Synthesis of new fluorinated non-ionic surfactants derived from lactose: the *N*-[2-(*F*-alkyl)ethyl]-lactosylamines and -lactobionamides

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Abstract

The synthesis of new fluorinated non-ionic surfactants derived from α-lactose, the *N*-[2-(*F*-alkyl)ethyl]-lactosylamines (**3**) and -lactobionamides (**4**), is described. These derivatives are readily prepared in good yield in an aza-Wittig reaction from: (i) 2-(*F*-alkyl)ethyl azides which are readily obtained from the corresponding 2-(*F*-alkyl)ethyl iodides; and (ii) α lactose (for compounds **3**) and lactobionic acid (for compounds **4**) without prior protection of the sugar hydroxy groups.

Introduction

The growing importance of non-ionic perfluorinated surfactants has encouraged the search for improved synthetic routes to compounds with good surface active properties [1–3]. Surfactants with fluorinated or hydrogenated chains and sugars as polar heads have potential pharmaceutical (biocompatible formulations) and biochemical (extraction of membrane proteins) applications [4, 5]. Generally, these derivatives are not readily synthesized as the starting sugars require protection, which makes the overall process rather costly. Nevertheless, few studies have been devoted to the regioselective alkylation or acylation of unprotected sugars. Although new non-ionic hydrocarbon surfactants have been prepared in good yield (one or two steps) [6, 7], the reaction was found to be less selective with fluorinated derivatives, and the compounds were less readily purified, which limited the overall yield (25–40%) [8].

We present here a route, avoiding protection of the starting sugars, to a new series of fluorinated surfactants derived from α-lactose (cheap starting material) or lactobionic acid which is obtained on an industrial scale by simple oxidation of α-lactose.

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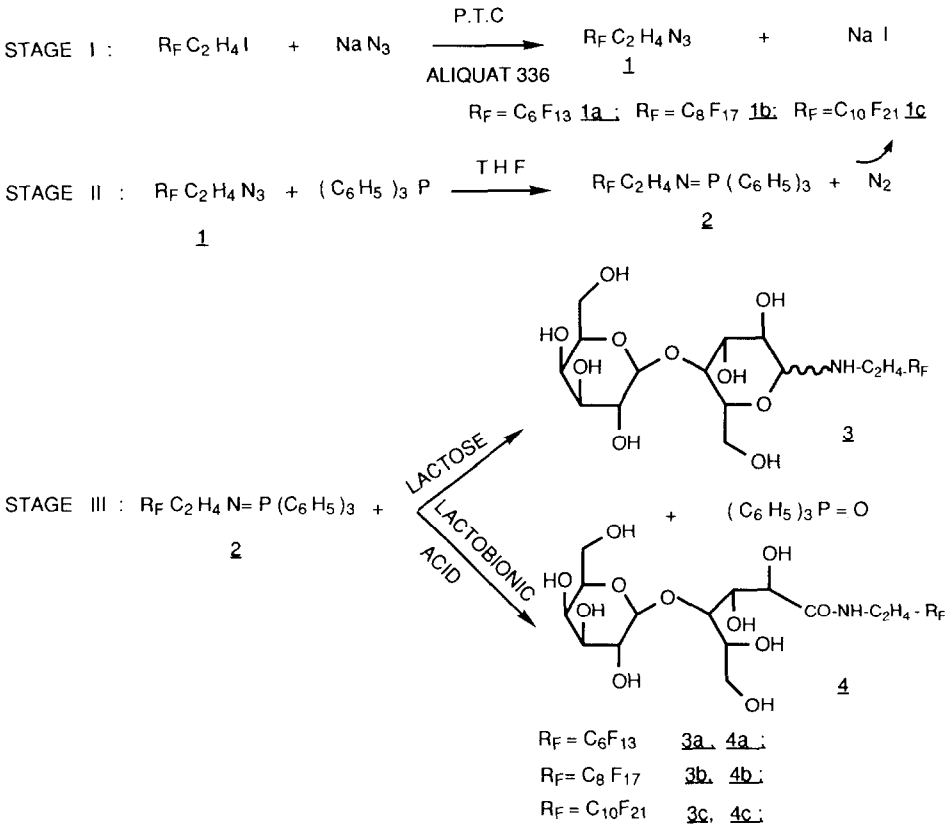
Results

The route involves a long-chain fluoroalkyl azide proceeding via an iminophosphorane intermediate according to the following reaction scheme:



Stage I was carried out under phase-transfer conditions [9, 10], the fluoroalkyl azides being isolated in greater than 70% yield (Table 1). The iminophosphorane intermediate formed in stage II was used directly in stage III without isolation.

