Simple and Convenient Method for Synthesis of 3-*O*-Sulfonyl-γ-cyclodextrin

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3-*O*-(2-Naphthylsulfonyl)-γ-cyclodextrin was prepared together with 2-*O*-(2-naphthylsulfonyl)-γ-cyclodextrin by a reaction of γ-cyclodextrin with 2-naphthalenesulfonyl chloride in aqueous CH_3CN, isolated, and structurally determined.

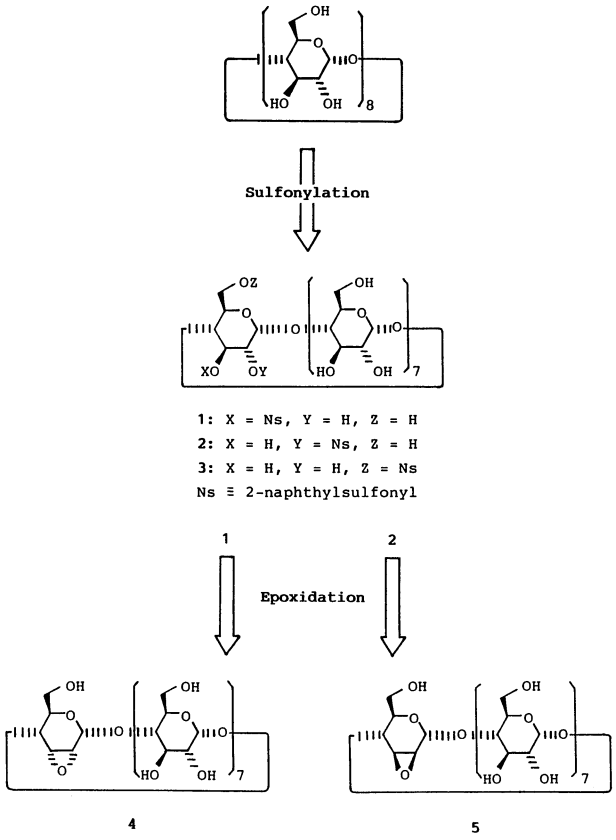
γ-Cyclodextrin (γ-CD) has unique characteristics such as large solubility in water, binding of large guest molecules,[1] and binding of two guests.[2] Therefore, attachment of various functional groups to γ-CD is valuable to construct unique enzyme (or receptor) models. Generally, hydroxyl groups of CDs must be sulfonylated before the respective functionalization. Initial studies were focused on the sulfonylation of the primary hydroxyl (6-OH) of γ-CD[3] since sulfonyl chloride had been well known to react exclusively with the primary hydroxyl of α- or β-CD in pyridine. Since a functional group introduced on the secondary hydroxyl side of β-CD demonstrated quite different enzyme-like properties from that on the primary hydroxyl side,[4] sulfonylation of the secondary hydroxyl (2-OH or 3-OH) of γ-CD should be investigated for the sake of wide development of construction of enzyme (or receptor) models. Recently, Murakami et al. reported that the 2-*O*-sulfonate was synthesized by the reaction of γ-CD with *p*-toluenesulfonyl chloride using dibutyltin oxide in dry DMF.[5] Fujita et al. also reported that the 2-*O*-sulfonates were obtained by the reaction of γ-CD with 1- or 2-naphthalenesulfonyl chloride in aqueous alkali.[6] However, the 3-*O*-sulfonate of γ-CD cannot be synthesized by their methods.

The enzymatic hydrolysis of 2-*O* or 6-*O*-sulfonylated γ-CD by Taka amylase A is a novel synthetic method for specifically modified linear oligosaccharides which can not be isolated in the enzymatic hydrolysis of the corresponding sulfonate of α- or β-CD.[6–8] Furthermore, the results of the hydrolyses afford more detailed knowledge with respect to the reactive site of Taka amylase A than those with α or β-CD derivatives.[6,7] Therefore, in the two points mentioned above, the synthesis of the 3-*O*-sulfonate of γ-CD is necessary.

