

SYNTHESIS AND CATIONIC RING-OPENING POLYMERIZATION OF 1, 4-ANHYDRO-2, 3-DI-O-(*P*-AZIDOBENZYL)- α -D-RIBOPYRANOSE

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Abstract New highly stereoregular 2, 3-di-O-(*p*-azidobenzyl)-(1 $\rightarrow$ 5)- α -D-ribofuranan was synthesized by selective ring-opening polymerization of 1, 4-anhydro-2, 3-di-O-(*p*-azidobenzyl)- α -D-ribopyranose (ADABR) using phosphorus pentafluoride or tin tetrachloride as catalyst at low temperature in dichloromethane. The monomer was obtained by the reaction of *p*-bromomethyl-phenyleneazide with 1, 4-anhydro- α -D-ribose in DMF. The structure of poly(ADABR) was identified by specific rotation and ^{13}C -NMR spectroscopy. Acid chloride- AgCl_4 complex catalyst such as $\text{CH}_2=\text{C}(\text{CH}_3)\text{C}^+\text{OClO}_4^-$ used in the polymerization resulted in polymers with mixed structures, i.e. (1 $\rightarrow$ 5)- α -D-ribofuranosidic and (1 $\rightarrow$ 4)- β -D-ribopyranosidic units. However, with $\text{C}_6\text{H}_5\text{C}^+\text{OClO}_4^-$ as catalyst, pure (1 $\rightarrow$ 5)- α -D-ribofuranan was obtained. The effects of catalyst, polymerization temperature and time on polymer stereoregularity were examined, and the mechanism of the ring-opening polymerization was discussed.

Keyword Cationic ring-opening polymerization, Azido-containing polysaccharide, Lewis acid catalysts, 1, 4-anhydro-2,3-di-O-(*p*-azidobenzyl)- α -D-ribopyranose, Stereoregularity

INTRODUCTION

The ring-opening polymerization of anhydrous sugar derivatives is one of the most useful methods for preparing polysaccharide with well-defined structure^[1-3]. Various Lewis acids were used as catalysts in the polymerization, and they played an important role in controlling polymer stereoregularity^[4]. Until now, among the products from several investigations of ring-opening polymerization of 1,4-anhydro- α -D-ribose derivatives, only 1, 5- α -, 1, 5- β - furanosidic and 1, 4- β -pyranosidic units in the obtained polysaccharide have been found^[5].

Polysaccharides with azido group were synthesized by ring-opening polymerization of 1,6-anhydro-2, 3- or 4-azidoglucopyranose derivatives^[6], or 1, 4-anhydro-3-azido-2-benzyl-3-deoxy- α -D-xylopyranose^[7]. The azido-containing polysaccharides were then easily reduced to amino-containing polysaccharides. It was found that the sulfated derivatives of the 3-amino polysaccharides have high anticoagulant activities and low cytotoxicity^[8].

With the purpose of extending the range of structures of polyribose and its potential use in electron beam resists, we carried out the synthesis and selective ring-opening polymerization of

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1,4-anhydro-2, 3-di-O-(*p*-azidobenzyl)- α -D-ribopyranose (ADABR). We hoped that it would have the property of e-beam resist materials and at the same time be biodegradable.

EXPERIMENTAL

Materials

D-ribose is commercially available. 1, 4-Anhydro- α -D-ribopyranose (AHRP) was obtained by vacuum pyrolysis of D-ribose^[9]. AgClO_4 and $\text{RC}^+\text{OClO}_4^-$ were prepared according to the methods described in the literature^[10]. Other reagents were used without further purification.

Preparation of *p*-Bromomethylene Phenylene Azide

A solution of toluidine (10.7 g, 0.1 mol) in 60 mL of 6 mol/L HCl was made. 27.8% Aqueous NaNO_2 (27.7 g) was then added and stirred at 5°C. The cooled mixture was then added dropwise into 15% aqueous sodium azide (50.0 g) while stirring and cooling in an ice bath over a period of 2 h^[11]. The reaction mixture was allowed to stand at room temperature for 1 h and extracted with diethyl ether, and the organic layer was washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and 9.4 g *p*-azidotoluene was obtained with 71% yield.

AIBN (2.0 g) was added into a solution of N-bromosuccinimide (NBS, 17.8 g, 0.1 mol) in 100 mL carbon tetrachloride, then the mixture was heated to 65°C. *p*-Azidotoluene (13.3 g, 0.1 mol) was added dropwise within a period of 30 min, and the mixture was then stirred at 75°C for 3 h. After filtration, the filtrate was washed with 0.5 mol/L HCl twice, then with water till neutral pH was reached, and dried over anhydrous sodium sulfate. After the solvent was evaporated, the residue was distilled under reduced pressure to give *p*-bromomethylene phenylene azide (13.0 g, yield 70%), b.p. 59~61°C/7 Pa.

