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Effects of tail alkyl chain length (n), head group structure and junction (Z) on amphiphilic properties of 1-Z-R-D,L-xylitol compounds ($R = C_nH_{2n+1}$)

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Abstract

In the family of 1-Z-R-D,L-xylitol, we have determined the main amphiphilic properties of esters (Z = OCO) as a function of alkyl chain length ($R = C_nH_{2n+1}$, $n = 4–17$). A classical decrease of critical micelle concentration with the increase in the alkyl chain has been found. With water, esters displayed lamellar phases at temperatures of 25°C or higher. The extent of hydrophilic/lipophilic balance range obtained by emulsification method can be proven to be of interest for pharmaceutical applications. The results were compared with those obtained in previous investigations, i.e. for alkyl-substituted xylitol, with thioether (Z = S) and ether (Z = O) linking groups in order to discuss the role of the junction nature. Likewise, they were compiled with the results related to their D-glucose homologues, in order to put forward the effects of the head group configuration, cyclic or acyclic.

Keywords: Non-ionic surfactant; D,L-Xylitol; Critical micelle concentration; Emulsions; Hydrophilic/lipophilic balance; Lyotropic liquid crystal

1. Introduction

Surfactant properties are widely exploited in pharmaceutical and cosmetic formulations (Attwood and Florence, 1983; Rieger, 1986; Lawrence, 1994). More so than simple adjuvants, surfactants play a decisive role for drug delivery because of their peculiar ability to organize heterogeneous systems under associated structures as versatile as micelles, lyotropic liquid crystals,

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emulsions, multiple emulsions, microemulsions or vesicles (Tiemessen et al., 1988; Friberg, 1990; Lawrence, 1994; Denine et al., 1996; Garti and Aserin, 1996; Kovarik et al., 1996; Riess and Weers, 1996; Saettone et al., 1996; Thevenin et al., 1996; Van Hal et al., 1996; Vanlerberghe and Morancais, 1996).

As a consequence of their use in organism, the surfactants for pharmaceutical purposes are required to possess a low allergenic and irritation potential associated to high biocompatibility. With regard to these requirements of innocuosness, the sugar-based surfactants, because of their low toxicity and excellent biodegradability, can offer an attractive alternative to more conventional ethyleneoxide based surfactants (Shinoda et al., 1996). They are prepared from natural and renewable resources which allow us to devise manifold structural combinations suited for modulating surfactant properties (Schmidt and Jankowski, 1996). Furthermore, the phase behavior of this class of non-ionic surfactants is much less influenced by temperature variations than that of typical nonionic surfactants (Stubenrauch et al., 1996).

Many investigations have explored the amphiphilic nature of this new generation of surfactants, often by adopting a systematic strategy in order to correlate the influence of structural changes with physical properties (Van Doren et al., 1989; Eastoe et al., 1994; Sakya et al., 1994; Auvray et al., 1995; Costes et al., 1995; Söderberg et al., 1995; Raaijmakers et al., 1995; Van Doren and Terpstra, 1995; Boullanger and Chevalier, 1996; Eastoe et al., 1996; Zhang and Marchant, 1996; Hato and Minamikawa, 1996).

In connection with this research field, we have recently prepared several series of monosaccharide derivatives according to the general formula shown in Fig. 1 (type I) (Gouéth et al., 1994; Bikanga et al., 1995, 1996). They are defined by aliphatic chains of varied length, (R) attached to a carbohydrate substrate (Su) via linking group (Z) in position 1. Compound hydrophilicity is attributed to the free hydroxyl group number borne by head part (p) rather than ethyleneoxide group number in conventional nonionic surfactants. The hydrophobicity depends on the atom carbon number (n) in the alkyl chain (R). The surfactant properties are estimated by the determination of physical parameters arising from fundamental concepts linked to the amphiphilic structure of molecules: 'abnormal' solubility, critical micelle concentration (CMC), lyotropic liquid crystal and hydrophilic/lipophilic balance (HLB).

In this article, we describe the results obtained with eleven alkyl esters issued from 1-Z-R-D,L-xylitol family ($p = 4$; Z = OCO; $n = 4$–17 in Fig. 1 type II). They are abbreviated X–C_n. In addition of the influence of tail length, we show the role of junction nature, Z = O; OCO; S, and the role of head group conformation, cyclic or acyclic. For the former, the behavior of X–C_n compounds is compared with the available data previously reported on their thio (X–S_n) (Van Roekeghem et al., 1997a) and ether (X–O_n) (Van Roekeghem et al., 1997b) derivatives (Fig. 1 type II) and for the latter the comparison is established between the D,L-xylitol derivatives and their D-glucose homologues (Glu-Z_n with $p = 4$; Z = OCO; $n = 8$,12, 16 and 18 in Fig. 1 type III) (Bikanga et al., 1995).

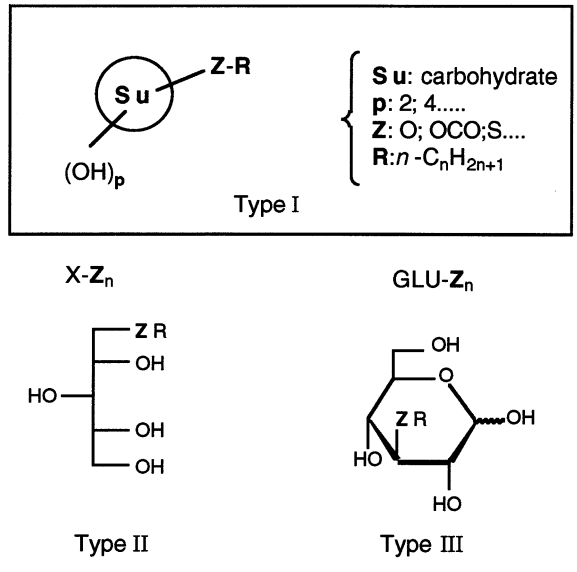

Fig. 1. Top: General formula of carbohydrate-based surfactants (type I). Bottom: Amphiphilic structures issued from acyclic substrate (type II where 'X' is D,L,-xylitol) and from cyclic substrate (type III where 'GLU' is D-glucose). In both series, Z corresponds to OCO for esters abbreviated to C, to O for ethers and to S for thioethers.

