

NOTES

Polymeric Phospholipid Analogs XXIX.† Synthesis and Polymerization of 2-(Methacryloyloxy)ethyl Dipalmitoyl-DL- α -phosphatidylethanolamide

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Within the past 15 years, a considerable amount of our effort has been directed toward the synthesis of polymers containing phosphatidylethanolamine^{1,2} and choline^{3,5} analogs in the side chains and phosphatidylcholine analogous moieties in the main chains and the studies of their properties.⁶⁻⁸ In a paper of this series,⁹ we reported a convenient preparation of a vinyl monomer containing a phosphatidylethanolamine unit, that is, dipalmitoyl-DL- α -phosphatidylethanolmethacrylamide, which was polymerized by UV and γ -radiation, but could not be homopolymerized by radical initiators. In order to improve this point and provide a high-molecular weight vinyl polymer bearing cephalin units in the side chains, we prepared 2-(methacryloyloxy)-ethyl dipalmitoyl-DL- α -phosphatidylethanolamide (III).

The present note is mainly concerned with the synthesis and radical polymerization of III and with the properties of the resulting polymer.

EXPERIMENTAL

Reagents

Thionyl chloride, pyridine, chlorobenzene, *o*-dichlorobenzene, chloroform, acetone, diethyl ether, and AIBN were commercially obtained and purified by distillation or recrystallization. DL- α -Phosphatidylethanolamine dipalmitoyl (Sigma Chemical Co.), methacrylic acid, benzoyl chloride, 3-hydroxypropionitrile, cuprous chloride, hydroquinone, and ferric trichloride were commercially obtained and used without further purification. Methacryloyl chloride was prepared by reaction of methacrylic acid with benzoyl chloride in the presence of a small amount of cuprous chloride. 3-Hydroxypropionic acid was prepared by reacting 3-hydroxypropionitrile with 25% sodium hydroxide, according to the procedure of Read.¹⁰

† For Part XXVIII of this series, see ref 11.

3-Methacryloyloxypropionic Acid (I)

Into a dried 500 ml three-necked round bottomed flask, equipped with a mechanical stirrer, calcium chloride drying tube, and dropping funnel, were placed 150 g (1.67 mol) of 3-hydroxypropionic acid and 133.2 g (3.33 mol) of sodium hydroxide in 100 ml of water. After cooling the solution in an ice bath (at 0°C), 174.1 g (1.67 mol) of methacryloyl chloride were slowly added to the stirred solution over a period of 1 h. The reaction mixture was stirred at room temperature for 12 h, and then acidified with hydrochloric acid to pH 2. The solution was extracted with chloroform. After drying over anhydrous sodium sulfate, the solution was filtered and evaporated *in vacuo* at room temperature to give crude product. To the crude product were added a small amount of hydroquinone and ferric chloride. The mixture was distilled under reduced pressure to give I as a colorless liquid: bp (96–98°C)/1 mmHg. Yield: 39.5 g (15.0%):

IR (neat): 1725 ($\overset{\text{O}}{\parallel}\text{C}-$), 1700 ($-\text{COOH}$), 1630, 1320, and 1295 cm^{-1} ($\text{C}=\text{C}$). ^1H NMR (CDCl_3): δ 1.91 (3H, s, $-\text{CH}_3$), 2.72 (2H, t, $-\text{CH}_2\text{CO}_2-$), 4.39 (2H, t, $-\text{CO}_2\text{CH}_2-$), 5.52 (1H, m, $-\text{CH}=\text{}$), 6.05 (1H, s, $-\text{CH}=\text{}$), 11.40 ppm (1H, s, $-\text{COOH}$).

