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Propyl-Ended Hemifluorinated Surfactants: Synthesis and Self-Assembling Properties

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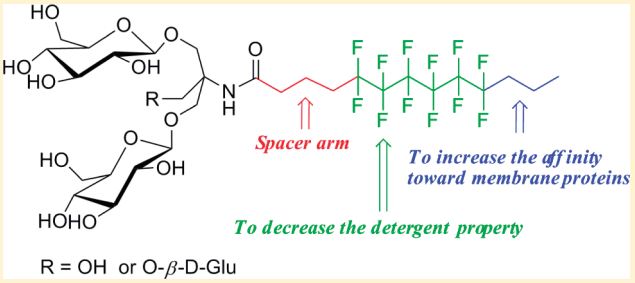
Supporting Information

ABSTRACT: The advantages of using hemifluorinated surfactants as an efficient alternative to detergents for manipulating membrane proteins in aqueous solution have been demonstrated in recent reports. However, the large-scale synthesis of these surfactants is still considered as a major matter and has limited their use for biochemical purposes. We report herein the synthesis of a novel series of perfluorohexane-based surfactants endowed with a short propyl hydrocarbon tip and whose polar head size is modulated by the presence of two or three glucose moieties. The synthetic route is based on the radical addition of two alkenes onto the 1,6-diiodoperfluorohexane using AIBN as a radical initiator, affording the surfactants in satisfactory overall yields. The self-assembling properties of these hemifluorinated surfactants were studied by surface tension measurements, dynamic light scattering, as well as their behavior upon reversed-phase chromatography and were compared with those of their perfluorinated analogues. Our findings strongly suggest the predominant influence of the propyl tip on both adsorption and micellization phenomena as well as on the hydrophobic character of the surfactants, whereas as previously observed, the shorter ethyl tip does not greatly affect these properties when compared to the perfluorinated analogues. Moreover, all the surfactants reported here self-assemble into small and monodisperse aggregates, a feature of crucial importance for biochemistry applications.



INTRODUCTION

Membrane proteins (MPs), which correspond to about 30% of the proteome, perform a wide range of essential cellular functions and therefore have a considerable therapeutic importance. The extraction and isolation of MPs from their biological environment is a primordial step for the determination of their structures as well as a requirement for the understanding of their role and function. The recent findings have resulted from efforts undertaken in obtaining pure homogeneous membrane proteins and understanding protein−lipid and protein−detergent interactions for proper stabilization of the active form. Indeed, detergents, which are commonly used for MP extraction, can often lead to the destabilization and irreversible inactivation of MPs because of their dissociating effect.[1] To circumvent these problems, current research focuses on the development of alternative approaches to classical detergents.[2] Among these novel approaches, one can cite amphipathic peptides,[3] tripod amphiphiles,[4] tandem facial amphiphiles,[5] amphipathic polymers,[6−8] and fluorinated surfactants (FS).[9]

FSs have the same general structure as classical detergents, i.e., a hydrophilic headgroup and a hydrophobic tail, but the latter is fluorinated. Since hydro- and fluoroalkanes are poorly miscible,[10−12] FSs are expected to be less aggressive toward membrane proteins than detergents as their micelles are poor solvents for lipids and other stabilizing hydrophobic cofactors, and therefore, they would not induce their destabilization even at high concentration. Moreover, the bulky and rigid fluorinated tail would intrude less easily into the protein structure itself.[13] Since it was demonstrated that the extremity of the hydrophobic chain of the surfactant interacts with the hydrophobic part of MPs through multiple close contacts,[14] the affinity of fluorinated surfactants toward MPs has been improved by the addition of an ethyl tip to the fluorinated chain. This has led to a new class of surfactants, the so-called hemifluorinated surfactants (HFSs).[15,16]

Recently, we reported the synthesis of the first series of (hemi)fluorinated surfactants derived from glucosylated tris(hydroxymethyl)aminomethane (TRIS).[17] The design of this series was based on Israelachvili's concept,[18] and we showed that by varying the size of the headgroup, the type of aggregates formed by these amphiphiles could be modulated. While surfactants bearing two or three glucose moieties led to the formation of small and well-defined spherical micelles, large cylindrical ones were obtained with monoglucosylated derivatives.[17,19] We proved

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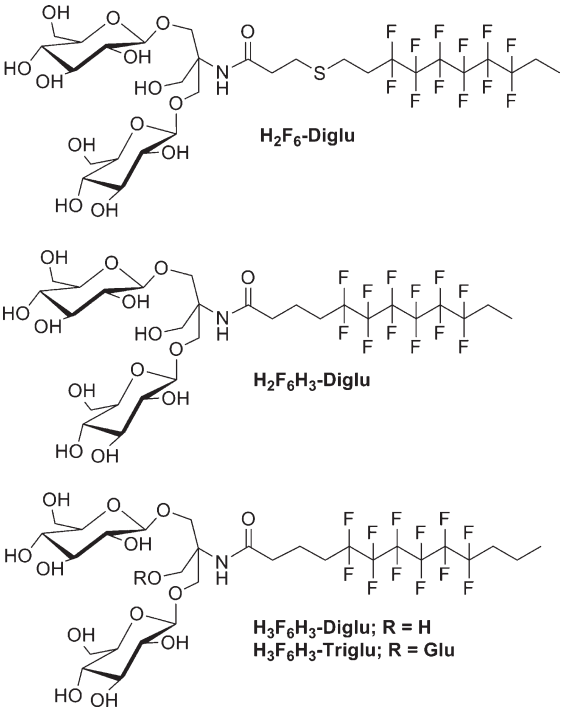
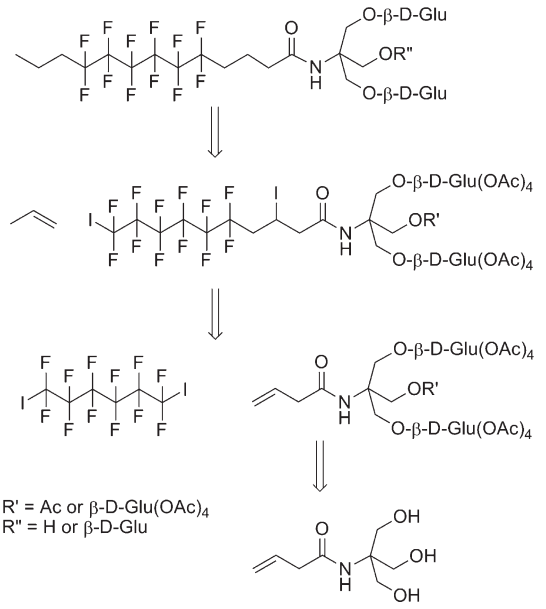


Figure 1. Chemical structures of the previously developed H_2F_6-Diglu and the new ethyl- and propyl-ended surfactants $H_2F_6H_3$-Diglu, $H_3F_6H_3$-Diglu, and $H_3F_6H_3$-Triglu.

that homogeneous complexes of two membrane proteins (bacteriorodopsine and cytochrome b_6f) and this series of glucose-based surfactants were obtained only with surfactants forming homogeneous micelles. Moreover, surfactants bearing one or two glucose moieties were found stabilizing, whereas those with three moieties were destabilizing.[19] The conclusion was that the diglucosylated hemifluorinated surfactant (H_2F_6-Diglu) and to a lesser extent its fluorinated analogue (F_6-Diglu)—both having an intermediate polar head size—are the best candidates for biochemistry and structural studies. In addition, first tests showed that bacteriorhodopsin could be successfully refolded in these compounds (unpublished data). However, although the synthesis of F_6-Diglu can be achieved in a satisfactory overall yield, the preparation of its hemifluorinated analogue H_2F_6-Diglu causes limitations for gram-scale synthesis, a requirement for biochemistry purposes. Moreover, since hemifluorinated surfactants are nowadays considered as a very promising alternative to classical detergents for handling MPs in aqueous solution, it is of importance to conceive synthetic routes that would allow both gram-scale synthesis and an easily tuning of the fluorine/hydrogen atoms distribution within the hydrophobic tail making possible the study of the physical−chemical and biochemical properties.

Therefore, we report herein the synthesis of a new series of glucose-based hemifluorinated surfactants bearing a hydrocarbon propyl tip using radical addition of two alkenes onto the commercially available 1,6 diiodoperfluorohexane. To the best of our knowledge, this is the first time that propyl-ended hemifluorinated surfactants have been reported. In order to confirm our previous findings on the effect of the size of the polar head on the physical-chemical and biochemical properties, di- and triglucosylated derivatives respectively labeled $H_3F_6H_3$-Diglu and $H_3F_6H_3$-Triglu were synthesized (Figure 1). For the sake of comparison perfluorinated analogues as well as an ethyl-ended

Scheme 1. Retrosynthetic Route for the Synthesis of the Propyl-Ended Surfactants



hemifluorinated surfactant $H_2F_6H_3$-Diglu were also synthesized. The comparative physical−chemical properties in aqueous solution were studied by surface tension measurement and dynamic light scattering (DLS) as well as their behavior upon reversed-phase chromatography.

RESULTS AND DISCUSSION

Synthetic Strategy. The convergent synthetic route for the synthesis of the propyl-ended surfactants is based on three key steps (Scheme 1): (i) synthesis of the polar head precursors by condensation of the commercially available butenoic acid and trishydroxymethyl aminomethane (TRIS), followed by selective *O*-glucosylation of the TRIS moiety; (ii) radical addition of the polar head precursors onto 1,6-diiodoperfluorohexane; (iii) second radical addition of the propylene which will constitute the hydrocarbon propyl tip. Since butenoic acid was used as a connector, a spacer arm comprising three methylene groups is inserted between the polar head and the alkyl chain of the surfactant.

