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Ring-Opening Polymerization of Modified 1,4-Anhydrodeoxyribose Derivatives and Synthesis of 3-Deoxy-(1→5)-α-D-ribofuranan

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ABSTRACT: Selective ring-opening polymerization of a 1,4-anhydro-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α-D-ribopyranose (A3DSR) was carried out by a number of Lewis acid catalysts to give stereoregular 3-deoxyribofuranans. It was found that the polymerization by phosphorus pentafluoride catalyst at −78 °C gave a poly(A3DSR) with $[\alpha]_D = +85°$ consisting of 1,5-α-linked furanosidic units in the polymer backbone, while the polymerization at 0 °C gave a poly(A3DSR) with $[\alpha]_D = -46°$ which was composed of 1,5-β-linked furanosidic units. 1,4-Anhydro-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-D-ribopyranose (A2DSR) was also polymerized by Lewis acid catalysts to give stereoirregular polymers consisting of mixed structures of α- and β-units. The desilylation of the poly(A3DSR) was carried out by a fluoride ion in THF to give a 3-deoxy-(1→5)-α-D-ribofuranan. The structure analysis of polymers was performed by ^{13}C NMR spectroscopy, specific rotation, and hydrolysis studies. The effects of catalyst, polymerization temperature, and time on the polymer stereoregularity were examined, and the mechanism of the stereoregular polymerization was discussed.

Introduction

Although the synthesis of polysaccharides is one of the important research projects to elucidate the biological mechanism of naturally occurring polysaccharides, only a few methods such as a condensation polymerization, an orthoester method, a Koenigs-Knorr glycosylation, and a ring-opening polymerization are available.[1] Among them, the ring-opening polymerization of anhydro sugar derivatives is one of the most successful methods to obtain stereoregular polysaccharides with high molecular weights.[2] Some of the polysaccharides were converted to sulfated polysaccharides with a blood anticoagulant activity[3] and a potent anti-AIDS virus activity.[4-6] Recently, curdlan sulfates which were prepared by sulfation of naturally occurring curdlan inhibited completely the infection of AIDS virus to MT-4 cells in the concentration of 3.3 μg/mL in vitro.[7,8]

Deoxy sugars not only are biologically important but also are of chemical interest; in particular, 2-deoxy-D-ribose is a constituent of DNA.[9] Several investigations on the ring-opening polymerization of benzylated deoxy[10-12] and dideoxy[13,14] 1,6-anhydroglucose derivatives have been reported to give stereoregular polysaccharides. So far, the ring-opening polymerization of 1,4-anhydrodeoxypentose derivatives has not been reported. Recently, we reported the synthesis of such polymerizable anhydrodeoxyribose derivatives as 1,4-anhydro-2(or 3)-*O*-(*tert*-butyldimethylsilyl)-3(or 2)-deoxy-α-D-ribopyranoses (1,4-anhydro-2(or 3)-*O*-(*tert*-butyldimethylsilyl)-3(or 2)-deoxy-α-D-*erythro*-pentofuranoses) from 1,4-anhydro-α-D-ribopyranose via a reduction of the imidazolyl precursors.[15]

In this paper, the ring-opening polymerization of the 1,4-anhydro-3(or 2)-deoxyribose monomers was investigated for their steric controlling factors and electronic effects of substituents on the ring-opening mode. In the polymerizability of 1,4-anhydro sugar derivatives, it is of great interest to investigate the influence of the substitution at the C2 carbon which is situated near the propagating center.

Experimental Section

1,4-Anhydro-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α-D-ribopyranose (A3DSR) and 1,4-Anhydro-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-D-ribopyranose (A2DSR).[15] 1,4-Anhydro-α-D-ribopyranose was treated with *tert*-butyldimethylsilyl chloride to afford a 1:1 mixture of 2-*O*- and 3-*O*-silylated anhydroriboses. The mixture was treated with *N,N'*-thiocarbonyldiimidazole to give the corresponding imidazolyl(thiocarbonyl) derivatives, which were separated by silica gel column chromatography. After reduction of the imidazolyl derivatives with tributyltin hydride, 2-*O*-silylated 1,4-anhydro-3-deoxy-α-D-ribopyranose (A3DSR) and 3-*O*-silylated 1,4-anhydro-2-deoxy-

