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Chemical Synthesis of Amino-Group-Containing (1→6)-α-D-Glucan Derivatives by Ring-Opening Polymerization of 1,6-Anhydro Azido Sugars

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Received September 2, 1982

ABSTRACT: In an approach toward the regioselective synthesis of aminated polysaccharides, the cationic polymerization of 1,6-anhydro-β-D-glucopyranose derivatives containing azido groups was studied, followed by transformation of the azido groups to amino groups to yield aminated 1,6-α-linked glucopyranans. The 1,6-anhydro sugars were 1,6-anhydro-2-azido-3,4-di-*O*-benzyl-2-deoxy- (2-ABG), -3-azido-2,4-di-*O*-benzyl-3-deoxy- (3-ABG), and -4-azido-2,3-di-*O*-benzyl-4-deoxy-β-D-glucopyranose (4-ABG). The polymerization of 3-ABG with phosphorus pentafluoride–benzoyl fluoride complex as catalyst at low temperatures gave a new highly stereoregular (1→6)-α-D-glucan derivative with number-average molecular weights of 15.1×10^3 to 55.0×10^3, while the polymerization of 2-ABG and 4-ABG provided only oligomers. Reduction of stereoregular poly(3-ABG) with lithium aluminum hydride gave amino-group-containing O-benzylated (1→6)-α-D-glucan, which was then debenzylated with sodium in liquid ammonia to give a stereoregular 3-amino-3-deoxy-(1→6)-α-D-glucopyran. The difference in the polymerizability of the three azido monomers is also discussed. The polysaccharide structures were analyzed by means of 400-MHz ^{1}H and 100-MHz ^{13}C NMR spectrometers.

Natural amino sugars have been found as constituents of lipopolysaccharides, mucopolysaccharides, and antibiotics, which are distributed in microorganisms, plants, and invertebrates.[1] 2-Amino-2-deoxy-D-glucose (D-glucosamine) and its derivatives occur abundantly in nature as structural units of chitin, which is composed of 2-*N*-acetyl-2-deoxy-(1→4)-β-D-glucopyranan and is a principal component in the exoskeletons of crustaceans and insects.[2] 3-Amino-3-deoxy-D-glucose is isolated from the antibiotic kanamycin[3,4] and 4-amino-4-deoxy-D-glucose is found as a constituent of antibiotics P-2563(P), P-2563(A),[5] and apramycin.[6] It is also reported that amino-group-containing anthracycline antibiotics are effective as antitumor agents.[7-9]

The synthesis of aminated polysaccharides has been investigated recently. For instance, the selective oxidation of the C-2 position of amylose and cellulose and its subsequent oximation and reduction of lithium aluminum hydride give 2-amino-2-deoxyamylose (degree of substitution (DS) 0.69)[10] and 2-amino-2-deoxycellulose (DS 0.37),[11] respectively, but the degree of substitution is low. The synthesis of an amino-group-containing polymer (DS 0.5; number-average molecular weight 1100) can be carried out by ring-opening polymerization of 6,8-dioxabicyclo[3.2.1]oct-3-ene and by subsequent epoxidation and ammonolysis of the polymer obtained to examine the anticoagulant activity of its sulfated derivative.[12]

Dextran-type polysaccharides with hydroxyl groups have been prepared by ring-opening polymerization of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-hexopyranoses, followed by debenzylation of the resulting polymers.[13-16] Other synthetic polysaccharides having free hydroxyl groups such as (1→2)-D-glucan,[17] (1→2)-D-mannan,[18] (5→6)-D-glucan,[22] (3→5)-D-xylan,[20] (1→4)-β-D-ribopyranan,[21] (1→4)-D-glucan,[22] and (1→5)-α-D-xylofuranan[23] have also been obtained. However, the ring-opening polymerization of a 1,6-anhydro-β-D-glucopyranose moiety with a protected amino group failed to give high molecular weight polymers.[24]

In this paper, we report the synthesis and cationic ring-opening polymerization of 1,6-anhydro-3-azido-2,4-di-*O*-benzyl-3-deoxy-β-D-glucopyranose (**1**) into 3-azido-2,4-di-*O*-benzyl-3-deoxy-(1→6)-α-D-glucopyranan with high molecular weight and report the first synthesis of stereoregular 3-amino-3-deoxy-(1→6)-α-D-glucopyranan by conversion of the protected polysaccharide. In addition, the ring-opening polymerizations of 1,6-anhydro-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranose (**2**) and 1,6-anhydro-4-azido-2,3-di-*O*-benzyl-4-deoxy-β-D-glucopyranose (**3**) are attempted to elucidate the effects of the azido groups on the ring-opening polymerizability of 1,6-anhydro sugars. The structural analysis of the polysaccharides is mainly carried out by 400-MHz ^{1}H and

