SYNTHETIC RECEPTORS : A MODULAR APPROACH TO LARGE STRUCTURES

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ABSTRACT. Combination of medium-sized building blocks comprises a new strategy for the synthesis of artificial receptor molecules. These building blocks should have relatively rigid structures to which functional groups can be attached, such as calix[4]- and -[6]arenes, resorcin[4]arenes, porphyrins, and cyclodextrins. Combination of a β-cyclodextrin with a calix[4]arene moiety resulted in water soluble receptor molecules. Large multifunctional receptors have been prepared by the covalent combination of two calix[4]arenes and one Zn-tetraarylporphyrin. The controlled conformation of *p-tert*-butylcalix[6]arenes which are alternately substituted with methoxy groups, was used to synthesize a cryptocalix[6]arene consisting of a calix[6]arene and a cyclotriveratrylene unit. A new type of diastereoisomerism (*carceroisomerism*) was found during the synthesis of carceplexes constructed from one calix[4]arene and one resorcin[4]arene. In a (2+2)-mode of coupling, the combination of calix[4]arenes and resorcin[4]arenes gave a large rigid receptor molecule of nanosize dimensions *(holand)*. The combination of two calix[4]arenes with one resorcin[4]arene resulted in three different compounds (*endo-endo, endo-exo*, and *exo-exo*) with large hydrophobic surfaces to which steroids can be complexed.

G. Tsoucaris et al. (eds.), Crystallography of Supramolecular Compounds, 347–368.

1. Introduction

Nature constructs receptors 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 difficult 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 sub-units that are organized by non-covalent bonds.

Most synthetic receptors have been prepared by *de novo* synthesis using modern synthetic methodologies, which allow an almost unlimited variation. This strategy focuses on the complementarity of functional groups of receptor and guest. The drawback is that for each individual guest molecule a new synthetic pathway has to be developed.

In recent years we have developed a new strategy for the synthesis of artificial receptors which is a compromise between the two extremes described above. We use medium-sized, relatively rigid molecules to which functional groups can be attached. Calix[4]- and -[6]arenes, resorcin[4]arenes, and cyclodextrins have the required structures for such building blocks.

In addition to coupling via covalent bonds these building blocks can be connected by non-covalent bonds to give *objects* with molecular weights of more than 5000 D.

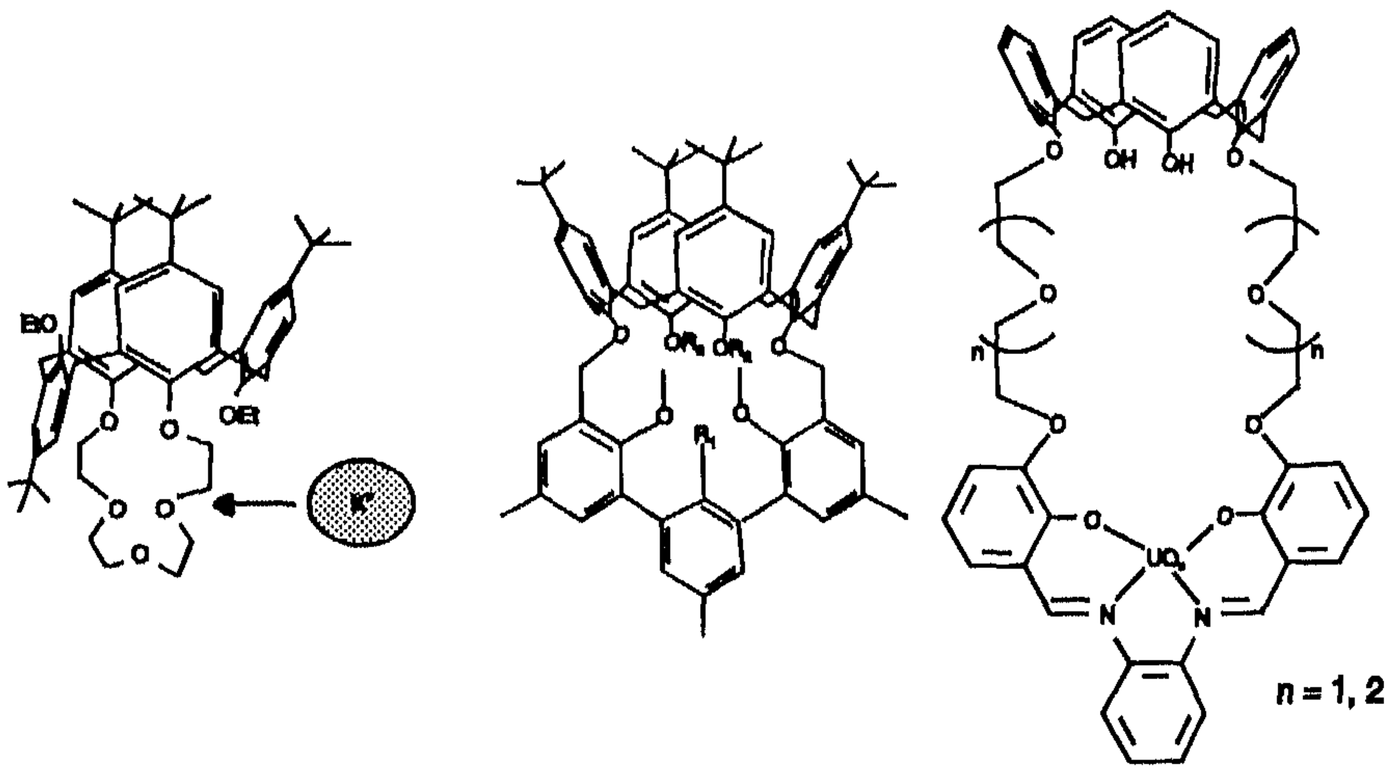
In this article we will illustrate our new strategy with a few examples of the synthesis of receptor molecules by the covalent linkage of medium-sized, relatively rigid molecules to which functional groups can be attached. Examples of the combination of calix[4]arenes with macrocycles and building blocks such as β-cyclodextrins, porphyrins, and resorcin[4]arenes are presented.

2. Combination of Calix[4]arenes with Macrocycles

Calix[4]arenes have been combined with polyethylene glycols, terphenyls, metallosalophenes and metallosalenes to give calixcrown ethers, calixspherands, anion, and ditopic receptors, respectively.

2.1. CALIXCROWN ETHERS

Calixcrown ethers can be synthesized by the selective bridging of *p-tert*-butylcalix[4]arene with glycol derivatives. The obtained 1,3-dihydroxy-*p-tert*-butylcalixcrown ethers can be rigidified by subsequent alkylation of the two remaining phenolic groups with substituents larger than C_2H_5; the resulting compounds can be formed as (a mixture of) different stereoisomers. All ligands are selective towards potassium cations with a surprisingly high K^+/Na^+ selectivity, as high as 1.18×10^4 for **1** (Chart 1). The partial cone isomer is in all cases the preferred conformation for binding of cations and showed the highest free energy of complexation [1].



(1) **(2)** $R_1 = CH_2CH_3$, $R_2 = CH_3$ **(4)**

(3) $R_1 = CH(CH_3)_2$, $R_2 = CH_3$

Chart 1

2.2. CALIXSPHERANDS

Calixspherands can be synthesized by reaction of *p-tert*-butylcalix[4]arenes with terphenyl derivatives and subsequent alkylation of the remaining hydroxyl groups (Chart 1). Appropriately substituted calixspherands form kinetically stable complexes with Na^+, K^+, and Rb^+, the complexes being present in the partial cone conformation. The kinetic stability was determined both by ^1H NMR spectroscopy and a method based on the exchange of radioactive rubidium or sodium in the complexes for nonradioactive sodium in different solvents. Both methods showed that the kinetic stability of the different complexes is strongly increased when the size of the group on the central aromatic ring of the *m*-terphenyl is increased. The latter showed that the rate of decomplexation is the rate-limiting step in the exchange of rubidium in the complex for sodium present in solution. In $CDCl_3$ saturated with D_2O, the Rb^+ complexes exhibit half-lives of decomplexation, of 139 h and 180 d, for $[\mathbf{2}\cdot Rb]^+$ and $[\mathbf{3}\cdot Rb]^+$, respectively. The complexes with Na^+ and K^+ have half-lives of decomplexation of several years [2].

