

Thermophysical and bionotox properties of solvo-surfactants based on ethylene oxide, propylene oxide and glycerol

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Thermophysical and bionotox properties of a new class of natural solvo-surfactants, glycerol 1-monoethers, were investigated in comparison with widespread but harmful glycol ethers. Vapour pressures and heats of vaporization were measured between 25 °C and 50 °C, and calculated thanks to two group contribution methods. Evaporation rates and Hansen parameters, evaluated from TGA measurements and group contributions respectively, were compared as well. Bionotox properties, *i.e.* cytotoxicity, irritating power and biodegradability, were evaluated experimentally. Glycerol 1-monoethers turned out to be less volatile than glycol derivatives, but contrary to the latter they will not be considered as VOCs. Toxicities and irritating powers are equivalent and increase with increasing alkyl chain length, *i.e.* with increasing amphiphilicity. Glycerol ethers are degradable at lower concentrations compared to glycol compounds, which is related to their higher interfacial activity.

Introduction

Among the huge number of available organic solvents some, such as glycol ethers, have the advantage of possessing an amphiphilic structure and exhibit some affinity for both hydrophilic and lipophilic compounds. These solvents are particularly appropriate for hard surface cleaning where volatility and interfacial activity are both required. By comparison, the degreasing power of aqueous solutions of polar solvents (MeOH, DMSO, DMF...) is generally poor, whereas “true” surfactants, though efficient, leave smears on the surface after evaporation of water.

Amphiphilic solvents may be considered as hydrotropes.¹ They are nicknamed solvo-surfactants² because they are volatile, unlike ionic hydrotropes. Their potential industrial interest is wide since they may be used in every application requiring a controlled evaporation (windows, floor, or kitchen cleaning, coatings...). Their performance results directly from their physico-chemical properties a knowledge of which is thus very important.

Glycol monoethers (C_iE_j) are the main solvo-surfactants on the market (Fig. 1). Historically, C_1E_1 was the first introduced under the denomination methylcellosolve in 1930, as a solvent of cellulose polymers. Their use became widespread in the 1970s with the development of polyurethane based epoxydic and aqueous (acrylic, vinylic) paints.^{3–5} Until 1980 their propylene glycol counterparts (C_iP_j) (Fig. 1), were totally ignored, but in 1985 the genotoxicity of C_1E_1 and C_2E_1 was

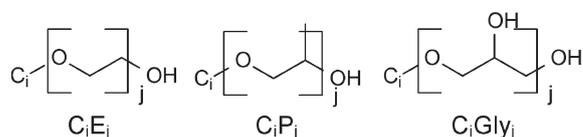


Fig. 1 Molecular structures of the solvo-surfactants studied in this work. Glycerol 1-monoethers (C_iGly_j) are potential green substitutes of the controversial ethylene glycol ethers (C_iE_j) and the moderately efficient propylene glycol ethers (C_iP_j).

put forward^{6–9} and they became of major importance. They will soon become more widespread than C_iE_j .

Even if four glycol ethers are today forbidden in Europe in medicines, cosmetics and household products, others are still very common in many applications. However, the whole family is tarnished in consumers' minds and manufacturers try to replace them in their formulations. C_iP_j , which are at present their main substitutes, exhibit satisfying properties¹⁰ but also derive from petrochemistry and suffer from the label “glycol ethers” as well. The growing green tendency encourages the development of molecules based on renewable resources. Among them, glycerol is more and more abundant as a major by-product of the biodiesel industry. We described recently in this journal¹¹ the synthesis and the aqueous behaviour of a new family of solvo-surfactants, glycerol 1-monoethers (C_iGly_1), in comparison with glycol ethers C_iE_j and C_iP_j . Their main characteristics are higher water solubility and amphiphilicity and a strong sensitivity to salt effects but not to temperature. Their excellent efficiency in the field of hard surface cleaning was also described recently.¹² In the present paper we report on our investigations concerning their so-called thermophysical and bionotox properties, which are of utmost relevance for many applications of these new green solvents. Results will systematically be discussed in comparison with C_iE_j and C_iP_j . The first part of this work will

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be dedicated to boiling points, vapour pressures and heats of vaporization that were determined experimentally. Results will be compared with theoretical estimates, calculated from molecular structures thanks to a group contribution method (Joback method—calculation of critical parameters P_c and T_c) and two analytical methods (Lee–Kesler and Kirschhoff–Reducted methods—estimation of vapour pressures). The second part of the paper will report on the comparison of evaporation rates, deduced from simple thermogravimetric analysis (TGA) measurements. In the third part, we will focus on solubility parameters. Hansen and Hildebrand parameters were calculated thanks to group contributions, and Hildebrand's parameter was also deduced from experimental heats of vaporization. Finally, we will describe in the last part of this work the bionotox properties of the molecules, *i.e.* their cytotoxicity, their irritant effects to skin and eyes, and their biodegradability.

Materials and methods

Materials

Ethylene glycol and propylene glycol derivatives were all purchased from Sigma–Aldrich at the highest grades available (C₄E₁ 99+%, C₄E₂ 99+%, C₃P₁ 98.5% and C₄P₁ 99%) and used without further purification. Glycerol 1-monoethers were synthesized according to a procedure described elsewhere.¹¹ Their purity was checked by GC/FID on an Agilent 6890N apparatus and by ¹H and ¹³C NMR on a Bruker AC200 spectrometer. *n*-Butyl acetate (99.5%) for TGA experiments was also purchased from Sigma–Aldrich.

