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Oana M. Martin[a]; Sandro Mecozzi[b]
[a] School of Pharmacy, [b] Department of Chemistry, University of Wisconsin - Madison, Madison, USA

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Synthesis and Self-assembly of Amphiphilic Semifluorinated Calix[4]arenes

OANA M. MARTIN[a] and SANDRO MECOZZI[a,b,*]

[a]*School of Pharmacy;* [b]*Department of Chemistry, University of Wisconsin - Madison, 777 Highland Ave., Madison, WI 53705, USA*

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A new amphiphilic molecule based on the calix[4]arene scaffold was synthesized by. appending perfluoroalkyl chains on the upper rim and polar groups on the lower rim of the macrocycle. This molecule self-assembles in water and methanol due to formation of a super-hydrophobic fluorous phase. Bilayer assemblies were observed using dynamic light scattering (DLS) and transmission electron microscopy (TEM). The aggregate architecture is strongly influenced by the solvent. Fibers formed by stacked disks were observed in methanol, whereas spherical aggregates were favored in an aqueous environment.

Keywords: Calix[4]arenes; Fluorophobic effect; Fluorous phase; Vesicles; Stacked disks; Self-assembly

INTRODUCTION

The physical and chemical properties of organic compounds are deeply affected by the introduction of fluorine substituents [1–5]. While the introduction of one single atom of fluorine in an organic molecule is sufficient to change the properties of a molecule, perfluorination of organic molecules can generate a new phase of liquid matter, the so-called fluorous phase. This phase does not mix with both polar and non-polar hydrogenated phases. The formation of a fluorous phase is at the origin of the unusual behavior of heavily fluorinated molecules and polymers[4]. Segregation of highly fluorinated molecules into a fluorous phase is a phenomenon that has come to be known as the fluorophobic effect [1,2,6–8]. The fluorophobic effect has found important applications in various fields, from fluorous supramolecular polymer and materials chemistry [9], to fluorous synthesis [10,11] and fluorous bioorganic chemistry and medical sciences [12]. The fluorophobic effect thus has enormous potential and can be possibly applied to the self-assembly of various classes of molecules functionalized with perfluoroalkyl chains.

Calix[4]arenes are adaptable scaffolds widely used to generate a variety of supramolecular entities [13–22]. Their three-dimensional, concave and relatively rigid structure, together with a well-developed synthetic chemistry, made them attractive platforms for development of new self-assembled systems. A variety of self-assembled systems based on the versatile calixarene scaffold have been studied, from dimeric capsules [19–22] to mono- and multilayers [14,23,24] and vesicles [17,18].

A consequence of the larger van der Waals radius of fluorine compared to hydrogen is that perfluoroalkyl chains, in spite of the weak van der Waals interactions between them, pack in a much more orderly manner compared to alkyl chains. Perfluoroalkyl chains exhibit reduced conformational freedom compared to alkyl chains, and consequently the incidence of gauche defects is significantly lower, facilitating stacking and ordering [25]. Fluorous chains are considerably more hydrophobic than alkyl chains and have the unique property of being lipophobic as well. These peculiar properties result in self-aggregation, phase separation and formation of an ordered fluorous phase. The situation is different when fluorinated amphiphilic molecules are considered. Due to the increased hydrophobicity of perfluoro-derivatives and to the concomitant presence of water-solubilizing groups, these amphiphiles form a special class of surfactants. Fluorinated surfactants are characterized by a high surface activity and a strong tendency to self-organize into ordered, stable