2. Experimental part

2.1. Materials

The 1-*O*-*n*-acyl-D,L-xylitol compounds, designated $X-C_n$, were prepared in our laboratory according to the following general synthetic pathway which was described in previous papers (Regnault et al., 1989; Goodby et al., 1997). The diacetal substrate, 1,2:3,4-di-*O*-isopropylidene-D,L-xylitol was prepared using the method reported by Regnault et al. (1989). Then, the diacetal esterification was subsequently realized with various acid chlorides in presence of triethylamine (C_nH_{2n+1}/TEA). The conditions for the deacetalization were selected in order to obtain the desired products (Fig. 1 type II with Z = OCO).

Distilled water was filtered through a 0.45 μm millipore medium before to be used and its surface tension was equal to 70. 5 ± 1 mN/m at 25°C.

Oily phase was liquid paraffin oil (Primol 352 Exxon). Brij 56 (decaethyleneglycol hexadecylether; with a hydrophilic/lipophilic balance of 12.9), Brij 52 (diethyleneglycol hexadecylether; with a hydrophilic/lipophilic balance of 5.3) and Tween 60 (Sorbitan stearate 20 ethyleneoxide; with a hydrophilic/lipophilic balance of 14.9) were purchased from Fluka. Span 60 (Sorbitan stearate; with a hydrophilic/lipophilic balance of 4.7) was supplied by Aldrich. The commercial products were used without further purification.

2.2. Methods

2.2.1. Water solubility

Two methods were performed on the ester series according to the disparity of water solubility. For very water soluble compounds, solubility at 25°C (S_w) was determined in round-bottom tubes by progressive titration with water of a determined surfactant amount previously weighted. The tubes were regularly stirred until whole clarification.

For other compounds, solubility was determined by stirring excess surfactant in water for 3 h at 50°C and then leaving it for two days at room temperature as reported previously (Van Roekeghem et al., 1997a,b). Solubility values were obtained from the difference between initial surfactant weight and the residue recovered on a glass filter with an experimental error estimated at 10%. With this process, none of the compounds, particularly the esters, are hydrolyzed.

2.2.2. Surface tension and critical micelle concentration (CMC)

For each compound, a primary solution S_0 (often saturated) was prepared in water at 25°C. Several samples were obtained by dilutions of S_0 in the range $3S_0/4$, $S_0/2$, $S_0/5$, $S_0/10$, $S_0/25$, $S_0/50$, $S_0/100$ and $S_0/250$. Surface tension (γ) was measured for each solution, after attaining thermal equilibrium in a thermostated bath, by use of the Wilhelmy method (TD 2000 Prolabo tensiometer). Each measurement of surface tension was repeated until two identical successive values were obtained. The critical micelle concentration value (CMC) was performed using graph $\gamma = f(\log C)$, in which C indicates molar concentration of the solution.

2.2.3. Microscopy

The optical observations of the lyotropic cristalline phases were made using an Olympus BX 50 polarizing microscope equipped with a Mettler FP 82 HT hot stage coupled to a Mettler FP central processor. The penetration technique described by Lawrence (1969) was used to form concentration gradients: a few milligrams of pure sample was placed on a glass slide beneath a cover slip, heated and cooled to form a glassy solid. Water was then added around the edges of the cover slip and allowed to penetrate the solid. A video camera connected to tape recorder was used to record the various textures produced by the two (surfactant/water) components as a function of temperature (between 25 and 95°C).

2.2.4. Determination of hydrophilic/lipophilic balance the emulsification method

This method consisted in preparing an emulsion range composed of constant water to oil ratio and stabilized by two surfactant combinations, A and B, one lipophilic e.g. A, with a hydrophilic/

lipophilic balance (HLB_A) which is rather low, and the other hydrophilic, e.g. B with a hydrophilic/lipophilic balance (HLB_B) which is rather high. By varying their respective weight percentages in each emulsion, a hydrophilic/lipophilic balance scale was set up and the hydrophilic/lipophilic balance value of the A and B mixture (HLB_m) was:

$$HLB_m = [HLB_A\ x + HLB_B\ (a - x)]/a \quad (1)$$

where x is the weight of the lipophilic surfactant and a the weight of the entire surfactant mixture A and B. For a specific oil, we can define the hydrophilic/lipophilic balance required (HLB_c) as the hydrophilic/lipophilic balance of surfactant mixture, which would give a more stable emulsion. In this case, the equation $HLB_m = HLB_c$ is satisfied.

Switching the lipophilic surfactant A to a lipophilic surfactant of an unknown hydrophilic/lipophilic balance, A′ in the previous system, the more stable emulsion obtained with x' of surfactant A′ allows the computation of $HLB_{A'}$ using the equation:

$$HLB_{A'} = [a(HLB_c - HLB_B)/x'] + HLB_B \quad (2)$$

Likewise, the substitution of hydrophilic surfactant B by an hydrophilic surfactant B′ with an unknown hydrophilic/lipophilic balance in the previous system serves to calculate the $HLB_{B'}$ value using the equation:

$$HLB_{B'} = (aHLB_c - x''\ HLB_A)/(a - x'') \quad (3)$$

In Eqs. (1)–(3), values of $HLB_{A'}$, $HLB_{B'}$, x, x' and x'' are known. The compositions exhibited by each emulsion were: lipophilic surfactant/hydrophilic surfactant/oil/water = x: $5 - x$: 20: 75 (w/w/w) where $0 \leq x \leq 5$.

Prior to HLB determination of $X - C_n$ compounds, the HLB_c of liquid paraffin oil used in emulsions has been set with the same water to oil ratio (75/20) and two type surfactant mixture, either Brij 52 (HLB = 5.3)/Brij 56 (HLB = 12.9) or Span 60 (HLB = 4.7)/Tween 60 (HLB = 14.9). The HLB_c assigned to oil was 10 for the first and 9 for the second one. The discrepancy obtained with these usual commercial products could be due to their different chemical nature, respectively ether and ester products, and could also result from their polydispersity.

Emulsions were prepared by coupling each X–C_n compound with its antagonist, Span 60 for $n = 4$–11 or Tween 60 for $n = 13$–17. This distribution was determined by taking into account water solubility of compounds at 25°C that can be used to obtain a rough approximation of their HLB values (Becher, 1965). Tween 60 was incorporated in water phase (or Brij 56 if emulsifiation was not achieved with previous one), the X–C_n compound in the oily phase and conversely for Span 60 (or Brij 52). Emulsification was achieved at 70°C by phase inversion using a mixer (Rayneri type 1144) at 200 r/m. for 30 min. The examination of emulsions was made by visual and microscopic inspection and the stability control was analysed over a 2-week period at 4, 25 and 40°C.

