

What can isothermal titration microcalorimetry experiments tell us about the self-organization of surfactants into micelles?

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The aim of the present review is to give a concise analysis of the thermodynamic parameters obtained from isothermal titration microcalorimetry (ITC) experiments for the characterization of the self-organization of surfactants into micelles. This review is also focused on works describing some methods allowing to overcome ITC limitation and to extract accurate thermodynamic values from ITC data. Copyright © 2009 John Wiley & Sons, Ltd.

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INTRODUCTION

The self-organization of surfactants into micelles is a widely studied phenomenon and many techniques have been used to explore this process, including surface tension measurements (Zhang *et al.*, 2008), Fourier transformed infrared spectroscopy (Su *et al.*, 2002), ¹H-NMR relaxation studies (Cau and Lacelle, 1996; Ma *et al.*, 2007), dynamic light scattering, fluorescence spectroscopy (Jiang *et al.*, 2008), and differential scanning calorimetry experiments in which the enthalpy change related to the micellization process can be calculated from the integration of the heat capacity versus temperature (Alexandridis and Hatton, 1995a; Artzner *et al.*, 2007).

Nowadays, isothermal titration microcalorimetry (ITC) is becoming a powerful technique for acquiring information on the self-organization of surfactants into micelles. ITC allows the determination of the critical micelle concentration (CMC) and the enthalpy of micellization (ΔH_{mic}) of a surfactant in a single experiment without the necessity of any probe. Other thermodynamic parameters related to the micellization, namely the free energy (ΔG_{mic}), the entropy (ΔS_{mic}) and the heat capacity of micellization ($\Delta C_{p,mic}$) can be calculated from the experimentally determined CMC and ΔH_{mic} . Furthermore, it is considered that micellar aggregation number (i.e., the average number of surfactant molecules involved in a micelle) can be obtained from a single set of experiments and by employing an appropriate model (Ohta *et al.*, 2008).

Interpretation of calorimetric data resulting from the isothermal titrations of surfactant solution into pure solvent (water, buffer, ...) is necessarily based on models describing micellization process. So far, there are two main approaches to the thermodynamic analysis of the micellization process: the mass-action model that considers micelles and unassociated unimers to be in an association–dissociation equilibrium (Attwood and Florence, 1983; Alexandridis *et al.*, 1995b) and the

phase separation model, which regards micelles as a separate phase at the CMC and assumes that the micellization process is strongly cooperative (Moroi, 1992). The phase separation model is the simplest model for describing micelle formation assuming that this process is akin to the precipitation of a separate phase. Although in reality micelles can be polydisperse (Tanford, 1980), this model assumes a monodisperse micellar solution.

In the present review, we will not go into the practical applications of ITC for the investigation of interactions of surfactant micelles with drugs, polymers, nucleic acids or proteins, as these aspects have been recently reviewed (Bouchemal, 2008). Here, the aim is to give a concise analysis of the thermodynamic parameters obtained from ITC experiments for the characterization of micellar system self-organization. This review starts with a description of typical ITC experiment followed by the explanation of how to analyze the obtained titration curves. The review will also be focused on works which aimed to interpret thermodynamic parameters obtained from ITC experiments and those devoted to the development of mathematical models to overcome ITC limitations.

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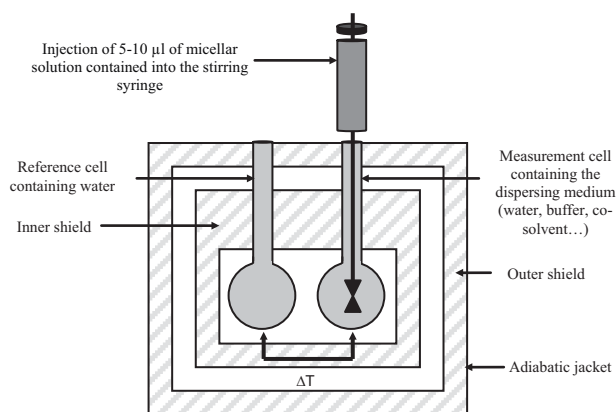


Figure 1. Schematic representation of the ITC apparatus.

TYPICAL ITC EXPERIMENT

From a technical point of view, ITC experiments are relatively simple. They consist in consecutive injections of small volumes (5–10 μl) of an aqueous micellar solution of surfactant (contained in the stirring syringe) into water contained in the measurement cell (Figure 1). The measurement cell is maintained at a constant temperature and the heat of processes occurring during dilution is monitored for each injection and plotted as a function of surfactant concentration in the cell. In commercial ITC apparatuses, the experimentally accessible range of temperature is comprised between 2 and 80°C, but experimental temperatures investigated are usually varied from 4°C (Roques *et al.*, 2009) to 60°C (Bijma and Engberts, 1994; Ropers *et al.*, 2003; Beyer *et al.*, 2006; Bouchemal *et al.*, 2009). Water which serves as the dispersing medium for the micellar solution and water initially contained into the measurement cell can be replaced by phosphate buffer (Diab *et al.*, 2007) or added with electrolytes such as NaCl (Raju *et al.*, 2001; Roques *et al.*, 2009), tyrode solution (Roques *et al.*, 2009) or co-solvents such as propanediol-1,2 (Bouchemal *et al.*, 2009).

Importantly, the surfactant concentration in the syringe has to be chosen in such a way that the increase in surfactant concentration in the measurement cell has to reach progressively the CMC during the experiment. However, a difficulty is related to the choice of the concentration of the micellar solution in the syringe when no information is available about the CMC or the critical micelle temperature (CMT) of the surfactant. In this case, various ITC experiments have to be conducted by varying the concentrations of the surfactant in the stirring syringe or the temperature of the experiment.

CRITICAL MICELLE CONCENTRATION (CMC) AND ENTHALPY OF MICELLIZATION (ΔH_{mic})

The process of self-organization of surfactants into micelles can be induced by increasing the surfactant concentration in order to be above the CMC and/or adjusting the temperature to exceed the CMT. When experimental parameters are adequately chosen, at low surfactant concentrations, heats are recorded and the CMC is progressively reached during the injection of surfactant solution into the measurement cell (Figure 2A). After integration

of heats released after each injection, enthalpograms (also called thermograms) are obtained. They consist in plots of heats as a function of surfactant concentration in the measurement cell. The composition of the medium contained in the stirring syringe and the one contained in the measurement cell being different, the integrated heats have to be corrected by subtracting adequate controls. Typically, controls consist on the titration of the two media without surfactant.

