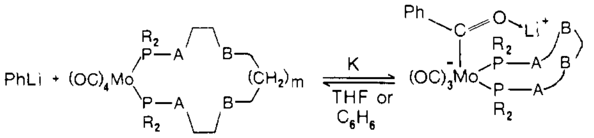
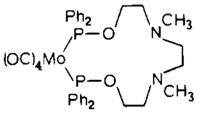
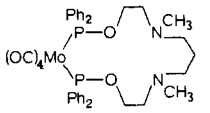
the diphosphinite ligand together with the "benzoylate-acylate-type" oxygen in the product molecule. In order to assess the magnitude of this effect and factors which favor it we have prepared and fully characterized the series of complexes **3**–**6** (yields 5–50%) via procedures analogous to the preparation of **1**. Stable benzoylate and acylate complexes structurally analogous to **2** (see Figure 2) have been isolated from the reaction of RLi with **3**, **4**, and **5a**, **b**. Infrared spectroscopy (ν_{CO} region) may be used to study the solution equilibrium 2 for the series of complexes **1** and **3**–**6** (e.g., see Figure 3).



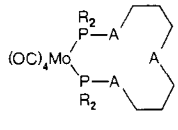
(2)



3



4



5a, R = Ph; A = O
b, R = Et; A = O
6a, R = Ph; A = NCH₃
b, R = Et; A = NCH₃

Selected equilibrium constants K (defined as ([Mo(CO)$_3$(RCOLi)P$_2$]/([Mo(CO)$_4$P$_2$][RLi])) are given in Table I together with ν_{CO} data for the Mo(CO)$_4$P$_2$ complexes. Values of K vary from $<10^{-2}$ L mol^{-1} for **6**/PhLi systems to $>10^5$ L mol^{-1} for the **3**/PhLi system. The data indicate that the benzoylate product in reaction 2 is favored by B = NMe > O and A = O ≫ NMe and the 2,2,2 ligand > 3,3 ligand > 2,3,2 ligand. Features which favor Li$^+$ binding in the product molecule are the following: (i) A ligand should be one donor atom short of providing Li$^+$ with a "full" coordination sphere [compound **1** (n = 4) complexes Li$^+$ but does not react to a significant extent with RLi). (ii) The ligand should be of a suitable size (12–14 atom ring). (iii) The ligand must accommodate the stereochemical requirements of the bridging M-C=O→Li$^+$ unit (molecular models indicate that steric interactions between PPh$_2$ and NMe groups for **6a** effectively prevent this complex from meeting this requirement). (iv) Atoms A and B should be as basic as possible. Thus B = NMe > O [e.g., compare **3** with **1** (n = 3)] and A = O ≫ NMe (e.g., compare **5b** with **6b**). [N→P π delocalization of the nitrogen lone pair effectively reduces the basicity of the P-N unit below that for P-O.[17] Delocalization of one of the P-O oxygen lone pairs onto phosphorus is also apparent in the molecular structure of **2** (M = Mo, R = Ph; Figure 2). The bond angles about the phosphinite oxygens are consistent with trigonal planar oxygen (e.g., ∠POC = 123, ∠POLi = 120, ∠LiOC = 117°)].

A comparison of the equilibrium data (Table I) for the reaction of **3** with PhLi vs. **6** with PhLi indicates that *preferential Li$^+$ binding in the product molecule can contribute ca. 9 kcal mol^{-1} of additional stabilization for the* **3** *system.* Thus cation binding by suitably designed ligands can provide *very significant* additional activation with respect to the reactions of coordinated carbon monoxide. Synthetic studies and investigations of metal carbonyls containing mono- and di-P-donor ligands with "pseudo-crown-ether" characteristics and capable of complexing Li$^+$, Mg^{2+}, and Al^{3+} are currently in progress.

Acknowledgment. Financial assistance from the Natural Sciences and Engineering Research Council of Canada is greatly appreciated.

Supplementary Material Available: A list of atomic coordinates and thermal parameters for (OC)$_3$Mo(PhCOLi)[Ph$_2$P(OCH$_2$CH$_2$)$_3$OPPh$_2$], complex **2** (M = Mo, R = Ph) (5 pages). Ordering information is given on any current masthead page.

---

[17] Grec, D.; Hubert-Pfalzgrat, L. G.; Riess, J. G.; Grand, A. *J. Am. Chem. Soc.* **1980**, *102*, 7133 and references therein.

