Regiospecific Sulfonation of Secondary Hydroxyl Groups of α-Cyclodextrin. Its Application to Preparation of 2A2B-, 2A2C-, and 2A2D-Disulfonates

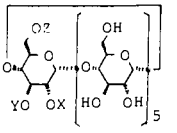
Kahee Fujita,*[1] Satoru Nagamura,[1] Taiji Imoto,[1] Tsutomu Tahara,[2] and Toshitaka Koga[2]

Contribution from the Faculty of Pharmaceutical Sciences, Kyushu University 62, Maidashi, Higashi-ku, Fukuoka 812, Japan, and Daiichi College of Pharmaceutical Sciences, Tamagawa, Minami-ku, Fukuoka 815, Japan. *Received November 13, 1984*

Abstract: Specific sulfonation on a secondary hydroxyl group (C-2–OH or C-3–OH) of α-cyclodextrin was elucidated. A reaction of α-cyclodextrin with *m*-nitrobenzenesulfonyl chloride exclusively gave the C-2-sulfonate, while β-naphthalenesulfonyl chloride selectively afforded the C-3-sulfonate. The former reaction also gave selectively 2A2B-, 2A2C-, and 2A2D-disulfonates as the products of disulfonation. They were well separated by reversed-phase column chromatography, isolated, and converted to corresponding di-*manno*-epoxides. Structural determinations of the disulfonates and the diepoxides were made from their spectral data and enzymatic conversion by Taka amylolysis to the linear oligosaccharides, whose structures were determined by FDMS, FABMS, and EIMS spectra.

Successful specific disulfonations on primary C-6-hydroxyls of cyclodextrins[3] have developed a new aspect of construction of enzyme (receptor) mimics, having a collaborative property of the two functional groups derived from the sulfonate groups. Since a functional group introduced onto the secondary hydroxyl side of β-cyclodextrin demonstrated quite different enzymelike properties from that onto the primary hydroxyl side,[4] it is valuable to prepare disulfonates of the secondary hydroxyls. However, sulfonation reactions utilized in this process should be really (not seemingly) regiospecific, because the secondary sulfonates (C-2- and C-3-sulfonates) decompose under the alkaline condition where sulfonations are carried out and, moreover, because the decomposition products are not parent cyclodextrins but the epoxides (the manno-epoxides and the allo-epoxides, respectively).[4,5] Although there are few studies on sulfonation on a secondary hydroxyl,[5-7] they do not give suitable conditions for disulfonation reaction because of long reaction times under alkaline conditions and/or at high temperature. We describe here a highly regiospecific sulfonation of a secondary hydroxyl under a condition where the decomposition (epoxidation) is minimized. This regiospecificity is dependent on the kind of the sulfonating reagent. Moreover, this method is applicable to regiospecific disulfonation of secondary hydroxyls.

Powdered *m*-nitrobenzenesulfonyl chloride was added in one portion to an aqueous solution (pH 12.0, adjusted by addition of aqueous NaOH) of α-cyclodextrin. The mixture was vigorously stirred, and the pH of the mixture was allowed to decrease rapidly. After the mixture became neutral (pH 7–8), it was filtered, analyzed by reversed-phase HPLC[8] (Figure 1), and each monosulfonate (**1a–3a**) was isolated from the filtrate by preparative reversed-phase column chromatography (Lobar column LiChroprep RP18, 25 × 310 mm, Merck Ltd.) (Table I). The structural assignments of **1a–3a** were made by FABMS spectra, by comparing their ^{13}C NMR spectra with those of known C-2-,[5] C-3-,[5] and C-6-tosylates[4] of α- or β-cyclodextrin, and by conversion of **1a** and **2a** to the corresponding epoxides whose structures were assigned by their ^{1}H NMR, ^{13}C NMR, and FABMS[9] spectra.[10]



1a; Y=m-NBs, X=Z=H **2a**; X=m-NBs, Y=Z=H **3a**; Z=m-NBs, X=Y=H
b; Y=p-NBs, X=Z=H b; X=p-NBs, Y=Z=H b; Z=p-NBs, X=Y=H
c; Y=α-Ns, X=Z=H c; X=α-Ns, Y=Z=H c; Z=α-Ns, X=Y=H
d; Y=β-Ns, X=Z=H d; X=β-Ns, Y=Z=H d; Z=β-Ns, X=Y=H

(NBs≡nitrobenzenesulfonyl, Ns≡naphthalenesulfonyl)

