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Spacer arm influence on glucidoamphiphile compound properties

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Abstract

We prepared glucidoamphiphile derivatives from D-glucose, D-galactose and xylitol, in which the glucidic moiety and the hydrophobic alkyl chain are separated by spacer arm E (E = glyceryl, $(OEt)_2$-α-polypropyleneglycyl and butyloxy). Their amphiphile characteristics are compared to those of the corresponding analogs 3-*O*-alkyl-D-glucopyranoses, 6-*O*-alkyl-D-galactopyranoses and 1-*O*-alkyl-D,L-xylitols. We discussed the spacer arm influence on hydrophobic lipophilic balance (HLB), critical micellar concentration (CMC), water solubility (S_w) and phase transition temperatures of thermotropic and lyotropic mesophases.

Keywords: Glucidoamphiphiles; Hydrophilic lipophilic balance; Critical micellar concentration; Thermotropic liquid crystals; Lyotropic liquid crystals

1. Introduction

In a previous work (Savelli et al., 1999), we showed that both water solubility (S_w) and critical micellar concentration (CMC) of 3-*O*-alkyl-D-glucopyranose compounds **1** satisfy the linear relationships:

$$\log S_w = an + b \quad (1)$$

$$\log \mathrm{CMC} = a'n + b' \quad (2)$$

$$\mathrm{HLB} = a''n + b'' \quad (3)$$

when the alkyl chain length $R = n\text{-}C_nH_{2n+1}$ varies from $\tilde{n} = 6$ to $\tilde{n} = 16$. In contrast, relationships (1) and (2) show an abrupt diminution, from $n = 8$–9 to $n = 9$–10 of both water solubility and CMC values for the glucidoamphiphile analogs 6-*O*-alkyl-D-galactopyranoses **2** (this work) and 1-*O*-alkyl-D,L-xylitols **3** (Savelli et al., 1999).

We wish to rationalize this phenomenon by comparing the amphiphile properties of compounds **1**–**3** to those of the analogs having a spacer arm E between the alkyl chain and the glucidic moiety.

2. General synthesis

3-*O*-Alkyl-D-glucopyranoses **1a**–**d**, 6-*O*-alkyl-D-galactopyranoses **2a**-**c** and 1-alkyl-D,L-xylitols **3a**–**d** were prepared as previously indicated (Bault et al., 1998; Goodby et al., 1997).

3-*O*-(3-*O*-Alkyl-glycer-1-yl)-D-glucopyranoses **1′a**–**d** in which the alkyl chain and the glucose moiety are separated by the glyceryl spacer arm, were synthesized as described in Scheme 1 ($R = n\text{-}C_nH_{2n+1}$ with $n = 8$ (**a**), 10 (**b**), 12 (**c**), 14 (**d**)). The epoxidation of the allyl derivative **4** (Goueth, Ronco & Villa, 1994) was performed using *m*-chloroperbenzoic acid; pure epoxide **5** was obtained in 79% yield. Reaction of **5** with appropriate alcohol ROH and potassium hydroxide in toluene–Me_2SO gave the ethers **6a**–**d** in 70% yield. Subsequent deprotection in CF_3COOH–H_2O gave the products **1′a**–**d** (Table 3), each as an anomeric mixture (α/β; 2:3). **6a**–**d** and **1′a**–**d** products are diastereoisomeric mixtures.

6-*O*-[2-*O*-*n*-Dodecylpoly-(α-propyleneglycol)-diethyleneglycol]-α-D-galactopyranose (**2′c**) was prepared as described in Scheme 2. To perform regiospecific alkylation at the secondary site of the commercial polypropyleneglycol, we first protected the primary site via selective tritylation in pyridine to give 1-*O*-tritylpoly-(α-propyleneglycol) (**7**) (95%). Etherification of **7** with *n*-dodecyl bromide in toluene–Me_2SO with potassium hydroxide gave the 2-*O*-*n*-dodecyl-1-*O*-tritylpoly-(α-propyleneglycol) (**8c**) (60%). Subsequently **8c** was deprotected with aqueous acetic acid to give 2-*O*-*n*-dodecylpoly-(α-propyleneglycol) (**9c**) (93%). The diethyleneglycol ditosylate **10** was prepared using *p*-toluenesulfonyl chloride in triethylamine–acetone (45%). The reaction of the resulting compound with 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose

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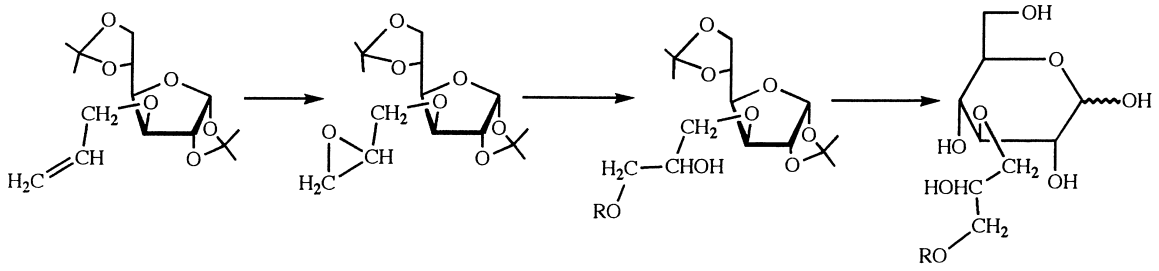


4 **5** **6a-d** **1'a-d**

R = *n*-C_nH_{2n+1} with n = 8 (**a**), 10 (**b**), 12 (**c**), 14 (**d**)

