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The kinetics and mechanism of micelle-vesicle transitions in aqueous solution

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Abstract. Bi-chained surfactants, e.g. sodium dialkylbenzenesulphonates, can spontaneously form vesicles when salts (e.g. NaCl) are added to water. Critical vesicle concentrations can be readily determined. The kinetics and mechanism for the breakdown and formation of vesicles will be discussed. A mechanism for assembly/disassembly is proposed. Organic dyes can be encapsulated inside the vesicles and their release rates can be monitored using flow experiments. It is found that the vesicle bilayer provides a rather low energy barrier to the transport of the dye from the vesicle core to the external aqueous medium.

1. Introduction

It is well known that synthetic surfactants (detergents) form micelles at low concentration in aqueous solution. It is also well established that phospholipids form vesicles (liposomes) although an input of energy (by sonication) is usually required. There are many significant differences between micelles and vesicles. The most obvious is that micelles are (in the general case) spherical with a radius (nm) determined by the length of the surfactant molecule. Vesicles are closed bilayer structures (normally considered spherical) enclosing an aqueous pool and surrounded by an aqueous solution, with a radius of the order of 1 μm.

This paper is concerned with synthetic surfactants which can spontaneously self-assemble to vesicles simply on addition of a salt electrolyte (e.g. NaCl) to water. The surfactant employed in our studies is sodium 6-phenyltridecanesulphonate (figure 1). The molecular structure is based on two relatively short alkyl chains with a benzenesulphonate head group. Classical arguments based on the Israelachvili packing parameter approach [1], which considers simply the geometrical (shape) properties of an isolated surfactant molecule, suggest a fine balance between an aggregate morphology based on micelles and lamellar structures (vesicles), and this is indeed found to be the case. We would suggest that vesicle formation by bi-chained surfactants is much more common than previously supposed, and assignments of large rod- and disc-like micelle structures when salt is added to an aqueous solution may in fact be due to the formation of vesicles.

This paper deals primarily with dynamic aspects associated with the rate and mechanism of breakdown of vesicles and of formation of vesicles by spontaneous self assembly.

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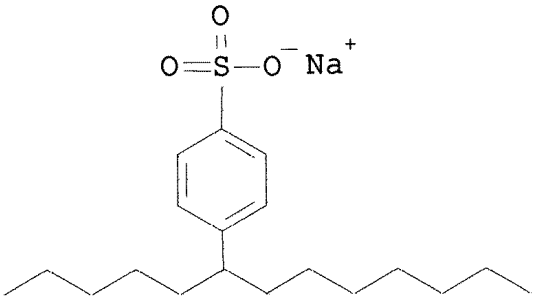


Figure 1. Sodium 6-phenyltridecanesulphonate (SURF).

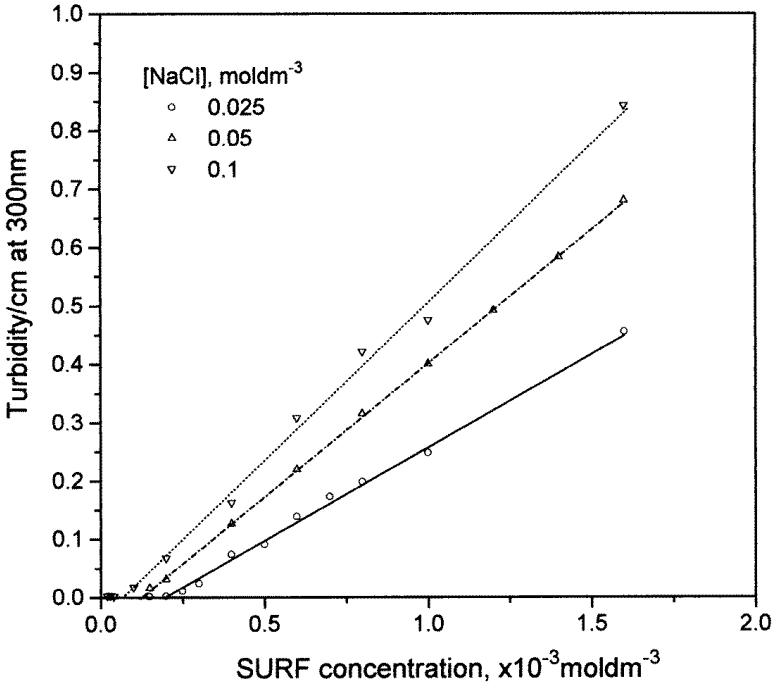


Figure 2. Plot of τ_{300} versus [SURF] at 25 °C.

