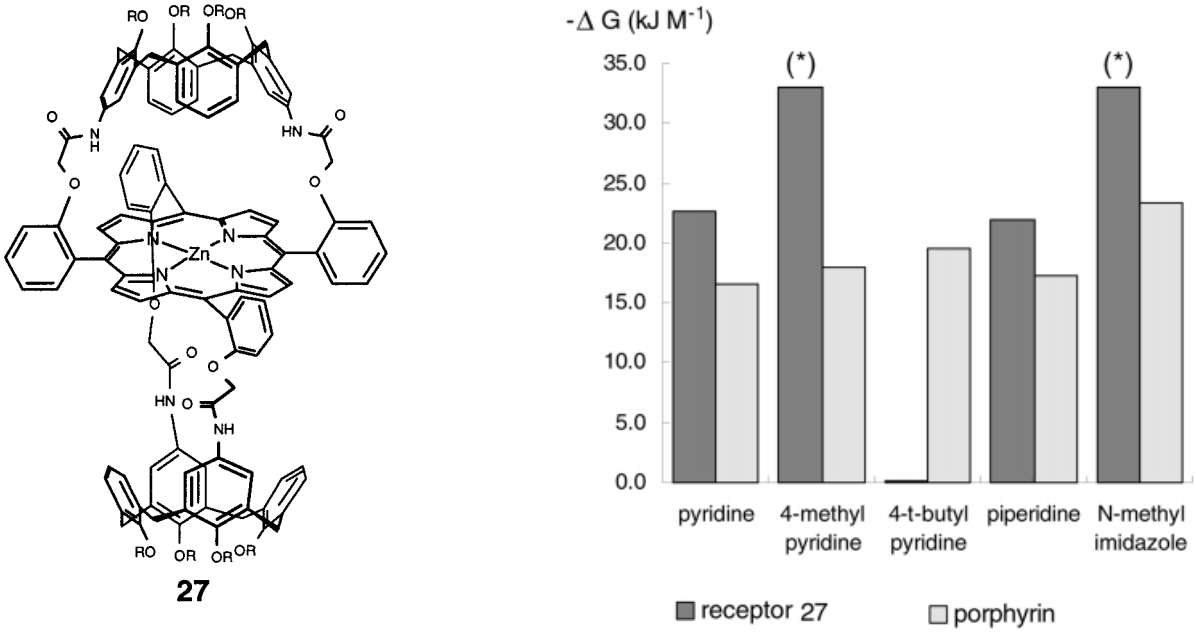
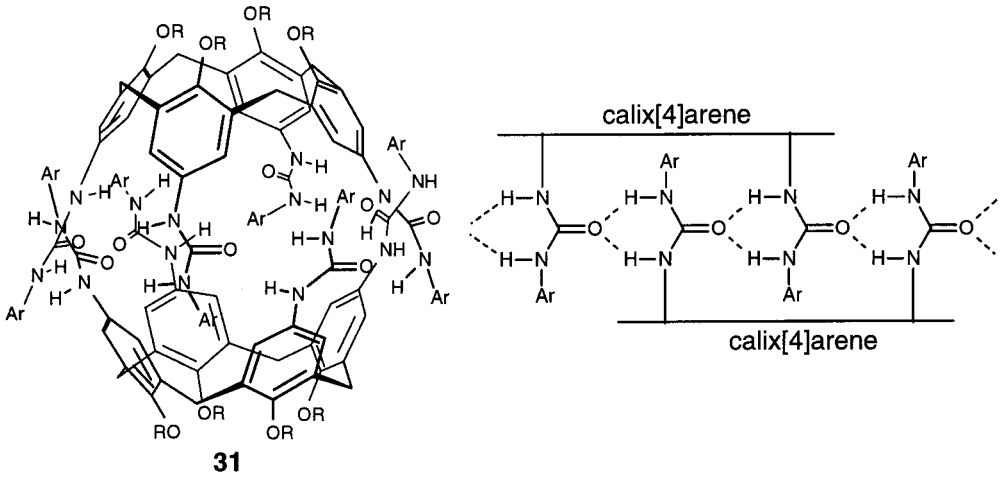


Figure 5. Dimerization of tetraureacalix[4]arene **31**; at the right the hydrogen-bonding pattern is shown

