Synthesis of $6^A,6^X$-Di-*O*-(*p*-tosyl)-γ-cyclodextrins and Their Structural Determination through Enzymatic Hydrolysis of $3^A,6^A;3^X,6^X$-Dianhydro-γ-cyclodextrins

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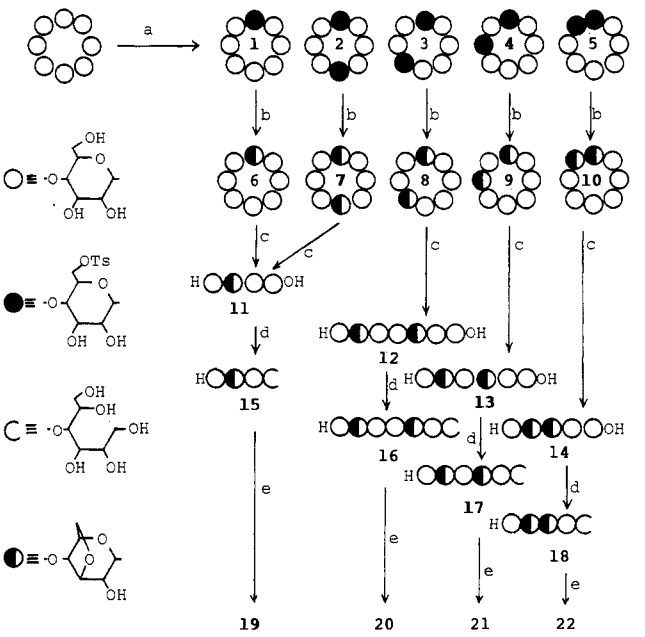
$6^A,6^X$-Di-*O*-(*p*-tosyl)-γ-cyclodextrins (X = B, C, D, and E) were prepared by the reaction of γ-cyclodextrin and *p*-tosyl chloride in pyridine and isolated by reversed-phase column chromatography. From the results of Taka amylolyses of $3^A,6^A;3^X,6^X$-dianhydro-γ-cyclodextrins which were obtained from the corresponding ditosylates, the regiochemistry of the ditosylates was determined.

Specific disulfonylations on primary C-6 hydroxyls of α- and β-cyclodextrins have successfully developed a new aspect of construction of enzyme (receptor) mimics.[1] Since γ-cyclodextrin has unique characteristics such as large solubility in water,[2] binding of large guest molecules[3], and binding of two guests,[4] it is valuable to prepare 6-*O*-disulfonates of γ-cyclodextrin and to determine their regiochemistry for the purpose of construction of bifunctional γ-cyclodextrins. We have already reported isolation of $6^A,6^B$-, $6^A,6^C$-, and $6^A,6^D$-disulfonates of α- or β-cyclodextrin from their mixture by reversed-phase column chromatography, where we applied Körner's method to regiochemical determination of the disulfonyl-α-cyclodextrins[1d,e] and used an enzymatic hydrolysis method based upon of Taka amylase to determine the structure of $6^A,6^B$-di-*O*-disulfonyl-β-cyclodextrin.[1c,f] The former method correlating the disulfonates to the trisulfonates through additional monosulfonylation does not seem promising in the regioisomer determination of the γ-cyclodextrin analogues because there are many isomers, i.e. four disulfonates and six trisulfonates, compared with three disulfonates and four trisulfonates in the α-cyclodextrin case. The latter method, a direct enzymatic hydrolysis, is not applicable to determination of $6^A,6^X$-disulfonyl-β-cyclodextrins (C and D), since the effectiveness is limited to a $6^A,6^B$ isomer, i.e. this method gave a common product, 6′-substituted maltose from the other isomers, $6^A,6^C$ and $6^A,6^D$ isomers (probably, $6^A,6^E$ isomer, too). We describe here the preparation and isolation of all of the isomeric 6-*O*-disulfonylated γ-cyclodextrins (**2–5**) and the determination of their regiochemistry by their chemical conversion to di-3,6-anhydro derivatives followed by Taka amylolysis (Scheme I).

Experimental Section

General. ^1H NMR spectra (400 MHz) were determined with a JEOL GX-400 spectrometer. ^{13}C NMR spectra (25 MHz) were obtained with a JEOL FX-100 spectrometer. Field desorption mass (FDMS), fast atom bombardment mass (FABMS), and electron impact mass (EIMS) spectra were recorded with a JEOL JMS DX-300/JMA 3500 data system. Thin-layer chromatography was run with precoated silica gel plates (Merck, Art 5557). 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)). The solvent for TLC development was n-C_3H_7OH/AcOEt/H_2O (7/7/5 (v/v/v). A Merck Lobar prepacked column (LiChroprep RP18 or RP8 column, size A or B) was used for reversed-phase column chromatography. High-performance liquid chromatography was performed on a Hitachi 635A with a TSKgel LS-410 ODS SIL column (4 × 300 mm, 5 μm, Toyo Soda, Japan).

Scheme I. Synthesis and Structure Determination of $6^A,6^X$-Di-*O*-(*p*-tosyl)-γ-cyclodextrins[a]



[a] (a) *p*-TsCl/Py; (b) 1 N NaOH; (c) Taka-amylase (d) $NaBH_4$; (e) Ac_2O/Py.