Preparation of 1,4-Anhydro-2,3-Di-O-(*p*-Azidobenzyl)- α -D-Ribopyranose (ADABR)

Sodium hydride (3 g) was added into a solution of 1, 4-anhydro- α -D-ribopyranose (4 g, 0.03 mol) in DMF (200 mL). After stirring at room temperature for 1 h. *p*-bromomethylene phenylene azide (16 g, 0.076 mol) was added dropwise and stirred for 26 h. After evaporation of DMF, the residue was extracted with chloroform. The organic layer was washed with water several times, then dried over anhydrous magnesium sulfate. The solvent was evaporated, and the residue was purified chromatographically on a silica column with benzene-ethyl acetate (volume ratio, 12:1) as eluant to give 1,4-anhydro-2,3-di-O-(*p*-azidobenzyl)- α -D-ribopyranose (ADABR, 4.5 g, yield 45%) $[\alpha]_D^{25} = -23.8^\circ$ (C 1% in CHCl_3).

Polymerization

High vacuum technique was used^[11] as the typical procedure for polymerization. ADABR (0.3 g) was dried in a polymerization ampoule by evacuating for several hours, then dissolved in dichloromethane (2 mL). PF_5 (4.0 mole % to the monomer) was added, and the reaction was carried out at -20°C for 5 h. The polymerization was terminated by adding methanol. The polymer solution obtained was washed with sodium bicarbonate solution, then with water, dehydrated over sodium sulfate, and concentrated to approximately 10 mL. A copolymer was purified by reprecipitation from a methanol-chloroform system three times and freeze-dried from benzene.

Measurement

The ^1H and ^{13}C -NMR spectra were recorded on a JEOL GX-270 spectrometer in CDCl_3 solution. Specific rotation measurements were carried out on the polymer solution in CHCl_3 at 25°C with a DIP-360A polarimeter. The molecular weight of the polymers was determined by VPO on a QX-08 vapor pressure osmometer or Corona-117 molecular weight apparatus with CHCl_3 as solvent.

RESULTS AND DISCUSSION

Synthesis of ADABR

ADABR was prepared by the reaction of 1, 4-anhydro- α -D-ribofuranose (AHRP) with *p*-bromomethylene phenylene azide (see Scheme 1). When the mole ratio of the *p*-bromomethylene phenylene azide to AHRP was 2:1, notable monosubstituents on C-2 or C-3 was found in the product. However, when the ratio was higher than 2.5:1, the elution chromatographic separation became difficult. Only the middle fraction collected from the silica gel column contained ~45% ADABR.

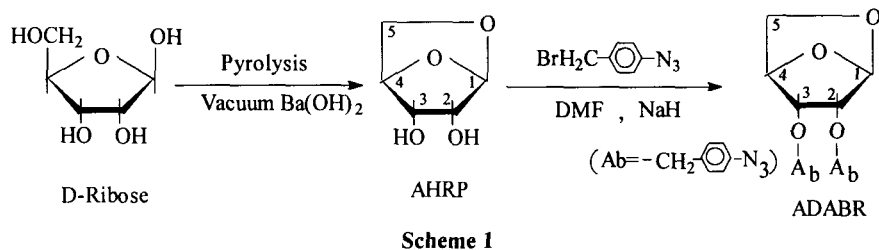


Figure 1 shows the IR spectrum of ADABR; the appearance of a strong absorption at 2105 cm^{-1} can be assigned to the N_3 stretching vibration peak. The absence of OH stretching vibration around 3000 cm^{-1} indicates that the original OH group percentage in AHRP was completely consumed in the reaction. Table 1 summarizes the chemical shifts of ^1H and ^{13}C of AHRP and ADABR. The results verified their structures.

