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Polymeric Phospholipid Analogs. XV. Polyacrylamides Containing Phosphatidyl Cholines

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ABSTRACT

p-Acryloylaminophenyl-2-(trimethylammonium)ethyl phosphate, p-methacryloylaminophenyl-2-(trimethylammonium)ethyl phosphate, and p-methacryloylbenzoylaminophenyl-2-(trimethylammonium)ethyl phosphate were prepared, characterized, and polymerized with 2,2'-azobisisobutyronitrile (AIBN). The properties of the resultant polymers are described.

INTRODUCTION

A great amount of interest has been shown in the phospholipids as essential components of biological membranes [1-3]. Accordingly, it appeared of interest to prepare vinyl polymers containing phospholipid analogs. In recent years, numerous reports [4-10] have appeared concerning the syntheses and properties of vinyl polymers containing phosphatidylethanolamines or cholines in sidechains. In continuation of

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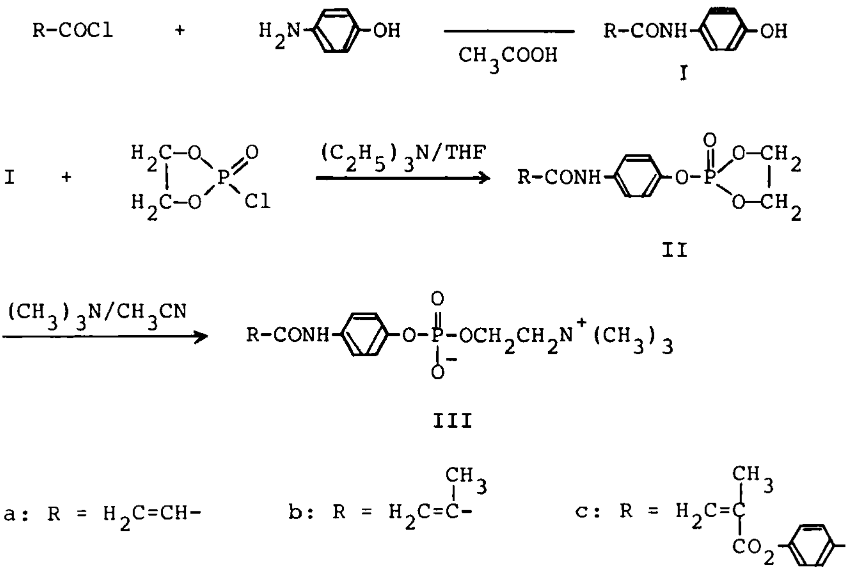
these studies, we have now prepared p-acryloylaminophenyl-2-(trimethylammonium)ethyl phosphate (IIIa) and p-methacryloylaminophenyl-2-(trimethylammonium)ethyl phosphate (IIIb). In order to provide an improved model compound resembling natural phospholipids, we have prepared p-methacryloyloxybenzoylaminophenyl-2-(trimethylammonium)ethyl phosphate (IIIc) in which a benzoyl group is introduced into IIIb to let it have a more hydrophobic character. In addition, some properties of the resultant polymers are described.

RESULTS AND DISCUSSION

Monomers IIIa, IIIb, and IIIc were prepared according to the following reaction scheme:



Compounds Ia, Ib, and Ic were synthesized by a modification of the method of Greiger [11], and Compounds IIIa, IIIb, and IIIc were prepared according to the method of Thuong and Chabrier [12]. Monomers IIIa and IIIb were very hygroscopic and soluble in water, methanol, and ethanol, but almost insoluble in acetone as well as benzene. Monomer IIIc was also hygroscopic and soluble in DMF and DMSO, but almost insoluble in methanol, ethanol, and benzene.

