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Glucose-Based Surfactants with Hydrogenated, Fluorinated, or Hemifluorinated Tails: Synthesis and Comparative Physical-Chemical Characterization

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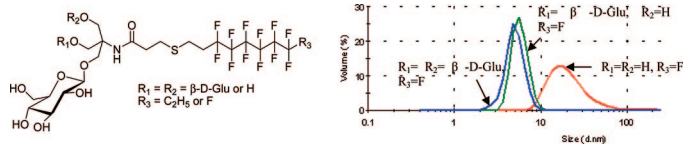

(Hemi)fluorinated hydrophobic chains have been found to minimize the denaturating propensity of surfactants toward membrane proteins. The work reported herein deals with the synthesis of a new series of non-ionic glucose-based surfactants endowed with a hybrid hemifluorocarbon chain. The convergent synthesis is based on a one-pot reduction/alkylation of hemifluorinated thioacetate and glucosylated trishydroxymethyl acrylamidomethane using $NaBH_4$ in methanol. This "mild" alkylation was studied in order to improve yields and to pass up the use of an excess of commercially unavailable hemifluorinated thiols. The physical-chemical properties in aqueous solution of this novel series were studied by surface tension measurement and dynamic light scattering (DLS), as well as their behavior upon reverse-phase chromatography, and were compared with those of their hydrogenated and perfluorinated analogues. The atypical effect of the additional ethyl tip to the fluorinated chain was demonstrated by higher critical micellar concentration values and abnormal hydrophobicities measured by reverse-phase chromatography. Moreover, according to Israelachvili's concept, DLS studies showed that surfactants bearing bulkier polar head self-assemble into small and well-defined aggregates, suggesting the formation of spherical micelles rather than the cylindrical ones usually observed with classical fluorinated surfactants.

Introduction

Obtaining membrane proteins (MPs) that are soluble, active, and stable so as to be able to study in vitro their function and structure is of major scientific and biomedical importance, given that MPs represent more than half of the targets of pharmaceutical drugs and 20−40% of proteins encoded by genomes.[1] However, there is currently a dearth of information on their function and structure (less than 1% of the entries in the Protein Data Bank are of MPs). MPs, which may comprise either one or several polypeptide chains (subunits) and hydrophobic cofactors, need to be extracted from the membrane for most in vitro studies. This is commonly done by using detergents, which bind, in place of the lipids, to the transmembrane (TM) surface of the proteins, making them soluble in water. Detergents are dissociating compounds, a specificity that allows them to solubilize membranes, to compete with lipid−lipid and lipid−protein interactions, and therefore to extract MPs. However, the dissociating effect of detergents can be difficult to control, and this results in the destabilization and irreversible inactivation of the protein. Specific interactions between TM segments belonging to the same or to different polypeptides are essential to the folding and assembly of MPs, and in many cases, bound lipids or other hydrophobic cofactors are required for the stability and function of MPs. It is therefore a delicate task to stop dissociation at the desired stage, namely, that of a discrete entity that needs to be purified and studied in vitro while retaining its biological activity and a modicum of stability.[2−4] The two likely mechanisms leading to inactivation are the intrusion of the detergent into the TM region of the protein and/or the dissociation of stabilizing lipids, cofactors, or subunits.[2,5]

(1) Wallin, E.; Von-Heijne, G. *Protein Sci.* **1998**, *7*, 1029–1038.

(2) Bowie, J. U. *Curr. Opin. Struct. Biol.* **2001**, *11*, 397–402.

(3) Garavito, R. M.; Ferguson-Miller, S. *J. Biol. Chem.* **2001**, *276*, 32403–32406.

(4) Gohon, Y.; Popot, J.-L. *Curr. Opin. Colloid Interface Sci.* **2003**, *8*, 15–22.

(5) Breyton, C.; Tribet, C.; Olive, J.; Dubacq, J.-P.; Popot, J.-L. *J. Biol. Chem.* **1997**, *272*, 21892–21900.

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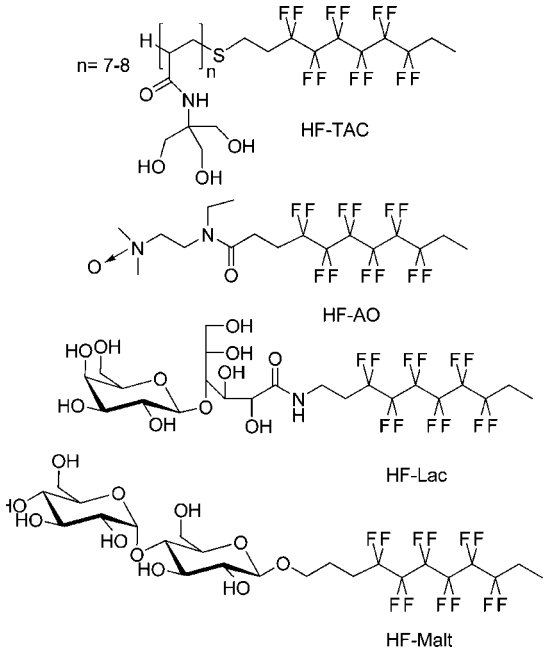


FIGURE 1. Chemical structures of previously developed hemifluorinated surfactants.

In an attempt at overcoming these problems, we have undertaken the charge to study the potentiality of fluorocarbon surfactants (FS).[6,7] These molecules have the same general structure as classical detergents (i.e., a hydrophilic headgroup and a hydrophobic tail), but the hydrophobic tail, rather than being a hydrogenated aliphatic chain, is a fluorinated chain. Our rationale was the following: alkanes and perfluorinated alkanes, while they are both hydrophobic, are poorly miscible; for this reason, surfactants with fluorinated alkyl chains are lyophobic−they do not partition well into biological membranes and therefore have little cytolytic effect.[7−10] For the same reason, they are poor solvents for lipids and hydrophobic cofactors and can be expected to be less delipidating. Their hydrophobic moieties being lyophobic, bulkier, and more rigid than their hydrogenated counterparts, they may also be expected to intrude less easily into the protein structure itself. However, by the same token, perfluorinated chains have little affinity for the hydrogenated TM surface of MPs. To improve the interaction between the hydrophobic, hydrogenated domain of integral membrane proteins and the surfactant, an ethyl hydrogenated tip has been grafted at the extremity of the surfactant tail, leading to hemifluorinated surfactants (HFSs).[11]

Among them, surfactants with a polymeric head derived from trishydroxymethyl acrylamidomethane (THAM), the HF-TAC family (Figure 1), proved to be particularly mild toward MPs.[12] MPs, initially extracted using hydrogenated detergents, remained soluble and active when transferred into HFSs with increased biochemical stabilities.[13] Recently, it has been demonstrated that HFSs can be used for in vitro synthesis of MPs or their insertion into a lipid bilayer.[14]

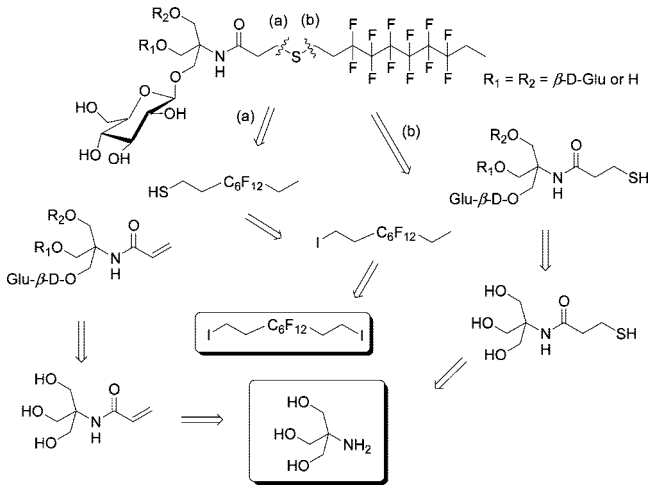
However, because the synthesis of the polar head of HF-TAC involves radical polymerization and leads to inevitable polydispersity, batch-to-batch variations can be observed. In order to circumvent this problem, we have thus synthesized hemifluorinated surfactants with chemically defined polar heads derived either from aminoxide[15] or lactose.[16] (Figure 1) The hemifluorinated zwitterionic aminoxide (HF-AO) was found to significantly decrease MPs stability, while hemifluorinated lactobionamide derivative (HF-Lac) was found to be much more efficient in keeping several MPs water-soluble and active. Interestingly, we underlined the inactivation character of the hydrogenated dodecyl homologue of HF-Lac, H_{12}-Lac, compared to dodecyl maltoside (DDM). This shows that the lactobionamide head and thus its galactose moiety are not particularly favorable to protein stability and leaves open the perspective of optimizing tail/head combinations so as to obtain yet milder fluorinated or hemifluorinated surfactants.

Thus we synthesized and examined the hemifluorinated (HF-Malt) analogue of this widely used detergent DDM.[17] The integrity of bacteriorhodopsine and cytochrom b_6f complex, as protein tests solubilized in this fluorinated surfactant, was investigated, and these two MPs were found in their native state and as active as in DDM. Their stability over time was either comparable to or higher than that in DDM. However, HF-Malt form large and polydisperse aggregates, which could be rod-like, disk, or cylindrical assemblies. Such aggregate formation seems to affect the nature of their complexes with MPs, causing a serious drawback for further studies. Indeed, having preparation homogeneous in size is a prerequisite for any functional and structural study of the protein: manipulating membrane proteins can lead to aggregation, dissociation, oligomerization, etc., and it is thus important to be able to check the homogeneity of the protein. If the heterogeneity of the sample is induced by the surfactant, we lose a precious means of monitoring the oligomeric state of the protein. Furthermore, no structural studies can be undertaken in these conditions.

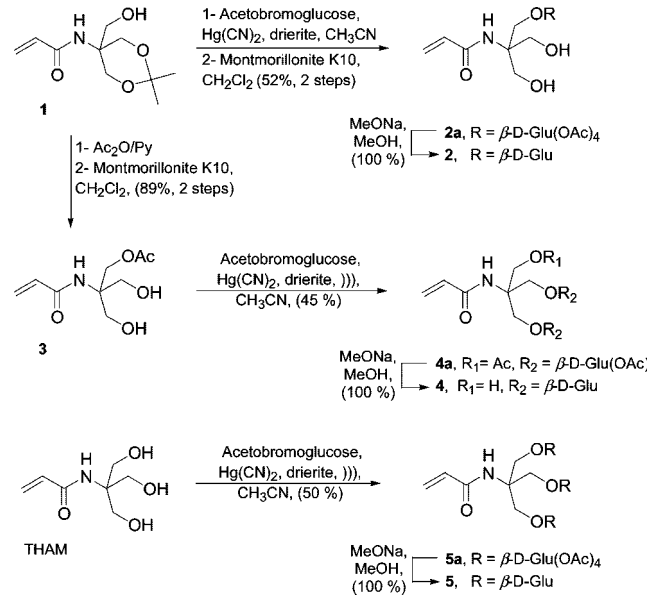
Therefore, these first results show that the use of fluorinated tails holds for various types of polar heads and also stress the impact of the volumetric ratio between the polar head and the hydrophobic tail of the FS on the micellar structure formed. Indeed, when comparing the chemical structures and physical-chemical properties of compounds of the HF-TAC, HF-Lac, and HF-Malt series and keeping in mind Israelachvili's concept[18] linking the nature of the aggregate formed by a surfactant to the volumetric ratio between its polar head and its hydrophobic tail, one is led to conclude that the introduction of a bulkier polar head for (hemi)fluorinated surfactants should induce an increase of the interfacial curvature of the aggregates and thus favor the formation of small and monodisperse micelles rather