*Corresponding author. E-mail: smecozzi@pharmacy.wisc.edu

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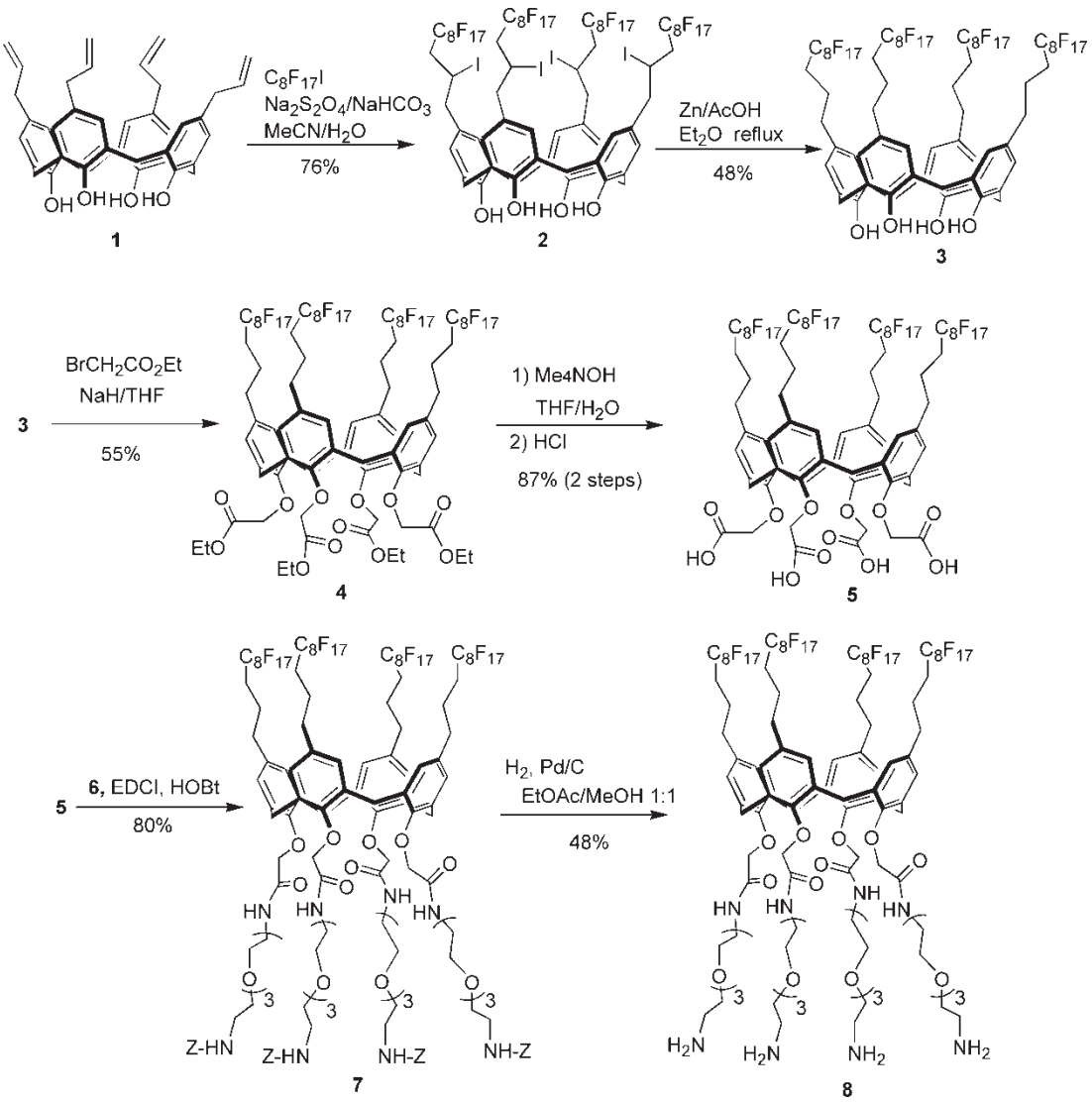
supramolecular complexes. Microtubules, vesicles, bilayers and complex three-dimensional ordered assemblies can be formed by organic molecules bearing perfluorinated substituents [26–34].

Exploring the unique properties of fluorous phase-driven self-assembly, we have prepared a novel semi-fluorinated amphiphilic calix[4]arene, which self-assembles into bilayer aggregates of various morphologies depending on the nature of the solvent.

