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6-O-Trisubstituted β-Cyclodextrins Whose Substituents Are Different from One Another

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6^A-S-phenyl-6^F-O-(β-naphthalenesulfonyl)-6^X-O-(p-toluenesulfonyl)-6^A-thio-β-cyclodextrins (X = B, X = C, X = D, X = E, and X = G) were prepared from the reaction of 6^A-S-phenyl-6^F-O-(β-naphthalenesulfonyl)-6^A-thio-β-cyclodextrin with p-toluenesulfonyl chloride in pyridine. The structures were determined through their Taka amylase A-catalyzed hydrolyses.

Introduction of plural same or different kinds of substituents onto the desired positions of cyclodextrins is one challenging approach to the construction of artificial enzyme or receptor.

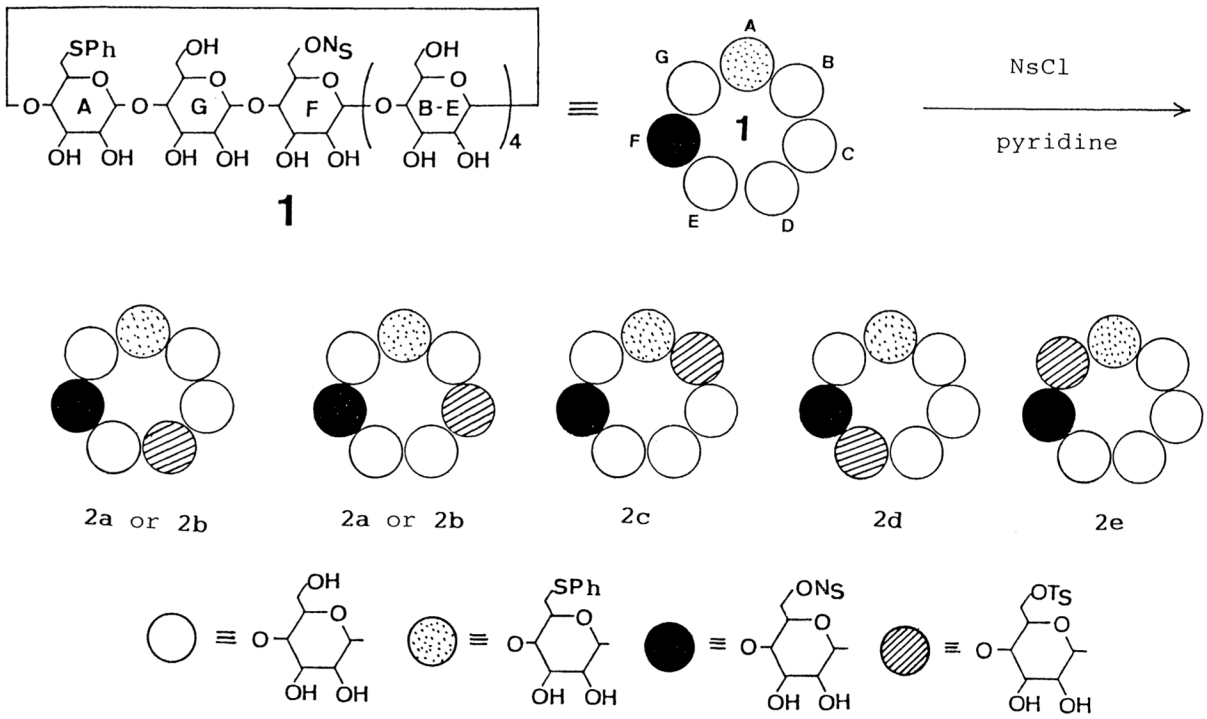
We have reported preparation, isolation, and structure determination of regioisomeric 6-O-poly(arenesulfonyl)-α (or β or γ)-cyclodextrins,[1-3] regioisomeric 6^A-S-phenyl-6^X-O-(β-naphthalenesulfonyl)-6^A-thio-β-cyclodextrins (X = B, X = C, X = D, X = E, X = F, and X = G),[4,5] and regioisomeric 6^A-S-(tert-butyl)-6^X-O-(β-naphthalenesulfonyl)-6^A-thio-β-cyclodextrins (X = B, X = C, X = D, X = E, X = F, and X = G).[5,6]