TABLE 1

Yields of fluoroalkyl azides

Compound	Yield (%)
1a	71
1b	76
1c	93

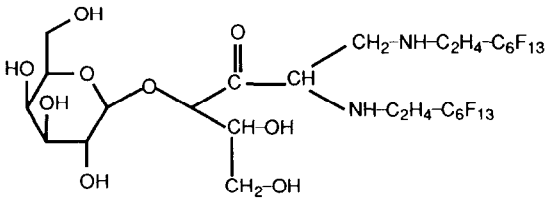
TABLE 2

Yields of fluorinated derivatives of lactose and lactobionic acid

Compound	Yield (%)
3a	50
3b	52
3c	55
4a	95
4b	95
4c	95

Stage III is an aza-Wittig [11] reaction between the iminophosphorane and the aldehyde form of lactose or the lactone form of lactobionic acid. The lactose $\underset{II}{\overset{I}{\rightleftharpoons}}$ aldehyde and lactobionic acid $\underset{II}{\overset{I}{\rightleftharpoons}}$ lactone equilibria are shifted in the I direction as the reaction progresses due to the formation of the products **3** or **4**.

The derivatives **3a–c** and **4a–c** were isolated in good yield (Table 2). In the condensation with lactose, secondary products were formed via an Amadori rearrangement, which tends to limit the overall yield. For compound **3a**, for example, the following secondary product formed by an Amadori rearrangement was isolated by chromatography on a cellulose column:



This secondary product was identified by ^{1}H NMR, ^{13}C NMR and mass spectrometry.

All products were identified by ^{1}H NMR ^{19}F NMR and mass spectrometry (cf. Experimental).

Preliminary experiments on the surfactant properties of these compounds showed that they have very low critical micellar concentrations (around 10^{-4} M) in water at 25 °C, and that they reduce the surface tension of pure water from 73 mN m^{-1} to 15 mN m^{-1}. A plot of the surface tension versus concentration for compound **3a** is shown in Fig. 1.

Conclusions

A new series of non-ionic fluorinated surfactants derived from lactose (or lactobionic acid), which were readily obtained in good yield without prior protection of the starting sugars, have been described. These compounds

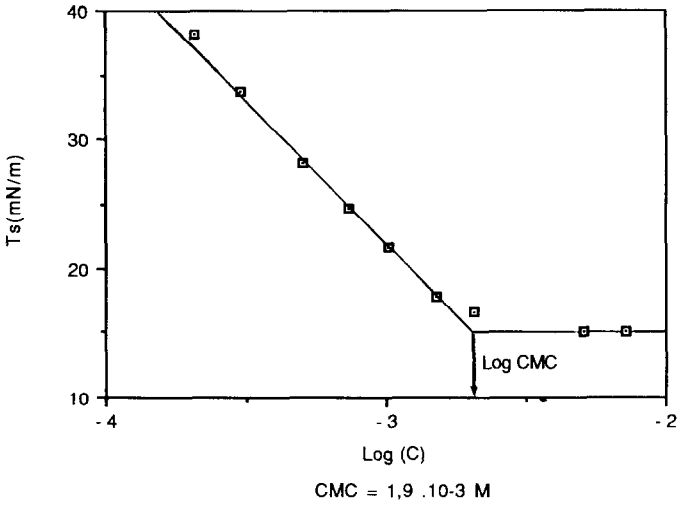


Fig. 1. Plot of surface tension against the logarithm of the concentration for compound **3a** in water at 25 °C.

have good surfactant properties and are currently under study for pharmaceutical applications.