2. Materials and methods

Sodium 6-phenyltridecane sulphonate [SURF] was supplied by Unilever-PSL. It was a particularly pure sample in terms of isomer distribution with >98.5% C_{13}. Micelles form in the absence of salt and the critical micelle concentration (CMC) is readily determined by the change in extinction coefficient (ϵ) of the solution at 262 nm (CMC $= 1.5 \times 10^{-3}$ mol dm^{-3} at 25 °C). The CMC is independent of temperature over the range 15–45 °C. Kinetic measurements were determined on a Hi-Tech Scientific Stopped-Flow Instrument (Model SF-4OC).

3. Results

3.1. The effect of added salt on aggregate formation:

On addition of salt to a surfactant solution, surfactant aggregates dramatically increase in size and their formation is associated with an increase in turbidity (absorbance). Absorbance measurements were made at 300 nm, a wavelength where the surfactant does not absorb.

Plots of τ_{300} versus [SURF] enable the so-called critical aggregation concentration (CAC) to be determined (figure 2). Addition of salt results in a dramatic decrease in the surfactant concentration at which aggregates form (e.g. CAC $\sim 10^{-4}$ mol dm^{-3} at an added NaCl concentration of 0.1 mol dm^{-3}). This is a much greater effect than is normally measured for NaCl addition to single-chain surfactants (e.g. sodium dodecylsuphate) where large changes in aggregate size are not observed.

Evidence for the existence of vesicles in salt solution has been obtained using a variety of techniques including cryoelectron microscopy, photon correlation spectrometry, video-enhanced microscopy and small-angle neutron scattering. Typically the vesicle radius is of the order of 250 nm, and some polydispersity of vesicle size is indicated. By working at low surfactant concentrations ($\leqslant 1 \times 10^{-3}$ mol dm^{-3} SURF), formation of multiwalled vesicles is essentially eliminated.

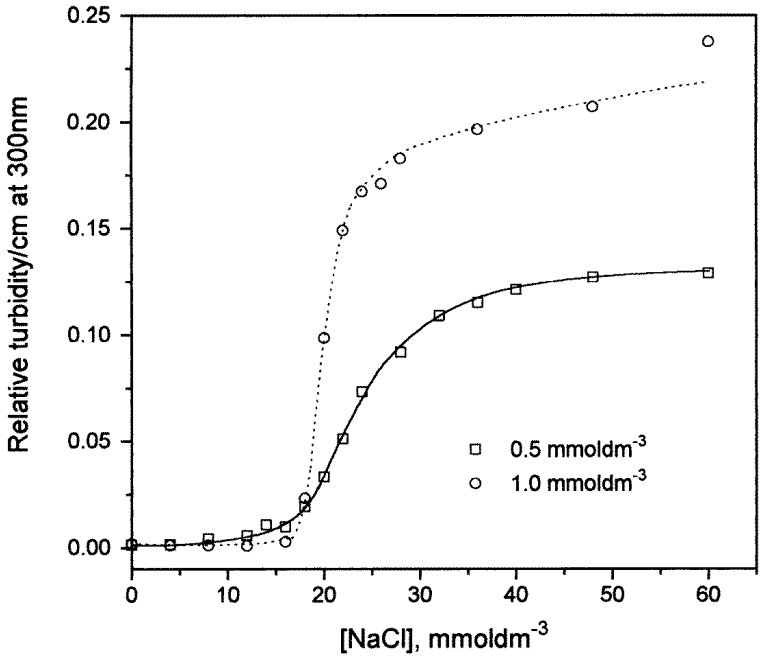


Figure 3. Plot of τ_{300} versus [NaCl] at two different surfactant concentrations as shown in plot. $T = 25\,^{\circ}$C.

