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Nonpolar Gemini Amphiphiles Self-Assemble into Stacked Layers of Nano-Objects

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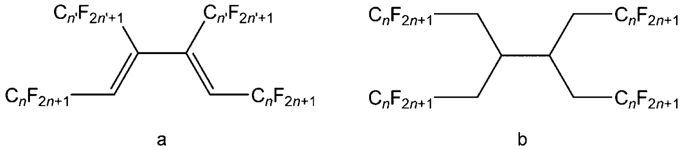
The first "nonpolar" fluorophilic/lipophilic gemini tetrablock amphiphiles $(C_nF_{2n+1}CH_2)(C_{m-2}H_{2m-3})CH{-}CH(C_nF_{2n+1}CH_2)(C_{m-2}H_{2m-3})$ (di(*FnHm*)) are reported, as well as the first example of thin films made of stacked self-assembled surface hemimicelles. Recent work has established that $C_nF_{2n+1}C_mH_{2m+1}$ (*FnHm*) diblocks, when spread on water, self-assemble into monodisperse nano-objects called surface micelles. When compressed, these hemimicelles form highly organized close-packed hexagonal arrays.[1–3] Further compression can induce a transition between a highly organized monolayer of surface micelles and less-organized composite multilayers.[4] Thus, *F*8*H*20 forms an upper bilayer of diblocks in coexistence with a lower carpet of surface micelles. *F*10*H*16 forms crystalline-like inflorescences that also coexist with a carpet of surface micelles. These findings raised the question of whether covalent association of two diblock molecules, thus forming a gemini-type amphiphile,[5,6] in which the number of opposed amphiphilic chains within the same molecule would be doubled, would facilitate film formation, enhance self-assembling capacity, further stabilize or modify the resulting self-assemblies and their stacking behavior, or generate unforeseen different behavior.

n-Perfluoroalkyl chains ($C_nF_{2n+1,}$ *F*-chains) exhibit larger cross sections, higher stiffness, and lower interchain cohesiveness than their *n*-alkyl chain counterparts, resulting in specific behavior.[7,8] Sustained efforts are being devoted to exploring, understanding, and controlling the self-assembling potency of *F*-alkylated compounds, in relation to applications in medicine and materials science.[9,10]

The pronounced lipophobic character of *F*-chains causes semifluorinated alkanes to display amphiphilic behavior, in spite of the absence of a hydrophilic moiety.[7,8] Although these compounds are apolar in the sense that they do not have a hydrophilic polar group and do not dissolve in protic solvents, they have a significant dipole moment due to the strong electron-withdrawing character of the *F*-chains. As noted earlier, *FnHm* diblocks tend to self-assemble into remarkably sturdy surface hemimicelles when spread on water,[3] as well as on solid supports.[1,2,11] Such nanostructures may be useful for surface patterning for biosensor engineering[8] and catalysis.[12] When used in conjunction with phospholipids, *FnHm* diblocks behave as co-surfactants,[13] providing considerable stabilization of fluorocarbon-in-water emulsions.[13,14] Diblock/lipid combinations also allow preparation of compartmented fluorinated bilayers as in fluorinated vesicles and tubules.[15–18]

Gemini[19] and hybrid fluorocarbon/hydrocarbon[20,21] amphiphiles with a polar sulfate or sulfonate head and fitted with an *F*-chain and an alkyl chain or with two *F*-chains have been reported. However, these compounds all comprise a strongly hydrophilic group. Moreover, to the best of our knowledge, no formation of surface micelles has been reported for these amphiphiles, which, therefore, cannot help predict the behavior of the nonpolar tetrablock amphiphiles reported herein. Tetrablocks **a** and **b** (Scheme 1), in which all four chains are perfluorinated, have been reported.[22,23] However, these compounds are not amphiphilic and have no potential for self-assembly.



Scheme 1. Nonamphiphilic tetrablocks in which all four chains are perfluoroalkylated.

Our fluorocarbon/hydrocarbon gemini tetrablocks di(*FnHm*) **1** to **10** (Scheme 2) comprise two lipophobic fluorinated (*Fn*) and two fluorophobic hydrogenated (*Hn*) blocks

