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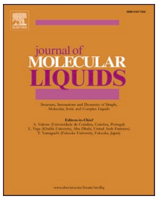

Micellization of dodecyldimethyl-N-2-phenoxyethylammonium bromide (domiphen) in aqueous solution. Comparison with other alkyl ammonium surfactants

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ABSTRACT

Dodecyldimethyl-N-2-phenoxyethylammonium bromide (domiphen) is a quaternary ammonium salt which has been used in oral hygiene long time ago. The published studies on its characterization as surfactant evidence several contradictory results. In this paper, measurements of surface tension, conductimetry, fluorescence and mainly isotermal titration calorimetry (ITC) have been performed at different temperatures. The enthalpy of demicellization, ΔH^o_{dem}, varies linearly with temperature in the interval 15–45 °C, from which a value of 704 ± 39 J mol^{-1}K^{-1} in water has been determined for the change of heat capacity, $\Delta C^o_{P,dem}$. The obtained results are compared with published values for alkyltrimethylammonium bromides with different alkyl chain lengths (C_nTAB). For instance, its critical micelle concentration, *cmc*, is almost ten times lower than that of C_{12}TAB. The substitution of one methyl group by the phenoxyethyl has a strong influence on the behavior of domiphen making it equivalent to a C_nTAB surfactant with n = 15–19 methylene groups, the number depending on the studied property. From ITC an average aggregation number of 45 ± 3 is obtained in good agreement with the one from fluorescence quenching of pyrene equal to 44.5–47.6. From the analysis of specific conductivity, the fraction of bound counterions to micelles was obtained, the values linearly decreasing with temperature. Below *cmc* domiphen behaves as a strong 1:1 electrolyte without association of monomers. Other themodynamic parameters have also been obtained. The fjord and reef hydration models are used to propose a structure for domiphen micelles.

1. Introduction

Dodecyldimethyl-*N*-2-phenoxyethylammonium bromide or domiphen bromide (domiphen) (Fig. 1) is a quaternary ammonium salt which long ago is known for the treatment of oral infections and dental diseases [1–3]. During the last two decades new important biological applications have been explored. For instance, Gao *et al.* [4] have shown that domiphen inhibits M. smegmatis growth by over-expressing or down-regulating 4-diphosphocytidyl-2-C-methyl-*d*-erythritol synthase (IspD), a key enzyme in the methylerythritol phosphate (MEP) pathway, common to Mycobacterium tuberculosis which usually causes tuberculosis in humans. It has potent activity on blockade of human ether-a-go-go related gene (HERG) channels in a dose-dependent manner [5], for precipitation of DNA from adenovirus [6], and as antimicrobial biofilms in combitation with AgNps [7] or miconazole [8].

Previous facts evidence the importance of this surfactant and consequently it has been the focus of various studies on its physicochemical characterization in aqueous solution. Unfortunately, incongruent results have been found. For instance, Khatua *et al.* [9] have determined micellization enthalpies at different temperatures (range 293.0–323 K), the values being in the range −16.38/-18.02 kJ mol^{-1}. From them, a value of 56.2 J mol^{-1}K^{-1} for the change of heat capacity of micellization, $\Delta C^o_{P,dem}$, may be obtained. However Yan *et al.* [10] have published enthalpy values in the range −14.81/−22.10 kJ mol^{-1}

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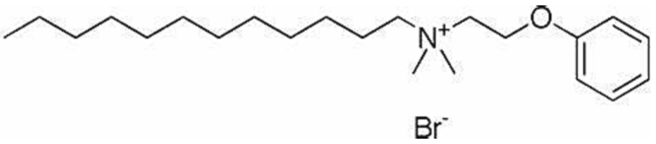


Fig. 1. Chemical structure of dodecyldimethyl-*N*-2-phenoxyethylammonium bromide (domiphen).

(20–40 °C), from which $\Delta C^{o}_{P,dem} = 364$ J $\text{mol}^{-1}\text{K}^{-1}$ is calculated. Both research groups have derived the values from the analysis of the dependence of the critical micelle concentration, *cmc,* with temperature. On the other hand, from spectral shifts observed in UV spectroscopy, Kopecká *et al.* [11,12] suggest the existence of two *cmc* values as a consequence of two different arrangements of the phenoxyethyl group.

The main aim of this work is the clarification of previous incongruencies, as well as improving the general knowledge about domiphen behavior in water. For such purposes, surface tension measurements, conductivity, spectrofluorometry (with pyrene as a probe) and, mainly, the isothermal titration calorimetry technique (ITC) have been employed for the characterization of the aggregation process of domiphen. This last technique is very precise as it has recently demonstrated in the analysis of the compensation temperature for micellization of surfactants in the enthalpy–entropy relationships [13]. The obtained results are compared with published values for alkyltrimethylammonium bromides with different alkyl chain lengths (C_nTAB).

2. Experimental

Domiphen bromide (Glentham Life Sciences, UK, >98 % purity) was used as received and directly dissolved in water (Milli Q-grade).

Pyrene (Merck) as a probe and hexadecylpiridinium chloride (Sigma) were used for fluorescence quenching experiments recorded on a Cary Eclipse spectrometer (Agilent Technologies, Santa Clara, California). Experimental parameters: excitation wavelength 336 nm, excitation slit 2.5 nm, emission wavelength 383 nm, emission slit 2.5 nm.

Surface tension measurements were carried out using a Drop volume Tensiometer TVT2 from Lauda (Lauda GMBH, Lauda-Königshofen, Germany). The surface tension was determined as the average value of four sets of 4–6 drops each. Conductivity was measured in a Crison BasiC 30 conductimeter calibrated with a 0.100 M KCl solution (Crison) with a specific conductivity of 12.88 mS cm^{-1} at 25 °C. For both techniques, sets of solutions were prepared according to the step-by-step dilution-extraction method [14].

In all these experiments the temperature was kept constant by recirculating water equipment (PolyScience 9100).

