Short chain glycerol 1-monoethers—a new class of green solvo-surfactants

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The synthesis of short eco-friendly amphiphilic compounds derived from glycerol was carried out. These compounds, called solvo-surfactants, are of great interest since they exhibit both properties of solvents, *e.g.* volatility, solubilization of organics, and surfactants, *e.g.* reduction of interfacial tensions, formation of emulsions and microemulsions. Their surface activity was studied, and binary phase diagrams with water were drawn. Their sensitivity to various electrolytes from Hofmeister's series was also investigated. Short chain glycerol 1-monoethers constitute a new class of green solvo-surfactants with excellent properties, that should be seriously considered for the replacement of reprotoxic glycol ethers. They have, moreover, the advantage of helping to solve the problem of an over-production of glycerol, which is a major side-product of the biocarburant industry.

Introduction

The dissolution of inorganic and organic compounds is an essential operation in chemistry. It can be achieved by molecular solubilization in water or organic solvents, but for different reasons (toxicity, biodegradability, simultaneous solubilization of both polar and unpolar compounds, *etc.*), chemists and formulators often prefer solubilization in micellar systems or microemulsions with the help of added surfactants. Today, both processes are well understood and controlled in most applications.

The use of amphiphilic solvents is an attempt to combine the advantages of solvents and surfactants. They are commonly used in the fields of coatings, degreasing, and numerous other applications (perfumery, inks, *etc.*). They exhibit properties both of solvents, such as volatility and solubilization of organics, and of surfactants, *e.g.* surface activity, self aggregation in water, co-micellization with surfactants, *etc.* They are sometimes nicknamed "solvo-surfactants".[1] The term hydrotrope is also commonly used, but it emcompasses a broader range of amphiphilic compounds, including low molecular weight aromatic salts.[2]

The most widespread hydrotropes today are the ethers derived from ethylene glycol, which are commonly called glycol ethers (C_iE_j). They have been studied extensively[3,4] because they exhibit interesting properties, mainly due to the fact that they are soluble not only in water but also in most organic solvents. However, recent toxicological studies have put forward a possible reprotoxic activity.[5] Therefore, some of them have been banned from pharmaceuticals, medicines, and domestic products.

Consequently, there is a need for new harmless amphiphilic solvents possessing comparable physico-chemical properties.

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Propylene glycol derivatives (C_iP_j) are today the main substitutes. Although less amphiphilic than their ethylene glycol counterparts, their functionnal properties are found to be satisfying.[6,7] However, they also derive from petrochemistry, whereas the "green" tendency encourages the development of new environmentally friendly products, bearing at least a natural polar moiety. In the field of surfactants, for example, sugar-based compounds, such as alkylpolyglucosides, have gained some importance within the last decade.[8] Within this context, we prepared and studied ethers of glycerol (that will be called C_iGly_j to distinguish them from alkylpolyglucosides C_iG_j) as potential substitutes for glycol ethers.

Glycerol is a natural molecule, also available synthetically (from petrochemicals[9] or by microbial fermentation[10]). The development of bio-carburants and particularly biodiesels (fatty acid methyl esters) will generate, until 2010, an annual glycerol over-production of more than 500 000 tons. To prevent a huge decrease of glycerol prices, which could destabilize the free market of oleochemicals, new uses of glycerol have to be found. The development of solvo-surfactants derived from glycerol could constitute a good opportunity to take advantage of this abundant resource, and to replace the more and more controversial glycol ethers.

Although polyglycerol based surfactants are already well known[11,12] and common, especially in the food and cosmetic industries,[13,14] low molecular weight glycerol derivatives have been almost totally ignored during the last century. Only a few of them are used, *e.g.* to deliver drugs,[15] or in degreasing and detergency.[16] Very little attention has been paid to them with respect to their physico-chemical properties and phase behaviour.

In the present paper we focus on short chain glycerol 1-monoethers (C_iGly_1, $4 \leqslant i \leqslant 6$) (Fig. 1). First, their synthesis will be described, followed by a presentation of their aqueous phase behaviour, which is compared to those of common ethylene glycol and propylene glycol derivatives. From the surface activity, minimal aggregation concentrations (MACs) will be determined. Next binary water/solvo-surfactants phase diagrams will be given and discussed. Attention
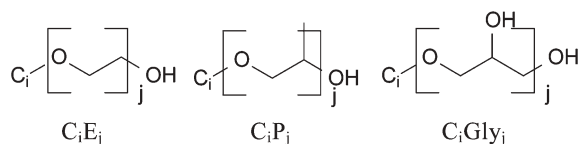
Fig. 1 Molecular structure of the solvo-surfactants studied in this work. Glycerol 1-monoethers (C_iGly_j) are potential substitutes for the controversial ethylene glycol ethers (C_iE_j) and propylene glycol ethers (C_iP_j).

will be paid to the thermodynamics of clouding, which yields information about the influence of temperature on the phase behaviour. In the last part of this paper, salt effects will be studied. A series of salts are chosen and their influence on the cloud points of the solvo-surfactants will be investigated and discussed in terms of the Hofmeister series. Salinity is indeed an important "formulation variable" (a parameter that can be used to balance the hydrophilicity and the lipophilicity of the amphiphile), since these molecules are almost insensitive to temperature, contrary to glycol ethers.

Experimental

Materials

For the synthesis of glycerol 1-monoethers, solketal (98%) was purchased from Aldrich (USA), as well as 1-bromoalkanes (all the highest grade available) and sodium sulfate (99+%). Tetrabutylammonium bromide (>98%) was purchased from Fluka (USA), whereas dichloromethane (99.8%) and cyclohexane (99.8%) were purchased from Acros (USA) and SDS (France) respectively.

