Synthesis of Monodisperse Perfluoroalkyl–Oxyethylene Surfactants with Methoxy Capping: Surfactants of High Chemical Inertness

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Monodisperse fluoroalkyl non-ionic surfactants with a methoxy group capping the hydrophilic head, and having a high chemical inertness and surface properties typical of perfluorinated non-ionic surfactants, have been synthesized.

Within the scope of our research work on the synthesis of chemically defined perfluorinated amphipathic compounds,[1,2] we have already reported the synthesis and surfactive properties of different types of structures: perfluoroalkoxyethylenes,[1,3] perfluoroalkylamides,[2,4] and perfluorolipopeptides.[5] All these compounds allow complex media[6] with fluorinated oils (perfluorodecalin for example) and a polar phase (aqueous or other) to be obtained, and in particular microemulsions.[1,7] These have been proposed as possible alternatives to fluorocarbon emulsions used presently as respiratory gas carriers.[8,9]. Another aspect that is just developing is the use of complex systems as reaction media.[10,11] For all these reasons, surfactants having high chemical inertness could be interesting. We present here a family of compounds possessing a structure which assures their stability with respect to reagents in general.

Effectively, the structures of these products consist of a chemically nearly non-reactive perfluoroalkyl chain[12] which constitutes the hydrophobic tail; the hydrophilic head is a polyoxyethylene unit having a well defined chain length with a methoxy terminal function. This monodisperse structure is composed of only ether type functions which are generally of low reactivity. Our previous observations on a two-chain headed hydrophilic moiety capped with a methoxy group[2] showed that the loss of hydrophilicity due to the replacement of the terminal OH by the OMe group had no drastic effect. A recent study by Tiddy *et al.*[13] on some perhydrogenated compounds of the type C_nH_{2n+1}–O–$(C_2H_4O)_p$–Me indicates that terminal hydroxy groups give rise to products whose surfactive behaviour is equivalent to that of compounds having the same hydrophobic tail but an additional two to three oxyethylene (EO) units with methoxy capping. We have

$$\mathrm{HO(EO)}_p\text{–H} \xrightarrow{\text{i}} \mathrm{BzlO}\text{–}\mathrm{(EO)}_p\text{–H} \xrightarrow{\text{ii}} \mathrm{BzlO}\text{–}\mathrm{(EO)}_p\text{–Me}$$

$$\mathrm{BzlO}\text{–}\mathrm{(EO)}_p\text{–Me} \xrightarrow{\text{iii}} \mathrm{HO}\text{–}\mathrm{(EO)}_p\text{–Me} \xrightarrow{\text{iv}} \mathrm{TsO}\text{–}\mathrm{(EO)}_p\text{–Me}$$

$$\mathrm{Y}\text{–}\mathrm{C}_n\mathrm{F}_{2n}\text{–}\mathrm{CH_2}\text{–}\mathrm{OH} + \mathrm{TsO}\text{–}\mathrm{(EO)}_p\text{–}\mathrm{CH_3} \xrightarrow{\text{v}} \mathrm{Y}\text{–}\mathrm{C}_n\mathrm{F}_{2n}\text{–}\mathrm{CH_2}\text{–O–}\mathrm{(EO)}_p\text{–}\mathrm{CH_3}$$

EO = $-C_2H_4O-$; Ts = p-$MeC_6H_4SO_2$; Py = Pyridine;
solvent = tetrahydrofuran (THF) or dioxane; Bzl = benzyl.

Scheme 1. *Reagents and conditions:* i, BzlCl, aq. NaOH, 90—95% yield; ii, Me_2SO_4, aq., NaOH, 95—98%; iii, H_2/Pd, 97%; iv, TsCl, Py, 90—95%; v, solid KOH, solvent.

prepared some linear molecules having the following general structure: $Y-(CF_2)_n-CH_2-O-(C_2H_4O)_p-Me$.

