Synthesis of (1→6)-2,5-Anhydro-3,4-di-*O*-methyl-D-glucitol via Highly Regio- and Stereospecific Cyclopolymerization of 1,2:5,6-Dianhydro-3,4-di-*O*-methyl-D-mannitol with Potassium *tert*-Butoxide

Toshifumi Satoh† **and Kazuaki Yokota***

Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060, Japan

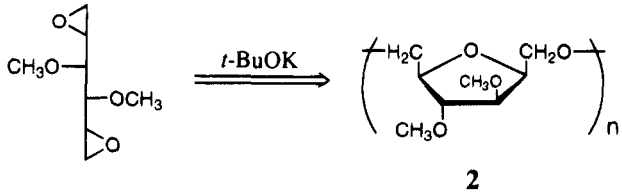
Toyoji Kakuchi*

Division of Bioscience, Graduate School of Environmental Earth Science, Hokkaido University, Sapporo 060, Japan

Received February 15, 1995
Revised Manuscript Received April 24, 1995

Ring-opening polymerization is widely used for producing highly stereoregular polysaccharides from various types of anhydro sugars.[1–3] For example, (1→6)-α-D-glucopyranan from 1,6-anhydro-β-D-glucopyranose,[4,5] (1→4)-β-D-ribopyranan and (1→5)-α-D-ribofuranan from 1,4-anhydro-α-D-ribopyranose,[6,7] and (1→3)-α-D-glucopyranan from 1,3-anhydro-β-D-glucopyranose.[8,9] These polysaccharides exhibit biological activity,[10] and, in particular, the sulfated ones are widely noticed in terms of an inhibitory effect toward AIDS (Acquired Immunodeficiency Syndrome).[11–14] Cyclopolymerization also presents a new method of synthesizing polysaccharides. Recently, we reported that 3,4-di-*O*-alkyl substituted 1,2:5,6-dianhydro-D-mannitols cyclopolymerized with a cationic initiator yield polymers consisting of mainly 2,5-anhydro-D-glucitol repeating units.[15,16] These polymers acted as hosts in the host–guest complexation and exhibited molecular discrimination properties toward alkali-metal ions, large organic cations as dyes, and racemic amino acids.[15,17] The polymerization method, however, requires extensive improvements in the relatively low polymer yield, the formation of oligomers, and the difficulty in obtaining certain molecular weights. In addition, the polymer contained some irregular cyclic units as a minor component together with the 2,5-anhydro-D-glucitol unit. The (1→6)-linked 2,5-anhydro-D-glucitol is a new type of polysaccharide that lacks the anomeric linkage. Therefore, highly sophisticated control is desired during the cyclopolymerization of such a dianhydro monomer as a synthesis method for the novel polymeric sugar. Here we report the successful synthesis of (1→6)-2,5-anhydro-D-glucitol by the highly regio- and stereospecific cyclopolymerization of 1,2:5,6-dianhydro-D-mannitol using an anionic initiator.

Scheme 1



1 **2**

The cyclopolymerizations of 1,2:5,6-dianhydro-3,4-di-*O*-methyl-D-mannitol (**1**)[18] were carried out in THF, 1,4-dioxane, benzene, and toluene at 60 °C for 48 h using *t*-BuOK.[19] Table 1 lists the results of the anionic polymerization. The reaction system was homogeneous up to complete consumption of the monomers. The resulting polymers were sticky semisolid and soluble in benzene, chloroform, methanol, and tetrahydrofuran but insoluble in *n*-hexane. The yield and number-average molecular weight (M_n) of the polymers were slightly affected by the solvents. When the [**1**]/[*t*-BuOK] molar ratio of 20 was used, the polymers were obtained in relatively high yield which was the highest value of 98% in toluene. The M_n was 5100–8000 which corresponds to a 29–46 degree of polymerization (DP). For the polymerization with a [**1**]/[*t*-BuOK] ratio of 40 in toluene, the M_n attained 12 900 (DP = 74), which was almost twice that with using the [**1**]/[*t*-BuOK] ratio of 20. The molecular weight distribution (M_w/M_n) was relatively narrow with a value in the range of 1.31–1.65. The specific rotations ($[\alpha]^{23}_{546}$) of the polymers were +72.2 to +93.9, but no obvious correlation was found with the M_n.

