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Akio Furukawa[a]; Tadao Nakaya[a]; Minoru Imoto[a]
[a] Department of Applied Chemistry Faculty of Engineering, Osaka City University, Sumiyoshi-ku, Osaka, Japan

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NOTE
POLYMERIC PHOSPHOLIPID ANALOGS. XXIV. POLYMERIC PHOSPHOLIPID ANALOGS WITH URIDINE UNITS*

AKIO FURUKAWA, TADAO NAKAYA,† and MINORU IMOTO

Department of Applied Chemistry
Faculty of Engineering
Osaka City University
Sumiyoshi-ku, Osaka 558, Japan

Since phospholipids are of considerable interest as essential components of biological membranes [1, 2], it has seemed promising to investigate the behavior of polymeric phospholipid analogs. For over 10 years, a large part of our efforts has been to prepare polymers containing phosphatidylethanolamine [3, 4] or choline [5-7] analogs in the side chains and phosphatidylcholine analogs [8-10] in the main chains. A part of this programs was to synthesize polymeric phospholipid analogs containing nucleosides [11, 12], e.g., uridine, as in the work reported here.

The polymeric phospholipid analog with uridine units (IV) was prepared as shown in Scheme 1.

The starting material, 2′,3′-*O*-isopropylideneuridine, was commercially obtained and reacted with 2-chloro-2-oxo-1,3,2-dioxaphosphate in THF in the presence of triethylamine to give 2′,3′-*O*-isopropylidene-5′-*O*-(2-oxo-1,3,2-dioxaphospholan-2-yl)-uridine (I). Product I, obtained as a white solid in nearly quantitative yield, was characterized by IR spectroscopy. According to the method of Thoung and Chabrier [14], I was reacted with 2-dimethylaminoethyl methacrylate in DMF to afford in good yield the corresponding 2-[2-(methacryloyloxy)ethylammonium] ethyl-2′,3′-*O*-isopropylidene)-5′-

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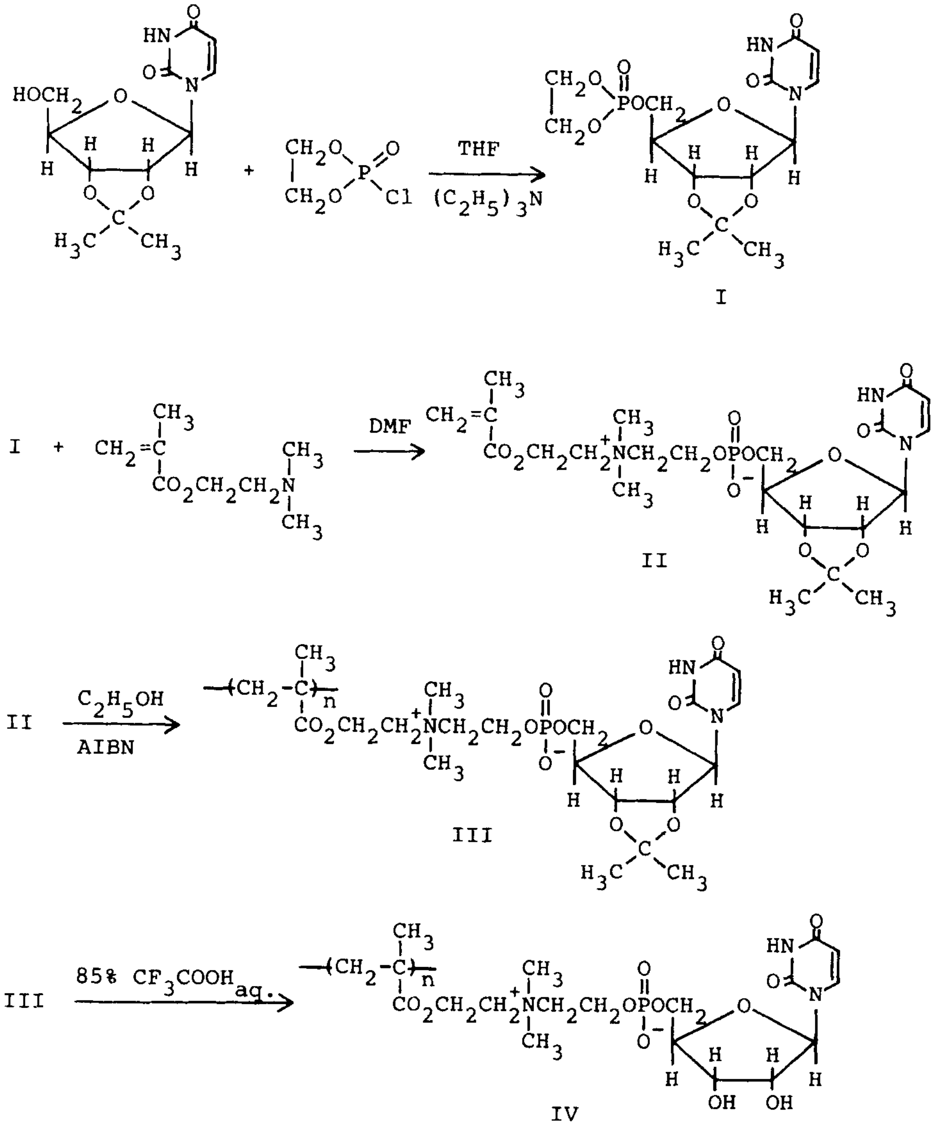
*See Ref. 13 for Part XXIII.