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Scheme 1

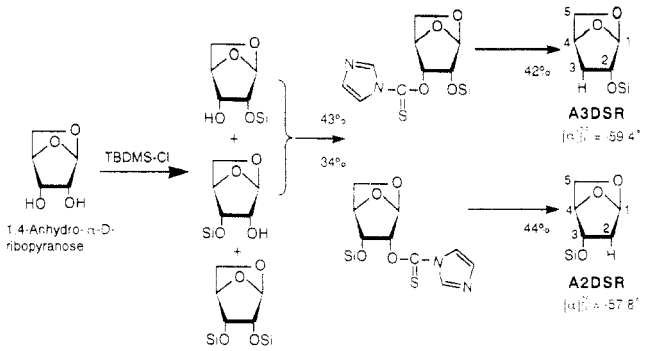


Table 1. Ring-Opening Polymerization of A3DSR

no.[a]	catalyst kind	catalyst amt, mol %	temp, °C	time, h	yield, %	$10^{-4}\bar{M}_n$[b]	$[\alpha]^{25}_D$,[c] deg	α content,[d] %
1	BF_3·OEt_2	3	−40	1	82	3.8	+98	95
2		3	−60	1	66	2.8	+96	94
3		20	−78	2	55	3.4	+95	96
4	$SnCl_4$	5	−40	1	73	5.8	+108	98
5		5	−60	1	69	7.2	+106	97
6	$SbCl_5$	3	−40	1	48	2.3	+51	71
7		3	−60	1	42	2.4	+60	72
8		3	−78	2	67	2.3	+85	87
9	$TaCl_5$	5	−40	2	63	2.2	+95	91

[a] Monomer, 0.25–0.28 g; solvent, CH_2Cl_2, 0.5 mL. [b] Determined by GPC (polystyrene standard). [c] Measured in $CHCl_3$ (c 1%). [d] Calculated from the ^{13}C NMR spectrum.

Table 2. Ring-Opening Polymerization of A3DSR by PF_5 Catalyst

no.[a]	amt of PF_5, mol %	temp, °C	time, h	yield, %	$10^{-4}\bar{M}_n$[b]	$[\alpha]^{25}_D$,[c] deg	α content,[d] %
10	2	0	0.5	45	0.8	−46	13
11	2	−20	0.5	52	0.6	−42	12
12	2	−30	0.5	51	0.7	−30	16
13	2	−40	0.5	80	1.3	+32	56
14	2	−40	1.0	82	2.8	+44	75
15	2	−60	0.5	61	2.4	+61	81

[a] Monomer, 0.25–0.28 g, solvent, CH_2Cl_2, 0.5 mL. [b] Determined by GPC (polystyrene standard). [c] Measured in $CHCl_3$ (c 1%). [d] Calculated from the ^{13}C NMR spectrum.

Table 3. Ring-Opening Polymerization of A2DSR

no.[a]	catalyst kind	catalyst amt, mol %	temp, °C	time, h	yield, %	$10^{-4}\bar{M}_n$[b]	$[\alpha]^{25}_D$,[c] deg	α content,[d] %
1	BF_3·OEt_2	3	−40	1	63	2.4	+113	78
2		3	−60	1	64	2.3	+102	74
3		20	−78	2	18	1.3	+93	82
4	$SnCl_4$	5	−60	2	61	3.3	+115	84
5	$SbCl_5$	3	−60	1	22	2.1	+78	73
6	$TaCl_5$	5	−40	2	53	1.1	+77	72
7		3	−60	3	26	2.6	+63	69
8	PF_5	3	0	0.5	57	1.1	+58	57
9		2	−40	0.5	48	1.8	+85	73
10		3	−60	0.5	52	0.8	+69	64

[a] Monomer, 0.25–0.28 g; solvent, CH_2Cl_2, 0.5 mL. [b] Determined by GPC (polystyrene standard). [c] Measured in $CHCl_3$ (c 1%). [d] Calculated from the ^{13}C NMR spectrum.

α-D-ribopyranose (A2DSR) were obtained in 42 and 38% overall yields, respectively, from 1,4-anhydroribose.

