SYNTHESIS OF A NOVEL POLYMERIC CARBOHYDRATE VIA REGIO- AND STEREOSELECTIVE CYCLOPOLYMERIZATION OF 1,2:5,6-DIANHYDROHEXITOL

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Abstract: The selective cyclopolymerization of 1,2:5,6-dianhydrohexitols corresponding to diepoxides was a new synthetic strategy for polycarbohydrates, though the polymer is a lack of the anomeric linkage which is found in the naturally occurring polysaccharides. 1,2:5,6-Dianhydro-3,4-di-*O*-methyl-D-mannitol, L-iditol, and D-glucitol were polymerized using *t*-BuOK and BF_3•OEt_2 to produce the polymers consisting of five-membered rings. On the other hand, the polymers consisting of six-membered rings were obtained by the cationic and anionic polymerizations of meso allitol and galactitol monomers, respectively.

INTRODUCTION

Methods for synthesizing polycarbohydrates fall into three categories: sequential condensation polymerization, ring-opening polymerization, and enzymatic polymerization. The cyclopolymerization of diepoxides derived from hexitols, namely, 1,2:5,6-dianhydrohexitols presents a new preparative method for polycarbohydrates [Refs. 1,2]. Diepoxides with suitable structure come in a type of monomers to undergo cyclopolymerization. 1,2:5,6-Dianhydrohexitols derived from naturally occurring hexitols correspond to the diepoxides. There are ten hexitols that contain four pairs of optical enantiomers and two meso forms. Two pairs of D- and L-isomers in mannitol and iditol are C_2 symmetric and the other pairs are asymmetric. D-Glucitol with C_1 symmetry consists of

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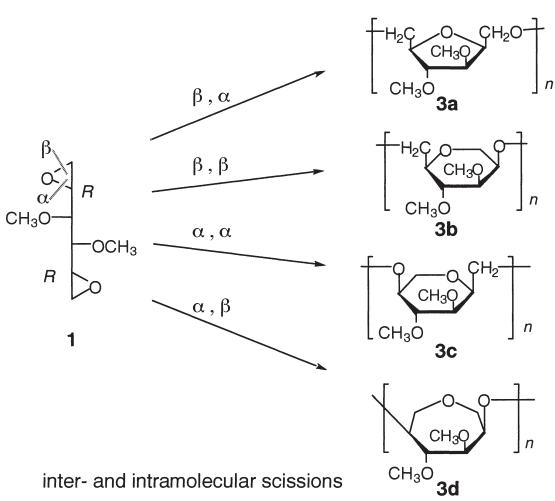
the structure combined two halves of D-mannitol and L-iditol. D-Altritol is constructed by two halves of meso allitol and galactitol. 1,2:5,6-Dianhydro-3,4-di-*O*-methyl-D-mannitol and L-iditol (**1** and **3**) of which the two epoxy groups in a molecule are equal in reactivity polymerize to yield the polycarbohydrates without the anomeric linkage, unlike the naturally occurring polysaccharides. 1,2:5,6-Dianhydro-3,4-di-*O*-methyl-D-glucitol (**7**) possesses two epoxy groups whose reactivities are nonequivalent, thus yielding two directions for polymerization. 1,2:5,6-Dianhydro-3,4-di-*O*-methyl-allitol and galactitol (**11** and **13**) with a plane of symmetry through the C3-C4 bond form the polymers consisting of a pair of enantiomeric cyclic units.

Cyclopolymerization of 1,2:5,6-dianhydro-3,4-di-*O*-methyl-D-mannitol (1)

The anionic cyclopolymerization of **1** was carried out in THF and toluene at 60 °C for 48 h using *t*-BuOK to yield the polymer (**2a**) [Refs. 3,4]. The reaction system was homogeneous up to complete consumption of the monomers. For the polymerization with a [**1**]/[*t*-BuOK] ratio of 40 in toluene, the $\overline{M}_n$ of the polymer attained to 12900 ($\overline{P}_n$ = 74). The sparing solubility of *t*-BuOK in toluene lowered the initiator efficiency. The complexation of *t*-BuOK with 18-crown-6 increased the initiator efficiency from 0.3 to 1.0. Since the linearity in the plot of $\overline{P}_n$ versus conversion showed little participation of side reactions in polymerization, e.g., chain transfer to monomer, the living-like nature of the system was found [Refs. 4,5]. Polymer **2a** was sticky semisolid and soluble in common organic solvents.

