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Polynucleotide Analogues. 3.[1] Synthesis, Characterization, and Physicochemical Properties of Poly(thymidylic acid) Analogues

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ABSTRACT: Poly[{(*R*)-(−)-2-thymin-1-yl-2,3-dihydrofuran}-*alt*-(maleic anhydride)] (**3**) and poly[{(*R*)-(−)-2-thymin-1-yl-2,3-dihydrofuran}-*alt*-(vinylene carbonate)] (**6**) have been synthesized by radical copolymerizations of the relevant monomer pairs. Their alternating sequences have been confirmed by elemental analyses, titrations of functional groups and NMR spectra. Low M_n values of these polymers, 1700 for **3** and 1630 for **6**, correspond to six repeating units per chain. Hydrolysis of copolymers **3** and **6** gives poly[(2-thymin-1-yltetrahydrofuran-4,5-diyl)(1,2-dicarboxyethylene)] (**4**) and poly[(2-thymin-1-yltetrahydrofuran-4,5-diyl)(1,2-dihydroxyethylene)] (**7**), respectively. These products are analogues of poly(thymidylic acid) in which the methylene phosphate groups are substituted by dicarboxy or dihydroxyethylene groups. Copolymers **4** and **7** exhibit 52 and 45% hypochromicities, respectively, in neutral aqueous solutions. These values are obtained by comparison of the UV absorption of the monomers. The hypochromicities are due to the base stacking. CD and ORD curves of the polymers showed several extrema with wavelength and magnitude different from those of the monomers. These differences are due to the atactic polymerization at the dihydrofuran ring of the monomer. Additionally, polymer **4** exhibits a typical polyelectrolyte behavior in concentration dependence of the reduced viscosity in aqueous solution. Sodium salt of polymer **4** migrates to the anode by electrophoresis showing three separated bands.

Introduction

Over the past decade there has been considerable interest in the synthesis of polynucleotide analogues (PNA) in the hope of elucidating structures of natural polynucleotides and of utilizing their biological activities in polymeric drugs for chemotherapy. Several methods of PNA synthesis have been developed. For example, one method involves attaching nucleic acid bases (NAB) to vinyl monomers followed by polymerization. Another example involves attaching NABs on the polymer chain as pendant groups with the aid of reactions of NAB derivatives with the functional groups of the selected polymers, such as poly(α-amino acid),[9,10] poly(vinyl alcohol),[11–14] and poly(ethyleneimine).[15–20] Yet another example of the method involves condensation polymerization of ω-hydroxy carboxylic acid[21] or α-amino acid derivatives[22,23] containing the NABs. In spite of numerous attempts, there has been no success in the past in the synthesis of PNAs with structures and physical properties closely resembling those of natural ones. Most of the previously synthesized PNAs have exhibited neither good solubilities in water, due to the lack of hydrophilic groups, nor optical properties due to the absence of sugar moieties on the polymer chain. Additionally, the alternating sequences between nucleosides and phosphate, observed in the natural polynucleotides, have rarely been realized in the previously syntheses of PNAs.

In an effort to obtain a PNA closely resembling a natural polymer, we have synthesized the monomer (*R*)-(−)-2-thymin-1-yl-2,3-dihydrofuran (**1**)[24] and copolymerized it with maleic anhydride (**2**) or vinylene carbonate (**5**). The resulting alternating copolymers, poly[{(*R*)-(−)-2-thymin-1-yl-2,3-dihydrofuran}-*alt*-{maleic anhydride}] (**3**) and poly[{(*R*)-(−)-2-thymin-1-yl-2,3-dihydrofuran}-*alt*-{vinylene carbonate}] (**6**), were hydrolyzed to give poly[(2-thymin-1-yltetrahydrofuran-4,5-diyl)(1,2-dicarboxyethylene)] (**4**) and poly[(2-thymin-1-yltetrahydrofuran-4,5-diyl)(1,2-dihydroxyethylene)] (**7**), respectively. These products, **4** and **7**, are analogues of poly(thymidylic acid), in which the methylene phosphate groups are substituted by dicarboxy- or dihydroxyethylene groups, respectively (Scheme I). We have previously reported these results in a short paper.[1] In this paper we describe the synthetic procedures of the monomer and polymers and the analysis of their physicochemical properties in detail.

