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SYNTHESIS AND STRUCTURE DETERMINATION OF $3^A,6^X$-Di-O-ARENESULFONYL-α-CYCLODEXTRINS

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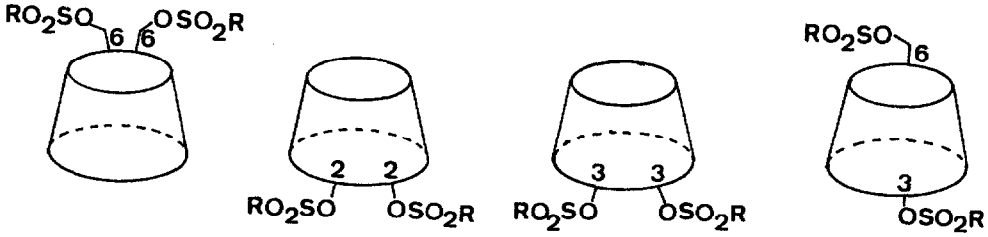
Summary: A regioisomeric mixture of 3^A-O-(β-naphthylsulfonyl)-6^X-O-mesitylsulfonyl-α-cyclodextrins (X = A-F) was prepared by the reaction of 3-O-(β-naphthylsulfonyl)-α-cyclodextrin with mesitylenesulfonyl chloride in pyridine. Each isomer was isolated and assigned.

Bifunctionalization of cyclodextrins has attracted much attention in construction of artificial enzymes and receptors.[2] The hydroxyl groups of cyclodextrins should be activated usually before their functionalization.

Regiospecifically transannular disulfonylation methods were developed for activation of two primary (6-OH) hydroxyl groups of β-cyclodextrin by Tabushi.[3] $6^A,6^X$-Di-O-sulfonylation followed by effective separation of each regioisomer was reported with α-, β-, and γ-cyclodextrins by Fujita et al.[4] With respect to disulfonylation of the secondary hydroxyl group (2-OH or 3-OH), there are a few reports; $2^A,2^X$-Di-O-sulfonylation of α-cyclodextrin[5a] and $3^A,3^X$-di-O-sulfonylation of β-cyclodextrin[5b] were reported by Fujita et al.[6]

The two activated hydroxyls in these disulfonates are located on the same side of cyclodextrin cavity (see **1**, **2**, and **3**). Therefore, the artifi-

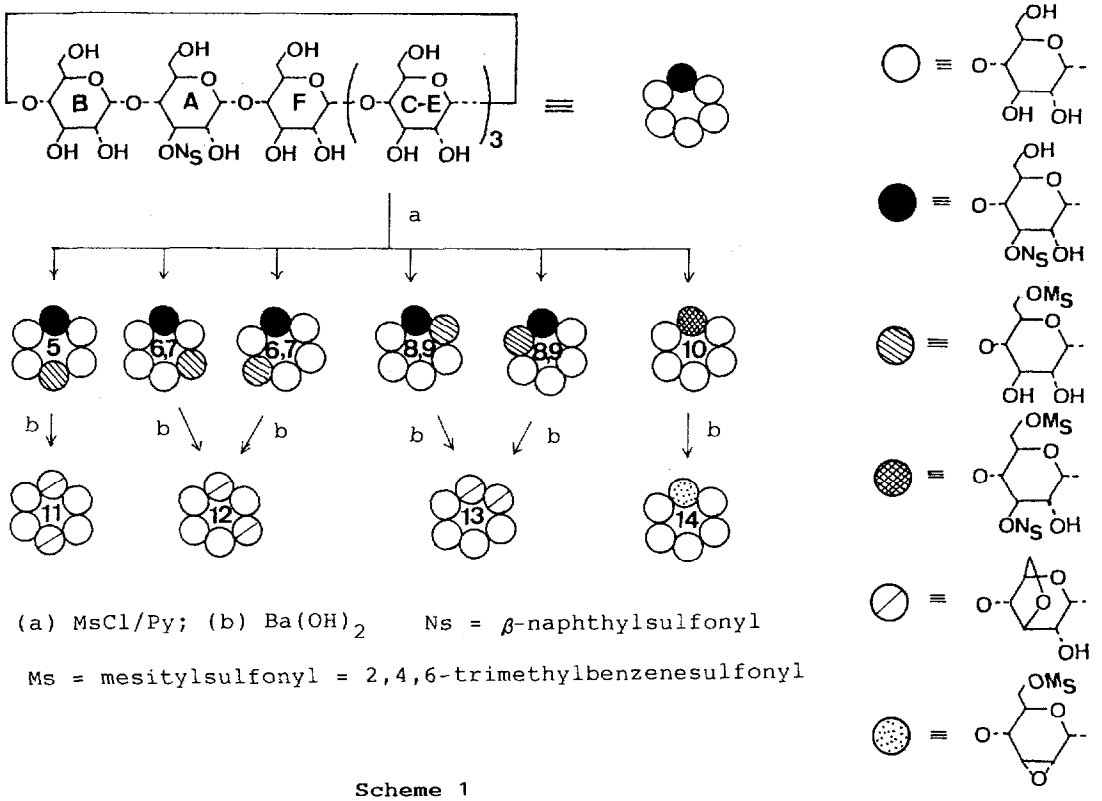


1 **2** **3** **4**

cial enzymes and receptors derived from these disulfonates will possess two functional groups at the same side of cyclodextrin cavity which is the binding site of substrate. These systems are extremely interesting, but it is necessary to develop a method that enables two functional groups to locate on the opposite sides of cyclodextrin cavity for the sake of wide study on construction of artificial enzymes and receptors.