3. Results and discussion

3.1. Water solubility determination

Water solubility data (S_w) at 25°C for the ester D,L-xylitols, X–C_n, are included in Table 1. They are compiled with the results obtained in previous investigations for two other series of alkyl substituted xylitol with thioether (Van Roekeghem et al., 1997a) and ether (Van Roekeghem et al., 1997b) linking groups noted X–S_n and X–O_n on the one hand and, on the other hand, for their cyclic homologues issued from D-glucose noted GLU-Z_n with Z = C, S and O (Bikanga et al., 1995).

As for the compounds earlier studied, the extension of aliphatic chain of ester D,L-xylitols, i.e. of the hydrophobic moiety, induces an expected water solubility decrease. The phenomenon presents the singularity to be unmonotonous for overall alkyl chain length, which it is clearly seen in plots of log S_w against carbon atom number (n) (Fig. 2). From four to eight carbon atoms in the alkyl chain, water solubility moderately decreases. In contrast, by the only change from eight to nine carbon atoms, water solubility of ester D,L-xylitols undergoes an abrupt inflexion which distinctly divides the ester series into two categories

Table 1
Solubility S_w in water at 25°C of X–C_n compounds and of its thio and ether derivatives previously studied (Van Roekeghem et al., 1997a,b) gathered with solubility values of their respective cyclic homologues issued from D-glucose also previously reported (Bikanga et al., 1996). The compounds corresponding to dashes were not studied

n	Water solubility S_w (in 10^{-4} M)					
	X–C_n	X–O_n	X–S_n	GLU-C_n	GLU-O_n	GLU-S_n
4	490 000	1 300 000	360 000	–	–	–
5	360 000	1 200 000	100 000	–	–	–
6	170 000	300 000	79 000	–	–	–
7	94 000	120 000	120	23.2	–	–
8	81 000	76 000	36	–	18.4	12.2
9	28	48 000	7.2	–	–	–
10	5.8	16	1.9	–	–	–
11	1.8	9.5	0.9	11.7	–	–
12	–	5.6	0.7	–	9.8	9.9
13	0.5	–	–	–	–	–
14	–	2.0	0.2	–	–	–
15	0.5	–	–	6.8	–	–
16	–	4.2	0.8	–	8.4	6.9
17	0.9	–	–	7.0	–	–
18	–	6.4	1.2	–	6.1	5.7

of compounds with opposite behaviour: the very soluble ones ($>10^3$ g/l) for $n=4$–8 and the very low soluble (<1 g/l) for $n=9$–17. The poor water solubility of the latter group is attributed to their relatively high hydrophobic to hydrophilic ratio. The break of the water solubility curve with respect to alkyl chain length should express a shift of Krafft points towards higher temperatures than 25°C as it was shown for 3-*O*-alkyl-D-glucitol (Raaijmakers et al., 1995) and alkyl 2-amino-2-deoxy-β-D-glucopyranosides (Boullanger and Chevalier, 1996). In short, the Krafft temperature should be less or equal than 25°C for the products with short alkyl chain length and higher for the products with long alkyl chain length.

A similar trend was described for other xylitol derivatives but it is shown in Fig. 2 that the transition between high and low solubility occurs at shorter alkyl chain length—between six and seven carbon atoms—for thioethers and, at longer alkyl chain length—between nine and ten carbon atoms—for ethers. Thus, for this range of alkyl chain length, even if the linking unit is not the preponderant factor, results lead to indicate the following order of efficiency of the functional group in solubilizing aliphatic substituted xylitols in water:

(R–O–) > (R–COO–) > (R–S–).

It is consistent with the hydrophilic nature of each atom. Indeed, sulphur has considerably less

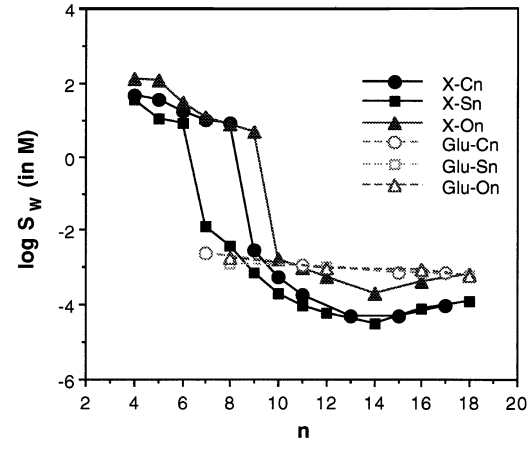

Fig. 2. Decimal logarithm of water solubility (S_w) at 25°C (in M) versus carbon atom number (n) in alkyl chain of D,L-xylitol and D-glucose derivatives.

Table 2
Critical micelle concentration (CMC) with respective surface tension (γ) at 25°C for X–C_n series, gathered with results previously reported for X–O_n (Van Roekeghem et al., 1997b), X–S_n (Van Roekeghem et al., 1997a) and GLU-C_n (Bikanga et al., 1996). The compounds corresponding to dashes were not studied

n	X–C_n		X–O_n	X–S_n	GLU-C_n
	CMC (in 10^{-4} M)	γ (mN/m)	CMC (in 10^{-4} M)	CMC (in $10-^{4}$ M)	CMC (in $10-^{4}$ M)
4	1200	30.0	580	1 800	–
5	580	33.2	380	460	–
6	100	30.0	94	160	–
7	180	28.6	92	–[a]	16.0
8	44	25.4	67	–[a]	–
9	18	26.0	21	–[a]	–
10	–[a]	<31.6	8.1	–[a]	–
11	–[a]	<26.4	3.0	–[a]	2.3
12	–		–[a]	–[a]	
13	–	<37.2	–	–	–
14	–		–[a]	–[a]	
15	–[a]	<43.4	–	–	1.4
16	–		–[a]	–[a]	–
17	–[a]	<43.3	–	–	2.0
18	–		–[a]	–[a]	–

[a] No break in the slope of $\gamma = f(\log c)$, γ is minimum surface tension.

ionic character than oxygen, and so forms hydrogen bonds only weakly if at all (Sakya et al., 1994). The ester functional group appears to develop intermediate behaviour between the one of ethers and thioethers. Though the carbonyl can act as an extra point for hydrogen bonding interactions, the more rigid nature of the ester group (Goodby et al., 1997) may also affect water solubility especially for longest alkyl chain.

