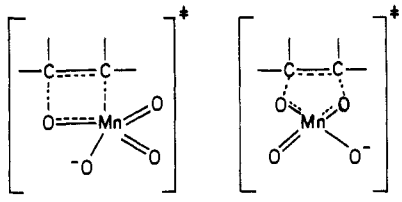
deuterium kinetic isotope effect (k_H/k_D = 0.95) from the oxidation of **3** and **4** indicates a change in hybridization from sp^2 at C-3 in the ground state to sp^3 in the activated complex.[13-15,18,30,59,60] A cycloaddition mechanism between permanganate ion and the carbon–carbon double bond is also supported by the large negative values for the entropy of activation (Table III).[20,26,28,30,53,61,62]



16 **17**

(*E*)-3-(2-Thienyl)-2-propenoate (**3**, 1341 M^{-1} s^{-1}) and (*E*)-3-(3-thienyl)-2-propenoate (**13**, 1071 M^{-1} s^{-1}), which react with permanganate ion at essentially the same rates (Table III and IV), are oxidized faster than (*E*)-2-butenoate (**18**, 286 M^{-1} s^{-1})[1,8] and (*E*)-3-phenyl-2-propenoate (**19**, 590 M^{-1} s^{-1}).[1,8,61] If the attack of permanganate ion on the carbon–carbon double bonds in **13**, **15**, **18**, and **19** were electrophilic in nature, **13** and **15** would be expected to react fastest owing to the strong resonance donor ability of the thiophene ring system which overrides its inductive withdrawal effect.[63]

Substitution of methyl for hydrogen at C-2 in **3** to give **5** and in **13** to give **14** slows the rate of oxidation owing to steric effects (eclipsing of the cis substituents in the activated complex). Substitution of a larger phenyl group for methyl in **5** to give **7** also slows the rates of oxidation. Thus, steric factors are important in the permanganate ion oxidation of carbon–carbon double bonds.[1]

Replacement of hydrogen by cyano at C-2 in **3** to give **8** and in **13** to give **15** also slows the rates of oxidation because of steric factors and electron-withdrawal effects (Tables III and IV). These data are consistent with an electrophilic attack by permanganate ion on the carbon–carbon double bond.

The relatively small substituent effects observed with ring-substituted 3-(2-thienyl)-2-propenoates (Table IV) may suggest a cycloadditions mechanism between oxidant and substrate. Resonance stabilization of the ground state by electron-attracting substituents would increase the activation energy and lead to reduced rates of oxidation. Permanganate ion reacting as an ambiphile may also account for the small substituent effects.[1,8,64-66] Thus, the transmission effects in the thiophene system are similar to those observed in the permanganate ion oxidation of phenyl-substituted α,β-unsaturated carboxylate ions.[8,13-15,31,65]

Acknowledgment. We thank Professor Robert Taft for helpful discussions, Monica C. Keindl for expert technical assistance, the Alexander von Humboldt Foundation for partial support of this work, and the National Science Foundation for the purchase of the stopped-flow spectrometer (CHE 77-07970) and for financial assistance toward the purchase of the NMR spectrometers. Fillmore Freeman thanks the Fulbright Commission and the Alexander von Humboldt Foundation for fellowships.

(57) Formation of π and/or σ complexes may precede the formation of intermediate **1** or **2**. Although formation of metallacycle **1** is consistent with the observed steric factors,[26,28] it does not account for the amount of oxygen transfer in the oxidation of alkenes[53] and alkynes.[58]

(58) Jáky, M.; Simándi, L. I. *J. Chem. Soc., Perkins Trans. 2* **1972**, 1481.

(59) Halevi, E. A. *Prog. Phys. Org. Chem.* **1963**, *1*, 109.

(60) Freeman, F.; Yamachika, N. J. *J. Am. Chem. Soc.* **1972**, *94*, 1214.

(61) Littler, J. S. *Tetrahedron* **1971**, *27*, 81.

(62) The rate-determining step may be preceded by rapid reversible formation of a π complex. Rearrangement of this complex to the product-determining cyclic manganate(V) diester is consistent with oxygen-18 and stereochemical studies in other unsaturated systems.

(63) On the other hand, phenyl, 2-thienyl, and 3-thienyl conjugation are expected to stabilize the ground state of the substrates and raise the energies of activation.

(64) The limited solubility of substrates precluded a more extensive study of substituent effects on the thiophene ring system. A concave upward LFER plot is expected if permanganate ion is ambiphilic.

(65) Small ρ values have been reported for the permanganate ion oxidation of several unsaturated systems.

(66) Since the reaction rates are determined by the difference in energy between the ground state and transition state, there may not be any merit in specifying the first step of a multistep reaction as being electrophilic or nucleophilic.

6-Polysubstituted α-Cyclodextrins. Application of Körner's Absolute Method of Isomer Determination

Kahee Fujita,*† Hatsuo Yamamura,‡ Atsuo Matsunaga,‡ Taiji Imoto,‡ Kunihide Mihashi,§ and Toshihiro Fujioka§

Contribution from the Faculty of Pharmaceutical Sciences, Kyushu University 62, Maidashi, Higashi-ku, Fukuoka 812, Japan, and the Faculty of Pharmaceutical Sciences, Fukuoka University, Nanakuma, Jonan-ku, Fukuoka 814-01, Japan. *Received January 29, 1986*

Abstract: A rigioisomeric mixture of C-6 polysulfonated α-cyclodextrins was prepared by the reaction of α-cyclodextrin with mesitylenesulfonyl chloride in pyridine. All regioisomers in di-, tri-, and tetrasubstituted cyclodextrins were separated by reversed-phase column chromatography and assigned as to their regiochemistries by Körner's method.

