CONVERGENT STRATEGIES FOR SYNTHETIC RECEPTORS

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ABSTRACT. Combination of medium-sized building blocks such as calix[4]- or resorcinarenes comprises a new strategy for the synthesis of receptor molecules with unique complexation properties. Calix[4]arenes bridged at the lower rim with a polyglycol chain show very high association constants for K^+ (8.9×10^9 M^{-1} in $CDCl_3$). Kinetically stable Rb^+-complexes (half-life time in $CDCl_3$ of 180 days) can be prepared with calix[4]arenes bridged at the lower rim with a *m*-terphenyl moiety. The combination of calix[4]arenes with a uranyl containing salophen unit is used for the synthesis of lipophilic carriers for selective transport of urea through supported liquid membranes. Connecting the salophen unit via the upper rim of a calix[4]arene carrying four ester groups at the lower rim a ditopic receptor able to selectively complex NaH_2PO_4 is synthesized. Calix[4]arenes can also be incorporated in carcerands via combination with resorcinol-based cavitands. Inclusion of dissymmetrical solvent molecules introduces a new type of diastereoisomerism with potential application in the preparation of molecular switches. The combination of calix[4]arenes with resorcinol-based cavitands is also used in the synthesis of the first holand, a molecule with a rigid organized cavity of nanosize dimensions.

1. Introduction

Supramolecular chemistry is a relatively new field in which specific interactions between molecules constitute the central theme. Its main source of inspiration is found in biological life which is almost entirely governed by very specific interactions.

Nature constructs biological receptors by the combination of a limited number of components. Amino acids are combined to proteins, nucleosides to DNA or RNA and

C. Chatgilialoglu and V. Snieckus (eds.), Chemical Synthesis, 245–261.

monosaccharides to carbohydrates. The linear structures fold in a three-dimensional way in order to form a recognition site which size and dimensions largely depend upon the sequence of the monomeric components. Systematic variation of the monomer sequence gives access to an almost infinite number of different receptors. However, this is achieved at the expense of a high molecular weight.

One of the aims of supramolecular chemistry is the mimicry of biological processes with synthetic molecules. Since the discovery by Pedersen in 1968 that certain crown ethers show a high affinity for alkali metal cations [1,2], the field of molecular recognition has developed rapidly.

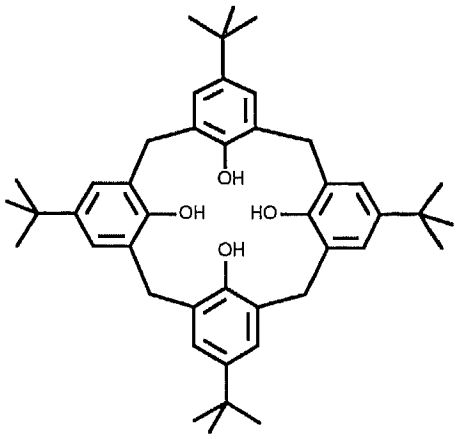
The first studies mainly concerned the complexation of cations which is based on the relatively strong ion-dipole interactions. Lehn and Cram introduced their cryptands [3] and spherands [4] which show substantially higher affinities for alkali and alkaline-earth metal cations compared to simple crown ethers. With these new macrocyclic host molecules they exemplified the importance of *preorganization* in the host and *complementarity* between host and guest [5].

Complexation of organic molecules requires a totally new set of electronical and structural demands for the synthesis of appropriate receptor molecules, because in most cases *neutral* guest molecules are involved that are generally larger and less symmetrical than cations. Much weaker interactions, like hydrogen bonding, π-π stacking and (induced) dipole - (induced) dipole interactions, account for the complexation but the larger size of the guest molecules permits multiple binding-site interactions which usually act in a cooperative way, resulting in a high *selectivity* in the binding of structurally related guest species.

Most synthetic receptors are prepared via *de novo* synthesis using modern synthetic methodologies, which allow almost unlimited variation. The strategy focusses on the complementarity of functional groups between receptor and guest species and aims for minimal reaction steps and molecular weights. The drawback is that for each individual guest molecule a new synthetic pathway has to be developed; the learning process is not efficiently accumulated.

A new strategy for the synthesis of artificial receptor molecules which is a compromise between the two extremes described above, starts from medium-sized molecules that can be used as platforms to which functional groups for intermolecular interactions can be attached [6]. Several of these components can be combined to build up larger structures. The components must have a well-defined shape, be readily available from cheap starting materials and easily functionalizable. Examples of such

molecular building blocks are calix[4]arenes (**1**) [7] and resorcinarenes (**2**) [8].