Monomers IIIa and IIIb were polymerized, and the characterizations of these polymers are based on spectral data or elemental analysis. As can be seen from Fig. 2, the IR spectrum showed the disappearance of the absorption bands due to the vinyl band in the monomer, but otherwise the spectrum was unchanged. As can be seen from Figs. 1 and 3, the

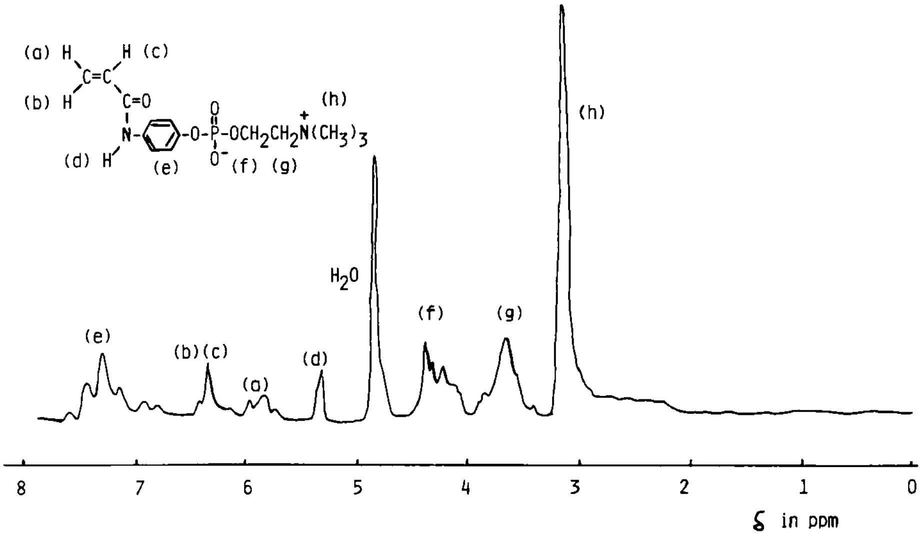


FIG. 1. ^{1}H-NMR spectrum of p-acryloylaminophenyl-2-(trimethylammonium)ethyl phosphate (IIIa) in D_2O.

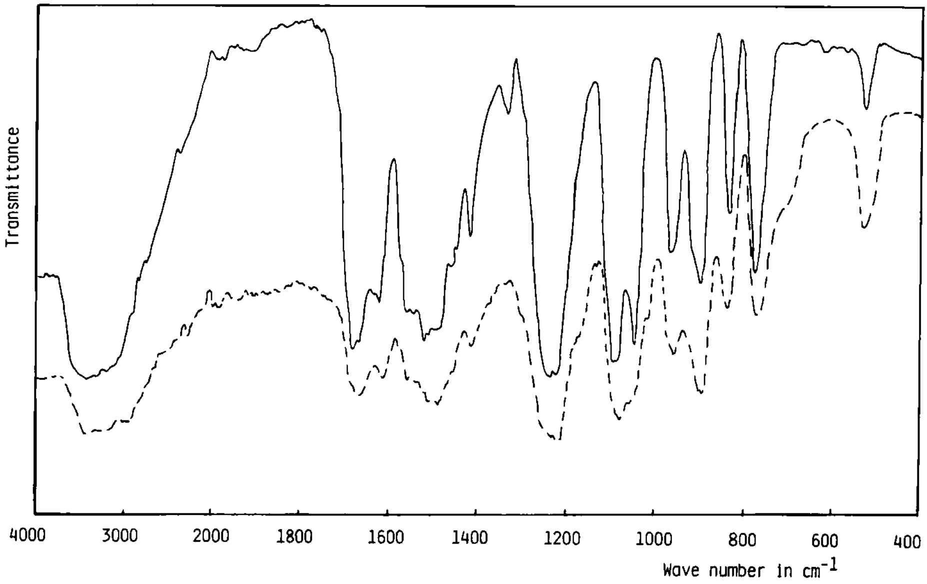


FIG. 2. Infrared spectra of (—) p-acryloylaminophenyl-2-(trimethylammonium)ethyl phosphate (IIIa) and (- -) poly(IIIa).