In the past decade, specific preparation of primary di- (or poly-) substituted β-cyclodextrins has been studied in order to construct refined and sophisticated models of enzymes.[1] Transannular disulfonate capping methods have been developed to activate 6A,6B-, 6A,6C-, or 6A,6D-primary hydroxyls of β-cyclodextrin.[2] For α-cyclodextrin, sulfonation on three (6A,6C,6E) primary hydroxyls[3] and transannular sulfonation on two primary hydroxyls[4] were reported, but the position of the substituent was left unclear

†Kyushu University. Present address: Faculty of Pharmaceutical Sciences, Fukuyama University, Sanzo, Higashimuramachi, Fukuyama 729-02, Japan.
‡Kyushu University.
§Fukuoka University.

(1) (a) Tabushi, I.; Kuroda, Y.; Yamada, M.; Higashimura, H.; Breslow, R. *J. Am. Chem. Soc.* **1985**, *107*, 5545. (b) Tabushi, I.; Kuroda, Y. *Ibid.* **1984**, *106*, 4580. (c) Tabushi, I.; Kuroda, Y.; Mochizuki, A. *Ibid.* **1980**, *102*, 1152. (d) Breslow, R.; Bovy. P.; Hersh, C. L. *Ibid.* **1980**, *102*, 2115. (e) Breslow, R.; Doherty, J. G.; Guillot, G.; Lipsey, C. *Ibid.* **1978**, *100*, 3227. For reviews, see: Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66. Tabushi, I.; Kuroda, Y. *Adv. Catal.* **1983**, *32*, 417. Tabushi, I. *Tetrahedron* **1984**, *40*, 269. Breslow, R. *Science (Washington, D.C.)* **1982**, *218*, 532. Bender, M. L; Komiyama, M. *Cyclodextrin Chemistry*; Springer Verlag: Berlin, 1978.

0002-7863/86/1508-4509$01.50/0

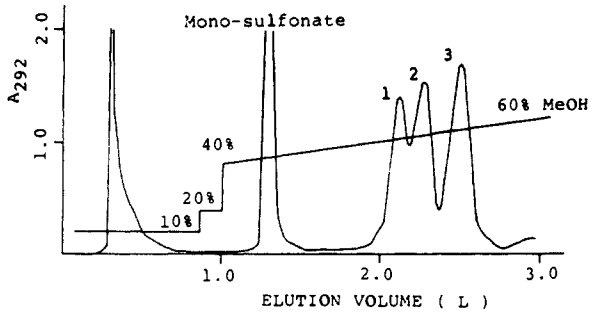
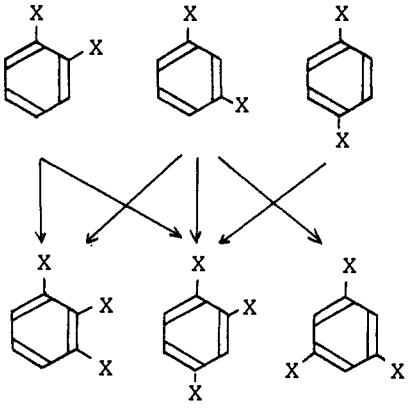


Figure 1. Reversed-phase column chromatography of the mixture of mono and di- (**1–3**) sulfonates. A stepwise followed by a linear gradient elution of MeOH was applied. "Monosulfonate" represents 6-deoxy-6-[(mesitylsulfonyl)oxy]-α-cyclodextrin.

Scheme I. Isomer Determination of Di- and Trisubstituted Benzenes by Körner[6]



in the latter case. There have been a few methods on the regioisomer determination of cyclodextrins. Additional reaction of a disulfonyl dichloride (a capping reagent) with a transannularly disulfonated β-cyclodextrins was employed as a criteria of the assignments of 6A,6C- and 6A,6D-disulfonations by Tabushi.[2b] The symmetric nature of the ^{13}C NMR spectrum was also used in a limited case, i.e., in the assignment of 6A,6C,6E-trisubstituted α-cyclodextrin by Knowles.[3] We also developed enzyme-based isomer determination where 6A,6B-disubstituted cyclodextrins give specifically 6′,6″-disubstituted maltotrioses and 6A,6C- and 6A,6D-isomers afford two molecules of 6′-monosubstituted maltose in the hydrolyses with Taka-amylase.[2f,5] However, in spite of the necessity of such specifically polysubstituted cyclodextrins to construct the more refined enzyme mimics, there have been no general methods for regiochemical determination of all isomers and preparations (isolations) of polysubstituted cyclodextrins.

About 100 years ago, Körner disclosed an elegant and unique method of isomer determination of substituted benzenes, where the number and the kind of the trisubstituted benzenes formed by an additional monosubstitution of the disubstituted benzenes determined not only the structures of the disubstituted benzenes but also the structures of the trisubstituted benzenes (Scheme I).[6] This method does not require the authentic specimens. This absolute method will be widely applicable to the determination of regioisomeric substitutions on the compounds, such as cyclodextrins, which are constructed of several of the same building blocks.

