Self-assembly of amphiphilic calixarenes and resorcinarenes in water

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The calixarenes and resorcinarenes are macrocyclic phenolic molecules that can be modified "*à façon*" and a wide range of chemical modification strategies have been published over the last 30 years. Because of their remarkable structural properties and their relative ease of chemical modification, they represent excellent and highly versatile bases to design complex building blocks capable of self-assembly and molecular recognition. They have been widely studied for their ability to form supramolecular structures targeting a wide range of applications. The possibility to regio(rim)-selectively modify these macrocycles with different polar and apolar moieties provides synthetic chemists with an unlimited range of possibilities for the design of complex amphiphiles with a high control over the position of the grafted moieties in the three dimensions. These amphiphiles have been shown to possess outstanding self-assembling and/or molecular recognition properties. This short review describes the developments of the chemistry of amphiphilic calixarenes and resorcinarenes with a clear focus on the synthetic paths used for their production and their self-assembly properties in water.

1. Introduction

1.1 Amphiphiles

Self-assemblies of amphiphiles, in addition to their tremendous theoretical interest, have found their place in the exponentially growing fields of drug delivery[1] and more recently of bio-nanotechnology.[2] Indeed, these assemblies give the possibility to encapsulate a pharmaceutically active compound in their core (or at their surface) and to cargo this compound to its therapeutic target.[3] This strategy presents the following advantages: (i) protection of the carried compound against degradation (*e.g.* enzymatic); (ii) possibility of controlled or triggered release; (iii) transport of the drug to its therapeutic target with the main benefit to decrease the doses given to the patient and therefore the possible side effects of these compounds.

In addition to a vast series of natural amphiphiles, a number of "engineered" synthetic amphiphiles have been designed. They include large molecules such as polymers[4] and peptides,[5] amphiphiles designed using a macrocyclic core such as cyclodextrins,[6] and crown-ethers,[7] to name but a few. An additional class of macrocycle that can serve as a basis to design amphiphiles are the calixarenes; the present review focuses on the use of calixarene (or resorcinarene) as an organizing basis

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for the design of synthetic amphiphiles and the study of the self-assembly of these molecules in water.

1.2 Introducing calixarenes and resorcinarenes

Generalities. The historical origin of calixarenes and resorcinarenes might be attributed to Adolf von Baeyer and the results he reported in 1902 on the reaction of pyrogallol and resorcinol with aldehydes.[8] The development of calixarene chemistry has seen the involvement of a number of chemists over the 20th century such as Lederer and Manasse, Baeckeland, Zinke and Ziegler, to name but a few. The detailed history of the discovery of calixarenes has been described in detail elsewhere.[9] The modern age of calixarene chemistry certainly started with the understanding and rationalization of the synthetic procedures by Gutsche and Muthukrishnan in the late 1970s.[10] The 1980s have seen the emergence of supramolecular chemistry[11] as a field of modern chemical sciences and a proof of the recognition of this new field is the Nobel prize shared by Lehn,[12] Cram[13] and Pedersen[14] for their pioneering work in the field. Supramolecular chemistry aims at designing complex multi-molecular systems where all the components are held together by non-covalent interactions.[11] As these interactions are widespread in biological systems, supramolecular chemistry largely overlaps biomimetic chemistry and numbers of supramolecular architectures mimicking or inspired by natural systems have been developed.[15] In this context, the calixarenes, because of their outstanding structural properties, rapidly took a predominant position in the field.

Calix[*n*]arenes[16,17] are macrocyclic molecules produced by the base-catalyzed reaction of *para*-substituted phenols and formaldehyde; *n* refers to the number of phenolic units that form the macrocycle and depends on the synthetic conditions and the ionic template used for their synthesis, *cf*. Fig. 1. The most commonly studied calixarenes, certainly because of their ease of synthesis, are that composed of 4, 6 or 8 phenolic units; their chemical modifications have been widely studied and reviewed recently.[18] The resorcinarenes (also called resorcinolarenes or resorcarenes) are commonly produced by the Brønsted acid-catalyzed reaction of resorcinol and an aromatic or aliphatic aldehyde in the absence of template;[19] synthetic strategies based on Lewis acid-promoted condensation have also been reported, *cf*. Fig. 1.[20]

Synthetic strategy. The use of macrocyclic compounds as a basis to design synthetic amphiphiles is mainly driven by the possibility given by these molecules to act as organizing entities for introducing and orienting, in the same complex

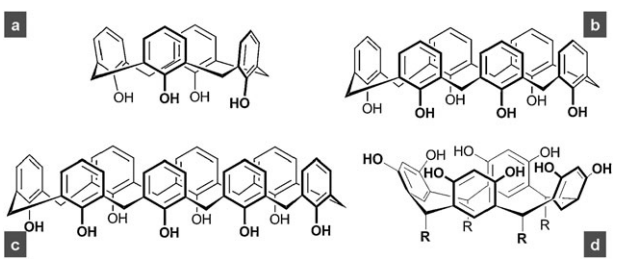


Fig. 1 Molecular formulas of calix[4]arene (a), calix[6]arene (b), calix[8]arene (c) and general formula of resorcinarenes (d).

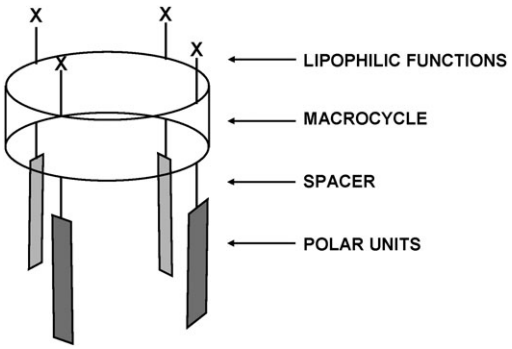


Fig. 2 Schematic representation of a macrocyclic amphiphile.

molecule, lipophilic and polar (molecular recognition) functions. Good candidates should exhibit, in addition to a relative conformational rigidity, the possibility to be chemically modified in a regio-selective fashion. The synthetic strategy may then be adapted in order to introduce on one rim of the macrocycle the needed lipophilic moieties and on the other rim the polar molecular recognition functions with or without spacing groups; a schematic representation is given in Fig. 2.

The calix[4]arenes, composed of four phenolic units, form a fairly rigid truncated cone-shaped molecule when adequately modified to "lock" the structure to avoid conformational changes to partial cone conformations.[16] In this molecule, the aromatic alcohol functions are exposed at the narrow rim, and the *para*-phenolic positions at the wide rim. Applying different chemistries, the macrocycle can be selectively modified either on one rim or the other. The regio-selectivity of the chemical modifications is not restricted to the selection of the modified rim, the number and the position within a rim could also be controlled.

