Table II. Autorecycling Oxidation of Cyclopentanol and *l*-Menthol by II at 120 °C for 25 h

oxidant (0.04 mmol)	product yield,[a-c] %	
	cyclopentanone[d]	*l*-menthone[e]
IIa	11 353 (13.06)	2776 (5.78)
IIb	11 274 (12.97)	3296 (6.87)
IIe	11 808 (13.59)	6279 (13.08)
IIf	15 929 (18.33)	9550 (19.90)
IIg	17 613 (20.27)	10611 (22.11)

[a] Yields have not been optimized. Based on the pyridodipyrimidines. [b] Isolated as the 2,4-dinitrophenylhydrazone. [c] Yields based on the starting alcohols are given in parentheses. [d] Starting alcohol is cyclopentanol (3 mL). [e] Starting alcohol is *l*-menthol (3 mL).

On the other hand, 3,7,9,10-tetramethylpyrido[2,3-*d*;6,5-*d'*]-dipyrimidine-2,4,6,8(3*H*,10*H*,7*H*,9*H*)-tetrones (IV), a fully substituted pyridodipyrimidine, almost never oxidized alcohols. This result indicates that the presence of acidic hydrogen (moving proton) at the nitrogen would be crucial for pyridodipyrimidines to act as an autorecycling oxidizing agent.

Similarly II oxidized several alcohols to give the corresponding carbonyl compounds in almost the same yields as in the oxidations by I. Table II shows an example of the autorecycling oxidation toward cyclopentanol and *l*-menthol by II.

It would be interesting that the above oxidation proceeded essentially until the alcohol substrates were almost exhausted; for example, in the reaction using Im (0.031 mmol) and cyclopentanol (2 mL) at 120 °C, the yield of cyclopentanone reached 56 602% (74.7% based on cyclopentanol) after 150 h. In control experiments without I or II in the above alcohols, at most, only a trace of carbonyl compounds was detected. Furthermore it should be noted that I and II used for reactions can be recovered in high yields (70–95%) and high state purity.

Therefore, the present method would be significant from the viewpoints of resource saving and environmental preservation as well as synthetic organic chemistry.

Acknowledgment. We are indebted to Kaoru Yoshino, Noriko Yano, and Etsuko Nagao for their technical assistance.

Vesicles of Polymeric Bilayer and Monolayer Membranes[1]

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We wish to report the first example of polymeric vesicles that retain the intrinsic bilayer and monolayer characteristics. We have been interested in the polymeric bilayer membrane since our discovery of a totally synthetic bilayer membrane,[2] because some of the basic instability element of bilayer vesicles (liposomes) might be eliminated by means of polymerization. Our initial attempts were polymerization of dialkyl amphiphiles which possess the vinyl group at the hydrophilic head group[3] or the alkyl tail end.[4,5] These approaches, however, did not give satisfactory results, as discussed below. In the subsequent approach, water-soluble copolymers shown in Chart I were prepared and some of them were shown to have typical bilayer characteristics in water. These polymers

