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# SUPRAMOLECULAR STRUCTURES FOR SWITCHING AND SENSING

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## Abstract

The synthesis of calix[4]arene-based carceplexes via two different methods is described, as well as a method for modifying the behavior of guests after incarceration. Furthermore, the sensing abilities of self-assembled monolayers of receptor molecules on gold is discussed. The expertise of the two different fields is combined for the development of a molecular switch.

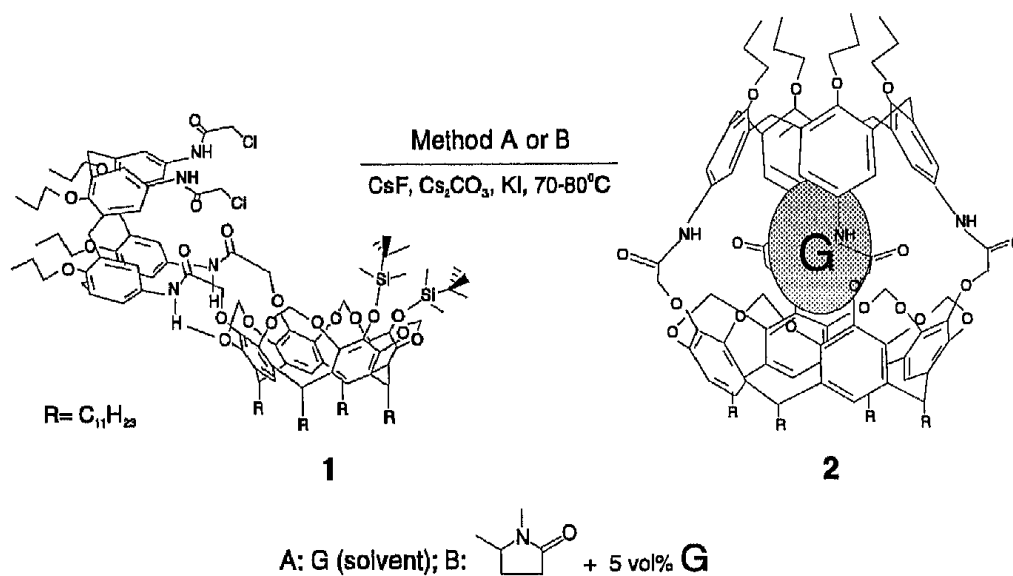
## 1. Introduction

In our group new receptor molecules have been synthesized via the combination of known building blocks, calix[4]arenes and resorcin[4]arenes. Furthermore, self-assembled monolayers have been prepared using cavitands and calix[4]arenes. In this review it is shown that combining the knowledge concerning the synthesis of receptor molecules

with a well defined cavity and the preparation and characterization of self-assembled monolayers can be used for the development of new molecular switches.

## 2. Calix[4]arene-based Carcerands

Cram *et al.* [1] 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 **2** which possess a non-symmetric cavity [2]. Therefore different orientations of incarcerated guests lead to different diastereoisomers. This makes these molecules of interest because of their potential use as molecular switches. Due to the flexibility of the calix[4]arene skeleton direct coupling between a tetra-functionalized calix[4]arene and a tetrol cavitand does not result in the formation of a calix[4]arene-based carcerand. Therefore, a new method for the introduction of amino groups from iodo-substituted calix[4]arenes was developed [3]. Reaction of 1,2-bis(chloroacetamido)-3,4-



Scheme 1

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 **1** via reduction of the remaining nitro groups and reaction with chloroacetyl chloride. This compound can be used for the synthesis of calix[4]arene-based carceplexes either via *solvent* or *doped* inclusion.

## 2.1. SYNTHESIS VIA SOLVENT INCLUSION

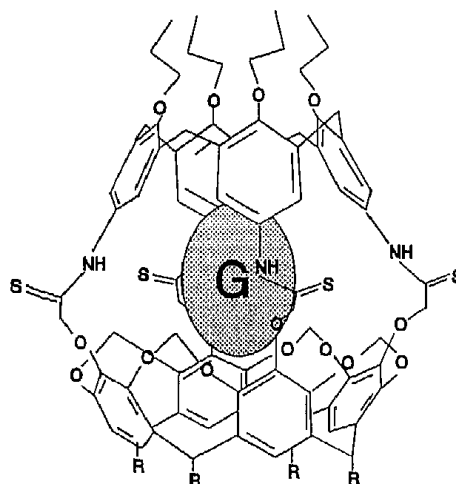
One method for the synthesis of calix[4]arene-based carceplexes comprises the formation of the final two bridges in an appropriate solvent (method A). During this reaction one solvent molecule is permanently incarcerated. Only highly polar solvents such as amides and sulphoxides can be used, *e.g.* DMF and ethyl methyl sulphoxide, respectively. Increasing the size of the solvent going from DMF to 1,5-dimethyl-2-pyrrolidinone leads to a dramatic decrease of the yield from quantitative to only 5%, respectively [4].