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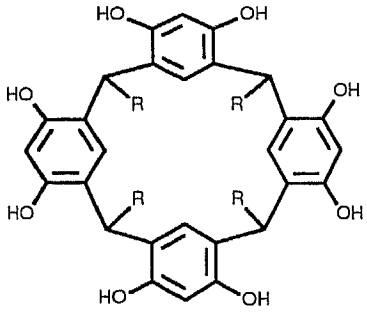

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In this article we will illustrate our new strategy with a few examples of receptor molecules composed of calix[4]arenes in combination with several other building blocks that exhibit unique complexation properties. Moreover we have found new routes for the selective introduction of functional groups both in calix[4]arenes and resorcinarenes. One of these methods comprises the key step in the synthesis of calix[4]arene-based carcerands in which guest molecules are permanently encapsulated in an asymmetric environment. Finally, the first example of a holand, a molecule with a large rigid cavity of nanosize dimensions, will be described.

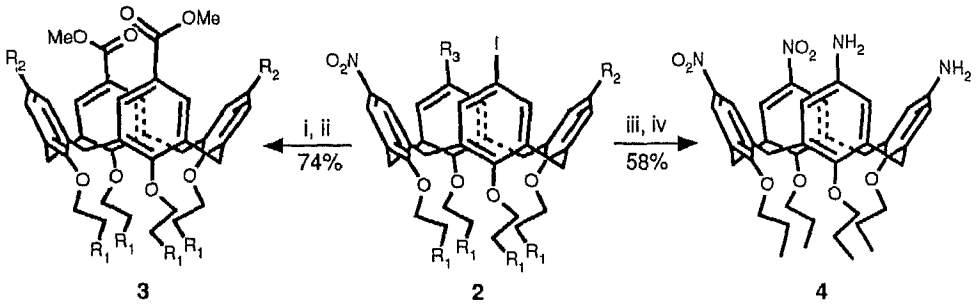
2. Selective Functionalization

2.1. SELECTIVE FUNCTIONALIZATION OF CALIX[4]ARENES

Calix[4]arenes (**1**) represent a class of synthetic molecules that has been a subject of research in our group for the past decade. Several methods have been developed for the selective functionalization of calix[4]arenes both at the lower and the upper rim; most of them have been summarized in a review article [9]. In this section only a recent example will be described.

Nitrocalix[4]arenes iodinated at the upper rim via treatment with CF_3COOAg/I_2 are

excellent starting materials for the synthesis of calix[4]arenes carrying a combination of carboxylic ester, amino and nitro groups at the upper rim [10]. Treatment of 1,3-diiodo-2,4-dinitrocalix[4]arene **2a** with CO and MeOH at 100 °C under 10 atm for 24 h using NEt_3 as a base gave the corresponding calix[4]arene **3a** carrying both carboxylic ester groups and nitro groups at the upper rim in 74% yield. The nitro groups could be cleanly reduced to amino groups without affecting the ester groups to give **3b** in quantitative yield.



3 **2** **4**

a R_1=OCH_2CH_3, R_2=NO_2 **a** R_1=OCH_2CH_3, R_2=NO_2, R_3=I

b R_1=OCH_2CH_3, R_2=NH_2 **b** R_1=CH_3, R_2=I, R_3=NO_2

i) CO (10 atm), MeOH, NEt_3, $Pd(PPh_3)_2Cl_2$, anisole, 100 °C, 24 h; ii) $NH_2NH_2.H_2O$, Raney Ni, MeOH, reflux, 2 h; iii) phthalimide, $Cu(I)_2O$, collidine, 190 °C, 24 h; iv) $NH_2NH_2.H_2O$, EtOH, reflux, 2 h, conc. HCl, reflux, 0.5 h.

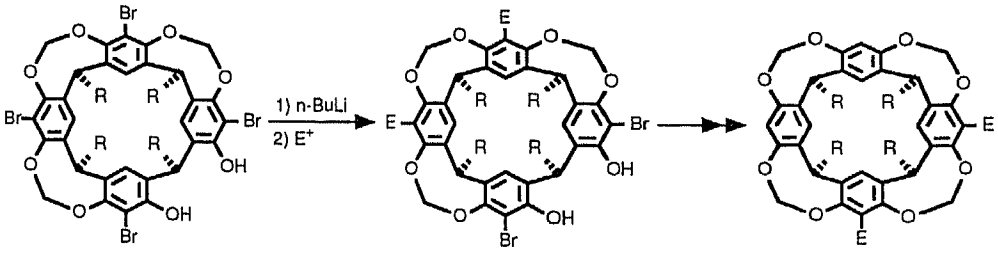
Scheme 1

Reaction of iodonitrocalix[4]arenes with phthalimide in the presence of $Cu(I)_2O$ followed by treatment with hydrazine and conc. HCl provides an easy route into calix[4]arenes carrying both nitro and amino groups at the upper rim. In this way 1,2-diiodo-3,4-dinitrocalix[4]arene **2b** was converted to the corresponding aminonitro-calix[4]arene **4** in 58% yield.

