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

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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 298.2, 304.2 and 310.2 K. From these data, thermodynamic parameters associated with the micellisation process (ΔG_{mic}, ΔH_{mic} and ΔS_{mic}) 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.

Keywords: calorimetry; ITC; micelles; drugs; PEG; CMC; NaDC

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 (ΔH_{mic}) 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 (ΔG_{mic}) and entropy (ΔS_{mic}) that accompany the process. Using isothermal calorimetry the standard free energy of micelle formation per mole of monomer (ΔG_{mic}) 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].

$$\Delta G_{mic} = RT(1+m/n)\ln X_{CMC} \quad (1)$$

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

$$\Delta G_{mic} = \Delta H_{mic} - T\Delta S_{mic} \quad (2)$$

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 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/mol. Interestingly, the change in entropy upon demicellisation was always negative and increased with increasing temperature. Work presented in the current study 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; 8; 9; 10; 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 kJ/mol at 298 K to -3.0 kJ/mol at 308 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 molecular weight 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, little scientific data has 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.

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 purity of 99 %, as stated in Table 1.

TABLE 1

Suppliers and stated purities (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

Stock solutions of the model drugs (60.0 ± 0.3 mmol/kg for paracetamol, 20.0 ± 0.2 mmol/kg for the other drugs) were prepared by by weighing the appropriate mass of the material on a 5-figure balance (Sartorius, 0.01 mg sensitivity, tolerance ± 0.01mg) and dissolving in 100 mL of deionised (Grade A 100 mL volumetric flask, tolerance ± 0.1 mL). Solutions of 200.0 ± 0.3 mmol/kg SDS and 50.0 ± 0.3 mmol/kg 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 ± 0.3 mmol/kg 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 deionized 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 K (±0.05)), all in triplicate to ensure reproducibility. Data was analysed to determine the critical micellar concentration (CMC) and enthalpy of micellisation (ΔH_{mic}) with Equation 1 and 2 employed to determine the associated changes in Gibbs free energy (ΔG_{mic}) and entropy (ΔS_{mic}), respectively.

3. Results & Discussion

3.1 Factors affecting the micellisation of SDS

Previous studies by the author have confirmed the influence the presence of additional compounds can have on the micellisation of SDS, affecting both the CMC and enthalpy of micellisation[2]. This data has now been expanded, through the application of Equation 1 and 2, to explore a full thermodynamic profile for the micellisation of SDS in the presence of five model compounds at three specific temperatures to obtain the values displayed in Table 2.

TABLE 2

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

Temp. / (K) (±0.05)	**Sample Cell Composition**	**SDS CMC/mmol/kg**	**ΔH°_{mic} /(KJ.mol^{-1})**	**ΔG°_{mic} /(KJ.mol^{-1})**	**$T\Delta S^{\circ}_{mic}$ /(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)	7.9 (± 0.02)	-29.7 (± 1.80)	-38.0 (± 0.02)	8.3 (± 0.1)
	diprophylline (20 mmol/kg)	8.3 (± 0.01)	-12.1 (± 0.60)	-37.8 (± 0.01)	25.7 (± 0.4)
	etofylline (20 mmol/kg)	8.3 (± 0.02)	-11.9 (± 0.80)	-37.8 (± 0.02)	25.9 (± 0.1)
	paracetamol (60	7.6 (± 0.01)	-40.9 (± 0.50)	-42.2 (± 0.04)	1.3 (± 0.2)

	mmol/kg)				
	theophylline (20 mmol/kg)	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)	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)	8.4 (± 0.24)	-10.3 (± 0.40)	-38.5 (± 0.24)	28.2 (± 0.2)
	paracetamol (60 mmol/kg)	6.9 (± 0.001)	-10.6 (± 0.30)	-39.3 (± 0.001)	28.7 (± 0.3)
	theophylline (20 mmol/kg)	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)	7.9 (± 0.01)	-29.1 (± 1.60)	-39.5 (± 0.01)	10.4 (± 0.1)
	diprophylline (20 mmol/kg)	8.3 (± 0.20)	-12.3 (± 0.90)	-39.3 (± 0.20)	27.0 (± 0.1)
	etofylline (20 mmol/kg)	7.8 (± 0.20)	-12.6 (± 0.50)	-39.6 (± 0.20)	26.3 (± 0.6)
	paracetamol (60 mmol/kg)	8.2 (± 0.20)	-16.6 (± 1.40)	-39.4 (± 0.20)	22.7 (± 0.4)
	theophylline (20 mmol/kg)	8.3 (± 0.01)	-28.4 (± 0.70)	-39.3 (± 0.01)	10.9 (± 0.1)