The cavity of the calixspherands is also complementary to Ag^+. Although the calixspherands lack the soft donor ligands (sulfur and nitrogen) which are preferred for the complexation of the soft silver cation, the calixspherands form kinetically stable complexes with Ag^+, in $CDCl_3$ saturated with D_2O. The half-lives of decomplexation are 51 h ($[\mathbf{2}\cdot Ag]^+$) and 131 h ($[\mathbf{3}\cdot Ag]^+$) [3].

2.3. CALIXSALOPHEN CROWN ETHERS

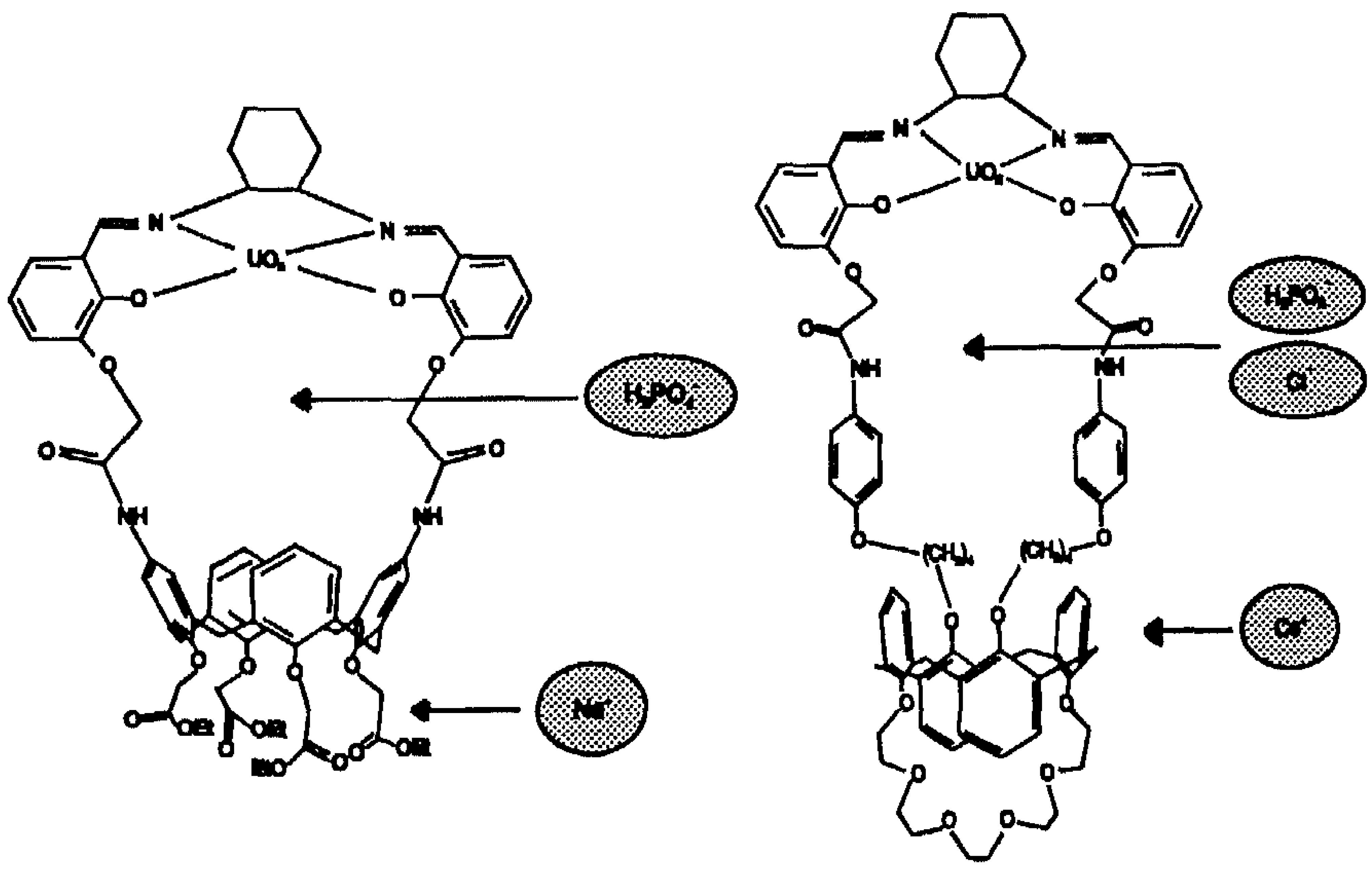
Macrocycles that contain a uranyl containing salen or salophen unit are known as complexing agents for urea or other neutral molecules that contain a nucleophilic group [4]. Calixsalophen crown ether (**4**, Chart 1) was obtained by macrocyclization of a dialdehyde functionalized calix[4]arene and a suitable diamine. The resulting receptor molecules are highly lipophilic and consequently useful as carriers for urea in supported liquid membranes. Furthermore, they have a phenolic group on either side of the crown ether ring, which can in principle be used for the

incorporation of functional groups, either as additional binding sites or for catalyzing reactions of a complexed substrate [5].

2.4. CALIX[4]ARENE BASED BIFUNCTIONAL RECEPTOR

By combination of anionic and cationic binding sites in one molecule, bifunctional receptors can be obtained which are capable to complex simultaneously anionic and cationic species. Calix[4]arenes containing four preorganized esters at the lower rim complex alkali metal cations with a high selectivity for Na^+ [6]. Neutral metalloclefts and metallomacrocycles containing both an immobilized Lewis acidic UO_2-center and amido C(O)NH groups as additional binding sites, are excellent receptors for anions with a high selectivity for dihydrogen phosphate $H_2PO_4^-$ [7].

Using calix[4]arene as a molecular platform, both four ester groups and a uranyl containing salen moiety were attached to one calix[4]arene to give a neutral calix[4]arene-based bifunctional receptor which contains both anionic and cationic sites, see **5** in Chart 2.



(5) (6)

Chart 2

A study of the binding ability of this receptor showed that it selectively binds dihydrogen phosphate $H_2PO_4^-$; only weak binding was observed for the divalent HPO_4^{2-} anion. From ^1H NMR dilution experiments, an association constant of 3.5 x 10^2 M^{-1} in DMSO-d_6 was calculated . In the positive FAB mass spectrum of the 1:1 complex of the ditopic receptor with NaH_2PO_4 an intense peak corresponding to the [host + Na^+]$^+$ was observed, while the corresponding negative FAB mass spectrum of the same sample yielded an intense peak for [host + $H_2PO_4^-$]$^-$. This proves the complexation of both cation and anion in one bifunctional receptor molecule [8].

Our strategy to combine the anion and the cation binding sites in one receptor molecule was also the basis of a neutral bifunctional receptor which can be used for carrier-assisted cotransport in which the anion and cation of a hydrophilic salt are bound and transported simultaneously through a membrane. As in the previous example, the combination of a Lewis acid UO_2-center and amido C(O)NH moieties was used as receptor site for dihydrogen phosphate ($H_2PO_4^-$) or chloride anions. The calix[4]arene crown-6 (1,3-alternate) fragment was used for the selective complexation of cesium cations (**6**, Chart 2). The transport of CsCl by the monofunctional carriers (anion and cation) exhibits low flux values (0.07-0.42 x 10^{-7} mol m^{-2} s^{-1}). This can be expected because when only one of the ionic species is complexed, the uncomplexed chloride cannot sufficiently penetrate the lipophilic membrane. For the bifunctional carrier with CsCl a significant flux (1.20 x 10^{-7} mol m^{-2} s^{-1}) was observed. This carrier showed a surprisingly low flux (0.89 x 10^{-7} mol m^{-2} s^{-1}) for $CsNO_3$, although NO_3^- is more lipophilic than Cl^-. This proves that *both* anion and cation binding sites are involved in the complexation and that the presence of only an anion or a cation binding site in the receptor molecule is not sufficient for effective transport of a *hydrophilic* salt such as CsCl. This also suggests a preference of hydrophilic CsCl over lipophilic $CsNO_3$ [9].