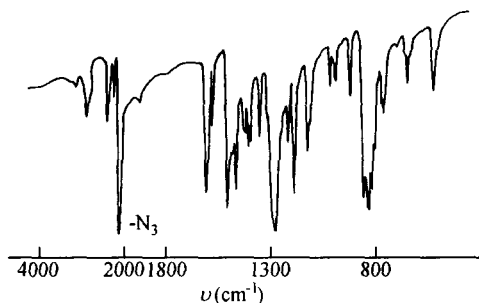


Fig. 1 IR Spectrum of 1, 4-anhydro-2, 3-di-O-(*p*-azidobenzyl)- α -D-ribofuranose (ADABR)

Ring-Opening Polymerization of ADABR

The results of the ring-opening polymerization of ADABR with PF_5 and SnCl_4 as catalysts are listed in Table 2. It indicates that ADABR is readily ring-opening polymerized into the polymers with high molecular weights ($M_n = 5.1 \times 10^3 \sim 58 \times 10^3$) in moderate yields. The temperature of polymerization does not show significant effect on the yield of polymer obtained. Longer polymerization times, i.e. 36 h and 46 h, increase the yield and molecular weight (No. 4: 42%, $M_n = 11 \times 10^3$ and No. 10: 64 %, $M_n = 58 \times 10^3$). Compared with PF_5 , SnCl_4 catalysts (Nos. 8, 9, and 10) resulted in polymers with higher yield (more than 50%), higher molecular weight (31×10^3 to 58×10^3), and higher positive specific rotation ($+141^\circ$ to $+146^\circ$). The results of ring-opening polymerization of ADABR with acid chloride- AgClO_4 complex as catalyst are summarized in Table 3. The obtained polymers have higher positive specific rotations of $+126^\circ$ to $+134^\circ$ and moderate molecular weights of 7.6×10^3 to 10.1×10^3 using benzoyl- ClO_4^- as catalyst. When polymerization was carried out using methylacryloyl- ClO_4^- as catalyst, the resulting polymers had higher molecular weights of 59.9×10^3 to 44.7×10^3 and moderate positive specific rotations of

+57° to +65°. These experimental results indicate that the type of catalysts play an important role in the polymerization.

Table 1. The chemical shifts of ¹H and ¹³C-NMR of AHRP and ADABR

Compound	Chemical shift δ ^a					
	C1, H1	C2, H2	C3, H3	C-4, H4	C5,H5	CH ₂ -C ₆ H ₅ -N ₃
AHRP ^b (¹ H)	5.35(1H)	3.99(1H)	3.99(1H)	4.60(1H)	3.42(2H)	
ADABR ^c (¹ H)	5.45(1H)	3.79(1H)	3.79(1H)	4.70(1H)	3.32(2H)	4.58
ADABR (¹³ C)	100.02	79.68	78.51	81.78	64.67	72.47

a. C1 to C5, H1 to H5 represent the carbon and hydrogen on the corresponding position of AHRP and ADABR (see Scheme 1); b. AHRP: 1,4-anhydro-α-D-ribofuranose; c. ADABR: 1,4-anhydro-2,3-di-O-(*p*-azidobenzyl)-α-D-ribofuranose

Table 2. Ring-opening polymerization of ADABR with PF₅ or SnCl₄ as catalyst

No. ^{a)}	Catalyst (mol%)	T (°C)	t (h)	Yield (%)	[α] _D ^{25b)} (deg.)	M _n ^{c)} (× 10 ³)
1	PF ₅ (4)	-20	5	13	+98	9.3
2	PF ₅ (4)	-20	5	26	+114	6.6
3	PF ₅ (4)	-30	5	38	+125	9.2
4	PF ₅ (4)	-30	36	42	+140	11.0
5	PF ₅ (4)	-30	5	35	+100	5.1
6	PF ₅ (4)	-78	5	15	+97	7.2
7	PF ₅ (4)	-78	5	17	+72	6.5
8	SnCl ₄ (6)	-30	5	52	+146	47.0
9	SnCl ₄ (6)	-30	36	62	+141	31.0
10	SnCl ₄ (6)	-30	46	64	+142	58.0

a) Monomer,0.3 g; solvent, dichloromethane (1 mL); b) Measured in CHCl₃ (c 1%); c) Determined by VPO

Table 3. Ring-opening polymerization of ADABR with acyl-ClO₄⁻ complex

No. ^{a)}	Catalyst (mol%)	T (°C)	t (h)	Yield (%)	[α] _D ^{25b)} (deg.)	M _n ^{c)} (× 10 ³)
1	C ₆ H ₅ C ⁺ OClO ₄ ⁻ (5)	-30	30	45	+134	10.1
2	C ₆ H ₅ C ⁺ OClO ₄ ⁻ (7)	0	30	42	+126	7.6
3	CH ₂ =C(CH ₃)C ⁺ OClO ₄ ⁻ (5)	-30	20	43	+65	60.0
4	CH ₂ =C(CH ₃)C ⁺ OClO ₄ ⁻ (7)	-30	20	60	+57	45.0

a) Monomer,0.3 g; solvent, dichloromethane (1 mL); b) Measured in CHCl₃ (c 1%); c) Determined by VPO