Vapour pressure measurements

Measurements of vapour pressure were performed at the University of Regensburg with a precise vapour pressure apparatus that was designed especially for vapour pressure measurements of pure fluids and of electrolyte solutions over a wide temperature range (278.15 to 473.15 K) with an overall uncertainty in temperature of 0.01 K and a reproducibility of 0.1% in pressure. Owing to uncertainties of the zero point pressure of the manometer, volatile impurities, incomplete degassing of the samples, and leakage, an overall uncertainty of about 5 Pa can be estimated. The temperature is based on the international temperature scale ITS-90. The apparatus and the measuring method, as well as the degassing procedure, are described in detail elsewhere.¹³ For each compound and at each temperature, between 2 and 5 measurements were performed and the mean value was taken as the final result. The building of $\ln P_{\text{vap}} = f(1/T)$ curves allowed us to evaluate ΔH_{vap} .

TGA experiments

Measurements were performed at the University of Lille on a TA Instruments TGA Q50 apparatus. The atmosphere was composed of a nitrogen–oxygen mixture with a ratio of 60:40 (V/V). Two drops (about 20 mg) of product were poured into a Pt crucible and a temperature ramp of 5 °C min⁻¹ was applied from 20 °C. The decrease of the mass was followed as a function of time and temperature.

Cytotoxicity

Cytotoxicity was assessed in the human embryonic fibroblast cell line MRC5 using the MTT assay.¹⁴ This test is based on the reduction of the yellow MTT salt (dimethylthiazoldiphenyltetrazolium bromide) to a blue formazan dye by mitochondrial dehydrogenase in viable cells. It is notably used to express the irritating power towards skin of pharmaceutical or cosmetic products.^{15–18} Its ability to describe irritancy towards eyes is lower.¹⁹ Cells were grown in 96-well tissue culture plate in a 5% CO₂ atmosphere and exposed to serially diluted solutions of the different solvo-surfactants ranging from 0.001 to 1% over 24 h. After washing with PBS to remove test materials MTT was added, and after an extra incubation time of 3 h, the percentage of living cells was evaluated. The concentration of surfactant that induced a 50% loss of viability (IC₅₀) relative to untreated control cells was determined. Detailed procedures to perform this assay are available elsewhere.^{15–19}

Eye-irritancy

MTT assay being inaccurate in the case of eye-irritancy, another test called RBC (red blood cell test) was performed. This *in vitro* assay has been assessed by COLIPA (European Cosmetic and Fragrance Association) and is associated with models to estimate equivalent *in vivo* results that would be obtained with the reference Draize test. The detailed procedure to carry it out is available in reference publications. Rabbit red blood cells are mixed with the studied molecules, and spectrophotometric measurements allow the determination of the concentration H50 where a 50% hemolysis is obtained and the denaturation level obtained with a 1% solution, relative to sodium dodecyl sulfate. Estimates of corresponding *in vivo* results allow the irritancy of the molecules to be evaluated.

Biodegradability

Biodegradability was studied in accordance with the OCDE 301F norm. Sludges from a local wastewater treatment plant were used to provide the required amount of bacteria. An IBUK respirometer allowed the detection of oxygen consumption during the degradation process. Experiments were performed at 20 °C for 28 d. A reference solution, sodium acetate, was used to check the validity of the measurements.

Results and discussion

Estimation and measurement of thermophysical parameters

The evolution of the vapour pressure of any organic compound as a function of temperature can be described by the well known Clausius–Clapeyron equation (eqn 1):

$$\frac{d \ln P_{\text{vap}}}{dT} = \frac{\Delta H_{\text{vap}}}{RT^2} \quad (1)$$

ΔH_{vap} being the molar heat of vaporization in J mol⁻¹.

ΔH_{vap} , directly linked to the cohesive energy within the liquid, can be deduced from vapour pressure measurements or calculated from different equations containing more or less serious approximations.²⁰

The integrated form of the Clausius–Clapeyron equation is given by eqn 2:

$$\ln P_{\text{vap}} = \frac{-\Delta H_{\text{vap}}}{R} \times \frac{1}{T} + \text{cste} \quad (2)$$

According to this relationship, plotting P_{vap} as a function of $1/T$ gives a straight line whose slope is proportional to ΔH_{vap} . Solving for ΔH_{vap} is thus possible if at least two (P_{vap}, T) couples are known, with the assumption that it remains constant within the considered temperature range. This assumption is valid as long as the temperature is far from the critical point.

To estimate new P_{vap} values, it is possible to get rid of ΔH_{vap} with the use of Trouton's rule (eqn 3) which presupposes that the vaporization entropy ΔS_{vap} is constant and links ΔH_{vap} to the boiling point T_b :

$$\Delta S_{\text{vap}} = \frac{\Delta H_{\text{vap}}}{T_b} \approx 85 \text{ Jmol}^{-1} \text{ K}^{-1} \quad (3)$$

According to this rule, P_{vap} can be calculated with temperature as sole variable if T_b is known. This assumption led to the building of so-called temperature–pressure nomographs, very handy but often inaccurate since Trouton's rule is valid only for very simple organic compounds and not for molecules bearing hydroxyl groups.

More efficient predictive methods exist. They can be divided into 2 main families. The first one gathers all quantitative structure properties relationships. These equations are built from several molecular descriptors which make the link between the structure of the compound and its properties. Such relationships have already been settled for many different parameters (melting and boiling temperatures,²¹ solvent polarities,²² critical micellar concentration of surfactants²³...) and give excellent results. However, their use requires the knowledge of the value taken by each of the molecular descriptors, which is difficult for new and original compounds.