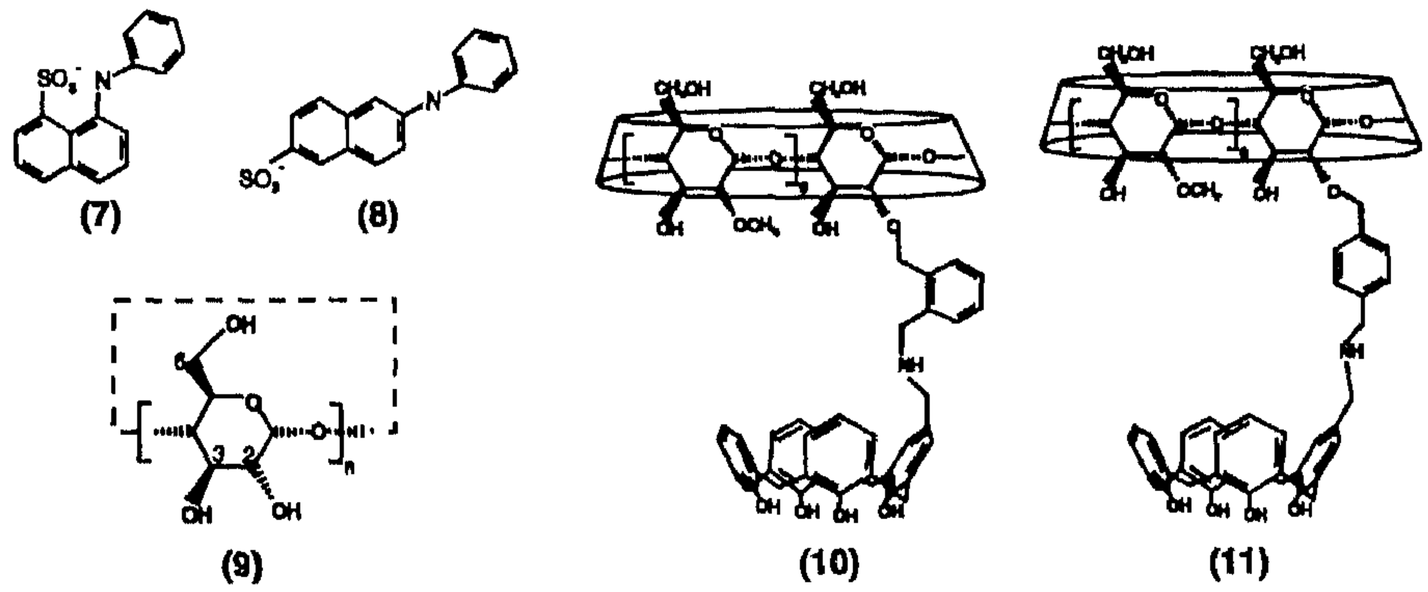
3. Combination of Calix[4]arenes with Other Building Blocks

More recently we have investigated combinations of β-cyclodextrins and calix[4]arenes, of porphyrins and calix[4]arenes, of cyclotriveratrylene and calix[6]arenes and of resorcin[4]arenes and calix[4]arenes.

3.1. CALIX[4]ARENES COMBINED WITH β-CYCLODEXTRINS

Cyclodextrins are known as a unique group of naturally occurring cyclic D-glucose oligomers, capable of the complexation of hydrophobic guest molecules in aqueous solution by predominantly hydrophobic interactions [10].

Modification of β-cyclodextrins with a calix[4]arene moiety at the secondary face resulted in receptor molecules which are very effective hosts for the fluorescent dyes 1-anilino-8-naphthalenesulphonate (ANS, **(7)** in Chart 3) and 2-*p*-toluidino-6-naphthalenesulphonate (TNS, **(8)** in Chart 3) with association constants much higher than reported thus far in the literature for cyclodextrins capped at the primary or secondary hydroxyl face. The strongly increased binding capacity is attributed to the additional shielding of the guest by the upper rim of the calix[4]arene which can cover the secondary hydroxyl face of the cyclodextrin cavity [11].



(7) **(8)** **(9)** **(10)** **(11)**

Chart 3

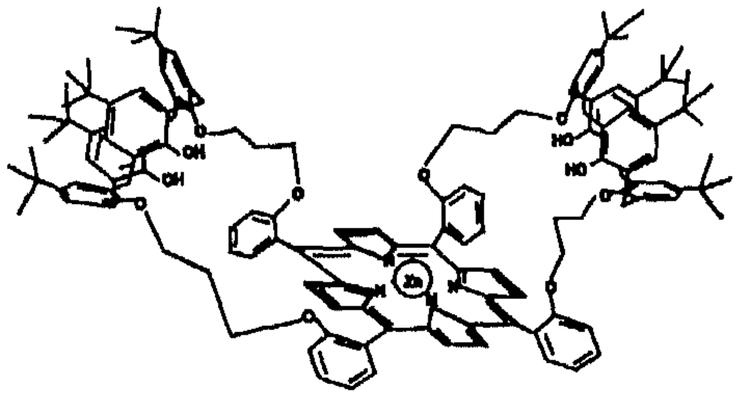
For the combination of calix[4]arenes with cyclodextrins it is necessary to monofunctionalize the cyclodextrins at the secondary face. Two methods have been reported for this monofunctionalization. In the first method a functional group is introduced at the C(3) position (see **9** in Chart 3) of the cyclodextrin by first tosylation of a secondary hydroxyl group of a silylated cyclodextrin and subsequent nucleophilic ring opening of the intermediate cyclodextrin mannoepoxide. The second method comprises the direct and selective introduction of functional groups at the secondary hydroxyl face of silylated cyclodextrins via monoalkylation of the C(2)-oxyanion, leaving the configuration of all glucose units in the cyclodextrin unaffected. The second method was also followed in the synthesis of a secondary face tethered cyclodextrin dimer and for the synthesis of two novel cyclodextrin-calix[4]arene host molecules. For the latter compounds, silylated β-cyclodextrins, functionalized with an *ortho*- or *para*-aminoxylyl spacer, were coupled to a calix[4]arene monoformyl derivative by reductive amination. After desilylation of the cyclodextrin residues two water soluble cyclodextrin-calix[4]arene receptors (**10** and **11** in Chart 3) were obtained of which the opening of the hydrophilic cavity at the secondary hydroxyl face is flexibly shielded by the aryl residues of the calix[4]arene moiety [12].

3.2. CALIX[4]ARENES COMBINED WITH PORPHYRINS

Large multifunctional receptors for molecular recognition have been prepared by covalent combination of two calix[4]arenes and one Zn-tetraarylporphyrin. Zn-porphyrins are being used in biomimetic chemistry for recognition of biologically important molecules such as nucleotides and amino acids.

Covalent combination of porphyrin and calix[4]arene building blocks may lead to receptors with multifunctional complexing properties. Two biscalix[4]arene-Zn-tetraarylporphyrins were prepared by the condensation of pyrrole with 1,3-diformylcalix[4]arenes. The aldehyde moieties were immobilized either at the *lower* or the *upper* rim of the calix[4]arene platform, (**12** and **13** (M=Zn) in Chart 4). These receptors possess an

active metallocenter which is able to complex anions and neutral species, and two lipophilic calix[4]arene moieties in a large preorganized cavity [13].