Polymerization. Deoxy monomers, A3DSR and A2DSR, were polymerized with Lewis acid catalysts under high vacuum at low temperatures according to an earlier paper.[16] After polymerization was terminated by addition of methanol, the reaction mixture was dissolved in chloroform. The chloroform layer was neutralized with sodium bicarbonate, washed with water several times, dried over anhydrous sodium sulfate, and concentrated. Purification was carried out by dissolution–reprecipitation three times by using a chloroform–methanol system, and the polymer was freeze-dried from benzene.

Deprotection of Poly(A3DSR). Desilylation of poly(A3DSR) was carried out with the fluoride ion in THF under reflux. To a THF solution (5 mL) of poly(A3DSR) (0.62 g) was added 1 M tetra-*n*-butylammonium fluoride in THF solution (8 mL), and then the mixture was stirred under reflux for 1 h. The reaction was terminated by addition of water (30 mL), and the resulting mixture was dialyzed with deionized water. Finally, the free 3-deoxyribofuranan was freeze-dried from water to give a white mass.

Hydrolysis. The hydrolysis of polymers was carried out according to the procedures described by Kops and Schuerch.[17] Using a 2-mL volumetric flask, the polymer (20.0 mg) was dissolved in 1.9 mL of THF and then 0.1 mL of 12 N hydrochloric acid was added. The solution (1 mL) was quickly transferred to a 1-mL polarimeter cell, and the temperature of the polarimeter cell was maintained at 55 °C. The optical rotation was recorded on a Perkin-Elmer 241 polarimeter until a constant value was attained.

Measurements. ^{13}C NMR (67.8 MHz) and ^1H NMR (270 MHz) spectra were recorded on solutions in $CDCl_3$ or D_2O by means of a JEOL GX-270 spectrometer. TMS or DSS was used as an internal reference. Specific rotations were measured in chloroform, THF, or water at 25 or 55 °C by a Perkin-Elmer 241 polarimeter. Molecular weights of THF-soluble and water-soluble polymers were estimated by GPC with standard polystyrene and standard pullulan as references, respectively.

Results and Discussion

Ring-Opening Polymerization of 1,4-Anhydro-2-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-α-D-ribopyranose (A3DSR) and 1,4-Anhydro-3-*O*-(*tert*-butyldimethylsilyl)-2-deoxy-α-D-ribopyranose (A2DSR). Cationic ring-opening polymerization of a 3-deoxy monomer, A3DSR, was carried out in methylene chloride at different temperatures between −78 and 0 °C by such Lewis acid catalysts as boron trifluoride etherate, tin tetrachloride, antimony pentachloride, and tantalum(V) chloride. Results are summarized in Table 1. The A3DSR monomer had a high polymerizability. When A3DSR was polymerized with BF_3·OEt_2 as catalyst at low temperatures from −40 to −78 °C, polymers with positive specific rotations of +95 to +98° were obtained in high yields. Tin tetrachloride catalyst also gave polymers with the highest positive specific rotation of +108°. The poly(A3DSR)s with high positive specific rotations of more than +85° were almost stereoregular 3-deoxy-(1→5)-α-D-ribofuranans, which were proved by measuring the NMR spectrum. Antimony pentachloride as catalyst provided polymers with considerably lower specific ratations of +51 to +85° in relatively low yields. Tantalum(V) chloride exhibited catalytic behavior similar to that of BF_3·OEt_2. The number-average molecular weights of the polymers (Table 1) were in the range 2.2×10^4 to 7.2×10^4, and a higher molecular weight was attained with 5 mol % $SnCl_4$ catalyst at −60 °C (no. 5).

The cationic behaviors of phosphorus pentafluoride in the polymerization of A3DSR were different from those of other Lewis acid catalysts, as summarized in Table 2. It was found that the specific rotation decreased from positive to negative with increasing polymerization temperature. A polymer obtained at −78 °C had a positive specific rotation of +85°. On the other hand, the polymerization at temperatures above −30 °C afforded polymers with negative specific rotations (−30, −42, and −46°), suggesting that the polymers were composed mainly of 1,5-β-linked 3-deoxyribofuranose units as described in the hydrolysis section. The molecular weights of the polymers