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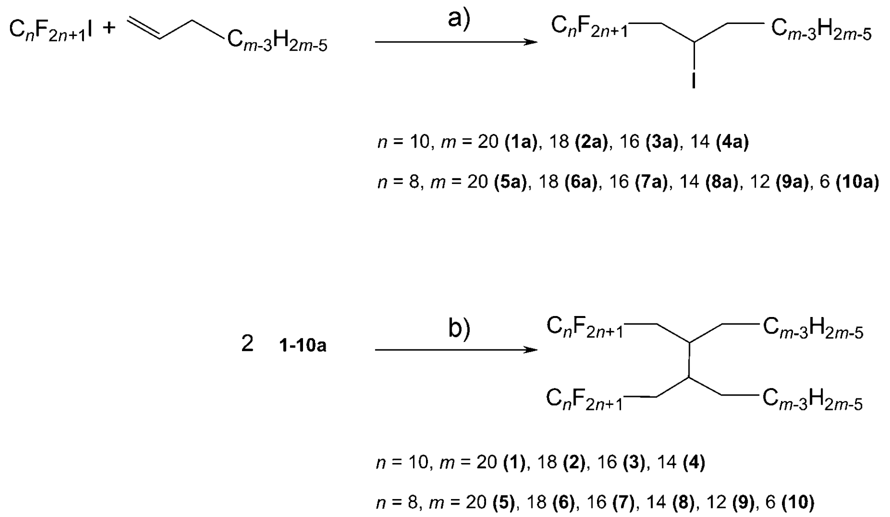

Scheme 2. Synthesis of di(*FnHm*) gemini amphiphiles. a) 2,2′-azobisisobutyronitrile (AIBN), 80 °C, 6 h, 80–97 %; b) Zn nanopowder in Ac_2O, 65 °C, 2 h, 80–98 %.

(and no hydrophilic moiety). By construction, they are amphiphilic (the *Fn* and *Hm* blocks exhibit different affinities), amphisteric (the *Fn* and *Hm* chains have different cross-sections, space requirements, and conformations (helical vs. planar zigzag)), and amphidynamic (one is stiff, rodlike, and prone to crystallization, yet “slippery”, the other more flexible and prone to kinks and defects).[8] The flexibility of the central six-carbon linking unit should also be noted, as it should facilitate conformational adjustments as needed for self-assembly. The modular structure of the new compounds should help control their behavior.

Their two-step synthesis involves the radical addition of an *F*-alkyl iodide, $C_nF_{2n+1}I$, to a linear terminal alkene, followed by the coupling of two molecules of the resulting iodo-adduct by using activated zinc (Scheme 2). The compounds were isolated in 80 to 97 % yield. Experimental details are given in the Supporting Information.

The iodo-adducts **6a**, **8a**, and **10a** have already been prepared,[24] using tetrakis(triphenylphosphine)palladium(0)-catalyzed addition of *F*-alkyl iodides to alkenes.[25] Addition of the *F*-chain on the double bond for **1a** to **10a** was confirmed by ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy. The characteristic resonance of C*H*I is observed at $\delta = 4.34$ ppm in the ^{1}H NMR spectra. The asymmetric carbon was found at $\delta = 41$ ppm in the ^{13}C NMR spectra. A multiplet at $\delta = 2.86$ ppm is characteristic of CH_2–CF_2 in ^{1}H NMR spectra. In ^{13}C NMR spectra, the H_2C in the α position relative to the CF_2 is a triplet at $\delta \approx 42$ ppm with a typical coupling constant, ^2J(C,F), of 21 Hz. The ^{19}F NMR signals of the two fluorines in the α position relative to the CH_2 appear as an AB quartet at approximately $\delta \approx -111$ and -114 ppm (^2J(F,F) ≈ 260 Hz) (see the ^{19}F NMR spectrum in the Supporting Information, p. 14). As a result of the proximity of the asymmetric carbon, these fluorines are diastereotopic and therefore nonequivalent. Consequently, additional splittings due to the couplings between these fluorines and the two diastereotopic protons are seen (^3J(H,F) ≈ 20, ≈ 10 Hz). At ambient temperature, the ^{19}F nuclei of all other CF_2 groups are equivalent, as evidenced by nonambiguous singlets. It is noteworthy that there are only very few examples of AB systems formed by diastereotopic fluorines in a CF_2.[26] The closest example has been reported for 1-*F*-hexyl-1-phenylethanol.[27]

The Wurtz-type coupling reaction used activated zinc nanopowder (< 50 nm)[28] at 65 °C (2 h) and was performed in acetic anhydride. The formation of ZnI_2 as a byproduct in the acidic medium allowed easy separation of the tetrablocks from the aqueous phase by extraction with *F*-*n*-hexane or *n*-heptane. The dimers have been isolated in good to excellent yields (80 to 98 %).

The presence of the two asymmetric linking carbon atoms entails the possible formation of diastereoisomers. Due to the plane of symmetry there are only three stereoisomers, one *meso* (*erythro*) and a pair of enantiomers (*threo*) (see the Supporting Information, p. 17).