RESULTS AND DISCUSSION

The present study is focused on the synthesis and characterization of the self-assembly patterns of a new calix[4]arene amphiphilic molecule. The target semi-fluorinated calix[4]arene was synthesized by functionalizing the upper rim of the macrocycle with four perfluorooctyl linear chains, while attaching four water-solubilizing groups on the lower rim. The rigid helical conformation of the fluorous chains[25], coupled with the complexity of the hydrophilic segment of the molecule, results in various aggregate architectures in solution, depending on the nature of the solvent. Intercalation of a short alkyl chain between the calixarene scaffold and the perfluoroalkyl chains imparts increased flexibility to the fluorophilic portion of the molecule, driving the assembly towards bilayer structures. Due to extensive hydration, the hydrophilic chains are expected to assume an expanded conformation in water. Therefore the molecules are expected to adopt a conical shape, which determines the formation of a curved bilayer membrane, possibly closing up into vesicles or tubules. The presence of four perfluoroalkyl chains greatly increases the hydrophobicity of the molecules. Water solubility was achieved by functionalizing the lower rim of the calix[4]arene with extended hydrophilic groups, composed of a tetra(ethylene oxide) linker ending with a charged group.



SCHEME 1 Chemical synthesis of amphiphilic calix[4]arene (**8**). Z = carbobenzyloxy.

The synthesis of this complex molecule is depicted in Scheme 1. *p-tert*-Butylcalix[4]arene was first obtained using a simplified Gutsche procedure which involves the base-induced condensation of *p-tert*-butylphenol with formaldehyde [35]. After removal of the *tert*-butyl groups, calix[4]arene was alkylated on the lower rim using the method of Stoochnoff and Benoiton [36], and converted to *p*-allyl-calix[4]arene (**1**) via a Claisen rearrangement in N,N-diethylaniline [37]. The addition of perfluorooctyl iodide to the *p*-allyl groups proceeded with 76% yield, and was followed by hydrodeiodination with zinc and acetic acid to finally give the desired calix[4]arene (**3**) functionalized at the upper rim with perfluorooctyl chains [38,39]. Tetraester (**4**) was then prepared by alkylating the phenol groups with ethyl bromoacetate and sodium hydride [40] and was subsequently transformed into the tetraacid (**5**) by basic hydrolysis (47% yield for 3 steps). Standard carbodiimide conditions for amide bond formation were used for coupling tetraacid (**5**) with amine (**6**). Finally, the carbobenzyloxy (*Z*) protecting groups were cleaved by hydrogenation, giving the amphiphilic target molecule (**8**).

The lower-rim water-solubilizing chains were synthesized starting from the azido-amine (**9**) which was prepared according to literature procedures [41]. Further conversion of (**9**) to 1-(carbobenzyloxy-amino)-11-amino-3,6,9-trioxaundecane (**6**) was achieved by protecting the amine functionality with a carbobenzyloxy group, followed by a Staudinger reduction of the azide (Scheme 2).

Dynamic light scattering of solutions of (**8**) in water and methanol indicated the presence of aggregates of different sizes (Figure 1). Two different distributions were observed in water, centered around 67 nm and 250 nm, whereas in the methanol solution, only larger aggregates with an average diameter of 217 nm were measured.

These aggregates were studied by transmission electron microscopy. Spherical particles with diameters of 50–70 nm were observed in water (Figure 2a). The morphology of these particles suggests that they are vesicles. These small particles can further aggregate into larger assemblies with diameters around 200 nm or even larger through what appears to be a time-dependent process.

