Perfluoroalkylated poly(oxyethylene) thiols: Synthesis, adsorption dynamics and surface activity at the air/water interface, and bubble stabilization behaviour

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ARTICLE INFO

ABSTRACT

We report the synthesis of four new perfluoroalkylated thiols, $C_nF_{2n+1}(CH_2)_2(OCH_2CH_2)_ySH$ ($FnH2(OE)_y$) with $n = 4$ and 6; $y = 4$ and 6, that have a hydrophilic poly(oxyethylene) (POE) segment inserted between the hydrophobic fluorinated chain and the thiol functional group. The dynamics of adsorption and surface activity of these compounds at the air/water interface were studied using bubble profile analysis tensiometry. The adsorption kinetics profiles show that all compounds diffuse rapidly to the air/water interface and decrease the interfacial tension of water to values ranging from 16.5 to 31.6 mN m^{-1}, which qualifies them as potential components of microbubble shells. Their ability to self-assemble and stabilize gaseous microbubbles in the presence or absence of a fluorocarbon gas (perfluorohexane) was investigated by optical microscopy. Three out of the four compounds (the two $F6$ derivatives and $F4H2(OE)_6$) were able to form and stabilize microbubbles. Microbubbles based on both $F6$ PEG thiols are more stable than those based on the $F4$ derivative. The number of oxyethylene (OE) groups substantially influences bubble stability; the higher the number of OEs, the more stable the microbubbles. Finally, the most important stabilising effect was obtained by introducing an internal fluorocarbon gas, whose presence in the bubble increases bubble stability from 6 h to 5 days for the most promising candidate, $F6H2(OE)_6SH$.

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1. Introduction

Partially fluorinated thiols have proved to be effective components for the elaboration of 2D self-assembled monolayers (SAMs) adsorbed at the surface of metals or metal oxides for nanomaterials fabrication. Such SAMs provide nanoscale surface coatings useful in various technologies such as corrosion inhibition and microelectromechanical systems (MEM) and biomaterials coatings [1,2]. Series of partially fluorinated thiols $C_nF_{2n+1}(CH_2)_mSH$, with $n = 6–10$; $m = 2–17$ have been synthesized and have produced nano-coatings with controlled wettability [2]. SAMs assembled on 2D flat surfaces have been shown to allow selective immobilization of proteins [3]. In the latter case, the SAMs were obtained from partially fluorinated disulfides with a poly(oxyethylene) (POE) chain grafted in terminal position (Scheme 1a) [3]. More recently, other POE fluorinated thiols have been used as ligands to protect gold nanoparticles in

contrast agents for ^{19}F magnetic resonance imaging (MRI) (Scheme 1b) [4]. The POE chains were intended to increase the dispersibility of gold nanoparticles grafted with perfluoroalkyl (F-alkyl) chains via the thiol function. However, to the best of our knowledge, all the F-alkylated thiols reported so far carry the POE moiety in terminal position, the fluorinated chain being inserted between the latter and a hydrocarbon segment.

Here, we report the synthesis of four F-alkylated thiols, $C_nF_{2n+1}(CH_2)_2(OCH_2CH_2)_ySH$ ($F_nH_2(OE)_y$ with $n = 4$ and 6; $y = 4$ and 6), in which a POE spacer is inserted between a terminal F-alkyl chain and the thiol function (Scheme 1c). We expected that changing the molecular topology of these compounds would modify their behaviour in terms of adsorption at the air/water interface and their molecular organization at this interface, as compared to the previously reported compounds. Molecular organization is known to depend strongly on the position of the self-assembly-promoting F-alkyl chains [5,6]. More generally, there is a critical need for new components specifically designed for controlling interfacial film properties [7–9]. The mechanical properties of thin surfactant films, such as stability and viscoelasticity, are preeminent parameters that determine the practicability

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a) $\left[S(CH_2)_2OCH_2(CF_2)_8CH_2(OCH_2CH_2)_yOH \right]_2$ $y = 1, 4$

b) $CH_3O(CH_2CH_2O)_yCH_2(CF_2)_8CH_2SH$ $y = 3, 4, 6, 12\text{-}13$

c) $C_nF_{2n+1}(CH_2)_2(CH_2CH_2O)_ySH$ $n = 4, 6; y = 4, 6$

Scheme 1. Molecular formulae of *F*-alkylated disulfides (a) and thiols (b) bearing a poly(oxyethylene) (POE) chain in terminal position; from [3] and [4], respectively. (c) Molecular formula of *F*-alkylated thiols carrying a POE spacer inserted between the thiol function and a terminal *F*-alkylated chain (this work).