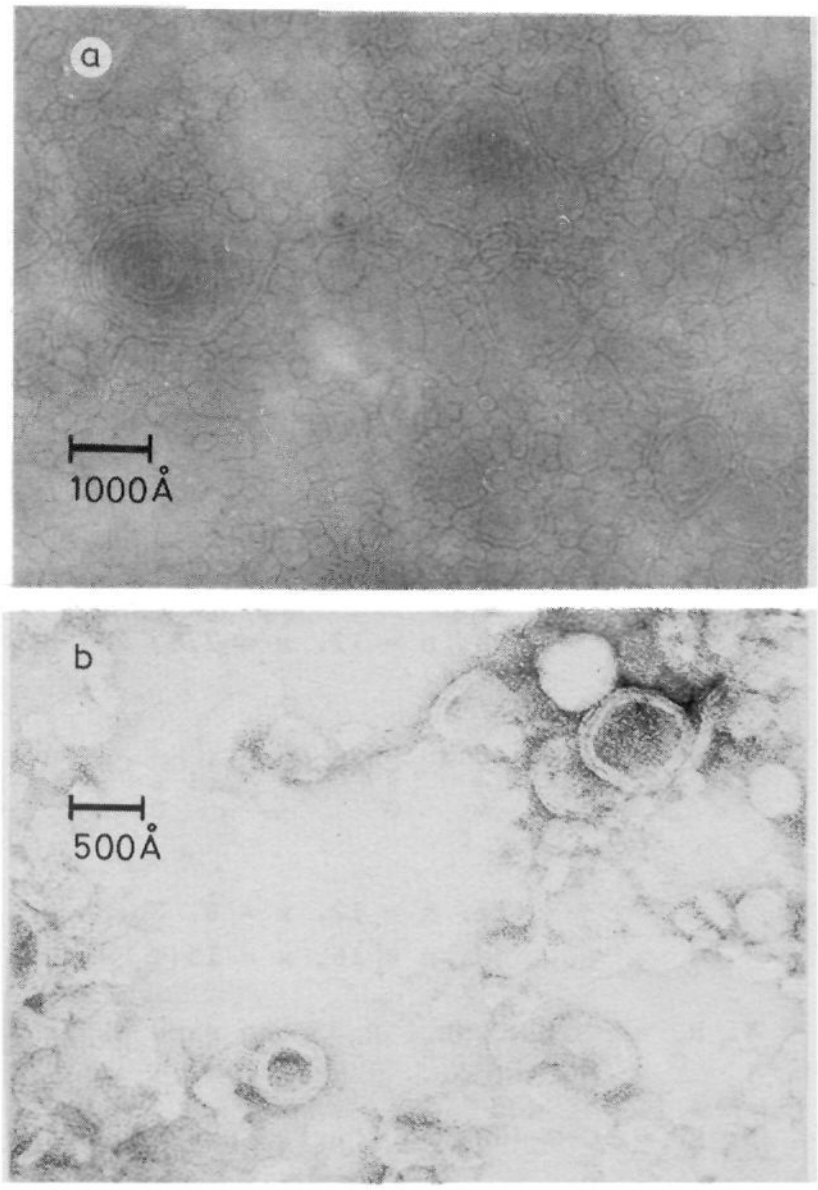

Figure 1. Electron micrographs of samples stained by uranyl acetate: (a) copolymer **3b**, 10^{-2} M of dialkyl unit (×80 000 as provided); (b) ionene polymer **7** (n = 20), 10^{-2} unit M (×150 000 as provided).

were obtained by radical copolymerization of hydrophilic monomers (acrylamide, *N*-acetamidoacrylamide, etc) and hydrophobic monomers with dialkyl side chains.[6] The dialkyl group is connected to the polymer backbone by the amide linkage as in **1** or via the glutamic acid residue as in **2** and **3**. The hydrophilic spacer (oxyethylene chain) is introduced except in the case of **2** in order to avoid the interference of the main chain with alignment of dialkyl groups. The hydrophilic unit may be nonionic (**1**–**4**), cationic (**5**), or anionic (**6**).

Copolymers **1**–**6** gave clear aqueous dispersions (1–2 × 10^{-2} M in the dialkyl group) by sonication for 0.5–2 min with a Branson cell disruptor 185 (sonic power, 60 W). Clear dispersions were not obtainable when acrylamide was used in place of *N*-acetamidoacrylamide or when the hydrophilic spacer was eliminated in **1**. In contrast, clear dispersions were obtained in the absence of the spacer, when the dialkylamide group was replaced with the dialkyl glutamate group.

