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6A6B, 6A6C, AND 6A6D-DITOSYLATES OF β-CYCLODEXTRIN

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Regio-isomers, 6A6B, 6A6C, and 6A6D-ditosylates of β-cyclodextrin prepared by the reaction of β-cyclodextrin with tosyl chloride were easily and effectively separated through reversed phase column chromatography and assigned.

In the past decade, designs of enzyme (or receptor) mimics by use of cyclodextrins have attracted much attention[1]. Since enzymes (or receptors) have at least two functional groups at the active site, more sophisticated enzyme (or receptor) mimics should be constructed to possess two (or more) functional groups at desirable positions of cyclodextrins. Separation of a tri-substituted α-cyclodextrin (6A6C6E-isomer) from a mixture of the positional isomers by means of silica gel column chromatography was carried out to make a model of a receptor for a phosphate anion[2], although structures of the other regio-isomers were not determined. Specific activation of two hydroxyls of β-cyclodextrin has been attained through specific preparations of several 6A6C and/or 6A6D-capped β-cyclodextrins from which 6A6C and/or 6A6D-difunctionalized β-cyclodextrins are easily obtained[3]. However, the complement, 6A6B-disubstituted β-cyclodextrin is not yet synthesized.

We wish to describe here a convenient preparation method and a structural assignment of the 6A6B-ditosylate of β-cyclodextrin as well as a highly effective separation of β-cyclodextrin-6A6C- and 6A6D-ditosylates by means of reversed phase column chromatography.

A solution of β-cyclodextrin (3 g) and p-toluenesulfonyl chloride (2.4 g)[4] in pyridine (4 mL) was stirred for 1.5 h at room temperature followed by addition of water (1 mL) and concentration in vacuo. The crude mixture was applied on a reversed phase column (Lobar column LiChroprep RP 8, Merck Ltd., 25 x 310 mm). Gradient elutions of ethanol gave 6-deoxy-6-tosyloxyl-β-cyclodextrin (400 mg, 12 %), and di-tosylates, **1** (370 mg, 10 %), **2** (390 mg, 11 %),and **3** (220 mg, 6 %) (Figure 1). Assignments of **1~3** were made as shown in Scheme 1. ^{1}H-NMR (100 MHz) and FAB mass spectra indicated that **1~3** were di-tosylates. ^{1}H-NMR spectra of the deoxy derivatives (**4~6**) which were obtained by the $NaBH_4$ reduction of **1~3** showed the presence of two methyl groups (δ 1.2, doublet, J = 6 Hz), demonstrating that **1~3** were the primary di-tosylates. The di-tosylates (**1~3**) were converted to the corresponding diphenylthio-derivatives (**7~9**) by treatment with thiophenol. The authentic 6A6C and 6A6D-diphenylthio-derivatives were prepared by the reaction of thio-

phenol with the β-cyclodextrin capped with diphenylmethanedisulfonate[3c] and isolated by use of the reversed phase column. By comparing the ^{1}H-NMR spectral patterns of the phenyl groups and the retention times in reversed phase HPLC[5] with those of the corresponding 6A6C and 6A6D-isomers, **7** (**1**) and **8** (**2**) were identified as 6A6D and 6A6C-isomers, respectively. Therefore, **3** was reasonably assigned to the 6A6B-isomer since there are only three

