Thermodynamics of Micelle Formation

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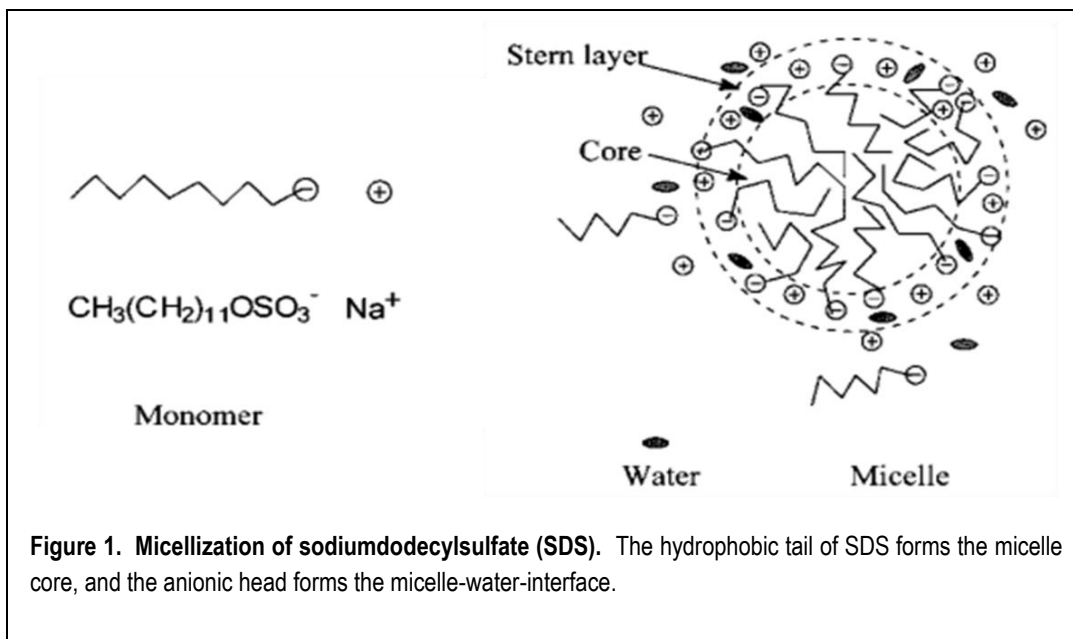
Abstract

Micelles are organized molecular assemblies of surfactants. In aqueous solution, the hydrophilic head of the surfactant is in contact with solvent, and the hydrophobic tail is sequestered within the center of the micelle. Micelles are usually spherical in shape, and can be cationic, anionic, ampholitic (zwitterionic), or nonionic depending on the chemical structure of the surfactant. Knowledge of the micellar phases of naturally occurring molecules or drugs is essential for determining how they may influence biological events. Mixed micelle formations that include amphipathic drug molecules, may result in decreased biological activity, and hence decreased therapeutic response. The propensity of drug molecules to aggregate is of great biological importance, and identifying the chemical details of the aggregation process could enhance control of micelle-encapsulated drugs. Enthalpies of micelle formation and critical micelle concentration were determined with isothermal titration calorimetry (ITC) for two model micelle systems, sodiumdodecylsulphate (SDS) and cetyltrimethylammonium bromide (CTAB).

Introduction

Surfactants, sometimes called surface-active agents or detergents, are extremely versatile chemicals with applications in chemistry, biology, and pharmaceutical science [1]. Surfactants contain both a non-polar long-chain hydrocarbon "tail" and a polar "head" group. This amphiphilic character of surfactants allows for self-association or micellization, whereby the hydrophobic portion forms the micelle core and the polar head groups form the micelle-water-interface (Fig. 1).

The critical micelle concentration (CMC) is the concentration of surfactant above which a surfactant aggregates into micelles [2]. Thus, the CMC represents a phase separation between single molecules of surfactant and surfactant aggregates in dynamic equilibrium [3].

Figure 1. Micellization of sodiumdodecylsulfate (SDS). The hydrophobic tail of SDS forms the micelle core, and the anionic head forms the micelle-water-interface.