All ethylene and propylene glycol ethers were purchased from Sigma–Aldrich (USA) and were the highest grade available (C_3E_1 99.4%, C_4E_1 99+%, C_5E_1 97%, C_4E_2 99+%, C_3P_1 98.5% and C_4P_1 99%). Glycerol 1-monoethers were synthesized according to the procedure described below.

Millipore water with 13 $m\Omega^{-1}$ cm^{-1} conductivity was used for all experiments. Sodium thiocyanate NaSCN 98%, sodium perchlorate NaClO$_4$ (98+%), sodium iodide NaI (99+%), sodium bromide NaBr (99+%), sodium chloride NaCl (99.5%) and sodium sulfate Na$_2$SO$_4$ (99%) were all purchased from Sigma–Aldrich (USA).

Synthesis of short chain glycerol 1-monoethers

0.5 mol (64.3 g) of solketal, 180 mL of KOH 33% and 0.025 mol (8 g) of tetrabutylammonium bromide were successively introduced in a 1 L two-neck round bottom flask, and stirred vigorously for 15 minutes at 25 °C. 0.5 mol of bromoalkane ($C_iH_{2i+1}Br$) was then added dropwise. At the end of the addition, the temperature was raised to 100 °C, and the mixture was stirred vigorously for 24 hours. The organic phase was then separated, dried over sodium sulfate, and distilled under reduced pressure to obtain pure alkylsolketal.

The pure alkylsolketal was then added, in a 1 L round bottom flask, to 500 mL HCl (2 M). After 4 hours vigorous stirring at room temperature, the mixture was neutralized with aqueous NaOH, and extracted 3 times with 200 mL of CH$_2$Cl$_2$. CH$_2$Cl$_2$ was chosen here because of its high efficiency.

However, cyclohexane can also be used, as well as other "greener" solvents. The organic phases were collected, dried over sodium sulfate, and CH$_2$Cl$_2$ was removed under reduce pressure. Finally, the residue was distilled under vacuum (Table 1) and under argon to obtain pure 1-*O*-alkylglycerol, which was stored on molecular sieves under argon. Purity was checked by ^{1}H and ^{13}C NMR, and by gas chromatography.

Yields obtained with different alkyl chain lengths are collected in Table 1. They slowly increase because the aqueous solubility of the final compound decreases with increasing alkyl chain length, resulting in an rise of the CH$_2$Cl$_2$/water partition coefficient.

Chemical shifts of ^{1}H and ^{13}C NMR spectra are given in Tables 2 and 3.

Surface activity, phase diagrams and salt effects

Solvo-surfactants solutions were obtained by precise dilution of the most concentrated one, prepared by weighing the product. The "rising bubble" mode was chosen to measure

Table 1 Yields[a] of the synthesis of glycerol 1-monoethers, and boiling points Eb measured during the distillation[b]

	C_4Gly_1	iC_5Gly_1	C_5Gly_1	C_6Gly_1
Yield	35	48	52	63
Eb	124/0.23	120/0.40	136/0.31	144/0.77

[a] In %. [b] In °C mmHg^{-1}.

Table 2 ^{1}H NMR chemical shifts[a] of glycerol 1-monoalkyl ethers, compared to TMS in CDCl$_3$ (δ, multiplicity, coupling constant)

	C_4Gly_1	iC_5Gly_1	C_5Gly_1	C_6Gly_1
1	0.92, t, 7.0	0.98, m	0.90, t, 6.1	0.89, t, 6.4
2	1.34, m		1.31, m	↑
3	1.54, q, 6.8	1.66, m		1.29, m
4	3.47, t, 6.7	1.50, m	1.58, q, 6.7	↓
5	—	3.49, t, 6.7	3.47, t, 6.1	1.54, q, 6.4
6	—	—	—	3.48, t, 6.4
1′	3.52, m	3.53, m	3.50, m	3.50, m
2′	3.86, m	3.85, m	3.85, m	3.86, m
3′	3.62, m	3.65, m	3.68, m	3.62, m

[a] In ppm.

Table 3 ^{13}C NMR chemical shifts[a] of glycerol 1-monoalkyl ethers, compared to TMS in CDCl$_3$

	C_4Gly_1	iC_5Gly_1	C_5Gly_1	C_6Gly_1
1	13.89	22.62	14.04	14.03
2	19.26		22.51	22.63
3	31.64	25.06	28.23	25.77
4	72.34	38.32	29.25	29.56
5	—	70.17	72.40	31.69
6	—	—	—	72.40
1′	71.52	72.44	71.82	71.88
2′	70.74	70.58	70.59	70.71
3′	64.18	64.21	64.21	64.22

[a] In ppm.

surface tensions. Surface activity was studied with a drop shape analysis tensiometer (model Tracker from IT Concept, France).

Binary phase diagrams were drawn by visual observation of a series of test tubes closed tightly and placed in a thermostated bath built at the University of Regensburg (Germany) combined with a RT5 multiple places magnetic stirrer from Fisher Bioblock Scientific (USA). Temperature was controlled at $T \pm 0.1$ °C. Samples were prepared by weighing on precision scales.

Salt effects were studied following the same procedure.