Calorimetric studies on the demicellization of domiphen were carried out by ITC in a MicroCal ITC200 titration calorimeter at constant temperature. The heat exchange for each injection was calculated by the Origin program supplied by MicroCal which accepts a fast mixing in the measuring cell during each injection from the syringe. In a typical experiment, 2 μL of a 10 mM solution of domiphen in water were injected into water. Experiments were at least duplicated at each temperature. Experimental titration curves were analyzed as indicated below.

The structural models of domiphen micelles were created with Cm2 using vesiclebuilder plugin (Cell microcosmos membrane editor 2.2.2.2 by Bjorn Summer https://www.cellmicrocosmos.org, last access 05/07/2023). Solvation clusters were created with VegaZZ (available at https://www.ddl.unimi.it/cms/index.php?Software_projects:VEGA_ZZ, last access 05/07/2023).

3. Results and discussion

As indicated, domiphen has been the focus of several studies for its characterization as surfactant. Fig. 2 shows the plot of the surface tension γ *vs* the logarithm of domiphen concentration, ln S_{tot}. It can be observed the typical profile dependence of γ with ln S_{tot}. From the breaking point, the *cmc* was obtained, the value being 1.690 mM. Other *cmc* values, from conductimetry and ITC measurements, are reported below. This value is slightly lower than the one (1.78 mM) published by Khatua *et al.* [9]. Kopecka *et al.* [12] have reported the existence of two *cmc* values at 1.50 and 2.72 mM.

Oremusová [15] has compiled *cmc* values of alkyltrimethylammonium bromides surfactants, C_nTAB, at 25 °C. The average values obey the equation $\ln(cmc/mM) = (11.13 \pm 0.07) - (0.698 \pm 0.006)n_c$, n_C being the number of carbon atoms of the alkyl chain. By using previous equation for domiphen, its *cmc* value would be equivalent to that of an alkyl trimethyl ammonium surfactant with $n_C = 15.1$. It is to say, if only the *cmc* value is considered, domiphen behaves as an alkyl surfactant with three additional CH_2 groups instead of the phenoxyethyl group. This estimation constitutes a first indication of a strong influence of the phenoxyethyl residue on the behavior of domiphen as surfactant. This aspect will be further discussed when analyzing the change in heat capacity of demicellization, $\Delta C^{o}_{P,dem}$.

According to the mass action law, the formation of a micelle, M_n, constituted by the association of *n* surfactant monomers (or aggregation number), S^{+}, and *m* counterions X^{-}, may be written as the equilibrium of eq. (1),

$$nS^{+} + mX^{-} \rightleftharpoons (S_nX_m)^{+(n-m)} \tag{1}$$

where, $X^{-} = Br^{-}$ for domiphen, and (*n-m*) is the charge of micelles. In solution, the positive charge of micelles is neutralized by an equivalent number of negative counterions. The ratio $\alpha = (n - m)/n$ is the degree of dissociation of the micelles and $\beta = 1 - \alpha = m/n$ is the degree of counterion binding.

Conductimetry is an experimental technique frequently used for the determination of *cmc* and the degree of counterion binding, as well as the effect of temperature on both parameters. Ideally, two straight lines, above and below a threshold concentration, are obtained when plotting the specific conductivity, κ, *vs* S_{tot}. This threshold concentration is accepted as the *cmc* of the surfactant, which is calculated as the intersection point of both straight lines. Fig. 3 shows the experimental results obtained for domiphen at temperatures between 15 °C and 45 °C. Table 1 shows the results for *cmc*, κ at *cmc*, and intercepts and slopes below and above the *cmc*. All R^2 values are above 0.9995.

Below *cmc,* domiphen behaves as a 1:1 strong electrolyte. In this case, λ^{o}_{m} (the molar conductivity in the limit of zero concentration) is equal to the slope of κ *vs* S_{tot} plot, $\lambda_m = \kappa/S_{tot}$, since the slope of the Kohlrausch's plot is not statistically different from zero. Values are given in Table 1. At 25 °C, $\lambda^{o}_{m} = 108.32$ $\text{Scm}^2\text{mol}^{-1}$, which is close to the one (=113.5 $\text{Scm}^2\text{mol}^{-1}$) obtained by Bakshi [16] for C_{14}TAB. From

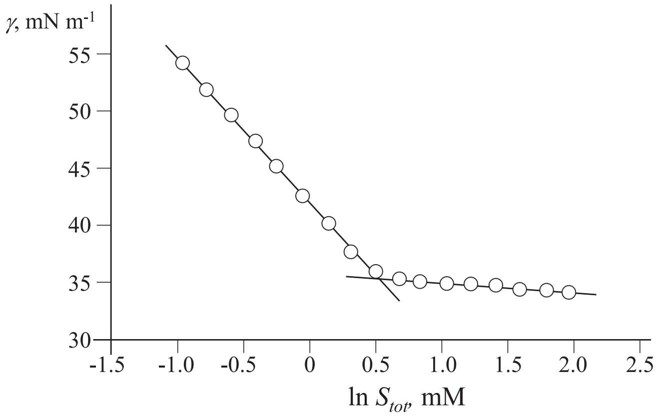


Fig. 2. Surface tension of solutions of domiphen in water at 25 °C.

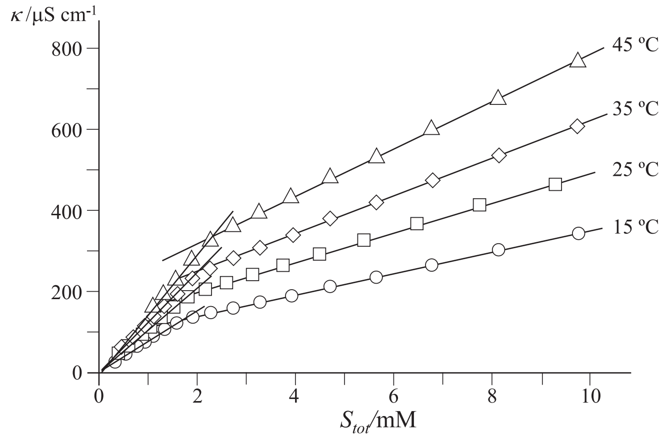


Fig. 3. Specific conductivity *vs* total concentration of domiphen at the indicated temperatures.

