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Synthesis and self-assembling behavior of F-amphiphilic functionalized amines

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ABSTRACT

A simple route to fluoroalkylated functionalized secondary amines is proposed by the treatment of 2-perfluoroalkylprop-2-enoic acids with various primary amines. Two of these compounds were obtained from oxyethylenic diamine and present an amphiphilic structure.

These compounds exhibit an excellent surface activity since they are lowering the surface tension to 18–20 mN/m and this, at very low concentrations (around 10^{-5} M). DLS measurements and TEM studies show an original behavior of the monocatenar fluorinated surfactants **5n** and **5o**, which are able to spontaneously self-assembles into vesicles, and therefore it makes them suitable candidates as carriers in drug or gene delivery systems.

1. Introduction

In the field of bioactive molecules, fluoroorganic compounds have received a great deal of attention and many studies showed that the incorporation of one, two, three or several F atoms into an organic compound modify its physical, chemical and biological properties [1–6]. Their properties make them suitable for various applications in organic synthesis, medicinal chemistry, plant health chemistry, as well as in material science. Perfluoroalkylated amphiphilic compounds are excellent emulsifiers for water colloidal systems, *i.e.* microemulsions or vesicles. They have been proposed as biocompatible surfactants in medical area. Perfluorocarbon emulsions can thus be used for drug delivery systems, vaccines, or genes [7,8]. Some of them have been proposed as biocompatible oxygen carriers, for example, in storage of tissues and organs or in cell culture. In general, they are functionalized with a variety of structures including sugars, amino acids, pseudo-peptides, etc. [9–12].

A specific interest has been focused on the development of synthetic methods for the preparation of fluorinated building blocks as synthons for functionalized fluorocarbon molecules. Among them, fluorinated amines are of interest as scavengers or precursors in the synthesis of fluorinated molecules or catalysts [13]. The synthesis of perfluoroalkylated primary amines has been developed by several methods such as the Gabriel method, the azido derivatives, reductive amination of fluorine-containing carbonyl compounds [14–16]. For some of these methods, the difficulty is to avoid the deshydrofluorination. Secondary amines are more difficult to be obtained. Previous syntheses of fluorinated amines are relatively few and include Mitsunobu reaction [17], hydroamination of *in situ* generated arylacetylenes [9], reaction of perfluoroalkyl Grignard reagents with N(α-aminoalkyl)benzotriazole) [18], or boron trifluoride reaction of perfluoroalkyllithiums with imines [19,20]. In this context, we propose a simple pathway to these compounds by heating a mixture of modified commercial perfluoroalkylethanols and a primary amine. Two of these compounds, **5n** and **5o**, exhibit particular amphiphilic properties, and their self-assembling properties are underlined.

2. Results and discussion

2.1. Synthesis

We showed, in previous work, the reactivity of ester derivatives of 3-fluoro-3-fluoroalkylpropenoic acids with different nucleophiles such as alcoholates, amines, azides, affording to acetals, enol ethers and enamines [21–25].

Since the corresponding acids can also directly react with primary amines [26], this kind of reaction could be extended to functionalized amines (amino acids, hydrophilic amines) in order to further label the molecules with additional functionalities.

Unsaturated acids were prepared as previously reported by our group, from commercially available 2-perfluoroalkylethanols, by oxidation with chromic acid and dehydrofluoration with aqueous NaOH [27]. In contact with a primary amine in refluxing toluene,

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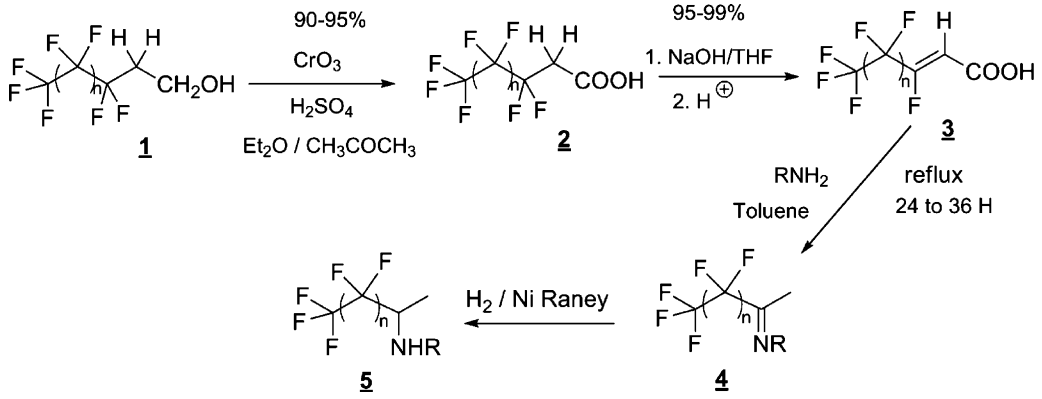
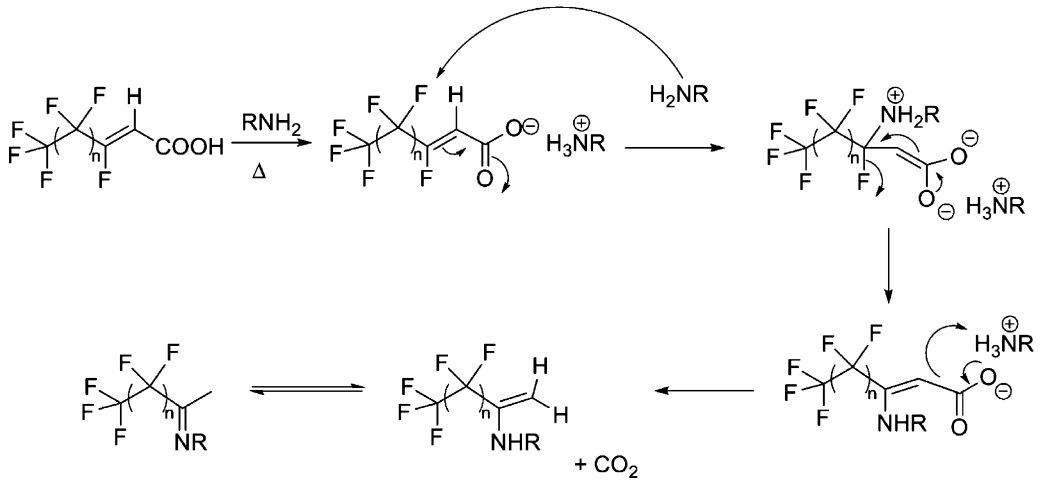