Results and discussion

Synthesis of short chain glycerol 1-monoethers

No efficient direct synthesis of glycerol 1-monoethers from glycerol and an alcohol or an alcohol derivative is known today. Two steps are generally required to obtain pure compounds. Usually, an initially "protected" or "modified" glycerol is preferred to the use of glycerol itself, which gives rise to mixtures of various mono- and polyethers that are difficult to purify. Historically, syntheses have been performed from allyl alcohols,[17] glycidol (2,3-epoxy-1-propanol),[18] or epichlorhydrin (2,3-epoxypropyl chloride),[19–21] but the most common reactant is solketal (1,2-isopropylideneglycerol).[17,20–22] In most cases, solketal is firstly etherified by an activated (halogenated, mesylated, tosylated) alcohol, and the resulting acetal is hydrolyzed (boric acid, hydrochloric acid, acid resins *etc.*) to give the target compound. The first step is problematic for several different reasons (use of harmful or expensive organic solvents, reactants that are not commercially available). A promising alternative was formulated by Rivaux *et al.* who used a phase-transfer catalysis[20] procedure, which was first introduced by Nouguier many years earlier.[23] This method allows the use of solketal and available halogenated alkanes as reactants, and avoids the use of any organic solvent. Solketal is solubilized in a concentrated KOH solution, etherified by an halogenated alcohol using a phase transfer catalyst, and the hydrolysis of the acetal is carried out with an acid resin. We chose to carry out the etherification of solketal on the basis of Rivaux's work. The subsequent hydrolysis was performed with an aqueous hydrochloric acid solution.

Surface activity of short chain glycerol 1-monoethers

The self-association of surfactants is a well known phenomenon. Hydrophobic interactions are the driving forces which induce the adsorption of the surfactant at the water/air interface. Once this interface is saturated, *i.e.* when the concentration reaches the CMC, the surfactant molecules self-associate to minimize the free energy of the whole system. The size and shape of the aggregates are governed not only by surfactant concentration, but also by other physical parameters such as temperature,[24] pH,[25] salinity,[26] *etc.*

According to their amphiphilic nature, solvo-surfactants or hydrotropes also adsorb at the interface and lower surface tension. However, their self-association is still a matter of debate.[27] Historically, the term hydrotrope was coined to describe short chain aromatic salts[2] that aggregate according

to a stack-type mechanism.[28] This stacking phenomenon was assumed to be responsible for their ability to solubilize organic compounds in water. However, molecules without an aromatic ring (*e.g.* sodium alkanoates)[29] and even without charge (*e.g.* glycol ethers) turned out to possess similar properties, although stacking cannot occur in this case. A progressive aggregation is more probable, but is hardly detected. Direct vizualisation by SANS, SAXS, or light scattering[30,31] has already been carried out but is difficult because aggregates are in general small and polydispersed. The easiest way to detect the onset of aggregation is to follow the evolution of some physico-chemical properties, such as surface tension, with increasing solvo-surfactant concentration. The levelling-off of the corresponding curves is reached at concentrations that are much higher than typical CMC, and may not always correspond to aggregation but only to the saturation of the surface. To distinguish them clearly from CMC, they will be called minimal aggregation concentrations (MACs). The denomination MHC[32] (minimal hydrotropic concentration) will not be used here because it usually corresponds to the concentration above which the solubilization of organic solute in water increases dramatically, a concentration which is generally similar but not systematically identical to the one where the surface tension levels-off.

To determine such MACs, surface tension measurements were carried out for a series of solvo-surfactants including ethylene glycol and propylene glycol ethers as references, and short chain glycerol 1-monoethers synthesized in the laboratory. The MAC is best determined, in the case of such low molecular weight compounds, by plotting the surface tension against the logarithm of the mole fraction[33] x (Fig. 2).

Table 4 summarizes the minimal aggregation concentrations deduced from these curves. As Strey *et al.* showed recently,[34] the activity should be used for such short amphiphiles instead of the molar concentration because of the extremely high MAC compared to typical CMC (generally $10^{-3}–10^{-4}$ mol L^{-1}). With the activity, the levelling-off of the curves is less obvious and can even totally disappear. Consequently, we did not perform calculations of the surface excesses (Γ) and areas at the interface (a_0) because we did not measure activity coefficients. However, the surface tension curves are presented to give, in each case, the surface tension reduction (also collected in Table 4) and the corresponding MAC characteristic of the efficiency of this reduction.

The value of the MAC is clearly dependent on the length of the alkyl chain. The nature of the polar head has less influence but is also relevant; for the same alkyl chain, it can be expected to be responsible for the classification of the MAC. The order found here is $C_4E_2 \geqslant C_4E_1 > C_4Gly_1$. It is quite surprising that C_4Gly_1 seems to be more hydrophobic than C_4E_1. On the basis of the molecular structure, the presence of two hydroxyl groups is expected to induce a high hydrophilicity. It seems that strong interactions between the glycerol polar heads exist and lower the global hydrophilicity of the molecule. The presence of one ether function and two hydroxyl groups make the formation of hydrogen bonds probable.

