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Supramolecular behavior of fluorous polyglycerol dendrons and polyglycerol dendrimers with perfluorinated shells in water^{†‡}

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In this article, we describe the synthesis of a perfluoro-tagged polyglycerol dendron and its aggregation behavior in the presence of polyglycerol dendrimers with perfluorinated shells in water. The perfluoro-alkyl-perfluoro-alkyl interactions between the perfluorinated shells of the dendrimers and the perfluorinated tags of the dendrons lead to highly stable supramolecular architectures, due to self-assembly of the perfluorinated moieties. Furthermore, we show that the size of the resulting supramolecular complexes can be tuned by simple variation of the dendrimer-dendron ratio. Complexes at various ratios are characterized by optical microscopy, DLS, and TEM. In general, the results presented herein demonstrate that perfluoro-alkyl interactions are applicable for the formation of stable supramolecular structures in water and thus provide a new tool for the design of supramolecular architectures in addition to traditional non-covalent interactions.

Introduction

One of the major challenges in supramolecular chemistry is the prediction and control of molecule aggregation used to develop new molecular architectures and materials. In recent years, fluorous interactions have been investigated as alternatives to traditional noncovalent interactions, such as dipole interactions, hydrogen bonding, metal coordination, and electrostatic interactions. Among noncovalent interactions, fluorous interactions are unique because of the physicochemical properties of fluorocarbons, including weak intermolecular dispersion interactions, high gas solubilities, combined hydro- and lipophobicity, and the large miscibility gaps that occur in solvent systems composed of fluorocarbons and hydrocarbons.¹ As a consequence of the physicochemical properties of fluorocarbons, compounds with heavy perfluoro-tags (ponytails) preferentially partition into the fluorous phase of a biphasic solvent system. In 1994 Horváth and Rabai generalized this partitioning in their "fluorous biphase concept" (FBC).² This partitioning of perfluoro-tagged compounds into a fluorous phase was further exploited in the so-called "light fluorous technology" where fluorous silica gels provide stationary fluorous phases for

solid-phase extraction of light perfluoro-tagged compounds.³ In addition, these methods have been effectively used in the fields of proteomics, microarray analysis, and catalyst immobilization on solid supports.⁴ In a similar manner dendritic macromolecules with perfluorinated shells can serve as fluorous phase and thus have been used as a homogeneous support for perfluoro-tagged catalysts in cross-coupling reactions.⁵ However, although the self-assembly of perfluoro-tagged compounds has been welldescribed, interactions between perfluoro alkyl chains (fluorous interactions) of different compounds have been scarcely used as a tool to design supramolecular architectures.⁶ Recently, we have reported size-tunable supramolecular complexes that consist of polyglycerol (PG) dendrimers with perfluorinated shells and perfluoro-tagged molecules.⁷ These supramolecular complexes are soluble even in polar organic solvents such as DMF or DMSO, although the PG dendrimers with perfluorinated shells are only soluble in fluorinated solvents.⁷

In this article, we present water-soluble supramolecular architectures based on fluorous interactions. For this purpose, we have used an amphiphilic PG dendron that consists of two perfluoro-alkyl chains that are coupled by a bridging unit to the core of a [G3] PG dendron 1 (Fig. 1). The perfluoro-tagged PG dendron has been obtained by synthesis of a precursor and consecutive addition of the perfluorinated chains to its bridging unit. The perfluoro-tagged PG dendron is well soluble in protic solvents such as methanol and water. To investigate formation of supramolecular complexes in water, [G3.5] PG dendrimers with perfluorinated shells 2 are chosen as the fluorous counterpart to the PG dendrons (Fig. 2). These dendrimers are insoluble in water and only soluble in fluorinated solvents, because of the

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 Fig. 1 Perfluoro-tagged [G3] glycerol dendron 1.



Fig. 2 [G3.5] polyglycerol dendrimer with perfluorinated shell 2.

fully functionalized periphery of the PG core.⁷ To obtain structural information of supramolecular complex formation, various ratios between compounds **1** and **2** are studied in water by dynamic light scattering (DLS), optical microscopy, and TEM. We find that supramolecular complexes are formed by these compounds in water; moreover we find that the dendron-dendrimer ratio has a significant influence on the structure of the resulting complexes.

Results and discussion

Design and synthesis of perfluoro-tagged [G3] polyglycerol dendron

We have designed the perfluoro-tagged [G3] PG dendron 1 to form supramolecular complexes with [G3.5] PG dendrimers with perfluorinated shells 2 in water.

