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SELECTIVE SULFONATION OF A SECONDARY HYDROXYL GROUP OF β-CYCLODEXTRIN

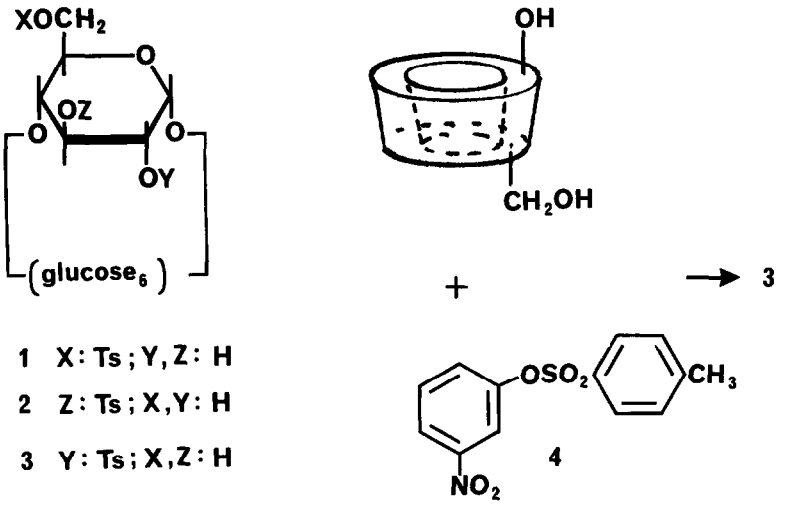
Akihiko Ueno[1] and Ronald Breslow*

Department of Chemistry
Columbia University
New York, New York 10027

Abstract: Tosylation of the secondary side of β-cyclodextrin, which has previously been incorrectly reported, can be achieved by tosyl transfer from 3-nitrophenyl toluenesulfonate to the C-2 hydroxyl of the cyclodextrin.

Cyclodextrins are toroidal cyclic oligosaccharides with the secondary hydroxyls of glucose C-2 and C-3 on their more open face and the primary C-6 hydroxyl on the other face. Their ability to bind good-sized organic molecules in the central cavity has provided a basis for the construction of models for receptor binding and for enzymatic catalysis.[2] Selective sulfonation of primary hydroxyl groups of α-cyclodextrin (cyclohexaamylose) and of β-cyclodextrin (cycloheptaamylose) have permitted the attachment of functional groups for modified binding[3] or catalysis.[4] Selective functionalization of the secondary side has normally been possible only by acyl transfer reactions of bound substrates.[5] For this reason, the reports[6] that α- and β-cyclodextrin could be selectively sulfonated on the secondary side with tosyl chloride in aqueous medium have excited considerable attention. We have examined the reported process carefully, and unfortunately we find[7] that the reported "secondary" monotosylate of β-cyclodextrin (2) is identical in all respects with the known primary β-cyclodextrin-6-tosylate (1). However, we have devised an authentic procedure for the preparation of the secondary β-cyclodextrin-2-tosylate (3). The properties of this material are very different from those of 1, or reported[6] for "2".

Tosylate 3 was prepared by reaction of 12 g β-cyclodextrin with one equiv. of 3-nitrophenyl tosylate (4) in 120 ml DMF by adding 72 ml of 0.2 M carbonate buffer (pH 9.9) and stirring the reaction mixture at 60° C for 1 hour. Then the mixture was neutralized with 1 N HCl, and one liter of acetone was added to precipitate cyclodextrin derivatives other than 3. The filtrate was concentrated almost to dryness; addition of one liter of acetone produced solid 3 in ca. 10% yield. It was further purified by Sephadex chromatography, to furnish the pure pentahydrate. Found (Calc'd. for $C_{49}H_{76}O_{37}S \cdot 5\ H_2O$): C, 42.79 (42.66); H, 6.10 (6.30); S, 2.35 (2.32).



1 X: Ts; Y,Z: H

2 Z: Ts; X,Y: H

3 Y: Ts; X,Z: H

The R_f value on silica (n-butanol, ethanol, water 5:4:3 by volume) was 0.52 for the secondary tosylate 3, but 0.49 for authentic primary tosylate 1 and for "secondary" tosylate 2. Furthermore, the solubility of 3 in water is strikingly good (> 35 g/100ml) in contrast to the poor solubility of 1 (< 0.04 g/100ml). Thus in the reported[6] procedure for the preparation of 2, any secondary tosylate 3 would have been lost. The great difference in solubilities of 1 and 3 presumably reflects differences in crystal packing. Both 1 and 2 afforded 6-deoxy-β-cyclodextrin ($-CH_3$ signal in the ^1H NMR) by reaction with KI, followed by $NaBH_4$. However, 3 is recovered unchanged from the KI reaction (85°C, 2 hr in DMF).