Enthalpograms can exhibit varying shapes. When sigmoidal curves are obtained (Figure 2B), they can be divided into three concentration ranges showing successively:

- (i) The dissociation of the micelles into unimers. The heat generated in this case corresponds to the enthalpy of dilution of the unimers ($\Delta H_{(i)}$).
- (ii) The micellization range of the surfactant. The heat generated during this phase corresponds to the enthalpy of micellization ($\Delta H_{(ii)}$ also denoted ΔH_{mic}).
- (iii) The dilution of the micelles. The heat generated during this phase corresponds to the enthalpy of micelle dilution ($\Delta H_{(iii)}$).

Figure 2B represents a typical enthalpogram corresponding to the dilution of pluronic F127 solution into water when the temperature of the experiment is fixed at 30°C (Bouchemal *et al.*, 2009). The CMC corresponds to the surfactant concentration at which the enthalpogram representing the enthalpy of dilution versus total surfactant concentration curve shows an inflection (Figure 2B). More accurately, the CMC is defined as the concentration for which the first derivative of the curve displays a maximum as presented in Figure 2C.

Although the start of the micellization process can be rather easily determined from ITC experiments, the end of micellization can be somewhat more difficult to determine precisely. Some authors have assumed that the plateau of the titration curve (phase (iii) in Figure 2) does not correspond to the end of the micellization process and that micellization would be effectively completed when the concentration of the surfactant was approximately ten times the CMC (Taboada *et al.*, 2003). Combining ITC experiments to other techniques such as DSC or Micro-DSC allows a correct determination of the temperatures corresponding to the start and to the end of the micellization process for thermosensitive surfactants.

For ITC experiments, when sigmoidal curves are obtained, most amphiphiles show only one extremum in the first derivative of the titration curve, which corresponds to one CMC value. This is the case of many surfactants such as alkyltrimethylammonium bromides (Beyer *et al.*, 2006), 1-methyl-4-alkylpyridiniumhalide surfactants (Bijma and Engberts, 1994), alkyl phenol ethoxylates (Dai and Tam, 2003), pluronic F127 (Bouchemal *et al.*, 2009), sodium dodecylsulfate (Paula *et al.*, 1995; Dai and Tam, 2004; Liu and Guo, 2007), β -casein (Portnaya *et al.*, 2006), tetriconic 304 (Roques *et al.*, 2009), amino-acid-type surfactants (Ohta *et al.*, 2008), oligo(ethylene oxide) alkyl ethers (Heerklotz *et al.*, 1996), the steroid CHAPS (Heerklotz and Seelig, 2000) and bile salts (Hildebrand *et al.*, 2003; Garidel and Hildebrand, 2005). However, some other amphiphilic molecules clearly show the appearance of two extrema, indicating two CMC values. This is characteristic of two-step aggregation process when the surfactant concentration is increased in the measurement cell (Hildebrand *et al.*, 2003).

Many works have reported the interest of ITC to study the variation of CMC and ΔH_{mic} with various parameters such as addition of co-solvents, type of counterion and temperature.

