Communications to the Editor

Polynucleotide Analogues. Synthesis, Characterization, and Optical Properties

There has been considerable interest in the synthesis of polynucleotide analogues to help elucidate the structures of natural polynucleotides and utilize their biological activities in polymeric drugs for chemotherapy. Despite numerous attempts, it has not previously been possible to synthesize polynucleotide analogues whose structures and physical properties have a close resemblance to those of natural polymers; most of the synthesized polynucleotide analogues 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.[1-6] The alternating sequences between nucleoside and diphosphate, observed in the natural polynucleotide, have also been rarely realized in the synthesis of polynucleotide analogues.[7] In this report we describe the synthesis of polynucleotide analogues closely resembling a natural one.

The monomer, (*R*)-(−)-2-thymin-1-yl-2,3-dihydrofuran (1),[8] was synthesized by decarboxyhydration of thymidine-5′-carboxylic acid obtained by oxidation of thymidine.[9,10] 1 was copolymerized with either maleic anhydride or vinylene carbonate to give 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). Hydrolysis of 3 and 6 gave 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), both of which are analogues to poly(thymidylic acid) in which the methylene diphosphate groups are substituted by dicarboxy- or dihydroxyethylene groups, respectively, as shown in Scheme I.

The hydrophilic groups on the polymer chain make polymers 4 and 7 water-soluble. The chiral atom of C-1′ in thymidine is intact during the synthesis of monomer 1 as well as during the copolymerization, so that its chirality is retained to render the polymers optically active. The nucleoside analogues 1 are linked by C–C bonds instead of phosphate linkages susceptible to hydrolysis, which deteriorates the biological activities of polynucleotide analogues.[7]

The radical copolymerization of 2,3-dihydrofuran derivatives with 2 or 5 is known to give alternating copolymers by forming charge-transfer complexes of the monomer pairs during the copolymerization.[11,12] As the electron-donating character of the vinyl ether group of 1 is negligibly influenced by the thymin-1-yl group substituted on the C_2 position, copolymers 3 and 6 are expected to have alternating sequences.

The copolymerizations of 1 with 2 or 5 were carried out in DMF in the presence of a radical initiator (AIBN), and the data are given in Table I. Neither 1 nor 2 homopolymerized under the same condition. Equimolar amounts of the comonomer pairs in polymers 3 and 6 were confirmed by titrations of anhydride or carbonate groups incorporated into the copolymers[13] and ^{1}H NMR spectra; e.g., 3 revealed a typical polymer spectrum with broad peaks from THF ring protons centered at $\delta = 2.4$ (ppm) for C_3 and C_4, at 3.4 for C_5, and at 6.9 for C_2 as well as the peaks from thymine protons at 1.75 for methyl, at 7.0 for C_6, and at 10.7 for NH. The integral ratios of these peaks indicated a 1:1 1–2 composition, which corroborated the C, H, and N elemental analysis data. Identical results were also

Scheme I

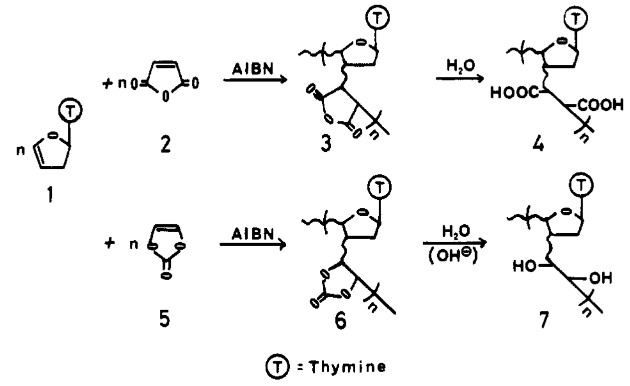

Table I
Copolymerization Data in DMF at 100 °C

copolymer	monomer (mol/L)		AIBN, mol/L	time, h	yield, %	M_n[a]
3	1[b] (2.03)	2[c] (2.03)	8.1×10^{-2}	24	88	1700
6	1 (12.83)	5[d] (8.58)	0.43	48	35	1630

[a] Number-average molecular weight measured by VPO. [b] (*R*)-(−)-2-Thymin-1-yl-2,3-dihydrofuran. [c] Maleic anhydride. [d] Vinylene carbonate.