Experimental

The ^{1}H and ^{19}F NMR spectra were recorded at 300 MHz on a Bruker AM 300WB instrument. Chemical shifts are expressed in ppm with respect to TMS for ^{1}H and CF_3CO_2H for ^{19}F spectra. IR spectra were recorded on a Perkin-Elmer 683 spectrophotometer and the frequencies are expressed in cm^{-1}. Mass spectra were recorded on a Nermag R10-10 instrument (DCI/NH_3 mode). Microanalyses were carried out by the CNRS central facilities in Vernaison (France) and are in accord with the structures proposed. Surface tensions were measured at 25 °C using the stirrup detachment method with a Prolabo Tensiomat No. 3 instrument.

Synthesis of azides ***1*** *[9, 10]*

The 2-(*F*-alkyl)ethyl iodide (8 mmol) was added to a 25% solution of sodium azide (16 mmol) in water or formamide. Aliquat 336 (0.4 mmol) was added, and the mixture heated and stirred at 100 °C for 6 h. The mixture was extracted with ether, the organic phase dried and evaporated under vacuum. The residue was either distilled (**1a**, **1b**) or recrystallized (**1c** in ether).

^{19}F NMR $CDCl_3$ δ: **1a** $C_6F_{13}-C_2H_4-N_3$: −5.60 (3F, s, CF_3); −38.65 (2F, s, $CF_2\alpha CH_2$); −46.54 (2F, s, $CF_2\beta CH_2$); −47.55 (2F, s, $CF_2\gamma CH_2$); −48.21 (2F, s, $CF_2\delta CH_2$); −50.87 (2F, s, $CF_2\epsilon CH_2$) ppm.

1b $C_8F_{17}-C_2H_4-N_3$: −5.80 (3F, s, CF_3); −38.78 (2F, s, $CF_2\alpha CH_2$); −46.45 (2F, s, $CF_2\beta CH_2$); −46.70 (4F, s, $CF_2\gamma$ and δCH_2); −47.53 (2F, s, $CF_2\gamma CF_3$); −48.29 (2F, s, $CF_2\beta CF_3$); −50.99 (2F, s, $CF_2\alpha CF_3$) ppm.

1c $C_{10}F_{21}-C_2H_4-N_3$: −5.49 (3F, s, CF_3); −38.58 (2F, s, $CF_2\alpha CH_2$); −46.40 (10F, s, $CF_2\beta$, γ, δCH_2 and δ, ϵCF_3); −47.35 (2F, s, $CF_2\gamma CF_3$); −48.11 (2F, s, $CF_2\beta CF_3$); −50.79 (2F, s, $CF_2\alpha CF_3$) ppm.

^{1}H NMR $CDCl_3\delta$: 3.59 (2H, m, CH_2-N_3); 2.37 (2H, m, CH_2-R_F) ppm.

B.p. (°C/mbar): **1a** 66/13; **1b** 89/13.

Synthesis of N-*[2-(F-alkyl)ethyl]-lactosylamines (3)*

Triphenylphosphine [5.15 mmol in 5 ml tetrahydrofuran (THF)] was added to a solution of the 2-(*F*-alkyl)ethyl azides (5.6 mmol) in 5 ml anhydrous THF under argon. The reaction mixture was stirred for 1 h at 0 °C, and then for 3 h at room temperature. Nitrogen was evolved. The solvent was evaporated and the residue taken up in 7.5 ml 2-propanol. Lactose (3.07 mmol in 4.2 ml water) was added, and the solution stirred for 7 d at room temperature and then at 75 °C for 2 h. The solvent was evaporated, the residue washed with toluene and filtered. The precipitate was extracted with a mixture of water and butanol. The two phases were separated and the aqueous phase freeze-dried. The residue was purified by chromatography on a cellulose column (eluent = butanol/ethanol/water, 5:2:3 v/v/v). Compound **3** was obtained as a white powder.