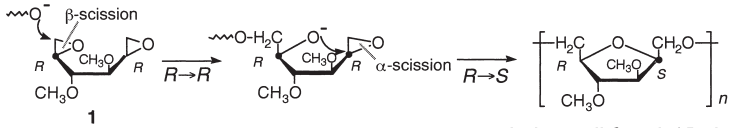


Scheme 1

The specific rotation ($[\alpha]_{546}^{22}$) of the polymer ranged from +72.2 to +93.9 deg•cm^2•dag^{-1} (concentration, 10 g•dm^{-3} in $CHCl_3$).

There are four possible cyclic units (**3a** - **3d**) by combination of the inter- and intramolecular reactions in the cyclopolymerization of **1** (Scheme 1). To confirm the structure of polymer **2a**, therefore, model compound **4**,

2,5-anhydro-1,3,4,6-tetra-*O*-methyl-D-glucitol was synthesized by hydrolysis of **1** and then treatment with dimethyl sulfate. The signals for the ^{13}C NMR spectrum of polymer **2a** fairly agreed with the chemical shifts for the model compound. Polymer **2a**, therefore, was exclusively (1→6)-2,5-anhydro-3,4-di-*O*-methyl-D-glucitol (**3a**).



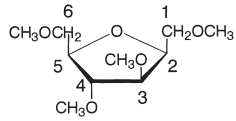
Scheme 2

For the cyclopolymerization of **1** using *t*-BuOK, the stereochemically-controlled polymer **2a** should be produced through the mechanism proposed in Scheme 2. For the intermolecular reaction, the growing alkoxy anion cleaves 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 cleaves the α-bond of the second epoxide to form a 5-membered ring. For the stereoselectivity during the cyclization, the configuration of the α-carbon is inverted from *R* to *S*. The cyclopolymerization **1** using *t*-BuOK was highly regio- and stereospecific through β,α-scissions in the inter- and intramolecular reactions.

With BF_3•OEt_2 in toluene or methylene chloride, the *n*-hexane-insoluble polymer (**2b**) was obtained together with *n*-hexane-soluble low molecular weight products [Ref. 6]. Polymer **2b** was a sticky semisolid soluble in $CHCl_3$, MeOH, THF, and H_2O and was optically active with a specific rotation $[\alpha]^{22}_{546}$ in the range from +41.3 to +71.3 deg•cm^2•dag^{-1}. The $\overline{M}_n$ was 1000 - 3400 ($\overline{P}_n$ = 6 - 20). Although polymer **2b** contained some irregular cyclic units as a minor component together with 2,5-anhydro-D-glucitol unit **3a**, the polymerization also proceeded mainly through β,α-scissions.

Cyclopolymerization of 1,2:5,6-dianhydro-3,4-di-*O*-methyl-L-iditol (5)

The polymerization systems of **5** using *t*-BuOK were homogeneous up to a very high conversion [Ref. 7]. The polymer (**6a**) had the $\overline{M}_n$ ranging from 2600 to 6100 ($\overline{P}_n$ = 15 - 35). Chain transfer to monomer placed the upper limit to the $\overline{M}_n$ of polymer **6a** [Ref. 8]. In the ^{13}C NMR spectrum of polymer **6a**, the signals agreed fairly well with the chemical shifts for model compound **4**. The cyclic constitutional unit in polymer **6a**,



