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Synthesis of 3,5-Bis(2,5,8-trioxaeicosyl)-18-crown-6 and Its Formation of Bilayer Membranes

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Dialkyl crown ether (**4**) containing oligooxyethylene group which can be dispersed in water to form a stable opalescent solution by sonication was synthesized. Transparency of the aqueous solution of **4** was enhanced by the addition of KCl, showing the salt-in effect. Electron microscopy suggested that **4** forms the myelin-like fingerprint structure and vesicle-like aggregates.

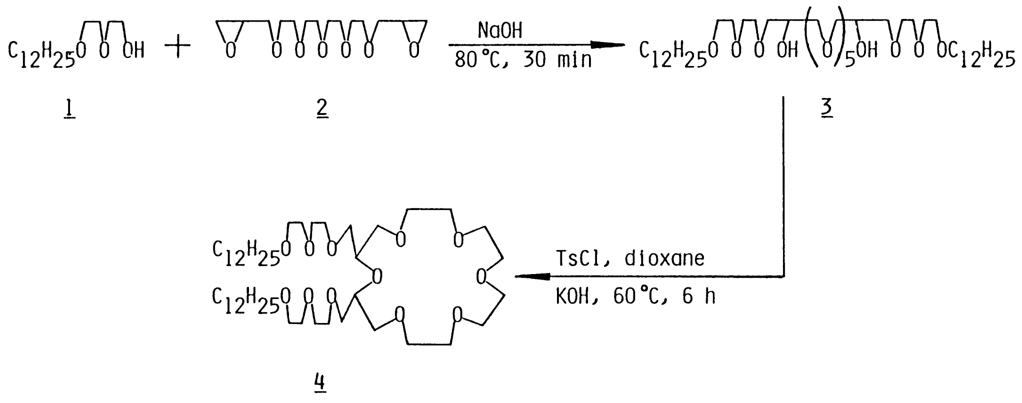
Since the first report on totally synthetic bilayer membranes by Kunitake and his co-workers in 1977,1) artificial bilayer membranes have been investigated widely due to their many interesting functions such as phase separation, phase transition and formation of vesicles etc. There have been found various materials which can form bilayer membranes. Especially, the crown compounds bearing two long hydrophobic chains have attracted some attention recently for their selective complexing ability with a specific metal cation.2-5)

The dialkyl crown ethers are suspected to be unable or difficult, at least, to form well-ordered aggregates because of its low hydrophilicity. Shinkai and his co-workers resolved this problem properly by introducing an anion-cap as the main hydrophilic group into crown ring-containing dialkyl amphiphile to increase the hydrophilicity of molecule, and presented the electron microscope photographs of lamellar and rod-like structure.5)

We have obtained many informations about the surface active crown compounds. It was found that the complexing ability of these compounds with alkali metal cations are strong and selective even in aqueous solutions. Cloud points of aqueous solution of long-chain crown ethers were selectively and greatly raised by the addition of a series of alkali salts.6,7) Namely, the hydrophilicity of long alkyl chain crown ether can be improved remarkably by addition of the suitable salt to the solution, as well as by introduction of oligooxyethylene group between the alkyl group and crown ether ring.8-10)

Now, we wish to report a finding that a double-chain 18-crown-6 ether was dispersed stably in water by sonication, and the state of the solution was affected by added alkali cation, and wish to present the electron microscope photographs of bilayer structure constructed with this amphiphile bearing a crown ether ring as the main hydrophilic group. This double-alkyl chain crown ether may retain the unique character of typical crown ether concerning the strong and selective complexing ability toward metal cations,[10)] and can keep this compound nonionic. It may be expected that the HLB (Hydrophile-Lipophile Balance) of this crown ether amphiphile and the stability of the dispersed system and bilayer membrane, if formed, can be properly controlled by the addition of different kinds of salts.

Preparation of 3,5-bis(2,5,8-trioxaeicosyl)-18-crown-6 (**4**) is described in the following scheme: after sodium hydroxide 8 g (0.2 mol, powdered) was dissolved in 3,6-dioxa-octadecanol (**1**) 82.2 g (0.3 mol) at 90 °C, tetraethylene glycol diglycidyl ether (**2**)[11)] 15.3 g (0.05 mol) was added dropwise during 10 minutes at 80 °C, then the stirring was continued for additional 20 minutes. After adding water (200 ml), the reaction mixture was neutralized with 10% aqueous hydrochloric acid, and extracted with ether. Excess amount of **1** was removed by distillation at reduced pressure (145 °C/0.03 Torr) to leave polyether diol **3** as a residue in yield of 77% (32.8 g).



3,5-Bis-(2,5,8-trioxaeicosyl)-18-crown-6 (**4**) was then prepared by the intramolecular cyclization[12)] of diol **3**. Thus, into a suspension of powdered potassium hydroxide 1.1 g (0.02 mol) in dioxane (200 ml), was added dropwise **3** 4.3g (0.005 mol) and tosyl chloride 0.95 g (0.005 mol) in dioxane (100 mol) at 60 °C during 5 hours, and the mixture stirred for another 1 hour. Solid material was removed by filtration through a short column filled with silica gel. Compound **4** was isolated as a colorless viscous liquid in yield of 25% (1.0 g) by reversed phase liquid column chromatograpy with methanol as eluent. The structure and purity of **4** were identified from spectral and elemental analyses. ^1H NMR ($CDCl_3$) δ 0.80-1.00 (t, 6H), 1.20-1.70 (m, 40H), 3.40-4.00 (m, 46H); MS, m/e (relative intensity) 836 (M^+), 57 (100), 45 (67), 43 (67). IR (liquid film) 2950, 1470, 1140 cm^{-1}. Anal.

