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 x 10^9 M⁻¹ in CDCl₃). Kinetically stable Rb⁺-complexes (half-life time in CDCl₃ 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 salphen unit is used for the synthesis of lipophilic carriers for selective transport of urea through supported liquid membranes. Connecting the salphen 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 NaH₂PO₄ is synthesized. Calix[4]arenes can also be incorporated in carcerands via combination with resorcinol-based cavats. 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 cavats 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

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 neural 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].

![Chemical Structures](image-url)

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 CF₃COOAg/I₂ 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 NEt3 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.

\[ \text{Scheme 1} \]

Reaction of iodonitrocalix[4]arenes with phthalimide in the presence of Cu(I)$_2$O 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 aminonitrocalix[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$_3$BrCl 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 $\text{H}^+$ to give 6a in 76% yield [11]. When the reaction was quenched with $\text{B(OMe)}_3$ 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.

![Scheme 2](image)

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.

![Structures 8, 9, 10](image)
3.1. CALIXCROWN ETHERS

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. \(^1\)H 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.

![Diagram of 11, 12, 13b, 13c](image)

2,4-Dihydroxycalixcrown-5 11 was dialkylated with ethyl iodide in THF/DMF in almost quantitative yield. Preparative thin layer chromatography (Al\(_2\)O\(_3\)) 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**

![Chemical structures](image)

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 decomposition 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 CDCl₃ saturated with D₂O, 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 CDCl₃ saturated with D₂O, 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 CDCl₃ saturated with D₂O, with half-life times of decomposition of 51 and 131 h, respectively [19].
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$_2$O, 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 metallocliefs 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$_2$PO$_4^-$ [23,24]. By combination of anionic and cationic binding sites in one molecule, a bifunctional receptor can be obtained which is able to complex
Scheme 4

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 NaH₂PO₄ has been proven by FAB mass spectrometry. ¹H NMR dilution experiments showed a selectivity of H₂PO₄⁻ over Cl⁻, HSO₄⁻, and ClO₄⁻ anions.


The work on the combination of calix[4]arenes and resorcinol-based cavitands was initiated primarily for the synthesis of disymmetric 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
(25b) and exo-exo (25c) in a total yield of 64% [30]. These 2:1 products show very selective complexation of the corticosteroid prednisolone acetate ($K_{\text{ass}}=6.0-8.5 \times 10^2 \text{ M}^{-1}$ in CDCl$_3$ at 25 °C), a compound that is often used because of its anti-inflammatory effect [31].
4.2. SYNTHESIS OF CALIX[4]ARENES-BASED CARCERANDS

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 cavatand 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 cavatand 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.

![Diagram](image)

**Scheme 7**

When compound 29 was reacted under high dilution conditions with CsF and Cs$_2$CO$_3$
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 DMP-d7 no exchange of the incarcerated DMF was observed. Compound 21 is the first example of a disymmetrical 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.

When 29 was desilylated with CsF in DMF for 2 h at 70 °C and subsequently reacted with Cs2CO3/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 Cs₂CO₃ 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 nm³ (1000 Å³). 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.

7. References

18. Iwema Bakker, W. I.; Haas, M.; den Hertog, Jr., H. J.; Verboom, W.; de Zeeuw,


32. Timmerman, P.; Verboom, W.; Reinhoudt, D. N. unpublished results.