ponents were rather short (with the PVP assumed to be the anchoring block) no hysteresis was observed.

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Viscoelastic Properties of Lipid Surfactant/Polymer Composite Films

Water-insoluble polyion complexes are formed from ionic lipids and ionic polymers with opposite charges.[1] By casting the solution of the polyion complexes in common halogenated organic solvents, lipid surfactant/polymer composite films are prepared. The aggregation state of the lipid in the films has already been examined by differential scanning calorimetry (DSC) and X-ray diffraction, and it was confirmed that the films are composed of lipid multilamellae, in which lipids aggregate in a manner similar to lipid bilayers (Figure 1).[1] For this reason, the composite films have been referred to as immobilized lipid bilayers. The films thus obtained are expected to exhibit unique properties based on the highly ordered structures similar to biomembranes. Membrane transport experiments were carried out for several solutes, and marked changes in permeation were observed near the phase-transition temperature of the lipid bilayers.[1b,c,e] However, the physical state of the lipid bilayers and the influence of ionic polymers on lipid bilayers are not fully known. In this paper, we report for the first time that dynamic viscoelastic measurement, which is effective to study the aggregation state and the phase state of polymers, is also very useful to know the fundamental properties of the lipid/polymer composite films. ESR studies of a spin probe incorporated into the films were also carried out to obtain information about molecular motion of the lipids.

According to the procedure of the previous reports,[1] the polyion complexes were obtained as precipitates by mixing a 2% aqueous dispersion of dialkyldimethylammonium bromide ($[CH_3(CH_2)_{n-1}]_2N^+(CH_3)_2Br^-$, n = 14, 16, 18) and a 0.5% aqueous solution of high molecular weight sodium poly(styrenesulfonate) (lipid/polymer repeating units 1.5:1 (mol/mol)) and purified by reprecipitation twice from chloroform with ethanol (recovery 30–50%). Polyion complexes consited of almost stoichiometric composition of lipids and polymer as determined by elementary analysis.[3] About 5% chloroform solutions of the polyion complexes were cast on flat glass plates and were evaporated to dryness at room temperature. Transparent films with thicknesses of 200–300 μm were obtained after vacuum drying.

Dynamic mechanical measurements of the composite films were made with a nonresonance, forced vibration instrument,[2] Rheovibron viscoelastmeter Model DDV-II-C (Toyo Baldwin Co. Ltd.) in water at a heating rate of 0.5 °C/min at a frequency of 110 Hz after aging the films at 60 °C in water for 10 min.

DSC measurements were performed with a Du Pont DSC 9900 system at a scanning rate of 10 °C/min in the presence of a small amount of water.

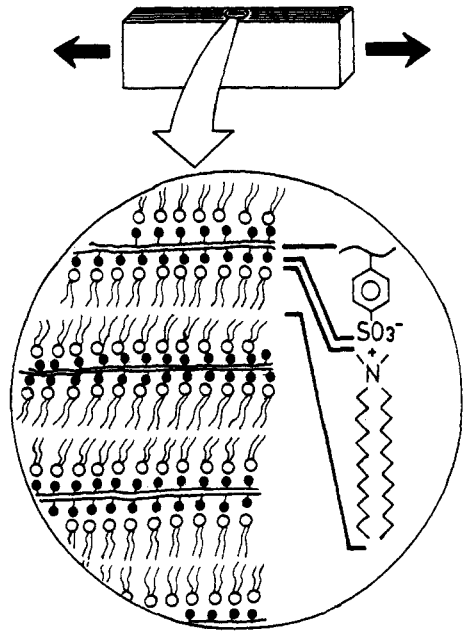


Figure 1. Schematic illustration of the structure of the lipid/polymer composite films. Arrows indicate the direction of oscillating stress and strain applied on the films. The specimen size was 5 mm in width, 10–15 mm in length, and 0.2–0.3 mm in thickness.

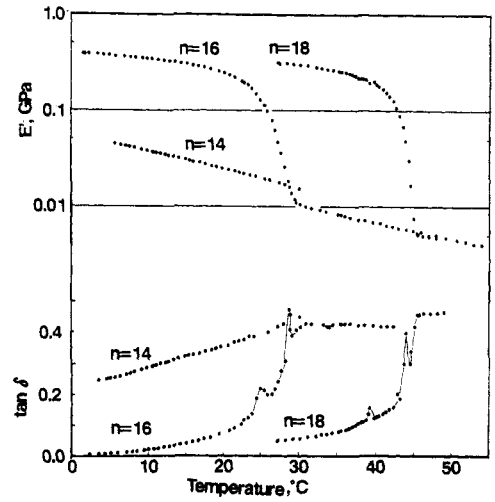
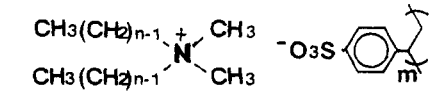


Figure 2. Thermomechanical behavior of the composite films, 2Cn2C1-PSS, n = 14, 16, 18.