Scheme 1. Reactivity of 3-fluoro-3-fluoroalkylpropenoic acids with primary amines.



Scheme 2. Proposed mechanism of the imine formation.

these perfluoroalkylated acids lead after decarboxylation to imines (Scheme 1).

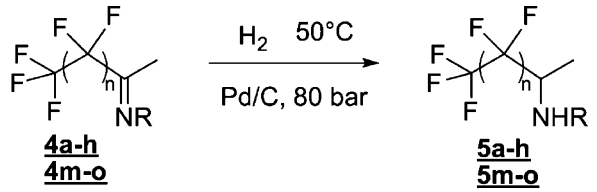
The proposed mechanism is described in Scheme 2. After the acid–base reaction between the fluorinated acid **2** and the triethylamine, the vinylic fluorine can be substituted by the R-NH_2 amine, certainly in two steps mechanism: Michael addition and elimination of fluoride. The formed enamine is then participating as proton donor to catalyze the decarboxylation. The imine is obtained by tautomerism from the enamine.

Table 1
Yields of formation and reduction of imines.

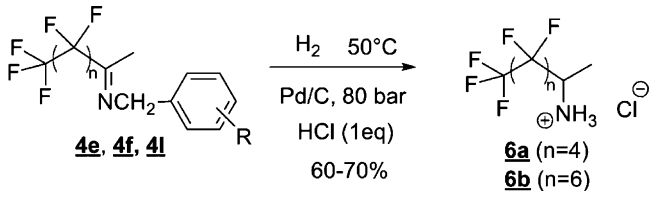
Series	*n*	R	Yield **4**	Yield **5**
a	4	$-(CH_2)_5CH_3$	84	68
b	6	$-(CH_2)_5CH_3$	90	70
c	4	$-(CH_2)_7CH_3$	92	72
d	6	$-(CH_2)_7CH_3$	80	85
e	4	$-CH_2C_6H_5$	83	/
f	6	$-CH_2C_6H_5$	82	/
g	4	$-CH_2CH_2OH$	75	73
h	6	$-CH_2CH_2OH$	83	78
i	4	$-CH(COOEt)(CH_2)_4NHZ$	82	92
j	6	$-CH(COOEt)(CH_2)_4NHZ$	77	94
k	8	$-CH(COOEt)(CH_2)_4NHZ$	81	91
l	6	$-CH_2C_6H_4OMe$	86	/
m	6	$-CH(CH_2Ph)COOMe$	93	70
n	6	$-(CH_2CH_2O)_2(CH_2)_2NH_2$	83	90
o	8	$-(CH_2CH_2O)_2(CH_2)_2NH_2$	85	70

The reaction is efficient with all tested primary amines and the yields are higher than 80% even with sterically hindered amines such as the amino acids (Table 1).

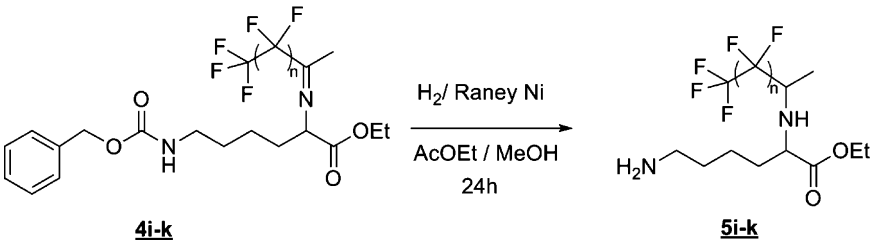
The reduction of imines **4a–h** and **4m–o** by hydrogen with palladium on charcoal needed a high pressure and a moderated temperature (Scheme 3). Secondary amines **5** have been obtained with excellent overall yields. Compounds **5a–d** are interesting building blocks for hybrid surfactants with a fluorocarbon and a



Scheme 3. Reduction of the imines.



Scheme 4. Reduction of the benzylic imines.



Scheme 5. Reduction of imine from protected lysine.

hydrocarbon chain, and **5m** allows to envisage the introduction of an N-perfluoroalkylated amino acid in a peptide (Scheme 4).