The resorcinarenes, in addition to their rigid structure and the possibility to perform rim-selective modification, possess the advantage to exhibit, on the wide rim, sites of different chemical nature which may thus be differentially modified, giving the possibility to access more straightforwardly the molecules having on their polar side two different kinds of hydrophilic functions. Indeed, the native macrocycle, in addition to the 8 aromatic alcohol functions, can be also modified at the *ortho*-position in order to introduce up to 4 additional polar functions. A number of synthetic routes to amphiphilic calixarenes and resorcinarenes have been published and their self-assembly in water as liposomes, micelles and nanoparticles studied. The present manuscript will detail those three different classes of self-assembly; the formation of amphiphilic concentrated phases such as liquid crystalline phases will not be reviewed here.

2. Calixarene-based vesicles

The first report describing the possibility to form unilamellar vesicles with calixarenes has been published by Regen *et al*.[21] The self-assembly of the native calix[6]arene (unmodified on both rims) has been achieved by injecting a tetrahydrofuran (THF) solution of this macrocycle in water. Dynamic light scattering and transmission electron microscopy (TEM) revealed the monolamellar vesicular structure of the formed

objects with a broad size distribution ranging from 0.5 to 1 μm in diameter. Regarding resorcinarenes, the first report describing the possibility to self-assemble an amphiphilic derivative in water was published by Tanaka *et al.*[22] In this paper, it was described that a resorcinarene bearing C_{16} alkyl chains at the lower rim, previously shown to form ion channels when embedded in lipid bilayers,[23] has the ability to form vesicular systems in water. The self-assembly process used is fairly simple and similar to that used by Regen *et al.*[21] The amphiphile, dissolved in THF, was injected in a buffer at 60 °C which spontaneously led to the formation of a colloidal suspension. After removal of the organic solvent, the formed objects had been analyzed by negative staining TEM and atomic force microscopy (AFM). The results confirmed the unilamellar structure of the produced vesicles that, when dried on a surface, are flattening to form structures having a height of around 4 resorcinarene molecules (*ca.* 10 nm, 2 bilayers).

Lee *et al.* have demonstrated that a series of calix[4]arenes, bearing aliphatic (C_{10}) chains at the lower rim and tertiary amino-alcohol functions at the upper rim, possess amphiphilic self-assembly properties in water.[24] The modification of the parent calix[4]arene has been carried out as follows: (i) alkylation of the lower rim in basic conditions; (ii) chloromethylation of the *para*-positions; (iii) nucleophilic substitution of the chlorine by an amino alcohol, *cf.* Fig. 3.

The self-assembly of these amphiphiles in water had been studied by photon correlation spectroscopy, scanning and transmission electron microscopy. The results showed that these amphiphiles can self-assemble into stable colloidal suspensions with a narrow size distribution and decreasing hydrodynamic diameter (D_H) with increasing the size of the hydrophobic moieties. Indeed, when R′ = H (**1a**), the vesicles have a D_H of 200 nm; while the amphiphiles with R′ = $(CH_2)_2OH$ (**1b**) and R′ = $(CH_2)_2O(CH_2)_2OH$ (**1c**) self-assemble in structures having D_H values of 36 and 6 nm, respectively. The evidence that **1a** and **1b** form vesicles was obtained from the contrast observed in TEM, *cf.* Fig. 4. Because of the small D_H measured for **1c** that corresponds to the double length of the amphiphile, the authors postulated on the micellar structure of the formed aggregates. Using calcein as a hydrophilic fluorescent tag encapsulated into the vesicles, it was demonstrated that the amphiphiles undergo a phase transition and the vesicles transform into micelles of smaller D_H.

Two calix[8]arenes bearing 8 propyl chains at the lower rim and 8 *N*-acetyl glucosamine functions at the upper rim have

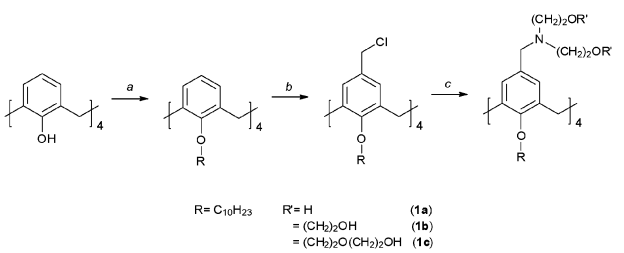


Fig. 3 Synthetic route to amino-alcohol-modified calix[4]arenes **1a**, **1b** and **1c** [a: *n*-$C_{10}H_{23}Br$, NaH; b: $ClCH_2OC_8H_{17}$, $SnCl_4$, c: Na_2CO_3, Bu_4NI, $(R'O(CH_2)_2)_2NH$].

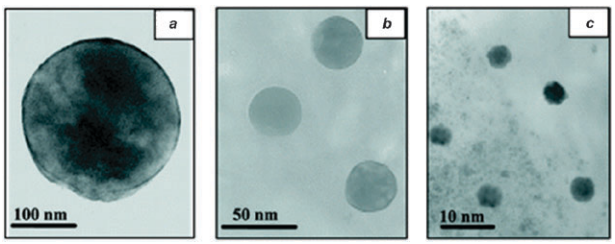


Fig. 4 TEM images of *p*-amino-alcohol-modified calix[4]arenes self-assembled in water (a: **1a**, b: **1b** and c: **1c**, as described in Fig. 3). [Reproduced with permission from ref. 24. Copyright 2004, the American Chemical Society.]

been synthesized,[25] *cf.* Fig. 5. The synthetic route followed consists of an *ipso*-nitration of the *O*-alkylated *p*-*tert*-butyl-calix[8]arene and the catalytic reduction of the *para*-nitro functions to yield the *para*-amino derivative that can be further modified to introduce the *N*-actetyl glucosamine units on the upper rim of the macrocycle. The produced molecules have been shown to form vesicles at neutral and basic pH. Interestingly, these assemblies are undergoing a vesicle-to-micelle phase transition at acidic pH. This phenomenon was attributed to the protonation of the polar groups of the amphiphiles and the changes of surface charge density.[26]

Reinaud and co-workers have produced[27–29] and studied the self-assembly in water of a calix[6]arene functionalized at the lower rim with three imidazolyl moieties and at the upper rim with sulfonato groups.[30] The synthesis was achieved by first alkylating the lower rim of the macrocycle at three alternate positions following the procedure described by Janssen *et al.*[28] The modification of the three remaining phenolic functions had been carried out using sodium hydride as basis and 2-chloromethyl-1-methyl-1*H*-imidazole hydrochloride.[29] The *ipso*-substitution of the positions in *para* of the methylated