The dendrimers have a molecular weight of 15648 g mol^{-1} and are highly hydrophobic due to the 32 perfluoro-hexyl chains that form the shell.⁸ We assume that relatively large



hydrophilic moieties in the amphiphiles are necessary to obtain water soluble dendron-dendrimer complexes even at low ratios. Therefore, we choose a [G3] PG dendron as a hydrophilic moiety. Two perfluoro-octyl chains are selected to enhance the probability of the amphiphiles to form supramolecular complexes with the dendrimers *via* fluorous-fluorous interactions.

To generate the perfluoro-tagged [G3] PG dendron 1, precursor 5 is synthesized by "click" reactions of the diallyl azide compound 3 and the protected propargyl [G3] PG dendron 4 (Scheme 1). Compound 3 forms the bridging unit in the perfluoro-tagged dendron 1. The synthesis of 3 is described in the ESI.[‡] The synthesis of the propargyl [G3] dendron 4 has been previously described.9 For the "click" reaction between the compounds 3 and 4, we use 15 mol% of CuSO₄, 30 mol% of sodium ascorbate, and 15 mol% of N,N-diisopropylethylamine (DIPEA) to generate the desired product in very good yields. These reaction conditions have already been optimized to avoid partial cleavage of the acetal groups.9 Radical addition of 1H,1H,2H,2H-heptadecafluorodecan-1-thiol to the allyl moieties of the precursor 5 and consecutive deprotection by the use of an acidic ion exchange resin afforded the perfluoro-tagged [G3] PG dendron 1 in good yields. The synthesis of [G3.5] dendrimers with perfluorinated shells 2 has been reported previously.8

Formation of supramolecular complexes in water

The [G3] bi-perfluoro-tagged glycerol dendron 1 is highly soluble in protic solvents, such as methanol and water. It has a critical



Fig. 3 Microscope picture of micron sized bubbles formed by self-assembly of perfluoro-tagged [G3] PG dendron 1 and [G3.5] PG dendrimer with perfluorinated shell 2: (left) optical micrograph of a dendron-dendrimer ratio of 2:1 in water; (right) proposed structure of dendrimer stabilized micron-bubbles.

micellar concentration (CMC) of 10⁻⁴ M in water. PG dendrimers with perfluorinated shells 2 that are usually insoluble in polar solvents can be fully dissolved in aqueous solutions of the perfluoro-tagged dendron 1 upon ultrasonication; this is an indication of the formation of supramolecular complexes. Similar to our previous studies of supramolecular structures in organic solvents, the dendron-dendrimer ratios in this study are 1:1, 2:1, and 4:1 based on a dendrimer concentration of 1 mM.⁷ DLS measurements of these solutions indicate the presence of particles larger than 1 µm. Optical microscopy reveals that the supramolecular complexes self-assemble around residual air in water in a similar manner as it was observed in organic solvents (Fig. 3).⁷ We assume that the structure of the observed micron-bubbles corresponds to the structures that have been observed in organic solvents. The dendrimers form a first layer around air. A second layer around the dendrimer layer is formed by the dendrons with the perfluoro alkyl chains of the dendron inserted into the perfluorinated shells of the dendrimers and the PG domain oriented towards the water. There is a clear trend in the average diameters ([M]) of the micron-bubbles assembled in water; they decrease with increasing dendron-dendrimer ratio. At a 1:1 ratio, the average diameter is 4.57 µm (coefficient of variation (CV) = 24.07).¹⁰ The average diameter is decreased about 40% at the ratio of 2:1 ($[M] = 2.80 \ \mu m$, CV = 55.78). In the sample containing the highest dendron-dendrimer ratio (4:1), no micron-bubbles are detected by optical microscopy.

Although micron-bubbles are observed at low dendrondendrimer ratios in water, they cannot be found at increased ratios (>4:1) in water. DLS measurements point to aggregates around 1 µm. The same phenomenon has been found in organic solvents.⁷ These results indicate that other supramolecular structures are favored at increased guest-host ratios. To investigate the supramolecular behavior at increased guest-host ratios, we use the complex system consisting of a 16:1 ratio of [G3] bi-perfluoro-tagged glycerol dendron 1 and [G3.5] dendrimer with perfluorinated shell 2 in water. As a control, an aqueous solution that contained only the dendron 1 is also prepared. It is noteworthy that the dendron concentration $(1.6 \times 10^{-2} \text{ M})$ in both samples is above its CMC of 10⁻⁴ M. Dynamic light scattering (DLS) measurements reveal aggregates of 9.8 nm (CV = 4.08) corresponding to pure surfactant micelles containing only dendron, and aggregates of 11.5 nm (CV = 6.09) corresponding to



