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The Chemical Synthesis of a Cyclic Oligosaccharide Derivative with Branching

Maria Carmelita Kasuya and Kenichi Hatanaka*

Department of Biomolecular Engineering, Tokyo Institute of Technology
4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8501, Japan

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Abstract: A cyclic oligosaccharide derivative was synthesized by cationic ring-opening polymerization of an anhydrodisaccharide derivative under high vacuum in dichloromethane with 20 mol% of PF_5 as initiator. Analysis of the spectral results showed that the oligomer chain is composed of only 3 glucose units connected by α-1,6 linkages with a glucopyranosyl branching unit at C-4 of each sugar residue in the main chain.

Keywords: glycosidation; polymerization; oligomer

Cyclic oligosaccharides are not very common, but their importance as hosts for predefined guests has sustained interest for continued research. Methods for their synthesis underwent rapid development. Recently, cyclodextrin homologues with dp<6 were reported to have been prepared chemically or enzymatically. Houdier and Vottero synthesized benzylated cyclomaltotriose and hexaose[1] by cycloglycosylation based on the n-pentenyl glycoside method introduced by Fraser-Reid. Cyclization to give a cyclomaltopentaose[2] via successive glycosidations was also reported by Nakagawa et.al. Moreover, Gagnaire and his co-workers reported the synthesis of a β-(1→6)-linked cyclic dimer and tetramer[3] via self-condensation of a disaccharide derivative.

In our on-going study on the effective chemical synthesis of branched polysaccharides[4] by cationic ring-opening polymerization,[5] a mixture of a comb-shaped polysaccharide[6] and a branched oligosaccharide was obtained from the polymerization of an anhydrodisaccharide monomer. Initial investigation of the structure of the oligosaccharide revealed it to be a cyclic trimer. This communication is a preliminary report on the key features involved in the chemical synthesis of the cyclic oligosaccharide i.e., (a) the preparation of the anhydrodisaccharide monomer by Schmidt's trichloroacetimidate method of glycosylation[7] of an anhydroglucose derivative and, (b) the preparation of the cyclic oligosaccharide derivative with branching by cationic ring-opening polymerization of the anhydrodisaccharide derivative.

The glycosyl acceptor, 1,6:2,3-dianhydro-β-D-mannopyranose (**1**),[8] was prepared from 1,6-anhydro-β-D-glucopyranose[9] by the method developed by Cerny et al. Glycosylation of compound **1** with 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl trichloroacetimidate (**2**) in CH_2Cl_2 was carried out with *tert*-butyldimethylsilyl

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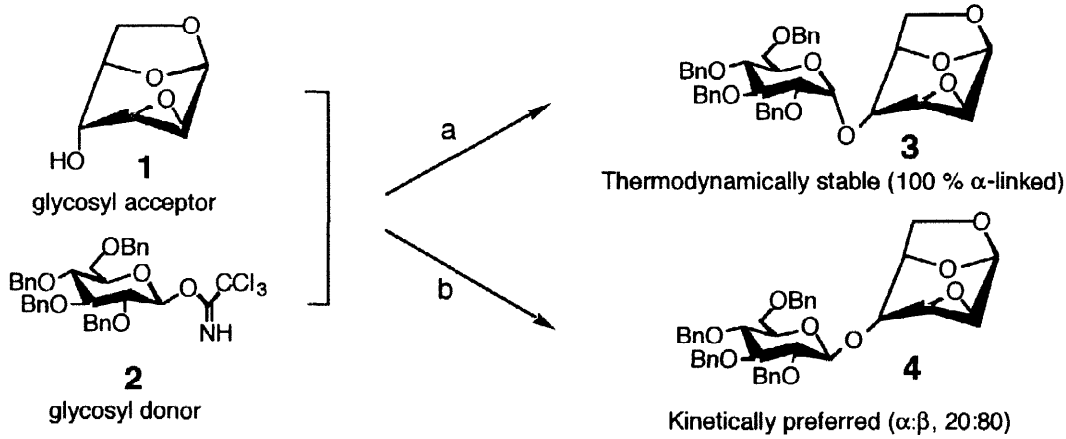
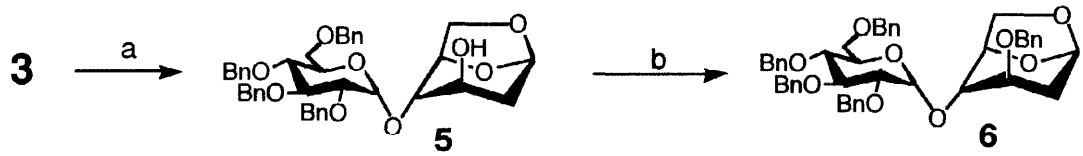
triflate as catalyst (Scheme 1). Glycosylation (acceptor:donor=1:2, 1.80 g and 17.12 g, respectively) in 250 ml dry CH_2Cl_2 at room temperature for 5 hours proceeded with a 100% α-anomeric selectivity to give the thermodynamically stable product 1,6:2,3-dianhydro-4-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-mannopyranose (**3**)[10] which has been purified by column chromatography using benzene:ethyl acetate (9:1, v/v)). On the other hand, high β-anomeric selectivity[11] (20:80, α:β) was favored at -30°C for 15 minutes.