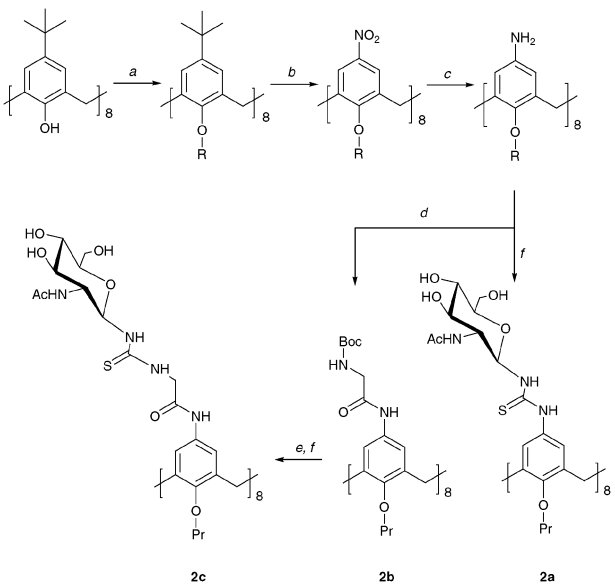


Fig. 5 Synthetic route to *N*-acetyl-glucosamine-bearing-calix[8]-arenes **2a**, **2b** and **2c** (a: NaH, *n*PrI; b: HNO_3, AcOH; c: Pd/C, H_2; d: *N*-Boc-Gly; e: TFA, f: sugar-NCS).[25]

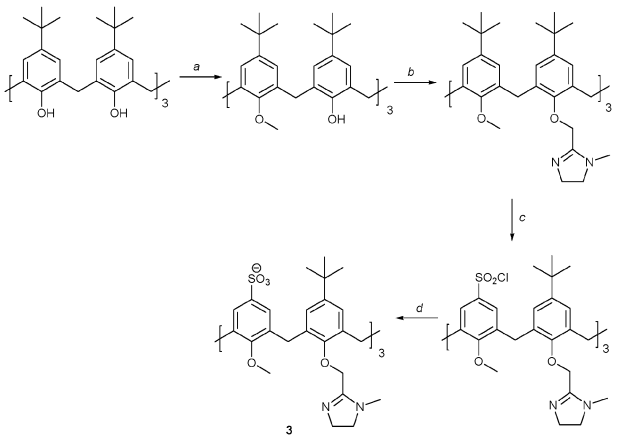


Fig. 6 Synthetic route to imidazolyl-sulfonato-calix[6]arenes, **3** (a: K_2CO_3, MeI; b: NaH, 2-chloromethyl-1-methyl-1*H*-imidazole, c: $ClSO_2OH$; d: TRIS).

phenols had been carried out using chlorosulfonyl acid, *cf*. Fig. 6.

In addition to their properties of biomimetic receptors for neutral molecules, it has been demonstrated that this macrocycle, even if it does not have a "typical" amphiphilic structure, does self-assemble as fairly polydisperse multilamellar vesicles. Ultrasonic treatment of this colloidal suspension has been shown to cause a diminution not only of the size of these assemblies but also of the polydispersity of the suspension. It has also been demonstrated that while decreasing the pH, monodisperse small vesicles are produced, an increase of pH causes the formation of giant vesicles (450 nm). The presence of silver ions drastically affects the self-assembly process causing the formation of micelles. This was attributed to the fact that the complexation with silver ions causes a conformational change of the calixarene which has a more pronounced conical shape and therefore is more prone to form micellar than layered systems, as schematized in Fig. 7.

Calix[4]arenes, modified at the upper rim with carboxy-functions, have been shown to form vesicles in water; interestingly at high concentrations they form layered lyotropic liquid crystalline phases.[31] A calix[4]arene, modified with perfluoro-alkyl chains, has also been shown to form vesicles in water while forming fiber-like structures in methanol.[32]

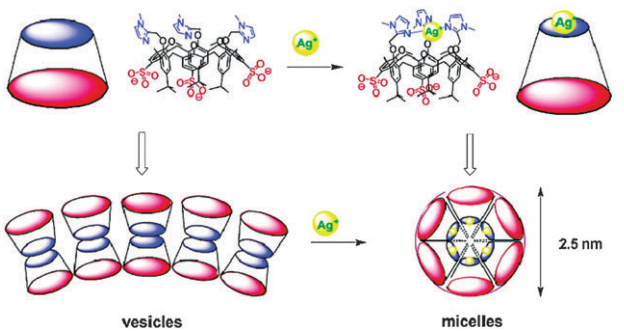
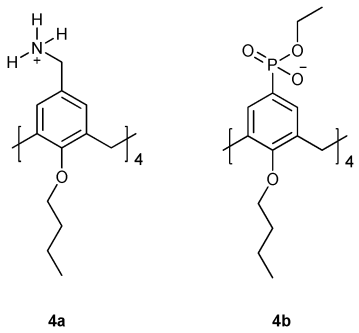


Fig. 7 Schematic representation of the effect of silver ions on the self-assembly of an imidazolyl-modified calix[6]arene. [Reproduced with permission from ref. 30. Copyright 2007, the American Chemical Society.]



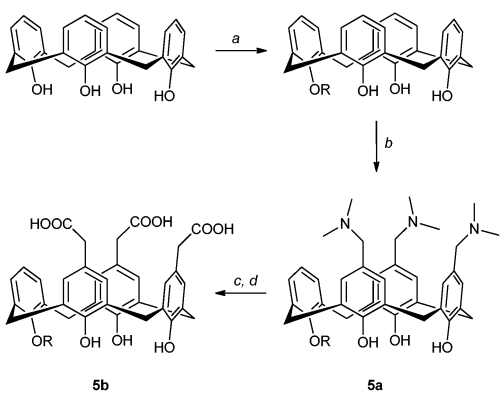
4a **4b**

Fig. 8 Methylammonium (**4a**) and phosphonate (**4b**) modified calixarenes.

The group of Schräder has developed a series of charged calixarene bearing phosphonate (**4a**) or methylammonium (**4b**) groups. It has been shown that these receptors, when embedded in membranes, have the ability to form a "charge imprint" of the target proteins, *cf*. Fig. 8.[33] Using a similar approach but embedding the calixarenes in vesicles comprising phospholipids and a chromatic polydiacetylene polymer, it has been demonstrated that micromolar protein concentrations cause a specific colorimetric response.