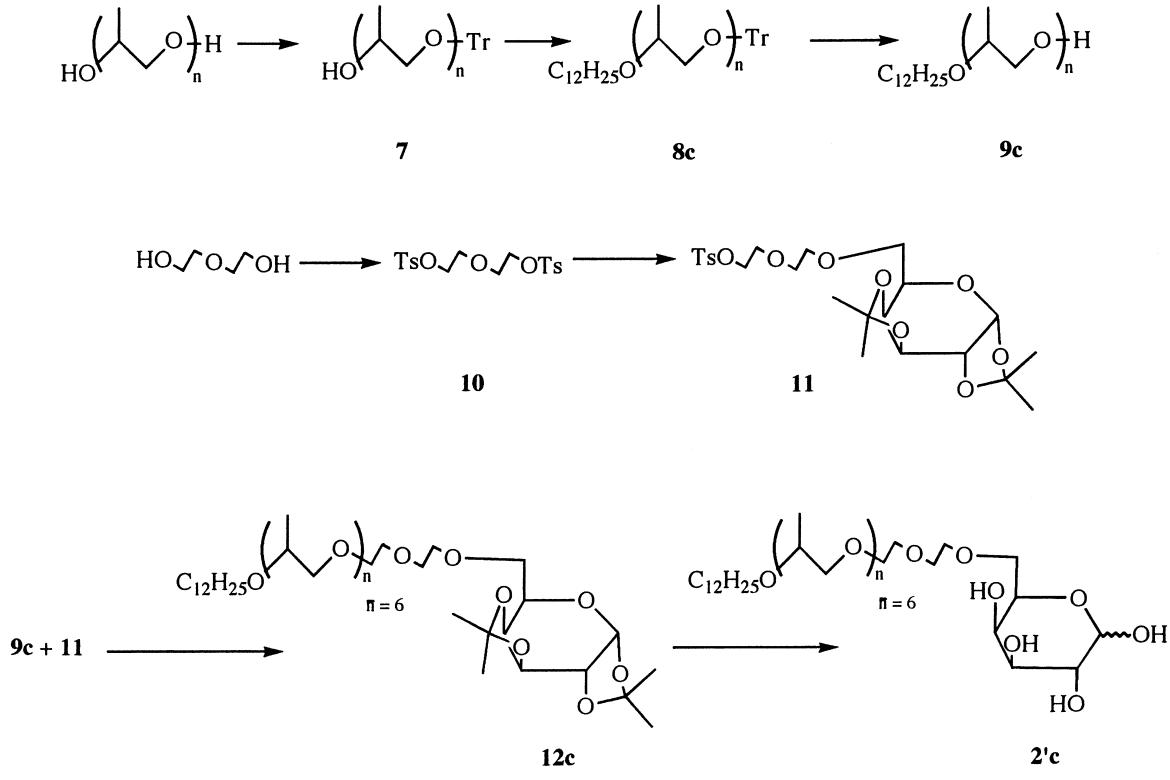
Scheme 1.

(Regnault, Ronco & Villa, 1989) in toluene–Me_2SO in the presence of potassium hydroxide gave the activated glucidic compound **11** (94%). The final condensation of the alcohol **9c** with the tosylate derivative **11** was carried out in the above conditions to yield the protected derivatives **12c** (56%). This product was subsequently deprotected in CF_3COOH–H_2O to obtain **2′c** (67%).

1-*O*-(4-*O*-Alkyl-butyleneglycol-1-yl)-D,L-xylitols **3′a,c** in which the alkyl chain and the xylitol moiety are separated by the butyleneglycol spacer arm, were synthesized as described in Scheme 3. The selective monoalkylation of the busulfan (bis-methylsulfonybutyleneglycol) with the appropriate alcohol ROH and potassium hydroxide in toluene–Me_2SO gave the ethers **13a,c** in 84 and 71% yield, respectively. Condensation of **13a,c** with 2,3:4,5-di-*O*-isopropylidene-D,L-xylitol in toluene–Me_2SO with potassium hydroxide gave the corresponding products **14a,c** (65%), which were subsequently deprotected in dioxane–water in the presence of amberlyst $15H^+$ resin to yield **3′a,c** (70 and 60%, respectively). In these conditions, a small amount of partial deprotected products **15a,c** was obtained.

3. Results and discussion

Table 1 reports HLB, CMC, γ and water solubility (S_w) values of the studied products.

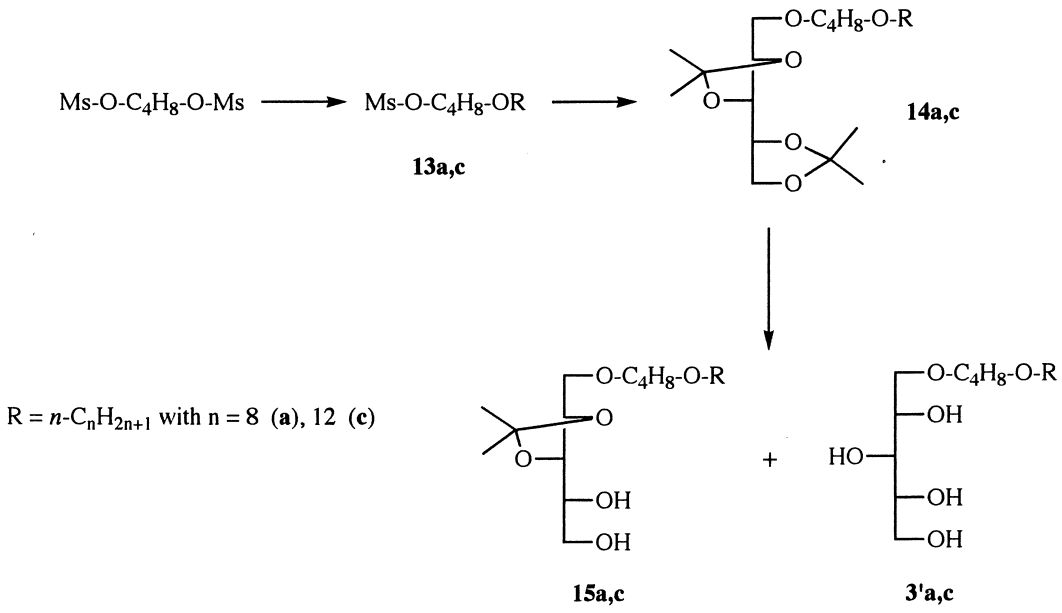


7 **8c** **9c**

10 **11**

9c + 11 **12c** **2'c**

Scheme 2.



Scheme 3.