Table 2 considers aggregation data with the incorporation of thermodynamic data for SDS. At all three temperatures and in the absence, or presence of all five model drugs, there is little influence on the change in Gibbs free energy observed. These findings imply that the overall energetics behind the aggregation phenomenon are not significantly altered by temperature or drugs, in agreement with the lack of change in the concentration at which it occurs. Interestingly, more substantial changes in the change in enthalpy and entropy for the micellisation event were observed implying an entropy-enthalpy compensation phenomenon. In general, a similar pattern of results was found to that previously published[2] in that structurally similar compounds produced similar thermodynamic profiles yet the most structurally dissimilar compound (paracetamol) displayed a rather different profile, particularly the change in entropy and enthalpy at 298.2 K.

To further investigate the effects additional compounds may have on the micellisation event, a second compound was added to the system in the presence of each model drug in turn, namely PEG.

Previous work has implied that the interaction between SDS and PEG is dependent upon the molecular weight of the PEG and known to be thermodynamically 'peculiar' exhibiting both endothermic and exothermic effects[15]. Our titration calorimetry results appeared to follow this expectation, as exemplified in Figure 1 for the micellisation of SDS in the presence of PEG whereby the first derivative of the titration curve corresponds to the CMC of SDS whilst the second broad inflection can be attributed to the PEG-SDS interaction (Figure 1).