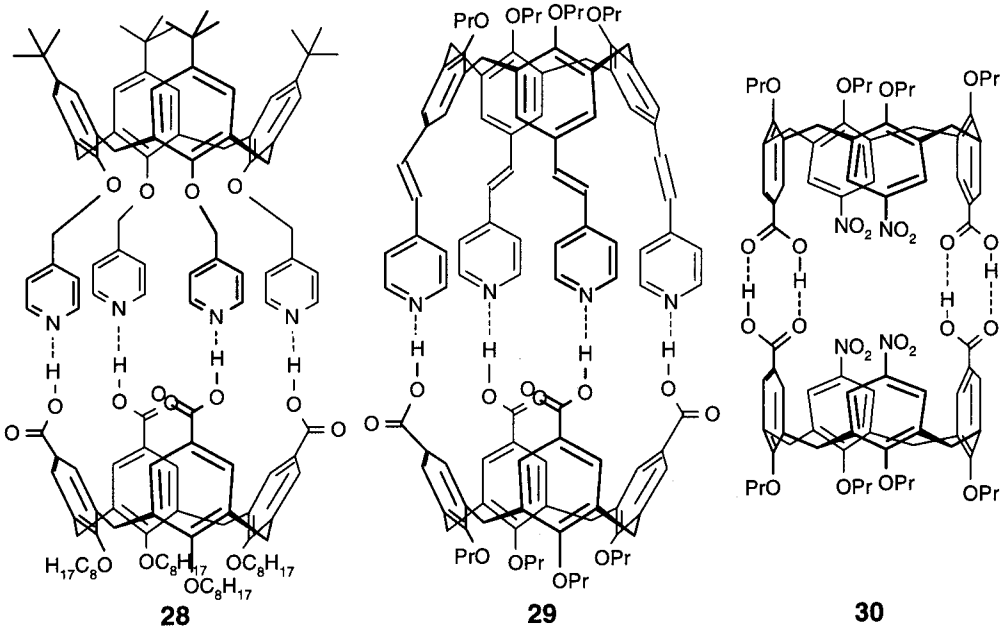


Non-Covalently Linked Calix[4]arene Dimers

A class of calix[4]arenes that form homodimers are the tetraurea derivatives. A head-to-tail hydrogen-bonding pattern containing sixteen hydrogen bonds holds the two units together (see **31** in ; R = $-CH_2C_6H_5$). Slow rotation around the aryl−urea bonds introduces asymmetry in the dimer. Inclusion of solvent molecules can be observed with ^{1}H-NMR spectroscopy, smaller molecules such as benzene or chloroform fit better than xylenes or ethylbenzene[64].

The flexible tetramethoxycalix[4]arene with four nitro groups at the upper rim mainly adopts the partial-cone conformation. However, conversion of the nitro into urea moieties (**31** in Figure 5; R = $-CH_3$) leads to dimerization of two calix[4]arenes in the cone conformation[65]. Böhmer et al.[66] have shown that in apolar solvents a mixture of two different urea derivatives forms beside homodimers AA and BB, a heterodimer AB. X-ray analysis of homodimer **31** (R = $-CH_2CO_2CH_2CH_3$) showed an array of eight urea moieties (see right side of Figure 5). By using a calix[4]arene with two different ether functionalities at the lower rim ($-CH_3$ and $-C_5H_{11}$) a dimer was obtained with C_2 instead of C_4 symmetry. In that case the exchange rates for four sets of protons could be determined by NOESY experiments. The rate constant for the dimerization is $k_d = 0.26 \pm 0.06$ s^{-1}[67].

Also the interaction between a carboxylic acid and a pyridine allows the association of two different components via hydrogen bonds. We[68] have connected a calix[4]arene functionalized at the upper rim with four carboxylic acid units with lower-rim-substituted tetrapyridylcalix[4]arene (*meta* and *para*) to give well-defined 1:1 hydrogen-bonded associates in chloroform (see formula **28**). The formation of these adducts was studied by extraction experiments in which the rather insoluble tetracarboxylic acid component



28 **29** **30**

is extracted into the chloroform layer by the tetrapyridylcalix[4]arene. Association constants determined by ^{1}H-NMR dilution experiments in $CDCl_3$ are $7.6 \cdot 10^3$ and $1.3 \cdot 10^3$ M^{-1} for the *para*-pyridyl and the *meta*-pyridyl derivative, respectively.

