J. Chem. Thermodynamics 77 (2014) 77–81

Contents lists available at ScienceDirect

J. Chem. Thermodynamics

journal homepage: www.elsevier.com/locate/jct

Thermodynamics of micellisation: Sodium dodecyl sulfate/sodium deoxycholate with polyethylene glycol and model drugs

Laura J. Waters *, Talib Hussain, Gareth M.B. Parkes

Department of Pharmacy, School of Applied Science, University of Huddersfield, Queensgate, Huddersfield HD1 3DH, UK

ARTICLE INFO

Article history:
Received 12 March 2014
Received in revised form 8 May 2014
Accepted 12 May 2014
Available online 21 May 2014

Keywords:
Calorimetry
ITC
Micelles
Drugs
PEG
CMC
NaDC

ABSTRACT

Variations in the critical micelle concentration (CMC) have been determined for sodium dodecyl sulfate and sodium deoxycholate (NaDC) in the presence of five drugs and polyethylene glycol (PEG) at temperatures (298.2, 304.2 and 310.2) K. From these data, thermodynamic parameters associated with the micellisation process ($\Delta_{mic}G$, $\Delta_{mic}H$ and $\Delta_{mic}S$) were calculated. In the presence of some drug-based compounds, the CMC of SDS was affected, for example the presence of PEG dramatically reduced the CMC in all cases. Furthermore, PEG appeared to reduce the enthalpy of micellisation for all scenarios with only comparatively minor variations in the change in Gibbs free energy for the processes observed. For NaDC, the calorimetric results were far less predictable. A primary aggregation event recorded at a comparatively low concentration failed to appear for NaDC in the presence of a secondary compound, such as a drug or PEG. For NaDC, the presence of PEG had little effect on the CMC and corresponding thermodynamic data.

1. Introduction

Micellisation of surfactants is a thermodynamically driven event that can be monitored using several analytical techniques, most recently, using isothermal titration calorimetry (ITC) [1]. It has been found that the process by which micelles become saturated with additional compounds can be monitored, particularly hydrophobic compounds, and this can be measured using the aforementioned technique. With respect to pharmaceutical compounds in particular, it has been discovered that the presence of such compounds can affect the concentration at which surfactants spontaneously form micellar based structures, *i.e.* the critical micellar concentration (CMC) [2], although the changes reported were only moderate. Furthermore, this specific application of ITC has permitted calculation of the change in enthalpy associated with the micellisation event ($\Delta_{mic}H$) and found to be dependent upon the physicochemical properties of the drug present, implying a large entropic effect is involved in the micellisation event which is affected by the drugs functionality. To thermodynamically characterise the micellisation event fully it is necessary to consider the associated changes in Gibbs free energy ($\Delta_{mic}G$) and entropy ($\Delta_{mic}S$) that accompany the process. Using isothermal calorimetry the standard free energy of micelle formation per mole of monomer ($\Delta_{mic}G$) can be calculated using equation (1) where m/n is a fraction of the charge of the surfactant ions, also known as the counterion binding constant [3].

$$\Delta_{mic}G = RT(1 + m/n)\ln X_{CMC}. \quad (1)$$

From this, the change in entropy upon micellisation (ΔS_{mic}) can be calculated for any temperature under investigation using equation (2).

$$\Delta_{mic}G = \Delta_{mic}H - T\Delta_{mic}S. \quad (2)$$

Variations in the CMC for selected surfactants have been determined in mixed systems, for example for alcohol/surfactant mixed micelles. In such cases it has been found that as a function of increasing temperature there is a clear shift in the direction of decreasing enthalpy for the formation of micelles. However, as a function of increasing alcohol concentration, the enthalpic values obtained using two separate methods are not comparable [4]. Not all studies have focused on the use of SDS based surfactants, for example, in the same year results were published for other surfactants as a function of temperature, determining values for the CMC, ΔH_{mic}, ΔG_{mic} and ΔS_{mic} [5]. At T = 292 K, the CMC for one surfactant was at a minimum of 7.8 mM, and the demicellisation enthalpy (*i.e.* the opposite of the micellisation enthalpy) was reportedly $-2.4\ kJ \cdot mol^{-1}$. Interestingly, the change in entropy upon demicellisation was always negative and increased with increasing temperature. Work presented in the current study

* Corresponding author. Tel.: +44 1484 472190.
E-mail address: l.waters@hud.ac.uk (L.J. Waters).