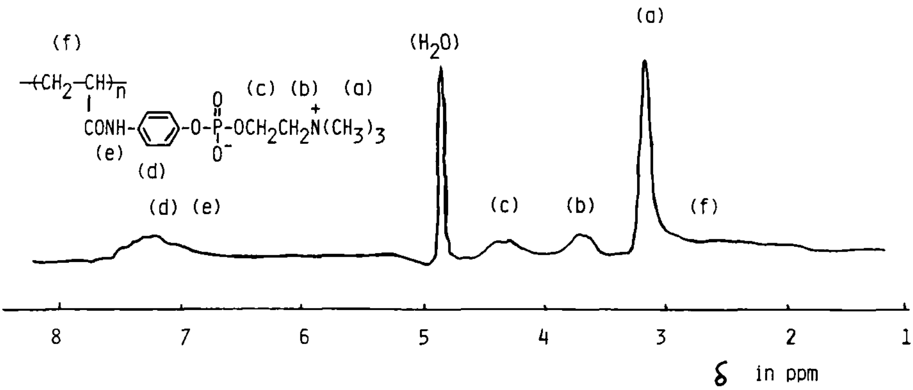


FIG. 3. ^{1}H-NMT spectrum of poly(IIIa) in D_2O.

^{1}H-NMR spectrum of poly(IIIa) showed the disappearance of the signals due to the three protons of the vinyl group in the monomer and the appearance of the signals due to the methylidene and methylene protons of the polymer backbone. Poly(IIIa) and poly(IIIb) were hygroscopic and soluble in water, methanol, and DMF, but almost insoluble in acetone and benzene. Poly(IIIc) was slightly soluble in hot DMSO, but almost insoluble in water and acetone. This polymer was found to exhibit a liquid crystalline phase in the range 210-290°C as observed with a polarizing optical microscope.

Gel permeation chromatography (GPC) of poly(IIIb) indicated a weight-average molecular weight of 9 500, apparently rather low.

In order to check whether the water-soluble poly(IIIa) and poly(IIIb) are polyelectrolytes, we examined the viscosity behavior of a water solution of poly(IIIa) with and without addition of sodium chloride. In pure water the reduced viscosity, η_{sp}/c, has a tendency to increase rapidly upon dilution (Curve A in Fig. 4), whereas the addition of sodium chloride eliminates this increase (Curve B in Fig. 4). The general trend of these plots agrees with that which has been reported by a number of investigators for various polyelectrolytes [13-15]. Accordingly, it is concluded that the resulting poly(IIIa) is a polyelectrolyte.

EXPERIMENTAL

Materials

Acrylic acid, methacrylic acid, benzoyl chloride, p-aminophenol, ethylene glycol, triethylamine, phosphorus trichloride, acetic acid,