We describe here the first preparation of cyclodextrin derivatives, which have three different substituents at the given positions, through arenesulfonylation on 6^A-S-phenyl-6^F-O-(β-naphthalenesulfonyl)-6^A-thio-β-cyclodextrin mentioned above.[5]

p-Toluenesulfonyl chloride (170 mg) was added to a solution of 6^A-S-phenyl-6^F-O-(β-naphthalenesulfonyl)-6^A-thio-β-cyclodextrin (**1**) (195 mg) in pyridine (5 mL) and the mixture was stirred at room temperature for 0.5 h. After the formation of the trisubstituted cyclodextrins was confirmed on TLC, the reaction was stopped by addition of water and the mixture was concentrated in vacuo. The residue was chromatographed on reverse-phase column (Lobar column LiChroprep Rp18, 25 mm x 310 mm, Merck) with gradient elution from 40% aqueous methanol (1 L) to 75% aqueous methanol (1 L) to give **2**a (9 mg, 4.2%), **2**b (7.8 mg, 3.6%), **2**c (6.3 mg. 2.9%). **2**d (11 mg, 5.1%), and **2**e (6.6 mg, 3.0%) together with the recovered **1** (44 mg, 22%).[7]

We have already demonstrated that 6^A,6^B-O-bis(arenesulfonyl)-cyclodextrins and 6^A,6^B-S-diphenyl-6^A,6^B-dithio-cyclodextrin give the corresponding 6',6"-

disubstituted maltotrioses whereas the $6^{A},6^{C}$- and $6^{A},6^{D}$-isomers give two molecules of the corresponding 6'-substituted maltoses in the enzymatic hydrolysis by Taka amylase A.[1,3,8] This knowledge is useful to differentiate the structure of **2**a-e. Thus, **2**a,b, **2**c, **2**d, or **2**e is expected to give three kinds

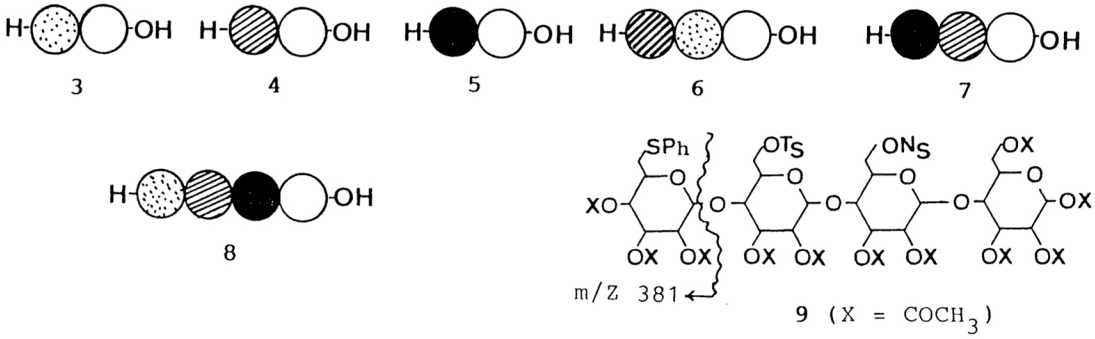


ph; phenyl, Ns; β-naphthalenesulfonyl, Ts; p-toluenesulfonyl

Scheme 1. Preparation of trisubstituted β-cyclodextrins.

of 6'-substituted maltoses (**3**-**5**), one kind of 6'-substituted maltose (**5**) and one kind of disubstituted oligosaccharide (**6**), one kind of 6'-substituted maltose (**3**) and one kind of disubstituted oligosaccharide (**7**), or one kind of trisubstituted oligosaccharide (**9**), respectively. The monosubstituted, the disubstituted, and the trisubstituted oligosaccharides in this case can be easily differentiated from each other by comparing their retention percentages of acetonitrile in reverse-phase HPLC with gradient elution from 10% aqueous acetonitrile to 60% aqueous acetonitrile.[9] The authentic 6'-substituted maltoses **3**-**5** were prepared from the Taka amylase A-catalyzed hydrolyses of the corresponding monosubstituted β-cyclodextrins.[3,8,10]