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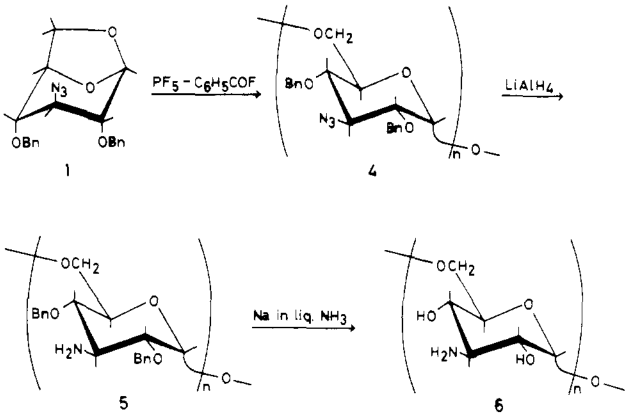
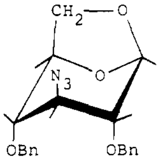
Scheme I



100-MHz ^{13}C NMR spectroscopies and optical rotation.

Results and Discussion

Polymerization of 1,6-Anhydro-3-azido-2,4-di-O-benzyl-3-deoxy-β-D-glucopyranose (3-ABG) (1). In the irst series of experiments, polymerizations of 3-ABG were attempted with Lewis acids phosphorus pentafluoride and boron trifluoride etherate as catalyst. The polymerization of 3-ABG at −60 °C by phosphorus pentafluoride, which s the best catalyst for the ring-opening polymerization of 1,6-anhydro sugars,[25] gave a polymer with high specific otation (+129.7°) and with high molecular weight ($\overline{M}_n$ 39.9 × 10^3) in fairly high yield, while the polymerization at 0 °C by boron trifluoride etherate resulted in low conver-ions. The results of polymerizations are summarized in Table I. Although it was first found that the azido-sub-tituted anhydro sugar can be polymerized by the cationic catalyst PF_5, the IR spectrum of the polymer indicated the existence of weak absorptions due to imino and carbonyl groups at 1610 and 1720 cm^{-1}, respectively. This might ndicate that PF_5 reacted partially with the azido groups o form the imino groups, a part of which was then changed nto carbonyl groups, possibly by hydrolysis.



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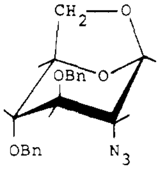

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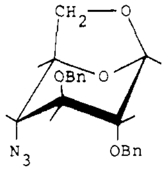

3

Thus, in order to avoid the use of a strong Lewis acid as catalyst, a benzoyloxycarbenium ion formed by the eaction[20,26] ($C_6H_5COF + PF_5 \rightleftarrows C_6H_5CO^+PF_6^-$) was used as catalyst, giving high yields of polymers (71.5–80.9%) at −40 to −60 °C (no. 306–308). The IR spectra of the esulting polymers showed no imino or carbonyl groups. The 400-MHz proton NMR spectrum of the polymer (no. 308) reveals that individual proton absorptions correspond to a single structure, indicating high stereoregularity and no irregular structure. The specific rotation of the polymers ranged from +127.0° to 131.7°, suggesting that they have an α-configuration. Accordingly, it was found that 3-azido-2,4-di-O-benzyl-3-deoxy-(1→6)-α-D-glucopyranan (4) was obtained by ring-opening polymerization with the PF_5–C_6H_5COF complex catalyst as shown in Scheme I. The elementary analysis on nitrogen also supported that he azido group is stable during polymerization.

The number-average molecular weights of the polymers prepared at −40 to −60 °C were high, in the range of 47.5 × 10^3 to 55.0 × 10^3 ($\overline{DP}_n$ 129–150). When the polymerization was performed at −78 °C for 20 h, both conversion and molecular weight were considerably lower, probably because of the slow rate of polymerization. The BF_3·OEt_2–C_6H_5COF complex was also an effective catalyst for the polymerization at 0 °C, affording a stereoregular polymer in high yield, but the molecular weight (18.6 × 10^3) of the resulting polymer was lower (no. 302).

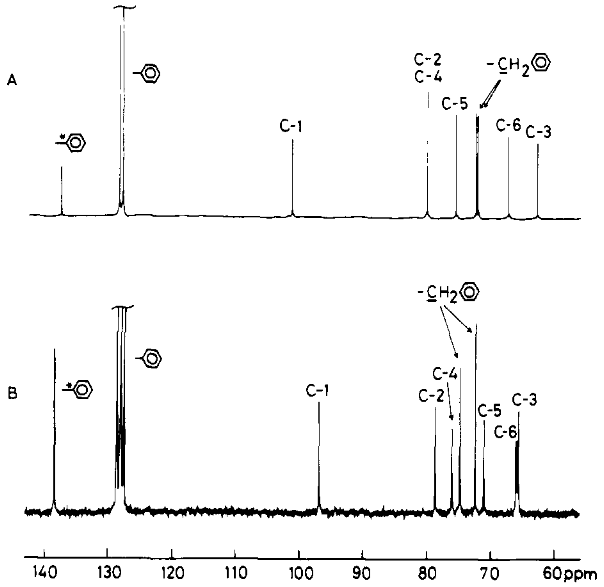

Figure 1. 100-MHz ^{13}C NMR spectra of (A) 3-ABG and (B) poly(3-ABG) (CD_2Cl_2 as solvent).

