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CONVENIENT PREPARATION AND EFFECTIVE SEPARATION OF THE C-2 AND C-3 TOSYLATES OF α-CYCLODEXTRIN

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Secondary tosylates of α-cyclodextrin were conveniently prepared by the reaction of the cyclodextrin with tosyl chloride in alkaline water where pH of the mixture should be allowed to decrease as the proceeding of reaction, and were effectively separated by reversed-phase column chromatography.

In the past decade, activation of the primary hydroxyls of cyclodextrin has been successfully carried out to construct enzyme mimics[1]. However, there are few studies on the activation of the secondary hydroxyls. The secondary p-toluenesulfonates (tosylates) of cyclodextrins have been attempted to be prepared by the reaction of cyclodextrins with p-toluenesulfonyl chloride (tosyl chloride) in alkaline aqueous solutions[2]. A critical report on these result has been published where the C-2 tosylate, 2-deoxy-2-tosyloxyl-β-cyclodextrin (**1**, n=7) was synthesized by the reaction of β-cyclodextrin with m-nitrophenyl tosylate in aqueous DMF (pH 9.9, 60°C)[3]. However, the reactions of α, β, and γ - cyclodextrins with tosyl chloride in alkaline aqueous solutions were recently reinvestigated to give mainly the C-2 tosylate (**1**, n=6), the C-6 tosylate (**3**, n=7), and the C-2 tosylate (**1**, n=8), respectively[4]. We wish to report here our result obtained by the reaction of α-cyclodextrin with tosyl chloride, which is quite different from the results mentioned above.

Powdered tosyl chloride (1.4 g) was added in one portion to 5 mL of an aqueous solution (pH 12.0, adjusted by addition of aqueous NaOH) of saturated α-cyclodextrin (1.4 g). The mixture was vigorously stirred at room temperature and the pH of the mixture was allowed to decrease rapidly. The pH of the reaction mixture should not be maintained (See later). After 5 min, the mixture became acidic (pH 6.5) and was filtered. An analysis of the filtrate

by reversed-phase HPLC[5] showed the formation of three mono-tosylates of α-cyclodextrin, I, II, III. For preparative separation of each tosylate, the filtrate was applied on a reversed-phase column (Lobar Column LiChroprep RP-18, 25 x 310 mm, Merck Ltd.). After eluting with 300 mL of water, a gradient elution of 500 mL of water and 500 mL of 40% aqueous EtOH was applied (Figure 1). The pure tosylates, I (270 mg, 17%), II (90 mg, 6%), and III (30 mg, 2%) were obtained after lyophilization[6]. The minor product, III, was identified as the primary tosylate (**3**, n=6) by comparing its 100 MHz ^{1}H-NMR spectrum, R_f value on silica gel TLC, and the retention time in HPLC[5] with those of the authentic compound[7]. The product, II, was assigned to the C-2 tosylate (**1**, n=6) on the basis of its 100 MHz ^{1}H-NMR and 25 MHz ^{13}C-NMR spectra which were quite similar to those of the reported **1** (n=7)[3a]. The product, I, was assigned to the C-3 tosylate (**2**, n=6) since there are only three kinds of hydroxyls in a cyclodextrin. Moreover, the ^{13}C-NMR spectrum of I was clearly different from that of II and showed no upfield-shifted C-1 absorption (101.9 ppm), demonstrating that the tosyl group was located at C-3. The tosylate (I) was degraded to its glucose unit by acidic methanolysis. The products, methyl glucoside and methyl 3-deoxy-3-tosyloxyl-glucoside were isolated by use of the reversed-phase column. The ^{13}C-NMR spectrum of the tosylate showed that the α-anomer was a main product and the β-anomer was minor one. Chemical shifts of C-1 of the α and β-anomers were not shifted from those of α and β-methyl glucosides, respectively, demonstrating the tosylation on C-3. The other chemical shifts of the α-anomer were reasonably understood on the basis of the deshielding effect (+12.9 ppm) of the tosyl group on C-3 (α-carbon of the tosyl group) and the shielding effects (-2.5 and -2.6 ppm) on C-2 and C-4 (β-carbons), respectively. The chemical shifts of the β-isomer were similarly reasonably understood. Thus, I was assigned to **2** (n=6). Moreover, the structures of II and I were confirmed through chemical conversions to the corresponding epoxides, **4** and **5**, respectively, by treatment with aqueous K_2CO_3. The FAB mass spectra showed M/Z 955 ($M + H^+$) for both epoxides and the ^{13}C-NMR spectra (DMSO-d_6) showed absorptions of epoxide carbons for **4** or **5** at 48.2 and 52.9 ppm, or at 52.6 and 55.9 ppm, respectively. 270 MHz ^{1}H-NMR spectra (D_2O, internal

standard : acetone, δ2.1) of **4** and **5** showed singlet 1H-absorption at δ5.15 and doublet 1H-absorption at δ5.22 (J = 3.7 Hz)as the C-1 protons, respectively[8]. These results indicate that **4** and **5** were the manno-epoxide and the allo-epoxide, respectively, confirming the structural assignments of **I** to **2** (n=6) and **II** to **1** (n=6).