2.2. SELECTIVE FUNCTIONALIZATION OF RESORCINARENES

Tri-bridged resorcinarene **5**, prepared in 54% yield by reaction of the corresponding resorcinarene with CH_2BrCl in DMSO, could be selectively debrominated at two of the four aromatic rings by treatment with 5 equiv of *n*-BuLi at -70 °C for 15 seconds

followed by quenching with H^+ to give **6a** in 76% yield [11]. When the reaction was quenched with $B(OMe)_3$ followed by oxidative workup, tetrol **6b** could be obtained in 47% yield. After incorporation of the fourth methylene bridge in **6a**, the two remaining bromo atoms could be substituted by carboxylic ester, cyano or hydroxyl groups to give compounds **7** in 60-95% yield.



5 **6** **7**

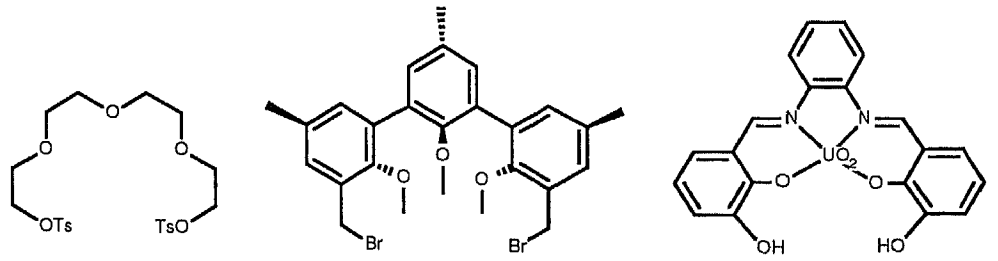
a E=H (76%)
b E=OH (47%)

a E=C(O)OMe (>95%)
b E=CN (60%)
c E=OH (62%)

Scheme 2

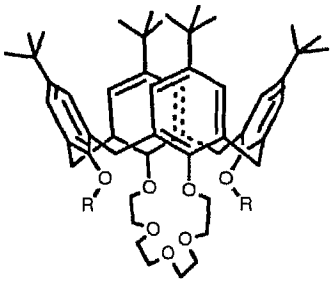
3. Combination of Calix[4]arenes with Other Building Blocks

For the design of new receptor molecules with unique complexation properties calix[4]arenes have been combined with several other building blocks making use of the methods for their selective functionalization that were developed. In this paragraph the combination of calix[4]arenes with glycol chains (**8**), a terphenyl (**9**), and a uranyl containing salophen moiety (**10**) will be discussed.

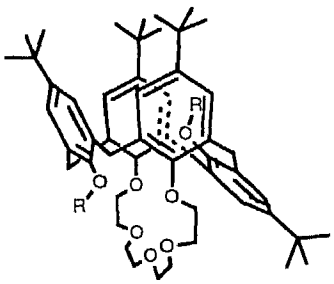


8 **9** **10**

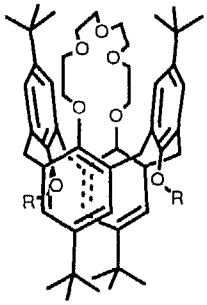
Reaction of calix[4]arene **1** with tetraethylene glycol ditosylate (**8**) gave calixcrown ether **11** in 53% yield. Subsequent methylation of **11** afforded the 2,4-dimethoxycalixcrown-5 **12** which shows a surprisingly high K^+/Na^+ selectivity in extraction experiments [12]. The preferred conformation for binding in **12** appeared to be a flattened partial cone, in which one of the methyl groups is located inside the apolar cavity of the calix[4]arene and the other near the polyether ring. ^1H NMR studies revealed that the flexible **12** undergoes a conformational reorganization from cone to partial cone upon complexation. Calixcrown-5 **12** has been used as potassium-selective carrier in supported liquid membranes [13]. In order to investigate whether the complexing properties of **12** could be improved by reducing the conformational mobility, we also prepared the corresponding 2,4-diethoxycalixcrown-5 **13a**.



