Pure & Appl. Chem., Vol. 68, No. 6, pp. 1273–1277, 1996.
Printed in Great Britain.

Synthesis of supramolecular structures via combination of calix[4]arenes with other medium-sized building blocks

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Abstract The synthesis of receptor molecules via combination of calix[4]- and calix[6]arenes with other known medium-sized building blocks such as cyclodextrins, resorcin[4]arenes, and cyclotriveratrylene is described.

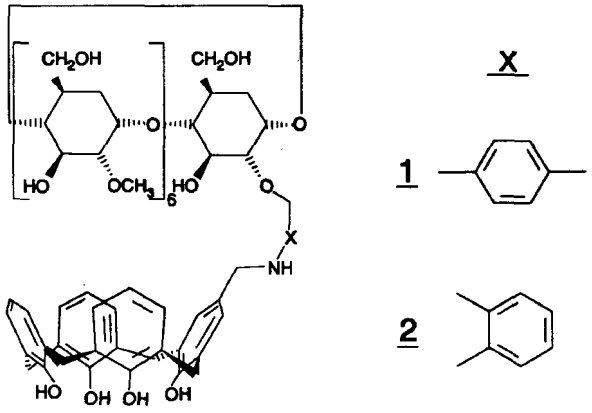
Introduction

Artificial receptors are commonly obtained by *de novo* synthesis, whereas Nature constructs a wide variety of biological receptors from a limited set of building blocks. We are currently investigating an analogous approach for the synthesis of host molecules via combination of (known) building blocks. This approach has already been proven to be very useful for the synthesis of calixspherands, calixcrown ethers and calixsal(oph)enes by combination of calix[4]arenes with spherands, crown ethers, and sal(oph)enes, respectively (1). In this paper we describe our results on the preparation of new receptor molecules with a molecular weight as high as 4500 synthesized via combination of calix[4]- or calix[6]arenes, resorcin[4]arenes, cyclodextrins, and porphyrins.

Calix[4]arene combined with Cyclodextrins

Cyclodextrins are a unique group of naturally occurring cyclic D-glucose oligomers, capable of complexing hydrophobic guest molecules in aqueous solvents predominantly by hydrophobic interactions. In order to link a β-cyclodextrin with a calix[4]arene a monofunctionalized β-cyclodextrin was synthesized (2). Reaction of hexakis(6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin with 1.2 equivalents of α-bromo-*p*- or α-bromo-*o*-tolunitrile and 1.5 equivalents of sodium hydride in refluxing THF gave monofunctionalized β-cyclodextrins at the secondary face in 35% and 18% yield, respectively. After methylation of the remaining secondary hydroxyl groups and subsequent reduction of the cyano group, the resulting monoamino functionalized β-cyclodextrins were reacted with monoformylcalix[4]arene under reductive conditions. After desilylation water-soluble calix[4]arene-linked cyclodextrins 1 and 2 were obtained in quantitative yields.

The complexation behaviour of the water-soluble receptors 1 and 2 was studied by fluorescence spectroscopy using 1-anilino-8-naphthalenesulphate (ANS) and 2-*p*-toluidino-6-naphthalenesulphate (TNS) as fluorescent guests. In a pH 7.0 buffered aqueous solution an increase in fluorescence intensity of ANS and TNS was observed upon addition of 1 or 2. For TNS complexation constants of 153,000 M^{-1} and 74,000 M^{-1} were calculated for 1 and 2, respectively. This is much higher than observed for β-cyclodextrin (K_{ass} 2000 M^{-1}) indicating the importance of the calix[4]arene moiety which provides additional shielding of the guests by means of the aryl units.