Similar reactions of α-cyclodextrin with some sulfonyl chlorides were carried out (Table I). Sulfonation on a C-2-hydroxyl of α-cyclodextrin was achieved by use of *m*-nitrobenzenesulfonyl chloride. The maximum yield of the C-3-sulfonate (**1a**) is estimated to be less than 6% on the basis of the sulfonation reaction period (1.8 min) and the half time of its decomposition (1.8 min at pH 12).[11] This value is still far smaller than the yield of the C-2-sulfonate (**2a**) (28%) which is an underestimated value, demonstrating that the sulfonation with *m*-nitrobenzenesulfonyl chloride was specific to a C-2-hydroxyl of α-cyclodextrin. Sulfonation on a C-3-hydroxyl was attained by use of β-naphthalenesulfonyl chloride in aqueous CH_3CN solution. Since the C-3-sulfonate (**1d**) was less stable than the C-2-sulfonate (**2d**), sulfonation with β-naphthalenesulfonyl chloride was specific to the C-3-hydroxyl.[11] When this reaction was carried out in an alkaline aqueous solution, the specificity was aparently absent, demonstrating that the longer reaction time under the alkaline condition reduced the amount of the C-3-sulfonate (**1d**). Other sulfonating reagents were also tested with respect to the specificity. *m*-Nitrobenzenesulfonyl chloride was specific to a C-2-hydroxyl of α-cyclodextrin, but its para isomer showed no specificity. Although β-naphthalenesulfonyl chloride exclusively gave a C-3-sulfonate of α-cyclodextrin (**1d**), α-naphthalenesulfonyl chloride gave only a C-2-sulfonate (**2c**). These results demonstrate that the sulfonation specificity is dependent on the molecular structure of the sulfonating reagent, i.e., probably on the geometry of the inclusion complex of α-cyclodextrin with the reagent.

(1) Kyushu University.
(2) Daiichi College.
(3) (a) Tabushi, I. *Tetrahedron* **1984**, *40*, 269. (b) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66. (c) Breslow, R. *Science (Washington, D.C.)* **1982**, *218*, 532. (d) Bender, M. L.; Komiyama, M. "Cyclodextrin Chemistry"; Springer Verlag: Berlin, 1978. (e) Fujita, K.; Matsunaga, A.; Imoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 5740.
(4) Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390.
(5) Fujita, K.; Nagamura, S.; Imoto, T. *Tetrahedron Lett.* **1984**, 5673.
(6) Ueno, A.; Breslow, R. *Tetrahedron Lett.* **1982**, 3451.
(7) Takahashi, K.; Hattori, K.; Toda, F. *Tetrahedron Lett.* **1984**, 3331.
(8) TSKgel LS 410 ODS SIL column (4 × 300 mm, 5 μm, Toyo Soda, Japan).
(9) FABMS, FDMS, and EIMS represent "fast atom bombardment mass", "field desorption mass", and "electron impact mass", respectively.
(10) The *allo*- and *manno*-epoxides of α-cyclodextrin are known compounds (see ref 5).
(11) The half-life of the C-3-sulfonate (**1a**) at pH 11 was 8.0 min at 20 °C, while the value of the C-2-sulfonate (**2a**) at pH 12 or 11 was 13.9 or 54.6 min, respectively. Generally, a C-3-sulfonate showed shorter half-life than the corresponding C-2-sulfonate. These will be reported elsewhere in the near future.

0002-7863/85/1507-3233$01.50/0

Table I. Products Obtained by the Reaction of α-Cyclodextrin with Sulfonyl Chloride

cyclodextrin (g)	sulfonyl chloride[a] (g)	solvent (mL)	reaction time[b]	yield of sulfonate, % C-2 (**2**)	C-3 (**1**)	C-6 (**3**)
α-CD (1.4)	*m*-NbsCl (1.4)	H_2O (5)	1.8 min	28	3	1
α-CD (2.8)	*p*-NBsCl (2.8)	H_2O (10)	16 s	7.2	4.4	0
α-CD (1.0)	α-NsCl (1.0)	H_2O (20)	63 min	11.1	0.2	1.1
α-CD (1.0)	β-NsCl (1.0)	H_2O (20)	66 min	4.8	7.3	0.8
		10% CH_3CN (20)	13 min	3.9	29	0.4

[a] NBs and Ns represent nitrobenzenesulfonyl and naphthalenesulfonyl, respectively. [b] Reaction time required for the pH of the reaction mixture to change from 12 to 8.