(6) Pucci, B.; Maurizis, J. C.; Pavia, A. A. *Eur. Polym. J.* **1991**, *27*, 1101–1106.
(7) Chabaud, E.; Barthelemy, P.; Mora, N.; Popot, J. L.; Pucci, B. *Biochimie* **1998**, *80*, 515–530.
(8) Barthelemy, P.; Tomao, V.; Selb, J.; Chaudier, Y.; Pucci, B. *Langmuir* **2002**, *18*, 2557–2563.
(9) Mukerjee, P. *Colloids Surf., A* **1994**, *84*, 1–10.
(10) Nakano, T. Y.; Sugihara, G.; Nakashima, T.; Yu, S. C. *Langmuir* **2002**, *18*, 8777–8785.
(11) Barthelemy, P.; Ameduri, B.; Chabaud, E.; Popot, J. L.; Pucci, B. *Org. Lett.* **1999**, *1*, 1689–1692.
(12) Breyton, C.; Chabaud, E.; Chaudier, Y.; Pucci, B.; Popot, J. L. *FEBS Lett.* **2004**, *564*, 312–318.
(13) Park, K. H.; Berrier, C.; Lebaupain, F.; Pucci, B.; Popot, J.-L.; Ghazi, A.; Zito, F. *Biochem. J.* **2007**, *403*, 183–187.
(14) Palchevskyy, S. S.; Posokhov, Y. O.; Olivier, B.; Popot, J. L.; Pucci, B.; Ladokhin, A. S. *Biochemistry* **2006**, *45*, 2629–2635.
(15) Chaudier, Y.; Zito, F.; Barthelemy, P.; Stroebel, D.; Ameduri, B.; Popot, J.-L.; Pucci, B. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1587–1590.
(16) 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.
(17) Polidori, A.; Presset, M.; Lebaupain, F.; Ameduri, B.; Popot, J.-L.; Breyton, C.; Pucci, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5827–5831.
(18) Israelachvili, J. M., D.; Ninham, B. J. *Biochim. Biophys. Acta* **1977**, *470*, 185–201.

SCHEME 1. Retrosynthetic Routes for Hemifluorinated Surfactants



SCHEME 2. Synthesis of THAM Derivatives



than rod-like or cylindrical micelles. Smaller and well-defined surfactant aggregates should lead to monodisperse MP/surfactant complexes, while preserving if not improving the useful biochemical properties exhibited thus far by fluorinated surfactants.

This led us to design a new class of surfactants that would make it possible to easily tune the polar head/hydrophobic tail volumetric ratio of the surfactant in order to study its effect on the physical-chemical properties. We chose THAM as the basic structure for the polar head synthesis where one, two, or three glucose moieties, respectively, were grafted on the hydroxyl groups. The hemifluorinated hydrophobic chain was synthesized from 1,10-diiodo-3,3,4,4,5,5,6,6,7,7,8,8-dodefluorodecane and was linked to the polar head through a thioether bond leading to a new series of hemifluorinated surfactants having different volumetric ratios. For the sake of comparison, perfluorinated and hydrogenated analogues were also synthesized following the same synthetic route. 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 reverse-phase chromatography.

Results

Synthesis. Our convergent synthetic strategy relies on the formation of the C−S bond of the surfactant. This thioether bond links the polar headgroup to the hydrophobic chain, and its formation is considered as the key step in this synthesis. Retrosynthetically, such a bond can be disconnected at two positions (Scheme 1). The first strategy involves the condensation of a hemifluorinated thiol onto an acrylamide-type polar head, which is easily obtained from THAM. Hemifluorinated thiol, structurally made of a fluorinated core end-capped with an ethyl and a thiol ethyl groups, is prepared from the monoiodide hemifluorinated chain. On the other hand, the second strategy involves the condensation of a thiol-derived polar head on the hemifluorinated monoiodide compound. Condensation of mercaptopropionic acid on tris(hydroxymethyl)-aminomethane (TRIS) followed by selective glucosylation led to the thiol-derived polar head.

(1) First Strategy. Synthesis of THAM-Derived Polar Head. The synthesis of THAM glucosylated derivatives required selective protections of the hydroxyl groups. Two hydroxyl groups of THAM[1] were protected by reaction with the 2,2-dimethoxypropane as previously published[20] to lead after purification to compound **1**. Grafting of the β-D-glucose was performed following the Helferich's method[21] using tetra-*O*-acetyl-D-glucopyranosyl bromide, previously prepared according to the Rosevear's method.[22] Then, hydrolysis of the 1,3-acetonide in the presence of Montmorillonite K10 led to monoglucosylated compound **2a**. Acetylation of **1** followed by removal of 1,3-acetonide under acidic condition led to compound **3**. Diglucosylation of compound **3** was performed in the presence of an excess of tetra-*O*-acetyl-D-glucopyranosyl bromide under ultrasonic activation leading to compound **4a**. We previously reported that the synthesis of THAM galactosylated derivatives using the Helferich method was improved under ultrasounds conditions.[23] Furthermore, the application of ultrasound was found to increase the solubilization of the reagents and the reaction was almost immediate. Finally, THAM bearing three β-D-glucose moieties **5a** was obtained by a direct glucosylation of THAM under ultrasounds activation. As it was expected, the synthesis of the tetra-*O*-acetyl-glucosylated tris polar head was achieved in good overall yields from THAM of 38%, 27%, and 50% for compounds **2a**, **4a**, and **5a**, respectively. Finally, removal of the acetyl protective groups was performed under Zemplén[24] conditions and afforded compounds **2**, **4**, and **5** in quantitative yields.

Synthesis of Hemifluorinated Thioacetate. The second part of the synthesis represents the major task. It consists of the preparation of the nonsymmetrical hemifluorinated thiol made of a fluorinated core and bordered by an ethyl and a thiol ethyl groups. As previously described, the bis monoethylenation of diiodoperfluorohexane[25] led to 1,10-diiodo 3,3,4,4,5,5,6,6,7,7,8,8

(19) Jedlinsky, J.; Paprotivy, J. *Rocz. Chem.* **1966**, *40*, 1487–1491. Pucci, B.; Maurizis, J. C.; Pavia, A. A. *Eur. Polym. J.* **1991**, *27*, 1101–1106.

(20) Polidori, A.; Braun, O.; Mora, N.; Pucci, B. *Tetrahedron Lett.* **1997**, *38*, 2475–2478.

(21) Helferich, B.; Zimmer, J. *Chem. Ber.* **1962**, *95*, 2604–2611.

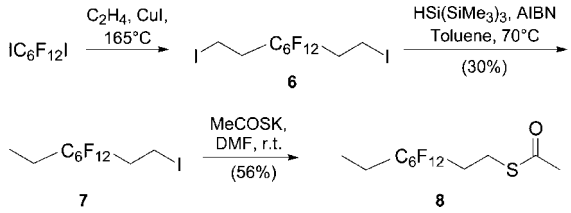
(22) Rosvear, P.; Vanken, T.; Baxter, J.; Miller, S. F. *Biochemistry* **1980**, *19*, 4108–4115.

(23) Polidori, A.; Pucci, B.; Maurizis, J. C.; Pavia, A. A. *New J. Chem.* **1994**, *18*, 839–848.

(24) Zemplen, G. *Chem. Ber.* **1927**, *60*, 1555–1564.

(25) Manseri, A.; Ameduri, B.; Boutevin, B.; Kotora, M.; Hajek, M.; Caporiccio, G. *J. Fluorine Chem.* **1995**, *73*, 151–158.

SCHEME 3. Synthesis of Hemifluorinated Thioacetate



dodecafluorodecane **6**, which was chosen as starting material for the synthesis of the commercially unavailable hemifluorinated thiol[11] (Scheme 3).

The first step involves a selective monoreduction of one iodide using $HSi(SiMe_3)_3$, in the presence of a catalytic amount of AIBN as radical initiator, affording after purification on silica gel pure 1-iodo 3,3,4,4,5,5,6,6,7,7,8,8 dodecafluorodecane **7** (30%), pure unreacted diiodo compound **6** (40%), and a small amount of bis reduced compound (10%). The remaining diiodo compound **6** can be recovered and reused to complete the reaction. It should be noted that the use of $HSi(SiMe_3)_3$ was preferred to Bu_3SnH. The use of the latter reducing agent suffers from several drawbacks such as the well-known toxicity[26] of the tributyltin-containing compounds, as well as the difficulties concerning the purification of such tin derivatives.

The second step in the synthesis of the hemifluorinated part consists in the conversion of the iodide into a thiol. A rapid search in the literature shows that monohalide compounds react with thiourea[27] to afford after hydrolysis the corresponding thiol; however, some previous experiments have revealed the weak reproducibility of this method (yields ranging between 17% and 90%).[28,29] Moreover, some other alternative routes to generate perhydrogenated or perfluorinated alkanethiols from their corresponding halides, using either thiolacetic acid[30] or potassium thioacetate,[31] have been largely described in the literature. In our case, monoiodide compound reacted with potassium thioacetate (1.5 equiv) in anhydrous DMF and afforded the desired compound **8** (56%). It has to be underlined that the use of a larger excess of potassium thioacetate led to secondary reactions (possibly elimination reactions due to the acidity of the methylene linked to perfluoroalkyl moiety) and subsequently decreased the yield to 30%. In addition to the good yield of formation of the thioacetate derivatives, the presence of the acetyl as protecting group of thiol is at the same time appreciated since thiols are extremely vulnerable to oxygen and can be easily oxidized in sulfoxide in the presence of very low traces of O_2. Furthermore, thioacetate can be quickly converted into corresponding thiol under the Zemplén[24] conditions.

Thioether Bond Formation. The synthesis of hemifluorinated thioether galactosylated surfactants using radical condensation has already been published.[23] However, radical condensations of alkane thiol onto acrylamide require a large excess of thiol (3 equiv) to get satisfactory yields. Taking into account the difficulties to synthesize hemifluorinated thiol, the radical condensation presents some limitations concerning large scale synthesis. In a first attempt at overcoming this problem, we used radical condensation of the hemifluorinated thiol and monoglucosylated THAM **2a** in equimolar conditions. Unfortunately only a low yield was obtained in such condition (9%). So instead of using thiol consuming radical condensation, we chose to use the Michael acceptor character of acrylamide to react with nucleophilic hemifluorinated thiol.

Michael reaction is commonly carried out using acid catalysts[32] or Lewis acids[33] or under alkaline conditions.[34] While the acidic mediums were found to give satisfactory results, they cannot be applied in the presence of acetal functions such as *O*-glucosyl. On the other hand, thiols are known to be sensitive to basic media as a result of the formation of disulfide bonds leading to a decrease of the yield. Moreover, as stated above, due to the acidic character of the hydrogen vicinal to the fluorinated core, fluorinated thiols are highly vulnerable to bases. Thus, performing the Michael reaction in basic medium seemed to be a limited solution. Fall et al.[35] pointed out the ability of the one-step reduction/alkylation of thioacetate compounds, using NaOH and $NaBH_4$ in EtOH, to afford the corresponding thioether in very good yield.