^{19}F NMR DMSO-d_6 δ: **3a** *N*-[2-(*F*-hexyl)ethyl]-lactosylamine (yield = 50%): −5.50 (3F, s, CF_3); −38.17 (2F, s, $CF_2\alpha CH_2$); −47.00 (2F, s, $CF_2\beta CH_2$); −47.93 (2F, s, $CF_2\gamma CH_2$); −48.53 (2F, s, $CF_2\delta CH_2$); −51.04 (2F, s, $CF_2\epsilon CH_2$) ppm. ^{1}H NMR DMSO-d_6 δ: 7.6 (1H, m, NH); 5.2–3.00 (25H, m, H sugar and $CH_2-CH_2-R_F$) ppm. MS *m/z*: 688 (MH^+); 508 (MH^+ − Gal); 364 ($C_6F_{13}C_2H_4NH_3^+$).

^{19}F NMR DMSO-d_6 δ: **3b** *N*-[2-(*F*-octyl)ethyl-lactosylamine (yield = 52%): −5.44 (3F, s, CF_3); −38.14 (2F, s, $CF_2\alpha CH_2$); −46.94 (6F, s, $CF_2\beta$, γ and δCH_2); −47.70 (2F, s, $CF_2\gamma CF_3$); −48.48 (2F, s, $CF_2\beta CF_3$); −50.96 (2F, s, $CF_2\alpha CF_3$) ppm. ^{1}H NMR DMSO-d_6 δ: 5.2–3.00 (25H, m, H sugar and $CH_2-CH_2-R_F$) ppm. MS *m/z*: 788 (MH^+); 608 (MH^+ − Gal); 464 ($C_8F_{17}C_2H_4NH_3^+$).

^{19}F NMR DMSO-d_6 δ: **3c** *N*-[2-(*F*-decyl)ethyl]-lactosylamine (yield = 55%): −5.44 (3F, s, CF_3); −38.19 (2F, s, $CF_2\alpha CH_2$); −46.80 (10F, s, $CF_2\beta$, γ, δCH_2 and δ, ϵCF_3); −47.72 (2F, s, $CF_2\gamma CF_3$); −48.51 (2F, s, $CF_2\beta CF_3$); −51.00 (2F, s, $CF_2\alpha CF_3$) ppm. ^{1}H NMR DMSO-d_6 δ: 7.6 (1H, m, NH); 5.2–3.00 (25H, m, H sugar and $CH_2-CH_2-R_F$) ppm. MS *m/z*: 888 (MH^+); 708 (MH^+-Gal); 564 ($C_8F_{17}C_2H_4NH_3^+$).

Synthesis of N-*[2-(F-alkyl)ethyl]-lactobionamides (4)*

A solution of 3.45 mmol 2-(*F*-alkyl)ethyl azide in 5 ml anhydrous THF, placed in a 100 ml two-necked flask equipped with stirrer, was cooled to 0 °C. A solution of 0.82 g (3.16 mmol) triphenylphosphine in 5 ml anhydrous THF was added dropwise under argon. The reaction mixture was stirred for

1 h at 0 °C and then for 3 h at room temperature. Nitrogen was evolved. The THF was evaporated and the residue taken up in 10 ml methanol. Lactobionic acid (0.95 g, 2.65 mmol) and 100 μl water were added and the mixture heated at 75 °C for 4 h. The solvent was evaporated and the residue washed in copious hot toluene. The precipitate was filtered and dried.

^{19}F NMR DMSO-d_6 δ: **4a** *N*-[2-(*F*-hexyl)ethyl]-lactobionamide (yield = 95%): −5.60 (3F, s, CF_3); −38.80 (2F, s, $CF_2\alpha CH_2$); −47.06 (2F, s, $CF_2\beta CH_2$); −47.99 (2F, s, $CF_2\gamma CH_2$); −48.63 (2F, s, $CF_2\delta CH_2$); −51.12 (2F, s, $CF_2\epsilon CH_2$) ppm. ^1H NMR DMSO-d_6 δ: 7.90 (1H, m, NH); 5.2–3.0 (25H, m, CHOH, CH_2OH and $CH_2-CH_2-R_F$) ppm. MS *m/z*: 704 (MH^+); 542 ($MH^+ - Gal$); 364 ($C_6F_{13}C_2H_4NH_3^+$). IR (KBr) ν: 1660 (CONH) cm^{-1}.