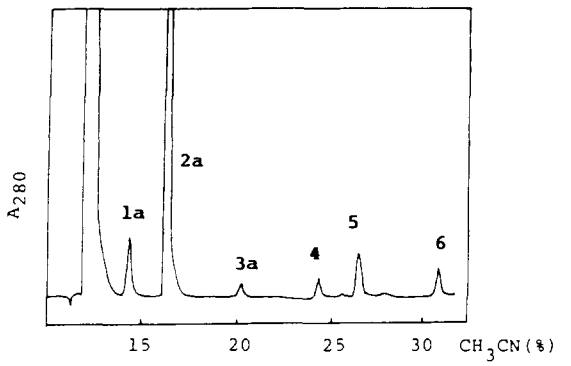
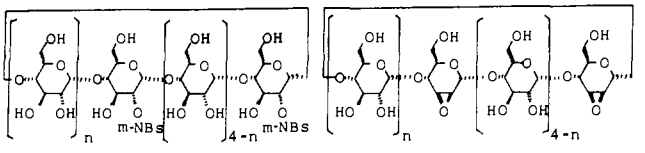
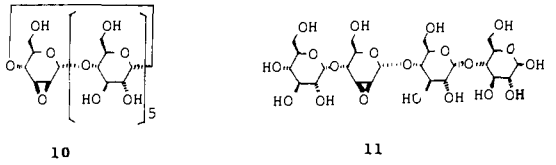


Figure 1. Reversed-phase HPLC of the mixture obtained from the reaction of α-cyclodextrin with *m*-nitrobenzenesulfonyl chloride. A gradient elution with 10% aqueous CH_3CN–40% aqueous CH_3CN was applied.

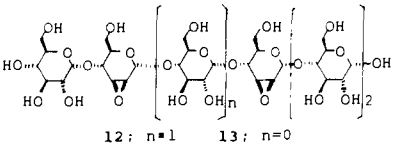
The high regiospecificity in sulfonation of the secondary hydroxyl of α-cyclodextrin with *m*-nitrobenzenesulfonyl chloride was supported by the simplicity of the elution pattern in Figure 1 which showed the formation of three bis(nitrobenzenesulfonates), **4** (2%),[12] **5** (6.4%),[12] and **6** (4.5%).[12] The disulfonates **4–6** were



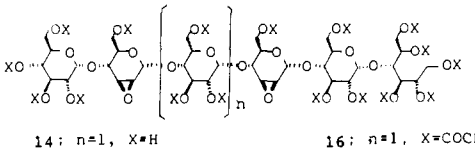
4; n=2 **5**; n=1 **6**; n=0 **7**; n=2 **8**; n=1 **9**; n=0



10 **11**



12; n=1 **13**; n=0



14; n=1, X=H **16**; n=1, X=$COCH_3$
15; n=0, X=H **17**; n=0, X=$COCH_3$

also effectively separated by reversed-phase column chromatography: **4** (38 mg, 1%), **5** (112 mg, 4%), and **6** (74 mg, 2%). The ^1H NMR, ^{13}C NMR, and FABMS spectra showed that they were disulfonates of C-2-hydroxyls.[13] Treatment of each disulfonate with aqueous K_2CO_3 gave a corresponding diepoxide, **7–9**. The ^1H NMR spectra showed that they were di-*manno*-epoxides,[14] confirming the disulfonation on C-2-hydroxyls. The FABMS and ^{13}C NMR spectra (Figure 2) also confirmed the structural assignment. Only **7** showed ^{13}C NMR (Figure 2) and ^1H NMR[14] spectra of a symmetrically substituted cyclodextrin, demonstrating that **7** (therefore, **4**) was the AD isomer. Moreover, the structures of **7–9** were independently determined as follows. We have found that Taka amylolysis of the α-cyclodextrin *manno*-epoxide (**10**) gave a tetraose epoxide (**11**) as a main product.[15] From this result, we expected Taka amylolyses of **7**, **8**, and **9** to give **7**, **12**, and **13**, respectively. Actually, **8** and **9** were hydrolyzed to give a hexaose diepoxide (**12**) and a pentaose diepoxide (**13**), respectively, as main products whose molecular weights were obtained by FABMS spectra, while unreactive **7** was recovered from the enzymatic reaction. In order to determine the positions of the diepoxides, **12** and **13** were reduced with 1% aqueous $NaBH_4$ to give **14** and

