Synthesis of a Comb-Shaped Branched Polysaccharide via Ring-Opening Polymerization of a Reactive Anhydro Disaccharide Derivative

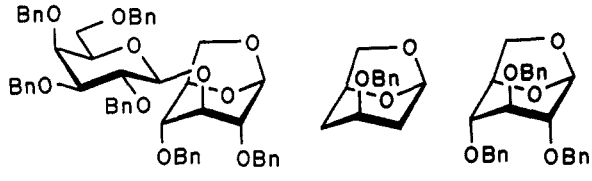
HARUO ICHIKAWA, KAZUKIYO KOBAYASHI,* AND HIROSHI SUMITOMO

Faculty of Agriculture, Nagoya University, Chikusa, Nagoya 464, Japan. *Received December 28, 1988; Revised Manuscript Received September 12, 1989*

This paper deals with a comb-shaped branched polysaccharide, which has a linear backbone and pendant monosaccharide units regularly substituted on each sugar unit in the main chain.[1,2] Naturally occurring polysaccharides often have branched structures, and their physical and biological functions are influenced by the nature of the branches.[3] It has also been noted that branched oligosaccharides on glycoproteins and glycolipids in cell surface membranes are key participants in cell–cell recognition during development.[4] In these respects, well-defined comb-shaped polysaccharides are expected to serve as model substances for physicochemical and biological studies and as cell-specific biomedical materials using carbohydrates as a recognition marker.[5,6]

Synthesis of comb-shaped branched polysaccharides has been attempted by two different routes via ring-opening polymerization of anhydro sugar derivatives: (1) polymerizatioin of anhydro disaccharide derivatives followed by deprotection[1,2] and (2) synthesis of regiospecifically protected linear polysaccharides followed by stereoselective glycosidation and deprotection.[7,8] The former route is favorable for the synthesis of polysaccharides that are substituted completely and stereospecifically with monosaccharide moieties. However, anhydro disaccharide derivatives seem less reactive in polymerization than the corresponding anhydro monosaccharide derivatives,[1,2,9] and hence highly reactive disaccharide anhydrides are required to lead to high molecular weight polysaccharides.

In this paper, we gave attention to the high polymerization reactivity of dideoxygenated anhydro ring structures[10] and to the role of a β-galactopyranose unit as a recognition marker. According to Scheme I, these two moieties were coupled to give 1,6-anhydro-3-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-2,4-dideoxy-β-D-*threo*-hexopyranose (**1**). The ring-opening polymerization of **1** followed by deprotection of the resulting polymer (**2**) was carried out, and a well-defined comb-shaped polysaccharide, 2,4-dideoxy-3-*O*-(β-D-galactopyranosyl)-(1→6)-α-D-*threo*-hexopyranan (**3**) was obtained. The polymerization reactivity of **1** is discussed in comparison with those of analogous anhydrides and their parent compounds including 1,6-anhydro-2,4-di-*O*-benzyl-3-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl)-β-D-glucopyranose (**4**), 1,6-anhydro-3-*O*-benzyl-2,4-dideoxy-β-D-*threo*-hexopyranose (**5**),[10] and 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**6**).



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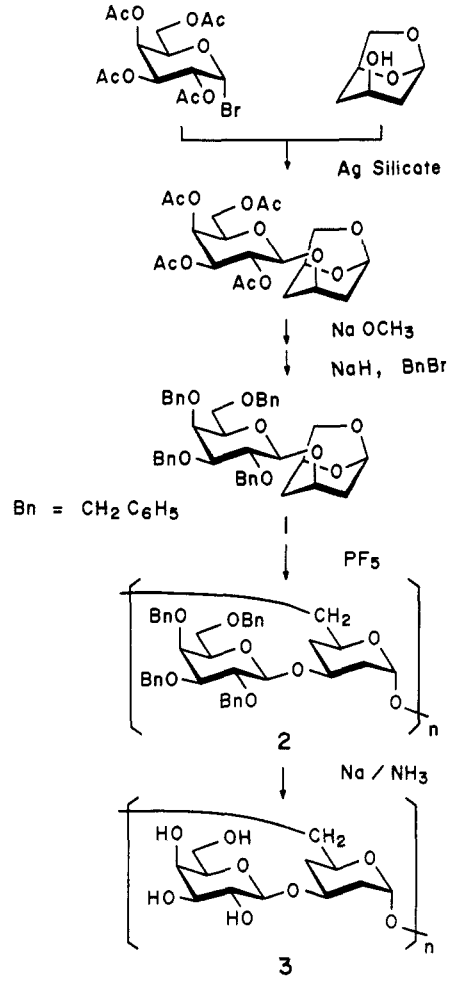
Scheme I
Synthesis of 2,4-Dideoxy-3-*O*-(β-D-galactopyranosyl)-(1→6)-α-D-*threo*-hexopyranan (3)