Table 1. Anionic Cyclopolymerization of 1,2:5,6-Dianhydro-3,4-di-*O*-methyl-D-mannitol (1) with *t*-BuOK[a]

solvent	[1]/[Cat.]	yield, %	M_n[b]	M_w/M_n[b]	DP	$[\alpha]^{23}_{546}$[c]
THF	20	84.3	5100	1.31	29	+78.0
1,4-dioxane	20	96.1	8000	1.48	46	+93.9
benzene	20	95.4	6400	1.64	37	+84.9
toluene	20	98.5	6400	1.53	37	+84.5
toluene	40	94.1	12900	1.65	74	+72.2

[a] [1]= 1 mol·L^{-1}; temp, 60°C; time, 48 h. [b] Measured in THF by GPC using PSt as the standard. [c] Measured in $CHCl_3$ (*c* 1.0).

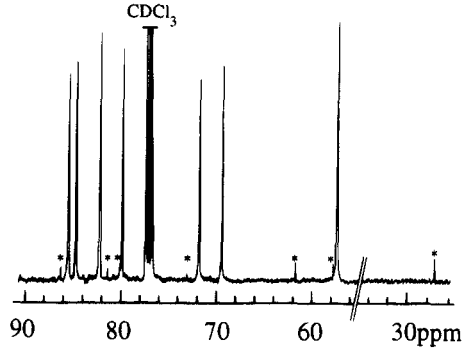


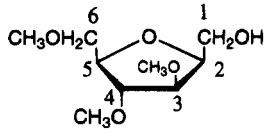
Figure 1. ^{13}C NMR spectrum of polymer **2** prepared from 1,2:5,6-dianhydro-3,4-di-*O*-methyl-D-mannitol (**1**) with *t*-BuOK in toluene. The asterisked signals are due to carbons for polymer ends.

In the ^1H NMR spectrum of polymer **2**, the characteristic absorption at 2.5–3.3 ppm due to the epoxy protons completely disappeared, i.e., the polymerization proceeded according to a cyclopolymerization mechanism, leading to the polymers consisting of cyclic constitutional repeating units. Figure 1 shows the ^{13}C NMR spectrum of the polymer prepared in toluene at a [**1**]/[*t*-BuOK] ratio of 20. The signals at 85.43, 84.70, 82.23, 79.83, 57.35, and 57.26 ppm for the polymer fairly agreed with the chemical shifts of the C3, C4, C2, C5, and two CH_3O carbons for 2,5-anhydro-1,3,4,6-tetra-*O*-methyl-D-glucitol (**4**),[20] respectively (Chart 1). In addition, seven small signals, which are asterisked in Figure 1, were observed. The signals at 73.58 and 27.47 ppm are assigned to the quaternary and methyl carbons of the *t*-butoxy group, respectively, and the signals at 86.21, 81.38, 80.02, 61.57, and 57.69 ppm were very close to the chemical shifts of the C3, C5, C2, C1, and

* To whom all correspondence should be addressed.
† *Research Fellow of the Japan Society for the Promotion of* Science.

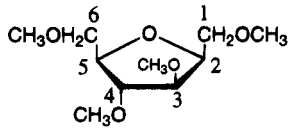
0024-9297/95/2228-4762$09.00/0

Chart 1



3

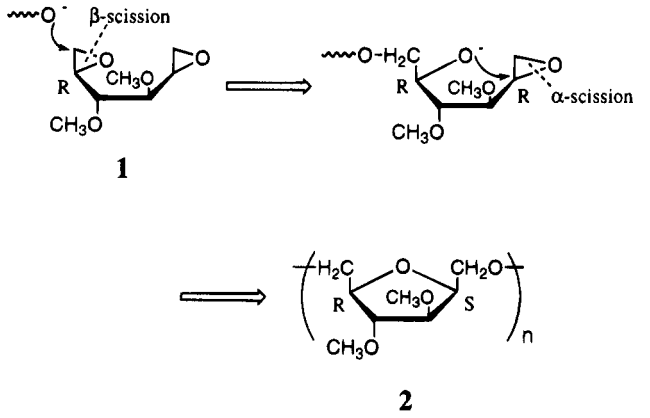
C	δ/ppm
1	61.47
2	80.06
3	86.04
4	84.97
5	81.32
6	73.20
CH_3O	59.25
CH_3O	57.71
CH_3O	57.65