The change over from linear hydrophilic headgroup to cyclic one issued from D-glucose provokes several effects. Firstly, it levels off the junction influence and secondly it reduces the hydrophobic effect produced with increasing the alkyl chain length. The less magnitude of water solubility values obtained for glucose derivatives with short alkyl chains ($n \leq 7–8$) compared to their acyclic homologues, suggests that the conformational stability of cyclic system restricts the ability of forming hydrogen bonds with water molecules. In return, the reverse situation observed for longer alkyl chains ($n \geq 9$) could be interpreted by the fact that, beyond a certain carbon atom number, the final part of such alkyl chains could come near hydroxyl sites by carbon-carbon rotation. This proximity could disturb the formation of intermolecular hydrogen bonds with water molecules. Due to steric reason, the phenomenon could occur more readily in the case of xylitol than in the case of glucose compounds because the acyclic head group allows the free carbon-carbon rotation whereas it could be less effective with the cyclic one.

3.2. Critical micelle concentration and interfacial parameters

The critical micellar concentrations (CMC) of ester xylitols, listed in Table 2, were determined via surface tension measurements (γ) using the Wilhelmy method. The measured values were plotted against the logarithm of surfactant molar concentration (c) in aqueous solution at 25°C as seen in Fig. 3. In this classical diagram, the CMC corresponds to the concentration from which surface tension stabilizes at a minimum by saturation at water surface and becomes independent on surfactant amount in water. The minimum surface tensions (γ_{min}) are also given in Table 2.

The slope discontinuity was only observed for the ester compounds having from four to nine carbon atoms in the alkyl chain. Above nine carbon atoms, surface tension regularly decreases with increasing log c until the concentration of saturated aqueous solution is reached. At the saturation, the surface tension reduction of water appears still efficient for $n = 10$ and 11 and a little less for $n = 13$–17 (Table 2), therefore demonstrating real surface activity. The poor water solubility of this range of ester xylitols does not allow to detect micellization phenomenon at 25°C. From this aspect, it would be confirmed the aforesaid assumption according to that Krafft point would be above 25°C. However, an other hypothesis can be put forwards; micellization could occur in the bulk water phase over the entire range of concentrations before achieving the complete adsorption at the air/water interface as it has been mentioned for surfactants derived from bile salts (Azéma et al., 1995).

Below ten carbon atoms in the alkyl chain, X–C_n compounds display CMC data which typically decrease as n increases. This trend with respect to the alkyl chain length was already reported for thioether (Van Roekeghem et al., 1997a) and ether (Van Roekeghem et al., 1997b) derivatives, as well as glucose derivatives (Bikanga et al., 1995). An important factor on the micellization phenomenon is often referred to as the hydrophobic effect. The mutual attraction forces exerted between the hydrocarbon chains provide an energetically favourable situation in the interior of micelles. These driving forces of micellization are higher for a long alkyl chain than a short one and, therefore, a lower CMC results (Rosen, 1988).

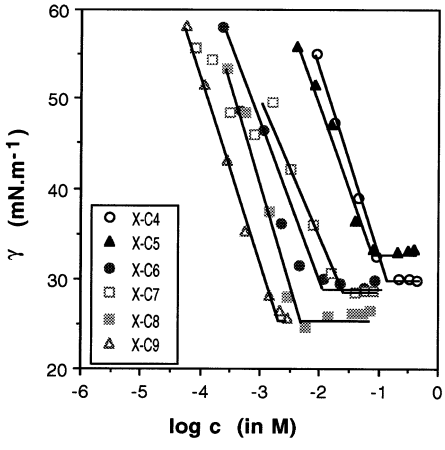

Fig. 3. Surface tension (γ) at the air/water interface versus the decimal logarithm of X–C_n molar concentration at 25°C.

In the range covering the alkyl chain from six to nine carbon atoms, and especially eight and nine, the propensity to micellize can be compared with literature data of other nonionic surfactants. The CMC determined for X–C_8 ($4.4\ 10^{-3}$ M) is in the vicinity of the one of some polyoxyethylene surfactants such as C_8E ($4.9\ 10^{-3}$ M) and C_8E_3 ($7.5\ 10^{-3}$ M) (Rosen, 1988), close to the values found for some other sugar-based surfactants, linear such as 3-*O*-decyl-D-glucitol ($2.8\ 10^{-3}$ M) (Raaijmakers et al., 1995) or cyclic as alkyl 2-amino-2-deoxy-β-D-glucopyranosides having nine carbon atoms ($7\ 10^{-3}$ M) (Boullanger and Chevalier, 1996).

It has to be pointed out the low surface tension obtained at the CMC ($\gamma_{min} < 30$ mN/m) for most of X–C_n products which attests their adsorption performance at air/water interface.

The hydrophobic fragment contribution to CMC was further analysed through the empirical relation (Rosen, 1988):

$$\log_{10} \text{CMC} = A - B\,n \quad (4)$$

where A is a constant strongly influenced by the hydrophilic group and B is related to the change in free energy when a methylene group is transferred from an aqueous environment to the micelle. The latter constant also depends on which hydrophilic group is present and can vary between about 0.3 and 0.5 (Rosen, 1988). This relation is illustrated for ester xylitols in Fig. 4. The fit to a straight line only gives a compatible correlation when $n > 6$ carbon atoms, with the values admitted in literature (Rosen, 1988). Indeed, the A and B constants, given in Table 3 for all D,L-xylitol series, are in agreement with data in particular refering to non-ionic ethoxylates, C_nE_m with $m =$ 6 and 8 (Huibers et al., 1996). When $n < 7$, the molecules are so soluble in water, because of the disproportion between hydrophilic and hydrophobic parts, that they behave more like 'salts' than

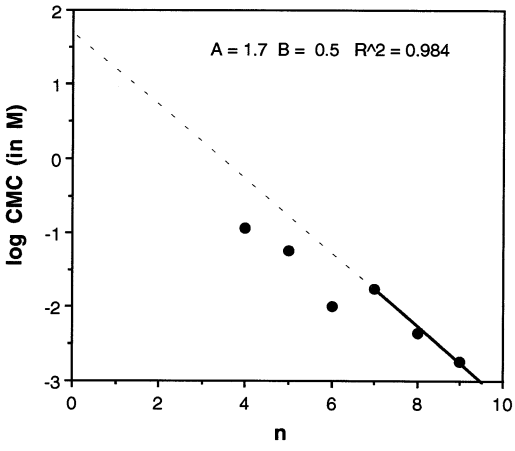

Fig. 4. Variation of log CMC (in M) versus the carbon atom number (n), in the alkyl chain of X–C_n compounds.

surfactants. The deviation corresponding to X–C_n compounds with shorter alkyl chain can be attributed to the high surfactant concentration at which ideal solution behaviour does not hold (Zhang and Marchant, 1996). Similar trend was observed for ether derivatives of which log CMC values are only well correlated for $n > 7$ (Table 3) (Van Roekeghem et al., 1997b). For thioethers, it was not possible to study correlation for longer alkyl chains because the CMC of the products in question was not detected.