Structure of Polymers and Polymerization Mechanism

There are four possible units in the poly(ADABR) prepared by the ring-opening polymerization of ADABR. They are (1→4)-α- and (1→4)-β-D-ribofuranosidic units, and (1→5)-α- and (1→5)-β-D-ribofuranosidic units. Figure 2 shows the C-H COSY spectrum of the poly(ADABR) prepared with PF₅ as catalyzer at -30°C. Individual carbon absorption due to the sugar moiety appeared as a single peak, indicating that the obtained polymer is a stereoregular polysaccharide. Taking into account the highly positive specific rotation (+125°), it can be concluded that the polymer is 2,3-di-(*p*-azidobenzyl)-(1→5)-α-D-ribofuranan and all NMR absorptions have been assigned^[11].

Figure 3 shows the ¹³C-NMR spectra of poly(ADABR)s prepared with PF₅ or C₆H₅C⁺OClO₄⁻ (A), SnCl₄(B), and CH₂=C(CH₃)C⁺OClO₄⁻ (C) as catalysts, respectively. When the polymerization was carried out with PF₅ or SnCl₄, almost all the obtained polymers had 1, 5-α- linked specificity (Fig. 3A, B). A peak at δ = 101.6 was assigned to the C-1 carbon of 1, 5-α-linked stereoregularity.

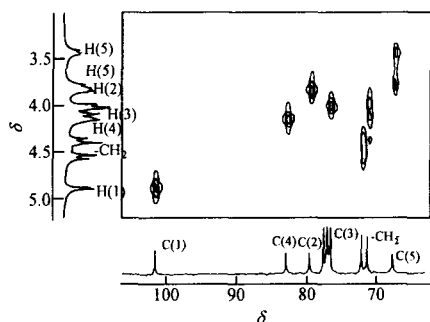


Fig. 2 C-H COSY spectrum of 2,3-di-O-(*p*-Azidobenzyl)-(1→5)-α-D-ribofuranan

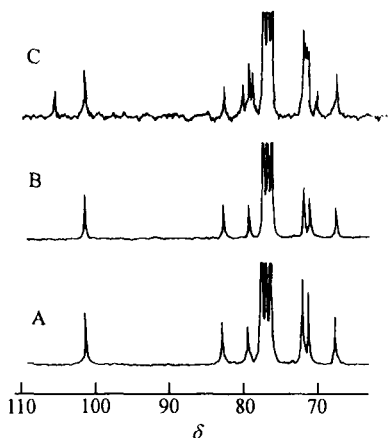
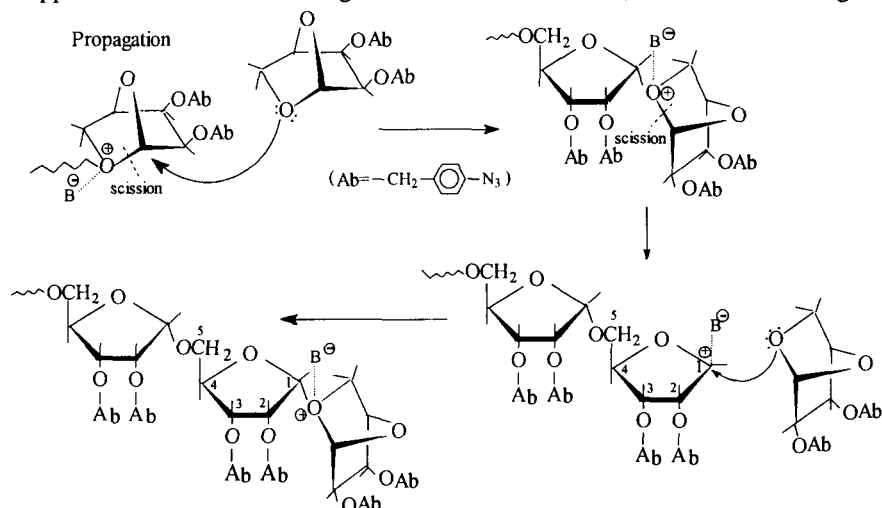


Fig. 3 67.8 MHz ^{13}C -NMR spectra of poly-(ADABR) obtained by different Lewis acid catalysts (A) PF₅ (or $\text{C}_6\text{H}_5\text{C}^+\text{OClO}_4^-$); (B) SnCl_4 (No 8 in Table 2); (C) $\text{CH}_2=\text{C}(\text{CH}_3)\text{C}^+\text{OClO}_4^-$ (No.3 in Table 3)