The composite films for ESR measurement were prepared by casting the chloroform solutions of polyion complexes and 12-doxylstearic acid (spin probe concentration: 10^{-4} mol/1000 g of polyion complex). Samples were dried in vacuo and annealed in water at 60 °C prior to measurement. ESR spectra were recorded on a Varian E-line 9.5-GHz ESR spectrometer with a temperature control unit in the presence of a very small amount of water which does not interfere with measurement.

Figure 2 shows the dynamic mechanical storage modulus, E', and tan δ measured for the three composite films (2CnN2Cl-PSS, n = 14, 16, 18). These films have tensile



2CnN2C1-PSS n=14, 16, 18

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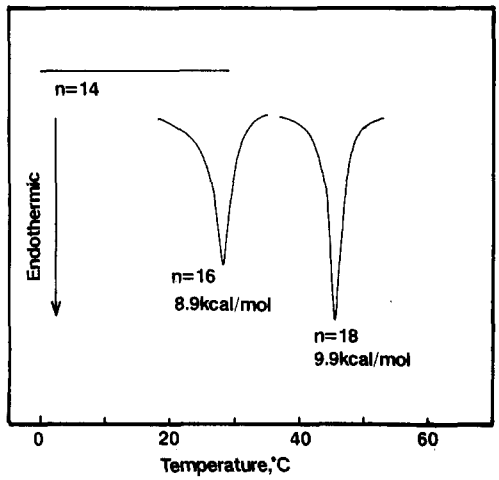

Figure 3. DSC thermogram of the composite films, 2CnN2C1-PSS, n = 14, 16, 18.

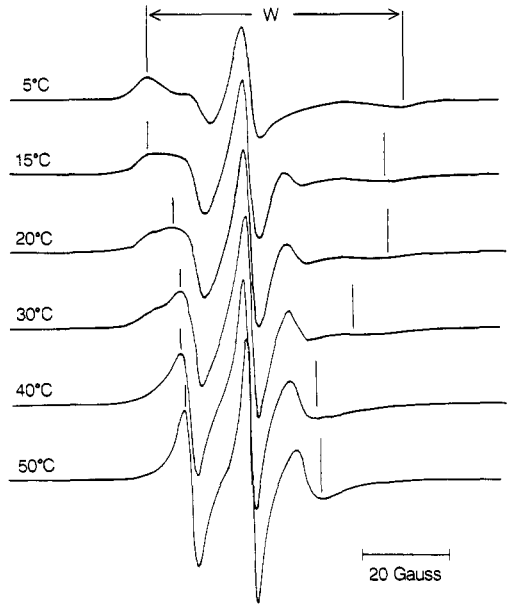

Figure 4. ESR spectra of 12-doxylstearic acid in the composite film at different temperatures.

strength enough to withstand the tension on measurement even in the liquid crystalline state. E' for 2C16N2C1-PSS decreased abruptly by about 2 orders of magnitude around 25 °C, which temperature corresponds to the phase transition observed in DSC thermogram (Figure 3). In the tan δ curve two narrow peaks were found around the phase transition temperature (T_c). The dynamic mechanical properties of 2C18N2C1-PSS, which has a higher T_c, were similar to those of 2C16N2Cl-PSS except for the temperature shift. The characteristic viscoelastic behavior was not found in the case of 2C14N2Cl-PSS because of the absence of the phase transition in the range of measurement. The temperature dependence of E' was moderate except around T_c. In the gel state of lipid bilayers below T_c, E' is 0.2–0.4 GPa (relatively soft polymer) and, in the liquid crystalline state above T_c, 0.005–0.05 GPa (gummy state of polymer), regardless of the alkyl chain length of the lipids. Temperature changes in tan δ were also not large except around T_c: tan δ is small below T_c (<0.2) and relatively large above T_c (0.4). Temperature variations of the ESR spectra of 12-doxylstearic acid in 2C16N2C1-PSS are shown in Figure 4. The spectra were not substantially different from that observed in vesiclar systems.[4] Significant changes in the line shape were not found at temperature below 0 °C and above 50 °C. The extrema separation was used as an indication of the movement of lipid bilayers. The decrease in the extrema separation from 60 to 30 G with increasing temperature indicates that enhancement in the thermal movement of lipid molecules in the films are attended by the phase transition from the gel state to the liquid crystalline state.[4]

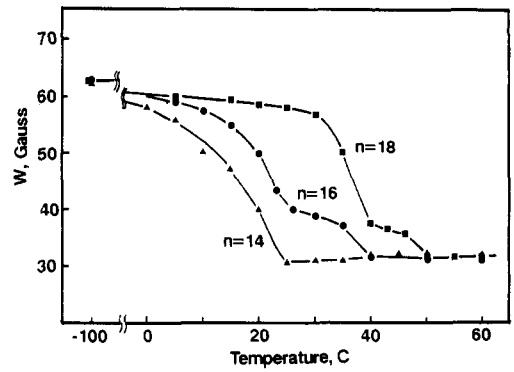

Figure 5. Extrema separation vs temperature plots for the composite films, 2CnN2C1-PSS, n = 14, 16, 18.

