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Note

Synthesis of partially 3-deoxygenated (1→6)-α-D-glucopyranan*

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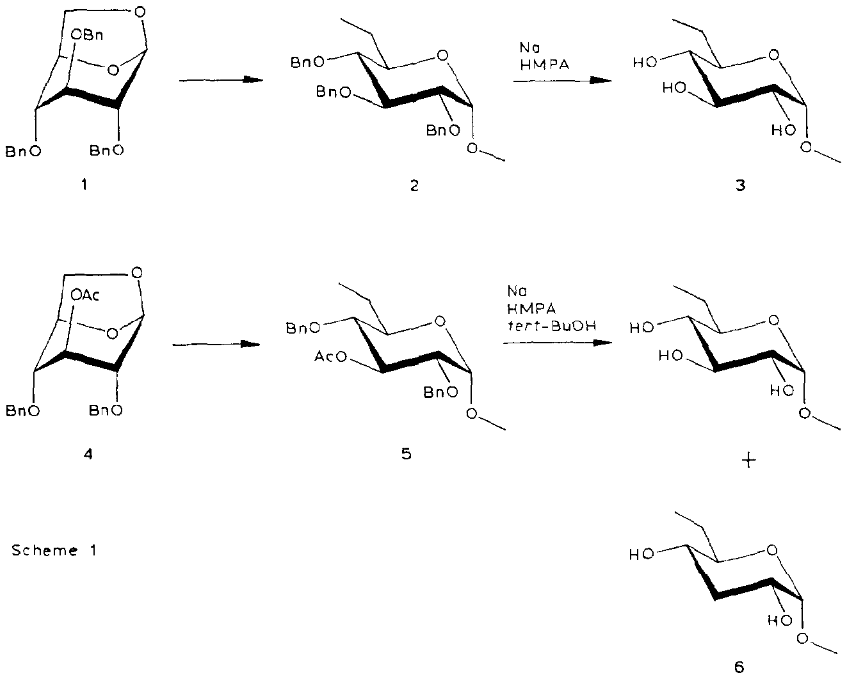
As shown in Scheme 1, the synthetic polysaccharide derivatives, 2,3,4-tri-*O*-benzyl-(1→6)-α-D-glucopyranan (**2**) and 3-*O*-acetyl-2,4-di-*O*-benzyl-(1→6)-α-D-glucopyranan (**5**), were reduced by sodium in hexamethylphosphoramide (HMPA) to give (1→6)-α-D-glucopyranan (**3**) and 3-deoxygenated (1→6)-α-D-glucopyranan (**6**), respectively. In addition to effective debenzylation, the ester in position 3 was reduced to the corresponding alcohol or alkane.



Scheme 1

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*Part 4 of the series: Regioselectively Modified Stereoregular Polysaccharides.

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Regioselective modification of polysaccharides is an attractive target for developing useful polysaccharides having novel properties. For this purpose, we have conducted ring-opening polymerization of 1,6-anhydro sugars having two different types of substituent in the molecule[1–6]. Thus, high-molecular-weight 3-*O*-methyl-(1→6)-α-D-glucopyranan was prepared by polymerization of 1,6-anhydro-2,4-di-*O*-benzyl-3-*O*-methyl-β-D-glucopyranose with subsequent debenzylation[4]

During the course of these investigations, attention has been directed to reduction of the polymer **5**. We previously reported that reduction of **5** by sodium in liquid ammonia yielded (1→6)-α-D-glucopyranan; both debenzylation and deacetylation took place. According to Deshayes and Pete[7], esters of alcohols are reduced by sodium in HMPA (containing *tert*-butyl alcohol as a proton source) to give mixtures of the corresponding alcohols and alkanes. HMPA has a remarkable ability to dissolve alkali metals, forming blue solutions of solvated electrons, and these exhibit stronger reducing power than solutions of alkali metals in liquid ammonia[8,9]. The reduction system may therefore be expected to bring about debenzylation as well as partial reduction of the ester of the polymer **5**.

To our knowledge, no data on debenzylation of carbohydrates by sodium in HMPA have yet been published. Prior to its application to the intended polymer **5**, the reagent was employed with the polymer **2** to confirm the effectiveness of debenzylation.

Deoxy sugars are biologically important, and selective deoxygenation processes of carbohydrates have been investigated extensively, but there have been only a few studies on deoxygenation of polysaccharides[10–14]. Recently, a fully 3-deoxygenated glucan, 3-deoxy-(1→6)-α-D-*ribo*-hexopyranan, has been prepared by polymerization of 1,6-anhydro-2,4-di-*O*-benzyl-3-deoxy-β-D-*ribo*-hexopyranose followed by debenzylation[15]. In contrast, 2,3,4-trideoxy-(1→6)-α-L-*glycero*-hexopyranan possessing a completely deoxygenated backbone structure and opposite absolute configurations of the asymmetric carbon atoms was obtained by polymerization of the corresponding bicyclic compound derived from noncarbohydrate sources[16]. Other polysaccharide-type polymers, of mixed D and L configurations and having two and one hydroxyl groups per repeating unit have also been reported[17–20].