The most significant difference between **1** and **1′** series is the much higher solubility (S_w) in water of compounds **1′** which are more than 20 times soluble than corresponding **1**. Moreover both series satisfy the CMC relationship (2) (Fig. 1) and HLB relationship (3) (Fig. 2). Nevertheless for compounds **1**, the corresponding a' and a'' slopes are higher than for compounds **1′**. These results indicate that the glyceryl spacer arm diminishes the influence of the hydrophobic chain. Compounds **2** and **3**, which have four OH groups as analogs **1** do not satisfy the (1)–(3) relationships. In both series, the water solubility decreases strongly when the number n of carbon atoms in the alkyl chain is higher than 8. In parallel, it was impossible to obtain CMC values for $n > 10$ (no break in the slope of $\gamma = \log c$) and HLB values diminished strongly from $n = 8$ (**2a**, **3a**) to $n = 10$ (**2b**, **3b**).

For D-galactose derivatives **2**, these data can be interpreted as a result of the intramolecular hydrogen bonds between two OH groups in *cis* position near the alkyl chain, which decreases the hydrophilic character. Thus the hydrophobic alkyl chain, with a sufficient length, can "invade" the region of the above OH groups and hence prevents intermolecular hydrogen bonding with water molecules. A similar interpretation can be proposed for xylitol derivatives **3** since the non-cyclic structure allows to obtain conformations with C-2 and C-3 OH groups in *cis* position near the alkyl chain. This phenomenon can be suppressed when the hydrophobic tail R and the glucidic polar head are separated by an appropriate spacer arm E. The comparison between **2c** and **2′c** and between **3c** and **3′c** results, seem to satisfy the above hypothesis. For compound **2′c** in which the spacer arm E = –O–Et–Et–$(OPPG)_n$ ($n = 6$) imposes a large distance between the polar head and the dodecyl chain, we obtained a measurable CMC (impossible for **2c**) and a water solubility more than 100 times higher than for analog **2c**. For compound **3′** (E = –O–$(CH_2)_4$)–, data are incomplete, however **3′c** CMC was measurable (impossible for the analog **3c**).

The last significant result in Table 1 is that surface tension

Table 1
HLB, CMC, γ and S_w values of type I and type II compounds at 25°C

Product		HLB	CMC (10^{-3} M)	γ[a]	S_w (10^{-3} M)
3-OR–Glu	**1a**	10.7	1.20	29.5	1.84
	1b	9.6	0.78	29.5	1.20
	1c	8.5	0.23	31.4	0.98
	1d	7.2	0.18	31.3	0.91
3-E–OR–Glu	**1′a**	9.0	1.04	28.7	22.4
(E = –O–CH_2–CHOH–CH_2–)	**1′b**	8.8	0.12	30.5	20.0
	1′c	8.6	0.09	28.3	22.0
	1′d	8.2	0.05	28.4	4.3
6-OR–Gal	**2a**	11.2	34	31.2	>100
	2b	9.6	0.37	32.4	0.2
	2c	9.2	[b]	[b]	0.05
6-E–OR–Gal (E = –O–Et–O–Et–$(OPPG)_n$)–	**2′c**	11.4	0.05	31.4	>5
1-OR–Xyli	**3a**	8.6	6.7[c]	28.2	7600[c]
	3b	7.4	0.81[c]	29.5	1.6[c]
	3c	7.0	[b,c]	29.0[b]	0.56[c]
	3d		[b]	[b]	0.42[c]
1-E–OR–Xyli (E = –O–$(CH_2)_4$–)	**3′a**		0.28	27.6	
	3′c		0.03	28.0	

[a] At CMC value, in mN m^{-1}.
[b] No break in the slope of $\gamma = f(\log c)$; γ value corresponds to saturated solution (S_w).
[c] Savelli et al., 1999.

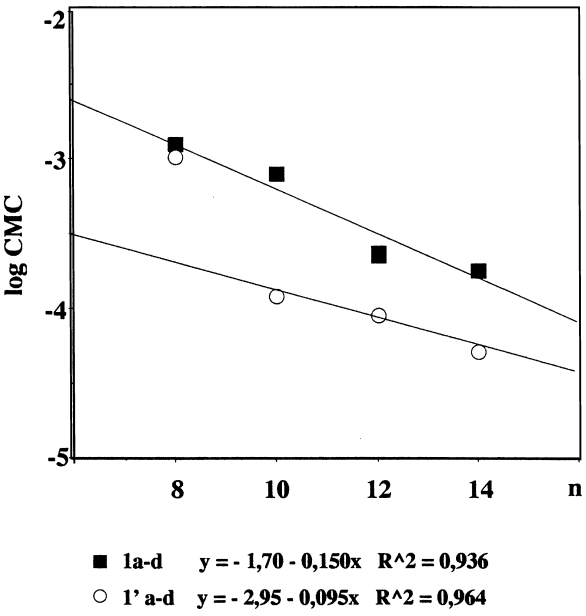


Fig. 1. log CMC = $f(n)$.

γ at CMC values is not sensitive to both structural parameter changes and alkyl chain length (all the compounds have $\gamma = 28$–31 mN m^{-1}).

Table 2 reports mesophase transition temperatures of type I and type II compounds.

For all these compounds, we observed thermotropic and lyotropic mesophases (smectic A* and lamellar, respectively). The comparison between **1′a–d** and **1a–d** shows that glyceryl spacer arm affects the phase transition temperatures strongly since we note on the one hand a large diminution of both melting point (m.p.) and T_1 temperatures and on the other hand a large increase in both thermotropic and lyotropic phase temperature intervals (ΔT = C.p − M.p.; $\Delta T = T_2 - T_1$). Also we observed above that compounds **1′a–d** were less sensitive to hydrophobic chain influence than the corresponding **1a–d** derivatives (a' and a'' slope values, Figs. 1 and 2). These results can be interpreted as the influence of the supplementary OH group brought by the glyceryl spacer arm, which favors organized aggregates as micelles (CMC) or liquid crystals.

The absence of liquid crystals for the galactose derivative **2′c** can result from many conformations of the (spacer arm — alkyl chain) groups, which inhibit organized structure formation because the spacer arm is an oligomer mixture (α-propyleneglycol)$_n$ with average degree $\tilde{n} = 6$.