3-Methacryloyloxypropionoyl Chloride (II)

To a solution of 39.5 g (0.25 mol) of I in 100 ml of dry THF, 89.1 g (0.75 mol) of thionyl chloride and 39.5 g (0.50 mol) of pyridine were added. The mixture was heated at 50°C for 1 h. After the excess unreacted thionyl chloride and THF were distilled off under reduced pressure, the mixture was distilled under reduced pressure to give the desired product (II) as a pale yellow liquid. bp (75–76°C)/1 mmHg. Yield:

18.5 g (42.0%): IR (neat): 1800 ($\overset{\text{O}}{\parallel}\text{C}-\text{Cl}$), 1725 ($\overset{\text{O}}{\parallel}\text{C}-\text{O}$), 1630, 1200, and 1295 cm^{-1} ($\text{C}=\text{C}$). ^1H NMR (CDCl_3): δ 1.91 (3H, s, $-\text{CH}_3$), 3.22 (2H, t, $-\text{CH}_2\text{COCl}$), 4.39 (2H, t, $-\text{CO}_2\text{CH}_2-$),

5.52 (1H, m, $-\text{CH}=\text{}$), 6.05 ppm (1H, s, $-\text{CH}=\text{}$).

2-(Methacryloyloxy)ethyl Dipalmitoyl-DL- α -phosphatidylethanolamide (III)

Into a thoroughly dried 100 ml three-necked round bottomed flask equipped with a mechanical stirrer, drying tube, and dropping funnel were placed 0.20 g (0.29 mmol) of DL- α -phosphatidylethanolamine dipalmitoyl in 40 ml of chloroform and 0.11 g (1.45 mmol) of pyridine. After cooling the solution in an ice bath (at 0°C), 0.204 g (1.16 mmol) of II were slowly added to the stirred solution over a period of 1 h. The reaction mixture was maintained at 0°C under stirring for 6 h and then allowed to warm to 20°C. After being kept at this temperature for 12 h, 20 ml of water were added to the reaction mixture. The solution was extracted with 80 ml of chloroform. After drying over sodium sulfate, the solution was filtered and evaporated under reduced pressure. The residue was dissolved in 0.3 ml of chloroform. The solution was then slowly added to 120 ml of acetone, whereby a white solid formed gradually. After the mixture was cooled in a freezer for 28 h, the solid formed was collected, washed successively with 20 ml of acetone, and dried. The crude product was reprecipitated twice from chloroform solution with acetone to give III as a pale yellow solid. Yield: 60.1 mg (25.0%). The thermal properties are listed in Table I. Its ^1H NMR (CDCl_3) is shown in Figure 1. IR (KBr): 2925, 2850, 1460 ($-\text{CH}_2-$), 1730 ($-\text{CO}_2-$), 1655 ($-\text{CONH}-$), 1630, 1320, 1295 ($\text{C}=\text{C}$), 1255 ($\text{P}=\text{O}$), 1070

Table I. Thermal properties of monomer III and of poly(III)

Samples	$T_m/^\circ\text{C}$	$T_1/^\circ\text{C}$
III	42 (35) ^a	139 (130) ^a
Poly(III)	67 (50) ^a	158 (150) ^a

^a Determined by optical microscopy.