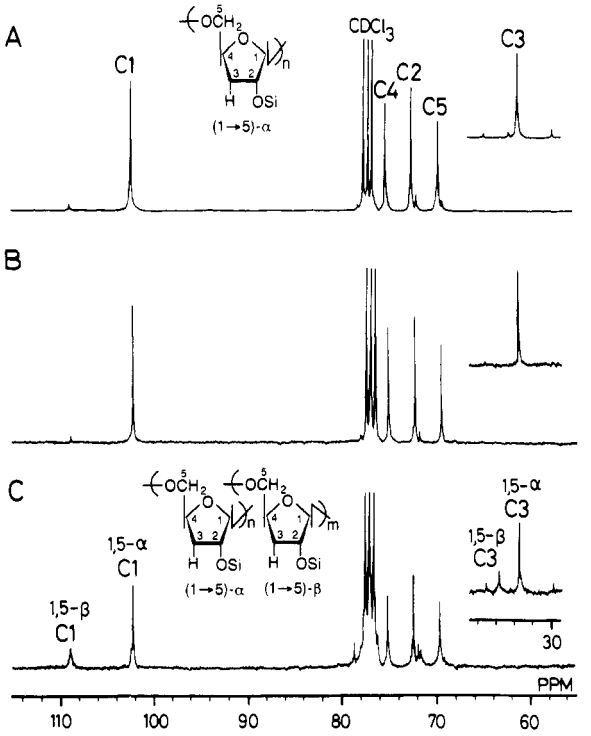


Figure 1. 67.8-MHz ^{13}C NMR spectra of poly(A3DSR)s prepared by (A) BF_3·OEt_2 at −78 °C ($[\alpha]^{25}_D$ = +95°), (B) $SnCl_4$ at −40 °C ($[\alpha]^{25}_D$ = +108°), and (C) $SbCl_5$ at −40 °C ($[\alpha]^{25}_D$ = +51°) ($CDCl_3$ as solvent).

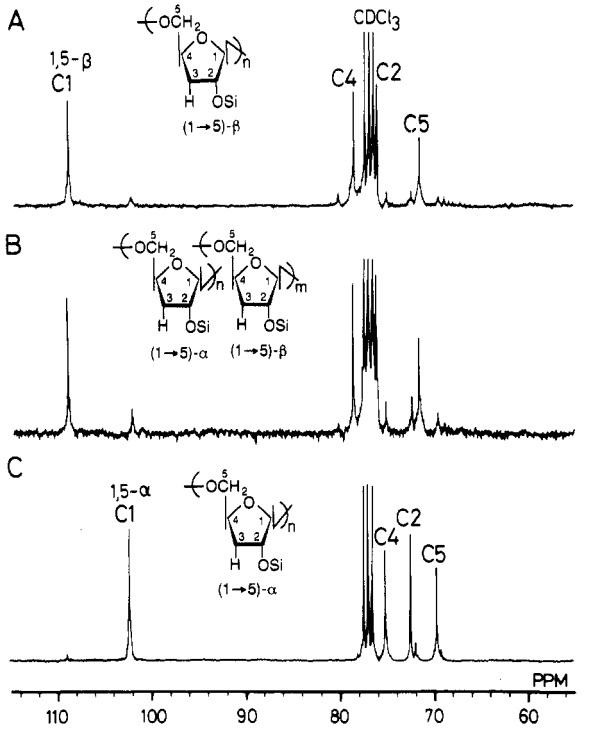


Figure 2. 67.8-MHz ^{13}C NMR spectra of poly(A3DSR)s prepared by PF_5 at (A) −20 °C ($[\alpha]^{25}_D$ = −42°), (B) −30 °C ($[\alpha]^{25}_D$ = −30°), and (C) −78 °C ($[\alpha]^{25}_D$ = +85°) ($CDCl_3$ as solvent).

in the range 0.6×10^4 to 2.8×10^4 were lower than those of polymers obtained by BF_3·OEt_2 and $SnCl_4$.

Table 3 shows the results of the ring-opening polymerization of the 2-deoxy monomer, A2DSR, by Lewis acid catalysts. The polymerization of A2DSR showed somewhat different results from that of A3DSR. The polymers were obtained in moderate yields (22–63%). Polymer structures represented by the specific rotation and the number-average molecular weight were considerably varied by polymerization temperature, time, and catalyst in the range +58 to +115° and 0.8×10^4 to 3.3×10^4, respectively. Although higher specific rotations give higher α-stereoregularity of the polymer backbone (nos. 1–4), contrary to the 3-deoxy homolog, the A2DSR monomer gave no stereoregular polymers, as described in the next section.