In compounds **3′a,c** the oxybutylene spacer arm is not only an additional group to increase the hydrophobic chain length since phase transition temperatures of **3′a** (total $n = 8 + 4$) are very different to those of **3c** ($n = 12$). Moreover, **3′a,c** have ΔT mesophase temperature intervals higher than those of the analogs **3a,c**. These results show that the oxybutylene spacer arm has a specific influence on the aggregate organization as liquid crystals and as micelles (**3′c** have measurable CMC value in contrast to the analog **3c**).

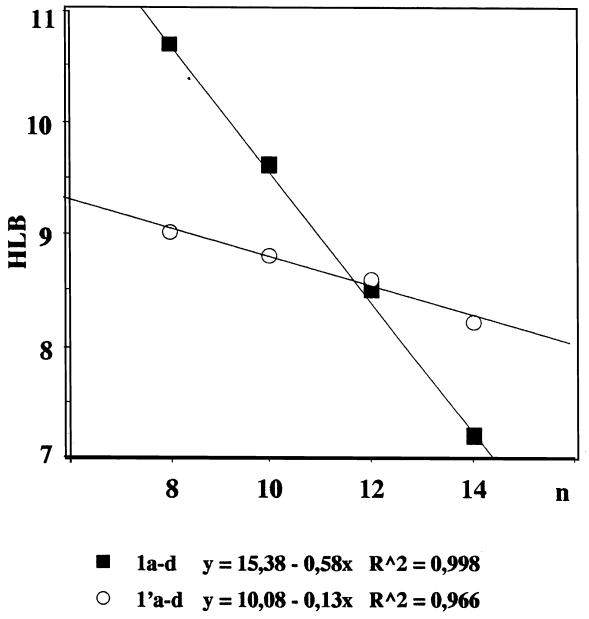


Fig. 2. HLB = $f(n)$.

Table 2
Mesophase transition temperatures of type I and II compounds

Product		Thermotropy m.p. (°C)		Lyotropy	
		M.p. (°C)	C.p. (°C)	T_1 (°C)	T_2 (°C)
3-OR–Glu	**1a**	112.0	135.0	–	–
	1b	114.0	138.0	69.0	118.0[a]
	1c	133.1	156.0	59.0	164.0[a]
	1d	130.7	158.1	–	–
3-E–OR–Glu	**1′a**	−12.5[b]	–	<RT	56.0
(E = –O–CH$_2$–CHOH–CH$_2$–)	**1′b**	−11.6[b]	–	<RT	89.0
	1′c	−9.5	126.9	<RT	138.0[a]
	1′d	19.2	154.8	<RT	156.0[a]
6-OR–Gal	**2a**	113[c]	169[c]	62.0	120.0[a]
	2b	117[c]	172[c]	71.0	112.0[a]
	2c	119[c]	171[c]	109.0	140.0[a]
6-E–OR–Gal (E = –O–Et–O–Et–(OPPG)$_n$–)	**2′c**	No		No	
1-OR–Xyli	**3a**	48.9[d]	98.0[d]	< RT	95.0
	3b	56.2[d]	109.8[d]	< RT	> 95.0
	3c	43.6[d]	112.0[d]	30.0	> 95.0
	3d	68.9[d]	112.5[d]	48.5	> 95.0
1-E–OR–Xyli (E = –O–(CH$_2$)$_4$–)	**3′a**	11.5	112.6	< RT	114.5
	3′c	50.0	120.0	25.0	112.0[b]

[a] Isotropic liquid.
[b] With ethylene glycol.
[c] Bault et al. (1998).
[d] Goodby et al. (1997).

4. Experimental

4.1. General methods

Melting points were determined on an electrothermal automatic apparatus and are uncorrected. Optical rotations, for solutions in $CHCl_3$ or methanol, were measured with a digital polarimeter JASCO model DIP-370 at 25°C. NMR spectra were recorded with a Bruker WP-300 instrument for solutions in $CDCl_3$, C_5D_5N or Me_2SO-d_6 (internal Me_4Si). Elemental analyses were performed by the Service Central de Micro-Analyse du Centre National de la Recherche Scientifique (Vernaison, France). Reactions were monitored either by HPLC (Waters 721) using either the reverse phase columns RP-18 (Merck) or PN 27-196 (Waters) or by CPG (Girdel) with either the columns OV 17 or SE 30. Column chromatography was performed on silica gel (60 mesh, Matrex) by usual gradient elution with hexane–acetone (in each case, the ratio of silica gel to product mixture to be purified was 30:1).

The water solubility S_w was performed for each sample at 25°C. In order to obtain CMC values, a solution scale was prepared for each compound by successive dilutions of a primary solution S_0. S_0 was equal to S_w for low water-soluble compounds. Surface tension measurements were performed for each solution at 25°C by Wilhelmy plate method (Prolabo TD 2000 tensiometer).

The HLB values were obtained using both the optimum formulation method (HLB_{form}) proposed by Salager and Anton (1983). The optimum formulation method is based on the occurrence of an optimum formulation on a simple formulation scan, which allows the calculation of the optimum formulation on a simple formulation scan, which allows the calculation of the surfactant parameter in a given physico-chemical environment and precisely ascertains the difference between a new surfactant and a known one with similar behavior. The accuracy of this method is based on the fact that for a surfactant/cosurfactant–oil–water system, the optimum is precisely identify by ultra-low interfacial tension (10^{-4} mN m^{-1}) values, three-phase behavior and maximum solubilization of water (brine) and oil by the surfactant/cosurfactant mixture. Exhaustive experimental studies have shown that an optimum formulation is attained whenever a certain balance between the formulation variables is satisfied. Correlations for optimum formulation for anionic (Salager, Morgan, Schechter, Wade & Vasquez, 1979) and non-ionic (Bourrel, Salager, Schechter & Wade, 1980) surfactants have been proposed, which relate numerically the effect of the physico-chemical parameters representing each component. A generalized correlation may be written as:

$$P = a\mathrm{ACN} + bf(A) + cS + d(T - 25)$$

where P is the parameter characteristic of the surfactant structure; the contribution of the oil phase is represented by the ACN or Alkane Carbon Number; $f(A)$ is a function of the alcohol type and concentration; S the salinity in wt%, and T the temperature (°C); a, b, c and d are empirical constants that depend on the system.