## 2.2. SYNTHESIS VIA DOPED INCLUSION

The possibility to use only highly polar solvents for the synthesis of calix[4]arene-based carceplexes limits the number of potential guests. Therefore we developed a synthesis method called *doped* inclusion (method B) [4]. By using 1,5-dimethyl-2-pyrrolidinone as a solvent, which itself is a bad template for the closure reaction, and adding potential guests, *e.g.* 2-butanone or 3-sulfolene (5-10 vol%) the carceplex with the added guest is exclusively formed. The ability to synthesize carceplexes via doped inclusion enlarges the scope of potential guests to solids, *e.g.* 3-sulfolene, and deuterated guests, *e.g.* DMF- $d_7$  and DMSO- $d_6$ .

### 2.3. MODIFICATION OF THE BRIDGES AFTER INCARCERATION OF GUESTS

The orientation of the guests inside the carcerand was studied by 2D NOESY and 2D ROESY NMR spectroscopy. With exception of *N,N*-dimethyl acetamide and *N*-methyl-2-pyrrolidone the guests either rotate fast on the NMR chemical shift timescale (DMF, DMSO) or preferably adopt one orientation in a temperature range of  $-40^{\circ}$  to  $100^{\circ}$  C (ethyl methyl sulfoxide, 2-butanone). Therefore it is interesting to have a method for changing the behaviour of guests after incarceration. An apparent position for modification are the amide bridges between the resorcin[4]- and calix[4]arene moiety. The amide bridges in carceplexes **2** could be converted into thiamides in essentially quantitative yields using Lawessons reagent in refluxing xylene giving thiacarceplexes **3** [4]. The incarcerated guests *do not react* which means that they are not reactive under the reaction conditions. This indicates that the guests are very well shielded.



**3**  
Chart 1

The energy barriers ( $\Delta G^{\ddagger}$ ) for the interconversion between the different diastereoisomers were determined by 2D EXSY NMR spectroscopy. As shown in TABLE 1 the conversion of the amide bridges into thioamides results in an increase of the energy

barriers for interconversion by 1.8-2.5 kcal mol<sup>-1</sup>. An explanation for this behaviour may be the stronger hydrogen bond donating character of thioamides compared to amides. Furthermore, molecular modelling studies revealed that in the calix[4]arene-based carceplexes with thioamide bridges the distance between the diametrical NH protons (across the cavity) is significantly smaller [5].

**TABLE 1.** Energy barriers ( $\Delta G^\ddagger_{273}$ ) for interconversion between different diastereoisomers of guests inside calix[4]arene-based carcerands determined by 2D EXSY NMR spectroscopy in CDCl<sub>3</sub> at 273 K and distance between diametrical NH protons determined using molecular mechanics calculations.

Guest	Bridge	$\Delta G^\ddagger_{273}$ (kcal/mol)	d (NH...HN) (Å)
<i>N,N</i> -Dimethylacetamide	Amide	12.7 ± 0.5	9.29 ± 0.73
	Thioamide	15.2 ± 0.5	8.56 ± 0.24
<i>N</i> -Methyl-2-pyrrolidinone	Amide	15.7 ± 0.5	9.60 ± 0.69
	Thioamide	17.5 ± 0.5	8.85 ± 0.51

### 3. Self-Assembled Monolayers on Gold

Self-assembled monolayers have been investigated extensively during the past decade [6], in particular because of the potential applications, like in piezoelectrical devices, nonlinear optics, and microsensors [7]. Highly ordered monolayers were obtained of resorcin[4]arene [8] and calix[4]arene [9] derivatives, substituted with four dialkylsulfides for the adsorption to gold as depicted in Chart 2. The driving force for the formation of a monolayer is the Au-S interaction, while van der Waals forces between the alkyl chains provide a high degree of order. Essential in the design of the

adsorbates is that the alkyl chains cover a space which is comparable in size to the area covered by the 'arene' unit [10].