The second main family of predictive methods gathers those which have been developed from a huge number of experimental measurements. In the case of vapour pressure, the best example is the well known Antoine's equation (eqn 4) whose expression is the following:

$$\log P_{\text{vap}} = A - \frac{B}{T + C} \quad (4)$$

where A , B , and C are experimental coefficients available for many compounds in specialized databanks.²⁴

Apart from this equation, more general methods exist, among which some are based on group contributions. These methods are handy because thermodynamic properties can be determined even if only the molecular structure is known. The different structural elements considered can be atoms, links, atom groups or chemical functions.²⁵ In the case of liquid–vapour equilibria, all relationships rely on reduced temperature and pressure T_r and P_r . This is interesting because only one single equation is required for all compounds, but in return critical parameters T_c and P_c have to be known (because $P_r = P/P_c$ and $T_r = T/T_c$). The critical point is the limit of the

liquid–gas equilibrium curve above which one single phase, called the supercritical phase, is present.

Critical parameters have been determined experimentally only for very common molecules and have to be calculated to be used for the determination of P_{vap} and ΔH_{vap} . For this purpose the best method is Joback's,²⁶ which is also based on group contributions. This method, introduced in 1984, is used to calculate not only P_c and T_c , but also T_b using the following equations (eqns 5–7):

$$T_b = 198 + \Sigma(\Delta T_b) \quad (5)$$

$$\frac{T_b}{T_c} = \theta = 0.584 + 0.965 \times \Sigma(\Delta T_c) - \Sigma(\Delta T_c)^2 \quad (6)$$

$$P_c = (0.113 + 0.0032 \times \text{na} - \Sigma(\Delta P_c))^2 \quad (7)$$

na being the global number of atoms of the molecule, T_b and T_c being expressed in K and P_c in bars. ΔT_b , ΔT_c and ΔP_c are the group contributions.

When T_c and P_c are known, two main methods are available to calculate P_{vap} : Kirchoff (the reduced form below was used)²⁷ and Lee–Kesler²⁸

The Kirchoff–Reduced method (eqn 8):

$$\ln P_{\text{vap,r}} = h \times \left(1 - \frac{1}{T_r}\right) \text{ with } h = \frac{\theta}{1-\theta} \times \ln(P_c/\text{atm}) \quad (8)$$

$$\text{and } \theta = \frac{T_b}{T_c}$$

The Lee–Kesler method (eqn 9):

$$\ln P_{\text{vap,r}} = f^0(T_r) + \omega \times f^1(T_r) \quad (9)$$

f^0 , f^1 and ω being expressed as follows (eqns 10–12):

$$f^0(T_r) = 5.92714 - \frac{6.09648}{T_r} - 1.28862 \ln(T_r) + 0.169347 T_r^6 \quad (10)$$

$$f^1(T_r) = 15.2518 - \frac{15.6875}{T_r} - 13.4721 \ln(T_r) + 0.43577 T_r^6 \quad (11)$$

$$\omega = \frac{-\ln(P_c/\text{atm}) - 5.92714 + 6.09648/T_r + 1.28862 \ln(T_r) - 0.169347 T_r^6}{15.2518 - 15.6875/T_r - 13.4721 \ln(T_r) + 0.43577 T_r^6} \quad (12)$$

The volatility of C_iE_j , C_iP_j and C_iGly_1 was studied experimentally, but also with the methods presented above. Vapour pressures measured at different temperatures are reported in Table 1.

Table 1 Experimental vapour pressures of some C_iE_j , C_iP_j and C_iGly_1

Compound	P_{vap}/Pa					
	25 °C	30 °C	35 °C	40 °C	45 °C	50 °C
C_4E_1	160.1	224.6	318.6	454.0	619.5	833.9
C_4E_2	30.1	40.8	54.4	72.7	96.8	124.7
C_3P_1	355.2	501.3	703.3	964.5	1306.7	1755.9
C_4P_1	132.3	195.4	277.7	392.0	545.9	746.6
C_4Gly_1	15.4	17.4	23.8	34.5	46.9	54.5
iC_5Gly_1	8.3	15.2	23.6	34.4	47.6	64.1
C_5Gly_1	13.4	21.3	29.7	44.5	57.0	76.8

The experimental values are compared with those obtained from L–K and K–R equations in Fig. 2 and 3 where $P_{\text{vap}} = f(T)$ curves were drawn for C_4E_1 and C_4Gly_1 respectively. Experimental values obtained between 25 and 50 °C were extrapolated to higher temperatures by using the Clausius–Clapeyron equation.

Generally speaking, calculated values match experimental ones quite well for each compound. The best method for prediction varies according to the solvo-surfactant. In the case of C_4E_1 , the L–K equation is better at higher temperatures, whereas the K–R one is more appropriate at lower ones. In the case of C_4Gly_1 the K–R equation is on the contrary better at high temperatures and both predictions are equivalent at lower ones. Globally, both methods are quite reliable for predicting the behaviour of any unknown compound. One has, however, to take into account the fact that experimental values were extrapolated at high temperatures assuming that ΔH_{vap} is constant, which is only a very crude approximation. The experimental curves shown in Fig. 2 and 3 are consequently not exactly representative of the results that would have been obtained if measurements had been carried out above 50 °C.

From these values the heats of vaporization ΔH_{vap} were in each case evaluated by plotting $\ln P_{\text{vap}}$ as a function of $1/T$ according to the Clausius–Clapeyron equation. Table 2

Table 2 Comparison of ΔH_{vap} of different solvo-surfactants

	C_4E_1	C_4E_2	C_3P_1	C_4P_1	C_4Gly_1	iC_5Gly_1	C_5Gly_1
ΔH_{vap} exp/kJ mol ⁻¹	53.3	45.7	51.2	55.3	44.2	64.3	55.4
ΔH_{vap} L–K/kJ mol ⁻¹	91.0	75.2	60.2	63.8	97.4	105.1	104.0
ΔH_{vap} K–R/kJ mol ⁻¹	45.9	54.1	46.5	48.6	69.4	75.6	71.6

gathers the resulting values at 25 °C. The heats of vaporization determined from experimental P_{vap} are well correlated by K–R calculations, whereas the L–K equation gives less accurate results.