When the pH of the reaction mixture was maintained around the pKa (ca. 12) of the cyclodextrin hydroxyls (pH 12.5, 12.0, or 11.0) with aqueous NaOH or buffer solution, **2** (n=6) could not be obtained, suggesting rapid conversion of **2** (n=6) to **5** in the alkaline condition. The kinetics of the disappearance of **1** (n=6) and **2** (n=6) in phosphate buffer (pH 12.0, 20°C) revealed that **2** (n=6) was more unstable ($t_{1/2}$: 4.8 min) than **1** (n=6) ($t_{1/2}$: 239 min). Under this condition, the primary tosylate **3** (n=6) was stable for at least 4 h.

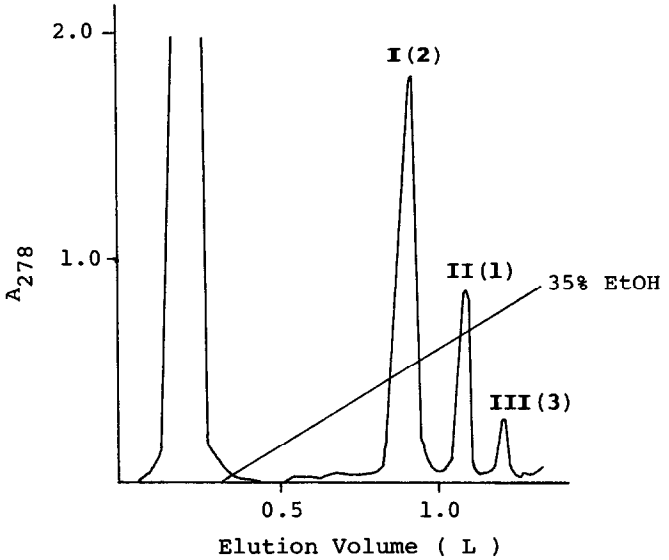
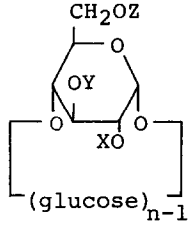


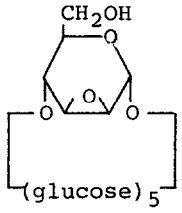
Figure 1. Reversed-phase column chromatography of the mixture obtained from the reaction of α-cyclodextrin with tosyl chloride. A linear gradient elution of EtOH was applied.

Because of the instability of the main product, the C-3 tosylate (**2**, n= 6) under alkaline conditions, tosylation of α-cyclodextrin may give different results depending on slight differences in reaction conditions and work-up procedures. However, the procedure where pH is not maintained and the simple separation method by use of the reversed-phase column gave reproducible results and are convenient for the preparation of the secondary tosylates.

Acknowledgement. We are indebted to Japan Maise Products Co. Ltd. for generous gift of α-cyclodextrin.



1 X : Ts ; Y,Z : H
2 Y : Ts ; X,Z : H
3 Z : Ts ; X,Y : H



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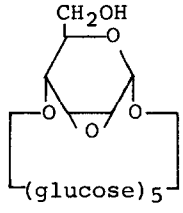

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References and Notes

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(5) TSK-GEL LS 410 ODS SIL Column (4 x 300 mm, 5 μm, Toyo Soda, Japan).

(6) FAB mass spectra showed M/Z 1127 ($M + H^+$) for I, II, and III, showing that they were indeed mono-tosylates.

(7) L. D. Melton and K. N. Slessor, Carbohyd. Res. 1971, 18, 29.

(8) β-Cyclodextrin-manno-epoxide has been prepared from β-cyclodextrin-2-tosylate (**1**, n=7) by a similar procedure to the present one. The ^{1}H-NMR spectrum of this epoxide was reported to show singlet 1H-absorption at δ5.1 for the C-1 proton of the manno-epoxide residue. In glucose-manno-epoxide, $J_{1,2}$ is normally close to 0 Hz, while in allo-epoxides it is 2.5～4.5 Hz. See ref (3b) and the references cited therein.

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