Understanding micelle behaviour in biological systems is important because the state of aggregation or micelle phase of naturally occurring molecules, drug molecules or added surfactant may influence the biological effects [4]. Many drug molecules have a propensity to aggregate knowing the chemical details of these aggregation processes could allow for precise control of drug transport across polymer membranes in the form of microcapsules or implant-capsules [5]. Stable micelle systems have remained elusive; however, through the determination of micelle formation constants and the enthalpy associated with drug-micelle interaction, it is possible to improve and obtain more stable systems and increase biological activity and availability of a drug. Titration calorimetry is a reliable, simple and rapid technique for obtaining the enthalpy, entropy, heat capacity and equilibria changes that accompany micelle formation. In combination with structural data, knowledge of the underlying thermodynamic process completes the understanding of the chemical and structural details for micellization and allows determination of the mechanism for micelle formation.

Materials and Methods

SDS (sodiumdodecylsulfate) was prepared at 100mM in water, and CTAB (cetyltrimethylammonium bromide) was prepared at 10mM in water. Titration experiments were performed in a Nano ITC (Isothermal Titration Calorimeter) Standard Volume with a gold reaction vessel. The reference cell was filled with water. Each titration experiment consisted of fifty, 5µL injections of surfactant into water at 300-second intervals with a stirring speed of 350 rpm. A 300-second baseline was collected before the first injection

and after the last injection. Prior to starting the titration experiment, the calorimeter was equilibrated to a baseline with a drift of less than 100nW over a ten-minute period.

Temperature stability measurements for SDS were performed in a Nano DSC (Differential Scanning Calorimeter) with a platinum capillary reaction vessel by scanning from 0°C to 100°C at a rate of 1°C/minute at three atmospheres. The reference cell was filled with water and the surfactant sample was degassed for 10 minutes at 400 mmHg prior to experimentation.

Data analysis of ITC data and DSC data was performed with TA Instruments NanoAnalyze™ software. The integrated data points from ITC experiments were fit with Independent- and Blank (linear) or Blank
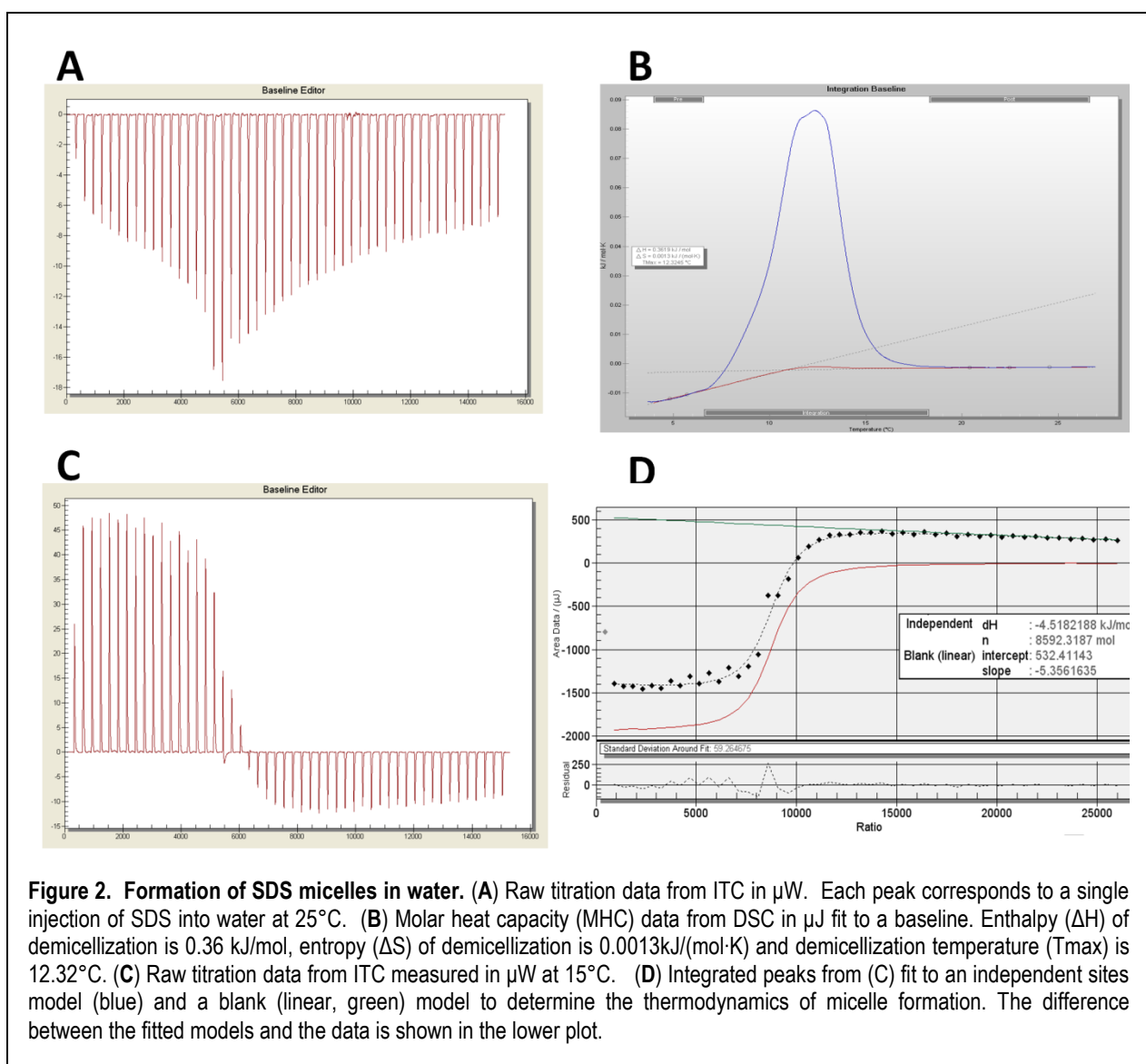