The volatility of C_7Gly_1 is clearly lower compared to other solvo-surfactants. C_5Gly_1 and C_4E_2 have equivalent molecular weights but P_{vap} is two times lower for C_5Gly_1 . Differences are less important for heats of vaporization. This hints at equivalent interactions within the liquid phase. The influence of hydrogen bonding is important. The $\Delta H_{\text{vap}}/T_b$ ratio reaches values up to 109 for iC_5Gly_1 , whereas Trouton's rule yields only 85 J mol⁻¹K⁻¹. The 109 value is similar to those of water and ethanol. It is however interesting to notice that the heats of vaporization of 1,2-diols obtained by replacing the oxygen atom of the ether function by a carbon atom are much higher with values up to 90 kJ mol⁻¹ at 25 °C.²⁹ The ether function provides, as expected, some volatility, unlike the alcohol functions.

Regulations³⁰ concerning solvents specify that every organic compound exhibiting a vapour pressure of 0.01 kPa (10 Pa) or more at 20 °C or in particular conditions of use is considered as a volatile organic compound (VOC). According to our data every C_iE_j and C_iP_j has to be considered as a VOC, whereas C_iGly_1 are not VOCs, except C_4Gly_1 . This is interesting because C_iGly_1 remains relatively volatile but will not, as a non-VOC, be subject to the same restrictions as competing solvents.

Evaporation rates

The volatility of an organic compound is often evaluated by the determination of its evaporation rate relative to a reference compound which is in general in Europe *n*-butyl acetate. There is no direct relationship between the evaporation rate and the boiling point. Within a homogeneous family of solvents volatility decreases as the boiling point rises,³¹ but hydrogen bonded solvents (alcohols, amines...) are in general less volatile than others with similar boiling points.

Globally, the evaporation rate of a liquid depends on its vapour pressure, but also on its heat of vaporization, its surface tension or its hygroscopic nature. Moreover, these factors are inter-dependent so that it is almost impossible to predict theoretically an evaporation rate.³² From experiments it can be inferred by calculating the ratio between the time required by a known quantity of the solvent to evaporate and the time required by the same quantity of the reference solvent to evaporate under the same experimental conditions. Evaporation rates have already been determined for a great number of organic compounds, among which are some glycol ethers.

To compare the rates of evaporation of C_iGly_1 and some C_iE_j and C_iP_j , TGA measurements were carried out. This

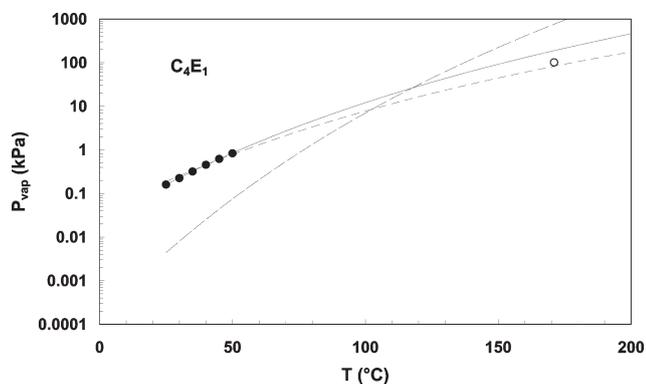


Fig. 2 comparison of experimental vapour pressures (—) of C_4E_1 with values calculated using the Lee–Kesler equation (— —) and Kirschhoff–Reducted equation (— — —). The experimental boiling point is also included (○).

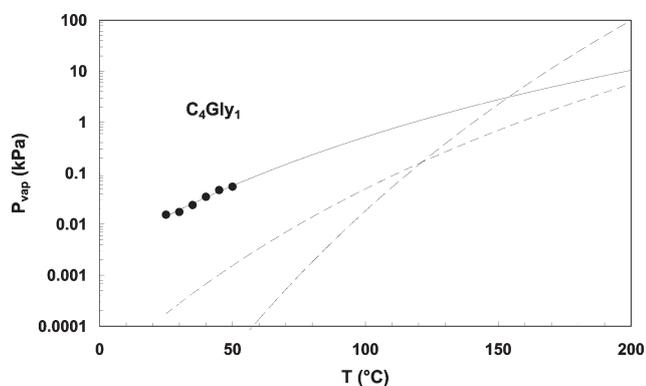


Fig. 3 comparison of experimental vapour pressures (—) of C_4Gly_1 with values calculated using the Lee–Kesler equation (— —) and Kirschhoff–Reducted equation (— — —).

technique has already been used to investigate the thermal stability of C_7Gly_1 which turned out to be stable up to quite high temperatures.³³ Moreover, the comparison between experiments carried out under an air and a helium stream showed that these compounds are not subject to thermal oxidation. The temperatures used here were much lower than temperatures of the thermal degradations so that only evaporation was observed. Similar conditions were used for every molecule, with an atmosphere containing 60% v/v of nitrogen and 40% of oxygen. A temperature ramp of $5\text{ }^\circ\text{C min}^{-1}$ was applied in each case from $20\text{ }^\circ\text{C}$. Two drops of liquid, *i.e.* around 20 mg, were used for each product. Evaporation curves are collected in Fig. 4.

The shape of the curves are all similar, the evolution being slow at first and then very fast above a threshold temperature. We calculated in each case the time corresponding to a loss of 90% of the weight and deduced evaporation rates relative to *n*-butyl acetate C_4Ac (Table 3).

