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SHORT COMMUNICATION

Kinetics of vesicle formation

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Abstract The kinetics of vesicle formation from a hydrotrope (sodium xylenesulfonate) solution of a surfactant (Laureth 4) is studied by the use of a stopped-flow apparatus combined with a dynamic light scattering device to determine vesicle size in the system. The hydrotrope system studied presents a system with a high surfactant solubilization combined with vesicle formation simply by dilution with water. The kinetic results show a single exponential decay time. The kinetic analysis indicates that the vesicles are formed from a molecular solution which resulted from the shear in the stopped-flow device and grow by monomeric association.

Key words Vesicle – self-assembly – hydrotrope – stopped-flow – kinetics

Introduction

Amphiphilic association structures such as micelles, microemulsion droplets, vesicles, and liquid crystals have been extensively studied due to their interesting fundamental properties [1–5] and their wide applicability in the biomedical [6–9], agricultural, and chemical industries [10–13]. The kinetics of formation play a decisive role in almost all applications and has been intensely studied for these structures [14–16] with the exception of vesicles, which have remained elusive in spite of their obvious importance in a wide range of applications [17, 18]. The electron micrographs from the Upsala group [19, 20] and others are only concerned with the shape of vesicles and not with the formation kinetics. In previous studies reporting time scales, the process observed was multi-step [21] involving exchange of solubilized materials between vesicles [22]. These provide no information about vesicle formation from a molecular dispersion which we have observed using the stopped-flow technique to occur at a rate at least five orders of magnitude slower than that for micelles.

Using the traditional method of vesicle generation, by mechanical disintegration of a lamellar liquid crystal in a fluid [23], the size and distribution dependance as a function of time and intensity of agitation is understood [17]. Later developments include dilution to sub-cmc conditions or osmosis of vesicle forming surfactants solubilized into micelles [17]. These approaches constitute a significant improvement, but suffer from the fact that the ratio between the micelle and vesicle forming surfactants is large requiring time consuming osmosis. The problem of vesicle preparation was alleviated by a recent introduction of hydrotrope solutions of vesicle forming surfactants. The ratio between hydrotrope and vesicle forming surfactant is small (1/5), and in addition, the hydrotrope molecule does not adsorb strongly to any interface. Such a system, combined with the stopped-flow method, offers a unique opportunity to study the kinetics of formation of vesicles, because rates developed during the mixing process are sufficiently large to convert molecular assemblies [24] to

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monomers. This fact combined with the low surface activity of the hydrotropic molecule provides strong justification for the assumption that the vesicles associate without influence from other amphiphiles.

Experimental

Materials

Sodium xylenesulfonate (Aldrich, Milwaukee, less than 9% Na_2SO_4) was rinsed with hexane (3 times), acetone (twice), and ethanol (twice) and then filtered. After filtration, the sodium xylenesulfonate (SXS) was dried in a vacuum oven for 72 h at 50 °C. Polyoxyethylene (4) lauryl ether (Brij® 30, ICI Surfactants, Wilmington) was used as received. Water was doubly distilled.

Stopped-flow measurements

The device designed to make the stopped-flow measurements has been extensively described elsewhere [25]. All measurements were made at 550 nm with a 2 mm inlet for the light.

Dynamic light scattering

Light scattering was performed on a custom built instrument. The laser is a 2.5 W argon ion laser (Model 85, Lexel laser) operating at a wavelength of 514.5 nm. A stepper-motor controlled goniometer (BI-2000SM, Brookhaven Instruments) is used in conjunction with a BI-DS photomultiplier tube and a BI-2030AT digital correlator to collect the autocorrelation function. A majority of the dynamic light scattering (DLS) was performed at 90° with other angles used to detect artifacts in the data. The analysis of the data was performed using the version of CONTIN provided by Brookhaven Instruments. For the light scattering, all solutions were passed through a 0.2 μm filter prior to mixing. For DLS, the samples were contained in an optical quality cuvette placed in a vat using toluene as the index matching liquid. Each sample was measured at least at three different times (immediately after preparation, after 24 h, and after 1 week). All experiments were thermostatically controlled.

Results and discussion

The complete phase diagram of our system (Laureth 4, sodium xylene sulfonate, and water) is shown in Fig. 1. The features are typical of a water/hydrotrope system combined with a surfactant not soluble in water [26]. The solubilization of the surfactant to 42% by weight should be contrasted with values in the range of 10–15% in pure surfactant systems. For the region of interest in the present study, shown in the inset in Fig. 1, the equilibrium tie lines all run to a composition with no significant amount of SXS in the LLC phase. The noteworthy feature is the low concentration of SXS both in the vesicles and in the total system.