We describe here the application of Körner's absolute method to isomer determination as well as the isolation of each disulfonate (6A,6B-, 6A,6C-, or 6A,6D-isomer), each trisulfonate (6A,6B,6C-, 6A,6B,6D-, 6A,6B,6E-, or 6A,6C,6E-isomer), each tetrasulfonate (6A,6B,6C6D-, 6A,6B,6C,6E-, or 6A,6B,6D,6E-isomer), a pentasulfonate, and a hexasulfonate of α-cyclodextrin.[7]

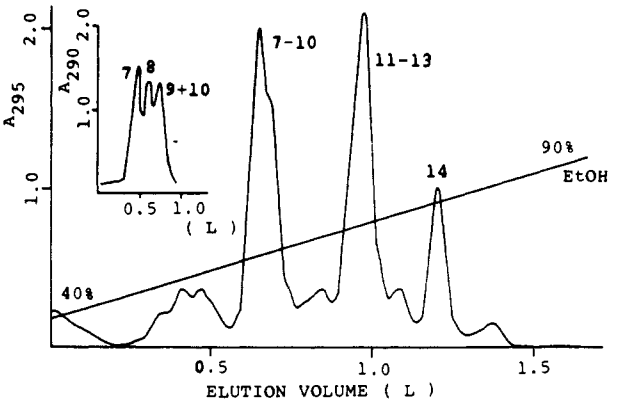


Figure 2. Reversed-phase column chromatography of the mixture of tri-, tetra-, and pentasulfonated α-cyclodextrins (**7–14**). A gradient elution of EtOH was applied. Inset: reversed-phase column rechromatography of the mixture of **7–10**. An elution of 75% aqueous MeOH was applied.

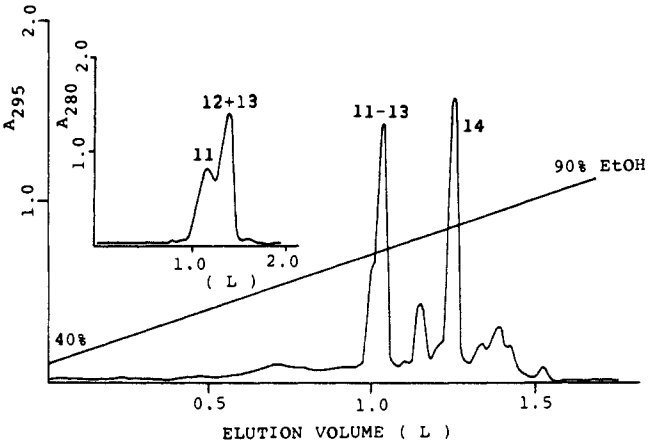


Figure 3. Reversed-phase column chromatography of the mixture of tetra and pentasulfonated α-cyclodextrins (**11–14**). A gradient elution of EtOH was applied. Inset: reversed-column rechromatography of the mixture of **11–13**. An elution of 57% CH_3CN was applied.

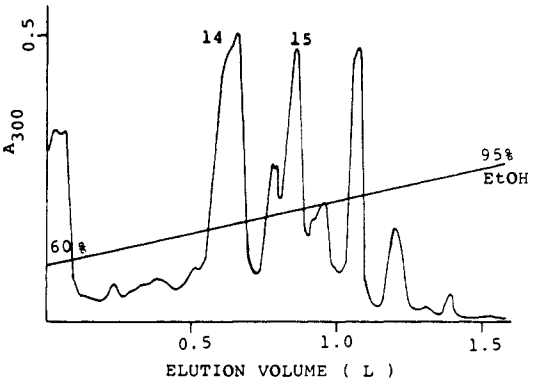


Figure 4. Reversed-phase column chromatography of the mixture of penta-, hexa-, and higher-sulfonated α-cyclodextrins (**14**, **15**, and many products). A gradient elution of EtOH was applied.

(2) (a) Tabushi, I.; Shimokawa, K.; Shimizu, N.; Shirakata, H.; Fujita, K. *J. Am. Chem. Soc.* **1976**, *98*, 7855. (b) Tabushi, I.; Kuroda, Y.; Yokota, K.; Yuan, L. C. *Ibid.* **1981**, *103*, 711. (c) Tabushi, I.; Yuan, L. C. *Ibid.* **1981**, *103*, 3574. (c) Tabushi, I.; Nabeshima, T.; Kitaguchi, H.; Yamamura, K.; *Ibid.* **1982**, *104*, 2017. (e) Tabushi, I.; Yamamura, K.; Nabeshima, T. *Ibid.* **1984**, *106*, 5267. (f) Tabushi, I.; Nabeshima, T.; Fujita, K.; Matsunaga, A.; Imoto, T. *J. Org. Chem.* **1985**, *50*, 2638.

(3) Boger, J.; Brenner, D. G.; Knowles, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7630.