The free energy decrease caused by the transfer of a methylene from the water to the hydrophobic core of the micelle (ΔG^0_{mic}) can be calculated through the expression (Rosen, 1988):

$$\Delta G^0_{mic} = 2.303\ RT\ (\log CMC/\omega) \quad (5)$$

where ω is the molar concentration of water (55.3 at 25°C). The introduction of a methylene group to the alkyl chain contributes for -2.85 KJ/mol to ΔG^0_{mic} for esters.

Concerning the influence of linking group on CMC, there is no evident variation rule from comparisons of A and B constants listed in Table 3 for the three D,L-xylitol series. Nevertheless, the lower CMC and the extent of the range of products exhibiting CMC (Table 3) put forwards that the tendency of forming micelles is better for ethers than the one of esters and then of thioethers: (R–O–) > (R–COO–) > (R–S–). This efficiency order for micellization, similar to water solubility, suggests that only the krafft point of the X–O_n compounds is reached at 25°C for longer alkyl chain ($n \leq 11$).

The configuration of the head group also plays an important role in micellization. Indeed, for a same alkyl chain length, i.e. $n = 7$, CMC of the D-glucose ester is about ten times less than the one of D,L-xylitol ester. Despite a poor water solubility, of a same order amplitude than water solubility of D,L-xylitol derivatives, D-glucose derivatives with longer alkyl chains have CMC. A cyclic hydroxyl bearing group, instead of a linear one as D,L-xylitol appears to promote strongly self-assembly of molecules: GLU > X. This result incites us to assume again that the affinity for water is stronger for xylitol head group. The hydrophilic head group might be spaced out to allow as much as water possible to solvate them. The acyclic structure of D,L-xylitol, less rigid than the cyclic one would lend to this phenomenon.

From surface tension plots, it is possible to get additional information by determining some parameters which tackle other characteristic features of surfactants. The maximum surface (excess) concentration of surfactant at the air/water

Table 3
Influence of the junction nature (Z) on the empirical A and B constants (Rosen, 1988) at 25°C for alkyl substituted xylitols

X–Z_n series	Range of products having CMC (n)	Empirical relationship		
		A	B	n range used
X–O_n	$n = 4$–11	1.4	0.45	$n = 8$–11
X–C_n	$n = 4$–9	1.7	0.50	$n = 7$–9
X–S_n	$n = 4$–6	1.3	0.50	$n = 4$–6

Table 4
Air/water surface tension data at 25°C for X–C_n, X–O_n (Van Roekeghem et al., 1997b) and X–S_n (Van Roekeghem et al., 1997a) compounds

n	CMC (in 10^{-4} M)	Γ 10^{10} (mol/cm^2)	A_0 (Å^2/molecule)	CPP	pC20
X–C_n					
4	1200	3.8	44	0.5	1.9
5	580	3.2	52	0.4	2.1
6	100	3.5	48	0.4	3.2
7	180	3.2	52	0.4	2.8
8	44	4.5	37	0.5	3.3
9	18	3.7	45	0.5	3.9
X–O_n					
7	92	4.6	36	0.6	2.9
8	67	3.4	49	0.4	3.4
9	21	5.7	29	0.7	3.4
10	8.1	4.6	36	0.6	4.0
11	3.0	4.4	38	0.6	4.5
X–S_n					
4	1800	2.9	58	0.4	1.8
5	460	3.7	45	0.5	2.2
6	160	4.2	34	0.5	2.7

interface, Γ_{max}, is a parameter which accounts for effectiveness of air/water interface adsorption, i.e. the extent of surface reduction attained at CMC. The Γ_{max} data were calculated from simplified Gibbs adsorption equation (Rosen, 1988):

$$\Gamma_{max} = \lim_{c \to CMC} [-1/(2.303\ RT)]\ (d\gamma/d\ \log\ c) \quad (6)$$

Surface area occupied per molecule at the air/water interface, A_0 (in Å^2/molecule) is directly inferred from Γ_{max} parameter (in mol/cm^2) according to the relation:

$$A_0 = 10^{16}/(N\ \Gamma_{max}) \quad (7)$$

where N is the Avogadro's number.

Results for Γ_{max} and A_0 are included in Table 4. In the ester series, the variation of alkyl chain length does not affect significantly the surfactant adsorption more or less stabilized at an average value of (3.7 ± 0.5) mol/cm^2, which leads to an area occupied per molecule of about (46 ± 6) Å^2. For ethers, the A_0 values are on the order of (38 ± 7) Å^2. and for the thioethers on the order of (46 ± 12) Å^2, irrespective of the alkyl chain. Even taking into account the large uncertainty of the values, it is suggested that the ether derivatives are more adsorbed at the air/water interface than two other surfactant series do. This conclusion is supported by the lower values of surface tension obtained at CMC for ethers ($\gamma_{min} = 26 \pm 3$ mN/m) (Van Roekeghem et al., 1997b) with regard to esters and thioethers ($\gamma_{min} = 29 \pm 3$ mN/m). The small oxygen size relative to sulphur or to ester group (Sakya et al., 1994) combined with the different conformation of molecules imposed by each junction (Goodby et al., 1997) contributes likely to modify the characteristic of the surfactant monolayer adsorbed at the air/water interface. The ether junction appears as the more appropriate to form a well-ordered monolayer.

The calculated parameters of D,L-xylitol amphiphiles (Table 4) are included in the range of values commonly mentioned in literature for non-ionic surfactants (Rosen, 1988). Compared to glucose-based surfactants, the surface area occupied per molecule is similar or intermediate to that reported for dodecylglucosides (36 Å^2) (Zhang and Marchant, 1996) for glucose-6-dodecanoate (37 Å^2) (Söderberg et al., 1995) and for alkyl 2-amino-2-deoxy-β-D-glucopyranosides (50 Å^2) (Boullanger and Chevalier, 1996).