RESULTS AND DISCUSSION

Debenzylation of 2,3,4-tri-O-benzyl-(1→6)-α-D-glucopyranan (**2**). — Debenzylation of **2** was performed by adding the polymer solution in oxolane (tetrahydrofuran, THF) dropwise to a blue solution of sodium in HMPA (Table I). The reduction was exothermic. The reaction temperature of Experiment A rose spontaneously, and hence experiment B was conducted at 10°. At this temperature, however, a fraction of the starting polymer was deposited because of its low solubility in cold HMPA, thus lowering the yield. No such proton source as *tert*-butyl alcohol was necessary, as the sodium alkoxide formed by reduction could be made neutral during the subsequent dialysis in water.

TABLE I

REDUCTION OF 2,3,4-TRI-*O*-BENZYL-(1→6)-α-D-GLUCOPYRANAN (**2**) AND 3-*O*-ACETYL-2,4-DI-*O*-BENZYL-(1→6)-α-D-GLUCOPYRANAN (**5**) BY SODIUM IN HMPA

Expt.	*Polymer*	*(g)*	*Na*[a] *(g)*	*HMPA (mL)*	*tert-BuOH (mL)*	*THF (mL)*	*Temp. (°C)*	*Time (min)*	*Yield (%)*	$[\alpha]_D^{25}$[b] *(deg)*	*Deoxygenation*[c] *(%)*
A	**2**	0.50	0.68	30	0	5	R.T.[d]	50	95	170	
B	**2**	0.51	0.43	30	0	15	10	60	62	177	
C	**5**	0.50	0.33	30	0	5	10	20	56		5
D	**5**	0.44	1.40	100	14.4	4.4	10	27	62		23

[a]Sodium consumed during the reaction. [b]Determined in water. [c]Percent of deoxygenation determined by the signal intensity [1'/(1 + 1')] of the ^{13}C-n.m.r. spectrum. [d]The reaction was performed at room temperature, but an exothermic process was observed.

TABLE II

DECREASE IN D.P.$_n$ VALUES DURING THE REDUCTION

Expt.	*Starting polymer*			*Product*			x[k]
		$[\eta]$[b]	$\overline{D.p.}_n$		$[\eta]$	$\overline{D.p.}_n$	
A	**2**	0.77	570[c]	**3**	0.08_5[j]	33[h]	35
B	**2**	0.95	790[c]	**3**	0.18[f]	110[h]	128
E[a]	**2**	0.95	769[d]	**3**	0.29[g]	149[i]	185
C	**5**	0.19	52[e]	**6**	—	27[j]	56
D	**5**	0.19	52[e]	**6**	—	5.6[j]	6.2

[a]Data from ref. 21. [b]Determined in chloroform at 25°. [c]Calculated from the equation $[\eta] = 2.12 \times 10^{-4}\ \bar{M}_n^{0.66}$ (ref. 21). [d]Determined by membrane osmometry in toluene at 37°. [e]Estimated from the g.p.c. retention time–molecular weight relationship derived for standard polystyrenes. [f]Determined in water at 25°. [g]Determined in Me_2SO at 25°. [h]Calculated from the equation $[\eta] = 4.93 \times 10^{-4}\ \bar{M}_n^{0.60}$ (ref. 24). [i]Determined by membrane osmometry in Me_2SO at 37°. [j]Determined by the signal intensity [(6 + 6')/6''] of the ^{13}C-n.m.r. spectrum. [k]Chain scission occurred once per x units.

The water-soluble polymers obtained were stereoregular (1→6)-α-D-glucopyranans: debenzylation proceeded completely without any configurational change. Their i.r., and ^{1}H- and ^{13}C-n.m.r. spectra were identical respectively with those of the products prepared by debenzylation with sodium–liquid ammonia[21]. The ^{13}C-n.m.r. spectra showed only six signals, assignable to the six carbon atoms of (1→6)-α-D-glucopyranan[22] (compare Table III). No resonances for a β-anomeric carbon atom or for terminal glucopyranose residues were detected. The specific rotations agree with those for linear, stereoregular (1→6)-α-D-glucopyranans if a correction for content of retained water is made[21,23].

