Synthesis of Novel Perfluoroalkyl Nonionic Surfactants with a Bipodal Hydrophilic Moiety

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Monodisperse perfluoroalkyl *N,N'*-polyethoxylated amides, synthesized as dimethyl ether derivatives, $C_nF_{2n+1}CH_2C(O)N([C_2H_4O]_mMe)_2$ are efficient bipodal nonionic fluorinated surfactants.

Aqueous microemulsions of fluorocarbons have been obtained for the first time in this laboratory by using well-defined monodisperse fluorinated polyoxyethylene surfactants.[1,2] These solutions may offer an alternative to commercial macroemulsions at present used as temporary blood substitutes because of their long-term stability and their better solubilization of fluorocarbons, and, consequently, of molecular oxygen.[3] However it seems that these solutions have short-term toxicity after intravenous infusion to animals.[1a] Among many possible causes, toxicity could be due primarily to membrane-damaging effects from the surfactant.[4] Nonionic polyoxyethylenic surfactants are known to decrease the resistance of lipid bilayers in liposomes. Membrane disorganization effects seem to pass through a maximum corresponding to the number (n = 6—13) of oxyethylene units in the hydrophilic part of the surfactant molecule.[4] On the other hand values of n = 4—6 were necessary in our studies to ensure the accessibility of microemulsions.[2] A simple way of making these two requirements mutually compatible would be to share the total number of oxyethylene glycol units necessary to achieve the appropriate hydrophilic/lipophilic balance of the surfactant molecule between several chains. The resulting shorter oxyethylene chains would be expected to be less prone to modify the permeability of biological membranes. These compounds also have a potential use as multidentate neutral ligands for cation complexation[5] in micellar solutions.

The multi-chain structures envisaged required multivalent bridging units between the fluorinated hydrophobic part and the hydrophilic ends in the surfactant molecule. This prompted us to use amide bonds in the place of ether[1b] or thioether[6] bridges in the two series of surfactants previously investigated to prepare fluorinated microemulsions. We obtained in this way surfactant molecules containing two hydrophilic ends (bipodal surfactants), of the general type (**1**). The possibility of using an amide bond to assemble the two moieties of an amphiphilic molecule has been previously demonstrated in the case of monosubstituted amides[7,8] $C_nF_{2n+1}CH_2C(O)NH[C_2H_4O]_mH$ and $C_nF_{2n+1}C(O)NH[C_2H_4O]_mH$.

However, all these compounds suffer slow degradation, as easily inferred from their i.r. spectra. This is not unexpected, in view of the behaviour of the analogous hydroxyalkanamides, which are known to equilibrate with the isomeric amino esters, which further rearrange into a series of undesired side-products.[9] As the surface-active properties of non-ionic surfactants, and especially the formulations of microemulsions, are very sensitive to the purity of compounds,[10] we decided to mask the hydroxylic functions in (**1**) by *O*-methylation, as in (**2**; R = Me). This prevents equilibration with aminoesters, while the decrease of hydrophilicity is sufficiently small for the surface-active nature of the molecule to be retained.

The strategy for the synthesis consisted of building up the corresponding amine (**3**), which was then condensed with an activated form (chloride in general) of the corresponding perfluorinated acid. In this way, the fluorinated starting material was consumed most economically in one reaction with high yield, and purification of the final surfactant was easy. The intermediate (**3**) itself was obtained by treating protected iminodiethanol with activated polyethylene glycol monomethyl ether of rank ($m-1$).

The set of compounds prepared in this way, together with their surface-active properties, are displayed in Table 1. Their purity was checked by elemental analysis, i.r. (absorption of amide carbonyl at 1650 cm^{-1}) and ^1H n.m.r. spectrocopy, and semi-logarithmic plots of γ *vs.* concentration in aqueous solution, which are typical of monodisperse surfactants.

$$C_nF_{2n+1}CH_2C(O)N([C_2H_4O]_mR)_2$$
(**1**) R = H
(**2**) R = Me

$$HN(C_2H_4OH)_2 \xrightarrow{Ph_3CCl,\ 80\%} Ph_3CN(C_2H_4OH)_2$$
(**4**)

$$MeO[C_2H_4O]_{m-1}H \xrightarrow{p\text{-}MeC_6H_4SO_2Cl} MeO[C_2H_4O]_{m-1}SO_2C_6H_4Me\text{-}p$$
(**5**)

$$(4) + (5) \xrightarrow[85\%]{KOH,\ heat,\ THF} Ph_3CN([C_2H_4O]_mMe)_2 \xrightarrow[96\%]{H^+} HN([C_2H_4O]_mMe)_2$$
(**3**)

$$(3) + R_FC(O)X \longrightarrow (2)$$
X = Cl or *N*-oxybenzotriazole

Table 1. Bipodal non-ionic surfactants (**2**).

n	m	Yield[a] (%)	n_D^{20}	10^4 (c.m.c.)[b] /mol dm^{-3}	λ[c] /mN m^{-1}
6	2	94	1.395	3.63	16
6	3	86	1.405	8.7	18
6	4	84	1.415	10.0	24
8	2	89	1.385	0.10	18.5
8	3	85	1.398	0.14	20.5
8	4	85	1.406	0.23	24
10	2	80	1.383	[d]	[d]
10	3	87	1.392	0.12	21
10	4	82	1.402	0.17	24

[a] Computed with respect to the activated form of the perfluorinated acid. [b] Critical micelle concentration. [c] Surface tension above c.m.c. [d] Insoluble.

C.m.c. values were of the magnitude expected for nonionic surfactants. The surface tension of water in binary solutions was lowered to values characteristic of fluorinated surfactants, *i.e. ca.* 20 mN m^{-1}. In one case ($n = 6$, $m = 2$), the surface tension reached the exceptionally low value of 16 mN m^{-1}. Clear and isotropic solutions were obtained in ternary systems involving water and perfluorodecalin. The synthesis of the corresponding hydrogenated surfactants is being studied for the sake of comparison with the fluorinated analogues.

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