Experimental Section

Materials. Thymidine (Aldrich Chemical Co.) was recrystallized from ethyl acetate (mp 185 °C). Maleic anhydride was sublimed under vacuum. Vinylene carbonate was distilled before use (bp 162 °C). DMF was refluxed over anhydrous $CaCl_2$ and distilled under reduced pressure. AIBN was recrystallized from methanol. Other commercially available reagent chemicals were used without further purification.

Synthesis of Monomer. Thymidine-5′-carboxylic acid was synthesized according to a modified method of Zemlicka[25] and Moss.[26] A mixture of thymidine (8.6 g, 3.5×10^{-2} mol), Na_2CO_3 (0.34 g, 3.23×10^{-3} mol), $NaHCO_3$ (2.97 g, 3.54×10^{-2} mol), and PtO_2 on charcoal (5%, 5 g) in 1.4 L of distilled water was stirred rapidly, and oxygen was bubbled through the mixture for 48 h at 100 °C. After the catalyst was removed by filtration, the solution was acidified with Amberlite IR-120 and filtered. The filtrate was concentrated to 25 mL under reduced pressure and kept for 24 h at 0 °C. A solid product was collected, washed in acetone by refluxing for 10 min, filtered, and recrystallized from water. This procedure produced 3.1 g: yield 34%; mp 263–265 °C; UV max (H_2O) 267 (9490), 206.5 (9600) nm; NMR (DMSO-d_6) δ 12.26 (s, 1 H, NH), 8.08 (br s, 1 H, H_6), 6.36 (t, 1 H, H_1'), 4.48 (m, 1 H, H_3'), 4.33 (m, 1 H, H_4'), 2.10 (m, 2 H, H_2'), 1.82 (s, 3 H, CH_3).

(*R*)-(−)-2-Thymin-1-yl-2,3-dihydrofuran was synthesized according to the method of Zemlicka et al.[25] with extended reaction time (24 h). The melting point and NMR spectrum of the compound coincided with those reported in the literature.[25]

General Copolymerization Procedure. The calculated amounts of monomers, solvent, and initiator (AIBN) were charged into the polymerization tubes (Table I), which were then immersed in a Dewar flask containing dry ice and acetone. After conventional freeze–thaw treatments under N_2, the tubes were sealed and placed in an oil bath at 100 °C for a period of time listed in Table I. The polymer solution in DMF was precipitated in benzene twice. The polymer was collected and dried in vacuum over P_2O_5 at 50 °C in a drying pistol.

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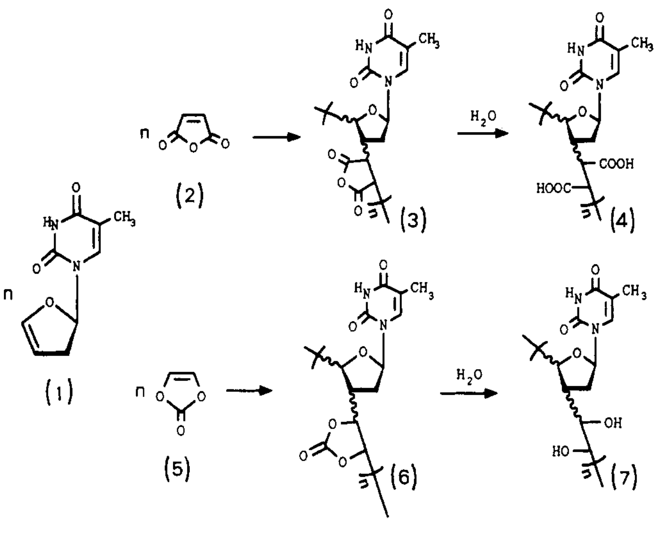
Scheme I



Titration. Analysis of anhydride groups in polymer **3** was performed by dissolving the polymer in DMF and titrating the solution with a solution of sodium methoxide (0.1 N) in DMF–methanol with the aid of a potentiometer.[27] Carboxyl groups in polymer **4** were analyzed by dissolving polymer **3** in water with stirring for 2 h and by titrating the solution with aqueous NaOH (0.1 N) solution.