(a) Synthesis of the Glucosylated Olefins. A connected synthetic pathway as that previously reported for trishydroxymethyl acrylamidomethane (THAM) derivatives was used for the preparation of the polar head precursors (Scheme 2).[17] Condensation of the commercially available butenoic acid onto TRIS was achieved using EEDQ in refluxing ethanol to afford **1** in good yield (82%). Compound **1** was further used as basic structure for the synthesis of the polar heads. The triglucosylated TRIS-based polar head **2** was obtained in 59% yield by direct glucosylation of compound **1** using the Helferich method in the presence of mercury cyanide and an excess of tetra-*O*-acetyl-β-D-glucopyranosyl bromide under ultrasonic activation. Compound **2** was thus prepared in 46% overall yield in two steps from butenoic acid. The diglucosylated TRIS-based polar head **5** was prepared as shown in Scheme 2. First, two hydroxyl groups of compound **1** were protected by reaction with 2,2-dimethoxypropane to lead to compound **3**. The remaining free hydroxyl group

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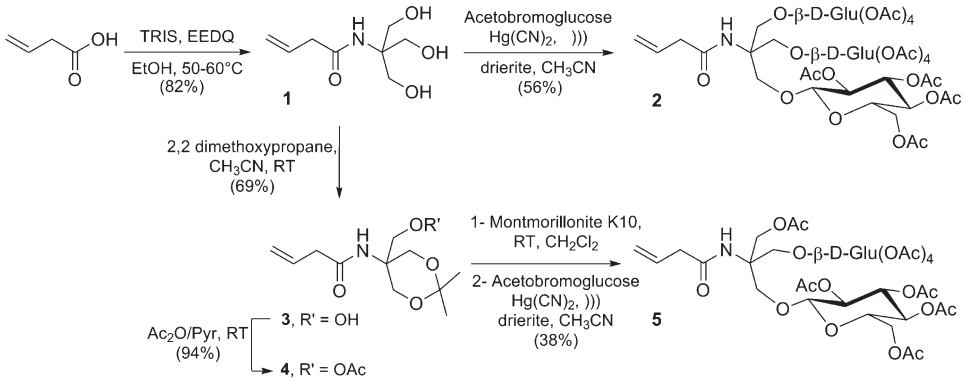
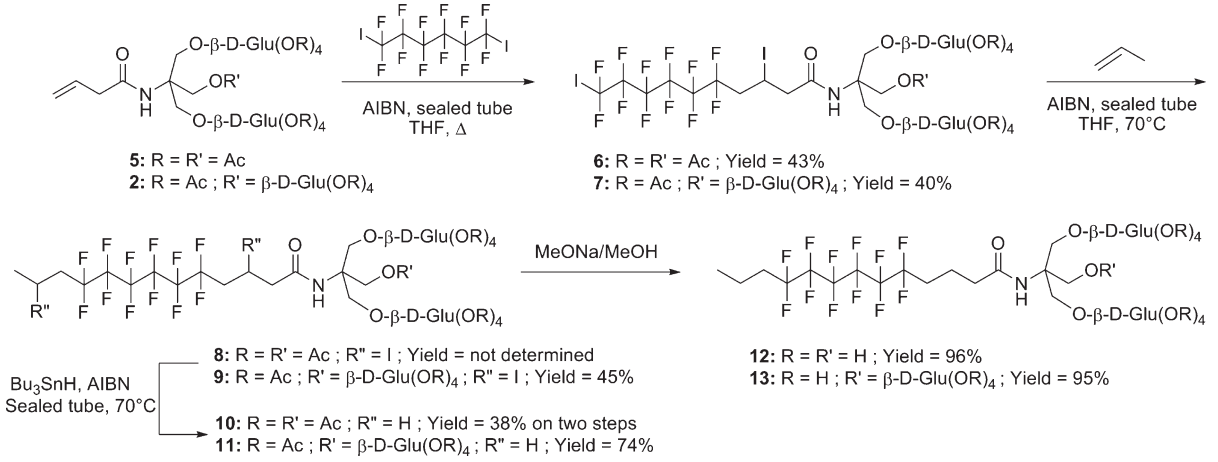
Scheme 2. Synthesis of Polar Heads



Scheme 3. Synthesis of Propyl-Ended Hemifluorinated Surfactants



was further protected by reaction with a 1:1 v/v mixture of Ac_2O/pyridine to yield compound **4**. Finally, hydrolysis of the 1,3 acetonide under mild acidic conditions yielded the monoacetylated derivative which was next diglucosylated using the Helferich method under ultrasonic activation. Compound **5** was thus prepared in 21% overall yield in five steps from butenoic acid.

(b) Radical Addition of Perfluoroakyl Iodide onto Alkenes. The second key step in the synthesis of this novel series of hemifluorinated surfactants relied on the connection of the fluorinated core onto glucosylated olefins. This was achieved by radical addition of 1,6-diiodoperfluorohexane onto compounds **2** and **5** in the presence of AIBN as radical initiator (Scheme 3). Free-radical addition of perfluoroalkyl iodide (R_fI) on unsaturated compounds such as olefins using a radical initiator[20] is a very convenient method for the introduction of fluorinated segments. Radical reactions using AIBN as initiator generally proceed in high yields, and the purification of the crude product is usually easy. The choice of the solvent is also critical to mediate iodofluoroalkylation in good yield.[21] Whereas some authors proscribe the use of solvents in such reactions, in our case, due to the solid state of the glucosylated olefins and their possible degradation at high temperatures, we used THF as reaction solvent. THF has the advantage of a low boiling point (66 °C) allowing a relatively slow decomposition of AIBN and at the same time a limited degradation of the glucose moieties.

However, an important point consists in the presence of two terminal CF_2I of the 1,6-diiodoperfluorohexane, which could lead to bis-addition instead of simple monoaddition. In order to circumvent this problem, the radical addition onto glucosylated olefins was performed with a 2−2.5-fold excess of 1,6-diiodoperfluorohexane $IC_6F_{12}I$. Following these conditions, the yields of addition were ranging between 40 and 43%. The remaining excess of fluorinated compound was recovered after purification and was reused. It should be noted that the yields were not significantly improved when larger excess of $IC_6F_{12}I$ (3-fold excess) were used. Nevertheless, we found that higher yields and faster reactions were obtained when AIBN was added in small fractions to the milieu (0.5 equiv every 2 h); this observation is in agreement with the work by Lahiouhel et al.[22]

The reaction was monitored by NMR, and after 24 h, the ^1H NMR spectrum showed the presence of a multiplet at 4.53−4.63 ppm assigned to CHI and the absence of vinylic protons at 5.83−5.94 ppm, demonstrating the formation of the C−C bond between the polar head and the fluorinated core and the complete consumption of the olefinic compound. This was also confirmed by ^{19}F NMR, with a high-field shift from −58.82 ppm to −113.24 ppm, as well as by ^{13}C NMR, which allowed the observation of the characteristic triplet of the methylene adjacent to the fluorinated core. However, in all our experiments, the NMR spectra showed that the monoaddition was produced

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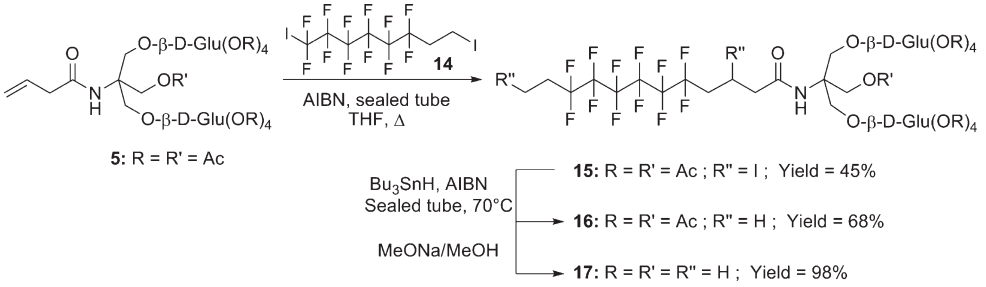
Scheme 4. Synthesis of Ethyl-Ended Hemifluorinated Surfactants



selectively and only traces of bis-addition compounds were detected. During the course of our work, we also noticed that the radical reaction was limited by the steric hindrance of the alkene. Indeed, while with the diglucosylated and triglucosylated compounds **6** and **7** the yields of addition reached 43 and 40%, respectively, those obtained with the commercially butenoic acid or the nonglucosylated TRIS-based compound **1** reached 75−80% (data not shown).

(c) Radical Addition of Propylene. The third important task in the synthesis of this novel series of hemifluorinated surfactants consisted of the insertion of the propyl tip at the end of the hydrophobic tail. This was achieved following a radical addition of propylene onto the free CF_2I group of compounds **6** and **7** using AIBN as radical initiator in THF as described earlier. The introduction of the olefin was carried out at −80 °C, and the reaction mixture was then heated progressively up to 66 °C to afford after 24 h compounds **8** and **9** (Scheme 3). Because of the difficulties encountered during the purification procedures compound **8** was not isolated and was used directly in the next step, while pure compound **9** was isolated in 45% yield. Once again, the reaction was monitored by ^{19}F NMR until the complete disappearance of CF_2I signal at (−60 ppm) as it was described earlier. Furthermore, it was noted that despite the presence of a larger excess of propylene, polyadducts were not produced.