The aggregate morphology of the copolymers was examined by electron microscopy for negatively stained samples[7] and freeze-fracture replicas.[8] Copolymers **2**–**4** gave well-developed bilayer vesicles in comparison with **1**. This is consistent with our previous observations that the ammonium amphiphiles with the

(1) Contribution No. 635 from Department of Organic Synthesis.
(2) Kunitake, T.; Okahata, Y. *J. Am. Chem. Soc.* **1977**, *99*, 3860–3861.
(3) Kunitake, T.; Okahata, Y. *Chem. Lett.* **1977**, 1337–1340.
(4) Fujiki, M. Master Thesis, Faculty of Engineering, Kyushu University, 1978. Hayashida, S. Master Thesis, Faculty of Engineering, Kyushu University, 1980.
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(6) The polymerization procedure is given for **3b** as a typical example: 1.0 g (1.2 mmol) of the dialkyl monomer, 0.35 g (5.0 mmol) of acrylamide, and 0.01 g (0.06 mmol) of azobis(isobutyronitrile) (initiator) dissolved in 20 mL of 1:1 ethanol–benzene were placed in an ampule, which was sealed upon subjecting to the freeze–pump–thaw cycle. The ampule was kept at 70 °C for 4 h and then the solvent removed, and the white residue was reprecipitated from dimethyl sulfoxide and acetone. The yield was 20%, and the polymer composition was determined by elemental analysis.
(7) The sample preparation procedure has been described elsewhere.[2] The staining agent (2% in water) was ammonium molybdate (pH 7) for copolymers **1** and **4**, uranyl acetate (pH 4) for copolymers **2**, **3**, and **5**, and phosphotungstic acid (pH 7) for copolymer **6**.
(8) Kunitake, T.; Okahata, Y.; Shimomura, M.; Yasunami, S.; Takarabe, K. *J. Am. Chem. Soc.* **1981**, *103*, 5401.

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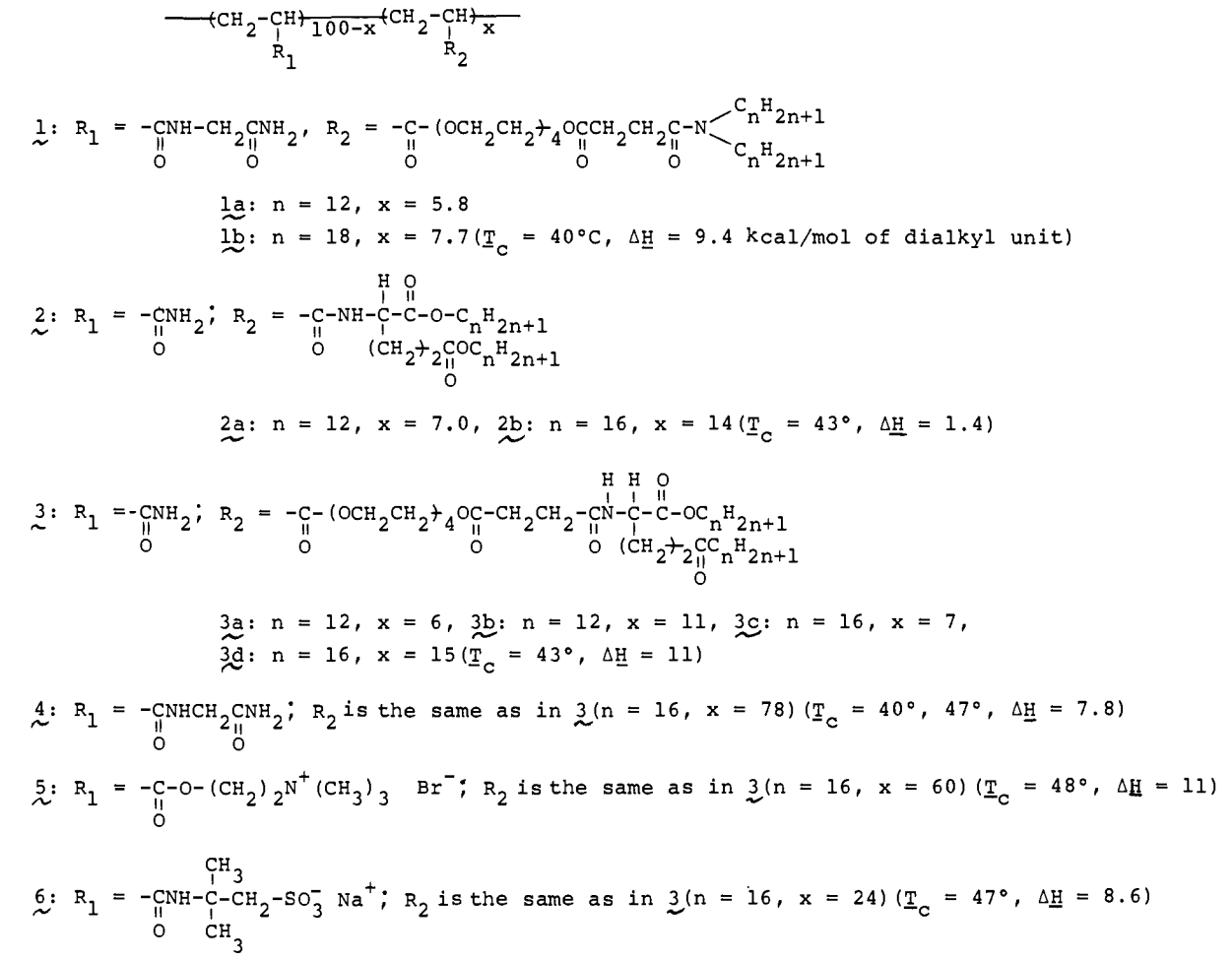
Chart I