Kohlrausch's law of independent ionic migration and $\lambda^o_{Br^-} = 78.14$ S cm^{2}mol^{-1} [17], a value of $\lambda^o_{S^+} = 30.18$ Scm^{2}mol^{-1} is obtained for the molar conductivity at infinite dilution of the monomer cation of domiphen.

Walden [17] has noticed that the molar conductivity at infinite dilution is proportional to the reciprocal dynamic viscosity of solvent (η), i.e, $\lambda^o_m\eta = constant$. Although Walden's assumption has been challenged, it suggests that the dependence of λ^o_m with temperature must be Arrhenius type, i. e., $\ln\lambda^o_m vs T^{-1}$ must be linear, allowing the calculation of the activation energy. Its value should be equal to the activation energy of water viscosity (17.8 kJ mol^{-1}). As $\lambda^o_m = S_1$, from values of Table 1, a value of 16.4 ± 4.2 kJ mol^{-1} is calculated for domiphen solutions. This is within the range observed for different ions (15–19 kJ mol^{-1}) [18]. According to Kallay *et al*, this temperature effect is an additional prove that no association takes place below *cmc*. On the other hand, Stokes's equation, at constant viscosity, establishes a reciprocal relationship between the radius of the ion and the limiting molar conductivity, which here will be used as an empirical one. Daggett *et al.* [19] have obtained the limiting molar conductivity for several tetra-alkyl ammonium cations (Table2). Similarly Masterton *et al.* [20] from equations derived from the scaled particle theory of the salt effect have obtained the effective radii of tetra-alkyl ammonium ions in aqueous solution. Values are also shown in Table 2.

The proposed empirical relationship is given by $r(\text{Å}) = (1.68 \pm 0.20) + (41.9 \pm 5.2)(\lambda^o_{S^+}/[\text{Scm}^2\text{mol}^{-1}])^{-1}$ ($R^2 = 0.970$, data from Masterton *et al*) or $r(\text{Å}) = (2.440 \pm 0.083) + (48.6 \pm 1.9)(\lambda^o_{S^+}/[\text{Scm}^2\text{mol}^{-1}])^{-1}$ ($R^2 = 0.995$, data from Robinson and Stokes). The substitution of the $\lambda^o_{S^+}$ value for domiphen in these equations provides values of 3.1 ± 0.4 Å and 4.05 ± 0.15 Å, respectively. This values must be understood as if the domiphen cation behaved as a hard-sphere in aqueous solution.

For the calculation of β, Evans [21] proposed that above *cmc* the specific conductivity of a solution of an amphiphilic salt may be regarded as divisible into three components: that due to the single ions at *cmc*, that due to the micellar ions, and that due to the counterions in excess.

Table 2
Molar conductivities at infinite dilution and radii of tetra-alkyl ammonium cations in aqueous solution.

Cation	$^+NMe_4$	$^+NEt_4$	$^+NPr_4$	$^+NBu_4$	$^+NAm_4$	ref
$\lambda^o_{S^+}$, S cm^{2}mol^{-1}	44.92	32.66	23.45	19.13	17.13	[19]
Radius, Å	2.51	3.08	3.49	3.81		[20]
Radius, Å	3.47	4.00	4.52	4.94	5.29	[17]

The application of Evans's equation requires the use of Stokes's law (the conductance of an ion in unit electrical field is proportional to the square of charge divided by the radius of the ion assumed spherical). For micelles this radius is estimated as the length of the extended alkyl chain of the surfactant, l_c, by l_c/Å=1.5 + 1.265 n_c (n_c, number of carbon atoms), as proposed by Tanford [22]. Other equations which have into account the contribution of the head group to the micelle radius have been proposed [15]. Several authors have used this approach for obtaining α for C$_n$TAB surfactants [23–25], the values being in the range 0.25–0.30.

Alternatively, it has been proposed [26] the calculation of α as the ratio of the slopes of the κ *vs* S_{tot} above and below the *cmc*, that is, $\alpha = S_2/S_1$. The main advantage of this method is that only conductivity-concentration data are required for the calculation. It has been used by Oremusová [15] for C$_n$TAB surfactants and by Khatua *et al.* [9] and Yan *et al.* [10] for domiphen. Table 1 shows the values obtained by us, expressed as β.The values obtained by this method are normally higher than those obtained from the micelle radius [24]. As observed by Kathua *et al.* [9], for domiphen α slightly increases with temperature. From data in Table 1, the dependence is given by $\alpha = (0.256 \pm 0.002) + (3.3 \pm 0.06) \times 10^{-3}t/^\circ C$. A similar dependence have been found by Chakraborty and Moulik [27] for C$_{10}$TAB and by Oremusová [15] for C$_{12}$TAB. Kopecká *et al.* [11,12], from their UV spectroscopic results, proposed two *cmc* values for domiphen and from Corrin-Harkins relationships obtained values for β of 0.66 and 0.75 for each *cmc*.

It is important to notice that the fractional micellar ionization has only influence on the calculation of the Gibbs free energy or the equi-

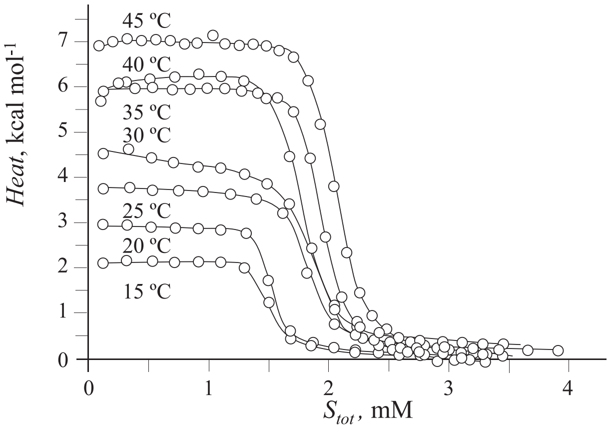


Fig. 4. Calorimetric titration curves from addition of domiphen in water. S_{tot} is the total surfactant concentration in the cell.

