

A MODULAR APPROACH TO LARGE FUNCTIONAL STRUCTURES

DAVID N. REINHOUDT,* DMITRY M. RUDKEVICH,
WILHELM T. S. HUCK, PAUL J. A. KENIS, REMKO H. VREEKAMP
*Laboratory of Organic Chemistry, University of Twente,
P.O. Box 217, 7500 AE Enschede, The Netherlands*

ABSTRACT. In this review a modular approach to design of functional (receptor) molecules, nanostructures, and molecular materials is described. Covalent combination of medium-sized functional building blocks (i.e., modules) results in highly effective bifunctional receptors, superstructured porphyrins and large hydrophobic surfaces. Noncovalently assembled bifunctional receptor systems and large well-defined aggregates (molecular objects) based on calixarene modules are discussed. Self-assembly of modules into NLO films and of large metallo-spheres into defined aggregates is described.

1. Introduction

Nature constructs receptors by the combination of a limited number of building blocks. Amino acids are combined to proteins, nucleotides to DNA and RNA, and monosaccharides to carbohydrates. Systematic variation of the monomer sequence gives access to an almost infinite number of functional bioreceptors. This is achieved at the expense of a high molecular weight which may be even larger when the biologically active species is composed of several sub-units that are connected 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 needs to be developed.

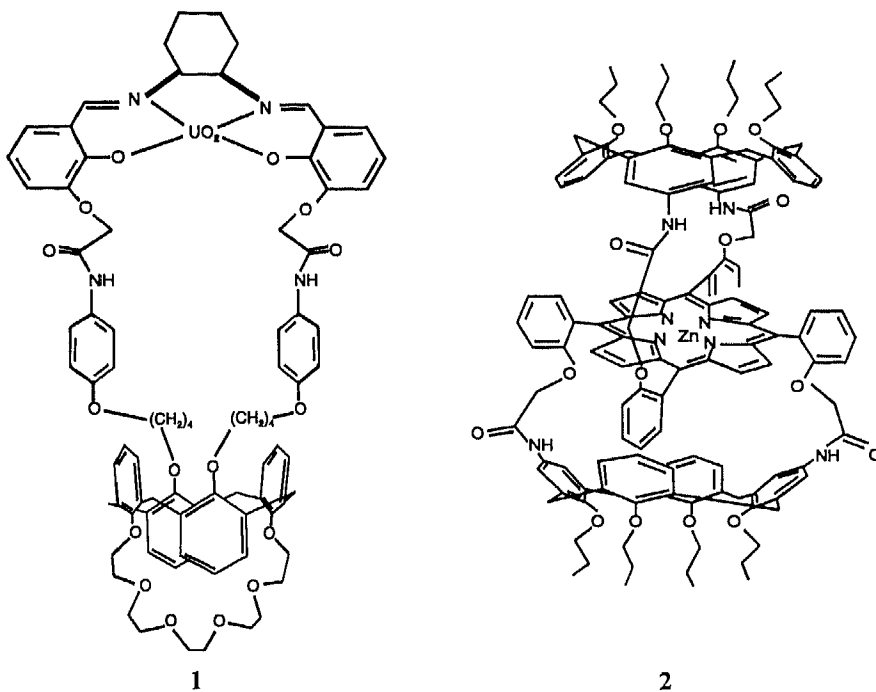
Over the past years we have developed a new strategy for the synthesis of artificial receptors which is a compromise between the two extremes described above. We use medium-sized, relatively rigid molecules (i.e., *modules*) to which functional groups can be attached. Calix[4]- and -[6]arenes, resorcin[4]arenes, cyclodextrins, and porphyrins have the required structures for such building blocks. Previously we have covalently combined calix[4]arene with polyethylene glycols and with terphenyls to give calixcrown ethers and calixspherands, respectively [1a,b]. Calix[4]arene connected to cyclodextrins gives water-soluble receptors for organic substrates [1c]; metallocalixarenes immobilized on a calixarene platform exhibit anion binding properties [2]. More recently, we have studied (covalent

and noncovalent) combinations of different calixarenes with metallosalens, (metallo)porphyrins, and resorcin[4]arenes.

In this paper we describe three different approaches to combining modules into functional (receptor) molecules, nanostructures and molecular materials. The first approach is based on *covalent* combination of modules to (multi)functional molecules. The second approach deals with *noncovalent* (self-)assembly of modules into functional systems and/or well-defined molecular aggregates of nanosize dimensions. Finally, we demonstrate *self-organization* of modules into highly functional films and (nano)surfaces.

