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SYNTHESIS AND PROPERTIES OF POLYURETHANES CONTAINING PHOSPHATIDYLCHOLINE ANALOGUES IN THE SIDE CHAINS

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ABSTRACT

Several polyurethanes containing phosphatidylcholine analogues in the side chains were synthesized by reaction of oleyl-2-[*N*-(methyldiethanolammonium) ethyl phosphate (**3a**) or (*p*-nonylphenyl)-2-[*N*-(methyldiethanolammonium) ethyl phosphate (**3b**) with diisocyanates such as 2,4-tolylene diisocyanate (TDI), 4,4′-methylene diphenyl diisocyanate (MDI), and *m*-xylylene diisocyanate (XDI), respectively. The new diols **3a** and **3b** were characterized by their IR and ^{1}H-NMR spectral data and elemental analyses. Polyurethanes were characterized by their IR spectral data. Polyurethanes with properties similar to the usual polyelectrolytes are described.

INTRODUCTION

There is considerable interest in polyurethanes as biomaterials because they are reported to exhibit excellent mechanical properties, resistance to biodegradation, and favorable biocompatibility [1–3]. However, the inherent thrombogenicity of polyurethanes still causes some problems and limits their greater widespread application. A variety of approaches has been taken to improve the blood compatibility of polymer surfaces [4–6]. On the other hand, considerable attention has been paid to phospholipids because they are known to be the important building units of

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biological membranes [7, 8]. From this point of view, it seemed very attractive to investigate the behavior of polymers containing phospholipid analogues. During the past 20 years a great amount of our effort has been directed toward the synthesis and properties of polymeric phospholipid analogues [9–14]. As a part of our general survey on biomembrane models, we have synthesized a series of new polyurethanes containing phosphatidylcholine analogues in the polymer backbones and in the side chains. The synthesis and properties of polyurethanes containing phosphatidylcholine analogues in their polymer backbones have been reported elsewhere [15]. The present paper is mainly concerned with the synthesis and properties of polyurethanes containing phosphatidylcholine analogues in their side chains.

EXPERIMENTAL

Materials

Oleyl alcohol, ethylene glycol, phosphorus trichloride, triethylamine (TEA), DMSO, *N*-methyldiethanolamine, 2,4-tolylene diisocyanate (TDI), 4,4′-methylene diphenyl diisocyanate (MDI), and *m*-xylylene diisocyanate (XDI) were commercially obtained and purified by vacuum distillation. Methanol was distilled in the presence of magnesium methoxide to ensure dryness. Dichloromethane and benzene were dried by distillation from phosphorus pentoxide. THF and diethyl ether were distilled from lithium aluminum hydride to ensure dryness. DMF was distilled in the presence of calcium hydride. Acetone was dried by distillation from anhydrous potassium carbonate. All solvents were dried over Molecular Sieves (Nakarai Chemicals, M4M7034). *p*-Nonylphenol and di-*n*-butyltin dilaurate were commercially obtained and used without further purification.

2-Chloro-1,3,2-dioxaphospholane [bp 45.5–46.5°C (15 mbar); Ref. 19: bp 45.5–47.0°C (15 mbar)] was prepared in 66% yield by the reaction of ethylene glycol with phosphorus trichloride in dichloromethane, according to the method of Lucas et al. [19], and oxidized to 2-chloro-2-oxo-1,3,2-dioxaphospholane; bp 103.5–105.0°C (1 mbar) [Ref. 20: bp 79°C (0.4 mbar)] in 90% yield with oxygen, according to the procedure of Edmundson [20].

2-Oleyloxy-2-oxo-1,3,2-dioxaphospholane (2a)

Into a thoroughly dried 500 cm^3 three-necked round-bottomed flask, equipped with a mechanical stirrer, drying tube, and dropping funnel, were placed 26.85 g (0.10 mol) oleyl alcohol and 12.14 g (0.12 mol) triethylamine in 150 cm^3 dry THF. After cooling with dry-ice/methanol (−20°C), 14.25 g (0.10 mol) 2-chloro-2-oxo-1,3,2-dioxaphospholane was added slowly to the stirred solution over a period of 1 hour. Triethylamine hydrochloride began to precipitate. The reaction mixture was maintained at −20 to −15°C for 1 hour with stirring and then allowed to warm to 0°C. After being kept at this temperature for 1.5 hours, the precipitate formed was filtered off and washed with 30 cm^3 dry THF. The filtrate and the THF solution were evaporated in a stream of nitrogen. To the residue, 50 cm^3 dry THF was added. The mixture was shaken for 30 seconds and then filtered through a glass filter to remove the small amount of triethylamine hydrochloride present. The fil-

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trate was evaporated in a stream of nitrogen for 1.5 hours to give **2a** as a pale brown semisolid. Yield: 36.7 g (98%).