^{19}F NMR DMSO-d_6 δ: **4b** *N*-[2-(*F*-octyl)ethyl]-lactobionamide (yield = 95%): −6.01 (3F, s, CF_3); −39.04 (2F, s, $CF_2\alpha CH_2$); −47.28 (6F, s, $CF_2\gamma$ and δCH_2); −48.09 (2F, s, $CF_2\gamma CF_3$); −48.75 (2F, s, $CF_2\beta CF_3$); −51.42 (2F, s, $CF_2\alpha CF_3$) ppm. ^1H NMR DMSO-d_6 δ: 7.90 (1H, m, NH); 5.1–3.2 (25H, m, CHOH, CH_2OH and $CH_2-CH_2-R_F$) ppm. MS *m/z*: 804 (MH^+); 642 ($MH^+ - Gal$); 464 ($C_8F_{17}C_2H_4NH_3^+$). IR (KBr) ν: 1660 (CONH) cm^{-1}.

^{19}F NMR DMSO-d_6 δ: **4c** *N*-[2-(*F*-decyl)ethyl]-lactobionamide (yield = 95%): −7.64 (3F, s, CF_3); −39.73 (2F, s, $CF_2\alpha CH_2$); −47.70 (10F, s, $CF_2\beta$, γ, δCH_2 and δ, ϵCF_3); −49.01 (2F, s, $CF_2\gamma CF_3$); −49.16 (2F, s, $CF_2\beta CF_3$); −52.61 (2F, s, $CF_2\alpha CF_3$) ppm. ^1H NMR DMSO-d_6 δ: 7.90 (1H, m, NH); 4.5–3.0 (25H, m, CHOH, CH_2OH and $CH_2-CH_2-R_F$) ppm. MS *m/z*: 904 (MH^+); 742 ($MH^+ - Gal$); 564 ($C_{10}F_{21}C_2H_4NH_3^+$). IR (KBr) ν: 1660 (CONH) cm^{-1}.

References

1 C. Selve, S. Achilefu and L. Mansuy, *Synth. Commun.*, *20* (1990) 799, and refs. therein.
2 C. Selve, E. M. Moumni and J. J. Delpuech, *J. Chem. Soc., Chem. Commun.*, (1987) 1437.
3 (a) M. Gautier, I. Rico and A. Lattes, *J. Fluorine Chem.*, *44* (1989) 419; (b) I. Rico, A. Lattes, K. P. Das and B. Lindman, *J. Am. Chem. Soc.*, *111* (1989) 7266; (c) M. Gautier, I. Rico and A. Lattes, *J. Org. Chem.*, *55* (1990) 1500.
4 A. Milius, J. Greiner and J. G. Riess, *New J. Chem.*, *55* (1991) 337.
5 (a) G. W. Stubbs and B. J. Litman, *Biochemistry*, *17* (1978) 215, and refs. therein; (b) T. Shimamoto, S. Saito and T. Tsuchiya, *J. Biochem.*, *97* (1985) 1807.
6 P. Latgé, I. Rico, R. Garelli and A. Lattes, *J. Dispers. Sci. Technol.*, *12* (1991) 227.
7 P. Leon-Ruaud and D. Plusquellec, *Tetrahedron*, *47* (1991) 5185.
8 S. Abouhilale, J. Greiner and J. G. Riess, *Carbohydr. Res.*, *212* (1991) 55.
9 F. Szonyi and A. Cambon, *J. Fluorine Chem.*, *42* (1989) 59.
10 B. Escoula, N. Hajjaji-Srhiri, M. J. Marti, I. Rico and A. Lattes, *J. Com. Esp. Deterg.*, *21* (1990) 381 [*Chem. Abst.*, *113* (1990) 233 741j].
11 P. Molina, M. Alajarin, C. Lopez-Leonard and I. Madrid, *Tetrahedron*, *45* (1989) 1823, and references therein.