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SYNTHESIS OF HOMOGENEOUS POLYOXYETHYLENE PERFLUORCALKYL SURFACTANTS

A NEW METHOD

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Abstract—Polyoxyethylene perfluoroalkyl surfactants are synthesized from polyoxyethylene glycols using an appropriate intermediate monooxyphosphonium salt. In contrast with methods involving the polyaddition of ethylene oxide to a fluoroalcohol, the present procedure allows us to obtain surfactant molecules with a definite number of oxyethylene units, i.e. with a well-defined hydrophile lipophile balance (HLB). Fluorinated microemulsions could thus be prepared for the first time by mixing the surfactant of appropriate HLB to water and a fluorocarbon.

An interesting feature of fluorinated compounds is their high solubility of gases, such as O_2 or CO_2. This property has suggested a probable utility of fluorinated solvents as O_2 carriers in artificial blood and liquid breathing.[1,2] They must be used fror this purpose as aqueous solutions so as to dissolve other compounds of biological importance. As fluorocarbons are highly hydrophobic molecules, this requirement can be reached only as emulsions[3] of fluorocarbons using an appropriate amphiphile. As the solubility of O_2 seems to depend mainly on the molar ratio of fluorinated compounds in the emulsion, we have devised to use surfactant molecules whose hydrophobic moiety is itself a highly fluorinated alkyl chain. Another objective of these investigations was to obtain *microemulsions*—instead of emulsions as it is the case in the procedures presently known—which are expected to be easier to prepare from their components and much more stable in the course of time. This requires in turn as a first step to have at our disposal a synthesis method which allows us to prepare a collection of pure surfactants, in which the lengths of the hydrophobic and hydrophilic moieties can be adjusted at will.

In this work, we describe a procedure to synthesize surfactants with a general formula $R_f(CH_2)_m(OCH_2CH_2)_nOH$, where $R_f = C_nF_{2n+1}$. General methods are existing in the literature[4] to prepare ethers from two alcohols—Williamson's synthesis,[5] or etherification of the tosylate.[6] However, when the pair of alcohols involves a polyol, such as ethyleneglycol, polyetherification is generally occuring and thus results into inextricable mixtures of compounds. The same is true for polyaddition of ethylene oxide to the corresponding fluoro-alcohol $R_f(CH_2)_mOH$.[7] It thus appears necessary to devise a new procedure to prepare unambiguously pure surfactants of the type described above.

Using a monosalt of polyoxyethylene oxy (trisdimethylamino)phosphonium (ATDP)[8] as an activated intermediate opens a new way to the synthesis of the desired molecules. Monosalts of ATDP are selectively obtained with high yields (Table 1) using a two-step reaction (Scheme 1)

$$HO(C_2H_4O)_nH \xrightarrow{PY_3CCl_4} HO(C_2H_4O)_nPY_3Cl \xrightarrow{KPF_6} HO(C_2H_4O)_nPY_3PF_6$$

n = 4 1		n = 4 4
n = 5 2	Y = $N(CH_3)_2$	n = 5 5
n = 6 3		n = 6 6

Scheme 1

They are submitted in a further experiment to nucleophilic substitution by the appropriate polyfluoroalkoxide. Nucleophilic substitution is actually prefered to elimination reactions if the nucleophilic reagent is not too basic. In the present case, although polyfluoroalkoxides are poor nucleophiles, their basic character is fortunately much weaker yet.[9] The latter property is the more important as the reacting alkoxide should not ionize through proton exchange the hydroxyle functions in the ATDP salt or in the newly formed ether. The desired product was effectively obtained, free from polymerization products and dialkylether.

The choice of the solvent is of great importance. It should allow the sodium hexafluorophosphate formed in the reaction to precipitate and the ion pair $HO(C_2H_4O)_nPY_3^{\oplus}R_f(CH_2)_mO^{\ominus}$ to be formed so as to promote a facile further nucleophilic substitution.[10] On the basis of the above mentioned conditions and of previous results from kinetic studies,[10] (by reacting the anion with its counter ion in a solvent of low polarity we attain the optimal conditions for the nucleophilic reaction), dioxane proved to be the best reacting medium. The analysis of by-products at the end of the reaction actually shows the presence of $NaPF_6$ and HMPA

Table 1 $H(OC_2H_4)_nOPY_1PF_4$* (obtained following Scheme 1)