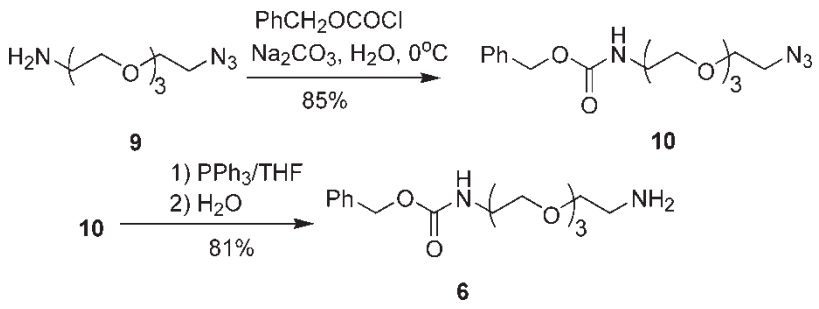
The self-assembly behavior of compound (**8**) in methanol was remarkably and surprisingly different, compared to the aqueous solution. In this case, the semifluorinated amphiphilic calixarenes appear to form long fibers having an average length of 200 nm. A more careful analysis of the structure of the fibers reveals that they are formed by discoid-shaped structural elements that appear to be stacked one above the other. The final layered structure of the aggregates can be clearly observed in the electron micrograph (Figure 2b). The formation of these structures could be explained by the intermediate formation of disks characterized by an inner fluorous phase (Figure 3). Segregation of the fluorous phase in the hydrophilic methanol would then result in the stacking of these disks to form fiber-like aggregates.

CONCLUSIONS

We have synthesized a novel amphiphilic semifluorinated calix[4]arene which self-assembles in water and methanol. The results indicate that the water solution consists of mainly spherical particles with uniform diameters, presumably vesicles. The behavior in methanol is drastically different; tubular aggregates are preferred to spherical ones. The dramatic change in self-assembly pattern observed in water and methanol, two hydrogen-bonding solvents, is an example of the variety of structures and possibilities offered by fluorous-phase driven recognition. Further studies on the self-assembly behavior and structure generation of fluorinated calix[4]arenes are currently underway.

EXPERIMENTAL

All procedures were carried out under inert gas in oven-dried glassware, unless otherwise indicated. Proton, carbon and fluorine NMR spectra were obtained on Varian NMR 400 MHz or 500 MHz instruments with TMS as an internal reference



SCHEME 2 Chemical synthesis of 1-(carbobenzyloxy-amino)-11-amino-3,6,9-trioxaundecane (**6**).

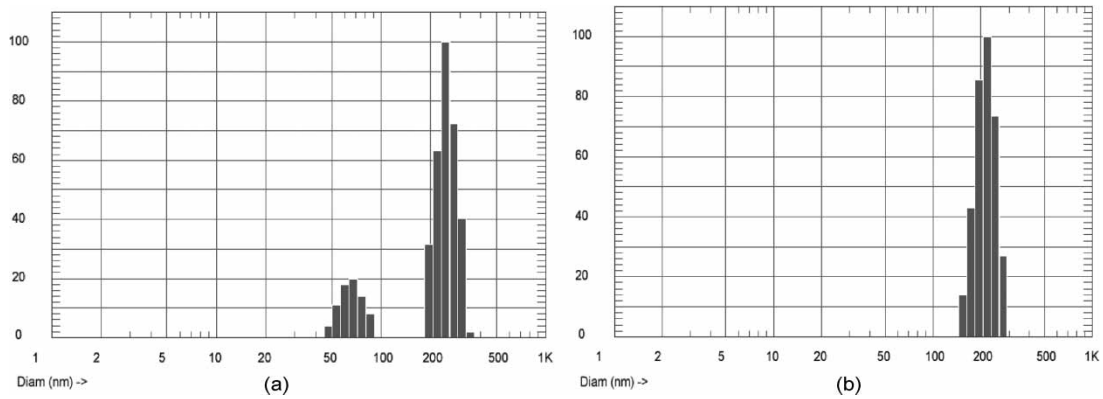


FIGURE 1 Volume-weighted NICOMP distribution analysis for solutions of compound (**8**): (**a**) 100 μM in water and (**b**) 100 μM in methanol.

standard. Mass spectra were measured with MALDI-TOF mass spectrometer (2,5-dihydroxybenzoic acid as the matrix) or ESI mass spectrometer. Analytical thin layer chromatography (TLC) was performed on E. Merck (Darmstadt) glass-backed plates pre-coated with silica gel 60 F_{254} (250 μm layer thickness) and visualized by ultraviolet light, a solution of polyphosphomolybdic acid in ethanol or ninhydrin in ethanol. Preparatory thin layer chromatography (prep-TLC) was performed on Whatman glass-backed plates pre-coated with silica gel 60 (1000 μm layer thickness). Flash column chromatography (CC) was performed on EM Science silica gel 60 (230–400 mesh). Organic solvents were purified and dried through alumina columns.