Hydrolysis. (a) Polymer 4. A 0.1 g portion of polymer **3** was stirred in 20 mL of 0.1 M NaOH for 1 h at room temperature. The solution was acidified to pH 3.5 with 0.1 M HCl and concentrated under reduced pressure. After the residue was dissolved in DMF, the sodium chloride crystals were removed by filtration. Polymer **4** was obtained by precipitating the filtrate in benzene and drying (yield 65%).

(b) Polymer 7. Polymer **6** (75 mg) was stirred in 30 mL of 0.1 M NaOH for 24 h at room temperature. After the solution pH was adjusted to 3.5 with 0.1 M HCl, water was evaporated. The residue was dissolved in DMF, and NaCl was removed by filtration. Polymer **7** was obtained by precipitating the filtrate in benzene and drying (yield 87%).

Hypochromicity (*h*, %). UV absorption was recorded using a Hitachi 200-20 spectrophotometer. The concentration of solutions was approximately 10^{-4} M of base residues. The percent hypochromicity (*h*, %) was calculated from

$$h\,(\%) = [|\epsilon_m - \epsilon_p|/\epsilon_m] \times 100 \qquad (1)$$

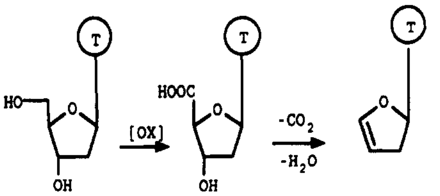
where ϵ_m and ϵ_p denote the molar extinction coefficients of monomer and base residues of polymer, respectively.

Electrophoresis. Thin-layer electrophoresis was carried out on a cellulose sheet (25 cm × 2 cm, Toyo Roshi Kaisha, sheet 51A), which was immersed in a buffer solution of pH 7.4 at a constant 250 V for 3 h. The separated bands were identified in an I_2 chamber.

Measurements. ^{1}H NMR (300 or 60 MHz) and ^{13}C NMR (25 MHz) spectra were measured on a Bruker AM-300 spectrometer or a Varian-T60 spectrometer. ORD and CD spectra were recorded on a Jasco Model J-20 with 10-mm cells at room temperature (2.4×10^{-2} g/L, H_2O). Viscosities of the polymer solution were measured by a Ubbelohde viscometer at 30 °C in H_2O. Elemental analyses were performed at KRICT.

Results and Discussion

Synthesis and Optical Properties of Monomer. The monomer, (*R*)-(−)-2-thymin-1-yl-2,3-dihydrofuran,[24] was synthesized according to a modified method of Zemlicka et al.[25,26] This method involved oxidation of thymidine followed by decarboxy dehydration of the resulting thymine-5′-carboxylic acid.



Since chiral atom C_1' in thymidine remained intact during the reactions, its chirality was retained to render the monomer optically active. The UV, ORD, and CD spectra as well as their data are given in Figures 1–3 and Table II, respectively.

Copolymerization and Characterization of the Copolymers. The radical copolymerization of 2,3-dihydrofuran with maleic anhydride (**2**) or vinylene carbonate (**5**) is known to give alternating copolymers by forming charge-transfer complexes of the monomer pairs during the copolymerization process.[28,29] As the electron-donating character of the vinyl ether group of **1** is negligibly influenced by thymin-1-yl groups on the C_2 position, both copolymers, poly[{(*R*)-(−)-2-thymin-1-yl-2,3-dihydrofuran}-*alt*-{maleic anhydride}] (**3**) and poly[{(*R*)-(−)-2-thymin-1-yl-2,3-dihydrofuran}-*alt*-(vinylene carbonate)] (**6**), are expected to give alternating sequences.