4

C	δ/ppm
1	73.15
2	82.26
3	85.69
4	84.75
5	79.83
6	70.66
CH_3O	59.25
CH_3O	59.19
CH_3O	57.42
CH_3O	57.35

Scheme 2



1

2

CH_3O carbons for 2,5-anhydro-3,4,6-tri-*O*-methyl-D-glucitol (**3**),[21] respectively. These signals diminished for the polymer prepared at the [**1**]/[*t*-BuOK] ratio of 40. These results indicate that the polymer obtained from the cyclopolymerization of **1** using *tert*-BuOK is exclusively composed of (1→6)-2,5-anhydro-3,4-di-*O*-methyl-D-glucitol (**2**) with the *t*-butoxy and hydroxymethyl groups at both ends of the polymer chain (Scheme 1).

The cyclopolymerization of the enantiomeric and diastereomeric mixtures of 1,2:5,6-diepoxyhexane, which correspond to 3,4-deoxy-1,2:5,6-dianhydro-D-mannitol, using cationic and anionic catalysts was reported.[22,23] However, the cyclic constitutional units in the resulting polymers were insufficiently confirmed and also stereoisomeric mixtures.

For the cyclopolymerization of **1** using *t*-BuOK, the stereochemically controlled polymer **2** should be produced through the mechanism proposed in Scheme 2. The regioselectivity in the oxirane polymerizations significantly depended on the nature of the initiator systems in which anionic catalysts mostly cleaved the CH_2–O bond (β-bond) to form the head-to-tail linkage. For the intermolecular reaction, therefore, the growing alkoxy anion cleaved the β-bond of the first epoxide, resulting in retention of the R configuration of the α-carbon. On the other hand, for the intramolecular cyclization, the alkoxy anion cleaved the α-bond of the second epoxide to form a 5-membered ring. The regioselectivity in the cyclization follows the Baldwin rules which explain ring closure on the basis of the stereoelectronic effect. For the stereoselectivity during the cyclization, the configuration of the α-carbon is inverted from the R to the S.

In summary, the cyclopolymerization of 1,2:5,6-dianhydro-3,4-di-*O*-methyl-D-mannitol using *t*-BuOK was highly regio- and stereospecific and the produced polymer was (1→6)-2,5-anhydro-3,4-di-*O*-methyl-D-glucitol which has the *tert*-butoxy and hydroxymethyl groups as each of the chain ends. The selective cyclopolymerization of 1,2:5,6-dianhydrohexitol is a new synthetic strategy for the artificial polycarbohydrate, which is exactly opposite from the ring-opening polymerization of the anhydro sugar. Further studies are currently in progress to investigate the cationic and anionic cyclopolymerizations of 1,2:5,6-dianhydro-L-iditol, D-glucitol, and dulcitol, and (2*S*,5*S*)- and (2*R*,5*R*)-diepoxyhexanes in order to clarify the scope and limit of the cyclopolymerization method.

Acknowledgment. This work was supported by a Research Fellowship of the Japan Society for the Promotion of Science for Young Scientists.