The coupling reaction was evidenced in ^{1}H NMR spectroscopy by the disappearance of the multiplet characteristic of the C*H*I signal at $\delta = 4.3$ ppm, and in ^{13}C NMR spectroscopy by the disappearance of the *C*HI triplet at $\delta = 41$ ppm. The *C*H signal in the dimerized compounds is a triplet at $\delta = 29.3$ ppm (^3J(C,F) = 11 Hz). In the ^{1}H NMR spectra, the multiplet seen for the diastereotopic protons results from the coupling to the single proton on the chiral center (^3J(H,H) ≈ 16 Hz) and from the couplings to the two diastereotopic fluorines (^3J(H,F1) ≈ 36 Hz, ^3J(H,F2) ≈ 54 Hz) (see the ^{1}H NMR spectrum in the Supporting Information, p. 15). Although each diastereotopic proton should give a multiplet, the two corresponding chemical shifts were not detectable. In the ^{19}F NMR spectra, the chemical shift difference (Δδ) between the two diastereotopic fluorines of CF_2–CH_2 was reduced to about 1 ppm, versus about 3 ppm in the adducts **1a**–**10a**, thus preventing determination of ^2J(H,F).

Five out of the ten gemini diblocks were obtained in isomerically pure form. TLC monitoring and ^{1}H NMR spectroscopy indicated indeed that, depending on the length of the fluorinated and hydrogenated blocks, one or two diastereoisomers were formed. For di(*F*8*H*20) and for all of the di(*F*10*Hm*) compounds, only one spot was observed on the TLC plates and a single set of signals in the ^{1}H spectra, supporting the formation of only one of the diastereoisomers. For the di(*FnHm*) compounds with $n = 8$, $m = 6$, 12, 14, 16, and 18, a second spot, very close to that of the predominant product, was seen on the TLC plates. The ^{1}H NMR spectra of the corresponding compounds exhibited two close and partially overlapping, but nevertheless distinct broad signals for the two protons in the α position relative to the CF_2, instead of the doublet of triplet observed for di(*F*8*H*20) and for the di(*F*10*Hm*) tetrablocks. All of the signals in the ^{13}C spectra of the isomerically pure diastereoismers were assigned (see the ^{13}C NMR spectra in the Supporting information, p. 16). On the other hand, the nonisomerically pure compounds present two overlapping triplets for the CH_2CF_2 and, in the case of di(*F*8*H*6), most of the signals are split. In the ^{19}F NMR spectra, the single signals seen for all the CF_2 (except CF_2–CH_2) also indicate the purity of the compounds.

Assignment of the NMR signals has been achieved by comparing the minimal energy of the two diastereoisomers, as calculated by using molecular mechanics computations (AMBER potential, HyperChem 8.0, Hypercube, Gainesville, FL, USA). The difference in energy between the *threo* and *erythro* configurations was small ($\approx 0.5\,kcal\,mol^{-1}$) for di(*F*8*H*6), for which CH_2–CF_2 gave two signals in the ^{1}H NMR spectrum. In contrast, the *threo* configuration was clearly favored for the compounds that displayed only one signal. For example, the difference in energy in favor of the *threo* isomer was around $3.5\,kcal\,mol^{-1}$ for di(*F*10*H*20). Consequently, the signal in the ^{1}H NMR spectrum of di(*F*10*H*20) for CH_2–CF_2 at $\delta = 2.06$ ppm was assigned to the *threo* diastereoisomer and the additional ^{1}H NMR signal of di(*F*8*H*6) at $\delta = 1.96$ ppm to the *erythro* diastereoisomer.

The *threo*/*erytho* isomer ratios (see the Supporting Information, p. 17), as quantified from the ^{1}H spectra by measuring the area under the curve, show that the shorter the H-block, the higher the amount of *erythro* isomer. Chemical characterization (^{1}H, ^{19}F, ^{13}C NMR spectroscopy, MALDI-TOF mass spectrometry and elemental analysis) is consistent with the expected structures.

Altogether, the isomeric purity of compounds **1** to **5** was securely established 1) by TLC, which definitely presents two spots when two diastereoisomers are present; 2) by the detailed analysis of ^{1}H, ^{19}F and ^{13}C NMR spectra (provided in the Supporting Information); and 3) by the fact that, when isomers are present and the mixture spread at the air/water interface, they are revealed by a kink in their compression isotherm (see Figure 1 in the Supporting Information); in contrast the monolayer made of isomerically pure compounds presents a monotonous increase of surface pressure upon compression.

