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Interglucosyl Attack of Hydroxyl Group to Epoxy Ring of $2^A,3^A$-Anhydro-(2^AS)-α-cyclodextrin. Selective Preparation of $3^A,2^B$-Anhydro-α-cyclodextrin

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$2^A,3^A$-Anhydro-(2^AS)-α-cyclodextrin was isomerized exclusively to $3^A,2^B$-anhydro-α-cyclodextrin by the reaction with aqueous alkali. This implies the selective and interglucosyl attack of 3^F-OH to the epoxy ring.

Sugar epoxide are synthetically the most useful class of anhydro-sugars. Reactions of sugar 2,3-epoxides with aqueous alkali are summarized in following two cases. (i) Attacks of hydroxide anion give trans-2,3-diols according to socalled trans-diaxial opening rule. (ii) Backside-attacks by hydroxyl groups of the same sugar unit cause isomerization of the epoxides into anhydrosugars such as 3.6-anhydrides and 3,4-epoxides.[1] In this context, we describe here a novel type of epoxide isomerization, i.e., selective attack of a hydroxyl group of the neiboughring sugar unit.

With the aim of preparing cyclodextrin derivatives which possess altrose units as the components of the macrocyclic rings, we tried a reaction of $2^A,3^A$-anhydro-(2^AS)-α-cyclodextrin **1**[2] with hydroxide anion. Although we expected type (i) reaction, such a reaction did not occur and an unexpected cyclic oligosaccharide **2** was exclusively obtained. Through the structure determination of **2**, we disclose intramolecular and interglucosyl selective attack of 3^F-OH to the epoxy ring.

A solution of $2^A,3^A$-anhydro-(2^AS)-α-cyclodextrin **1** (50 mg) in 0.25N aqueous $Ba(OH)_2$ (1 mL) was kept at 80 °C for 48 h. After neutralized with 1N H_2SO_4 and filtered, the solution was chromatographed on a reverse-phase column with gradient elution from water to 30% aqueous ethanol to give $3^A,2^B$-anhydro-α-cyclodextrin **2** (37.8 mg, 75.6%). The structure determination of **2** was carried out as follows. Its fast-atom-bombardment (FAB) mass spectrum showed the corresponding molecular ion. The Taka amylase A-catalyzed hydrolysis[3] of **2** (250 mg) gave an anhydromaltopentaose **3** (95.6 mg, 45.0%) whose molecular ion

was observed in its FAB mass spectrum. The completely acetylated compound **4**, which was obtained by the reduction of **3** with $NaBH_4$ followed by acetylation with acetic anhydride/pyridine, was analyzed by mass spectrometry. The FAB mass spectrum of **4** showed the molecular ion and the mass spectral fragmentation pattern demonstrated that anhydration occurred between the second and third glucose units from the nonreducing end. However, from these data, two terminal positions of the anhydro-bridge can not be determined. The acidic methanolysis of **2** (550 mg) gave two methyl anhydrodisaccharides **5a** (85.3 mg, 43.7%) and **5b** (68.0 mg, 34.9%) together with methyl D-glucoside. Since the acidic hydrolysis of **2** followed by $NaBH_4$ gave only two compounds (an anhydromaltitol **6** and glucitol), **5a,b** were suggested to be α- and β-anomers. The molecular ions in their FAB mass spectra and the reasonable chemical shift differences between their ^{13}C NMR absorptions confirmed this conclusion. The ^{13}C and ^{1}H NMR of the anomer **5a** are shown in Fig. 1. By comparing the chemical shifts of the C-1 absorptions of **5a** with those of **5b** and **6**, the absorptions of C-1 and C-1' were easily assigned. On the basis of these assignments, other absorptions were assigned with the aid of the $^{1}H,^{13}C$- and $^{1}H,^{1}H$-COSY NMR spectra. The $^{1}H,^{1}H$ coupling constants $J_{1,2}$, $J_{1',2'}$, $J_{2,3}$ (= $J_{3,4}$), and $J_{2',3'}$ (= $J_{3',4'}$) are 3.57, 3.47, 9.58, and 9.34 Hz, respectively, as shown in Fig. 1. These show that H-2, H-2', H-3, H-3', H-4, and H-4' are the axial protons and that H-1 and H-1'