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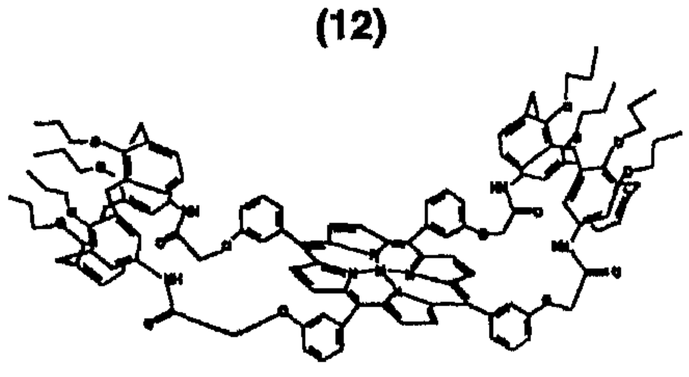

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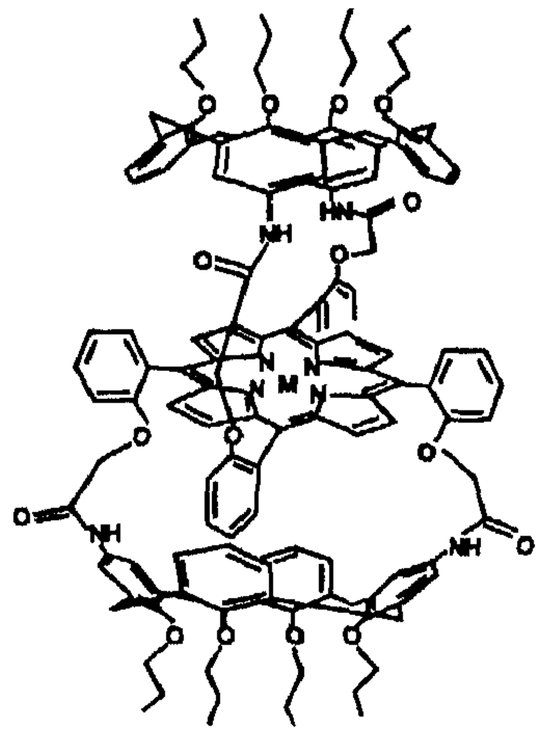


(14)

Chart 4

The active metalloporphyrin core in biscalix[4]arene-Zn-porphyrin **14** (M=Zn) is covalently incorporated into a hydrophobic and rigid *egg-shaped* biscalix[4]arene cavity. The difference with the biscalix[4]arene-Zn-tetraarylporphyrins **12** and **13** is that in **14** the calix[4]arenes are coupled via distal positions, and in the former cases via the proximal positions of the porphyrin. For this reason the core of biscalix[4]arene-Zn-porphyrin **14** provides a more effective shielding and encapsulation of a substrate [14].

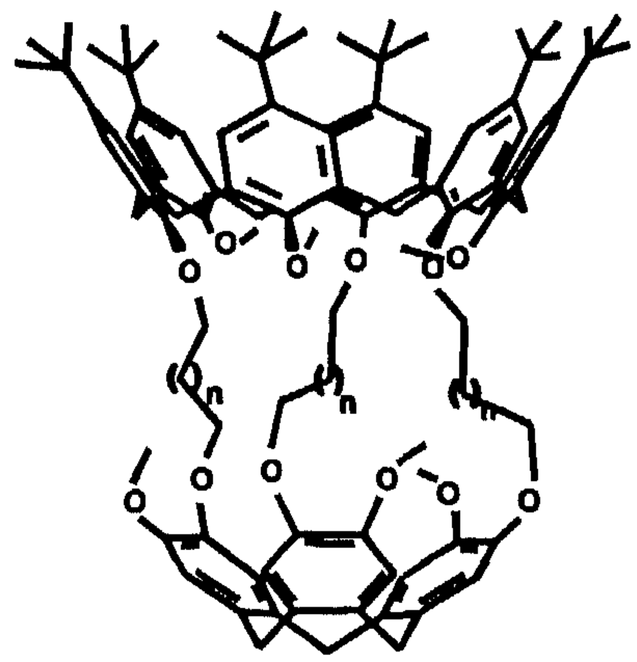
3.3. CRYPTOCALIX[6]ARENES

Since calix[6]arenes are even more flexible than calix[4]arenes, capping would provide a method to obtain conformationally more defined calix[6]arene derivatives.

In a detailed study of the conformational properties and dynamic behavior of calix[6]arenes, we found that *p-tert*-butylcalix[6]arenes which are alternately substituted with methoxy groups and bulky substituents predominantly exist in a flattened cone conformation [15]. The *syn*

arrangement of the bulky substituents in space provides an ideal stereochemistry to cap the lower rim of calix[6]arene via an intramolecular cyclotrimerization. Veratryl alcohol can be easily derivatized and cyclotrimerized to cyclotriveratrylenes in reasonable to good yields [16].

Cryptocalix[6]arenes **15** (Chart 5) containing both a calix[6]arene and a cyclotriveratrylene unit, were prepared via three-point capping of calix[6]arenes to give compounds with an increased rigidity and a well-defined conformational and dynamic behavior.



(15)

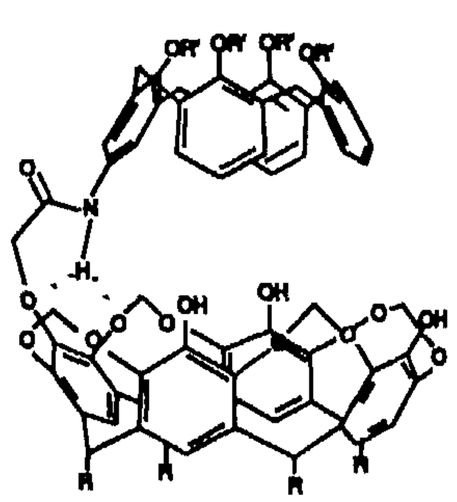
Chart 5

The ^{1}H NMR spectra of these cryptocalix[6]arenes clearly prove the C_3 symmetry of these molecules. Low temperature ^{1}H NMR spectra showed the existence of a minor conformer beside the major C_3 conformer, whose resonances coalesce upon raising the temperature. In the minor conformer one anisole moiety has rotated in such a way that its *tert*-butyl group is located in the cavity [17].

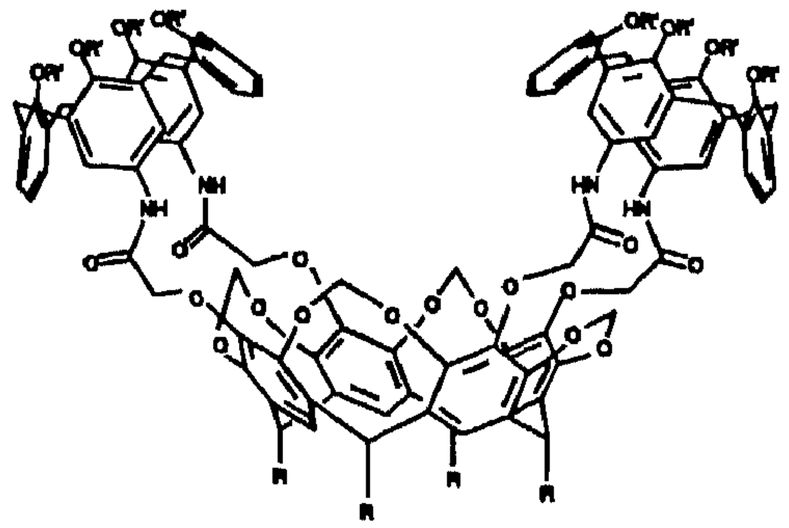
4. Combination of Calix[4]arenes with Resorcin[4]arenes

Coupling reactions of calix[4]arenes and modified resorcin[4]arenes have also been investigated. Direct combination of *upper rim* tetrafunctionalized

calix[4]arenes (with alkoxy groups at the *lower rim*) with tetrafunctionalized resorcin[4]arenes is not possible because of the flexibility of the calix[4]arenes. Reaction of mono(chloroacetamido)calix[4]arene with a tetrahydroxycavitand gave the 1:1 coupled product (calix-resorcinarene **16** in Chart 6) in 61% yield. Combination of an *upper rim* 1,3-difunctionalized calix[4]arene with a tetrahydroxycavitand afforded predominantly the 2:1 calix-resorcinarene **17** (Chart 6) in 47% yield [18].