A comparison of the conversions and molecular weights of poly(3-ABG)'s with those of polymers from 1,6-anhydro-2,3,4-tri-O-benzyl-β-D-glucopyranose[25] and 1,6-anhydro-2,4-di-O-benzyl-3-O-crotyl-β-D-glucopyranose[27] in which the substituents at C-3 carbon are O-benzyl and O-crotyl groups, respectively, shows that the presence of a C-3 azido group results in a considerable decrease in polymerizability.

As can be seen in the 100-MHz ^{13}C NMR spectra of 3-ABG and 3-azido-2,4-di-O-benzyl-3-deoxy-(1→6)-α-D-glucopyranan, shown in Figure 1, the azido substitution causes an upfield shift of the C-3 carbon, indicating that the azido substituent has an electron-releasing effect on the pyranose ring rather than an electron-withdrawing effect as was the case with the O-benzyl group. This might explain partly the lower polymerizability of azido-substituted 1,6-anhydro sugars. Assignments of the ^1H and ^{13}C NMR absorptions of 3-ABG and 4 are given in Table II.

Polymerization of 1,6-Anhydro-2-azido-3,4-di-O-benzyl-2-deoxy-β-D-glucopyranose (2-ABG) (2). Polymerizations of 2-ABG were attempted with Lewis acids and their complexes as catalyst under various conditions; the results are summarized in Table I. Although the cationic polymerizations of 2-ABG by PF_5 or BF_3·OEt_2 catalyst at concentrations of 10–20 mol % with respect to the monomer did not give a polymer, oligomers with molecular weights of 1000–2000 ($\overline{DP}_n$ 3–6) could be obtained in low yields by using antimony pentafluoride, antimony pentachloride, or a large amount of PF_5 as catalyst (no. 203, 204, 206, and 208). Even PF_5–C_6H_5COF, which was successful with 3-ABG, only gave a very low yield of oligomer (no. 205).

It is obvious from the polymerization results of 2-ABG and 3-ABG that the azido substituent in the 1,6-anhydro sugars decreases the ring-opening polymerizability, but the result on 2-ABG suggests that there is another factor preventing the 1,6-anhydro sugar from polymerizing cat-

Table I
Polymerization of 1,6-Anhydro-3-azido-2,4-di-*O*-benzyl-3-deoxy-β-D-glucopyranose (3-ABG), 1,6-Anhydro-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranose (2-ABG), and 1,6-Anhydro-4-azido-2,3-di-*O*-benzyl-4-deoxy-β-D-glucopyranose (4-ABG)[a]

polymer no.	monomer	catalyst	[catalyst]/[monomer] mol %	monomer/solvent g/100 mL	temp, °C	time, h	conversion, %	$[\alpha]^{25}{}_{D}$,[b] deg	$\overline{M}_n$,[c] $\times 10^3$	$\overline{DP}_n$
301	3-ABG	$BF_3 \cdot OEt_2$	20	50	0	50	13.3			
302	3-ABG	$BF_3 \cdot OEt_2$-C_6H_5COF	20	50	0	50	72.6	+138.2	18.6	51
303	3-ABG	PF_5	5	50	−60	24	68.3	+129.7	39.9	109
304	3-ABG	PF_5-C_6H_5COF	5	40	0	20	15.5	+126.0	15.1	41
305	3-ABG	PF_5-C_6H_5COF	5	40	−20	20	42.7	+127.0	23.1	63
306	3-ABG	PF_5-C_6H_5COF	5	40	−40	20	71.5	+129.8	55.0	150
307	3-ABG[d]	PF_5-C_6H_5COF	5	40	−60	2	80.9	+131.7	48.2	131
308	3-ABG[d]	PF_5-C_6H_5COF	5	40	−60	20	72.6	+129.0	47.5	129
309	3-ABG	PF_5-C_6H_5COF	5	40	−78	20	39.2	+130.3	31.8	87
201	2-ABG	$BF_3 \cdot OEt_2$	20	30	0	96	trace			
202[e]	2-ABG	$BF_3 \cdot OEt_2$-C_6H_5COF	10	30	0	75	10.7			
203	2-ABG	SbF_5	9	30	−40	28	7.3		1.0	3
204	2-ABG	SbF_5	20	30	−40	28	10.7		1.3	4
205	2-ABG	PF_5-C_6H_5COF	5	30	−40	50	3.3			
206	2-ABG	PF_5	100	20	−60	80	28.7		2.1	6
207	2-ABG	$SbCl_5$	5	30	−40	47	3.9			
208	2-ABG	$SbCl_5$	10	30	−78	47	6.2			
401	4-ABG	PF_5-C_6H_5COF	10	35	0	41	27.4	+190.2	46.	13
402	4-ABG	$BF_3 \cdot OEt_2$-C_6H_5COF	30	35	0	21	42.9	+204.0	3.3	9
403	4-ABG	$BF_3 \cdot OEt_2$-C_6H_5COF	30	35	−10	65	57.4	+203.8	3.8	10
404	4-ABG	SbF_5	20	35	−40	19	18.4			
405	4-ABG	PF_5-C_6H_5COF	10	35	−40	22	18.9	+178.1	4.9	13
406	4-ABG	TaF_5-C_6H_5COF	25	35	−40	17	7.1		3.6	10
407	4-ABG	PF_5-C_6H_5COF	5	35	−60	20	6.9		3.5	9