Fig. 4 TEM images of the dendron-dendrimer mixture (16:1) (A) and perfluoro-tagged [G3] PG dendron 1 (B) in water upon 50-fold dilution negatively stained with 4.5% aqueous phosphotungstic acid/ 0.1% trehalose.

complexes containing the dendron-dendrimer mixture. TEM measurements confirm this (Fig. 4). The PDI value of the samples is 0.5 because of the presence of few large aggregates. In both samples, the small aggregates are the dominant species and there are only few large spherical aggregates; TEM measurements show sizes for the large aggregates from 50 to 100 nm. Upon 50-fold dilution, these larger aggregates are no longer present in the sample containing a pure amphiphile. However, the number and size of aggregates decrease in the sample containing the dendron-dendrimer mixture. Sizes of residual aggregates range from 20 to 30 nm in diameter. This implies that the formation of large aggregates is concentration dependent, since there are no effects on the sizes of the smaller complexes.

Based on these results, we concluded that increasing guest-host ratios led to smaller aggregates (Scheme 2). This can only be explained by favored fluorous-fluorous interactions between the perfluoro alkyl chains of the guest molecules and the perfluorinated shell of the dendrimers compared to



Scheme 2 Structures of supramolecular aggregates based on fluorous– fluorous interactions between dendrimers with perfluorinated shell and perfluoro-tagged guest molecules in dependence of the guest–host ratio.

Table 1 Effective sizes of supramolecular aggregates in water

System	Ratio	Average diameter of aggregates	Coefficient of variation
Dendron : dendrimer ^{a,b}	1:1 2·1	$4.75 \pm 0.16 \ \mu m$ $2.80 \pm 0.22 \ \mu m$	24.07 55.78
Dendron : dendrimer ^a	4:1	$\sim 1 \ \mu m$	_
Dendron : dendrimer ^{<i>a,c</i>}	16:1	$11.5 \pm 0.10 \text{ nm}$	6.09
Dendron ^d		$9.8\pm0.06~\mathrm{nm}$	4.08

^{*a*} Measured at a constant dendrimer concentration of 1.06×10^{-3} M; size determination by optical microscopy. ^{*b*} Errors represent the standard deviation of the mean. ^{*c*} Measured at a constant dendrimer concentration of 1.06×10^{-3} M; size determination by DLS and TEM. ^{*d*} Measured at a dendron concentration of 1.06×10^{-3} M; size determination by DLS and TEM.

interactions only between dendrons. Since smaller aggregates of the dendrimers offer a larger fluorous surface and thus more binding sites for perfluoro-tagged guest molecules such as amphiphile **1**, this finding is reasonable. These results are summarized in Table 1.

Conclusions

We have shown that supramolecular complexes, which consist of perfluoro-tagged PG dendrons 1 and PG dendrimers with perfluorinated shells 2, can be formed in water. In addition the size of the resulting complex structures can be tuned by variation of the dendron-dendrimer ratio. The size-tunability of the supramolecular particles formed by fluorous-fluorous interactions between dendrimers and dendrons is highly attractive and can be controlled by the dendron-dendrimer ratio. Studies on the use of these systems as pore forming agents for polymeric materials are currently in progress. In general, the results observed also demonstrated that fluorous-fluorous interactions are applicable for the formation of stable supramolecular structures in water. Thus, they provide a new tool for the design of supramolecular architectures in addition to charge neutral non-covalent interactions, such as hydrogen bonding, dipole interactions, and arene-arene interactions. In contrast to other non-covalent interactions, fluorous interactions are highly stable in aqueous environments. Therefore, it is reasonable to assume that greater structural complexity and functionality in supramolecules can be achieved by the hierarchical use of these interactions.

Experimental

Methods

CMC determination. The critical micelle concentration (CMC) of the [G3] bi-perfluoro-tagged glycerol dendron was determined by measuring the surface tension of the amphiphiles in deionized water (Millipore system Milli-Q plus) by the pendant drop method. The contact angle tensiometer OCA20 (DataPhysics Instruments GmbH, Filderstadt, Germany) was used for these measurements and the temperature was set at 25 ± 0.5 °C. Calculation of the surface tension was done by using the Young–Laplace-equation. The accuracy of measurements, checked by one replicate experiment and by control of the surface tension for pure water, was ± 0.4 mN m⁻¹. The behaviour of the

amphiphiles in water was studied over the concentration range of 4×10^{-7} to 1×10^{-3} M. Aqueous solutions were prepared 24 h before measurement. The surface tension was determined twice per minute and the measurement was stopped when the value did not change by more than 0.1 mN m⁻¹ over three minutes. Equilibration time was generally between 50–80 min below the CMC and 25–50 min at higher concentrations.