The copolymerization of **1** with **2** or **5** has been carried out with different concentrations of monomers in the presence of the radical initiator AIBN in DMF at 100 °C. The data are given in Table I. Higher yields and molecular weight of copolymers **3** and **6** have been obtained with higher monomer concentration at the beginning of the copolymerization reactions. These copolymers are yellowish powder, soluble only in highly polar solvents such as DMF and DMSO; they are insoluble in THF, acetone, acetonitrile, chloroform, methylene chloride, and other less polar solvents.

The number-average molecular weights of copolymers **3** and **6** have been measured by VPO in DMF and found to be 1700 and 1630, respectively. These values correspond to six repeating units per chain for both copolymers. The anhydride groups incorporated into polymer **3** and carboxyl groups of polymer **4** are found to be 48 and 47 mol %, respectively, by titrating them with either sodium methoxide[27] or aqueous HCl (0.1 N). The elemental analyses (Table I) have corroborated the equimolarity of the monomer pairs for polymers **3** and **6**. Note that monomer **1** as well as **2** is not homopolymerizable under the condition used. All of these results indicate that both polymers, **3** and **6**, have the alternating sequences.

Simple hydrolysis of polymer **3** in distilled water at room temperature gave poly[(2-thymin-1-yltetrahydrofuran-4,5-diyl)(1,2-dicarboxyethylene)] (**4**) without difficulty. However, hydrolysis of polymer **6** was possible with the aid of 0.1 M aqueous NaOH at room temperature, producing poly[(2-thymin-1-yltetrahydrofuran-4,5-diyl)(1,2-dihydroxyethylene)] (**7**). The completion of these reactions was monitored by following the disappearance of the carbonyl IR peaks at 1810 cm^{-1} of anhydride groups in polymer **3** and at 1760 cm^{-1} of carbonate groups in polymer **6**.

NMR spectra of monomer **1** and polymers **3**, **4**, and **7** are shown in Figure 1. In the NMR spectra of polymers **3**, **4**, and **7**, the signals of double bond protons (δ 6.73, q, 5.09, q) in dihydrofuran rings of monomer **1** have completely disappeared, while broad signals of succinic acid (δ 2.8) and ethylene glycol (δ 3.2) emerged. Both polymers, **4** and **7** are soluble in water and insoluble in organic solvents.

Hypochromicity. According to the Tinoco[30] and Rhodes[31] theory, induced dipole–dipole interactions in the

Table I
Copolymerization Data for Polymers 3 and 6 in DMF at 100 °C

	concn, mol/L								elem anal[d] calcd (found)		
polymer	1	2 or 5	AIBN	polym time, h	yield, %	$[\eta]$,[a] dL/g	M_n[b]	MA,[c] mol %	C	H	N
3	0.20	0.20	8.0×10^{-3}	26	25	0.05					
	1.96	1.96	7.8×10^{-2}	24	86						
	2.03	2.03	8.1×10^{-2}	24	88	0.12	1700	48	51.90	4.13	9.58
									(51.90)	(4.55)	(10.0)
6	3.02	2.01	8.1×10^{-2}	47	40						
	5.15	3.43	1.4×10^{-1}	47	41						
	12.83	5.58	3.4×10^{-1}	48	45	0.08	1630		51.40	4.32	10.00
									(51.30)	(4.69)	(10.60)

[a] Intrinsic viscosity in DMF at 30 °C. [b] Number-average molecular weight measured by VPO in DMF. [c] Mole percent of maleic anhydride incorporated into the polymer. [d] Elemental analysis calculated for the alternating copolymers.