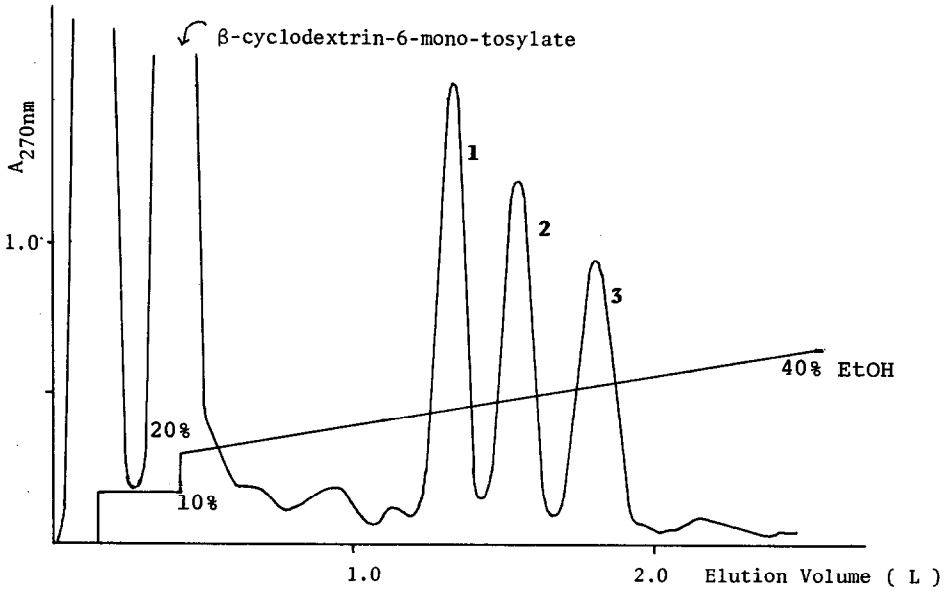
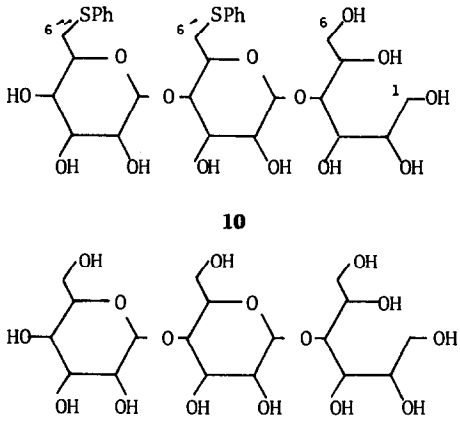


Figure 1. Reversed phase column chromatography of the mixture obtained by the reaction of β-cyclodextrin with p-toluenesulfonyl chloride. A stepwise followed by a linear gradient elution of ethanol was applied.



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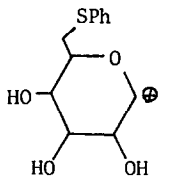

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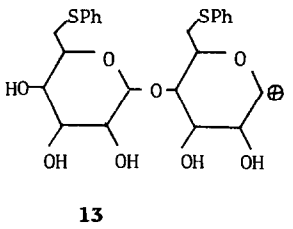

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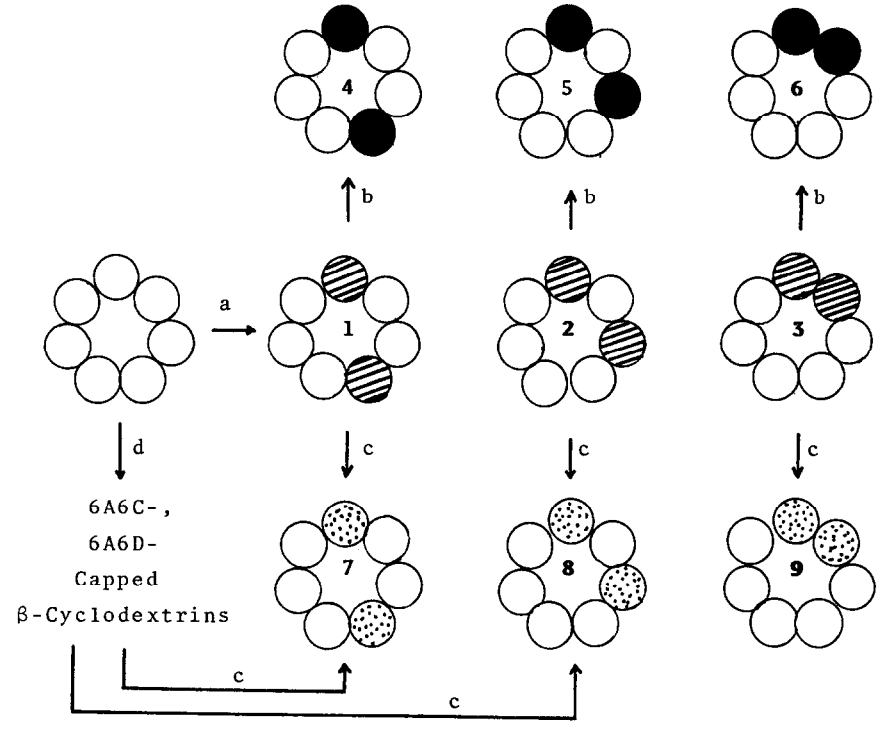
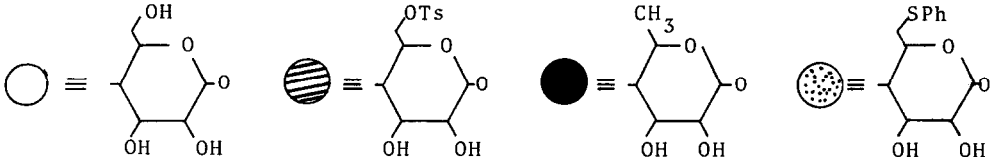
kinds of di-substitutions on the primary hydroxyls of β-cyclodextrin. Moreover, the 6A6B structure of **3** was confirmed by an enzymic degradation of **9** with Taka-amylase[6] followed by $NaBH_4$ reduction to give **10**. By comparing the ^{13}C-NMR spectrum (25 MHz) of **10** with that