Autorecycling Oxidation of Alcohols Catalyzed by Pyridodipyrimidines as an NAD(P)$^+$ Model

Fumio Yoneda,* Hirotake Yamato, and Masami Ono

Faculty of Pharmaceutical Sciences, Kumamoto University
Oe-honmachi, Kumamoto 862, Japan

Received January 28, 1981

The alcohol dehydrogenases catalyzing the interconversion between carbonyl compounds and alcohols require NAD(P)$^+$/NAD(P)H as coenzymes. In the biomimetic reactions, both classes of the N-substituted 1,4-dihydronicotinamides and the Hantzsch esters have been widely used as models of NAD(P)H.[1] However, there are few examples for the NAD(P)$^+$ model oxidation of alcohol substrates,[2-5] because thermodynamically the redox equilibrium favors the formation of the pyridinium ion. Furthermore these model oxidations of alcohols proceeded only with the aid of very strong base[6] and gave the carbonyl compounds in stoichiometric yields.

Recently we reported that 5-deazaflavins[7] and their analogues such as 4-deazatoxoflavins[8] were considered to be NAD(P)$^+$ models which oxidized alcohols under weakly basic conditions and thereupon exhibited some recycling in the oxidation giving carbonyl compounds in more than 100% yield.

We here report an efficient and autorecycling oxidation of alcohols which is catalyzed by the new type NAD(P)$^+$ model working *under neutral conditions*. The NAD(P)$^+$ models used in the present study are two kinds of pyridodipyrimidines, 3,7,10-trisubstituted pyrido[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6,8-(3*H*,10*H*,7*H*,9*H*)-tetrones (I) and 3,8,10-trisubstituted pyrido-[2,3-*d*:6,5-*d*′]dipyrimidine-2,4,6(3*H*,10*H*,7*H*)-triones (II).

The pyridodipyrimidines (I and II) are structurally cyclized compounds of the amino analogues of the Hantzsch esters and also have a conjugated system similar to that of 5-deazaflavins. Furthermore, one of canonical forms can be considered as a model of the nicotinamide nucleotide protected by annelation ("masked NAD$^+$ analogue") (Scheme I). Thus it was expected that I and II abstract hydrogen (or its equivalents) from alcohol substrates. In fact, I and II have been found to oxidize a variety of alcohols under neutral conditions (in the absence of base) to yield the corresponding carbonyl compounds, and, furthermore, a remarkable autorecycling in the oxidation was observed.

Compounds I and II were synthesized by the condensation of the corresponding 6-chloro-5-formyluracils[9] with appropriate 6-(substituted-amino)uracils (for Ia–n) or with appropriate 6-(alkylamino)-2-phenylpyrimidine-4(3*H*)-ones[10] (for IIa–h) in

---

[1] (a) R. J. Kill and D. A. Widdowson, in "Bioorganic Chemistry", Vol. 4, E. E. van Tammelen, Ed., Academic Press, 1978, p 239; (b) T. J. van Bergen, D. M. Hedstrand, W. H. Kruizinga, and R. M. Kellog, *J. Org. Chem.*, **44**, 4953 (1979); (c) A. Ohno, K. Ikeguchi, T. Kimura, and S. Oka, *J. Am. Chem. Soc.*, **101**, 7036 (1979); (d) R. A. Gase and U. K. Pandit, *ibid.*, **101**, 7059 (1979).

[2] K. Wallenfels and W. Hanstein, *Angew. Chem., Int. Ed. Engl.*, **4**, 869 (1965).

[3] A. Shirra and C. J. Suckling, *Tetrahedron Lett.*, 3323 (1975); *J. Chem. Soc. Perkin Trans. 2*, 759 (1977).

[4] Y. Ohnishi and M. Kotami, *Tetrahedron Lett.*, 4035 (1978).

[5] S. Shinkai, H. Hamada, H. Kuroda, and O. Manabe, *Chem. Lett.*, 1235 (1980).

[6] Exceptionally, Wallenfels and Hanstein[2] reported the oxidation of fluorenol to fluorenone by *N*-methyl-3,4,5-tricyanopyridinium perchlorate under neutral conditions. Although this unusual NAD(P)$^+$ model has very high electron affinity by virtue of the three cyano groups, the yield of fluorenone was still only 8%.