Structure of the Polymers. The structures of the poly(A3DSR)s with high positive specific rotations of +95° (Table 1, no. 3) and +108° (no. 4), and those with a low positive specific rotation of +51° (no. 6), were examined by means of ^{13}C NMR spectroscopy (Figure 1). The C1 carbon absorption appeared as two peaks around 102 and 109 ppm, indicating that the polymers were composed of α- and β-configurations. When the polymerization was carried out with BF_3·OEt_2 and $SnCl_4$ as catalyst, the obtained polymer had almost 1,5-α-linked stereoregularity (Figure 1A,B). A peak at 102 ppm was assigned to the C1 carbon of the 3-deoxy-(1→5)-α-ribofuranosidic unit. The polymer obtained by $SbCl_5$ as catalyst (Figure 1C) showed relatively low stereoregularity, consisting of 71% 3-deoxy-(1→5)-α-furanosidic unit. The C3 deoxy carbon absorption appeared around 33.5 ppm. All carbon absorptions were assigned by means of 2D NMR spectroscopy.

As revealed by the ^{13}C NMR spectra shown in Figure 2, the poly(A3DSR)s polymerized by PF_5 catalyst were two different stereoregular 3-deoxy-(1→5)-ribofuranans. The C1 carbon absorption of the polymers with negative specific rotations (Figure 2A,B) appeared as two peaks around 102 and 109 ppm, the intensities of which, 12 and

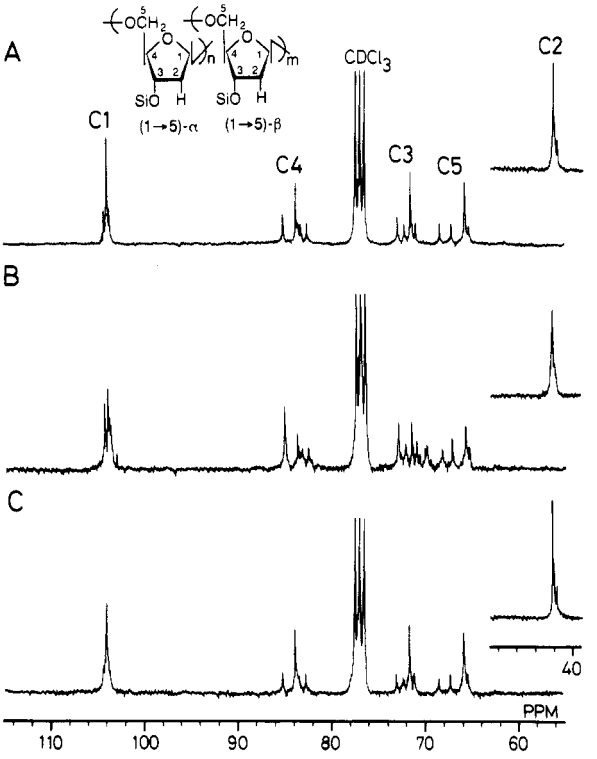


Figure 3. 67.8-MHz ^{13}C NMR spectra of poly(A2DSR)s prepared by (A) BF_3·OEt_2 at −78 °C ($[\alpha]^{25}_D$ = +93°), (B) PF_5 at 0 °C ($[\alpha]^{25}_D$ = +58°), and (C) $SnCl_4$ at −60° C ($[\alpha]^{25}_D$ = +115°) ($CDCl_3$ as solvent).

16 mol % of α-monomeric units, were opposite those of the polymers obtained at −78 °C (Figure 2C). Taking into account the large negative specific rotation, the strong absorption at 109 ppm must be originated from a β-configuration, i.e., a 3-deoxy-(1→5)-β-ribofuranosidic or 3-deoxy-(1→4)-β-ribopyranosidic unit. The polymer had the former structure, which was established in the next hydrolysis section. As shown in Figure 2C, when the polymerization was carried out at a low temperature (−78

