SYNTHESIS OF A β-(1→6)-LINKED POLYSACCHARIDE VIA RING-OPENING POLYMERIZATION WITH NEIGHBORING-GROUP PARTICIPATION*

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ABSTRACT

(1→6)-β-D-Galactopyranan was synthesized by cationic ring-opening polymerization of 1,6-anhydro-2-*O*-benzoyl-3,4-di-*O*-benzyl-β-D-galactopyranose and subsequent deprotection. The polymerization proceeded at 0° and 20°, using 10–50 mol% of phosphorus pentafluoride as initiator in dichloromethane, to give the polymer of $\overline{M}_n$ 2.6–3.6 × 10^3. The benzyl and benzoyl groups were removed by using sodium in liquid ammonia and an exclusively (1→6)-linked β-D-galactopyranan oligosaccharide of average d.p. 7 was obtained. The formation of the β-(1→6)-linkage was explained by a neighbouring-group effect on the steric control of the propagation step: BzO-2 in the growing terminal unit reacted with the cyclic trialkyloxonium ion to form a stable dioxacarbenium (dioxolenium) ion, which allowed exclusive β-side attack of the incoming monomer.

INTRODUCTION

A variety of stereoregular polysaccharides have been synthesized *via* ring-opening polymerization of anhydro sugar derivatives[1,2] and polycondensation of cyclic orthoester derivatives[3]. In stepwise glycoside synthesis, glycopyranosyl halides with an acetyl or benzoyl group at position 2 are often used as glycosyl donors to control the anomeric configuration through neighboring-group participation[4,5]. An application of neighboring-group participation to ring-opening polymerization will be useful for chemical synthesis of polysaccharides that are not presently accessible. We now report on the ring-opening polymerization of an anhydro sugar derivative (**1**, 1,6-anhydro-2-*O*-benzoyl-3,4-di-*O*-benzyl-β-D-galactopyranose[6]) with a neighboring participating group to lead to the synthesis of (1→6)-β-D-galactopyranan[7].

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*Dedicated to Professor Bengt Lindberg.

EXPERIMENTAL

Polymerization. — Monomer **1**[6] and **4**[8] were synthesized and purified by previously reported methods. Compound **1** had m.p. 93–94°, $[\alpha]_D^{25}$ +1.6° (*c* 1, chloroform); lit.[6] m.p. 89–90°, $[\alpha]_D^{23}$ +0.8° (*c* 2.5, chloroform). (*Anal.* Calc. for $C_{27}H_{26}O_6$: C, 72.63; H, 5.87. Found: C, 72.59; H, 5.83). Compound **4** had m.p. 53.5–54.5°, $[\alpha]_D^{25}$ −45.3° (*c* 1, chloroform); lit.[8] m.p. 55–56°, $[\alpha]_D^{25}$ −46.1° (*c* 1, chloroform).

Polymerization was carried out using the high vacuum technique[9]. The product was reprecipitated thrice from solution in chloroform with methanol and chromatographed on silica gel [hexane–ethyl acetate (1:1) and then benzene]. The eluate was concentrated and the residue was freeze-dried from benzene.

Deprotection. — A solution of polymer **2** (0.40 g) in toluene (15 mL) and 1,2-dimethoxyethane (5 mL) was added to 50 mL of liquid ammonia. Small pieces of freshly cut sodium metal were added to the mixture until the dark blue color of the solution persisted. Water (20 mL) was added dropwise, the mixture was stirred overnight at room temperature, and the water layer was passed through a column of Amberlite IR-120 (H⁺) resin. The eluate was concentrated, and the residue was precipitated from a solution in water with tetrahydrofuran and freeze-dried from water to give a white hygroscopic powder (0.15 g, ~100%).

Characterization. — ¹³C-N.m.r. spectra were recorded with a JEOL JNM-FX-200 Fourier-transform n.m.r. spectrometer operating at 50 MHz for solutions in $CDCl_3$ (internal Me_4Si) or D_2O (internal MeOH, 49.0 p.p.m.). Optical rotations were determined in a Japan Spectroscopic Co. DIP-181 digital polarimeter, using a water-jacketed 1-dm cell. Number-average molecular weights ($\overline{M}_n$) of protected polysaccharides were estimated by h.p.l.c. with a Hitachi 634A with a column (8 mmϕ × 1000 mm) of Shodex GPCA 803–804, using chloroform with polystyrene as the standard.

RESULTS AND DISCUSSION

Polymerization of 1,6-anhydro-2-O-benzoyl-3,4-di-O-benzyl-β-D-galacto-pyranose (**1**). — The results of polymerization of **1**, using phosphorus pentafluoride (10–50 mol% to monomer) as the initiator in dichloromethane, are summarized in Table I. The polymerization proceeded only above −20°. The white powdery product **2**, soluble in benzene and chloroform but insoluble in hexane, methanol, and water, had a $\overline{M}_n$ in the range of 2.6–3.6 × 10³ corresponding to d.p. 6.0–8.3 [*Anal.* Calc. for $(C_{27}H_{26}O_6)_n$: C, 72.63; H, 5.87. Found: C, 72.59; H, 5.83].