Scheme 1. Glycosylation. (a) TBDMSOTf, CH_2Cl_2, $NaHCO_3$, room temp., 5 h, 12.6% yield. (b) TBDMSOTf, CH_2Cl_2, $NaHCO_3$, -30°C, 15 min, 38.0% yield.

The preparation of the deoxy sugar derivative (1,6-anhydro-2-deoxy-4-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranose[12] (**5**) was accomplished through the 2,3-epoxide scission of the 1,6:2,3-dianhydrosugar derivative (**3**) using lithium aluminum hydride in accordance with Seib's procedure.[13]

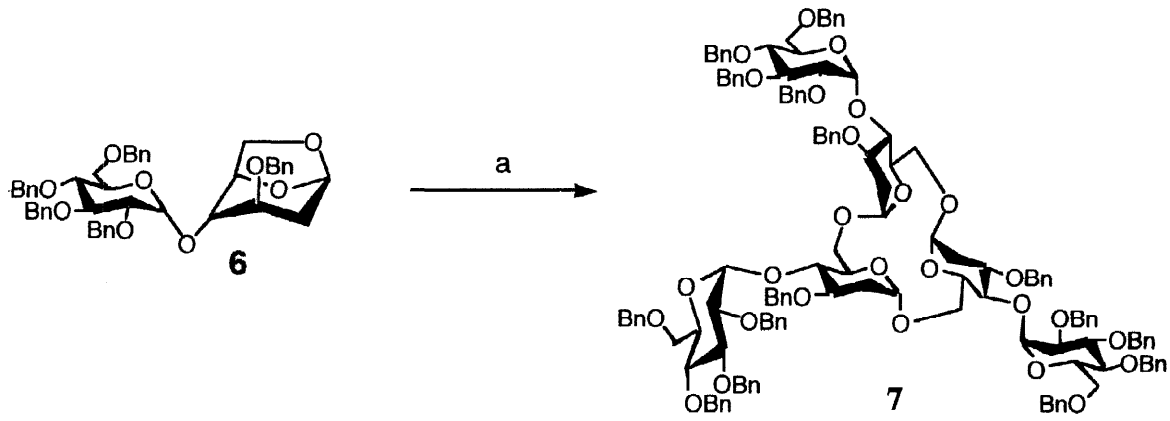


Scheme 2. Synthesis of anhydrodisaccharide monomer. (a) LAH, Et_2O, reflux, 4 h, 82.6% yield (b) BnBr, NaH, DMF, room temp., 4 h, 88.1% yield.

Finally, benzylation of the free hydroxyl group at C-3 position of compound **5** afforded the anhydrodisaccharide monomer 1,6-anhydro-3-*O*-benzyl-2-deoxy-4-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-*arabino*-hexopyranose[14] (**6**) (Scheme 2). Silica gel column chromatography with $CHCl_3$-EtOAc (9:1,v/v) and recrystallization from petroleum benzine and hexane gave the pure white monomer crystals.

Ring-opening polymerization of the prepared anhydrodisaccharide monomer was carried out under high vacuum in dichloromethane with 20 mol% of phosphorous pentafluoride as initiator (Scheme 3). Polymerization at lower temperatures (-60~-40 °C) and at shorter period of time (15 min~24 hours) gave a mixture of polymerization products, i.e., a comb-shaped polysaccharide (having a pendant sugar moeity on each monosaccharide residue in the backbone chain) and a branched trimer as detected from the gel permeation chromatography results. However, polymerization at a higher temperature of 0 °C, or at a reaction time of 48

hours (or even longer) gave only the oligomer in 89.0% yield. These results highlight the dramatic effects of time and temperature in the polymerization reaction. The polymerization was terminated by the addition of MeOH and the product was purified by reprecipitation of the chloroform solution into methanol three times, and then freeze dried from benzene solution. Separation of the polysaccharide from the oligosaccharide was accomplished by HPLC.



