



Delta-8: Note on solubility and critical micelle concentration

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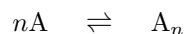
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Overview

Many compounds precipitate at ambient temperature instead of forming micelles. This is particularly common for drug molecules, which in comparison to surfactants, exhibit relatively more polar groups and complex shape that both favor precipitation instead of micelle formation. This note discusses similarities between these phenomena, and highlights some implications that should be considered when making measurements.

Thermodynamic similarities between precipitation and micelle formation

Typically, above the critical micelle concentration (CMC) or the solubility limit the concentration of free compound in solution is constant. This stems from thermodynamic similarities. Consider the following reaction where a molecule A, agglomerates:



where n is the number of molecules in the agglomerate. The equilibrium constant for this reaction is given by:

$$K = \frac{[A_n]}{[A]^n} \quad (1)$$

Typically for micelles n ranges between 10's and 100's, while in the case of precipitation n is unbounded. The larger n becomes, the more the concentration of the monomeric species determines the equilibrium, and consequently micelle formation is commonly considered as a quasi-phase separation.

These simplified arguments are obscured by several factors. The existence of multiple micellar equilibria, corresponding to a range of micelle sizes results in a transition with increasing concentration, however, this is commonly not observed in a surface tension experiment. The precipitation reaction is affected by the so called nucleation barrier, which leads to supersaturation that must be surpassed before the precipitation occurs. This can for some compounds be observed as a rise in surface tension for concentrations above the precipitation point.

Example isotherms and comments

Figure 1 shows an adsorption isotherm of sodium dodecylsulfate (SDS) which forms spherical micelles. The CMC of SDS is seen at ca 6.3 mM.

Figure 2 shows an adsorption isotherm of clomipramine, a tricyclic antidepressant. Clomipramine precipitates at 0.2 mM. Comparing Figure 1 and 2 shows that the solubility limit and the CMC appear in as a similar feature in the adsorption isotherms.

The features of the solubility limit and the CMC observed in surface tension experiments cannot usually be distinguished from each other based on the surface tension vs. concentration data. There are some features that are indicative. The formation of precipitates frequently causes more noise in the data above the solubility limit, since some crystals may interact with the probe. The nucleation barrier can cause a rise in the surface tension above the solubility limit as the concentration passes through a supersaturation before equilibrating at the level determined by the solubility. However, precipitates can be visually observed on the detection plate.

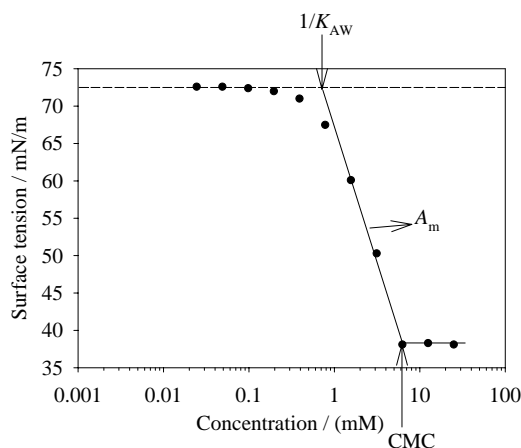


Figure 1: Adsorption isotherm of SDS in water. The critical micelle concentration and air/water partitioning coefficient are determined as shown. The cross-sectional molecular area is determined from the slope

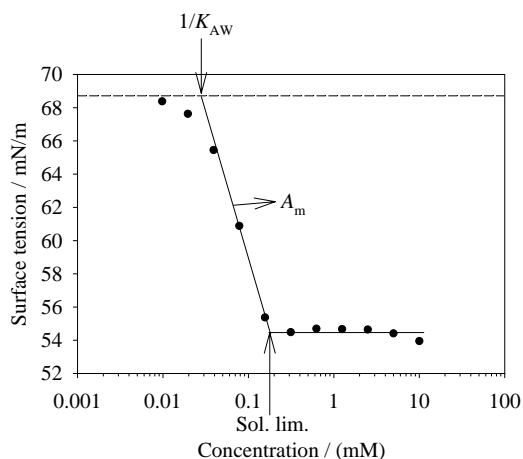


Figure 2: Adsorption isotherm of clomipramine in a TRIS buffer (pH 8). Clomipramine precipitates instead of forming micelles.

Many surfactants precipitate at lower temperatures and forms micelles at higher temperatures. The transition temperature is commonly referred to as the Krafft temperature.

Some pharmaceuticals precipitate before they become significantly surface active, In such cases it can be difficult to determine the air/water partitioning coefficient and the cross-sectional area accurately since the slope of the surface tension vs. $\log c$ has not reached a constant or nearly constant value. Thus, as the surface tension decreases the molecules are expected to pack more densely on the surface. As a rule of thumb, caution should be exercised if the surface tension has been lowered by less than 5 mN/m in comparison to the pure solvent system.

Implications on sample preparations

In the Delta-8 the samples are typically prepared by serial dilution. For a sample that precipitates it is important to first prepare the dilution series in a solvent where the compound dissolves completely and then mix the dilution series with the buffer on the detection plate, *e.g.* preparing the dilution series in DMSO and then mixing it with an aqueous buffer at a ratio of 1:10 detection plate. In this way the precipitation occurs on the detection plate and the amount of compound in each well is exactly known.

It should be noted that the co-solvent affects the solubility also in the mixture, and the fraction should therefore be kept small.

Conclusions

The critical micelle concentration and the solubility limit are phenomena with many similarities. Consequently, they appear with similar features in a surface tension vs. concentration experiment. Precipitating compounds can be measured and useful data extracted from adsorption isotherms provided that the dilution series can be made accurately. This usually requires that the dilution steps are made in a co-solvent.