We described here preparation and structure determination of 3^{A}-O-(β-naphthylsulfonyl)-6^{X}-O-mesitylsulfonyl-α-cyclodextrins (X = A-F) whose sulfonylated hydroxyl groups are located on the opposite sides of the cyclodextrin cavity to each other (see **4**).

Mesitylsulfonyl chloride (2.17 g) was added to a solution of 3-O-(β-naphthylsulfonyl)-α-cyclodextrin[5a] (1.087 g) in pyridine (18 mL) at room temperature. The solution was stirred for 3 h. After addition of water, the solution was concentrated in vacuo, dissolved in 10% aqueous CH_3CN, and chromatographed on a reverse-phase column (Lobar column, size C, Merck) with gradient elution from 10% aqueous CH_3CN (1 L) to 25% aqueous CH_3CN (1 L) followed by gradient elution from 25% aqueous CH_3CN (2 L) to 35% aqueous CH_3CN (2 L) to give the recovered starting material (596.7 mg, 54,9%), **5**



(a) MsCl/Py; (b) $Ba(OH)_2$ Ns = β-naphthylsulfonyl

Ms = mesitylsulfonyl = 2,4,6-trimethylbenzenesulfonyl

Scheme 1

(65.5 mg. 5.2%), **6** (76.1 mg, 6.1%), **7** (49.9 mg, 4.0%), **8** (31.8 mg, 2.5%), **9** (59.5 mg, 4.7%), and **10** (75.7 mg, 6.0%). The numbers of the compounds **5-10** are given in order of increasing retention time in HPLC on a reverse-phase column (Cosmosil $5C_{18}$, 4.6 mm x 100 mm, Nakarai) with gradient elution from 10% aqueous CH_3CN to 40% aqueous CH_3CN.

The structures of **5-10** were determined as follows. The ^1H and ^{13}C NMR spectra and fast-atom-bombardment mass (hereafter abbreviated as FABMS) spectra of **5-10** showed that each of them possessed one β-naphthylsulfonyl group at C-3 and one mesitylsulfonyl group at C-6. However, these spectral data did not clarify their regiochemistry.

Fujita et al. reported that 6-O-arenesulfonyl-cyclodextrins and 3-O-arenesulfonyl-cyclodextrins were easily and exclusively converted to 3,6-anhydrocyclodextrins and 2,3-anhydro-3(R)-cyclodextrins, respectively, by treatment with 0.1 N $Ba(OH)_2$ at 40 °C.[6a,b,7] They also showed that the latter products were further converted to 3,6-anhydrocyclodextrins by treatment with 0.25 N $Ba(OH)_2$ at 90 °C.[8] These results were used for determination of the regiochemistry of **5-10**.

A solution of each $3^A,6^X$-disulfonate in 0.1 N $Ba(OH)_2$ was kept at 40 °C for 4 h. The R_f values on silica gel TLC of the reaction mixtures demonstrated that **5-9** afforded respectively cyclodextrin derivatives without any arenesulfonyl group and that only **10** gave a monosulfonate **14**. Furtheremore, reactions of **5-9** with 0.25 N $Ba(OH)_2$ at 90 °C for 48 h were carried out. The reaction mixture was neutralized with diluted H_2SO_4, filtered, concentrated in vacuo, and chromatographed on the reverse-phase column to give **11-14**. The results are summarized in Scheme 1.

The FABMS spectra of **11-14** showed that they were dianhydro-α-cyclodextrins. By comparing their ^1H NMR spectra and HPLC retention times with those of the authentic $3^A,6^A;3^X,6^X$-dianhydro-α-cyclodextrins (X = B, X = C, and X = D) which were easily prepared by the reactions of $6^A,6^X$-di-O-arenesulfonyl-α-cyclodextrins (X = B, X = C, and X =D) with $Ba(OH)_2$,[4d,8] the compounds **11-13** were assigned to $3^A,6^A;3^D,6^D$-dianhydro-α-cyclodextrin, $3^A,6^A;3^C,6^C$-dianhydro-α-cyclodextrin, and $3^A,6^A;3^B,6^B$-dianhydro-α-cyclodextrin, respectively.

The ^1H NMR and FABMS spectra of the sulfonate **14** demonstrated that it was 6-O-mesitylsulfonylated 2,3-anhydro-α-cyclodextrin. While only 3^A-O-(β-naphthylsulfonyl)-6^A-O-mesitylsulfonyl-α-cyclodextrin can give 6-O-mesitylsulfonylated 2,3-anhydro-α-cyclodextrin as a major product of the reaction under alkaline conditions, all other regioisomers can be convertible to 2,3;3,6-dianhydro-α-cyclodextrins and then to 3,6-dianhydro-α-cyclodextrins under the conditions. Therefore, **10** should be assigned to 3^A-O-(β-naphthylsulfonyl)-6^A-O-mesitylsulfonyl-α-cyclodextrin.

The assignment of **5** to 3^A-O-(β-naphthylsulfonyl)-6^D-O-mesitylsulfonyl-α-cyclodextrin is confirmed by symmetry of ^{1}H NMR spectrum of **11**[9] showing that **11** must be a symmetric compound, $3^A,6^A;3^D,6^D$-dianhydro-α-cyclodextrin.

In conclusion, **5-10** are assigned to $3^A,6^D$-, $3^A,6^C$- (or $3^A,6^E$-), $3^A,6^E$- (or $3^A,6^C$-), $3^A,6^B$- (or $3^A,6^F$-), $3^A,6^F$- (or $3^A,6^B$-), and $3^A,6^A$-disulfonates, respectively.

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