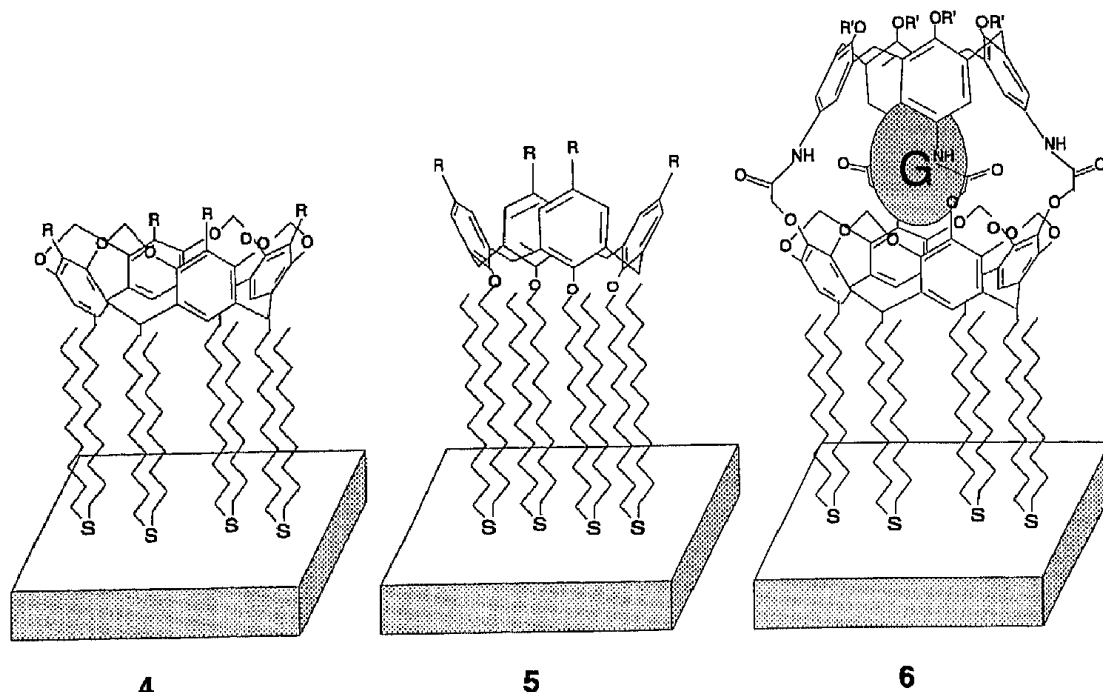


Chart 2

### 3.1. MONOLAYERS AS SENSING INTERFACE

In the highly ordered monolayers of cavitand **4** the cavity is exposed to the outer interface. It was shown in sensing experiments that in contact with various (halogenated) hydrocarbons the cavity acts as a molecular recognition site. The specific interactions were detected both by the use of a quartz crystal microbalance (QCM) [11] and surface plasmon resonance (SPR) measurements [12]. The cavity effect was further evidenced by comparison with an inert disulfide, for which a ten times smaller response was obtained compared to the monolayer with the cavity. Due to the short diffusion lengths, very fast response times could be obtained ( $t_{90} < 1$  sec). Both the QCM and SPR are very sensitive techniques, of which SPR appears to be more stable in time. Therefore,

SPR enabled us to study the adsorption behavior more closely, to find that an increasing response occurs upon adsorption. As the sensing results with these layers is very promising, new recognition sites are under development. The calix[4]arene self-assembled monolayers (**5**, R = H, *t*-butyl) are important in this regard, as the modification of these compounds is more advanced than of resorcin[4]arenes.

### 3.2. DEVELOPMENT OF SWITCHING MONOLAYER

The experience with self-assembled monolayers was recently combined with the calix[4]arene-based carcerands. The carcerand can be oriented in space in a controlled manner by assembling this compound in a monolayer on gold. Thus the orientation of the carcerand is fixed, while the guest remains free to be switched independently between two different orientations. As appeared from the systematic study of guests described before, different energy barriers between the two states can be obtained, depending on the size of the cavity and of the incarcerated guest. Self-assembled monolayers of carceplex **6** (synthesized via method A with DMF as guest as shown in Scheme 1, R = C<sub>10</sub>H<sub>20</sub>-S-C<sub>10</sub>H<sub>21</sub>) were prepared from a 0.1 mM solution in ethanol on gold [13]. The monolayers were characterized by a number of surface sensitive techniques (like FTIR, ellipsometry, contact angle measurement, XPS, and SIMS). Well-ordered monolayers were obtained, for which a structure is proposed as depicted in Chart 2.

The monolayer infrared spectrum provides clear information about the order and orientation of the carceplex **6**.DMF on the monolayer (Table 2). The methylene C-H stretches have the same absorption maxima in the monolayer as in the bulk, which indicates a high degree of order. The amides in the carceplex appear in the bulk infrared spectrum as amide I (predominantly C=O stretch) and amide II. In the monolayer spectrum, however, only amide II appears at 1537 cm<sup>-1</sup> as a clear absorption, while amide I is very weak or absent. The orientation of the transition dipole of amide I is in

the proposed monolayer structure parallel to the gold, and therefore is not absorbed by the (p-polarized) infrared beam. This confirms that the orientation of the carceplex **6.DMF** is 'upright', similar to the previously reported adsorbates.

**TABLE 2.** Selected infrared peak positions for carceplex **2** in the bulk and the monolayer.

vibration	bulk [cm <sup>-1</sup> ]	monolayer [cm <sup>-1</sup> ]
-CH <sub>2</sub> -, symmetrical	2853	2853
-CH <sub>2</sub> -, asymmetrical	2924	2926
Amide I	1696	n.o.
Amide II	1526	1537

#### 4. Summary

It has been shown that calix[4]arene-based carceplexes can be obtained *via* solvent or doped inclusion. Furthermore, the behavior of incarcerated guests can be altered after incarceration by modification of the bridges between the resorcin[4]- and calix[4]arene moiety. Self-assembled monolayers are an elegant tool to control molecular orientation. Thus resorcin[4]arene monolayers were formed, for which sensing applications based on molecular recognition were shown. The calix[4]arene-based carceplex was confined in space by means of self-assembly to gold. This approach is a step toward a new type of molecular switch.



**References and notes**

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