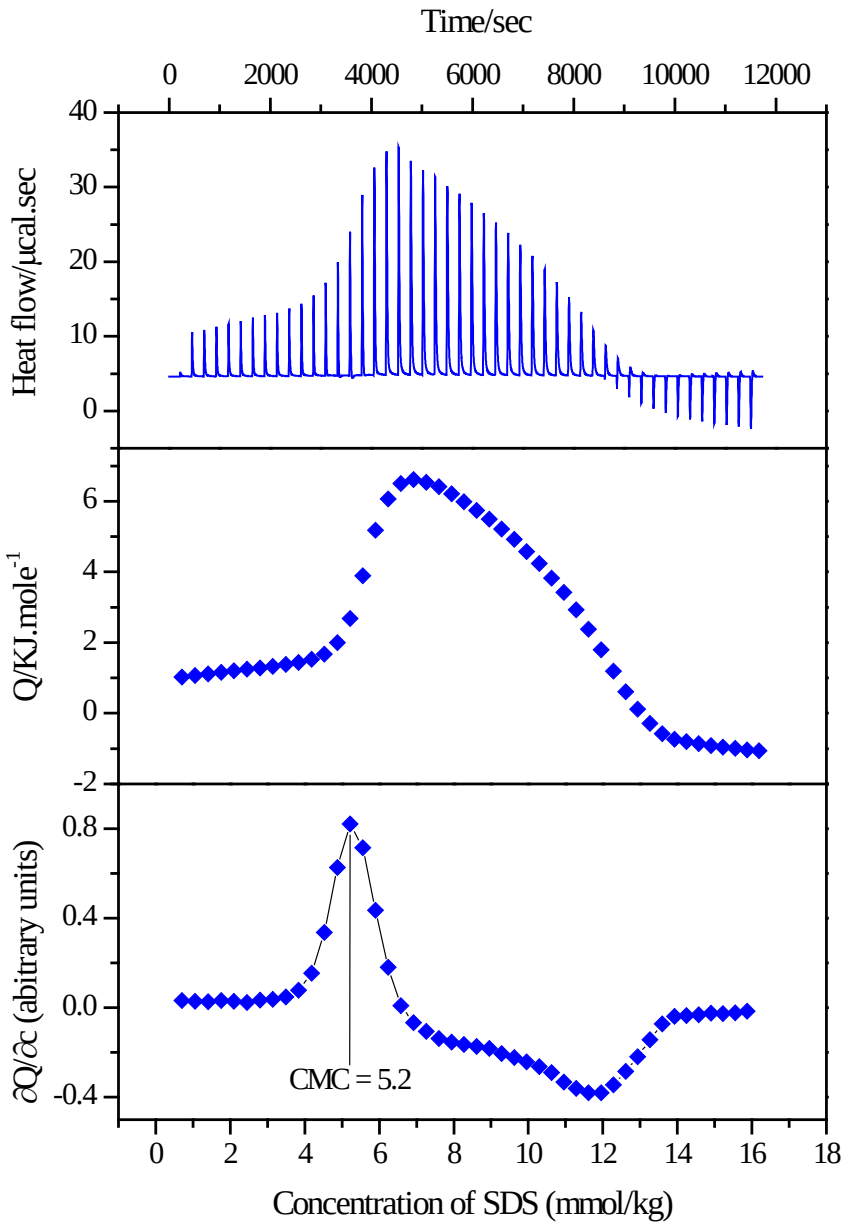

FIGURE 1. Raw ITC data and subsequent data analysis to determine the CMC of SDS in the presence of 0.2 mmol/kg PEG-6000 at T = 298.2 (±0.05) K.

A summary of the CMC values and associated thermodynamic behaviour for SDS in the presence of PEG for all five systems studied at the three temperatures can be seen in Table 3. Whereas Table 2 indicates a significant variation in some data based on the structure of the drug, this phenomenon does not appear to occur in the presence of PEG in Table 3. For example, data for paracetamol compares well with the remaining four drugs.

TABLE 3

Critical micellar concentrations and thermodynamic values associated with the aqueous micellisation of SDS in the presence of 0.2 mmol/kg PEG and five model compounds at 298.2, 304.2 and 310.2 (±0.05) K at atmospheric pressure. The expanded uncertainty (0.95 confidence) is indicated for each value.

Temp. /(K) (±0.05)	**Sample Cell Composition (0.2 mmol/kg PEG and ...)**	**SDS CMC/mmol/kg**	**$\Delta^{\circ}H_{mic}$ /(KJ.mol^{-1})**	**$\Delta^{\circ}G_{mic}$ /(KJ.mol^{-1})**	**$T\Delta^{\circ}S_{mic}$ / (KJ.mol^{-1})**
298.2	no drug present (i.e. water and PEG only)	5.2 (± 0.20)	-11.3 (± 0.20)	-39.6 (± 0.10)	28.4 (± 0.1)
	caffeine (20 mmol/kg)	5.5 (± 0.01)	-10.8 (± 0.40)	-39.5 (± 0.001)	28.7 (± 0.4)
	diprophylline (20 mmol/kg)	5.5 (± 0.01)	-10.0 (± 0.90)	-39.5 (± 0.08)	29.5 (± 0.9)
	etofylline (20 mmol/kg)	5.3 (± 0.40)	-11.0 (± 0.20)	-39.7 (± 0.42)	28.7 (± 0.6)
	paracetamol (60 mmol/kg)	4.5 (± 0.12)	-11.7 (± 0.04)	-40.5 (± 0.12)	28.7 (± 0.1)
	theophylline (20 mmol/kg)	5.4 (± 0.26)	-11.0 (± 0.10)	-39.6 (± 0.22)	28.6 (± 0.2)
304.2	no drug present (i.e. water and PEG only)	4.7 (± 0.30)	-7.9 (± 0.20)	-41.0 (± 0.30)	33.1 (± 0.4)
	caffeine (20 mmol/kg)	4.9 (± 0.20)	-8.5 (± 0.10)	-40.8 (± 0.06)	32.3 (± 0.1)
	diprophylline (20 mmol/kg)	5.1 (± 0.17)	-8.1 (± 0.20)	-40.6 (± 0.15)	32.6 (± 0.2)
	etofylline (20 mmol/kg)	5.1 (± 0.20)	-8.3 (± 0.01)	-40.7 (± 0.20)	32.4 (± 0.2)
	paracetamol (60 mmol/kg)	4.0 (± 0.12)	-8.6 (± 0.04)	-41.8 (± 0.47)	32.3 (± 0.4)
	theophylline (20 mmol/kg)	4.7 (± 0.27)	-8.5 (± 0.10)	-40.7 (± 0.32)	32.1 (± 0.3)
310.2	no drug present (i.e. water and PEG only)	4.3 (± 0.20)	-10.3 (± 0.20)	-42.2 (± 0.20)	31.9 (± 0.1)
	caffeine (20 mmol/kg)	4.4 (± 0.40)	-10.7 (± 0.10)	-42.1 (± 0.40)	31.4 (± 0.5)
	diprophylline (20 mmol/kg)	4.7 (± 0.27)	-10.7 (± 0.01)	-41.8 (± 0.27)	31.2 (± 0.3)
	etofylline (20 mmol/kg)	4.4 (± 0.24)	-10.7 (± 0.10)	-42.2 (± 0.25)	31.5 (± 0.3)
	paracetamol (60 mmol/kg)	3.1 (± 0.01)	-11.0 (± 0.01)	-43.6 (± 0.15)	32.6 (± 0.2)