An alternative way to express the onset of vesiculation is to plot τ_{300} versus [NaCl] at a fixed concentration of surfactant (figure 3). In this way a critical salt concentration, or CSC, for formation of vesicles may be determined ($\sim 20 \times 10^{-3}$ mol dm^{-3} NaCl).

The CSC is found to depend on the nature of the salt chosen, especially the charge on the cation.

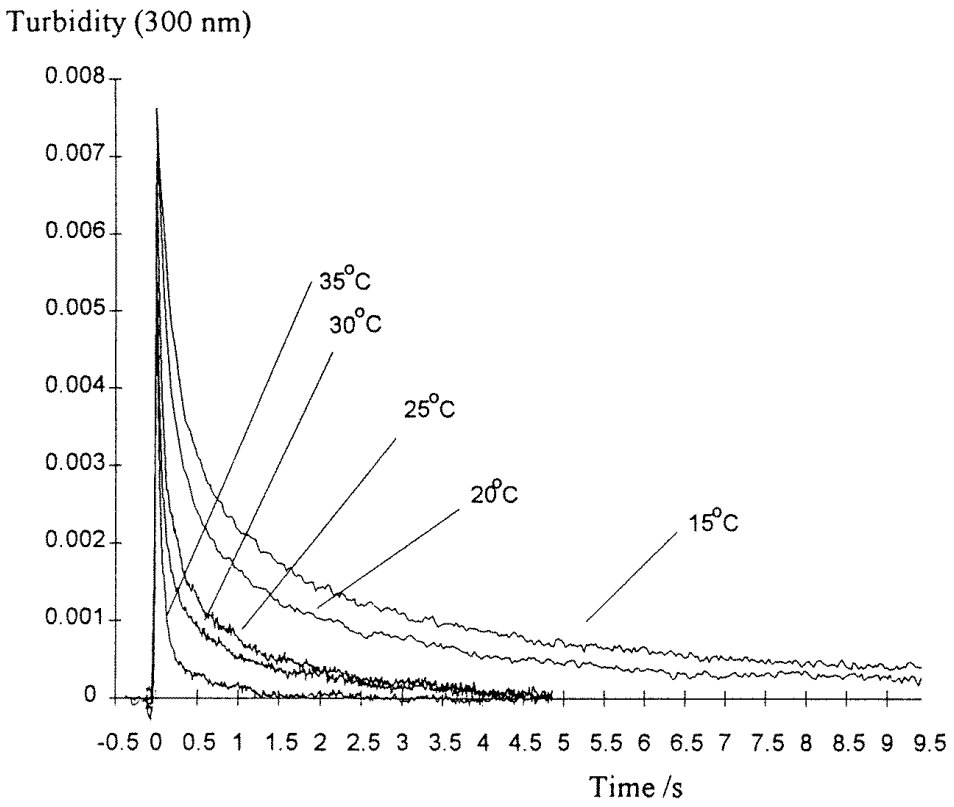


Figure 4. Kinetic transients for breakdown of vesicles on dilution >CVC to <CVC over the temperature range 15–35 °C.

3.2. The kinetics of vesicle breakdown

Vesicle breakdown was measured by rapid dilution of a surfactant solution, at a concentration >CVC with an equal volume of water, while maintaining the ionic strength (salt concentration) constant. In this type of experiment, the time for breakdown of vesicles is much slower than that for breakdown of micelles, which was measured using a very fast mixing technique (the so-called continuous-flow method with integrating observation) [2]. For micelle breakdown (no added salt), the breakdown rate constant k_{diss} was ~ 5000 s^{-1}, implying a micelle lifetime <1 ms.