Figure 2. Formation of SDS micelles in water. (**A**) Raw titration data from ITC in µW. Each peak corresponds to a single injection of SDS into water at 25°C. (**B**) Molar heat capacity (MHC) data from DSC in µJ fit to a baseline. Enthalpy (ΔH) of demicellization is 0.36 kJ/mol, entropy (ΔS) of demicellization is 0.0013kJ/(mol·K) and demicellization temperature (Tmax) is 12.32°C. (**C**) Raw titration data from ITC measured in µW at 15°C. (**D**) Integrated peaks from (C) fit to an independent sites model (blue) and a blank (linear, green) model to determine the thermodynamics of micelle formation. The difference between the fitted models and the data is shown in the lower plot.

(constant) models. The peak area from DSC data was analyzed by fitting to a combination, straight (1st order polynomial) and variable (2nd order polynomial), baseline.
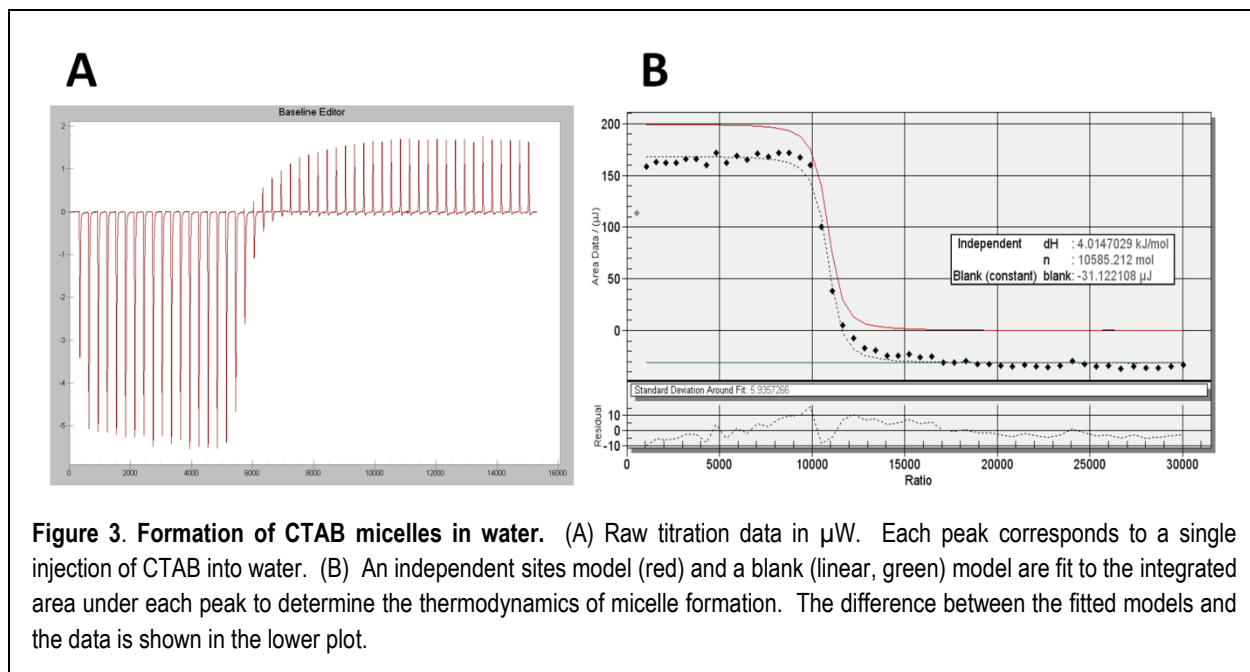
Results