The reduction of the C−I bonds formed during the double-radical addition was next carried out using tributyltin hydride in the presence of a catalytic amount of AIBN as radical initiator. Despite its toxicity and the difficulties encountered for the removal of its derivatives,[23] tributyltin hydride (Bu_3SnH) is considered as one of the most useful radical reducing agent for alkyl halides because of the low dissociation energy[24,25] of the Sn−H bond which facilitates the formation of triorganotin radicals. Another advantage of using Bu_3SnH is the high kinetic[24] balance of the steps of dehalogenation by tributyltin radical and hydrogen donation of tributyltin hydride[26,27] at high concentration, which favors the termination step on the propagation step. After purification, compounds **10** and **11** were obtained in 38% and 34% yields from compounds **6** and **7**, respectively. Finally, removal of the acetyl protective groups of the hydroxyls was performed under Zemplén conditions and afforded the final surfactants **12** and **13** in very high yields (Scheme 3).

(d) Synthesis of Ethyl-Ended Hemifluorinated and Perfluorinated Analogues. To extend the physical−chemical investigation of these surfactants, the hemifluorinated analogue $H_2F_6H_3$-Diglu bearing an ethyl tip and the perfluorinated analogues of Di- and Triglu compounds were synthesized following connected synthetic routes. The ethyl-ended hemifluorinated Diglu compound was synthesized in three steps as shown in Scheme 4. As previously described,[15] the monoethylenation of diiodoperfluorohexane led to 1,1,2,2,3,3,4,4,5,5,6,6-dodecafluoro-1,8-diiodooctane **14**, which was chosen as starting material. The first step involves a radical addition of compound **14** onto the olefin **5** using AIBN as it was described in a previous section to afford compound **15** in satisfactory yield (45%). Reduction of iodine atoms using tributyltin hydride, followed by deprotection of the hydroxyl groups, led to the desired compound **17** in 30% overall yield in three steps. On the other hand, the synthesis of perfluorinated compounds was carried out using the commercially available 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-1-iodohexane as starting material (Scheme 5). Once again, the radical addition was achieved using AIBN and was followed by iodide reduction and hydroxyl groups deprotection. Compounds **22** and **23** were obtained in satisfactory overall yields (31 and 26% for Diglu and Triglu compounds, respectively).

O-Acetylated surfactants were all purified by flash chromatography on silica gel and Sephadex LH-20 size-exclusion chromatography, while de-*O*-acetylated compounds were only purified by size-exclusion chromatography and then lyophilized to give pure surfactants. They were fully characterized by ^1H, ^{13}C, ^{19}F DEPT, COSY, and HMQC NMR experiments as well as mass spectrometry (see the Supporting Information). Their purity was checked by C18-reversed-phase HPLC and was higher than 98%. All perfluorinated surfactants were labeled by F_6H_3 according to the number and the distribution of fluorinated and hydrogenated carbons of the hydrophobic chain, followed by Di- or Triglu according to the number of glucose moieties grafted onto the polar head. In order to distinguish hemifluorinated surfactants from their perfluorinated analogues, H_n was added to the given name of these latter surfactants, indicating the presence of a hydrocarbon tip; where "*n*" indicates the number of carbons of the hydrocarbon tip.

Physical−Chemical Characterization. With the aim to study the physical−chemical properties of these surfactants, three different parameters were considered: (a) log k'_W determination, which is correlated to the hydrophobic character of the surfactant; this parameter was measured by RP-HPLC; (b) surface tension activity, which was determined by the Wilhelmy plate technique; (c) size of the supramolecular assemblies formed by the surfactants in aqueous media measured by dynamic light scattering.

(a) log k'_W Determination. log k'_W values are reported in Table 1. This parameter, which is closely related to the molecule water/octanol partition coefficient, is used to reflect the hydrophobic character of the surfactant and was obtained from reversed-phase HPLC.[28] As expected, for a surfactant the value of this parameter increases with increasing the number of carbons within the hydrophobic tail. However, we previously found that in the case of ethyl-ended hemifluorinated surfactants the addition of the ethyl tip did not significantly affect the value of log k'_W,

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Scheme 5. Synthesis of Perfluorinated Surfactants

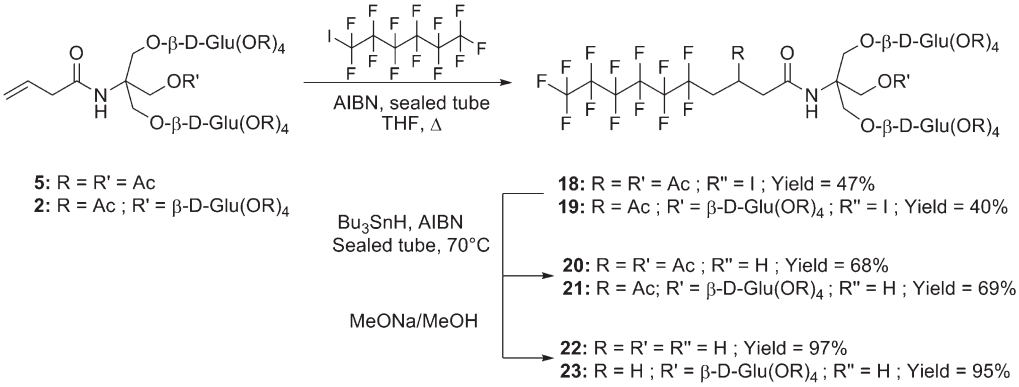

Table 1. Physical-Chemical Data[a]

surfactant	log k'_W	CMC (mM)	γ_{CMC}(mN/m)	D_H[b] (nm)	HHW[c] (nm)	conc[d] (mM)
$H_3F_6H_3$-Diglu (**12**)	5.2	0.08	32.9	6.0	1.6	5.4
$H_3F_6H_3$-Triglu (**13**)	5.0	0.07	33.4	5.5	1.4	4.6
F_6H_3Diglu (**22**)	4.5	1.10	24.7	6.6	1.6	1.2
F_6H_3-Triglu (**23**)	4.4	2.78	32.5	5.7	3.4	13.8
$H_2F_6H_3$-Diglu (**17**)	4.7	0.37	31.3	5.8	1.3	1.8
H_2F_6Diglu [e]	4.9[e]	0.35[e]	36.0[e]	6.5[e]	1.6[e]	5[e]
F_6Diglu [e]	4.8[e]	0.23[e]	28.3[e]	5.8[e]	1.3[e]	4[e]
F_6Triglu [e]	4.7[e]	0.95[e]	32.3[e]	5.1[e]	1.2[e]	4[e]

[a] Data presented are the average of two or three experiments. [b] D_H: hydrodynamic diameter of particles of the main peak. The values reported are the average of 10 runs. [c] HHW, the width of the peak at half-height, an indication of the degree of polydispersity of the aggregates. [d] Concentration used for DLS measurements. [e] Data from ref 17.

with for instance H_2F_6-Triglu having the same value as F_6-Triglu. On the contrary, as we can observe with $H_3F_6H_3$-Diglu and F_6H_3-Diglu, exhibiting log k'_W of 5.2 and 4.5, respectively, the addition of a propyl-end group results in a greater hydrophobicity of the surfactant. A similar trend was observed with the Triglu series. As suggested in previous reports on hemifluorinated surfactants, the hydrophobicity of the additional ethyl group may be compensated by the pseudoacidity of the methylene adjacent to the fluorocarbon, a direct consequence of the electron-withdrawing effect of the fluorine atoms.[17,29,30] Such an effect could favor hydrogen bonding with the aqueous phase and shift the partition coefficient of the surfactant toward water. Moreover, the unfavorable interactions between hydrocarbon and fluorocarbon segments belonging to the same or to different chains may also play a role. An opposite behavior was observed in this work with the addition of a propyl tip to the fluorocarbon chain, where in this case, the hydrophobicity brought by the propyl as demonstrated by a higher log k'_W value seems to be predominant.

(b) Surface Tension Measurements. The surface activity data are summarized in Table 1, and the curves of diglucosylated surfactants are represented in Figure 2. The most important parameters this technique can provide are the critical micellar concentration (CMC) and the limit surface tension attained at the CMC (γ_{CMC}). The CMC is obtained from the intersection of the two straight lines for the linear concentration-dependent section and for the baseline of the limit surface tension (γ_{CMC}).

Contribution of the Polar Head. As frequently reported,[31] for a given hydrophobic tail, the CMC of a surfactant increases while increasing the number of sugar moieties of its polar head. This was actually observed for the perfluorinated F_6H_3-Diglu and F_6H_3-Triglu compounds, with CMC values of 1.10 and 2.78 mM, respectively, and confirmed our previous observations on the first series of glucose-based surfactants, with F_6-Diglu and F_6-Triglu compounds having CMC values of 0.23 and 0.95 mM, respectively.[17] On the contrary, propyl-ended hemifluorinated $H_3F_6H_3$ surfactants did not follow the same rule. Indeed, $H_3F_6H_3$-Diglu and $H_3F_6H_3$-Triglu compounds, despite the presence of an additional glucose moiety in the latter surfactant, exhibited similar CMC values (0.08 and 0.07 mM, respectively). It has to be underlined that, our previous findings on ethyl-ended hemifluorinated surfactants demonstrated that the influence of the number of glucose moieties on the value of the CMC was not striking. For instance, while the H_2F_6-Diglu exhibited a CMC value of 0.35 mM, that of its analogue bearing an additional glucose group only reached 0.75 mM. This shows that as the chain of the surfactant becomes longer, the effect of an additional sugar on the polar head does not affect much the CMC. A similar observation was made on a series of galactosylated surfactants having a long perfluorinated tail (C_8F_{17}). For instance, the CMC value of the digalactosylated derivative (0.04 mM) was found in the same range to that of the trigalactosylated derivative (0.037 mM).[32] This was further confirmed with a series of galactosylated ethyl-ended hemifluorinated surfactants.[15]

The limit surface tension of a surfactant is essentially related to lateral interactions between the hydrophobic chains of the surfactant,[33] the greater the packing of surfactants at the