Results and Discussion

Synthesis of a Comb-Shaped Branched Polysaccharide, 2,4-Dideoxy-3-*O*-(β-D-galactopyranosyl)-(1→6)-α-D-*threo*-hexopyranan (3). Polymerization data of **1** are summarized in Table I. A relatively large amount of the initiator was required. The molecular weight of the disaccharide derivative was high (MW = 653), and hence the monomer concentration could not be made higher than those employed. The polymerization of **1** at −78 °C was more satisfactory than that at −60 °C in terms of polymerization rate, conversion, and molecular weight and stereoregularity of the products.

The polymerization using 20 mol % PF_5 at −78 °C proceeded rapidly to give a methanol-insoluble polymer of $M_n = 2.7 \times 10^4$ ($DP_n = 40$) in 67% yield. The powdery polymer was soluble in organic solvents such as benzene, chloroform, tetrahydrofuran, acetone, and ethyl acetate. In the ^{13}C NMR spectrum of the polymer, there appeared two anomeric carbon signals at 103.1 and 98.2 ppm: the former was assignable to the pendant β-galactopyranose unit and the latter to the backbone (1→6)-α-glycosidic chain.

The polymer (**2** in Scheme I and no. 101 in Table I) was debenzylated with sodium in liquid ammonia at −33 °C and a white powdery product (**3** in Scheme I) was obtained in a 90% yield. It was partially soluble in water

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Table I
Polymerization of 1,6-Anhydro-3-O-(2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl)-2,4-dideoxy-β-D-*threo*-hexopyranose (1) and 1,6-Anhydro-2,4-di-O-benzyl-3-O-(2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl)-β-D-glucopyranose (4)[a]

exptl no.		monomer, mol/L	PF_5, mol %	temp, °C	time, min	yield,[b] %	$10^{-3}M_n$[c]	$[\alpha]_D^{25}$,[d] deg
101	1	0.7	20	−78	6	67[f]	27	+59.5
100	1	0.7	20	−78	60	71	18	+57.9
99	1	0.7	20	−60	60	42	4.3	+50.8
96	1	1.0	10	−60	60	57	5.9	+28.1
95	1	0.7	10	−60	60	33	5.1	+52.4
94	1	0.5	10	−60	24[e]	56	4.3	+29.8
70	4	0.5	10	0	24[e]	0		
67	4	0.5	10	−60	100[e]	0		
102[g]	1 + 6	0.5	6	−78	4	10[h]		
103[i]	4 + 6	0.5	6	−78	8	0		
104[j]	4 + 6	0.5	10	−60	120	61[k]		

[a] Monomer, 0.5 mmol; solvent, dichloromethane. [b] Methanol-insoluble fraction. [c] Determined by GPC. [d] In chloroform; c, 1.0 g/dL. [e] Hour. [f] Anal. Calcd for $(C_{40}H_{44}O_8)_n$: C, 73.60; H, 6.79. Found: C, 73.57; H, 6.87. [g] Copolymerization of 1 (0.41 mmol) with 6 (0.41 mmol). [h] Copolymer composition, 0.68:0.32. [i] Copolymerization of 4 (0.41 mmol) with 6 (0.41 mmol). [j] Copolymerization of 4 (0.20 mmol) with 6 (0.80 mmol). [k] Homopolymer of 6.

