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MONOTOSYLATED α- AND β-CYCLODEXTRINS PREPARED IN AN ALKALINE AQUEOUS SOLUTION

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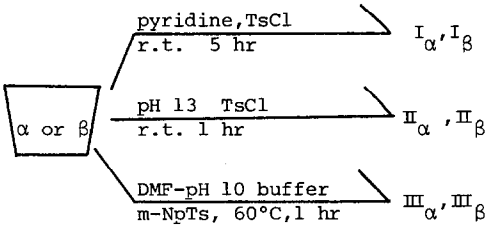
In order to establish the tosylated positions of α- and β-cyclodextrins, ^{13}C-nmr spectra for the monotosyl-derivatives prepared in an alkaline aqueous solution were examined and determined to be in the 6-position of one glucose unit for β-cyclodextrin and to be in the C-2 position for α-cyclodextrin.

Cyclodextrins(CD) are torodial cyclic oligosuccharides with the primary hydroxyl glucose C-6 on their more closed side and the secondary C-2 and C-3 hydroxyls on the other side. They provide their central cavities as hydrophobic or sterically restricted reaction fields. Within the complex there may be a reaction with the hydroxyl group of CD. Many derivatives of CD have also been studied in which catalytic or reactive functional groups are present to attack the bound substrate.[1] The first important step to attach the functional groups to hydroxyls of CD is selective sulfonation. However, the preparation method and substituted position of the popular sulfonated CD have not been clear. We have already reported that α- and β-CD could be selectively mono-sulfonated with tosyl chloride in an alkaline aqueous solution.[2),3)] In this letter we wish to report the determination of substituted positions on the glucose ring of the mono-tosylated cyclodextrins prepared under some different conditions based on ^{13}C-nmr spectroscopy, paper chromatography and HPLC. We also wish to suggest that the substituted position in CD under our original alkaline condition was dependent upon the geometry of the complex.

Various mono-tosylates(I_α, I_β, II_α, II_β, III_α, III_β) were prepared under three different conditions. (scheme 1). In each pathway, tosylation of both α- and β-CD were carried out in the same manner. The first pathway has already been reported as the method for attaching a tosyl residue at the primary C-6 hydroxyl group of the CD moiety[4] which was treated with 1.8 eq. of tosyl chloride in dry pyridine at 5°C for 5 hr. The second pathway was treated with 6 eq. of tosyl chroride and CD in an alkaline aqueous solution at room temperature for 1 hr. As this reaction proceeded it was accompanied by a 1:1 complex formation between tosyl chloride



(scheme 1) monotosylation of α- and β-cyclodextrin.