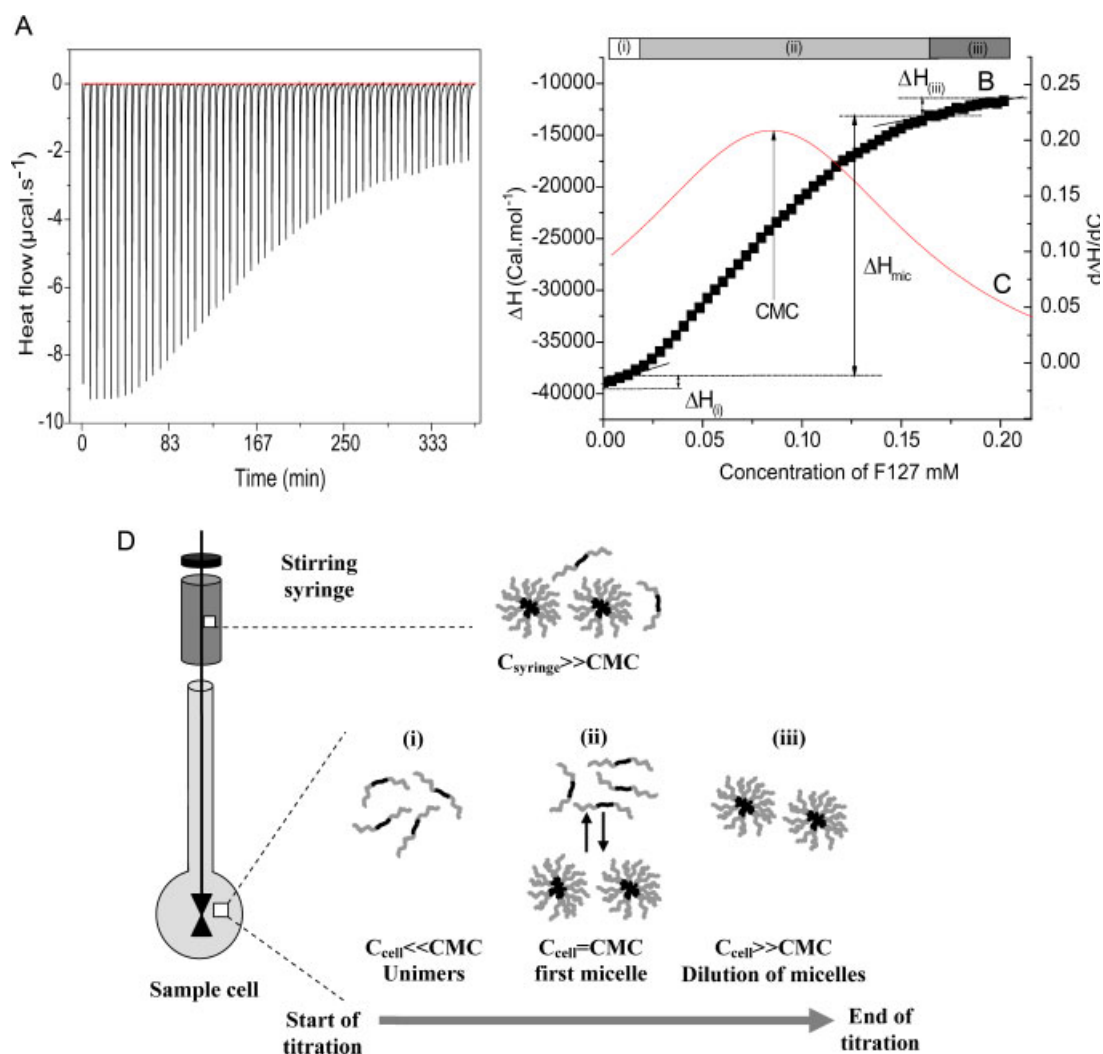


Figure 2. Typical data obtained from ITC experiments performed with a pluronic solution of F127 at a concentration of 1.187 mM in water when the temperature of the experiment is fixed at 30°C (i.e., above the CMT of the 1.187 mM F127 solution). Panel (A) shows exothermic heats released upon injection of F127 solution. Panel (B) shows integrated heat data, leading to a sigmoidal micellization curve. The CMC is defined as the concentration where the first derivative of the curve (A) reaches a maximum (C). Panel (D) is a schematic representation of the events in the measurement cell during the ITC experiment. $\Delta H_{(i)}$: the enthalpy of unimer dilution, ΔH_{mic} (also named $\Delta H_{(ii)}$): the enthalpy of micellization, $\Delta H_{(iii)}$: the enthalpy of micelle dilution. (Adapted from Bouchemal *et al.*, 2009).

Concerning the effect of temperature on the CMC, in some cases, the CMC decreases upon temperature increase. This was observed with block copolymers such as pluronic F127 (Bouchemal *et al.*, 2009) and tetronic 304 (Roques *et al.*, 2009). In other cases, the CMC decreases upon increasing the temperature, then, goes through a minimum, and increases at high temperatures (Paula *et al.*, 1995; Beyer *et al.*, 2006; Łuczak *et al.*, 2009). This was observed in the case of ionic surfactants such as sodium oleate (Hildebrand *et al.*, 2004) and sodium dodecyl sulphate (Paula *et al.*, 1995), non-ionic surfactants such as octyl glucoside (Paula *et al.*, 1995) as well as in the case of mixed micelles (Hildebrand *et al.*, 2004). It was demonstrated that the variation of $\ln CMC'$ (CMC' is the critical micelle concentration (CMC) expressed in mole fraction terms) with temperature can be empirically approximated by a second degree polynomial (Nusselder and Engberts, 1992; Paula *et al.*, 1995; Majhi and Blume, 2001):

$$\ln CMC'(T) = AT^2 + BT + C \quad (1)$$

When sigmoidal curves are obtained, the heat of micellization ΔH_{mic} was equal to the enthalpy difference between the two extrapolated lines in Figure 2B. The total enthalpy of reaction $\Delta H_{observed}$ includes in addition, dilution contributions of the unimers ($\Delta H_{(i)}$) and the dilution of micelles ($\Delta H_{(iii)}$):

$$\Delta H_{(ii)} = \Delta H_{mic} = \Delta H_{observed} - \Delta H_{(i)} - \Delta H_{(iii)} \quad (2)$$

In many works, results were expressed in terms of enthalpy of demicellization (ΔH_{demic}) (Paula *et al.*, 1995; Garidel *et al.*, 2000; Raju *et al.*, 2001), or in terms of enthalpy of micellization (ΔH_{mic}) (Bijma and Engberts, 1994; Majhi and Moulik, 1998; Dai and Tam, 2003; Bouchemal *et al.*, 2009; Roques *et al.*, 2009). Since results obtained from these two considerations are similar ($\Delta H_{mic} = -\Delta H_{demic}$), we suggest that it is thermodynamically more significant to comment this review in terms of "the enthalpy of micellization" which is the effective studied phenomena.

It is worth noting that the enthalpy of micellization of a thermosensitive nonionic surfactant (pluronic F127) obtained

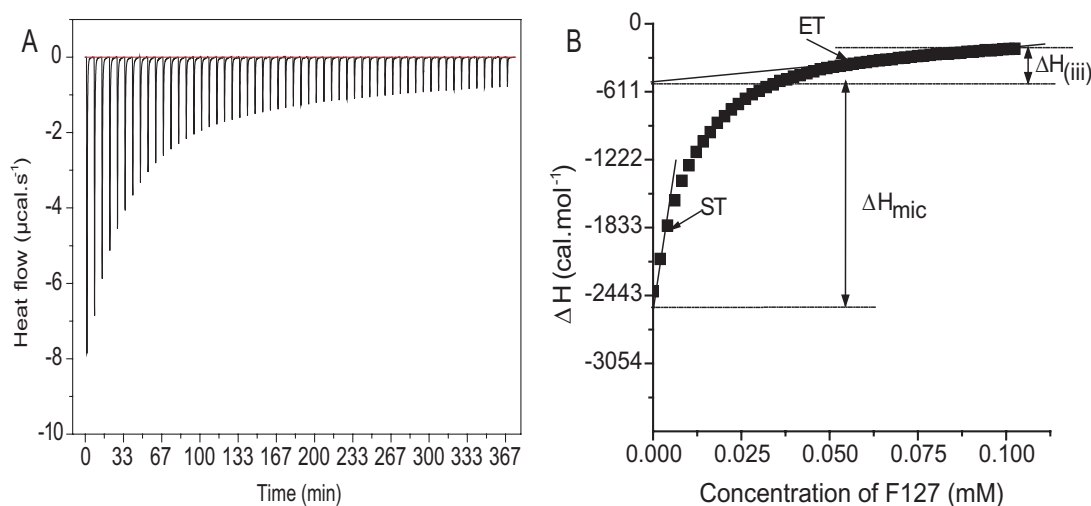


Figure 3. Typical non-sigmoidal curves obtained from ITC experiments performed with a pluronic solution of F127 at a concentration of 1.187 mM in water when the temperature of the experiment is fixed at 34 °C. Panel (A) shows exothermic heat released upon injection of F127 solution. Panel (B) shows integrated heat data, giving a sigmoidal micellization curve. ST and ET represent respectively the start and the end of the micellization. ΔH_{mic} (also named $\Delta H_{\text{(ii)}}$): the enthalpy of micellization, $\Delta H_{\text{(iii)}}$: the enthalpy of micelle dilution. (Adapted from Bouchemal *et al.*, 2009).

using other methods such as Micro-DSC (Pham Trong *et al.*, 2008) does not correspond to that obtained by using ITC (Bouchemal *et al.*, 2009). Certainly, the difference between the two ΔH_{mic} values is due to the fact that the heat measured by Micro-DSC and the one measured by ITC do not reflect the same events. Indeed, in Micro-DSC, the surfactant concentration remains unchanged while the temperature of the experiment is progressively increased. However, in ITC measurements, the temperature of the experiment remains unchanged while the surfactant concentration is progressively increased in the measurement cell. However, other research works (Saito *et al.*, 2000) reported very slightly different values of ΔH_{mic} for chlorpromazine hydrochloride (ionic surfactant) determined from DSC and ITC experiments. The amplitude of the discrepancy might thus depend on the nature of the surfactant. Unfortunately, there is no research work to date which explores the origin of this discrepancy and the relationship between the two determinations of ΔH_{mic} values. The signification of the observed enthalpy from both experiments thus remains an open question.