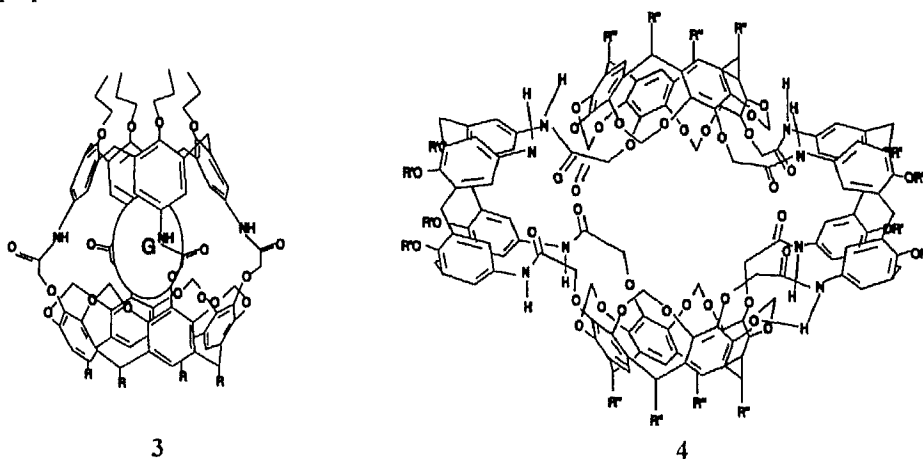
2. Covalently Linked Modules

For bifunctional recognition of inorganic salts we have covalently attached both cation and anion binding sites to the rigid lipophilic calix[4]arene platform. Bifunctional receptor **1** containing a UO_2 -salen center for anion recognition and crown ether moiety for cation complexation has been prepared and used as a carrier to investigate the transport of hydrophilic salts such as cesium chloride across a supported liquid membrane [2].



Multifunctional metalloreceptors have been prepared by covalent combination of two calix[4]arenes and one Zn tetraarylporphyrin core [3]. Porphyrins are being used in biomimetic chemistry for oxygen carrying and storage, and for recognition of biologically significant structures such as nucleic bases, amino acids, and anions.

Covalent combination of porphyrin and calix[4]arene building blocks in one preorganized molecular shape leads to receptors with a highly specific complexing ability. "Capped" metalloreceptor **2** in which the active Zn porphyrin fragment is for the first time covalently incorporated into a hydrophobic and rigid "egg-shaped" bis-calix[4]arene cavity has been prepared.



Searching for large hydrophobic surfaces of nanosize dimensions, we have been studying the combination of resorcin[4]arenes and calix[4]arenes in different ratios [4]. Combined in a 1:1 ratio we have obtained calix[4]arene-based carceplexes **3** which possess a non-symmetrical cavity that is completely closed. These molecules exist as two different diastereomers. NMR and computational studies have revealed a good relation between experimental and calculated activation energies of the isomerization process.

Reaction of two calix[4]arenes with one resorcin[4]arene gives three 2:1 coupling products having different configurations: endo-endo, endo-exo, and exo-exo. These molecules have a large hydrophobic surface on which steroids can be complexed; at least three functional groups are involved in complexation. The acetoxy group and the two hydroxyl groups are responsible for the complexation of steroids by these 2:1 addition products, most probably via CH- π and hydrogen bonding.

In a (2+2)-mode of coupling, the calix[4]arene and resorcin[4]arene give a rigid receptor **4** with a cavity of more than 1000 \AA^3 [4].

3. Noncovalent Assembly of Modules into Functional Aggregates and Molecular Objects

Molecular self-assembly is an important part of life processes and biological systems. It results in a wide variety of complex structures, such as double-stranded DNA, viral protein coatings, lipid membranes, and globular proteins. Self-assembling processes have also found applications in the design of nanosize structures such as inorganic clusters, tubes and

channels, monolayers, and hydrogen-bonded networks. The functions of such assemblies can be extrapolated from molecular properties.

In addition to coupling of the above described modules via covalent bonds, they can be also connected by non-covalent bonding to give *self-assembled functional receptor systems* and *objects* with molecular weights as large as 8000.