(16)



(17)

Chart 6

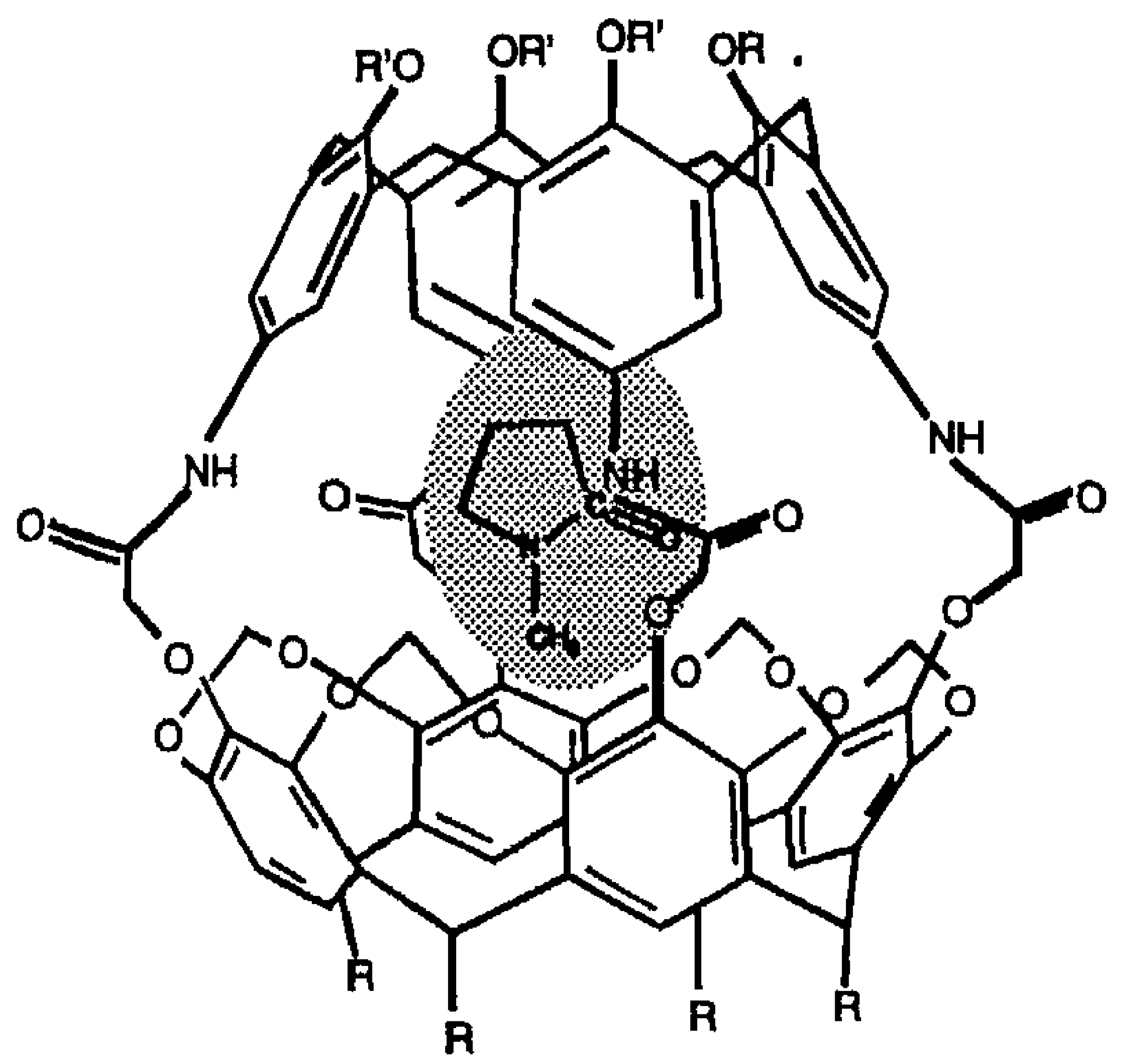
The combination of tetrahydroxycavitand and *upper rim* 1,2-difunctionalized calix[4]arenes is possible in different ratios depending on the reaction conditions.

4.1. CALIX[4]ARENE BASED CARCEPLEXES

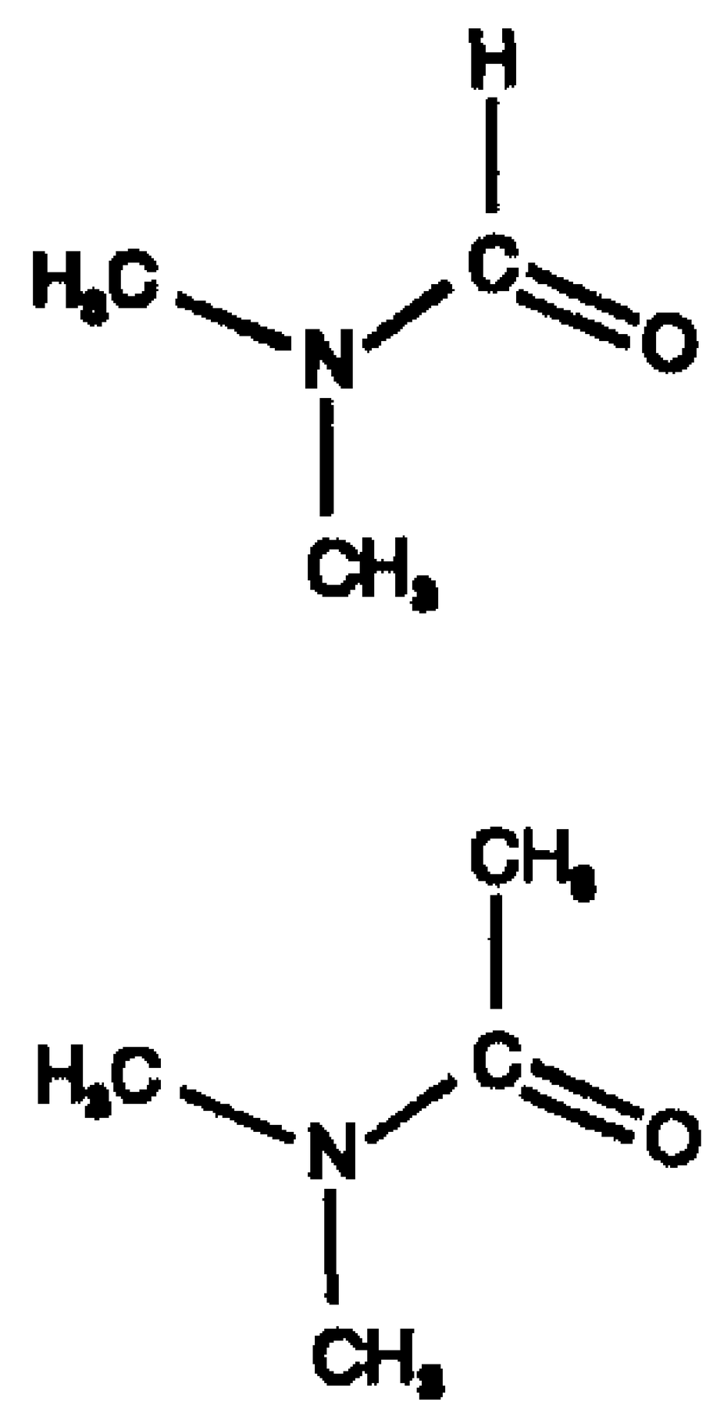
Carcerands are characterized by their ability to trap guest molecules in their interior space [19]. During synthesis they form carceplexes by capturing guest molecules from the medium that cannot leave the cavity without the rupture of at least one covalent bond of the host. Carcerands are usually formed by combination of two resorcinarene-based cavitands; these carcerands have D_{4h} symmetry. Different orientations of the guest molecule inside such cavities do not lead to diastereomeric structures due to the overall symmetry of the carceplex. However, a carceplex constructed from both a calix[4]arene and a resorcin[4]arene has C_{4v} symmetry which could lead to diastereomeric structures caused by

different orientations of the guest [20].