The thermodynamics of micellization as well as the critical micelle concentration (CMC) can be determined in a single titration experiment. To illustrate this, concentrated surfactant solution of two micelle systems, SDS or CTAB, were titrated into aqueous solution in a Nano ITC. At concentrations below the CMC in the reaction vessel the reaction is

> **micelles → monomers**,   (**Reaction 1**)

and at concentrations above the CMC, the reaction is

> **concentrated micelles → dilute micelles**.   (**Reaction 2**)

At 25°C, titration of concentrated SDS into water elicits a titration profile with a peak inflection at 4800 seconds (injection 18) (Fig. 2A). All peaks are endothermic and the heat effects are caused by Reaction 2. Analysis in the NanoDSC (Differential Scanning Calorimeter) indicated a thermal transition from approximately 7°C to 18°C (Fig. 2B). Repeating the titration experiment at 15°C, a temperature that falls within the range of the thermal transition, yields a titration curve consistent with the dissociation of micelles, Reaction 1, up through injection 20 (Fig. 2C). Peaks 1 through 20 are exothermic and peaks 21 to 50 are endothermic.   The exothermic peaks represent the dispersion of the concentrated micelle solution (demicellization) upon titration into water. The peaks become less exothermic as they approach the critical micelle concentration (the midpoint of the inflection).   The integrated area under each peak is plotted

Figure 3. **Formation of CTAB micelles in water.** (A) Raw titration data in µW. Each peak corresponds to a single injection of CTAB into water. (B) An independent sites model (red) and a blank (linear, green) model are fit to the integrated area under each peak to determine the thermodynamics of micelle formation. The difference between the fitted models and the data is shown in the lower plot.

against the injection number (Fig. 2D). The solid lines represent the fit to an independent sites model and blank (linear) fitting model. The standard deviation around the fit of the sum of the models is 59.26 µJ. The blank, due to heat of dilution of titrant, is linear with a slope of -5.36. The CMC is the molar concentration of SDS at the inflection point of the titration-curve, n=8592.13. Analysis of the tabulated data revealed a CMC of 7.8 mM SDS at the inflexion midpoint, and approximates the literature value for the at 25°C (8.2 mM [6]). The enthalpy change of demicellization is -4.52 kJ/mol

To determine the degree with which different surfactants exhibit variable thermodynamic profiles, we performed a titration of CTAB (cetyltrimethylammonium bromide) into aqueous solution. Peaks 1 through 20 are endothermic and peaks 21 to 50 are exothermic (Fig. 3A). This data was unexpected as the titration data is opposite to that seen with SDS. It is not precisely known what accounts for this difference, but one possibility is the cationic charge in the head group of CTAB leads to distinct structural perturbations at the water-micelle-interface compared to SDS, which is anionic.

The integrated area under each peak is plotted against the injection number (Fig. 3B). The solid lines show the fit to an independent sites model and blank (linear) fitting model. The blank, due to heat of dilution, is contant at -31.1 µJ. The standard deviation around the fit of the sum of the models is 5.94 µJ. From the tabulated data, the CMC was 0.95 mM from this titration, which corresponds to the literature value for the CMC of CTAB in water determined by NMR (0.92 mM [7]).

Conclusion

Thermodynamics of micelle formation is essential to better understand how to develop stable micelles for use in pharmaceutical and industrial applications. ITC and DSC are versatile and sensitive techniques that allow simultaneous determination of CMCs, enthalpy changes, entropy changes, stoichiometry, and dissociation temperature. This study provides a proof of concept that can be applied to novel micelle systems. In combination with structural data, knowledge of the thermodynamics could lead to a more complete understanding of micelle dynamics.

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