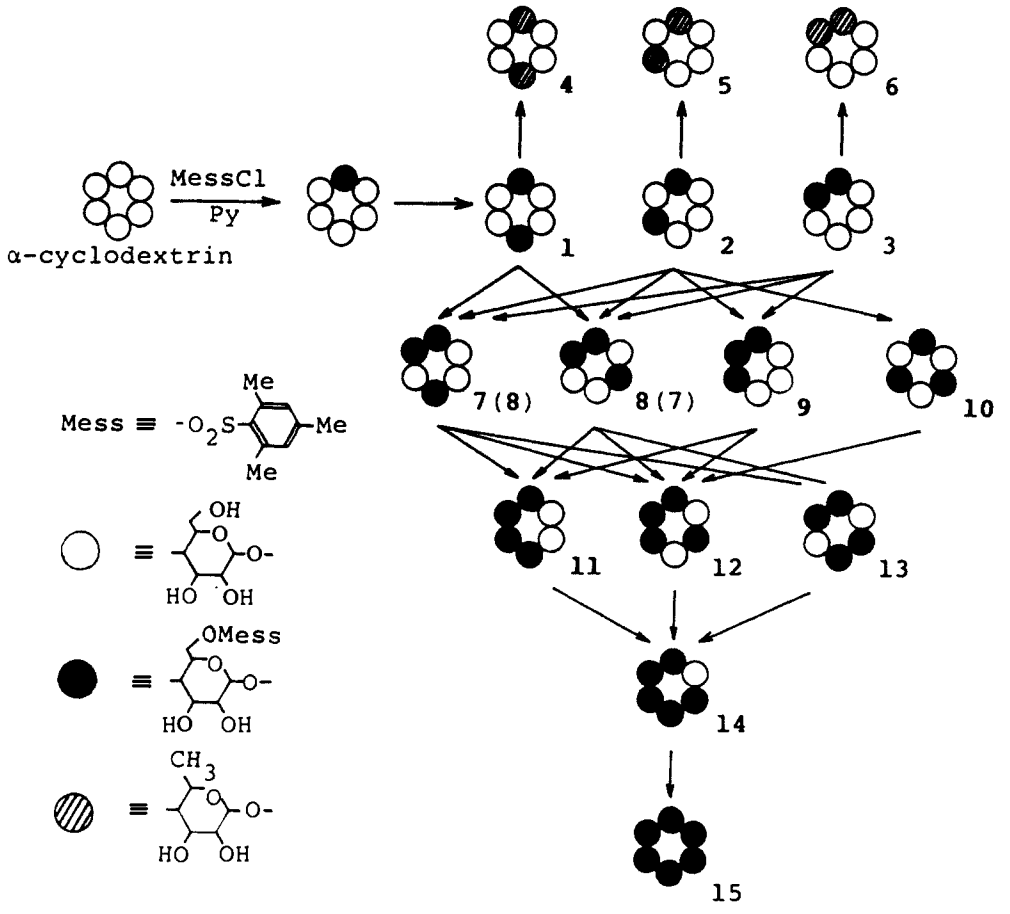
(4) Tabushi, I.; Shimokawa, K.; Fujita, K. *Tetrahedron Lett.* **1977**, 1524.

(5) Fujita, K.; Matsunaga, A.; Imoto, T. *Tetrahedron Lett.* **1984**, 5533.

(6) Körner, G. *Gazz. Chim. Ital.* **1874**. *4*, 305.

(7) A part of this report has been published as a communication. Fujita, K.; Matsunaga, A.; Imoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 5740.

Scheme II



Results and Discussion

Preparation and Isolation of Polysulfonted α-Cyclodextrins. Regioisomeric mixtures (I–IV) of C-6 sulfonated α-cyclodextrins were prepared by the reaction of α-cyclodextrin with mesitylenesulfonyl chloride in pyridine by monitoring the progress of the reaction with TLC and regulating the amount of the sulfonyl chloride. The mixtures I, II, III, and IV were made to contain disulfonates, trisulfonates, tetrasulfonates, and penta- and hexasulfonates as the main components, respectively. The products were separated from the mixture by reversed-phase column chromatography with a gradient elution of aqueous alcohol (Figure 1–4). Figure 1 shows good separation of disulfonates (**1–3**) and Figures 2 and 3 show separation of tri- (**7–10**) and tetra- (**11–13**) sulfonates. Separation of four trisulfonates (**7–10**) by column rechromatography (Figure 2, inset) gave pure **7**, **8**, and a mixture of **9** and **10**, from which pure **9** and **10** were isolated by silica gel column chromatography. Column rechromatography of the mixture of **11–13** with an elution of aqueous CH_3CN was somewhat poor but gave pure **11** and a mixture of **12** and **13** (Figure 3, inset), from which pure **12** and **13** were isolated by reversed-phase HPLC. The penta (**14**) and the hexa- (**15**) sulfonates were easily separated from mixture IV by reversed-phase column chromatography as shown in Figure 4.