Taking the rate of the reference compound to be 1, compounds with the highest rates are the most volatile. From our results, the following classification can be established, from the most to the least volatile compound:



The rates deduced here from TGA measurements can obviously only be compared with other rates calculated under the same conditions. Classical evaporation rates are generally determined by the “transpiration” method,^{34–36} where a small quantity of vapour is carried by a nitrogen stream and then condensed and weighed. The comparison with literature data is consequently reliable only if a correlation is shown between TGA rates and evaporation rates. Whereas our TGA rates are not clearly linked to boiling points or heats of vaporization, a linear tendency ($R^2 = 0.96$) is observed with experimental

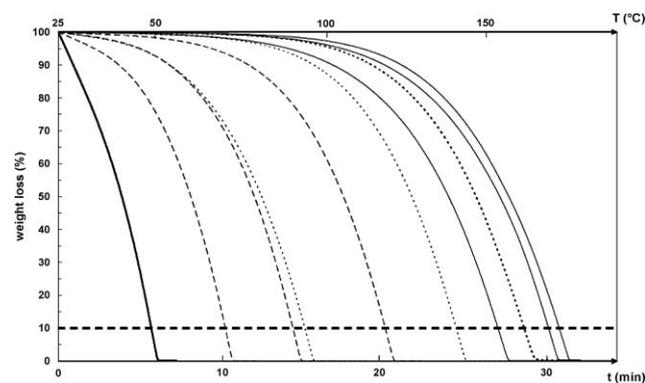


Fig. 4 TGA evaporation curves of a series of C_iE_j , C_jP_i and C_iGly_j . By increasing evaporation time: *n*-butyl acetate $AcOBu$ (ref.), C_3P_1 , C_4P_1 , C_4E_1 , C_3P_2 , C_4E_2 , C_4Gly_1 , C_6E_2 , iC_5Gly_1 , C_5Gly_1 .

Table 3 Evaporation rates deduced from TGA measurements, relatively to *n*-butyl acetate, after correlation with vapour pressures at $20\text{ }^\circ\text{C}$

Compound	C_4Ac	C_3P_1	C_4P_1	C_3P_2	C_4E_1	C_4E_2	C_6E_2	C_4Gly_1	iC_5Gly_1	C_5Gly_1
Rate	1	0.56	0.40	0.28	0.38	0.23	0.20	0.21	0.19	0.19

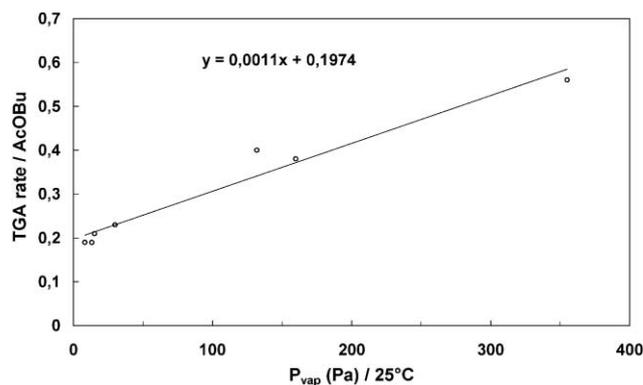


Fig. 5 Evolution of the TGA evaporation rate of glycol and glycerol ethers as a function of vapour pressure measured at $25\text{ }^\circ\text{C}$.

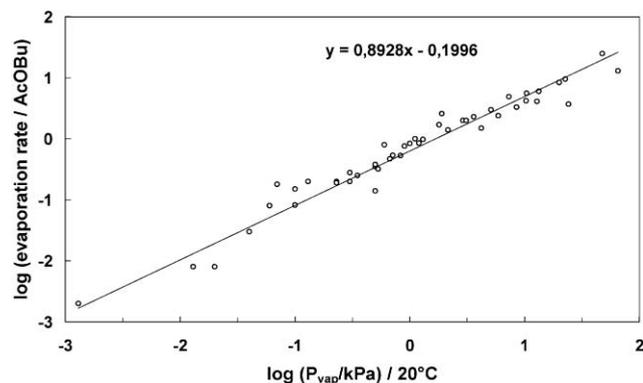


Fig. 6 Evolution on a log-log scale of the evaporation rate (literature data³⁷) as a function of vapour pressure at $20\text{ }^\circ\text{C}$.

vapour pressures at $25\text{ }^\circ\text{C}$, see Fig. 5. If literature evaporation rates³⁷ are correlated with vapour pressures, a linear log-log relation ($R^2 = 0.94$) is found, see Fig. 6. It is thus possible to predict evaporation rates not only from experimental vapour pressures but also from TGA measurements. The values collected in Table 4 were calculated and compared to literature data.

C_4E_1 and C_4E_2 were used to check the validity of our method since their evaporation rates are available in the literature. In the case of C_4E_1 , the correlation is excellent: almost the same value is found. It is much worse for C_4E_2 for which literature data of 0.004 was found. However our value seems more in agreement with all our observations and reflects better the behaviour of C_4E_2 , which is intermediate between those of C_3P_2 and C_4Gly_1 . Our method appears to be appropriate for the prediction of evaporation rates and has the advantage of supplying an evaluation of P_{vap} at $20\text{ }^\circ\text{C}$ from a simple and rapid experiment only, carried out with a common apparatus.