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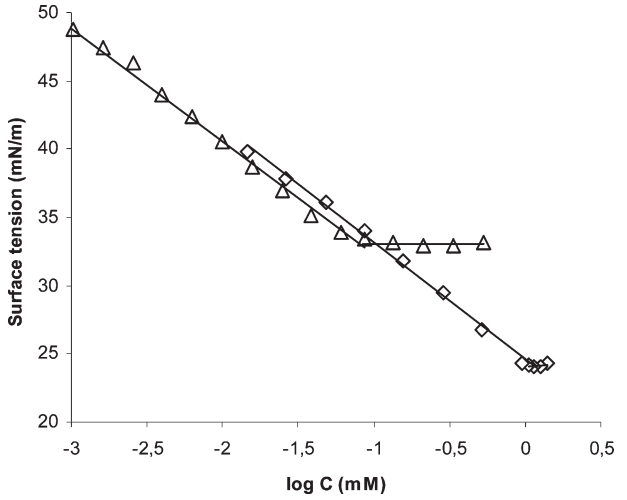

Figure 2. Surface tensions versus log *C* plot for (Δ) $H_3F_6H_3$-Diglu and (◊) F_6H_3-Diglu.

air/water interface, the lower the limit surface tension. For a given perfluorinated hydrophobic chain, γ_{CMC} rises while increasing the polar head size as a result of weaker packing at the surface caused by an increase of the gap between the fluorinated chains at the air/water interface. This was observed with F_6H_3-Diglu and F_6H_3-Triglu with respective values of 24.7 and 32.5 $mN \cdot m^{-1}$; however, no significant variation was observed in the limit surface tension of the propyl-ended $H_3F_6H_3$-Diglu and $H_3F_6H_3$-Triglu surfactants. The absence of correlation between the size of the polar head and the limit surface tension of hemifluorinated surfactants was previously observed with the ethyl-ended series in agreement with this latter observation.

Contribution of the Alkyl Tip. Whereas, as a rule of thumb, the addition of an ethyl group to a classical surfactant leads to a dramatic drop of the CMC,[34] we have previously demonstrated that the addition of a terminal ethyl group to a hydrophobic fluorinated chain does not greatly affect the CMC value of the corresponding surfactant. On the contrary, we found that the addition of a propyl end group to the fluorinated chain of a surfactant drastically reduces the CMC as we can observe for F_6H_3 and $H_3F_6H_3$-Diglu (1.10. and 0.08 mM, respectively) and F_6H_3 and $H_3F_6H_3$-Triglu (2.78 and 0.07 mM, respectively). This demonstrates for the first time that the number of carbons within the terminal tip of hemifluorinated surfactants can dramatically affect the value of the CMC. This is in full agreement with the values of log k'_W reported previously, thereby confirming the high influence of the propyl tip on both hydrophobicity of the surfactant and micellization. The more classical behavior of the propyl-ended hemifluorinated surfactants compared to the singular one of the ethyl-ended derivatives was also demonstrated with the limit surface tension values (γ_{CMC}), which are usually found between the lower values of the fluorinated surfactants and the higher values of the hydrogenated ones. As shown in Table 1, for a given polar head, the limit surface tension value of the propyl-ended hemifluorinated derivative compared to its perfluorinated analogue was increased in the Diglu series with 32.9 and 24.7 $mN \cdot m^{-1}$, respectively, while no significant difference was observed with the Triglu series. A similar trend was observed with the first series of glucose-based surfactants, F_6-Diglu and H_2F_6-Diglu compounds exhibiting limit surface tension of 28.3 and 36.0 $mN \cdot m^{-1}$, respectively.

Contribution of the Spacer. When comparing $H_2F_6H_3$-Diglu to its first series analogue H_2F_6-Diglu,[17] one can observe that these two surfactants, despite the presence of a longer spacer in the latter compound (i.e., C_2H_4-S-C_2H_4), exhibit very close CMC values (0.37 and 0.35 mM for $H_2F_6H_3$-Diglu and H_2F_6-Diglu, respectively). Surprisingly, a more striking difference was observed for the perfluorinated surfactants, with for instance the diglucosylated compound of the first series, F_6-Diglu, having a CMC of ∼0.23 mM while that of F_6H_3Diglu is ∼5 times higher. This latter point indicates that the length and the structure of the spacer should also be considered for the design of future hemifluorinated surfactants.

(c) Dynamic Light Scattering. Table 1 shows values of hydrodynamic diameter of the autoassemblies formed by the surfactants at relatively high concentrations (from 1.2 to 13.8 mM depending on the surfactant). The reported results show that perfluorinated surfactants bearing two or three glucose moieties self-assemble in water into small and monodisperse particles with apparent hydrodynamic diameter ∼5−6 nm, suggesting the formation of globular micelles.[35] However, F_6H_3-Triglu led to slightly smaller particles than its analogue F_6H_3-Diglu. The addition of a propyl-end group to the fluorocarbon chain did not affect the spatial geometry of the particles, yet the micelles of $H_3F_6H_3$-Diglu were found bigger than those of $H_3F_6H_3$-Triglu. This confirms the impact of the volume of the polar head on the size and the shape of the self-assemblies formed by a surfactant in aqueous media, the bigger the polar head of the surfactant, the smaller the hydrodynamic diameter of the micelle. When comparing $H_3F_6H_3$-Diglu and $H_2F_6H_3$-Diglu, the one-carbon longer chain of the former surfactant led to a small decrease of the interfacial curvature and thus to slightly larger aggregates.

Compared to the first series of glucose-based surfactants, the hydrodynamic diameter values of the novel series were found approximately 10% higher, with, for instance, F_6-Diglu and F_6H_3-Diglu forming micelles of 5.8 and 6.6 nm diameters, respectively. The same observation was noted with F_6-Triglu and F_6H_3-Triglu (5.1 and 5.7 nm, respectively). Due to the shorter spacer of the F_6H_3 series (C_3H_6) compared to that of the first series (C_2H_4−S-C_2H_4), a decrease of the volumetric ratio was expected, which in turn should have induced a smaller hydrodynamic diameter of the micelle. An opposite result was observed with a slight decrease of the interfacial curvature of the aggregates of the new series. This may be explained by the lack of flexibility of the shorter spacer, which could result in a more difficult assembling.

CONCLUSION

We have reported herein a simple route for the synthesis of a new series of hemifluorinated sugar-based surfactants bearing a propyl tip. This synthetic route is based on the radical addition of two olefins onto the commercially available 1,6-diiodoperfluorohexane using AIBN as radical initiator. The first radical addition allowed the grafting of the polar head onto the fluorinated core of the molecule, whereas the second radical addition was used for the insertion of the propyl tip on the hydrophobic tail. This synthetic pathway is a convenient access for upcoming syntheses of hemifluorinated surfactants where we could easily change the hydrocarbon/fluorocarbon distribution within the hydrophobic part and study their influence on the physical−chemical and biochemical properties of these compounds. Whereas in previous works we had shown that the addition of an ethyl tip to fluorinated surfactants did not significantly affect the CMC values, we found

that the addition of a propyl tip resulted in another trend. With these newly designed propyl-ended surfactants, the hydrophobicity brought by the propyl, as demonstrated by higher log k'_W values, is predominant, and therefore, the CMC values of $H_3F_6H_3$-surfactants were significantly lower than those of their perfluorinated analogues. Finally, as demonstrated by DLS experiments, we showed that propyl-ended hemifluorinated surfactants self-assemble into small and well-defined aggregates with diameter ~5−6 nm. Such a feature makes this novel series of surfactants very promising as tools for handling membrane proteins in aqueous solutions. Biochemical investigations are currently under progress and will be reported soon.

EXPERIMENTAL SECTION

***N*-1,1-Di[(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]acetoxyethyl-5,5,6,6,7,7,8,8,9,9,10,10-dodecafluoro-3,10-diiododecanamide (6).** 1,6-Diiodoperfluorohexane (1.54 g, 2.78 mmol, 2.5 equiv) and compound **5** (1.0 g, 1.12 mmol, 1 equiv) were dissolved in 2 mL of anhydrous THF in a sealed tube and heated up to 66 °C. To this was added 0.11 g (0.67 mmol, 0.6 equiv) of AIBN in three portions (0.2 equiv every 2 h). After 24 h of being stirred at 66 °C, the reaction mixture was cooled at room temperature and the solvent was removed under reduced pressure. The resulting crude compound was next purified by flash chromatography (EtOAc/cyclohexane, 6:4 v/v) and by size-exclusion chromatography (CH_2Cl_2/MeOH, 1:1 v/v) to give 0.7 g (0.48 mmol, 43%) of **6** as a white solid: R_f = 0.43 (EtOAc/cyclohexane, 6:4 v/v); mp = 64.3−65.2 °C; MS (ESI+) m/z = 1446 $[M + H]^+$, m/z = 1468 $[M + Na]^+$; HRMS (ESI+) calcd for $C_{44}H_{54}NO_{23}F_{12}I_2$ ($[M + H]^+$) 1446.0985, found 1446.1002; ^{1}H NMR ($CDCl_3$) δ 6.12 (NH, s, 1H), 5.31−4.98 (H_2, H_3, H_4, m, 6H), 4.65−4.46 (CHI, H_1, m, 3H), 4.36−3.97 (H_6, $H_{6'}$, CH_2O, m, 10H), 3.75−3.71 (H_5, m, 2H), 3.03−2.81 (CH_2, m, 4H), 2.11−2.02 (CH_3, 9s, 27H); ^{13}C NMR ($CDCl_3$) δ 170.6−169.3, 101.0, 72.5, 71.9, 71.4, 68.6, 68.2, 62.8, 61.6, 59.5, 47.2, 40.6 ($CF_2\underline{C}H_2$, t, J = 19.3 Hz), 20.8−20.6, 13.2; ^{19}F NMR ($CDCl_3$) δ −58.9 (2F), from −111.4 to −115.1 (2F), −112.9 (2F), −120.9 (2F), −121.5 (2F), −123.5 (2F).