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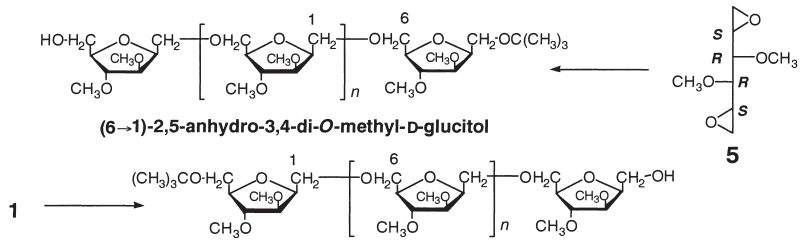
thereby, was recognized as 2,5-anhydro-3,4-di-*O*-methyl-D-glucitol, analogous to polymer **2a**. The formation of the 2,5-anhydro-3,4-di-*O*-methyl-D-glucitol units is based on β,α-scissions of the two epoxy groups in the monomer. The anionic cyclopolymerization of **5**, thus, is regio- and stereoselective, like that of 1. However, there is an essential difference in structure between polymers **2a** and **6a**. Although both polymers have apparently the same constitutional repeating units, their units differ from one another in direction. The ^{13}C NMR spectra of polymers **2a** and **6a** showed the small signals attributable to the ends in the polymer chain. Polymer **2a**, therefore, is (1→6)-2,5-anhydro-3,4-di-*O*-methyl-D-glucitol with tert-butoxy and hydroxymethyl groups at both ends, but polymer **4a** by the (6→1)-bonded glucitol, as shown in Scheme 3. The copolymerization between monomers **1** and **5** offered a solution to the problem of direction.

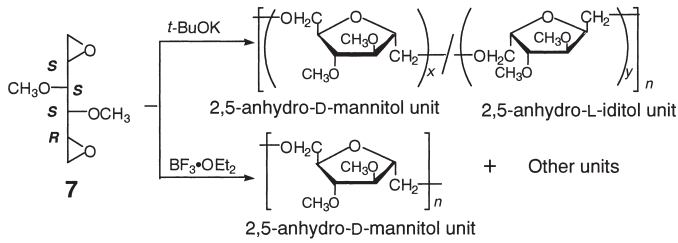


Scheme 3

In the cationic polymerization of monomer **5** with BF_3•OEt_2, the yields and $\overline{M}_n$s for the polymer (**6b**) were lower than those for **2b** [Ref. 6]. The ^{13}C NMR spectrum of polymer **6b** indicated that the major structure of the polymer was identical to polymer **6a**, but some irregular units were formed.

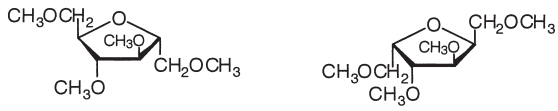
Cyclopolymerizations of 1,2:5,6-dianhydro-3,4-di-O-methyl-D-glucitol (7)

The anionic polymerization of **7** using *t*-BuOK yielded the polymer (**8a**) with the $\overline{M}_n$ in the range of 4530 to 5510 ($\overline{P}_n$ = 26 - 32) [Ref. 9]. The polymer (**8b**) obtained by the cationic polymerization with BF_3•OEt_2 had the $\overline{M}_n$s of 3770 ($\overline{P}_n$ = 22). The specific rotations ($[\alpha]^{22}_{546}$) were +69.2 to +81.4 deg•cm^2•dag^{-1} for polymer **8a**, and +40.6 to +62.7 deg•cm^2•dag^{-1} for polymer **8b**. The characteristic signals due to the epoxy groups in the ^1H NMR spectra of both polymers completely disappeared. The ^{13}C NMR spectrum of polymer **8a** comprised of the signals similar to those of the model compounds, 2,5-anhydro-3,4-di-*O*-methyl-D-



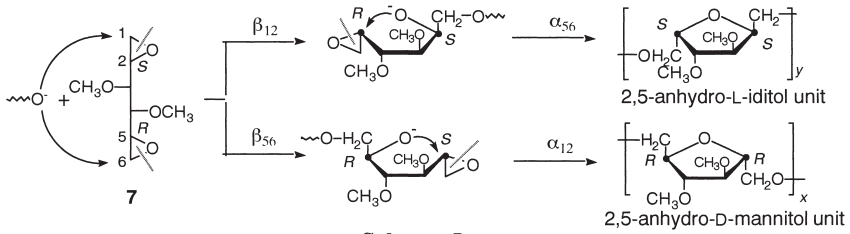
Scheme 4

mannitol (**9**) and L-iditol (**10**). Polymer **6a**, thus, consists of two kinds of cyclic repeating units, as shown in Scheme 5. The ratio of the D-mannitol unit to the L-iditol unit (x/y) was 0.40/0.60 for the polymerization in toluene. The ratio changed from 0.27/0.73 in the system of 18-crown-6/toluene to 0.47/0.53 in DMSO according to the polymerization conditions. On the other hand, in the structure of polymer **8b**, there might exist six- and seven-membered rings as minor constitutional units together with the 2,5-anhydro-3,4-di-*O*-methyl-D-mannitol as major unit.



