Synthesis of a Novel Asymmetric Gemini Surfactant and pH-controlled Vesicle Aggregation

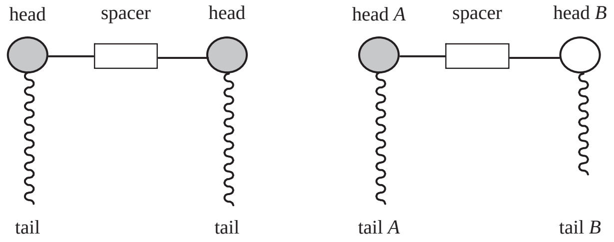
Feng Yan,*[1] Ming Huo,[1] Mingxia Wang,[1] Haibin Yao,[1] Lu Zhang,[2] and Jiayong Yu[2]
[1]*College of Materials Science and Chemical Engineering, Tianjin Polytechnic University, Tianjin 300160, P. R. China*
[2]*Technical Institute of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100080, P. R. China*

(Received January 14, 2009; CL-090052; E-mail: yanfeng@tjpu.edu.cn)

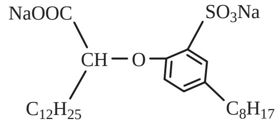
A novel asymmetric Gemini surfactant, comprising two nonidentical hydrocarbon chain lengths and two different hydrophilic groups, abbreviated as $C_{13}COONa–O–C_8BSO_3Na$, has been synthesized. The unique aggregation behavior was investigated by transmission electron microscopy in aqueous solution. Spontaneous vesicle formation (approximately 100–300 nm) was observed. The reversible morphological change of vesicle aggregation took place by varying the solution pH. These results indicated the potential application of the present amphiphile, which may be used as a model for cell membranes and drug delivery systems.

Supramolecular aggregation, such as vesicles, derived from small molecular amphiphiles have become increasingly interesting due to their many potential applications, for example, as models for cell membranes, drug delivery systems, and microreactors.[1–4] Generally, different function relies on different properties of vesicles. For example, it is desirable for vesicles to be stable when they are used as templates,[5] while vesicle aggregation and fusion are usually beneficial to the release of entrapped drugs.[6] Living cells in a multicellular organism preserve their individuality. However, in certain physiological conditions their aggregation or fusion occurs. In the past few decades, the aggregation of vesicles has attracted special attention not only for its close relation to these biological processes as an analogous model, but also for its practical importance in pharmacy and so on.

As a new type of surfactant, Gemini surfactants, which contain two hydrocarbon chains and two hydrophilic groups in a molecule and make up two amphiphilic moieties having the structure of conventional monomeric surfactants connected by a spacer group, as shown in Figure 1a, have attracted increasing attention over recent years, owing to their superior properties, such as much lower critical micelle concentrations (cmc), higher efficiency in lowering the surface tension of water, and unusual aggregation morphologies.[7–12] The majority of studies on Gemini surfactants have been conducted using symmetrical surfactants that possess identical hydrocarbon chain lengths and identical polar headgroups. In recent years, new classes of Gemini surfactants have been designed and synthesized, namely, asymmetric Gemini having two nonidentical hydrocarbon chain lengths or two nonidentical headgroups, Figure 1b. Only a few reports are available with regard to research on asymmetric Gemini surfactants. Until now, asymmetric Gemini surfactants such as ammonium/carboxylate (cationic/anionic),[13] ammonium/phosphodiester (cationic/anionic),[14,15] sulfate/polyoxyethylene (anionic/nonionic),[16] ammonium/gluconamide (cationic/nonionic),[17] and hydroxy/polyoxyethylene (nonionic/nonionic)[18] as two nonidentical headgroups were designed and synthesized, and their adsorption and micellization properties were investigated. So far, few attempts have made to synthesize those with two different anionic headgroups (anionic/anionic) probably owing to the difficulty of synthesis.



a, symmetric gemini surfactant b, asymmetric gemini surfactant



c, $C_{13}COONa-O-C_8BSO_3Na$

Figure 1. The structure models of Gemini surfactants, and the structure of $C_{13}COONa–O–C_8BSO_3Na$.

In the present study, we describe the synthesis of a novel anionic/anionic-type asymmetric Gemini surfactant with nonidentical headgroups containing carboxylate and sulfonate $C_{13}COONa–O–C_8BSO_3Na$, where –O– is the spacer and B stands for benzene ring, as shown in Figure 1c. The aggregate morphology in aqueous solution was investigated by transmission electron microscopy (TEM). It is possible to control the shape of the aggregate by varying pH for molecules containing –COONa.

Figure 2 shows the synthetic route of $C_{13}COONa–O–C_8BSO_3Na$.

The starting material **I** was prepared according to a previous paper.[19] Compound **I** (9.21 g, 0.02 mol) was dissolved in 20 mL of 1,2-dichloroethane in a 100-mL three-necked flask equipped with a dropping funnel and thermometer. After the mixture

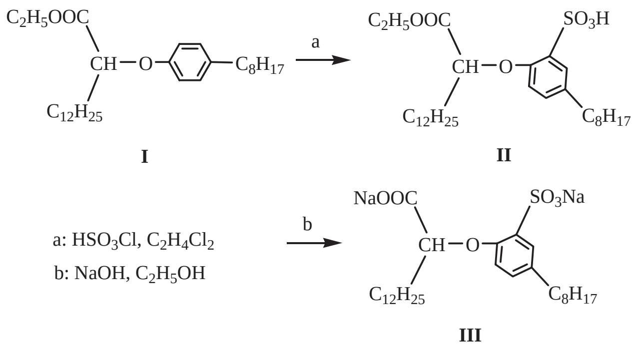


Figure 2. Synthetic route of $C_{13}COONa–O–C_8BSO_3Na$.

