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Synthesis and Characterization of Poly[(5,6-dideoxy- α -D-xylo-hex-5-enofuranose)-alt-(maleic acid)]

Man Jung Han*, Kyung Soo Yoo, Young Heui Kim,
and Sung Hwa Yoon

Department of Applied Chemistry, Ajou University,
Suwon 441-749

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There has been considerable interest in the application of polymers in medicine either as polymer drugs or as polymeric drug carriers¹. The synthetic polyanions containing carboxylate groups are one kind of polymer drugs², which exhibit a broad range of biological activities. They are particularly active against bacteria, viruses, and tumors. Recently we have reported that, among the polyanions, the alternating copolymers of dihydropyran or dihydrofuran rings with maleic anhydride showed very high antitumor activity³⁻⁷.

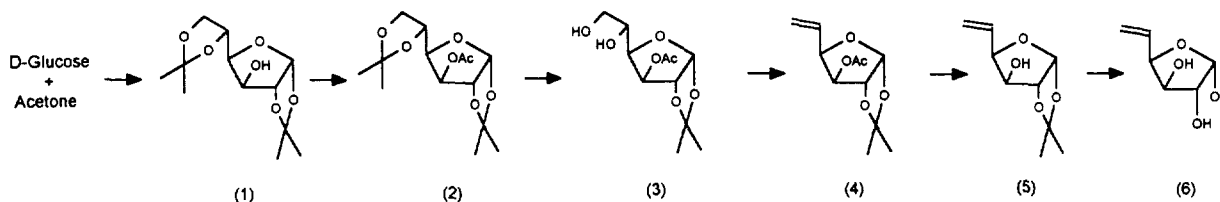
In this paper we report on the synthesis and characterization of monomers, 3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene- α -D-xylo-hex-5-enofuranose (**4**) and its derivatives **5** and **6**, and their alternating copolymers with maleic anhydride **8**, **9**, **10**, and **11** as shown in Scheme 1. Since polymer **11** is a polyanion, composed of furanose sugar and maleic acid, it may show high biological activities and be applicable for the backbone of polymeric carrier in the liver-specific delivery system. Recently it was found that sugar derivatives attached on the polymer chain had high affinities to liver hepatocyte as its membrane contains a receptor which recognizes them⁸⁻¹⁰. For example, galactose has been used as a homing device in the liver-specific delivery of polymeric antitumor agents¹⁰.

Experimental

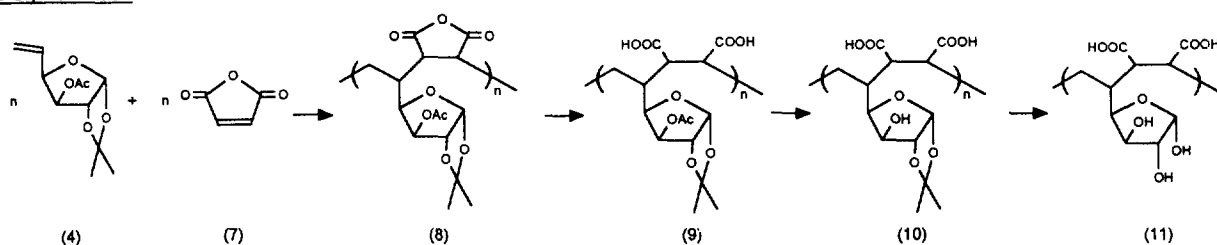
Materials and measurement. D-glucose (Aldrich Co.) and N,N-dimethyl formamide dimethyl acetal were used as delivered. Maleic anhydride was sublimed under vacuum. Acetone was distilled over P₂O₅. AIBN was recrystallized from methanol. Other commercially available reagent chemicals were used without further purification. ¹H and ¹³C-NMR spectra were recorded on a Varian T-60 or a Bruker AMX-500 spectrometer. IR spectra were obtained with a Perkin-Elmer Model 238B spectrometer. UV spectra were recorded with a Hitachi Model 200-20 spectrometer. CD and ORD spectra were obtained with a Jobin-Yvon spectrometer. Measurements of M_n were carried out in acetone at 40°C using a vapour-pressure osmometer (Knauer Co.). Elemental analysis was performed at KRICT.