Interestingly, ΔH_{mic} obtained from Micro-DSC is always positive. However, ΔH_{mic} determined from ITC titration curve of ionic surfactant can take negative values (Bijma and Engberts, 1994; Diab *et al.*, 2007; Bai *et al.*, 2008; Poša *et al.*, 2008), positive values (Raju *et al.*, 2001; Bouchemal *et al.*, 2009; Roques *et al.*, 2009), or both negative and positive values depending on the temperature. For instance, it was reported for octylglucoside surfactants that ΔH_{mic} was positive at high temperatures, decreased upon lowering the temperature, then, passed through zero, and became negative at low temperatures (Paula *et al.*, 1995; Majhi and Moulik, 1998). Conversely, ΔH_{mic} of amino-acid-type surfactants was positive at low temperatures and decreased with increasing temperature to ultimately become negative at high temperatures (Ohta *et al.*, 2008).

In some cases, the shape of the ITC enthalpogram obtained at a given temperature cannot be exploited directly (Dai and Tam, 2003; Bouchemal *et al.*, 2009; Roques *et al.*, 2009). For instance, when no break in the enthalpy versus concentration curve is observed, the determination of ΔH_{mic} and CMC becomes

inaccurate or even impossible (Paula *et al.*, 1995; Garidel *et al.*, 2000; Rozycka-Roszak *et al.*, 2008). In such circumstances, curve analysis is requested for determining the concentrations corresponding to the start and to the end of the micellization process (Klijn *et al.*, 2000; Raju *et al.*, 2001; Bouchemal *et al.*, 2009; Roques *et al.*, 2009). As explained in Figure 3, linear fits of the data sets in the lower and the upper concentration domains were performed. The abscissa of the last (highest) value in the fitted raw data of the lower concentration range (ST: start of transition), and of the first (lowest) value in the fitted data of the higher concentration domain (ET: end of transition), were taken as the polymer concentrations corresponding to the start and to the end of micellization process, respectively (see Figure 3). It is worth noting that the accuracy of the determination of the ST and the ET, remains approximate using this method (Bouchemal *et al.*, 2009).

An other possibility for the determination of ΔH_{mic} and CMC at the desired temperature consists in determining a set of experimental values of ΔH_{mic} at various temperatures and extrapolating the CMC value at the corresponding temperature (Paula *et al.*, 1995; Garidel *et al.*, 2000; Beyer *et al.*, 2006). For many surfactants, the experimentally determined ΔH_{mic} values are well fitted to a second degree polynomial (Paula *et al.*, 1995; Garidel *et al.*, 2000; Beyer *et al.*, 2006) and the CMC can then be calculated from van't Hoff equation

$$\left(\frac{\partial \ln \text{CMC}'}{\partial T}\right) = -\frac{1}{RT^2} \Delta H_{\text{mic}}(T) \quad (3)$$

where R is the ideal gas constant ($8.3144 \text{ J mol}^{-1} \text{ K}^{-1}$) and T the absolute temperature. $\Delta H_{\text{mic}}(T)$ represents the enthalpy of micellization as a function of temperature, which is an experimentally determined quantity.

Alternatively, for a known value of CMC, the calculation of ΔH_{mic} can be achieved by using Gibbs–Helmholtz equation derived from van't Hoff equation

$$\Delta H_{\text{mic}} = -RT^2 \left(\frac{\partial (\ln \text{CMC}')}{\partial T}\right)_p \quad (4)$$

However, differences between experimentally determined data and that obtained using Gibbs–Helmholtz or van't Hoff equations have been reported (Bijma and Engberts, 1994; Chatterjee *et al.*, 2001). Indeed, agreement between calculated and experimentally determined ΔH_{mic} is usually poor in the case of ionic surfactants, whereas better agreement is obtained for non-ionic surfactants (Moroi, 1992). For ΔH_{mic} determined from ITC experiments, the consequence of these effects and others, such as the heats of solvation–desolvation of surfactants, ionization, molecular rearrangement, and mixing, are included in the calorimetric measurements. The calculated ΔH_{mic} is dependent on the aggregation number, micelle shape, and these effects are not considered in Gibbs–Helmholtz or van't Hoff analyses. Furthermore, specific counterion effects (e.g., counterion binding originated from the surfactant or from added salts, acids, or bases) and aggregation number are not taken into account in the monodisperse phase separation model.

FREE ENERGY OF MICELLIZATION: ΔG_{mic}

In general, micellization process obeys the closed association model, which assumes an equilibrium between molecularly dispersed unimers and multimolecular aggregates (micelles). Aggregation process can be described by Equation 5 in which (n) molecules of surfactant S form one aggregate of aggregation number (n), (Tanford, 1980; Armstrong *et al.*, 1996):



The equilibrium constant of the association process can be written as $K = \frac{[S_n]}{[S]^n}$. The relation between K , ΔG_{mic} , and ΔG_{demic} (the free energy of demicellization) is expressed by Equation 6

$$\Delta G_{\text{demic}} = -\Delta G_{\text{mic}} = -RT \ln K \quad (6)$$

It can easily be deduced that

$$\Delta G_{\text{mic}} = -\frac{RT}{n} \ln[S_n] + RT \ln[S] \quad (7)$$

When the aggregation number (n) is sufficiently large, the term $\frac{RT}{n} \ln[S_n]$ can be omitted from Equation 7 and ΔG_{mic} can be expressed by the simple equation

$$\Delta G_{\text{mic}} = nRT \ln(\text{CMC}') = n\Delta G_0 \quad (8)$$

However, for low aggregation numbers, the pseudo-phase-separation model becomes a crude approximation because the term $\frac{RT}{n} \ln[S_n]$ cannot be omitted from Equation 7. In this case, the aggregation process can be better described using mass action model as explained by many researchers (Garidel *et al.*, 2000; Lah *et al.*, 2000; Poša *et al.*, 2008).