Table 5
Critical micelle concentration (CMC) with the corresponding surface tension (γ) of X–C_n compounds for various temperatures

X–C_n	CMC (in 10^{-4} M)				γ (mN/m)			
	25°C	35°C	45°C	55°C	25°C	35°C	45°C	55°C
X–C_4	1200	1100	770	640	30.0	29.9	29.4	29.2
X–C_5	580	540	440	410	33.2	32.5	32.3	32.0
X–C_7	180	170	150	130	28.6	28.0	27.4	27.0
X–C_8	44	40	32	39	25.4	24.7	24.6	24.2

To give an other insight into surface adsorption of D,L-xylitol-based surfactants at the air/water interface, the efficiency of reduction in surface tension, designated pC20, was determinated. The pC20 parameter is defined as the value of the negative logarithm of the bulk concentration required to reduce the surface tension by 20 mN/m (Rosen, 1988). The pC20 values are gathered in Table 4 for ester, ether and thioether series. The increase of the alkyl chain length involves a better efficiency in surface tension reduction. The relation between the pC20 parameter and the carbon atom number in the alkyl chain is linear as it is shown in Fig. 5 for esters compounds. The slope of the straight line only differs a little from that obtained for the two other series, showing that the junction nature is not the preponderant factor for efficiency. The variation of pC20 is associated to the variation of free energy (ΔG_{tr}) when a methylene unit of the alkyl chain is transferred from the bulk phase to the interface by the following equation (Rosen, 1988):

$$pC20 = (-\Delta G_{tr}/2.303\ RT)\ n - K \quad (8)$$

where n is the number of carbon atom number in the alkyl chain and K is a constant for a given hydrophilic group. The ΔG_{tr} value calculated for D,L-xylitol surfactants is (-2.3 ± 0.1) KJ/mol at 25°C. This value falls near that of nonionic polyoxyethylene surfactants (Rosen, 1988).

The effect of temperature on micellization process was examined for ester compounds by performing surface tension determination at 25, 35, 45 and 55°C. The CMC results are listed in Table 5. The increase of temperature from 25 to 55°C leads to decrease CMC values, but without affecting significantly their respective minimum surface tension (γ_{min}). The changes observed with temperature could be a consequence of decreased hydration of the hydrophilic group, facilitating micellization (Rosen, 1988). The dependence of CMC on temperature was also characteristic of their D-glucose homologues (Bikanga et al., 1996) whereas it was not evidenced for glucosamine-based surfactants (Boullanger and Chevalier, 1996).

The relationship between CMC and temperature can be expressed by the equation (Meguro et al., 1987):

$$\text{Ln CMC} = A'\ (1/T) + B' \quad (9)$$

where A' and B' are constants. The experimental A' and B' constants for ester xylitols were determined from the linear regression of Ln CMC versus $1/T$ plots (Fig. 6). This expression combined with the Eq. (5) and the classic one:

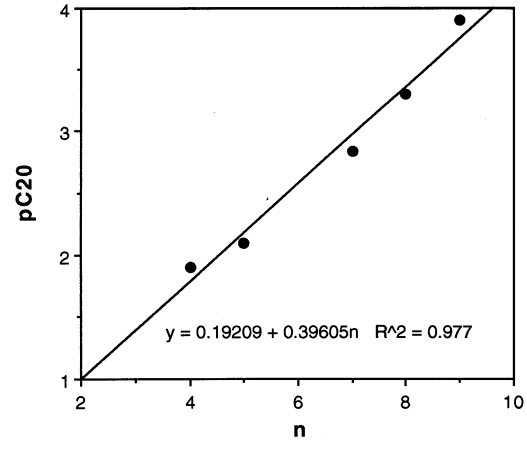

Fig. 5. Plot of surface tension efficiency (pC20) of X–C_n compounds against carbon number (n) in the alkyl chain at 25°C.

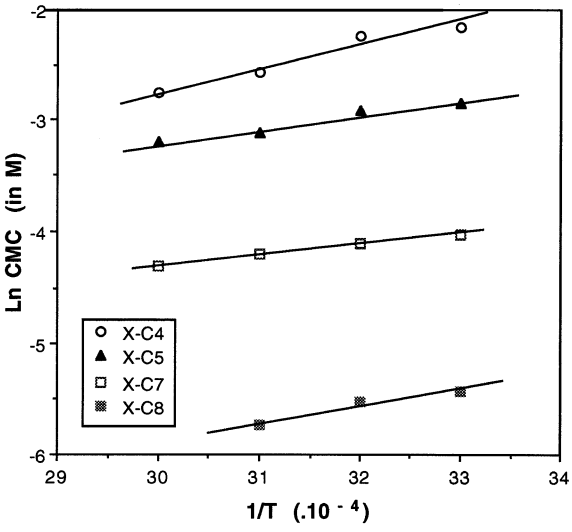

Fig. 6. Ln CMC (in M) versus $1/T$ for X–C_n compounds.

$$\Delta G^0_m = \Delta H^0_m - T\ \Delta S^0_m \quad (10)$$

allows to express the micellization thermodynamic ΔG^0_m, ΔH^0_m and ΔS^0_m parameters from A' and B' values:

$$\Delta G^0_m = R\ A' + RTB' \quad (11)$$

$$H^0_m = R\ A' \quad (12)$$

$$\Delta S^0_m = -R\ B' \quad (13)$$

The thermodynamic parameters calculated for the three xylitol series are given in Table 6. The negative ΔG^0_m values indicate that micellization is spontaneous and especially by increasing alkyl chain length. Thus, the lipophilic surfactant moiety is the main driving force involved in aggregate formation. The larger contribution of positive ΔS^0_m values to G^0_m, compared to H^0_m values, proves that the entropic gain governs primarily the micellization process with a dependence of the linking group nature in the following order: ΔS^0_m (X–O_n) > ΔS^0_m (X–C_n) ≈ ΔS^0_m (X–S_n).