The enzymatic hydrolysis of **2**a or **2**b gave **3**, **4**, and **5** in equimolar amount, demonstrating that they are either 6^{A}-S-phenyl-6^{C}-O-(p-toluenesulfonyl)-6^{F}-(β-naphthalenesulfonyl)-6^{A}-thio-β-cyclodextrin or 6^{A}-S-phenyl-6^{D}-(p-toluenesulfonyl)-6^{F}-(β-naphthalenesulfonyl)-6^{A}-thio-β-cyclodextrin. The hydrolysis of **2**c or **2**d afforded **5** and a disubstituted oligosaccharide, or **3** and another disubstituted oligosaccharide, respectively.[9,11] The cyclodextrin derivative



2e was enzymatically hydrolyzed to give a trisubstituted oligosaccharide **8** whose structure was determined by complete acetylation with acetic anhydride in pyridine followed by mass spectral analyses. The fast atom bombardment mass spectrum of **8** showed that **8** was a trisubstituted maltotetraose and the field desorption mass spectrum of the acetylated compound **9** showed that it was a trisubstituted undecaacetyl maltotetraose. From these structures and the knowledge about the action pattern of Taka amylase A, it is reasonably deduced that **8** is a 6',6",6'"-trisubstituted maltotetraose. This implies that **9** must be 6'-O-(β-naphthalenesulfonyl)-6"-O-(p-toluenesulfonyl)-6'"-S-phenyl-6'"-thiomaltotetraose since the starting compound is the 6^{A}-S-phenyl-6^{F}-O-(β-naphthalenesulfonyl)-6^{A}-thio-β-cyclodextrin. This was confirmed by the electron impact mass spectrum of **9**, which gave an intense fragmentation ion at m/Z 381 showing that the phenylthio group was located on the non-reducing end.

Therefore, **2**a-e are assigned as shown in Scheme 1, except that the exact assignment of **2**a and **2**b was not successful; however, **2**a or **2**b is either the A,C,F- or the A,D,F-isomer.

Thus, the trisubstituted β-cyclodextrins where the substituents are on the given positions and different from one another were prepared and assigned for the first time.

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References

1) K. Fujita, A. Matsunaga, and T. Imoto, J. Am. Chem. Soc., 106, 5740 (1984).
2) K. Fujita, H. Yamamura, A. Matsunaga, T. Imoto, K. Mihashi, and T. Fujioka,

J. Am. Chem. Soc., 108, 4509 (1986); K. Fujita, H. Yamamura, T. Imoto, T. Fujioka, and K. Mihashi, J. Org. Chem., 53, 1943 (1988).

3) K. Fujita, A. Matsunaga, and T. Imoto, Tetrahedron Lett., 25, 5533 (1984).

4) K. Fujita, A. Matsunaga, Y. Ikeda, and T. Imoto, Tetrahedron Lett., 26, 6439 (1985).

5) K. Fujita, A. Matsunaga, H. Yamamura, and T. Imoto, J. Org. Chem., 53, in press (1988).

6) K. Fujita, A. Matsunaga, T. Imoto, K. Hirotsu, S. Kamitori, and T. Higuchi, J. Am. Chem. Soc., 107, 1790 (1985).

7) The numbers (**2**a-**2**e) of the compounds are given in order of increasing retention time in reverse-phase HPLC on TSKgel LS 410 ODS (4 mm x 300 mm, 5 μm, Toyo Soda) with gradient elution from 10% aqueous CH_3CN to 60% aqueous CH_3CN.

8) I. Tabushi, T. Nabeshima, K. Fujita, A. Matsunaga, and T. Imoto, J. Org. Chem., 50, 2638 (1985).

9) The retention percentages of acetonitrile on reverse-phase HPLC in these cases are as follows. the monosubstituted oligosaccharides, 20-25%; the disubstituted oligosaccharides, 30-35%; the trisubstituted oligosaccharides, 40-45%.

10) L. D. Melton and K. N. Slessor, Can. J. Chem., 51, 327 (1973).

11) The fast atom bombardment mass spectrum of the disubstituted oligosaccharide showed the molecular ion corresponding to the expected disubstituted maltotriose.

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