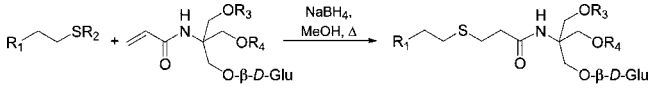
Despite the fact that our work is essentially devoted to the synthesis of the hemifluorinated surfactants and taking into consideration the difficulties concerning the synthesis of the hemifluorinated thioacetate, we performed the first attempts using the perfluorinated one ($C_6F_{13}CH_2CH_2SCOCH_3$), which was prepared from the commercially available $C_6F_{13}CH_2CH_2I$ in one step with 75% yield (see Supporting Information for further details). A first attempt using 1 equiv of perfluorinated thioacetate and compound **2** using the method of Fall et al. led to the desired compound **9** but in a low yield (9%). Compared to the high yields reported by these authors, we assumed that basic conditions (NaOH) might be responsible to the fluorinated thiol degradation. Furthermore the use of other bases such as TEA or KOH did not improve significantly the yield (20−24%). Therefore we applied the same experimental conditions as previously reported, including some modifications in the process: (i) the use of $NaBH_4$ without any additional base and (ii) the use of methanol as solvent. In these conditions the yield was improved and compound **9** was isolated with 60% yield (Scheme 4).

Thus, the condensation of perfluorothioacetate on mono-, di-, or triglucosylated THAM derivatives **2**, **4**, or **5** provided the desired compounds **9**−**11** with satisfactory yields ranging between 52% and 60%. In comparison to the yield obtained using Fall's method and those obtained with different bases, these results encouraged us to apply this method to the hemifluorinated series. Even with hemifluorinated compounds the yields were in the same range (44% and 60%, respectively, for di- and triglucosylated THAM). Finally, to extend our physical-chemical investigation, hydrogenated analogues were also synthesized following the same synthetic route. However the synthesis of the hydrogenated analogues was directly carried out using the commercially available decanethiol and dodecanethiol, demonstrating the extent of this procedure.

All of the amphiphilic compounds were purified by Sephadex LH-20 size exclusion chromatography and most of them by C18

(26) Boyer, I. J. *Toxicology* **1989**, *55*, 253–298.
(27) Brace, N. O. U.S. Patent 3,172,910, 1965.
(28) Chaudier, Y., Thesis, Université d'Avignon et des Pays de Vaucluse, France, 2002.
(29) Olivier, B., Thesis, Université d'Avignon et des Pays de Vaucluse, France, 2004.
(30) Naud, C.; Calas, P.; Blancou, H.; Commeyras, A. *J. Fluorine Chem.* **2000**, *104*, 173–183.
(31) Hong, H. G.; Park, W. *Langmuir* **2001**, *17*, 2485–2492.
(32) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M.; Ghaderi, A. *J. Mol. Catal., A* **2006**, *249*, 98–102.
(33) Alam, M. M.; Varala, R.; Adapa, S. R. *Tetrahedron Lett.* **2003**, *44*, 5115–5119.
(34) Martinelli, M. J.; Vaidyanathan, R.; Khau, V. V.; Staszak, M. A. *Tetrahedron Lett.* **2002**, *43*, 3365–3367.
(35) Fall, Y.; Diouf, O.; Gomez, G.; Bolano, T. *Tetrahedron Lett.* **2003**, *44*, 6069–6072.

SCHEME 4. Thioether Bond Formation



Compound	R_1	R_2	R_3	R_4	Yield (%)	Name[b]
9[a]	C_6F_{13}	$COCH_3$	H	H	9	F_6-Monoglu
9	C_6F_{13}	$COCH_3$	H	H	60	F_6-Monoglu
10	C_6F_{13}	$COCH_3$	Glu	H	55	F_6-Diglu
11	C_6F_{13}	$COCH_3$	Glu	Glu	52	F_6-Triglu
12	$C_2H_5C_6F_{12}$	$COCH_3$	Glu	H	44	H_2F_6-Diglu
13	$C_2H_5C_6F_{12}$	$COCH_3$	Glu	Glu	60	H_2F_6-Triglu
14	C_8H_{17}	H	Glu	H	51	H_{10}-Diglu
15	C_8H_{17}	H	Glu	Glu	57	H_{10}-Triglu
16	$C_{10}H_{21}$	H	Glu	H	53	H_{12}-Diglu
17	$C_{10}H_{21}$	H	Glu	Glu	44	H_{12}-Triglu

[a] Reaction performed following Fall et al.[35] experimental conditions. [b] See the physical-chemical characterization section below for further details.

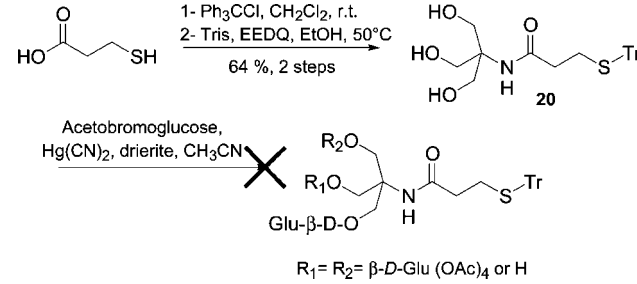
reverse-phase HPLC and then lyophilized to give pure surfactants as white powder. They were fully characterized by ^1H, ^{13}C, ^{19}F, DEPT, and HMQC NMR experiments as well as high resolution mass spectrometry, allowing the observation of characteristic adducts (see Supporting Information). The purity of the samples was checked by RP-HPLC and was higher than 98%.

In the aim to study the role of the methanol in such one-pot alkylation, two experiments using fluorinated thioacetate ($C_6F_{13}CH_2CH_2SCOCH_3$) and commercially available benzyl bromide in either methanol or acetonitrile as solvent were performed in the presence of $NaBH_4$ (1.5 equiv). Whereas the reaction in methanol afforded the desired compound in a very good yield (91%), only unreacted starting materials were recovered after 48 h of reflux in acetonitrile. Furthermore, we found that the reaction of $C_6F_{13}CH_2CH_2SH$ with benzyl bromide in acetonitrile afforded the desired compound (86%). Finally, the reaction of $C_6F_{13}CH_2CH_2SH$ with benzyl bromide in methanol without using $NaBH_4$ did not lead to the thioether bond formation. These latter experiments clearly demonstrate that the methanol in the presence of $NaBH_4$ is capable of transesterification of the thioacetate group, yielding therefore to the thiol, which is subsequently converted in thiolate due to the excess of $NaBH_4$.

(2) Second Strategy. Despite the success of the first strategy, we also investigated an alternative synthetic route using 3-mercaptopropionic acid and TRIS as starting materials. The thiol group was first protected by reaction with triphenylmethylchloride in dichloromethane, and then TRIS was grafted through an amide bond onto the protected 3-mercaptopropionic acid in the presence of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoleine (EEDQ) in refluxing ethanol.[36] Nevertheless, glycosylation of the hydroxyl groups under the same conditions used in the first strategy using $Hg(CN)_2$ was not possible. The triphenylmethyl group as well as most of the commonly used thiol protecting groups are usually cleavable in the presence of strong acids. During the glucosylation reaction under ultrasound

(36) Sharma, K. S.; Durand, G.; Giusti, F.; Olivier, B.; Fabiano, A.-S.; Bazzacco, P.; Dahmane, T.; Ebel, C.; Popot, J.-L.; Pucci, B. *Langmuir*Accepted for publication.

SCHEME 5. Synthesis of Thiol-Derived Polar Head



activation we observed that the thioether bond was partially cleaved, suggesting that even mild Lewis acid catalysis such as $Hg(CN)_2$ are able to deprotect trityl groups. Furthermore, in addition to the consumption of $Hg(CN)_2$ in the deprotection reaction, the formation of the thiol at this step leads to other secondary thioglucosylation reactions. Currently, the use of acetyl group as protective agent of mercapto propionic acid derivatives and their one-pot mild reduction/alkylation with 1-iodo-3,3,4,4,5,5,6,6,7,7,8,8-dodecafluorodecane **7** in the presence of $NaBH_4$ is under investigation as an alternative synthetic route.

Physical-Chemical Characterization. All fluorinated surfactants were labeled by F_6, according to the number of fluorinated carbons of the hydrophobic chain followed by Mono-, Di-, or Triglu according to the nature and number of sugar moieties grafted onto the polar head. In order to differentiate perfluorinated surfactants from their hemifluorinated analogues, "H_2" was added to the given name of these latter surfactants, indicating the presence of an ethyl tip. Perhydrogenated surfactants were labeled by H_n, where n indicates the number of the hydrogenated carbons in the corresponding thiol starting material, followed by the nature of the polar head as described for fluorinated surfactants. All surfactants were very soluble in water up to at least 4−5 mM at room temperature, and the solutions were very clear (4−5 mM is the maximum concentration used for the physical-chemical assays; however, it does not reveal the maximum solubility of the surfactants). Only H_{12}-Diglu and H_{12}-Triglu at 5 mM were subjected to heating at 50 °C for 10−20 min in order to complete solubilization and then kept at room temperature at least 12 h before any physical-chemical measurement. In these conditions, both H_{12}-surfactant solutions remain clear after cooling at room temperature and no precipitation was observed.

(a) Surface Tension Measurement. The surface tension data are summarized in Table 1, and the curves for diglucosylated surfactants are represented in Figure 2. From this technique we determined different parameters: (i) the critical micellar concentration (CMC); (ii) the surface tension attained at the CMC (γ_{CMC}); (iii) the concentration of surfactant in the bulk phase that produces a reduction of 20 mN/m in the surface tension of the solvent (C_{20}) and its corresponding logarithm pC_{20}, which measure the adsorption efficiency; (iv) the surface excess concentration at the CMC (Γ_{max}), which measures the maximum concentration of adsorbed species; (v) the minimum area occupied by a surfactant at the air/water interface at the CMC when the surface is saturated (A_{min}); and (vi) the ratio CMC/C_{20} measuring the relative effect of structural or microenvironemental factor on micellization and on adsorption.

As frequently reported,[37,38] for a given polar head the addition of two methylene to the hydrocarbon chain of a surfactant usually decreases 5−15 times the CMC. Such a rule is followed

TABLE 1. Surface Active Data[a]

surfactant	CMC (mM)	γ_{CMC} (mN/m)	A_{min}[b] (Å^2)	Γ_{max} 10^{-12} (mol/mm^2)[b]	C_{20} 10^{-3} (mM)[c]	pC_{20} [d]	CMC/C_{20}	log k'_W
F_6-Monoglu	0.113 ± 0.006	18.3 ± 0.6	52.7 ± 1.5	3.13 ± 0.07	1.37 ± 0.06	2.86	82.8	5.2
F_6-Diglu	0.233 ± 0.012	28.3 ± 0.6	97.5 ± 2.1	1.79 ± 0.14	1.54 ± 0.37	2.81	151.8	4.8
F_6-Triglu	0.947 ± 0.042	32.3 ± 0.6	114.0[e]	1.46[e]	4.60[e]	2.34	205.9	4.7
H_2F_6-Diglu	0.347 ± 0.029	36.0 ± 1.0	104.5 ± 2.5	1.50 ± 0.13	5.4 ± 2.7	2.27	64.3	4.9
H_2F_6-Triglu	0.747 ± 0.084	36.0 ± 3.6	131.5 ± 14.8	1.47 ± 0.57	6.6 ± 1.6	2.18	112.8	4.7
H_{12}-Diglu	0.039 ± 0.001	40.7 ± 2.3	102.7 ± 10.1	1.61 ± 0.17	3.4 ± 0.4	2.47	11.5	5.6
H_{12}-Triglu	0.102 ± 0.007	41.5 ± 0.7	125.0 ± 17.0	1.34 ± 0.18	5.00 ± 0.17	2.30	20.4	5.4
H_{10}-Diglu	0.555 ± 0.005	36.0 ± 1.4	92.0 ± 17.0	1.84 ± 0.33	17.5 ± 6.7	1.76	31.8	4.4
H_{10}-Triglu	1.175 ± 0.037	38.5 ± 2.1	107.7 ± 6.4	1.55 ± 0.09	22.5 ± 15.4	1.65	52.3	4.2

[a] Data presented are the average of two or three experiments except when noted otherwise. [b] A_{min} and Γ_{max} were estimated from the slope of the surface tension curve. [c] C_{20} values were obtained by extrapolation of the surface tension versus log C to 52 mN/m. [d] pC_{20} = −log C_{20}. [e] Data from one experiment only.