Optical microscopy. The images of the micron-sized bubbles formed in water were recorded on a Zeiss Axioskop 40 Pol. The images were recorded at rt and were evaluated with AxioVision[®] 3.1. Objectives used were LD EC-Epiplan-NEOFLUAR 20x/0.22DIC and EC-Epiplan-NEOFLUAR 50x/0.55DIC. Samples of the various dendron-dendrimer ratios were prepared by dissolving a certain amount of polyglycerol dendrimer with perfluorinated shell (1.06×10^{-3} M) in a solution of the [G3] bi-perfluoro-tagged glycerol dendron in water. To ensure proper mixing and dissolution of the compounds all solutions were homogenized by ultrasonication for half an hour. As solvents, distilled water was used. 20 µL of the samples were placed on a microscope slide (76 × 26 mm) and covered with an additional thinner slide for visualization.

Dynamic Light Scattering (DLS). Dynamic Light Scattering measurements were conducted in Millipore filtered water using a Zetasizer Nano (Malvern Instruments Ltd.). Aqueous solutions were prepared 24 h before measurement. Samples of dendron–dendrimer ratios were prepared by dissolving a certain amount of polyglycerol dendrimer with perfluorinated shell $(1.06 \times 10^{-3} \text{ M})$ in a solution of the [G3] bi-perfluoro-tagged glycerol dendron in water.

Transmission Electron Microscopy (TEM). Transmission Electron Microscopy samples were prepared on copper grids (400 mesh) coated with 0.1% collodion/C-film. Samples were blotted (drop of 5 μ L) after 60 s and stained with 4.5% aqueous phosphotungstic acid/0.1% trehalose after 30 or 60 s and visualized using a FEI CM12 Electron Microscope at 100 kV high tension.

Syntheses

Diallyl [G3] polyglycerol dendron (5). To a solution of 1.0 equiv. protected propargyl [G3] PG dendron 4 (2.21 g, 1.48 mmol) and compound 3 (0.32 g, 1.63 mmol, 1.1 equiv.) dissolved in THF 15 mol% of DIPEA (diisopropylethyl amine) (36.8 µL, 0.22 mmol) was added. After stirring for 5 min 30 mol% of sodium ascorbate (0.09 g, 0.44 mmol) was added, followed by the addition of 15 mol% CuSO₄·5H₂O (0.056 g, 0.22 mmol). A THF/H₂O mixture has to be in a 1:1 ratio (v/v). The heterogeneous mixture was stirred vigorously up to the point, at which TLC analysis indicated complete consumption of the starting material. The reaction mixture was diluted with water and extracted three times with CH₂Cl₂. The combined organic layers were washed with a small amount of saturated solution of EDTA, dried with Na₂SO₄ and concentrated in vacuo. Purification by column chromatography with 20% isopropanol in *n*-hexane followed by 3% MeOH in CH₂Cl₂ gives the desired product 5 (2.31 g, 92%). (A stock solution of sodium ascorbate and $CuSO_4$ ·5H₂O in water was prepared in a concentration of 100 mg mL⁻¹.)

¹H NMR (500 MHz, CDCl₃, 25 °C): δ = 7.73 (m, 1 H, C*H*-aromatic), 5.86–5.76 (m, 2 H, OCH₂C*H*=CH₂), 5.25–5.14 (m, 4 H, OCH₂CH=CH₂), 4.86 (m, 1 H, N–C*H*-(CH₂O)₂), 4.78 (s, 2 H, O–C*H*₂–Ar), 4.21 (m, 8 H, –C*H*CH₂–O–C(CH₃)₂), 4.05–3.94 (m, 12 H, –CHC*H*₂–O–C(CH₃)₂, OC*H*₂CH=CH₂), 3.84 (m, 4 H, N–CH–(C*H*₂O)₂), 3.75–3.40 (m, 59 H, C*H*₂C*H*O backbone), 1.38 (2 s, 24 H, –C*H*₃), 1.32 (2 s, 24 H, –C*H*₃) ppm; ¹³C NMR (100 MHz, CDCl₃, 25 °C): δ = 144.98, 133.89, 122.81, 117.42, 109.17, 78.49, 78.23, 74.62, 74.48, 72.36, 72.11, 71.81–71.13, 70.50, 69.97, 68.66, 66.64, 63.87, 60.52, 26.68, 25.31 ppm; ESI-TOF MS: calculated for C₈₁H₁₄₁N₃O₃₃ (1683.9447); found 864.9635 [M+Na]²⁺, 1684.9552 [M+H]⁺, 1706.9375 [M+Na]⁺.