11 R=H
12 R=Me
13a R=Et



13b R=Et

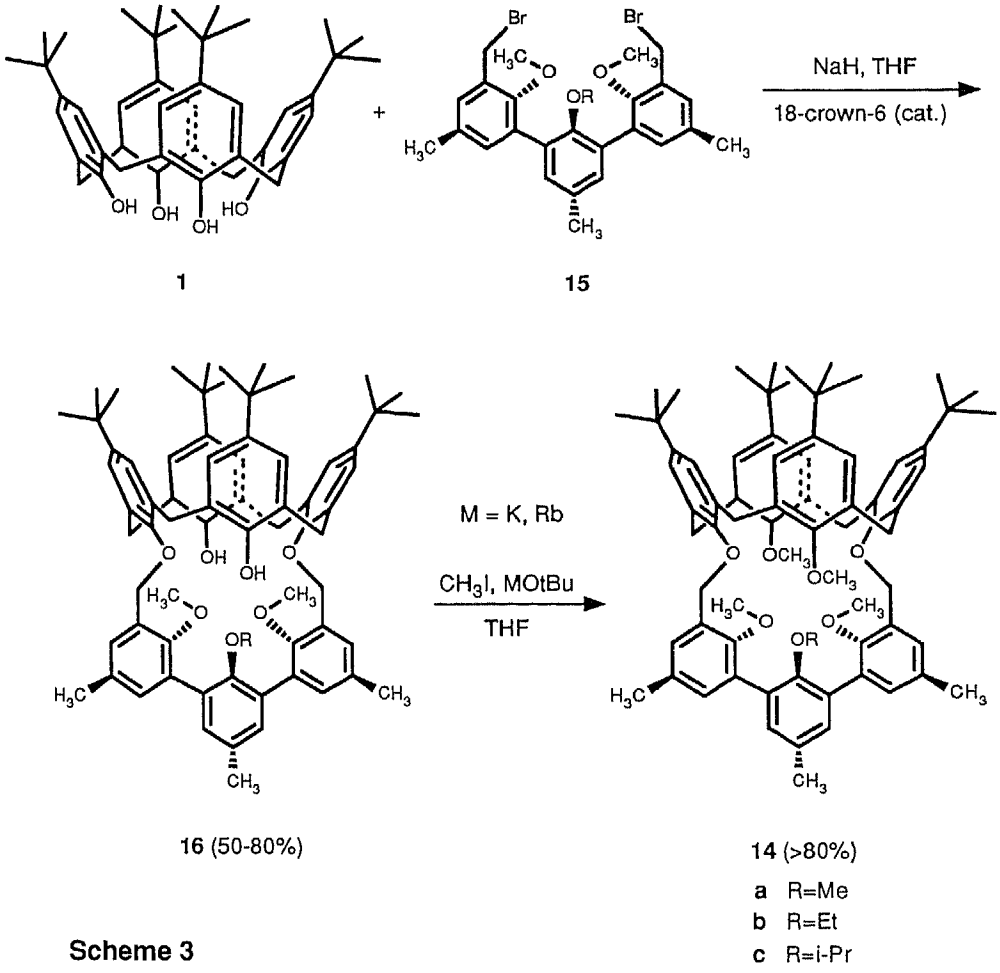


13c R=Et

2,4-Dihydroxycalixcrown-5 **11** was dialkylated with ethyl iodide in THF/DMF in almost quantitative yield. Preparative thin layer chromatography (Al_2O_3) of the crude mixture gave **13** as pure flattened cone (**13a**), partial cone (**13b**), and 1,3-alternate (**13c**) conformers in isolated yields of 53%, 28%, and 13%, respectively [14]. All ligands exhibit selectivity toward K^+ cations, whereas, as expected, the partial cone stereoisomer **13b** shows the highest K_{ass} value (8.9 x 10^9 M^{-1} in $CDCl_3$ at 22 °C) for the complexation of K^+. This clearly demonstrates that in highly preorganized ligands such as **13** the stability of the complexes can be strongly affected by subtle changes in the geometry

around the binding region. The superiority of the partial cone stereoisomer **13b** in K^+/Na^+ selectivity has also been found in chemically modified field effect transistor (CHEMFET) and membrane ion selective electrode (ISE) measurements [15].

3.2. CALIXSPHERANDS



1 **15**

16 (50-80%)

14 (>80%)

a R=Me
b R=Et
c R=i-Pr

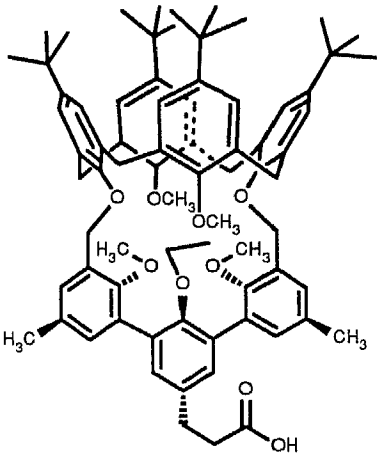
Scheme 3

Some years ago we reported the synthesis of calixspherand **14a** by reaction of 26,28-dimethoxy-*p-tert*-butylcalix[4]arene with *m*-terphenyl **15** in a yield of less than 30% [12]. This calixspherand forms complexes with Na^+ and K^+ which are kinetically

