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A COMPLETE SET OF 6^A-AZIDO-6^A-DEOXY-6^X-*O*-SULFONYL-β-CYCLODEXTRINS

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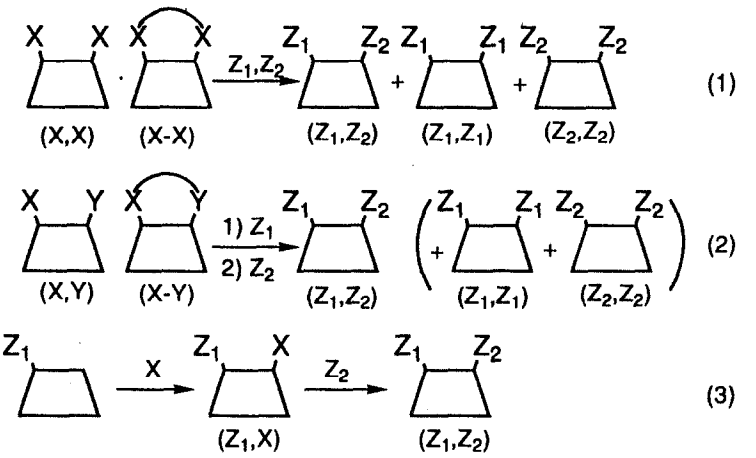
Key Words: Cyclodextrin; Enzyme Model; Receptor Model; Unsymmetrically Bifunctional Cyclodextrin

Abstract: Each of 6^A-azido-6^A-deoxy-6^X-O-(2-naphthalenesulfonyl)-β-cyclodextrins (X=B~G) was prepared by the reaction of 6-azido-6-deoxy-β-cyclodextrin with 2-naphthalenesulfonyl chloride, isolated, and structurally determined.

Construction of artificial enzymes (or receptors) by chemical modification of cyclodextrins has been extensively studied. While monosubstitution of primary hydroxyls of cyclodextrins allowed simple designing of enzymes (or receptors),[2] Ttransannular disulfonylation (disulfonate capping) developed new aspect of synthesis of symmetrically bifunctionalized enzyme (or receptor) mimics.[2,3] We also developed convenient preparation and effective separation of $6^A,6^X$-bis(*O*-arenesulfonyl)-cyclodextrins.[4] However, more sophisticated artificial enzymes (or receptors) should possess two different functional groups at desirable positions.

Strategy of preparation of these artificial enzymes (or receptors) may be divided into three types as shown in Scheme 1, where X and Y are activated primary hydroxyls such as sulfonates and Z_1 and Z_2 are functional groups. Since the product composition of the type (1) reaction is statistical, particular association between Z_1 and Z_2 (neither between Z_1 and Z_1 nor between Z_2 and Z_2) should be necessary for the formation of (Z_1,Z_2) in a composition more than 50% (statistical value). The type (2) reaction utilizing an unsymmetrically, transannularly disulfonylated cyclodextrin (X-Y) has been reported. This method permitted predominant production of (Z_1,Z_2), although information was not given with respect to the relative positions of Z_1 and Z_2.[5] Recently, we reported preparation and isolation of regiochemically pure (X,Y) where X has more reactive than Y.[6]

Six years ago, we reported the type (3) method, i.e., the 6-*O*-sulfonylation of 6-azido-6-deoxy-β-cyclodextrin with mesitylenesulfonyl chloride in pyridine.[7] Although this type method permitted isolation of (Z_1,X) which was pure with respect to the *relative* positions ($6^A,6^B$-, $6^A,6^C$-, or $6^A,6^D$-positions) of the substituents, each isomer (for example, the $6^A,6^B$-isomer) was most likely a mixture of two positional isomers ($6^A,6^B$- and $6^A,6^G$-isomers) which were not separable. In this paper, we describe preparation of a complete set of



X,Y; activated hydroxyl Z_1,Z_2; functional group

Scheme 1. Strategy for Preparation of Unsymmetrically Bifunctionalized Cyclodextrin (Z_1,Z_2)