	theophylline (20 mmol/kg)	4.4 (± 0.20)	-10.4 (± 0.30)	-42.1 (± 0.20)	31.8 (± 0.2)

For SDS and PEG based systems, the addition of PEG reduced the CMC in all cases with this phenomenon becoming more apparent as the temperature increased (highlighted in Figure 2).

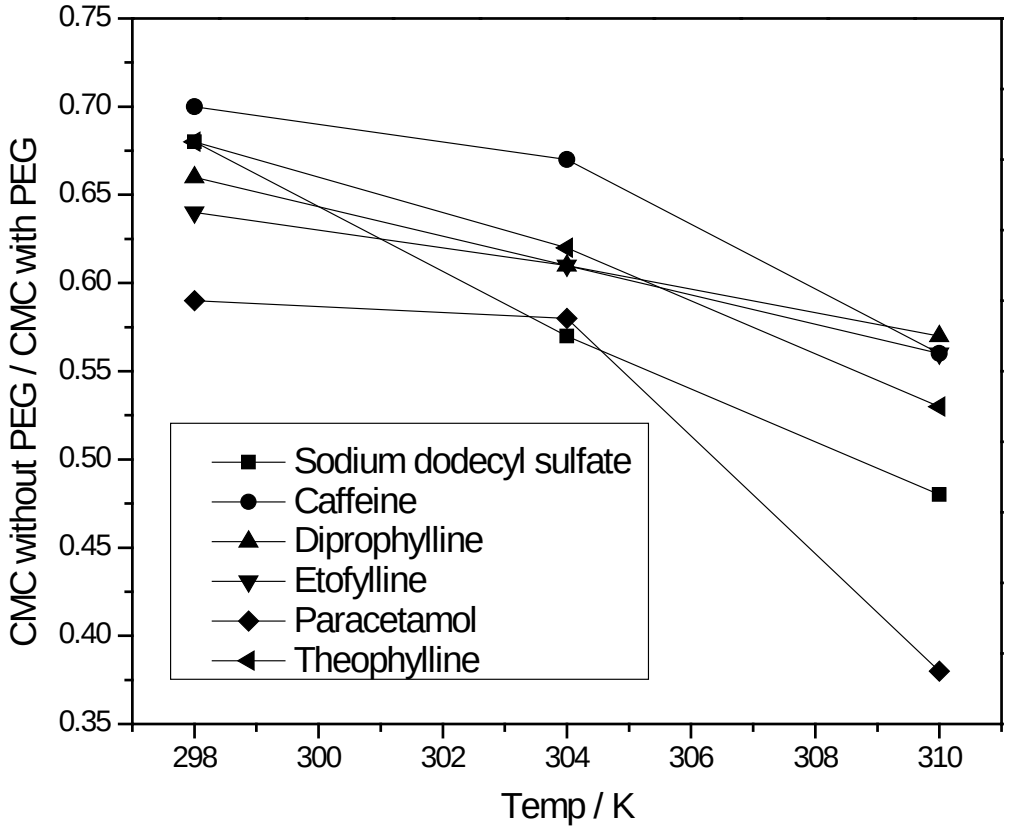

FIGURE 2. The effect upon micellisation of SDS in the presence of 0.2 mmol/kg PEG and five model compounds.

Figure 2 exemplifies how the presence of PEG encouraged the micellisation process at lower concentrations with values for the CMC with PEG/without PEG all below 1. Although PEG is known to self-aggregate under certain conditions[18], it is not believed to be the process being observed in these studies with the use of low concentrations (0.2 mmol/kg) and a high molecular weight PEG. A more

plausible explanation is the observance of hydrophobic interactions between SDS and PEG leading to the formation of a stable complex, similar to that previously reported in literature[19].