Assignment of Regiochemistry of Sulfonates. Sulfonations with sulfonyl chlorides in pyridine generally occur on primary hydroxyl groups of cyclodextrins, and positions of the sulfonation were confirmed by reduction of **1–3** with $NaBH_4$ in DMF to **4–6** which showed doublet absorptions of two methyl groups at δ 1.21 or 1.24 (J = 5.0 Hz) in their ^1H NMR spectra. The numbers of the sulfonations in **1–3** and **7–14** were determined by their ^1H NMR spectra. Moreover, their FABMS or FDMS spectra showed the correct molecular ions. Although di-, tri-, and tetrasulfonates (**1–3** and **7–13**) could be obtained in pure state as mentioned above, there are no specimens for the regiochemical determinations. Therefore, we applied Körner's method to these assignments. Theoretically, additional monosulfonates of 6A,6B-, 6A,6C-, or

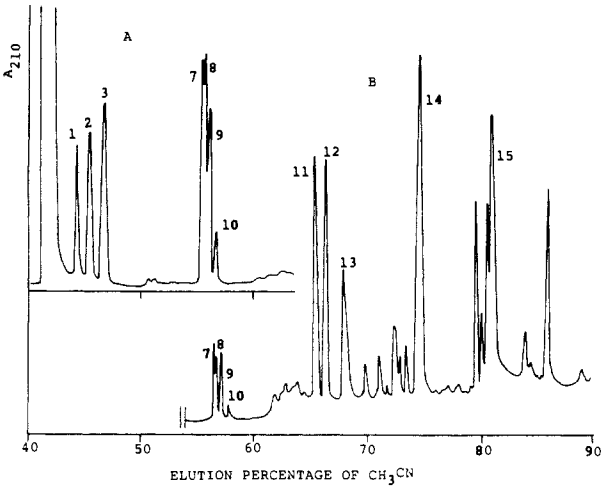


Figure 5. Reversed-phase HPLC of the mixtures (A and B) of polysulfonated α-cyclodextrins. Mixture A or B was prepared to contain mainly **1–3** and **7–9** or **11–15**, respectively. A gradient elution of CH_3CN was applied.

6A,6D-disulfonates should produce three (6A,6B,6C-, 6A,6B,6D-, and 6A,6B,6E-), four (6A,6B,6C-, 6A,6B,6D-, 6A,6B,6E-, and 6A,6C,6E-), or two (6A,6B,6D- and 6A,6B,6E-) trisulfonates, respectively (Scheme II). Similarly, additional monosulfonation of 6A,6B,6C-, 6A,6B,6D-, 6A,6B,6E-, or 6A,6C,6E-trisulfonates should provide two, three, or one tetrasulfonates, respectively (Scheme II). On the basis of these expectations, additional monosulfonations of **1–3** and **7–10** were carried out.

The HPLC retention times of the products obtained from **1–3** and **7–10** were compared with those of **7–10** and **11–13**, respectively. From well-separated HPLC patterns (Figure 5), **1–3** were assigned to 6A,6D-, 6A,6C-, and 6A,6B-disulfonates, respectively, **7–10** to 6A,6B,6D- (6A,6B,6E-), 6A,6B,6E- (6A,6B,6D-),

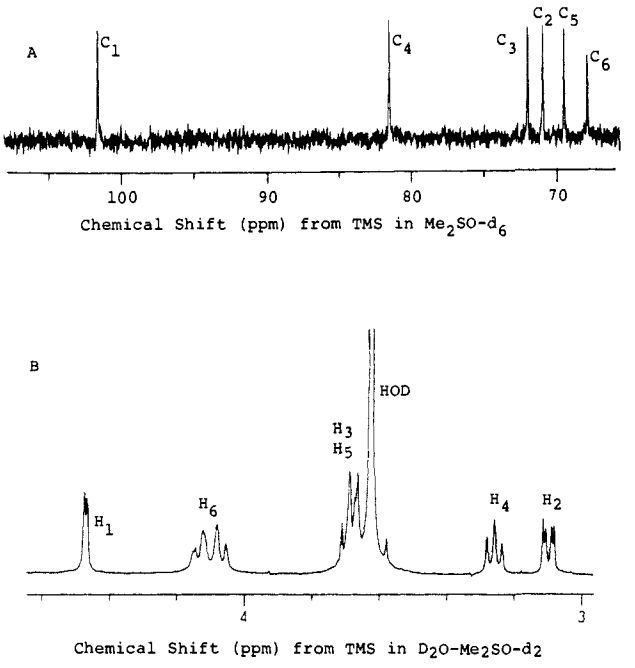
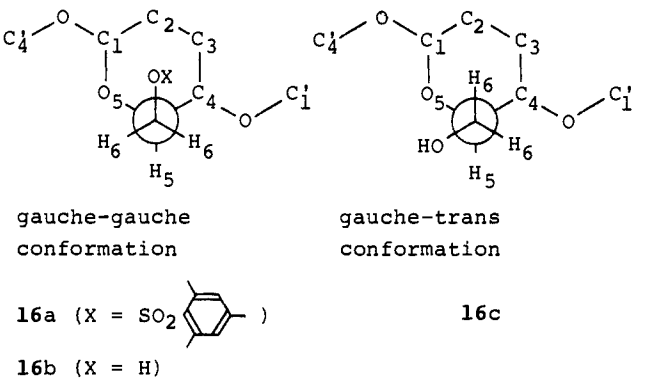


Figure 6. 100 MHz-^{13}C NMR (6A) and 400 MHz-^{1}H NMR (6B) spectra of the cyclodextrin part of 6A,6B,6C,6D,6E,6F-hexadeoxy-6A,6B,6C,6D,6E,6F-hexakis[(mesitylsulfonyl)oxy]-α-cyclodextrin (**15**).