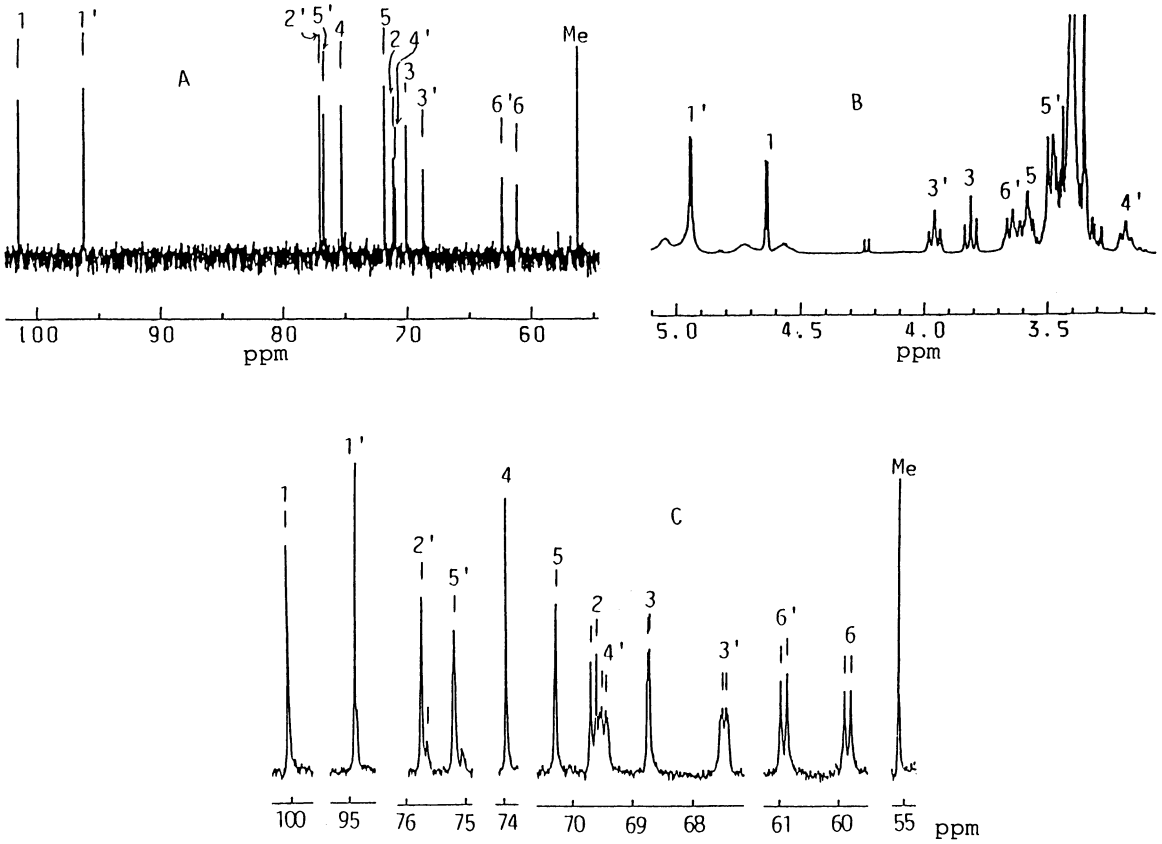
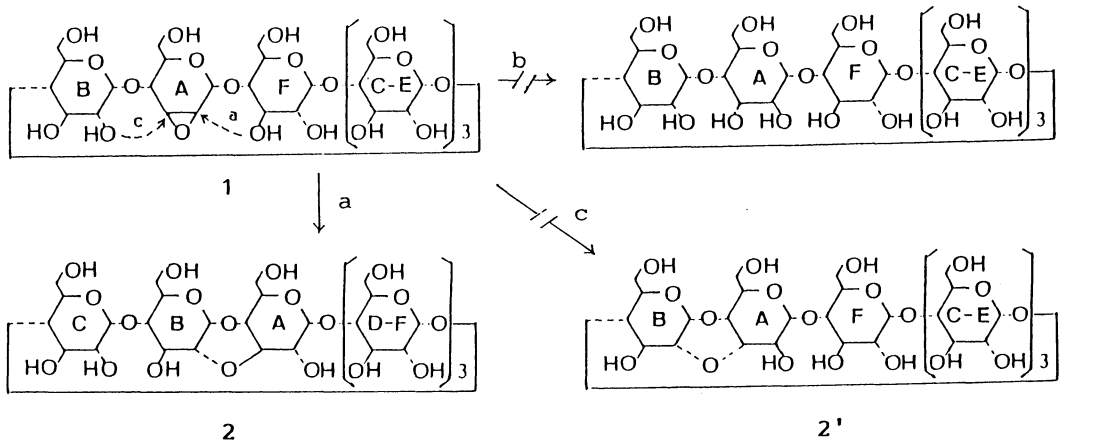
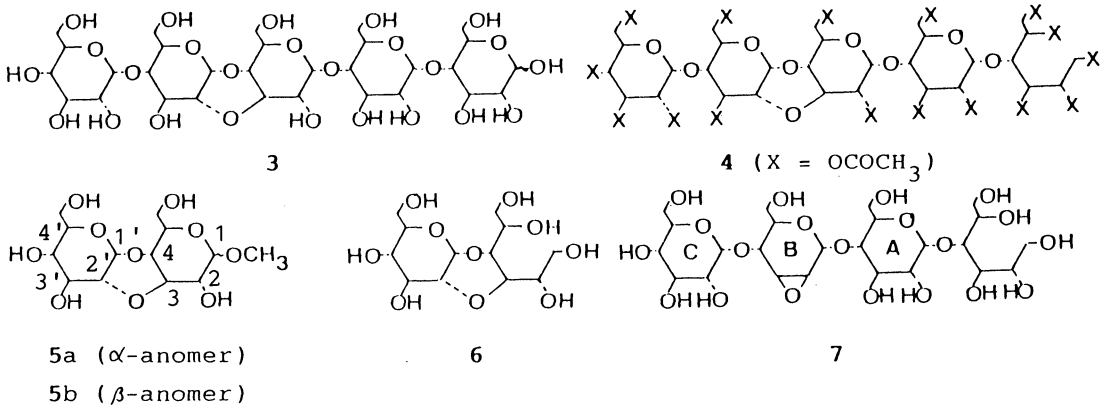