It is shown that many reported studies did not use the correct relationship to evaluate the free energy of micellization. In particular, the counterion was often neglected, which resulted in large errors. In the case of ionic surfactants, many models have been proposed to calculate ΔG_{mic} (Zana, 1996; Goldsipe and Blankschtein, 2006). Probably, the simplest one consists in the calculation of ΔG_{mic} by the following relation:

$$\Delta G_{\text{mic}} = \left(1 + \frac{m}{n}\right)RT \ln(\text{CMC}') = (1 + \beta)RT \ln(\text{CMC}') \quad (9)$$

where the terms m and β are the number of counterions bound per micelle and the fraction of counterion bound to a micelle, respectively. The term " β " is also called the effective micellar

charge fraction (Dai and Tam, 2003) or degree of counterion condensation (Beyer *et al.*, 2006). Because the correct evaluation of the counterion binding is quite difficult, values of " β " can be calculated from the ionization degree (α) defined as the fraction of counterions not bound to a micelle ($\alpha = 1 - \beta$). The value of " α " can be experimentally determined from the slopes of the conductivity plots below and above the CMC (Benrraou *et al.*, 2003; Jiang *et al.*, 2004; Bai *et al.*, 2008).

In the case of cationic gemini surfactants ($[\text{C}_{12}\text{H}_{25}(\text{CH}_3)_2\text{N}(\text{CH}_2)_6\text{N} - (\text{CH}_3)_2\text{C}_{12}\text{H}_{25}]X_2$), the calculated " β " parameter values have been estimated to be 0.46, 0.51, 0.56, 0.58, 0.59, and 0.6 for $X = \text{F}^-$, Cl^- , Ac^- , Br^- , NO_3^- , and $\frac{1}{2} \text{SO}_4^{2-}$, respectively at 298.15 K (Jiang *et al.*, 2004). For the anionic sodium dodecylsulphate surfactant, " β " parameter values were 0.50, 0.55, and 0.74 for Li^+ , K^+ , and Cs^+ , respectively (Maiti *et al.*, 2009). We will not go through the origin of the variation of " β " value with the size of the counterion because this point has been well explained in many previous research works (Benrraou *et al.*, 2003; Ropers *et al.*, 2003; Jiang *et al.*, 2004; Maiti *et al.*, 2009).

The lowering of CMC values obtained from ITC experiments in presence of salts is well known and was discussed in detail (Paula *et al.*, 1995; Garidel *et al.*, 2000; Hildebrand *et al.*, 2004; Roques *et al.*, 2009). Indeed, the higher value of " β " when increasing counterion concentration means the higher ability of counterion to bind to micelles. Consequently, the electrostatic repulsions between the headgroups of the ionic surfactant molecules are reduced by increasing the counterion concentration. The micellization process becomes thermodynamically more favorable in the presence of counterions, and ΔG_{mic} is shifted toward lower values (Ropers *et al.*, 2003).

Increasing temperature leads to a similar decrease of ΔG_{mic} indicating a larger driving force for micellization and a greater propensity to form micelles. As a result, the aggregation process is thermodynamically favored and becomes spontaneous at higher temperatures. This was observed in the case of many surfactants such as pluronic F127 (Bouchemal *et al.*, 2009), Tetronic 304 (Roques *et al.*, 2009), *N*-cetyl-*N,N*-diethanolyl-*N*-methyl ammonium bromide (CDMAB) (Chatterjee *et al.*, 2002). However, in some cases, the variation of the temperature of the experiment does not affect ΔG_{mic} (Hildebrand *et al.*, 2004). This is a manifestation of the hydrophobic effect with its enthalpy–entropy compensation (Tanford, 1980; Moroi, 1992; Paula *et al.*, 1995). Importantly, the linear correlation between enthalpy and entropy has been observed when the temperature and the composition of the micellization medium are varied in a systematic way (Figure 4) (Jolicoeur and Philip, 1974; Paterson *et al.*, 1997; Tsui *et al.*, 2008; Bouchemal *et al.*, 2009).

CHANGE OF ENTROPY DURING MICELLIZATION: ΔS_{mic}

The change in entropy ΔS_{mic} during micellization process of a surfactant can be easily obtained from the second law of thermodynamics

$$\Delta S_{\text{mic}} = \frac{\Delta H_{\text{mic}} - \Delta G_{\text{mic}}}{T} \quad (10)$$

From the comparison of ΔS_{mic} and ΔH_{mic} , the major driving force for surfactant micelle formation can be revealed. In most cases, the major driving forces for micelle formation are

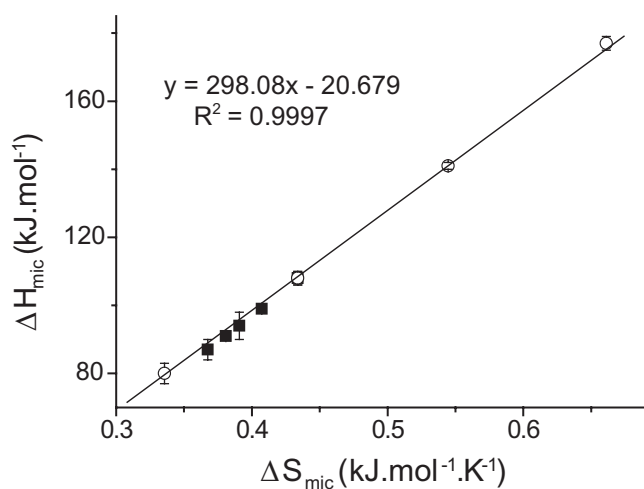


Figure 4. Enthalpy–entropy compensation plot corresponding to the micellization of F127 (1.187 mM). (i) In water at various temperatures (○). Data available in Table 1. (ii) In presence of propanediol-1,2 at 29°C (■). (Adapted from Bouchemal *et al.*, 2009).

hydrophobic interactions. In these cases, the entropy contribution usually dominates the micellization process in aqueous surfactant solutions, with the enthalpy playing a minor role ($|T\Delta S_{mic}| > |\Delta H_{mic}|$). At room temperature, the hydrophobic forces are produced when water molecules in hydration shells around the hydrophobic parts of the monomeric amphiphiles are released during the micellization process. This is reflected by positive entropy values of micellization. The entropic contribution that dominates the hydrophobic effect at room temperature is reduced at higher temperatures. The association is becoming more and more enthalpy-driven at elevated temperatures (Moroi, 1992; Paula *et al.*, 1995). This so-called enthalpy–entropy compensation is characteristic for aggregation processes which can be observed for ionic (Paula *et al.*, 1995; Hildebrand *et al.*, 2004; Beyer *et al.*, 2006) and non-ionic (Majhi and Blume, 2001) surfactants.