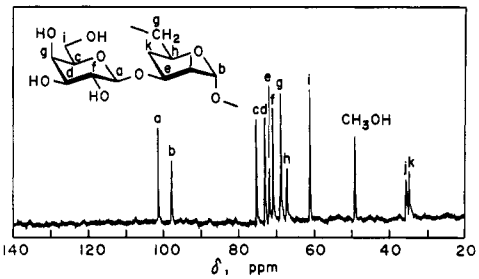

Figure 1. ^{13}C NMR spectrum of 2,4-dideoxy-3-O-(β-D-galactopyranosyl)-(1→6)-α-D-*threo*-hexopyranan (3) (in D_2O, 5%; reference, methanol, 49.00 ppm; 50 MHz).

and dimethyl sulfoxide (Me_2SO) and insoluble in other common organic solvents.

Its ^{13}C NMR spectrum (Figure 1) shows that 2,4-dideoxy-3-O-(β-D-galactopyranosyl)-(1→6)-α-D-*threo*-hexopyranan (3) has been successfully obtained. The assignments are as follows: α-D-Threose main chain:[10] C-1, 97.63; C-2, 35.27; C-3, 71.72; C-4, 34.45; C-5, 67.12; C-6, 68.62. β-D-Galactose branch:[11] C′-1, 101.23; C′-2, 70.75; C′-3, 72.85; C′-4, 68.62; C′-5, 75.14; C′-6, 60.94. The following coupling constants confirmed that the main chain had α-stereoregularity and the branch β-stereoregularity.[12] $J(^{13}C-^{1}H)$: α-C-1, 171.4 Hz; β-C′-1, 155.8 Hz. $J(^{1}H-^{1}H)$: α-H-1 (5.18 ppm), less than 1 Hz; β-H′-1 (4.57 ppm), 7.6 Hz. It was also of interest to note that the absorptions due to the hydrophilic galactose branch were more sharp and higher than those of the hydrophobic threose main chain.

Polymerization Reactivity of a Disaccharide Derivative Having a Dideoxygenated Anhydro Ring (1). Stereoregular polymerization of 1 proceeded at −78 °C. In contrast, none of the polymer was obtained from the galacto glucose monomer 4 under attempted conditions (nos. 70 and 67 in Table I), but the monomer 4 was recovered unchanged. Polymerizations of hexabenzyl derivatives of 1,6-anhydro maltose and cellobiose were reported to be sluggish (at −60 °C),[1,2] and hence the monomer with the (1→3)-glycosidic linkage was less reactive than those with the (1→4)-glycoside linkage.

Copolymerization of 1 with 1,6-anhydro-2,3,4-tri-O-benzyl-β-D-glucopyranose (6) in 0.50:0.50 M feed gave a copolymer of 0.68 M of the disaccharide unit at 10% conversion (experimental no. 102). The monomer 1 was more incorporated into the polymer backbone than monomer 6. The galacto glucose monomer 4 gave no copolymer (no. 103), but the homopolymer of 6 was produced (no. 104).[13] It has also been reported that, under similar conditions on copolymerization with 6 (0.50:0.50 M feed), 0.98 M of the parent compound 1,6-anhydro-3-O-benzyl-2,4-dideoxy-β-D-*threo*-hexopyranose (5) was incorporated into the copolymer,[10] and 0.38 M of the 1,6-anhydro maltose derivative was incorporated.[9,14]

The high reactivity of 1 relative to 4 was probably due to the 2,4-dideoxygenated anhydro structure.[10] Both the acetal oxygen of the monomer and the trialkyloxonium ion of the growing terminal in 1 are less sterically hindered and more basic and nucleophilic than those in the corresponding dibenzyloxylated compound (4). On the other hand, a low reactivity of 1 relative to 5 was explained by assuming that the large side-chain group hindered both reaction centers.

Inspection of CPK molecular models suggested that the polymer backbone was very crowded with large pendant tetrabenzylated sugar units, and as a result, the polymer sequence was thermodynamically less stable. We assumed that the instability of the polymer backbone was reflected in the ease of disordering of the polymer structure during polymerization.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded with a JEOL JNM-FX-200 Fourier-transform NMR spectrometer operating at 200 and 50 MHz, respectively. Optical rotations were determined in a Japan Spectroscopic Co. DIP-181 digital polarimeter, using a water-jacketed 1-dm cell. Number-average molecular weights (M_n) of protected polysaccharides were estimated by gel-permeation chromatography with a Hitachi 634A with a column (8-mm i.d. × 1000 mm) of Shodex GPCA 803-804, using chloroform with polystyrene as the standard.