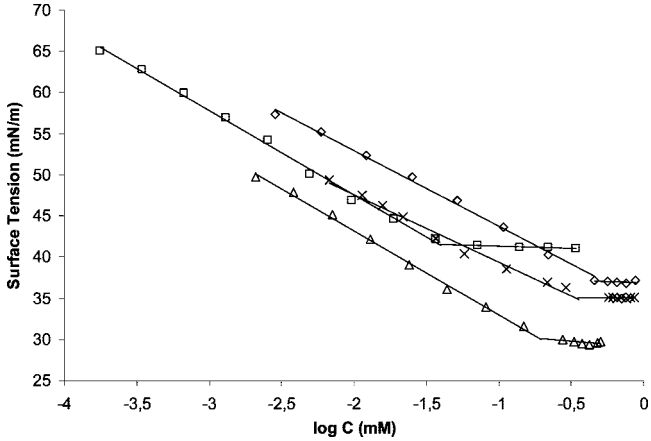


FIGURE 2. Surface tensions versus log CMC plot for H_{10}-Diglu (◇), H_{12}-Diglu (□), H_2F_6-Diglu (×), and F_6-Diglu (Δ).

by hydrogenated di- and triglucosylated surfactants. However, hemifluorinated surfactants do not follow the same rule. H_2F_6-Diglu, despite the additional ethyl tail, exhibits a CMC (0.347 mM) close to that of the F_6-Diglu (0.233 mM). A similar trend was observed with F_6-Triglu and H_2F_6-Triglu (0.947 and 0.730 mM, respectively), which is in perfect agreement with our previous observations.[11,16] Fluorocarbon surfactants are known to exhibit CMCs lower than those of their hydrocarbon analogues.[39,40] On an other hand, we noted herein that increasing the number of glucose moieties induces an increase of the CMC. Thus, the CMC of F_6-Triglu is ∼8 times higher than that for F_6-Monoglu; nevertheless the CMC of F_6-Diglu is only 2 times higher than that measured for F_6-Monoglu. Finally, whatever the nature of the hydrophobic chain, the general trend is that the CMC for Triglu derivatives is 2−4 times higher than that of the Diglu compounds.

Limit surface tensions (γ_{CMC}) of surfactants are known to decrease with increasing fluorine content of the hydrophobic chain, the result of a higher order of packing of the fluorocarbon layer at the air/water interface.[40] In agreement with this observation H_{10}- and H_{12}-Diglu and Triglu compounds exhibited γ_{CMC} values higher than those of F_6 derivatives. For a given polar head, γ_{CMC} for the hemifluorinated surfactants is between those of the hydrogenated and perfluorinated surfactants as previously observed[16] confirming the particular properties of ethyl-ended fluorinated surfactants. It has also to be underlined that an increase of the polar head size (demonstrated by an evolution of the surface area per molecule at the air/water interface, A_{min}) induces a significant increase of the limit surface tension for F_6 compounds, as observed with F_6-Monoglu and F_6-Diglu. Such a phenomenon could be explained by an increase of the gap between fluorocarbon chains at the air/water interface.

The results for Γ_{max} and the surface area per molecule A_{min} were estimated from the slope of the surface tension curves. A_{min} gives information about the space that every molecule needs to accommodate at the air/water interface. For a given polar head (Di- or Triglu, for instance), the length and the nature of the hydrophobic chain have almost no effect on Γ_{max}, whereas for a given chain the surface concentration Γ_{max} decreases as the size of the headgroup increases. For instance, F_6-Monoglu has the highest surface concentration and this value significantly decreases as the number of glucose increases. An opposite trend is obviously observed regarding A_{min}. When comparing the values obtained for the hemifluorinated derivatives with those of the perfluorinated ones, it appears that the occupied area per molecule is slightly higher when adding the ethyl tip, as we previously observed,[16,17] and subsequently the surface concentration is slightly lower.

The efficiency of the surfactant is defined by the value of the negative logarithm of the bulk concentration necessary to reduce its surface tension by 20 mN/m and is designed by pC_{20}. The values listed in Table 1 clearly show that the efficiency of a hydrocarbon or fluorocarbon surfactant increases by increasing the length of the hydrophobic chain and decreases by increasing the volume of the polar head. However, the efficiency of H_2F_6-surfactants do not follow the same trend as we can observe with Diglu-surfactants where the value of pC_{20} of the F_6-surfactant drops from 2.81 to 2.27 with the addition of the ethyl tip (similar behavior was observed for Triglu-surfactants). Finally, we determined the CMC/C_{20} ratio.[41] This ratio gives information about which of the micellization or the adsorption phenomenon at the air/water interface is favored. Usually, an increase in the CMC/C_{20} ratio indicates that adsorption phenomenon is more facilitated than micellization (or micellization more inhibited than adsorption). Table 1 shows that CMC/C_{20} ratio increases when replacing the hydrogen chain by a fluorinated chain and/or with the introduction of a bulkier hydrophilic head. However, for a given polar head, it decreases with increasing the hydrogenated chain length.

(b) Dynamic Light Scattering. All measurements were taken at a concentration at least 4 times above the CMC of the

(37) Zhang, T.; Marchant, R. *J. Colloid Interface Sci.* **1996**, *177*, 419–426.
(38) Shinoda, K.; Hato, M.; Hayashi, T. *J. Phys. Chem.* **1972**, *76*, 909–914.
(39) Sadtler, V. M.; Guilleri, F.; Krafft, M. P.; Riess, J. G. *Chem. Eur. J.* **1998**, *4*, 1952–1956.
(40) Kissa, E. *Fluorinated Surfactants: Synthesis, Properties, Applications*; Dekker: New York, 1994; Vol. 7.
(41) Rosen, M. J. *Surfactants and Interfacial Phenomenon*; John-Wiley: New York, 1989.

TABLE 2. Size of Aggregates in Aqueous Solutions

surfactant	D_H[a] (nm)	% vol[b]	HHW[c] (nm)	concn (mM)
F_6-Monoglu	25.3	99.8	34.8	4
F_6-Diglu	5.8	99.8	1.3	4
F_6-Triglu	5.1	99.7	1.2	4
H_2F_6-Diglu	6.5	99.9	1.6	5
H_2F_6-Triglu	5.1	99.3	1.4	5
H_{12}-Diglu	5.9	99.9	1.4	5
H_{12}-Triglu	5.2	99.9	1.2	5
H_{10}-Diglu	5.4	100	1.3	5
H_{10}-Triglu	4.5	100	1.2	5

[a] D_H: hydrodynamic diameter of particles of the main peak. The values reported are the average of 10 runs. [b] Volume particle size distribution. [c] HHW, the width of the peak at half-height, an indication of the degree of polydispersity of the aggregates.

corresponding surfactant. Stock solutions were stored at room temperature overnight before measurements. The values recapitulated in Table 2 show that all surfactants bearing two or three glucose moieties, despite the nature of the hydrophobic chain or its length, self-organize in water into well-defined monodisperse particles (see Figures S38−S40, Supporting Information) with apparent hydrodynamic diameters ∼5−6 nm as expected for globular micelles.[42] Nevertheless, the diameter of the particles formed by the Triglu compounds is 12−22% lower than that found for the Diglu compounds. Only F_6-Monoglu self-aggregates into larger and polydisperse micelles (diameter ∼25 nm). Since F_6-Monoglu gives large and polydisperse micelles, there was no need for the synthesis of its hemifluorinated analogue.

(c) log k'_W Determination. Table 1 reports values of log k'_w, a parameter closely related to the molecule's water/octanol partition coefficient, which can be obtained from reverse-phase HPLC.[43] This parameter is usually considered to reflect the hydrophobic character of the surfactant, and we previously found that the volume and/or the nature of the polar group have only a low impact on this parameter.[44] Indeed, H_{10}-Diglu and H_{10}-Triglu exhibit similar log k'_w values, whereas those of the H_{12} are significantly higher. The addition of the ethyl tip at the end of the fluorinated chain does not affect significantly the hydrophobicity of the surfactant, as we can observe in the case of F_6-Diglu and H_2F_6-Diglu (log $k'_w = 4.8$ and 4.9, respectively). Furthermore, whereas H_{10}-Diglu and H_2F_6-Diglu can be considered as having the same hydrophobic chain length (10 C up to the sulfur group), the hemifluorinated surfactant exhibits a higher log k'_w value and therefore appears to be more hydrophobic than its hydrogenated analogue (4.4 and 4.9, respectively). Similar observation was noted with the TriGlu surfactants (4.2 and 4.7, respectively, for H_{10}-Triglu and H_2F_6-Triglu). By the same token, we observed that to a given polar head, even though perfluorinated F_6 surfactants have a shorter hydrophobic chain, they exhibit a higher log k'_W, such a behavior of the fluorinated surfactants is conformable to previous observations on other series of surfactants.[16]

Discussion

Synthesis. We described herein the synthesis of a new class of hemifluorinated glucose-based surfactants derived from THAM. The synthesis is based on a one-pot reduction/alkylation of a hemifluorinated thioacetate (using $NaBH_4$ in methanol) and THAM derivatives. The interest of this procedure and the modifications we brought about lie in three major points: (i) the mildness of this Michael addition that avoids using bases that can be aggressive toward thiol such as fluorinated ones; (ii) the role of $NaBH_4$/MeOH, which can avoid secondary reactions such as oxidation or disulfide bond formation and lead to the formation of the thiolate in situ; (iii) finally, the efficient thioether bond formation that can be performed with a slight excess (1.2−1.5 equiv) of acryloyl monomer, allowing us to circumvent the necessity of a large excess (3 equiv) of thiol as required in radical condensations.[23] Following the same strategy, the syntheses of the perfluorinated and hydrogenated analogues were also achieved in satisfactory yields.

Physical-Chemical Characterization. Three different parameters were considered for the study of the physical-chemical properties of this novel series: determination of the surface activity (CMC, the limit surface tension γ_{CMC}, and the occupied area per surfactant molecule A_{min}); determination of log k'_W, which is correlated to the hydrophobic character of the surfactant, and finally, determination of the size of the supra-molecular assemblies formed in aqueous solution. The physical-chemical properties recorded were in agreement to previous observations on other series of hydrogenated, fluorinated, and hemifluorinated surfactants.[16,17]

Effect of the Sulfur Atom. It is important to note that a sulfur atom inserted within the hydrophobic chain of a surfactant is usually considered as a hydrophobic unit. Evidence for this assertion comes from the unfavorable affinity toward water of the sulfur atom owing to its poor hydrogen bond acceptor properties[45] and the Hansch[46] partition constant between octanol and water (i.e., $\pi = 0.45$ and -0.47 for the SCH_3 and OCH_3 group, respectively). The sulfide group might be considered as a methylene regarding its behavior in aqueous media. For instance, the CMC of *n*-octyl-β-D-glucopyranoside is in the range of 20−25 mM, whereas its thio analogue, the *n*-octyl-β-D-thioglucopyranoside, exhibits a CMC value of 9 mM that is close to the CMC of the *n*-nonyl-β-D-glucopyranoside (6.5 mM).[47] Furthermore, Menger and co-workers [48,49] found that the insertion of a sulfide group causes an increase in the CMC, the magnitude of which depends on the position of the sulfur atom. In our case, as the location of the sulfur atom remains constant for the whole series, distant by only two methylenes from the polar head, we consider the thioether unit as a part of the hydrophobic entity. Thus, the hydrogenated (H_{10} and H_{12}), the perfluorinated, and the hemifluorinated surfactants presented in this article have to be considered bearing a hydrophobic chain made of the alkyl group as well as the sulfur atom and the two methylene from the THAM.