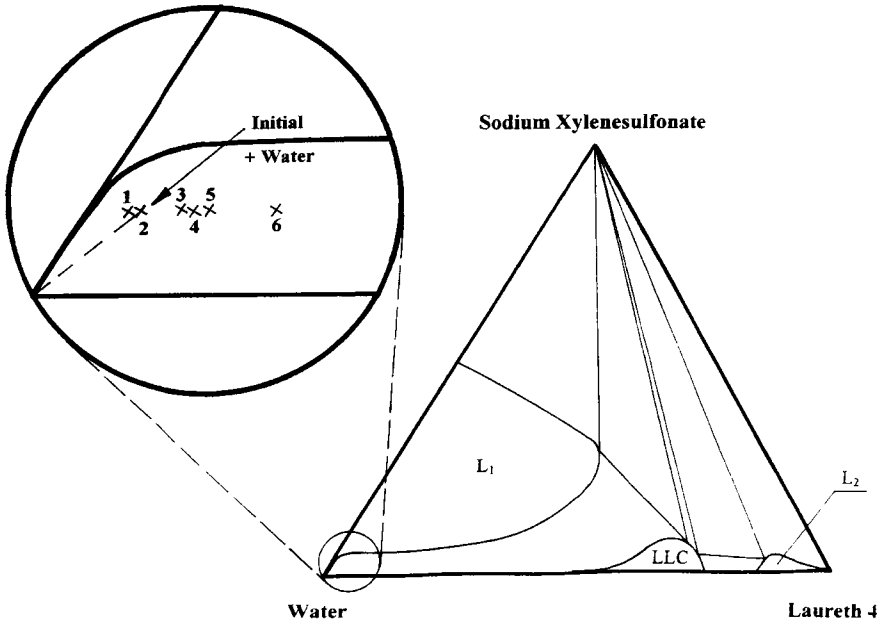


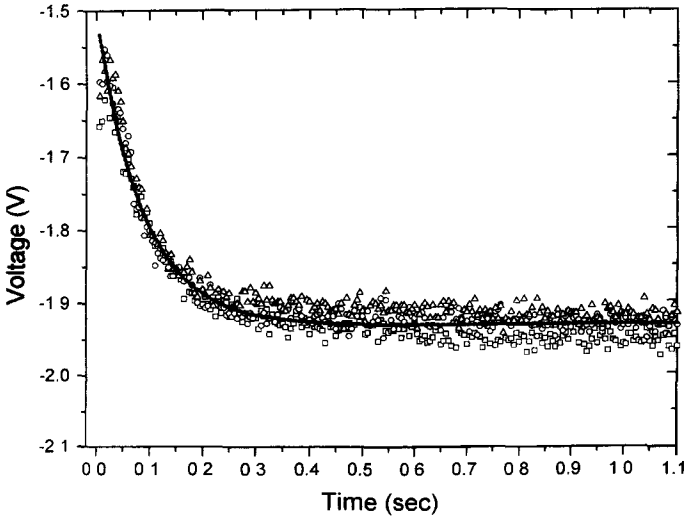
Fig. 1 The phase diagram for the system water, Laureth 4, and sodium xylenesulfonate. L_1 = isotropic solution of hydrotrope/Laureth 4 combination micelles; LLC = lamellar liquid crystal; L_2 = surfactant solution. Inset: Composition of vesicle solutions within the two-phase region L_1-LLC. The vesicles were formed by combining equal amount of water and a solution within L_1. The arrows for sample 2 exemplify the principle

From the phase boundaries, initial solutions which would yield vesicles upon dilution were determined. The inset in Fig. 1 shows the final total concentration after dilution. To determine the original solution, the distance from the water corner to the final composition is determined. The initial composition is located at twice this distance along the same line as shown for sample #2. Note that all the original solutions were stable with time as determined both visually and by dynamic light scattering. The final solutions had limited stability, but no sedimentation was found after one week at room temperature. The stability of the original solutions, lends credence to the solution being in an equilibrium micellar configuration. The separation of the other solutions clearly indicates that the structures resulting from mixing are nonequilibrium and exist in two phase region (as also seen on the phase diagram). All the final solutions were opalescent and turbid giving an indication of large structures.

A representative result from the stopped-flow [25] runs is presented in Fig. 2. The response curves show a single exponential decay. The summary of stopped-flow measurements is reported in Table 1.

In addition to the stopped-flow measurements, dynamic light scattering measurements were made on the initial and final solutions. The analysis is based upon the program CONTIN; questions still surround the proper interpretation of light scattering data for vesicles [27]. The analysis used did assume that the vesicles were spherical in shape and noninteracting thus using the well known Stokes–Einstein relationship [28]. The light scattering results are also summarized in Table 1.