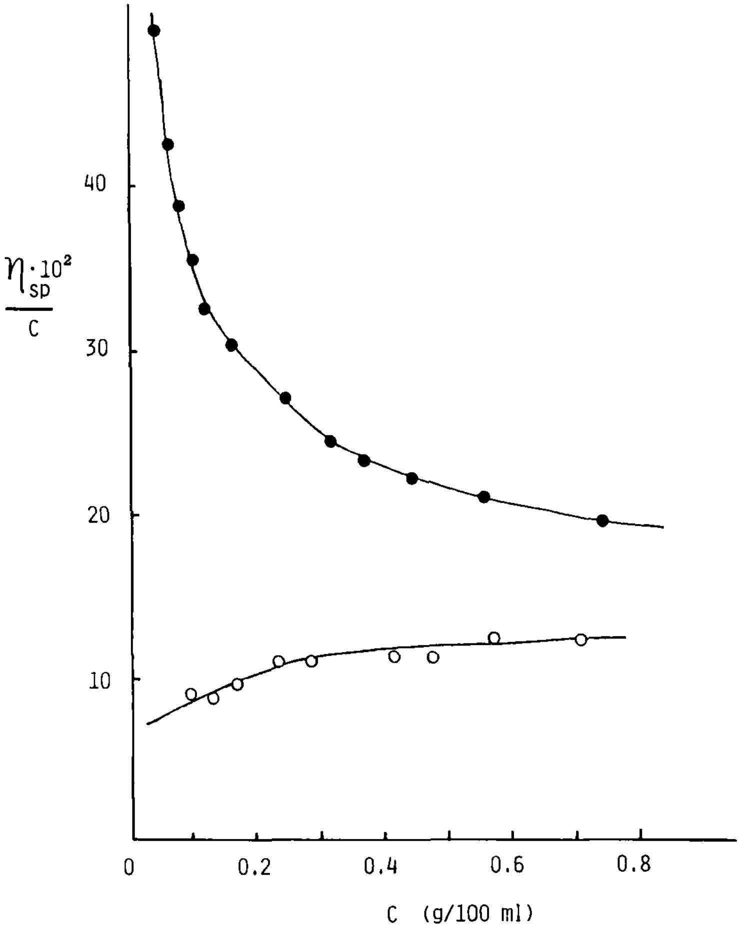


FIG. 4. Reduced viscosity of poly(IIIa) in aqueous solutions at 21°C; (●) in pure water; (○) in 0.0525 mol/L NaCl.

dichloromethane, diethyl ether, acetone, THF, and methanol were commercially obtained and purified by distillation and recrystallization. Oxygen, trimethylamine hydrochloride, copper(I) chloride, thionyl chloride, and p-hydroxybenzoic acid were commercially obtained and used without further purification. Trimethylamine was prepared by the reaction of trimethylamine hydrochloride with 40% sodium hydroxide by the procedure of Adams and Brown [16]. 2-Chloro-1,3,2-dioxaphospholane, bp 45.5-46.5°C/15 torr (Ref. 17: bp 45.5-47.0°C/15 torr), was prepared in 66% yield by the reaction of ethylene glycol with phosphorus trichloride in dichloromethane, according to the method of Lucas et al. [17]. 2-Chloro-2-oxo-1,3,2-dioxaphospholane, bp 103.5-105.0°C/1 torr (Ref. 18: bp 79°C/0.4 torr), was prepared in 90% yield by oxidation of 2-chloro-1,3,2-dioxaphospholane with oxygen, according to the method of Edmundson [18]. p-Methacryloyloxybenzoic acid was prepared by the reaction of p-hydroxybenzoic acid with methacryloyl chloride in sodium hydroxide solution by the method of Amerik et al. [19]. p-Methacryloyloxybenzoyl chloride was prepared by the reaction of p-methacryloylbenzoic acid with thionyl chloride in the presence of pyridine.

p-Acryloylaminophenol (Ia)

According to a modification of the method of Greiger [11], Ia was prepared by the reaction of p-aminophenol with acryloyl chloride in acetic acid at 55°C for 3 h. The reaction mixture was cooled in cold water, and then 1 N hydrochloric acid was added to the mixture. The solution was extracted with diethyl ether. The extract was washed three times with water. After drying over sodium sulfate, the solution was filtered and evaporated in vacuo. Recrystallization of the residue from ethanol afforded Ia as pale yellow crystals in 67% yield, mp 193°C (Ref. 10: mp 192-193°C).

p-Methacryloylaminophenol (Ib)

In a similar manner, Ib was prepared from p-aminophenol and methacryloyl chloride in acetic acid at 55°C for 3 h. Recrystallization from ethanol afforded Ib as pale yellow crystals in 67% yield, mp 155°C.

p-Methacryloyloxybenzoylaminophenol (Ic)

In the same manner, Ic was prepared from p-aminophenol and p-methacryloyloxybenzoyl chloride in acetic acid at 65°C for 3.5 h. Recrystallization from methanol/ethanol (volume ratio 2:1) afforded Ic as pale yellow crystals in 20% yield, mp 226°C.