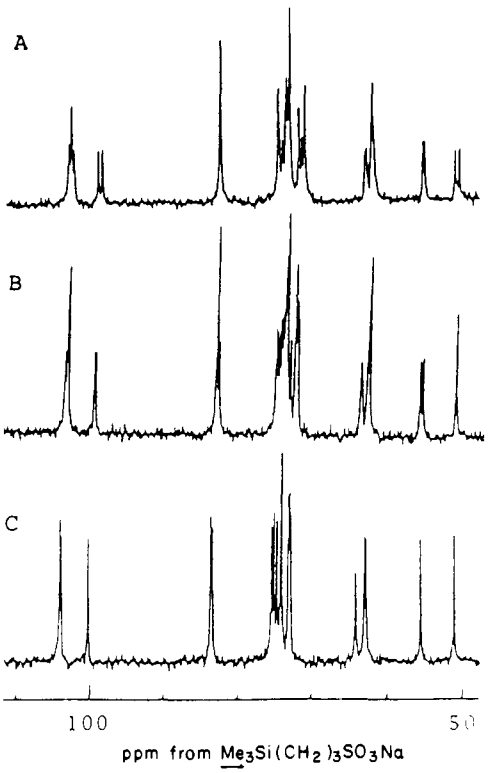


Figure 2. ^{13}C NMR spectra of AB-di-*manno*-epoxide of α-cyclodextrin (**9**) (2A), AC isomer (**8**) (2B), and AD isomer (**7**) (2C) in D_2O.

(12) The yields of **4–6** were obtained by use of HPLC, where phenol was used as the internal standard.

(13) ^{13}C NMR spectra (Me_2SO-d_6) of **4–6** showed the downfield-shifted absorption of C-2 and the upfield-shifted absorptions of C-1 and C-3 similarly to that of **2a**. ^1H NMR spectra (Me_2SO-d_6) of **4–6** were different from one another in the pattern of the aromatic absorptions.

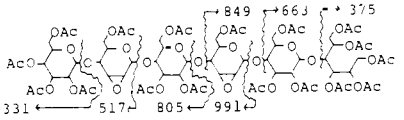
(14) Chemical shifts (D_2O, internal standard; acetone, δ 2.07) of two C-1 protons of the epoxide parts were as follows: δ 5.15 for **7**, δ 5.13 and 5.14 for **8**, and δ 5.12 and 5.18 for **9**. They were singlet absorptions, showing that the stereochemistry of the epoxide was a *manno*-epoxide type. See ref 4 and 5.

(15) This will be reported elsewhere in near future.

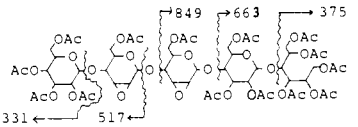
15 followed by complete acetylation with acetic anhydride in pyridine to give **16** and **17**, respectively. While FABMS spectra of **14** and **15** and FDMS[9] spectra of **16** and **17** showed the correct molecular ions of them, EIMS[9] fragmentations of **16** and **17** demonstrated that the epoxides were located on the second and fourth glucose units from the nonreducing end of **16** and on the second and third units for **17**.[16] Therefore, **8** and **9** are assigned to AC and AB isomers, respectively. In conclusion, the disulfonates **4–6** are assigned to 2A2D, 2A2C, and 2A2B isomers, respectively.

Thus, we could find highly regiospecific sulfonating reagents for secondary hydroxyls of α-cyclodextrin and obtain disulfonates of the secondary C-2-hydroxyls and the di-*manno*-epoxides, which will develop a new aspect of studies on construction of artificial enzymes and receptors having novel properties of molecular recognition and catalysis. Also, the present study suggests the wide application of Taka amylolysis to isomer determination of various polysubstituted cyclodextrins.

(16) The following fragmentation ions were observed.



16



17

Acknowledgment. We are indebted to Japan Maise Products Co. Ltd. for generous gift of α-cyclodextrin.

Registry No. 1a, 95784-30-8; **1b**, 95784-31-9; **1c**, 95784-32-0; **1d**, 95784-33-1; **2a**, 95784-34-2; **2b**, 95784-35-3; **2c**, 95784-36-4; **2d**, 95784-37-5; **3a**, 95784-38-6; **3b**, 95784-39-7; **3c**, 95784-40-0; **3d**, 95784-41-1; **4**, 95784-42-2; **5**, 95784-43-3; **6**, 95784-44-4; **7**, 95784-45-5; **8**, 95797-81-2; **9**, 95797-82-3; **12**, 95784-46-6; **13**, 95784-47-7; **14**, 95784-48-8; **15**, 95784-49-9; **16**, 95784-50-2; **17**, 95784-51-3; *m*-NBsCl, 121-51-7; *p*-NBsCl, 98-74-8; α-NsCl, 85-46-1; β-NsCl, 93-11-8; α-cyclodextrin, 10016-20-3.