In some cases, besides hydrophobic interactions, other forces such as electrostatic can contribute to micellization process (Portnaya *et al.*, 2006). For example, the formation of a micelle from monomeric ionic surfactants results on a balance between

- attractive molecular driving forces between the hydrophobic surfactant tails arising from the hydrophobic interactions,
- attractive and repulsive electrostatic interactions between their hydrophilic charged headgroups, and
- with and between the counterions.

Furthermore, it is well understood that there exists hydrogen bonding between water and some surfactant molecules. For example, in the case of benzyl(2-acylaminoethyl)dimethyl ammonium chloride, the presence of amide group may form direct and/or water mediated intermolecular hydrogen bonds, while poly(*N,N*-dimethylaminoethylate) (PDMA) block presents a weak hydrophilic property deriving from the hydrogen bond between water molecules and deprotonized amine residues (Kang *et al.*, 2009).

Finally, hydrogen bonds may result from changes of the solvent composition. For example, during the investigation of the effect of propanediol-1,2 on the micellization of F127, we have confirmed that inter-molecular hydrogen bonds occur between water and propanediol-1,2. The hydrogen bonds could also be responsible for a lower degree of freedom and in turn, a lower value of ΔS_{mic} (Bouchemal *et al.*, 2009).

THERMAL HEAT CAPACITY OF MICELLIZATION: $\Delta C_{p_{mic}}$

The determination of the temperature dependence of ΔH_{mic} helps to decide whether more hydrophobic surface is exposed to water when the aggregates associate into micelles. Probably, the most reliable thermodynamic quantity for the extent of hydrophobic hydration is the change in thermal heat capacity of micellization $\Delta C_{p_{mic}}$ obtained from the slope of the ΔH_{mic} versus temperature plot. The $\Delta C_{p_{mic}}$ can be also evaluated from the following relationship:

$$\Delta C_{p_{mic}} = \left(\frac{\partial \Delta H_{mic}}{\partial T} \right)_p \quad (11)$$

In aqueous solutions, the hydrophobic part of surfactant molecules in the unimer form, are surrounded by water, which tend to form a kind of net around surfactant molecules and is generally referred as hydrophobic hydration. The variations of $\Delta C_{p_{mic}}$ contain information on the change in hydration of apolar surfaces during micellization. For some amphiphiles, $\Delta C_{p_{mic}}$ has been found to be a linear function of the hydrophobic surface area of amphiphiles that become excluded from water through micellization (Jolicœur and Philip, 1974). In other words, $\Delta C_{p_{mic}}$ scales linearly with the hydrophobic surface area buried upon micellization. Thus, from the positive values of the $\Delta C_{p_{mic}}$, one can conclude that the association of unimers to form aggregates leads to the decrease of the exposed hydrophobic surface area. In contrast, negative values of $\Delta C_{p_{mic}}$ suggest that the dissociation of aggregates leads to the exposure to the aqueous environment of additional hydrophobic surface area (Garidel *et al.*, 2000). In the case of ionic surfactants, the condensation of ions onto micelles during micellization process reduces the number of water molecules in the solvation shell. Indeed, ions can share hydration water with the headgroups resulting in a positive value of the heat capacity associated with the dehydration process of counterions (Marcus and Rashin, 1994).

CONCLUSION

As shown in this review, ITC experiments allowed the direct determination of the CMC values, and ΔH_{mic} from which other thermodynamic parameters are calculated. However, depending on the shape of the titration curve, data determination can be more or less easy. In some cases, when CMC (or ΔH_{mic}) cannot be derived directly from the enthalpograms, it can be necessary to take advantage of the dependency of CMC (or ΔH_{mic}) to variables such as temperature to be able to determine a CMC (or ΔH_{mic}) values in the desired conditions.