On the other hand, when the polymerization of ADABR with $\text{CH}_2=\text{C}(\text{CH}_3)\text{C}^+\text{OClO}_4^-$ as catalyst, the poly(ADABR) obtained would have mixed structures (No. 4 in Table 3). Poly-(ADABR) with specific rotation of $+57^\circ$ (Fig. 3C) shows relatively low stereoregularity. Two peaks of C-1 appeared respectively at $\delta = 102$ and $\delta = 106$, indicating that the polymer was composed of α - and β - configurations, namely, (1→4)- β -D-ribofuranosidic and (1→5)- α -D-ribofuranosidic units. The content of (1→5)- α -D-ribofuranosidic unit in two poly(ADABR)s (No. 3 and No. 4 in Table 3) were 65% and 62% calculated from the C-1 absorption in their ^{13}C -NMR spectra. When $\text{C}_6\text{H}_5\text{C}^+\text{OClO}_4^-$ was used as catalyst, the obtained poly(ADABR)s with pure (1→5)- α -configurations were obtained (The ^{13}C -NMR spectrum of which shows in Fig. 3A, only one peak appeared at $\delta = 101.6$ was assigned to the C-1 carbon of 1, 5- α -linked stereoregularity).

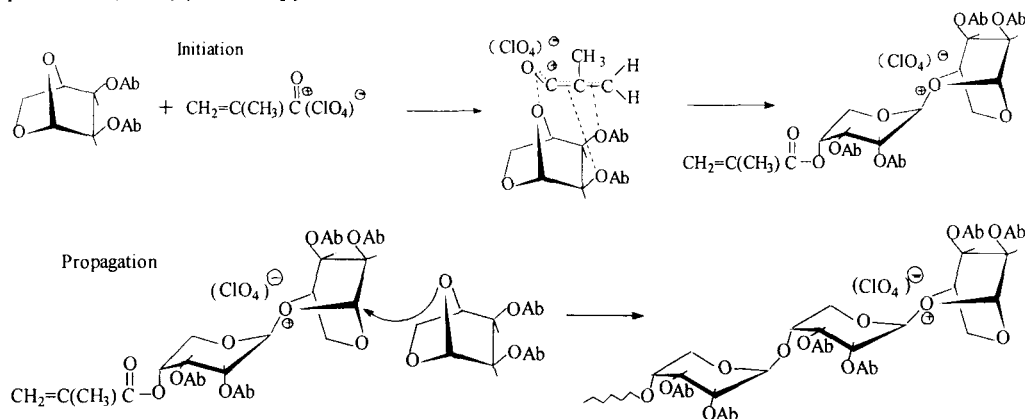


Scheme 2

The ring-opening polymerization of ADABR was thought to proceed *via* both a trialkyloxonium ion mechanism ($\text{S}_{\text{N}}2$ type) and a carbennium ion mechanism ($\text{S}_{\text{N}}1$ type). It was

revealed that in the stereoregular polymerization of 1, 4-anhydro- α -D-ribose derivatives, the substituents at C-2 and C-3 position play an important role in the formation of 1, 4- β -linkage and 1,5- α -linkage. The benzyl and *tert*-butyldimethylsilyl groups led to 1, 4- β -linkage^[10], while the benzylidene and isopropylidene groups led to the 1, 5- α -linkage^[12]. As shown in Scheme 2, the selective 1, 5-ring-opening of ADABR can be interpreted as due to a possibly higher nucleophilicity of the 1, 5-linked oxygen than that of 1, 4-linked oxygen.

The mechanism leading to the formation of (1 $\rightarrow$ 4)- β -D-ribopyranan macromer is proposed in Scheme 3. Selective coordination of $\text{CH}_2=\text{C}(\text{CH}_3)\text{CO}^+$ and the 1, 4-linked oxygen with the aid of O-2 and O-3 oxygen is to give the oxonium ion. Then, an approaching monomer attacks the C-1 carbon from the direction opposite to the C-1—O-4 bond. The successive addition of monomer produced (1 $\rightarrow$ 4)- β -D-ribopyranan macromer^[13].



Scheme 3

The mechanism affording (1 $\rightarrow$ 5)- α -D-ribofuranan when $\text{C}_6\text{H}_5\text{COCl}$ was used as catalyst may be the same as that for the benzylated monomer^[11]. When different carbenium ions were used as the initiating cation for the polymerization of ADABR, even with the same gegenion such as ClO_4^- , two types of selective ring-opening polymerization occurred.

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