When a carbon atom is added to the alkyl chain, the hydrophilicity and consequently the MAC decrease, *c.f.* C_4Gly_1 and C_5Gly_1. When the compound becomes too
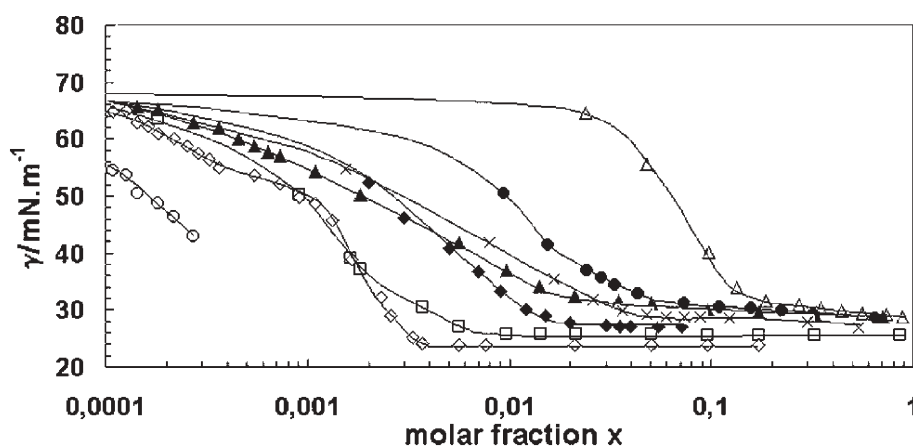
Fig. 2 Surface tension curves for a series of C_iE_j, C_iP_j, and C_iGly_j. ● C_3E_1, ◆ C_4E_1, ▲ C_4E_2, × C_3P_1, △ C_4Gly_1, □ iC_5Gly_1, ◇ C_5Gly_1, ○ C_6Gly_1.

Table 4 Minimal aggregation concentrations MAC[a] and corresponding surface tensions γ_{MAC}[b] for some C_iE_j, C_iP_j, and C_iGly_j

	C_3E_1	C_3P_1	C_4E_1	C_4E_2	C_4Gly_1	iC_5Gly_1	C_5Gly_1
MAC	1.22	1.56	0.83	0.88	0.60	0.36	0.15
γ_{MAC}	33.4	26.5	27.2	28.0	28.6	25.3	23.9

[a] In mol L^{-1}. [b] In mN m^{-1}.

hydrophobic, *c.f.* C_6Gly_1, it reaches its solubility limit before its MAC, and no value can be given. However, solvo-surfactants that are soluble below their MAC reduce γ very efficiently. Glycerol derivatives with C_5 alkyl chains are particularly interesting because their relatively low MACs allow a very efficient surface tension reduction compared to other solvo-surfactants. The advantage of the glycerol head-group is evident here: its high water solubility allows the use of longer alkyl chains that will aggregate at lower concentrations and will interact more strongly with the organic compounds solubilized for various applications.[35]

Binary phase diagrams

Binary phase diagrams (water/amphiphile/temperature diagrams) were drawn for several solvo-surfactants. They are less complicated than diagrams involving "true" surfactants, mainly because of the absence of liquid crystals. They are simply composed of two distinct regions, one corresponding to stable, isotropic solutions, and the other corresponding to unstable solutions that unmix into two phases at equilibrium.[6] In the case of nonionic amphiphiles, the separation curve has the shape of a loop. As the temperature is increased, the molecules become less hydrophilic because of the dehydration of their oxygenated groups. This results in a phase separation, the minimum temperature associated with this unmixing being called the *cloud point* or LCST (lower critical solubility temperature).

Fig. 3 and 4 show the binary phase diagrams of common ethylene and propylene glycol ethers, and of 1-hexylglycerol, respectively. In the case of glycerol ethers bearing C_4, iC_5 and C_5 alkyl chains, we could not observe any unmixing until the temperature was above 90 °C.
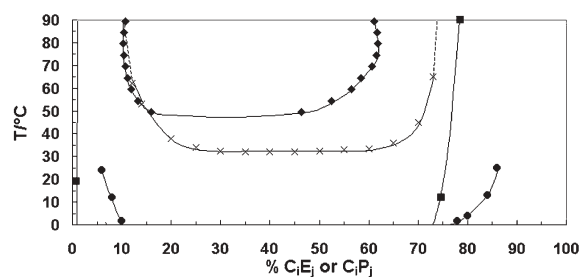

Fig. 3 Binary phase diagrams of common C_iE_j and C_iP_j in water. × C_4E_1, ■ C_5E_1, ◆ C_3P_1, ● C_4P_1.
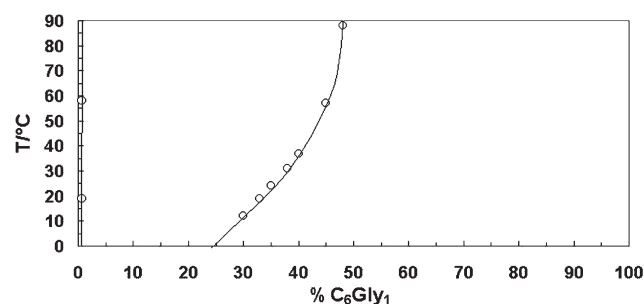

Fig. 4 Binary phase diagram of C_6Gly_1 in water. C_4Gly_1, iC_5Gly_1 and C_5Gly_1 are miscible with water up to 90 °C.

The shapes of the diagrams are significantly different. They are quite symmetric for glycol ethers, whereas glycerol ethers diagrams are strongly "shifted" to the left. This is obvious in the case of C_6Gly_1, but also for shorter homologues, whose hypothetical cloud points can be revealed with the addition of salting-out agents (see Fig. 6 and 7). In the case of glycol ethers, the behaviour is typical of solvents, whereas it is more characteristic of nonionic surfactants in the case of glycerol 1-monoethers. The solubility of C_6Gly_1 in water is very poor, but the solubility of water in this solvo-surfactant is huge. Long-chain C_iE_j have similar behaviours.

The phase diagrams confirm that the alkyl chain length has a major influence on the phase behaviour of short amphiphiles. Whereas C_4, iC_5 and even C_5 glycerol ethers are totally

miscible with water at least from -20 °C to 95 °C, the linear C_6 ether has a very low cloud point. We could not determine it experimentally, even by decreasing the temperature down to -20 °C. The difference in the cloud point is thus larger than 120 °C for a difference of one carbon atom, which is remarkable.