[a] Monomer, 0.15–0.50 g; solvent, CH_2Cl_2; benzoyl fluoride was used in the mol ratio of 2 to Lewis acid catalyst. [b] Cl, $CHCl_3$. [c] Determined by membrane osmometry for poly(3-ABG) and approximated by gel permeation chromatography for poly(2-ABG) and poly(4-ABG). [d] Monomer, 1 g. [e] $BF_3 \cdot OEt_2$-C_6H_5COF, mol ratio 1:1.

Table II
^1H and ^{13}C Chemical Shifts (ppm) of 3-ABG and Polymers

substance	H-1	H-2	H-3	H-4	H-5	H-6a	H-6b	C-1	C-2	C-3	C-4	C-5	C-6
3-ABG[a]	5.38 (s)	3.20 (d)	3.63 (t)	3.20 (q)	4.50 (d)	3.62 (q)	3.59 (q)	101.49	80.23	62.85	80.23	75.73	67.43
poly(3-ABG)[a]	4.81 (d)	3.06 (q)	3.78 (t)	3.40 (t)	3.61 (d)	3.72 (q)	3.54 (d)	96.96	78.72	65.66	76.14	70.99	65.95
poly(4-ABG)[a]	4.87 (d)	3.40 (q)	3.85 (t)	3.69 (t)	3.59 (d)	3.87 (d)	3.57 (d)						
3-amino-2,4-di-*O*-benzyl-3-deoxy-(1→6)-α-D-glucopyranan[b]	4.91 (d)	3.06 (q)	3.32 (t)	3.46 (t)	3.68 (d)	3.83 (q)	3.57 (d)	96.62	79.89	53.79	78.86	70.81	66.16
HCl salt of 3-amino-3-deoxy-(1→6)-α-D-glucopyranan[c]	5.06 (d)	3.87 (q)	3.46 (t)	3.84 (t)	3.96 (d)	4.06 (q)	3.83 (d)	99.63	72.96	58.37	68.67	70.56	68.12

[a] Solvent $CDCl_3$ (^1H), CD_2Cl_2 (^{13}C). [b] Solvent $CDCl_3$. [c] Solvent D_2O.

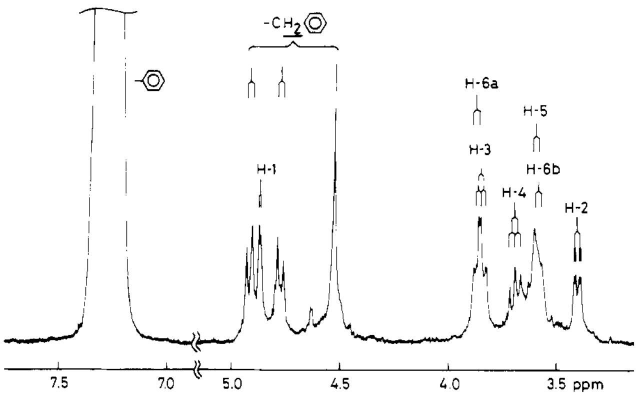

Figure 2. 400-MHz ^{1}H NMR spectrum of poly(4-ABG) ($CDCl_3$ as solvent).

ionically, that is, a complexation of Lewis acid PF_5 with the azido group at C-2. This assumption was confirmed by measuring ^{31}P NMR spectra of the polymerization system. Moreover, the extremely low polymerizability of 2-ABG might be due to an intramolecular interaction of the azido group with the electron-deficient C-1 carbon at the propagating chain end. In the case of 3-ABG, this interaction could not take place because of the configuration of azido group at the C-3 carbon.