†To whom correspondence should be addressed.



SCHEME 1.

uridine phosphate (II) as a crystalline solid. Monomer II was characterized by ^1H NMR, IR spectra, and elemental analysis. It is hygroscopic and soluble in methanol, ethanol, acetone, chloroform, DMF, and water, but almost insoluble in diethyl ether.

Monomer II was polymerized in ethanol at 65°C for 7 h with 2,2′-azobisisobutronitrile (AIBN) to give the corresponding poly-(II) (III) in good yield. The absorption bands at 1280, 1310, and 1630 cm^{-1}, due to the vinyl double bond in the monomer, have disappeared in the IR spectrum. Polymer III is soluble in methanol, ethanol, and water, but almost insoluble in acetone and diethyl ether. It was deisopropylidenated with 85% trifluoroacetic acid at 15°C for 4 h to afford the corresponding Polymer IV, a colorless solid, in 49% yield. As can be seen from Fig. 1, its IR spectrum showed the disappearance of the absorption band at 1375 cm^{-1} due to the isopropylidene group, but otherwise the spectrum was unchanged. Polymer IV is hygroscopic and soluble in chloroform as well as DMF, but almost insoluble in acetone as well as diethyl ether. The inherent viscosity $[\eta]$ of Polymer IV was found to be 0.36 dL/g (at 25°C in ethanol).

EXPERIMENTAL

Materials

Most of the reagents were commercially obtained and used without further purification. 2′,3′-*O*-isoprolylidene uridine, 2-dimethylaminoethyl methacrylate, phosphorus pentoxide, oxygen, lithium aluminum hydride, and calcium hydride were commercially obtained and used without further purification. THF and diethyl ether were dried by distillation from lithium aluminium hydride. DMF was distilled from calcium hydride and ethanol from magnesium ethoxide to ensure dryness. 2-Chloro-1,3,2-dioxaphospholane, bp 45.5-46.5°C/15 torr (Ref. 15: by 45.5-47.0°C/15 torr) was prepared in 65% yield by the method of Lucas et al. [15]. 2-Chloro-2-oxo-1,3,2-dioxaphospholane, bp 102.5-105.0°C/1 torr (Ref. 15: bp 79°C/0.4 torr), was prepared in 86% yield by oxidation of 2-chloro-1,3,2-dioxaphospholane with oxygen, following the method of Edmundson [16].