http://dx.doi.org/10.1016/j.jct.2014.05.004
0021-9614/

includes two surfactants, namely sodium dodecyl sulfate (SDS) and sodium deoxycholate (NaDC), both of which have reported values for their CMC and thermodynamic profiles [5]. As a comparison, the former generally has a greater CMC value (yet a similar thermodynamic profile) than the latter. Sodium deoxycholate is used in pharmaceutical formulations to solubilise poorly soluble molecules and is known to form micelles and mixed micelle systems such as with Tweens [6]. The aggregation behaviour of NaDC has been reported with CMC values in the range 5.3 to 10.5 [7–11] with a clear temperature dependence. From a thermodynamic perspective, several values have been reported for the enthalpy of micellisation, for example, from $-0.5\ \mathrm{kJ \cdot mol^{-1}}$ at $T = 298\ \mathrm{K}$ to $-3.0\ \mathrm{kJ \cdot mol^{-1}}$ at $T = 308\ \mathrm{K}$ [12]. No such studies have been conducted prior to this work regarding the effect of additional compounds on the values obtained for these two particular micelles, with respect to their CMC values and thermodynamic profiles.

Limited previous work has investigated isothermal titration calorimetric studies on the interaction between SDS and polyethylene glycols (PEGs) and the consequences on micellar properties. Unusual profiles have been attributed to the structural reorganisation of SDS/PEG aggregates with the effect observed at a critical PEG molar mass with subsequent influences on the binding isotherms [13]. This 'peculiar' behaviour includes endothermic and exothermic effects, including the binding of multiple micellar clusters on single polymeric chains [14]. Furthermore, increasing the polymeric concentrations can cause the polymer saturation concentration, C_2, and CMC to increase although the concentration of those bound to polymer does not vary [15].

For some surfactant based systems, not only can the presence of a second compound, such as PEG, affect aggregation but the micelles themselves are known to form a wide variety of assemblies ranging from rodlike structures, bilayers and even cubic phases [16]. It is for this reason that caution should be observed, particularly in the case of NaDC, where a primary aggregation phenomenon has been reported at a concentration not much lower than the main CMC [9]. Furthermore, even the drugs themselves are potentially capable of self-aggregating which has been previously observed for similar compounds [17].

In summary, few scientific data have been reported concerning the effects of the presence of both PEG and model drugs on the micellisation of either SDS or NaDC. This is of particular value if such systems are to be employed to help solubilise pharmaceutical compounds.

TABLE 1
Suppliers and mass fraction stated purity (by supplier) of chemicals used in this study.

Component	Supplier	Mass fraction purity
Sodium dodecyl sulfate	Sigma Aldrich	>0.99
Caffeine	Fisher Scientific	>0.99
Diprophylline	Acros Organics	>0.99
Etofylline	TCI	>0.99
Paracetamol	Sigma Aldrich	>0.99
Polyethylene glycol 6000	Sigma Aldrich	>0.99
Sodium deoxycholate	Fisher Scientific	>0.99
Theophylline	TCI	>0.99

2. Experimental

A Microcal calorimetric unit (ITC) linked to a Microcal MCS observer was employed for all experiments with data analysed using Origin 8.5 software. All chemicals were used as purchased with a minimum mass fraction purity of 0.99, as stated in table 1.

Stock solutions of the model drugs $(60.0 \pm 0.3)\ \mathrm{mmol \cdot kg^{-1}}$ for paracetamol, $(20.0 \pm 0.2)\ \mathrm{mmol \cdot kg^{-1}}$ for the other drugs were prepared by weighing the appropriate mass of the material on a 5-figure balance (Sartorius, 0.01 mg sensitivity, tolerance ± 0.01 mg) and dissolving in 100 mL of deionised (Grade A 100 mL volumetric flask, tolerance ± 0.1 mL). Solutions of $(200.0 \pm 0.3)\ \mathrm{mmol \cdot kg^{-1}}$ SDS and $(50.0 \pm 0.3)\ \mathrm{mmol \cdot kg^{-1}}$ NaDC were prepared in a similar manner. A 0.02 ± 0.002 mmol/kg stock solution of PEG was produced by preparing 100 mL of a $(20 \pm 0.3)\ \mathrm{mmol \cdot kg^{-1}}$ solution and diluting 10 mL of this up to a 1000 mL (Grade A 1000 mL volumetric flask, tolerance ± 1.0 mL).