Influence of temperature

The binary phase diagrams show that temperature does not have the same influence on the different molecules. At room temperature, the polar groups of glycol ethers (C_4E_1, C_3P_1) are hydrated, forming hydrogen bonds with water molecules, and an increase of temperature breaks these bonds, inducing the unmixing. C_4Gly_1 and even C_5Gly_1, on the contrary, are miscible with water up to more than 90 °C. Temperature has little influence on their desolvation. C_6Gly_1 is also not very temperature-sensitive, since the right branch of its phase diagram looks like a small section of a very wide loop. In the first part of this discussion, we suggested the existence of hydrogen bonds between the glycerol polar heads. It is well known that intermolecular hydrogen bonds are dependent on temperature, whereas intramolecular bonds are much more stable.[36] In the light of the phase diagrams, it is probable that, in the case of glycerol ethers, hydrogen bonds are essentially *intra*molecular. Therefore hydrophobicity remains almost constant as the temperature rises, whereas it increases strongly for glycol ethers, a cloud point being detectable in the temperature range between 0 and 100 °C.

Thermodynamic parameters associated with the clouding phenomenon can be determined from the shape of the unmixing curve, but have been very seldomly calculated.[37–40] The micellization process has been much more widely studied.[41,42] The clouding can be described by eqn 1, allowing the calculation of the standard Gibbs free energy of clouding ΔG°_c:

$$\Delta G^\circ_c(T) = RT \ln(X_c(T)) = \Delta H^\circ_c(T) - T\Delta S^\circ_c(T) \quad (1)$$

where X_c is the mole fraction of solvo-surfactant corresponding to the phase separation at the temperature T. X_c values are calculated from the w/w% of the phase diagrams (Fig. 3 and 4). Eqn 1 is obtained with the hypothetical state of unit mole fraction as reference.

To calculate the enthalpy of clouding ΔH°_c, the Gibbs–Helmholtz equation (eqn 2) has to be considered.

$$[\partial(\Delta G^\circ_c(T)/T)/\partial(1/T)] = -T^2 [\partial(\Delta G^\circ_c(T))/\partial T] = \Delta H^\circ_c(T) \quad (2)$$

Replacing ΔG°_c (T) in eqn 2 by the expression given in eqn 1 yields

$$\Delta H^\circ_c(T) = -RT^2 [\partial \ln(X_c(T))/\partial T] \quad (3)$$

To calculate numerically ΔH°_c, experimental ($\ln X_c$, T) values are fitted with a polynomial equation (eqn 4), to give finally eqn 5.

$$Ln(X_c(T)) = a + bT + cT^2 + dT^3 \quad (4)$$

$$\Delta H^\circ_c(T) = -RT^2(b + 2cT + 3dT^2) \quad (5)$$

Once the enthalpy of clouding is known, the entropy ΔS°_c (T) is simply obtained by eqn 6 to give eqn 7.

$$\Delta S^\circ_c(T) = (\Delta H^\circ_c - \Delta G^\circ_c)/T \quad (6)$$

$$\Delta S^\circ_c(T) = -R(a + 2bT + 3cT^2 + 4dT^3) \quad (7)$$

ΔH°_c, ΔS°_c and ΔG°_c were calculated at different temperatures for C_4E_1 (whose behaviour is also representative of the one of C_3P_1 because of the similarity of their diagrams) and C_6Gly_1. Due to the insignificant solubility of C_6Gly_1 in water, the calculations were performed only on the right branch of the phase diagram, *i.e.* for the unmixing that occurs when water is progressively added to the pure solvo-surfactant. In the case of C_4E_1, both branches of the phase diagram were considered. Data are collected in Table 5.

The process is obviously spontaneous, and endothermic at low temperatures. The energy needed to break interactions between the molecules and water surrounding them is higher than the one gained by the creation of interactions between the molecules themselves ($\Delta H^\circ_c > 0$). As the temperature rises, the solvation of headgroups by water decreases and the process becomes progressively exothermic. The entropy of clouding ΔS°_c is also positive at lower temperatures, and drops down to negative values as temperature increases. When it reaches 0,

Table 5 Thermodynamic parameters $\Delta H_c^{\circ a}$, $\Delta S_c^{\circ b}$ and $\Delta G_c^{\circ c}$ associated to the clouding process in water for C_4E_1 and C_6Gly_1, as a function of T^d

C_4E_1							C_6Gly_1			
	Water rich branch			C_4E_1 rich branch			C_6Gly_1 rich branch			
T	ΔH°_c	ΔS°_c	ΔG°_c	ΔH°_c	ΔS°_c	ΔG°_c	T	ΔH°_c	ΔS°_c	ΔG°_c
322.5	4.23	46.2	−10.66	5.93	19.4	−0.33	285	4.63	19.2	−0.85
327.5	4.87	48.2	−10.94	4.93	16.4	−0.43	292	4.61	19.1	−0.97
332.5	4.24	46.3	−11.16	3.94	13.4	−0.50	297	4.57	19.0	−1.06
337.5	2.21	40.3	−11.39	2.97	10.4	−0.55	304	4.43	18.6	−1.21
342.5	−1.33	29.7	−11.50	2.01	7.6	−0.61	310	4.26	18.0	−1.32
347.5	−6.51	14.7	−11.61	1.08	4.9	−0.64	330	3.21	14.7	−1.64
352.5	−13.47	−5.2	−11.63	0.19	2.4	−0.65	361	−0.23	4.8	−1.96
357.5	−22.33	−30.0	−11.59	−0.67	0.0	−0.66				
362.5	−33.23	−60.2	−11.40	−1.48	−2.3	−0.65				
367.5	−46.31	−96.4	−10.89	−2.24	−4.4	−0.63				

[a] In kJ mol^{-1}. [b] In J mol^{-1} K^{-1}. [c] In kJ mol^{-1}. [d] In K.