Synthesis of 3-O-acetyl-5,6-dideoxy-1,2-O-isopropylidene- α -D-xylo-hex-5-enofuranose (4**).** N,N-dimethylformamide dimethyl acetal (20.0 mL, 15.0 mmol) was added to the solution of **3**¹³ (6.6 g, 28.9 mmol) in 20 mL of methylene chloride, and the mixture was stirred at room temperature for 3 h. After evaporation under reduced pressure, the residue was redissolved in 40 mL of acetic anhydride. The solution was refluxed for 100 min and then neutralized with

Synthesis of Monomer



Polymerization



Scheme 1.

Table 1. Copolymerization of Monomer **4** and **5** (2 : 1 by mole) in Bulk for 20 h

AIBN ^a (mol%)	Temperature (°C)	Conversion (%)	Mn ^b	$[\eta] \times 10^2$ dl/g	MA ^d (%)
1	80	36.6	—	—	—
2	80	54.7	—	—	—
1	90	41.9	—	—	—
2	90	69.6	3500	4.3	50.2

^aInitiator concentration: mol% of total monomer. ^bNumber-average molecular weight measured by VPO. ^cmeasured in methyl ethyl ketone at 30°C. ^dmole% of maleic anhydride (MA) incorporated into the polymer measured by titration.

a saturated sodium bicarbonate solution. The solution was concentrated and the residue was dissolved in 20 ml of water. The aqueous layer was extracted with diethyl ether (4 × 40 ml). Organic layer was washed with a saturated NaCl solution, and dried with anhydrous magnesium sulfate. After filtration and concentration, the resulting oil was chromatographed on silica gel (1 : 4 ethylacetate : hexane) to give 1.3 g of product (22.8% yield).

¹H-NMR (DMSO-d₆): 1.53-1.4 (6H, d, methyl), 2.1 (3H, s, methyl of acetyl), 4.55 (1H, d, 2-H), 4.75 (1H, m, 4-H), 5.2 (1H, d, 3-H), 5.29 (1H, d, 6-H), 5.43 (1H, d, 6-H), 5.76 (1H, m, 5-H), 5.95 (1H, d, 1-H).

Anal. Calc. for C₁₁H₁₆O₅: C, 57.89; H, 7.07; O, 35.04. Found: C, 57.50; H, 7.15; O, 35.35.

Synthesis of 5,6-dideoxy-1,2-O-isopropylidene-α-D-xylo-hex-5-enofuranose (5). Deacetylation of **4** was accomplished according to the literature¹¹. Mp.: 60-62°C (ref. mp. 61-65°C)

Synthesis of 5,6-dideoxy-α-D-xylo-hex-5-enofuranose (6). The mixture of **5** (700 mg, 3.76 mmol) in 3.0 ml of dimethoxyethane (DME) and 4.0 ml of 2 N HCl was stirred at room temperature for 96 h. After the reaction mixture was neutralized with a saturated NaOH solution, it was concentrated and added with acetone. Acetone layer was filtered and concentrated. The product was purified by column chromatography on silica gel (10 : 1, methylene chloride : methanol) to give 350 mg. (63.6% yield)

¹H-NMR (neat): 3.6 (1-OH, s), 4.17 (2H, s, 2,3-OH), 4.8 (2H, 2-H and 4-H), 5.3 (1H, 3-H), 5.6 (2H, 6-H), 5.85 (1H, 1-H), 6.0 (1H, 5-H).

IR (neat, cm⁻¹): 3420, 3020, 2980, 1680, 1430, 1100-910.

Anal. Calc. for C₆H₁₀O₄: C, 49.31; H, 6.90; O, 43.79. Found: C, 49.17; H, 6.97; O, 43.86.

General polymerization procedure. The calculated amounts of monomers, solvents, and initiators (AIBN or BPO) were charged into the polymerization tubes (Table 1), which were then immersed in a Dewar flask containing dry-ice and acetone. After conventional freeze-thaw treatments under nitrogen, the tubes were sealed and placed in an oil bath at a definite temperature for 20 h. The products were dissolved in acetone and precipitated in diethyl ether twice. The polymers were collected and dried *in vacuo* over P₂O₅ at 50°C in a drying pistol.

Hydrolysis of polymers. Polymer **9**. Polymer **8** (0.1 g) was dissolved in 6 ml of 0.1 N NaOH aqueous solution

and stirred for 0.5 h at room temperature. Polymer was precipitated by adjusting pH 3.5, filtered and dried (yield: 70%). Polymer **10**. Polymer **8** (100 mg) was dissolved in 20 ml of 0.1 N NaOH aqueous solution and stirred for 6 h at room temperature. After adjusting pH 3.5, the precipitate was filtered and dried (yield: 57%). Polymer **11**. Polymer **8** (150 mg) was dissolved in 5 ml of 0.1 N NaOH aqueous solution and stirred for 4 h at 70°C. After 6 ml of 2 N HCl was added, the solution was stirred for 12 h at room temperature, and dialyzed with a cellulose membrane (Spectrum Medical Ind. Inc. MWCO-1000) using a constant flow of distilled water for 24 h at room temperature. The retentate was lyophilized to give 116 mg of the product (yield: 82%).