The sample cell comprised of an aqueous solution and, where appropriate, a solution of the model drug and/or PEG. Alongside this was the reference cell which contained deionised water. The 290 μL syringe contained either SDS or NaDC and was stirred at 307 rpm. Experiments were conducted at three temperatures (298.2, 304.2 and 310.2 (±0.05)) K, all in triplicate to ensure reproducibility. Data were analysed to determine the critical micellar concentration (CMC) and enthalpy of micellisation ($\Delta_{mic}H$) with equations (1) and (2) employed to determine the associated changes in Gibbs free energy ($\Delta_{mic}G$) and entropy ($\Delta_{mic}S$), respectively.

TABLE 2
Critical micellar concentrations and thermodynamic values associated with the aqueous micellisation of SDS in the presence of five model compounds at temperatures (298.2, 304.2 and 310.2 (±0.05)) K (expanded from previous studies [2] at atmospheric pressure 0.1 MPa). The expanded uncertainty (0.95 confidence) is indicated for each value.

T/K (±0.05)	Sample cell composition	SDS CMC/mmol · kg^{-1}	$\Delta_{mic}H°$/(kJ · mol^{-1})	$\Delta_{mic}G°$/(kJ · mol^{-1})	$T\Delta_{mic}S°$/(kJ · mol^{-1})
298.2	No drug present (*i.e.* water only)	7.9 (±0.34)	−20.4 (±1.30)	−38.0 (±0.34)	17.6 (±0.2)
	Caffeine (20 mmol · kg^{-1})	7.9 (±0.02)	−29.7 (±1.80)	−38.0 (±0.02)	8.3 (±0.1)
	Diprophylline (20 mmol · kg^{-1})	8.3 (±0.01)	−12.1 (±0.60)	−37.8 (±0.01)	25.7 (±0.4)
	Etofylline (20 mmol · kg^{-1})	8.3 (±0.02)	−11.9 (±0.80)	−37.8 (±0.02)	25.9 (±0.1)
	Paracetamol (60 mmol · kg^{-1})	7.6 (±0.01)	−40.9 (±0.50)	−42.2 (±0.04)	1.3 (±0.2)
	Theophylline (20 mmol · kg^{-1})	7.9 (±0.01)	−7.8 (±0.20)	−38.0 (±0.01)	30.2 (±0.4)
304.2	No drug present (*i.e.* water only)	8.3 (±0.001)	−10.1 (±0.01)	−38.6 (±0.001)	28.5 (±0.3)
	Caffeine (20 mmol · kg^{-1})	7.3 (±0.001)	−10.5 (±0.24)	−39.1 (±0.001)	28.6 (±0.2)
	Diprophylline (20 mmol/kg)	8.4 (±0.24)	−11.1 (±1.54)	−38.5 (±0.24)	27.5 (±0.3)
	Etofylline (20 mmol · kg^{-1})	8.4 (±0.24)	−10.3 (±0.40)	−38.5 (±0.24)	28.2 (±0.2)
	Paracetamol (60 mmol · kg^{-1})	6.9 (±0.001)	−10.6 (±0.30)	−39.3 (±0.001)	28.7 (±0.3)
	Theophylline (20 mmol · kg^{-1})	7.6 (±0.001)	−10.6 (±0.20)	−38.9 (±0.001)	28.4 (±0.5)
310.2	No drug present (*i.e.* water only)	8.9 (±0.20)	−20.7 (±1.10)	−39.0 (±0.20)	18.3 (±0.1)
	Caffeine (20 mmol · kg^{-1})	7.9 (±0.01)	−29.1 (±1.60)	−39.5 (±0.01)	10.4 (±0.1)
	Diprophylline (20 mmol · kg^{-1})	8.3 (±0.20)	−12.3 (±0.90)	−39.3 (±0.20)	27.0 (±0.1)
	Etofylline (20 mmol · kg^{-1})	7.8 (±0.20)	−12.6 (±0.50)	−39.6 (±0.20)	26.3 (±0.6)
	Paracetamol (60 mmol · kg^{-1})	8.2 (±0.20)	−16.6 (±1.40)	−39.4 (±0.20)	22.7 (±0.4)
	Theophylline (20 mmol · kg^{-1})	8.3 (±0.01)	−28.4 (±0.70)	−39.3 (±0.01)	10.9 (±0.1)