Table 1. Structure information of compounds **I** and **III**

Compound	FT-IR[a] /cm^{-1}	^{1}H NMR[b] δ	Elemental analyse
I	2927, 2855, 1738, 1612, 1510, 1465, 1237, 1180, 826	7.05 (d, 2H), 6.78 (d, 2H), 4.54 (t, 1H), 4.22 (m, 2H), 2.52 (t, 2H), 1.92 (m, 2H), 1.57 (m, 2H), 1.22–1.54 (m, 33H), 0.88 (t, 6H).	
III	2924, 2853, 1608, 1488, 1463, 1421, 1246, 1195, 904, 816	7.59 (s, 1H), 7.04 (d, 1H), 6.75 (d, 1H), 4.59 (t, 1H), 2.47 (t, 2H), 1.79 (m, 2H), 1.45 (m, 2H), 1.07–1.14 (m, 30H), 0.75 (t, 6H).	Anal. Calcd: C, 60.41; H, 8.33%. Found: C, 60.66; H, 8.10%.

[a] **I** was layered on KBr plates directly; **III** dissolved in CH_3OH was layered on KBr plates. [b] Solvent: **I**, $CDCl_3$; **III**, D_2O.

was cooled to below 5 °C in an ice bath, a solution of chlorosulfonic acid (2.9 g, 0.025 mol) in 5 mL of 1,2-dichloroethane was added dropwise while stirring. After this addition, the reaction mixture was stirred for another 1.5 h in an ice-bath and for 3.5 h at room temperature to complete reaction. The resulting mixture was poured into crushed ice with fast stirring. The organic layer was separated and 1,2-dichloroethane was removed by evaporation. The obtained compound **II** was mixed with excess NaOH in 20 mL of ethanol, and then was heated to reflux for 2 h. After it cooled to room temperature, the solution was adjusted to pH 8, and solvent was evaporated. The residue was then re-dissolved with anhydrous ethanol and filtered to provide the crude product. This crude product was recrystallized from anhydrous ethanol and dried by lyophilization to yield $C_{13}COONa–O–C_8BSO_3Na$.

The FT-IR spectra, ^{1}H NMR spectra,[20] and elemental analysis results are listed in Table 1. As for compound **I**, 2927 and 2855 cm^{-1}, ν-CH$_2$; 1738 cm^{-1}, ν-C=O; 1612 cm^{-1}, ν-C=C; 1237 and 1189 cm^{-1}, ν-C–O–C. As for compound **III**, the disappearance of band 1738 cm^{-1} suggests that the ester group was hydrolyzed. The appearance of the wide strong band from 1195 to 1246 cm^{-1} indicates that the sulfonation reaction was successful.

The aggregation behavior of asymmetric Gemini surfactant $C_{13}COONa–O–C_8BSO_3Na$ in aqueous solution was investigated at a concentration of 1.25 mmol/L. Spontaneous vesicle formation with a wide distribution size of 100–300 nm diameter was observed, as shown in Figure 3a. It is very unusual that Gemini surfactant molecules with two nonidentical anionic headgroups spontaneously form vesicles in solution without external forces such as supersonic waves,[17] although much research on vesicle formation for Gemini surfactants[13–18] and fatty acids[21,22] has been reported. This unusual aggregation morphology (Spontaneous vesicle) is not observed with sodium octylbenzenesulfonate and sodium myristate, which are the two monomeric surfactants comprising $C_{13}COONa–O–C_8BSO_3Na$. It also indicates the advantage of Gemini surfactants.

Controlling the aggregates formed by the amphiphiles has attracted special attention over the past few decades. Normally, the formation and transition of amphiphile self-assemblies is induced by external additives, such as salt or polymer, variation of pH or temperature.[23–25] It is not surprising that pH-induced vesicle aggregation occurred in aqueous solution of $C_{13}COONa–O–C_8BSO_3Na$. The aqueous solution of $C_{13}COONa–O–C_8BSO_3Na$ was transparent and clear. As a small quantity of dilute hydrochloric acid was added, the solution turned to light blue but transparent still. Figure 3b shows the aggregation morphology at pH 3.5 of the above solution. By TEM, giant vesicles (approximate 2.5 µm) were observed, which reveals that the increase of the turbidity was attributed to the vesicle aggregation in acid solution. Subsequent addition of NaOH into the turbid solution quickly eliminated the turbidity of the solution under alkaline conditions. This process could be repeated by alternate addition of HCl and NaOH, which indicates that the aggregation process is reversible.

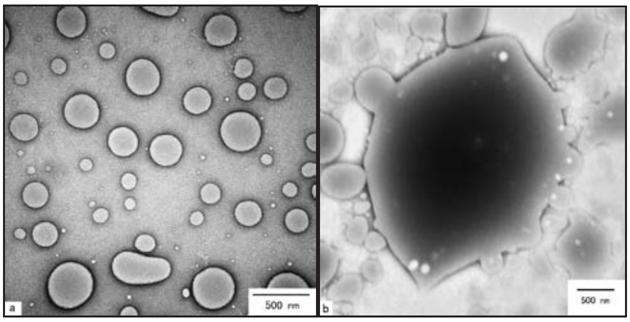


Figure 3. TEM image of $C_{13}COONa–O–C_8BSO_3Na$ in aqueous solution (a) and in acid solution pH 3.5 (b).

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