REFERENCES

- Alexandridis P, Hatton TA. 1995a. Poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) block copolymer surfactants in aqueous solutions and at interfaces: thermodynamics, structure, dynamics, and modelling. *Colloids. Surf. A* **96**: 1–46. DOI:10.1016/0927-7757(94)03028-X
- Alexandridis P, Nivaggioli T, Hatton TA. 1995b. Temperature effects on structural properties of pluronic P104 and F108 PEO-PPO-PEO block copolymer solutions. *Langmuir* **11**: 1468–1476. DOI:10.1021/la00005a011
- Armstrong J, Chowdhry B, Mitchell J, Beezer A, Leharne S. 1996. Effect of cosolvents and cosolutes upon aggregation transitions in aqueous solutions of the Poloxamer F87 (Poloxamer P237): a high sensitivity differential scanning calorimetry study. *J. Phys. Chem.* **100**: 1738–1745. DOI:10.1021/jp951390s
- Artzner F, Geiger S, Olivier A, Allais C, Finet S, Agnely F. 2007. Interactions between poloxamers in aqueous solutions: micellization and gelation studied by differential scanning calorimetry, small angle X-ray scattering, and rheology. *Langmuir* **23**(9): 5085–5092. DOI:10.1021/la062622p
- Attwood D, Florence A. 1983. *Surfactant Systems: Their Chemistry, Pharmacology and Biology*. Chapman & Hall: London; 794.
- Bai G, Lopes A, Bastos M. 2008. Thermodynamics of micellization of alkylimidazolium surfactants in aqueous solution. *J. Chem. Thermodynamics* **40**(10): 1509–1516. DOI:10.1016/j.jct.2008.05.016
- Benraou M, Bales BL, Zana R. 2003. Effect of the nature of the counterion on the properties of anionic surfactants. 1. Cmc, ionization degree at the Cmc and aggregation number of micelles of sodium, cesium, tetramethylammonium, tetraethylammonium, tetrapropylammonium, and tetrabutylammonium dodecyl sulfates. *J. Phys. Chem. B* **107**: 13432–13440. DOI:10.1021/jp021714u
- Beyer K, Leine D, Blume A. 2006. The demicellization of alkyltrimethylammonium bromides in 0.1 M sodium chloride solution studied by isothermal titration calorimetry. *Colloid Surf. B* **49**: 31–39. DOI:10.1016/j.colsurfb.2006.02.003
- Bijma K, Engberts JBFN. 1994. Thermodynamics of micelle formation by 1-methyl-4-alkylpyridinium halides. *Langmuir* **10**: 2578–2582. DOI:10.1021/la00020a015
- Bouchemal K. 2008. New challenges for pharmaceutical formulations and drug delivery systems characterization using isothermal titration calorimetry. *Drug. Discov. Today* **13**(21/22): 960–972. DOI:10.1016/j.drudis.2008.06.004
- Bouchemal K, Agnely F, Koffi AA, Ponchel G. 2009. A concise analysis of the effect of temperature and propanediol-1,2 on Pluronic F-127 micellization using isothermal titration microcalorimetry. *J. Colloid Interf. Sci.* **338**: 169–176.
- Cau F, Lacelle S. 1996. ¹H NMR relaxation studies of the micellization of a poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) triblock copolymer in aqueous solution. *Macromolecules* **29**: 170–178. DOI:10.1021/ma950976+
- Chatterjee A, Moulik SP, Sanyal SK, Mishra BK, Puri PM. 2001. Thermodynamics of micelle formation of ionic surfactants: a critical assessment for sodium dodecyl sulfate, cetyl pyridinium chloride and dioctyl sulfosuccinate (Na salt) by microcalorimetric, conductometric, and tensiometric measurements. *J. Phys. Chem. B* **105**: 12823–12831. DOI:10.1021/jp0123029
- Chatterjee A, Maiti S, Sanyal SK, Moulik SP. 2002. Micellization and related behaviors of *N*-cetyl-*N*-ethanolyl-*N*, *N*-dimethyl and *N*-cetyl-*N*, *N*-diethanolyl-*N*-methyl ammonium bromide. *Langmuir* **18**: 2998–3004.
- Dai S, Tam KC. 2003. Isothermal titration calorimetric studies of alkyl phenol ethoxylate surfactants in aqueous solutions. *Colloids. Surf. A* **229**: 157–168. DOI:10.1016/j.colsurfa.2003.09.007
- Dai S, Tam KC. 2004. Isothermal titration calorimetric studies on the temperature dependence of binding interactions between poly(propylene glycol)s and sodium dodecyl sulfate. *Langmuir* **20**: 2177–2183. DOI:10.1021/jp030907
- Diab C, Winnik FM, Tribet C. 2007. Enthalpy of interaction and binding isotherms of non-ionic surfactants onto micellar amphiphilic polymers (amphipols). *Langmuir* **23**: 3025–3035. DOI:10.1021/la062522j
- Garidel P, Hildebrand A, Neubert R, Blume A. 2000. Thermodynamic characterization of bile salt aggregation as a function of temperature and ionic strength using isothermal titration calorimetry. *Langmuir* **16**: 5267–5275. DOI:10.1021/la9912390
- Garidel P, Hildebrand A. 2005. Thermodynamic properties of association colloids. *J. Therm. Anal. Calorim.* **82**: 483–489.
- Goldspie A, Blankschtein D. 2006. Molecular-thermodynamic theory of micellization of pH-sensitive surfactants. *Langmuir* **22**: 3547–3559. DOI:10.1021/la052896x
- Heerklotz H, Lantzsh G, Binder H, Klosse G. 1996. Thermodynamic characterization of dilute aqueous lipid/detergent mixtures of POPC and C₁₂EO₈ by means of isothermal titration calorimetry. *J. Phys. Chem.* **100**: 6764–6774.
- Heerklotz H, Seelig J. 2000. Correlation of membrane/water partition coefficients of detergents with the critical micelle concentration. *Biophys. J.* **78**: 2435–2440. DOI:10.1006/biophys.2000.02001
- Hildebrand A, Beyer K, Neubert R, Garidel P, Blume A. 2003. Temperature dependence of the interaction of cholate and deoxycholate with fluid model membranes and their solubilization into mixed micelles. *Colloid. Surf. B* **32**(4): 335–351. DOI:10.1016/j.colsurfb.2003.02.001
- Hildebrand A, Garidel P, Neubert R, Blume A. 2004. Thermodynamics of demicellization of mixed micelles composed of sodium oleate and bile salts. *Langmuir* **20**: 320–328. DOI:10.1021/la035526m
- Jiang X, Lavender CA, Woodcock JW, Zhao B. 2008. Multiple micellization and dissociation transitions of thermo- and light-sensitive poly(ethylene oxide)-*b*-poly(ethoxytri(ethylene glycol) acrylate-*co*-*o*-nitrobenzyl acrylate) in water. *Macromolecules* **41**: 2632–2643. DOI:10.1021/ma7028105
- Jiang N, Li P, Wang Y, Wang J, Yan H, Thomas RK. 2004. Micellization of cationic gemini surfactants with various counterions and their interaction with DNA in aqueous solution. *J. Phys. Chem. B* **108**: 15385–15391. DOI:10.1021/jp0488057
- Jolicoeur C, Philip PR. 1974. Enthalpy-entropy compensation for micellization and other hydrophobic interactions in aqueous solutions. *Can. J. Chem.* **52**: 1834–1839.
- Kang H, Peng B, Liang Y, Han X, Liu H. 2009. Study of the interaction between a diblock polyelectrolyte PDMA-*b*-PAA and a gemini surfactant 12-6-12 in basic media. *J. Colloid. Interf. Sci.* **333**: 135–140.
- Klijin JE, Kevelam J, Engberts JBFN. 2000. Aggregation behavior of mono-endcapped hydrophobically modified poly(sodium acrylate)s in aqueous solution. *J. Colloid. Interf. Sci.* **226**: 76–82. DOI:10.1006/jcis.2000.6616
- Lah J, Pohar C, Vesnaver G. 2000. Calorimetric study of the micellization of alkylpyridinium and alkyltrimethylammonium bromide in water. *J. Phys. Chem. B* **104**: 2522–2526. DOI:10.1021/jp9928614
- Liu Y, Guo R. 2007. Interaction between casein and sodium dodecyl sulfate. *J. Colloid. Interf. Sci.* **315**: 685–692. DOI:10.1016/j.jcis.2007.07.018
- Łuczak J, Jungnickel C, Joskowska M, Thöming J, Hupka J. 2009. Thermodynamics of micellization of imidazolium ionic liquids in aqueous solutions. *J. Colloid. Interf. Sci.* **336**: 111–116. DOI:10.1016/j.jcis.2009.03.017
- Ma J-H, Guo C, Tang Y-L, Liu H-Z. 2007. ¹H NMR spectroscopic investigations on the micellization and gelation of PEO-PPO-PEO block copolymers in aqueous solutions. *Langmuir* **23**: 9596–9605. DOI:10.1021/la701221f
- Maiti K, Mitra D, Guha S, Moulik SP. 2009. Salt effect on self-aggregation of sodium dodecylsulfate (SDS) and tetradecyltrimethylammonium bromide (TTAB): physicochemical correlation and assessment in the light of Hofmeister (lyotropic) effect. *J. Mol. Liq.* **146**: 44–51. DOI:10.1016/j.molliq.2009.01.014
- Majhi PR, Blume A. 2001. Thermodynamic characterization of temperature-induced micellization and demicellization of detergents studied by differential scanning calorimetry. *Langmuir* **17**: 3844–3851. DOI:10.1021/la001660k
- Majhi PR, Moulik SP. 1998. Energetics of micellization: reassessment by a high-sensitivity titration microcalorimeter. *Langmuir* **14**: 3986–3990. DOI:10.1021/la9707437
- Marcus Y, Rashin A. 1994. A simple empirical model describing the thermodynamics of hydration of ions of widely varying charges, sizes and shapes. Discussion. Response. *Biophys. Chem.* **51**: 111–127.
- Moroi Y. 1992. *Micelles*. Plenum Press: New York.