The reference surfactants were used as received from the manufacturer and their HLB values are those reported in the literature. They were the sorbitan derivatives provided by ICI Americas Inc. SPAN 20 (HLB = 8.6), TWEEN 85 (11.0) and TWEEN 80 (15.0). Heptan (ACN = 7), Decan (ACN = 10), NaCl and the alcohols were analytical grade provided by Merck; water was distilled and deionized. Heptan and decan were used as the oil phase; the brine electrolyte concentration was 0.1 (wt%) of NaCl; the alcohol used as cosurfactant was a mixture of *sec*-butanol and *n*-pentanol (2:1, v/v) at a concentration of 4.3% (v/v); water-to-oil ratio was unity (v/v). The variable was the HLB of the surfactants and intermediate values were obtained by mixing neighboring species assuming a linear mixing rule on a mass fraction basis (Griffin, 1949) and the surfactant concentration was 1% (wt%). HLB values were obtained using the following relation:

First, a reference P scan (HLB in this case) was carried out at 25°C. At optimum

$$\mathrm{HLB}_{op} = a\mathrm{ACN} + bf(A) + cS + d(T - 25)$$

and

$$\mathrm{HLB}_{op} = x_1\mathrm{HLB}_1 + x_2\mathrm{HLB}_2; \qquad (x_1 + x_2 = 1)$$

Secondly, 20% of the surfactant used as reference was replaced with the tested surfactant. As HLB_{op} is determined by the value of the remaining experimental parameters, it remains constant at optimum so that

$$\mathrm{HLB}_{op} = 0.8(x'_1\mathrm{HLB}_1 + x'_2\mathrm{HLB}_2) + 0.2\mathrm{HLB}_x(x'_1 + x'_2)$$

and

$$\mathrm{HLB}_x = (\mathrm{HLB}_{op} - 0.8(x'_1\mathrm{HLB}_1 + x'_2\mathrm{HLB}_2))/0.2$$

Phase transition temperatures were determined by DSC (differential scanning calorimetry) using Mettler FP85 furnace and by thermal polarized light microscopy using Olympus BX50 polarizing transmitted light, equipped with a Mettler FP82 microfurnace. Both Mettler apparatus were recorded to an FP90 central processor. For thermotropic liquid crystals, transition temperatures, noted m.p. (solid → liquid crystal) and c.p. (liquid crystal → isotropic liquid) are T_{onset} measured at 2°C min^{-1} by DSC. For lyotropic liquid crystals, transition temperatures, noted T_1 (liquid crystal apparition) and T_2 (liquid crystal disappearence) are determined by simply allowing crystals of the test material to dissolve in water, thereby creating a concentration gradient, which supports mesophase formation.

Table 3
Physicochemical and microanalytical data for derivatives **6**, **1′**, **13**, **14** and **3′**

Product	Yield (%)	M.p.[a] (°C)	$[\alpha]_D^{25}$	Formula	Cald		Found	
					C	H	C	H
6a	60	Oil	−11.5[b] (*c* 1.1)	$C_{23}H_{42}O_8$ (446.58)	61.85	9.48	61.73	9.57
6b	57	Oil	−18.1[b] (*c* 1.2)	$C_{25}H_{46}O_8$ (474.61)	63.26	9.77	62.98	9.84
6c	48	63.0	−27.2[b] (*c* 1.3)	$C_{27}H_{50}O_8$ (502.66)	64.51	10.02	64.17	10.17
6d	56	95.0	−24.6[b] (*c* 1.4)	$C_{29}H_{54}O_8$ (530.72)	65.63	10.25	65.90	10.14
1′a	68	−12.5	22.4[c] (*c* 1.3)	$C_{17}H_{34}O_8$ (366.45)	55.72	9.35	55.58	9.50
1′b	70	−11.6	23.4[c] (*c* 1.8)	$C_{19}H_{38}O_8$ (394.50)	57.84	9.70	58.05	9.57
1′c	73	−9.5	39.1[c] (*c* 1.1)	$C_{21}H_{42}O_8$ (422.56)	59.69	10.01	59.83	9.93
1′d	67	19.2	34.3[c] (*c* 1.2)	$C_{23}H_{46}O_8$ (450.61)	61.30	10.29	61.62	10.15
13a	84	Oil	–	$C_{13}H_{28}O_4S$ (280.43)	55.68	10.06	55.87	10.21
13c	71	Oil	–	$C_{17}H_{36}O_4S$ (336.53)	60.67	10.78	60.43	10.62
14a	68	Oil	–	$C_{23}H_{44}O_6$ (416.60)	66.31	10.64	66.18	10.81
14b	65	Oil	–	$C_{27}H_{52}O_6$ (472.70)	68.60	11.09	68.75	10.95
3′a	70	11.5	–	$C_{17}H_{36}O_6$ (336.47)	60.68	10.78	60.49	10.95
3′c	60	50.0	–	$C_{21}H_{44}O_6$ (392.58)	64.24	11.29	64.49	11.52

[a] Measured by thermal microscopy.
[b] In $CHCl_3$.
[c] In MeOH.

4.2. Synthesis

4.2.1. 3-O-(2,3-Epoxyglycer-1-yl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranose **5**

To a stirred solution of allyl derivative **4** (10 g, 0.033 mol) in 100 ml CH_2Cl_2 was added *m*-chloroperbenzoic acid (8.65 g, 0.050 mol). After 24 h at reflux, the mixture was concentrated under reduced pressure and extracted with ethyl ether. The organic phase was separated, washed with aq. NaOH 4% and water (twice), dried (Na_2SO_4) and concentrated under reduced pressure. The anhydro **5** was isolated without purification in 79% yield (8.2 g) as an oil. $[\alpha]_D^{25}$ −18.1° (*c* 1.1, $CHCl_3$). ^{13}C NMR ($CDCl_3$): 111.4 and 108.6 (C-*iso*); 104.9 (C-1); 82.6, 82.4 and 82.2 (C-2 and C-3); 80.8 (C-4); 72.2 (C-5); 71.6 and 70.4 (C-1 glyceryl); 66.9 (C-6); 50.3 and 50.1 (C-2 glyceryl); 43.9 and 43.6 (C-3 glyceryl); 26.5, 25.9 and 25.1 (CH_3-*iso*).