Supplementary Material Available: Experimental data for α-cyclodextrins (8 pages). Ordering information given on any current masthead page.

Palladium-Catalyzed Double Carbonylation of Aryl Halides To Give α-Keto Amides. Mechanistic Studies

Fumiyuki Ozawa,[†] Hidehiko Soyama,[†] Hisayoshi Yanagihara,[†] Issei Aoyama,[†] Hiroaki Takino,[‡] Kunisuke Izawa,[‡] Takakazu Yamamoto,[†] and Akio Yamamoto*[†]

Contribution from the Research Laboratory of Resources Utilization, Tokyo Institute of Technology, 4259 Nagatsuta, Midori-ku, Yokohama 227, and Central Research Laboratories, Ajinomoto Co., Inc., Suzuki-Chyo 1-1, Kawasaki-ku, Kawasaki 210, Japan.
Received September 11, 1984

Abstract: Various aryl halides are catalytically converted into α-keto amides and amides on treatment with secondary amines and carbon monoxide. Palladium complexes containing tertiary phosphine ligands, particularly diphenylmethylphosphine and 1,4-bis(diphenylphosphino)butane, are most effective among other transition-metal complexes. Detailed examination of factors controlling the reaction rates and selectivity for α-keto amide formation revealed the following characteristics of the reactions. (a) Reactivity of phenyl halide decreases in the order PhI > PhBr ≫ PhCl. (b) Oxidative addition of phenyl bromide constitutes the rate-determining step in double carbonylation of phenyl bromide, whereas in the reaction of phenyl iodide the rate-determining step is associated with the reaction of a catalytically active palladium species with carbon monoxide. (c) Introduction of an electron-withdrawing substituent into the para position of phenyl halide enhances the reactivity but decreases the selectivity for α-keto amide. (d) Employment of amines of high basicity ($pK_b \leq 4$) is essential for accomplishing the catalytic double carbonylation. (e) When highly basic secondary amines are used, less sterically demanding amines seem to favor the formation of amide. Decrease of selectivity for the α-keto amide formation in the order Pr_2NH > Et_2NH > piperidine > hexamethyleneimine > Me_2NH > pyrrolidine probably reflects the decrease in steric bulkiness of amines. (f) Although primary amines are in general not suitable for the double carbonylation, *tert*-butylamine can be used because of its inertness to the product α-keto amide. Reactivity of *trans*-PdPh(I) $(PMePh_2)_2$ and *trans*-Pd(COPh)I$(PMePh_2)_2$, supposed intermediates in the catalytic reaction of PhI, toward amines and CO was examined. The relative reactivity of six secondary amines with the benzoylpalladium complex increasing in the order Pr_2NH < Et_2NH < piperidine < Me_2NH < hexamethyleneimine < pyrrolidine was found to be inversely correlated with decreasing selectivity order for α-keto amide formation in the catalytic systems. On the basis of the experimental results, a mechanism consisting of two catalytic cycles to produce α-keto amides and amides has been proposed.

The recently discovered double-carbonylation reaction of aryl halides catalyzed by palladium complexes provides synthetic means useful for introducing two carbonyl groups into organic compounds[1,2]

$$ArX + 2HNR_2' + 2CO \xrightarrow{[Pd]} ArCOCONR_2' + R_2'NH_2X \quad (1)$$

The α-keto amides prepared by this method have potential applications to synthesis of a variety of useful products including α-amino acids, α-hydroxy acids, and heterocyclic compounds.

Previous papers[3,4] focused on stoichiometric reactions of aryl- and alkylpalladium halides with carbon monoxide, and amines indicated involvement of elementary processes in the double-

[†] Tokyo Institute of Technology.
[‡] Ajinomoto Co., Inc.

(1) Ozawa, F.; Soyama, H.; Yamamoto, T.; Yamamoto, A. *Tetrahedron Lett.* **1982**, *23*, 3383.
(2) Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1982**, *233*, C64.
(3) Ozawa, F.; Yamamoto, A. *Chem. Lett.* **1982**, 865.
(4) (a) Ozawa, F.; Sugimoto, T.; Yuasa, Y.; Santra, M.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1984**, *3*, 683. (b) Ozawa, F.; Sugimoto, T.; Yamamoto, T.; Yamamoto, A. *Ibid.* **1984**, *3*, 692.

0002-7863/85/1507-3235$01.50/0