In the case of benzylic imines (**4e**, **4f**, **4l**), primary amines are directly obtained because of simultaneous hydrogenolysis of benzylic group.

As for the lysine derivatives, hydrogenolysis of N-protecting group benzyloxycarbonyl occurs at the same time as the hydrogenation of the imine with Nickel Raney (Scheme 5). N(α)-perfluoroalkylated lysine is obtained with excellent yield.

2.2. Amphiphilic properties of compounds 5n and 5o

Surface tension measurements of aqueous solutions of **5n** and **5o** were realized in pure water and in TRIS buffer (pH = 7.4) in order to determine the critical aggregative concentration (CAC) (Fig. 1). The results gathered in Table 2 show the CAC and the minimal surface tension values. Moreover, surface tension measurements allowed us to estimate the mean surface area per molecule, A, of the absorbed non ionic surfactant, from the inverse of the surface excess concentration, Γ (calculated according to the Gibbs equation, Fig. 1c).

The minimal surface tension reaches a plateau at 20 and 18 mN/m, respectively in water and in buffer solution and this value seems to be independent of the length of the perfluorinated chain. However, when increasing the F-tag length the CAC values decrease in agreement with what is usually observed for surfactants. Also, the CAC values are higher in buffer solution than pure water. At this pH, the lipid is cationic (the primary amine is protonated). Usually, the addition of salt compresses the double electric layer of the polar head of ionic surfactants. This can produce a screening of the electrostatic repulsions between neighboring hydrophilic groups and, therefore, enables the aggregation to a lower surfactant concentration.

The estimated molecular area in pure water, 34 (**5n**) and 32 (**5o**) Å^2, respectively are slightly higher than the cross section area of the fluoroalkyl chain (27–30 Å^2). Thus, the molecular area at the interface seems to be governed by the contribution of both fluorinated and ethylene oxide segments, which are slightly tilted with respect to the normal at the interface (Fig. 1d). This might be due (i) to the stiffness of the fluorinated chain and the absence of the any "gauche" defects and (ii) to the flexibility to the ethylenoxide moiety. In addition, area per molecules are higher

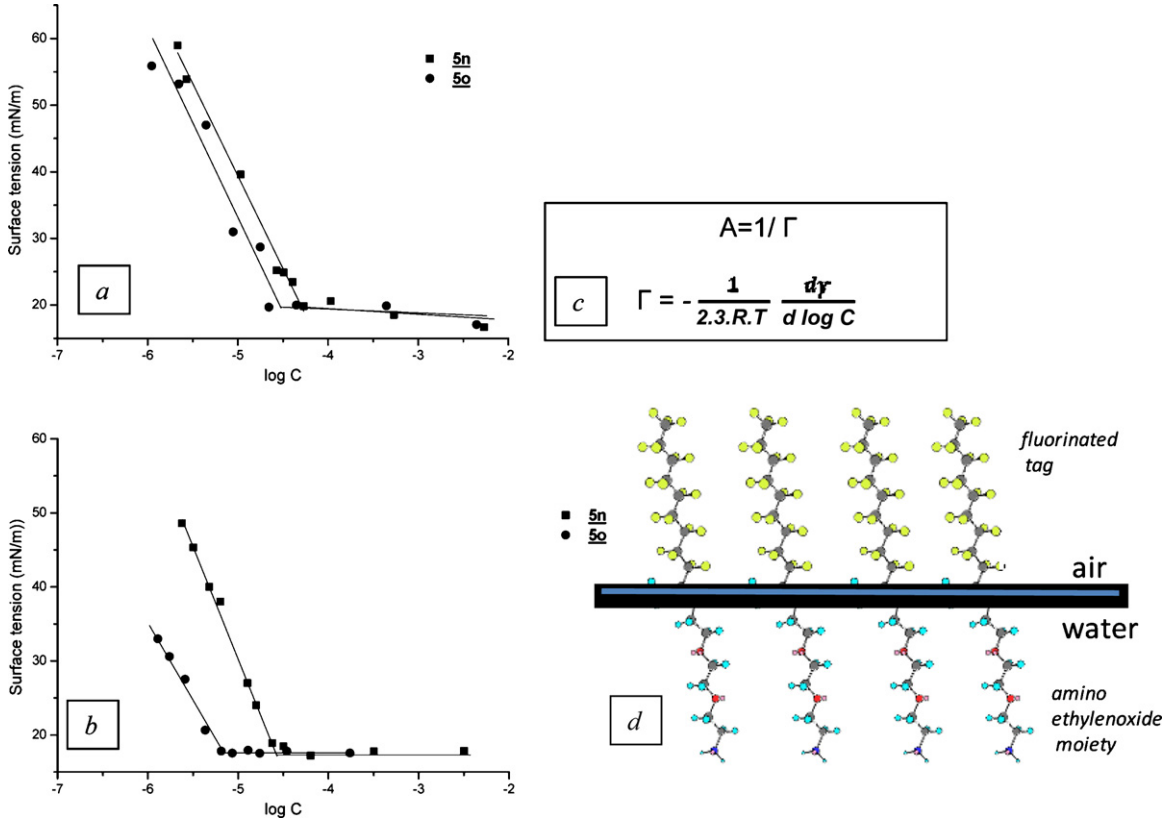


Fig. 1. Surface tension measurements of **5n** and **5o** (a) in pure water and (b) in TRIS buffer (pH 7.4). Equations of the estimated molecular area and Gibbs surface excess (c). Suggested self-assembled Gibbs layer of molecular modeled fluorinated surfactant **5o** as with MOPAC method, CS Chem Office (d).