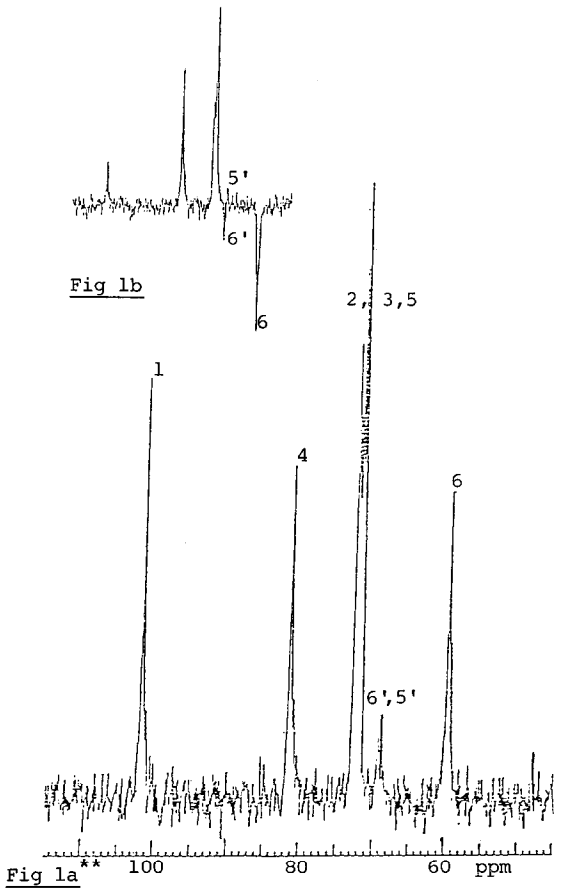


Fig 1b

Fig 1a

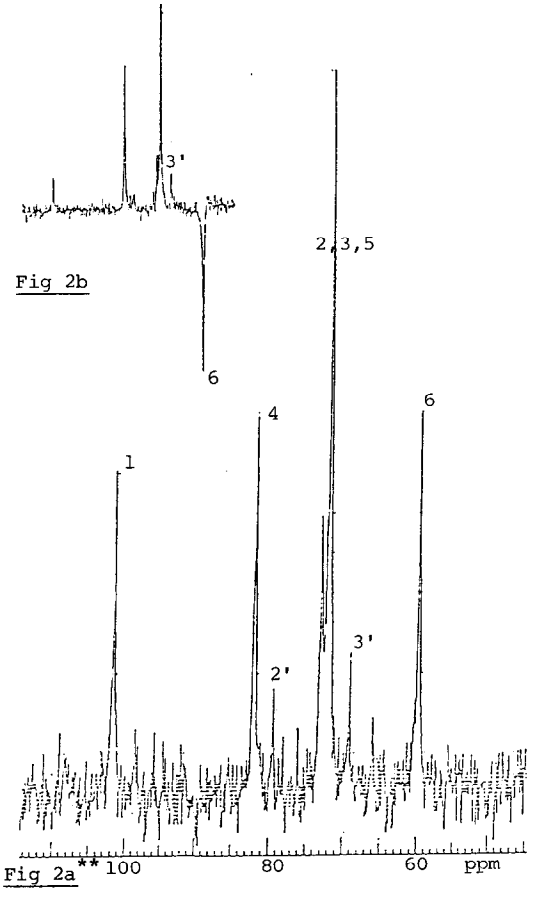


Fig 2b

Fig 2a

** ^{13}C-nmr specra of II_{β} (Fig 1) and of II_{α} (Fig 2); solvent:DMSO-d_6,reference:ext(TMS), temperature:70°C, instrument:JEOL-90Q;
a):using by usual techninique,b):using by INEPT method technique.

and CD moiety. The final pathway has been reported by Breslow et al.[5] III_{α} and III_{β} were prepared by treating α- or β-CD with 3-nitrophenyltosylate(m-NpTs) in DMF-buffer solution. Each crude product was purified by reported preparative HPLC using an ODS-silicagel column. The purity of the products was confirmed by HPLC, elemental analysis, ^{1}H-nmr and thin-layer chromatography. Elemental analysis data and ^{1}H-nmr estimation by peak area comfirmed that all of the purified products were monotosylated compounds. ^{13}C-nmr spectra of these compounds showed much precise information about the structure concerning the located site. The rule of shift by sulfonyl group substitution is said to be by Breslow, that the substituted carbon will be downshifted and the other neighboring carbons of both sides will be upshifted. Anther nmr technique called the INEPT method[6] was used to determine whether the peak was due to the methine carbon at the C-2 or C-3 position or due to the methylene carbon at the C-6 position. The ^{13}C-nmr spectra of I_{α} and I_{β} which were treated in pyridine show two small peaks around 65 and 69 ppm corresponding to a downfield shift of C-6' and an upfield shift C-5'. These compounds

also showed the expected signals for tosyl groups, so the tosyl moiety in the compounds I_α and I_β was attached at the C-6 hydroxyl position. In the case of the III method, the spectrum of III_β showed four small peaks, corresponding to a downfield shift of C-2' and an upfield shift of C-1', C-4' and C-3'. III_α was much the same; the tosyl moiety in III_α and III_β was substituted at the C-2 position. The ^{13}C-nmr spectrum of II_β in DMSO-d_6 is shown in Fig 1. All peaks were identified with the peaks of I_β. The tosyl moiety was introduced onto the C-6 hydroxyl position. On the other hand, the spectrum of II_α was different from I_α, compared with III_α.(Fig 2). There was no peak corresponding to shifted C-6' carbon(Fig 2b),therefore the tosyl group in II_α must be located at the C-2 position. HPLC data of various tosylated compounds supported the above determination.(Fig 3). In the case of α-CD, retention volumes were the same for both the products prepared in aqueous solution(II_α) and for the product prepared in DMF-buffer (III_α); however, the retention volume of the product prepared in pyridine(I_α) was larger than that of II_α and III_α. On the other hand, in the case of β-CD, the retention volumes of the main product prepared in aqueous solution(II_β) and in pyridine(I_β) were the same and the retention volume of the product prepared in DMF-buffer(III_β) was larger. The evidence from the analysis by partial hydrolysis of the compounds assured the determination of substituted position.(Table 1). Tosylates II_α, II_β and III_β were hydrolyzed in 2N-HCl solution at 80°C for 3 hr. The contents in the hydrolyzate were examined by the use of paper chromatography with a solvent of butanol, ethanol and water in the ratio of 5:4:3. Detection was carried out with a diphenylamine spray. Rf values of the hydrolyzate of II_α prepared in an aqueous solution and of the hydrolyzate of III_β apparently differ from both the hydrolyzate of 6-tosyl form(hydrolyzate of II_β) and the authentic C-3 tosyl glucose prepared according to the previous literature.[7]