In contrast, typical breakdown times for vesicles were in the time range 0.1–10 s. Figure 4 shows some typical data obtained as a function of temperature at a sodium chloride concentration of 0.025 mol dm^{-3}. The activation energy (measured from a plot of $\ln k_{diss}$ versus T^{-1} is ~60 kJ mol^{-1}.

Further measurements are required to substantiate a breakdown mechanism but a plausible pathway would involve initial loss of surfactant from the outside wall of the vesicle leading to a critically unstable bilayer structure which disrupts into smaller disc fragments, followed by further dissolution into monomers, as shown in scheme I.

$$V_{x_o x_i} \xrightarrow{slow} V^*_{(x_o-\Delta X_o)x_i} \xrightarrow{fast} D \xrightarrow{fast} (x_o + x_i)\text{Mon} \qquad \text{(I)}$$

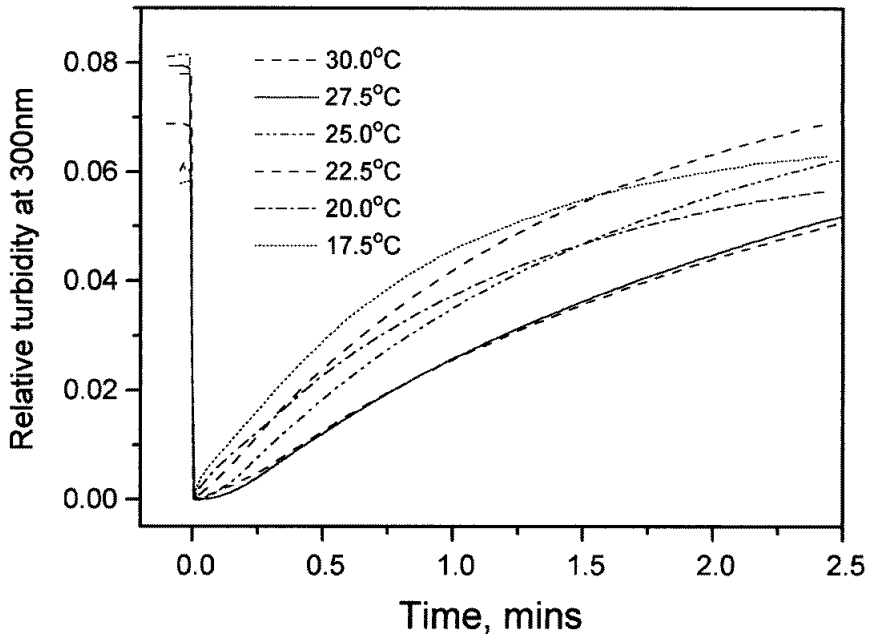


Figure 5. Kinetic transients for increase in turbidity following a salt concentration jump. Mixing (*a*) 1×10^{-3} mol dm^{-3} SURF, 15×10^{-3} mol dm^{-3} NaCl with (*b*) 45×10^{-3} mol dm^{-3} NaCl. The reaction was studied over the temperature range 15–35 °C.

where x_o is the number of 'outside' surfactants in vesicle, x_i is the number of inside surfactants in vesicle and $x_o \sim x_i$, Δx_o is the number of surfactants lost from outside wall in forming transition state $*$, D are the disc fragments and Mon represents the monomer surfactant.

3.3. Kinetics and mechanism of vesicle formation

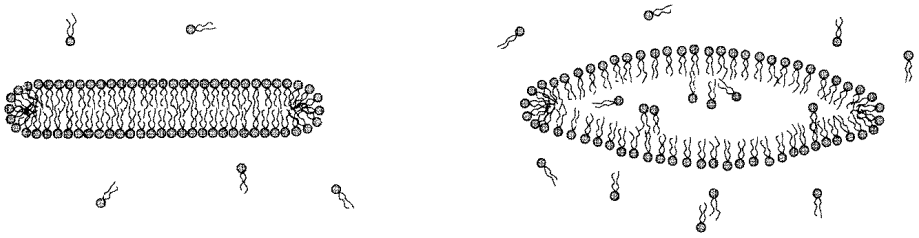
Vesicles may be spontaneously generated by rapidly ($t \sim 1$ ms) increasing the ionic strength (salt concentration) in a mixing experiment. The kinetics of vesicle formation are then conveniently followed (as previously) by the increase in (180°) turbidity τ at 300 nm. In this case the time course of reaction is of the order of a few minutes (figure 5). Significantly, the process becomes more difficult as the temperature is increased. It is interesting to hypothesize whether the mechanism of vesicle formation proceeds by the reverse of I above, according to the principle of microscopic reversibility. At first sight this would seem to be unlikely.