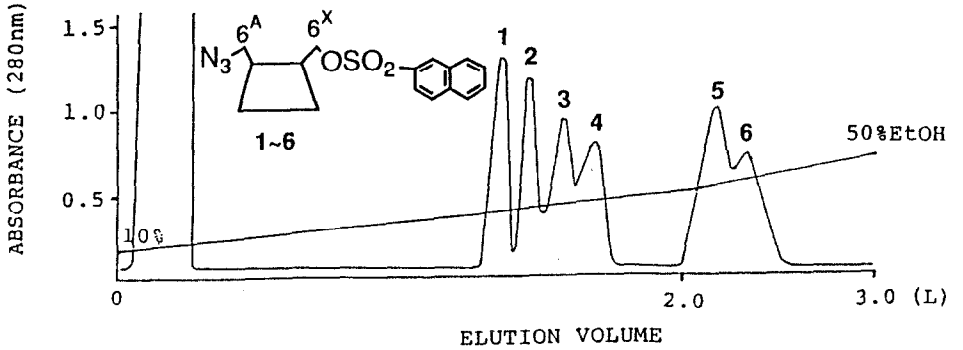
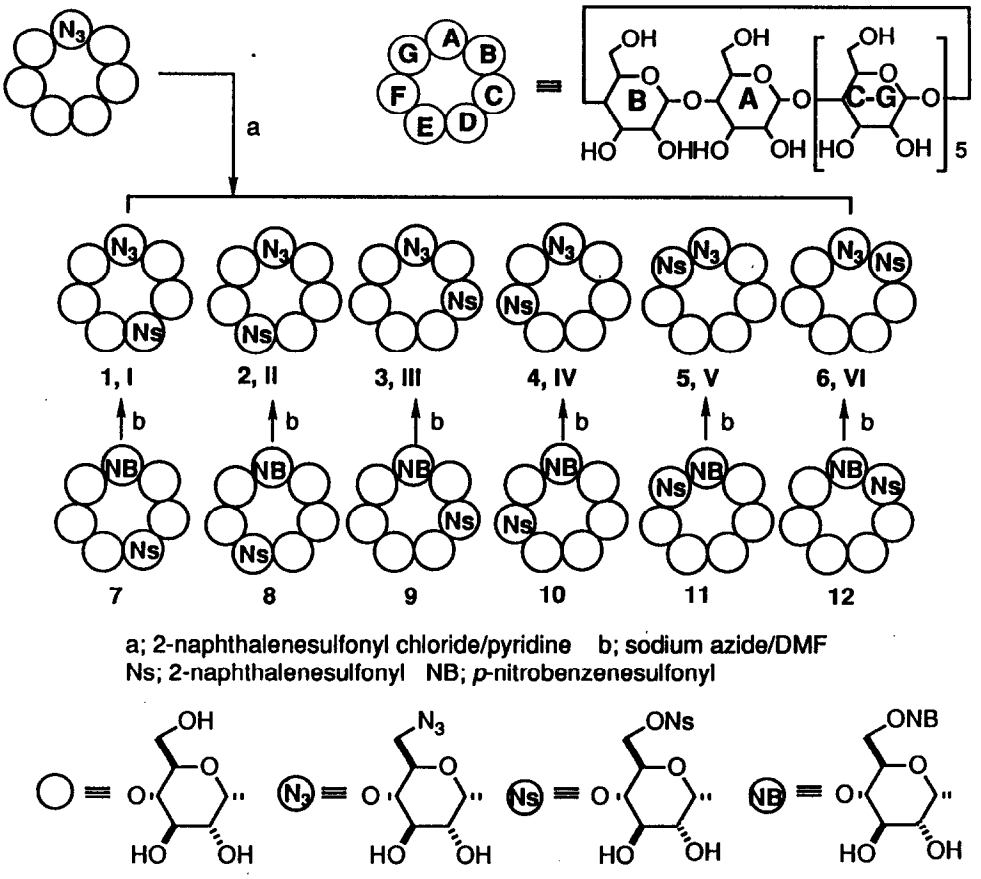


Figure 1. Reverse-phase column chromatography of 6^A-azido-6^A-deoxy-6^X-*O*-(2-naphthalenesulfonyl)-β-cyclodextrins **1~6**. A gradient elution of ethanol (EtOH) was applied.