We present here their preparation, some of their surfactive properties, and the first evaluation of their biological aggressiveness. We shall compare the properties observed for these compounds with those of their analogues having a terminal hydroxy function. The strategy for the synthesis is summarized in Scheme 1. The perfluorinated alcohols which are normally expensive are economically consumed in the ultimate step of the reaction.

It should be noted that this reaction uses solid–liquid phase transfer which allows the bridging of the perfluorinated tail and the hydrophilic head by the ether function. The monomethylethylene glycol acts as both reagent and phase transfer agent. The Williamson condensation is the key step of the synthesis and compared with our previous procedures[1,3] better yields are obtained.

The results of the Williamson condensation using the solid–liquid phase transfer reaction are presented in Table 1. All new compounds gave the expected IR and ^1H NMR spectra, one spot on TLC, and satisfactory elemental analyses.

The surfactive properties were evaluated by surface tension measurements (γ) of their aqueous solutions. Plots of γ *vs.* log [C] (concentration of surfactant) give rise to curves typical of monodisperse surfactants. The minimum of γ(CMC) as well as critical micelle concentration (CMC) values which can be obtained from these curves are shown in Table 1. The γ(CMC) and CMC values of the corresponding compounds having a terminal hydroxy function are also included. It is found that the γ values of the two series are relatively similar. The surface tension of their aqueous solutions is within the usual range observed for perfluorinated surfactants, *i.e. ca.* 20 mN m^{-1}.

The CMCs obtained are characteristic of those observed for fluorinated non-ionic surfactants. These values between the two series are relatively close. Only a slight decrease in CMC was observed for homologous products.

The compounds in which one terminal fluorine atom (Y = F) is replaced by a hydrogen (Y = H) in the fluorinated tail have distinctly lower surfactant activity. The presence of the hydrogen, which is likely to be acidic in nature, causes important changes in the binary structures of the system.

Having examined the existence of ternary systems (water/perfluorodecalin/surfactant) with these different surfactants, isotropic solutions (microemulsions) were observed with some compounds.

The biological aggressiveness of these compounds has been evaluated for the first time. No haemolytic effect on a suspension of red blood cells in an isotonic solution was observed by the addition of these compounds up to a concentration of 10 g dm^{-3}. The addition of increasing amounts of the synthesized surfactants to hybridoma culture medium enabled us to assess their aggressiveness by cell viability measurements.[14] At 0.3 g dm^{-3} these cells have normal growth and viability.

Table 1. Surfactants of the general formula: $Y-C_nF_{2n}-CH_2-O-(EO)_p-Z$.

Compounds[a]							
Y	n	p	Z	Yield/%[b]	n_D (20 °C)	γ(CMC)[c]/ mN m^{-1}	10^4CMC[d]/ mol dm^{-3}
F	6	3	H	—	—	17[e]	1.1
F	6	3	Me	71	1.359	20	1.06
F	6	4	H	—	—	17.5[e]	1.65
F	6	4	Me	70	1.373	18.5	1.15
F	6	5	H	—	—	18[e]	2.4
F	6	5	Me	68	1.386	19.5	1.3
F	7	3	Me	73	1.357	[18][f]$_{\mathrm{sat}}$	(f)
F	7	4	H	—	—	16.5[e]	0.41
F	7	4	Me	69	1.377	17	0.39
F	7	5	Me	67	1.379	17.5	0.5
H	6	3	Me	76	1.372	36	3.4
H	10	3	Me	77	1.352	[29][f]$_{\mathrm{sat}}$	(f)

[a] Y = F or H on terminal carbon tail; n = number of fluorinated carbons; p = number of ethoxy groups (EO = C_2H_4O) per chain in the polar head. Z = terminal group head. [b] Yields calculated on the basis of fluorinated alcohol. [c] Surface tension beyond the CMC. [d] CMC evaluated at the intersection of γ *vs.* log [C]. [e] Ref. 6. [f] These compounds are sparingly soluble in water, hence the absence of CMC at 25 °C. However, we have measured the maximum lowering of the γ of their saturated aqueous solution (γ_{sat}).

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