Table II summarizes the intrinsic viscosities and $\overline{\text{d.p.}}_n$ values determined before and after the reduction. The data collected are based on different methods and solvents, but seem adequate for the following discussion. The term x in the last column was introduced to compare the decrease in $\overline{\text{d.p.}}_n$. It represents the reciprocal of the probability of observing a chain scission in one glucosidic linkage. In other words, the scission occurs once per x glucose residues. It was found that lower reaction temperature resulted in a higher value of x. Data for conventional debenzylation by sodium in liquid ammonia are also listed for comparison. We preferred the earlier data by Schuerch and Uryu[21], while more recent procedures[22,23] have been improved to minimize the decrease in $\overline{\text{d.p.}}_n$. The sodium–HMPA debenzylation caused scission of the main chain more often than the sodium–liquid ammonia method.

In conclusion, the sodium–HMPA reduction has proved satisfactory for debenzylation of the synthetic polysaccharide to give stereoregular (1→6)-α-D-glucopyranan, although there is still room for improvement in the yield and the $\overline{\text{d.p.}}_n$ of the resulting polymer. The simple procedure has advantages over the conventional method, but a demerit is that HMPA is carcinogenic.

Reduction of 3-O-acetyl-2,4-di-O-benzyl-(1→6)-α-D-glucopyranan (**5**). — Polymer **5** was reduced by sodium–HMPA in the absence and in the presence of *tert*-butyl alcohol at 10°, as summarized also in Table I. Compared with the reduction of **2**, the blue color of the mixture tended to disappear more readily, especially in the

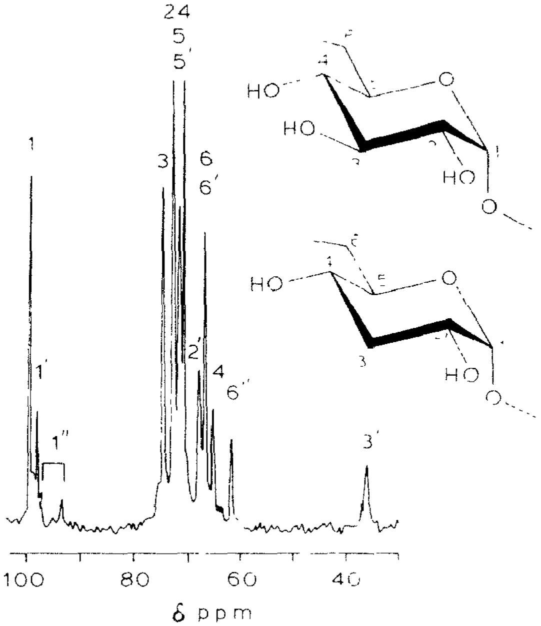

Fig. 1. ^{13}C-N.m.r. (25.05 MHz) spectrum of partially 3-deoxygenated (1→6)-α-D-glucopyranan prepared by reduction of 3-*O*-acetyl-2,4-di-*O*-benzyl-(1→6)-α-D-glucopyranan (**5**) by sodium in HMPA–*tert*-butyl alcohol (product D). The spectrum was recorded at room temperature after 35000 transients with a tube (10-mm diameter) containing an 8% solution in D_2O with Me_4Si as the external standard.

TABLE III

^{13}C-N.M.R. CHEMICAL SHIFTS (p.p.m.) OF REDUCTION PRODUCTS[a]

Sample	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	
A	98.83	72.56	74.56	70.71	71.34	66.76	
D	98.83	72.51	74.51	70.66	71.34	66.66	Glucose residue
	97.75	67.64	36.01	65.20			3-Deoxy residue
	97.7, 93.3					61.60	Terminal residue

[a] All shifts are relative to the external reference of Me_4Si.

presence of *tert*-butyl alcohol, where the tendency was marked and more sodium was consumed. For experiment D, larger quantities of sodium and HMPA were used, and the reaction was terminated immediately after the color disappeared.

The product was characterized by ^{13}C-n.m.r. spectroscopy, including the off-resonance technique. Fig. 1 is the proton-noise-decoupled spectrum of product D, and the chemical shifts are listed in Table III. Benzyl and acetyl resonances were absent. The six signals of relatively high intensity were found superposable on those of linear, high-molecular-weight (1→6)-α-D-glucopyranan. Assignments are shown by unprimed numbers in Fig. 1.

The signals designated by primed numbers were attributed to the 3-deoxy-(1→6)-α-D-*ribo*-hexopyranosyl residues. Comparison between (1→6)-α-D-glucopyranosyl residues and the 3-deoxy analogs shows that replacement of the 3-OH group by hydrogen causes a large upfield shift (38.5 p.p.m.) for the C-3 resonance and intermediate upfield shifts of 4.9 and 5.5 p.p.m. for the adjacent C-2 and C-4, respectively. The C-1 resonance was also shifted upfield by 1.1 p.p.m. These values are in accord with the corresponding differences between α-D-glucopyranose[25] and 3-deoxy-α-D-*ribo*-hexopyranose[26]. The C-5 and C-6 signals were assumed to overlap those of the non-deoxygenated unit.