Table 2
Amphiphilic properties of **5n** and **5o** as determined by surface tension measurements.

Compound	CAC (mol l^{-1})	Area per molecule (Å^2)	$\gamma_{(CAC)}$ (mN m^{-1})
5n/water	6×10^{-5}	34	20
5o/water	2×10^{-5}	32	20
5n/buffer	3×10^{-5}	38	18
5o/buffer	6×10^{-6}	42	18

Table 3
Hydrodynamic diameter values of **5n** and **5o** as determined by DLS measurements in water and in buffer solution, respectively.

Compound	Hydrodynamic diameter (nm) in pure water	Hydrodynamic diameter (nm) in buffer solution
5n	65 and 220–300	60 and 200–230
5o	70 and 300–360	65 and 275

in buffer solution, 38 (**5n**) and 42 (**5o**) Å^2, respectively, which could be due to the electrostatic repulsions between the ethylenoxide moieties and the phosphate anions.

DLS measurements were carried out on 1 mM solutions of **5n** and **5o**, respectively in pure water and in buffer solutions and the hydrodynamic size and the polydispersity of the aggregates were determined. In all cases, the measurements show two populations, centered on around 60–70 nm and 200–360 nm (Table 3), depending on surfactant chain length and on the aqueous solution, and these aggregates were stable at room temperature for at least 48 h. Moreover, TEM micrographs allow us to visualize these aggregates (Fig. 2e and f).

Thus, **5n** and **5o** have the ability to spontaneously self-assemble into vesicles in aqueous solutions, which is rare for monocatenar surfactants. Indeed, to date, only several examples are reported in the literature [7,8,28–30]. This phenomenon seems to be related to the particular features of fluorinated chains and to the asymmetry of the molecule [31–35].