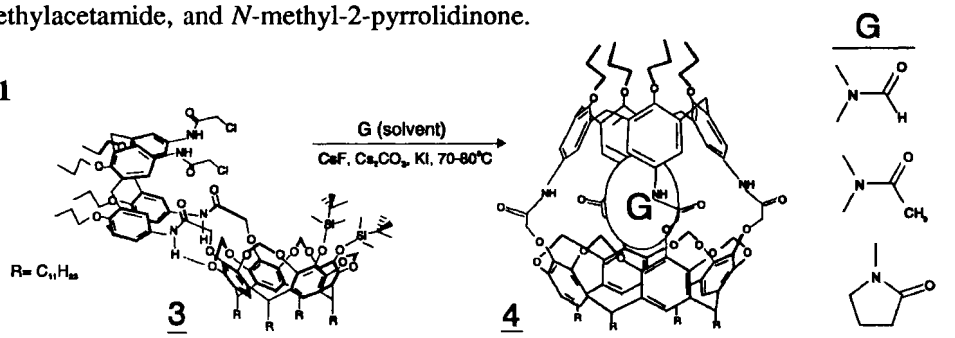
Calix[4]arene combined with Resorcin[4]arene

Calix[4]arenes and resorcin[4]arenes have been combined to give new (concave) receptor molecules with an extended hydrophobic cavity. Furthermore, new receptor molecules with a well defined cavity have been synthesized.

Calix[4]arene-based carcerands

Cram *et al.* (3) have shown that resorcin[4]arene-based carcerands can permanently incarcerate guest molecules. Although incarcerated guests can adopt different orientations this does not lead to different stereoisomers due to the symmetry of the carcerand. Combination of calix[4]arenes with resorcin[4]arenes leads to calix[4]arene-based carcerands 4 which possess an asymmetric cavity (4). Therefore different orientations of incarcerated guests lead to different diastereoisomers. This makes these molecules of interest because of their potential use as molecular switches. In order to synthesize a calix[4]arene-based carcerand a new method for the introduction of amino groups from iodo-substituted calix[4]arenes was developed (5). Reaction of 1,2-bis(chloroacetamido)-3,4-dinitrocalix[4]arene with tetrol-resorcin[4]arene predominantly leads to an 1:1 *endo* coupled product. This preference for the *endo* orientation is probably a result of electrostatic interactions between the nitro groups on the calix[4]arene and the hydroxyl groups on the resorcin[4]arene. The 1:1 coupled product is converted into 3 via reduction of the remaining nitro groups and reaction with chloroacetyl chloride. During the formation of the final two bridges in an appropriate solvent, one solvent molecule is incarcerated (Scheme 1). Solvents that can be used are DMF, *N,N*-dimethylacetamide, and *N*-methyl-2-pyrrolidinone.

Scheme 1



The amide bridges in carceplexes 4 could be converted to thioamides using Lawessons reagent in refluxing xylene (6). The incarcerated guests *do not react* which means that they are not reactive under the reaction conditions. In the ^{1}H NMR spectra all carceplexes show a 2-4 ppm upfield shift for the guest protons with respect to the free guest in $CDCl_3$ solution due to the shielding of the calix[4]- and resorcin[4]arene moiety (see Fig. 1).