Figure 5 shows the temperature dependence of the extrema separation for the films having different T_cs. As the length of long alkyl chain of lipids increases, that is, T_c increases, the decrease region of the extrema separation was shifted to higher temperature.

ESR data indicate that the decrease of E' and the increase in tan δ at the phase transition correspond to the movement of lipid molecules. However, the composite films are appreciably different from that of a number of polymers reported, so detailed discussion of E' and the peak assignment of tan δ should be given after further investigation.

In order to investigate the basic properties of the lipid surfactant/polymer composite films, dynamic mechanical measurement is a very useful and easy method as shown in the preliminary results. The aggregation structures of lipids in aqueous media have been studied industriously for several decades by the use of various physical methods.[5] Evan Evans and his co-workers reported micromechanical methods to provide direct measurements of elasticity and rigidity of lipid bilayer membranes in aqueous media.[6] Viscoelastic measurement of the composite films can be expected to be another method to study the lipid bilayer itself; e.g., thermal movement of lipid molecules and miscibility of two lipids and lipid–protein interactions, although it is necessary to take into account the influences of the polymer main chain on the bilayer structure.

Registry No. Dimethyldi(tetradecyl)ammonium bromide–poly(styrenesulfonic acid) complex, 116911-37-6; dimethyldi(hexadecyl)ammonium bromide–poly(styrenesulfonic acid) complex, 116911-38-7; dimethyldi(octadecyl)ammonium bromide–poly(styrenesulfonic acid) complex, 116911-39-8; 12-doxylstearic acid, 29545-47-9.

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(3) Anal. Calcd for $C_{38}H_{71}NO_3S\cdot H_2O$ (2C14N2C1-PSS): C, 71.4; H, 11.4; N, 2.2. Found: C, 74.0; H, 11.7; N, 1.9; Br, 0.33. Calcd for $C_{42}H_{79}NO_3S\cdot H_2O$ (2C16N2C1-PSS): C, 72.5; H, 11.7; N, 2.0.

Found: C, 70.7; H, 11.1; N, 2.2; Br, —. Calcd for $C_{46}H_{87}NO_3S{\cdot}H_2O$ (2C18N2C1-PSS): C, 73.7; H, 11.6; N, 1.9. Found: C, 74.0; H, 12.2; N, 1.6; Br, 0.10.
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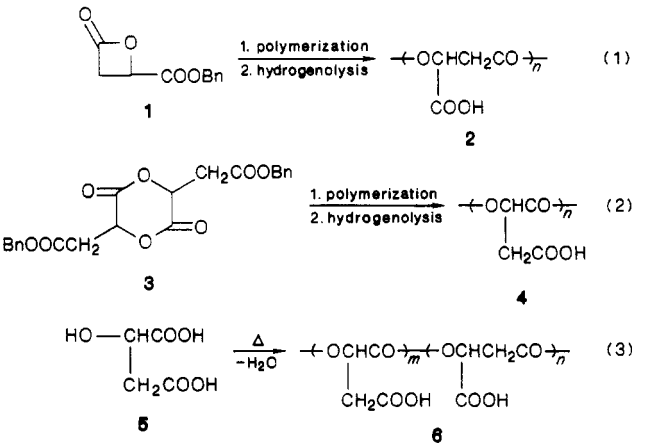
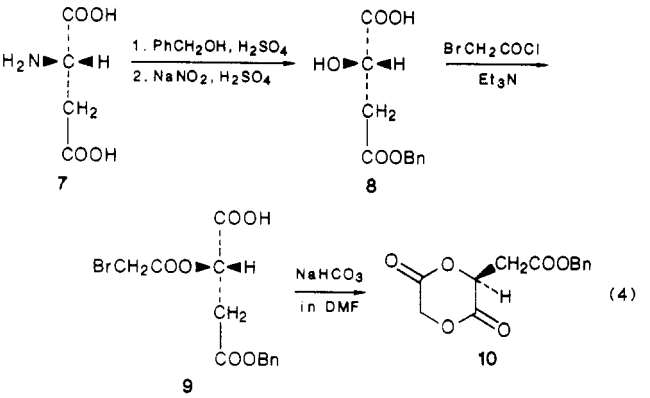
Ring-Opening Polymerization of 3(*S*)-[(Benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione: A New Route to a Poly(α-hydroxy acid) with Pendant Carboxyl Groups