IR (neat): 2925, 2850, 1460 ($-CH_2-$), 1220 ($P=O$), and 1040 cm^{-1} ($PO-CH_2-$).

2-(*p*-Nonylphenyloxy)-2-oxo-1,3,2-dioxaphospholane (2b)

In a similar manner, **2b** was prepared from *p*-nonylphenol and 2-chloro-2-oxo-1,3,2-dioxaphospholane in THF in the presence of triethylamine at −20 to −15°C. The product **2b** was a pale brown semisolid in 98% yield.

IR (neat): 2925, 2850, 1460 ($-CH_2-$), 1600, 1500 (arom.), 1220 ($P=O$), and 1060 cm^{-1} ($PO-CH_2-$).

Oleyl-2-(*N*-methyldiethanolammonium) Ethyl Phosphate (3a)

Into a 300-cm^3 glass pressure bottle (Top Model E 1435, Type A) were placed 35.0 g (0.093 mol) **2a** and 100 cm^3 dry DMF. *N*-Methyldiethanolamine, 16.68 g (0.14 mol), was rapidly added to the solution. The pressure bottle was closed and then shaken in a thermostat maintained at 75°C for 24 hours. After the bottle was opened, the solvent was evaporated in a stream of nitrogen. To the residue, 100 cm^3 dry acetone was added. After the mixture was shaken for 1 minute, the solvent was discarded by decantation. The residue was collected and dried in vacuum to give a crude product which was dissolved in dry methanol and reprecipitated from dry diethyl ether. The reprecipitation procedure was repeated three times to give pure **3a** as a pale brown semisolid. Yield: 39.2 g (85%).

IR (neat): 2925, 2850, 1460 ($-CH_2-$), 1220 ($P=O$), and 1050 cm^{-1} ($PO-CH_2-$).

^{1}H NMR ($CDCl_3$): δ = 0.88 (t; $C-CH_3$, 3H), 1.26 (s; $-CH_2-$, 28H), 3.12 (s; N^+-CH_3, 3H), 3.70-4.55 (m; $-OCH_2-$, N^+-CH_2-, 14H), 5.2 (t; $-CH=CH-$, 2H), 5.8-6.1 (m; $-OH$, 2H).

$C_{25}H_{52}NO_6P \cdot 2H_2O$ (529.7). Calculated: C, 56.69; H, 10.66%. Found: C, 56.45; H, 10.48%.

(*p*-Nonylphenyl)-2-(*N*-methyldiethanolammonium) Ethyl Phosphate (3b)

This was synthesized in a manner similar to **3a**. Yield: 80%.

IR (neat): 2925, 2850, 1460 ($-CH_2-$), 1600, 1500 (arom.), 1220 ($P=O$), and 1060 cm^{-1} ($PO-CH_2-$).

$C_{22}H_{40}NO_6P \cdot 2H_2O$ (481.6). Calculated: C, 54.87; H, 9.21%. Found: C, 54.37; H, 9.20%.

Polyurethane 1 (P1)

Into a 100-cm^3 round-bottomed flask, equipped with a reflux condenser with a drying tube and a Teflon-coated magnetic stirring bar, were placed 4.94 g (10.0 mmol) of **3a**, 1.75 g (10.0 mmol) TDI, and a drop of di-*n*-butyltin dilaurate in 70 cm^3 DMSO under a nitrogen atmosphere. The mixture was stirred at 80°C for 12 hours. At the end of the reaction the mixture was concentrated to one-third of its

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original volume. The concentrate was poured into 200 cm^3 acetone and polymer **P1** precipitated. It was purified by reprecipitation from DMSO with acetone three times. Yield: 5.75 g (86%); mp: 198–203°C.