1,6-Anhydro-3-O-(2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl)-2,4-dideoxy-β-D-*threo*-hexopyranose (1). A solution of 1,6-anhydro-2,4-dideoxy-β-D-*threo*-hexopyranose[10] (2.4 g, 18 mmol) in dry 1,2-dichloroethane (2 mL) was added to a stirred suspension of 2,3,4,6-tetra-O-acetyl-α-D-galactopyranosyl bromide (7.2 g, 18 mmol), silver silicate[15] (12 g), magnesium sulfate (7.2 g), and powdered molecular sieve 4A (10 g) in dry 1,2-dichloroethane (38 mL). The mixture was stirred for 4 h at room temperature, filtered, washed with water, and then chromatographed over silica gel. A viscous liquid product was obtained in 85% yield (7.0 g).

The glycoside (2.3 g, 5 mmol) was treated with small pieces of sodium in methanol (30 mL) at room temperature and was concentrated to dryness. The product was dissolved in dry Me_2SO (40 mL) and sodium hydride (0.80 g) and benzyl bromide (2.4 mL) were added successively. The solution was stirred at 70 °C for 2 h. Excess water was added and the mixture was washed with benzene. The organic layer was dried, concentrated, and chromatographed over silica gel. A viscous liquid was obtained (1.5 g, 46%). $[\alpha]_D^{25}$, −16.0° (c, 1.0 g/dL in chloroform). Anal. Calcd for $C_{40}H_{44}O_8$: C, 73.60; H, 6.79. Found: C, 73.60; H, 6.80.

^{13}C NMR ($CDCl_3$): 138.6, 138.3, and 137.7 (phenyl ipso); 128.2, 128.0, 127.5, and 127.3 (phenyl ortho, meta, and para); 103.2 (C′-1); 99.8 (C-1); 82.2 (C′-3); 79.2 (C′-2); 74.8 (C′-5); 74.4 (C′-4); 73.6, 73.4, and 73.2 (benzyl CH_2); 71.5 (C-3); 70.5 (C-6); 69.0 (C-5); 67.3 (C′-6); 35.8 (C-2); 35.3 (C-4). (The primed carbons are of the β-galactopyranose moiety and the nonprimed ones of the β-*threo*-hexopyranose moiety.)

^{1}H NMR coupling constant J(H′-1,H′-2) = 10.5 Hz was evidence of the β-configuration.

1,6-Anhydro-2,4-di-O-benzyl-3-O-(2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl)-β-D-glucopyranose (4). 2,3,4,6-Tetra-O-acetyl-α-D-galactopyranosyl bromide was glycosidated to 1,6-anhydro-2,4-di-O-benzyl-β-D-glucopyranose[16] according to procedures similar to those described above. Overall yield based

on the dibenzyl glucose was 41%. $[\alpha]_D^{25}$, +5.3° (*c*, 1.0 g/dL in chloroform). Anal. Calcd for $C_{54}H_{56}O_{10}$: C, 70.37; H, 6.20. Found: C, 70.36; H, 6.16.

^{1}H NMR: *J*(H′-1,H′-2), 11.6 Hz. ^{13}C NMR ($CDCl_3$): 138.5, 138.4, 138.2, 138.1, 137.7, and 137.5 (phenyl ipso); 127.9, 127.5, and 127.3 (phenyl ortho, meta, and para); 103.8 (C′-1); 100.0 (C-1); 81.8 (C′-3); 78.9 (C′-2); 76.2 (C-2); 76.0 (C-4); 75.2 (C-3); 74.6 (C′-5); 74.4 (C′-4); 74.2 (C-5); 73.4, 73.3, 73.2, 72.9, 72.1, and 70.8 (benzyl CH_2); 68.6 (C′-6); 64.7 (C-6). (The primed protons and carbons are of the β-galactopyranose moiety and the nonprimed ones of the β-glucopyranose moiety.)