Compound	n	reaction solvent	θ °C	hrs	Yields %
4	4	THF	-40	2.5	93
5	5	THF-Et_2O 3/1	-35	3.5	92
6	6	THF-Et_2O 3/1	-28	3.5	92

a. Y = NMe_2

Conditions of operation had to be carefully optimized to obtain good yields of products. Using an excess of alkoxide ion does not improve the quantity of product. A temperature of 60° was found most convenient. It allowed us to reduce the time of reaction to 24 hr without the production of undesirable by-products (from elimination reactions), as it was observed on increasing the temperature up to the boiling point of dioxane. The substitution step (Scheme 2; method A) was therefore carried out by heating equimolar quantities of reactants in dioxane at 60° for 24 hr. Polyfluorinated ethers with n = 4,5,6 ethyleneglycol units have been prepared according to this procedure (Table 2)

$$R_f(CH_2)_mO^{(-)}Na^{(+)} + HO(C_2H_4O)_nPY_1PF_4 \xrightarrow{\text{dioxane}}$$

$$R_f(CH_2)_mO\text{–}CH_2\text{–}CH_2\text{–}(OC_2H_4)_{n-1}\text{–}OH + NaPF_4 \longrightarrow$$

$$R_f(CH_2)_m\text{–}O\text{–}(CH_2CH_2O)_n\text{–}OH + OPY_1$$

8 to 14

Y = $N(CH_3)_2$; $R_f = C_6F_{2m+1}$

Scheme 2 Method A

The purity of each surfactant is examined by thin layer chromatography on silicagel (using three eluents: EtOAc–cyclohexane 80:20, EtOAc, and EtOAc-MeOH 92:8) and centesimal analysis.

Surfactants with n > 6 cannot however be obtained in this way, as the corresponding ethylene glycol molecules are not commercially available. We have therefore devised an extension of the above method using alkoxide ions derived from the compounds prepared above (Scheme 3).

$$R_f(CH_2)_m(OC_2H_4)_nO^{(-)}Na^{(+)} + HO(C_2H_4O)_pPY_1PF_4 \rightarrow$$

$$R_f(CH_2)_m(OC_2H_4)_{n+p}OH$$

Scheme 3

In fact, it is impossible to obtain the pure alkoxide without simultaneously ionizing the OH group of the ATDP salt. In order to avoid undesirable side-reactions (see above), the OH function of the ATDP salt was protected by a tetrahydropyrane substituent[11,12] (Scheme 4).

$$HO(C_2H_4O)_nPY_1PF_4 \xrightarrow[CH_2Cl_2]{\text{DHP APTS}} THPO(C_2H_4O)_nPY_1PF_4$$

Y = $N(CH_3)_2$; DHP = dihydropyran; THP = tetrahydropyran; APTS = paratoluenesulfonic Acid; n = 4 7

Scheme 4

This protecting group was chosen so as to resist to the basicity of the reaction medium and to be easily removed by acidification (Scheme 5, method B)

$$R_f(CH_2)_m(OC_2H_4)_nO^{(-)}Na^{(+)} + THPO(C_2H_4)_pPY_1PF_4 \rightarrow$$

$$R_f(CH_2)_m(OC_2H_4)_{n+p}OTHP \xrightarrow{H^+} R_f(CH_2)_m(OC_2H_4)_{n+p}OH$$

Scheme 5 Method B

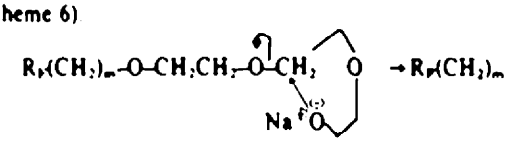
Table 2 Compounds $F(CF_2)_q\text{–}(CH_2)_m\text{–}(OC_2H_4)_nOH$*

Compound	type q	m	n	method[a]	Yields %	n_D^{21}
8	6	1	4	A	42	1.375
8	7	1	4	B	40	1.375
9	6	1	5	A	41	1.385
10	7	1	5	A	40	1.382
11	6	1	6	A	39	1.393
12	7	1	6	A	39	1.389
13	6	3	6	B	19	-
14	7	1	8	B	5	1.402

a. Scheme 2 or Scheme 5

b. I.R. Spectrum ν_{max} 3650-3200 OH, 2300-1120 (CF), 860-800 CF_3. ^1H NMR ($CDCl_3$ or CCl_4/TMS) : δ = 3.65 (m.2H) ; 4.15 (dd. J^4_{HF}=14, J^5_{HF}= 1.5. $(H_4)_n$).

Yields were however much lower in this variant, by about a factor of one half. We checked that the presence of the protecting tetrahydropyrane group was not responsible for this matter of fact (by performing method A, with n = 6, using a protected ATDP salt and obtaining an unchanged 92% yield). This is presumably due to the higher basicity of the alkoxide ion used in variant B, this results into a higher participation of elimination reactions. Moreover we observed a self-degradation of the alkoxide ion which is segmented, under the conditions of the reaction, into dioxane and the alkoxide ion with a chain length decreased by two oxyethylenic units (Scheme 6)



$$-O-CH_2-CH_2O^-Na^+ + \text{dioxane}$$

Scheme 6 Self degradation

We are currently investigating new routes for the synthesis of long-chain ethers keeping the same high yields as those presently obtained by method A.