Comparison of Contributive Effects of the Hydrogenated and the Fluorinated Chains. While the addition of an ethyl tail to a hydrogenated surfactant decreases (∼10 times) the CMC value without affecting the γ_{CMC}, the substitution of hydrogen to fluorine results in lowering significantly both the CMC and the γ_{CMC} at a constant chain length. This has been explained by the larger absolute value of the free energy of micellization for a fluorinated compound.[16,50] Moreover, as the energy of

(42) Zana, R. *Colloids Surf. A* **1997**, *123−124*, 27–35.
(43) Braumann, T. *J. Chromatogr., A* **1986**, *373*, 191–225.
(44) Durand, G.; Poeggeler, B.; Boeker, J.; Raynal, S.; Polidori, A.; Pappolla, M. A.; Hardeland, R.; Pucci, B. *J. Med. Chem.* **2007**, *50*, 3976–3979.
(45) Allen, F. H.; Bird, C. M.; Rowland, R. S.; Raithby, P. R. *Acta Crystallogr., Sect. B* **1997**, *B53*, 696–701.
(46) Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971**, *71*, 525–616.
(47) Wenk, M. R.; Seelig, J. *Biophys. J.* **1997**, *73*, 2565–2574.
(48) Menger, F. M.; Shi, L. *J. Am. Chem. Soc.* **2006**, *128*, 9338–9339.
(49) Lundberg, D.; Shi, L.; Menger, F. M. *Langmuir* **2008**, *24*, 4530–4536.

transfer to the air/water interface becomes more favorable with fluorinated derivatives, the pressure of the film at the CMC becomes higher. The effect of the polar head size on A_{min} and Γ_{max} is obviously demonstrated when we compare the Diglu and Triglu hydrogenated and fluorinated compounds. The efficiency parameter (pC_{20}) of the fluorinated series increases with the order F_6-Triglu < F_6-Diglu < F_6-Monoglu, demonstrating that the proneness to adsorb at the air/water interface increases with the hydrophobic character of the molecule. This is dramatically confirmed with the values recorded for the Diglu compounds, 2.81, 2.47, and 1.76 for the F_6, H_{12}, and H_{10} chains, respectively. As an evaluation of the hydrophobic character of surfactants, the log k'_W parameter has also been used.[16,51,44,52] Logically, the values of log k'_W increase with the length of the chain, and thus H_{10} derivatives exhibit values of log k'_W lower than those of H_{12} ones, while as previously reported, the volume and/or the nature of the polar group have only a low impact. This is confirmed by the much closed values exhibited for H_{10}-Diglu and H_{10}-Triglu (the same observation was made for H_{12} and F_6 derivatives).

Atypical Behavior of Hemifluorinated Surfactants. The hemifluorinated surfactants exhibit atypical behavior when compared to the H- or F-surfactants in several respects: (i) Whereas an increase of the hydrophobic chain length induces a decrease of the CMC, we observed that hemifluorinated surfactants display CMC values very similar to those of their fluorocarbon analogues devoid of ethyl tip. Similar observations have already been made for the TAC, the Lac, and the Malt series.[11,16,17] (ii) The limit surface tension values are between the expected much lower values of the fluorinated compounds and the higher values of the hydrogenated ones. (iii) Whereas the efficiency parameter would be expected to dramatically increase as the fluorine content of the chain increase or as the chain length increase, the H_2F_6 compounds exhibit intermediate values. (iv) Finally, despite the addition of an ethyl tip, the log k'_W values are closer to that of the parent fluorinated compound. However, it has to be underlined that the surface area per molecule was slightly affected by the additional ethyl tip, as has been already reported for the Lac and Malt series.[16,17]

Among the contributions that lead to the unexpected hydrophobicity and the paradoxical behavior of the surface activity of such hemifluorinated surfactants, two are likely to be[16] (i) poorer packing induced by either unfavorable van der Waals interactions between fluorinated and hydrogenated atoms and/or steric hindrance in the core of H_2F_6-surfactants micelles and (ii) the acidic character of the methylene group vicinal to the fluorocarbon core, a consequence of the electron-withdrawing effect of fluorine atoms, which favors hydrogen bonding with the aqueous phase. Such an effect would increase the energy of transfer of the hemifluorinated chain of H_2F_6-surfactants to a hydrophobic phase and shift its partition coefficient toward water.

Hydrophobic and Hydrophilic Effects toward the Micellization. The CMC/C_{20} ratio is a measure of the tendency of the surfactants to adsorb at the air/water interface relative to its tendency to form micelles. Rosen and Shulthana reported that the decyl-β-glucoside (CMC/C_{20} = 11.1) has a greater tendency to adsorb at the air/water interface than its maltoside analogue (CMC/C_{20} = 6.5).[53] This was explained by an inhibition of the adsorption at the interface of the latter surfactant, due to its greater hydrophilicity, as it has also been reported for glucocationic surfactants[54] and gemini surfactants.[55] We found opposite results as shown with the F_6 series with the following order: F_6-Triglu > F_6-Diglu > F_6-Monoglu. Confirmation of this observation was made with the H_{10} and H_{12} series, while no significant difference was observed for the H_2F_6 series. This suggests that both the steric effect and the hydrophilicity of the polar head have to be considered. Indeed, in the case of linear glycosidic polar head, the number of the sugar moieties has limited effect on the volume of the polar head while the hydrophilicity is obviously increased with the number of sugars. Thus, the most contributively effect of the number of sugar on the CMC/C_{20} ratio is the hydrophilicity. On the contrary, with ramified or branched polar head, the steric hindrance appears to be more contributive than the hydrophilicity as observed in this work. The nature of the tail is also a determinant parameter toward the tendency to adsorb or to micellize. For a given glucosylated polar head, fluorinated surfactants exhibit highest values while intermediate values are found for the hemifluorinated and the lowest for the hydrogenated surfactants. Such a trend occurs likely because the substitution of hydrogen by fluorine atoms within the tails favors the adsorption at the interface as previously reported[41] leading to a higher order of packing and thus a compact film.

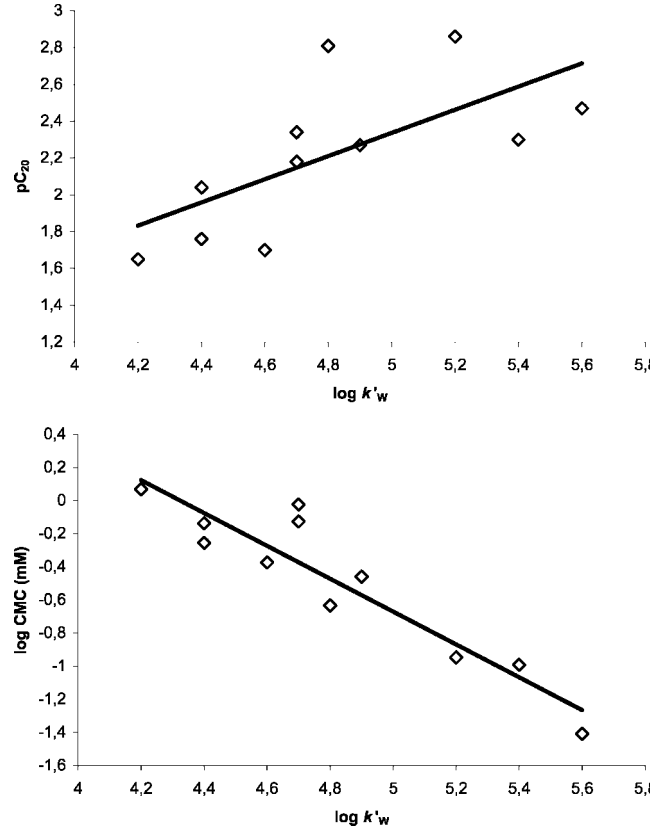


FIGURE 3. Correlation of the hydrophobic characters (log k'_W) determined by reverse-phase HPLC with (a) the efficiency parameter (pC_{20}) ($a = 0.63$, $R^2 = 0.45$) and (b) the critical micellar concentration (CMC) ($a = -0.99$, $R^2 = 0.86$).

(50) Ravey, J. C.; Stébé, M. J. *J. Coll. Surf., A* **1994**, *84*, 11–31.
(51) Durand, G.; Polidori, A.; Ouari, O.; Tordo, P.; Geromel, V.; Rustin, P.; Pucci, B. *J. Med. Chem.* **2003**, *46*, 5230–5237.
(52) Ortial, S.; Durand, G.; Poeggeler, B.; Polidori, A.; Pappolla, M. A.; Boker, J.; Hardeland, R.; Pucci, B. *J. Med. Chem.* **2006**, *49*, 2812–2820.
(53) Rosen, M. J.; Sulthana, S. B. *J. Colloid Interface Sci.* **2001**, *239*, 528–534.
(54) Quagliotto, P.; Viscardi, G.; Barolo, C.; D'Angelo, D.; Barni, E.; Compari, C.; Duce, E.; Fisicaro, E. *J. Org. Chem.* **2005**, *70*, 9857–9866.
(55) Li, F.; Rosen, M. J.; Sulthana, S. B. *Langmuir* **2001**, *17*, 1037–1042.

The peculiar behavior of the hemifluorinated chain, i.e., unfavorable interactions between the ethyl tip and the fluorocarbon core as well as the acidity of the methylene close to the fluorinated core[16] could explain the lower propensity of these compounds to adsorb at the air/water interface comparatively to their fluorinated analogues.

A relatively marked correlation between the log k'_W and the log CMC or the pC_{20} is shown in Figure 3. A significant correlation was observed in the plot of the hydrophobic character with the CMC ($R^2 = 0.86$). As regards their efficiency (which measures in fact the ability of a surfactant to decrease the surface tension by 20 mN/m), the adsorption phenomenon increases with the hydrophobicity. Similarly, Zhang and Marchant demonstrated that the efficiency of *N*-alkylmaltosamides increases linearly with the length of the chain.[37] However, a less significant correlation ($R^2 = 0.45$) was found with pC_{20}, suggesting that this parameter does not depend only on the nature of the hydrophobic part but also on the hydrophilicity of the polar head while the log k'_W is unaffected by the nature and by the volume of the polar head.

Aggregation Behavior. The results of DLS experiments were in perfect agreements with Israelachvili's concept[18] and confirmed the impact of the volumetric ratio on the nature and the size of the aggregates formed in aqueous solutions. The interfacial curvature of the aggregates increased with the size of the polar head, leading to the formation of smaller and well-defined aggregates (~5−6 nm diameter). Moreover, for a given type of polar head, fluorocarbon surfactants usually exhibit a propensity to form structures with less curvature than hydrocarbon surfactants and thus larger aggregates; this was verified with lactobionamide[16] or maltoside[17] surfactants, for instance. Thus, whereas F_6-Monoglu self-aggregated into large particles that might possibly be rod-like or cylindrical micelles, F_6-Diglu and F_6-Triglu formed smaller and well-defined monodisperse particles as expected for globular micelles.[42] Finally, the interaction between the ethyl tip and the fluorinated core of the HF-surfactants did not significantly affect the size of the aggregates as we previously found for hemifluorinated surfactants with smaller polar head.[16,17] Again, one can expect that an increase of the polar head size should induce the formation of globular micelles.