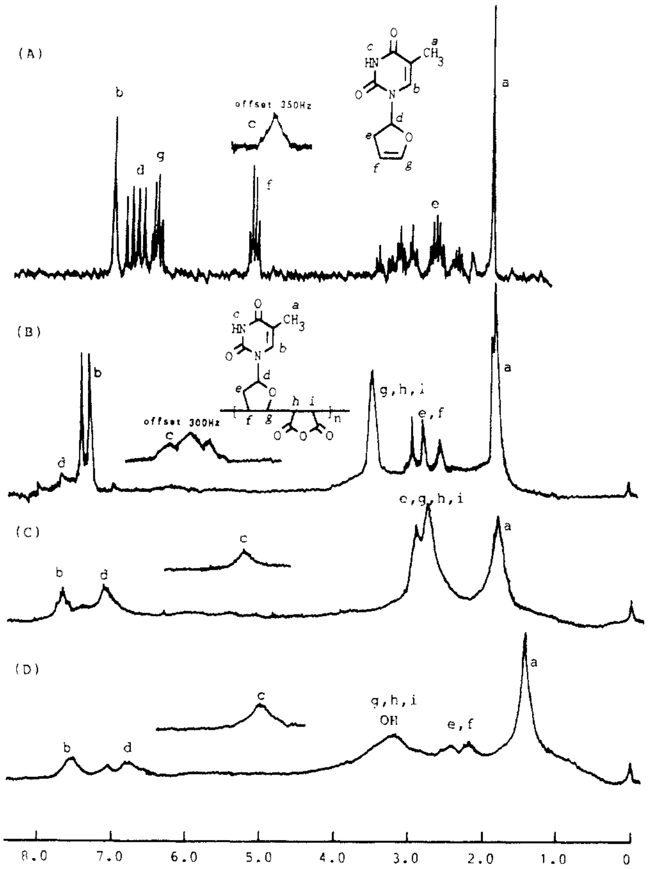


Figure 1. ^1H NMR spectra: (A) monomer 1 in $CDCl_3$; (B) polymer 3; (C) polymer 4; (D) polymer 7 in DMSO-d_6.

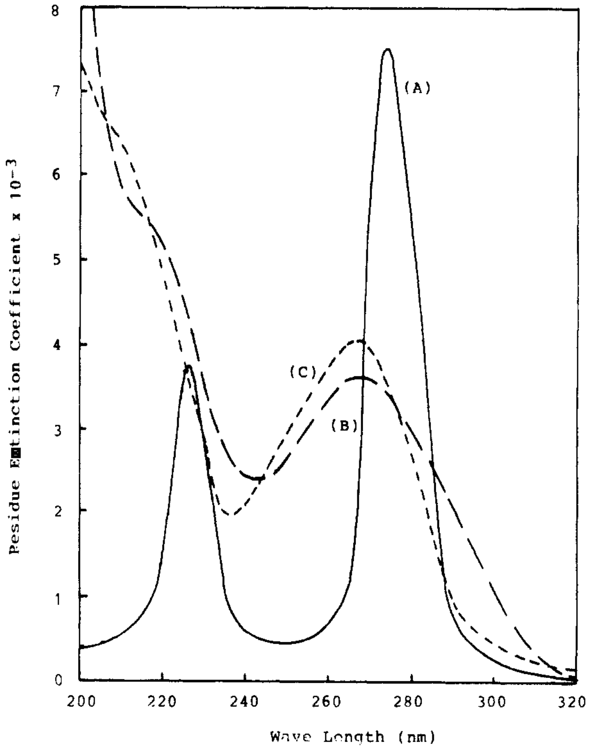


Figure 2. UV spectra: (A) monomer 1; (B) polymer 4 at pH 7; (C) polymer 7 in H_2O at room temperature.

chromophores of maleic acid bases can result in either hypochroism or hyperchroism, depending on the relative geometry of the stacked chromophores. Hypochroism is common to systems with the chromophores stacked one on top of another like a deck of cards,[30,31] which systems with the chromophores in an end-to-end aggregate are generally predicted to be hyperchromic.[32] To determine the hypochromicity of polymers, the UV spectra of monomer 1, polymer 3 in DMF, and polymers 4 (at pH 7.0) and 7 in H_2O have been measured (Figure 2). Their data are given in Table II. Polymers 4 and 7 have shown hypochromicities of 52 and 45%, respectively, in neutral aqueous solution. These values are obtained in comparison to the UV absorption of monomer 1. This result indicates that the carboxylate groups of polymers 4 at pH 7.0 and the hydroxyl groups of polymer 7 in aqueous solution protrude outward, interacting with the aqueous environment. Consequently, the thymines are stacked one upon another to cause such high hypochromicity. On the contrary, polymer 3, containing anhydride groups, has exhibited no hypochromicity in DMF since the pendant bases could not be stacked under these conditions (Table II).