2-(p-Acryloylaminophenoxy)-2-oxo-1,3,2-dioxaphospholane (IIa)

Into a thoroughly dried 500-mL three-necked round-bottomed flask equipped with a mechanical stirrer, drying tube, and dropping funnel were placed 32.0 g (196 mmol) of Ia and 19.8 g (196 mmol) of triethylamine in 300 mL of dry THF. After cooling the solution in a Dry Ice/methanol bath (-30°C), 27.9 g (196 mmol) of 2-chloro-2-oxo-1,3,2-dioxaphospholane was added slowly to the stirred solution over a period of 0.5 h, by which procedure triethylamine hydrochloride began to precipitate from the solution. The reaction mixture was maintained at -20 to -10°C during the addition and then allowed to warm to 0°C. After being kept at this temperature for 1 h, the precipitate was filtered off and washed with 30 mL of THF. The filtrate and the THF solutions were evaporated in vacuo in a stream of nitrogen. To the residue, 10 mL of dry THF were added. The mixture was shaken for 1 min and then filtered through a glass filter to remove a small amount of triethylamine hydrochloride. The filtrate was evaporated in vacuo in a stream of nitrogen for 1.5 h to give IIa as a viscous, transparent liquid. Yield: 46.4 g (98.5%). It was identified by IR spectroscopy.

IR (neat) showed absorptions at 1 670 (CONH), 1 635 (C=C), 1 300 (P=O), 1 220 and 960 cm^{-1} ($P-OCH_2$).

p-Acryloylaminophenyl-2-(trimethylammonium)-ethyl Phosphate (IIIa)

Into a 300-mL glass pressure bottle (Top Model E 1435, Type A) were placed 40.0 g (149 mmol) of IIa and 100 mL of dry acetonitrile. After the pressure bottle was cooled in cold water, 8.8 g (149 mmol) of trimethylamine was rapidly added to the cold solution. The pressure bottle was closed and then shaken in a thermostat maintained at 60°C for 15 h. After it had been allowed to cool to 0°C, a pale yellow, transparent, viscous product precipitated from the solution. The precipitate formed was removed, washed with 30 mL cold THF, and dried in vacuo to give a caramel-like product. The crude product was dissolved in dry methanol and reprecipitated from diethyl ether. This procedure was repeated three times to afford pure IIIa as a pale yellow solid, which was very hygroscopic. Yield: 15.6 g (32.0%). ^1H-NMR and IR spectra are shown in Figs. 1 and 2.

Analysis: Calculated for $C_{14}H_{21}O_5N_2P.2H_2O$: C, 46.15; H, 6.86; N, 7.69%. Found: C, 46.57; H, 7.29; N, 7.43%.

p-Methacryloylaminophenyl-2-(trimethylammonium)-ethyl Phosphate (IIIb)

Using the same procedure given for the preparation of IIa, the reaction of Ib with 2-chloro-2-oxo-1,3,2-dioxaphospholane in dry THF in the presence of triethylamine gave 2-(p-methacryloylaminophenoxy)-2-oxo-1,3,2-dioxaphospholane (IIb) as a viscous, transparent liquid in 98.3% yield. Its characterization was made by IR spectroscopy, which showed absorptions at 1 670 (CONH), 1 635 (C=C), 1 230 (P=O), 1 220 and 960 cm^{-1} ($P-OCH_2$).

Using the same method as described for the preparation of IIIa, the product IIb was reacted with trimethylamine in dry acetonitrile to give product IIIb in 40.0% yield as a pale yellow solid, which was very hygroscopic.

IR (KBr) showed absorptions at 1 675 (CONH), 1 635 (C=C), 1 235 and 1080 cm^{-1} (PO–O^-).

^{1}H-NMR (D_2O) showed δ = 2.02 (s, –CH_3, 3H), 3.17 (s, –CH_3, 9H), 3.50-3.85 (m, –CH_2N^+, 2H), 4.05-4.70 (m, –OCH_2–, 2H), 5.60 (s, –NH, 1H), 5.75 (s, –CH=, 1H), 5.90 (s, –CH=, 1H), and 7.10-7.60 (m, aromatic ring protons, 4H).