Table 1
Slope and intercept values of the linear dependence below and above *cmc* of domiphen at different temperatures. The values of the specific coductivities at *cmc* are shown, as well as the fraction of bound counterions to micelles.

T/°C	$S_{tot} < cmc$		$S_{tot} > cmc$		*cmc*/mM	κ at *cmc* (μS cm^{-1})	$\beta = 1 - \alpha$
	Intercept	Slope, S_1	Intercept	Slope, S_2			
15	2.0 ± 1.0	78.7 ± 1.1	86.66 ± 0.91	26.32 ± 0.17	1.615	129.2	0.696 ± 0.011
25	0.78 ± 0.58	108.32 ± 0.65	126.6 ± 2.4	36.67 ± 0.45	1.756	191.0	0.661 ± 0.012
35	1.33 ± 0.39	124.7 ± 1.3	159.5 ± 2.3	46.42 ± 0.39	2.020	253.0	0.628 ± 0.007
45	2.2 ± 1.0	143.94 ± 0.88	203.8 ± 2.2	57.99 ± 0.36	2.346	339.9	0.597 ± 0.007

brium contant but not on enthalpy of micellization (or equivalently, demicellization) ΔH^o_{dem}, determined from ITC measurements.

Fig. 4 shows the results of the ITC measurements for determining the thermodynamic parameters corresponding to the demicellization process of domiphen micelles in water. The enthalpies of demicellization, ΔH^o_{dem}, can be directly measured from these curves [28]. The obtained values are in Table 3 and Fig. 5 shows the plot of ΔH^o_{dem} *vs* temperature.

Within the interval of temperatures 15–45 °C, the dependence of ΔH^o_{dem} with T is linear and the change in heat capacity, $\Delta C^o_{P,dem} = (\partial \Delta H^o_{dem}/\partial T)_P$, is easily obtained as the slope of the straight line, the value being 704 ± 39 J mol^{-1}K^{-1} in water. This value is far from published values. Khatua *et al.* [9] have determined ΔH^o_{dem} values in the range 16.38/18.02 kJ mol^{-1} from 20 °C to 50 °C, from which a value of 56.2 J mol^{-1}K^{-1} is obtained for $\Delta C^o_{P,dem}$. Similarly Yan *et al.* [10] have published ΔH^o_{dem} values in the range 14.81/22.10 kJ mol^{-1} from 293.15 K to 313.15 K, $\Delta C^o_{P,dem}$ being 364 J mol^{-1}K^{-1}. However, from enthalphy data published by Yan *et al.* [29] for domiphen DL-mandelic acid, we have obtained a value of$\Delta C^o_{P,dem} = 655 \pm 10$ J mol^{-1}K^{-1} in water, which is comparable with the one measured here.

The positive value of $\Delta C^o_{P,dem}$ means that the hydrophobic surface of monomers, being exposed to water, increases upon demicellization. Therefore the transfer of surfactant monomers from an aggregate to the bulk water has many facts in common with the dissolution of liquid alkanes [30] and other alkyl derivatives [31,32] into water. High values of $\Delta C^o_{P,dem}$ suggest large changes in the exposed hydrophobic surface to water after demicellization. The values of $\Delta C^o_{P,dem}$ in Table 4 for several alkyl ammonium halides surfactants are in agreement to this assert as, within of each head group, an increase in $\Delta C^o_{P,dem}$ with increasing alkyl chain length is easily recognizable.

There is some controversy [42] about the degree of water penetration towards the micelle hydrophobic core. According to some authors [43–45] water permeates deeply towards the center of the micelles, while others [46] stated that water meets an abrupt interface at the micelle surface. These two models have been named as “fjord” and “reef” hydration models by Menger *et al.* [45].

Independently of previous controversy, the demicellization process implies the hydration of the alkyl chains of monomers. Baar *et al.* [47], from dielectric relaxation measurements, have obtained hydrophobic hydration numbers for alkyltrimethylammonium surfactants (which would be a measure for the degree of hydrocarbon-water contacts), the values (extrapolated to zero concentration) being C_8TAB, 19.7 > C_{12}TAC, 14.2 > C_{12}TAB, 11.4 > C_{16}TAB, 9.7. Previous sequence indicates that the number of water molecules approaching the micelle core diminishes with the alkyl chain length. Therefore in the sequence a larger number of water molecules have to reorganize to interact with methylene and methyl groups of monomers after demicellization. Furthermore, for surfactants with identical alkyl chain length and similar micelle size but different aggregation number, it is reasonable to accept that more space for water will be available for the micelle with lower aggregation number.

Table 3
Critical micelle concentration, expressed as mole fraction, x_{cmc}, aggregation number, n, and thermodynamic parameters obtained from ITC experiments for the demicellization of domiphen at different temperatures.

Temp/K	$10^5 x_{cmc}$	ΔH^o_{dem}/kJ mol^{-1}	n	ΔG^o_{dem}/kJ mol^{-1}	ΔS^o_{dem}/J mol^{-1}K^{-1}
288.43	2.71	8.84	43	41.70	−113.9
293.15	2.71	12.19	49	42.48	−104.3
298.18	3.14	14.48	43	41.59	−90.9
303.15	3.44	17.91	45	41.55	−78.0
308.15	3.13	24.15	46	42.19	−58.5
313.15	3.48	25.47	49	42.05	−53.0
318.15	3.71	29.23	40	41.86	−39.7

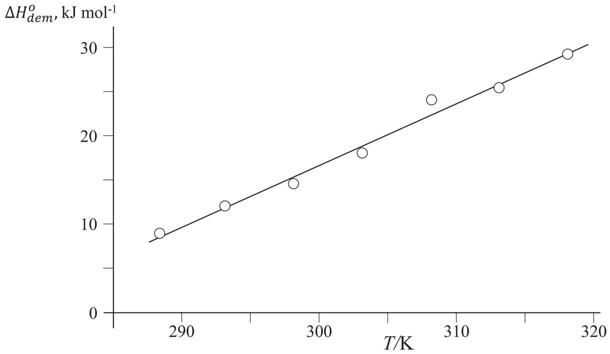


Fig. 5. Enthalpy of demicellization ΔH^o_{dem} of domiphen in water as function of temperature.