9 **10**

The anionic cyclopolymerization of **7** produced the polymer consisting of two kinds of cyclic repeating units. The β_{12},α_{56}-scissions form the cyclic D-mannitol unit with *S,S*-configuration, and the β_{56},α_{12}-scissions form the cyclic L-iditol unit with *R,R*-configuration (Scheme 5). As a result, the two processes competitively proceeded to produce the



Scheme 5

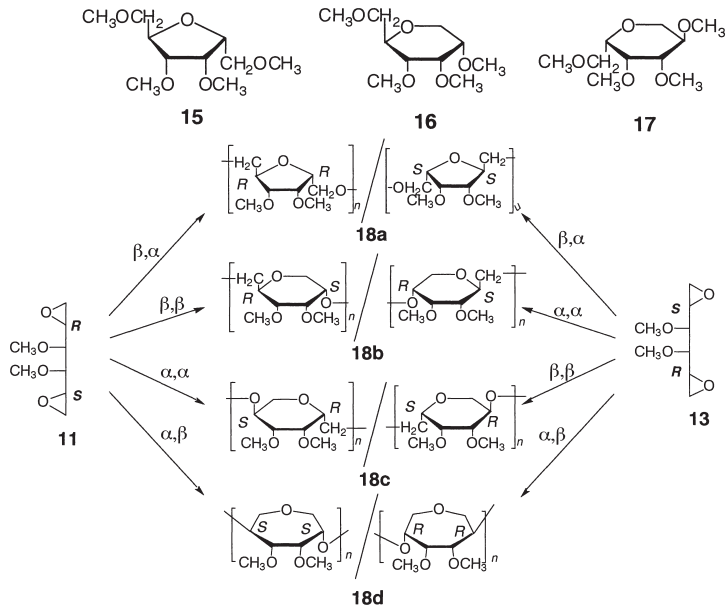
copolymer consisting of 2,5-anhydro-3,4-di-*O*-methyl-D-mannitol and L-iditol units. Although involving two processes, the polymerization was regio- and stereoselective in each process. On the other hand, the cationic cyclopolymerization of **7** induced the intermolecular reaction preferentially at the 1,2-epoxide moiety as a nucleophile. Therefore, the formation

of 2,5-anhydro-3,4-di-*O*-methyl-D-mannitol results from β_{56},α_{12}-scissions.

Cyclopolymerizations of meso 1,2:5,6-dianhydro-3,4-di-*O*-methyl-allitol (11) and galactitol (13)

The anionic polymerization systems using *t*-BuOK were homogeneous for **11** and heterogeneous for **13** [Ref. 10]. The obtained polymers (**12a** and **14a**) were soluble in chloroform and THF. For **12a** obtained in toluene, the $\overline{P}_n$s were 7.6, 14.4, and 25.1 relative to the values of 5, 10, and 20 calculated from the ratio of [M]/[*t*-BuOK]. The polymerization of **11**, thus, had a living-like nature similar to that of **1**. On the other hand, the polymerization of **13** suggested some participation of the chain transfer to monomer similar to those of **5** and **7**. The cationic polymerizations of **11** and **13** with BF_3•OEt_2 gave the polymers (**12b** and **14b**) with the lower $\overline{P}_n$s of 13 and 6, respectively. The extent of cyclization (f_c) was 1.0 for each of polymers **12a**, **14a**, and **11b**, but 0.89-0.93 for **14b**. All of the polymers consist of a pair of enantiomeric cyclic units, thus being optically inactive.