ΔG°_c, which was decreasing before, begins to increase. If measurements had been realized under pressure so that higher temperatures could have been attained, entropy would probably have become so predominant that ΔG°_c would finally have reached 0, so that the clouding would have disappeared. The evolution of ΔS°_c is the consequence of the dehydration of polar headgroups on the one hand and the high motion of the molecules on the other hand that make the disorder more and more important in the homogeneous phase.

The final states being identical, the comparison between the two side branches of the diagram of C_4E_1 provides information about the initial states, i.e. the monophasic solutions just before the phase separation. Important differences are observed. First ΔH°_c, which is of the same order of magnitude at lower temperatures, becomes much more negative at higher temperatures for the left branch. This is not surprising given that there are 60 times more water molecules than C_4E_1 ones. The energy of the highly solvated C_4E_1 molecules is very important at high temperature, so they release more energy when they escape from their aqueous environment, breaking their unfavourable interactions with water. In the vicinity of the right branch, C_4E_1 molecules are much more concentrated, which explains the lower enthalpy values. The same explanation can be given concerning the entropy ΔS°_c. It becomes more negative for the left branch, once again because the dehydration of the highly solvated glycol headgroups creates an important disorder. The one induced by the breaking of interactions between water and C_4E_1 on the right branch is lower.

The comparison between C_4E_1 and C_6Gly_1 leads to the conclusion that a similar evolution is observed in both cases, but that C_6Gly_1 is less sensitive to temperature. Indeed values are of the same order of magnitude for each parameter at lower temperatures, but their variations are then clearly less pronounced for C_6Gly_1. The loop drawn by the demixing curve is wider, the lower critical solubility temperature (LCST) being below −20 °C and the upper critical solubility temperature (UCST) being above 100 °C, so that the right branch of the diagram looks almost straight.

For many processes involving small molecules in aqueous solution such as solubilization of actives,[43] complexation,[44] oxidation and reduction reactions,[45] micellization of surfactants[46] etc., a linear relationship between the entropy change ΔS and the enthalpy change ΔH is observed. This linear relationship is called the compensation phenomenon. According to Lumry and Rajender,[47] ΔH°_c can be written as shown in eqn 8.

$$\Delta H^{\circ}_c = \Delta H^{*}_c + T_{comp}\Delta S^{\circ} \qquad (8)$$

The slope T_{comp} is called the compensation temperature, since it corresponds to the particular temperature, where the process is purely enthalpy-driven ($\Delta G^{\circ}_c = \Delta H^{*}_c$). Consequently, the intercept ΔH^{*}_c is representative of the "chemical" part of the process. The meaning of T_{comp} and the intercept ΔH^{*}_c have never been investigated in the case of clouding, but T_{comp} is usually assumed to be characteristic of the solute–solute and solute–solvent interactions. In aqueous solution it reflects the desolvation of the polar headgroups of
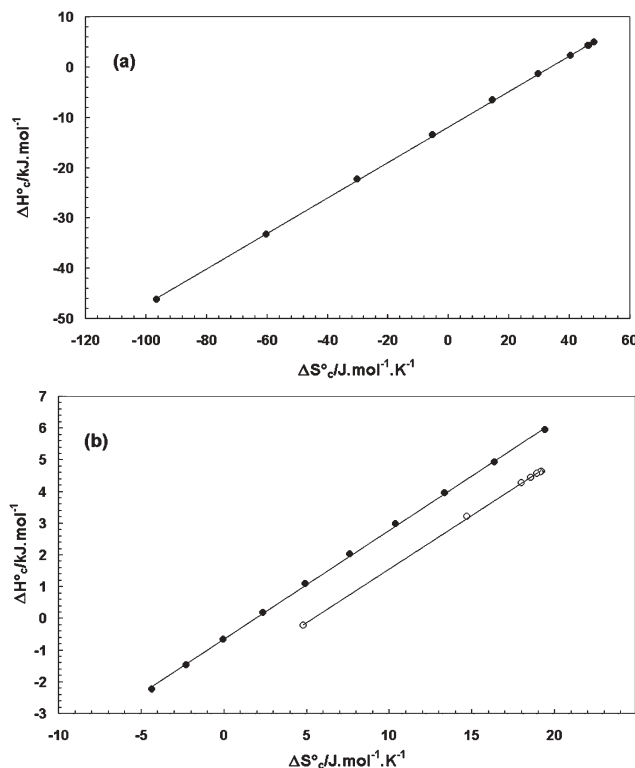
Fig. 5 $\Delta S^{\circ}_c/\Delta H^{\circ}_c$ plots for C_6Gly_1 and C_4E_1. (a) Left branch of the phase diagram for C_4E_1. (b) Right branches for ● C_4E_1 and ○ C_6Gly_1. The compensation phenomenon is nicely observed.

the solute. The "chemical" term ΔH^{*}_c represents, for example, in the case of micellization, the strength of the interactions created between the molecules within the micelles, in other words the stability of the micelles. Here it can be assumed to reflect the stability of the biphasic system after the phase separation.

In Fig. 5, ΔH°_c is plotted against ΔS°_c for both molecules. Water-rich and solvo-surfactant-rich sides are presented on separated figures. The compensation phenomenon is nicely observed.

Table 6 gives the compensation temperatures T_{comp} and the intercepts ΔH^{*}_c, deduced from the plots.