Table 4
Published values for $\Delta C^o_{P,dem}$ of domiphen and some N-alkyl ammonium halide surfactants. Values with (*) were calculated by present authors from ΔH^o_{dem} values published by Tong *et al.* [33].

Surfactant	$\Delta C^o_{P,dem}$ J mol^{-1}K^{-1}	Ref
Domiphen	704 ± 39	This paper
[a]C_{10}TAB	302	[34]
[a]C_{12}TAB	334.4	(*), [33]
	406	[34]
[a]C_{14}TAB	499	[34]
	629.6	(*), [33]
[a]C_{16}TAB	573	[34]
[b]C_{12}EDAB	426	[35]
	471	[36]
[c]$C_{12}C_8$DAB	436	[37]
[d]$C_{14}C_8$DAB,	476	[37]
[e]C_{12}HDAB	297.5	(*)
[f]C_{12}DHAB	297.2	[33]
[e]C_{14}HDAB	522.3	
[f]C_{14}DHAB	520.4	
[e]C_{16}HDAB	584.2	
[f]C_{16}DHAB	640.1	
[g]C_{10}TAC	348 ± 21	[38]
[g]C_{12}TAC	417.9	[39]
	420	[40]
[g]C_{14}TAC	540 ± 21	[38]
[h]C_{12}BeMC	630	[40]
[i]C_{12}MeMC	440	[40]
[j,k]C_{12}BDAB	493	[41]
[j,k]C_{14}BDAC	651	

[a] C_nTAB (n = 10, 12, 14, 16): alkyltrimethylammonium bromides.
[b] C_{12}EDAB: dodecyldimethylethylammonium bromide.
[c] $C_{12}C_8$DAB: dodecyloctyldimethylammonium bromide.
[d] $C_{14}C_8$DAB: tetradecyloctyldimethylammonium bromide.
[e] C_nHDAB: alkyl-2-hydroxyethyldimethyl ammonium bromides.
[f] C_nDHAB: alkyl-2-dihydroxyethylmethyl ammonium bromides.
[g] CnTAC: alkyltrimethyl ammonium chlorides.
[h] C_{12}BeMC: dodecylbenzylmorpholinium chloride.
[i] C_{12}MeMC: dodecylmethylmorpholinium chloride.
[j] C_nBDAB: alkylbenzyldimethylammonium bromides.
[k] Temperature range 288–308 K.

The substitution of a methyl group at the ammonium group by other organic functions clearly has a strong influence on the thermodynamic properties of surfactants. Tong *et al.* [33] have measured the micelle formation in aqueous solutions by ITC of eight quaternary ammonium surfactants [*N*-alkyl-*N*-2-hydroxyethyl-*N*,*N*-dimethyl ammonium bromides (C_nHDAB, n = 12, 14, and 16), *N*-alkyl-*N*,*N*-2-dihydroxyethyl-*N*-methyl ammonium bromides (C_nDHAB, n = 12, 14, and 16), *N*-dodecyl-*N*,*N*,*N*-trimethyl ammonium bromide (DTAB), and *N*-cetyl-*N*,*N*,*N*-trimethyl ammonium bromide (CTAB)]. Their ΔH^o_{dem} data fitted well to a second-order polynomial, meaning that $\Delta C^o_{P,dem}$ decreases when temperature increases. However, for direct comparative purposes data perfectly fitts a straight line in the range 25–35 °C (central part of the range of temperatures studied here). The behavior of these surfactants is complex as the number of hydroxyethyl substituents on the nitrogen atom of the head group diminishes $\Delta C_{P,dem}$ for derivatives with C_{12} and C_{14} alkyl chains, but the opposite behavior is observed for the C_{16} derivative.

Anyhow, the structure of the head group has a strong influence on the hydration and mobility of water molecules. Baar *et al.* [47] have indicated that the effective hydration number of the cation group should increase in the order $C_8TAB < C_{12}TAB < C_{12}TAC < C_{16}TAB$, it is to say, both the length of the alkyl chain and the counterion binding have influence on the hydration of micelles and consequently on $\Delta C^o_{P,dem}$, as demicellization requires additional water molecules for complete hydration of counterions and the polar surface of monomers [28]. From surfactants in Table 4, the effect of the substitution of a methyl group by a benzyl one at the cationic ammonium head may be evaluated.

Różycka-Roszak and Fisicaro [40] have studied the micellization of N-dodecyl-N-benzylmorpholinium chloride (C_{12}BeMC), N-dodecyl-N-methylmorpholinium chloride (C_{12}MeMC) and dodecyltrimethylammonium chloride (C_{12}TAC). The difference between $\Delta C^o_{P,dem}$ values between C_{12}BeMC and C_{12}TAC is 210 J mol^{-1}K^{-1}, while the one between C_{12}MeMC and C_{12}TAC is only 20 J mol^{-1}K^{-1}. From these differences, Różycka-Roszak and Fisicaro concluded that the benzyl group of C_{12}BeMC behaves as a second chain with respect to the micellization process, behaving in fact as an alkyl chain of five carbon atoms. Similarly, Tyczyńska and Wasiak [41] have studied by ITC the demicellization of dodecylbenzyldimethylammonium bromide (C_{12}BDABr) and tetradecylbenzyldimethylammonium chloride (C_{14}BDACl) in a wide range of temperature (278.15–333.15 K). The dependence of ΔH^o_{dem} with temperature obeys a second order polynomial, but (for comparative purposes) considering only the central interval of temperature (around 25 °C) the dependence is perfectly linear, the slope being $\Delta C^o_{P,dem}$. The experimental values are 493 and 651 J mol^{-1}K^{-1} (Table 4). From previous values, the average effect due to the substitution of a methyl group in the cationic head by a benzyl one is$\Delta(\Delta C^o_{P,dem}) = 136 \pm 65$ J mol^{-1}K^{-1}.