For purposes of comparison, the polymerization of 1,6-anhydro-2,3,4-tri-O-benzyl-β-D-galactopyranose (**4**) was also carried out at −20° and 0° (Table I); at −60°, a (1→6)-linked α-D-galactopyranan derivative (**5**) was obtained[8,10] with $\overline{M}_n$ 2.1 × 10⁵ (d.p. 500) and $[\alpha]_D^{25}$ +104.2°. The molecular weight and stereoregularity of the product decreased with increase in the temperature of polymerization. The

TABLE I

POLYMERIZATION OF 1,6-ANHYDRO-2-O-BENZOYL-3,4-DI-O-BENZYL-β-D-GALACTOPYRANOSE (1) AND 1,6-
ANHYDRO-2,3,4-TRI-O-BENZYL-β-D-GALACTOPYRANOSE (4)[a]

Expt.	Monomer	PF_5 (mol%)	Temp. (°)	Time (h)	Yield (%)	β-Form[b] (%)	$\overline{M}_n$[c] ($\times 10^{-3}$)	$[\alpha]_D^{25}$[d] (°)
I-76	1	10	0	6	24	100	3.6	+32
I-77	1	10	0	48	66	100	2.6	+27
I-82	1	50	−20	6	22	100	2.8	+29
I-85	4	10	0	6	88	28	3.1	+68
I-86	4	10	−20	0.5	86	0	7.7	+91

[a]Monomer, 1.0 mmol; 1.5 mol/L in dichloromethane. [b]Determined by ^{13}C-n.m.r. spectroscopy. [c]Determined by gel-permeation chromatography (see Experimental). [d]In chloroform (c 1).
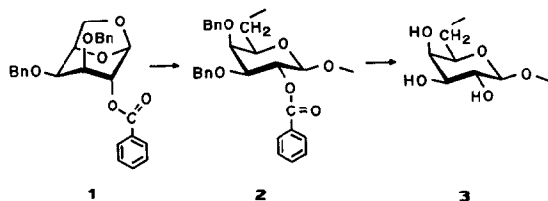
rate of polymerization of **1** was lower than that of **4** as was the molecular weight of the product.

As judged from the optical rotation and ^{13}C-n.m.r. spectrum, the configuration of the polymer **2** was distinct from that of α-(1→6)-linked polymer **5** but similar to that of a tetrasaccharide composed of 2-O-benzoyl-3,4-di-O-benzyl-(1→6)-β-D-galactopyranosyl units ($[\alpha]_D^{25}$ +25.8°) and prepared[11] by a stepwise glycosidation method. In the region for anomeric carbons of the ^{13}C-n.m.r. spectrum of **2**, there appeared a strong signal at 101.3 p.p.m. and a weak signal at 97.7 p.p.m. The chemical shift of the former signal was in agreement with that (101.67 p.p.m.) of the C-1β signal of the model compound[11]. The latter signal was assignable to the C-1β of the reducing terminal unit and the ratio of the intensities of these signals agreed with the d.p. value. Confirmation of the β-stereoregularity is described below.

Synthesis of (1→6)-β-D-galactopyranan. — Deprotection of **2** (I-77 in Table I) was carried out with sodium in liquid ammonia, and the unsubstituted polysaccharide **3** was obtained quantitatively as a hygroscopic powder, which was soluble in water, partially soluble in methyl sulfoxide, insoluble in common organic solvents, and had $[\alpha]_D^{25}$ +27° (c 1, water) [*cf.* +20° (water) for (1→6)-β-D-galactotriose[12]].

Fig. 1 shows the ^{13}C-n.m.r. spectrum of **3**. The set of six strong signals were assigned to the central β-D-galactopyranosyl residues (C-1, 103.38; C-5, 73.78; C-3, 72.69; C-2, 70.80; C-6, 69.29; C-4, 68.69 p.p.m.). These chemical shifts were in
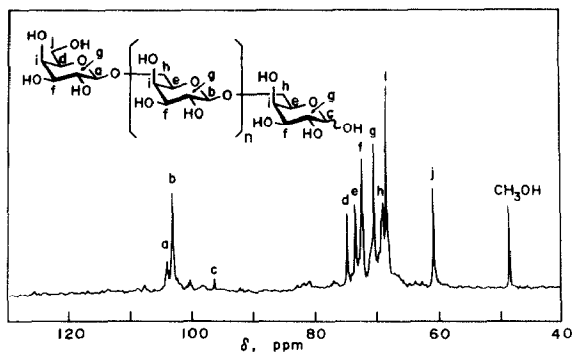
Fig. 1. ^{13}C-N.m.r. spectrum (50 MHz) of a solution of (1→6)-β-D-galactopyranan (3) in D$_2$O (internal MeOH).

agreement with those (C-1, 103.46; C-5, 73.79; C-3, 72.66; C-2, 70.77; C-6, 69.23; C-4, 68.70 p.p.m.) of the central units of the methyl β-glycoside of (1→6)-β-D-galacto-hexaose[13]. The $J_{C-1,H-1}$ value of 162.6 Hz confirmed the β linkage[14]. Other signals were assigned as follows: non-reducing terminal unit: C-1, 104.25; C-5, 75.17; C-6, 61.06 p.p.m.; reducing terminal unit: C-1β, 96.43 p.p.m. When the polysaccharide was oxidized with hypoiodite to an aldonic acid[15], only the signal for reducing C-1β disappeared. The d.p., estimated from the ratio of the intensities of the signals for C-1 in central and non-reducing residues, was 7.