Dynamic Light Scattering

Measurements were carried out at 20°C using a Zeta Potential/Particle Sizer Nicomp™ 380 ZLS. The samples were prepared in water or methanol by sonication of a thin film, obtained by slow rotary evaporation of a chloroform solution. The final concentrations were 100 μM and all solutions were filtered through a 450 nm microfilter before the measurements.

Transmission Electron Microscopy

Samples were prepared in a similar manner as described above for the DLS study, deposited on pioloform powder grids, negatively stained with methylamine tungstate and analyzed on a Philips CM120 electron microscope operating at 80 kV.

5,11,17,23-tetra-(Heptadecafluoro-10-iodo-undecyl)-calix[4]arene-25,26,27,28-tetrol (2)

To an acetonitrile suspension of 1 g (1.71 mmol) 5,11,17,23-tetra-allyl-calix[4]arene-25,26,27,28-tetrol, 2M NaOH solution was added dropwise until the starting material dissolved. After addition of 20 ml water, the solution was cooled to 0°C, then 4.5 ml (17.1 mmol) perfluorooctyl iodide was added, followed by a mixture of 2.38 g (13.68 mmol) $Na_2S_2O_4$ and 1.8 g (21.88 mmol) $NaHCO_3$. The reaction mixture was stirred at 0°C for 4 hours and then was left to warm to room temperature and stirred for 20 hours. 10% HCl was added to pH 2-3, followed by extraction of the product in diethyl ether. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated down to a yellow solid. Purification by column chromatography (petroleum

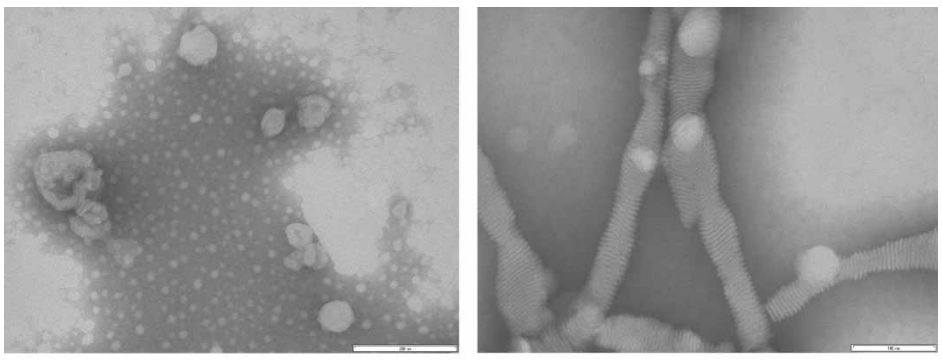


FIGURE 2 Transmission electron micrographs of (**a**) (**8**) in water, (the scale bar represents 200 nm) (**b**) (**8**) in methanol (the scale bar represents 100 nm). Samples were stained with methylamine tungstate. (Small dots in Figure 2a are an artifact of sample preparation.)