Stepwise 1:1 coupling of the respective building blocks gave calix[4]arene-based carceplexes which possess a non-symmetrical cavity that is completely closed. In this way the calix[4]arene-based carceplexes with *N,N*-dimethylformamide (DMF), 1-methyl-2-pyrrolidinone (NMP) **(18)**, and *N,N*-dimethylacetamide (DMA) as guests were isolated (Chart 7).



(18) carceplex • NMP



DMF

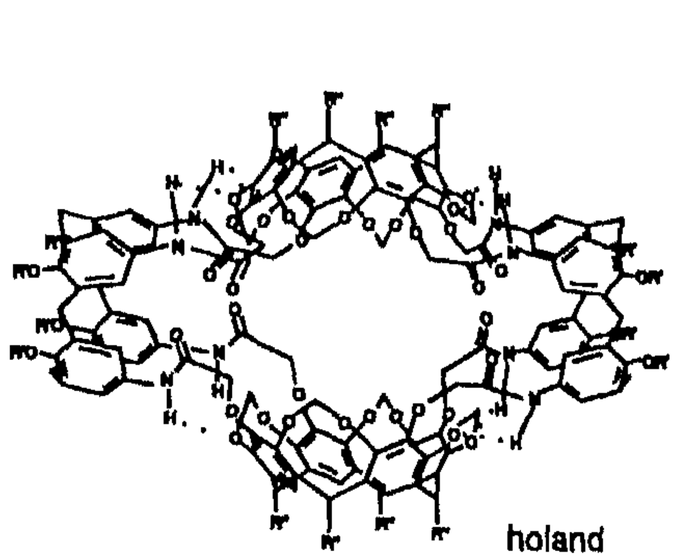
DMA

Chart 7

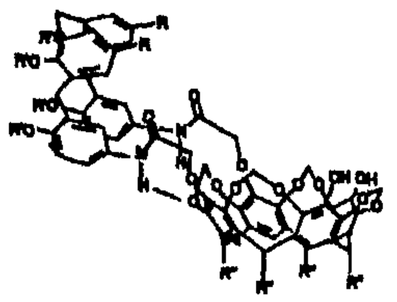
These carceplexes contain one guest molecule inside the cavity and they can be present as two different diastereomers (*carceroisomerism*). NMR and computational studies have revealed a good relation between experimental and calculated activation energies of the isomerization process [21].

4.2. HOLANDS

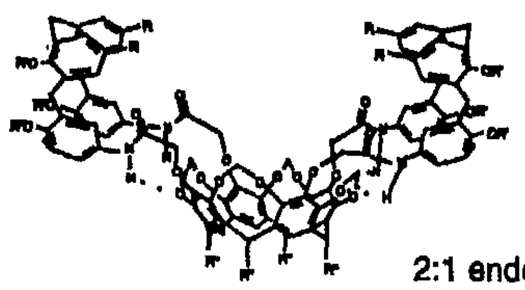
In a (2+2)-mode of coupling, the calix[4]arene and resorcin[4]arene building blocks give a large, rigid receptor molecule. This molecule **19**, a holand, can be synthesized starting either from the *endo* 1:1 isomer **20** or the *endo-endo* 2:1 isomer **21** (see Chart 8).



holand
(19)



1:1 endo
(20)



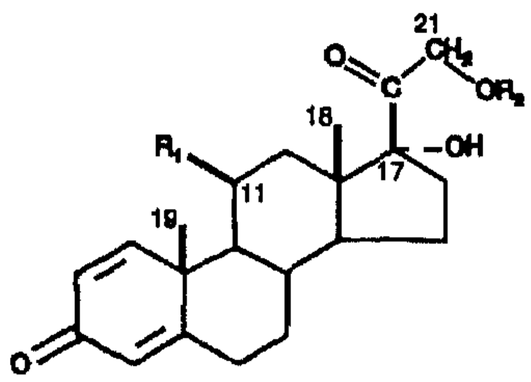
2:1 endo-endo
(21)

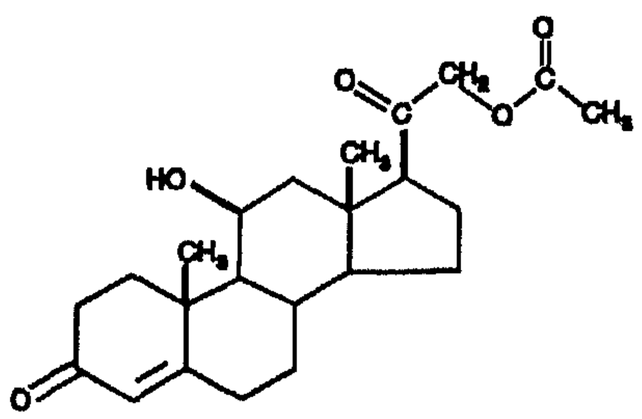
Chart 8

The formation of the 2:2 structure was proven by FAB mass spectrometry; its ^{1}H NMR spectrum reflects the high degree of symmetry as expected for the holand. For its size, the molecule is extremely rigid: the calix[4]arene and cavitand moieties, which are intrinsically rigid, are connected by highly preorganized spacers. The holand contains a cavity of nanosize dimensions. According to CPK models, the axes are 1.5 and 2.0 nm and the molecule has a calculated internal volume of approximately 1.0 nm^3 (1000 Å^3). During a 50 ps dynamics simulation (at 300 K in a $CHCl_3$ box with 46 Å edges) of the energy-minimized structure of this molecule, four chloroform molecules entered the cavity and stayed there during the entire simulation without changing the shape of the cavity, supporting the rigid structure of the holand [20].

4.3. SYNTHETIC RECEPTORS THAT COMPLEX STEROIDS

The chemistry of synthetic receptors for a variety of cations, anions, and small neutral molecules is well known, but the synthesis of receptor molecules for larger guest molecules is relatively unexplored. The holand, with a large and rigid cavity of nanosize dimensions, was studied for suitable guest molecules using the computer simulation program DOCK. This systematic search revealed an excellent fit for a number of steroids, in particular prednisolone-21-acetate **(22)** (see Chart 9).





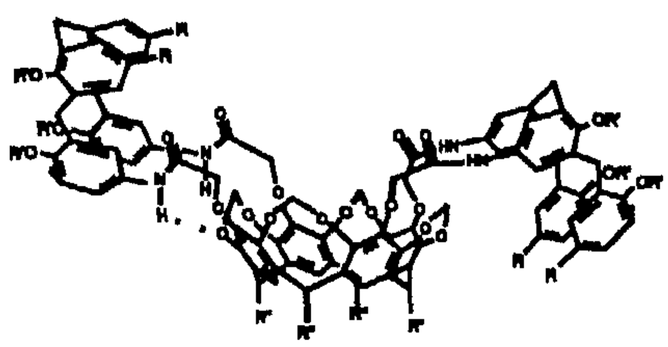
	R_1	R_2
(22) prednisolone acetate	-OH	$-C(O)CH_3$
(23) prednisolone	-OH	-H
(24) prednisone acetate	=O	$-C(O)CH_3$

(25) Corticosterone acetate

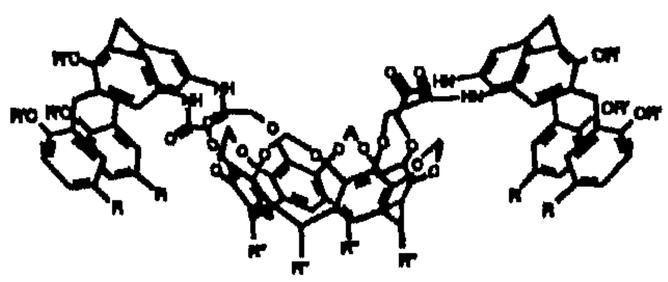
Chart 9

The complexation of steroids in *apolar* solvents has hardly been studied, in contrast with that in polar solvents. The complexation of steroids in aqueous solution by water soluble azacyclophanes [22] or cyclodextrins [23] is well known and the stability and selectivity is mainly governed by hydrophobic interactions.