Percent hypochromicity increases with the increasing molecular weight of the polynucleotide analogues.[33] Although the average degree of polymerization for both polymers 4 and 7 is 6, they have exhibited unusually high hypochromicity in comparison to the typical hypochromism range (20–40%) of natural polynucleotide in neutral water,[34] suggesting that these polymers can be used as a model system for the hypochroism change of polynucleotides.

Optical Properties. It is well documented that ORD spectra of thymidine and its α-anomer show nearly symmetrical curves on the base line; they have crossover points at a close wavelength and opposite sign of Cotton effect with similar amplitude[35] (Table II). The stereochemistry at C_3' of thymidine and the phosphate groups of 3′-thymidylic acid has little effect on the sign and magnitude of the Cotton effect on ORD curves of thymidine.[36] The ORD curve of poly(thymidylic acid) has shown a larger amplitude in optical rotation with the same sign of Cotton effect than that of thymidylic acid. This difference is due to the ordered structural formation of the polymer[37] (Table II).

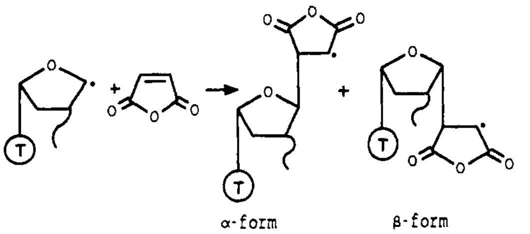
Table II
Optical Data of Monomer and Polymers

compound	solvent	UV λ_{max} ($\epsilon \times 10^{-3}$)	h,[a] %	ORD extrema λ ([m] $\times 10^{-3}$)	CD extrema λ ([θ] $\times 10^{-3}$)
monomer 1	H_2O	226 (3.8) 274 (7.5)		210, 234, 267 (−3.7) (5.4) (−3.3)	222, 257 (1.5) (−3.7)
polymer 3	DMF	268 (7.4)			
polymer 4	H_2O (pH 7)	268 (3.6)	52	214, 247, 262 (−2.1) (0.2) (−0.9)	212, 249 (0.8) (−0.3)
polymer 7	H_2O (pH 7)	266 (4.1)	45	210, 227, 252, 267 (−1.9) (−0.4) (−1.5) (0.5)	236, 262 (0.3) (2.8)
thymidine				255, 282[35] (−7.50) (1.89)	218, 235, 273[40] (−4.6) (−3.3) (4.3)
α-thymidine				264, 286[35] (6.78) (−3.66)	
poly(thymidylic acid)[b]				264, 288[37] (−13.0) (7.0)	252, 276[41] (−4.0) (5.5)

[a] Hypochromicity. [b] Measured at pH 7 and room temperature.

As shown in Figure 3 and Table II, the ORD spectrum of monomer 1 shows one peak at 234 and two troughs at 211 and 267 nm that are different from those of thymidine with a peak at 282 nm and a trough at 255 nm.[35] These results may be explained by the fact that the replacement of 4′-hydroxymethyl and 3′-hydroxy groups by a double bond on the furanosyl ring has a significant effect on the ORD curve. Additionally, monomer 1 has two crossover points at 217 and 254 nm, which are not coincident with the UV maxima (226, 274 nm). ORD curves of polymers 4 and 7 have three extrema with different wavelengths and reduced magnitudes from those of the monomer.

These results suggest that an atactic addition polymerization has occurred at the double bonds of monomer 1. The sign of the Cotton effect is decided by the C_4' configuration, and a decreased amplitude results from an anomeric mixture formed during copolymerization. As shown, oxyalkyl radicals on the furanosyl rings are formed during copolymerization, as they are more stable than alkyl radicals. The addition of monomers 2 or 5 on the radical can lead to α- or β-anomeric forms. However, under the high polymerization temperature (100 °C) used, a stereoregular addition has rarely been obtained, and a mixture of α- and β-forms in the polymer results. These mixtures have caused the reduced amplitude with several extrema due to overlapping of the optical rotation with different signs arising from α- and β-forms in polymer.