of self-assembled colloids in a wide range of applications [9]. Gas microbubbles are, for example, promising theranostic agents susceptible to crossing physiological barriers with limited damage under focalized application of ultrasound [10–12]. Shell film viscosity and elasticity, and hence, shell composition, determine the inertial cavitation threshold so as to either achieve or avoid cavitation at a given operating pressure [13,14]. Control of surfactant film elasticity is therefore highly desirable. The surface activity of the new *F*-alkyl POE thiols was investigated by bubble profile analysis tensiometry, and their kinetics of adsorption at the air/water interface were determined. Their ability to stabilize microbubbles of air or perfluorohexane-saturated air was also investigated.

2. Experimental part

2.1. General

All starting materials were purchased from Sigma (See Supporting Information) including *F*-hexane (purity > 99%) and Pluronic F-68 (a polyoxyethylene-polyoxypropylene triblock copolymer, MW ∼ 8300, purity > 99%). Water was purified using a Millipore system (surface tension: 72.1 mN m^{-1} at 20 °C, resistivity: 18.2 MΩ cm). ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded in CDCl$_3$ with a Bruker AM 400 spectrometer. Chemical shifts are reported in parts per million (δ in ppm) relative to Me$_4$Si (^{1}H, ^{13}C) and CFCl$_3$ (^{19}F).

The detailed procedure for the synthesis of *F*6H2(OE)$_4$SH is described below.

2.2. Synthesis of 15,15,16,16,17,17,18,18,19,19,20,20,20-tridecafluoro-3,6,9,12-tetraoxaicosane-1-thiol 7 (F6H2(OE)$_4$SH).

2.2.1. 1-Phenyl-2,5,8,11-tetraoxatridecan-13-ol 1

The benzyl protected compound **1** was synthesized following an earlier report.[15] ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 7.27–7.38 (m, 5*H*), 4.57 (s, 2*H*), 3.55–3.7 (m, 16*H*). ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 137.8, 128.0, 127.5, 127.3, 72.9, 72.4, 70.2, 70.2, 70.2, 69.9, 69.1, 61.2.

2.2.2. 1-Phenyl-2,5,8,11-tetraoxatridecan-13-yl 4-methylbenzenesulfonate 2

To a stirred solution of the benzyl-protected compound **1** (10.00 g, 35.17 mmol) and triethylamine (7 mL) under argon, was added dropwise *p*-toluenesulfonyl chloride (6.91 g, 36.22 mmol, 1.03 eq) in dry CH$_2$Cl$_2$ (15 mL) over 5 min. The reaction mixture was stirred for 16 h and diluted with diethyl ether (25 mL). The organic phase was washed with a 1 N HCl solution, a 5% NaHCO$_3$ solution, water and dried over Na$_2$SO$_4$, filtered and the solvent was evaporated to give compound **2** (14.95 g, 97%) as a light brown liquid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 7.8 (m, 2*H*), 7.27–7.4 (m, 7*H*), 4.56 (s, 2*H*), 4.15 (m, 2*H*), 3.5–3.7 (m, 14*H*), 2.44 (s, 3*H*). ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 144.7, 138.2, 133.0, 129.8, 128.3, 127.9, 127.7, 127.5, 73.2, 70.7, 70.6, 70.5, 69.4, 69.2, 68.6, 21.6.