stable, with decomplexation half-life times at room temperature of 3.7 and 2.2 years, respectively. With Rb^+ a complex is formed with a much lower kinetic stability; the half-life time of decomplexation at room temperature is only 2.8 h. Since we are particularly interested in the formation of kinetically stable Rb^+-complexes with the ultimate goal to immobilize rubidium for organ imaging, we have prepared calixspherands having a more shielded cavity [16]. Therefore we developed a new synthetic route giving higher overall yields (Scheme 3). First calix[4]arene **1** was bridged with the functionalized *m*-terphenyl **15**, the presence of a catalytic amount of 18-crown-6 being essential for a good yield, whereupon the resulting calixspheranddiol **16** was alkylated. ^1H NMR spectroscopy and X-ray crystallography showed that all the complexes are in a *partial cone* conformation. All the calixspherands form *kinetically* stable complexes with Na^+, K^+, and Rb^+. The kinetic stability was determined both by ^1H NMR spectroscopy, in $CDCl_3$ saturated with D_2O, and by a new method based on the exchange of radioactive rubidium or sodium in the complexes for non-radioactive sodium in different solvents [17]. 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. This effect is the most pronounced for the rubidium complexes. The half-life times for decomplexation, in $CDCl_3$ saturated with D_2O, increased from 2.8 hours for **[14a.Rb]**$^+$ to 139 hours and 180 days for **[14b.Rb]**$^+$ and **[14c.Rb]**$^+$, respectively. The "exchange method" shows that the rate of decomplexation is the rate-limiting step in the exchange of rubidium in the complex for sodium present in solution. These results can be explained in terms of increased shielding of the cavity from solvent molecules. The kinetic stabilities of the complexes of calixspherands **14c** with Na^+, K^+, and Rb^+ are the highest ever reported [16].

Since for practical use coupling to an organ-specific carrier is mandatory, functionalized calixspherand **17** has been prepared in a multi-step synthesis. The formation of a conjugate between **17** and the low-molecular-weight protein (LMWP) lysozyme was confirmed by ion-spray mass spectrometry [18].

Recently, we found that calixspherands **14b** and **14c** form kinetically stable complexes with Ag^+, in $CDCl_3$ saturated with D_2O, with half-life times of decomposition of 51 and 131 h, respectively [19].



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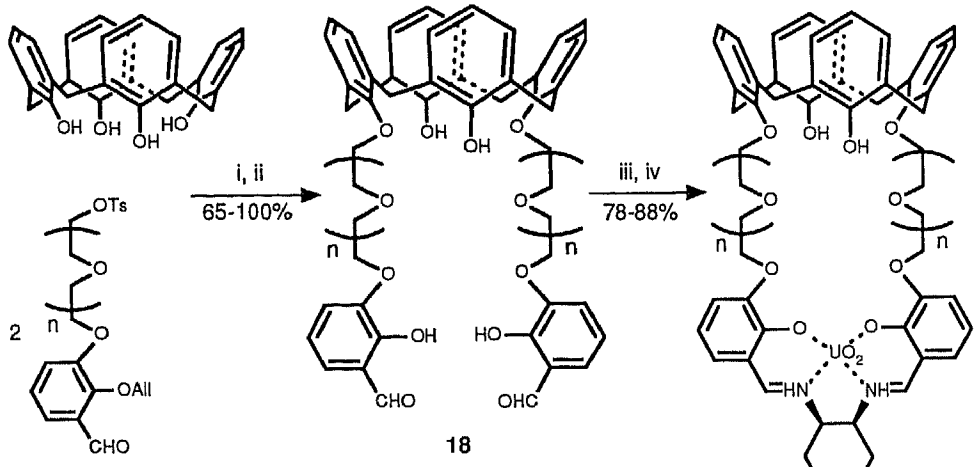
3.3. CALIX SALOPHEN CROWN ETHERS

Macrocycles that contain a uranyl containing salen or salophen unit are very good complexing agents for urea and other neutral molecules containing a nucleophilic center [20]. The synthesis of calix salophen crown ethers **19** is outlined in Scheme 4 [21]. The key step involves the macrocyclization of dialdehyde **18** by addition of 1 equiv of *cis*-1,2-cyclohexanediamine to a solution of **18** and 2 equiv of $Ba(OTf)_2$, which serves as a template, in THF. Subsequent addition of uranyl acetate gave the crude product which after purification afforded pure calix salophen crown ethers **19** in 78-88% yield. Complexation of neutral molecules has been demonstrated by the X-ray structures of the H_2O, MeOH, and DMSO complexes. Due to the presence of the calix[4]arene unit receptors **19** are highly lipophilic, making them useful as carriers for urea in supported liquid membranes [22].

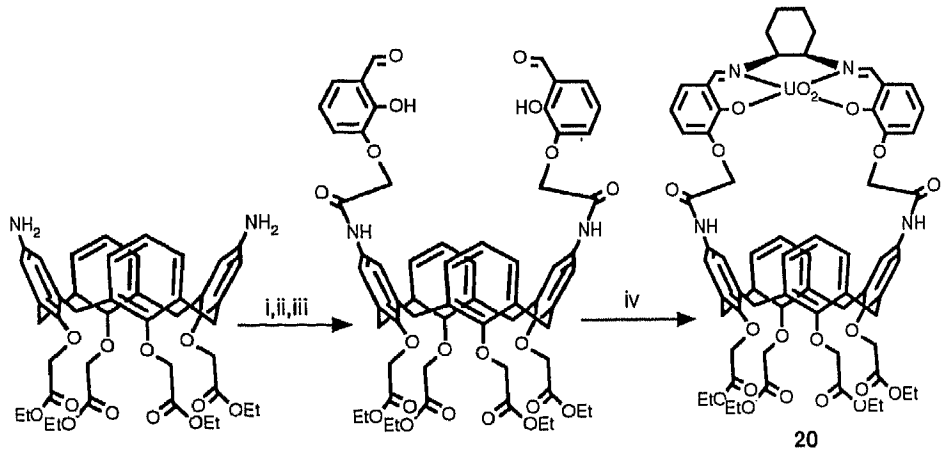
3.4. CALIX[4]ARENE BASED DITOPIC RECEPTOR