Calcd for $C_{46}H_{92}O_{12}$: C, 66.13; H, 11.20. Found: C, 65.99; H, 11.08.

Dialkyl crown ether **4** was dispersed in water (10 mM/l) to form a stable opalescent solution by sonication. On the contrary, more hydrophilic compound **3** only formed a turbid solution under the same sonication conditions, and greasy material separated gradually after several days. Upon the addition of potassium chloride or potassium phosphotungstate as a staining agent for transmission electron microscopy, the solution of **4** turned translucent, showing the salt-in effect.

In electron microscope (JEOL, 1200-EX) photographs of this solution (Figure 1), myelin-like fingerprint structures (a) and round water phase surrounded by single to multilayered membranes (b) can be clearly seen depending on the conditions for preparation. The thickness of the unit layer is about 4.5 nm.

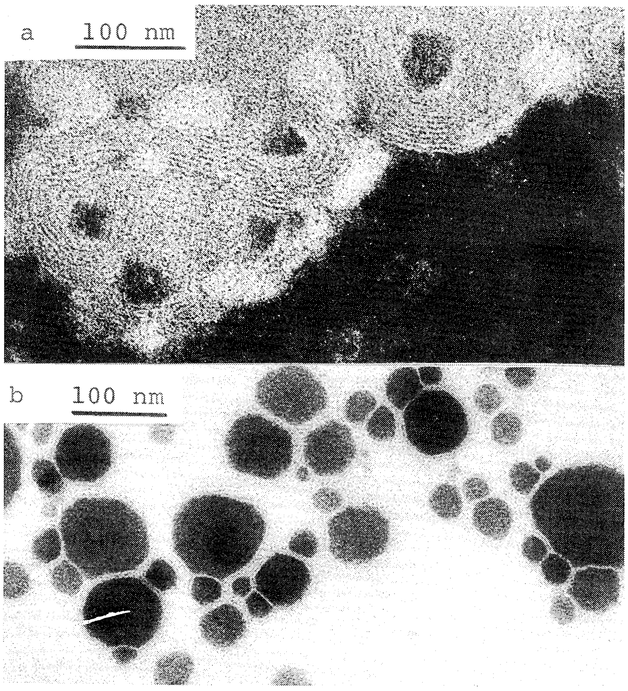


Fig. 1. Electron micrograph of **4** (10 mM): (a) sample stained by sodium phosphotungstate (150,000 as provided). (b) sample stained by potassium phosphotungstate (130,000 as provided).

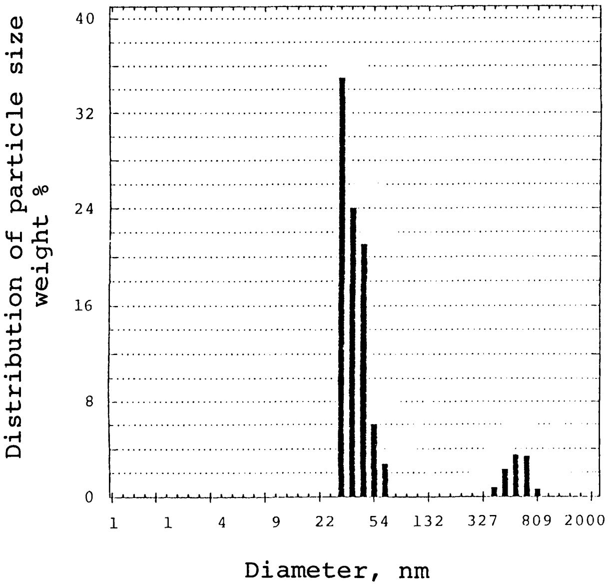


Fig. 2. Distribution of particle size of **4** dispersed in aqueous solution (10^{-3} mol/l)

The light scattering experiment (Union Giken Co., Japan, Model DLS-700) with a translucent solution (1 mM/l) of compound **4** prepared by sonication and filtered through a 1μm Sartorius filter (Type MF 4) is shown in Figure 2. There are observed two kinds of aggregate groups with different sizes in the dispersing solution of this dialkyl crown ether. The average diameters are about 40 nm and 600 nm, respectively.

The differential scanning calorimetry (Daini Seikosha Co., Ltd., SSC-560) with 60 μl of aqueous solution of **4** (1.5 wt%) did not show any significant endo- or exothermic peak between the range of 10-45 °C. But an exothermic phenomenon appeared at 46 °C, which may mean the degradation of aggregate structure occurred at this temperature. This phenomenon could also be observed by naked eye. Thus, when the sample solution was warmed to 46 °C, the solution became turbid and small oily particles arose gradually, similarly to the clouding phenomenon of the monoalkyl crown ethers,[13] but the original opalescent state can not be restored by cooling without sonication. On the other hand, the solution turned also turbid below 5 °C, which might be attributable to the occurrence of phase transition. This phenomenon can be considered that the liquid crystalline state transformed to the crystalline state at 5 °C, because it became opalescent again with the rise of temperature beyond this point, quite different from that of monoalkyl crown ethers, which did not show this kind of phenomenon with the lowering of temperature.[13]

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