Scheme 3. Synthesis of cyclic oligosaccharide. (a) 20% PF_5, CH_2Cl_2, -40°C, 48 h, 89.0% yield.

Analysis of the trimer gave a relatively high positive specific rotation value, $[\alpha]^{25}_D$ +63.8° (c1,$CHCl_3$) which implies α stereoregularity. The ^{13}C NMR spectral result showed a single sharp resonance at 96.7 ppm with integration values equivalent to 2 carbon atoms signifying the overlapping of the signals for the anomeric carbon of the glucose unit in the main chain and the anomeric carbon of the α-linked branching unit. Moreover, the resonances at 81.7 ppm and 79.5 ppm corresponding to C-2' and C-3' positions, respectively, show that the branching unit was intact even after polymerization. From the ^{13}C NMR spectrum, we estimated the possibility of the trimer having a cyclic structure with a three-fold symmetry in the molecule. The NMR results coupled with the specific rotation value obtained for the trimer suggested that the 3 glucose units may be 1-6 α–linked with polymerization proceeding via the oxonium ion mechanism.[15]

The MADLI TOF mass spectrum further confirmed the cyclic nature of the trimer by giving the signal at 2300.4 [calculated molecular weight of the cyclic trimer (2276.9) plus Na reference (Atomic mass: 23.0) is equal to 2299.9]. Examination of molecular models supported the possibility of the cyclic structure and showed a stable tripod-like structure with the 3 glucose units connected by glycosidic α-1-6 linkages and a branching glucose unit attached to the carbon at C-4 position of each of the three glucose units forming the ring.

The prescence of the tetrabenzyl glucopyranosyl branching unit is considered as a major factor influencing the formation of the cyclic trimer since in a previous report by Hatanaka et al., no trimer was produced after the ring-opening polymerization of an anhydromonosaccharide monomer, 1,6-anhydro-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranose.[16] This monomer has a benzyl group at the C-4 position while the anhydrodisaccharide monomer has a tetrabenzyl glucose unit. Another interesting point is the effect of time since at shorter polymerization time, the comb-shaped polysaccharide is the dominating product while at longer polymerization time, only the trimer was produced. This suggests possible internal ring closure which may be due to the over-crowding of the polysaccharide caused by the tetrabenzylated branching units.

Although further investigation is required to fully establish the mechanism of cyclization, the synthesis of this cyclic oligosaccharide may open new avenues for research directed towards cyclooligomerization - its

methods of preparation and mechanism of cyclization.

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[10] **1,6:2,3-dianhydro-4-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-mannopyranose (3)** : mp 134-135 °C, $[\alpha]^{25}_{D}$ +3.7° (c1, $CHCl_3$), calcd for $C_{40}H_{42}O_9$: C, 72.04; H, 6.36, found: C, 71.49; H, 6.36. The ^{1}H NMR spectrum of **3** showed a sharp resonance at 5.68 ppm corresponding to the absorption of the anomeric proton of the anhydroglucose unit. The ^{13}C NMR spectrum shows the anomeric carbon signals for the α-branching unit and the anhydroglucose unit at 99.0 ppm and 97.5 ppm, respectively. The resonances at 81.8 ppm and at 80.1 ppm corresponds to the branching unit's C2' and C3', respectively. (200 MHz ^{1}H and ^{13}C NMR spectra of all compounds were taken in $CDCl_3$.)

[11] As regards the β-linked disaccharide, research is currently in progress to purify, reduce, benzylate C-3 and finally, polymerize.

[12] **1,6-anhydro-2-deoxy-4-*O*-(2',3',4',6'-tetra-*O*-benzyl-α-D-glucopyranosyl)-β-D-glucopyranose (5)** : mp 114-115 °C, $[\alpha]^{25}_{D}$ +1.9° (c1,$CHCl_3$), calcd for $C_{40}H_{44}O_9$: C,71.83; H,6.64, found: C,71.18; H,6.63. The ^{1}H NMR of compound **5** showed the peaks at 1.81 ppm and 2.20 ppm for the axial and equatorial protons, respectively, at C-2 position of the anhydrodeoxy-glucose unit. The ^{13}C NMR spectrum shows the resonance at 36.2 ppm for the methylene C-2 of the anhydrodeoxy glucose unit.

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