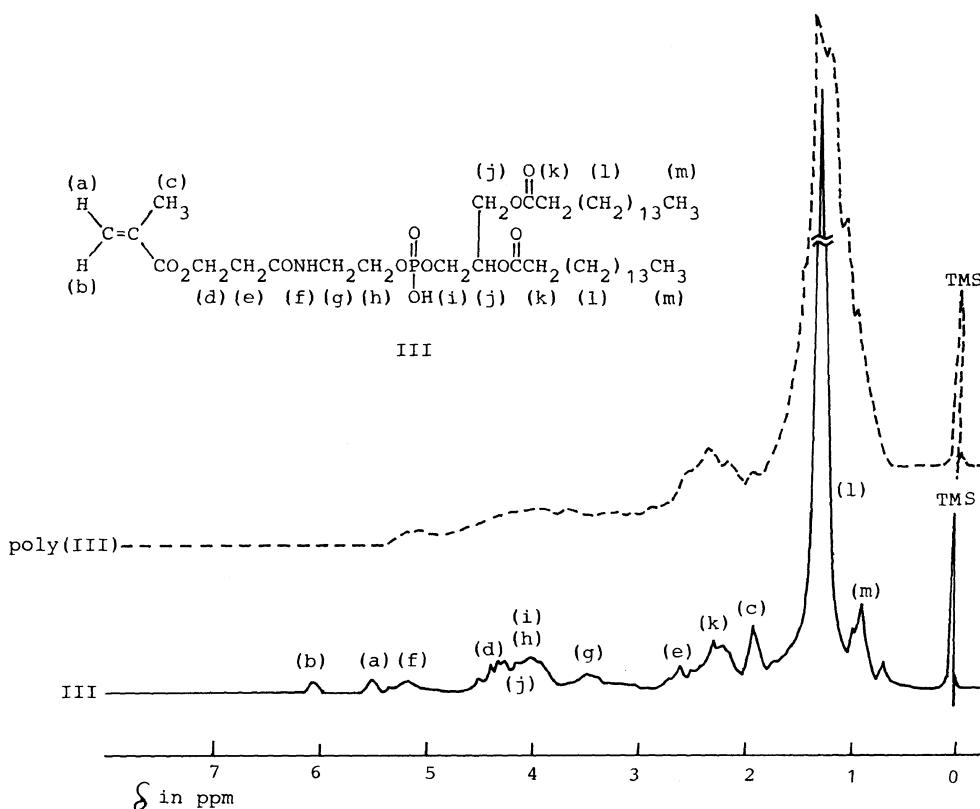


Figure 1. ^1H NMR spectra (60 MHz) of III and poly(III) (in CDCl_3) TMS as the internal standard.

cm^{-1} ($\text{PO}-\text{O}^-$).

Polymerization of III

The polymerization of III was carried out in chlorobenzene with AIBN as initiator. A solution of 60.1 mg of III, 0.24 mg of AIBN, and 2 ml of chlorobenzene were placed in a glass tube, which was flushed three times with nitrogen, sealed *in vacuo*, and then shaken at 80°C for 24 h. After the polymerization, the content of the tube was concentrated to one-tenth its original volume. The concentrate was poured into an excess of acetone to affect the precipitation of poly(III). It was washed with acetone and purified by reprecipitation from chloroform solution with acetone to give 45.7 mg (76.1%) of pure polymer as a pale yellow powder. The thermal properties of the polymer are listed in Table I. Its ^1H NMR

(CDCl_3) is shown in Figure 1. Its IR spectrum (KBr) showed the disappearance of absorption bands at 1630, 1320, and 1295 cm^{-1} due to the methacrylic ($\text{C}=\text{C}$) double bond in the monomer, but otherwise the spectrum was unchanged. Its inherent viscosity $[\eta]$ was found to be 0.23 dl g^{-1} at 25°C in *o*-dichlorobenzene.

Viscosity Measurements

Measurements were carried out at 25°C using an Ubbelohde type viscometer.

DSC Measurements

DSC measurements were conducted with a Rikagaku instrument Model TAS100 DSC 8230.

Polarization Microscopy

This was carried out with a polarizing optical microscope using a Yanaco Model MP with heating stage.

