Preparation and Characterization of Double-Chain Destructible Surfactants and Derived Vesicles

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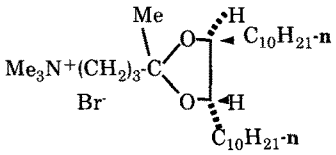
Double-chain destructible surfactants 1 and 2 were prepared, and vesicles derived from them were characterized. The hydrolyses of 1 and 2 to nonsurfactant compounds were demonstrated, and the application of 1 and 2 in preparative chemistry and in pH-controlled delivery is discussed.

Vesicles are spherical or ellipsoidal, closed bilayer structures formed by double-chain surfactants in water (1). Numerous reactions have been performed in vesicular media (1), and in several instances (2,3) impressive reactivity control has been realized which is unobtainable in conventional solvents. Such control results from the ability of vesicles to solubilize, orient and compartmentalize reactants. The application of vesicular media to preparative chemistry, however, has been hindered by the difficulty inherent in the isolation of products from surfactant-based media. Normal extraction procedures are generally precluded because of the likely formation of troublesome emulsions. We have, therefore, prepared 1 and 2 as the first examples of double-chain surfactants specifically designed for application in synthetic chemistry and have characterized vesicles derived from them. After their use in vesicular form, 1 and 2 can be converted to nonsurfactant compounds to facilitate product isolation.



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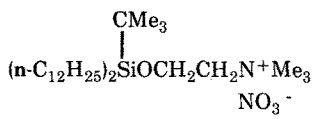
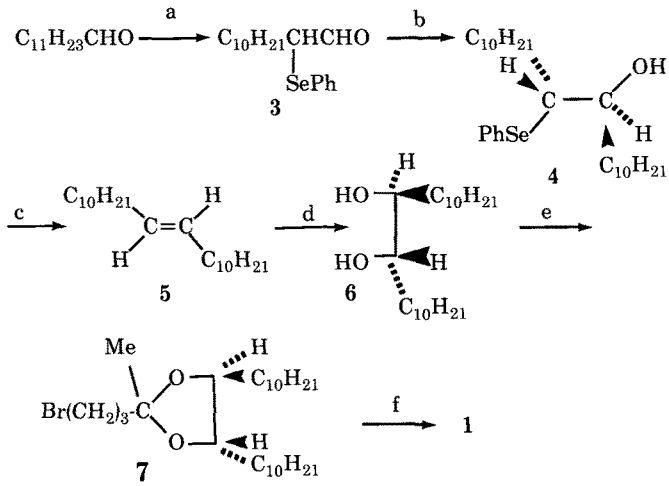


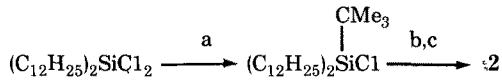
2

The preparation of 1 is summarized in Scheme I. New compounds, except for some intermediates, were fully characterized by ^1H NMR and IR spectroscopy, and by carbon and hydrogen analyses and/or high resolution mass spectral measurements. Aldehyde 3, derived from dodecanal and phenylselenenyl chloride (4), yielded alcohol 4 on reaction with decyl magnesium bromide (5), which followed Cram's rule. Alkene 5, formed by anti-elimination of the methanesulfonate derivative of 4 (6), gave threo diol 6 (7) by *cis*-hydroxylation with osmium tetroxide/4-methylmorpholine N-oxide (8). Diol 6 gave bromo ketal 7 on reaction with 5-bromo-2-pentanone (9), which was then converted to 1, mp 89→150 C, with trimethylamine in methanol.



Scheme I. (a) PhSeCl, EtOAc, trace H_2SO_4, 25 C, 66% yield; (b) $C_{10}H_{21}MgBr$, Et_2O, -109 C; 75%; (c) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 C 90%; (d) 4-methylmorpholine N-oxide, OsO_4, 3:5:1 (v/v/v) tert-BuOH:THF:H_2O, 25 C, 25%; (e) $Br(CH_2)_3COMe$, p-$MeC_6H_4SO_3H$, C_6H_6, Dean-Stark, 74%; (f) Me_3N, MeOH, 25 C, 66%.

The synthesis of 2 is summarized in Scheme II. Chlorosilane 9 resulted from the reaction of dichlorosilane 8 (Petrarch Systems, Inc.) with tert-butyllithium (10). On reaction with choline chloride (11), followed by metathesis with silver nitrate, 9 gave 2 as viscous oil.