Polymerization. 1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**6**) was prepared according to the prescribed method.[9,10,17] Purification of *p*-chlorobenzenediazonium hexafluorophosphate and dichloromethane was followed by usual methods.[17] Polymerization was carried out by using high-vacuum techniques.[17]

Debenzylation. Polymer was debenzylated with sodium in liquid ammonia according to the method described previously.[17]

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Registry No. 1, 125076-61-1; 1 acetylated analogue, 125076-60-0; 2, 125076-63-3; 4, 125076-62-2; 5 debenzyl derivative, 14241-58-8; 6, 10548-46-6; 6 3-debenzyl derivative, 33208-48-9; 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide, 3068-32-4.

Chemical Nature of Conduction in Iodine-Doped *trans*-1,4-Poly(buta-1,3-diene) and Some of Its Derivatives: The Presence of I_3^- and the Effect of Double-Bond Configuration

QUAN-YUAN SHANG, SHEKHAR PRAMANICK, AND BRUCE HUDSON*

Department of Chemistry and Chemical Physics Institute, University of Oregon, Eugene, Oregon 97403.

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Conductive polymers have been extensively studied following the discovery of Shirakawa et al.[1,2] that polyacetylene (PA) could be prepared as films having a metallic luster and conductivity. This conductivity can be increased by 9–13 orders of magnitude by doping with various donor or acceptor species to give p-type and n-type semiconductor and conductor charge-transfer complexes. Many modifications of PA have been prepared including substitutions[3] and conjugation length variations.[4,5] Conjugation of the polymer backbone was thought to be a prerequisite for the formation of a conductive charge-transfer complex upon doping.[6]

Recently it was found that several 1,4-poly(butadiene) polymers having a nonconjugated backbone could be halogen doped to form semiconductors.[7] Both *cis*- and *trans*-1,4-poly(2-methylbuta-1,3-diene) (natural rubber and gutta percha or synthetic rubber) and *cis*-1,4-poly(2,3-dimethylbuta-1,3-diene) became dark and conductive when treated with iodine but *cis*-1,4-poly(buta-1,3-diene), without methyl substitution at the double bond, did not change color on doping or become conductive. This difference was proposed to be due to an inductive effect of the methyl substituent. It was proposed that radical cation polaron formation is responsible for the increased conductivity and that the electron transports through interchain hopping. These results have received editorial comment[8] because they call into question basic assumptions concerning the mechanism of conductivity in doped polymers. The simplicity of polybutadiene backbone deserves more study to clarify the physical and chemical nature of this system as the results will likely help us gain more insight into polymer conduction mechanisms.

The technique of inclusion polymerization[9–11] has been applied to synthesize poly(butadiene) and its methyl and chloro derivatives. The product from inclusion polymerization has well-characterized trans stereochemistry and crystal structure[9,10] that have long been recognized as important to characterize the chemical and physical properties of conductive polymers. The availability of *trans*-poly(butadiene) and its derivatives from inclusion polymerization permits us to extend the work of Thakur[7] so as to investigate the effect of stereochemistry on conductivity. The availability of chloro as well as methyl derivatives permits further examination of inductive effects.

Experimental Section

Synthesis of Polymers. Monomers were of commercial origin and were used without further purification except 2,3-dichlorobutadiene which was synthesized following a published procedure.[12] *trans*-1,4-Poly(buta-1,3-diene) (PBD) was obtained through urea inclusion polymerization while deoxycholic acid (DCA) inclusion polymerization was applied to synthesize *trans*-1,4-poly(2,3-dimethylbuta-1,3-diene) (PDMBD) and *trans*-1,4-poly(2,3-dichlorobuta-1,3-diene) (PDCBD).[13] γ-Ray irradiation was provided by a ^{60}Co source for 15 h with a dose rate of 40 Mrad/h. The sample was maintained at −78 °C. The polymer structures were verified by infrared spectra.

Doping with Iodine and Conductivity Measurements. For initial evaluation, the pressed pellet of synthesized polymer was

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