T_{comp}, which is representative of the hydration of the molecules, confirms that, for C_4E_1, molecules are highly hydrated on the left branch, at lower concentrations. On the right branch, the solvation is lower, and sligly more important for C_4E_1 than C_6Gly_1. ΔH^{*}_c is, as expected, much higher on the left branch. It is, on the right side, lower for C_4E_1 than for C_6Gly_1. This is probably due to the longer alkyl chains

Table 6 $T_{comp}{}^a$ and $\Delta H^{*}_c{}^b$ calculated from $\Delta H^{\circ}_c - \Delta S^{\circ}_c$ plots for C_4E_1 and C_6Gly_1

	C_4E_1		C_6Gly_1
Branch	Left	Right	Right
T_{comp}	353	343	338
ΔH^{*}_c	−11.95	−0.66	−1.83

^{a} In K. ^{b} In kJ mol^{-1}.

creating stronger interactions in the case of C_6Gly_1, which results in a higher stability of the separated phases.

Influence of electrolytes on the phase behaviour of short chain glycerol 1-monoethers

The role played by ions is essential in many chemical and biological processes. Their influence has been studied extensively, but their mode of action is quite complex, and is still not clearly understood. The work of Hofmeister,[48] performed at the end of the 19th century, comprises a large amount of information, the main result being the classification of ions either in "salting-in" or in "salting-out" agents. Salting-in agents are able to increase the solubility of proteins in water, whereas salting-out agents decrease it. For anions, Hofmeister's classification, known as Hofmeister series, is $SO_4^{2-} >$ OH$^- >$ F$^- >$ CH$_3$COO$^- >$ Cl$^- >$ NO$_3^- >$ I$^- >$ ClO$_4^- >$ SCN$^-$, the most salting-out agents being on the left and the most salting-in on the right. This classification turned out to be valid for a great number of processes in biology[49] as well as surface chemistry.[50,51] But in spite of a huge amount of experimental data, it is still very difficult to explain clearly these specific ion effects, mainly because they result simultaneously from several interactions such as dielectric, steric, and dispersion forces, but also from a specific hydration of ions at interfaces.[52]

The specific effects of ions on the phase behaviour of short chain amphiphilic compounds were scarcely considered in the last century. Only few results have been published. In 1930, Motoo reported on the influence of various salts on the surface tension of sodium taurocholate solutions.[53] In 1942, Reber and coworkers studied their effects on the mutual solubilities of butyl alcohol and water[54] but these one-off studies were not included in a global approach. More recently, some of us studied Hofmeister effects on water/propylene glycol ethers mixtures.[55] From the shift of the lower critical solubility temperatures, Bauduin et al. calculated a specific coefficient for each salt, and compared these coefficients for two different propylene glycol ethers, namely propylene glycol propyl ether (C_3P_1) and dipropylene glycol propyl ether (C_3P_2). Following their methodology, we measured the evolution of the cloud points and calculated equivalent coefficients for our newly

Table 7 Salt coefficients a^a according to eqn 9 for some glycerol 1-monoethers and other solvo-surfactants. * from ref. 54. LCSTs^b are also given

	C_5Gly_1	C_6Gly_1	C_4E_1	C_3P_1	C_3P_2
NaSCN	—	8.20	8.60	3.42*	3.17*
NaClO$_4$	—	5.39	6.26	2.64*	2.38*
NaI	—	0.92	1.31	0.35*	1.74*
NaBr	−1.61	−0.32	−1.18	−2.54	−1.02*
NaCl	−2.57	−2.15	−2.42	−2.80	−2.07*
Na$_2$SO$_4$	−12.12	−14.88	−15.32	−11.95	−9.62*
LCST	(158)	<-20 °C	48	35	14

^{a} In mmol of salt per mole of water in solvo-surfactant mixture. ^{b} In °C.

synthesized glycerol 1-monoethers, namely 1-pentylglycerol (C_5Gly_1) and 1-hexylglycerol (C_6Gly_1), as well as for a common ethylene glycol ether, 2-butoxyethanol (C_4E_1). We tested 3 salting-in agents (sodium thiocyanate NaSCN, sodium perchlorate NaClO$_4$ and sodium iodide NaI) and 3 salting-out agents (sodium chloride NaCl, sodium bromide NaBr and sodium sulfate Na$_2$SO$_4$). Measurements with C_3P_1 and NaClO$_4$, NaI and NaBr, that had not been performed previously, were also carried out for the sake of comparison.

The LCST/salt concentration curves appear to be perfectly linear. According to Bauduin's methodology, they were represented as

$$LCST = LCST_0 + a \times c \qquad (9)$$

where c is the salt concentration in mmole of salt per total number of moles of solvents (water + solvo-surfactant). The characteristic coefficients a are given for each experiment in Table 7. Note that in the case of C_5Gly_1 and iC_5Gly_1 the LCSTs are above 100 °C. Therefore we chose a composition of 15% solvo-surfactant and 85% water instead of the true composition of the hypothetical LCST, see Fig. 6 and 7. We added only salting-out agents, because salting-in agents would further increase the LCSTs.