***N*-Tris[(2′,3′,4′,6′tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]methyl-5,5,6,6,7,7,8,8,9,9,10,10-dodecafluoro-3,10-diiododecanamide (7).** The synthetic route was essentially the same as for compound **6**. 1,6-Diiodoperfluorohexane (1.99 g, 3.59 mmol, 2.5 equiv), compound **2** (1.7 g, 1.44 mmol, 1 equiv), and AIBN (0.14 g, 0.86 mmol, 0.6 equiv) were used as starting materials. Purification by flash chromatography (EtOAc/cyclohexane, 6:4 v/v) and by size-exclusion chromatography (methanol) led to 0.98 g (0.57 mmol, 40%) of compound **7** as a white solid: R_f = 0.28 (EtOAc/cyclohexane, 6:4 v/v); mp = 81.3−82.1 °C; MS (ESI+) m/z = 1734.1 $[M + H]^+$, m/z = 1751.2 $[M + NH_4]^+$; ^{1}H NMR ($CDCl_3$) δ 6.11 (NH, s, 1H), 5.26−4.94 (H_2, H_3, H_4, m, 9H), 4.63−4.53 (CHI, m, 1H), 4.48 (H_1, d, J = 7.9 Hz, 3H), 4.35 (H_6, dd, J = 4.7 Hz, J = 12.4 Hz, 3H), 4.25−4.11 ($H_{6'}$, CH_2OGlu, m, 6H), 3.81−3.73 (CH_2OGlu, H_5, m, 6H), 3.02−2.76 (CH_2, m, 4H), 2.18−2.02 (CH_3, 12s, 36H); ^{13}C NMR ($CDCl_3$) δ 170.6−169.4, 101.2, 72.4, 71.6, 71.5, 68.9, 68.2, 61.5, 59.6, 47.5, 40.2 (CF_2CH_2, t, J = 24.3 Hz), 20.8−20.6, 15.6; ^{19}F NMR ($CDCl_3$) δ −58.9 (2F), from −111.4 to −115.1 (2F), −112.9 (2F), −120.9 (2F), −121.51 (2F), −123.5 (2F).

***N*-1,1-Di[(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]acetoxyethyl-5,5,6,6,7,7,8,8,9,9,10,10-dodecafluoro-3,12-diiodotridecanamide (8).** Compound **6** (0.6 g, 0.41 mmol, 1 equiv) and AIBN (34.1 mg, 0.21 mmol, 0.5 equiv) were dissolved in 5 mL of anhydrous THF in a sealed tube. The solution was then cooled at −80 °C in a dry ice−acetone bath, and 3 mL of propylene was injected under argon atmosphere. The reaction mixture was then heated progressively up to 66 °C. After 24 h of being stirred at 66 °C, the solvent was removed under reduced pressure. *Despite several attempts to purify the resulting crude compound by flash chromatography and size-exclusion chromatography, compound* **8** *was not isolated with a sufficient purity to be properly characterized, and therefore, the impure fraction (0.38 g) was then used as is in the next reaction.*

***N*-Tris[(2′,3′,4′,6′tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]methyl-5,5,6,6,7,7,8,8,9,9,10,10-dodecafluoro-3,12-diiodotridecanamide (9).** The synthetic route was essentially the same as for compound **8**. Compound **7**(0.85 g, 0.49 mmol, 1 equiv), 3 mL of propylene, and AIBN (40.2 mg, 0.24 mmol, 0.5 equiv) were used as starting materials. Purification by flash chromatography (EtOAc/cyclohexane, 6:4 v/v) and by size-exclusion chromatography (MeOH) led to 0.39 g (0.22 mmol, 45%) of compound **9** as a white solid: R_f = 0.32 (EtOAc/cyclohexane, 6:4 v/v); mp = 90.3−91.2 °C; MS (ESI+) m/z = 1776.5 $[M + H]^+$;^{1}H NMR ($CDCl_3$) δ 6.09 (NH, s, 1H), 5.22−4.91 (H_2, H_3, H_4, m, 9H), 4.59−4.57 (CHI, m, 2H), 4.44 (H_1, d, J = 7.9 Hz, 3H), 4.31 (H_6, dd, J = 4.7 Hz, J = 12.4 Hz, 3H), 4.21−4.08 ($H_{6'}$, CH_2O-Glu, m, 6H), 3.76−3.69 (CH_2OGlu, H_5, m, 6H), 3.01−2.77 (CH_2, m, 6H), 2.10−2.02 (CH_3OAc and CH_3, 39H); ^{13}C NMR ($CDCl_3$) δ 170.7−169.3, 101.0, 72.5, 71.8, 71.4, 68.6, 68.2, 68.1, 61.6, 59.5, 59.3, 47.4, 40.6 (CF_2CH_2, t, J = 25.8 Hz), 37.4 (CF_2CH_2, t, J = 24.3 Hz), 21.4−20.5, 14.2. 11.8; ^{19}F NMR ($CDCl_3$) δ from −111.4 to −114.9 (4F), −121.7 (4F), −123.6 (4F).

***N*-1,1-Di[(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]acetoxyethyl-5,5,6,6,7,7,8,8,9,9,10,10-dodecafluorotridecanamide (10).** The crude compound **8** (0.38 g), Bu_3SnH (0.18 g, 0.98 mmol, 2.4 equiv), and a catalytic amount of AIBN (~0.005 g, 0.03 mmol, 0.07 equiv) were dissolved in 1.5 mL of anhydrous THF, and the mixture was heated at 66 °C for 24 h. The solvent was removed under reduced pressure, and the crude was purified by flash chromatography (EtOAc/cyclohexane, 6:4 v/v) to give 0.2 g (0.16 mmol, 38% *in two steps from compound* **6**) of **10** as a white solid: R_f = 0.45 (EtOAc/cyclohexane, 5:5 v/v); mp = 65.7−67.1 °C; ^{1}H NMR ($CDCl_3$) δ 5.99 (NH, s, 1H), 5.24−4.99 (H_2, H_3, H_4, m, 6H), 4.49 (H_1, d, J = 7.8 Hz, 1H), 4.48 (H_1, d, J = 7.8 Hz, 1H), 4.44−4.14 (H_6, $H_{6'}$,CH_2OGlu, m, 6H), 3.98 (CH_2OAc, s, 2H), 3.83−3.75 (H_5, CH_2OGlu, m, 4H), 2.26 (CH_2CO, t, J = 7.1 Hz, 2H), 2.12−2.03 (CH_3, 9s, 27H), 1.96−1.93 (CH_2CF_2, m, 2H), 1.69−1.64 (CH_2, m, 2H), 1.44−1.27 (CH_2 and CH_2CF_2, m, 4H), 1.04 (CH_3, t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.9, 170.8−169.4, 101.0, 72.5, 72.4, 72.0, 71.9, 71.3, 68.2, 68.1, 61.7, 58.7, 35.4, 32.8 (CF_2CH_2, t, J = 21.1 Hz), 29.9 (CF_2CH_2, t, J = 23.6 Hz), 20.7−20.6, 16.4−14.1, 13.8; ^{19}F NMR ($CDCl_3$) δ −114.3 (4F), −121.8 (4F), −123.6 (4F).

***N*-Tris[(2′,3′,4′,6′tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]methyl-5,5,6,6,7,7,8,8,9,9,10,10-dodecafluorotridecanamide (11).** The synthetic route was essentially the same as for compound **10**. Compound **9** (0.32 g, 0.18 mmol, 1 equiv), Bu_3SnH (1.12 g, 0.43 mmol, 2.4 equiv), and a catalytic amount of AIBN (~0.005 g, 0.03 mmol, 0.16 equiv) were used as starting materials. Purification by flash chromatography (EtOAc/cyclohexane, 6:4 v/v) and by size-exclusion chromatography (MeOH) led to 0.2 g (0.13 mmol, 74%) of compound **11** as a white solid: R_f = 0.36 (EtOAc/cyclohexane, 6:4 v/v); mp = 89.2−89.7 °C; ^{1}H NMR ($CDCl_3$) δ 5.99 (NH, s, 1H), 5.24−4.93 (H_2, H_3, H_4, m, 9H), 4.45 (H_1, d, J = 7.9 Hz, 3H), 4.36 (H_6, dd, J = 4.7 Hz, J = 12.5 Hz, 3H), 4.20−3.97 (H_6, CH_2OGlu, m, 6H), 3.75−3.69 (CH_2OGlu, H_5, m, 6H), 2.17 (CH_2, t, J = 8.7 Hz, 2H), 2.25−2.10 (CH_2, m, 2H), 2.18−1.92 (CH_3, 12s, 36H), 1.65−1.55 (CH_2, m, 2H), 1.42−1.22 (CH_2CH_2, m, 4H), 1.26 (CH_3, t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.7−169.3, 101.0, 72.5, 71.8, 71.4, 69.8, 69.2, 68.6, 68.2, 67.8, 61.6, 61.4, 59.5, 47.4, 40.6 (CF_2CH_2, t, J = 25.8 Hz), 37.4 (CF_2CH_2, t, J = 23.7 Hz), 36.8, 31.5, 21.4−20.5, 14.2; ^{19}F NMR ($CDCl_3$) δ −115.3 (4F), −122.8 (4F), −124.5 (4F).