8 9

Scheme II[a]

[a](a) tert-BuLi, hexane/pentane, 60 C, 90% yield; (b) $HOCH_2CH_2N^+Me_3$ Cl^-, imidazole, DMF, 50 C, 63%; (c) $AgNO_3$, $EtOH/H_2O$, 25 C, 60%.

Differential scanning calorimetry of 1 and 2 gave phase transition temperatures of 7 C and 10 C, respectively (12, 13). Both small unilamellar and multilamellar vesicles (SUV's and MLV's, respectively) were formed from 1 and 2. The SUV's were prepared by sonication (50 W) of the surfactant (6 mg/ml) in aqueous 0.01 M sodium bicarbonate (pH 8) for 4 hr, at which time the turbidity of the solution reached a minimum, as detected at 400 nm with a UV spectrometer. Then the solution was filtered at 25 C through a 1.2-μm filter (Millipore RATF 013 00). When the sonication procedure was repeated in 0.008 M sodium carbonate in deuterium oxide, the methylene signals in the ^1H NMR spectra of 1 and 2 were monitored. Increases in their intensities and decreases in their linewidths with time indicated the formation of vesicles (14). The MLV's

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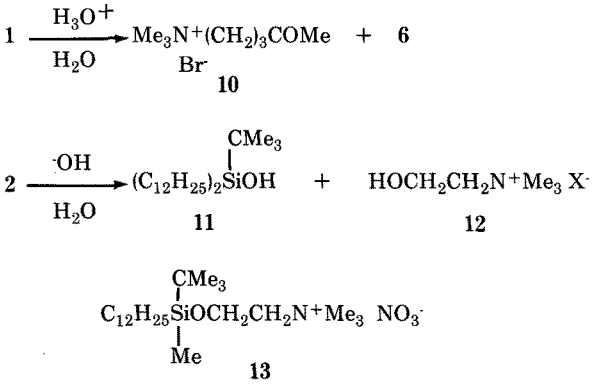
were prepared by injection of an ethanolic solution of the surfactant (6 mg/25 μl) into 1 ml of rapidly stirred aqueous 0.01 **M** $NaHCO_3$ at 60 C. The solution was then held at 60 C for 0.5 hr and filtered at 25 C through a 1.2-μm filter.

Entrapment studies using 5(6)-carboxyfluorescein, a fluorescent dye (15), and ^{14}C-glucose (16) as markers demonstrated the formation of vesicles from **1** and **2**. By the above procedures, SUV's and MLV's were prepared in aqueous 0.066 **M** 5(6)-carboxyfluorescein adjusted to pH 7.8 with sodium hydroxide, and in aqueous 0.01 **M** sodium bicarbonate containing 50 μCi of ^{14}C-glucose. Each of the preparations was chromatographed at 25 C through a column of Sephadex G-25-80 (17) with 0.01 **M** sodium bicarbonate as eluent, and a portion of the marker eluted in the void volume, consistent with its entrapment in vesicles, followed by the remainder in later fractions.

The cleavable natures of **1** and **2** as SUV's prepared by sonication were demonstrated by hydrolysis reactions at 25 C. Surfactant **1** was 50% and 100% hydrolyzed to **6** and **10** (9) after 4 hr and 24 hr, respectively, in 1.0 **M** hydrochloric acid. Surfactant **2** was 30% and 100% hydrolyzed to silanol **11** and **12** after 4 hr and 48 hr, respectively, in aqueous 1.0 **M** sodium hydroxide. It is interesting to note that at 25 C, the single-chain analogue **13** (18) required only 4.7 hr for 65% hydrolysis in 0.2 **M** sodium hydroxide. The reactivity differences between double-chain **2** and single-chain **13** may be due, in part, to their different aggregate characters, i.e., the former forms vesicles and the latter micelles.



Vesicles composed of cleavable surfactants such as **1** and **2** have a potential use in pH-controlled delivery of entrapped compounds. However, even without taking advantage of the cleavability of **1** and **2**, their vesicles released 5(6)-carboxyfluorescein rapidly at 20 C and pH 8 (>20% within 5 min), as determined by fluorescence spectroscopy (15). Further work on this application will focus on homologues of **1** and **2** with longer chain lengths. Derived vesicles should have higher phase transition temperatures and lower release rates (19) that will allow the realization of cleavage-induced delivery.

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