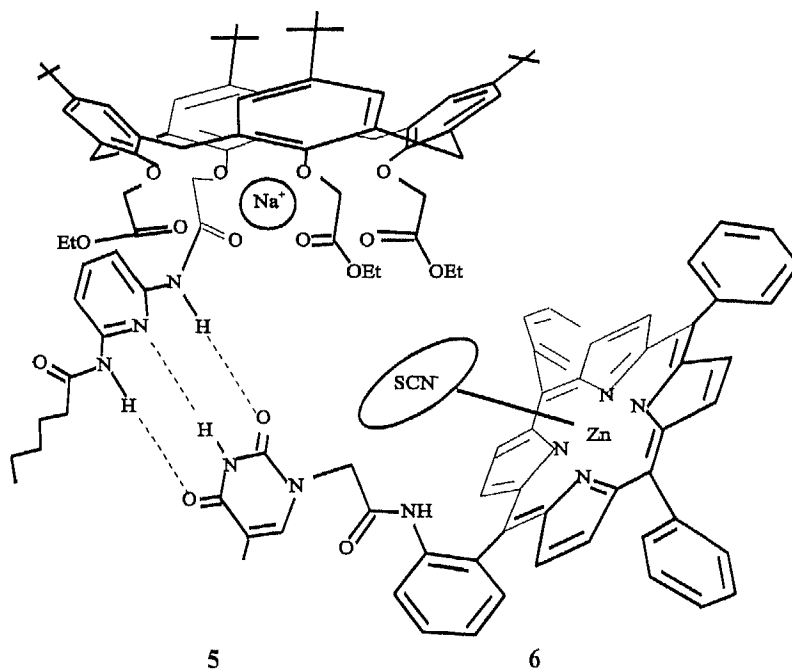


Figure 1. Noncovalently assembled bifunctional receptor 5•6 for NaSCN

In the *noncovalently* organized bifunctional receptor system (schematically represented in Figure 1) the Na^+ cation is complexed by calixarene 5, the SCN^- anion coordinates to the Zn porphyrin 6, and both cation and anion receptors 5 and 6 are connected via hydrogen-bonded aggregation ($K_{\text{ass}} = 2.8 \times 10^4 \text{ M}^{-1}$ in toluene) [5]. The unique feature of this assembly is that all four components (calix[4]arene 5, Zn porphyrin 6, Na^+ cation, and SCN^- anion) are fixed in solution with their positions determined by specific ion-dipole interactions and hydrogen bonding. Moreover, the assembly can be "switched on" by complexation of the Na^+ cation with receptor 5, and "switched off" by simply adding MeOH which will destroy the hydrogen bonds.

In the search for higher aggregates of functional molecules with well-defined geometry, Whitesides' cyanuric acid-melamine structural motif is currently being used. This "rosette" structure has the potential to function as a hydrogen-bonded platform for the aggregation of multiple calixarenes. The cyclic nature of the rosette provides substantial control over the degree of aggregation, and its highly ordered structure allows for the specific positioning of

substituents and functional groups. Three features of the calixarenes are currently exploited in the construction of rosette-based assemblies. The first is the (almost) parallel orientation of two opposing aromatic rings, especially when the pinched cone conformation is adopted. Secondly, the bulky nature of the calix[4]arene can direct the association process towards the formation of the cyclic structure (*vs.* linear aggregates), and closes the space that is generated between the rosettes, thus creating a cavity. Finally, positions on both the upper and the lower rim can be employed to introduce functional groups.

The formation and stability of double rosettes from bis(melamine)calix[4]arene **7** calix-isocyanurates **8** and **9** (Figure 2) has been investigated by ^1H NMR titrations, NOE spectroscopy, and vapor pressure osmometry (VPO).