Table 4 Evaporation rates calculated from experimental vapour pressures and from TGA (*italic*) in comparison with literature (**bold**)

Compound	C ₃ P ₁	C ₄ P ₁	C ₃ P ₂	C ₄ E ₁	C ₄ E ₂	C ₆ E ₂	C ₄ Gly ₁	iC ₅ Gly ₁	C ₅ Gly ₁
<i>P</i> _{vap} 20 °C	253.6	92.6	<i>160.5</i>	111.65	22.2	<i>1.586</i>	10.6	6.1	10.4
Evaporation rate/AcOBu	0.188	0.058	<i>0.123</i>	0.089/ 0.082	0.021/0.004	<i>0.002</i>	0.011	0.007	0.011

The evaporation rates of C_iGly₁ are among the lowest for liquid compounds, reflecting a volatility which is lower than that of most common organic solvents (NMP, DMF, acetone, cyclohexanone, hexane, octane, cyclohexane...) and also slightly lower than those of C_iP_j and some C_iE_j. The behaviour of C₄Gly₁ is similar to the one of C₄E₂ whose molecular weight is slightly higher (148 g mol⁻¹ compared to 162 g mol⁻¹). In terms of applications the use of these compounds is favourable when a slow evaporation is required but they must be heated to evaporate quickly.

Hansen solubility parameters

Solubility parameters are used to predict the behaviour of various substances and give some information about the miscibility of two or several solvents or the solubility of a compound.³⁸ They are very useful from a qualitative point of view and can be used for quantitative calculations, even if they are not systematically very accurate

When the parameters of a substance are not known, they may be calculated with group contribution methods. The contributions of different common groups were published by Fedors³⁹ and collected later by Barton⁴⁰ in the handbook of solubility parameters. Hansen's parameters are expressed by the following equations (eqn 13–15):

$$\delta_d = \frac{\Sigma F_D}{\Sigma V_i} \quad \delta_p = \frac{\sqrt{\Sigma F_p^2}}{\Sigma V_i} \quad \delta_h = \frac{\sqrt{\Sigma E_h}}{\Sigma V_i} \quad (13)$$

where *F_d*, *F_p* and *E_h* are the dispersive, polar and cohesive contributions respectively, and *V_i* are the group contributions to the molar volumes of the molecules. Calculations of the different solvo-surfactants gave the results collected in Table 5.

Table 5 Hansen solubility parameters of some C_iE_j, C_iP_j and C_iGly_j were calculated by group contributions. Values originally proposed by Hansen are given *in italic*. δ_{exp} values were calculated from experimental heats of vaporization. $\delta_{\text{exp}} = [(\Delta H_{\text{vap}} - RT)/V_m]^{1/2}$, *V_m* being the molar volume estimated from group contributions

Compound	MPa ^{1/2}					δ_{exp}			
	δ_d	δ_p	δ_h	δ	δ_{exp}				
C ₄ Gly ₁	16.0	5.5	17.0	24.0	16.8				
iC ₅ Gly ₁	15.6	4.9	16.0	22.9	19.2				
C ₅ Gly ₁	15.8	4.9	16.1	23.1	17.8				
C ₆ Gly ₁	16.0	4.5	15.4	22.7					
iC ₈ Gly ₁	16.8	3.8	14.15	22.3					
C ₈ Gly ₁	16.4	3.8	14.3	22.1					
C ₄ E ₁	15.8	<i>16.0</i>	4.9	<i>5.1</i>	13.2	<i>12.3</i>	21.2	<i>20.8</i>	19.7
C ₄ E ₂	15.9	<i>16.0</i>	4.4	<i>7.0</i>	12.3	<i>10.6</i>	20.6	<i>20.4</i>	15.9
C ₆ E ₂	16.0	<i>16.0</i>	3.7	<i>6.0</i>	11.3	<i>10.0</i>	20.0	<i>19.8</i>	
C ₃ P ₁	15.2	<i>15.8</i>	4.8	<i>7.0</i>	13.1	<i>9.2</i>	20.6	<i>19.6</i>	19.0
C ₄ P ₁	15.2	<i>15.3</i>	4.2	<i>4.5</i>	12.3	<i>9.2</i>	20.0	<i>18.4</i>	18.6
C ₃ P ₂	15.05		3.9		11.65		19.4		

C_iGly₁ have higher parameters than their E_j or P_j counterparts and theoretically show a better solubilizing power. Differences come mostly from δ_h and partly from δ_p . The dispersive part is not dependent on the nature of the polar head and is only a function of the length of the alkyl chain. The global number of carbon atoms in this chain is important, but branching has almost no effect. The glycerol head brings a higher polarity and above all a strong ability to create hydrogen bonds, and its derivatives have a better affinity with polar and protic solvents.

Hildebrand's parameter can also be obtained from experimental ΔH_{vap} values and molar volumes. It is interesting to notice that if δ is calculated from these values (Table 5), the results do not match group contribution values. δ is for example 16.8 against 24.0 for C₄Gly₁, 19.2 against 22.9 for iC₅Gly₁ and 17.8 against 23.1 for C₅Gly₁. Hansen had already noticed these differences many years ago but was unable to explain them. They show that these values have to be used with care, and that only δ determined by the same method can be compared.

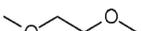
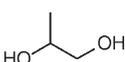
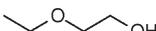
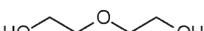
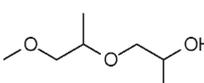
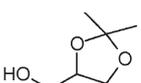
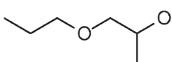
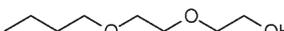
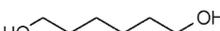
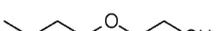
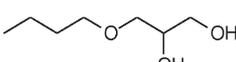
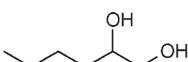
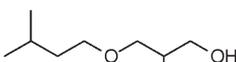
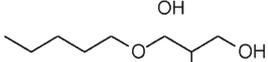
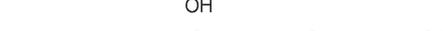
Cytotoxicity

Cytotoxicity was evaluated for some C_iGly₁, C_iE_j, C_iP_j, and a series of reference solvents. The same kind of cells was used in each case since IC₅₀ values can vary from one cell family to another.⁴¹ Results are collected in Table 6 and ordered according to increasing toxicity.