***N*-1,1-Di[(*O*-*β*-D-glucopyranosyl)oxymethyl]hydroxyethyl-5,5,6,6,7,7,8,8,9,9,10,10-dodecafluorotridecanamide (12).** Compound **10** (0.12 g 0.097 mmol) and a catalytic amount of MeONa

(~0.002 g, 0.036 mmol, 0.37 equiv) were dissolved in 10 mL of MeOH (pH ~8−9) and then the mixture stirred for 3 h at room temperature. Two spatulas of IRC 50 resin were added, the solution was filtered, and then the solvent was removed under reduced pressure. Purification of the crude compound by size-exclusion chromatography (MeOH) followed by lyophilization led to 80 mg (0.093 mmol, 96%) of **12** as a white solid: R_f = 0.59 (EtOAc/MeOH/H_2O, 7:2:1 v/v/v); mp = 150.2−151.1 °C; HRMS (ESI+) calcd for $C_{29}H_{44}NO_{14}F_{12}$ ($[M + H]^+$) 858.2565, found 858.2570; ^{1}H NMR (CD_3OD) δ 4.31 (H_1, d, J = 7.7 Hz, 1H), 4.30 (H_1, d, J = 7.7 Hz, 1H), 4.18−4.12 (CH_2OGlu, m, 2H), 3.89−3.81 (CH_2OGlu, H_6, CH_2OH, m, 6H), 3.68−3.65 ($H_{6'}$, m, 2H), 3.35−3.15 (H_2, H_3, H_4, H_5, m, 8H), 2.35 (CH_2CO, t, J = 7.3 Hz, 2H), 2.21−2.11 (CH_2CF_2, m, 4H), 1.91−1.85 (CH_2, m, 2H), 1.65−1.61 (CH_2, m, 2H), 1.04 (CH_3, t, J = 7.4 Hz, 3H); ^{13}C NMR (CD_3OD) δ 173.9, 103.5, 103.4, 76.6, 73.6, 70.2, 67.8, 67.7, 61.3, 60.8, 34.8, 32.3 (CF_2CH_2, t, J = 21.9 Hz), 29.8 (CF_2CH_2, t, J = 21.3 Hz), 19.4, 16.3, 13.5; ^{19}F NMR (CD_3OD) δ −115.5 (4F), −122.8 (4F), −124.7 (4F).

***N*-Tris[(*β*-D-glucopyranosyl)oxymethyl]methyl-5,5,6,6,7,7,8,8,9,9,10,10-dodecafluorotridecanamide (13).** The synthetic route was essentially the same as for compound **12**. Compound **11** (0.16 g, 0.104 mmol) and a catalytic amount of MeONa (~0.002 g, 0.036 mmol, 0.35 equiv) were used as starting materials. Purification by size-exclusion chromatography (MeOH) followed by lyophilization led to 0.1 g (0.098 mmol, 95%) of **13** as a white foam: R_f = 0.35 (EtOAc/MeOH/H_2O, 7:2:1 v/v/v); mp = 156.2−157.1 °C; HRMS (ESI+) calcd for $C_{35}H_{53}NO_{19}F_{12}$ ($[M + H]^+$) 1020.3093, found 1020.3111; ^{1}H NMR (CD_3OD) δ 4.36−4.33 (H_1, CH_2O, m, 6H), 3.95−3.87 (CH_2O, H_6, m, 6H), 3.75−3.65 ($H_{6'}$, m, 3H), 3.42−3.18 (H_2, H_3, H_4, H_5, m, 12H), 2.36 (CH_2, t, J = 7.7 Hz, 2H), 2.24−2.04 (CH_2, m, 4H), 1.93−1.88 (CH_2, m, 2H), 1.68−1.54 (CH_2, m, 2H), 0.96 (CH_3, t, J = 6.25 Hz, 3H); ^{13}C NMR (CD_3OD) δ 173.7, 103.5, 76.9, 76.6, 73.6, 70.2, 67.8, 67.5, 61.3, 59.8, 34.9, 32.3 (CF_2CH_2, t, J = 21.2 Hz), 29.5 (CF_2CH_2, t, J = 21.3 Hz), 19.4, 16.3, 12.9; ^{19}F NMR (CD_3OD) δ −114.4 (4F), −121.9 (4F), −123.7 (4F).

***N*-1,1-Di[(2′,3,′4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]acetoxyethyl-5,5,6,6,7,7,8,8,9,9,10,10-dodecafluoro-3,12-diiodododecanamide (15).** 1,1,2,2,3,3,4,4,5,5,6,6-Dodecafluoro-1,8-diiodooctane (1.0 g, 1.76 mmol, 1 equiv)[15] and compound **5** (1.56 g, 1.76 mmol, 1 equiv) were dissolved in 2 mL of anhydrous THF in a sealed tube and the mixture heated to 66 °C. To this was added 0.17 g (1.05 mmol, 0.6 equiv) of AIBN in three portions (0.2 equiv every 2 h). After 24 h of being stirred at 66 °C, the reaction mixture was cooled at room temperature, and the solvent was removed under reduced pressure. The crude compound was then purified by flash chromatography (EtOAc/cyclohexane, 6:4 v/v) and size-exclusion chromatography (CH_2Cl_2/MeOH, 1:1 v/v) to give 1.15 g (0.78 mmol, 45%) of compound **15** as a white solid: R_f = 0.56 (EtOAc/cyclohexane, 6:4 v/v); mp = 65.6−66.8 °C; MS (ESI+) m/z = 1474.2 $[M + H]^+$, m/z = 1496.2 $[M + Na]^+$; HRMS (ESI+) calculated for $C_{46}H_{58}NO_{23}F_{12}I_2$ ($[M + H]^+$) 1474.1298, found 1474.1240; ^{1}H NMR ($CDCl_3$) δ 6.14 (NH, d, J = 8.3 Hz, 1H), 5.24−4.95 (H_2, H_3, H_4, m, 6H), 4.51−4.49 (CHI, m, 1H), 4.50 (H_1, d, J = 6.5 Hz, 1H), 4.47 (H_1, d, J = 6.5 Hz, 1H), 4.32−3.94 (H_6, CH_2O, m, 10H), 3.73−3.65 (H_5, m, 2H), 3.26−3.19 (CH_2I, m, 2H), 2.94−2.72 (CH_2, m, 6H), 2.08−1.98 (CH_3, 9s, 27H); ^{13}C NMR ($CDCl_3$) δ 170.8−169.4, 100.9, 72.5, 72.3, 71.9, 71.8, 71.3, 71.2, 68.2, 68.1, 62.8, 61.6, 59.1, 47.2, 40.6 (CF_2CH_2, t, J = 19.3 Hz), 35.3 (CF_2CH_2, t, J = 19.3 Hz), 20.9−20.6, 19.3, 12.1; ^{19}F NMR ($CDCl_3$) δ from −112.4 to −113.9 (2F), −114.9 (2F), −121.7 (4F), −123.5 (4F).

***N*-1,1-Di[(2′,3,′4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]acetoxyethyl-5,5,6,6,7,7,8,8,9,9,10,10-dodecafluorododecanamide (16).** The synthetic route was essentially the same as for compound **10**. Compound **15** (0.41 g 0.28 mmol, 1 equiv), Bu_3SnH (0.19 g, 0.67 mmol, 2.4 equiv), and a catalytic amount of AIBN (~0.005 g, 0.03 mmol, 0.11 equiv) were used as starting materials. Purification by flash chromatography (EtOAc/cyclohexane, 6:4 v:v) and size-exclusion chromatography (CH_2Cl_2/MeOH, 1:1 v/v) led to 0.23 g (0.19 mmol, 68%) of compound **16** as a white solid: R_f = 0.34 (EtOAc/cyclohexane, 6:4 v/v); mp = 64.3−64.4 °C; HRMS (ESI+) calcd for $C_{46}H_{60}NO_{23}F_{12}$ ($[M + H]^+$) 1222.3365, found 1222.3350; ^{1}H NMR ($CDCl_3$) δ 5.89 (NH, s, 1H), 5.25−4.93 (H_2, H_3, H_4, m, 6H), 4.47 (H_1, d, J = 7.4 Hz, 2H), 4.29 (H_6, dd, J = 4.2 Hz, J = 12.3 Hz, 2H), 4.15−3.59 (H_6, H_5, CH_2O, m, 10H), 2.21 (CH_2CO, t, J = 7.2 Hz, 2H), 2.16−1.86 (CH_3, CH_2, m, 29H), 1.66−1.53 (CF_2CH_2, m, 2H), 1.36−1.22 (CF_2CH_2, m, 2H), 1.13 (CH_3, t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.5−169.1, 100.9, 72.4, 72.3, 72.1, 71.9, 71.8, 71.7, 71.2, 71.1, 68.1, 61.5, 60.2, 55.9, 35.3, 29.5 (CF_2CH_2, t, J = 22.3 Hz), 24.4 (CF_2CH_2, t, J = 22.9 Hz), 20.4, 18.1, 14.0; ^{19}F NMR ($CDCl_3$) δ −114.3 (2F), −116.4 (2F), −121.9 (4F), −123.7 (4F).