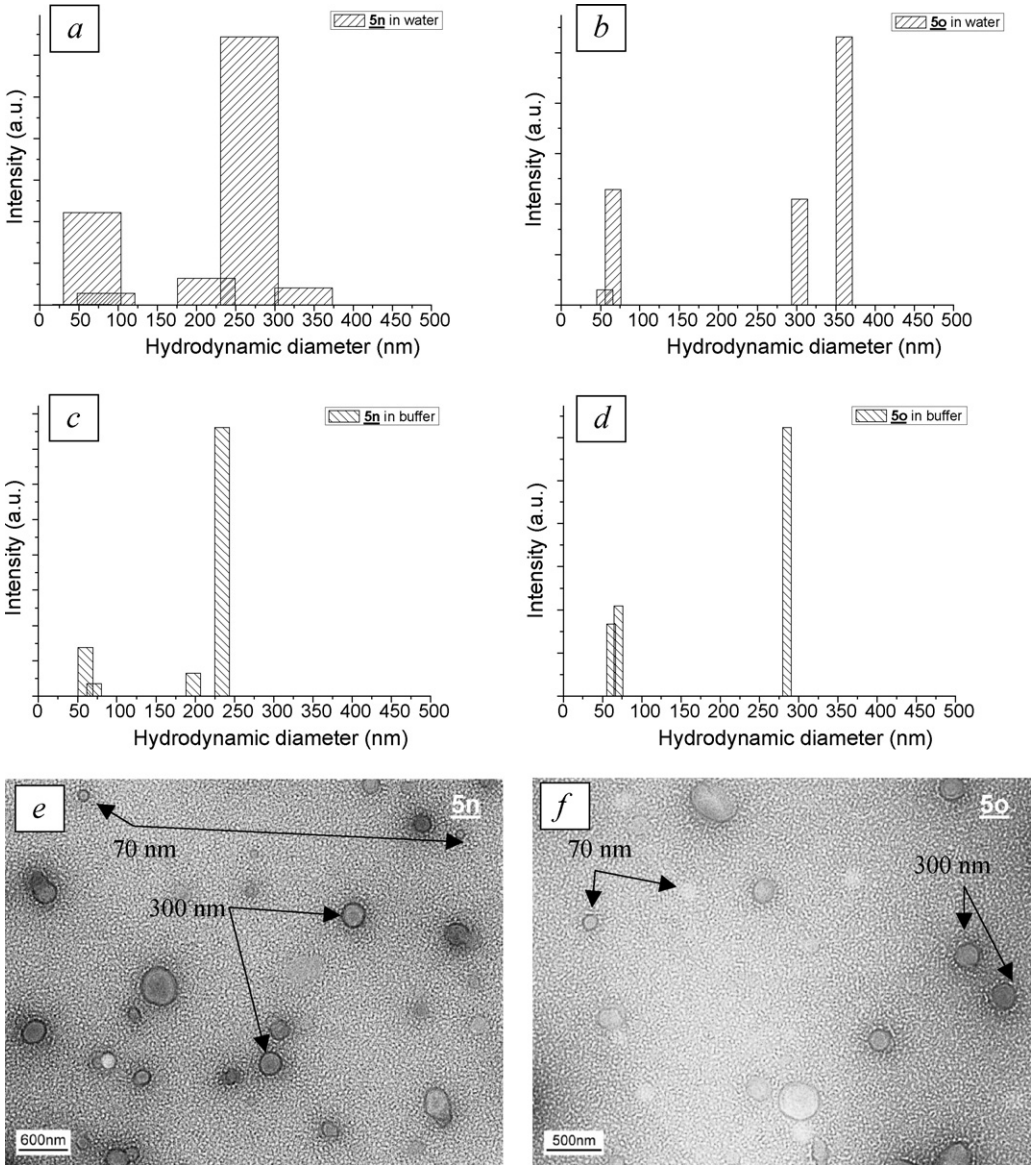


Fig. 2. DLS measurements of 1 mM solution of (a) **5n** in water, (b) **5o** in water, (c) **5n** in buffer, (d) **5o** in buffer, respectively show two populations of aggregates centered on 50 nm and 300 nm. TEM micrographs of (e) **5n** and (f) **5o** in water show vesicles of around 70 and 300 nm.

3. Conclusion

We reported in the present work the synthesis of novel fluorinated/hydrogenated secondary amines starting from commercially available fluorinated acids and a variety of primary hydrogenated amines, in a very simple and efficient method. In the key step, the Michael addition of the hydrogenated amine followed by the elimination of the vinylic fluorine was proposed as a possible mechanism.

By using diamino-diethyleneoxide, two amphiphilic compounds, **5n** and **5o**, were prepared and they exhibit excellent surface activity (minimal surface tension of 18–20 mN/m) and low critical concentration aggregation (around 10^{-5} M). By combining *a* rigid *fluorinated hydrophobic tag* responsible for self-assembling and *a* flexible *ethylenoxide moiety* sufficiently hydrophilic so that the compound could be soluble at high concentration (up to 1 mM), one can design original monocatenar lipids, which are able to spontaneously form vesicles in water.

This property makes them interesting candidates for biomedical applications, such as novel drug or gene carriers. This could be a new approach in the study of oligonucleotide/surfactant interactions, with respect to the communily used hydrogenated monocatenar surfactant-made micells or bicatenar surfactant-fabricated vesicles.

4. Experimental

4.1. Synthesis

All solvents were reagent grade and used without further purification. The progress of reaction was determined using FT-IR spectra. NMR spectra were recorded on a Bruker AM 400 or an AC 200 instrument. Chemical shifts are reported in ppm relative to TMS as internal standard for the ^{1}H spectra and to $CFCl_3$ for the ^{19}F spectra. Coupling constants (*J*) are in Hertz. IR spectra were recorded on a Perkin-Elmer FTIR "spectrum one" in ATR mode or transmission mode. Melting points were made on Kofler Bench and were not corrected. Elemental analyses were performed by C.N.R.S-Vernaison or at UHP on Thermofinnigan FlashEA 1112. 3-Fluoroalkyl-3-fluoro-2-enoic acids were synthesized from alcohol as method described [21].

4.1.1. Synthesis of imines 4a–m

A mixture of 1 g of 3-fluoroalkyl-3-fluoro-2-enoic acid, 1.1 eq. of amine (or lysine with appropriate protections) in 150 mL of toluene, was heated to reflux for 24 h (36 h in case of **4m**). Toluene was then removed under vacuum and the resulting mixture was redissolved in ether and the solution was filtrated. The filtrate was washed with 100 mL of aqueous HCl and saturated solution of sodium chloride until neutralization. Organic phase was dried on $MgSO_4$ and the solvent was evaporated. Final products were not purified (purity 95–98% according to NMR).

N-(perfluoro-alkan-2-ylidene)alkyl-1-amine, **4a** ($n = 4$, $n' = 4$), **4b** ($n = 6$, $n' = 4$), **4c** ($n = 4$, $n' = 6$), **4d** ($n = 6$, $n' = 6$), yellow liquids, IR (KBr) 1300–1100 cm^{-1} (C–F); ^{1}H NMR ($CDCl_3$) 0.90 (t, 3H, $-CH_2(CH_2)_{n-2}CH_3$, $^3J_{HH} = 7$ Hz), 1.30–1.80 (m, $2n'$H, $-CH_2(CH_2)_{n'}CH_3$); 2.00 (s, 3H, CH_3); 3.50 (t, 2H, $-CH_2(CH_2)_{n'}CH_3$, $^3J_{HH} = 7$ Hz); ^{19}F NMR ($CDCl_3$) −80.7 (t, 3F, CF_3); −117 (m, 2F, $CF_3(CF_2)_{n-1}CF_2C{=}N$); −122 to −128 (m, $2n-2$F, $CF_3(CF_2)_{n-1}CF_2C{=}N$). For **4a**, yield 84%; Anal. Calcd for $C_{13}H_{16}F_{11}N$: C, 39.50; H, 4.08. Found: C,39.80; H, 3.90.

1-phenyl-N-(perfluorofluoroalkan-2-ylidene)alcanamine, **4e** ($n = 4$), **4f** ($n = 6$), yellow liquid, IR (KBr) 1300–1100 cm^{-1}(νC–F); ^{1}H NMR ($CDCl_3$) 2.10 (s, 3H, CH_3); 4.70 (s, 2H, $-CH_2C_6H_5$) 7.30 (m, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) −80.5 (t, 3F, CF_3); −117 (m, 2F, $CF_3(CF_2)_{n-1}CF_2C{=}N$); −122 to −128 (m, 6F, $CF_3(CF_2)_{n-1}CF_2C{=}N$). For **4e**, yield 83%; Anal. Calcd for $C_{14}H_{10}F_{11}N$: C, 41.91; H, 2.51. Found: C, 41.50; H, 2.85.