Results and Discussion

Synthesis. The syntheses of monomers are shown in Scheme 1. Compounds **1**¹², **2**¹³, and **3**¹³ were prepared according to the literatures. Compound **3** was then converted into desired 5-enofuranose **4** with N,N-dimethyl formamide dimethyl acetal in methylene chloride. Hydrolysis of compound **4** under basic condition gave compound **5**, whereas hydrolysis in 2 N HCl in DME removed both acetal and acetate groups to give compound **6**.

Several runs of homopolymerizations for the monomers **4**, **5**, and **6** were attempted in bulk or in acetone (monomer **6** in water) in the presence of a radical initiator (AIBN, BPO or potassium persulfate) at 70-90°C and no polymer was found under these polymerization conditions.

Copolymerization of monomer **4** with maleic anhydride was attempted in acetone at 70°C for 20 h in the presence of a radical initiator (AIBN) to result in oligomer with a yield of 14%. In order to obtain high molecular weight of polymer with increased conversion, copolymerization was carried out in bulk with the mole ratio of monomer **4** to maleic anhydride 1 : 2. Due to its low melting point (52.8°C), excess maleic anhydride served as a solvent for the polymerization. The polymerization results are given in Table 1. The higher conversion was obtained with the increase of the temperature and initiator concentration. The copolymer **8** was a white powder, soluble in acetone, chloroform, methyl ethyl ketone, DMF, DMSO, and methylene chloride, and was insoluble in the nonpolar solvents such as diethyl ether and hexane.

Polymer **8** has several functional groups such as ester, anhydride, and acetal. Hydrolysis of them under different conditions resulted in three derivatives, polymers **9**, **10**, and **11**. Completion of hydrolysis was monitored by following the disappearance of the characteristic IR peaks at 1810 cm⁻¹ (C=O) for the anhydride groups, and NMR signals at δ=2.1 ppm (acetyl group) and 1.3, 1.5 ppm (isopropylidenene group) of the polymers.

Polymer **11** was insoluble either in polar or in nonpolar solvents, such as water, DMF, DMSO, acetone, chloroform, diethyl ether, and hexane. However, it was soluble in aqueous alkali. Polymer **11** has three hydroxyl and two carboxyl groups in one repeating unit. These groups can form intra- and/or intermolecular hydrogen bonding in the polymer, which renders the polymer insolubility.

Characterization of the copolymers. Since the homopolymerization of monomer **4** was found to be not success-

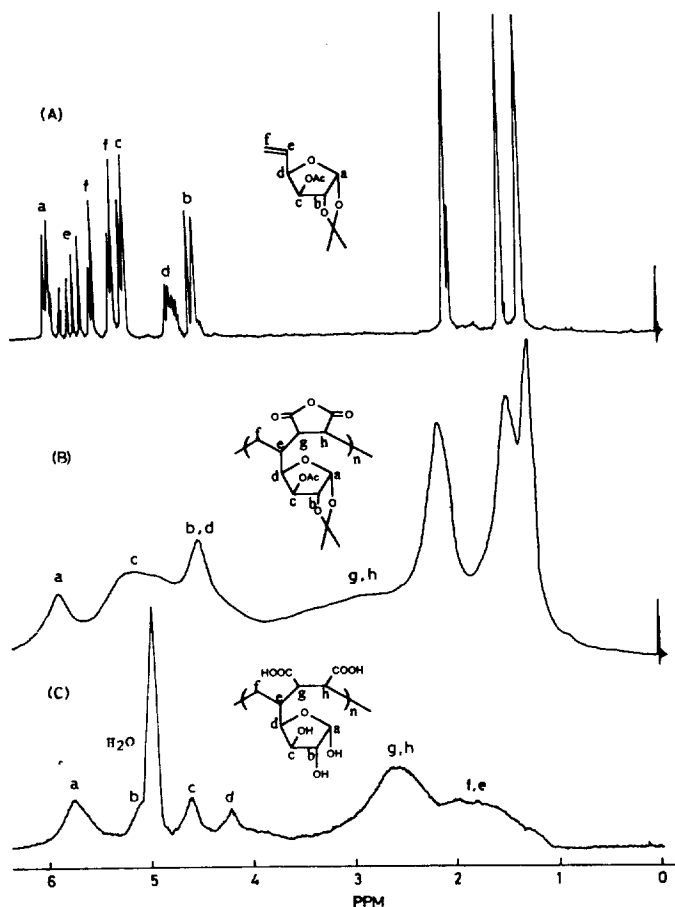


Figure 1. ¹H-NMR spectra: (A) monomer **4** in CDCl₃, (B) polymer **8** obtained by a bulk polymerization in CDCl₃, and (C) polymer **11** produced by hydrolysis of polymer **8** in D₂O and NaOD.