The 1″ and 6″ signals were similar in chemical shifts to the C-1 and C-6 resonances, respectively, of the terminal residues of low-molecular-weight dextran. The ratio of non-terminal to the terminal C-6 resonances in an expanded spectrum gave an approximate value for $\overline{\text{d.p.}}_n$. The area ratio of the 1′ and 1 signals also provided a rough estimate of the deoxygenation/deacetylation ratio.

The estimated percent of deoxygenation (Table I) and $\overline{\text{d.p.}}_n$ (Table II) depended upon the reaction conditions. The sodium–HMPA reduction in the absence of *tert*-butyl alcohol gave a (1→6)-α-D-glucopyranan having $\overline{\text{d.p.}}_n$ 27, in which ~5% of 3-deoxygenated residues was present. A polymer having a higher proportion of deoxygenated residues (23%) was obtained by the sodium–HMPA–*tert*-BuOH reduction, whereas the addition of *tert*-butyl alcohol lowered the $\overline{\text{d.p.}}_n$ to 5.6.

The molecular weights (determined by vapor-pressure osmometry) and optical rotations of the products were found to be smaller than those expected. The products probably still contained some salt, as thorough dialysis could not be performed because of leakage of the product through a cellulose membrane (cut off ~3500). Nevertheless, we consider that the evidence presented in this paper supports the formation of regioselectively deoxygenated, stereoregular polysaccharides of low molecular weight.

EXPERIMENTAL

General methods. — ^{13}C-N.m.r. spectra were recorded with a JASCO JNM-FX-100 Fourier-transform spectrometer for solutions in deuterium oxide. Tetramethylsilane was used as the external standard. Optical rotations were determined at 25° with a JASCO-DIP-181 digital polarimeter equipped with a jacketed, 1-dm cell. Solution viscosities were measured in Ubbelohde viscometers at 25°.

Materials. — The polymerization of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (**1**) and 1,6-anhydro-3-*O*-acetyl-2,4-di-*O*-benzyl-β-D-glucopyranose (**4**) was conducted according to the published procedures[1,21], except that an improved polymerization vessel was used to dry the liquid monomer **4** thoroughly[4,6]. Polymer **2** was obtained in 96.5% yield; $[\alpha]_D^{25}$ +113.8° (*c* 1, chloroform); polymer **5**: in 54.3% yield; $[\alpha]_D^{25}$ +141.4 (*c* 1, chloroform). HMPA was refluxed over calcium oxide for 3 h, stirred with sodium at room temperature until a dark-blue color persisted, and then distilled under diminished pressure (61–62°/0.39 mmHg). *tert*-Butyl alcohol was dried by distillation from calcium hydride. THF was distilled and stored over sodium.

Debenzylation of **2** *(experiment B).* — A mixture of small pieces of sodium (1.5 g) and freshly distilled HMPA (30 mL) was stirred for 60 min at room temperature under nitrogen. The blue mixture, in which some of the sodium had dissolved, was cooled to 10° with external cooling in an acetone–Dry Ice bath. A solution of **2** (0.51 g) in THF (15 mL) was added dropwise during 10 min at such a rate that the blue solution was never decolorized. The mixture was stirred for 50 min at room temperature. Unreacted sodium (1.07 g) was removed by decantation, and the solution was poured into 100 mL of ice–water and washed with five 25-mL portions of chloroform. The aqueous phase was dialyzed, concentrated, and freeze-dried to yield 0.12 g (62%) of (1→6)-α-D-glucopyranan.

Reduction of **5** *(experiment D).* — A partial solution of sodium (3.97 g) in HMPA (100 mL) was prepared with stirring for 60 min at room temperature, and was cooled to 10°. *tert*-Butyl alcohol (10 mL) was added and the mixture was stirred for 5 min. The polymer **5** (0.50 g), which had been previously dissolved in 5 mL of THF and then diluted dropwise with 5 mL of *tert*-butyl alcohol, was added slowly to the sodium–HMPA–*tert*-butyl alcohol mixture through a dropping funnel at such a rate that the blue color of the HMPA solution never completely disappeared. When 8.8 mL of the polymer solution had been added over 27 min, the blue color disappeared and did not reappear. The reaction was terminated immediately; unchanged polymer was recovered (78 mg), unreacted sodium (2.57 g) was removed by decantation, and the solution was treated with 100 mL of ice-water. The aqueous solution was washed with five 25-mL portions of chloroform, and then dialyzed, concentrated, and freeze-dried; yield, 0.11 g (62%).

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