Poly(α-hydroxy acid)s[1] such as poly(glycolic acid) (PGA) and poly(lactic acid) (PLA) are not only biocompatible but also bioresorbable. When they are implanted in living organisms including the human body, they are hydrolyzed to their constituent α-hydroxy acid which is eliminated by general metabolic pathways.[2] Based on these intriguing properties, various biomedical and pharmaceutical applications of poly(α-hydroxy acid)s have recently been developed including their use as polymeric drug carriers[3] and bioresorbable sutures.[4] The hydrolysis rates of the widely used poly(α-hydroxy acid)s are too slow because of their high crystallinity and water insolubility,[5] and this slow biodegradation interferes with the controlled release of drugs chemically bound to the polymers.[2,3,5] Consequently, recent work has focused on methods of imparting a hydrophilic nature to these polymers by suitable functionalization. For this purpose, Vert and Lenz have prepared poly(β-malic acid) (**2**) by the ring-opening polymerization of benzyl malolactonate (**1**) and the subsequent hydrogenolysis of the pendent benzyl ester.[6] Ouchi and Fujino have also prepared poly(α-malic acid) (**4**), from the cyclic diester **3** called malide,[7] although its preparation is quite difficult. Recently,[8] we have reported the preparation of the copolymer poly(α,β-malic acid) (**6**) by direct condensation of malic acid **5**. All these polymers have a pendant carboxyl group in every repeat unit which can be used to impart water solubility and to attach drugs for sustained release.

For the purpose of manipulating the hydrophilicity of these biodegradable polyesters, the copolymers containing a variable degree of functionality should be developed. Gross et al. have recently prepared such copolymers by the combination of **1** and other lactones.[9] However, the reactivities of the monomers **1**, **3**, and **5** are quite different from those of the common glycolide and lactide,[10] and application of the conventional copolymerization techniques fails to yield a copolymer. In this paper, we discuss the synthesis of a six-membered cyclic diester, 3(*S*)-[(benzyloxycarbonyl)methyl]-1,4-dioxane-2,5-dione (**10**), which polymerizes to the alternating copolymer **11** consisting of glycolic acid and benzyl α-(*S*)-malate units. This monomer has a comparable ring-opening polymerizability with glycolide and lactide. The pendant benzyl ester can readily be removed by catalytic hydrogenolysis after polymerization to yield poly[(glycolic acid)-*co*-(α-(*S*)-malic acid)] (**12**), which is a new carboxyl-functionalized poly(α-hydroxy acid).



The synthesis of the monomer **10** was accomplished according to eq 4. The optically pure benzyl α-(*S*)-malate



(**8**) ($[\alpha]^{25}_D$ = −8.6° (in MeOH, *c* = 1.0 g/dL), ref[12b] −8.6° (the same conditions)) was prepared from (*S*)-aspartic acid (**7**) by the methods reported previously.[11,12] Twenty grams of **8** was mixed with 18.4 g of bromoacetyl chloride in 300 mL of diethyl ether. With this mixture stirred vigorously, a solution of 9.9 g of triethylamine in 50 mL of diethyl ether was added dropwise at a temperature not exceeding 5 °C over a period of 30 min. After the addition was over, stirring was continued at room temperature for 6 h, and triethylamine hydrochloride precipitate was removed by filtration. The filtrate was then washed with the same volume of water several times, dried over sodium sulfate, and evaporated in vacuo. A pale yellow viscous liquid was obtained in a yield of 96%, which was identified as **9** by ^{1}H NMR spectroscopy (200 MHz in acetone-d_6): δ 3.02 (q, CH_2, 2 H), 4.02 (s, OCH_2CO, 2 H), 5.12 (s, CH_2Ph, 2 H), 5.50 (q, CH_2, 1 H), 7.35 (s, C_6H_5, 5 H). This compound **9** was not further purified, for the contaminant, bromoacetic acid, did not produce a side reaction in the following cyclization.

In the next step, a solution of 10 g of **9** in 50 mL of DMF was added dropwise to a mixture of 3.7 g of sodium bicarbonate in 950 mL of DMF with vigorous stirring at room temperature over a period of 8 h. The mixture was further stirred for 12 h and filtered to remove the crystals of NaBr and excess sodium bicarbonate. The filtrate was then evaporated in vacuo, and the residue was washed with isopropyl alcohol and sublimed at 0.01–0.001 mmHg. The sublimate was recrystallized from isopropyl alcohol to give

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