6A,6B,6C-, and 6A,6C,6E-trisulfonates, respectively, and **11**–**13** to 6A,6B,6C,6D-, 6A,6B,6C,6E-, and 6A,6B,6D,6E-tetrasulfonates, respectively. Moreover, these tetrasulfonates were converted to the same sulfonate (**14**) by an additional monosulfonation, which was followed by one more additional monosulfonations to give a hexasulfonate (**15**) as the main product. ^{13}C NMR spectra also confirmed these assignments, where the spectrum of **15** showed a quite simple pattern with only six absorptions for cyclodextrin carbons (Figure 6). In the spectrum, the absorption at δ 101.7 was easily assigned to that of C-1, and the absorption at δ 68.0 was assigned to that of C-6 by use of the DEPT technique. From the COSY ^{1}H NMR spectrum of **15** and the decoupling experiments, assignments of all proton absorptions were carried out (Figure 6). From these assignments and the CHSHF measurement, absorptions of the other carbons were assigned, where clear assignments of C-3 and C-5 were, however, very difficult. The expected substitution effect of sulfonate groups at C-6 on the chemical shifts of the β carbon (C-5) and the δ carbon (C-3)[8] made the discrimination between C-3 and C-5 absorptions possible as shown in Figure 6. From the coupling patterns of C-6 protons ($J_{6a,5}$,$J_{6b,5} \leq 2$ Hz), the two C-6 protons are expected to be in gauche conformation to the C-5 proton,[9] demonstrating the location of the mesitylenesulfonyl group on the opposite side to the cyclodextrin cavity (see **16a**). This conformation is somewhat different from that of α-cyclodextrin itself which has equilibrated conformations of gauche–gauche (**16b**) and gauche–trans (**16c**). This difference is probably due to the steric repulsion between the mesitylenesulfonyl group and the other part of the cyclodextrin.

Only one defect in the present application of Körner's method to isomer determination of α-cyclodextrin derivatives is that discrimination between the 6A,6B,6D- and the 6A,6B,6E-trisubstituted isomers is theoretically impossible.



16a (X = SO_2)

16c

16b (X = H)

In the present study, all 6-polysubstituted α-cyclodextrins were purely isolated and structurally assigned except two trisubstituted isomers as mentioned above. These polysubstituted α-cyclodextrins will serve as the starting materials for more refined enzyme mimics. Also, this type of structural determination, Körner's absolute method, will be applicable as a powerful method to positional isomer determination of the compounds whose skeletons are constructed of several of the same building blocks.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were determined with a JEOL FX-100 spectrometer and a JEOL GX-400 spectrometer. UV absorptions were recorded with a Hitachi Model 200-10 spectrophotometer. Fast atom bombardment mass (FABMS) and field desorption mass (FDMS) spectra were obtained with a JEOL JMS DX-300/JMA 3500 data system and a JEOL JMS DX-303/JMA 3500 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-dihydroxynaphthalene in EtOH/H_2O/H_2SO_4 (200/157/43 (v/v/v)). An elution solvent of TLC was n-C_3H_7OH/AcOEt/H_2O (7/7/5 (v/v/v)) or a lower layered solution which was obtained by mixing $CHCl_3$, MeOH, and H_2O (7/3/1 (v/v/v)). Prepacked columns (Merck, Lobar column LiChroprep RP18, 25 × 310 mm and LiChroprep RP8, 10 × 240 mm and 25 × 310 mm) were used for reversed-phase column chromatography. High-performance liquid chromatography (HPLC) was performed on a Hitachi 635A with a TSKgel LS-410 ODS SIL column (4 × 300 mm, 5 μm, Toyo Soda, Japan). Silica gel (Wako, C-200) was used for column chromatography.

Sulfonation of α-Cyclodextrin. In order to obtain mixtures mainly containing mono- and disulfonates, trisulfonates, tetrasulfonates, and penta- and hexasulfonates, four reactions (I, II, III, and IV) were employed, respectively.

Sulfonation I. A solution of α-cyclodextrin (3 g, 3.1 mmol) and mesitylenesulfonyl chloride (6 g, 27 mmol) in pyridine (230 mL) was stirred for 2 h at room temperature followed by addition of water (1 mL) and concentrated in vacuo. The crude concentrated mixture was applied on a reversed-phase column (RP8, 25 × 310 mm). After a stepwide elution from 10% aqueous MeOH (900 mL) to 20% aqueous MeOH (100 mL), a gradient elution from 40% aqueous MeOH (1 L) to 60% aqueous MeOH (1 L) was applied to give **1**(AD) (298 mg, 7.3%), **2**(AC) (374 mg, 9.1%), **3**(AB) 555 mg, 13.6%), and 6-deoxy-6-[(mesitylsulfonyl)oxy]-α-cyclodextrin (802 mg, 22.7%).

1(AD): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 59.5, 69.0, 71.9, 72.8, 81.3, 81.8, 101.3, 101.8, 102.1; ^{1}H NMR (Me_2SO-d_6, aromatic protons) δ 7.08; FABMS (m/z) 1375 (M + H^+), 1379 (M + Na^+).

