Synthesis and Evaluation of the Properties of Fluorinated Amphiphilic Amides of 2,2-Bis(hydroxymethyl)propionic Acid

Claude Selve,*[a] Christine Delestre,[a] Samuel Achilefu,[a] Michel Maugras[b] and Fatima Attioui[b]

[a] *Université de Nancy I, Domaine Scientifique Victor Grignard, Laboratoire d'Études des Solutions Organique et Colloïdales, LESOC, Associé CNRS, UA 406, BP 239, F, 54506 Vandoeuvre-lès-Nancy Cedex, France*
[b] *INSERM U 284, Université de Nancy I, Brabois CO 10 F, 54506, Vandoeuvre-lès-Nancy Cedex, France*

The generally fluorinated amides synthesized are shown to be surfactants with negligible haemolytic effect and biological aggressiveness to living cells.

Currently we are concerned with the synthesis and study of the properties of generally non-ionic and essentially fluorinated molecules.[1-3] The ultimate aim is the preparation of mostly biocompatible fluorinated surfactants.[4] In order to obtain products having negligible aggressive effects on cell membranes, we proposed a new family of compounds consisting of a two-chain ethyleneglycol head.[2,5,6] One hypothesis that led to the preparation of these structures rests on the fact that the aggressiveness of a surfactant molecule could be due, among other factors, to the penetration of the cell membranes by the hydrophilic head, which enhances its destructuration. By preparing molecules with a significant head volume, the penetration of the cell membrane becomes more difficult, hence the aggressiveness decreases[5] and the biocompatibility is raised. Within the scope of these investigations, we describe here an efficient synthesis of amides of 2,2-bis(hydroxymethyl)propionic acid using long chain or fluorinated amines. Hydrogenated amides were also prepared under the same conditions, in order to compare their properties. Such a hydrophilic head, based on a quaternary carbon, will have a significant head volume.

The syntheses were effected in a single-step reaction by activation of the acid function. In order to carry out the coupling, classical reagents such as thionyl chloride, should be avoided. We used BOP[7] [benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (Neosysteme, Strasbourg, France)] in the presence of one equivalent of tertiary amine. This reagent exhibits a general high selectivity in the presence of multifunctional products.[8] The surface properties observed for these amides is due to the presence of two primary alcohol groups and an amide function which renders them hydrophilic. The synthesis of fluorinated amides necessitated a preliminary preparation of fluorinated long chain amines. This was realised from commercial 2-fluoro-1-iodoethanes. As a result of the destabilising influence of the perfluoro group on the 2-methylene protons, these products are substrates for which the nucleophilic substitution of the iodide becomes delicate. However, using the azide ion in the phase-transfer method and well adapted experimental conditions allows its substitution with good yields.[9,10] Access to the fluorinated amines is effected by catalytic hydrogenation of the azides obtained. Commercial perhydrogenated long chain amines were used. All the amides obtained are solids.

$$R_F\text{-}CH_2\text{-}CH_2\text{-}I \xrightarrow[95\%]{N_3^-} R_F\text{-}CH_2\text{-}CH_2\text{-}N_3 \xrightarrow[96\%]{H_2/Pd} R_F\text{-}CH_2\text{-}CH_2\text{-}NH_2$$

$$R_F = C_6F_{13};\ C_8F_{17}$$

$$R\text{-}C_2H_4\text{-}NH_2 + HO\text{-}C(O)\text{-}C(CH_2OH)_2CH_3 \xrightarrow{BOP\ (94\text{-}97\%)} R\text{-}C_2H_4\text{-}NH\text{-}C(O)\text{-}C(CH_2OH)_2CH_3$$

$$R = R_F = C_6F_{13};\ C_8F_{17};\ \text{or } R = C_6H_{13};\ C_8H_{17};\ C_{10}H_{21}$$

Scheme 1

The results of the BOP condensation without preliminary protection of the primary alcohol functions, are presented in Table 1. All new compounds gave the expected IR, ^1H NMR, one spot in TLC and satisfactory elemental analyses.

The surfactant properties of the aqueous solutions were evaluated by surface tension measurements (γ) carried out using the Wilhelmy method (Dognon–Abribat tensiometer). The 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 CMC values that can be obtained from these curves are shown in Table 1. A good linearity of the points below, the constant values of γ above the CMC and the sharp change in the curve is in accordance with the purity of the studied compounds. The surface tension of their aqueous solutions and the CMC obtained is within the usual range observed for perfluorinated surfactants, *i.e. ca.* 20 mN m^{-1} and *ca.* 10^{-4} mol dm^{-3}, respectively.