Perfluoro-tagged [G3] polyglycerol dendron (2). To compound 5 (1.3 g, 0.77 mmol, 1.0 equiv.) four equiv. of R_{f8}CH₂CH₂SH per allyl group (2.96 g, 6.18 mmol) were added. The solution was stirred under reduced pressure (3 mbar) to remove oxygen from the solution. After heating to 80 °C, a catalytic amount of AIBN was added under an argon atmosphere and the reaction mixture was stirred for 2 h. After further addition of the same amount of AIBN, the mixture was stirred for another 24 h at 80 °C. Evaporation of an excess of R_{f8}CH₂CH₂SH was followed by flash column chromatography (petroleum ether (40-60 °C)/ CH_2Cl_2 (7:1, v/v) and then by AcOEt/*n*-hexane (10:1)). This afforded the desired protected perfluoro-tagged [G3] PG dendron (1.48 g, 73%). The protected perfluoro-tagged [G3] PG dendron was subsequently dissolved in a solvent mixture of MeOH/ CH₂Cl₂ (25 mL g⁻¹). To this solution Dowex-50W resin (2 g g^{-1}) was added after activation. The mixture was stirred and heated at reflux for 18 h. The crude product was filtered, concentrated, and dried under vacuum. The desired product 1 was obtained as a colorless wax (1.12 g, 86%).

¹H NMR (500 MHz, CD₃OD/CDCl₃, 25 °C): δ = 7.67 (s, 1 H, CH-aromatic), 4.72 (p, 1 H, J = 5.8 Hz, N-CH-(CH₂O)₂-), 4.60 (s, 2 H, -OCH₂-Ar), 3.69 (d, 4 H, J = 5.8 Hz, NCHCH₂O), 3.62 (m, 10 H, -CHCH₂-OH, -OCH(OCH₂)₂), 3.50 (m, 17 H, CH₂CHO backbone), 3.46-3.29 (br m, 66 H, CH₂CHO backbone, -OCH₂CH₂CH₂S-), 2.55 (m, 4 H, $-SCH_2CH_2CF_2$), 2.43 (t, 4 H, J = 7.1 Hz, -OCH₂CH₂CH₂S-), 2.20 (m, 4 H, -SCH₂CH₂CF₂-), 1.67 (p, 4 H, J = 6.5 Hz, OCH₂CH₂CH₂S-) ppm; ¹³C NMR (100 MHz, $CD_3OD/CDCl_3$, 2.5 °C): $\delta = 144.66$, 123.25, 122.00–107.00 $(C-R_{f8})$, 78.73, 78.50, 78.37, 78.00, 72.70, 71.78, 71.22, 70.97, 70.86, 70.66, 69.93, 69.60, 69.49, 69.32, 63.34, 60.54, 31.81 $(t, J = 22.4 \text{ Hz}), 28.92, 28.57, 22.41 \text{ ppm}; {}^{19}\text{F} \text{ NMR}$ (470 MHz, CD₃OD/CDCl₃, 25 °C): $\delta = -81.17$ (t, J = 9.8Hz, CF₃CF₂-), -114.59 (CF₃CF₂-), -121.98, -122.14 $(CF_3CF_2-CF_2CF_2CF_2-), -123.03 (-CF_2CF_2CF_2-CH_2), -123.60$ (-CF2CF2-CH2), -126.46 (-CF2CF2-CH2) ppm; ESI MS: calculated for $C_{77}H_{119}F_{34}N_3O_{33}S_2$ (2323.6624); found 1184.8215 $[M+2Na]^{+2}$, 2346.6524 $[M+Na]^{+}$, 2362.6282 $[M+K]^{+}$.

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- 10 Average diameter and coefficient of variation (CV) of all particles were calculated from the microscopy and TEM images by measuring the diameter of over 50 particles randomly selected from each sample. The value of CV is defined by $CV = \sigma/[M] \times 100$, where σ is the standard deviation and [M] is the average diameter.