3.3. Lyotropic liquid crystals

Surfactant phase behaviour in water is strongly influenced by the system variables as well as by the molecular structure of the surfactant (Israelachvili, 1985). The relationship between the geometric features of surfactants and amphiphilic association structures that will form these molecules have been approached in terms of packing parameter (Tanford, 1980):

$$CPP = v_H/(a_o \cdot l_c) \quad (14)$$

in which v_H is the lipophilic group volume of a surfactant molecule, a_0 is the cross-sectional area of its hydrophilic group and l_c is the approximate

Table 6
Micellization free energy, enthalpy and entropy at 25°C of X–C_n compounds and of X–O_n (Van Roekeghem et al., 1997b) and X–S_n (Van Roekeghem et al., 1997a) compounds previously reported

n	ΔH_m (kJ/mol)	ΔS_m (J/K.mol)	T ΔS_m (kJ/mol)	ΔG_m (kJ/mol)
X–C_n				
4	17.3 ± 2.1	75.4 ± 6.9	22.5 ± 2.1	−5.2 ± 4.2
5	10.1 ± 1.3	57.3 ± 4.2	17.1 ± 1.2	−7.0 ± 2.5
7	7.7 ± 0.7	59.1 ± 2.0	17.6 ± 0.6	−10.0 ± 1.3
8	12.4 ± 2.1	86.7 ± 6.9	25.8 ± 2.1	−13.4 ± 4.2
X–O_n				
6	22.3 ± 3.7	113.8 ± 12.0	33.9 ± 3.6	−11.6 ± 7.3
7	21.5 ± 4.2	112.0 ± 13.4	33.4 ± 4.0	−11.9 ± 8.2
8	20.2 ± 2.2	109.9 ± 7.1	32.7 ± 2.1	−12.5 ± 4.3
9	27.8 ± 5.1	144.8 ± 16.4	43.1 ± 4.9	−15.3 ± 10
X–S_n				
4	21.6 ± 0.4	85.8 ± 12.4	25.6 ± 3.7	−4.4 ± 4.1
5	2.4 ± 0.4	33.5 ± 1.2	10.0 ± 0.4	−7.6 ± 0.8
6	6.5 ± 1.1	55.8 ± 3.7	16.6 ± 1.1	−10.2 ± 2.2

length of the hydrocarbon chain. Tanford (1980) has established the following relations as a function of the carbon atom number in the alkyl chain:

$$v_H = 27.4 + 26.9\ n\ (Å^3) \quad (15)$$

$$l_c = 1.5 + 1.255\ n\ (Å) \quad (16)$$

The geometry of the aggregates may be predicted from the magnitude of CPP parameter:

- CPP < 1/3: spherical micelles;
- < CPP < 1/2: rods;
- < CPP < 1: lamellar structures;
- CPP > 1: inverted micelles.

To the calculated CPP data summarized in Table 4 for ester series, are joined the values of the two other series obtained in previous studies (Van Roekeghem et al., 1997a,b). They were calculated taking into account the area occupied per molecule at the air/water interface (A_0) as an approximate a_0 value. The assumption of $A_0 = a_0$ provides a reasonable prediction for the phase behaviour of surfactant in water concerning low or intermediate surfactant concentrations (Söderberg et al., 1995). On this basis, the CPP values of 0.4 or 0.5 relative to esters and thioethers suggest that cylindrical-like micelles or bilayers are expected. The CPP values of about 0.6 determined for ethers mean that in this case lamellar phase are preferentially formed. The effective size of the hydrophilic head group of ethers is less bulky than the one of esters and thioethers (Sakya et al., 1994) and likely the balance between head group and hydrophobic segment enables the surfactant to adopt a cylinder shape appropriate to promote bilayers.

The lyotropic liquid crystal properties were qualitatively investigated. The different phases, progressively developed on contacting a few crystals of each X–C_n compound with water, were observed by polarized optical microscopy. In the experiment, attention was restricted to the interval of temperature between 25°C and 95°C.

As for thioether and ether derivatives, the lyotropic phase displayed by ester series (see Table 7), except for $n = 4$, was lamellar phase ($L\alpha$) that was identified by its characteristic 'oily streak' texture (see Fig. 7). It expands over abroad range of temperature which is shifted to higher temperatures when the alkyl chain length increases, probably due to the respective decrease of water solubility of the products (Tables 1 and 7).

Table 7
Temperature range (determined by microscopic inspection) of lyotropic liquid crystals formed by X–C_n compounds. T_1 is crystal to lyotropic liquid crystal transition and T_2 is liquid crystal to liquid transition

n	T_1 (°C)	T_2[a] (°C)	Lyotropic phases
4	–	–	Dissolves
5	<25	45–55	Lamellar
6	<25	69	Lamellar
7	<25	>95	Lamellar
8	31	>95	Lamellar
9	<25	>95	Lamellar
10	42	>95	Lamellar
11	42	>95	Lamellar
13	40	>95	Lamellar
15	40	>95	Lamellar
17	58	>95	Lamellar

[a] The experimental device used does not allow to observe at $T > 95$°C because of water evaporation.

From $n = 11$, lamellar phase does not exist at room temperature for esters whereas for ethers it does (Van Roekeghem et al., 1997b). For thioethers we did not observed liquid crystals at this temperature. From the comparison drawn for the three series, the different linking groups can be arranged in the following order as a function of their efficiency of forming lyotropic phases: R–O– > R–OCO– > R–S–.

4. Hydrophilic/lipophilic balance determination

The hydrophilic/lipophilic balance of esters was determined by testing surfactant in emulsions of constant composition. In each emulsion, one X–C_n compound was coupled to a commercial surfactant of similar chemical nature (ester with ester), Span 60 or Tween 60. If the consecutive emulsion was unstable, Span 60 was substituted by Brij 52 or Tween 60 by Brij 56.

The results of hydrophilic/lipophilic balance and storage stability of emulsions are described in