2-(3,3,4,4,5,5,6,6,7,7,7-undecafluoroheptan-2-ylideneamino)ethanol, **4g** ($n = 4$), **4h** ($n = 6$), yellow liquid, IR (KBr) 1300–1100 cm^{-1}(νC–F); ^{1}H NMR ($CDCl_3$) 2.10 (s, 3H, CH_3) 3.20 (m, 2H, $-CH_2CH_2OH$) 3.900 (m, 2H, $-CH_2CH_2OH$); ^{13}C NMR ($CDCl_3$): 22.7($CH_3C{=}N$) 47.4($C{=}NCH_2$) 68.5(CH_2OH) 110–120(CF); ^{19}F NMR ($CDCl_3$) −80.7(t, 3F, CF_3); −116 to −124(m, 2F, $CF_3(CF_2)_3CF_2C{=}N$); −122 to −128(m, 6F, $CF_3(CF_2)_3CF_2C{=}N$). For **4g**, yield 75%, Anal. Calcd for $C_{13}H_{16}F_{11}N$: C, 39.50; H, 4.08. Found: C, 39.90; H, 3.95.

Ethyl-6-(benzyloxycarbonylamino)-2-(perfluoroalkanan-2-ylideneamino)hexanoate, **4i** ($n = 4$), **4j** ($n = 6$), **4k** ($n = 8$), yellow liquid, IR (KBr) 3350 cm^{-1}(νN–H); 1730 cm^{-1} (νC=O ester); 1715 cm^{-1} (νC=O carbamate);1300–1100 cm^{-1}(νC–F); ^{1}H NMR ($CDCl_3$): 0.9–1.2(m, 7H, CH_3 and $NHCH_2(CH_2)_2CH_2$ lysine) 1.42(m, 2H, $NHCH_2(CH_2)_2CH_2$ lysine) 1.83(m, 3H, CH_3) 3.07(m, 2, $NHCH_2(CH_2)_2CH_2$ lysine) 4.05(m, 2H, $COOCH_2CH_3$) 4.66(m, 1H, CH lysine) 4.97(m, 2H, $CH_2C_6H_5$) 7.23(m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$): 16.16 ($COOCH_2CH_3$) 26.72($CH_2(CH_2)_2CH_2NHZ$) 31.61($CH_2(CH_2)_2CH_2NHZ$) 42.18($CH_2(CH_2)_2CH_2NHZ$) 62.27($CHCH_2(CH_2)_2CH_2NHZ$) 60.24($COOCH_2CH_3$) 66.60($NHCOOCH_2C_6H_5$) 106–120(CF) 128 and 136.20 (C_6H_5) 155.07(C=N) 168.10($COOCH_2CH_3$); ^{19}F NMR ($CDCl_3$) −81.08(t, 3F, CF_3); −116(s, 2F, $CF_3(CF_2)_{n-1}CF_2C{=}N$); −121.49 to −126.52(m, 2n–2F, $CF_3(CF_2)_{n-1}CF_2C{=}N$). For **4i**, yield 82%, Anal. Calcd for $C_{23}H_{25}F_{11}N_2O_4$: C, 45.85; H, 4.18. Found: C, 45.10; H, 3.90.

1-(4-methoxyphenyl)-N-(3,3,4,4,5,5,6,6,7,7,7-undecafluoroheptan-2-ylidene)methanamine, **4l**, yellow liquid, IR (KBr) 1300–1100 cm^{-1}(νC–F); ^{1}H NMR ($CDCl_3$):1.90(s, 3H, CH_3) 3.70(s, 3H, $C_6H_4CH_3$) 6.70(dd, 4H, C_6H_4). ^{13}C NMR ($CDCl_3$): 15.4($CH_3C{=}N$) 55.4(CH_3O) 110–120(CF) 114.7–157.9 (Aromat) 158.5(C=N) Yield 83%. Anal. Calcd for $C_{15}H_{12}F_{11}NO$: C, 41.78; H, 2.80. Found: C, 42.20.10; H, 2.90

Methyl-3-phenyl-2-(3,3,4,4,5,5,6,6,7,7,7-undecafluoroheptan-2-ylideneamino) propanoate, **4m**, yield %, yellow liquid, IR (KBr) 1300–1100 cm^{-1}(C–F); 1740 (C=O); ^{1}H NMR (CD_3OCD_3): 1.80(s, 3H, CH_3) 3.20(dd, 2H, $CH_2C_6H_5$) 3.70(s, 3H, $COOCH_3$) 4.70(m, 1H, CH Phenylalanine) 7.20(m, 5H, C_6H_5). ^{19}F NMR (CD_3OCD_3): −80.7(t, 3F, CF_3) −116(m, 2F, $CF_3(CF_2)_5CF_2C{=}N$) −122 to −128(m, 10F, $CF_3(CF_2)_5CF_2C{=}N$) Yield 93%. Anal. Calcd for $C_{17}H_{12}F_{15}NO$: C, 38.43; H, 2.28. Found: C, 38.20.10; H, 2.50.