***N*-1,1-Di[(*O*-*β*-D-glucopyranosyl)oxymethyl]hydroxyethyl-5,5,6,6,7,7,8,8,9,9,10,10-dodecafluorotridecanamide (17).** The synthetic route was essentially the same as for compound **12**. Compound **16** (97 mg, 0.079 mmol) and a catalytic amount of MeONa (~0.002 g, 0.036 mmol, 0.45 equiv) were used as starting materials. Purification by size-exclusion chromatography (MeOH) followed by lyophilization led to 65 mg (0.077 mmol, 98%) of compound **17** as a white foam: R_f = 0.69 (EtOAc/MeOH/H_2O, 7:2:1 v/v/v); mp = 149.2−150.3 °C; HRMS (ESI+) calcd for $C_{28}H_{41}NO_{14}F_{12}$ ($[M + H]^+$) 844.2408, found 844.2416; ^{1}H NMR (CD_3OD) δ 4.34 (H_1, d, J = 7.7 Hz, 1H), 4.33 (H_1, d, J = 7.7 Hz, 1H), 4.21−4.15 (CH_2OGlu, m, 2H), 3.92−3.83 (CH_2OGlu, H_6, $H_{6'}$, m, 6H), 3.71−3.69 (CH_2OH, m, 2H), 3.38−3.18 (H_2, H_3, H_4, H_5, m, 8H), 2.38 (CH_2CO, t, J = 7.3 Hz, 2H), 2.30−2.11 (CF_2CH_2, m, 4H), 1.94−1.88 (CH_2, m, 2H), 1.16 (CH_3, t, J = 7.4 Hz, 3H); ^{13}C NMR (CD_3OD) δ 174.0, 103.5, 103.4, 76.6, 73.6, 70.2, 67.8, 67.7, 61.3, 60.8, 34.8, 29.8 (CF_2CH_2, t, J = 18.6 Hz), 24.1 (CF_2CH_2, t, J = 24.8 Hz), 16.3; ^{19}F NMR (CD_3OD) δ −115.4 (2F), −117.5 (2F), −122.9 (4F), −124.6 (4F).

***N*-1,1-Di[(2′,3,′4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]acetoxyethyl-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluoro-3-iododecanamide (18).** Compound **5** (0.75 g, 0.84 mmol, 1 equiv) and 0.79 g (1.68 mmol, 2 equiv) of 1-iodoperfluorohexane were dissolved in 2 mL of anhydrous THF in a sealed tube and heated to 66 °C. To this was added 82.7 mg (0.5 mmol, 0.6 equiv) of AIBN in three portion (0.2 equiv every 2 h). After 24 h of being stirred at 66 °C, the reaction mixture was cooled at room temperature and the solvent was removed under reduced pressure. The resulting crude compound was then purified by flash chromatography (EtOAc/cyclohexane, 6:4 v/v) to give 0.53 g (0.39 mmol, 47%) of **18** as a white solid: R_f = 0.65 (EtOAc/cyclohexane, 6:4 v/v); mp = 58.9−59.3 °C; HRMS (ESI+) calcd for $C_{44}H_{54}NO_{23}F_{13}I$ ($[M + H]^+$) 1338.1924, found 1338.1897; ^{1}H NMR ($CDCl_3$) δ 6.14 (NH, s, 1H), 5.28−4.97 (H_2, H_3, H_4, m, 6H), 4.70−4.60 (CHI, m, 1H), 4.54−3.77 (H_1,H_6, $H_{6'}$, and CH_2O, m, 12H), 3.76−3.72 (H_5, m, 2H), 3.04−2.80 (CH_2, m, 4H), 2.12−2.03 (CH_3, 9s, 27H); ^{13}C NMR ($CDCl_3$) δ 170.9−169.4, 101.0, 100.9, 72.5, 72.4, 72.0, 71.9, 71.3, 71.2, 68.8, 68.1, 61.7, 59.1, 47.2, 40.6 (CF_2CH_2, t, J = 25.9 Hz), 20.9−20.6, 19.3; ^{19}F NMR ($CDCl_3$) δ −80.7 (3F), from −111.4 to −115.0 (2F), −121.8 (2F), −122.8 (2F), −123.5 (2F), −126.1 (2F).

***N*-Tris[(2′,3′,4′,6′tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]methyl-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluoro-3-iododecanamide (19).** The synthetic route was essentially the same as for compound **18**. Compound **2** (1.5 g, 1.28 mmol, 1 equiv), 1-iodoperfluorohexane (1.21 g, 2.56 mmol, 1 equiv), and AIBN (0.13 g, 0.77 mmol, 0.6 equiv) were used as starting materials. Purification by flash chromatography (EtOAc/cyclohexane, 8:2 v/v) and by size-exclusion chromatography (MeOH) led to 0.82 g (0.5 mmol, 40%) of **19** as a white solid: R_f = 0.34 (EtOAc/cyclohexane, 6:4 v/v); mp = 62.2−63.4 °C; MS (ESI+) m/z = 1626.6 $[M + H]^+$; ^{1}H NMR ($CDCl_3$) δ 6.11 (NH, s, 1H), 5.56−4.93 (H_2, H_3, H_4, m, 9H), 4.65−4.59 (CHI, m, 1H), 4.47 (H_1, d, J = 7.9 Hz, 3H), 4.38−4.09 (H_6, $H_{6'}$, CH_2OGlu, m, 9H), 3.81−3.72 (CH_2Oglu, H_5, m, 6H), 3.03−2.86 (CH_2, m, 4H), 2.15−2.02

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(CH_3, m, 36H). ^{13}C NMR ($CDCl_3$) δ 170.6−169.3, 101.0, 72.5, 71.9, 71.4, 68.6, 68.2, 61.6, 59.4, 45.2, 40.3 ($CF_2\underline{C}H_2$, t, J = 23.3 Hz), 20.8−20.6, 14.2; ^{19}F NMR ($CDCl_3$) δ −80.7 (3F), from −111.4 to −115.1 (2F), −121.7 (2F), −122.8 (2F), −123.5 (2F), −126.1 (2F).

***N*-1,1-Di[(2′,3,′4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]acetoxyethyl-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluorodecanamide (20).** Compound **18** (0.45 g, 0.34 mmol, 1 equiv), Bu_3SnH (0.12 g, 0.41 mmol, 1.2 equiv), and a catalytic amount of AIBN (∼0.005 g, 0.03 mmol, 0.09 equiv) were dissolved in anhydrous THF in sealed tube and the mixture heated to 66 °C for 24 h. The reaction mixture was then cooled at room temperature, and the solvent was removed under reduce pressure. The crude compound was purified by flash chromatography (EtOAc/cyclohexane, 6:4 v/v) to give 0.28 g (0.23 mmol, 68%) of **20** as a white solid: R_f = 0.52 (EtOAc/cyclohexane, 7:3 v/v); mp = 51.5−52.2 °C; MS (ESI+) m/z = 1212 $[M + H]^+$, m/z = 1234 $[M + Na]^+$; HRMS (ESI+) calcd for $C_{44}H_{55}NO_{23}F_{13}$ ($[M + H]^+$) 1212.2957, found 1212.2936; ^1H NMR ($CDCl_3$) δ 5.98 (NH, s, 1H), 5.21−4.94 (H_2, H_3, H_4, m, 6H), 4.48 (H_1, d, J = 7.8 Hz, 1H), 4.47 (H_1, d, J = 7.8 Hz, 1H), 4.32−3,69 (CH_2O, $H_{6'}$, H_6, H_5, m, 10H), 3.96 (CH_2OAc, m, 2H), 2.24 (CH_2CO, t, J = 6.9 Hz, 2H), 2.08−1.94 (CH_2 and 9CH_3, m, 29H), 1.28−1.22 (CH_2, m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.8−169.3, 100.9, 72.5, 72.3, 71.9, 71.2, 68.8, 68.7, 68.2, 68.1, 62.9, 61.6, 58.7, 35.3, 29.9 (CF_2CH_2, t, J = 18.0 Hz), 21.0−20.5, 16.3; ^{19}F NMR ($CDCl_3$) δ −80.8 (3F), −114.3 (2F), −121.9 (2F), −122.9 (2F), −123.4 (2F), −126.2 (2F).

***N*-Tris[(2′,3′,4′,6′tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]methyl-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluorodecanamide (21).** The synthetic route was essentially the same as for compound **20**. Compound **19** (0.60 g, 0.37 mmol, 1 equiv), Bu_3SnH (0.13 g, 0.44 mmol, 1.2 equiv), and a catalytic amount of AIBN (∼0.005 g, 0.03 mmol, 0.08 equiv) were used as starting materials. Purification by flash chromatography (EtOAc/cyclohexane, 6:4 v/v) and size-exclusion chromatography (MeOH) led to 0.38 g (0.25 mmol, 69%) of compound **21** as a white solid: R_f = 0.52 (EtOAc/cyclohexane, 6:4 v/v); mp = 59.3−59.7 °Cm MS (ESI+) m/z = 1500 $[M + H]^+$, m/z = 1522 $[M + Na]^+$; HRMS (ESI+) calcd for $C_{56}H_{71}NO_{31}F_{13}$ ($[M + H]^+$) 1500.3802, found 1500.3809; ^1H NMR ($CDCl_3$) δ 5.97 (NH, s, 1H), 5.26−4.94 (H_2, H_3, H_4, m, 9H), 4.46 (H_1, d, J = 7.9 Hz, 3H), 4.35 (H_6, dd, J = 4.7 Hz and J = 12.3 Hz, 3H), 4.21−4.09 ($H_{6'}$ and CH_2O, m, 6H), 3.76−3.71 (H_5, CH_2O, m, 6H), 2.24 (CH_2CO, t, J = 6.8 Hz, 2H), 2.11−1.91 (CH_2 and 12CH_3, m, 38H), 1.39−1.25(CH_2, m, 2H); ^{13}C NMR ($CDCl_3$) δ 171.7−169.4, 100.9, 72.5, 72.3, 71.9, 71.2, 68.8, 68.7, 68.2, 68.1, 61.7, 60.5, 58.7, 35.3, 29.8 (CF_2CH_2, t, J = 18.0 Hz), 21.0−20.5, 16.3; ^{19}F NMR ($CDCl_3$) δ −80.7 (3F), −114.2 (2F), −121.9 (2F), −122.8 (2F), −123.3 (2F), −126.1 (2F).