ful and the maleic anhydride had not been homopolymerized under the same conditions, the copolymer formed was expected to be an alternating copolymer. The anhydride groups incorporated into the polymer **8** and the succinic acid moieties in polymer **11** were found to be 50.2 and 50.1 mol%, respectively, by titrating them with sodium methoxide¹⁴ and back titration with aqueous 0.1 N HCl after dissolving polymer **11** in a definite volume of aqueous 0.1 N NaOH, respectively. These results corroborated the alternating structures of polymer **8** and **11**.

The NMR spectra of polymer **8** and polymer **11** are shown and the chemical shifts of the protons assigned in Figure 1. Chemical shifts of furanose ring protons were found in the region of 4 to 6 ppm, whereas those of the other protons in the polymer **8** appeared at 1-4 ppm (curve B). The ratio of integration values of former to latter was found to be 4 to 14, which also corroborated the alternating structure of the polymer **8**. The proton signals of acetyl group 2.1 ppm and isopropylidene group at 1.2-1.4 ppm of polymer **8** disappeared in the NMR spectrum of polymer **11** (curve C), that confirmed the complete hydrolysis of polymer **8**.

The number-average molecular weights ($\bar{M}_n$) of polymer **8**, obtained by solution and bulk polymerization, were measured by vapour pressure osmometry at 40°C in acetone and found to be 1100 and 3500, respectively. The low $\bar{M}_n$ obtain-

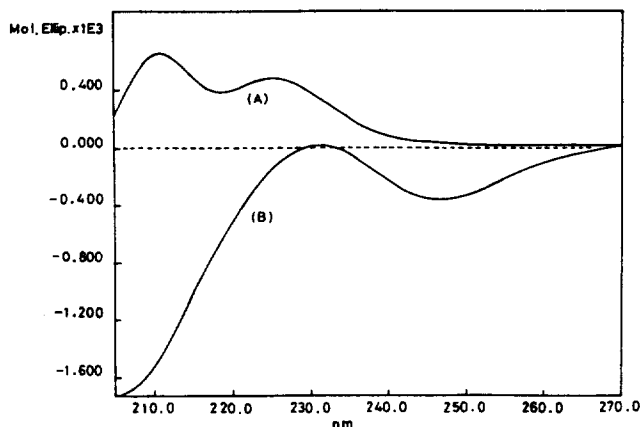


Figure 2. CD-curves: (A) monomer **4** and (B) polymer **9** in water.

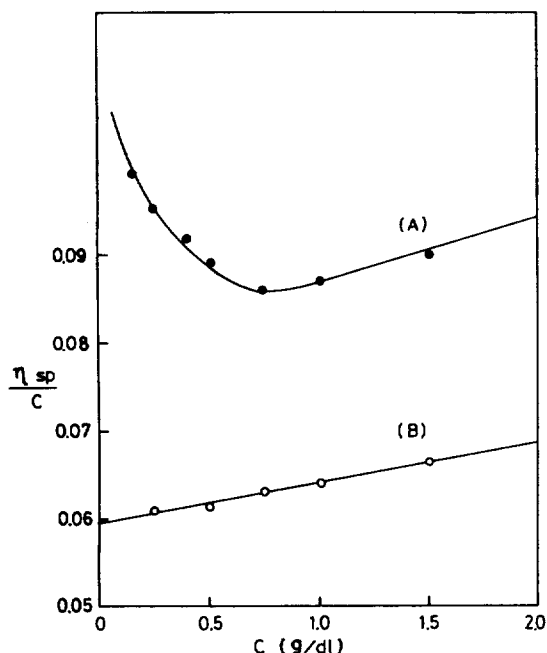


Figure 3. Reduced viscosity as a function of concentration: (A) sodium salt of the polymer **11** in water and (B) sodium salt in aq. 5% NaCl solution at 30°C.

ed either in solution or in bulk polymerization was attributable to the transfer reaction on monomers, as was generally in the case of a monomer having an allyl hydrogen.