Coupling of two calix[4]arenes with one resorcin[4]arene gives three different isomers: *endo-endo* **21**, *endo-exo* **26**, and *exo-exo* **27** (see Charts 8 and 10). These molecules have a large hydrophobic surface (which is in the case of **21** a part of the cavity of the holand) to which steroids can be complexed [24].



(26) endo-exo

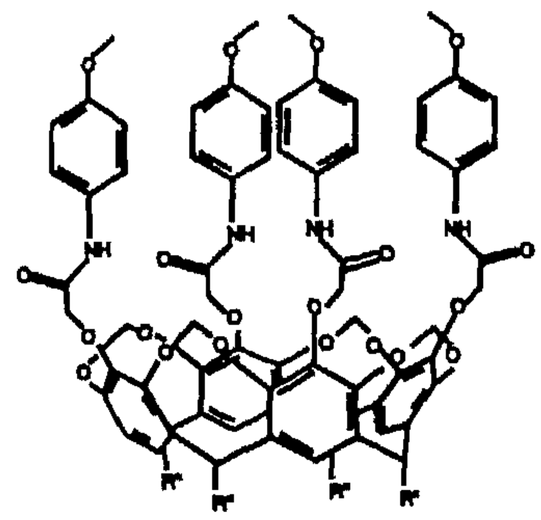


(27) exo-exo

Chart 10

Upon the addition of prednisolone-21-acetate **(22)** to solutions of these receptor molecules (**21**, **26**, or **27**, with R=H) in $CDCl_3$ at 25 °C, several host proton signals, *viz.* the amide resonances, split into two signals of equal intensity. The observed splitting is larger for the *exo* amide protons

(*ca.* 0.4 ppm) than for the *endo* amide protons (*ca.* 0.1 ppm). The signals of prednisolone-21-acetate **(22)** show considerable shifts. The singlet for the acetyl methyl group at δ 2.0 shifts and becomes much broader, even when the host is present in low concentrations (ratio 1:10). The AB quartet of the C-21 methylene group shifts upfield by *ca.* 0.2 ppm and also the singlets for both methyl groups (C-18 and C-19) show upfield shifts. The observed splitting of the amide proton signals of the receptor molecules upon complexation of prednisolone-21-acetate **(22)** is due to the chirality of the guest molecule. As a result of the complexation, enantiotopically related protons in the free host become diastereotopic in the chiral complex. However, in the case of the *endo-endo* conformer and the *exo-exo* conformer, which both exhibit C_{2v} symmetry, the homotopic amide protons give rise to only one signal as a result of fast exchange between the free host and the complex on the ^1H NMR chemical shift timescale.



(28)

Chart 11

Prednisolone-21-acetate **(22)** is complexed by receptors **21**, **26**, and **27** with association constants of 4.3 - 8.3 x 10^2 M^{-1} in $CDCl_3$ at room temperature. The relatively small difference in association constant between *endo-endo* **21** (R=H) and *exo-exo* **27** (R=H) suggests that the upper rim cavity of the calix[4]arene fragments contributes little to the binding. In order to prove that the calix[4]arene fragments in these receptor molecules play a crucial role in the complexation of prednisolone-21-acetate **(22)**, a cavitand carrying four *para*-methoxyphenyl-aminocarbo-

nyl-methoxy substituents **28**, was synthesized (see Chart 11).

Neither the signals of the host nor the guest signals shifted upon the addition of up to 10 equivalents of prednisolone-21-acetate **(22)** to a solution of host in $CDCl_3$. This unambiguously proves that complexation of prednisolone-21-acetate **(22)** by the diastereoisomeric 2:1 products is not simply a result of the presence of four amide moieties at the upper rim of a cavitand, but that preorganization of the amide spacers due to the presence of the calix[4]arene fragments is at least partially responsible for the observed complexation.

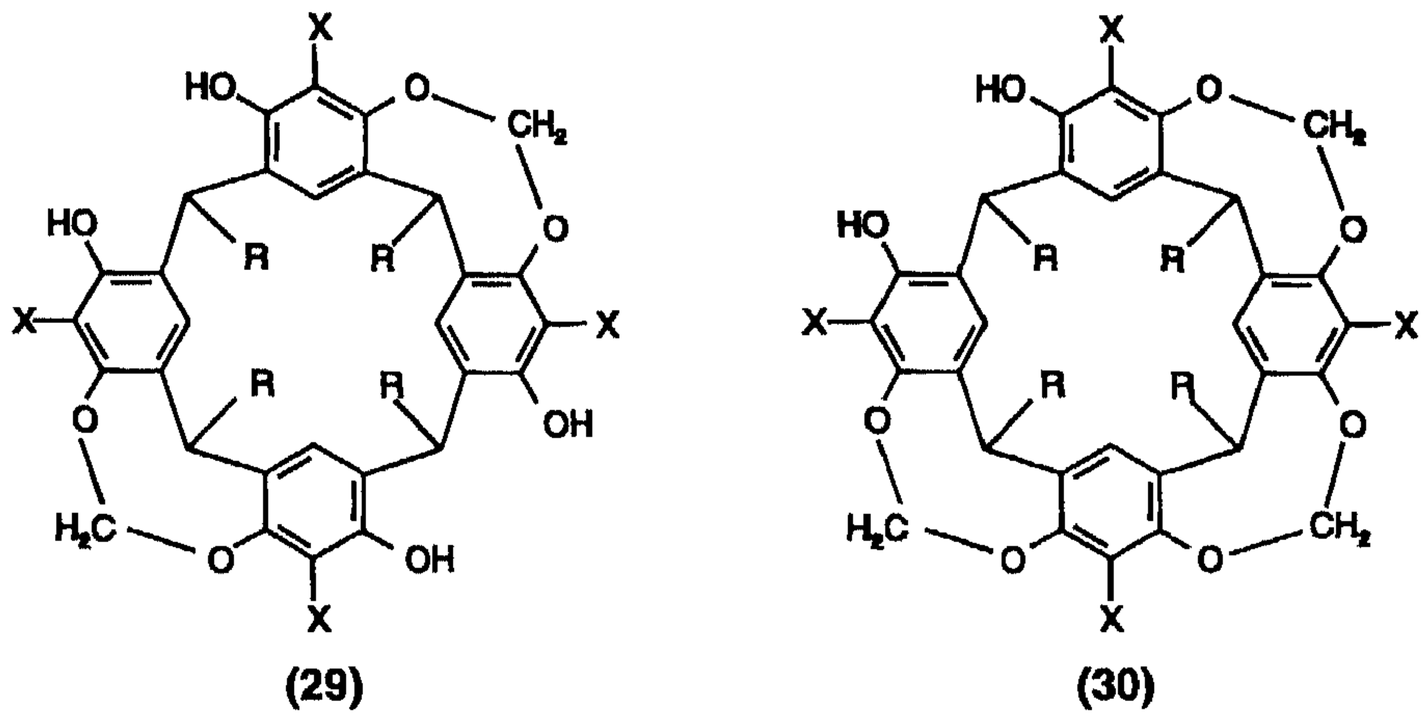
By comparison with other steroids it appeared that at least three functional groups are involved in complexation. In order to determine which functionalities in the guest favor complexation by these receptors, the related corticosteroids prednisolone **(23)**, prednisone-21-acetate **(24)** and corticosterone-21-acetate **(25)** were also studied. Addition of prednisolone **(23)** to a solution of any of the 2:1 products in $CDCl_3$ did not give rise to any significant shift of guest or host protons. With prednisone-21-acetate **(24)**, having a keto function at C-11 instead of a hydroxyl group, the splitting of the amide proton signals was absent in case of the *endo-endo* and strongly diminished in the cases of the *endo-exo* and *exo-exo* isomers ($\Delta\delta < 0.1$ for the *exo* amide protons). Significant shifts of guest proton signals were not observed for any of the three diastereoisomers. Very similar results were obtained with corticosterone-21-acetate **(25)** a steroid that lacks the hydroxyl group at C-17.