On the other hand, Bai *et al.* [37] have studied the thermodynamics of demicellization of a series cationic surfactants in which a dimethylammonium headgroup is attached to two alkyl chains of different lengths, the structure being $C_nH_{2n+1}\,C_mH_{2m+1}N(CH_3)_2Br$, with n = 12 or 14, and m in the range 1–12. For n = 12 and m varying from m = 1-to m = 8, the increment of $\Delta C^o_{P,dem}$ is only 90 J mol^{-1}K^{-1}, being even lower (10 J mol^{-1}K^{-1}) for n = 14. For both n values and m = 12, $\Delta C^o_{P,dem}$ increases sharply above 900 J mol^{-1}K^{-1}.

The $\Delta C^o_{P,dem}$ value in water for domiphen (with a C_{12} alkyl chain) is higher than those for all surfactants in Table 4 even with C_{16} alkyl chains. In fact it is comparable to the one observed for sodium oleate (C_{18} chain with a double bond) for which a value of 780 J mol^{-1}K^{-1} has been published [48]. The results for the C_nTAB series studied by Dearden and Woolley [34] ($\Delta C^o_{P,dem}(\mathrm{J\,mol^{-1}K^{-1}}) = -(144 \pm 32) + (45.3 \pm 2.4)n_C$) may be used to obtain the number or carbon atoms of a hypothetic surfactant with a long alkyl chain equivalent to domiphen. The obtained value is $n_C = 18.7$. It is to say, the equivalent alkyl surfactant would be C_{19}TAB, with seven additional methylene groups respect to the domiphen long alkyl chain. Let us recall that from *cmc* analysis, we observed that the aromatic residue $(CH_2)_2$–O–C_6H_5 let domiphen behave as an alkyl surfactant with three additional methylene groups.

From data of heat capacities of aqueous C_nTAB (n = 10, 12, 14, 16) obtained by Dearden and Woolley [34] the relationship $\Delta C^o_{P,dem} = -166.55 + 22.65n_H$ J mol^{-1}K^{-1} is obtained (n_H = 21–33 is the number of hydrogen atoms of the alkyl chain). Gill and Wadsö [49] analyzed heat capacities for the dissolution of hydrocarbons in water. If only aromatic derivatives are considered the following relationship is calculated $\Delta C^o_{P,dem} = 50.4 + 27.65n_H$ J mol^{-1}K^{-1} (n_H = 6–12), which when applied to the aromatic residue $(CH_2)_2$–O–C_6H_5 leads to a value of 299 J mol^{-1}K^{-1}. Therefore $\Delta C^o_{P,dem}$ may be estimate as the sum of the results of previous equations, resulting the value$\Delta C^o_{P,dem} = 699$ J mol^{-1}K^{-1}, in good agreement with the experimental one.

Krecheck [50] has calculated the water accessible surface area of methylene and methyl groups (29 and 89 Å^2, respectively). These values allow a theoretical estimation of the water accesible surface area for the hydrophobic tails of surfactants. On the other hand, Livingstone *et al.* [51] found a simple direct proportionality between heat capacity changes and accessible surface area, ΔA_{np}, for the burial of nonpolar groups during folding or interactions between macromolecules,

$$\frac{\Delta C^o_{P,dem}}{\Delta A_{np}} = b\mathrm{J\,mol^{-1}K^{-1}\mathring{A}^{-2}} \tag{2}$$

the value of b being 1.46 J mol^{-1} K^{-1} Å^{-2}. Krecheck and others [38] used this relationship to determine the number of buried methylene groups in a surfactant, n_{buried}, as

$$n_{buried} = \frac{\Delta C^o_{P,dem}/b - 89}{29} \tag{3}$$

the error of n_{buried} being estimated as 30 % [38]. The application of this equation to domiphen and C_{12}TAB [34] gives values of 13.6 and 6.5 for n_{buried}, respectively, i.e., a difference of 7.1. This value indicates that domiphen has 7.1 more carbon atoms than C_{12}TAB which do not interact with water. All previous estimations suggest that the aromatic residue is fully involved in the formation of micelles with low interation with water.

The application of previous equation to C_{12}BeMC and C_{12}MeMC (Table 4) gives values for n_{buried} of 11.8 and 7.32, respectively. The difference ($\Delta n_{buried} = 4.5$) should be adscribed to the benzyl group. However the value for C_{12}BDABr [41] and its comparison with C_{12}BDABr and C_{12}TAB gives a much lower value ($\Delta n_{buried} = 2.1$) for the effect of the benzyl group. However, it should be emphasized that the published values for $\Delta C^o_{P,dem}$ for a given surfactant evidence a wide scattering range of values, thus affecting any calculation. Data for C_{12}TAB and C_{14}TAB by Dearden and Woolley [34] and Tong *et al.* [33] are just two examples.

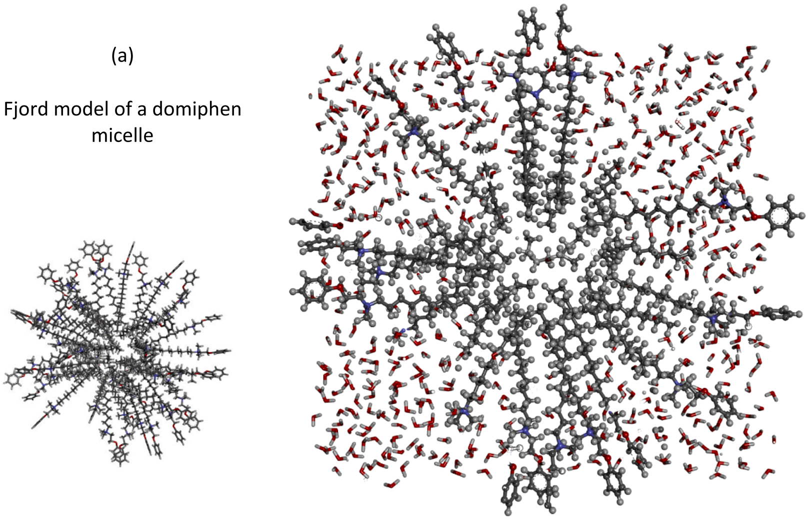
We have analyzed three domiphen micelle models, in which (1) the domiphen molecule is fully extended, (2) the phenoxyethyl group is folded towards the micelle core, and (3) the micelle is built with 50 % percentage of each conformation. In all cases, micelle have an aggregation number of 45 (see below). In all cases, micelle is within a sphere of radius 15 Å. In the first case, the model suggests that water could permeate deeply towards the center of the micelle (Fig. 6a) as in a fjord hydration model. In the second case (Fig. 6b), the micelle reminds the reef hydration model but the accommodation of all phenoxy groups in a folded conformation leaves an empty space in the micelle core. The third model (Fig. 6c) suggests that some water can enter and leave the micelle in a proportion relative to the degree of fjord or reef composition of the micelle. This mixed model is probably the most realistic one as it is in closer agreement with previous analysis about $\Delta C^o_{P,dem}$. Intuitively, this model would also be in better agreement with a dynamic micelle in which monomers live and enter the micelle.