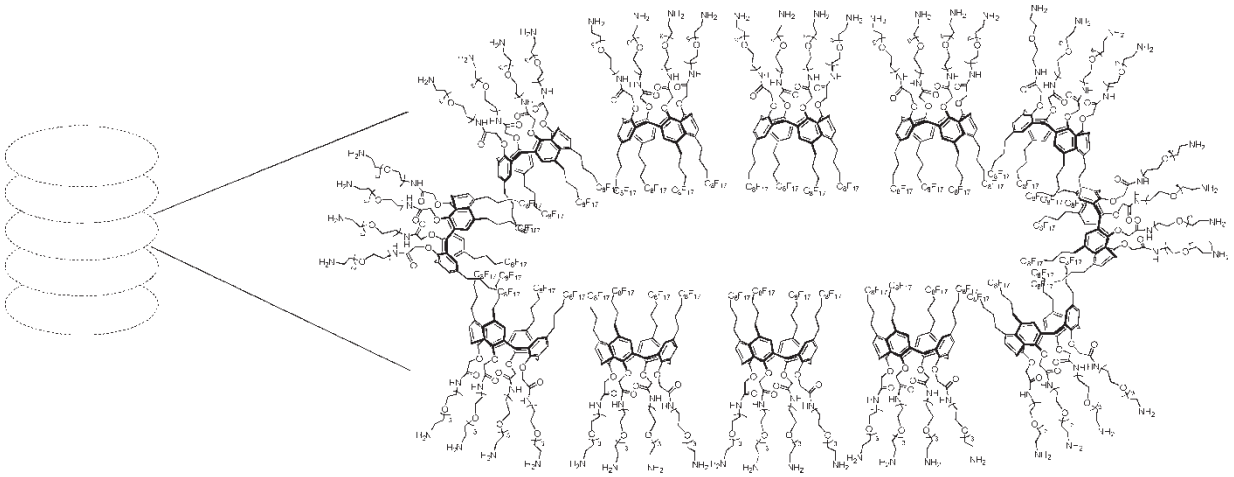


FIGURE 3 A potential disk-shaped structure formed in methanol. Stacking of similar disks would yield the fibers shown in Figure 2b.

ether/dichloromethane 3:1) yielded 3.5 g of product (76%). MALDI-TOF $(MNa)^+ = 2791$. ^{1}H-NMR ($CDCl_3$): δ 2.7–3.1 (m, 16H), 3.4–3.6 (br d, $J =$ 12.4 Hz, 4H), 4.2–4.3 (br d, $J = 12.4$ Hz, 4H), 4.3–4.4 (m, 4H), 6.8 (s, 8H), 10.1 (s, 4H). ^{19}F-NMR ($CDCl_3$): δ −81.25 (t, 12F), −111.73 (m, 2F), −112.44 (m, 2F), −113.94(m, 2F), −114.61(m, 2F), −122.01–122.35 (m, 24F), −123.19 (m, 8F), −123.92(m, 8F), −126.58 (m, 8F).

5,11,17,23-tetra-(Heptadecafluoro-undecyl)-calix[4]arene-25,26,27,28-tetrol (3):

5,11,17,23-tetra-(Heptadecafluoro-10-iodo-undecyl)-calix[4]arene-25,26,27,28-tetrol (50 mg, 0.018 mmol) was dissolved in a mixture of 10 ml anhydrous diethyl ether and 10 ml acetic acid. After addition of Zn dust, the mixture was refluxed for 5 hours. After filtration, the product was extracted in diethyl ether, the organic layer was washed with 10% $NaHCO_3$, water, dried over anhydrous $MgSO_4$, and concentrated down to a yellow oil. Purification by preparative TLC (petroleum ether/dichloromethane 3:1) yielded 19 mg of product (47%). MALDI-TOF $(MNa)^+ = 2287$. ^{1}H-NMR ($CDCl_3$): δ 1.8–1.9 (m, 8H), 1.9–2.1 (m, 8H), 2.4–2.5 (t, $J = 7.6$ Hz, 8H), 3.4–3.6 (br d, $J = 13.6$ Hz, 4H), 4.2–4.3 (br d, $J = 14.2$ Hz, 4H), 6.8 (s, 8H), 10.1 (s, 4H). ^{19}F-NMR ($CDCl_3$): δ −81.29 (t, 12F), −114.57 (m, 8F), −122.25 – −122.47(m, 24F), −123.22 (m, 8F), −123.76(m, 8F) −126.61(m, 8F).