3. Micelles

The self-assembly of amphiphilic molecules into micellar structures in aqueous solution is a spontaneous dynamic process which is usually described to occur when the concentration of the amphiphile reaches the critical micelle concentration (CMC). The conditions of self-assembly are controlled by several parameters in which the conical shape of the amphiphile is considered as a prerequisite for forming small spherical micelles. Calixarenes offer intriguing synthetic possibilities for achieving this condition, which has been demonstrated for instance by functionalizing monoalkylated calix[4]arenes with hydrophilic groups by Coleman *et al*.[34] A possible synthetic route to mono-alkylated aminomethyl (**5a**) and carboxymethyl (**5b**) calixarenes is given in Fig. 9. A systematic study of the effect of alkyl chain length and



5b **5a**

Fig. 9 Synthesis of monoalkylated calix[4]arene amphiphiles with dimethylaminomethyl (**5a**) and carboxymethyl (**5b**) functionalities, R = CH_3, C_2H_5, C_3H_7, C_4H_9, C_5H_{11}, C_6H_{13}, C_7H_{15}, C_8H_{17}, C_9H_{19}, $C_{10}H_{21}$, $C_{12}H_{25}$; a: K_2CO_3, RI, or CsF, RI; b: $NH(CH_3)_2$, CH_3COOH, HCHO; c: CH_3I; d: KOH.[34]

hydrophilic group on the aggregation properties of the amphiphiles in water revealed that all the calixarene amphiphiles bearing carboxylic acid groups studied form small micelles at physiological pH (*i.e.* 6–8) with CMC values depending on the alkyl chain length—for dodecyl group the value was identical to that of a common surfactant dodecylmaltoside, 0.1 μM. In contrast, for amphiphiles containing less polar aminogroups the micellization does not follow a similar trend.

Water-solubility can be conferred to the calixarenes and resorcinarenes by attaching polar groups to the molecules, which is an appealing approach since it might simultaneously confer the macrocycle the ability to interact with biomolecules and therefore to show a biological activity.[35,36] Amphiphilic calix[4]arenes with four 2′-deoxythymidine or 2′-deoxyadenosine groups were synthesized by linking four phosphoramidite activated nucleotides at the calix[4]arene lower rim (*cf.* Fig. 10) and these molecules were shown to inhibit *in vitro* DNA replication.[37] In aqueous solution, these molecules self-assemble as dimers, which aggregate into micellar structures with D_H of 3.8 and 3.9 nm, respectively.[38] Adenine bases show stronger π-stacking interactions which lead to lower CMC value of **6b**, 0.22 mM compared to 0.51 mM of the thymine functionalized amphiphile **6a**. In the solid state, only **6b** forms spherical well defined aggregates of 700 nm diameter whereas **6a** tends to form smaller clusters which assemble into grapelike superstructures, as observed by SEM.

Multistep synthesis, starting from hydroxy group alkylation of undecyl resorcinarene to produce resorcinarene octaamines which further reacted with maltooligosaccharide lactones, yields amphiphilic resorcinarenes with eight oligosaccharide groups attached at the upper rim with amide linkages, as shown in Fig. 11.[39] The so-produced oligosaccharide conjugates do not show surfactant properties when surface tension is considered but they aggregate in micellar structures in water which is a clear indication of their amphiphilic nature.

In addition, the apparently huge oligosaccharide part with 16–56 glucose residues strongly promotes the formation of

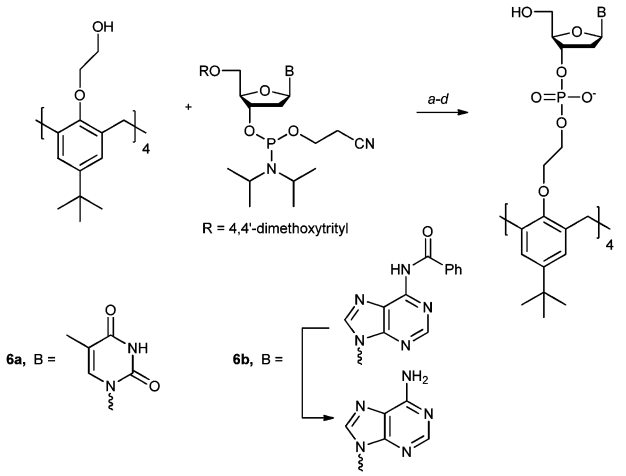


Fig. 10 Synthetic conditions for preparing calixarene nucleotide conjugates starting from *p*-(*tert*-butyl)-*O*-(2-hydroxyethyl) calix[4]arene and protected 2′-deoxynucleoside phosphoramidite; a: tetrazole; b: I_2; c: 30% NH_4OH, pyridine; d: 30% CH_3COOH. Adenosine base (**6b**) is protected with benzoyl group in the starting material.[37]

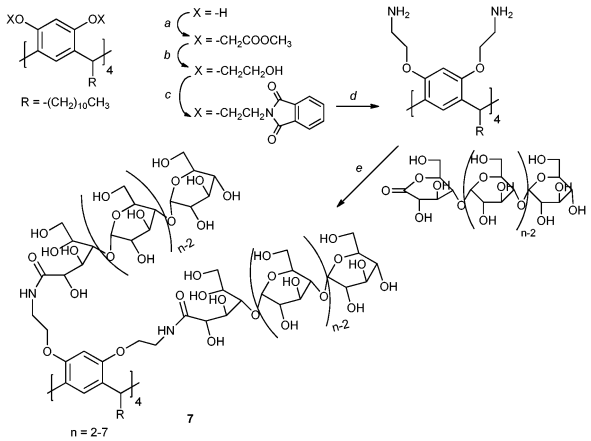


Fig. 11 Synthetic strategy leading to resorcinarene oligosaccharide conjugates; a: $BrCH_2CO_2CH_3$, K_2CO_3, acetone; b: $LiAlH_4$, THF; c: phthalimide, diethyl azodicarboxylate (DEAD), PPh_3, THF; d: $NH_2NH_2{\cdot}H_2O$, THF/EtOH; e: MeOH or MeOH/ethylene glycol.[39]

small micelles consisting of 4–6 molecules instead of lamellar assemblies. The formation of micelles cannot be explained by hydrophobic driving forces alone, since the micelle formation is found to be irreversible and the aggregates are not dissociating into monomers, but interactions between oligosaccharide moieties must also play a role. Phosphate ions promote agglutination of the micelles which indicates that this anion is effectively hydrogen bonded by the oligosaccharide moieties (Fig. 12). The glycosaccharide micelles and their interaction with DNA to form "artificial viruses" have been reviewed elsewhere.[40]