Polymerization of 1,6-Anhydro-4-azido-2,3-di-*O*-benzyl-4-deoxy-β-D-glucopyranose (4-ABG) (3). 4-ABG was polymerized with Lewis acid–benzoyl fluoride complex catalysts at −40 to −60 °C, resulting in the formation of polymers with low molecular weights ($\bar{M}_n$ 3.5 × 10^3 to 4.9 × 10^3) in low yields (no. 405–407 in Table I). The molecular weights of poly(4-ABG)'s were, however, approximately 2 times as high as those of poly(2-ABG)'s.

The ^{1}H NMR spectrum of the polymer with specific rotation of +178.1° indicated high α-configuration and no irregular structure, as shown in Figure 2. Accordingly, it was found that the ring-opening polymerization of 4-ABG with the Lewis acid–benzoyl fluoride complex catalysts at low temperatures afforded a stereoregular 4-azido-2,3-di-*O*-benzyl-4-deoxy-(1→6)-α-D-glucopyranan with low molecular weight.

When the polymerization temperature was raised to −10 to 0 °C, polymers with higher specific rotations (+190.2°–+204.0°) were obtained in relatively high yields (no. 401–403). However, since the IR spectra of the polymers prepared at the higher temperatures showed the presence of carbonyl groups, it is expected that the increase in the specific rotation of the polymers by 12°–26° was due to the presence of some irregular units.

As in the case of 2-ABG, the reason for low polymerizability of 4-ABG could be due to an intramolecular interaction between the 4-azido group and the electron-deficient C-1 carbon at the propagating chain end, which might be weaker than that between the 2-azido group of 2-ABG and the C-1 carbon.

Reduction of 3-Azido-2,4-di-*O*-benzyl-3-deoxy-(1→6)-α-D-glucopyranan (4) with Lithium Aluminum Hydride. In the first experiment, when 4 was reduced with sodium in liquid ammonia to prepare a free polysaccharide having amino and hydroxyl groups in one step, the resulting polymer was found to have lost a considerable amount of nitrogen. Thus, a two-step reduction was attempted. The lithium aluminum hydride reduction of the azido group of 4 into the amino group was carried out by refluxing in tetrahydrofuran for 1 h.

The ^{1}H NMR spectrum of the resulting polymer indicates that the azido groups were completely reduced into the amino groups, with amino-proton absorption appearing as a broad singlet at 1.43 ppm with an intensity corresponding to two protons per monomeric unit. Therefore, the polymer obtained was 3-amino-2,4-di-*O*-benzyl-3-deoxy-(1→6)-α-D-glucopyranan (5). The number-average degree of polymerization of 5 was 127 vs. 136 for 4, indicating that essentially no chain scission had occurred during the reaction.

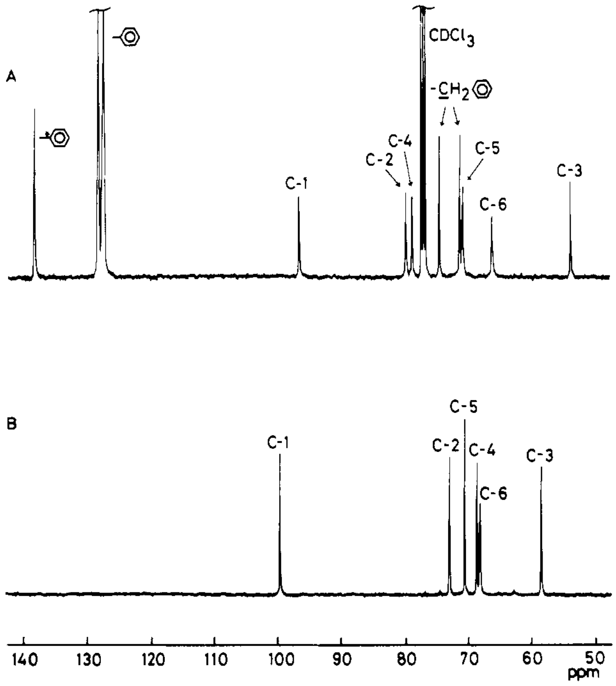

Figure 3. 100-MHz ^{13}C NMR spectra of (A) 3-amino-2,4-di-*O*-benzyl-3-deoxy-(1→6)-α-D-glucopyranan ($CDCl_3$ as solvent) and (B) HCl salt of 3-amino-3-deoxy-(1→6)-α-D-glucopyranan (D_2O as solvent).

The 100-MHz ^{13}C NMR spectrum of 5 also shows that the structure of the polymer is highly stereoregular (Figure 3A). The chemical shifts of individual protons and carbons of polymer 5 are shown in Table II. The assignment of ^{13}C absorptions was performed by means of the selective hetero-decoupling method using the previously determined assignment of ^{1}H absorptions, which was made by the homo-decoupling method.

3-Amino-2,4-di-*O*-benzyl-3-deoxy-(1→6)-α-D-glucopyranan was soluble in organic solvents such as chloroform, acetone, benzene, tetrahydrofuran, and 1,2-dimethoxyethane.