The ^1H NMR spectrum of 3 shows aromatic protons at δ 7.84, 0.1 ppm downfield from those of 1, while 1 shows anomeric protons at δ 4.82 with one of them shifted down to δ 4.76, but 3 shows no such shifted signal. Most striking is the evidence from ^{13}C NMR. The ^{13}C NMR spectrum of 3 in DMSO-d_6 is shown in Fig. 1; in the sugar region it is similar to that of β-cyclodextrin except for the single shifted carbons, denoted as primed numbers. Tosylation of a hydroxyl group leads to a downfield shift of the carbon carrying that hydroxyl (the α carbon), but a smaller upfield shift of the β carbon and a still smaller upfield shift of the γ carbon.[8] Since the position of the peak labelled 1' is such that it can only be an upfield-shifted C-1, with a magnitude of shift corresponding to a β carbon, the tosyl group in compound 3 must be located at C-2. This would lead to the large downfield shift of 2', the significant upfield shift of 3', and the small upfield shift of 4'. No other assignment is consistent with the known[8] shift effects of tosylation.

By contrast, the ^{13}C NMR spectra of the primary tosylate 1 and of the identical material 2 show two small peaks at 68.8 and 69.5 ppm, corresponding to a downfield shift of C-6' and an

upfield shift of C-5'. There is also a small upfield shift of C-4' to 80.8 ppm. All these compounds also showed the expected signals for the tosyl groups.

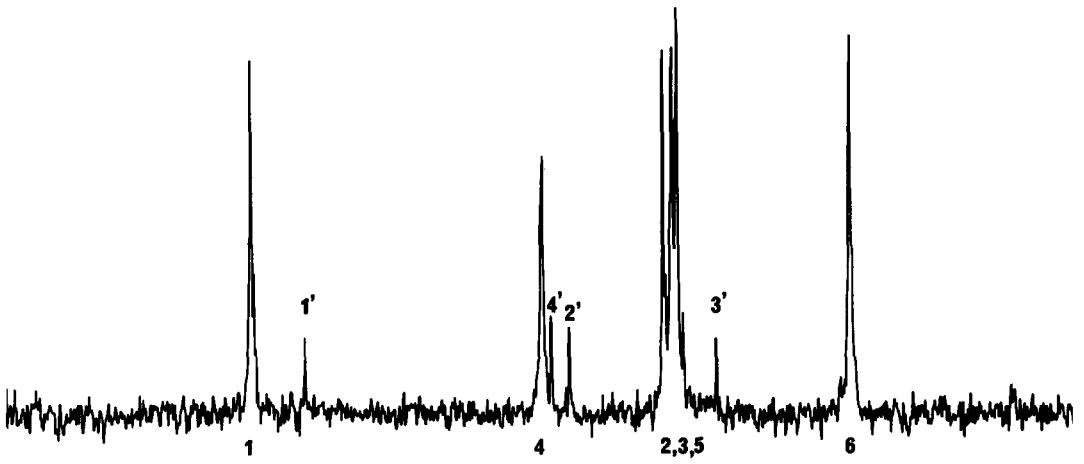


Fig 1. The ^{13}C NMR spectrum of 3 in DMSO-d_6 in the carbohydrate region. The shifts, in ppm, are 101.8 (C-1), 98.1 (C-1'), 81.4 (C-4), 80.9 (C-4'), 79.6 (C-2'), 72.9, 72.3, 71.9 (C-2, C-3, C-5) 69.2 (C-3'), and 59.8 (C-6). Signals for the toluenesulfonyl group are not shown.

Our tosyl transfer process is obviously related to the acyl transfer of the acetyl group of 3-nitrophenyl acetate to β-cyclodextrin[9], which involves a cyclodextrin-substrate complex. With acyl transfers we have found[10] that mixtures of C-2 and C-3 acylated products are formed, but since acyl migration in glycol esters is fast it is not clear whether attack is random or whether it goes specifically to one of the carbons, followed by equilibration. Our results with the tosyl group, which would not migrate once attached, suggest that at least with 3-nitrophenyl esters the acylation of β-cyclodextrin also occurs initially on the (intrinsically more acidic) C-2 hydroxyl. Further work will be needed to extablish the generality of this conclusion for other cyclodextrins and other esters.[11] However, the most important result is that an authentic secondary tosylate of β-cyclodextrin is now available for use in fabricating derivatives.[12]

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References and Notes

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7. The first finding that the "secondary" tosylate is really the known primary tosylate was by Dr. Robin Clark, shortly after publication of ref. 6a. We would like to thank Dr. Hattori for sending an authentic sample of his material. The report in ref. 6b that 2 hydrolyzes to glucose-3-tosylate must involve a mis-identification of the isomer.
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