3.2 Factors affecting the micellisation of NaDC

Sodium deoxycholate (NaDC) is a more complex surfactant than SDS, with published data often referring to a second aggregation event, similar in concentration to that for the main micellisation[9]. The ITC thermogram for NaDC, especially in the presence of PEG or drugs, cannot be determined directly as no clear break point in the heat (Q) versus concentration was observed leading to inaccurate CMC and ΔH_{mic} values. In such cases, curve analysis was used to determine the concentrations corresponding to the start (ST: start of transition) and to the end (ET: end of transition) of the micellisation process[20; 21]. This phenomenon is explained in Figure 3, the linear fitting of the data in the lower and the upper concentration domains provided the inflection point, corresponding to the CMC of NaDC alone and in the presence of PEG (Figure 3). The data points for the determination of the ST and the ET remained approximate using this method. A systematic thermodynamic study was undertaken for NaDC (with the same five compounds as SDS) presented in Table 4.

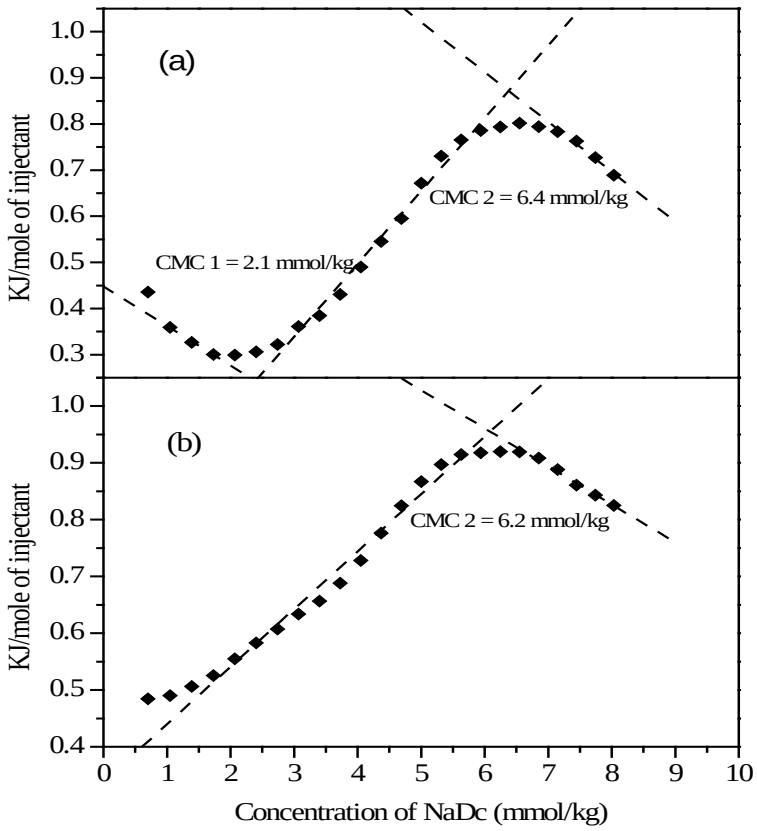

FIGURE 3. Integrated ITC heat data highlighting the micellisation point of (a) NaDC alone (CMC 1 and 2) and (b) in the presence of 0.2 mmol/kg PEG at 298.2 (±0.05) K.

TABLE 4

Critical micellar concentrations and thermodynamic values associated with the aqueous micellisation of NaDC in the presence of five model compounds at 298.2, 304.2 and 310.2 (±0.05) K at atmospheric pressure. The expanded uncertainty (0.95 confidence) is indicated for each value.

Temp. /(K) (±0.05)	**Sample Cell Composition**	**SDS CMC/mmol/ kg**	**$\Delta^{\circ}H_{mic}$ /(KJ.mol^{-1})**	**$\Delta^{\circ}G_{mic}$ /(KJ.mol^{-1})**	**$T\Delta^{\circ}S_{mic}$ /(KJ.mol^{-1})**
298.2	no drug present (i.e. water only)	2.1 (± 0.23), 6.4 (± 0.17)	-1.6 (± 0.05), 1.7 (± 0.01)	-33.0 (± 0.39), 29.2 (± 0.08)	31.5 (± 0.3), 27.5 (± 0.1)
	caffeine (20 mmol/kg)	5.4 (± 0.17)	-1.6 (± 0.04)	-30.1 (± 0.63)	28.1 (± 0.1)