In this paper, we report convenient method for preparation of the 3-*O*-sulfonate of γ-CD.

Results and Discussion

γ-CD was sulfonylated by addition of 2-naphthalenesulfonyl chloride to an alkaline aqueous CH_3CN solution of γ-CD at 30 °C, where the initial pH of the solution of γ-CD was adjusted to 12 and the pH was allowed to decrease during the reaction with 2-naphthalenesulfonyl chloride (Scheme 1). The reaction mixture was not a solution but a suspension of the sulfonyl chloride. The clear solution, which was obtained by filtration of the reaction mixture, was chromatographed on a reversed-phase column to afford sulfonates **1** (6.6%), **2** (12.6%), and **3** (1.1%) as shown in Fig. 1. Structural assignments of these compounds are as follows. The sulfonates **2** and **3** were assigned the 2-*O*-sulfonate and the 6-*O*-sulfonate, respectively, by comparing their HPLC retention



Scheme 1.

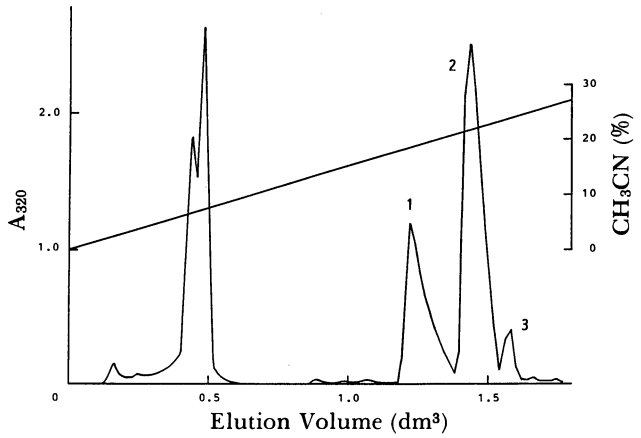


Fig. 1. Reversed-phase column chromatography of the mixture obtained from the reaction of γ-cyclodextrin with 2-naphthalenesulfonyl chloride in 30% aqueous CH_3CN. A linear gradient elution of CH_3CN was applied.

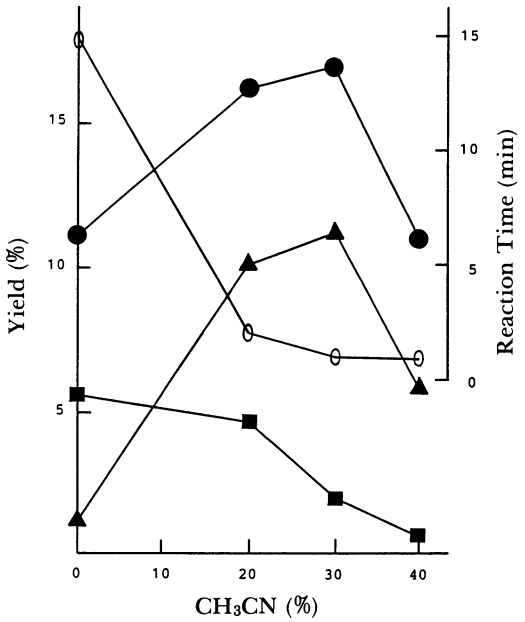


Fig. 2. Effect of CH_3CN content in the solvent (10 cm^3) on the yield of **1** (▲), **2** (●), or **3** (■) and on the reaction time (○) required for the pH change of the reaction mixture from 12 to 8 in the reaction of γ-cyclodextrin (2.0 g) with 2-naphthalenesulfonyl chloride (4.0 g) at 30 °C.

times and ^{13}C NMR spectra with those of the authentic specimens, 2-*O*-(2-naphthylsulfonyl)-γ-CD[6] and 6-*O*-(2-naphthylsulfonyl)-γ-CD.[7] The sulfonate **2** was converted to the corresponding manno-epoxide **5** (Scheme 1). The ^1H NMR spectrum of **5** showed a singlet absorption (δ=5.26) for an H-1 demonstrating its manno-epoxy structure. Also, its ^{13}C NMR and fast-atom bombardment (hereafter abbreviated to FAB) mass spectra confirmed that **5** was the epoxide of γ-CD.

