Polymer Bulletin 7, 431–437 (1982)

Polymer Bulletin

Polymerization of Bicyclic Acetals

10. Synthesis and Polymerization of (+)-(1R,4R,5S)-4-Bromo-6,8-Dioxabicyclo[3.2.1]Octane

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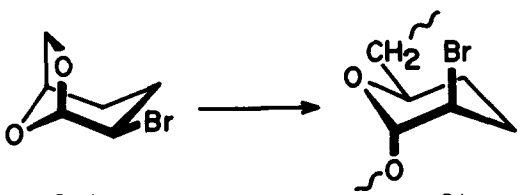
SUMMARY

An optically active, stereoregular polyacetal having a dextran-type backbone structure but opposite absolute configuration of the asymmetric carbons (the L-series) was prepared by the cationic ring-opening polymerization of (+)-(1R,4R,5S)-4-bromo-6,8-dioxabicyclo[3.2.1]octane (1e*). The optically active monomer 1e* was synthesized from sodium 3,4-dihydro-2H-pyran-2-carboxylate through the optical resolution of its diastereomeric dehydroabietylammonium salt followed by four step reactions. Polymerization of 1e* in methylene chloride at -90°C with antimony pentafluoride as an initiator provided a stereoregular polymer having a number average molecular weight of 2.9×10^4 and a specific rotation of $[\alpha]_D^{25}$ -163°(chloroform).

INTRODUCTION

Previously, we reported a convenient synthetic procedure for (+)-(1R,5S)-6,8-dioxabicyclo[3.2.1]octane and its cationic ring-opening polymerization leading to a polysaccharide analogue (KOMADA *et al.* 1979). The optically active polymer obtained at -78°C or below possessed a backbone structure similar to that of naturally occurring dextran but it was completely opposite in the absolute configuration of the asymmetric carbons. Namely, the polymer belongs to a category of the L-polysaccharide series (2,3,4-trideoxy-(1→6)-α-L-*glycero*-hexopyranan in the nomenclature of carbohydrate chemistry). As a continuation of the studies along this line, the present paper describes synthesis of (+)-(1R,4R,5S)-4-bromo-6,8-dioxabicyclo[3.2.1]octane (1e*) and its cationic ring-opening polymerization to a polysaccharide analogue of the L-series (2-bromo-



1e* 2*

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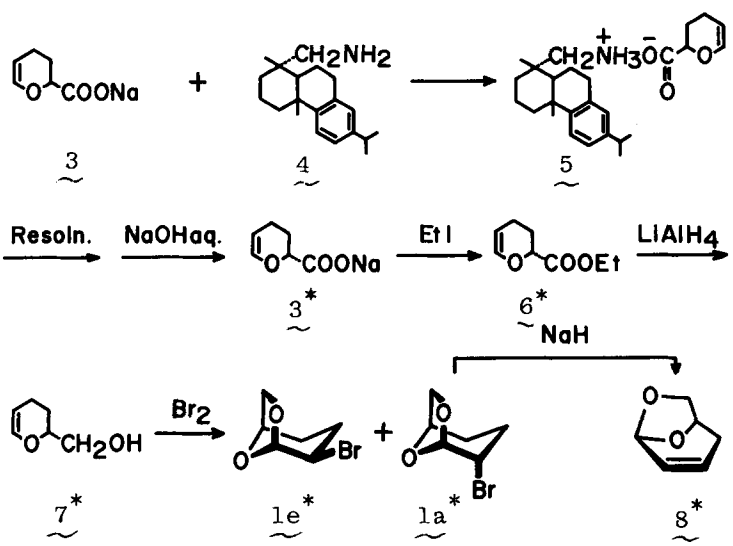
2,3,4-trideoxy-(1→6)-α-L-*erythro*-hexopyranan). The resulting polymer (2*) having a bromine atom in its repeating unit can be chemically modified in various ways, and therefore, it is a potential precursor for synthetic L-polysaccharides which are useful for better understanding of biological activities of natural polysaccharides.

RESULTS AND DISCUSSION

Synthesis of (+)-(1R,4R,5S)-4-Bromo-6,8-dioxabicyclo[3.2.1]octane (1e*). In the previous paper (*loc. cit.*), we described a synthetic procedure for (+)-(1R,5S)-6,8-dioxabicyclo[3.2.1]octane starting from sodium 3,4-dihydro-2H-pyran-2-carboxylate (3) through the optical resolution of its diastereomeric dehydroabietylammonium salt (5). This procedure was applied to the synthesis of (+)-(1R,5R,4S)-4-bromo-6,8-dioxabicyclo[3.2.1]octane (1e*). The synthetic route is given in Scheme 1.