Among our reference solvents, many have already been tested previously and can be used as references. Ethanol or propylene glycol exhibit for instance a very low toxicity, whereas Solketal is considered moderately toxic.⁴¹ In comparison C₃P₁ is also moderately toxic whereas C_iGly₁ are more harmful. Globally cytotoxicity increases with amphiphilicity and, more precisely, it seems that the alkyl chain length has a major influence. This hypothesis was already proposed when, recently, we evaluated the IC₅₀ of some carboxylated surfactants and correlated them with their CMC.⁴² Here the "true" surfactant C₁₀E₄ has the lowest IC₅₀, followed by C_iGly₁ which are the most amphiphilic solvo-surfactants. In the same way, it was observed that 1,2-hexanediol has a much lower IC₅₀ than its symmetrical isomer 1,6-hexanediol.

The fact that the most amphiphilic compounds exhibit the highest cytotoxicity is not surprising since the killing of cells is linked to the ability of the molecules to penetrate the membranes and thus make them less resistant. Cytotoxicity has already been correlated with $\log P_{\text{octane/water}}$ for a large number of molecules.⁴³ Glycerol ethers are particularly oil soluble and excellent solubilizers. Numerous studies in the literature refer to their ability to deliver medicines by helping them to cross cellular membranes.^{44–48} Consequently their relatively high cytotoxicity is not surprising. However, the validity of the *in vitro* tests carried out here can be discussed

Table 6 IC₅₀ measured by the MTT method

Compound	Formula	IC ₅₀ (%)	IC ₅₀ /mmol L ⁻¹
Ethanol		7.1	1540
Acetonitrile		7.2	1040
Dimethylsulfoxide		5.3	680
C ₁ E ₁ C ₁		6.1	675
Propylene glycol		5.0	660
C ₂ E ₁		2.1	230
Diethylene glycol		1.9	180
C ₁ P ₂		2.5	170
Solketal		2.0	150
C ₃ P ₁		1.2	101
C ₄ E ₂		1.3	80
1,6-Hexanediol		0.9	76
C ₄ E ₁		0.7	59
C ₄ Gly ₁		0.5	33
1,2-Hexanediol		0.3	25
iC ₅ Gly ₁		0.25	15
C ₅ Gly ₁		0.2	12
C ₁₀ E ₄		0.02	0.0006

for amphiphilic compounds which are highly oil soluble. According to this observed tendency, iC₈Gly₁ for instance may be expected to be harmful whereas it is commercially available as a skin-friendly cosmetic additive (Schulke & Mayr). Another example is C₄E₁ which is less toxic than C₇Gly₁ but which is labelled as irritating to skin and eyes. The results proposed here have consequently to be used with great care, the main conclusion being that C₇Gly₁ seem to be more cytotoxic than glycol ethers.

Eye-irritancy

The RBC test carried out in this work was assessed in 1999 by the European Cosmetic and Fragrance Association to estimate *in vivo* results obtained by the reference Draize test. Three

products were studied: C₄E₁, C₃P₁ and C₄Gly₁. Their H50 and %D were calculated and are reported in Table 7.

In order to discuss these results two classifications were used: Lewis's classification which links the H50 in mmol L⁻¹ to the *in vivo* result and Pape's which correlates the H50/%D ratio also with the *in vivo* values. Tables 8 and 9 show these classifications

Table 7 Results of the RBC test performed with C₄E₁, C₃P₁ and C₄Gly₁

Compound	H50 (ppm/mmol L ⁻¹)	%D	H50 (ppm)/%D
C ₄ E ₁	129 440/1095	15.1	8572
C ₃ P ₁	52 823/447	10.2	5179
C ₄ Gly ₁	52 570/355	10.2	5154

Table 8 Lewis's classification for RBC test (MMTS: maximum mean total Draize score)

Classification	<i>In vitro</i> result: H50 in mmol L ⁻¹	<i>In vivo</i> result: MMTS
Non irritating	>10	0–5
Very slightly irritating	1–10	>5–15
Slightly irritating	0.1–1	>15–25
Moderately irritating	<0.1	>25–50
Highly irritating	<<0.1	>50–80

Table 9 Pape's classification for RBC test (MIOI: mean index ocular irritation)

Classification	<i>In vitro</i> result: H50/%D ratio	<i>In vivo</i> result: MIOI
Non irritating	>100	<5
Slightly irritating	>10	<15
Moderately irritating	>1	<25
Irritating	>0.1	<40
Highly irritating	<0.1	>40

The three compounds have similar H50 and %D, C₃P₁ and C₄Gly₁ being nevertheless slightly more irritating than C₄E₁. According to both classifications, all compounds are non irritating since the values are far higher than the limits fixed by Lewis and Pape. However, these results have once more to be used with great care, since C₄E₁ is labelled as irritating. This makes it difficult to correlate forward, *in vitro* and *in vivo* results. In our case, the nature of the molecules may be problematic, since the RBC test is advised for amphiphilic molecules but not for solvents, whereas solvo-surfactants possess by definition similarities with solvents. It is thus wise to conclude that C₄Gly₁ has a similar effect compared to competing molecules, without drawing further conclusions.