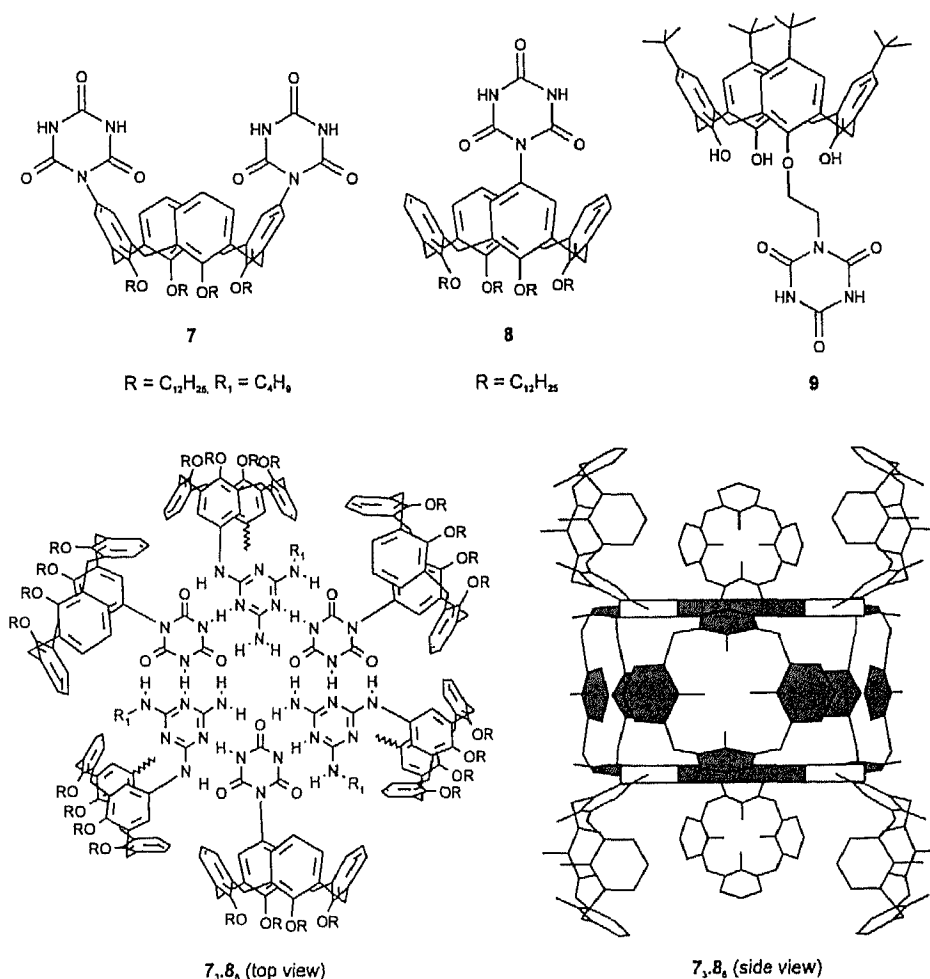


Figure 2. Schematic representation of the proposed structure of a double rosette consisting of **7** and **8** (for clarity, only the upper one of the two rosettes is drawn in the top view). In the side view the two rosettes are depicted as horizontal bars.

The results of the ^1H NMR titrations strongly support the formation of stable double rosettes as depicted in Figure 2. In these rosettes **7** and the cyanuric acid derivatives **8** and **9** are present in a ratio of 1:2. For the imido protons of the cyanuric acid derivatives two signals appear at very low field (14-16 ppm), indicating strong hydrogen bonding. Also the melamine NH's in the complexes are observed at lower field. The fact that only two signals are observed for the hydrogen bonded imido protons in situations where there is excess **7** indicates that the self-assembly is a highly cooperative process. NOE distances also are in accord with the proposed structures.

Mixing the bis-isocyanurate calix[4]arene **10** with flexible arms and tris-melamine calix[6]arene **11** with short and (rather) rigid arms in a ratio 3:2 in CDCl_3 also shows assembly; aggregates with expected masses of ca 8000 are formed (Figure 3).