Conclusion

A novel class of hemifluorinated glucose-based surfactants was synthesized, as well as their hydrogenated and perfluorinated analogues. The value of these syntheses lies in the efficient thioether bond formation in mild conditions using thioacetate (or thiol) and a slight excess of THAM-derived polar head. The surface properties and related parameters were found to be influenced by both the nature of the tail and the number of the glucose moieties, demonstrating once again the particular behavior of hemifluorinated surfactants. Finally, dynamic light scattering investigations confirmed the impact of the volumetric ratio on the nature and the size of the aggregates formed in aqueous solutions. Whatever the nature of the tail, Diglu and Triglu surfactants led to the formation of small and well-defined aggregates that may be globular micelles. Considering that such micelles should lead to monodisperse membrane proteins/surfactant complexes, these novel surfactants show promising structural features. Confirmation by neutron diffusion of the globular shape of these aggregates and their potency to maintain MP in their native form in an aqueous solution are underway.

Materials

Determination of log k'_W Values. The compounds were dissolved in MeOH at 1 g L^{-1} and injected onto a reverse-phase column (C_{18}, 5 μm granulometry, 250 × 4.6 mm) at room temperature. Compounds were eluted with various MeOH/H_2O mixtures (from 6:4 to 9:1 v/v). Linear regression analyses ($r^2 > 0.996$) were performed on three points for H_{12}-Diglu, H_{12}-Triglu, and H_{10}-Triglu (MeOH/H_2O from 7:3 to 9:1) and four points for the other compounds (MeOH/H_2O from 6:4 to 9:1). The measurements were performed at a flow rate of 0.8 mL min^{-1} and detected at 205 nm. The value of log k' was calculated as log $k' = \log((t - t_0)/t_0)$, where t is the retention time of the surfactant and t_0 is the elution time of MeOH, which is not retained on the column. log k'_W values were obtained by extrapolation of the linear regression to 0% MeOH.[43,51,56]

Surface Tension Measurements. The surface activity of surfactants in solution at the air/water interface was determined by the Wilhelmy plate technique. The surfactant solution was prepared 12 h prior to the measurements using Milli-Q water (resistivity of 18.2 MΩ cm, surface tension of 72.0 mN m^{-1} at 20 °C). Twenty milliliters initial volume of the surfactant solution was taken in a glass trough, and surface tensions were determined by dilution technique. The platinum plate was cleaned by flaming before experiments. All measurements were made at 25 ± 0.5 °C. Other conditions were identical as reported else where.[16,52] All measurements were repeated 2 or 3 times. An estimate of the area per molecule, A_{min}, at the interface is also given, as derived from the surface excess calculated using the Gibbs adsorption isotherm, $\Gamma_{max} = -(1/RT)(d\gamma/d(\ln C))$ where Γ_{max} is the surface excess (moles per unit area), R is the universal gas constant, T is the absolute temperature, γ is the surface tension, and C is the surfactant concentration. The A_{min} can be calculated as $A_{min} = 1/(N_A\Gamma_{max})$, where N_A is the Avogadro number. C_{20} values were obtained by extrapolation of the slope of the surface tension curve to 52 mN m^{-1}. The efficiency, pC_{20}, was calculated as the negative logarithm of C_{20}.

Dynamic Light Scattering. The hydrodynamic particle size distributions and polydisersity of surfactants at different concentrations and temperatures were determined by using a He−Ne laser (λ = 633 nm, 4.0 mW). In a typical experiment, stock solutions were made and stored at room temperature overnight before measurements. On the day of the experiment aqueous solutions of samples were passed through a 0.45 μm filter directly into scintillation vials of 1.0 cm diameter. A closed plastic cuvette was filled with 1.5 mL samples, and the size of the particles was measured 1 h after filtration. The experimental run time was 10.0 min. The time-dependent correlation function of the scattered light intensity was measured at a scattering angle of 173° relative to the laser source (backscattering detection). The hydrodynamic radius (R) of the particles was estimated from their diffusion coefficient (D) using the Stokes−Einstein equation, $D = k_BT/6\pi\eta R$, where k_B is Boltzmann's constant, T is the absolute temperature, and η is the viscosity of the solvent.

Experimental Section

***N*-1-Acetoxymethyl-1-[(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)oxymethyl]acetoxyethyl Acrylamide (2a).** First, 2.4 g (11.35 mmol, 1 equiv) of **1**, 7.0 g (17.03 mmol, 1.5 equiv) of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide, and 4.3 g of $HgCN_2$ (17.03 mmol, 1.5 equiv) were dissolved in CH_3CN in the presence of drierite. The reaction was stirred 24 h, filtered over a pad of Celite, and then concentrated under reduced pressure. The syrup residue was redissolved in EtOAc. The organic layer was successively washed with $NaHCO_3$, KI (10%), and saturated $Na_2S_2O_3$ solutions, dried over Na_2SO_4, and then concentrated under reduced

(56) Hseih, M. M.; Dorsey, J. G. *Anal. Chem.* **1995**, *67*, 48–57.

pressure. To this, 8.2 g of Montmorillonite K10 in CH_2Cl_2 was added, and the reaction was stirred overnight. The crude mixture was filtered over a pad of Celite and then concentrated under reduced pressure. The resulting crude compound was purified by flash chromatography (EtOAc/cyclohexane 90:10 v/v) to give 3 g (5.94 mmol, 52%) of **2a** as a white powder. R_f = 0.24 (EtOAc/cyclohexane 9:1 v/v). Mp = 42.9−44.3 °C. $[\alpha]^{25}_D$ = −10.95° (*c* 1, MeOH). HRMS (ESI+) calcd for $C_{21}H_{31}NO_{13}$ ($[M + H]^+$): 506.1868, found 506.1870. ^{1}H NMR ($CDCl_3$) δ 6.61 (br s, 1H), 6.34 (dd, ^2J = 1.66 Hz, $^3J_{trans}$ = 16.86 Hz, 1H), 6.21 (dd, $^3J_{cis}$ = 9.87 Hz, $^3J_{trans}$ = 16.86 Hz, 1H), 5.74 (dd, ^2J = 1.65 Hz, $^3J_{cis}$ = 9.75 Hz, 1H), 5.31−.95 (m, 3H, H_2, H_3, H_4), 4.52 (d, J = 7.93 Hz, 1H, H_1), 4.43−3.45 (m, 9H, CH_2OGlu, H_5, H_6, $H_{6'}$, CH_2OH), 2.11−2.02 (4s, 12H, $COCH_3$). ^{13}C NMR ($CDCl_3$) δ 170.7, 170.1, 170.0, 169.5, 166.7, 130.4, 127.8, 100.9, 72.1, 72.0, 68.2, 71.3, 70.0, 63.8, 63.2, 61.7, 60.9, 20.7.

A 0.72 g (1.42 mmol) portion of **2a** was dissolved in methanol in the presence of a catalytic amount of MeONa and stirred overnight at room temperature. Two spatulas of IRC 50 resin were added, and the solution was filtered then concentrated under vacuum to afford **2** in a quantitative yield, which was used without further purification.

***N*-1,1-Di[(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)oxymethyl]acetoxyethyl Acrylamide (4a).** First, 1 g (4.6 mmol, 1 equiv) of **3**, 7.27 g (17.48 mmol, 3.8 equiv) of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide and 3.48 g (13.8 mmol, 3 equiv) of $HgCN_2$ were dissolved in CH_3CN in the presence of drierite and sonicated for 1 h. The reaction mixture was filtered over a pad of Celite, and the solvent was removed under vacuum. Then, the residue was dissolved in EtOAc. The organic layer was successively washed with $NaHCO_3$, KI (10%), and saturated $Na_2S_2O_3$ solutions, dried over Na_2SO_4 and then concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/cyclohexane 6:4 v/v) to give 1.8 g (2.05 mmol, 45%) of **4a** as a white powder. R_f = 0.45 (EtOAc/cyclohexane 6:4 v/v). Mp = 52.7−54.5 °C. $[\alpha]^{25}_D$ = −25.10° (*c* 1, MeOH). HRMS (ESI+) calcd for $C_{37}H_{52}NO_{23}$ ($[M + H]^+$): 878.2925, found 878.2925. ^{1}H NMR ($CDCl_3$) δ 6.25 (dd, ^2J = 1.63 Hz, $^3J_{trans}$ = 17 Hz, 1H, CH_2), 6.17 (br s, 1H, NH), 6.21 (dd, $^3J_{cis}$ = 10.02 Hz, $^3J_{trans}$ = 17.5 Hz, 1H, CH), 5.63 (dd, ^2J = 1.62 Hz, $^3J_{cis}$ = 10 Hz, 1H, CH_2), 5.25−.94 (m, 6H, H_2, H_3, H_4), 4.50 (d, J = 9.5 Hz, 1H, H_1), 4.49 (d, J = 7.88 Hz, 1H, H_1), 4.41 (d, J = 13.56 Hz, 2H, CH_2OAc), 4.33−4.25 (m, 2H, H_6), 4.17−3.92 (m, 6H, $H_{6'}$, CH_2Oglu), 3.75−3.69 (m, 2H, H_5), 2.19−1.93 (9s, 27H, $COCH_3$). ^{13}C NMR ($CDCl_3$) δ 170.9, 170.7, 170.6, 170.2, 170.1, 169.5, 169.4, 169.3 165.5, 130.9, 126.9, 101.1, 101.0, 72.6, 72.4, 71.9, 71.8, 68.8, 68.6, 68.2, 68.1, 68.2, 68.1, 63.0, 61.7, 58.8, 20.8, 20.7, 20.6.

Deacetylation of compound **4a** was performed following the same procedure as described for **2a**, affording **4** in a quantitative yield, which was used without further purification.

***N*-Tris[(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)oxymethyl]-methyl Acrylamide (5a).** The synthetic procedure was essentially the same as for compound **4a**; 0.75 g (4.27 mmol, 1 equiv) of THAM, 10.54 g (25.66 mmol, 6 equiv) of 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide, and 6.48 g (25.66, 6 equiv) of $HgCN_2$ were used as starting materials. Purification by flash chromatography (EtOAc/cyclohexane 7:3 v/v) led to 2.5 g (2.16 mmol, 50%) of **5a** as a white powder. R_f = 0.47 (EtOAc/cyclohexane 8:2 v/v). Mp = 72.5−74.3 °C. $[\alpha]^{25}_D$ = −28.15° (*c* 1, MeOH). HRMS (ESI+) calcd for $C_{49}H_{68}NO_{31}$ ($[M + H]^+$): 1166.3770, found 1166.3772. ^{1}H NMR ($CDCl_3$) δ 6.25 (dd, ^2J = 1.67 Hz, $^3J_{trans}$ = 15 Hz, 1H, CH_2), 6.14 (br s, 1H, NH), 6.07 (dd, $^3J_{cis}$ = 9.99 Hz, $^3J_{trans}$ = 17.5 Hz, 1H, CH), 5.60 (dd, ^2J = 1.69 Hz, $^3J_{cis}$ = 12.5 Hz, 1H, CH_2), 5.26−4.94 (m, 9H, H_2, H_3, H_4), 4.48 (d, J = 7.9 Hz, 3H, H_1), 4.31 (dd, J = 4.54 Hz, J = 12.5 Hz, 3H), 4.19 (d, CH_2OGlu, J = 10.55 Hz, 3H), 4.11 (dd, J = 2.3 Hz, J = 12.5 Hz, 3H), 3.83 (d, J = 10.41 Hz, 3H, CH_2OGlu), 3.75−3.69 (m, 2H, H_5), 2.15−2.01 (12s, 36H, $COCH_3$). ^{13}C NMR ($CDCl_3$) δ 170.6, 170.2, 169.5, 169.4, 165.4, 131.0, 126.7, 101.2, 72.6, 71.8, 71.4, 68.6, 68.2, 61.7, 61.7, 59.3, 20.7, 20.6.