These results show that at least three functional groups in prednisolone-21-acetate **(22)** are involved in complexation. First of all, the acetoxy group at C-21 that can interact both *via* CH-π interactions of the slightly acidic acetyl group with the aromatic rings of the cavitand, and *via* hydrogen bonding interactions of the carbonyl group with the amide protons. Secondly, the hydroxyl groups at C-11 and C-17 seem also involved in the complexation, most probably via hydrogen bonding.

Addition of prednisolone-21-acetate **(22)** to a solution of holand **19** in $CDCl_3$ did not give significant shifts or splitting of signals in the ^1H NMR spectrum of both host and guest. Probably the extreme rigidity of the host prevents the molecule from accommodating the structural deformations necessary for complexation.

4.4. COMBINATION OF CALIX[4]ARENES WITH PARTLY BRIDGED RESORCIN[4]ARENES

Calix[4]arenes can also be combined with partly bridged resorcin[4]arenes. Combination of *upper rim* 1,3-difunctionalized calix[4]arenes with A,C-di-bridged **29** and tri-bridged resorcin[4]arenes **30** (Chart 12) yields both 1:1 and 2:1 calix-resorcin[4]arenes [25].

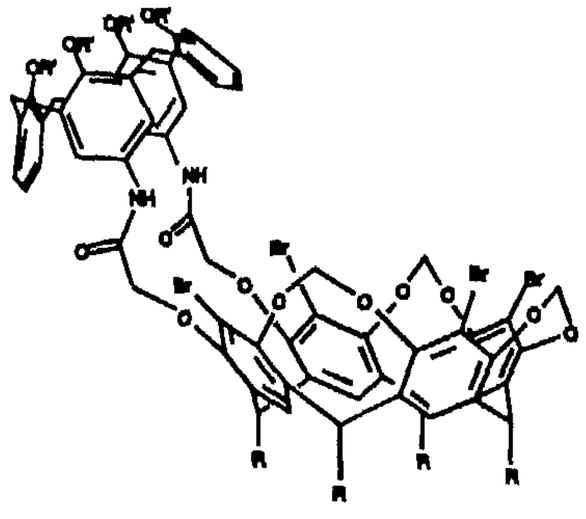


(29) **(30)**

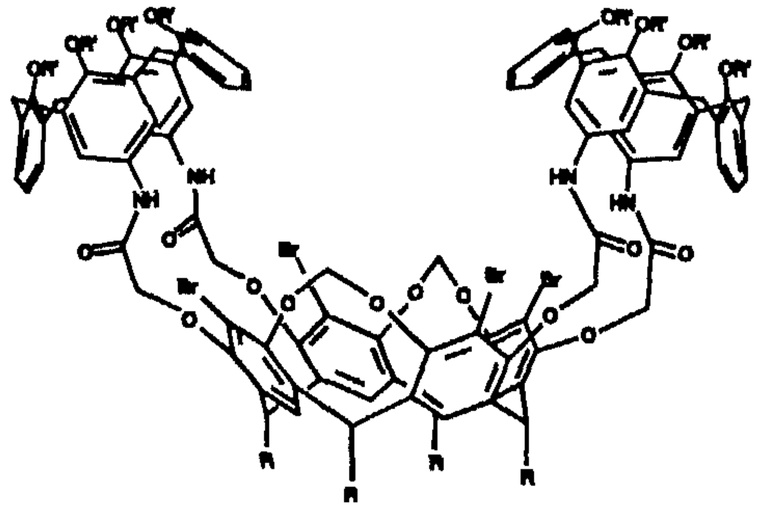
Chart 12

Partly bridged resorcin[4]arenes possess free phenolic hydroxyl groups which render them suitable candidates for combination with *upper rim* functionalized calix[4]arenes for the synthesis of receptor molecules with large hydrophobic surfaces. The simplest way to connect partly bridged resorcin[4]arenes to *upper rim* functionalized calix[4]arenes is to react the phenolic hydroxyl groups of the resorcin[4]arene *via* a nucleophilic substitution reaction with electrophilic sites at the *upper rim* of the calix[4]arene. However, the reactivity of electrophilic groups in electron-rich aromatic rings like those in cavitands and calix[4]arenes is rather low. For this reason we decided to introduce nucleophilic groups at the *upper rim* of calix[4]arenes, *viz.* hydroxyl or amino groups. In order to connect the two buiding blocks, a spacer containing two electrophilic end groups, like $-CH_2C(O)-$, is required, which can easily be incorporated using reagents like $BrCH_2C(O)OMe$ or $ClCH_2C(O)Cl$.

Tri-bridged resorcin[4]arene derivatives **30** were combined with several 1,3-difunctionalized calix[4]arenes. The coupling of a diacid dichloride resorcin[4]arene with 1,3-diaminocalix[4]arene afforded the 1:1 calix-resorcin[4]arene **31** in 46% yield, which was comparable to the coupling reaction of dihydroxyresorcin[4]arene with 1,3-bis(chloroacetamido)calix[4]arene. The reaction of a diacid dichloride resorcin[4]arene with 1,3-dihydroxycalix[4]arene gave a 1:1 calix-resorcin[4]arene in only 13% yield, which can be attributed to the enhanced flexibility of the 1,3-dihydroxycalix[4]arene. The yield could be increased to 48% when using Cs_2CO_3 as a base (cesium-template effect). The 1:1 calix-resorcin[4]arene mainly exists as one conformer, but at low temperatures a second conformer could be observed, which is only present in small amounts (<5%). Both conformers equilibrate via rotation about one of the C(arene)-N bonds, with an activation free energy ($\Delta G^{\neq}$) of 13 kcal•mol^{-1}.



(31)



(32)

Chart 13

The 2:1 calix-resorcin[4]arenes (**32** in Chart 13) were synthesized in 20% ($R=(CH_2)_2Ph$, $R'=(CH_2)_2OCH_2CH_3$) and 53% ($R=CH_3$, $R'=(CH_2)_2CH_3$) yield, in the same way as the 1:1 calix-resorcin[4]arene starting from the tetraacid tetrachlorides A,C-dibridged resorcin[4]arenes **29**. These are present in at least three different conformations of comparable energy. To rigidify the structure of these 2:1 calix-resorcin[4]arenes several 1,3-diaminocalix[4]arenes, functionalized at the residual aromatic rings with carboxylic ester, nitro, and cyano substituents, were synthesized [26].

With these calix[4]arene derivatives, three new functionalized 2:1 calix-resorcinarenes were synthesized. Although the yields are somewhat lower than that of the unsubstituted 2:1 calix-resorcin[4]arene, it can be concluded that the presence of the carboxylic ester, nitro, or cyano groups does not severely hinder the formation of 2:1 calix-resorcin[4]arenes, or alter the structure of these host molecules to a considerable extent.

5. Conclusions

A new strategy for the synthesis of artificial receptor molecules was developed by the covalent linkage of medium-sized, relatively rigid molecules to which functional groups can be attached. The validity of the concept has been demonstrated with several examples.

6. Acknowledgements

The authors are indebted to their colleagues, whose names appear in the references, for their contribution included in this paper. Part of this work has been performed in collaboration with the University of Parma (Professors Pochini and Ungaro). Financial support from the Technology Foundation (STW), Technical Science Branch of the Netherlands Organization for Scientific Research (NWO), and the EEC Science Program is gratefully acknowledged.

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