4.2.2. 3-O-(3-O-n-Alkylglycer-1-yl)-1,2:5,6-di-O-isopropylidene-α-D-glucofuranoses **6a–d**

To a stirred solution of anhydro **5** (1 equiv) and corresponding alcohol ROH (3 equiv) in 1:1 toluene–Me_2SO (100 g l^{-1}) was added KOH powdered (6 equiv). After 72 h at 40°C, the mixture was filtered and the filtrate neutralized with saturated aq. NH_4Cl. The organic phase was separated, washed with water (twice), dried (Na_2SO_4) and concentrated under reduced pressure. The 3-*O*-(3-*O*-*n*-Alkylglycer-1-yl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **6a–d** were isolated after purification by column chromatography with hexane–acetone (Table 3). ^{13}C NMR ($CDCl_3$): 111.7 and 109.1 (C-*iso*); 105.4 (C-1); 83.9 and 82.2 (C-3); 82.2 (C-2); 81.2 (C-4); 72.8 and 72.6 (C-1 glyceryl); 72.6 (C-5); 71.6 and 71.2 (C-3 glyceryl and C-α chain); 69.9 and 68.2 (C-2 glyceryl); 67.5 (C-6); 32.5–22.5 (CH_2 chain); 26.6, 26.0 and 25.0 (CH_3-*iso*); 14.0 (C-ω).

4.2.3. 3-O-(3-O-n-Alkylglycer-1-yl)-D-glucopyranoses **1′a–d**

Diacetal derivatives **6a–d** were added to a stirred solution of 9:1 CF_3COOH–H_2O (100 g l^{-1}). After 3 h, the solution was concentrated under reduced pressure. The 3-*O*-(3-*O*-alkylglycero-1-yl)-D-glucopyranoses **1′a–d** were isolated after purification by column chromatography with hexane–acetone (Table 3). ^{13}C NMR (C_5D_5N): α anomer; 94.1 (C-1); 85.7 (C-3); 74.0 (C-5); 73.9 (C-2); 71.4 (C-4); 62.2 (C-6); 31.7–22.6 (CH_2 chain); 14.0 (C-ω). β anomer; 98.8 (C-1); 88.5 (C-3); 78.3 (C-5); 76.3 (C-2); 70.8 (C-4); 62.6 (C-6); 31.7-22.6 (CH_2 chain); 14.0 (C-ω).

4.2.4. 1-O-Trityl-poly(α-propyleneglycol) **7**

Trityl chloride (19.2 g, 0.07 mol) in pyridine (80 ml) was added to a stirred solution of poly(α-propyleneglycol) (20 g, 0.047 mol) in pyridine (120 ml). After 3 h at reflux, the mixture was cooled, aq. H_2SO_4 (10%, 150 ml) was added and the solution was extracted with dichloromethane. The organic phase was separated, washed with water (twice), dried (Na_2SO_4) and concentrated under reduced pressure to give crude 1-*O*-trityl-poly(α-propyleneglycol) (**7**) as viscous liquid. The observed yield was 95% (29.6 g). n_{20}^D 1.5972. ^{13}C NMR ($CDCl_3$): 145.1 and 147.0 (C-*ipso*); 126.7 (C-*meta*); 127.4 (C-*ortho*); 129.6 (C-*para*); 86.7 (Ph_3–*C*–); 18.4, 18.1, 17.0 and 16.6 (–O–CH(*C*H_3CH_2–O–)$_n$; 72.7, 73.1, 74.3, 75.5 and 75.7 (–O–*C*H(CH_3)CH_2–O–)$_n$; (–O–CH(CH_3)*C*H_2)$_n$–OH; 65.5, 66.9, 75.0 and 76.4 (–O–CH(CH_3)*C*H_2–O–)$_n$; (HO–(*C*H(CH_3)CH_2–O–)$_n$).

4.2.5. 2-O-n-Dodecyl-1-O-trityl-poly(α-propyleneglycol) **8c**

Finely powdered potassium hydroxide (5.1 g, 0.091 mol) and *n*-dodecyl bromide (11.3 g, 0.045 mol) were added to a stirred solution of trityl derivative **7** (25 g, 0.039 mol) in 4:1 toluene–Me_2SO at room temperature. After 72 h, the mixture was filtered and the filtrate neutralized with saturated aq NH_4Cl. The organic phase was separated, washed with water (twice), dried (Na_2SO_4), and concentrated under reduced pressure. The 2-*O*-*n*-dodecyl-1-*O*-trityl-poly(α-propyleneglycol) (**8c**) was isolated as a viscous liquid after purification by column chromatography with 47:3 hexane–acetone. The observed yield was 60% (18.8 g). n_{20}^{D} 1.5059. ^{13}C NMR ($CDCl_3$): 127.0 and 127.6 (C-*ortho*); 145.1 and 147.0 (C-*ipso*); 126.7 and 125.2 (C-*meta*); 129.0 and 128.0 (C-*para*); 81.5 (Ph_3–C–); 18.4, 18.1, 17.1 and 16.6 (–O–CH(CH_3CH_2–O–)$_n$; 72.7, 73.1, 74.3, 75.5 and 75.7 (–O–CH(CH_3)CH_2–O–)$_n$; (–O–CH(CH_3)CH_2)$_n$–OH; 65.5, 66.9, 75.0 and 76.4 (–O–CH(CH_3)CH_2)–O–)$_n$; (HO–(CH(CH_3)CH_2–O–)$_n$); 13.9 ($CH_3(CH_2)_{11}$–O–); 22.5 and 32.6, ($CH_3(CH_2)_{11}$–O–). IR (NaCl) ν_{max} (cm^{-1}): 3069, 3059, 1718, 1542, 1490, 1450, 1109, 762.