[7] (a) F. Yoneda, Y. Sakuma, and P. Hemmerich, *J. Chem. Soc., Chem. Commn.*, 825 (1977); (b) F. Yoneda, K. Tsukuda, K. Shinozuka, F. Hirayama, K. Uekama, and A. Koshiro, *Chem. Pharm. Bull.*, **28**, 3049 (1980); (c) F. Yoneda, K. Mori, M. Ono, Y. Kadokawa, E. Nagao, and H. Yamaguchi, *ibid.*, **28**, 3576 (1980); (d) F. Yoneda, K. Mori, S. Matsuo, Y. Kadokawa, and Y. Sakuma, *J. Chem. Soc., Perkin Trans. 1*, 1836 (1981).

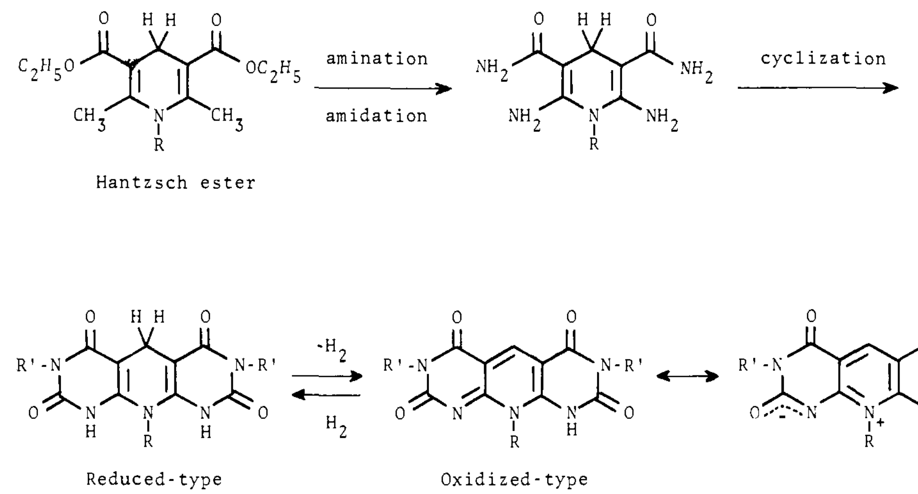
[8] (a) F. Yoneda and K. Nakagawa, *J. Chem. Soc., Chem. Comm.* 878 (**1980**); (b) F. Yoneda, K. Nakagawa, M. Noguchi, and M. Higuchi, *Chem. Pharm. Bull.*, **29**, 379 (1981).

[9] S. Senda, K. Hirota, G.-N. Yang, and M. Shirahashi, *Yakugaku Zasshi*, **91**, 1372 (1971).

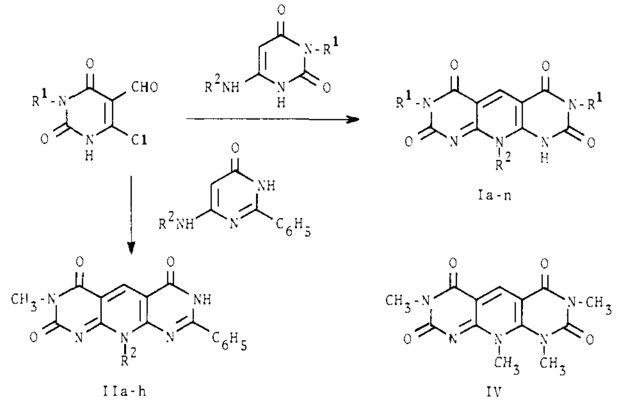
[10] F. Yoneda and T. Nagamatsu, *J. Chem. Soc., Perkin Trans. 1*, 1547 (1976).

0002-7863/81/1503-5943$01.25/0

Scheme I



Scheme II



Compd. No.	R^1	R^2	Mp (°C)
Ia	CH_3	CH_3	>330
Ib	CH_3	C_2H_5	>330
Ic	CH_3	$\underline{n}$-C_4H_9	>330
Id	CH_3	$\underline{n}$-C_8H_{17}	219
Ie	CH_3	$\underline{n}$-$C_{12}H_{25}$	206
If	CH_3	$C_6H_5(CH_2)_2$	>330
Ig	CH_3	C_6H_5	>330
Ih	CH_3	4-CH_3-C_6H_4	>330
Ii	CH_3	4-Cl-C_6H_4	>330
Ij	CH_3	4-Br-C_6H_4	312
Ik	CH_3	3,4-$(CH_3)_2$-C_6H_3	>330
Il	C_6H_5	C_6H_5	310
Im	C_6H_5	4-CH_3-C_6H_4	276
In	C_6H_5	4-Cl-C_6H_4	298