Scheme 2. Preparation and Structure Determination of All Regioisomers of 6^{A}-Azido-6^{A}-deoxy-6^{X}-*O*-activated β-Cyclodextrin

regiochemically pure 6^{A}-azido-6^{A}-deoxy-6^{X}-*O*-activated (X = B, C, D, E, F, and G) β-cyclodextrins by the type (3) method.

2-Naphthalenesulfonyl chloride (324 mg) was added to a solution of 6-azido-6-deoxy-β-cyclodextrin (330 mg) in pyridine (20 mL) and the solution was stirred at room temperature for 5 h. After usual workup procedure followed by concentration, the residue was chromatographed by a reverse-phase column to give **1** (19.9 mg, 5.2%), **2** (19.4 mg, 5.0%), **3** (8.7 mg, 2.6%), **4** (9.1 mg, 2.4%), **5** (10.8 mg, 2.8%), and **6** (8.0 mg, 2.1%) (Fig. 1).

Fast atom bombardment mass (FABMS) spectra of **1-6** contained the molecular ion (M/z 1350, $M+H^{+}$). The

IR spectra demonstrated the presence of an azide group in each compound (ν_{N_3} 2100 cm^{-1}). The ^1H NMR spectra showed the presence of a naphthalenesulfonyl group per the cyclodextrin moiety. The positions of the glucose moieties having the azido and the naphthalenesulfonyl groups were determined as follows.

As mentioned above, we have already reported preparation, isolation, and structure determination of 6^A-*O*-(*p*-nitrobenzenesulfonyl)-6^X-*O*-(2-naphthalenesulfonyl)-β-cyclodextrins (X = B, C, D, E, F, and G) **7-12**.[7] The authentic compounds (**I-VI**) for **1-6** were expected to be obtained by the selective reaction of **7-12** with sodium azide. To test this expectation, we examined nucleophilic substitution reaction of 6-*O*-(*p*-nitrobenzenesulfonyl)-β-cyclodextrin and 6-*O*-(2-naphthalenesulfonyl)-β-cyclodextrins with sodium azide in 50% aqueous dimethylformamide at 40°C. This study showed that the *p*-nitrobenzenesulfonyl group was more reactive by twelve-times than the 2-naphthalenesulfonyl group.

A mixture of 6^A-*O*-(*p*-nitrobenzenesulfonyl)-6^E-*O*-(2-naphthalenesulfonyl)-β-cyclodextrin **8** (16.2 mg, 1.01×10^{-2} mmol) and sodium azide (1.00 mg, 1.53×10^{-2} mmol) in DMF (0.1 mL) was stirred at 40°C for 10 h. The mixture was diluted with water and chromatographed by a reverse-phase column with a gradient elution from 20% aqueous MeOH (500 mL) to 35% aqueous MeOH (500 mL) to give the recovered material **8** (3.98 mg, 24%), **II** (4.72 mg, 32%), and 6^A,6^D-diazido-6^A,6^D-dideoxy-β-cyclodextrin (1.30 mg, 10%). The other authentic compounds **I** and **III-VI** were also prepared by the similar procedure. By comparing the HPLC retention time (and ^{1}HNMR, FABMS, and IR spectra in the case of **2**) of **1-6** with those of the authentic compounds **I-VI**, the compounds **1-6** were the 6^A,6^D-, 6^A,6^E-, 6^A,6^C-, 6^A,6^F-, 6^A,6^G-, and 6^A,6^B-isomer, respectively (Scheme 2).

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References and Notes

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