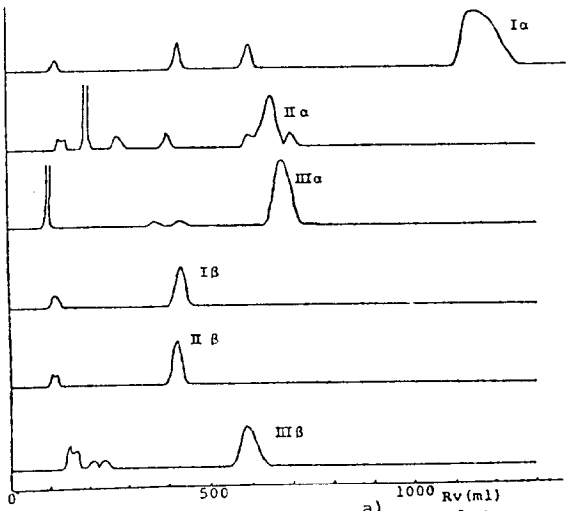


Fig.3 Preparative HPLC Date[a] of Tosylates

a) instrument: HLC-827(TOYO SODA), eluent: 10% acetonitrile in water, column: LS-410(ϕ= 25x300mm), detect:UV(254 nm)

Table 1 Paper Chromatography of Hydrolyzates*

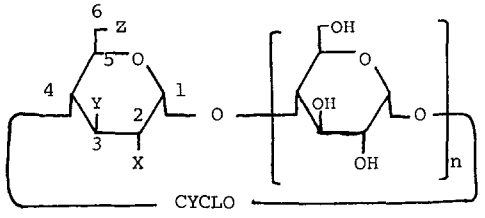
starting material	Rf value
II_β	0.51
II_α	0.61
III_β	0.61
authentic 3-tosyl glucose	0.71

*solvent; butanol:ethanil:water=5:4:3, coloring reagent; diphenylamine sprey and aniline-hydrogen-phthalic acid

The results of three pathway substitutions are summarized in Table 2. In the pyridine

Table 2 Specific Site of Modification in Tosylation of Cyclodextrin

method	solvent	α-CD	β-CD
I	pyridine	6	6
II	alkaline	2	6
III	DMF-buffer	2	2



solution, both α- and β-CD were modified on primary hydroxyl position of glucose C-6. In the DMF-buffer condition, both α- and β-CD were modified at the C-2 position stereospecifically. Remarkably, in the alkaline aqueous solution, there were differences between α-CD and β-CD depending on the ring size of the CD. In the alkaline solution, the product which was obtained as monotosyl-α-CD was the same as which was obtained in the DMF-buffer solution, meaning that we obtained C-2 monotosylated-α-CD. And in the case of β-CD, the product was the same as the one which was obtained as C-6 monotosylated-β-CD in pyridine. Our preliminary structual determination on the monotosyl-β-CD in the *previous paper*[3] *should be corrected.*

But our original condition in an alkaline aqueous solution has advantages in two points: 1) the experiment and purification in water is easy and simple, 2) few isomers were produced and a good yield of desired product was obtained; for the yield of monotosyl-α-CD and monotosyl-β-CD were 16% and 28% respectably. It is assured that the process will be acconpanied by host-guest complex formation between CD and tosyl chloride in an aqueous solution. This may cause the above mentioned advantages of this preparation and also the remarkable change of this regiospecificity at the modified site. In the DMF-buffer condition, tosylation may also proceed with the host-guest complex formation between CD and 3-nitrophenyltosylate, but the change of specificity at the modified site will not occur.

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