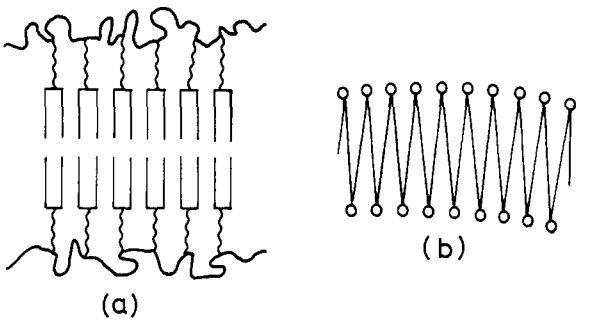


Figure 2. Schematic illustration of polymeric bilayer and monolayer membranes: (a) copolymers **1–6**; (b) ionene polymer **7**.

dialkyl glutamate residue produce better developed bilayer membrane than simple dialkylammonium amphiphiles.[9] Figure 1a is an electron micrograph of aqueous **3b**. Bilayer vesicles with diameter of 1000–2000 Å are seen. The layer width of 60–70 Å corresponds approximately to two times the alkyl chain length.

A freeze-fracture replica of aqueous **3b** also showed the presence of vesicles with diameter of 1000–2000 Å. It is obvious from these observations that the vesicles of **3b** are composed of the bilayer structure such as shown in Figure 2a.

The bilayer formation was confirmed by differential scanning calorimetry (DSC) (Daini-Seikosha, SSC/560) and molecular weight measurement (Toyo Soda Co., LS-8, laser light scattering apparatus). Aqueous dispersions (0.01–0.02 M in the dialkyl unit) of copolymers **1–6** show endothermic peaks in the DSC heating cycle, which apparently is derived from the gel-to-liquid crystal phase transition of the bilayer membrane. The phase transition temperature (T_c) and the transition enthalpy (ΔH) are given in Chart I. The T_c value is not affected much for a given alkyl chain length by the presence or absence of the spacer or the nature of the hydrophilic group, but the ΔH value is influenced by the spacer group and the copolymer composition.

The copolymers give molecular weight in the range of several millions in water: 1×10^6 for **3a**, 3×10^6 for **3d**, and 9×10^6 for **4**. On the other hand, the molecular weights of the same copolymers determined as $CHCl_3$ solutions are in the range of $(2–5) \times 10^4$. Since the polymers are supposedly not aggregated in $CHCl_3$, the latter value indicates molecular weight of the individual polymer molecule. It is thus concluded that the aqueous vesicles are composed of 100–200 polymer molecules.