It is generally accepted that in a non-perturbed system, i.e. a system at equilibrium, the forward and backward reactions will proceed throught the same intermediate states. However, in our system, reaction is induced by a finite perturbation, so that process (I) is effected by a dilution-jump, and the reverse process, of vesicle formation, is similarly induced by an ionic-strength jump. For this case, where the reaction is being driven externally, and under different driving forces for reaction in the two directions, the principle of microscopic reversibility may well not hold. It is possible to systematically reduce and thereby minimize the perturbation to the system by carrying out temperature-jump

measurements on the system in the vicinity of the CSC; these measurements will be reported in due course, which will further clarify the situation.

A possible mechanistic hypothesis for vesicle formation in homogeneous solution could again involve the intermediate formation of disc-like aggregates from growth of micelles/monomers. However, the aggregates could prefer a slight positive curvature rather than a planar structure resulting in disjoining of the disc bilayer film followed by adsorption of free surfactant cooperatively to the inner hydrophobic surface so exposed (scheme II)

$$\text{Mon} \xrightarrow{fast} D \xrightarrow{disjoining} D' \rightarrow \text{Vesicle} \qquad \text{(II)}$$

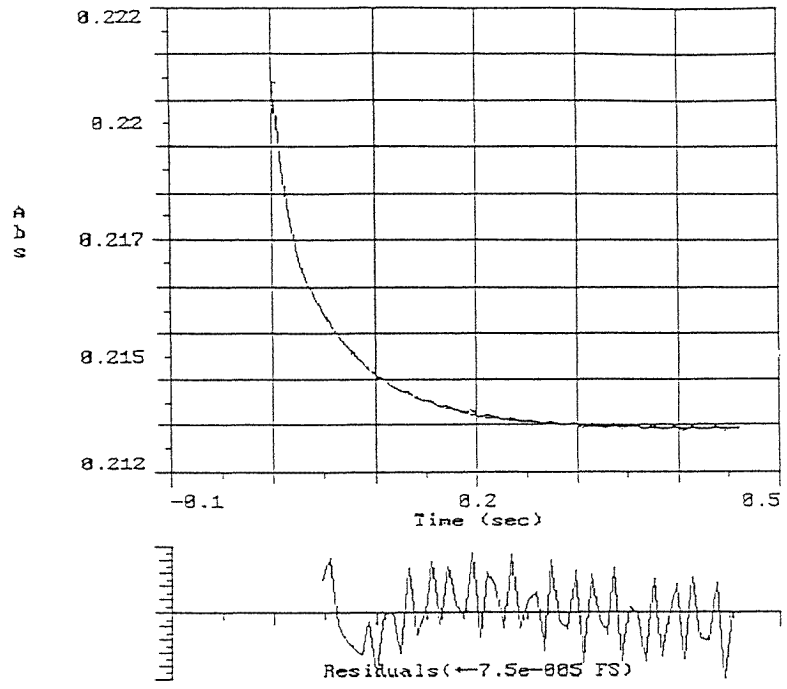


3.4. Permeation of the vesicles by organic dyes/drugs

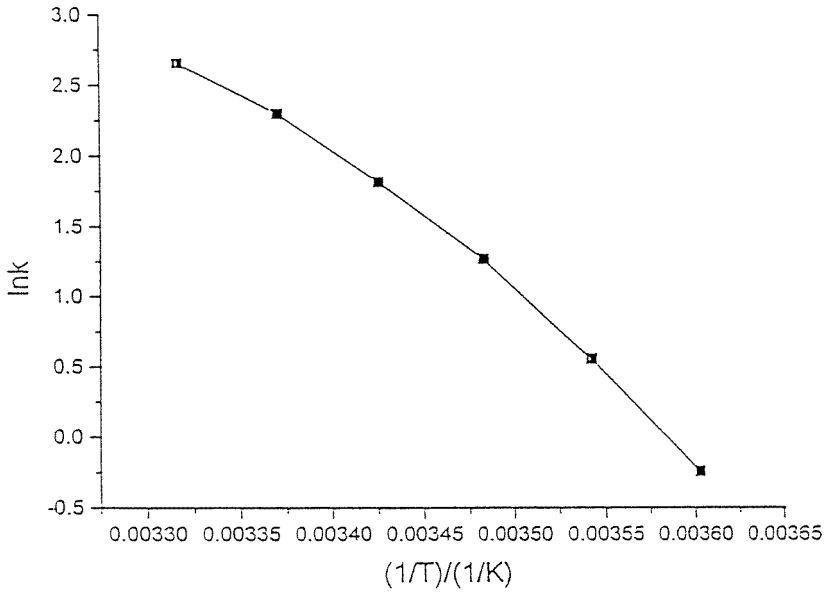
These experiments are relevant to the role of vesicles as drug- transporting vehicles. Ideally, it is desirable to retain the carrier molecule inside the vesicle and release it on a change in environment (e.g. ionic strength). Obviously for the systems already discussed, disruption of the vesicles (and release of contents) can occur on a time scale of $\sim$1 s. However, to test the ability of vesicles to retain a hydrophilic drug some model experiments have been performed using the dye methyl orange as a carrier. The essence of the experiment is to work with a protonated dye system. On suddenly increasing the pH external to the vesicle, all