Careful adjustment of the polarity of both the amphiphile and the environment can offer control over the aggregation and micelle formation as observed in systematic experiments conducted with resorcinarenes bearing carboxymethyl (**8**), 2-hydroxyethyl (**9**), methylamino acetal (**10**) or dialkylamino groups (**11–19**) in chloroform and 1,4-dioxane where they form inverted micelles (Fig. 13).[41,42] In addition, mixed micellization of tris(hydroxymethyl)amide resorcinarene with a common cationic surfactant cetyl trimethylammonium bromide has been shown to increase the catalytic activity of the micelles of hydrolysis of phosphoric ester in water when compared to a pure resorcinarene amphiphile (Fig. 14).[43]

Even though aggregation might be considered as a purely random and anarchic way of forming polydispersed material, scientists have recently put a lot of effort in attempts to control the aggregation of many interesting amphiphilic compounds in

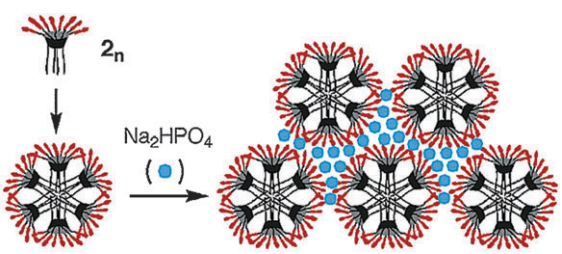


Fig. 12 Schematic representation of the self-assembly and phosphate induced agglutination of amphiphilic resorcinarene oligosaccharide conjugates.[39] [Reproduced with permission from ref. 39. Copyright 2003, the American Chemical Society.]

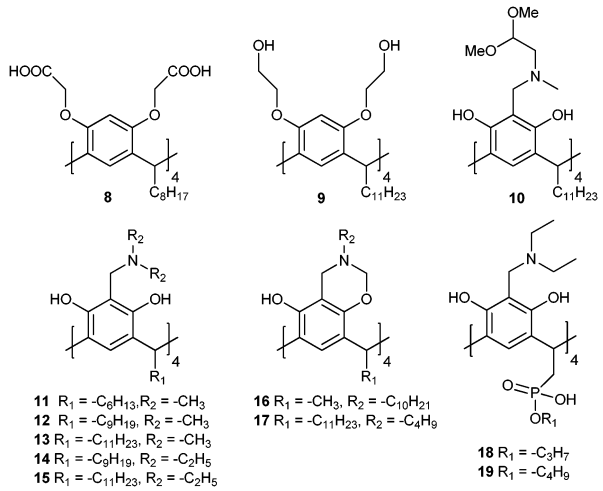


Fig. 13 Structures of amphiphilic resorcinarenes **8–19**.[42–44]

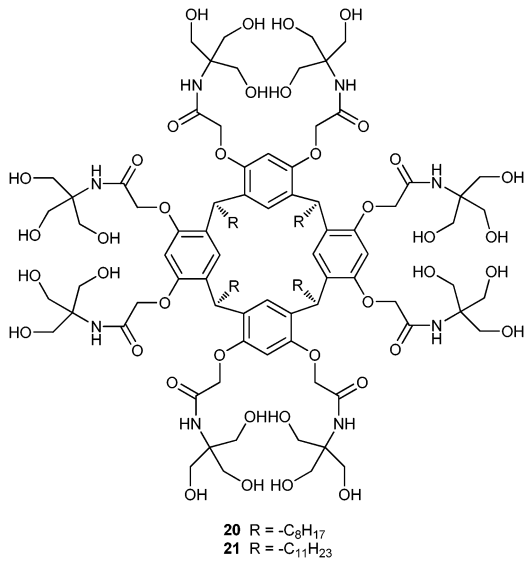


Fig. 14 Tris(hydroxymethyl)amide resorcinarene, **20** and **21**.[43]

order to fully exploit their potential. Aggregation of calix[4]-arene gadolinium chelate conjugates (Fig. 15) into micelles with a hydrodynamic radius of 2.2 nm has a remarkable consequence in improving their properties as a MRI contrast

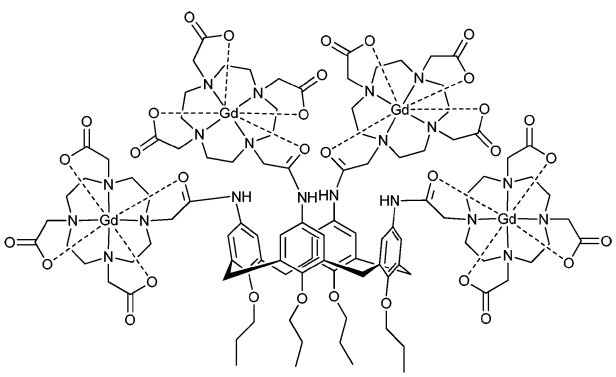


Fig. 15 Structure of calix[4]arene Gd–DOTA conjugate, DOTA = 1,4,7,10-tetra(carboxymethyl)-1,4,7,10-tetraazacyclododecane, **22**.[45]

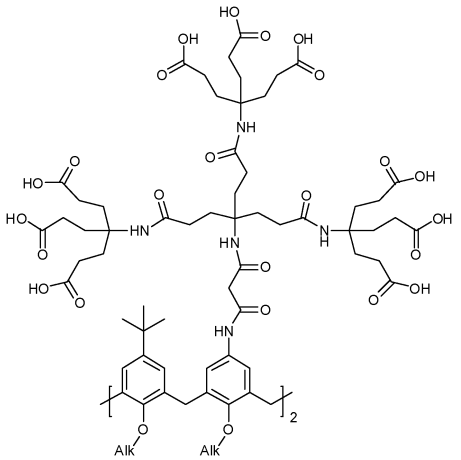


Fig. 16 Structure of amphiphilic dendrocalixarene, **23**.[46]

agent when compared to the monomer.[45] In MRI imaging, the toxic gadolinium must be strongly chelated to prevent its release in the body and therefore the chelator also has an effect on the performance of the substance. In the current study, relaxivity of 18.3 s^{-1} per mM Gd at 37 °C and 20 MHz was obtained for Gd bound to micelles, about twice as much when compared to the monomer.

