Determination of the Structures of Tris(6-*O*-mesitylenesulfonyl)-α-cyclodextrin Regioisomers by ^{1}H NMR Analyses of the Corresponding 3,6-Anhydrocyclodextrin Derivatives

Hatsuo Yamamura,*[1a] Hideki Nagaoka,[1a] Kazuki Saito,[1b] Masao Kawai,[1a] Yasuo Butsugan,[1a] Terumi Nakajima,[1b] and Kahee Fujita[1c]

Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466, Japan, Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan, and Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyo-machi, Nagasaki 852, Japan

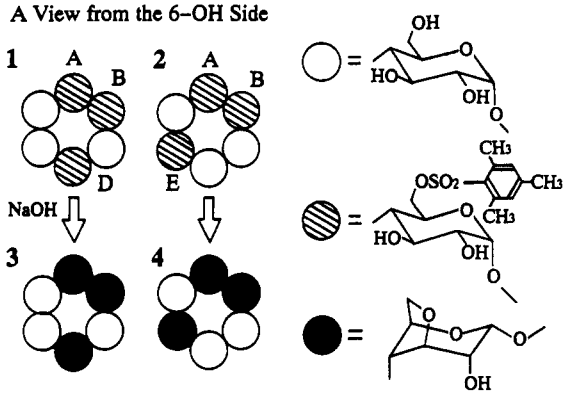
Received January 25, 1993

Summary: The structures of two regioisomers of tris(6-*O*-mesitylenesulfonyl)-α-cyclodextrin ($6^A,6^B,6^D$ and $6^A,6^B,6^E$) were assigned by conversion of the isomers to tris(3,6-anhydro)-α-cyclodextrins and analyses of the two-dimensional ^{1}H NMR spectra (DQF-COSY, HOHAHA, and ROESY) of the anhydrocyclodextrins.

Cyclodextrins can form inclusion complexes with guest compounds and can be used as artificial enzymes.[2] To construct more sophisticated artificial enzymes, chemical modifications have been studied to equip native cyclodextrins with active sites and/or the binding sites to suit a specific purpose.[3] Polysulfonylated cyclodextrins can be important synthetic intermediates for such enzyme mimics. However, it is quite difficult to separate the regioisomers of the sulfonylated mixture and to determine their structures. We have developed a separation method using reversed-phase chromatography.[4] We have also developed methods for the determination of the structures of the regioisomers by (a) additional sulfonylation,[4a] (b) Taka-amylolysis,[4b] and (c) conversion of the sulfonylated regioisomers to 3,6-anhydrocyclodextrins and subsequent Taka-amylolysis.[4c] We report here the determination of the structures of the regioisomers by means of two-dimensional ^{1}H NMR analyses of the corresponding 3,6-anhydrocyclodextrin derivatives.

Mesitylenesulfonylation of the primary OH groups of α-cyclodextrin yielded one mono-, three di-, four tri-, three tetra-, one penta-, and one hexasulfonylated derivatives, and all of these products were isolated by reversed-phase chromatography. Further mesitylenesulfonylation of the products revealed their structures, except for the two regioisomeric trisubstituted derivatives, namely, the $6^A,6^B,6^D$- and $6^A,6^B,6^E$-tris(*O*-mesitylenesulfonyl)-α-cyclodextrins.[4a] Discrimination between these two structures by means of additional sulfonylation is theoretically impossible since both of them can be derived from the same disulfonyl derivatives and can give the same tetrasulfonyl derivatives. Neither compound was hydrolyzed by Taka-amylolysis. For the purpose of determining their structures, the two tris(6-*O*-mesitylenesulfonyl)-α-cyclodextrins **1** and **2**[5] were converted into the corresponding tris(3,6-anhydro) derivatives **3** and **4**, respectively, by

Scheme I



treatment with 1 N aqueous NaOH at 40 °C followed by reversed-phase column chromatographic purification (Scheme I). The conversion of the 6-O-sulfonylated glucose unit into the 3,6-anhydroglucose unit brings about a marked change in the ^{1}H NMR signals because of the unusual $^4C_1$ conformation of the 3,6-anhydroglucose.[6] Because of the conformation of the bicyclic 3,6-anhydroglucose unit, its proton signals are more deshielded than those of the normal glucose units. The change in the shape of the signals is also remarkable: the vicinal axial-axial couplings commonly observed for protons of a normal glucose unit are replaced by much smaller equatorial-equatorial couplings. Unlike those of starting materials **1** and **2**, the 400-MHz ^{1}H NMR spectra of **3** and **4** in D_2O showed well-separated signals, as expected. Compound **3** especially exhibited well-defined spectra, and we were able to assign all of its signals by means of ^{1}H-^{1}H DQF-COSY and HOHAHA experiments. The most important point is that all of the H1 signals [δ 5.04, 5.07, and 5.19 (H1 of glucose units); 5.13, 5.27, and 5.29 (H1 of 3,6-anhydroglucose units)] and H4 signals [δ 3.59, 3.65, and 3.72 (H4 of glucose units); 4.14, 4.34, and 4.42 (H4 of 3,6-anhydroglucose units)] could be easily assigned. The distance between H1 in one glucose unit and H4 in the adjoining α(1→4)-linked glucose unit is small enough for the observation of an NOE. In fact, the ROESY spectrum of **3** showed six cross peaks corresponding to neighboring (H1, H4) pairs as shown in Figure 1, revealing the sequential relationship of the three glucose units and the three 3,6-anhydroglucose units in **3**. Thus, we established the structure of **3** to be A,B,D-tris(3,6-anhydro)-α-cyclodextrin and the structure of regioisomer **4** to be A,B,E. Consequently, parent compounds **1** and **2** were determined unambiguously to be $6^A,6^B,6^D$- and $6^A,6^B,6^E$-tris(*O*-mesitylenesulfonyl)-α-cyclodextrin, respectively.