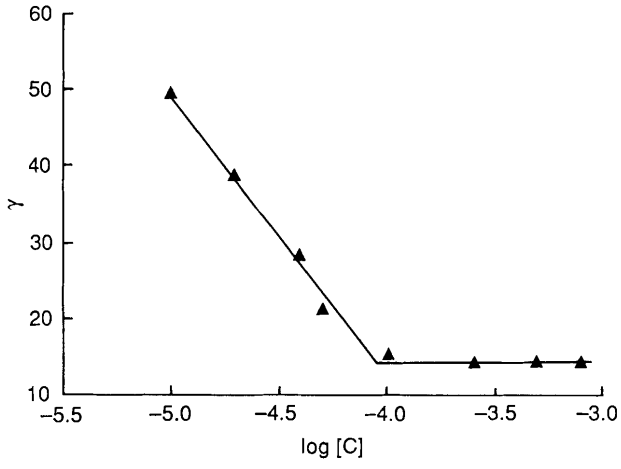

Fig. 1 Plot of γ *vs.* log [C] for binary system, water/C_6F_{13}–C_2H_4–NH–C(O)–$C(CH_2OH)_2CH_3$

Table 1 Surfactants of the general formula: C_nZ_{2n+1}–C_2H_4–NH–C(O)–$C(CH_2OH)_2CH_3$

Compounds[a] Z	*n*	M.p./°C[b]	Yield (%)[b]	γ_{CMC}[c]/ mN m^{-1}	CMC[d] /10^4 mol dm^{-3}
H	6	39	97	28.7	10
H	8	45	95	29	3
H	10	48	95	26	0.7
F	6	78	94	14.3[c]	0.95[c]
F	8	108	95	17.5	0.1

[a] Z = F or H on carbon tail. *n* = number of perhydrogenated or perfluorinated carbons. [b] All the compounds are solids; yields calculated on the basis of carboxylic acid. [c] Surface tension beyond the CMC at 37 °C in water; products are slightly soluble at 22 °C (except for F6 compound γ_{22} = 15.9 and CMC_{22} = 1.26 × 10^{-4} mol dm^{-3}). [d] Critical (micelle) concentration (CMC) evaluated at the intersection of γ *vs.* log [C] at 37 °C.

A biological evaluation of the agressiveness of these compounds has been carried out for the first time. With the perhydrogenated compounds, a haemolytic effect on a suspension of red blood cells in an isotonic solution was observed at 0.15 g dm^{-3}. But no such effect was observed by the addition of the fluorinated compounds up to their aqueous saturation concentration (~0.55 g dm^{-3}). The addition of increasing amounts of the synthesized fluorinated surfactants to hybridoma culture medium enabled us to assess their aggressiveness by cell viability measurements.[5] At 0.5 g dm^{-3} these cells have normal growth and viability. With hydrogenated compounds, in accordance with the results of haemolytic tests, the agressiveness was observed at 0.025 g dm^{-3}.

For comparison in the same conditions a haemolytic effect with the linear head compound [$C_{12}H_{25}$–$(OC_2H_4)_4$–OH = $C_{12}EO_4$] was observed at 0.03 g dm^{-3}, and no haemolytic effect with the fluorinated surfactant having the same linear head [C_6F_{13}–CH_2–$(OC_2H_4)_4$–OH = 614].[11] For hybridoma viability the agressiveness of $C_{12}EO_4$ was observed[11] at 0.003 g dm^{-3} and for 614 at 0.05 g dm^{-3}. In agreement with our first hypothesis, the biological results, thus, appear to confirm the possible role of the polar head volume in cell agressiveness.

We thank Professor J-J. Delpuech and Dr J-C. Ravey (CNRS) for their useful discussion. This work has been generously supported by G.D.R. (CNRS) 'Nouveaux Matériaux tensio-actifs' and research contract sponsored by 'Region Lorraine'.

Received, 13th February 1991; Com. 1/00689D

References

1 G. Mathis, P. Leempoel, J-C. Ravey, C. Selve and J-J. Delpuech, *J. Am. Chem. Soc.*, 1984, **106**, 6162.
2 C. Selve, E. M. Moumni and J-J. Delpuech, *J. Chem. Soc., Chem. Commun.*, 1987, 1437.
3 C. Selve and S. Achilefu, *J. Chem. Soc., Chem. Commun.*, 1990, 911.
4 J. Greiner, A. Manfredi and J-G. Riess, *New J. Chem.*, 1989, **13**, 247 and references cited therein.
5 M. Maugras, J-F. Stoltz, C. Selve, M. Moumni and J-J. Delpuech, *Innov. Technol. Med. Biol.*, 1989, **10/2**, 145.
6 C. Selve, J-C. Ravey, M-J. Stebe, C. El Moujahid, E. M. Moumni and J-J. Delpuech, *Tetrahedron*, 1991, **47/3**, 411.
7 B. Castro, J-R. Dormoy, G. Evin and C. Selve, *Tetrahedron Lett.*, 1975, 1219.
8 Y. Chapleur, B. Castro, R. Toubiana, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1940.
9 E. M. Moumni, PhD Thesis, University Nancy, 1988, p. 163.
10 F. Szönyi, PhD Thesis, University Nice-Sophia Antipolis, 1990, p. 211.
11 S. Ramzaoui, MSc Dissertation, University Nancy, 1989, p. 34.