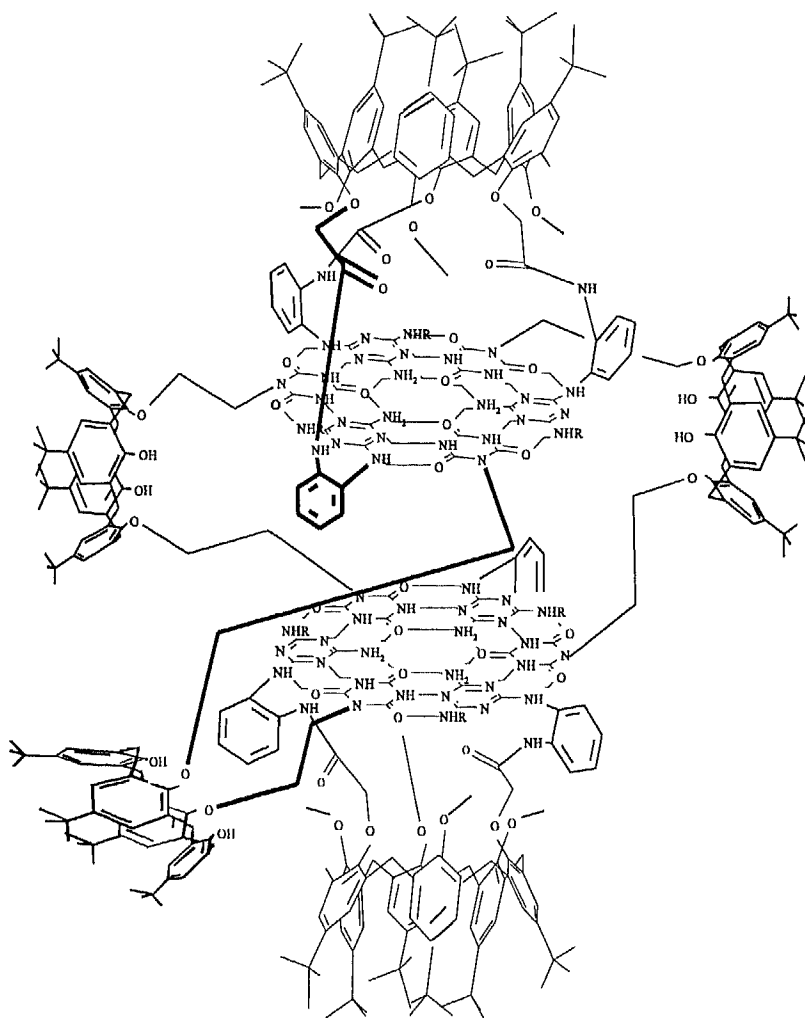


Figure 3. Double rosette from: calix[4]arene **10** and calix[6]arene **11**

The ^1H NMR spectrum of the mixture **10** and **11** (ratio 3:2) is sharp already at room temperature. At the same time, only a very broad signal of isocyanurate NH protons can be found at ca 14.0 ppm. At 0 °C sharpening of the signal occurs, and at -30 – -60 °C there are two pronounced singlets at 16.1 and 14.0 ppm for both isocyanurate NH protons. This implies that the formation of a double rosette takes place.

4. Assembly of NLO-phoric Modules in a Strong Electric Field

Calix[4]arenes are also suitable as building blocks for nonlinear optical (NLO) active materials. Possible applications for those materials are frequency doubling (conversion of red laser light to blue) or electro-optic switching (optical computers). Macroscopic NLO activity requires an aligned arrangement of non-centrosymmetric building blocks. Organic molecules which are functionalized non-centrosymmetrically with electron donating (D) and accepting (A) groups which are connected via a π -conjugated system, so called D- π -A molecules, meet the requirements for NLO active building blocks.

NLO active calix[4]arenes **12a,b** have been obtained by selective functionalization of the upper rim with electron accepting groups like nitro or *p*-nitrostilbene, and the lower rim with an electron donating group (*n*-propoxy), as depicted in figure 4. In this way four D- π -A-units are combined within one molecule.