CD curves of monomer 1 and polymers 4 and 7 are shown in Figure 4, and their data are given in Table II. Monomer 1 has shown a positive Cotton effect at 225 nm and a negative one at 257 nm. These Cotton effects are quite different from those of thymidine. The disappearance of chirality on the 3′ and 4′ carbon atoms of the furanosyl ring by formation of a double bond causes a significant change in the CD spectra. The CD curve of poly(thymidylic acid) has shown a similar trend with larger magnitude to that of thymidine (Table II). Therefore, if one anomeric form is exclusively formed during copolymerization, an increased magnitude of Cotton effect compared to those of thymidine is expected. However, magnitudes of the Cotton effect of polymer 4 are small, whereas that of polymer 7 is considerably larger. These phenomena can be explained by the fact that the atactic addition polymerization at the double bonds of monomer 1 has reduced the ellipticity by overlapping and by the fact that polymer 7 is probably more stereoregular than polymer 4. Ellipticity of the former is higher than that of the latter and ranges between those of thymidine and poly(thymidylic acid).

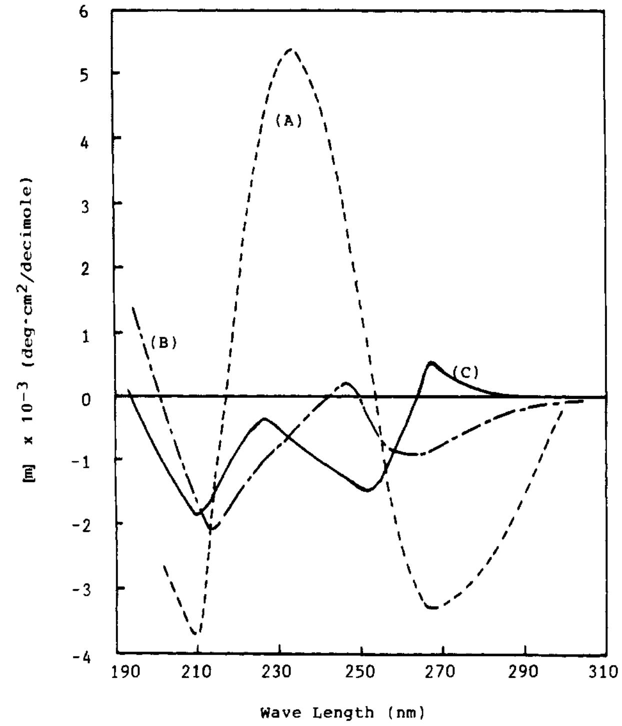


Figure 3. ORD spectra: (A) monomer 1; (B) polymer 4 at pH 7; (C) polymer 7 in H_2O at room temperature.

Polyelectrolyte Behavior. The sodium salt of polymer 4 is a polyelectrolyte which has viscosity as well as electrophoretic characteristics. Reduced viscosities of the sodium salt of polymer 4 exhibit typical polyelectrolyte behavior as a function of concentrations in H_2O (Figure 5). By continuous dilution the reduced viscosities of polymer 4 decreased steadily and increased rapidly at concentrations below 0.5 g/dL in water. In a neutral salt (NaCl, 5%) solution the reduced viscosity retains normal behavior.[38] Compared to polymer 3 (Table I), polymer 4 gives rather low intrinsic viscosity in neutral salt solution (NaCl, 5%). This decrease in viscosity is due to the chain flexibility introduced by cleaving anhydride groups of polymer 3. Base stacking compels polymer 4 in H_2O to be shaped into a spherical form, which also contributes to the viscosity reduction.