dye outside the vesicles is very rapidly (at the diffusion-controlled limit) deprotonated ($<$1 ms). It is then possible to measure the dye which becomes deprotonated after permeation through the vesicles. A typical trace for dye permeation is shown in figure 6(*a*). It should be noted that a vesicle made up of the short chains of our surfactant does not present much of a barrier to transport, release occurring on a time scale of $\sim$0.25 s. The effect of changing temperature (in the form of an Arrhenius plot) is shown in figure 6(*b*). The plot is curved, which suggests that the bilayer barrier to penetration decreases with increasing temperature. However, there is no evidence from this plot to indicate a phase transition in the vesicle over the temperature range studied (5–40 °C), such as is observed for phospholipid vesicles.

4. Concluding remarks

It is clear that addition of salt to an aqueous solution can dramatically change the type of aggregate which is present in solution. This is, however, generally in line with predictions based on the packing parameter concept proposed by Israelachvili *et al* [1]. It is also relevant to pose the question as to whether vesicles formed spontaneously, as described in this paper, can be thought of as thermodynamically stable. In any case, it is likely that many new cases will now be found where synthetic surfactants spontaneously form vesicles on pertubation of the ionic environment.



(a)



(b)

Figure 6. (*a*) Transient for release of methyl orange from vesicle. Mixing of solution (*i*) Dye/H^+ (5×10^{-3} mol dm^{-3})/SURF (0.5×10^{-3} mol dm^{-3})/NaCl (50×10^{-3} mol dm^{-3}) with (*ii*) OH^- (20×10^{-3} mol dm^{-3})/NaCl (50×10^{-3} mol dm^{-3})/SURF (0.5×10^{-3} mol dm^{-3}). (*b*) Curved Arrhenius Plot for release of methyl orange from SURF vesicle. Conditions as for 6(*a*).

Acknowledgments

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[1] Israelachvili J, Mitchell D J and Ninham B W 1976 *J. Chem. Soc. Faraday II* **72** 1525–87
[2] Holzwarth J F 1979 *Techniques and Applications of Fast Reactions in Solution* ed W J Gettins and E Wyn Jones (Dordrecht: Reidel) pp 13–24 and references therein.