Fig. 2 Response curves from the stopped-flow measurements based upon 90° light scattering [25]. Each set of symbols (circle, square, and triangle) represent a single experiment. The single exponential decay (solid line) Chi Square fitting parameter is less than 2×10^{-4}



The light scattering data show that all initial micelles were of the same size (21 nm), which is consistent with large micelles composed of both SXS and Laureth 4. The shape most consistent with the scattering data is a disk shaped micelle in which the hydrophilic heads of Laureth 4 form the upper and lower surface while the SXS associates along the edge of the disk stabilizing the hydrocarbon chains. This model conforms with the known behavior of SXS which exhibits associative behavior as is common for hydrotropes [29]. The final sizes (55–95 nm) are consistent with the formation of vesicles for the system. The trend in the width of the distribution is probably a reflection of the system, but may also be significantly influenced by the commercial grade of the surfactant used in this study.

In modelling the kinetics, the most essential factors are the combination of dilution and extremely high shear during the stopped-flow process. The dilution means that the concentration of the hydrotrope is less than that when association takes place with combined micelles and far below the concentration for eigen-association. At equilibrium, the association with Laureth 4 in the continuous phase is restricted to only small amounts of the surfactant, and it may reasonably be concluded that the small association structures have no significant influence on the kinetics of vesicle formation. This is especially true with regard to the assumption of the association taking place via monomer addition.

Hence, the analysis should decide on the main mechanism of association. Two consecutive mechanisms are possible: monomer association to form growing oligomers reaching a limit in the form of a vesicle, or aggregation of the oligomers with the identical limit.

The initial association is molecular, but the final stages which are captured by the experimental light scattering detection may also include oligomer association. The kinetics of surfactant molecular association to form micelles was clarified by Aniansson et al. [14] and later extended to oligomer aggregation by Kahlweit [15]. As expected, monomer addition dominates the process for low surfactant concentrations, while aggregation of oligomers is the

Table 1 Final composition, final size, and decay time at SXS = 2.8%

Sample	Laureth 4 (wt%)	Final size (nm)	Decay time (sec)
1	0.8	65 ± 12	0.0904 ± 0.0156
2	1.1	54 ± 16	0.122 ± 0.034
3	2.1	76 ± 20	0.196 ± 0.087
4	2.6	85 ± 25	0.324 ± 0.108
5	3.2	81 ± 21	1.24 ± 0.25
6	5.0	92 ± 28	8.34 ± 1.14

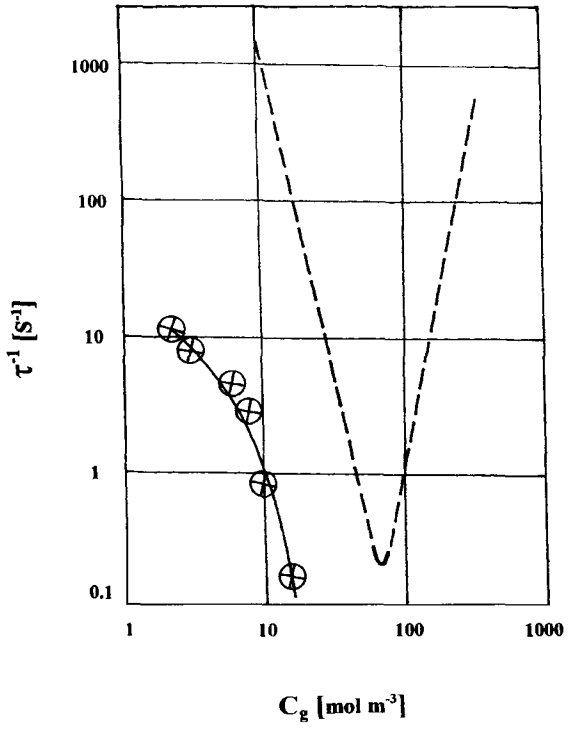


Fig. 3 A comparison of the trend for the present results (solid line) with those from earlier investigations (dashed line) [30]

main contribution at higher concentrations. The association is described by [15]

$$1/\tau = (MX^{n/m} + \beta_0 mx)/[1 + (\sigma^2/m)X] \quad (1)$$

in which τ is the relaxation time, M the molecular weight, X the ratio of associated to free molecules, n the number of molecules in the aggregate, m the number average for aggregates, β the dissociation constant for the aggregation reaction of oligomers, and σ the width of the size distribution. Plotting $1/\tau^2$ versus the logarithm of concentration of the surfactant, the change from one mechanism to another is characterized by a pronounced minimum (Fig. 3: dashed line). The present results (Fig. 3: solid line) reveal the nature of the association process to be governed by monomer addition. The reason for the absence of oligomer aggregation is not immediately obvious, and at present, a choice between different potential reasons would not be justified. Based upon the model of consecutive monomer addition, further studies may directly determine the fundamental thermodynamic properties resulting in the formation of vesicles.

Hence, the model of consecutive vesicle build-up by monomer addition appears strongly justified for the present surfactant and the decay times reported reflect that mechanism.

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