The sulfonate **1** was identified as the 3-*O*-sulfonate by comparing its ^{13}C NMR spectrum with those of the authentic homologues, 3-*O*-(2-naphthylsulfonyl)-α-CD[9] and 3-*O*-(2-naphthylsulfonyl)-β-CD.[10] These three sulfonates did not possess any up-field shifted C-1 signal, demonstrating that the position of sulfonylation was not 2-OH but 3-OH. Its FAB mass spectrum also confirmed the monosulfonylation in **1**. In order to ascertain the 3-*O*-sulfonate structure, **1** was converted to the allo-epoxide (**4**) (Scheme 1), whose structure was spectrally determined as shown below. Its FAB mass spectrum contained the molecular ion. Its ^{13}C NMR spectrum demonstrated the presence of the epoxide carbons at δ=56.6 and 58.5. A coupling constant (J=3.3 Hz) of a H-1 proton signal at δ=5.34 in the ^1H NMR spectra demonstrated that **4** was the allo-epoxide, and, therefore, its precursor **1** was the 3-*O*-sulfonate.

The present reaction in aqueous CH_3CN was selective for secondary hydroxyl groups. However, when the sulfonylation was carried out in water instead of 30% aqueous CH_3CN, the reaction was not very selective for secondary hydroxyl groups, i.e., a mixture of the 3-*O*-sulfonate (0.8%), the 2-*O*-sulfonate (8.9%), and the 6-*O*-sulfonate (2.0%) was obtained. The time (15 min) required for the pH change of the reaction mixture from 12 to 8 in water was longer than that in 30% aqueous CH_3CN at 30 °C (2.5 min). Our independent kinetic studies on the epoxidation of the various cyclodextrin sulfonates demonstrated that the half-times of the decomposition (the epoxidation) of **1** and **2** at 20 °C in a phosphate buffer (pH 12.0) were 0.3 min and 1.7 min, respectively. The 6-*O*-sulfonate was far more stable under the alkaline condition. These mean that the long reaction time under alkaline conditions decreases the yields of the secondary sulfonates. Short reaction time is, therefore, very important for selective production of the secondary sulfonates and this was achieved by use of CH_3CN as a cosolvent. The presence of CH_3CN must decrease the time for the pH change from 12 to 8 by increase of the solubility of 2-naphthalenesulfonyl chloride. Effect of the CH_3CN concentration on the yields of sulfonates is shown in Fig. 2. The maximum yield was obtained around the 30% CH_3CN concentration. The yield at the CH_3CN concentration larger than 40% could not be obtained because of insolubility of γ-CD in the mixed solvent.

The effect of the reaction temperature on the yields of secondary sulfonates was also investigated (Fig. 3). Heating the reaction suspension is expected to increase the solubilities of the reactants and the rate constants of the two consecutive reactions (the sulfonylation and the epoxidation). An optimum temperature for the production of secondary sulfonates (**1** and **2**) was 30 °C. Therefore, the optimum conditions mentioned above (30% aqueous CH_3CN and 30 °C) were employ-