	diprophylline (20 mmol/kg)	6 (± 0.17)	-1.6 (± 0.01)	-29.4 (± 0.08)	27.8 (± 0.1)
	etofylline (20 mmol/kg)	6.0 (± 0.18)	-1.5 (± 0.12)	-29.0 (± 0.09)	27.9 (± 0.1)
	paracetamol (60 mmol/kg)	3.9 (± 0.20)	1.8 (± 0.02)	-30.8 (± 0.14)	32.6 (± 0.2)
	theophylline (20 mmol/kg)	6.2 (± 0.52)	-1.7 (± 0.01)	-29.3 (± 0.26)	27.7 (± 0.3)
304.2	no drug present (i.e. water only)	1.6 (± 0.17), 5.1 (± 0.17)	-1.1 (± 0.12), 1.4 (± 0.02)	-34.4 (± 0.37), -30.6 (± 0.11)	33.3 (± 0.2) 29.2 (± 0.1)
	caffeine (20 mmol/kg)	4.5 (± 0.40)	-1.3 (± 0.06)	-31.2 (± 0.33)	29.7 (± 0.4)
	diprophylline (20 mmol/kg)	4.6 (± 0.17)	-1.0 (± 0.05)	-30.9 (± 0.12)	29.9 (± 0.1)
	etofylline (20 mmol/kg)	4.4 (± 0.19)	-1.1 (± 0.25)	-30.8 (± 0.12)	30.0 (± 0.2)
	paracetamol (60 mmol/kg)	3.5 (± 0.35)	-1.3 (± 0.02)	-31.8 (± 0.32)	30.5 (± 0.3)
	theophylline (20 mmol/kg)	4.8 (± 0.35)	-1.4 (± 0.02)	-30.8 (± 0.24)	29.4 (± 0.2)
310.2	no drug present (i.e. water only)	4.3 (± 0.23)	-1.3 (± 0.01)	-31.8 (± 0.17)	30.5 (± 0.2)
	caffeine (20 mmol/kg)	4.1 (± 0.51)	-1.1 (± 0.02)	-31.2 (± 1.22)	30.7 (± 0.4)
	diprophylline (20 mmol/kg)	4.2 (± 0.40)	-1.0 (± 0.05)	-31.9 (± 0.33)	30.8 (± 0.4)
	etofylline (20 mmol/kg)	4.0 (± 0.35)	-1.1 (± 0.17)	-32.0 (± 0.29)	30.9 (± 0.5)
	paracetamol (60 mmol/kg)	3.4 (± 0.57)	-1.2 (± 0.02)	-32.6 (± 0.60)	31.4 (± 0.6)
	theophylline (20 mmol/kg)	4.2 (± 0.51)	-1.2 (± 0.02)	-31.5 (± 0.38)	30.3 (± 0.4)

The observed CMC for NaDC appeared slightly lower than some published values[11], yet unlike SDS, was significantly affected by the presence of the drugs. Most notably, of the five drugs considered, paracetamol dramatically reduced the CMC, for example from 4.3 mmol/kg to 3.4 mmol/kg at 310.2 K. This finding suggests the drugs encourage the formation of micelles as in all cases the CMC in the presence of drugs was less than that in water alone. This finding can be seen at all three temperatures studied. Unlike SDS, little variation in the change in enthalpy and entropy can be seen in Table 4 (with the exception of the change in enthalpy for paracetamol at 298.2 K) and a consistent value for the change in Gibbs free energy was also found. Such consistency implies that although the CMC may have decreased to varying extents, the thermodynamics of the process has not altered. A comparison of Table 2 with Table 4 highlights the change in enthalpy change between the two surfactants, with a smaller modification to the remaining thermodynamic parameters.

As with SDS, the effect of the presence of PEG on the micellisation event was monitored for NaDC, as shown in Table 5.

TABLE 5

Critical micellar concentrations and thermodynamic values associated with the aqueous micellisation of NaDC in the presence of 0.2 mmol/kg PEG and five model compounds at 298.2, 304.2 and 310.2 (±0.05) K at atmospheric pressure. The expanded uncertainty (0.95 confidence) is indicated for each value.