- Nusselder JH, Engberts JBFN. 1992. Toward a better understanding of the driving force for micelle formation and micellar growth. *J. Colloid. Interf. Sci.* **148**: 353–361. DOI:10.1016/0021-9797(92)90174-K
- Ohta A, Toda K, Morimoto Y, Asakawa T, Miyagishi S. 2008. Effect of the side chain of *N*-acyl amino acid surfactants on micelle formation: an isothermal titration calorimetry study. *Colloids Surf. A.: Physicochem. Eng. Aspects* **317**: 316–322. DOI:10.1016/j.colsurfa.2007.10.028
- Paterson I, Armstrong J, Chowdhry B, Leharne S. 1997. Thermodynamic model fitting of the calorimetric output obtained for aqueous solutions of oxyethylene–oxypropylene–oxyethylene triblock copolymers. *Langmuir* **13**: 2219–2226. DOI:10.1021/la960432g
- Paula S, Sús W, Tuchtenhagen J, Blume A. 1995. Thermodynamics of micelle formation as a function of temperature: a high sensitivity titration calorimetry study. *J. Phys. Chem.* **99**: 11742–11751.
- Pham Trong LC, Djabourov M, Ponton A. 2008. Mechanisms of micellization and rheology of PEO-PPO-PEO triblock copolymers with various architectures. *J. Colloid. Interf. Sci.* **328**: 278–287. DOI:10.1016/j.jcis.2008.09.029
- Portnaya I, Cogan U, Livney YD, Ramon O, Shimoni K, Rosenberg M, Danino D. 2006. Micellization of Bovine β -Casein studied by isothermal titration microcalorimetry and cryogenic transmission electron microscopy. *J. Agric. Food. Chem.* **54**: 5555–5561. DOI:10.1021/jf060119c.
- Poša M, Kevrešan S, Mikov M, Ćirin-Novta V, Kuhajda K. 2008. Critical micellar concentrations of keto derivatives of selected bile acids: thermodynamic functions of micelle formation. *Colloid. Surf. B.* **64**: 151–161. DOI:10.1016/j.colsurfb.2008.01.017
- Raju BB, Winnik F, Morishima Y. 2001. A look at the thermodynamics of the association of amphiphilic polyelectrolytes in aqueous solutions: strengths and limitations of isothermal titration calorimetry. *Langmuir* **17**: 4416–4421. DOI:10.1021/la001554i
- Ropers MH, Czichocki G, Brezesinski G. 2003. Counterion effect on the thermodynamics of micellization of alkyl sulfates. *J. Phys. Chem. B.* **107**: 5281–5288. DOI:10.1021/jp0264329
- Roques C, Bouchemal K, Ponchel G, Fromes Y, Fattal E. 2009. Importance of formulations parameters of non-viral vectors based on amphiphilic copolymers on their in vivo efficiency. *J. Control Release.* **138**: 71–77. DOI:10.1016/j.jconrel.2009.04.030
- Rozycka-Roszak B, Misiak P, Woźniak E, Mozrzyms A, Dega-Szafran Z. 2008. Calorimetric and molecular modeling studies of *N*-alkoxycarbonylmethyl-*N*-alkyl-piperidinium chlorides. *Colloids Surf. A: Physicochem. Eng. Aspects* **318**: 301–306. DOI:10.1016/j.colsurfa.2008.01.006
- Saito YD, Tehrani S, Okamoto MM, Chang HH, Dea P. 2000. Calorimetry studies of chlorpromazine hydrochloride in solution. *Langmuir* **16**: 6391–6395. DOI:10.1021/la9912971
- Su Y-L, Wang J, Liu H-Z. 2002. Formation of a hydrophobic microenvironment in aqueous PEO-PPO-PEO block copolymer solutions investigated by fourier transform infrared spectroscopy. *J. Phys. Chem. B.* **106**: 11823–11828. DOI:10.1021/jp026160+
- Taboada P, Mosquera V, Attwood D, Yang Z, Booth C. 2003. Enthalpy of micellisation of a diblock copoly(oxyethylene/oxypropylene) by isothermal titration calorimetry. Comparison with the van't Hoff value. *Phys. Chem. Chem. Phys.* **5**: 2625–2627. DOI:10.1039/b303108j
- Tanford C. 1980. *The Hydrophobic Effect. Formation of Micelles and Biological Membranes.* (2nd edn), Wiley: New York.
- Tsui H-W, Hsu Y-H, Wang J-H, Chen L-J. 2008. Novel behavior of heat of micellization of pluronics F68 and F88 in aqueous solutions. *Langmuir* **24**: 13858–13862. DOI:10.1021/la803272y
- Zana R. 1996. Critical micellization concentration of surfactants in aqueous solution and free energy of micellization. *Langmuir* **12**: 1208–1211. DOI:10.1021/la950691q
- Zhang S, Li N, Zheng L, Li X, Gao Y, Yu L. 2008. Aggregation behavior of pluronic triblock copolymer in 1-butyl-3-methylimidazolium type ionic liquids. *J. Phys. Chem. B.* **112**: 10228–10233. DOI:10.1021/jp803513z