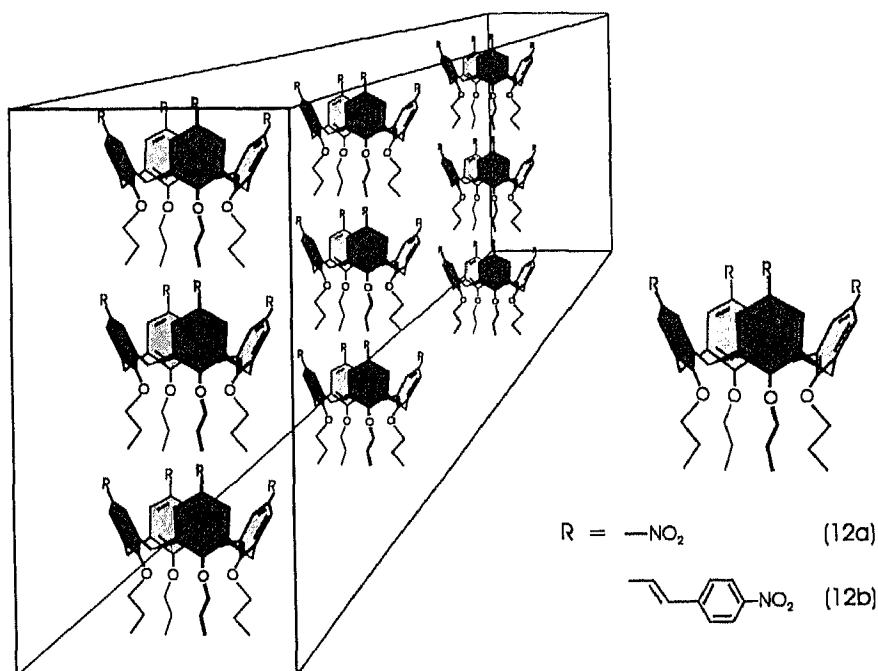


Figure 4. Assembly of calixarenes **12a** or **12b** after electrical field poting.

Spincoating of these building blocks (without a polymer matrix!) results in films (0.5-1.0 μm thick) which exhibit high NLO activity after poling [6]. The thermal stability of the d_{33} -values (frequency doubling parameter) of films consisting of neat **12a** and **12b** is high. At room temperature as well as at 80 °C (to which level the temperature can rise in photonic devices) no decay or less than 30 % decay of NLO activity is observed. After this initial decay a stable and still high d_{33} -value is reached. The origin of the high thermal stability of these NLO active films of calix[4]arenes alone is probably the stacking of these bowl-shaped molecules on top of each other (Figure 4). In this way very stable, large aggregates of columns are formed with very high dipole moments. Reorientation of these large aggregates which would mean decay of NLO activity, is difficult. Currently, dielectric measurements are in progress to prove the presence of these (columnar) aggregates of aligned molecules.

Another important property of NLO films used for frequency doubling, is transparency at both the fundamental (1064 nm) and the frequency doubled wavelength (532 nm). The maxima of the absorption bands of **12a** and **12b** are well below 532 nm (291 and 370 nm, respectively). Furthermore, there is hardly any residual tailing absorption at that wavelength.

5. Large Self-assembled Metallosheres

Nanophysical fabrication methods (nanolithography) which operate from the bulk 'down' are close to having reached their diffraction limits. Chemistry builds structures from the atom 'up' and should in principle produce materials which perfectly fit size requirements. Dendrimers have the well-defined structure to meet the requirements for new materials. They are prepared by stepwise growth, which may be divergent or convergent. Until recently dendrimers were fully organic in nature, but very recently also transition metal containing derivatives and organometallic dendrimers have been described.

Our approach to building dendrimers completely by self-assembly employs the combination of a kinetically inert tridentate ligand and kinetically labile cyano groups in a square planar Pd(II) complex [7]. The self-assembly process is based on the substitution of the labile acetonitrile molecules for cyanomethyl groups of the tridentate ligand thereby adding a new building block as is schematically depicted in Figure 5. The branching in the repeating units leads to a metallodendritic structure.

When all solvent molecules, including acetonitrile, were removed from a solution of **13** in nitromethane by gentle heating *in vacuo*, the cyanomethyl group of the bis-palladated complex **13** replaces the acetonitrile at the fourth coordination site of palladium. This coordination of the cyano group can be monitored by FT-IR spectroscopy in a nitromethane solution and in the solid state (KBr disc), because of the characteristic shift of the $\text{C}\equiv\text{N}$ stretch from 2250 cm^{-1} (free cyanomethyl group) to 2290 cm^{-1} upon coordination.

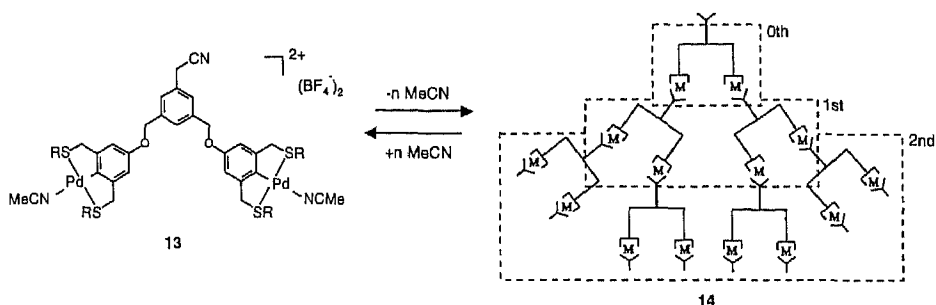


Figure 5. Schematic self-assembly of a second generation metallodendrimer.