Emulsifying properties of the prepared surfactants can be correctly described by establishing ternary phase diagrams of the systems surfactant, water and alkane at various temperatures. Such lengthy measurements are now in progress and are deferred to later publications. Meanwhile, the interest of these surfactants can be simply shown by displaying their hydrophile–lipophile balance (HLB)[13,14] and the cloud points of their aqueous solutions (Table 3). The emulsifying efficiency of a surfactant has been related to the polarity of the molecule, empirically defined as the HLB on various arbitrary scales (*cf* Table 3).[13,14] The HLB values for our fluorinated surfactants are smaller than their hydrogenated counterparts, this results from the much more lipophilic character of the CF_3 and CF_2 units, as compared to the analogous CH_3 and CH_2 units (by a factor of 1.8 using the increments of Davies). However good emulsifying properties can be expected towards fluorinated oils, since the hydrophilic tendency of the perfluorinated alkanes is much less pronounced than that of the homologous alkanes.

The influence of HLB is also reflected in the *cloud point* (CP) of the binary 1% (w/w) solutions of surfactant with water (Table 3). The cloud point is defined by the sudden onset of turbidity (separation into two phases) of a clear non-ionic micellar surfactant solution of raising the temperature.[15,17] This effect has been traced to the breaking of H-bonds within the polar heads of direct (O/W) micelles above a critical temperature. The cloud point is related to the polarity of the surfactant, and therefore increases in a parallel direction to the HLB. This is clear from our data for fluorinated surfactants where the cloud point decreases from 10° to 1° when the HLB is decreased from 5.18 to 4.85, and goes below the freezing point of solutions (*ca* 0°) for smaller HLB. This parallelism between CP and HLB values also accounts for the much higher CP values obtained for the analogous hydrogenated surfactant molecules. Most important, the solubilization of alkanes to obtain microemulsions is also related to the cloud point. Strongly hydrogen-bonded micelles with a high cloud point are less able to incorporate large quantities of oil. This means that an important degree of oil solubilization is possible just below the cloud point of a given surfactant.

Table 3 HLB[13,14] and cloud points of fluorinated surfactants and hydrogenated homologs

Compounds[a]		HLB_D[a,b]		HLB_G[a,c]		Cloud points[a] (°C)	
FE	HE	FE	HE	FE	HE	FE	HE
6:5	C_7E_5	4.85	7.23	8.31	14.10	1	75[14]
6:6	C_7E_6	5.18	7.56	9.15	14.80	10	83[15]
6:6	C_9E_6	4.24	6.60	8.76	13.80	<0	-
7:4	C_8E_4	3.65	6.42	6.71	12.60	<0	35.5[16]
7:5	C_8E_5	3.98	6.75	7.64	13.50	<0	55[16]
7:6	C_8E_6	4.31	7.08	8.46	14.30	<0	-
7:8	C_8E_8	4.98	7.74	9.81	15.31	6	-

a. FE fluorinated ethers and HE hydrogenated ethers homologs

b. Hydrophile-lipophile balance (HLB) calculated by equation of Davies[14] $HLB_D = 7 + \Sigma$ number of hydrophilic groups $+ \Sigma$ number of lipophilic groups.
Increments used in this calcul :
hydrophilic groups : $-OCH_2CH_2-$=0.33, -OH=1.9
hydrophobic groups : $-CF_3$=-0.87, $-CF_2$=-0.87, CH_3=-0.475, $-CH_2$=-0.475.

c. Hydrophile-lipophile balance calculated by equation of Griffin[13]

$$HLB_G = \frac{\text{Mass of hydrophilic part}}{\text{Molecular mass}} \cdot 20$$

Another factor is the simultaneous increase of the cloud point generally observed by addition of oil.[18] Thus incorporation of fluorocarbon to aqueous solutions of fluorinated surfactants may bring the cloud point up to *ca* 37° with simultaneously a high concentration of fluorinated compounds (oil plus surfactant), thus defining ideal conditions for using such solutions as convenient blood substitutes. This was not possible with polydisperse solutions of surfactants with n > 10, for which the cloud point is situated well above 37° thus allowing the formation of dispersions (emulsions) and not of stable microemulsions. This point explains our efforts to synthesize homogeneous polyoxyethilenic surfactants, in spite of the considerable experimental difficulty involved.