4.2.6. 2-O-n-Dodecyl-poly-(α-propyleneglycol) **9c**

2-*O*-*n*-Dodecyl-1-*O*-trityl-poly(α-propyleneglycol) (**8c**) (18.2 g, 0.021 mol)) was added to a stirred solution of 4:1 CH_3COOH–H_2O (91 ml). After 90 min at 100°C, the solution was filtered and concentrated to dryness under reduced pressure. The 2-*O*-*n*-dodecyl-poly(α-propyleneglycol) (**9c**) was isolated as a viscous liquid after purification by column chromatography with 4:1 hexane–acetone. The observed yield was 93% (12 g). n_{20}^{D} 1.4564. ^{13}C NMR ($CDCl_3$): 16.3–18.3 (CH_3 polymer); 75.6–76.0, 72.6–73.2 (–O–(CH(CH_3)CH_2–O)–); 75.0–75.2 (*n*-dodecyl–O–(CH(CH_3)CH_2–O); 65.5–67.0 (–O–(CH_2CH(CH_3)–O)–); 22.5–32.6 ($CH_3(CH_2)_{10}CH_2$–O–polymer); 13.9 ($CH_3(CH_2)_{10}CH_2$–O–polymer). IR (NaCl) ν_{max}.(cm^{-1}): 3460, 2927, 1456, 1109.

4.2.7. Bis-p-toluenesulfonyldiethyleneglycol **10**

p-Toluenesulfonyl chloride (79 g, 0.42 mol) in acetone (150 ml) was added dropwise to a solution of diethyleneglycol (20 g, 9.19 mol) and triethylamine (20.6 g, 0.20 mol) in acetone (100 ml) at 0°C. After 1 h at room temperature, the solution was filtered and concentrated under reduced pressure to give crude bis-*p*-toluenesulfonyldiethyleneglycol (**10**), which was recrystallized in MeOH. The observed yield was 45% (34.3 g). M.p. 78–79°C. ^{13}C NMR ($CDCl_3$): 21.5 (CH_3–Ph–); 68.6 (O–CH_2–CH_2–O–Ts); 69.0 (O–CH_2–CH_2–O–Ts); 127.8, 129.83, 132.7 and 144.9 (CH_3–Ph–).

4.2.8. 6-O-(p-Toluenesulfonyldiethyleneglycol)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **11**

Finely powdered potassium hydroxide (3 g, 0.053 mol) and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (6.3 g, 0.024 mol) were added to a stirred solution of the bis-tosylate **10** (20 g, 0.048 mol) in 4:1 toluene–Me_2SO at room temperature. After 2 h 30 min, the mixture was filtered and the filtrate neutralized with saturated aq. NH_4Cl. The organic phase was separated, washed with water (twice), dried (Na_2SO_4), and concentrated under reduced pressure. The 1-*O*-(*p*-toluenesulfonyldiethyleneglycol)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**11**) was isolated as a viscous liquid after purification by column chromatography with 97:3 hexane–acetone. The observed yield was 94% (11.8 g). n_{20}^{D} 1.4880. $[\alpha]_D^{23}$ −17.8° (*c* 0.9, $CHCl_3$),. ^{13}C NMR ($CDCl_3$): 127.6, 129.6, 132.7 and 144.8 (*p*-toluenesulfonyl); 108.6 and 109.1 (C-*iso*); 96.2 (C_1a): 69.2 and 69.6 (CH_2 dietoxy).

4.2.9. 6-O-[2-O-n-Dodecyl-poly(α-propyleneglycol)-diethyleneglycol]-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose **12c**

Finely powdered potassium hydroxide (1.6 g, 0.028 mol) and tosylate derivative **11** (11 g, 0.021 mol) were added to a stirred solution of alcohol **9c** (8.4 g, 0.014 mol) in 3:2 toluene–Me_2SO, at room temperature. After 72 h, the mixture was filtered and the filtrate neutralized with saturated aq. NH_4Cl. The organic phase was separated, washed with water (twice), dried (Na_2SO_4) and concentrated under reduced pressure. The 6-*O*-[2-*O*-*n*-dodecyl-poly(α-propyleneglycol)-diethyleneglycol]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**12c**) was isolated as a viscous liquid after purification by column chromatography with 97:3 hexane–acetone. The observed yield was 56% (7.5 g). n_{20}^{D} 1.4666. $[\alpha]_D^{23}$ −24.2° (*c* 1.1, $CHCl_3$),. ^{13}C NMR ($CDCl_3$): 109.6 and 108.7 (($C(CH_3)_2$); 96.2 (C-1); 69.2 (C-6); 16.3, 16.0, 17.3 and 17.2 (–O–CH(CH_3)CH_2–O–); 2.6, 25.1, 26.0, 29.2, 29.4, 30.0, 31.4 and 31.5 ($CH_3(CH_2)_{11}$–); 72.7 and 73.2 ((O–CH_2–CH(CH_3)–O–)$_n$). 24.3, 24.8, 25.1 and 25.0 ($C(CH_3)_2$).

4.2.10. 6-O-[2-O-n-Dodecy-poly(α-propyleneglycol)-diethyleneglycol]-D-galactopyranose **2′c**

6-*O*-[2-*O*-*n*-Dodecy-poly-(α-propyleneglycol)-diethyleneglycol]-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**12c**) (6.5 g, 0.007 mol) was added to a stirred solution of 9:1 CF_3COOH–H_2O (25 ml). After 2 h at room temperature, the solution was concentrated under reduced pressure. The 6-*O*-[2-*O*-*n*-dodecyl-poly(α-propyleneglycol)-diethyleneglycol]-α-D-galactopyranose (**2′c**) was isolated after purification by column chromatography with 95:5 hexane–THF. The observed yield was 67% (4 g). $[\alpha]_D^{23}$ 94.8° (*c* 0.6, MeOH). n_{20}^{D} 1.4232. ^{13}C NMR ($CDCl_3$): 96.2 (C-1); 70.5 (C-2, C-3); 71.0 (C-4); 66.7: (C-5); 69.2 (C-6); 75.1 (–O–CH(CH_3)CH_2); 72.6 (–O–CH_2CH(CH_3)–O–); 31.6–22.5 (CH_2 chain); 16.7 (CH_3 polymer); 13.9 (C-ω). IR (NaCl) ν_{max}.(cm^{-1}): 3387, 2927, 1456, 1377, 1343, 1216, 1170, 1104, 926, 779, 700.