Deacetylation of compound **5a** was performed following the same procedure as described for **2a**, affording **5** in a quantitative yield, which was used without further purification.

3,3,4,4,5,5,6,6,7,7,8,8-Dodecafluoro-1-iododecane (7). First, 3 g (4.92 mmol, 1 equiv) of 1,10-diiodo-3,3,4,4,5,5,6,6,7,7,8,8-dodecafluorodecane[25] and 1.23 g (4.92 mmol, 1 equiv) of tris(trimethylsilyl)silane were dissolved in 15 mL of toluene, under argon atmosphere, and then heated at 70 °C in the presence of a catalytic amount of AIBN. After 24 h of being heated, the mixture was cooled at room temperature, and 25 mL of CH_2Cl_2 was added. The organic layer was washed with $Na_2S_2O_3$ saturated solution and distilled water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were then dried over Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by silica gel chromatography (cyclohexane) to give 0.7 g (1.44mmol, 30%) of pure compound **7** as a translucent liquid. R_f = 0.35 (cyclohexane). ^{1}H NMR ($CDCl_3$) δ 3.27 (m, 2H, CH_2I), 2.84−2.63 (m, 2H, CH_2R_f), 2.22−2.05 (m, 2H, $CH_3CH_2R_f$), 1.17 (t, J = 7.47 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ 36.5, 24.5, 11.5, 4.4. ^{19}F NMR ($CDCl_3$) −114.8 (2F), −116.3 (2F), −121.8 (4F), −123.5 (4F).

In addition, 1.2 g (1.97mmol, 40%) of **6** and 0.17 g (0.49mmol, 10%) of bis reduced compound were isolated.

3,3,4,4,5,5,6,6,7,7,8,8-Dodecafluorodecane Thioacetate (8). First, 2.0 g (4.13 mmol, 1 equiv) of **7** was dissolved in 10 mL of anhydrous DMF under argon atmosphere. Next, 0.57 g (4.96 mmol, 1.2 equiv) of potassium thioacetate was added, and the mixture was stirred for 1 h at room temperature. Then 30 mL of water was added, and the aqueous layer was extracted with EtOAc. The organic layer was washed with distilled water, dried over Na_2SO_4, and then concentrated under reduced pressure. The crude compound was purified by flash chromatography (cyclohexane/CH_2Cl_2 95:5 v/v) to give 1.0 g (2.31 mmol, 56%) of **8** as a translucent liquid. R_f = 0.23 (cyclohexane/CH_2Cl_2 95:5 v/v).^{1}H NMR ($CDCl_3$) δ 3.12 (t, J = 8 Hz, 2H, CH_2S), 2.64−2.37 (m, 2H, CF_2CH_2), 2.37 (s, 3H, CH_3CO), 2.11−2.06 (m, 2H, CH_3CH_2), 1.16 (t, J = 7.4 Hz, 3H, CH_3 CH_2). ^{13}C NMR ($CDCl_3$) δ 194.8, 31.7, 30.5, 24.6, 20.3, 4.5. ^{19}F NMR ($CDCl_3$) δ −114.8 (2F), −116.6 (2F), −122.2 (4F), −123.8 (4F).

***N*-1-Acetoxymethyl-1-[(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)oxymethyl]acetoxyethyl-4-thia-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluorododecanamide (9, F_6-Monoglu).** First, 500 mg (1.18 mmol, 1 equiv) of 1*H*,1*H*,2*H*,2*H*-perfluorooctylthioacetate (see Supporting Information for further details) and 67.4 mg (1.78 mmol, 1.5 equiv) of $NaBH_4$ were dissolved in 3 mL of MeOH under argon atmosphere. After 15 min of being refluxed, a solution of 600 mg (1.78 mmol, 1.5 equiv) of **2**, in 9 mL of MeOH was added, and the reaction was stirred for 3 h. The reaction mixture was cooled at room temperature and then concentrated under reduced pressure. The crude mixture was purified by flash chromatography (EtOAc/MeOH 9:1 v/v) and by size-exclusion chromatography (MeOH), to give 510 mg (0.72 mmol, 60%) of **9** as a white powder. R_f = 0.7 (EtOAc/MeOH/H_2O 7:2:1 v/v/v). Mp = 153.7. $[\alpha]^{25}_D$ = −0.6° (*c* 1, MeOH). HRMS (ESI+) calcd for $C_{21}H_{28}NO_9SF_{13}$ ($[M + H]^+$): 718.1349, found 718.1351. ^{1}H NMR (CD_3OD) δ 4.32 (d, J = 7.69 Hz, 1H, H_1), 4.07 (d, J = 10.02 Hz, 1H, CH_2OGlu), 3.92−3.65 (m, 7H, CH_2OGlu, CH_2OH, H_6, $H_{6'}$), 3.42−3.20 (m, 4H, H_5, H_4, H_3, H_2,), 2.89−2.79 (m, 4H, CH_2SCH_2), 2.61−2.41 (m, 2H, CH_2R_f), 2.58 (t, J = 7.1 Hz, 2H, CH_2CO). ^{13}C NMR (CD_3OD) δ 173.4, 103.3, 76.6, 70.2, 73.6, 67.9, 61.7, 61.3, 60.9, 36.2, 31.6, 27.2, 21.9. ^{19}F NMR (CD_3OD) δ −82.4 (3F), −115.2 (2F), −122.9 (2F), −123.8 (2F), −124.3 (2F), −127.3 (2F).

***N*-1,1-Di[(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)oxymehtyl]acetoxyethyl-4-thia-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluorododecanamide (10, F_6-Diglu).** The synthetic procedure was essentially the same as for **9**. 250 mg (0.59 mmol, 1 equiv) of 1H,1H,2H,2H-perfluorooctylthioacetate, 34.5 mg (0.91 mmol, 1.5

equiv) of $NaBH_4$ and 420 mg (0.86 mmol, 1.45 equiv) of **4** were used as starting materials. Purification by flash chromatography (EtOAc/MeOH 8:2 v/v), by size-exclusion chromatography (MeOH), and RP-HPLC (H_2O/CH_3CN 65:35 v/v) followed by lyophilization led to 285 mg (0.32 mmol, 55%) of **10** as a white powder. R_f = 0.46 (EtOAc/MeOH/ H_2O 7:2:1 v/v/v). Mp = 169.4 °C. $[\alpha]^{25}_D$ = −10.25° (*c* 1, MeOH). HRMS (ESI+) calcd for $C_{27}H_{38}NO_{14}SF_{13}$ ($[M + H]^+$): 880.1878, found 880.1878. ^{1}H NMR (CD_3OD) δ 4.35 (d, J = 7.72 Hz, 1H, H_1), 4.34 (d, J = 7.73 Hz, 1H, H_1), 4.21−4.13 (m, 2H, CH_2OGlu), 3.96−3.84 (m, 6H, CH_2OGlu, CH_2OH, H_6,), 3.72−3.65 (m, 2H, $H_{6'}$), 3.38−3.19 (m, 8H, H_5, H_4, H_3, H_2), 2.85−2.79 (m, 4H, CH_2SCH_2), 2.60−2.44 (m, 2H, CH_2R_f,), 2.57 (t, J = 7.21 Hz, 2H, CH_2CO). ^{13}C NMR (CD_3OD) δ 173.2, 103.4, 103.3, 76.6, 70.3, 73.3, 67.8, 67.7, 61.3, 61.0, 60.9, 36.23, 31.5, 27.1−22.0. ^{19}F NMR (CD_3OD) δ −82.4 (3F), −115.3 (2F), −122.9 (2F), −123.9 (2F), −124.3 (2F), −127.3 (2F).

***N*-Tris[(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]-methyl-4-thia-7,7,8,8,9,9,10,10,11,11,12,12,12-tridecafluorododecanamide (11, F_6-Triglu).** The synthetic procedure was essentially the same as for compound **9**; 150 mg (0.4 mmol, 1 equiv) of 1*H*,1*H*,2*H*,2*H*-perfluorooctylthioacetate, 19.7 mg (0.52 mmol, 1.3 equiv) of $NaBH_4$, and 344 mg (0.52 mmol, 1.3 equiv) of **5** were used as starting materials. Purification by size-exclusion chromatography (MeOH) and RP-HPLC (H_2O/CH_3CN 65:35 v/v) followed by lyophilization led to 217 mg (0.21mmol, 52%) of **11** as a white powder. R_f = 0.35 (EtOAc/MeOH/ H_2O 7:2:1 v/v/v). Mp = 180.2 °C. $[\alpha]^{25}_D$ = −19.75° (*c* 1, MeOH). HRMS (ESI+) calcd for $C_{33}H_{48}NO_{19}SF_{13}$ ($[M + H]^+$): 1042.2406, found 1042.2411. ^{1}H NMR (CD_3OD) δ 4.14− 4.07 (m, 6H, H_1, CH_2OGlu), 3.74−3.64 (m, 6H, CH_2Oglu, H_6), 3.47−3.42 (m, 3H, $H_{6'}$), 3.19−2.95 (m, 12H, H_5, H_4, H_3, H_2), 2.64−2.61 (m, 4H, CH_2SCH_2), 2.32 (t, J = 7.46 Hz, 2H, CH_2CO), 2.35−2.29 (m, 2H, CH_2R_f). ^{13}C NMR (CD_3OD) δ 172.9, 103.5, 76.6, 70.2, 73.7, 67.8, 61.3, 59.9, 36.4, 31.5, 27.1, 22.0. ^{19}F NMR (CD_3OD) δ −82.4 (2F), −115.3 (2F), −122.9 (2F), −123.9 (2F), −124.3 (2F), −127.3.

***N*-1,1-Di[(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]acetoxyethyl-4-thia-7,7,8,8,9,9,10,10,11,11,12,12-dodecafluorotetradecanamide (12, H_2F_6-Diglu).** The synthetic procedure was essentially the same as for **9**; 450 mg (1.04 mmol, 1 equiv) of **8**, 53.8 mg (1.56 mmol, 1.5 equiv) of $NaBH_4$, and 727 mg (1.45 mmol, 1.4 equiv) of **4** were used as starting materials. Purification by size-exclusion chromatography (MeOH) and RP-HPLC (H_2O/CH_3CN 60:40 v/v) followed by lyophilization led to 399.9 mg (0.45 mmol, 44%) of **12** as a white powder. R_f = 0.54 (EtOAc/MeOH/H_2O 7:2:1 v/v/v). Mp = 160 °C. $[\alpha]^{25}_D$ = −3.95° (*c* 1, MeOH). HRMS (ESI+) calcd for $C_{29}H_{43}NO_{14}SF_{12}$ ($[M + H]^+$): 890.2285, found 890.2293. ^{1}H NMR (CD_3OD) δ 4.36 (d, J = 7.71 Hz, 1H, H_1), 4.34 (d, J = 7.77 Hz, 1H, H_1), 4.20−4.13 (m, 2H, CH_2OGlu), 3.94−3.84 (m, 6H, CH_2OGlu, CH_2OH, H_6), 3.70−3.67 (m, 2H, $H_{6'}$), 3.40−3.23 (m, 8H, H_5, H_4, H_3, H_2), 2.87−2.78 (m, 4H, CH_2SCH_2,), 2.61−2.45 (m, 2H, CH_2R_f), 2.58 (t, J = 7.08 Hz, 2H, CH_2CO), 2.21−2.11 (m, 2H, $CH_3CH_2R_f$), 1.16 (t, J = 7.41 Hz, 2H, CH_3CH_2). ^{13}C NMR (CD_3OD) δ 173.3, 103.4, 103.3, 76.5, 70.1, 73.3, 67.9, 67.7, 61.2, 60.9, 36.2, 31.6, 27.1, 24.1, 22.0, 3.3. ^{19}F NMR (CD_3OD) δ −115.2 (2F), −117.5 (2F), −122.9 (4F), −124.4 (2F), −127.7 (2F).