References and Notes

(1) Schuerch, C. *Acc. Chem. Res.* **1973**, *6*, 184.
(2) Schuerch, C. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 157.
(3) Uryu, T. In *Models of Biopolymers by Ring-Opening Polymerization;* Penczek, S., Ed.; CRC Press: Boca Raton, FL, 1990; p 133.
(4) Ruckel, E. R.; Schuerch, C. *J. Am. Chem. Soc.* **1966**, *88*, 2605.
(5) Ruckel, E. R.; Schuerch, C. *J. Org. Chem.* **1966**, *31*, 2233.
(6) Uryu, T.; Kitano, K.; Ito, K.; Yamanouchi, J.; Matsuzaki, K. *Macromolecules* **1981**, *14*, 1.
(7) Uryu, T.; Yamanouchi, J.; Kato, T.; Higuchi, S.; Matsuzaki, K. *J. Am. Chem. Soc.* **1983**, *105*, 6865.
(8) Ito, H.; Schuerch, C. *Macromolecules* **1981**, *14*, 246.
(9) Good, F. J. J.; Schuerch, C. *Macromolecules* **1985**, *18*, 595.
(10) Uryu, T. *Prog. Polym. Sci.* **1993**, *18*, 717.
(11) Nakashima, H.; Yoshida, O.; Tochikura, T.; Yoshida, T.; Mimura, T.; Kodo, Y.; Motoki, Y.; Kaneko, Y.; Uryu, T.; Yamamoto, N. *Jpn. J. Cancer Res.* **1987**, *78*, 1164.
(12) Yoshida, T.; Hatanaka, K.; Uryu, T.; Kaneko, Y.; Suzuki, E.; Miyano, H.; Mimura, T.; Yoshida, O.; Yamamoto, N. *Macromolecules* **1990**, *23*, 1.
(13) Hatanaka, K.; Nakajima, I.; Yoshida, T.; Uryu, T.; Yoshida, O.; Yamamoto, N.; Mimura, T.; Kaneko, Y. *J. Carbohydr. Chem.* **1991**, *10*, 681.
(14) Hatanaka, K.; Kurihara, Y.; Uryu, T.; Yoshida, O.; Yamamoto, N.; Mimura, T.; Kaneko, Y. *Carbohydr. Res.* **1991**, *214*, 147.
(15) Hashimoto, H.; Kakuchi, T.; Yokota, K. *J. Org. Chem.* **1991**, *56*, 6471.
(16) Kakuchi, T.; Satoh, T.; Umeda, S.; Hashimoto, H.; Yokota, K. *Macromolecules,* in press.
(17) Kakuchi, T.; Harada, Y.; Satoh, T.; Yokota, K. *Polymer* **1994**, *35*, 204.
(18) Kuszmann, J. *Carbohydr. Res.* **1979**, *71*, 123.
(19) A typical polymerization procedure is as follows: The polymerization was carried out in an H-shaped glass ampule. *t*-BuOK (9.6 mg, 0.0857 mmol) and dry toluene (3.4 mL) were added to the one side of the ampule, and monomer **1** (0.59 g, 3.39 mmol) was added to the other side of the ampule under a nitrogen atomosphere. After sealing, the monomer and the catalyst solution were mixed at 60°C. After 48 h, the reaction mixture was poured into a large amount of methanol and the solution was neutralized with diluted hydrochloric acid. After evaporating the solvent, the residue was purified by reprecipitation from chloroform–*n*-hexane to yield the polymer in 94.1% (0.555 g). The M_n and M_w/M_n were 12 900 and 1.65, respectively. $[\alpha]_D$ +61.8°, $[\alpha]_{577}$ +63.2°, $[\alpha]_{546}$ +72.2°, $[\alpha]_{435}$ +120.4°, and $[\alpha]_{405}$ +142.9° (*c* 1.0 in $CHCl_3$ at 23 °C). ^1H NMR (400 MHz, $CDCl_3$): δ 4.09 (td, J = 5.6 Hz, J = 4.2 Hz, H5, 1H), 3.93 (td, J = 6.0 Hz, J = 2.9 Hz, H2, 1H), 3.74 (dd, J = 6.3 Hz, J = 5.4 Hz, H6, 1H), 3.62–3.69 (m, H3, H4, H1, and H6, each 1H total

4H), 3.46–3.52 (m, H1, 1H), 3.38 (s, CH_3O, 3H), 3.36 (s, CH_3O, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 85.43 (C3), 84.69 (C4), 82.23 (C2), 79.83 (C5), 71.71 (C1), 69.23 (C6), 57.35 and 57.27 (CH_3O on C3 and C4).

(20) The synthesis is a procedure similar to that used for 2,5-anhydro-1,3,4,6-tetra-*O*-ethyl-D-glucitol in ref 15.

(21) To a stirred solution of **1** (0.5g, 2.87mmol) in methanol (100 mL) was added 2 drops of concentrated hydrochloric acid, and then the solution was kept for 24 h at room temperature. After neutralized by adding methanolic sodium methoxide, the mixture was evaporated to give a syrup. The residue was purified by column chromatography using ethyl acetate for elution. The fractions having R_F 0.4 gave **3** as a colorless syrup (0.41 g, 70%).

(22) Stille, J. K.; Culbertson, B. M. *J. Polym. Sci., Part A* **1964**, *2*, 405.

(23) Bauer, R. S. *J. Polym. Sci., Polym. Chem. Ed.* **1967**, *5*, 2192.

MA950197T