Scheme 1

Sodium 3,4-dihydro-2H-pyran-2-carboxylate (3) was converted with hydrochloric acid to its free acid, which was mixed in ethyl ether with dehydroabietylamine (4) to yield diastereomeric dehydroabietylammonium 3,4-dihydro-2H-pyran-2-carboxylate (5). Repeated recrystallization of 5 from methanol solution gave white crystals having a constant value of $[\alpha]_D^{25}$ +11.6° (ethanol). The ammonium salt was transformed to its sodium salt (3*),

which was then esterified with ethyl iodide in N,N-dimethylformamide to afford ethyl 3,4-dihydro-2H-pyran-2-carboxylate (6*) with $[\alpha]_D^{25}$ -71.4° (ethanol). Subsequent lithium aluminum reduction of 6* in ethyl ether gave 2-hydroxymethyl-3,4-dihydro-2H-pyran (7*) with $[\alpha]_D^{25}$ -80.7° (ethanol). Bromination of 7* in carbon tetrachloride produced optically active 4-bromo-6,8-dioxabicyclo[3.2.1]octane as a mixture of stereoisomers (1a* : 1e* = 49 : 51 by ^{13}C-NMR spectroscopy).

Previously, we attempted without success to separate a stereoisomer mixture of racemic 4-bromo-6,8-dioxabicyclo[3.2.1]octane into its components by conventional methods such as fractional distillation or column chromatography. Therefore, the stereoisomer mixture of the optically active monomer was dehydrobrominated with sodium hydride in 1,2-dimethoxyethane (Strivastava *et al.* 1970) and only 1a* was removed as 6,8-dioxabicyclo[3.2.1]oct-3-ene (8*). The unreacted 1e* was confirmed to be free from 1a* by ^{13}C-NMR spectroscopy. The overall yield of 1e* from racemic 3 was 2.1 %.

As described in the previous paper (*loc. cit.*), optically active 6,8-dioxabicyclo[3.2.1]octane derived from 7* possesses the absolute configuration of (1R,5S). As a consequence, its 4(e)-bromo derivative from the identical precursor 7* has the absolute configuration of (1R,4R,5S). The optical purity of 1e* was not determined directly, because 1e* or its enantiomer of a known optical purity has never been reported in the literature. Therefore, the optical purity of 1e* prepared in this work was estimated to be approximately 99 % on the basis of the observed specific rotation of 8*, $[\alpha]_D^{25}$ -136° (water) compared with a reported value of $[\alpha]_D^{25}$ +137° (water) of (-)-(1S,5R)-6,8-dioxabicyclo[3.2.1]oct-3-ene derived from D-glucose (Pecka *et al.* 1973).

Polymerization of (+)-(1R,4R,5S)-4-Bromo-6,8-dioxabicyclo[3.2.1]octane (1e*). Racemic 4(e)-bromo-6,8-dioxabicyclo[3.2.1]octane undergoes cationic polymerization in the presence of antimony pentahalides and trifluoromethanesulfonic acid at low temperature to yield a polymer almost entirely consisting of a structural unit in which the exocyclic acetal oxygen atom is axially oriented to the tetrahydropyran ring, in other words, the polymer is composed of "α-form" in the terminology of carbohydrate chemistry (OKADA *et al.* 1982). Therefore, the polymerization of the optically active monomer 1e* was carried out in methylene chloride at -90, -78, and -60°C by using antimony pentafluoride as the initiator. The results are summarized in Table I. The polymer of 1e* thus prepared showed a poor solubility and was barely soluble only in chloroform. It began to decompose at about 210°C in air.

TABLE I

Polymerization of (+)-(1R,4R,5S)-4-bromo-6,8-dioxabicyclo[3.2.1]octane (1e*)[a]

Exptl. No.	Temp., °C	Yield,[b] %	Mn[c] × 10^{-4}	$[\alpha]_D^{25}$,[d] deg	α-form,[e] %
S-127	-60	24(81)	2.9	-151	~100
S-128	-78	26(88)	3.2	-161	~100
S-129	-90	20(88)[f]	2.9	-163	~100

[a]Monomer, 0.75 g; solvent, CH_2Cl_2, 0.48 ml; initiator, SbF_5, 2 mol% to monomer; time, 48 h.
[b]Methanol-insoluble polymer; figures in parentheses denote hot chloroform-soluble fraction.
[c]By vapor pressure osmometry in chloroform at 37°C.
[d]In chloroform; c = 0.13~0.23 g/dl.
[e]By ^{13}C-NMR spectroscopy.
[f]Anal. Calcd. for $(C_6H_9BrO_2)_n$: C, 37.33%; H, 4.70%. Found: C, 38.05%; H, 4.72%.