***N*-1,1-Di[(*O*-*β*-D-glucopyranosyl)oxymethyl]hydroxyethyl-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluorodecanamide (22).** The synthetic procedure was essentially the same as for compound **12**. Compound **20** (0.21 g, 0.17 mmol) and a catalytic amount of MeONa (∼0.002 g, 0.036 mmol, 0.2 equiv) were used as starting materials. Purification by size-exclusion chromatography (MeOH) led to 0.13 g (0.15 mmol, 97%) of compound **22** as a white foam: R_f = 0.62 (EtOAc/MeOH/H_2O, 7:2:1 v/v/v); mp = 114.3 °C; HRMS (ESI+) calcd for $C_{26}H_{36}NO_{14}F_{13}$ ($[M + H]^+$) 834.2001, found 834.1992; ^1H NMR (CD_3OD) δ 4.31 (H_1, d, J = 7.8 Hz, 1H), 4.30 (H_1, d, J = 7.8 Hz, 1H), 4.16−4.12 (CH_2OGlu, m, 2H), 3.89−3.81 (H_6, CH_2OH, CH_2OGlu, m, 6H), 3.68−3.66 ($H_{6'}$, m, 2H), 3.34−3.15 (H_2, H_3, H_4, H_5, m, 8H), 2.35 (CH_2CO, t, J = 7.3 Hz, 2H), 2.19−2.06 (CF_2CH_2, m, 2H), 2.01−1.85 (CH_2, m, 2H); ^{13}C NMR (CD_3OD) δ 173.9, 103.5, 103.4, 76.6, 73.6, 70.2, 67.8, 61.3, 60.8, 34.7, 29.7 (CF_2CH_2, t, J = 18.8 Hz), 16.2; ^{19}F NMR (CD_3OD) δ −82.4 (3F), −115.4 (2F), −122.9 (2F), −123.9 (2F), −124.3 (2F), −127.3 (2F).

***N*-Tris[(*β*-D-glucopyranosyl)oxymethyl]methyl-5,5,6,6,7,7,8,8,9,9,10,10,10-tridecafluorodecanamide (23).** The synthetic procedure was essentially the same as for compound **12**. Compound **21** (0.21 g, 0.14 mmol) and a catalytic amount of MeONa (∼0.002 g, 0.036 mmol, 0.25 equiv) were used as starting materials. Purification by size-exclusion chromatography (MeOH) led to 0.13 g (0.13 mmol, 95%) of compound **23** as a white solid: R_f = 0.42 (EtOAc/MeOH/H_2O, 7:2:1 v/v/v); mp = 164.3−165.2 °C; HRMS (ESI+) calcd for $C_{32}H_{46}NO_{19}F_{13}$ ($[M + H]^+$) 996.2529, found 996.2526; ^1H NMR (CD_3OD) δ 4.36−4.33 (H_1, CH_2O, m, 6H), 3.95−3.88 (CH_2O, H_6, m, 6H), 3.71−3.65 ($H_{6'}$, m, 3H), 3.42−3.18 (H_2, H_3, H_4, H_5, m, 12H), 2.37 (CH_2CO, t, J = 7.7 Hz, 2H), 2.24−1.93 ($CF_2CH_2CH_2$, m, 4H); ^{13}C NMR (CD_3OD) δ 172.9, 103.5, 76.6, 73.7, 70.2, 67.8, 61.3, 60.0, 34.4, 29.6 (CF_2CH_2, t, J = 18.8 Hz), 16.3; ^{19}F NMR (CD_3OD) δ −82.4 (3F), −115.3 (2F), −122.9 (2F), −123.9 (2F), −124.3 (2F), −127.4 (2F).

■ ASSOCIATED CONTENT

Supporting Information. General experimental methods; experimental procedure for the synthesis of compounds **1**−**5**; ^1H and ^{13}C NMR spectra of compounds **1**−**5**; ^1H, ^{13}C, and ^{19}F NMR spectra of compounds **6**−**13** and **15**−**23**; HMQC NMR spectrum of compound **12**, DEPT 135, COSY and HMQC NMR spectra of compound **22**; high-resolution mass spectrometry data of compounds **12**, **13**, **17**, **22** and **23**; hydrodynamic distribution of compounds **12**, **13**, **17**, **22**, and **23**; surface tension curves of compounds **13** and **23**; HPLC partition coefficient linear regression analysis of compounds **12**, **17**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Bowie, J. U. *Curr. Opin. Struct. Biol.* **2001**, *11*, 397–402.
(2) Popot, J.-L. *Annu. Rev. Biochem.* **2010**, *79*, 737–775.
(3) Schafmeister, C.; Miercke, L.; Stroud, R. *Science* **1993**, *262*, 734–738.
(4) Chae, P. S.; Laible, P. D.; Gellman, S. H. *Mol. BioSyst.* **2010**, *6*, 89–94.
(5) Chae, P. S.; Gotfryd, K.; Pacyna, J.; Miercke, L. J. W.; Rasmussen, S. G. F.; Robbins, R. A.; Rana, R. R.; Loland, C. J.; Kobilka, B.; Stroud, R.; Byrne, B.; Gether, U.; Gellman, S. H. *J. Am. Chem. Soc.* **2010**, *132*, 16750–16752.
(6) Popot, J. L.; Berry, E.; Charvolin, D.; Creuzenet, C.; Ebel, C.; Engelman, D. M.; Flotenmeyer, M.; Giusti, F.; Gohon, Y.; Hervé, P.; Hong, Q.; Lakey, J. H.; Leonard, K.; Shuman, H. A.; Timmins, P.; Warschawski, D. E.; Zito, F.; Zoonens, M.; Pucci, B.; Tribet, C. *Cell. Mol. Life Sci.* **2003**, *60*, 1559–1574.
(7) Sharma, K. S.; Durand, G.; Giusti, F.; Olivier, B.; Fabiano, A.-S.; Bazzacco, P.; Dahmane, T.; Ebel, C.; Popot, J.-L.; Pucci, B. *Langmuir* **2008**, *24*, 13581–13590.

(8) Bazzacco, P.; Sharma, K. S.; Durand, G.; Giusti, F.; Ebel, C.; Popot, J.-L.; Pucci, B. *Biomacromolecules* **2009**, *10*, 3317–3326.
(9) Breyton, C.; Pucci, B.; Popot, J.-L. *Methods Mol. Biol.* **2009**, *601*, 219–245.
(10) Peyre, V. *Curr. Opin. Colloid Interface Sci.* **2009**, *14*, 305–314.
(11) Lo Nostro, P.; Chen, S.-W. *J. Phys. Chem.* **1993**, *97*, 6535–6540.
(12) Dorset, D. L. *Macromolecules* **1990**, *23*, 894–901.
(13) Rodnin, M. V.; Posokhov, Y. O.; Contino-Pépin, C.; Brettmann, J.; Kyrychenko, A.; Palchevskyy, S. S.; Pucci, B.; Ladokhin, A. S. *Biophys. J.* **2008**, *94*, 4348–4357.
(14) le Maire, M.; Champeil, P.; Møller, J. V. *Biochim. Biophys. Acta (BBA) - Biomembranes* **2000**, *1508*, 86–111.
(15) Barthélémy, P.; Ameduri, B.; Chabaud, E.; Popot, J.-L.; Pucci, B. *Org. Lett.* **1999**, *1*, 1689–1692.
(16) Breyton, C.; Chabaud, E.; Chaudier, Y.; Pucci, B.; Popot, J.-L. *FEBS Lett.* **2004**, *564*, 312–318.
(17) Abla, M.; Durand, G.; Pucci, B. *J. Org. Chem.* **2008**, *73*, 8142–8153.
(18) Israelachvili, J. N.; Mitchell, D. J.; Ninham, B. W. *Biochim. Biophys. Acta (BBA) - Biomembranes* **1977**, *470*, 185–201.
(19) Breyton, C.; Gabel, F.; Abla, M.; Pierre, Y.; Lebaupain, F.; Durand, G.; Popot, J.-L.; Ebel, C.; Pucci, B. *Biophys. J.* **2009**, *97*, 1077–1086.
(20) Brace, N. O. *J. Fluorine Chem.* **1999**, *93*, 1–25.
(21) Delon, L.; Laurent, P.; Blancou, H. *J. Fluorine Chem.* **2005**, *126*, 1487–1492.
(22) Lahiouhel, D.; Ameduri, B.; Boutevin, B. *J. Fluorine Chem.* **2001**, *107*, 81–88.
(23) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072–3082.
(24) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739–7742.
(25) Praly, J.-P. *Adv. Carbohydr. Chem. Biochem.* **2000**, *56*, 65–151.
(26) Pereyre, M. Q.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, 1987.
(27) Rajanbavu, T. V. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995; Vol. 7.
(28) Braumann, T. *J. Chromatogr. A* **1986**, *373*, 191–225.
(29) Lebaupain, F.; Salvay, A. G.; Olivier, B.; Durand, G.; Fabiano, A.-S.; Michel, N.; Popot, J.-L.; Ebel, C.; Breyton, C.; Pucci, B. *Langmuir* **2006**, *22*, 8881–8890.
(30) Polidori, A.; Presset, M.; Lebaupain, F.; Ameduri, B.; Popot, J.-L. Breyton, C.; Pucci, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5827–5831.
(31) Zhang, T.; Marchant, R. E. *Colloid Interface Sci.* **1996**, *177*, 419–426.
(32) Polidori, A.; Pucci, B.; Maurizis, J. C.; Pavia, A. A. *New J. Chem.* **1994**, *18*, 838–848.
(33) Adamson, A. W. *The Physical Chemistry of Surfaces*; Wiley Interscience: New York, 1990.
(34) Rosen, M. J. *Surfactants and Interfacial Phenomenon*; John-Wiley: New York, 2003.
(35) Zana, R. *Colloids Surf. A* **1997**, *123−124*, 27–35.