Analysis: Calculated for $C_{15}H_{23}O_5N_2P.2H_2O$: C, 45.45; H, 7.37; N, 7.07%. Found: C, 45.62; H, 7.34; N, 7.19%.

p-Methacryloyloxybenzoylaminophenyl-2-(trimethylammonium)ethyl Phosphate (IIIc)

Using the same procedure as described for the preparation of IIa, the reaction of Ic with 2-chloro-2-oxo-1,3,2-dioxaphospholane in dry THF in the presence of triethylamine gave 2-(p-methacryloyloxybenzoylaminophenoxy)-2-oxo-1,3,2-dioxaphospholane (IIc) as a white solid in 94.7% yield.

IR (KBr) showed absorptions at 1 670 (CONH), 1 635 (C=C), 1 300 (P=O), 1 200 and 960 cm^{-1} (P–$COCH_2$).

Using the same procedure given for the preparation of IIIa, the product IIc was reacted with trimethylamine in dry DMF to give product IIIc as a pale yellow solid, decomposing at 130°C, in 20% yield.

IR (KBr) showed absorptions at 1 720 (CO_2), 1 670 (CONH), 1 635 (C=C), 1 235 and 1 080 cm^{-1} (PO–O^-).

Analysis: Calculated for $C_{22}H_{27}O_7N_2P.2H_2O$: C, 53.01; H, 6.27; N, 5.62; P, 6.21%. Found: C, 53.03; H, 5.49; N, 4.90; P, 5.70%.

Polymerization of IIIa

The polymerization of IIIa was carried out in methanol with AIBN as initiator. A solution of 0.83 g (2.28 mmol) of IIIa, 8.2 mg (0.05 mmol) of AIBN, and 10 mL methanol were placed in a glass tube which was flushed three times with nitrogen, sealed in vacuo, and then shaken at 70°C. After 14 h the content of the tube was poured into an excess of diethyl ether and the polymer precipitated. The mixture was allowed to stand overnight, and the diethyl ether was decanted. The removal of the diethyl ether at reduced pressure left a white solid which was purified by reprecipitation from methanol solution with diethyl ether. This provided 0.63 g (73.9%) of a white polymer that decomposed at 240-250°C. Its IR and ^{1}H-NMR spectra are shown in Figs. 2 and 3. It was soluble in water, methanol, and ethanol, but almost insoluble in acetone and benzene. The polymer was hygroscopic.

Analysis: Calculated for $(C_{14}H_{21}O_5N_2P.2H_2O)_n$: C, 46.15; H, 6.86; N, 7.69%. Found: C, 46.04; H, 6.94; N, 6.96%.

Polymerization of IIIb

By the same procedure, the polymerization of IIIb gave poly(IIIb), decomposing at 220-230°C, as a white polymer in 46% yield. Its IR spectrum (KBr) showed the disappearance of the absorption band at 1 635 cm^{-1} due to the methacrylic C=C double bond in the monomer, but otherwise the spectrum was unchanged. It was hydroscopic and soluble in water, methanol, and DMF, but almost insoluble in acetone and diethyl ether.

Polymerization of IIIc

By the same procedure, the polymerization of IIIc afforded, in 40% yield, poly(IIIc), which showed liquid crystalline properties in the range 210-290°C by polarizing optical microscopy. Its IR spectrum (KBr) showed the disappearance of the absorption band at 1 635 cm^{-1}, due to the vinyl group, in the monomer, but otherwise the spectrum was unchanged. It was soluble in hot DMSO, but almost insoluble in water and acetone.

Measurements

Molecular weight was determined by GPC with TSK-GEL-G6000H/G5000H/G4000H/G3000H/G2000H columns based on narrowly distributed polystyrenes as standards. This GPC analysis was carried out with a Jasco Model TRI ROTER, Type I.

Viscosity measurements were carried out at 21°C with an Ubbelohde viscometer.

Polarization microscopy measurements were carried out with a polarizing optical microscope with a Yamaco Model MP heating stage.

^{1}H-NMR and IR measurements were carried out with a 60 MHz Hitachi-Perkin Elmer Model R-20 NMR spectrometer and a Jasco Model IR-G spectrometer. The chemical shifts were expressed in terms of δ-values downfield relative to TMS as the internal standard.

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