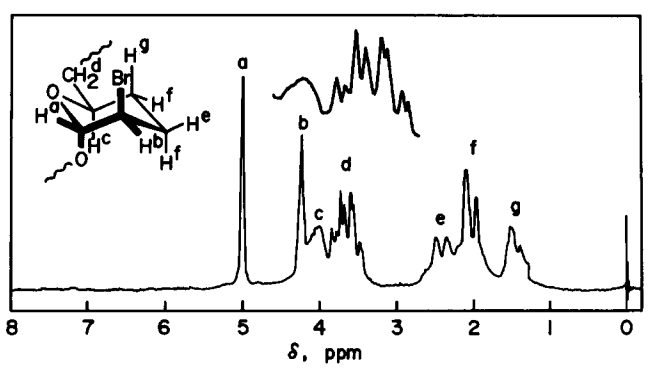


Figure 1. ^1H-NMR spectrum of (-)-poly((2R,3R,6R)-3-bromotetrahydropyran-6,2-diyloxymethylene) (S-129). Solvent, $CDCl_3$; temp., 50°C; 100 MHz; TMS.

The ^1H-NMR spectrum of the polymer prepared at -90 °C is shown in Figure 1. The appearance of only an equatorial acetal proton signal at δ 4.95 demonstrates that the polymer entirely consists of the α-form. The oxymethylene protons showed an ABX pattern in the region of δ 3.9~3.4 as shown in the expanded spectrum in Figure 1. The analysis of this pattern gave the estimated values of coupling constants, J_{AB} = 10.7 Hz, J_{AX} = 5.6

Hz, and J_{BX} = 3.7 Hz. The latter two values imply that the conformation around the exocyclic C-C bond is not fixed at one of the three noneclipsing conformations. The coupling constants above are very close to the corresponding vlaues for an optically active polymer derived from (+)-(1R,5S)-6,8-dioxabicyclo[3.2.1]octane (*loc. cit.*).

The ^{13}C-NMR spectrum of the polymer prepared at -90°C is shown in Figure 2, together with the assignments. The chemical shift values (δ, ppm from TMS) are: a" 99.10, b" 69.70, c" 68.03, d" 48.15,. e" 22.03, and f" 26.47. The spectrum consists of only six signals, indicating that the polymer is highly stereoregular.

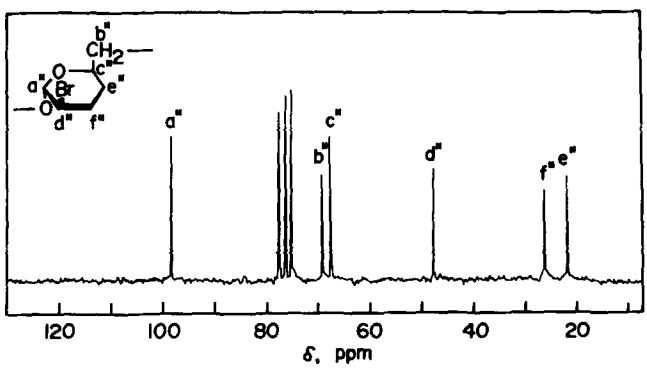


Figure 2. ^{13}C-NMR spectrum of (-)-poly((2R,3R,6R)-3-bromotetrahydropyran-6,2-diyloxymethylene) (S-129). Solvent, $CDCl_3$; temp., 50°C; 25MHz; TMS.

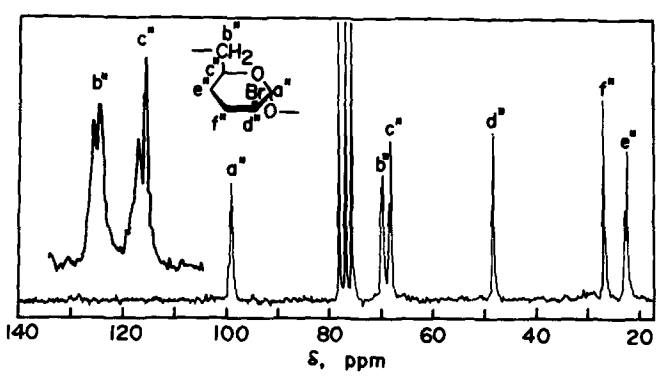


Figure 3. ^{13}C-NMR spectrum of (±)-poly(3(a)-bromotetrahydropyran-6,2-diyloxymethylene) prepared under similar conditions as those for S-129. Solvent, $CDCl_3$; temp., 50°C; 25MHz; TMS.