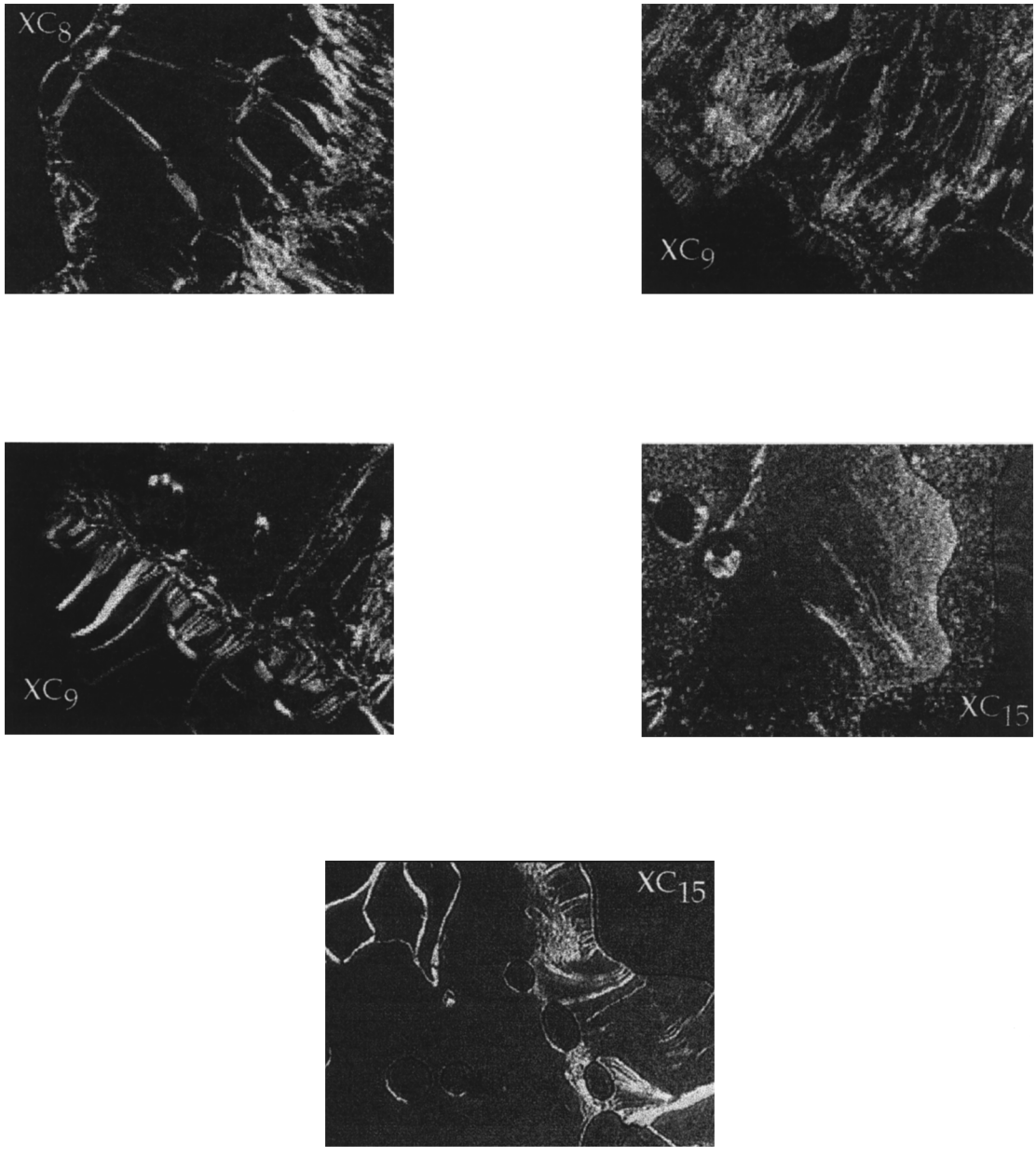

Fig. 7. The optical pattern, typical of a liquid crystalline phase of the lamellar type obtained with X–C_n compound.

Table 8 for esters. When alkyl chain length varies from $n = 4–17$, hydrophilic/lipophilic balance values decrease from 18 to 2. The more stable emulsions were obtained with X–C_6, X–C_7 and especially X–C_8, whose hydrophilic/lipophilic balance values are in the vicinity of 14.

Globally, the emulsions prepared with ethers were more stable and the drop size smaller (Van Roekeghem et al., 1997b) while the stability of emulsions formed with thioethers was mostly improved by the formation of gel-like structure (Van Roekeghem et al., 1997a).

The substitution of acyclic structure by a cyclic one in head group leads to increase stability of emulsions. The HLB values of GLU-C_n are less versatile than those of X–C_n since for $n = 7$–17, they only vary between HLB = 12 and HLB = 9, respectively. The large variation of ester HLB values and of emulsion stability is not quite surprising since the compounds of this same series exhibit extreme water solubility behaviour. Taking into account the discontinuity of the results, we should turn towards another process, such as the method described by Salager (1996). bringing into operation microemulsions.

5. Conclusion

In the context of 1-Z-R-D,L-xylitol study, we report the main amphiphilic properties of eleven esters (Z = OCO; R = C_nH_{2n+1} with $n = 4$–17), noted X–C_n. Their behaviour follows the classical trend expected in a homologous series of surfactants with the same hydrophilic group and different alkyl chain length. Tensiometric measurements at 25°C give a CMC conform to nonionic surfactant for $n = 8$ and 9 (about 10^{-3} M). For longer alkyl chain, CMC is not detected because of poor water solubility at 25°C. By means of emulsification method, we have shown the versatile HLB with the changes of alkyl chain length, from HLB 16 to HLB 2, which can be of interest for pharmaceutical applications.

Except for $n = 4$, all X–C_n compounds form lyotropic liquid crystal of the lamellar structure. By compiling ester results with the available data of their thioether (Z = S) and ether derivatives (Z = O) as well as of their D-glucose homologues, we have stated some generalizations about the influence of the connecting group and head group configuration, cyclic or acyclic, on amphiphilic properties. We have shown that ethers appear to have higher tendency for micellization, emulsification and for displaying lamellar phases at 25°C. The cyclic configuration of D-glucose with respect to acyclic of D,L-xylitol also contributes to improve micellization and emulsification.

Globally, the major fact that has emerged from the study of water solubility, of critical micelle concentration as well as hydrophilic lipophilic balance determination, is an important discontinuity in the experiment values of the studied parameters for the transition of compounds having an alkyl chain length from $n = 8$ to 9. The explanation put forward suggests that this behaviour would result from perturbations brought by alkyl chains of sufficient size when the head group is not rigid but acyclic as in the case of xylitol. These perturbations seem to decrease the hydrophilic character of the molecules. One of the consequences would be the difficulty to have criti-

Table 8
Hydrophilic/lipophilic balance (HLB) data of X–C_n derivatives by means of emulsification method

n	Co-surfactant	HLB	Storage stability at 25°C (days)	Droplet size (μm)
4[a]	Brij 52	14–18	<3	1–200
5[a]	Brij 52	14–16	<7	1–30
6	Span 60	14	>14	1–30
7	Span 60	15–16	<3	1–10
8	Span 60	13–14	>14	1–10
9[a]	Brij 52	14	<3	1–5
10[a]	Brij 52	14	>14	1–50
11[b]				
13[b]				
15	Tween 60	7	>14	1–200
17[c]	Brij 52	2	<3	1–50

[a] Coupled with Span 60: unstable just after emulsification.
[b] No emulsification (either with Brij 56 or Tween 60).
[c] Coupled with Tween 60: unstable just after emulsification.

cal micelle concentration and stable emulsions under the experimental conditions that were used in the present work (75 wt.% water and 20 wt.% oil). In ulterior studies, hydrophilic lipophilic balance determination should be proceeded with an other method taking into account the behaviour disparity between the compounds of a same series.

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