Compd. No.	R^2	Mp (°C)
IIa	CH_3	>330
IIb	C_2H_5	>330
IIc	$\underline{n}$-C_3H_7	>330
IId	$\underline{n}$-C_4H_9	>330
IIe	$\underline{n}$-C_8H_{17}	>330
IIf	$\underline{n}$-$C_{12}H_{25}$	>330
IIg	$\underline{n}$-$C_{18}H_{37}$	>330
IIh	$C_6H_5(CH_2)_2$	>330

N,*N*-dimethylformamide or acetic acid in 70–95% yields (Scheme II).

The experimental procedure for alcohol oxidation is quite simple. A mixture of I (0.04 mmol) in an appropriate alcohol (1–3 g) was just stirred in a flask joined with a refluxing condenser at an appropriate temperature (50–130 °C). The reaction mixture was diluted with ether, and the catalyst (I) [mixed with the reduced-type catalyst (vide infra)] thus separated was filtered off. The filtrate was treated with a 2 N HCl solution of 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylhydrazone of the corresponding carbonyl compound. Under these conditions, the 1,5-dihydropyridodipyrimidine (III) initially formed is reoxidized to the original I by adventitious air, and thus I acts as a turnover catalyst (Scheme III). In fact, III[11] was isolated from the reaction mixture and was identified with the authentic sample unequivocally synthesized by the sodium dithionite reduction of I. Furthermore, III also was effective for the oxidation of alcohols.

Scheme III

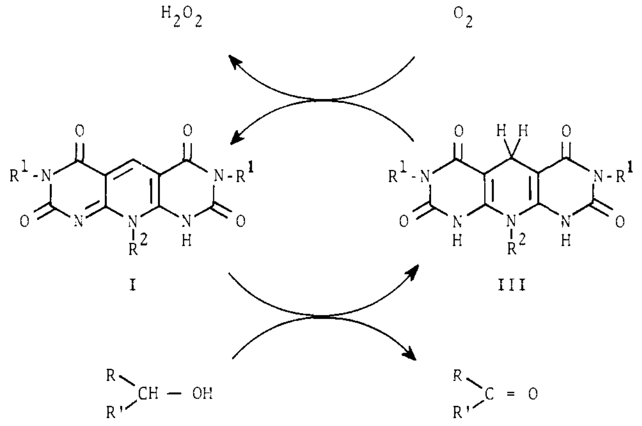


Table I. Autorecycling Oxidation of Alcohols by I at 90 °C for 25 h

alcohol substrate (amount, mL)	oxidant (0.04 mmol)	product	yield,[a-c] %
ethylene glycol (2)	Il	glycol aldehyde	2632 (3.27)
ethylene glycol (2)	Im	glycol aldehyde	3418 (4.24)
ethylene glycol (2)	In	glycol aldehyde	3795 (4.71)
benzyl alcohol (2)	Il	benzaldehyde	4855 (10.50)
benzyl alcohol (2)	Im	benzaldehyde	11345 (24.53)
benzyl alcohol (2)	In	benzaldehyde	6287 (13.60)
cyclopentanol (2)	Il	cyclopentanone	2017 (3.47)
cyclopentanol (2)	Im	cyclopentanone	3058 (5.27)
cyclopentanol (2)	In	cyclopentanone	2391 (4.12)
cyclohexanol (2)	Il	cyclohexanone	7505 (15.03)
cyclohexanol (2)	Im	cyclohexanone	22350 (44.77)
cyclohexanol (2)	In	cyclohexanone	12385 (24.81)
cycloheptanol (1)	Il	cycloheptanone	3396 (15.51)
cycloheptanol (1)	Im	cycloheptanone	5487 (25.06)
cycloheptanol (1)	In	cycloheptanone	10147 (46.34)
cyclooctanol (1)	Il	cyclooctanone	7320 (37.54)
cyclooctanol (1)	Im	cyclooctanone	9357 (47.99)
cyclooctanol (1)	In	cyclooctanone	7090 (36.36)

[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.