Figure 3 presents the ^{13}C-NMR spectrum of a polymer of racemic 4(e)-bromo-6,8-dioxabicyclo[3.2.1]-octane prepared in methylene chloride at -90°C with antimony pentafluoride as the initiator. It is noteworthy that the signals a", b", c", and e" are split into two peaks of different intensities as the expanded spectrum of the signals b" and c" shows. The chemical shift values (δ, ppm from TMS) are: a" 99.33, 99.10, b" 69.94, 69.70, c", 68.30, 68.03, d" 48.10, e" 22.42, 21.99, and f" 26.47. Comparison of the chemical shifts of these signals with those for the optically active polymer clearly indicates that the chemical shifts of the higher field peaks of a", b", c", and e" are in complete agreement with those of the corresponding signals of the optically active polymer.

Accordingly, the higher field peaks of a", b", c", and e" in the ^{13}C-NMR spectrum of the racemic polymer are assignable to the respective carbons in the dyad structures of D-D and L-L consecutive units (isotactic dyad). As the racemic polymer contained a negligibly small amount of another structural unit, that is, "β-form" in which the exocyclic oxygen lies in the equatorial position of the tetrahydropyran ring, the lower field peak of each signal pair can be reasonably ascribed to the respective carbons in the dyad structures consisting of D-L enantiomer pairs (syndiotactic dyad). Unfortunately, the difference in the chemical shifts of each signal pair is too small to allow an accurate measurement of the dyad tacticity of the racemic polymer from the relative peak areas of each signal pair. However, it has been recently found that the racemic polymer can be converted to poly(tetrahydropyran-6,2-diyloxymethylene) by reductive debromination using tributylstannane, and that the dyad tacticity of the original polymer can be determined from the ^{13}C-NMR spectrum of the debrominated polymer. Details of the reductive debromination and the determination of the stereoregularity of racemic poly(3-bromotetrahydropyran-6,2-diyloxymethylene) will be published elsewhere.

EXPERIMENTAL

Synthesis of (+)-(1R,4R,5S)-4-Bromo-6,8-dioxabicyclo[3.2.1]octane (1e*). Detailed procedures of the optical resolution of sodium 3,4-dihydro-2H-pyran-2-carboxylate (3) using dehydroabietylamine (4) as a resolving reagent and the subsequent reactions leading to 2-hydroxymethyl-3,4-dihydro-2H-pyran (7*) have been reported previously (KOMADA *et al.* 1979). Accordingly, only the synthetic procedures of 1e* from 7* is described here.

To a solution of 7* (8.0 g) in carbon tetrachloride (95 ml) was added dropwise a solution of bromine (13 g) in carbon tetrachloride (110 ml) at 24~26°C. Then the

reaction mixture was stirred at room temperature for 2.5 hours. During the addition of the bromine solution and the subsequent stirring, the reaction system was kept under a slightly reduced pressure by an aspirator in order to eliminate hydrogen bromide. The solvent was removed by a rotary evaporator, and the oily residue was distilled in vacuum to yield optically active 4-bromo-6,8-dioxabicyclo[3.2.1]octane (9.4 g, bp, 70~73°C/0.8 mmHg) as a mixture of stereoisomers (1a* : 1e* = 49 : 51 by ^{13}C-NMR spectroscopy). $[\alpha]_D^{25}$ +54.2° (ethanol).

To a stirred solution of the stereoisomer mixture (9.3 g) in 1,2-dimethoxyethane (65 ml) was added sodium hydride (50 % oil dispersion, 1.8 g) in small portions. The addition of one third of the sodium hydride was followed by 1 ml of dry ethanol. Then, another third of the sodium hydride was added, followed again by 1 ml of dry ethanol. The remainder of the sodium hydride was then added. The mixture was stirred at room temperature for 1 hour, then under reflux for 2 hours. Removal of 1,2-dimethoxyethane at atmospheric pressure by fractional distillation left a dark brown liquid which deposited a solid when cooled and diluted with ethyl ether. The solid was separated and the filtrate was fractionally distilled under reduced pressure to give optically active 6,8-dioxabicyclo[3.2.1]oct-3-ene (8*) (2.0 g, bp, 25~28°C/0.75 mmHg, $[\alpha]_D^{25}$ -136°(H_2O) and 4(e)-bromo-6,8-dioxabicyclo[3.2.1]-octane (1e*) (3.1 g, bp, 76~77°C/1.0 mmHg, $[\alpha]_D^{25}$ +111° (ethanol)).

Polymerization Procedure. Polymerization was carried out in an evacuated and sealed ampule at -90, -78, and -60°C with antimony pentafluoride as initiator. The detailed procedure has been described in the previous paper (OKADA *et al.* 1982). A crude product obtained by pouring the reaction mixture into methanol was extracted with hot chloroform for 24 hours. The chloroform extract was concentrated and poured into a large volume of methanol to give a white powdery polymer.

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Received May 24, accepted May 29, 1982

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