Physicochemical properties of the polymer. The monomer **4** had a furanose ring containing four chiral atoms. They were intact during the synthesis of the monomer, so that the monomer **4** had optical activity. The CD curves of **4** and the polymer **9** were recorded in aqueous solutions and given in Figure 2. The monomer **4** showed two positive extrema at the wavelength of 211 and 225 nm where the carbonyl groups absorbed. The polymer **9** was also optically active, since the chiral atoms of the monomer were intact during propagation. The polymer **9** showed two negative Cotton effects; one at 247 nm and the other with higher amplitude below 200 nm.

The sodium salt of the polymer **11** is a polyelectrolyte.

Reduced viscosities of the sodium salt of polymer **11** exhibited typical polyelectrolyte behavior as a function of concentrations in water (Figure 3). By continuous dilution the reduced viscosity of polymer **11** decreased steadily and increased rapidly at the concentrations below 0.6 g/dl in water. In a neutral salt solution (NaCl, 5%) the reduced viscosity retained normal behavior¹⁵.

Biological activities of the polymers **9**, **10**, and **11** and the sulfate of **11** as well as the body distribution of the polymer **11**-pharmakon conjugate are under investigation.

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Generation and Trapping of 2-Methyl-2-sila-naphthalene

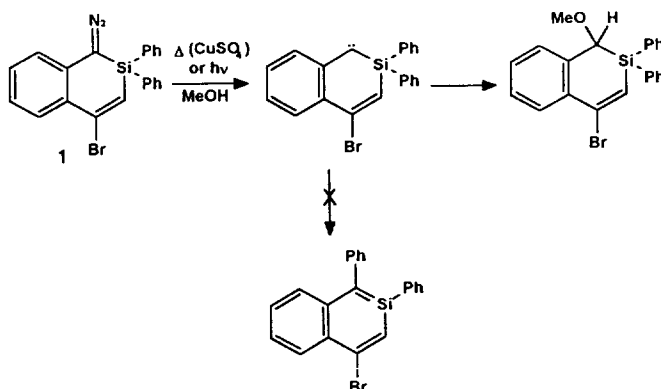
Young-Woo Kwak*, Jong-Bong Lee, Kyung-Koo Lee, Seong-Su Kim, and Bong Hyun Boo†

Department of Chemistry, Kyungpook National University, Taegu 702-701

†Department of Chemistry, Chungnam National University, Taejeon 305-764

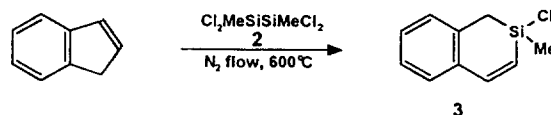
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There has been many reports of the generation and their reactions of silabenzene intermediate from the readily available allyl or chloro precursors.¹ The intramolecular reaction of 1-methyl-2,3,4,5-tetraphenylsilacyclopentadienylmethylene to give silatoluene was reported by Ando and Sekiguchi.^{1c} West and coworkers reported the existence of the intermediacy of hexamethyl-1,4-disilabenzene.^{1f} In 1978, Barton and Burns confirmed the first unambiguous generation and trapping of the silatoluene formed *via* a thermally induced retroene elimination of propene from the 1-allyl-1-methyl-1-silacyclohexa-2,4-diene.² There is precedent for the unsuccessful approach to produce 2-silanaphthalene intermediate from the thermolysis or photolysis of silyl diazo compound **1** in the presence of methanol.³



We now wish to report the first generation and its trapping of 2-methyl-2-silanaphthalene (**5**), a kind of new transient sila-aromatic intermediate, which could arise from the thermolytic reaction of the 2-allyl-2-methyl-2-sila-1,2-dihydronaphthalene (**4**) with methanol or methanol-*d*₁.

The chlorosilane **3** was produced in 45% yield from the coprolysis of 1,1,2,2-tetrachloro-1,2-dimethyldisilane (**2**)^{4,5} and indene at 600°C with a 55 ml/min flow of the nitrogen gas.^{1a,6}



The compound **4**, the possible precursor of the 2-methyl-2-silanaphthalene (**5**), was prepared with a yield of 65% by the reaction of 2-chloro-2-methyl-2-sila-1,2-dihydronaphthalene (**3**) with an allylmagnesium bromide in dry ether.⁷ We copolymerized the 2-methyl-2-silanaphthalene precursor **4** and