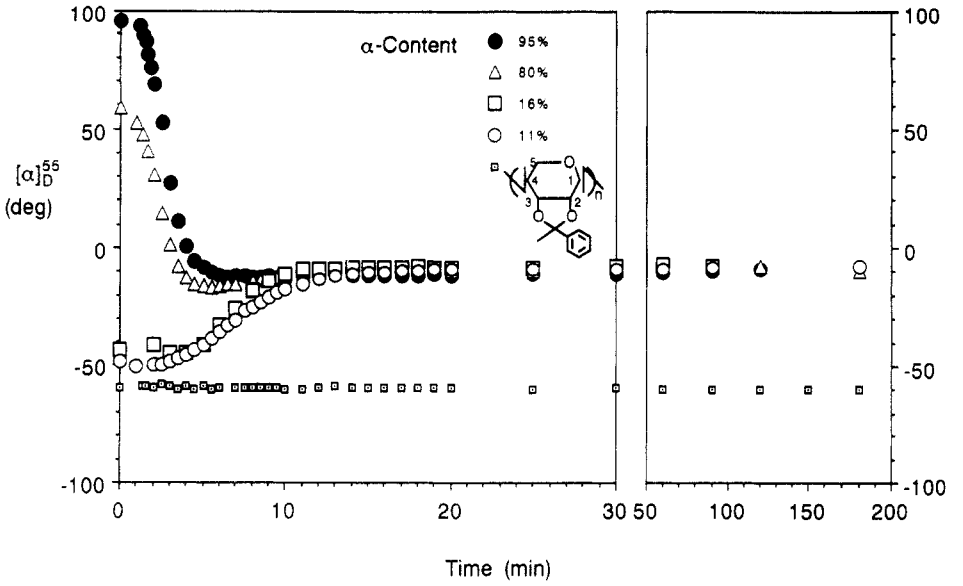


Figure 4. Hydrolysis of poly(A3DSR)s and 2,3-*O*-benzylidene-(1→4)-β-D-ribopyranan.

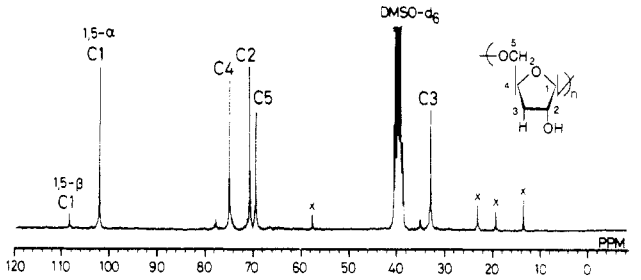


Figure 5. 67.8-MHz ^{13}C NMR spectrum of 3-deoxy-(1→5)-α-D-ribofuranan (DMSO-d_6 as solvent at 37 °C) (x, impurity).

°C), the obtained polymer with a positive specific rotation (+85°) almost had a 3-deoxy-(1→5)-α-furanosidic unit.

On the other hand, the ^{13}C NMR spectra of the poly(A2DSR)s, which were prepared by BF_3·OEt_2, PF_5, and $SnCl_4$ at different temperatures, showed that the individual absorptions due to C1–C5 carbons appeared as several peaks (Figure 3), suggesting that the polymers had mixed structures. In Figure 3B, when PF_5 was used, the obtained polymer showed a different NMR spectrum compared with those of the polymers prepared by BF_3·OEt_2 and $SnCl_4$. The C4 peak at 86 ppm should be due to a (1→5)-β-furanosidic unit. The splitting of the absorptions seems to be caused by a conformational difference in the polymer backbone consisting of such possible monomeric units as 1,5-α- and β-furanosidic units and 1,4-α- and β-pyranosidic units. As shown in Table 3, the stereoregularity of the polymers was determined from the intensity of the C4 carbon peaks.

Hydrolysis. In the former section, the absorption at 102 ppm was assigned to the C1 carbon of a 3-deoxy-(1→5)-α-ribofuranosidic unit. In order to assign whether the peak at 109 ppm is due to the β-furanosidic or β-pyranosidic unit, the hydrolysis of the poly(A3DSR)s with different specific rotations was performed (Figure 4). The hydrolysis of the four kinds of poly(A3DSR)s ($[\alpha]^{55}_D$ = +95.8, +58.4, −43.2, and −48.6°) and of a structurally proven benzylidenated (1→4)-β-D-ribopyranan ($[\alpha]^{55}_D$ = −59.5°)[18] were started initially in systems of THF/12 N HCl (9.5/0.5) at 55 °C. The specific rotation of the polymer with an α content of 95% ($[\alpha]^{55}_D$ = +95.8°) decreased rapidly to −10° in 5 min, and the value was maintained constant for more than 2 h. In contrast, the specific rotation of poly(A3DSR) with an α content of 11% ($[\alpha]^{55}_D$ = −48.6°) increased slowly, and after 15 min, the value became