Biodegradability

The evaluation of the biodegradability of organic compounds is important since it expresses their long term effect on the environment. The ultimate degradation in H₂O and CO₂ was studied according to the OCDE 301F standard that requires the measurement of the BOC (biological oxygen consumption) and the calculation of the TOC (theoretical oxygen consumption). The BOC is determined with a respirometer for 28 d in a medium containing diverse mineral substances (sodium and potassium phosphates, ammonium, calcium and iron chlorides, magnesium sulfate) and bacteria collected from the local wastewater treatment plant. The TOC (in mg of oxygen per mg of product) is calculated from the molecular structure of the molecule, according to eqn 14. It corresponds to the amount of oxygen required to oxidize totally the product.

$$\text{TOC} = 16 \times \frac{(2 \times C + 0.5 \times (H - Cl - 3 \times N) + 3 \times S + 2.5 \times P + 0.5 \times Na - O)}{\text{PM}} \quad (14)$$

The biodegradability is thus calculated using eqn 15:

$$\% \text{ biodeg} = \frac{\text{BOC}}{\text{TOC}} \times 100 \quad (15)$$

Four substances were tested in addition to a reference compound (sodium acetate): C₄E₁, C₃P₁, C₄Gly₁ and iC₅Gly₁.

Each of them was studied at several concentrations in order to detect a possible harmful effect on bacteria. Several parameters were checked to assess the validity of the experiment. (1) The degradation of sodium acetate had to be higher than 60% after 14 d. Here it reached 80%. (2) The oxygen consumption of the mineral medium had to be lower than 60 mg L⁻¹ after 28 d. In this work it was only 6 mg L⁻¹. (3) The pH had to be between 6 and 8.5 after 28 d, which we obtained in each case.

According to the OCDE standard, the biodegradation has to reach 60% 10 d after the attainment of the 10% level and globally at least 60% after 28 d in order to consider a molecule as biodegradable. In the case of surfactants, the European norm CE2004/648 requires only the attainment of at least 60% after 28 d. Fig. 7 shows the evolution of the biodegradation of the compounds after 28 d, as a function of their concentrations. A threshold concentration is observed in each case, around 70 and 55 mg L⁻¹ for C₄E₁ and C₃P₁ respectively, and around 20 mg L⁻¹ for C₄Gly₁. It could not be determined for iC₅Gly₁. This threshold expresses a harmful effect of the solvo-surfactants on the bacteria which are supposed to degrade them. It seems that it is linked to the cytotoxicity of the compounds, certainly through their ability to dissolve hydrophobic cellular membranes. Similar to the cytotoxic effect, it increases with the hydrophobicity and the alkyl chain length, iC₅Gly₁ being the most harmful. According to these results, amphiphilicity, cytotoxicity, irritancy and biodegradability are all linked and similar phenomena are certainly involved in each process.

According to the OCDE, products have to be tested at 100 mg L⁻¹ and the concentration can be decreased afterwards if necessary. Our results show that none of the products is degradable at 100 mg L⁻¹, the threshold concentration being 50 mg L⁻¹ for glycol ethers and lower for glycerol ethers (20 mg L⁻¹ max.)

Conclusion

The volatility of short chain glycerol 1-monoethers was investigated in comparison with two others families of solvo-surfactants, namely ethylene glycol and propylene glycol monoethers. Calculated and experimental boiling points and vapour pressures as well as deduced heats of vaporization were

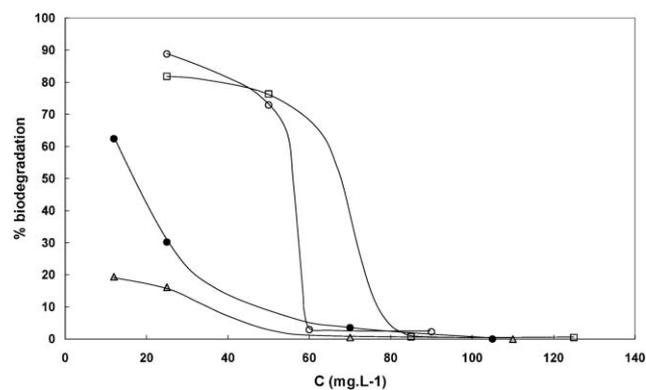


Fig. 7 Evolution of the biodegradability after 28 d as a function of the concentration for C₄E₁ (□), C₃P₁ (○), C₄Gly₁ (●) and iC₅Gly₁ (△).

compared and discussed, and evaporation rates were calculated from simple TGA experiments. Glycerol derivatives turned out to be less volatile than their glycol counterparts. Because of their great tendency to form hydrogen bonds, they have lower vapour pressures and higher boiling points even if their heats of vaporization are similar. Their evaporation rates also are lower, the rate of a given monoglycerol ether being similar to one of a diethylene glycol equivalent. These molecules are thus appropriate for applications where low evaporation is required at ambient temperature. Their low volatility can be seen as a drawback from a practical point of view, but the advantage is that contrary to glycol ethers, they will not be considered as VOCs because their vapour pressures at 20 °C are lower than 10 Pa.

Bionotox properties were also studied and compared with those of glycol ethers. Even if the validity of the cytotoxicity and irritancy tests can be in our particular case a matter of debate, they show that C_iGly_1 are not as interesting as C_iE_j and C_iP_j in terms of irritating power towards skin and eyes. Their biodegradability is also lower, more precisely they are degradable at lower concentrations. All solvo-surfactants have, above a threshold concentration, a harmful effect on the bacteria supposed to degrade them. This effect is detected at lower concentrations in the case of C_iGly_1 .

In spite of their poor volatility, glycerol 1-monoethers exhibit a theoretically high solubilizing power according to their Hildebrand and Hansen parameters. Their solubility in many organic solvents was assessed experimentally. Their high affinity for water has already been reported elsewhere. This results in their excellent ability to put initially insoluble compounds into solution in water and to co-solubilize water and organic solvents, with a consequently improved degreasing power, as we observed in a previous study.¹³ Taking into account the fact that most of them will not be considered as VOCs, they show an interesting potential as substitutes for genotoxic glycol ethers.

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