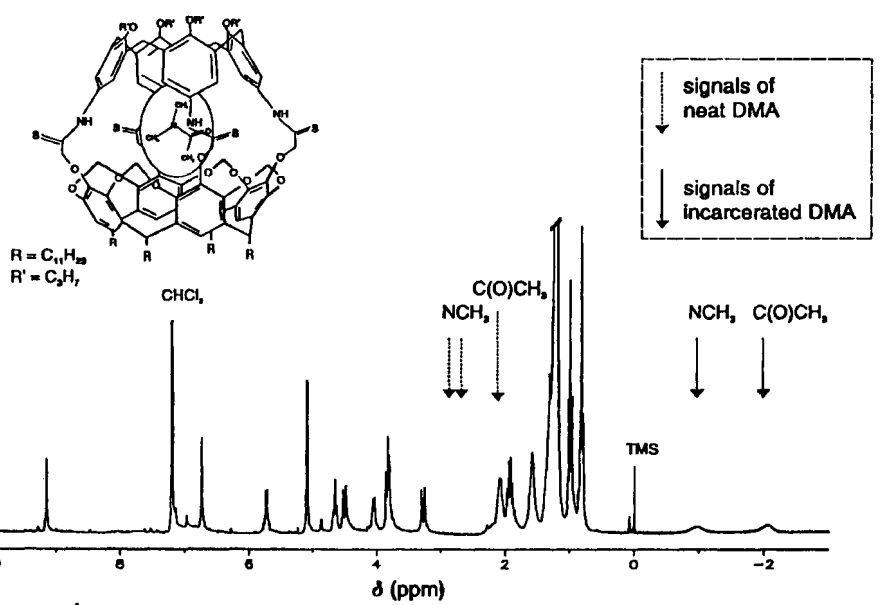


Figure 1. ^{1}H NMR spectrum (250 MHz, $CDCl_3$) of a calix[4]arene-based thiacarceplex with *N,N*-dimethylacetamide incarcerated.

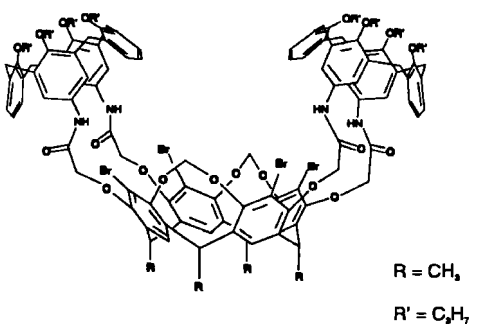
The orientation of the guests inside the carcerand was studied by 2D NOESY and 2D ROESY NMR spectroscopy. The energy barriers ($\Delta G^{\neq}$) for the interconversion between the different diastereoisomers were determined by 2D EXSY NMR spectroscopy and are summarized in TABLE 1. The conversion of the amide bridges into thioamides proves to be a useful method for increasing the energy barriers *after* incarceration of the guest.

TABLE 1. Energy barriers ($\Delta G^{\neq}_{273}$) for interconversion between different diastereoisomers of guests inside calix[4]arene-based carcerands determined by 2D EXSY NMR spectroscopy in $CDCl_3$ at 273 K.

Guest	Bridge	$\Delta G^{\neq}_{273}$ (kcal/mol)
N,*N*-Dimethylacetamide	Amide	12.7 ± 0.5
	Thioamide	15.2 ± 0.5
N-Methyl-2-pyrrolidinone	Amide	15.7 ± 0.5
	Thioamide	17.5 ± 0.5

Receptor molecules with an extended hydrophobic surface

Calix[4]arenes can be coupled to resorcin[4]arenes via distal and proximal positions of the calix[4]arene. Reaction of a 1,3-functionalized calix[4]arene with tetrol-resorcin[4]arene yielded 2:1 coupled product 5 in 47% yield (7). Furthermore, reaction of a 1,3-functionalized calix[4]arene with an A,C-bridged resorcin[4]arene carrying acid chloride groups gave 2:1 coupled product 6 in 25% yield (8).



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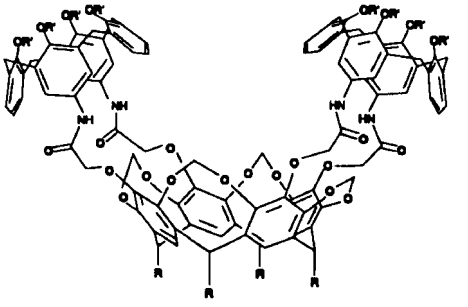

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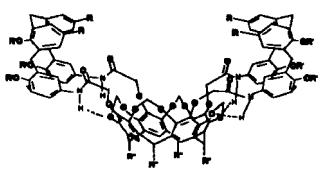
Concave receptor molecules with an extended hydrophobic surface were obtained by reaction of 1,2-functionalized calix[4]arenes and tetrol-resorcin[4]arene (8,9). Besides 1:1 coupled products mainly 2:1 coupled products were isolated as three diastereoisomers depending on the orientation of the calix[4]arene moiety with respect to the resorcin[4]arene moiety, *viz. endo-endo* (7), *endo-exo* (8) and *exo-exo* (9).