Thanks to the salting-out agents, it was possible to evaluate the hypothetical LCST of C_5Gly_1, as shown in Fig. 8. The value of 158 °C was found with an excellent accuracy (± 1 °C). This is obviously an unreachable cloud point at atmospheric
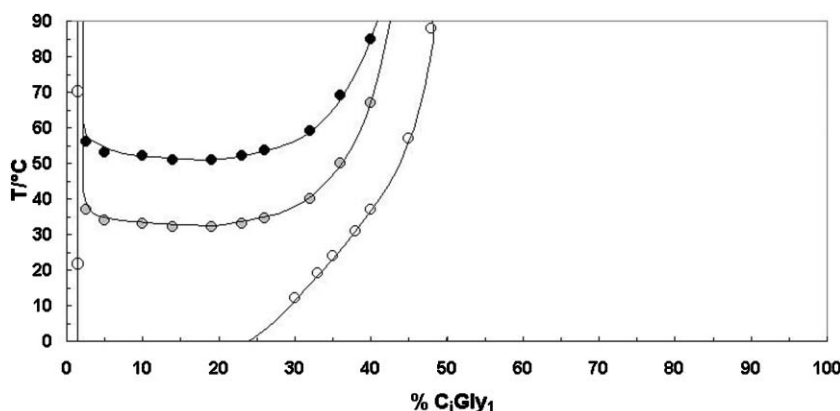
Fig. 6 Binary phase diagrams displaced to the available temperature window by addition of salt for C_6Gly_1. Curve minima are around 15%. The huge increase of the cloud point at very low salt concentrations is remarkable. ○ C_6Gly_1, ◉ C_6Gly_1 + NaSCN 1%, ● C_6Gly_1 + NaSCN 2%.
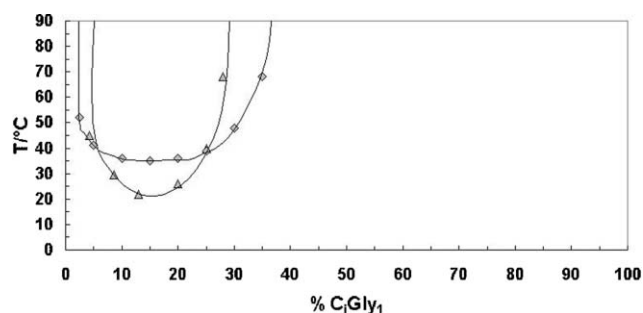
Fig. 7 Phase diagrams displaced to the available temperature window for iC_5Gly_1 and C_5Gly_1. Curve minima are once more around 15%. △ iC_5Gly_1 + Na_2SO_4 13.8%, ◇ C_5Gly_1 + Na_2SO_4 7.5%.

pressure, but it can be useful to compare the hydrophilicity of C_5Gly_1 with the one of other compounds.

The same composition, 15% of solvo-surfactant and 85% of water, was chosen for the aqueous mixture of C_6Gly_1—which has a hypothetical $LCST_0$ below 0 °C—when salting-in agents were added, whereas a composition of 40% C_6Gly_1 and 60% water was preferred when salting-out agents were added, see also Fig. 6.

As expected salting-in salts increase and salting-out salts decrease the LCST. In the first case, the ions go to the surface or even slightly into the organic component making it more polar or even partially charged. As a result, the compatibility of the two solvents increases. By contrast, salting-out salts, especially sodium sulfate, "salt out" the solvo-surfactant for the usual reason: the highly charged unpolarizable anion, *e.g.* sulfate, withdraws water molecules from the organic component and strongly binds them within its hydration shell. Similarly, and known for a long time, salts can considerably decrease the solubility of small polar but uncharged molecules like methanol.

The effect of the ions (Table 7) strictly follows the Hofmeister series without any exception and for all mixtures studied. However, the sensitivity of each system is quite different. Roughly speaking, the more hydrophilic solvo-surfactants are more sensitive to the addition of ions than the more hydrophobic ones. A notable exception is C_6Gly_1. According to the very low LCST, it should be very hydrophobic. Nevertheless, it is highly sensitive to salts. Since this is the case both for salting-in and salting-out agents, which should have very different effects, we currently have no
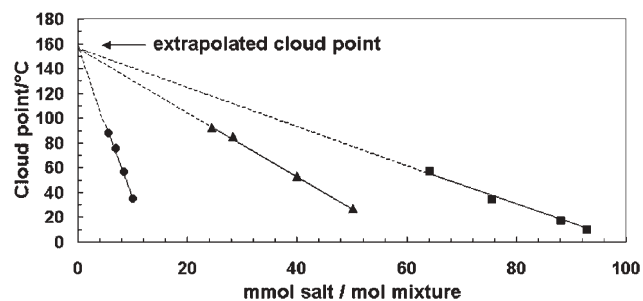
satisfactory explanation for this exception. Note that ions can have strong interactions with the glycerol headgroup, much as with water[56] and therefore the ions can efficiently break up intra- and intermolecular hydrogen bonds in glycerol.

Another interesting point is the different relative sensitivity of a given ion towards different solvo-surfactants. For all investigated sodium halides their influence on the LCSTs of mixtures considered here is relatively small and no clear trend among hydrophilic or hydrophobic solvo-surfactant is visible. More subtle hypotheses are difficult to infer from the global thermodynamic results that we present here.

Conclusions

Short chain glycerol 1-monoethers were synthesized and their surface activity was measured. The temperature-dependent phase diagrams of their mixtures with water and salts effects on these diagrams were also studied.

It turns out that this new class of molecules is a promising alternative to commonly used solvo-surfactants such as ethylene or propylene glycol ethers, showing similar properties. However, in contrast to them, glycerol ethers can be synthesized from natural products independently of petrochemistry. Since glycerol is a side product of the increasing biocarburant production, these new solvo-surfactants have the double advantage of being partly "green" products and also provide new uses of glycerol.

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Fig. 8 Effect of salting-out agents on the cloud point of C_5Gly_1. An extrapolated cloud point is determined to be 158 °C. ● Na_2SO_4, ▲ NaCl, ■ NaBr.

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