The calorimetric titration curves were analyzed according to Olesen *et al.* [52]. The method assumes a two-state reaction type in which the aggregation of n surfactant monomers, S, form the micelle, M_n, $nS \leftrightharpoons M_n$, i.e., monodispersity of micelles is considered. Furthermore, the counterions of the surfactant molecules are not explicitly considered, an approach commonly accepted in the analysis of ITC data [53]. After several transformations the following equation is derived

$$\frac{dln\{(d[S]/dS_{tot})^{-1} - 1\}}{dlnS_{tot}} = \frac{n-1}{n} + \frac{(n-1)^2}{n}\frac{dS}{dS_{tot}} \tag{4}$$

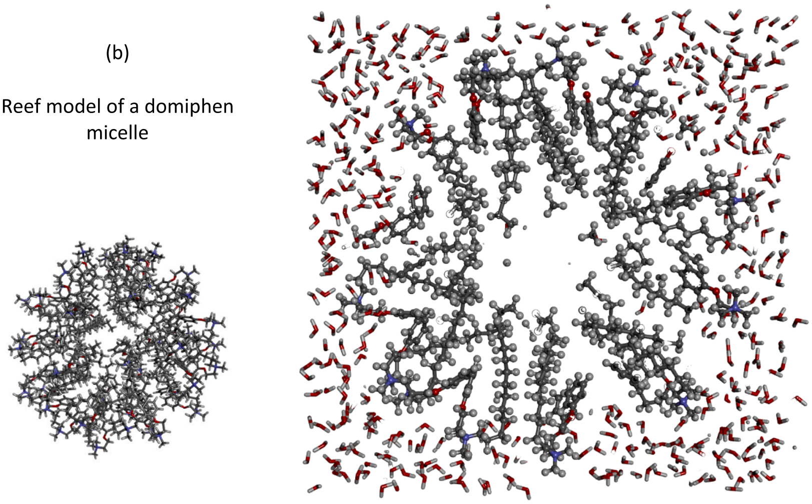
(a)

Fjord model of a domiphen micelle



(b)

Reef model of a domiphen micelle



(c) Fjord/reef 1:1 model

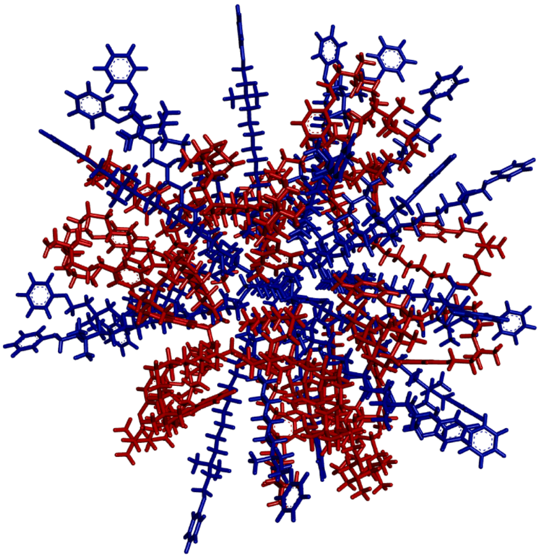


Fig. 6. Fjord (a), reef (b) and fjord/reef 1:1 models for domiphen micelles. In the fjord/reef model, extended domiphen molecules are in blue color and those with folded phenoxymethyl group are in red color. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In this equation n is the aggregation number S is the concentration of surfactant as monomers. The amount dS/dS_{tot} is obtained from calorimetric data as

$$\frac{dS}{dS_{tot}}=\frac{d\Delta H}{d\Delta H^{o}_{dem}} \tag{5}$$

where ΔH is the enthalpy change after adding a small amount of surfactant from the syringe into the measuring cell.

The fitting of the experimental results to previous equations allows the determination of the aggregation number, the enthalpy of demicellization and the involved enthalpy of dilution as optimization parameters. The optimization process is facilitated by considering that the intercept must be in the range 0.66–1 since $3 \leq n \leq \infty$, and that both the slope and intercept in equation (3) allow the calculation of the aggregation number. Obviously, the obtained values should be self-consistent. Fig. 7 shows an example of the calculation of the aggregation number for domiphen at 25 °C and Table 3 the values for n at several temperatures. It must be noticed that the aggregation number does not show any tendency with temperature, the average value being 45 ± 3.

The values of n and β were used to calculate the free energy change associated with demicellization, ΔG^o, according to Phillips's equation [54]

$$\frac{\Delta G^{o}}{RT}=\frac{\ln(3n^{2})}{n}+\left(1+\beta-\frac{1}{n}\right)\ln cmc \tag{6}$$

For n large, previous equation is simplified to the well-known equation $\Delta G^o/RT = (2-\alpha)\ln cmc$. The *cmc* (expressed as mole fraction of the surfactant) was obtained as the point corresponding to the maximum change in gradient in an ideal property-concentration relationship which means $d^3S/dS^3_{tot} = 0$ [54]. The fractional micellar ionization has only influence on the calculation of the Gibbs free energy or the equibrium constant but not on enthalpy of micellization (or equivalently, demicellization, ΔH^o_{dem}), determined from ITC measurements. Knowing ΔH^o_{dem} and ΔG^o_{dem}, the entropy of demicellization is easily derived. All these thermodynamic amounts are shown in Table 3. It may be noticed that ΔG^o_{dem} is fairly constant with an average value of 41.92 ± 0.34 kJ mol^{-1}. This fact often leads to the wrong idea of the existence of an enthalpy–entropy relationship and a compensation temperature [13]. Previous value is comparable with those reported (range 41.90–43.65 kJ mol^{-1}, 25–40 °C) by Yan *et al.* [10].