The copolymer vesicle is capable of retaining water-soluble substances in the inner water core. In the present study, glucosamine was used as a probe and detected after converting to a fluorescent compound by reaction with fluorescamine.[10] The extent of retention was 2.3% for vesicles of **3b** and 2.8% for vesicles of **4**. On the other hand, copolymer **3a** which produces lamellar aggregates cannot retain glucosamine. The aggregate morphology observed by electron microscopy is consistent with the results of the retention experiment as for the presence or absence of the inner water core. The extent of the glucosamine retention was close

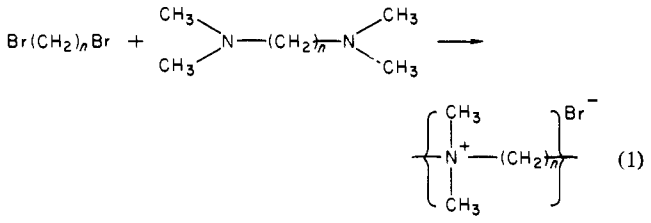
(9) Kunitake, T.; Nakashima, N.; Hayashida, S.; Yonemori, K., *Chem. Lett.* **1979**, 1413–1416.

(10) A vesicle solution (1×10^{-2} M in the dialkyl unit) and 0.39 mM of glucosamine were sonicated for 5 min in borate buffer (pH 7.9, $\mu = 0.02$ KCl) and aged for 30 min with ice cooling. The solution was subjected to gel chromatography (Sephadex G-50, 12 × 200 nm). Each fraction (1 mL) was added with 50 μL each of aqueous Triton X-100 (200 mM) and 0.9 mM fluorescamine in acetone, allowed to stand for 40 min, and the intensity of the fluorescence emission was determined at 480 nm (excitation wavelength 390 nm). This technique was previously used by Lee and Forte.[11]

(11) Lee, H. C.; Forte, J. G. *Biochim. Biophys. Acta* **1979**, *554*, 375–387.

to that found for typical dialkylammonium vesicles.[12,13]

Our second approach to the polymeric vesicle is the use of ionene polymers **7** prepared according to eq 1.[14]

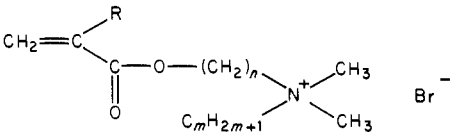


7 (n = 12, 16, 20)

Polymer **7** gave clear dispersions upon sonication. Electron microscopy indicated that vesicles are formed from **7** (n = 12, 20) and that vesicles and lamellae are present for aqueous **7** (n = 16). An electron micrograph of aqueous **7** (n = 20) is shown in Figure 1b. The observed layer width (ca. 25 Å) is consistent with the membrane formation by chain folding as illustrated in Figure 2b.

The polymer membranes of **7** undergo phase transition: T_c = 53 °C for n = 20, T_c = 27 °C for n = 16, and no transition detected for n = 12. The molecular weight of aqueous **7** (n = 20) was 2×10^6. As anticipated, ionene polymers composed of alkyl chains of different lengths do not form the membrane structure.

In our previous attempts mentioned above, we prepared amphiphilic monomers **8** and examined their polymerization behavior in water and the change in the aggregate morphology due to polymerization.[4,5,16]



8a, R = H (n, m = 10, 12; 10, 18; 16, 12; 16, 18)
b, R = CH_3 (n, m = 16, 18)

Unfortunately, the bilayer structure was not clearly seen by electron microscopy for the monomer aggregate and the polymerized aggregate. The T_c value of the aqueous aggregate lowered appreciably upon polymerization: T_c = 61 °C for **8a** (n, m = 16, 18) monomer and 31 °C upon polymerization; T_c = 46 °C for **8b** (n, m = 16, 18) monomer and 31 °C upon polymerization. These results suggest that polymerization promotes disorder in the bilayer assemblage.