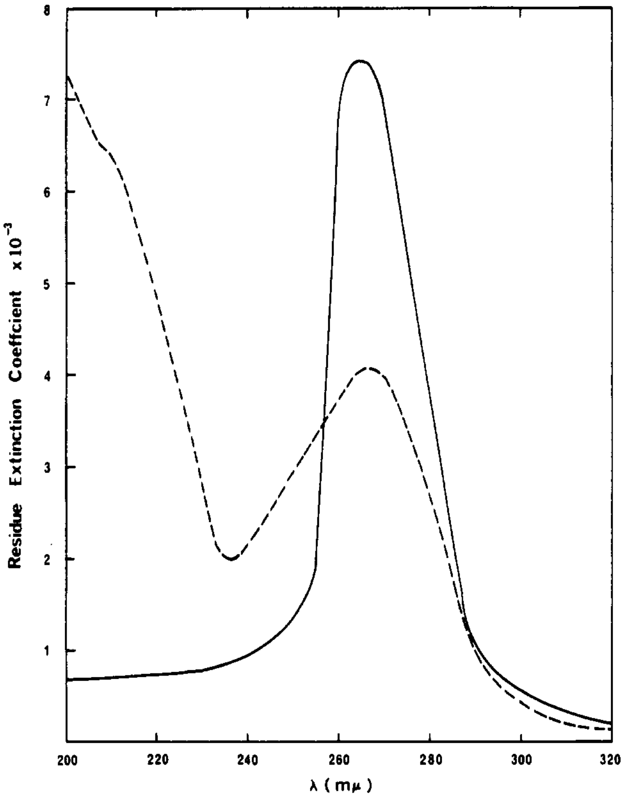

Figure 1. UV spectra of polymers 6 in DMSO (solid line) and 7 in water (dotted line).

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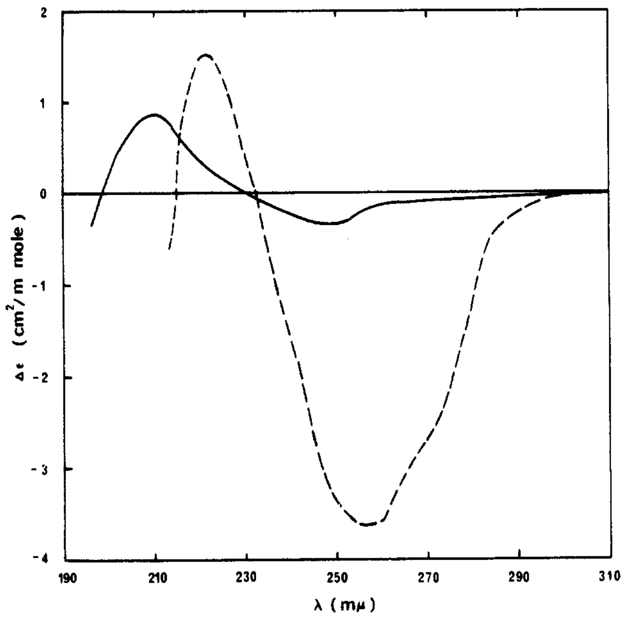

Figure 2. CD spectra of monomer 1 in H_2O (dotted line) and polymer 4 in H_2O at pH = 7 (solid line).

obtained for 6. The copolymers 3 and 6 therefore have alternating sequences. Number-average molecular weights of the polymers are rather low (Table I). Mean repeating units per chain were calculated to be 6 for both 3 and 6. Hydrolysis of 3 was simply accomplished by stirring 3 in water whereas that of 6 was carried out with the aid of hydroxide catalyst. Polymers 4 and 7 are soluble in H_2O.

UV spectra of polymers 6 in DMSO and 7 in water are shown in Figure 1. The hydroxyl groups of polymer 7 protrude outward to interact with the aqueous environment, and consequently the bases are stacked one upon another to cause the hypochromicity of 45.1%, which is generally observed in natural polynucleotides under the same conditions.[14]

The CD spectrum of monomer 1 exhibited two Cotton effects, negative at 257 nm and positive at 225 nm (Figure 2). The CD curve of polymer 4 showed the same trend with reduced ellipticities. As the configurations of the carbon atoms other than C-1′ in the furanose ring of the nucleosides influence the CD curve, even the sign of the Cotton effects,[15] the atactic addition polymerization at the double bond of monomer 1 apparently reduced the ellipticity by overlapping.

A detailed analysis of optical properties and experimental results as well as a more extensive discussion will be published elsewhere. The copolymerization of 2,3-dihydrofuran substituted with other nucleic acid bases is in progress.

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References and Notes

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