2(AC): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 59.6, 59.8, 68.8, 68.9, 71.6, 72.0, 72.8, 81.9, 101.5, 101.9; ^{1}H NMR (Me_2SO-d_6, aromatic protons) δ 7.04, 7.08; FABMS (m/z) 1375 (M + H^+), 1379 (M + Na^+).

3(AB): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 59.7, 69.1, 71.4, 71.9, 72.5, 72.7, 72.9, 73.1, 81.8, 101.9; ^{1}H NMR (Me_2SO-d_6, aromatic protons) δ 7.08; FABMS (m/z) 1375 (M + H^+), 1379 (M + Na^+).

Sulfonation II. A solution of α-cyclodextrin (1 g, 1 mmol) and mesitylenesulfonyl chloride (6 g, 2.75 mmol) in pyridine (80 mL) was stirred for 4 h at room temperature. After the workup procedure similar to that described above, the crude concentrated mixture was dissolved in 20% aqueous EtOH (200 mL) and applied on a reversed-phase column (RP18). After an elution with 40% aqueous EtOH (1 L), a gradient elution with 1 L of 40% aqueous EtOH–1 L of 90% aqueous EtOH was applied to give a mixture of trisulfonates, which were lyophilized after evaporation of EtOH. The mixture of **7**–**10** was dissolved in 60% aqueous

(8) Sulfonation of a hydroxyl group leads to the downfield shift of the carbon carring that hydroxyl (the α carbon), the smaller upfield shift of the β carbon, and still smaller upfield shift of the γ carbon. Such an effect is practically negligible for the δ carbon. Cf.: (a) Ueno, A.; Breslow, R. *Tetrahedron Lett.* **1982**, 3451 and references cited therein. (b) Fujita, K.; Nagamura, S.; Imoto, T. *Ibid.* **1984**, 5673. (c) Fujita, K.; Nagamura, S.; Imoto, T.; Tahara. T.; Koga, T. *J. Am. Chem. Soc.* **1985**, *107*, 3233. (d) Fujita, K.; Tahara, T.; Imoto, T.; Koga, T. *Ibid.* **1986**, *108*, 2030.

(9) Wood, D. J.; Hruska, F. E.; Saenger, W. *J. Am. Chem. Soc.* **1977**, *99*, 1735.

MeOH (200 mL) and rechromatographed by a reversed-phase column (RP8) with a stepwise gradient elution, 65% aqueous MeOH (500 mL), 70% aqueous MeOH (700 mL), 75% aqueous MeOH (700 mL), and 75% aqueous MeOH (1 L), to give pure **7**(ABD or ABE) (66 mg, 4.2%), pure **8**(ABE or ABD) (96 mg, 6.3%), and a mixture of **9**(ABC) and **10**(ACE) (73 mg). The mixture of **9** and **10** (73 mg) was chromatographed by a silica gel column (3.5 × 30 cm) with an elution with a lower layer of a mixture of $CHCl_3$, MeOH, and water to give pure **9** (33.9 mg, 2.2%) and pure **10** (8.2 mg, 0.5%).

7(ABD or ABE): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 59.6, 68.6, 69.0, 72.0, 72.6, 72.9, 81.3, 81.8, 101.2, 101.9, 102.1; ^1H NMR (Me_2SO-d_6, aromatic protons) δ 7.04, 7.10; FABMS (*m/z*) 1519 ($M + H^+$), 1541 ($M + Na^+$).

8(ABE or ABD): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 58.9, 59.6, 59.9, 69.1, 71.9, 72.7, 81.3, 81.7, 101.4, 101.6, 102.0; ^1H NMR (Me_2SO-d_6, aromatic protons) δ 7.06; FABMS (*m/z*) 1519 ($M + H^+$), 1541 ($M + Na^+$).

9(ABC): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 59.5, 68.3, 69.1, 69.3, 71.3, 71.9, 72.4, 72.9, 81.7, 101.8; ^1H NMR (Me_2SO-d_6, aromatic protons) δ 7.06; FABMS (*m/z*) 1519 ($M + H^+$), 1541 ($M + Na^+$).

10(ACE): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 59.5, 68.6, 69.0, 71.3, 71.6, 72.0, 72.6, 81.3, 81.8, 101.3, 102.1; ^1H NMR (Me_2SO-d_6, aromatic protons) δ 7.10; FABMS (*m/z*) 1519 ($M + H^+$).

Sulfonation III. A solution of α-cyclodextrin (1 g, 1 mmol) and mesitylenesulfonyl chloride (4 g, 18 mmol) in pyridine (80 mL) was stirred for 7 h at room temperature. After the workup procedure, the crude concentrated mixture was dissolved in 45% aqueous EtOH (2.5 L) and applied on a reversed-phase column (RP18). After an elution with 40% aqueous EtOH (1 L), a gradient elution with 40% aqueous EtOH (1 L)–90% aqueous EtOH (1 L) was applied to give a mixture of tetrasulfonates (318 mg, 18.2%) and the pentasulfonate (**14**)(ABCDE) (125 mg, 6.5%) (Figure 4). The lyophilized mixture of **11**–**13** (318 mg) was dissolved in 50% aqueous CH_3CN (318 mL) and chromatographed by a reversed-phase column (RP18). An elution with 57% aqueous CH_3CN (2 L) gave pure **11**(ABCD) (50.9 mg, 2.9%) and a mixture of **11**–**13** (184.4 mg). From the mixture, **11** (12.7 mg, 0.7%) **12**(ABCE) (63.6 mg, 3.6%), and **13**(ABDE) (38.2 mg, 2.2%) were purely isolated by HPLC (65% aqueous CH_3CN).