Previously we reported that neutral metalloclefts and metallomacrocycles containing both an immobilized Lewis acidic UO_2-center and amido C(O)NH units as additional binding sites are excellent receptors for anions with a high selectivity for dihydrogen phosphate $H_2PO_4^-$ [23,24]. By combination of anionic and cationic binding sites in one molecule, a bifunctional receptor can be obtained which is able to complex



i) K_2CO_3, CH_3CN; ii) $Pd(PPh_3)_4$, $HCOONHEt_3$, THF-EtOH-H_2O;
iii) $Ba(CF_3SO_3)_2$, cis-1,2-cyclohexanediamine, THF; iv) $UO_2(OAc)_2.2H_2O$

Scheme 4



i) $ClCH_2C(O)Cl$, NEt_3, CH_2Cl_2 ii) 2-allyl-3-hydroxybenzaldehyde, K_2CO_3, KI, MeCN(67%)
iii) $Pd(OAc)_2$, PPh_3, HCOOH, NEt_3, EtOH (aq) (90%) iv) cis-1,2-diaminocyclohexane
$UO_2(OAc)_2.2H_2O$, EtOH (20%)

Scheme 5

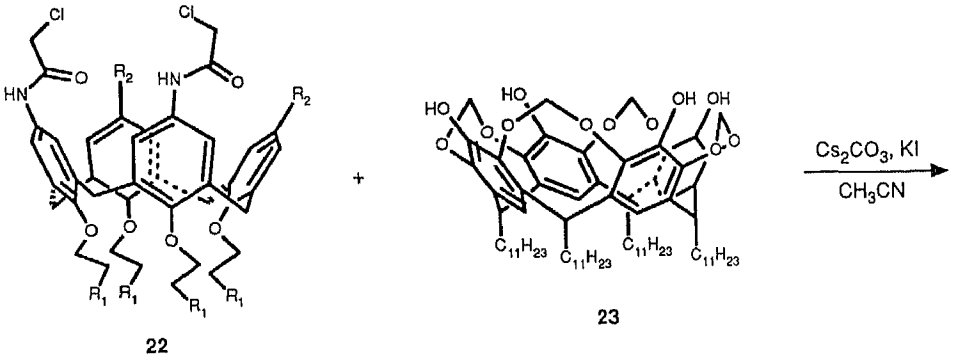
simultaneously anionic and cationic species [25]. It is well-known that calix[4]arenes containing four preorganized ester fragments at the lower rim complex alkali metal cations with a high selectivity for Na^+ [26]. Using calix[4]arene as a molecular platform we attached both four ester groups and a uranyl containing salen moiety to give the calix[4]arene based bifunctional receptor **20**, the synthesis of which is summarized in Scheme 5 [27]. The complexation of NaH_2PO_4 has been proven by FAB mass spectrometry. ^1H NMR dilution experiments showed a selectivity of $H_2PO_4^-$ over Cl^-, HSO_4^-, and ClO_4^- anions.

4. Combination of Calix[4]arenes with Resorcinol-based cavitands

The work on the combination of calix[4]arenes and resorcinol-based cavitands was initiated primarily for the synthesis of dissymmetrical carcerands with ellipsoidal shape that are able to encapsulate guest molecules with a dipole moment in two different orientations giving rise to a new type of diastereomerism. Therefore the coupling of upper rim functionalized calix[4]arenes to resorcinol-based cavitands was investigated. We developed a stepwise route for the synthesis of calix[4]arene-based carcerand **21** because the direct coupling analogously to the synthesis of previously reported symmetrical carcerands [28] was not successful.

4.1. RECEPTOR MOLECULES WITH EXTENDED SURFACES FOR THE COMPLEXATION OF PREDNISOLON ACETATE

First, we studied the reaction between upper rim 1,2-functionalized calix[4]arene **22a**, prepared in 72% overall yield by reduction of the corresponding 1,2-dinitro compound [29] and subsequent reaction with two equivalents of α-chloroacetyl chloride, and cavitand **23**. When this reaction was performed in a 1:1 ratio of **22a** and **23** the diastereomeric products **24a** and **b** in which the calix[4]arene moiety is coupled to the cavitand in a 1,2- (proximal) fashion with the *endo* and *exo* stereochemistry were isolated in 20 and 32% yield, respectively. In addition to these 1:1 reaction products small amounts of the three possible isomeric 2:1 products **25a-c** were formed. Products in which the calix moiety is coupled in a 1,3- (distal) fashion to the cavitand could not be detected. When the reaction between **22a** and **23** was carried out in 2:1 ratio only the 2:1 products **25** were isolated in an almost statistical ratio of endo-endo (**25a**), endo-exo