Another example of micelles forming calixarenes with perfect structural uniformity is presented by the self-assembly of seven subunits of dendrocalixarene (Fig. 16) in aqueous solution into robust and uniform micelles.[46] The structure of the micelles was determined at 12 Å resolution by cryo-TEM and 3D-reconstruction, *cf.* Fig. 17. The interior of these micelles was then probed using pyrene labels for time resolved spectroscopy experiments.[47] The results showed how hydrophobic guest molecule can experience environments inside the micelle, *i.e.* the aromatic part of calixarene macrocycle in addition to the hydrophobic tails. However, calixarene does not quench the pyrene fluorescence as efficiently as 2,6-dimethylanisole, which was used as a model for the calixarene

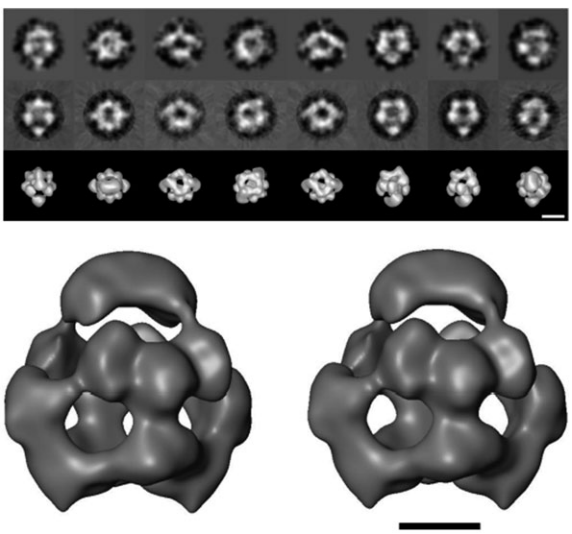


Fig. 17 Electron micrograph of dendrocalixarene micelles; reprojections.[46]

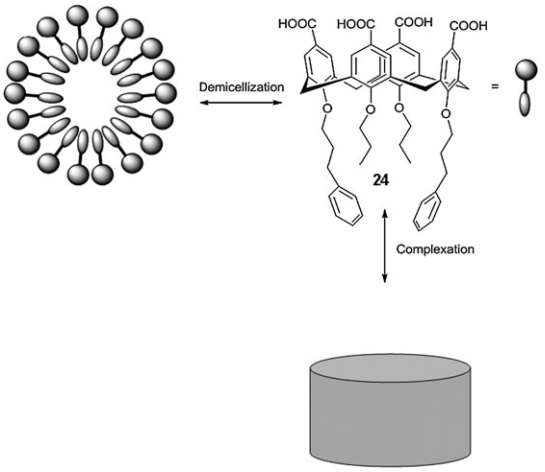


Fig. 18 Demicellization and complexation of calixarenes with γ-cyclodextrin.[48]

walls but rather protects the embedded fluorophore from the quenchers present in the solution. In this study, the CMC of the amphiphiles was found to be only 40 μM, which is 200 times less than for sodium dodecyl sulfate.

Formation of host–guest inclusion complexes in the presence of aggregates has been investigated using calix[4]arene bearing carboxylate groups and cyclodextrins in aqueous solution.[48] Fig. 18 shows a schematic representation of the complexation, where demicellization precedes the 1 : 1 complexation. The study revealed that initial micellization of the amphiphilic calixarenes (guest) did not disturb the inclusion complexation of phenyl groups of the guest inside γ-cyclodextrin cavity, and therefore equilibrium constants for the system could be determined reliably using isothermal titration calorimetry (ITC).

Calixarenes and resorcinarenes can be utilized as building blocks for true supramolecular amphiphiles, *i.e.* the hydrophobic and hydrophilic parts of the supramolecule are linked through weak force interactions.[49,50] Yu *et al.* demonstrated that a hydrophilic calix[4]arene PEG-conjugate forms an inclusion complex with hydrophobic phenyl palmitate (guest), which further assembles in water into vesicles, micelles or network like structure,[49] *cf.* Fig. 19. The elegance of this system lies in the simple way of controlling the equilibrium between each species by changing the ratio of hydrophobic and hydrophilic counterparts in the system. Increasing the amount of hydrophobic guest changes the equilibrium from vesicles with a diameter of 270 nm to micellar species with a diameter of 130 nm at the 1 : 1 ratio and finally the excess of guest leads to the formation of network aggregates.

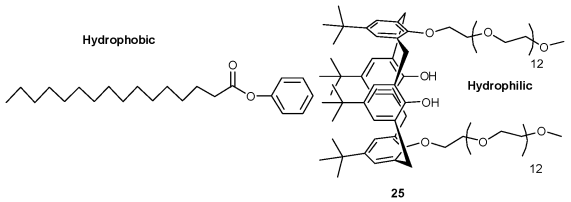


Fig. 19 Structure of a supramolecular amphiphile formed by inclusion complex of calix[4]arene PEG-conjugate and phenyl palmitate.[15]

4. Nanoparticles

The first calix-arene-based solid lipid nanoparticle systems were developed by one of us in the group of Anthony W. Coleman. Using a method pretty similar to that used by Tanaka *et al.* for producing resorcinarene-based liposomes,[22] and inspired from the work done in the group with amphiphilic cyclodextrins,[51] the self-assembly of a series of *p*-acyl-calixarenes in water was studied.[52] Briefly, the preparation method consists of adding water into a solution of the amphiphile dissolved in THF, to keep the formed suspension under stirring for a short time (typically 1 min) and to evaporate the organic solvent under reduced pressure.[53] The AFM studies[52] of these nanoparticles revealed some clear differences with the behaviour of the resorcinarene liposomes described by Tanaka *et al.*[22] Liposomes, when dried on a surface, either collapse to form supported bilayers[54] or get significantly flattened (down to the length of four constitutive amphiphiles in the case of unilamellar liposomes). For the studied systems, not a drastic flattening was observed and the particles revealed a very high stability over time. Indeed, AFM imaging on samples prepared for more than 12 months did not show any difference with the initial images of the fresh samples. From these considerations was postulated a non-lamellar structure of these systems that were then classified as nanoparticles. Additional ^{129}Xe NMR brought additional insights on the structure of these self-assemblies.[55] Having produced a series of *p*-acylated calix[4]arenes as analogues of natural phospholipids modified regioselectively at the lower rim with two phospho-ester groups,[56] it was demonstrated that all these amphiphiles have the ability to self-assemble as stable nanoparticles, *cf.* Fig. 20.

p-Acyl calixarenes have shown remarkable characteristics including high temporal and physical stability,[53] no hemolytic activity,[57] no aggregation in contact with serum albumin,[58] possibility of freeze-drying[59] or possibility of integration in gels used for formulation of topical creams.[60] This work has been recently summarized in a review article and will not be