5,11,17,23-tetra-(Heptadecafluoro-undecyl)-25,26,27,28-tetrakis-(ethoxycarbonyl) methoxy-calix[4]arene (4)

5,11,17,23-tetra-(Heptadecafluoro-undecyl)-calix[4]-arene-25,26,27,28-tetrol (0.3 g, 0.132 mmol) was dissolved in 10 ml anhydrous THF under an argon atmosphere. 0.032 g 95% NaH (1.32 mmol) was added, followed by 0.12 ml ethylbromoacetate (1.06 mmol) and the mixture was stirred at 80°C. Several portions of NaH and ethylbromoacetate were added to the reaction mixture over the course of 40 hours, while the mixture was heated at 80°C. After a total of 5 days, when no change was observed in the composition of the reaction mixture followed by TLC analysis, the mixture was cooled to room temperature, 1 ml water was added and the product was extracted in diethyl ether. The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated to a small volume. After purification by flash chromatography using 10% methanol in dichloromethane, 190 mg of product was isolated (55%) MALDI-TOF $(MNa)^+ = 2631.17$. ^{1}H-NMR: ($CDCl_3$) δ 1.54 (t, $J = 7.2$ Hz, 12H), 1.69–1.72 (m, 8H), 1.96–2.07 (m, 8H), 2.31 (m, 8H), 3.15–3.17 (d, $J = 13.5$ Hz, 4H), 4.18–4.23 (q, $J = 7$ Hz, 8H), 4.72 (s, 8H), 4.83–4.86 (d, $J = 13.5$ Hz, 4H), 6.46(s, 8H). ^{19}F-NMR: ($CDCl_3$) δ −81.57 (t, 12F), −114.80 (m, 8F), −122.53 – −122.71(m, 24F), −123.50 (m, 8F), −123.98(m, 8F) −126.93(m, 8F).

5,11,17,23-tetra-(Heptadecafluoro-undecyl)-25,26,27,28-calix[4]arene tetraacetic acid (5)

5,11,17,23-tetra-(heptadecafluoro-undecyl)-25,26,27,28-tetrakis (ethoxycarbonyl) methoxy) calix[4]arene (300 mg, 0.115 mmol) was dissolved in 10 ml THF and 5.7 ml 10% aqueous Me_4NOH was added (6.33 mmol), followed by refluxing for 24 hours. After cooling, 3 ml concentrated HCl were added and stirring was continued at room temperature overnight. After removing the THF, a yellow precipitate was filtered off, washed with water and dried under vacuum. 250 mg of product was obtained (87%). MALDI-TOF $(M + H)^+ = 2497.043$, $(MNa)^+ = 2519.0657$. ^{1}H-NMR: (THF-d_8) δ 2.02–2.15 (m, 8H), 2.35–2.38 (t, $J = 7.6$ Hz, 8H), 2.48 (m, 8H), 3.17–3.21 (d, $J = 13.5$ Hz, 4H), 4.68 (s, 8H), 4.96–4.99 (d, $J = 13.5$ Hz, 4H), 6.64(s, 8H), 10.82 (s, 4H).

^{19}F-NMR: (THF-d_8) δ −82.45(t, 12F), −115.12 (m, 8F), −122.89 – −123.11(m, 24F), −123.94 (m, 8F), −124.33 (m, 8F) −127.46(m, 8F).

1-(Carbobenzyloxy-amino)-11-azido-3,6,9-trioxaundecane (10)

1-Amino-11-azido-3,6,9-trioxaundecane (0.76 g, 2.98 mmol) was dissolved in 50 ml water and 1.58 g (14.9 mol) Na_2CO_3 was added. The solution was cooled to 0°C before adding 1.5 ml (10.43 mmol) benzyl chloroformate. Stirring was continued at 0°C for 45 minutes and was followed by neutralization to pH 6 using 1N HCl. The aqueous suspension was extracted with dichloromethane, the organic solvent was dried over anhydrous $MgSO_4$ and concentrated. After purification by flash chromatography (petroleum ether/ethyl acetate 1:1) 0.9 g of product was isolated as a yellow oil (85%). ^{1}H-NMR: ($CDCl_3$) δ 3.3–3.4 (m, 4H), 3.55–3.7 (m, 12H), 5.1 (s, 2H), 5.4 (br s, 1H), 7.3–7.4 (m, 5H).