11(ABCD): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 59.7, 68.1, 68.5, 69.2, 69.4, 71.2, 71.9, 72.8, 81.7, 101.7; ^1H NMR (Me_2SO-d_6, aromatic protons) δ 7.03, 7.07; FABMS (*m/z*) 1701 ($M + H^+$).

12(ABCE): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 59.4, 68.3, 69.2, 71.3, 71.8, 72.1, 81.7, 101.7, 102.0; ^1H NMR (Me_2SO-d_6, aromatic protons) δ 7.06; FABMS (*m/z*) 1701 ($M + H^+$).

13(ABDE): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 59.6, 68.6, 68.7, 69.0, 71.2, 71.6, 72.5, 81.5, 81.8, 101.1, 101.6, 102.1; ^1H NMR (Me_2SO-d_6, aromatic protons) δ 7.04, 7.08; FABMS (*m/z*) 1701 ($M + H^+$).

Sulfonation IV. A solution of α-cyclodextrin (1 g, 1 mmol) and mesitylenesulfonyl chloride (4 g, 18 mmol) in pyridine (80 mL) was stirred for 17.5 h at room temperature followed by addition of water (1 mL) and concentrated in vacuo. The residue was dissolved in 60% aqueous EtOH (1 L) and chromatographed by a reversed-phase column (RP18) with a gradient from 60% aqueous EtOH (1L) to 99% EtOH (1L) to give pure pentasulfonate (**14**)(ABCDE) (260 mg, 13.5%) and a mixture of hexasulfonates (252.5 mg). The mixture of hexasulfonates (252.5 mg) was dissolved in 60% aqueous CH_3CN (500 mL) and applied on a reversed-phase column (RP18). After the column was washed with 70%, 73%, and then 76% aqueous CH_3CN (400 mL each), 79% aqueous CN_3CN (1.2L) was developed to give pure **15**(ABCDEF) (77.2 mg, 3.6%).

14(ABCDE): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 59.4, 68.0, 69.3, 71.2, 72.2, 81.6, 101.6; ^1H NMR (Me_2SO-d_6, aromatic protons) δ 7.00, 7.04; FDMS (*m/z*) 1905 ($M + Na^+$), 1921 ($M + K^+$).

15(ABCDEF): ^{13}C NMR (Me_2SO-d_6, carbons other than mesityl group) δ 68.0, 69.5, 71.2, 72.2, 81.6, 101.7; ^1H NMR (Me_2SO-d_6, aromatic protons) δ 6.96; FDMS (*m/z*) 2087 ($M + Na^+$).

Reduction of Disulfonates 1–3. A solution of **1** (20 mg) and $NaBH_4$ (50 mg) in DMF (0.5 mL) was stirred at 70 °C for 2 h. After evaporation of DMF in vacuo, the residue was dissolved in water (10 mL), slightly acidified by addition of HCl, and chromatographed by a reversed-phase column (RP18) with a gradient elution from 10% aqueous EtOH (200 mL) to 30% aqueous EtOH (200 mL) to give pure **4** (12 mg, 64%). The dideoxy compounds **5** (10 mg, 53%) and **6** (10 mg, 53%) were obtained from **2** and **3**, respectively, by similar procedures.

4(AD): ^1H NMR (Me_2SO-d_6) δ 1.24 (CH_3, 6 H, d, J = 5.0 Hz), others are very similar to those of α-cyclodextrin. FABMS (*m/z*) 941 ($M + H^+$), 963 ($M + Na^+$), 979 ($M + K^+$).

5(AC): ^1H NMR (Me_2SO-d_6) δ 1.24 (CH_3, 6 H, d, J = 5.0 Hz), others are very similar to those of **4**. FABMS (*m/z*) 941 ($M + H^+$), 963 ($M + Na^+$), 979 ($M + K^+$).

6(AB): ^1H NMR (Me_2SO-d_6) δ 1.21 (CH_3, 6 H, d, J = 5.0 Hz), others are very similar to those of **4**. FABMS (*m/z*) 941 ($M + H^+$), 963 ($M + Na^+$), 979 ($M + K^+$).

Additional Sulfonation of Sulfonates. A solution of **1** (5 mg) and mesitylenesulfonyl chloride (26 mg) in pyridine (0.5 mL) was stirred at room temperature for 20 min. After addition of water (0.5 mL), the mixture was concentrated in vacuo. The residue was dissolved in water (1 mL) and applied on a short reversed-phase column (SEP-PAK, Waters). After washing the column with 30% aqueous EtOH (15 mL), 99% EtOH (15 mL) was applied to give a mixture of the sulfonates. The mixture, after dilution and lyophilization, was dissolved in 50% aqueous EtOH (1 mL), filtered with a membrane filter, and analyzed by reversed-phase HPLC. Similar procedures were carried out in the cases of **2**, **3**, and **7**–**13**.

Acknowledgment. We are indebted to Japan Maize Products Co. Ltd. (Japan) for a generous gift of α-cyclodextrin.