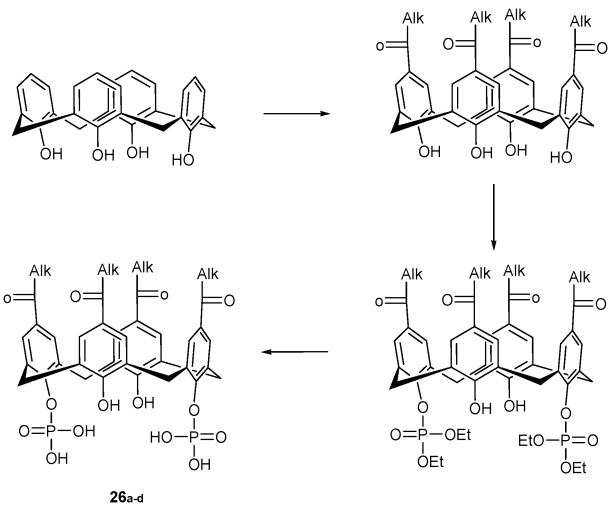


Fig. 20 Synthetic route to *p*-acyl-phospho-calixarenes **26a–d** (a: AlkCOCl, $AlCl_3$; b: $ClPO(OEt)_2$, Et_3N; c: (1) $BrSiMe_3$, (2) MeOH; Alk = $CH_3(CH_2)_n$, n = 5, 7, 9, 11).

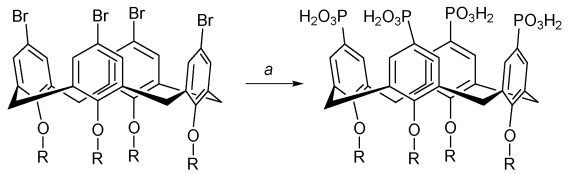


Fig. 21 Synthetic route to *p*-phospho-calix[4]arenes (a: (1) $PO(OiPr_3)$, $NiBr_2$, (2) Me_3SIBr).[62]

detailed here.[61] In a similar approach, the self-assembly of *p*-phospho-calix[4]arenes in water has been studied. Produced by the reaction of the *p*-bromoalkoxycalix[4]arenes with tri-isopropyl phosphite in the presence of $NiBr_2$ and consecutive deprotection with bromotrimethylsilane and methanol, these amphiphiles have been shown to self-assemble as nanoparticles, *cf.* Fig. 21.[62]

This self-assembly method has been expanded to a series of other calixarenes and resorcinarenes. For instance, a synthetic route to a chiral prolyl-bearing resorcinarene has been developed (Fig. 22). In addition to the proof of the chiral recognition properties of these molecules when self-assembled as Langmuir monolayer at the air–water interface *via* the formation of a ternary complex with Cu^{2+} ions,[63] we demonstrated that these molecules self-assemble as stable solid lipid nanoparticles.[64] We have also shown that the formed SLNs can be further modified, using a typical aqueous amide coupling procedure using *N*-hydroxysuccinimide (NHS) and a water soluble carbodiimide (1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide), at their surface with proteins. The integrity of the nanoparticles has been demonstrated by PCS. The *native* state of the protein at the surface of the SLNs has been shown by showing the ability of an antigene directed against this protein to recognize these proteo-SLNs, as demonstrated by surface plasmon resonance experiments.

The high stability of these nanoparticles also allowed us to image them without any further treatment to stabilize the SLNs by means of SEM, *cf.* Fig. 23.

The interest of calixarenes for biomedical applications[35] has shown rapid development during the past decade for applications including anti-viral,[65] anti-thrombotic activities,[66] enzyme inhibition[67] and protein complexation.[68] The first report on the interaction of calixarenes with nucleic acids dates back to 1999 when Shi and Schneider published the synthesis of four different calixarenes bearing (trimethylammonium)-methyl groups at the upper rim of the macrocycle.[69] It was demonstrated

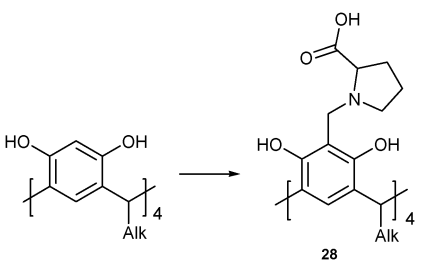
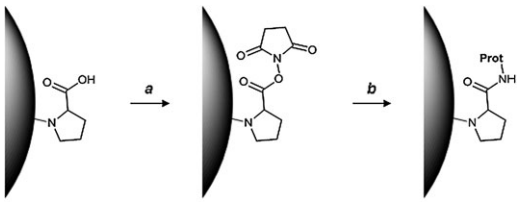


Fig. 22 Synthetic route to prolyl-modified resorcinarenes (HCHO, L-Pro).



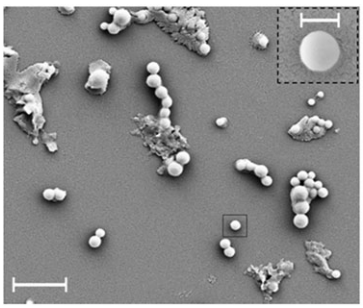


Fig. 23 Chemical modification of prolyl-bearing calix[4]arenes SLNs with serum albumin (top) and scanning electron micrograph of these SLNs spread on a mica surface at a pressure of 10^{-5} Pa (a: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, *N*-hydroxysuccinimide; b: bovine serum albumin).

that the two calix[4]arene derivatives produced show greater binding properties than linear polyamines (*e.g.* spermine) which also bear 4 amino functions, suggesting that the interaction was improved by a cooperative effect of the amine groups.[69] Based on these findings and the recent results published by Ungaro *et al.* on the possibility to compact DNA with cationic calixarenes,[70] the self-assembly properties of a polycationic calixarenes, 5,11,17,23-tetramino-25,26,27,28-tetradodecyl-oxycalix[4]arene, at the air–water interface and in water have been studied. The results revealed the ability of these molecules to interact with DNA not only when self-assembled at the air–water interface but also in the form of SLNs.[71] With the ambition to use these systems to cargo DNA for therapeutic purposes, a solution was needed to avoid the exposure of the DNA molecules at the surface of the SLNs to nucleases attacks. It was decided to wrap the DNA with an additional polyelectrolyte (chitosan) layer bound to the DNA *via* electrostatic interactions, this positively charged layer gives the possibility to add, *via* an iterative process, additional layers of DNA, as schematized in Fig. 24.[72] This approach, also known as layer-by-layer (LBL) assembly,[73] additionally allows a significant increase of the quantity of DNA loaded at the surface of the carrier; the choice of the polyelectrolyte used might also favor the uptake of the colloidal particles in the cells. It was demonstrated for the first time the possibility to load calixarene-based SLNs *via* a layer-by-layer assembly

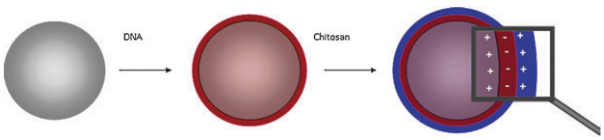


Fig. 24 Schematic representation of the LBL coating of amino-calixarenes.