The ^1H NMR spectrum in CD_3NO_2 of the acetonitrile-free compound **14** shows very broad signals, indicating association in solution. When small amounts of acetonitrile were added to this solution, all signals became sharp. This proves that the self-assembly of **13** and disassembly of **14** is a completely reversible process. QELS (Quasi Elastic Light-Scattering) measurements of nitromethane solutions showed particles with a modal hydrodynamic diameter of 200 nm.

The size of the aggregates was measured by Atomic Force Microscopy (AFM), after evaporation of the nitromethane solution on a gold surface. A representative part of the surface is shown in Figure 6. The globular shaped assemblies are clearly visible on a relatively rough gold substrate. The average diameter, as found by the grain size analysis routine of the instruments software of these aggregates is 205 nm, with a relatively narrow distribution: 80% (95%) of the diameters are found within s_d ($2 s_d$) of the mean value. Grazing angle FT-IR on the gold surface covered with the spheres showed the characteristic $\text{C}\equiv\text{N}$ signal of coordinated cyanogroups at 2290 cm^{-1} . When a glass substrate was used instead of gold, the same spheres were observed, of roughly the same size. This indicates that the interaction of the spheres with the surface does not significantly influence their size.

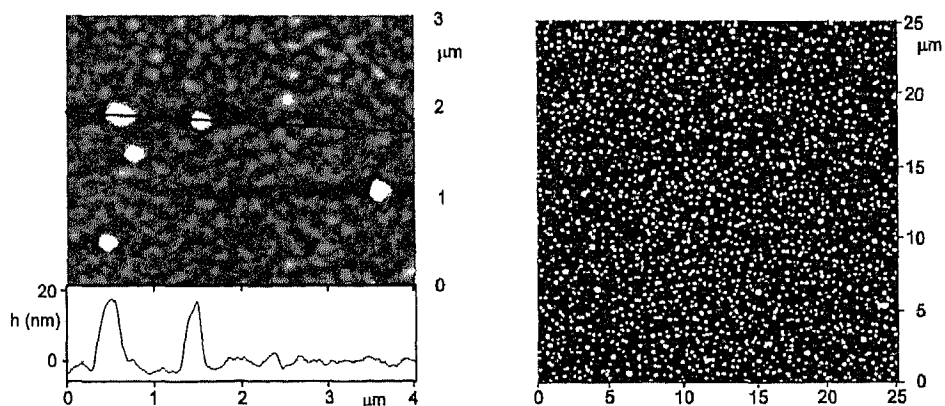


Figure 6. $25\times 25\ \mu\text{m}$ AFM scan of self-assembled spheres on a gold substrate (right) An enlargement of a representative $3\times 4\ \mu\text{m}$ area (left) is some isolated spheres (white dots). (Left): A line scan over two of the aggregates. The grey scale is 40 nm.

Samples for Transmission Electron Microscopy (TEM) were prepared by slow evaporation of a nitromethane solution on a carbon-coated copper grid. The pictures clearly show globular aggregates in the 150-200 nm range. This is in good agreement with the diameter measured with AFM (Figure 6) and indicates that Pd is present throughout the spherical assembly. Energy Dispersive X-ray Spectrometry (EDX) revealed the presence of the elements Pd and S in these aggregates, proving that these structures are no artifacts.

6. Conclusions

A modular approach to large functional structures has been described which applies either covalent or noncovalent combination of medium-size functional building blocks. This approach has produced bifunctional receptors, capped porphyrins, and large hydrophobic surfaces by covalent combination of the appropriate modules (e.g. calix[4]- and -[6]arenes, resorcin[4]arenes, cyclodextrins, porphyrins, and metallosalens). Noncovalent assembly of bifunctional receptor systems and large well-defined aggregates (molecular objects) based on calixarene modules have been 'synthesized'. Transparent and highly NLO active thin films, consisting of calix[4]arenes only, have been assembled. The perfect combination of high NLO activity and transparency makes these calix-films suitable materials for frequency doubling. By proper design of a branched repeating unit, large (metallo)spheres with well-defined dimensions can be formed by self-assembly. Self-assembly occurs not only in the solid state, but also in solution.

7. Acknowledgements

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8. References

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