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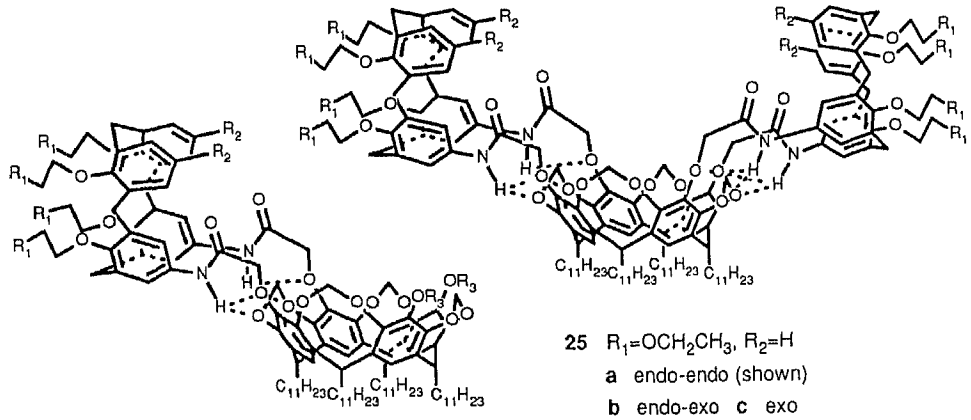
a $R_1=OCH_2CH_3$, $R_2=H$
b $R_1=CH_3$, $R_2=NO_2$

23



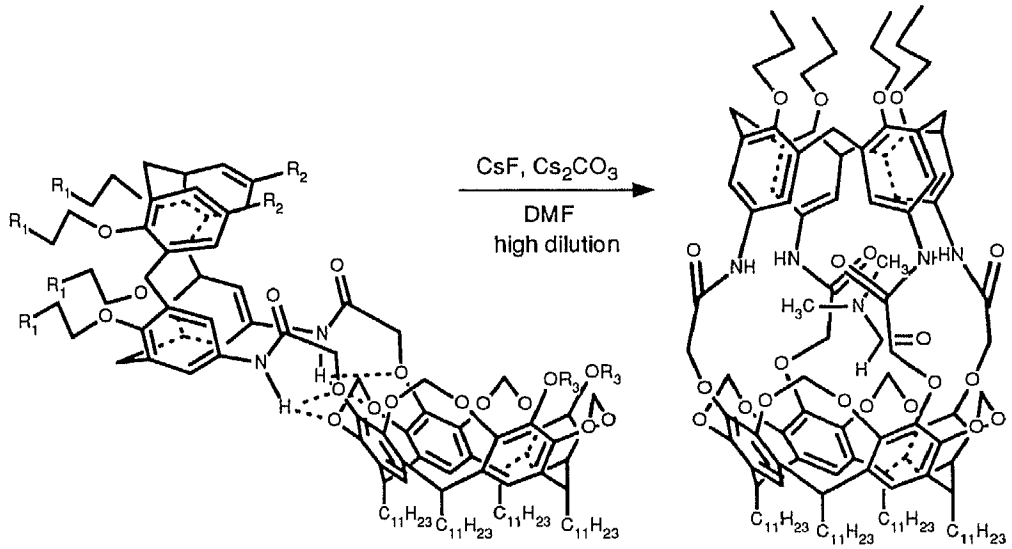
24 $R_1=OCH_2CH_3$, $R_2=R_3=H$
a endo (shown) **b** exo
26 $R_1=CH_3$, $R_2=NO_2$, $R_3=H$ endo
28 $R_1=CH_3$, $R_2=NO_2$, $R_3=Si(CH_3)_2C(CH_3)_3$ endo
29 $R_1=CH_3$, $R_2=NHC(O)CH_2Cl$
$R_3=Si(CH_3)_2C(CH_3)_3$ endo

25 $R_1=OCH_2CH_3$, $R_2=H$
a endo-endo (shown)
b endo-exo **c** exo
27 $R_1=CH_3$, $R_2=NO_2$
a endo-endo (shown) **b** endo-exo
30 $R_1=CH_3$, $R_2=NHC(O)CH_2Cl$ endo-endo

Scheme 6

(**25b**) and exo-exo (**25c**) in a total yield of 64% [30]. These 2:1 products show very selective complexation of the corticosteroid prednisolon acetate (K_{ass}=6.0-8.5 x 10^2 M^{-1} in $CDCl_3$ at 25 °C), a compound that is often used because of its anti-inflammatory effect [31].