IR (neat): 2920, 2850, 1460 ($-CH_2-$), 1700 ($-NHCO_2$), 1600, 1500 (arom.), 1230 ($P{=}O$), and 1060 cm^{-1} ($PO-CH_2-$).

Polyurethane 2 (P2)

Using the same procedure given for the preparation of **P1**, the reaction of **3a** with MDI by a 1:1 mole ratio in dry DMSO at 80°C for 12 hours afforded polyurethane **P2**. Yield: 91%.

IR (neat): 2920, 2850, 1460 ($-CH_2-$), 1700 ($-NHCO_2$), 1600, 1500 (arom.), 1230 ($P{=}O$), and 1060 cm^{-1} ($PO-CH_2-$).

Polyurethane 3 (P3)

Using the same procedure given for the preparation of **P1**, **3a** was reacted with XDI by a 1:1 mole ratio in dry DMSO at 80°C for 12 hours and afforded polyurethane **P3**. Yield: 82%.

IR (neat): 2920, 2850, 1460 ($-CH_2-$), 1700 ($-NHCO_2$), 1600, 1500 (arom.), 1230 ($P{=}O$), and 1060 cm^{-1} ($PO-CH_2-$).

Polyurethanes 4–6 (P4–P6)

The same procedure was applied for the preparation of polyurethanes **P4–P6**. **3b**, reacted with TDI, MDI, and XDI by a 1:1 mole ratio in dry DMSO at 80°C for 12 hours, afforded polyurethanes **P4–P6**, respectively. The results are listed in Table 1. The IR spectra of polyurethanes **P4–P6** were similar to those of polyurethanes **P1–P3**, respectively.

Measurements

IR spectra were recorded on a Jasco A 202 spectrometer, ^{1}H-NMR spectra were performed on a 60 MHz Hitachi-Perkin Elmer Model R-20 NMR spectrometer using TMS as an internal standard. The viscosity of polymers in DMSO at 25°C was measured with an Ubbelohde viscometer. Thermal property measurements were carried out with a Yamaco Model MP heating stage.

RESULTS AND DISCUSSION

The new diols, **3a** and **3b**, were prepared according to Scheme 1.

The starting materials, oleyl alcohol or *p*-nonylphenol, were reacted with the 2-chloro-1,3,2-dioxaphospholane in THF in the presence of triethylamine to give 2-oleyloxy-2-oxo-1,3,2-dioxaphospholane (**2a**) or 2-(*p*-nonylphenyloxy)-2-oxo-1,3,2-dioxaphospholane (**2b**) in nearly quantitative yield. They were characterized by their IR spectral data, according to the method of Nguyen Thanh and Chabrier [16]. The ring-opening reaction of **2a** and **2b** with *N*-methyldiethanolamine in polar

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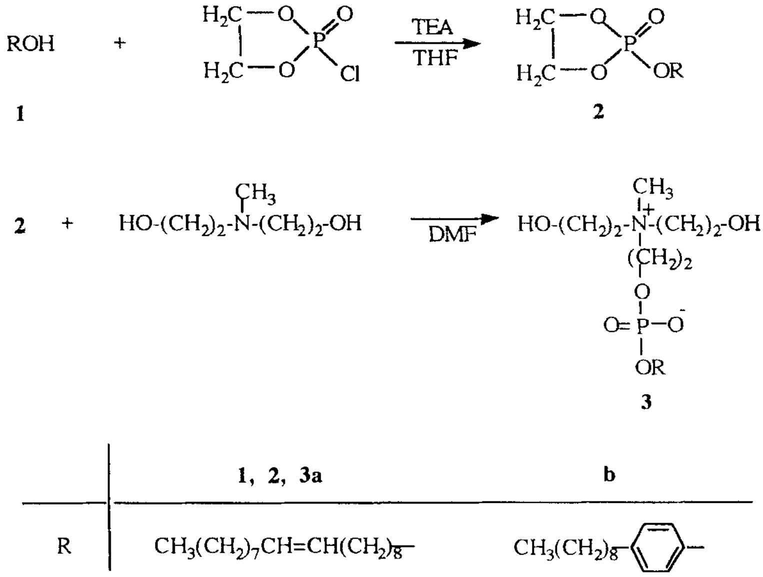