Debenzylation of 3-Amino-2,4-di-*O*-benzyl-3-deoxy-(1→6)-α-D-glucopyranan into 3-Amino-3-deoxy-(1→6)-α-D-glucopyranan (6). Debenzylation of polymer 5 was carried out with sodium in liquid ammonia by using the same method as for 2,3,4-tri-*O*-benzyl-(1→6)-α-D-glucopyranan.[28] The resulting polymer was soluble in dilute HCl and 2.5 N NaOH, but insoluble in water and organic solvents. Since the HCl salt of the synthetic aminoglucan (7) which was prepared by freeze-drying from the HCl (10 mol % excess to the polymer) solution was soluble in water, the ^{13}C NMR spectrum of the aminoglucan hydrochloride was measured in D_2O solution, as shown in Figure 3B. The debenzylation was found to be complete, and individual carbon absorptions correspond to a single stereoregular structure.

The specific rotation of 7 was +150.8° in water, and its molecular rotation of +29 800° was comparable to that of the synthetic dextran (+31 900°)[25] and higher than those of monosaccharides such as α-D-glucopyranose (+20 400°)[29] and 3-amino-3-deoxy-α-D-glucopyranose hydrochloride (+10 900°).[30]

Some chain scission occurred during the debenzylation of **5** as a polymer with a starting DP of 127 gave **7** with DP of 96 after reaction with sodium and liquid ammonia.

Since we recently found that 1,6-anhydro sugars which homopolymerize poorly can be incorporated into the backbone of copolymers by ring-opening copolymerization with 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose,[31] the copolymerization of 2-ABG with the tribenzylated monomer will be reported elsewhere.

Experimental Section

General. The 400-MHz ^{1}H and 100-MHz ^{13}C NMR spectra of monomers and polymers were recorded on JEOL FX-400 and GX-400 spectrometers in chloroform-*d* and methylene-d_2 chloride with tetramethylsilane as internal standard, except those of debenzylated polysaccharides, which were measured in deuterium oxide with sodium 4,4-dimethyl-4-silapentanesulfonate (DSS) as internal reference. Gel permeation chromatography was run on 1% solutions of polymers in tetrahydrofuran by means of a Toyo Soda high-speed liquid chromatograph (Model HLC 802UR). The optical rotation was measured in chloroform at 25 °C in a Perkin-Elmer Model 241 polarimeter with a 1-dm cell. Infrared spectra were obtained with a JASCO IRA-2 spectrometer. The number-average molecular weight of polymer was determined on the solution in toluene or water at 37 °C, by means of a Hewlett-Packard high-speed membrane osmometer, Model 502, and a Hewlett-Packard vapor pressure osmometer, Model 302B.

Synthesis of 3-ABG. A crystalline mixture of 1,6:2,3-dianhydro-β-D-allopyranose and 1,6:3,4-dianhydro-β-D-allopyranose was synthesized according to the procedure of Černý et al.[32,33] By comparison of the specific rotation of the mixture ($[\alpha]^{25}{}_\mathrm{D}$ −61.9° (*c* 0.69, water)) with those of the two pure dianhydro sugars ($[\alpha]_\mathrm{D}$ +55° and −134°),[33] the mole fractions of 1,6:2,3-dianhydro-β-D-allopyranose and 1,6:3,4-dianhydro-β-D-allopyranose were calculated as 0.38 and 0.62, respectively. This result was confirmed by ^{1}H and ^{13}C NMR analyses.

Benzylation of the mixture of dianhydro sugars was carried out with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide by using a modification of Hakomori's method.[34] Epoxide scission of the mixture of benzylated sugars with sodium azide gave a mixture of 1,6-anhydro-3-azido-2-*O*-benzyl-3-deoxy-β-D-glucopyranose and 1,6-anhydro-3-azido-4-*O*-benzyl-3-deoxy-β-D-glucopyranose, since oxirane rings that are attached to rigid six-membered ring systems tend to open so that the incoming groups are in axial positions in a chair form, that is, position 3 in this case.[35,36]

Benzylation of the mixture of azido sugars was carried out in the same manner as above. The syrupy product was chromatographed on silica gel, with hexane–ethyl acetate (5:1 v/v) as eluent, to afford crystalline 1,6-anhydro-3-azido-2,4-di-*O*-benzyl-3-deoxy-β-D-glucopyranose (3-ABG). 3-ABG was recrystallized twice from cyclohexane and then from thoroughly dried cyclohexane. The total yield of 3-ABG based on levoglucosan was 25%: mp 51.5–52.0 °C; $[\alpha]^{25}{}_\mathrm{D}$ −14.9° (*c* 1, CHCl$_3$).