***N*-Tris[(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]-methyl-4-thia-7,7,8,8,9,9,10,10,11,11,12,12-dodecafluorotetradecanamide (13, H_2F_6-Triglu).** The synthetic procedure was essentially the same as for **9**; 200 mg (0.46 mmol, 1 equiv) of **8**, 23.9 mg (0.69 mmol, 1.5 equiv) of $NaBH_4$, and 458 mg (0.69 mmol, 1.5 equiv) of **5** were used as starting materials. Purification by size-exclusion chromatography (MeOH) and RP-HPLC (H_2O/CH_3CN 65:35 v/v) followed by lyophilization led to 291 mg (0.28 mmol, 60%) of **13** as a white powder. R_f = 0.33 (EtOAc/MeOH/H_2O 7:2:1 v/v/v). Mp = 177.5 °C. $[\alpha]^{25}_D$ = −18.25° (*c* 1, MeOH). HRMS (ESI+) calcd for $C_{35}H_{53}NO_{19}SF_{12}$ ($[M + H]^+$): 1052.2813, found 1052.2826. −115.2 (2F), −122.8 (2F), −123.8 (2F), −124.2 (2F), −127.3. ^{1}H NMR (CD_3OD) δ 4.36−4.30 (m, 6H, H1, CH_2OGlu); 3.97−3.87 (m, 6H, CH_2OGlu, H6); 3.76−3.65 (H6', m, 3H); 3.42−3.18 (m, 12H, H5, H4, H3, H2); 2.86−2.78 (m, 4H, CH_2SCH_2); 2.58−2.45 (m, 2H, CH_2R_f; 2.55 (t, J = 6.96 Hz, 2H, CH_2CO); 2.26−2.06 (m, 2H, $CH_3CH_2R_f$); 1.16 (t, J = 7.43 Hz, 3H, $CH_3CH_2R_f$). ^{13}C NMR (CD_3OD) δ 172.9, 103.5, 76.6, 76.6, 70.3, 73.3, 67.8, 61.3, 59.9, 36.4, 31.6, 27.07, 24.10, 22.04, 3.3. ^{19}F NMR (CD_3OD) δ −115.32 (2F), −117.53 (2F), −122.89 (4F), −124.42 (2F), −124.70 (2F).

***N*-1,1-Di[(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]acetoxyethyl-4-thia-tetradecanamide (14, H_{10}-Diglu).** The synthetic procedure was essentially the same as for compound **9**; 118 mg (0.68mmol, 1 equiv) of 1-decanethiol, 33.3 mg (0.88 mmol, 1.3 equiv) of $NaBH_4$, and 440 mg (0.88 mmol, 1.3 equiv) of **4** were used as starting materials. Purification by size-exclusion chromatography (MeOH) and RP-HPLC (H_2O/CH_3CN 60:40 v/v) followed by lyophilization led to 232 mg (0.34mmol, 51%) of **14** as a white powder. R_f = 0.45 (EtOAc/MeOH/ H_2O 7:2:1 v/v/v). Mp = 129.9 °C, $[\alpha]^{25}_D$ = −9.55° (*c* 1, MeOH), HRMS (ESI+) calcd for $C_{29}H_{55}NO_{14}S$ ($[M + H]^+$): 674.3416, found 674.3422. ^{1}H NMR (CD_3OD) δ 4.35 (d, J = 7.72 Hz, 1H, H_1,), 4.34 (d, J = 7.64 Hz, 1H, H_1), 4.21−4.12 (m, 2H, CH_2OGlu), 3.94−3.83 (m, 6H, CH_2OGlu, CH_2OH, H_6), 3.72−3.66 (m, 2H, $H_{6'}$), 3.39−3.19 (m, 8H, H_5, H_4, H_3, H_2,), 2.77 (t, J = 7.29 Hz, 2H, CH_2CO), 2.59−2.51 (m, 4H, CH_2SCH_2), 1.63−1.44 (m, 2H, SCH_2CH_2,), 1.32 (s, 14H, CH_2), 0.93 (m, J = 5.66 Hz, 3H, CH_3). ^{13}C NMR (CD_3OD) δ 173.6, 103.4, 103.3, 76.6, 70.2, 73.6, 67.8, 67.7, 61.3, 61.0, 60.9, 36.6, 31.6, 31.4, 29.3, 29.1, 29.0, 28.5, 27.2, 22.3, 13.1.

***N*-Tris[(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]-methyl-4-thia-tetradecanamide (15, H_{10}-Triglu).** The synthetic procedure was essentially the same as for compound **9**; 175 mg (1 mmol, 1 equiv) of 1-decanethiol, 56.9 mg (1.5 mmol, 1.5 equiv) of $NaBH_4$ and 995 mg (1.5 mmol, 1.5 equiv) of **5** were used as starting materials. Purification by size-exclusion chromatography (MeOH) and RP-HPLC (H_2O/CH_3CN 65:35 v/v) followed by lyophilization led to 480 mg (0.57mmol, 57%) of **15** as a white powder. R_f = 0.20 (EtOAc/MeOH/ H_2O 7:2:1 v/v/v). Mp = 167 °C. $[\alpha]^{25}_D$ = −19.55° (*c* 1, MeOH). HRMS (ESI+) calcd for $C_{35}H_{65}NO_{19}S$ ($[M + H]^+$): 836.3944, found 836.3947.^{1}H NMR (CD_3OD) δ 4.22 (d, J = 7.71 Hz, 3H, H_1), 4.19 (d, J = 10.11 Hz, 3H, CH_2OGlu), 3.83 (d, J = 10.26 Hz, 3H, CH_2OGlu), 3.79−3.74 (m, 3H, H_6), 3.59−3.57 (m, 3H, $H_{6'}$), 3.26−3.06 (m, 12H, H_5, H_4, H_3, H_2), 2.60 (t, J = 7.27 Hz, 2H, CH_2CO), 2.47−2.36 (m, 4H, CH_2SCH_2,), 1.51−1.45 (m, 2H, SCH_2CH_2), 1.19 (s, 14H, CH_2), 0.80 (t, J = 6.32 Hz, 3H, CH_3). ^{13}C NMR (CD_3OD) δ 173.0, 103.4, 76.6, 76.6, 70.2, 73.3, 67.9, 61.4, 59.9, 36.8, 31.4, 29.3, 29.1, 29.1, 28.6, 27.1, 22.4, 13.1.

***N*-1,1-Di[(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]acetoxyethyl-4-thia-hexadecanamide (16, H_{12}-Diglu).** The synthetic procedure was the same as for **9**; 150 mg (0.57 mmol, 1 equiv) of 1-dodecanethiol, 27.6 mg (0.80 mmol, 1.4 equiv) of $NaBH_4$, and 0.4 g (0.80 mmol, 1.4 equiv) of **4** were used as starting materials. Purification by size exclusion chromatography (MeOH) followed by lyophilization led to 0.21 g (0.29 mmol, 53%) of **16** as a white powder. R_f = 0.43 (EtOAc/MeOH/H_2O 7:2:1 v/v/v). Mp = 125.4 °C. $[\alpha]^{25}_D$ = −1.65° (c,1,MeOH). HRMS (ESI+) calcd for $C_{31}H_{59}NO_{14}S$ ($[M + H]^+$): 702.3729, found 702.3727.^{1}H NMR (CD_3OD) δ 4.34 (d, J = 7.69 Hz, 1H, H_1), 4.33 (d, J = 7.71 Hz, 1H, H_1), 4.21−4.13 (m, 2H, CH_2OGlu), 3.96−3.83 (m, 6H, CH_2OGlu, CH_2OH, H_6), 3.72−3.65 (m, 2H, $H_{6'}$), 3.39−3.19 (m, 8H, H_5, H_4, H_3, H_2), 2.71 (t, J = 7.01 H, 2H, CH_2CO), 2.59−2.51 (m, 4H, CH_2SCH_2), 1.63−1.55 (m, 2H, SCH_2CH_2), 1.32 (s, 18H, CH_2), 0.92 (t, J = 6.25 Hz, 3H, CH_3). ^{13}C NMR (CD_3OD) δ 173.6, 103.4, 103.3, 76.6, 70.2, 73.6, 67.8, 67.7, 61.3, 61.0, 60.9, 36.6, 31.4, 29.4, 29.3, 29.1, 29.0, 28.6, 27.1, 22.4, 13.1.

***N*-Tris[(2′,3′,4′,6′-tetra-*O*-acetyl-*β*-D-glucopyranosyl)oxymethyl]-methyl-4-thia-hexadecanamide (17, H_{12}-Triglu).** The synthetic procedure was essentially the same as for compound **9**; 100 mg (0.49 mmol, 1 equiv) of 1-dodecanethiol, 24.29 mg (0.64 mmol, 1.3 equiv) of $NaBH_4$, and 424 mg (0.64 mmol, 11.3 equiv) of **5** were used as starting materials. Purification by size-exclusion

chromatography (MeOH) and RP-HPLC (H_2O/CH_3CN 55:45 v/v) followed by lyophilization led to 185 mg (0.21mmol, 44%) of **17** as white powder. $R_f = 0.29$ (EtOAc/MeOH/ H_2O 7:2:1 v/v/v). Mp = 164 °C. $[\alpha]^{25}_D = -6.7°$ (*c* 1, MeOH). HRMS (ESI+) calcd for $C_{37}H_{69}NO_{19}S$ ($[M + H]^+$): 864.4257, found 864.4257. ^1H NMR (CD_3OD) δ 4.22 (d, $J = 7.64$ Hz, 3H, H_1), 4.16 (d, $J = 9.89$ Hz, 3H, CH_2OGlu), 3.79 (d, $J = 10.27$ Hz, 3H, CH_2OGlu,), 3.79−3.74 (m, 3H, H_6), 3.59−3.53 (m, 3H, $H_{6'}$), 3.26−3.06 (m, 12H, H_5, H_4, H_3, H_2), 2.63 (t, $J = 7.16$ Hz, 2H, CH_2CO), 2.47−2.36 (m, 4H, CH_2SCH_2), 1.51−1.43 (m, 2H, SCH_2CH_2), 1.19 (s, 18H, CH_2), 0.80 (t, $J = 6.27$ Hz, 3H, CH_3). ^{13}C NMR (CD_3OD) δ 173, 103.5, 76.6, 76.6, 70.2, 73.3, 67.9, 61.4, 59.9, 36.8, 31.7, 31.5, 29.4, 29.3, 29.1, 29.0, 28.6, 27.1, 22.4, 13.1.

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Supporting Information Available: General experimental methods; experimental procedure for the synthesis of 1*H*,1*H*,2*H*,2*H*-perfluorooctylthioacetate; ^1H, ^{13}C, ^{19}F, DEPT 135, DEPT 90, DEPT 45, COSY and HMQC NMR spectra of F_6-Monoglu (compound **9**); ^1H and ^{13}C spectra of compounds **2**, **4**, **5**, **8**, and **10**−**17** and ^{19}F spectra of compound **8** and **10**−**13**; analytical RP-HPLC chromatogram and high resolution mass spectrum of F_6-Monoglu; hydrodynamic distribution and surface tension curves of all the surfactants. This material is available free of charge via the Internet at http://pubs.acs.org.

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