SCHEME 1.

aprotic solvents such as acetonitrile, DMF, and DMSO at 75°C for 24 hours afforded the new diols oleyl-2-[*N*-(methyldiethanolammonium) ethyl phosphate (**3a**) and (*p*-nonylphenyl)-2-[*N*-(methyldiethanolammonium) ethyl phosphate (**3b**) in good yield, respectively. The diols **3a** and **3b** were very hygroscopic and soluble in methanol, DMSO, and DMF, but insoluble in acetone and diethyl ether. The characterizations of diols **3a** and **3b** were based on their IR and ^{1}H-NMR spectral data and elemental analyses.

Polyurethanes **P1**–**P6** were synthesized by reaction of **3a** and **3b** with diisocyanates such as 2,4-tolylene diisocyanate (TDI), 4,4′-methylene diphenyl diisocyanate (MDI), and *m*-xylylene diisocyanate (XDI). Polyurethanes were obtained at 80°C in DMSO and in the presence of catalyst (di-*n*-butyltin dilaurate). The results are listed in Table 1.

The polyurethanes were characterized by their IR spectral data. The IR spectra of the synthesized polyurethanes **P1**–**P6** showed adsorption bands due to $-CONH-$ at 1700, $-P{=}O$ at 1230, and $-PO-CH_2-$ at 1060 cm^{-1}. Moreover, because synthesized polyurethanes and their intermediates containing phospholipid are very hygroscopic, adsorption bands due to H_2O at 3300 cm^{-1} also appeared in their IR spectra. As an example, Fig. 1 shows the IR spectra of polyurethane **P1** and its intermediate **3a**.

All the polyurethanes were soluble in DMSO and DMF but insoluble in acetone and diethyl ether. Thermal property investigation of polyurethanes was carried out with a Yamaco Model MP heating stage; for example, the melting point of polyurethane **P1** was 198–203°C.

The viscosity measurements of polyurethanes were performed at 25°C in DMSO. As an example, Fig. 2 shows the reduced viscosity of polyurethane **P1**.

TABLE 1. Polyurethanes **P1–P6** Obtained from **3a**, **3b**, and Diisocyanates (TDI, MDI, XDI)[a]

Polyurethanes	**3a**, g	**3b**, g	TDI, g	MDI, g	XDI, g	Yield, %
P1	4.94		1.75			86
P2	4.94			2.51		91
P3	4.94				1.89	82
P4		4.46	1.75			88
P5		4.46		2.51		93
P6		4.46			1.89	90

[a] Reaction condition: solvent, DMSO; 80°C; 12 hours. TDI, 2,4-tolylene diisocyanate; MDI, 4,4′-methylene diphenyl diisocyanate; XDI, *m*-xylylene diisocyanate.

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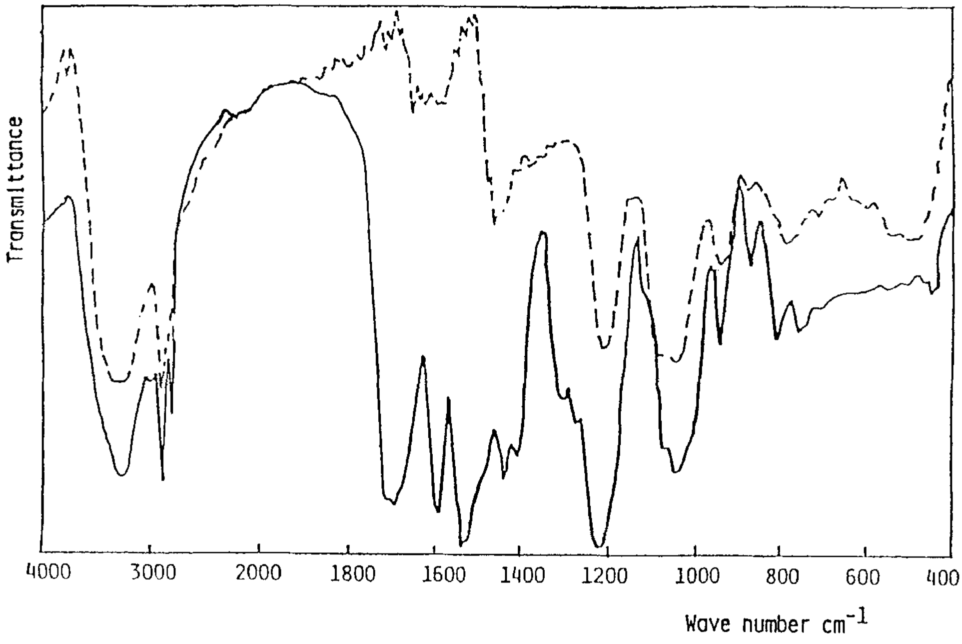