Apparently in the reaction between **22a** and **23** there is a slight preference for the formation of the 1:1 exo product **24b**. A possible way to stimulate the formation of the 1:1 endo product, the desired precursor for calix[4]arene-based carcerand **21**, is the introduction of functional groups at the calix[4]arene fragment that favorably interact with the cavitand moiety in the transition state. Reaction of a 1:1 mixture of calix[4]arene **22b**, prepared by acylation of **4** (Scheme 1) with 2 equiv of α-chloroacetyl chloride, and cavitand **22** exclusively gave the 1:1 endo isomer **26** together with small amounts of the 2:1 products **27a** (endo-endo) and **27b** (endo-exo). Because of its instability, **26** was isolated after silylation of the free hydroxyl groups as **28** in 41% yield. The nitro groups in **28** could easily be reduced to amino groups using Raney Ni/hydrazine [30] and after reaction with α-chloroacetyl chloride the bis(2-chloro-acetamido) derivative **29** was isolated in quantitative yield.



29 R_1=CH_3, R_2=$NHC(O)CH_2Cl$
R_3=$Si(CH_3)_2C(CH_3)_3$ endo

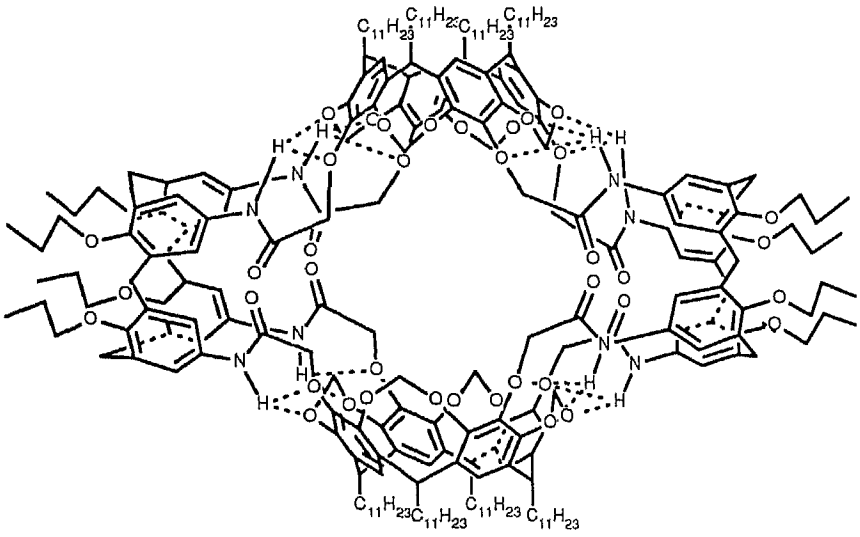
21

Scheme 7

When compound **29** was reacted under high dilution conditions with CsF and Cs_2CO_3

in DMF at 70 °C for 24 h calix[4]arene-based carcerand **21**, with one molecule of DMF inside its interior, was isolated in essentially quantitative yield [32]. The presence of the incarcerated solvent molecule is evident from both MS FAB [M^{+}_{obs} = 2126, (M+DMF+Na^{+}, 100%)] and ^{1}H NMR spectroscopy showing two different singlets for the two methyl groups of DMF at 0.66 and -0.86 ppm, respectively. Even after heating for 1 h at 100 °C in DMF-d_7 no exchange of the incarcerated DMF was observed. Compound **21** is the first example of a dissymmetrical carcerand. According to variable ^{1}H NMR and NOE experiments the incarcerated solvent molecule has a preferred orientation in the cavity, but exchange with other orientations is too fast to be measured even at low temperatures [32]. Studies are underway to complex solvent molecules that have such a high rotation barrier inside the cavity that different diastereomers can be isolated.

4.3. SYNTHESIS OF A HOLAND; a molecule with a shielded hole of nanosize dimensions.



31

When **29** was desilylated with CsF in DMF for 2 h at 70 °C and subsequently reacted with Cs_2CO_3/KI in a concentration of 5 mM, beside calix[4]arene-based carcerand **21** (27%) a second compound, characterized as holand **31**, was formed in 26% yield. The latter compound could also be synthesized by dropwise addition of an equimolar solution

of **30,** obtained from **27a** in quantitative yield in a similar way as **29** was obtained starting from **28,** and **23** in DMF to a suspension of Cs_2CO_3 and KI in DMF to give **31** in 35% yield. Holand **31** has a large rigid organized cavity. The rigidity is partly a result of a bifurcated hydrogen bond between the amide hydrogen atom and both the oxygen atoms in the spacer itself and an oxygen atom in the methylenedioxy bridge as indicated in **31** with dashed lines. Holand **31** contains a cavity of nanosize dimensions having, according to CPK-models, axes of about 1.5 and 2.0 nm long. The calculated internal volume is approximately 1.0 nm^3 (1000 $Å^3$). Holand **31** is expected to have unique complexation properties. The size of the cavity permits complexation of host molecules which themselves are good complexing agents.

5. Conclusions

An efficient strategy for the synthesis of new receptor molecules which exhibit unique complexation properties was developed by the covalent linkage of only a limited number of medium-sized molecules in many different ways. Several examples have been described showing the validity of the concept.

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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