4.1.2. Synthesis of imines 4n–o

A mixture of 1 g of 3-fluoroalkyl-3-fluoro-2-enoic acid, 10 eq. of 2,2′-(ethylenedioxy)bis(ethylamine) and 30 eq. of Et_3N, in 150 mL of toluene was heated to reflux for 24 h. Toluene and excess of Et_3N were then removed under vacuum and the resulting mixture was re dissolved in ether and solution was filtrated. The filtrate was washed 6 times with 100 mL of water. Organic phase was dried on $MgSO_4$ and the solvent evaporated. Final products were sufficiently pure.

2-(2-(2-aminoethoxy)ethoxy)-N-(perfluoroalkan-2-ylidene)ethanamine, **4n** ($n = 4$), **4o** ($n = 6$). Yellow liquid, IR (KBr) 1300–1100 cm^{-1} (C–F); 1682 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): 1.29(m, 2H, NH_2) 2.02(s, 3H, CH_3) 2.83(m, 2H, CH_2NH_2) 3.46(t, 2H, CH_2N = C, $^3J = 4$ Hz) 3.56–3.96(m, 8H, CH_2O). ^{13}C NMR ($CDCl_3$): 14.33($CH_3C{=}N$) 42.17(CH_2NH_2) 52.71($C{=}NCH_2$) 71.06–73.92 (CH_2O) 106–120(CF) 159.40(C=N). ^{19}F NMR ($CDCl_3$): −81.22(t, 3F, CF3) −116.19(m, 2F, $CF_3(CF_2)_{n-1}CF_2C{=}N$) N) −122 to −128(m, 2n–2F, $CF_3(CF_2)_{n-1}CF_2C{=}N$). **4n** Yield 83%. Anal. Calcd for $C_{15}H_{17}F_{15}N_2O_2$: C, 33.22; H, 3.16. Found: C, 32.850.10; H, 3.13

4.2. Reduction of imines

5 mmol of imine dissolved in 45 mL MeOH and catalytic amount of Palladium 10% on activated carbon, were introduced in a

hydrogenation reactor working under 80 bar H_2. After 16 h at 50 °C, the mixture was cooled down to room temperature, purged with N_2 and filtered on celite. The solvent was then removed under vacuum and the final product was used without further purification.

N-alkyl(1-perfluoroalkyl-ethyl)amine **5a** (n = 4, n' = 4), **5b** (n = 6, n' = 4), **5c** (n = 4, n' = 6), **5d** (n = 6, n' = 6) Yellow liquid, IR (KBr) 1300–1100 cm^{-1}(C–F); ^{1}H NMR ($CDCl_3$):0.90(t, 3H, $-CH_2(CH_2)_{n'}CH_3$) 1.30(m, $(2n'+3)$H, $-CH_2(CH_2)_{n'}CH_3$ and CH–CH_3) 2.70(m, 2H, $-CH_2(CH_2)_{n'}CH_3$) 3.30(m, 1H, CH–CH_3). ^{13}C NMR ($CDCl_3$): 13.9(CF_2CHCH_3) 14.8($NHCH_2(CH_2)_nCH_3$) 24.1($NHCH_2(CH_2)_nCH_3$) 33.4($NHCH_2(CH_2)_nCH_3$) 56(CF_2CHCH_3) 110–120(CF) **5a** Yield 68%. Anal. Calcd for $C_{13}H_{18}F_{11}N$: C, 39.30; H, 4.57. Found: C,39.90.10; H, 4.90.

2-(1-perfluoroalkyl-ethylamino)ethanol **5g** (n = 4), **5h** (n = 6), yellow liquid, IR (KBr) 1300–1100 cm^{-1}(C–F); ^{1}H NMR ($CDCl_3$):1.35(m, 3H, CH–CH_3) 2.95(m, 2H, CH_2OH) 3.65(m, 2H, CH_2NH). **5g** Yield 73%. Anal. Calcd for $C_9H_{10}F_{11}NO$: C, 30.27; H, 2.82. Found: C, 30.67.10; H, 3.20.

Ethyl 6-amino-2-(1-perfluoroalkyl-ethylamino)hexanoate **5i** (n = 4), **5j** (n = 6), **5k** (n = 8), yellow liquid, IR (KBr) 3350 cm^{-1}(νN–H); 1732 cm^{-1} (νC=O ester); 1300–1100 cm^{-1} (νC–F); ^{1}H NMR ($CDCl_3$): 1.09–1.43(m, 8H, NH–CH–CH_3 and $-COOCH_2CH_3$ and $H_2NCH_2CH_2CH_2CH_2CH$) 2.01(m, 4H, $H_2NCH_2CH_2CH_2CH_2CH$) 2.69(m, 2H, NH_2) 3.18–3.38(m, 4H, NH–CH–CH_3, and CH–COOEt and CH_2NH_2) 4.08(q, 2H, $-COOCH_2CH_3$). ^{13}C NMR ($CDCl_3$): 14.59(CF_2CHCH_3 and $COOCH_2CH_3$) 20.75–31.28(CH$(CH_2)_3CH_2NH_2$) 40.78(CH$(CH_2)_3CH_2NH_2$) 51.69(CH$(CH_2)_3CH_2NH_2$) 58.65(CF_2CHCH_3) 60.24($COOCH_2CH_3$) 106–120(CF) 170.11 ($COOCH_2CH_3$) **5i** Yield 92%. Anal. Calcd for $C_{15}H_{21}F_{11}N_2O_2$: C, 38.31; H, 4.50. Found: C, 38.20; H, 4.90.