In this way, I showed generally strong oxidizing power toward a variety of alcohols to yield the corresponding carbonyl compounds in several thousand or more percent yield. In particular, 2,7,10-triaryl derivatives (Il, -m, and -n) exhibited an excellent autorecycling as shown in Table I.

---

[11] 1,5-Dihydropyridodipyrimidines (III) showed a characteristic signal of C_5-H_2 at the 3.9-ppm region in the NMR (CF_3CO_2H) spectrum.

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]

T. Kunitake,* N. Nakashima, K. Takarabe, M. Nagai,
A. Tsuge, and H. Yanagi

Department of Organic Synthesis, Faculty of Engineering
Kyushu University, Fukuoka 812, Japan

Received May 12, 1981

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 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**).

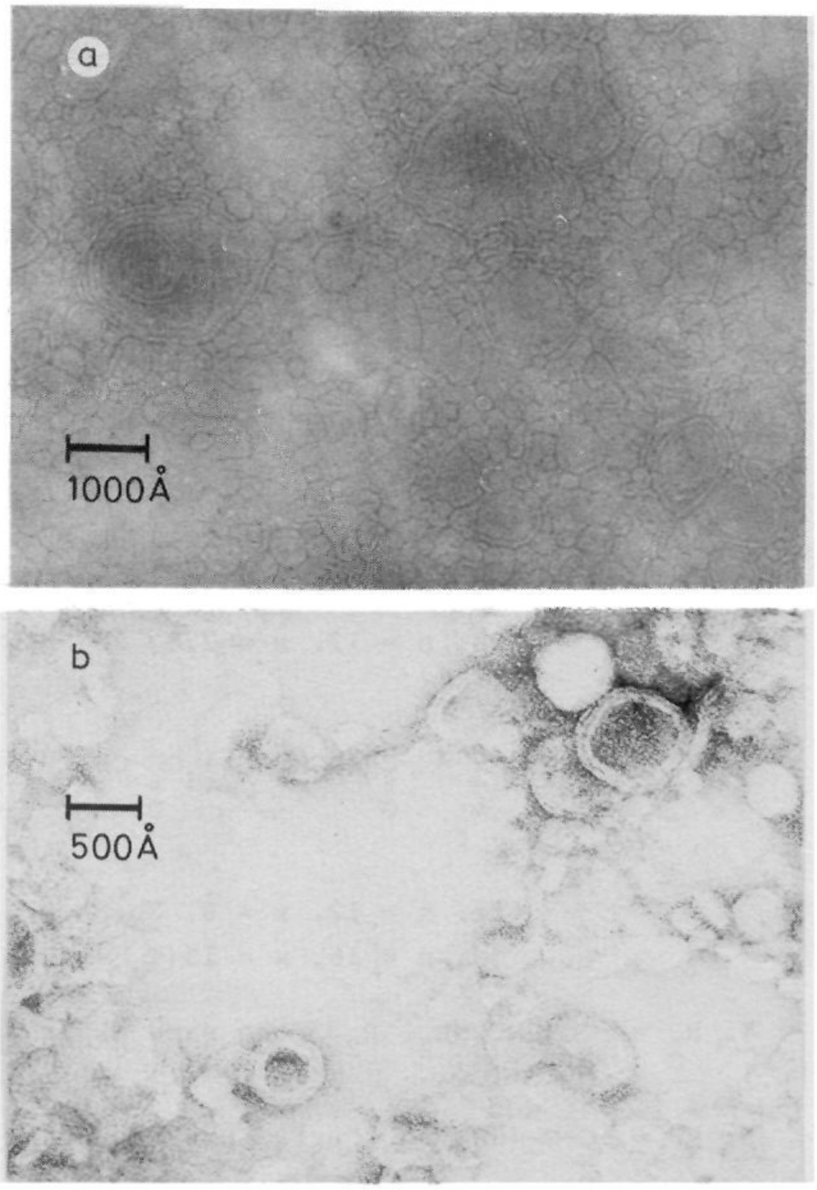


Figure 1. Electron micrographs of samples stained by uranyl acetate: (a) copolymer **3b**, 10^{-2} M of dialkyl unit (×80 000 as provided); (b) ionene polymer **7** (n = 20), 10^{-2} unit M (×150 000 as provided).

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.

(5) Hayashida, S.; Takarabe, K.; Fujiki, M.; Kunitake, T. *Polym. Prepr. Jpn.* **1979**, *28*(1), 107.

(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.

0002-7863/81/1503-5945$01.25/0