endo-endo

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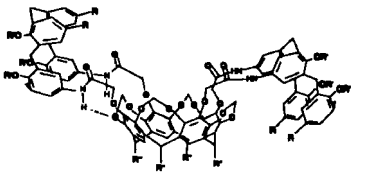

endo-exo

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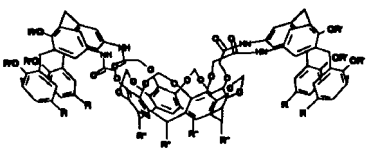

exo-exo

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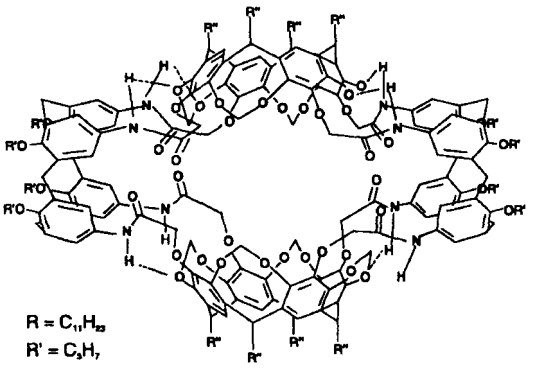
Complexation studies in $CDCl_3$ showed that these receptor molecules (7-9, R=H) are capable of complexing prednisolone-21-acetate (9). The association constants range from 430 M^{-1} for compound 7 to 830 M^{-1} for compound 8. This indicates the importance of the calix[4]arene cavity at the *endo* side as well as the NH-groups of the amide bridges at the *exo* side.

Receptor molecule with a cavity of nanosize dimensions

A receptor molecule with a nanometer size cavity (*holand*, 10) was obtained via combination of two calix[4]arenes and two resorcin[4]arenes (10). The synthesis was carried out via two different routes. The first one comprises the reaction of two molecules of 1:1 *endo* coupled product 3. The other route starts from 2:1 *endo-endo* coupled product 7 (R=NO_2). After reduction of the remaining nitro groups and reaction with chloroacetyl chloride the 2:1 coupled product is reacted with tetrol-resorcin[4]arene to give holand 10.



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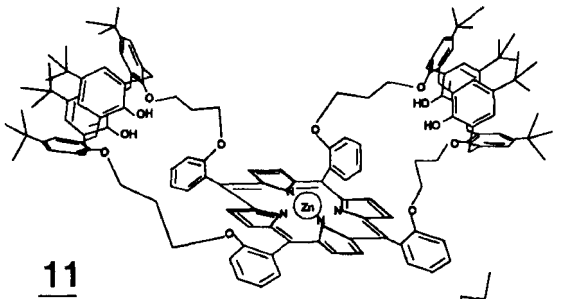
DOCK studies revealed that the cavity of 10 can accomodate molecules that are receptors themselves such as porphyrins and crown ethers. Molecular dynamics simulation showed that four solvent molecules ($CHCl_3$ or THF) occupy the cavity which do not leave during the period of the simulation.

Calix[4]arene-Porphyrins

Sterically hindered porphyrins are widely known as chemical models for metalloporphyrin-dependent proteins (11). Calix[4]arenes can be linked to a porphyrin either via distal or proximal positions of the porphyrin. Lower rim connected biscalix[4]arene porphyrin 11 was obtained via reaction of a diametrically substituted calix[4]arene with pyrrole in refluxing propionic acid (12). Using the same strategy upper rim functionalized biscalix[4]arene porphyrin 12 was synthesized.