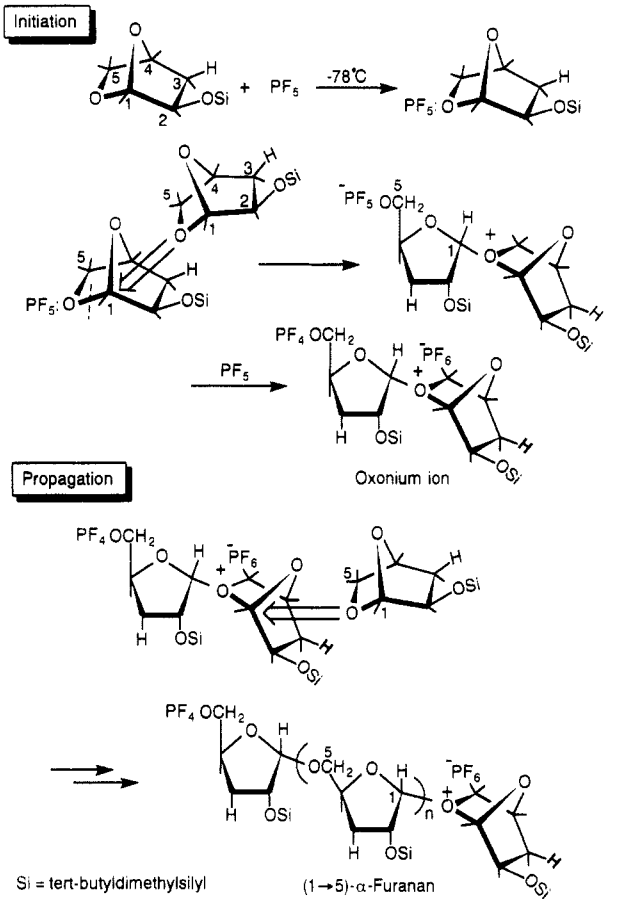


Figure 6. Proposed mechanism for (1→5)-α-D-ribofuranan derivatives via the oxonium ion intermediate.

constant (−10°). On the other hand, the hydrolysis of the (1→4)-β-D-ribopyranan derivative was very slow under the same conditions. After 3 h, the specific rotation was almost the same as the initial one. After 48 h, the specific rotation increased to −35° and the polymer decomposed after 72 h. It is well-known that a 1,5-glycofuranosidic linkage is much more labile to acidic conditions than a 1,4-glycopyranosidic linkage.[17] The rapid decrease in $[\alpha]_D$ of the polymer with D conformation from positive to negative at the initial stage of the hydrolysis suggests that a scission of the 1,5-α-linkage in the polymer occurred preferentially. On the other hand, the relatively slow increase in $[\alpha]_D$

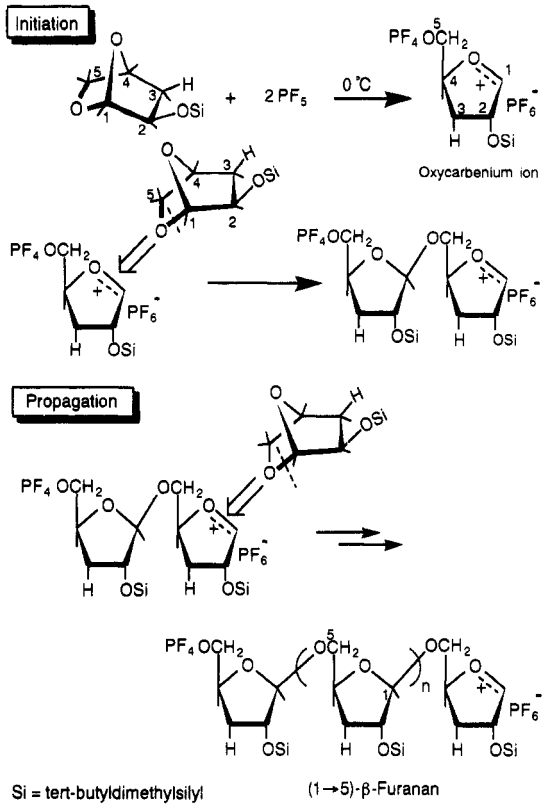


Figure 7. Proposed mechanism for (1→5)-β-D-ribofuranan derivatives via the oxycarbenium ion intermediate.