Methyl 3-phenyl-2-(1-perfluoroalkyl)amino-propanoate **5m**, yellow liquid, IR (KBr) 3350 cm^{-1}(νN–H); 1740 cm^{-1} (νC=O ester); 1300–1100 cm^{-1}(νC–F); ^{1}H NMR ($CDCl_3$): 1.30(d, 3H, NH–CH–CH_3) 2.90(m, 2H, $-CH_2C_6H_5$) 3.20(m, 1H, CH–$COOCH_3$) 3.70(m, 4H, NH–CH–CH_3, and $COOCH_3$) 7.20(m, 5H, $-CH_2C_6H_5$). ^{13}C NMR ($CDCl_3$):15.1(CF_2CHCH_3) 40.6(CH_2Ph) 52.1($COOCH_3$) 62.8($CHCOOCH_3$) 66.4(CF_2CHCH_3) 110–120(CF) 127–137(Aromat) 175.6($COOCH_3$). Yield 70%. Anal. Calcd for $C_{17}H_{16}F_{11}NO_2$: C, 42.96; H, 3.39. Found: C, 42.20; H, 3.90.

N-(2-(2-(2-aminoethoxy) ethoxy)ethyl)-(1-perfluoroalkyl)ethyl-2-amine **5n** (n = 4), **5o** (n = 6) yellow liquid, IR (KBr) 3375 cm^{-1}(νN–H); 1300–1100 cm^{-1}(νC–F); ^{1}H NMR ($CDCl_3$): 1.25(d, 3H, NH–CH–CH_3, ^3J = 6 Hz) 2.81(m, 4H, $-CH_2NH_2$ and $-CH_2NH$) 3.36(m, 1H, CH–NH) 3.59(m, 8H, $-CH_2O$) 4.07(m, 3H, NH and NH_2). ^{13}C NMR ($CDCl_3$): 14.56(CF_2CHCH_3) 40.36(CH_2NH_2) 50.37($NHCH_2$) 55.90(CF_2CHCH_3) 70.99(CH_2O) 105–120(CF). **5n**: Yield 90%. Anal. Calcd for $C_{15}H_{19}F_{15}N_2O_2$: C, 33.10; H, 3.52. Found: C, 32.86; H, 3.37.

1-perfluoroalkylethylammonium chloride **6a** (n = 4), **6b** (n = 6), IR (KBr) 3350 cm^{-1}(νN–H); 1300–1100 cm^{-1}(νC–F); ^{1}H NMR (CD_3OD): 1.57 (d, 3H, CH–CH_3, ^3J = 10 Hz), 4.40 (m, 1H, CH–CH_3). **6a**: Yield: 60%. Anal. Calcd for $C_7H_7ClF_{11}N$: C, 24.05; H, 2.02. Found: C, 23.85; H, 1.98.

4.3. Surface tension measurements

Surface tension (γ) measurements were carried out with a Digital tensiometer KRUSS K10ST using the Wilhelmy method. Surfactant solutions were prepared in pure water or in TRIS buffered solution (NaCl (0.15 M), TRIS (0.05 M), HCl, pH = 7.4). All the measures were carried out at 20 °C.

4.4. Light scattering measurements

The measurement of the particle size and polydispersity were performed by dynamic light scattering experiments, using a Zetasizer 3000 Has (Malvern Instruments Ltd.) with a light source He–Ne laser (wavelength 633 nm). The scattering angle was 90°. All solutions were filtered in nanopure water or in buffer solution before any measurement (filter 450 nm) and all the measures were carried out at 20 °C.

4.5. Transmission electron microscopy

TEM studies were performed using a Philips CM20 type microscope at 200 keV. Samples for TEM were prepared by the negative-staining technique with a 2% sodium phosphotungstate solution buffered at pH 7.4. A drop of the sample solution was left on the carbon-coated copper grids for 1 min. Then, excess liquid was sucked away with a filter paper. Then, a drop of sodium phosphotungstate solution was left on the cooper grid for 1 min and the excess liquid was sucked away with a filter paper.

Research topics

Our group is interested for more than twenty years in the synthesis and the physico-chemical characterization of fluorocarbon amphiphilic compounds. Different studies relative to the design and synthesis of F-amphiphilic compounds with specific properties (antibacterial, antioxidant, metal binding, antiviral...) have been investigated. We have described methodological developments for the synthesis of fluorocarbon and hybrid fluorocarbon/hydrocarbon series to produce molecular tailored amphiphiles for applications in the fields of drug or gene delivery, cosmetics, detergency, complexation. We have also developed access to different kinds of amphiphiles: fluorinated lipopeptides or peptidoamines analogues, triazoles and various original hydrophobic parts for surfactants. Specific characterization techniques for Langmuir monolayers, micelles, vesicles, hydrogels have been used and correlation between molecular structure and amphiphilic properties have been established. We have been also interested from some years ago on wood surface treatment with fluorinated compounds for hydrophobation purposes in order to limit its affinity for water and reduce its susceptibility to decay.

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