The ^{13}C-n.m.r. data of the (1→6)-α-D-galactopyranan **6** obtained[8,10] by de-benzylation of **5** (sample I-86, Table I) were as follows: C-1, 98.55; C-5, 70.23; C-3, 69.98; C-2, 69.12; C-4, 68.85; C-6, 66.83 p.p.m. Weaker signals at 71.43 and 61.47 p.p.m. were assignable to C-5 and C-6, respectively, of the non-reducing terminal unit. No signals due to an α-(1→6)-linked unit were detected in Fig. 1.


4   **5**   **6**
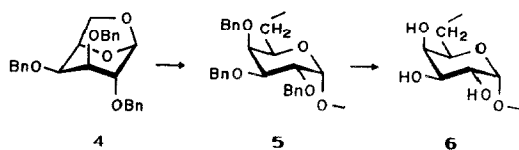
Mechanism of neighboring-group participation. — The stereospecific poly-merization of **4** leading to the formation of an α-(1→6)-linked sequence is explained by the trialkyloxonium ion mechanism[1-3,8,10] as shown in Scheme 1. At −60°, a monomer attacks the acetal carbon of the cyclic trialkyloxonium ion exclusively from the opposite (α) side of the C–O$^+$ bond.

The mechanism of the stereospecific polymerization of **1**, yielding β-(1→6)-linked polymer, is proposed in Scheme 2. The cyclic trialkyloxonium ion, tran-siently formed at the growing terminal unit, immediately interacts with the carbonyl oxygen of the neighboring benzoyl substituent to form the relatively stable cyclic
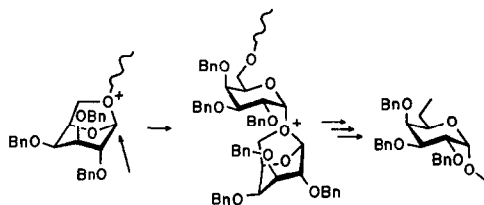
Scheme 1. Trialkyloxonium ion mechanism in the stereospecific polymerization of 1,6-anhydro-2,3,4-tri-O-benzyl-β-D-galactopyranose (4).
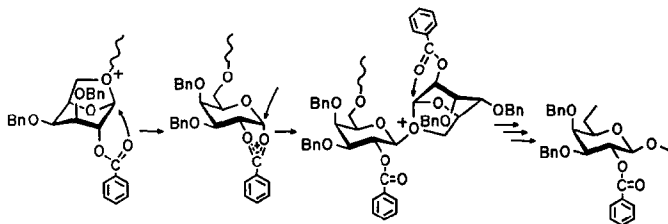
Scheme 2. The proposed mechanism for the neighboring-group effect in the steric control of the polymerization of 1,6-anhydro-2-O-benzoyl-3,4-di-O-benzyl-β-D-galactopyranose (1).

dioxacarbenium (dioxolenium or benzoyloxonium) ion with inversion of configuration at C-1. The α-side of the pyranose ring in the growing terminal unit is sterically blocked, and the approaching monomer can attack the reaction center only from the β-side. Repetition of oxonium ion–dioxolenium ion interchange yields the β-(1→6)-linked sequence. This reaction is in contrast to stepwise glycosidations in which the intermediate dioxolenium ion is destroyed by nucleophilic attack of an alcoholic component[4,5].

The dioxolenium ion is much more stable than the oxonium ion and hence the polymerization of 1 is more sluggish than that of 4. In addition, a portion of added Lewis acid initiator is consumed by coordination with carbonyl oxygen. As a result, the polymerization of 1 requires a larger amount of initiator and higher temperature, and the molecular weight of the polymer was low. It is also possible that some side reactions occur at the benzyl or benzoyl substituents during prolonged polymerization, which is suggested by the observation that some unassignable signals appeared around ~40 p.p.m. in the ^{13}C-n.m.r. spectrum of the protected polymer, which disappeared after deprotection. These problems may be avoided by using more reactive 2-O-acylated compounds as monomers.

Recently, an increase in the content of β-forms resulting from the polymerization of a bicyclic acetal (4-bromo-6,8-dioxabicyclo[3.2.1]octane) was explained in terms of bromonium ion participation[16]. A different type of polymerization with exclusive *cis* ring-opening has been reported for 1,6-anhydro-2,3-di-O-benzyl-4-deoxy-β-L-*ribo*-hexopyranose[17,18]. In the present investigation, exclusive *cis* ring-opening has been attained by neighboring-group participation. This is a useful and

convenient method for synthesizing β-(1→6)-linked oligo- and poly-saccharides[3,7,19,20].

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