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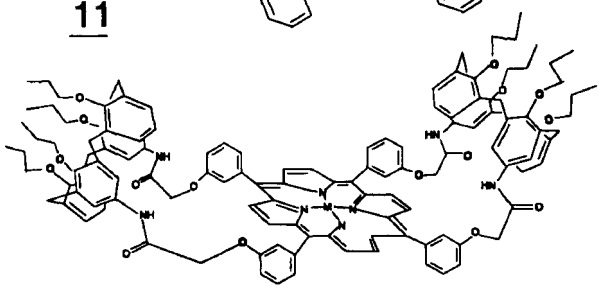

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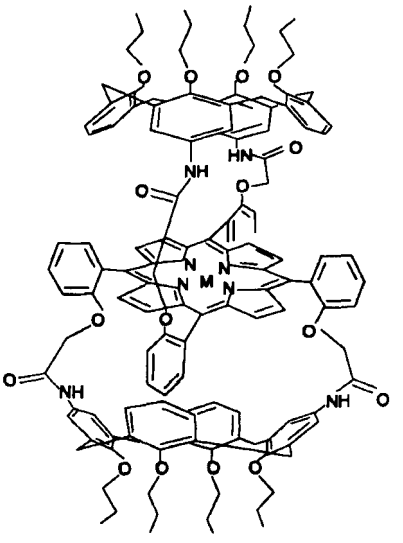

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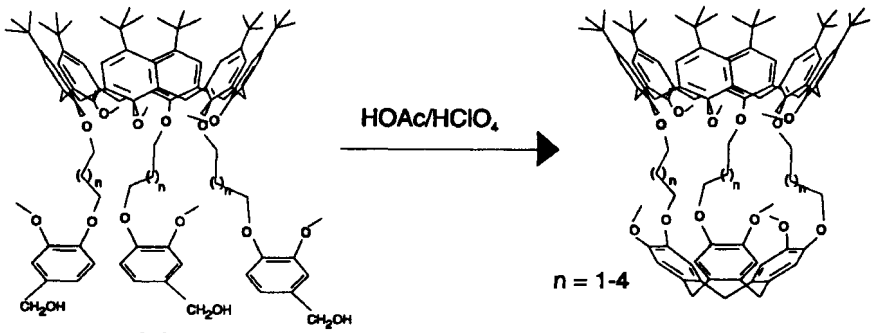
Biscalix[4]arene porphyrin 13 was synthesized starting from 5,17-bis((2-formylphenoxy)acetamido)-tetrapropoxycalix[4]arene (13). The corresponding Zn-complex showed enhanced binding for pyridine (K_{ass} 1.1 x 10^4 M^{-1}), 4-methylpyridine (K_{ass} >10^6 M^{-1}), piperidine (K_{ass} 7.9 x 10^3 M^{-1}) and *N*-methylimidazole (K_{ass} >10^6 M^{-1}) in $CDCl_3$ compared to non-capped Zn-porphyrins. Doubly calix[4]arene-capped porphyrin 13 is an excellent receptor for different aza-heterocycles due to the ideal combination of the properties of both building blocks.

Cryptocalix[6]arenes

Cyclotriveratrylene can easily be obtained via cyclotrimerization of veratryl alcohol and has been used for the synthesis of cryptophanes (14). Reaction of alkyl bromide- or alkyl tosylate-substituted veratryl alcohol with 1,3,5-trimethoxy-*p-tert*-butylcalix[6]arene in DMF at 60-80 °C with six equivalents of Cs_2CO_3 as a base resulted in veratryl alcohol-substituted calix[6]arenes 14 in 40-70% yield. Subsequent in situ cyclotrimerization in glacial acetic acid/perchloric acid gave cryptocalix[6]arenes 15 in 30-73% yield (15). Variable temperature ^1H NMR experiments showed that the calix[6]arene moiety mainly adopts a cone conformation (C_3 symmetry). However, also a minor conformer can be observed in which a *tert*-butyl group of one aromatic unit is directed towards the cyclotriveratrylene unit.

Scheme 2



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