2′,3′-*O*-Isopropylidene-5′-*O*-(2-oxo-1,3,2-dioxaphospholan-2-yl)-uridine (I)

Into a thoroughly dried 100-mL three-necked round-bottomed flask, equipped with a mechanical stirrer, drying tube, and dropping funnel, were

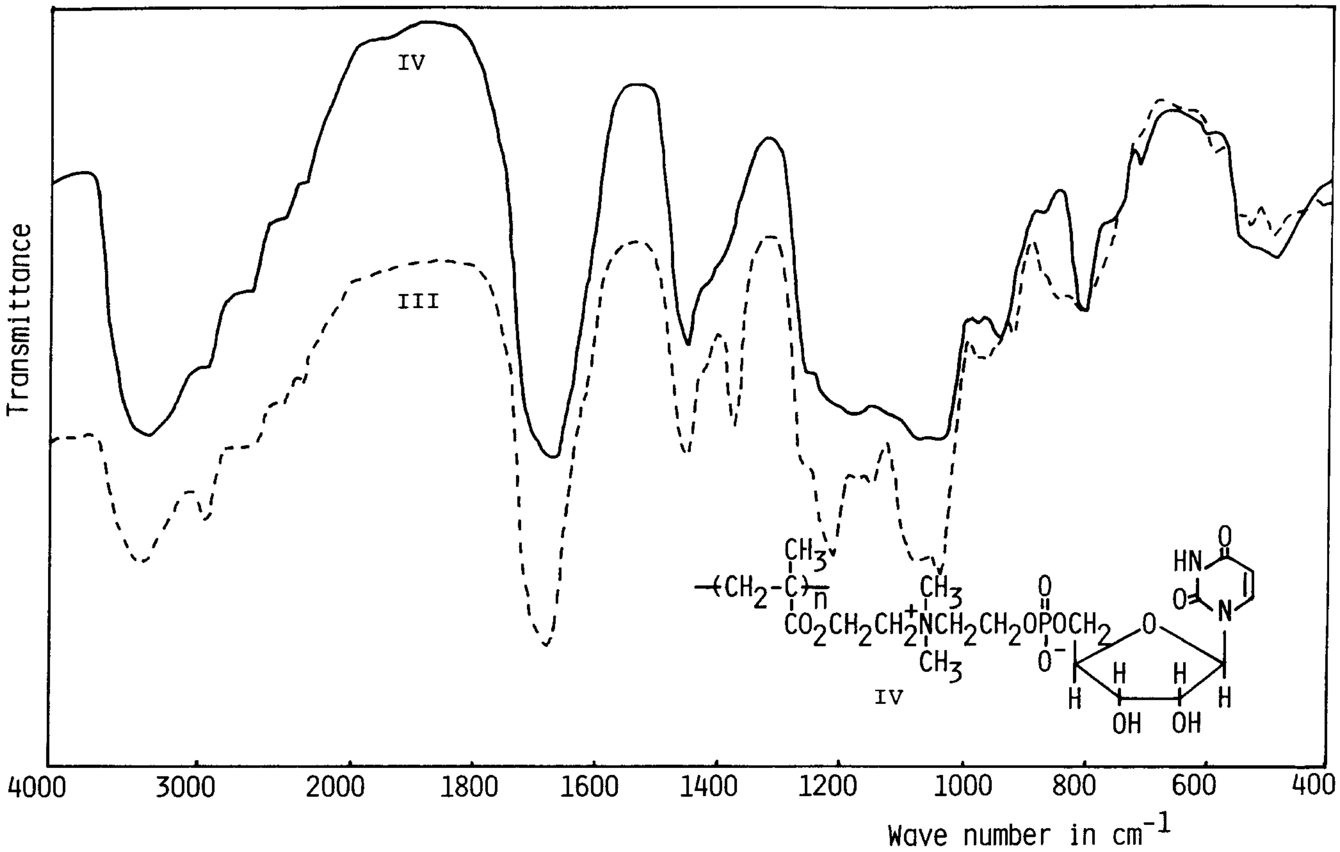


FIG. 1. IR spectra of Polymer III (KBr) (- -) and of Polymer IV (KBr) (——).

placed 1.00 g (3.50 mmol) 2′,3′-*O*-isopropylideneuridine, 0.43 g (4.20 mmol) triethylamine, and 50 mL dry THF. After cooling the solution in a Dry Ice/methanol bath (-20°C), 0.5 g (3.50 mmol) 2-chloro-2-oxo-1,3,2-dioxaphospholane in 10 mL dry THF was added slowly to the stirred solution over a period of 0.5 h, by which triethylamine hydrochloride began to precipitate from the solution. The reaction mixture was maintained at -20 to -15°C for 0.5 h during the addition and then allowed to warm up to 0°C. After 2 h at 0°C the precipitate was filtered off and washed with 30 mL dry THF. The filtrate and the THF solution were evaporated *in vacuo* in a stream of nitrogen for 1.5 h to give a white solid product in quantitative yield.