1-(Carbobenzyloxy-amino)-11-amino-3,6,9-trioxaundecane (6)

A solution of the above azide (1.1 g, 3.12 mmol) in anhydrous THF was cooled to 0°C, before adding 0.9 g (3.43 mmol) PPh_3. The mixture was then slowly warmed to room temperature and stirring was continued for 2 days. The intermediate phosphorus adduct was hydrolyzed with 0.1 ml H_2O and heating to 40°C for 5 hours, followed by stirring at room temperature for 20 hours. After dilution with water and removal of the THF, the aqueous suspension was extracted with dichloromethane. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. Purification by flash chromatography (dichloromethane followed by 10% methanol in dichloromethane) gave 0.75 g of the monoprotected diamine (81%). ^{1}H-NMR: ($CDCl_3$) δ 1.8 (br s, 2H), 2.9 (br s, 2H), 3.3–3.6 (m, 14H), 5.1 (s, 2H), 5.65 (br s, 1H), 7.3–7.4 (m, 5H). MS (ESI) *m/z* 327.2 (M + 1).

Calix[4]arene (7)

To an anhydrous THF solution of 5,11,17,23-tetra-(heptadecafluoro-undecyl)-25,26,27,28-calix[4]arene tetraacetic acid (180 mg, 0.072, mmol), 82.4 mg (0.43 mmol) 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride (EDCI) and 58.1 mg (0.43 mmol) 1-hydroxybenzotriazole hydrate (HOBt) were added, followed by anhydrous DMF dropwise until all the solids dissolved. After stirring at room temperature for 4 hours, a DMF solution of 1-(carbobenzyloxy-amino)-11-amino-3,6,9-trioxaundecane (140.3 mg, 0.43 mmol) was added and stirring was continued at room temperature for 2 days. After removal of all solvents in vacuo, the residue was taken up in dichloromethane and washed with 10% citric acid, saturated $NaHCO_3$, brine, dried over anhydrous $MgSO_4$ and concentrated down to a yellow solid, which was used without further purification. 216 mg of Z-protected product was obtained (80%). ^{1}H-NMR: ($CDCl_3$) δ 1.69–1.82 (m, 8H), 1.95–2.05 (m, 8H), 2.1–2.25 (m, 8H), 3.15–3.17 (d, $J = 13.5$ Hz, 4H), 3.25–3.65 (m, 56H), 4.45–4.50 (br s, 4H), 4.65–4.70 (d, $J = 13.5$ Hz, 4H), 5.05 (s, 8H), 5.25–5.35 (br s, 8H), 6.25–6.35 (br s, 8H), 7.3–7.4 (m, 5H), 7.9–8.0 (br s, 4H). ^{19}F-NMR: ($CDCl_3$) δ −81.57 (t, 12F), −114.80 (m, 8F), −122.53 – −122.71(m, 24F), −123.50 (m, 8F), −123.98(m, 8F) −126.93(m, 8F). MALDI-TOF $(MH)^+ = 2730.895$, $(M + Na)^+ = 3752.900$.

Calix[4]arene (8)

The Z-protected tetraamine (7) (216 mg) was dissolved in 20 ml 1:1 mixture ethyl acetate/methanol, excess Pd/C was added and a hydrogen balloon was then adapted to the flask. Stirring was continued for 4 days, after which the catalyst was filtered through Celite and the solvents removed to give 89 mg (48%) of the free tetraamine (8) as a yellow solid. ^{1}H-NMR: ($CDCl_3$) δ 1.6–2.1 (m, 24H), 3.15–3.17 (d, 4H), 3.25–3.65 (m, 56H), 4.45–4.60 (br s, 12H), 6.25–6.35 (br s, 8H). ^{19}F-NMR: ($CDCl_3$) δ −81.57 (t, 12F), −114.80 (m, 8F), −122.53 – −122.71(m, 24F), −123.50 (m, 8F), −123.98(m, 8F) −126.93(m, 8F). MALDI-TOF $(M4Na)^+ = 3286.656$.

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