Table 4. Desilylation of Poly(A2SDR) into Free 3-Deoxyribofuranan[a]

poly(A2SDR)			free deoxyribofuranan		
g	$10^{-4}\bar{M}$[b]	$[\alpha]^{25}_D$,[c] deg	g	$10^{-4}\bar{M}_n$	$[\alpha]^{25}_D$,[d] deg
0.62	3.1	94	0.13	1.9	96

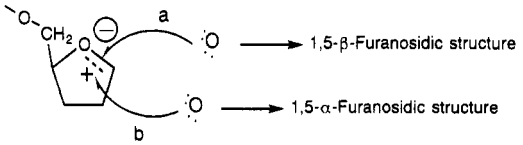
[a] 1 M (n-Bu)$_4$NF (THF solution; 8 mL); temperature, reflux; time, 1 h. [b] Determined by GPC (polystyrene standard). [c] Measured in $CHCl_3$ (c 1%). [d] Measured in H_2O (c 1%).

indicates that the scission of a β-linkage occurred. As seen in the hydrolysis of a stereoregular (1→4)-β-D-ribopyranan derivative, the scission of the (1→4)-β-D-pyranosidic linkage was very slow. Accordingly, poly(A3DSR)s with negative specific rotations were concluded to have mainly (1→5)-β-furanosidic units but not (1→4)-β-pyranosidic units.

Deprotection. The deprotection of the 2-*O*-silylated 3-deoxy-(1→5)-α-D-ribofuranan (Table 1, no. 2) was carried out with tetrabutylammonium fluoride in THF to give an OH-free 3-deoxyribofuranan (Table 4). The ^{13}C NMR spectrum of the free polymer (Figure 5) showed that the deprotection was complete and the polymer had mixed structures consisting of 3-deoxy-(1→5)-α-D-ribofuranosidic and β-D-furanosidic units in the ratio of 95 and 5%. The peaks at 102 and 33 ppm were assigned to the C1 and C3 carbon absorptions of the 3-deoxy-(1→5)-α-D-ribofuranosidic unit, respectively.

Proposed Mechanism of Polymerization. In the ring-opening polymerization of A3DSR and A2DSR, there are four possible monomeric units in the poly(A3DSR)s and poly(A2DSR)s, respectively, that is, the 1,5-α- and 1,5-β-furanosidic units and the 1,4-α- and 1,4-β-pyranosidic units, because a bicyclic 1,4-anhydro sugar is equally regarded as a 1,5-anhydro sugar.[18] However, from the results of the hydrolysis studies of poly(A3DSR)s, possibilities of the existence of pyranosidic structures are low. On the other hand, as seen in ^{13}C NMR spectra (Figure 3), poly(A2DSR)s were composed of the four units. A stereoregular structure consisting exclusively of the 3-deoxy-(1→5)-α-furanosidic unit can be attained by a trialkyloxonium ion mechanism, as illustrated in Figure 6. Complexation of Lewis acid occurred at the 1,5-linked oxygen O5 in the initiation step and then the 1,5-linked oxygen of the monomer attacks the propagating end from the backside of the C1–O–C5 bond.[2]

On the other hand, the mechanism leading to the formation of the (1→5)-β-furanosidic structure at 0 °C is assumed to follow Figure 7. An initiating oxycarbenium ion was attacked by the 1,5-linked oxygen of A3DSR from the α-side of the furanose ring to yield a (1→5)-β-linked unit and then the oxycarbenium ion is regenerated. In general, an approaching monomer can attack an active end carrying an oxycarbenium ion intermediate from two directions a and b, giving polymers with mixed structures



consisting of 1,5-α- and 1,5-β-linked furanosidic units. The reason that the proportion of 1,5-β-linked unit increased with elevating polymerization temperature is assumed to be due to a preferential attack from the a direction, because the counteranion (PF_6^-) positioned at the lower side of the furanose ring might lead to the attack. Since the 2-deoxy monomer cannot be polymerized into a stereoregular polymer, it was found that the protective group at the C2 position plays an important role in the stereoregulation of the ring-opening polymerization of the anhydro sugars.

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