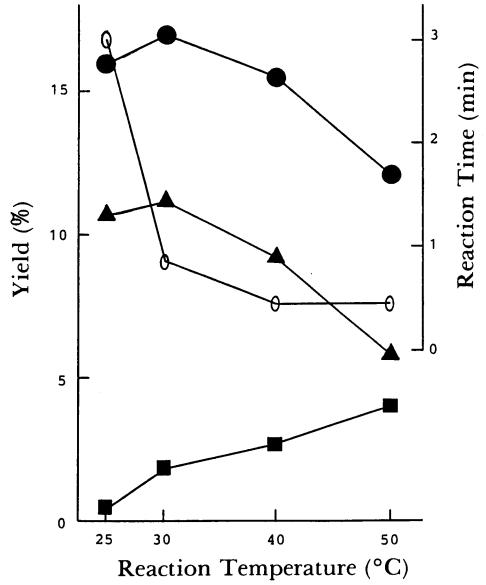


Fig. 3. Temperature effect on the yields of products and on the reaction time in the reaction of γ-cyclodextrin (2.0 g) with 2-naphthalenesulfonyl chloride (4.0 g): ▲, **1**; ●, **2**; ■, **3**; ○, reaction time required for the pH of the reaction mixture to change from 12 to 8.

ed for the selective preparation of secondary sulfonates (**1** and **2**).

Murakami et al. reported that the 2-*O*-sulfonate was synthesized by the tosylation of γ-CD via cyclic tin intermediate.[5] This reaction must be carried out under strict nonaqueous conditions, since the yield of 2-*O*-sulfonate depends on the amount of water in the reaction mixture. On the other hand, our method is very simple and convenient and can give constant yields of secondary 2-*O*- and 3-*O*-sulfonates. Moreover, this is only one method giving the 3-*O*-sulfonate of γ-CD.

Experimental

General. ^{1}H NMR (500 MHz) and ^{13}C NMR (25 MHz) were determined with a JEOL GX -500 and a JEOL FX-100 spectrometers, respectively. FAB mass spectra were recorded with a JEOL JMX DX-303/JMA 5000 data system. Thin-layer chromatography (TLC) was run with precoated silica-gel plates (Merck, Art 5554). Spot detection was carried out by UV light and/or staining with 0.1% 1,3-naphthalenediol in EtOH–H_2O–H_2SO_4 (200:157:43 v/v/v). A solvent of TLC development was *n*-C_3H_7OH–AcOEt–H_2O (7:7:5 v/v/v). A Merck Lobar prepacked column (Lichroprep Rp 18 column, 25 mm×310 mm) was used for reversed-phase column chromatography. High-performance liquid chromatography (HPLC) was performed on a Shimadzu LC3A with a Zorbax CN column (4.6 mm×150 mm, 5 μm, Du Pont).

Sulfonates of γ-Cyclodextrin (1—3). Powdered 2-naphthalenesulfonyl chloride (4 g) was added in one portion to 10 cm^3 of 30% aqueous CH_3CN solution (pH 12.0, adjusted by addition of aqueous NaOH) of γ-CD (2 g), which had been already thermostated at 30 °C. The suspension was vigorously stirred and its pH was allowed to decrease rapidly. During this reaction, the reaction vessel was kept in the bath thermostated at 30 °C. After the mixture became neutral, it was filtered, concentrated in vacuo, and chromatographed on a reversed-phase column with gradient elution from water (1 dm^3) to 30% aqueous CH_3CN (1 dm^3) to give **1—3**, which were lyophilized: **1** (150.8 mg, 6.6%), **2** (288.5 mg, 12.6%), **3** (25.8 mg, 1.1%).

1: ^{13}C NMR (25 MHz, D_2O, characteristic nonaromatic absorptions) δ=62.7, 72.6, 74.2, 74.8, 75.5, 79.6, 82.3, 83.4, 86.4, 103.0, 104.8; FABMS *m/z* 1487 ($M+H^+$), 1509 ($M+Na^+$).

A similar reaction was carried out in water at 30 °C. After filtration, the filtrate was chromatographed on a reversed-phase column. The products **1—3** were isolated in 0.8%, 8.9%, and 2.0% yields, respectively.

Effect of Acetonitrile on the Yields of Sulfonates. Powdered 2-naphthalenesulfonyl chloride (4 g) was added to a solution of γ-CD (2 g) in 10 cm^3 of water or aqueous CH_3CN (pH 12.0) and the suspension was stirred at 30 °C until the pH of the mixture became neutral. The mixture was filtered and analyzed by reversed-phase HPLC. The yields of products were obtained by HPLC with *p*-methoxyphenol as an internal standard. The results are shown in Fig. 2.