2.2.3. 17,17,18,18,19,19,20,20,21,21,22,22,22-Tridecafluoro-1-phenyl-2,5,8,11,14-pentaoxadocosane 3

A solution of compound **2** (3.28 g, 7.47 mmol, 1.20 eq) and *F*-hexylethanol (C$_6$F$_{13}$C$_2$H$_4$OH) (1.35 mL, 2.27 g, 6.23 mmol) in dry dioxane (30 mL) was stirred under argon. To this, powdered KOH (1.40 g, 24.9 mmol, 4 eq) was added, and the resulting reaction mixture was refluxed under argon for 48 h. The brown reaction mixture was cooled down to room temperature and water added. The mixture was extracted with diethyl ether (4 times) and the combined ether phases were washed with water and dried over Na$_2$SO$_4$. Solvent was evaporated to give a brown liquid, which was purified by flash column chromatography on silica gel using a 1:1 mixture of ethyl acetate and pentane to afford compound **3** (963 mg, 25%) as a light orange coloured liquid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ (ppm): 7.27–7.38 (m, 5*H*), 4.56 (s, 2*H*), 3.55–3.8 (m, 18*H*), 2.42 (m, 2*H*). ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 128.3, 127.9, 127.7, 127.6, 107–122 (m), 73.2, 70.6, 70.6, 70.6, 70.5, 70.4, 70.2, 69.4, 69.2, 63.1 (t), 61.6, 31.5 (t), 21.6.

2.2.4. 15,15,16,16,17,17,18,18,19,19,20,20,20-Tridecafluoro-3,6,9,12-tetraoxaicosan-1-ol 4

A solution of **3** (750 mg, 1.19 mmol) in methanol (25 mL) was thoroughly degassed by using repeated cycles of vacuum and argon. Pd/C (75 mg, 10% of the mass of the substrate) was added and degassed repeatedly. Finally, the flask was filled with hydrogen using a balloon and stirring was continued overnight under hydrogen. The reaction flask was then flushed with argon and the contents were filtered through celite and the celite was thoroughly washed with methanol. The solvent was evaporated to yield a colourless oil that was purified by flash column chromatography on silica gel; elution was achieved with a gradient of pure ethyl acetate to 5% methanol in ethyl acetate to get compound **4** (623 mg, 97%) as a colourless liquid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 3.5–3.8 (m, 18*H*), 2.43 (m, 2*H*). ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 107–122 (m), 72.5, 70.6, 70.5, 70.5, 70.4, 70.3, 63.1 (t), 61.6, 31.5 (t).

2.2.5. 15,15,16,16,17,17,18,18,19,19,20,20,20-Tridecafluoro-3,6,9,12-tetraoxaicosyl methanesulfonate 5

To a solution of **4** (619 mg, 1.15 mmol) and triethylamine (160 μL, 116 mg, 1.15 mmol) in dry THF (15 mL) under argon were added dropwise methanesulfonyl chloride (131 mg, 1.15 mmol) in THF (15 mL). The resulting turbid white reaction mixture was stirred for 2 h and ether (25 mL) was added. The mixture was washed with 2% HCl and water, dried over Na$_2$SO$_4$ and the solvent was evaporated to give **5** (668 mg) as a white turbid liquid that was used in the next reaction without further purification. ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 4.38 (m, 2*H*), 3.55–3.82 (m, 16*H*), 3.07 (s, 3*H*), 2.43 (m, 2*H*).

2.2.6. S-15,15,16,16,17,17,18,18,19,19,20,20,20-tridecafluoro-3,6,9,12-tetraoxaicosyl ethanethioate 6

A solution of mesylate **5** (650 mg, 1.05 mmol) and potassium thioacetate (240 mg, 2.1 mmol, 2 eq) in dry DMF (5 mL) was heated to 80 °C for 90 min under argon. The light orange coloured reaction mixture was cooled down and water was added. It was extracted with ethyl acetate (3 times) and the combined organic phase was washed with water and dried over Na$_2$SO$_4$. Evaporation of the solvent gave a yellow coloured liquid. This liquid was adsorbed onto a silica gel column and eluted with gradients of 10 to 13% ethyl acetate in dichloromethane to get **6** (460 mg, 73%) as a light yellow coloured liquid. ^{1}H NMR (CDCl$_3$, 400 MHz) δ: 3.78 (t, 2*H*), 3.55–3.7 (m, 14*H*), 3.09 (t, 2*H*), 2.42 (m, 2*H*), 2.33 (s, 3*H*). ^{13}C NMR (CDCl$_3$, 75 MHz) δ (ppm): 107–122 (m), 70.7, 70.6, 70.5, 70.3, 69.7, 63.1 (t), 31.5 (t), 30.5, 28.8.