IR (KBr) showed absorptions at 1375 ($(CH_3)_2CO$–), 1070, and 1030 cm^{-1} (P–OCH_2).

2-[2-(Methacryloyloxy)ethyldimethylammonium] ethyl 2′,3′-*O*-isopropylidene)-5′-uridine phosphate (II)

Into a 300-mL glass pressure bottle (Top Model E 1435 Type A) were placed the obtained I, 0.61 g (3.90 mmol) 2-dimethylaminoethyl methacrylate, and 50 mL dry DMF. The pressure bottle was closed and placed in a thermostat at 70°C for 48 h. Then it was cooled down in cold water to 10°C. After it was opened, the contents were filtered. The filtrate was evaporated *in vacuo* with a stream of nitrogen for 2 h to give 17.5 g of a white solid. The crude product was dissolved in a small amount of diethyl ether. This procedure was repeated three times to afford a pure product as a white hygroscopic solid of mp 15°C. Yield: 1.00 g (51.9%).

IR (neat) showed absorptions at 1630, 1310, 1290 (C=C), 1375 ($(CH_3)_2CO$–), 1210, 1075, and 1040 cm^{-1} (PO–O$^-$).

^{1}H NMR ($CDCl_3$) showed δ1.30-1.60 (m, $(CH_3)_2\overset{|}{C}O$–, 6H), 1.92 (s, –CH_3, 3H), 2.90 (s, N^+–CH_3, 6H), 2.10-4.95 (m, N^+–CH_2–, –OCH_2–, –CH, 11H), 5.53 (m, –$O\overset{|}{\underset{|}{C}}H$, 2H), 5.60 (m, –$\overset{|}{\underset{|}{C}}H$–, 1H), 5.94 (m, N–CH, 1H), 6.10-6.16 (m, N=CH, –$\overset{|}{C}H$–, 2H), 7.88 (m, $O\overset{|}{C}CH$=, 1H).

Analysis: Calculated for $C_{22}H_{34}N_3O_{11}P.2H_2O$: C, 45.28; H, 6.56; N, 7.20%. Found: C, 45.31; H, 6.73; N, 7.46%.

Polymerization of II

The polymerization of II was carried out in dry ethanol with AIBN as initiator. A solution of 90 mg (0.54 mmol) of AIBN and 10 mL of dry ethanol were mixed in a glass tubule, which was flushed three times with nitrogen, sealed *in vacuo,* and then shaken at 65°C for 7 h. After this, the content of the tube was concentrated to one-third of its original volume and the concentrate poured into an excess of ethyl ether, by which a white polymer precipitated. The crude product was collected, dissolved in methanol, and purified by reprecipitation from methanol solution with acetone. The yield was 538 mg (64.8%) of a white pure polymer III melting at 160-170°C and decomposing at about 240°C. Its IR spectrum (Fig. 1) showed the disappearance of the absorption bands (1630, 1310, and 1290 cm^{-1}) due to the methacrylic C=C double bond in the monomer, but otherwise the spectrum was unchanged.

Deisopropylidenation of Polymer III

Polymer III (60.2 mg) was dissolved in 1.0 mL of a trifluoroacetic acid/water mixture (volume ratio 85/15) with stirring. The mixture was allowed to stand at 15°C for 4 h. The solution was concentrated *in vacuo* in a stream of nitrogen, by which procedure a white precipitate gradually formed. The precipitate was collected by filtration, washed three times with 50 mL acetone, and dried *in vacuo* to give Polymer IV as a white solid. Yield: 25.0 mg (49.2%), mp 168-170°C. Its IR spectrum (Fig. 1) showed the disappearance of the absorption band (1375 cm^{-1}) due to the isopropylidene group, but otherwise the spectrum was unchanged.

Viscosity Measurements

The measurements were carried out at 25°C with a Ubbelohde-type viscometer.

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