4.2.11. 4-O-n-Alkyl-but-1-yl mesylates **13a**,**c**

To a stirred solution of busulfan (1 equiv) and the corresponding alcohol ROH (0.6 equiv) in 4:1 toluene–Me_2SO (100 g l^{-1}) was added KOH powdered (2.5 equiv). After 72 h, the mixture was filtered and the filtrate neutralized with saturated aq. NH_4Cl. The organic phase was separated, washed with water (twice), dried (Na_2SO_4) and concentrated under reduced pressure. The 4-*O*-*n*-alkyl-but-1-yl mesylates **13a**,**c** were isolated after purification by column chromatography with 90:10 hexane–acetone (Table 3). ^{13}C NMR ($CDCl_3$): 70.9 (C-α chain); 70.4 (C-4); 68.2 (C-1); 38.1 (CH_3 mesyl); 31.6–22.4 (CH_2 chain); 29.5 (C-3); 25.7 (C-2); 13.9 (C-ω).

*4.2.12. 1-O-(4-O-n-Alkyl-butyleneglycol-1-yl)-2,3:4,5-di-O-isopropylidene-*D,L*-xylitols* **14a**,**c**

To a stirred solution of alkyl derivatives **13a**,**c** (1 equiv) and 2,3:4,5-di-*O*-isopropylidene-D,L-xylitol (1.2 equiv) in 4:1 toluene–Me_2SO (100 g l^{-1}) was added KOH powdered (2.5 equiv). After 72 h, the mixture was filtered and the filtrate neutralized with saturated aq. NH_4Cl. The organic phase was separated, washed with water (twice), dried (Na_2SO_4) and concentrated under reduced pressure. The 1-*O*-(4-*O*-*n*-alkyl-butyleneglycol-1-yl)-2,3:4,5-di-*O*-isopropylidene-D,L-xylitols **14a**,**c** were isolated after purification by column chromatography with 85:15 hexane–acetone (Table 3). ^{13}C NMR ($CDCl_3$): 109.7 and 109.6 (C-*iso*); 77.6 (C-3); 76.4 (C-2); 75.2 (C-4); 71.4 (C-1); 70.2 (C-α chain); 70.1 (CH_2–O spacer arm); 65.6 (C-5); 31.6–22.4 (CH_2 chain); 29.1 (CH_2 spacer arm); 26.8–25.4 (CH_3-*iso*); 13.9 (C-ω).

*4.2.13. 1-O-(4-O-n-Alkyl-butyleneglycol-1-yl)-*D,L*-xylitols* **3′a**,**c**

To a stirred solution of diacetal derivatives **14a**,**c** in 9:1 dioxane–water (100 g l^{-1}) was added Amberlyst 15H^+ resin (weight ratio resin to substrate 4:1). After 24 h at 70°C, the mixture was filtered and the filtrate concentrated under reduced pressure. After purification by column chromatography the partial deprotected products **15a**,**c** were isolated with 60:40 hexane–acetone. The 1-*O*-(4-*O*-alkyl-butyleneglycol-1-yl)-D,L-xylitols **3′a**,**c** were isolated with 20:80 hexane–acetone (Table 3). ^{13}C NMR (Me_2SO-d_6): 72.7 (C-4); 72.1 (C-1); 71.5 (C-3); 71.0 (C-2); 70.4 (C-α chain); 70.2 (CH_2–O spacer arm); 63.6 (C-5); 31.7–22.5 (CH_2 chain); 28.8 (CH_2 spacer arm); 14.0 (C-ω).

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References

Bault, Ph., Godé, P., Goethals, G., Goodby, J. W., Haley, J. A., Kelly, S. M., Mehl, G. H., Ronco, G., & Villa, P. (1998). An homologous series of 6-*O*-*n*-alkyl-α-D-galactopyranoses: synthesis and thermotropic mesomorphic properties. *Liquid Crystals*, *24* (2), 283–293.

Bourrel, M., Salager, J. L., Schechter, R. S., & Wade, W. H. (1980). A correlation for phase behaviour of non-ionic surfactants. *Journal of Colloid and Interface Science*, *75*, 451–461.

Goodby, J., Haley, J., Watson, M., Mackenzie, G., Kelly, S., Letellier, P., Douillet, O., Godé, P., Goethals, G., Ronco, G., & Villa, P. (1997). Substitution effects on the liquid crystalline properties of D,L-xylitol amphiphiles. *Liquid Crystals*, *22* (3), 367–378.

Goueth, P. Y., Ronco, G., & Villa, P. (1994). Synthesis of ether-linked di- and trisaccharide derivatives. Part I. Synthesis of disaccharides from 5,6-anhydro-D-glucose derivatives. *Journal of Carbohydrate Chemistry*, *13* (5), 679–696.

Griffin, W. C. (1949). Classification of surface active agents by HLB. *Journal of the Society of Cosmetic Science*, *1*, 311–326.

Regnault, I., Ronco, G., & Villa, P. (1989). Procédé de synthèse d'acétonides de monosaccharides et/ou de leurs dérivés fonctionnalisés, à partir de (mono-, di-, poly-)saccharides. Fr Patent 89 15995.

Salager, J. L., & Anton, R. E. (1983). Physico-chemical characterization of a surfactant: a quick and precise method. *Journal of Dispersion Science and Technology*, *4*, 253–273.

Salager, J. L., Morgan, J., Schechter, R. S., Wade, W. H., & Vasquez, E. (1979). Optimum formulation of surfactant/water/oil systems for minimum interfacial tension or phase behavior. *Journal of the Society of Petroleum Engineers*, *19*, 107–115.

Savelli, M. P., Van Roeckeghem, P., Douillet, O., Cavé, G., Godé, P., Ronco, G., & Villa, P. (1999). Effects of tail alkyl chain length (*n*), head group structure and junction (*Z*) on amphiphilic properties of 1-*Z*-*R*-D,L-xylitol compounds. *International Journal of Pharmacy*, *182*, 221–236.