Investigation of spin-coated films of di(*F*8*H*20) on mica plates by using AFM shows that the di(*F*8*H*20) tetrablock spontaneously self-assembles into stratified nano-patterned surface films showing two levels of structuration. Figure 1 a clearly shows the presence of a lower carpet of essentially circular, toroidally shaped surface hemimicelles about 40 nm in diameter (see a magnification in Figure 1 d). The phase mode image (Figure 1 b) provides evidence that the upper level of surface micelles has surface-adhesion properties, or hardness, different from those of the lower carpet. This lower carpet is in contact with the mica surface and is surmounted by a second layer of micron-size domains (Figure 1 a). The height of these upper domains ((4.0 ± 0.5) nm, see AFM height profile in Figure 1 c) is close to that reported for a film of surface micelles of diblock *F*8*H*20.[4] The upper domains comprise both circular micelles, about 40 nm in diameter, and wormlike aggregates, half as large in cross-section (≈20 nm), comparable to those reported for monolayers of *FnHm* diblocks *F*8*H*20 and *F*8*H*18.[11] A magnification of the surface micelles of the upper level is seen in Figure 1 e.

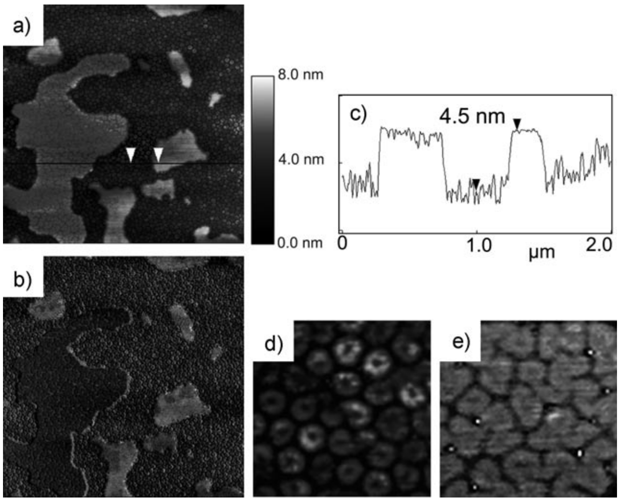

Figure 1. a) Height and b) phase AFM images (2×2 μm) of a film of di(*F*8*H*20) cast by spin-coating onto a mica substrate. c) AFM height profile taken between the two white arrows. Larger scale images (250×250 nm) d) of the lower carpet of surface micelles in contact with mica and e) of the upper layer of surface micelles are also shown.

It should be noted that when mixtures of isomers are present (i.e., for the shorter compounds), no stable films could be spin-coated.

The self-assembly behavior of the tetrablock is unique. It forms a first layer consisting of a continuous array of densely packed circular surface micelles (Figure 1 a and d) that are very similar to those reported for diblocks.[1] However, the tetrablock uniquely forms a second layer of discrete surface micelles on top of the layer that is in contact with the support (Figure 1 a and e). The two-level, self-organized arrangement of stacked micelles observed with the tetrablock is different from that of *FnHm* diblocks, which were recently reported to form a continuous upper bilayer or crystalline dendrites, depending on molecular structure.[4] Such a stacked arrangement of self-assembled discrete nano-objects has, to the best of our knowledge, never been reported. Figure 2 shows a representation of the two-storey films of di(*F*8*H*20) tetrablocks. Driving forces for self-assembly are likely to include hydrophobic segregation of *Fn* chains and dipole moment, as demonstrated with diblocks.[29]

Surfaces that present organization at several different spatial scales (molecules, micelles, arrays, and now vertical stacking), yet involving the same components and surface chemistry, may help understand the influence of surface

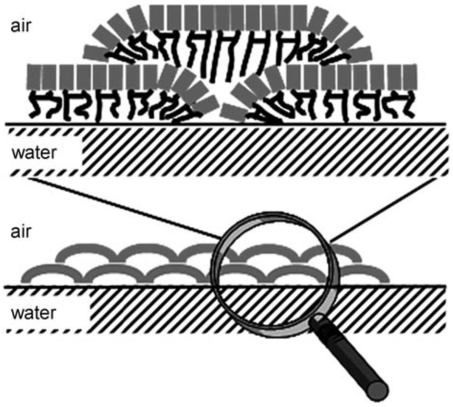

Figure 2. Schematic representation of the two-storey film of surface micelles obtained by spin-coating on mica of di(*F*8*H*20) gemini tetrablock.

nanopatterning on cells or bacteria,[30] and may play a role in material science and catalysis.

In summary, we report the synthesis of a series of the first apolar gemini fluorophilic/lipophilic amphiphiles. The self-assembly behavior of the di(*F*8*H*20) tetrablock differs substantially from that of the related diblock and appears to provide the first example of stacked, self-assembled, discrete nano-objects.

Experimental Section

All of the experimental details can be found in the Supporting Information, along with typical ^{1}H, ^{13}C, and ^{19}F NMR spectra and typical Langmuir film compression isotherms.

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Keywords: amphiphiles • fluorine • hemimicelles • nanostructures • self-assembly

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