Recently, Regen and co-workers[17] reported vesicle formation from **8b** (n, m = 11, 16) and its polymer, but the bilayer structure was not clearly visibile by electron microscopy. Attempts to stabilize bilayer vesicles by polymerization were also reported by Ringsdorf et al.,[18] Chapman et al.,[19] and O'Brien et al.[20] They synthesized dialkyl amphiphiles with the diacetylene moiety in the center of the alkyl chain. The polymerized vesicle showed enhanced stability, although the phase transition behavior was lost upon polymerization.

In conclusion, we could show that vinyl polymers with the hydrophilic main chain can form bilayer vesicles through the side-chain aggregation. The vesicle retains the liquid crystalline characteristics. This is important, since the peculiar property of the bilayer membrane is related to its liquid crystalline nature. The enhanced stability of polymer vesicles **1**–**7** is now under detailed investigation. For example, these vesicles undergo fusion less efficiently than ordinary bilayer vesicles. Our interests are directed to the use of the polymer vesicle as models of the vesicle–protein interaction and the vesicle–cell interaction and as carriers of drugs and other biologically active substances into the cell.

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(13) Kunitake, T.; Okahata, Y.; Yasunami, S., *Chem. Lett.*, in press.
(14) Ionene polymers were prepared according to the procedure of Rembaum and Noguchi.[15] A typical procedure is as follows: 2.64 g (6×10^{-3} mol) of 1,20-dibromoeicosane and 2.21 g (6×10^{-3} mol) of 1,20-bis(*N*,*N*-dimethylamino)eicosane were dissolved in 20 mL of purified tetrahydrofuran (THF) and stirred for 100 h at room temperature. The precipitates were washed with THF and reprecipitated from dimethyl sulfoxide and THF to give **7** as a colorless powder (n = 20) in 2.8 g (58%) yield.
(15) Rembaum, A.; Noguchi, H. *Macromolecules* **1972**, *5*, 261–269.
(16) Polymerization condition: monomer 10 mM in water; 11 °C; dose rate (^{60}Co) 9.5×10^4 R/h.
(17) Regen, S. L.; Czech, B.; Singh, A. *J. Am. Chem. Soc.* **1980**, *102*, 6638–6640.
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Nucleophilic Oxygen Atom Transfer Reactions by Persulfoxide and Persulfone[1]

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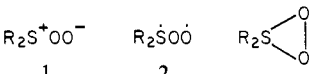
Oxygen atom transfer reactions are of current interest as a model of monooxygenase enzymes;[2] among them are those from carbonyl oxides,[3] pyridine *N*-oxide,[4] and unstable cyclic peroxides.[5] Especially, much attention has been concentrated on the structure[6] and reactions[3,7] of carbonyl oxides. In the course of studies on the photooxidation of benzoins[8] and diazoketones,[9] we could characterize a nucleophilic O-transfer reaction by intermediates formed in the sensitized photooxidation of sulfides and sulfoxides.

Foote et al.[10] have elegantly suggested that in the reaction of sulfide R_2S with $^1O_2$, a persulfoxide structure **1** is more appropriate than diradical **2** or cyclic dioxirane one **3** as an intermediate oxidizing another sulfide molecule to sulfoxide. Their rationale



1 2 3

is based on the trapping of the intermediate by Ph_2S and the dramatic acceleration of the photooxidation of R_2S by protic

(1) Contribution No. 287.
(2) G. A. Hamilton, "Molecular Mechanism of Oxygen Activation", O. Hayaishi, Ed., Academic Press, New York, 1974, p 405.
(3) (a) H. Kwart and D. M. Hoffman, *J. Org. Chem.*, **31**, 419 (1966); (b) G. A. Hamilton and J. R. Giacin, *J. Am. Chem. Soc.*, **88**, 1584 (1966); (c) T. A. Hinrichs, V. Ramachandren, and R. W. Murray, *ibid.*, **101**, 1282 (1979); (d) W. Ando, H. Miyazaki, and S. Kohmoto, *Tetrahedron Lett.*, 1317 (1979).
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