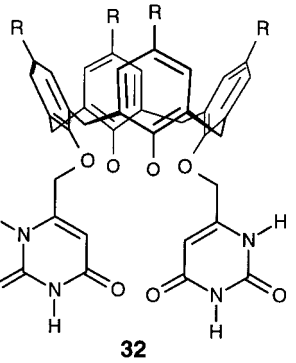
Shinkai et al.[69] attached pyridine ligands at the upper rim of a calix[4]arene to obtain the head-to-head non-covalent double calix[4]arene **29** in $CDCl_3$. A calix[4]arenetetracarboxylic acid was solubilized in chloroform by adding a tetrastilbazolecalix[4]arene. The associate was characterized by solubility and molecular-weight measurements and by fluorescence spectroscopy.

We studied the formation of homodimers of calix[4]arene-1,3-dicarboxylic acids in the solid state and in apolar solvents[70] (see **30**). NMR studies showed that the dimer adopts one of the two possible pinched-cone conformations while in polar solvents the monomer is present in the other pinched-cone conformation.

Also 1,3-bis(ureido)calix[4]arenes adopt a pinched-cone conformation in $CDCl_3$ solutions. This pinched-cone conformation is the result of diametrical, intramolecular hydrogen bonds. According to ^{1}H-NMR and FTIR experiments these bis(ureido)calix[4]arenes form hydrogen-bonded dimers[71].

The position and directionality of hydrogen-bonding moieties have a strong influence on the association of calix[4]arenes functionalized with uracil or diaminotriazine moieties. In the case of 1,3-bis(uracil)calix[4]arene **32**, self-association is observed ($K_{dimer} = 3.4 \times 10^3$ M^{-1} in $CDCl_3$) whereas, in the case of 1,3-bis(diamidotriazine)calix[4]arene **33** intermolecular association is hampered by the formation of intramolecular hydrogen bonds[72].

We have also synthesized larger aggregates of calix[4]arenes based on the 2,6-diaminotriazinimide system. 1,3-Bis(diaminotriazine)calix[4]arene formed hydrogen-bonded strands with a barbituric acid derivative resulting in the formation of a gel in chloroform[72].



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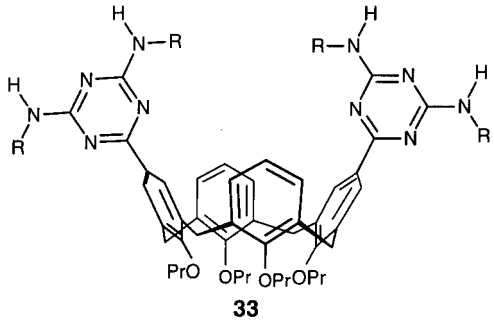

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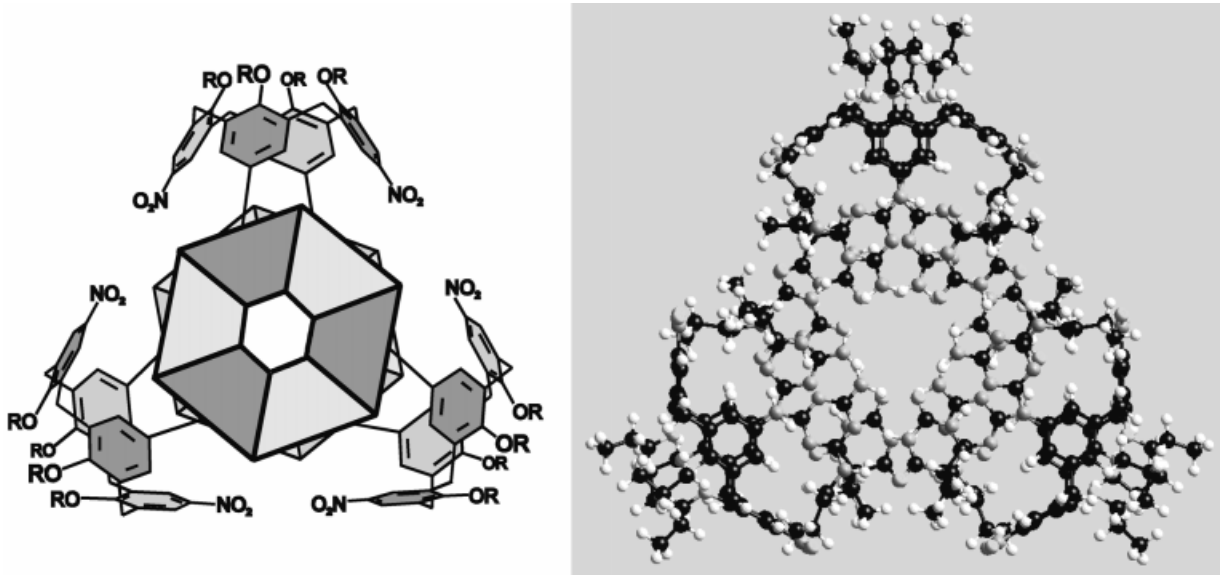
Better defined aggregates are formed by combining a bis(melamine)calix[4]arene with calix[4]arenes containing one isocyanuric acid moiety. In these cases self-assembled boxes are formed with a double-rosette structure in which the calix[4]arene serves as a spacer between the two rosettes (see Figure 6). The box-like assemblies consist of three calix[4]arenes and six barbituric acid derivatives and are held together by 36 hydrogen bonds, these are stable in apolar solvents at concentrations of up to 10^{-4} M. The assemblies are stereogenic as a result of an antiparallel orientation of the two rosette motifs[73].