Anal. Calcd for $C_{20}H_{21}O_4N_3$: C, 65.38; H, 5.76; N, 11.44. Found: C, 64.91; H, 5.74; N, 11.38.

Synthesis of 4-ABG. 1,6-Anhydro-4-azido-4-deoxy-β-D-glucopyranose was synthesized by the reaction of 1,6:3,4-dianhydro-2-*O*-tosyl-β-D-glucopyranose[32] with sodium azide followed by epoxidation and alkaline hydrolysis according to the procedure of Černý et al.[37] Benzylation of 1,6-anhydro-4-azido-4-deoxy-β-D-glucopyranose was carried out with benzyl bromide, barium oxide, and barium hydroxide in *N*,*N*-dimethylformamide to give 1,6-anhydro-4-azido-2,3-di-*O*-benzyl-4-deoxy-β-D-glucopyranose (4-ABG). Recrystallizations of 4-ABG were carried out twice from the mixture of ethyl ether and petroleum ether and finally from the mixture of thoroughly dried ethers. The yield of benzylation was 80%: mp 76.0–77.0 °C; $[\alpha]^{25}{}_\mathrm{D}$ −112.6° (*c* 1, CHCl$_3$).

Anal. Calcd for $C_{20}H_{21}O_4N_3$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.37; H, 5.73; N, 11.42.

Synthesis of 2-ABG. 1,6-Anhydro-2-azido-3,4-di-*O*-benzyl-2-deoxy-β-D-glucopyranose (2-ABG) was synthesized according to the procedure of Paulsen and Stenzel.[38] Crystallization of 2-ABG was performed from ethanol solution. Recrystallizations were carried out twice from cyclohexane and then from thoroughly dried cyclohexane: mp 68.5–69.5 °C (lit.[38] mp 68 °C); $[\alpha]^{25}{}_\mathrm{D}$ +40.7° (*c* 1, CHCl$_3$) (lit.[38] $[\alpha]^{20}{}_\mathrm{D}$ +37° (*c* 1, CHCl$_3$)).

Other Materials for Polymerization. Phosphorus pentafluoride was prepared by thermal decomposition of *p*-chlorobenzenediazonium hexafluorophosphate (Ozark-Mahoning Co.), which had been recrystallized from water. Commercial boron trifluoride etherate, antimony pentachloride, antimony pentafluoride, and benzoyl fluoride were used after purification by trap-to-trap distillation in vacuo. Tantalum pentafluoride (Ozark-Mahoning Co.) was used without purification. Methylene chloride was purified as described previously.[21,25]

Polymerization. The polymerizations were carried out under high vacuum at low temperature in anhydrous methylene chloride with cationic catalysts as described previously.[21,25,31] In the polymerization with the Lewis acid–benzoyl fluoride complex as catalyst, the reaction of the Lewis acid and benzoyl fluoride was carried out in methylene chloride at the polymerization temperature for 30 min, and then the monomer solution in methylene chloride was added. The polymerization was terminated by the addition of a small amount of methanol. The polymer was precipitated 3 times by adding petroleum benzin, petroleum ether, or methanol into a chloroform solution and it was finally dried from benzene.

Reduction of the Polymer with Lithium Aluminum Hydride. Two hundred milligrams of the stereoregular poly(3-ABG) was dissolved in 30 mL of thoroughly dried tetrahydrofuran, and 60 mg of lithium aluminum hydride was added. The mixture was magnetically stirred and immediately heated to reflux temperature. After refluxing for 1 h, 100 mL of saturated aqueous potassium sodium tartrate was added and then the mixture was extracted with three 100-mL portions of benzene. The combined extracts were washed with saturated aqueous Rochelle salt and water. The benzene solution was dried over anhydrous sodium sulfate and concentrated. The reduced polymer was isolated by freeze-drying from benzene (150 mg, 81%): $[\alpha]^{25}{}_\mathrm{D}$ +132.5° (*c* 1, CHCl$_3$); NH$_2$ (by ninhydrin) positive.

Anal. Calcd for $C_{20}H_{23}O_4N$: C, 70.36; H, 6.79; N, 4.10. Found: C, 68.41; H, 6.66; N, 4.10.

Debenzylation of the Polymer. 3-Amino-2,4-di-*O*-benzyl-3-deoxy-(1→6)-α-D-glucopyranan (200 mg) was dissolved in 10 mL of 1,2-dimethoxyethane and the solution was added dropwise to 30 mL of liquid ammonia containing 160 mg of sodium at −78 °C under nitrogen. After the solution was stirred for 1.5 h at −78 °C, the blue color disappeared by the addition of anhydrous ammonium chloride, and then a small amount of water was added. After evaporation of ammonia, the suspension of the polymer in water was washed 5 times with methylene chloride and the water-insoluble part was filtered out, washed with water, dried, and weighed (77.3 mg, 81.9%).