a : TsCl/Py, b : $NaBH_4$/DMSO, c : PhSH/DMF, d : p,p'-diphenylmethane-disulfonyl chloride/py

Scheme 1.

of **11**[7] and also by the FAB mass spectrum[8] of **10** showing the presence of the molecular ion and the fragments, **12** and **13**, the tosylate (**3**) was assigned to the 6A6B isomer.

Thus, we established here the convenient preparation method of 6A6B, 6A6C, and 6A6D-disulfonates of β-cyclodextrin and their isolation through single column chromatography. Our separation method by use of the reversed phase column is also quite suitable for elimination of the unreacted cyclodextrin and salts such as pyridinium tosylate. Taka-amylolysis might be generally applicable to the regio-assignment of 6A6B-structures of di-substituted cyclodextrins.

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(4) We added p-tosyl chloride to the pyridine solution, monitoring the formation of the tosylates. The amount of the sulfonyl chloride was dependent on the dryness of pyridine and β-cyclodextrin.

(5) TSK-GEL LS 410 ODS SIL Column (4 x 300 mm, 5 μm, Toyo Soda, Japan). A linear gradient elution of 20 % aqueous CH_3CN (20 mL) and 40 % aqueous CH_3CN (20 mL) was applied. Retention percentages of CH_3CN were as follows : **7** ; 27.3 %, **8** ; 28.5 %, **9** ; 30.7 %. The ^{1}H-NMR spectra of the phenyl parts of **7~9** differ from one another.

(6) 6-Substituted α-cyclodextrin has been reported to be hydrolyzed by Taka-amylase to give 6'-substituted maltose, where the substituent was tosyloxyl, azido, or halide group. L. D. Melton and K. N. Slessor, Can. J. Chem. 1973, 51, 327.

(7) The 25 MHz ^{13}C-NMR spectrum of **11** (DMSO-d_6) showed absorptions at 62.3 ppm for C-1, at 62.7 ppm for C-6, and at 60.0 and 60.7 ppm for C-6' (or C-6'') and C-6'' (or C-6'). In the ^{13}C-NMR of **10**, the absorptions of the glucitol part (C-1 and C-6) were observed at the same chemical shifts as those of **11**, while the absorptions corresponding to those of C-6' and C-6'' of **10** were not present and, instead, the upfield-shifted absorptions at 35.0 ppm for C-6' and C-6''. These observations demonstrated that the substitution of the hydroxyl group with the phenylthio group was not on the reducing end of maltotriose but on the non-reducing glucose units. Assignments of the ^{13}C-NMR absorptions of glucitol have been reported. K. P. G. Kieboom, A. Sinnema, J. M. van der Toorn, and H. van der Bekkum, Recl. Trav. Chim. Pays-Bas, 1977, 96, 35.

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