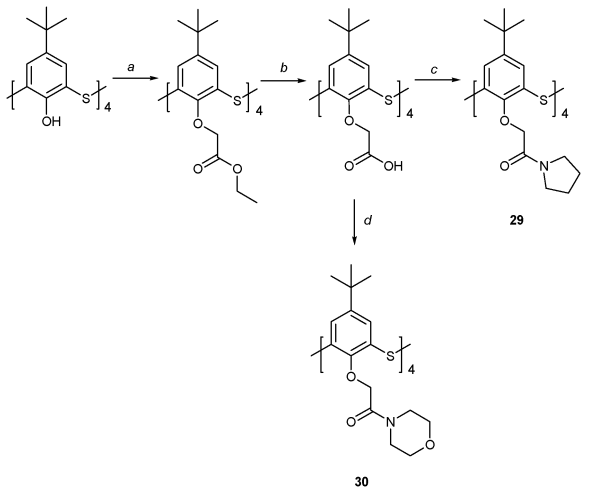


Fig. 25 Synthetic route to morpholine or pyrrolidine modified resorcinarenes; (a) LiOH, H_2O/THF, HCl; (b) $SOCl_2$, reflux; (c) pyrrolidine, RH, NEt_3, CH_2Cl_2, rt; (d) morpholine RH, NEt_3, CH_2Cl_2, rt [from ref. 74].

process and the ability of these systems to enter mammalian cells to release the DNA loaded at their surface.

Thiacalix[4]arenes bearing *p-tert*-butyl groups at the upper rim and functionalized at the lower rim with secondary amide groups have been studied for their ability to dimeric complexes and to recognize metal ions (Li^+, Na^+, K^+, Cs^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, Al^{3+}, Pb^{2+}, Fe^{3+}, Co^{3+}, Ni^{2+}, Cu^{2+}, Ag^+, Cd^{2+}, Hg^{2+}) by the picrate extraction method and photon correlation spectroscopy. Whereas the extraction capabilities have been shown to be fairly poor, these molecules have been shown to form nanoparticulate assemblies in water (Fig. 25).

We have recently reported on the self-assembly of 5,11,17,23-tetra-carboxy-25,26,27,28-tetradodecyloxycalix[4]arene at the air–water interface as monomolecular Langmuir layers and in water.[75] It has been demonstrated that these monolayers have the ability to interact with salicylic acid, acetylsalicylic acid and acetaminophene. As mentioned above, Meier *et al.* demonstrated that this calix-arene has the ability to self-assemble as monomolecular vesicular structures in aqueous medium when dissolved in aqueous ammonia.[31] When using the nanoprecipitation method, the formed assemblies possess properties that suggest that they possess a nanoparticulate structure. Nevertheless, AFM investigations of this calixarene revealed the presence of layered structures coexisting with the nanoparticles at the surface of mica after drying, *cf.* Fig. 26.

Among the relevant number of examples of calix-arenes and forming nanoparticles, one example can be considered non-typical because the macrocycle used as a building block is not amphiphilic but hydrophobic. Indeed, it was demonstrated that *O*-dodecyl-calix[4]arene, even if it does not possess polar functions can self-assemble as fairly stable nanoparticles.[76] This observation might have led to the conclusion that these nanoparticles are formed only because of the insolubility of the lipophilic macrocycle in water. Nonetheless, a series of observation including the ability of this calix-arene to form Langmuir monolayers and that incapacity of the non-cyclic building block (dodecyl-phenol) to form neither Langmuir monolayers nor nanoparticles brought us to qualify this molecule as "pseudo-amphiphilic" (Fig. 27). In other word, the amphiphilic behaviour of this molecule is not due to the presence of polar function but to the capacity of the calix-arene macrocycle to interact with water.[77]

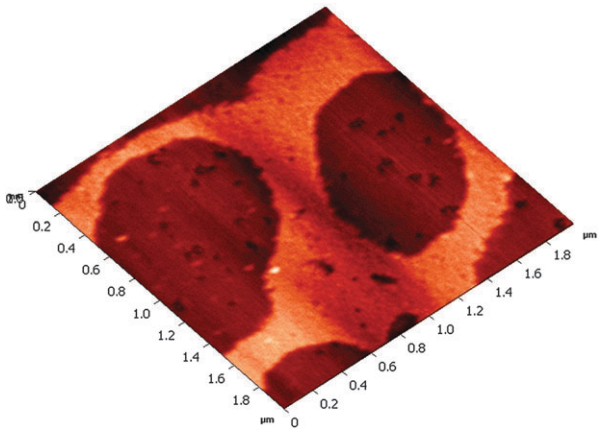


Fig. 26 Supported layer formed by 5,11,17,23-tetra-carboxy-25,26,27,28-tetradodecyloxycalix[4]arene on a mica surface imaged by non-contact AFM in air (2 × 2 µm scan range). [Reproduced with permission from *Chimia*.[75] Copyright 2010, the Swiss Chemical Society.]

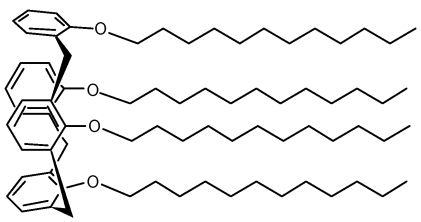


Fig. 27 Molecular formula of *O*-dodecyl-calix[4]arene shown to possess "pseudo-amphiphilic" properties.

5. Summary and outlook

Since the first proof of the possibility to self-assemble amphiphilic calixarenes in water, a relevant number of publications reported the ability of these systems to form self-assemblies in water. Nevertheless, compared to the wide amount of known calixarenes and resorcinarenes and the almost unlimited possibilities given by these macrocycles to design amphiphiles, one can realize that the amount of amphiphilic derivatives is still fairly limited. A more systematic approach of the structure/self-assembly property relations of a wider range of amphiphiles based on macrocyclic molecules might allow us to produce a set of general rules that would help to predict the self-assembly properties of this class of complex amphiphiles and thus allow a rational design of new amphiphiles possessing the desired properties.

As the foremost interest of producing synthetic amphiphilies is oriented toward the use of these self-assemblies for drug transport and targeting, one explanation of the limited amount of data available regarding amphiphilic calixarenes and resorcinarenes is the suspected toxicity of phenolic

compounds and their derivatives. Therefore, we believe that the development of new amphiphilic calixarenes should be accompanied by toxicity tests to definitely open the fertile ground that can represent the chemistry of self-assembled calixarenes and their applications.

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