In regarding the calculation of the aggregation number, Olesen *et al.* have already commented on the limitations and the advantages of their method. Experimental ITC enthalpograms are particularly sensitive to several calorimetric effects which may introduce different kinds of systematic errors, and there is a strong correlation between the equilibrium constant and the aggregation number. When studying demicellization processes the dilution enthalpy of monomers and micelles is particularly important.

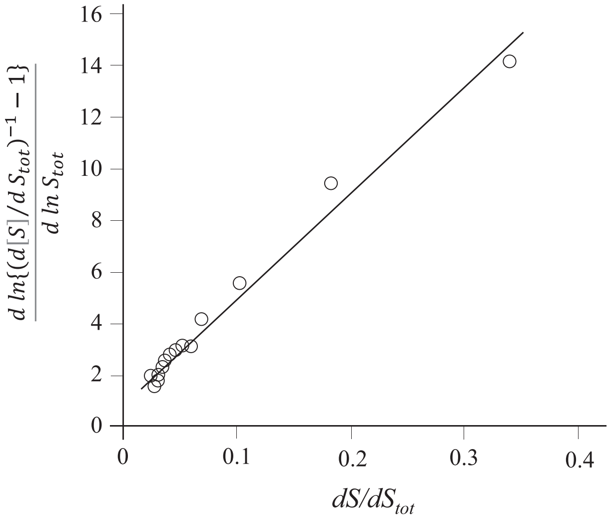


Fig. 7. Determination of the aggregation number, according to eq. (3), of domiphen in water at 25 °C.

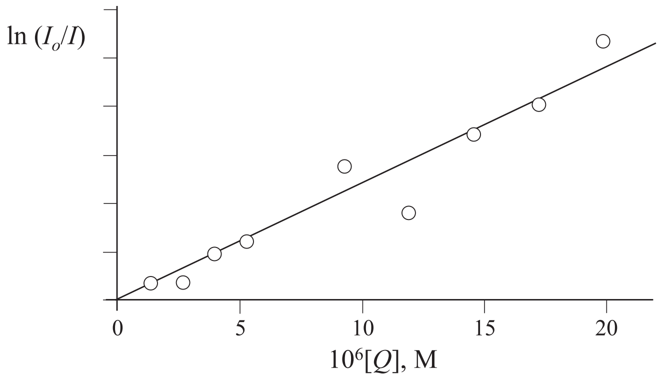


Fig. 8. Influence of quencher (cetylpiridinium chloride) concentration on the intensity of probe (pyrene) fluorescence in domiphen 2.686 mM in water at 25 °C. The concentration of pyrene probe was 10.14 × 10^{-6} M.

To confirm the validity of the aggregation number calculation, the fluorescence quenching of pyrene (incorporated into the aggregates) [55,56] by hexadecylpiridinium chloride (Q) was used. The experimental results were analyzed through the equation derived by Turro and Yekta

$$ln\frac{I_{o}}{I}=\frac{n[Q]}{S_{tot}-cmc} \tag{7}$$

From the slope (=47.9 ± 2.8 mM^{-1}, at 25 °C) of the $\ln(I_o/I) vs [Q]$ plot (Fig. 8) and *cmc* determined by surface tension measurements or conductimetry, n values of 47.6 ± 2.8 and 44.5 ± 2.8 are obtained, respectively, which closely agree with the average value given above (45 ± 3). Previous equation involves some restrictive assumptions [57,58], as well.

The values obtained for the aggregation number are close to those reported by Khatua *et al.* [9] of 52.0 ± 4.0 and 51.0, from fluorescence measurements, the values slightly depending on the fluorescence probe. Similarly an aggregation number of 38 has been published by Yan *et al.* [29] for domiphen DL-mandelic acid in water. For comparative purposes, we can recall that the value for C_{12}TAB reported by Oremusová [15] is 55.5.

4. Conclusions

In comparison to C_{12}TBA, the presence of the phenoxyethyl group in domiphen strongly reduces the *cmc* of this C_{12} alkyl ammonium surfactant and increases the value of $\Delta C^o_{P,dem}$. The analysis of *cmc*, the relationship between the heat capacity change and the number of hydrogen atoms of the alkyl and aromatic residues, and the number of buried methylene groups of the surfactant, strongly suggest that the behavior of domiphen is equivalent to that of a C_nTBA surfactant with n = 15–19 methylene groups, the number depending on the analyzed parameter. However, the aggregation number of the micelle and the fraction of bound counterions are close to those of the C_{12}TBA surfactant. Independently of the experimental technique (surface tension, conductimetry or ITC) only one *cmc* is observed, its value being in the range 1.69–1.76 mM. Within the range of temperature 288–318 K, demicellization is endothermic and the high positive value of $\Delta C^o_{P,dem}$ indicates that the hydrophobic surface of monomers, being exposed to water, increases upon demicellization and a fjord/reef 1:1 hydration is suggested for domiphen micelles. The activation energy of the surfactant monomer, close to the one observed for water viscosity, and the limiting molar conductivity of the salt suggest that below *cmc*, association of domiphen monomers does not take place and behaves as a 1:1 electrolyte.

CRediT authorship contribution statement

Silvia Vázquez-Gómez: Conceptualization, Investigation. **M. Pilar Vázquez-Tato:** Software. **Julio A. Seijas:** Software. **Francisco Meijide:** Investigation. **José Vázquez Tato:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. **Francisco Fraga:** Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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