Effect of the Reaction Temperature on the Yields of Sulfonates. The reaction was carried out in a bath thermostated at given temperature similarly to that described in the experiment on the effect of acetonitrile. The results are shown in Fig. 3.

Epoxides of γ-Cyclodextrin (4 and 5). A solution of **1** (100.0 mg) in 0.05 mol dm^{-3} $Ba(OH)_2$ (10 cm^3) was stirred at room temperature for 1 h, neutralized with 0.05 mol dm^{-3} H_2SO_4 and filtered. The filtrate was chromatographed on a reversed-phase column with gradient elution from water (1 dm^3) to 10% aqueous CH_3CN (1 dm^3) to give the allo-epoxide (**4**) (76.3 mg, 88.7%).

Similarly, **2** (117.0 mg) gave the manno-epoxide (**5**) (87.4 mg, 86.9%).

4: ^{1}H NMR (500 MHz, D_2O) δ=3.56—4.12 (48 H), 5.07—5.11 (H-1, 7 H), 5.34 (H-1, 1 H, d, *J*=3.3 Hz); ^{13}C NMR (25 MHz, D_2O, characteristic absorptions) δ=56.6, 58.5, 62.8, 71.6, 73.6, 74.2, 74.3, 74.8, 75.4, 76.9, 81.1, 82.9, 98.2, 103.6, 104.0, 104.2; FABMS, *m/z* 1279 ($M+H^+$), 1301 ($M+Na^+$).

5: ^{1}H NMR (500 MHz, D_2O) δ=3.47—3.94 (48 H), 5.08—5.13 (H-1, 7 H), 5.26 (H-1, 1 H, s); ^{13}C NMR (25 MHz, D_2O, characteristic absorptions) δ=51.9, 56.9, 62.7, 63.3, 71.7, 73.5, 74.2, 74.8, 75.4, 81.5, 82.1, 82.4, 82.8, 99.8, 102.6, 103.6, 104.0; FABMS, *m/z* 1279 ($M+H^+$), 1301 ($M+Na^+$), 1317 ($M+K^+$).

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References

1) F. Vögtle and W. M. Müller, *Angew. Chem., Int. Ed. Engl.*, **18**, 623 (1979).

2) a) N. Kobayashi, Y. Hino, A. Ueno, and T. Osa, *Bull. Chem. Soc. Jpn.*, **56**, 1849 (1983), and references cited there; b) K. Fujita, S. Ejima, and T. Imoto, *Chem. Lett.*, **1985**, 11.

3) a) A. Ueno, Y. Tomita, and T. Osa, *Chem. Lett.*, **1983**, 1635; b) K. Fujita, H. Yamamura, T. Imoto, T. Fujioka, and

K. Mihashi, *J. Org. Chem.*, **53**, 1943 (1988).
4) R. Breslow and A. W. Czarnik, *J. Am. Chem. Soc.*, **105**, 1390 (1983).
5) T. Murakami, K. Harata, and S. Morimoto, *Tetrahedron Lett.*, **28**, 321 (1987).
6) K. Fujita, T. Tahara, T. Koga, and T. Imoto, *Bull. Chem. Soc. Jpn.*, **62**, 3150 (1989).
7) K. Fujita, T. Tahara, T. Imoto, and T. Koga, *Chem. Lett.*, **1988**, 1329.
8) K. Fujita, T. Tahara, S. Nagamura, T. Imoto, and T. Koga, *J. Org. Chem.*, **52**, 636 (1987).
9) K. Fujita, S. Nagamura, T. Imoto, T. Tahara, and T. Koga, *J. Am. Chem. Soc.*, **107**, 3233 (1985).
10) K. Fujita, T. Tahara, T. Imoto, and T. Koga, *J. Am. Chem. Soc.*, **108**, 2030 (1986).