Hydrolysis of **11** and **13** yielded 2,5-anhydro-1,3,4,6-tetra-*O*-methyl-DL-altritol (**15**), 1,5-anhydro-2,3,4,6-tetra-*O*-methyl-DL-allitol (**16**), and 1,5-anhydro-2,3,4,6-tetra-*O*-methyl-DL-galactitol (**17**) corresponding to model compounds for the constitutional units. The signals

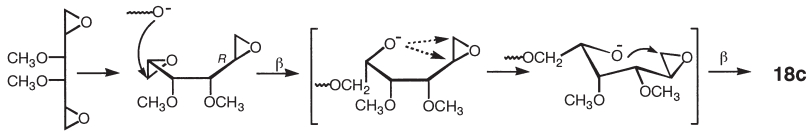


Scheme 6

observed in the ^{13}C NMR spectra of the polymers were split into two or more bands, which fact should be caused by the diversity of sequences of the two enantiomeric units. The signals for polymers **12a** and **14a** agreed very closely with those for **15** and **17**, respectively. The structure of the polymers was **18a** of five-membered rings for polymer **12a**, in contrast to **18c** of six-membered rings for polymer **14a** (Scheme 6).

The ^{13}C NMR spectra of polymers **12b** and **14b** were somewhat complex, which suggested that their structures were composed of plural repeating units. For polymer **12b**, the signals could be divided into two groups compatible with the spectra of **15** and **17**. Polymer **12b**, thus, had a structure consisting of **18c** as major unit and **18a** as minor unit. Polymer **14b** comprised **18a** and **18b** of five- and six-membered rings, respectively. In addition, the other unknown units along with the uncyclized unit were contained in the polymer.

During the anionic cyclopolymerizations of **11**, the constitutional unit **18a** was formed through β,α-scissions. The equality of reactivity at the 1,2- and 5,6-epoxides yielded a pair of enantiomeric units in polymer **12a**. On the other, the anionic polymerization of **13** proceeded mainly through β,β-scissions to form **18c**. The growing anion in cyclization should avoid the unfavorable conformation due to the eclipsed arrangements of three neighboring substituents in the five-membered ring to convert its conformation into the favorably staggered arrangements in the six-membered ring (Scheme 7).



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Scheme 7

The cationic cyclopolymerization of **11** comprised the process through α,α-scissions to form **18c**. The steric crowd in the growing oxonium ion is responsible for the formation of six-membered rings. The α,α-scissions in the cationic polymerization of **11** constructed the same constitutional units of six-membered rings as the β,β-scissions in the anionic polymerization of **13**.

Characteristics of (1→6)-2,5-anhydro-3,4-di-*O*-methyl-D-glucitol as a new macromolecular ionophore

The naturally occurring ionophore includes the polyether antibiotics such as monensin and nigericine consisting of a formally linear array of tetrahydrofuranyl and tetrahydropyranyl rings. The regio- and stereoselective cyclopolymerization of monomer **1** yielded the

polycarbohydrate consisting of tetrahydrofuranyl rings.

Polymer **2** strongly complexed with such larger organic cations as methylene blue and rhodamine 6G besides alkali metal ions, unlike the crown ether[Ref. 2]. In the transport experiment using the HPF_6 salt of methyl α-amino esters ($RCH(CO_2CH_3)NH_3^+ \cdot PF_6^-$), the steric requirements for higher enantioselectivity were the longer alkyl substituents at the 3,4 positions for the polymer and the bulkiness of the chiral center for the guest [Refs. 11,12]. Having a living-like character, the anionic polymerization of monomer **1** could be used for preparing stationary phase bound on silica gel for chromatographic optical resolution of racemic amines and amino acids [Ref. 13]

CONCLUSIONS

The anionic polymerizations of 1,2:5,6-dianhydrohexitols were highly regio- and stereoselective to produce the polycarbohydrates consisting of five-membered rings for D-mannitol, L-iditol, D-glucitol, and meso allitol monomers and six-membered rings for meso galactitol. The polymer consisting of six-membered rings was formed also by the cationic polymerization of allitol monomer. The same structures of six-membered rings were obtained through β,β-scissions for galactitol monomer and α,α-scissions for allitol monomer.

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