EXPERIMENTAL

Solvents and liquid reagents were purified and dried by standard procedures.[19] IR spectra were recorded on a Perkin–Elmer 457 spectrophotometer and NMR spectra on a Perkin–Elmer R12B or Cameca 250 MHz. Elemental analyses of the fluorinated compounds are in good agreement with the proposed structures.

Tetraethyleneglycol monooxy (trisdimethylamino) phosphonium hexafluorophosphate 4. The general procedure has already been described.[8] To a stirred mixture of 1 (9.71 g) and CCl_4 (19.25 g) in dry THF (40 ml) under N_2 at −40° was added dropwise during 2 hr a soln of hexamethylphosphorous triamide (8.16 g) in dry THF (10 ml), stirring was continued for another 30 min. The mixture was poured into water (100 ml), twice extracted with water (2 × 50 ml), and the combined aqueous phases were washed with ether (100 ml).

A soln of potassium hexafluorophosphate (18.4 g) in water (30 ml) was added to the aqueous phase, this phase was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and evaporated to give the crude product which was washed with ether. The salt 4 (23.30 g–93%) was obtained as an oil. ν_{max}: 3700 and 3200 (OH), 1325 (P–O), and 860 (PF_6). ^1H NMR (CD_2Cl_2) δ: 2.8 d J_{HP} = 10 Hz, $[N(CH_3)_2]_3$, 3.67 [m, $H(OCH_2CH_2CH_2)_4OCH_2$]. 4.31 [m, CH_2–O–P].

In the same conditions are prepared the other ATDP salts 5, 6 and 7. Spectroscopic data (IR, NMR) and elemental analysis agree with formulas.

Tetraethyleneglycol mono [1'H1'H perfluorooctyl] ether (714) 8. To a dioxane (80 ml) soln of 0.012 mol of the sodium 1H1H perfluorooctanolate, prepared by proton exchange between 1H1H perfluorooctanol with NaOMe and subsequent MeOH evaporation in vacuum, 0.01 mol (5.01 g) of 4 was added. The soln was heated to 60° for 24 hr under inert gas atmosphere. After reaction, the product was extracted with ether and the organic layer washed with a dil HCl aq and water, and dried over $MgSO_4$. Vacuum evaporation gave a crude product. The purification by chromatography on silicagel (eluting with EtOAc) gave 8 (2.40 g–42%).

Compound 8 with pyranil ATDP salt 7. Exactly the same procedure as above, replacing 4 by 7, was followed. The ether extraction was washed with a 20% trifluoroacetic acid soln under stirring for 4 hr (depyranilation). The organic phase was washed with water and dried over $MgSO_4$. Vacuum evaporation gave a crude product. The purification of a silicagel column gave 8 (2.3 g–40%) as an oil. n_D^{20} = 1.375. ν_{max}: 3650–3200 (OH), 1300–1120 (CF), 860–800 (CF_3). ^1H NMR (CD_2Cl_2) δ: 3.60–3.69 m (OC_2H_4)$_4$, 3.88 s (OH), 4.08 dd J_{HF}^4 = 14.1 Hz J_{HF}^5 = 1.4 Hz CF_2–CH_2. (Found: C, 33.25; H, 3.38; F, 49.08. $C_{16}H_{16}O_5F_{14}$ requires: C, 33.35; H, 3.32; F, 49.45%).

In the same conditions are prepared the other compounds 9 to 14 (Table 2).

Hexaethyleneglycol mono [1'H1'H, 2'H2'H, 3'H3'H perfluorononyl] ether (636) 13. To a dioxane (80 ml) soln of 0.012 mol of sodium diethyleneglycolate mono [1'H1'H, 2'H2'H, 3'H3'H perfluorononyl] ether prepared as above (preparation of 8), 0.01 mol of 7 was added. The soln was heated to 60° for 24 hr under inert gas atmosphere. After reaction, the product was extracted with ether. The organic layer was washed with a 20% trifluoroacetic acid soln under stirring for 4 hr (depyranilation). The organic phase was washed with water and dried over $MgSO_4$. Evaporation in vacuum gave a crude product. The purification on a silicagel column (eluting with EtOH) gave 13 1.22 g–19% oil; ν_{max}: 3640–3210 OH, 1295–1120 CF, 860–800 CF_3; ^1H NMR (CCl_4) δ: 1.83–2.2 m $CF_2(CH_2)_2$, 3.64 m $CH_2(OC_2H_4)_3$, 3.7 s,OH; (Found: C, 39.27; H, 4.82; F, 38.92. $C_{21}F_{17}H_{20}O_5$ requires: C, 39.32; H, 4.71; F, 38.50%).

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