FIG. 1. IR spectra of **P1** (neat) (——) and its intermediate **3a** (neat) (---).

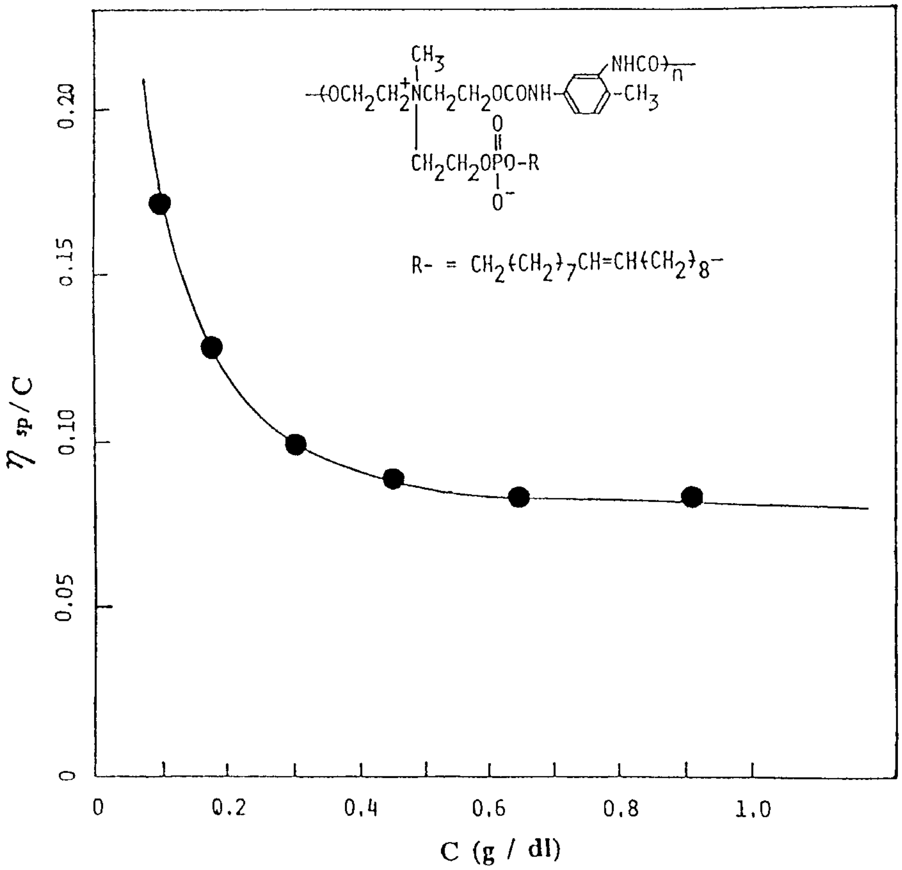

FIG. 2. Reduced viscosity of **P1** in DMSO at 25°C.

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As can be seen, the reduced viscosity has the tendency to increase rapidly upon dilution. Polyurethanes **P2–P6** have behaviors similar to **P1**. These findings suggest that polyurethanes containing phosphatidylcholine analogues in the side chains show properties similar to those of the usual polyelectrolytes. These phenomena may result from mutual repulsion between N^+ and N^+, particularly the possible chain expansion at low concentrations. These results agree with those obtained from various polyelectrolytes such as vinyl polymers containing phosphatidylethanolamines [17] or phosphatidylcholines [18] in the side chains, and poly(phosphatidylcholine) analogues [14].

CONCLUSION

Several new diols and polyurethanes containing phosphatidylcholine analogues in the side chains have been synthesized.

The viscosity measurement show that synthesized polyurethanes have properties similar to the usual polyelectrolytes.

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