Temp. /(K) (±0.05)	**Sample Cell Composition (0.2 mmol/kg PEG and ...)**	**SDS CMC/mmol/kg**	**$\Delta^{\circ}H_{mic}$ /(KJ.mol^{-1})**	**$\Delta^{\circ}G_{mic}$ /(KJ.mol^{-1})**	**$T\Delta^{\circ}S_{mic}$ /(KJ.mol^{-1})**
298.2	no drug present (i.e. water and PEG only)	6.2 (± 0.30)	-1.8 (± 0.05)	-29.3 (± 0.15)	27.6 (± 0.2)
	caffeine (20 mmol/kg)	5.1 (± 0.17)	-1.6 (± 0.02)	-30.3 (± 0.46)	28.3 (± 0.1)
	diprophylline (20 mmol/kg)	5.8 (± 0.17)	-1.6 (± 0.02)	-29.5 (± 0.10)	27.9 (± 0.1)
	etofylline (20 mmol/kg)	5.8 (± 0.17)	-1.5 (± 0.11)	-29.5 (± 0.98)	28.0 (± 0.2)
	paracetamol (60 mmol/kg)	3.7 (± 0.30)	1.7 (± 0.55)	-31.0 (± 0.26)	32.8 (± 0.3)
	theophylline (20 mmol/kg)	6.1 (± 0.34)	-1.7 (± 0.02)	-29.4 (± 0.17)	27.7 (± 0.2)
304.2	no drug present (i.e. water and PEG only)	4.9 (± 0.17)	-1.3 (± 0.02)	-30.7 (± 0.11)	29.4 (± 0.1)
	caffeine (20 mmol/kg)	4.4 (± 0.35)	-1.3 (± 0.04)	-31.4 (± 0.31)	29.8 (± 0.3)
	diprophylline (20 mmol/kg)	4.4 (± 0.35)	-1.0 (± 0.08)	-30.7 (± 0.34)	30.1 (± 0.3)
	etofylline (20 mmol/kg)	4.3 (± 0.23)	-1.1 (± 0.83)	-31.1 (± 0.18)	30.1 (± 0.1)
	paracetamol (60 mmol/kg)	3.4 (± 0.57)	-1.3 (± 0.01)	-32.0 (± 0.59)	30.6 (± 0.6)
	theophylline (20 mmol/kg)	4.7 (± 0.57)	-1.4 (± 0.10)	-30.5 (± 0.16)	29.5 (± 0.4)
310.2	no drug present (i.e. water and PEG only)	4.2 (± 0.35)	-1.2 (± 0.04)	-31.3 (± 1.32)	30.8 (± 0.3)
	caffeine (20 mmol/kg)	3.8 (± 0.51)	-1.2 (± 0.08)	-31.4 (± 1.70)	31.0 (± 0.5)
	diprophylline (20 mmol/kg)	4.1 (± 0.57)	-0.9 (± 0.06)	-31.9 (± 0.49)	31.0 (± 0.5)
	etofylline (20 mmol/kg)	3.9 (± 0.50)	-1.0 (± 0.13)	-32.1 (± 0.43)	31.0 (± 0.6)
	paracetamol (60 mmol/kg)	3.3 (± 0.75)	-1.2 (± 0.02)	-32.7 (± 0.84)	31.5 (± 0.85)
	theophylline (20 mmol/kg)	4.1 (± 0.40)	-1.2 (± 0.40)	-31.6 (± 0.31)	30.4 (± 0.3)

Little variation in the CMC of NaDC was observed with the additional presence of 0.2 mmol/kg PEG and the five model compounds again, with the exception of paracetamol. Similarly, the thermodynamics of the micellisation process did not dramatically alter with the addition of PEG. This finding is in contrast to that for SDS where PEG was found to be influential in the micellisation concentration and change in enthalpy associated with the process. This finding implies there is little, or no, interaction between NaDC and PEG to encourage the formation of micelles as was previously seen for SDS.

4. Conclusions

In summary, the influence of five model drugs on the micellisation phenomenon indicates there is little interaction between the drugs and SDS yet there is a more favourable interaction between the drugs and NaDC. In contrast, the presence of PEG appeared to encourage micellisation for SDS yet not for NaDC. These differences can be attributed to their subtle differing functionality as they are generally similar in that they are both anionic surfactants containing hydrophobic and hydrophilic sections. This work highlights the impact such small differences can have on their behaviour in solution.

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