The combination of coordination chemistry and hydrogen bonding can be used for the non-covalent synthesis of

Figure 6. Schematic representation of the non-covalently assembled calix[4]arene molecular boxes and top view of the X-ray crystal structure



nanostructures. The nanosized assemblies consist of a hydrogen-bonded rosette of three metallodendrimer wedges[74].

Non-Covalently Linked Carcerands

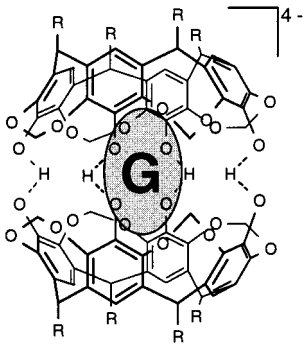
Sherman et al.[75] studied the templation and molecular encapsulation of carceplexes. During the synthesis of a carceplex (see formula **7**; X = $-OCH_2O-$) starting from two tetrahydroxycavitands, eight covalent bonds are formed and seven molecules are brought together, including the guest.

To investigate the guest-determining step they used a self-assembling structure consisting of two tetrahydroxycavitands with a guest molecule inside, which is formed in the presence of four equivalents of base (see **34**). This complex is reversible and strongly guest-selective; the complex with pyrazine is 580 times stronger than the benzene complex in $CDCl_3$[76]. Houk et al.[77] calculated relative free energies of the complexation of ternary complexes (two cavitands and a guest molecule) and found a good correlation between experimental template ratios and calculated complexation energies.

Non-Covalently Linked Combinations of Other Building Blocks

A non-covalent assembly of a calix[4]arene with a porphyrin was described by our group[78]. The melamine-barbiturate structural motif was introduced by attaching the melamine fragment to the calix[4]arene and the barbiturate fragment to a Zn porphyrin. This assembly was used as a ditopic receptor for NaSCN, NaN_3, and NaI (K_{ass} values up to $5 \cdot 10^4$ M^{-1} in CH_2Cl_2).

Other examples of complementarity of shape, size, and chemical surface is provided by Rebek but such "tennis balls" and "softballs" are not within the scope of this review[79].



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Concluding Remarks

The many examples discussed in this review of combinations of building blocks, either of *identical* or of *different* building blocks, illustrate that this new approach to combine larger subunits is a convenient method to obtain large (receptor) molecules. The use of relatively rigid, medium-sized, easily accessible building blocks to which functional groups can be attached simplifies the route to large, well-defined structures. Building blocks that are widely used in the field of supramolecular chemistry are cyclodextrins, cyclotriveratrylenes, cyclophanes, porphyrins, steroids, calix[4]arenes, and resorcin[4]arenes. For example, covalent combinations of calix[4]arenes and resorcin[4]arenes in a 1:1 ratio led to calix[4]arene-based carceplexes with a non-symmetric cavity showing a novel type of diastereoisomerism. Combinations of these building blocks in a 2:1 or 1:2

ratio gave receptor molecules selective for certain corticosteroids, alkaloids, and sugar derivatives.

So far mainly covalent bonds have been used for the connection of the different modules. Although the synthesis of receptor molecules is less demanding using this approach, it remains not-trivial. Therefore, currently this is changing to non-covalent bonds which makes this approach even more attractive on account of the often simpler synthesis.

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