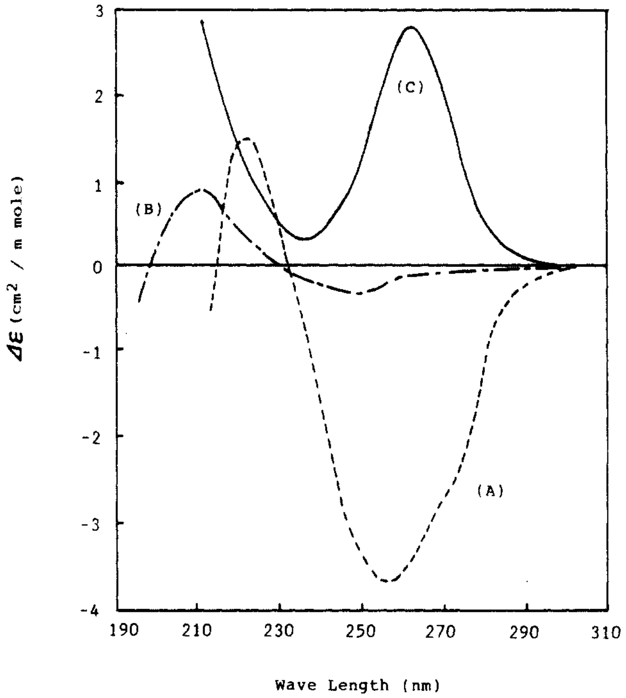


Figure 4. CD spectra: (A) monomer 1; (B) polymer 4 at pH 7; (C) polymer 7 in H_2O at room temperature.

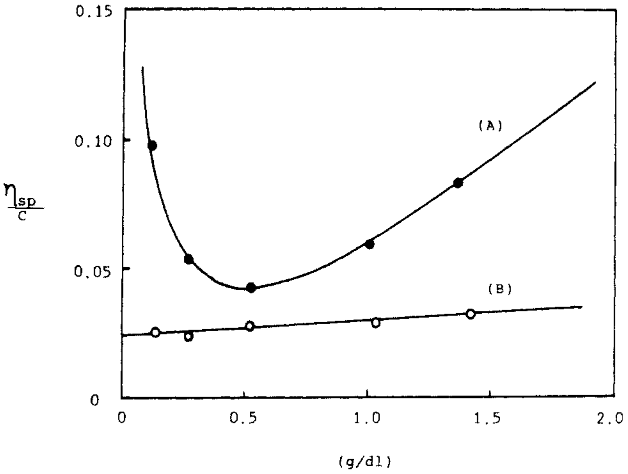


Figure 5. Reduced viscosity vs concentration: (A) polymer 4 in H_2O; (B) Na salt of polymer 4 in 5% NaCl aqueous solution at 30 °C.

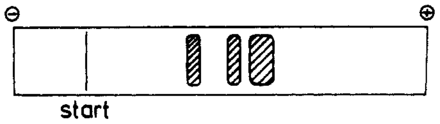


Figure 6. Electrophoresis diagram of sodium salt of polymer 4 at a constant 250 V for 2.5 h in a pH 7.4 buffer solution.

Migration of the polyanions of polymer 4 to an anode has been investigated in an electrical field according to eq 2.[39] Thin-layer electrophoresis diagrams of sodium salts of polymer 4 developed on electrophoresis cellulose sheets in a buffer solution (pH 7.4) have shown three separated bands (Figure 6). According to eq (2), the mobility (V) of charged polymers is proportional to the net charge (Z) and is inversely proportional to the two-thirds power of molecular weight (M)

$$V = kZM^{-2/3} \qquad (2)$$

where k is a constant. The increase of each repeating unit in polymer 4 is accompanied by an increase of two net charges. The polymer band at a farther distance from the starting line, therefore, corresponds to the polymer of higher molecular weight than a closer band.

Since the average degree of polymerization of polymer 4 has been found to be 6 by vapor-pressure osmometry, polymer 4 should be a mixture of penta-, hexa-, and heptamers. The narrow molecular weight distribution of the oligomer is attributable to the following points: transfer reactions generally occurred on the allyl protons of cyclic vinyl ethers which cut off high molecular weight portions,[28] and the precipitation processes after copolymerization and hydrolysis of the polymers resulted in the dissolving of the low molecular weight portion.

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