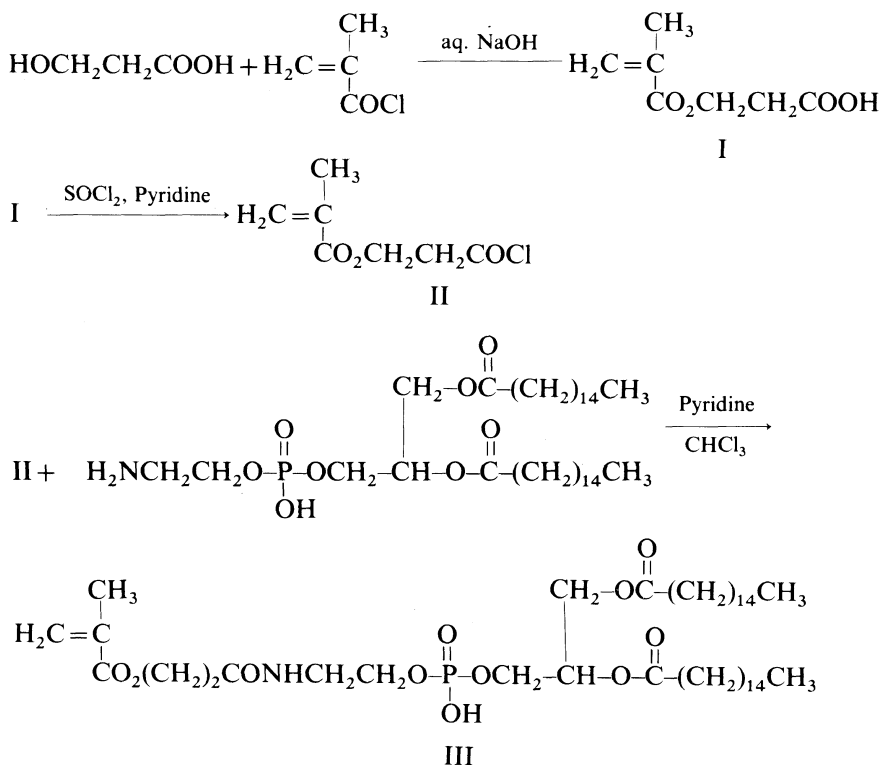
Spectroscopic Measurements

The ^1H NMR and IR were carried out on a 60 MHz Hitachi Model R-24B NMR spectrometer and a JASCO Model IR-G spec-

trometer.

RESULTS AND DISCUSSION

The monomer, 2-(methacryloyloxy)ethyl dipalmitoyl-DL- α -phosphatidylethanolamide (III), was prepared *via* the following reaction path:



3-Hydroxy propionic acid was reacted with methacryloyl chloride in aqueous sodium hydroxide to give 3-methacryloyloxypropionic acid (I) as a colorless liquid. I was characterized by IR and ^1H NMR spectroscopy. This compound was subsequently converted to its acid chloride (II) by heating it with thionyl chloride in THF in the presence of pyridine. The characterization of II was based on its IR and ^1H NMR spectra. 2-(Methacryloyloxy)ethyl dipalmitoyl-DL- α -phosphatidylethanolamide

(III) was prepared by reacting II with DL- α -phosphatidylethanolamine dipalmitoyl in chloroform in the presence of pyridine. III was obtained in 25.0% yield as a pale yellow solid and characterized by IR and ^1H NMR (Figure 1) spectroscopy. It was somewhat hygroscopic and soluble in chloroform, chlorobenzene, and hot ethanol, but virtually insoluble in acetone and diethyl ether.

Monomer III was polymerized in chlorobenzene with AIBN at 80°C for 24 h to give

the corresponding poly(III) in good yield. It was a pale yellow powder and characterized by ^1H NMR (Figure 1) and IR spectra. The IR spectrum showed the disappearance of absorption bands (1295, 1320, and 1630 cm^{-1}) due to the vinyl double bond in the monomer. The polymer was soluble in chloroform and chlorobenzene. The inherent viscosity $[\eta]$ of the polymer was 0.23 dl g^{-1} (at 25°C) in *o*-dichlorobenzene.

The thermal properties of the monomer III and poly(III) were examined by differential scanning calorimetry (DSC) and polarizing microscopy. Table I shows the phase transition temperatures T_m (crystalline \rightarrow nematic) and T_1 (nematic \rightarrow isotropic melt). The DSC thermograms of the transition temperature of the two samples are in good agreement with the microscopic observations.

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