Fig. 1. ^{13}C (100 MHz, A and C) and ^{1}H NMR (400 MHz, B) spectra of **5a** in DMSO-d_6. Hydroxyls of **5a** are partially (ca. 50%) deuterated in (C).

are the equatorial protons. Therefore, **5**a is methyl anhydro-α-D-maltoside in which the two glucose units have $^4C_1$ conformations, but the terminal positions of the anhydro-bridge cannot be determined from these spectral data. As shown below, this is clarified by the technique that deuterium exchanges of OH's of hydroxyl compounds change NMR chemical shifts of the carbons which are located at β and γ positions from the exchangeable protons.[4] After the hydroxyls of **5**a were partially (ca. 50%) labeled with D_2O, isotopic multiplets[4] in the proton-decoupled ^{13}C NMR spectrum were measured (Fig. 1). The splittings of absorptions of C-3 and C-2' showed only γ-effects, demonstrating the absence of hydroxyl groups on C-3 and C-2', i.e., the anhydration between C-3-OH and C-2'-OH. Other isotopic multiplets can be reasonably explicable on the basis of the anhydro-bridge between C-3-OH and C-2'-OH. Therefore, **5**a is methyl 3,2'-anhydro-α-D-maltoside. Similarly, the two glucose units in **2** are shown to possess $^4C_1$ conformations from its $^1H,^1H$ coupling constants ($J_{1A,2A}$ = 3.42 Hz,





Scheme 1

$J_{1^B,2^B}$ = 3.42 Hz, $J_{2^A,3^A}$ = $J_{3^A,4^A}$ = 9.53 Hz, and $J_{2^B,3^B}$ = $J_{3^B,4^B}$ = 8.78 Hz). Thus, **2** is assigned to $3^A,2^B$-anhydro-α-cyclodextrin, which is produced by attack of 3^F-hydroxyl on the epoxy ring (route a in Scheme 1).

There are following two other possibilities in opening the $2^A,3^A$-epoxide ring; formation of altroside by a reaction with hydroxide anion (b route) and formation of a $3^A,2^B$-anhydro-(2^AS),(3^AR)-α-cyclodextrin **2'** by a reaction with 2^B-OH (c route). The former reaction which is described in many books should be regarded as a rather limited reaction to simple monosaccharides on the basis of the present result. If the product of the present reaction were **2'**, the acidic methanolysis would give an anhydrodisaccharide in which both H-3 and H-4 are not axial protons. The anhydrodisaccharide **5**a has both axial H-3 and axial H-4 as mentioned above. Therefore, the reaction (c) did not occur in the present case. The reason is probably that the trans-diaxial opening of the epoxy ring by attack of 2^B-OH in formation of the $2^A,3^B$-anhydride **2'** was sterically hindered by the macrocyclic structure of the cyclodextrin derivative. In our preliminary study, similar treatment of **7** with aqueous alkali gave two types of anhydromaltoteraoses. The products were reduced with $NaBH_4$, completely acetylated, and then analyzed by mass spectrometry, which showed anhydration between A and B in one product and anhydration between B and C in another product. Probably, this implies that the epoxide ring openings through a and c routes in Scheme 1 are possible in the linear epoxy-oligosaccharide system. At least, formation of a trans diol in the reaction of glucose epoxide with hydroxide anion did not occur even in the linear oligosaccharide system and the result that **2** was an exclusive product in the cyclodextrin system must be brought about by the macrocyclic structure.

In conclusion, a novel cyclic oligosaccharide **2** was specifically produced by the novel intramolecular and interglucosyl epoxy-opening reaction of $2^A,3^A$-anhydro-(2^AS)-α-cyclodextrin **1** under alkaline conditions.

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