Anal. Calcd for $C_6H_{11}O_4N + 0.5H_2O$: C, 42.35; H, 7.11; N, 8.23. Found: C, 42.50; H, 7.18; N, 7.83.

Water-insoluble polymer was dissolved in 0.1 N HCl and freeze-dried. The polymer obtained was soluble in water: $[\alpha]^{25}{}_\mathrm{D}$ +150.8° (*c* 1, water); NH$_2$ (by ninhydrin) positive.

Registry No. **1**, 85011-00-3; **1** (homopolymer), 85553-31-7; **2**, 55682-48-9; **3**, 85553-30-6; **3** (homopolymer), 85553-35-1; **5** (homopolymer), 85553-33-9; **6** HCl (homopolymer), 85553-37-3; 1,6:2,3-dianhydro-β-D-allopyranose, 26423-96-1; 1,6:3,4-dianhydro-β-D-allopyranose, 26423-98-3; 1,6-anhydro-3-azido-2-*O*-benzyl-3-deoxy-β-D-glucopyranose, 85010-99-7; 1,6-anhydro-3-azido-4-*O*-benzyl-3-deoxy-β-D-glucopyranose, 54202-52-7; 1,6-anhydro-4-azido-4-deoxy-β-D-glucopyranose, 61784-10-9; $BF_3{\cdot}OEt_2$, 109-63-7; C_6H_5COF, 455-32-3; PF_5, 7647-19-0; SbF_5, 7783-70-2; $SbCl_5$, 7647-18-9; TF_5, 7783-71-3.

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Aminolysis and Ammonolysis Polymerizations of Spiro(acylpentaoxy)phosphoranes to Polyphosphate Derivatives

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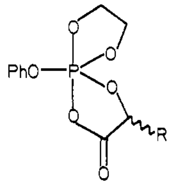
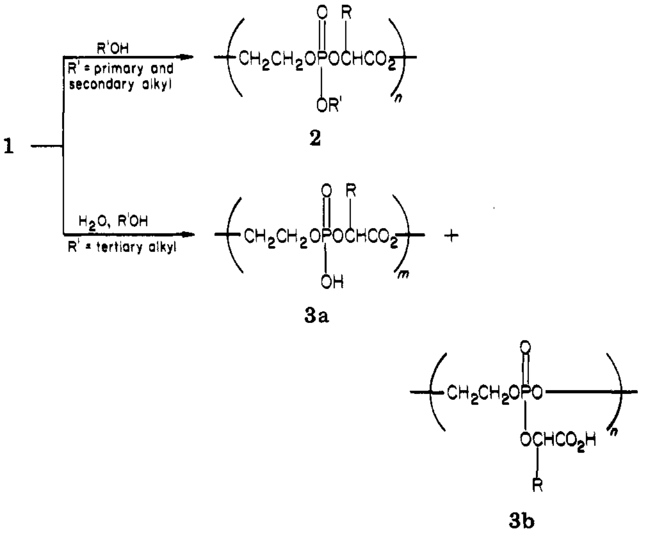
Received September 29, 1982

ABSTRACT: Polymerization of spiro(acylpentaoxy)phosphoranes (1) has been induced at room temperature by reaction of 1 with *N*-nucleophiles of amines and ammonia to give polyphosphate derivatives (4 and 9) having amine and ammonia components, respectively ("aminolysis and ammonolysis polymerizations"). Amines employed were primary and secondary ones. Product polymers contained an amide–phosphate type unit (4a or 9a) as the major component. A possible mechanism is proposed in which amine attacks the phosphorus atom of 1 to produce a spiro(acyloxyamino)phosphorane (12) as a predominant intermediate. Phenol is eliminated during the reaction. Then 12 rearranges to a cyclic phosphate (11), leading to unit 4a. Acute toxicities of the product phosphate derivatives were examined to investigate the derivatives' suitability as carrier polymers of drug amine components.

Spiro(acyloxy)phosphoranes are a new group of pentacovalent phosphorus species originally prepared and isolated by us via the reactions of cyclic phosphorus(III) compounds with α-keto acids[1,2] or glyoxylic acid[3] and with acrylic acid or β-propiolactone.[2,4] These phosphoranes are quite reactive monomers and produce various types of phosphorus-containing polymers.[5] Among them, spiro(acylpentaoxy)phosphoranes (1) have been studied most extensively.[5–7] Hitherto, we have found that 1 is a reactive amphiphile; i.e., 1 reacts with various nucleophiles and electrophiles.[8] 1 has been reacted with *O*-nucleophiles of primary and secondary alcohols to give poly(phosphoric acid triesters) 2 ("alcoholysis polymerization")[7] and also with *O*-nucleophiles of water ("hydrolysis polymerization")[8] and tertiary alcohols[7] to produce poly(phosphoric acids) consisting of diester (3a) and triester (3b) units. The



1a, R = Me
b, R = Ph



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