(1) (a) Nagoya Institute of Technology. (b) University of Tokyo. (c) Nagasaki University.

(2) Bender, M. L.; Komiyama, M.; *Cyclodextrin Chemistry*; Springer-Verlag: Berlin, 1978.

(3) For example, Ye, H.; Tong, W.; D'Souza, V. T. *J. Am. Chem. Soc.* **1992**, *114*, 5470. Breslow, R.; Zhang, B. *J. Am. Chem. Soc.* **1992**, *114*, 5882.

(4) (a) Fujita, K.; Yamamura, H.; Matsunaga, A.; Imoto, T.; Mihashi, K.; Fujioka, T. *J. Am. Chem. Soc.* **1986**, *108*, 4509. (b) Fujita, K.; Matsunaga, A.; Imoto, T. *Tetrahedron Lett.* **1984**, *25*, 5533. (c) Fujita, K.; Yamamura, H.; Imoto, T.; Fujioka, T.; Mihashi, K. *J. Org. Chem.* **1988**, *53*, 1943.

(5) These isomers are numbered according to their elution order in reversed-phase chromatography. See ref 4a.

(6) Fujita, K.; Yamamura, H.; Imoto, T.; Tabushi, I. *Chem. Lett.* **1988**, 543.

0022-3263/93/1958-2936$04.00/0

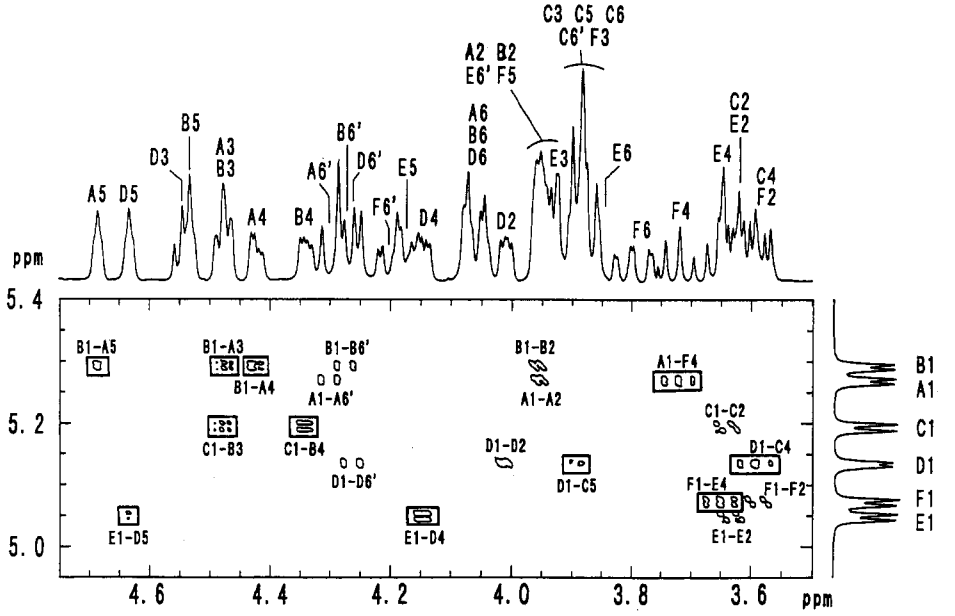


Figure 1. ROESY spectrum (τ_m = 250 ms) of **3** in D_2O. Peaks in boxes are interunit cross peaks.

The present study has led to the completion of the synthetic study of poly(6-*O*-mesitylenesulfonyl)-α-cyclodextrins. Now all the polysulfonylated α-cyclodextrins have known structures and are available to cyclodextrin chemists for a wide variety of uses. The sulfonyl groups can be easily converted to functional groups such as NH_2, SH, etc. The method described here for determining the structures of poly-6-*O*-sulfonylated cyclodextrins consists of conversion of the 6-*O*-sulfonylglucose units to 3,6-anhydroglucose units and detailed ^1H NMR analyses of the resulting poly(3,6-anhydro)cyclodextrins. Because of the NMR characteristics of the 3,6-anhydroglucose unit, ^1H NMR techniques such as ROESY can be used to determine interunit relationships. This method is widely applicable to the structural analysis of chemically modified cyclodextrins containing 6-*O*-sulfonyl groups.

Acknowledgment. We thank Japan Maize Products Co. Ltd. for a generous gift of α-cyclodextrin.

Supplementary Material Available: Experimental procedure for the conversion of **1** to **3** and DQF-COSY and HOHAHA NMR spectra of **3** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.