Preparation of $6^A,6^X$-Di-*O*-(*p*-tosyl)-γ-cyclodextrins. *p*-Tosyl chloride (10.1 g) was added to a solution of γ-cyclodextrin (10 g) in pyridine (100 mL) and stirred for 2 h at room temperature. The amount of the sulfonyl chloride was dependent on the dryness of γ-cyclodextrin and pyridine. After addition of ethanol (20 mL) and concentration in vacuo, the crude mixture was dissolved in water (200 mL) and chromatographed on a

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(1) (a) Tabushi, I.; Kuroda, Y.; Yokota, K.; Yuan, L. C.; *J. Am. Chem. Soc.* **1981**, *103*, 711. (b) Tabushi, I.; Yuan, L. C. *Ibid.* **1981**, *103*, 3574. (c) Tabushi, I.; Nabeshima, T.; Fujita, K.; Matsunaga, A.; Imoto, T. *J. Org. Chem.* **1985**, *50*, 2638. (d) Fjuita, K.; Matsunaga, A.; Imoto, T. *J. Am. Chem. Soc.* **1984**, *106*, 5740. (e) Fujita, K.; Yamamura, H.; Matsunaga, A.; Imoto, T. *Ibid.* **1986**, *108*, 4509. (f) Fjuita, K.; Matsunaga, A.; Imoto, T.; *Tetrahedron Lett.* **1984**, *25*, 5533. (g) Tabushi, I.; Shimokawa, K.; Fujita, K. *Ibid.* **1977**, 1527. (h) Breslow, R.; Doherty, J. N.; Guillot, C.; Lipsey, C. *J. Am. Chem. Soc.* **1978**, *100*, 3227. (i) Breslow, R.; Bovy, P.; Hersh, C. L. *Ibid.* **1980**, *102*, 2115. (j) Tabushi, I.; Kuroda, Y. *Ibid.* **1984**, *106*, 4580. (k) Tabushi, I.; Kuroda, Y.; Yamada, M.; Higashimura, M.; Breslow, R. *Ibid.* **1985**, *107*, 5545. (l) Tabushi, I.; Kuroda, Y.; Mizutani, T. *Ibid.* **1986**, *108*, 4514.

(2) 30 g/100 mL at 25 °C, compared with 13 g/100 mL of α-cyclodextrin and 1.85 g/100 mL of β-cyclodextrin.

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

(4) (a) Ueno, A.; Takahashi, K.; Osa, T. *J. Chem. Soc., Chem. Commun.* **1980**, 921. (b) Fujita, K.; Ejima, S.; Imoto, T. *Chem. Lett.* **1985**, 11.

0022-3263/88/1953-1943$01.50/0

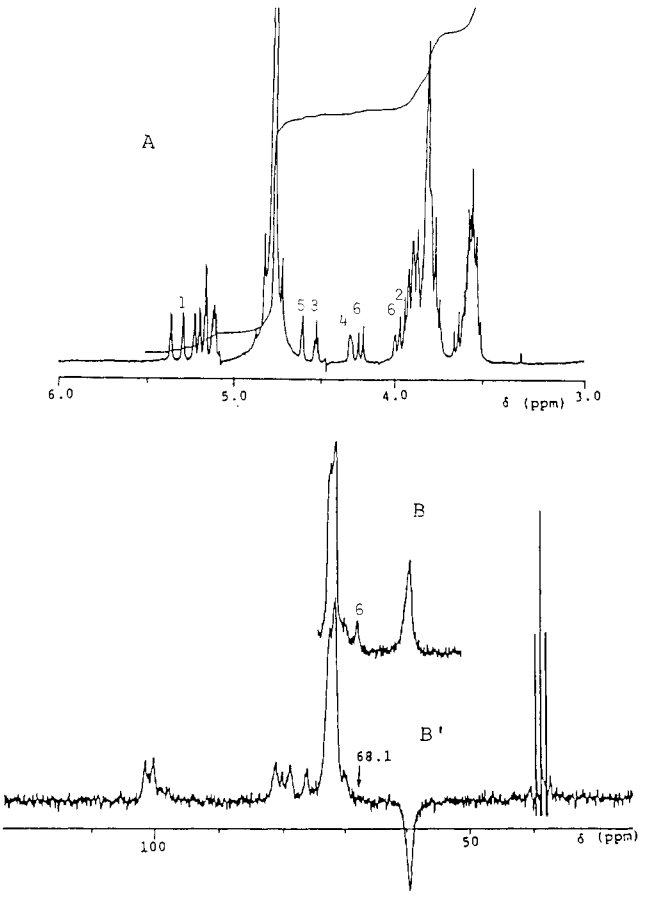

Figure 1. ^1H NMR (A, in D_2O), ^{13}C NMR (B, in Me_2SO-d_6), and INEPT ^{13}C NMR (B′, in Me_2SO-d_6) spectra of 3,6-anhydro-γ-cyclodextrin (**6**). The numbers for assignments represent the carbon numbers in the 3,6-anhydroglucose unit.

reversed-phase column. After stepwise elution from water (1 L) to 5% aqueous ethanol (1 L), linear gradient elution from 10% aqueous ethanol (1 L) to 40% aqueous ethanol (1 L) followed by linear gradient elution from 40% aqueous ethanol (1 L) to 60% aqueous ethanol (1 L) was applied to give **2** (340 mg, 2.6%), **3** (772 mg, 5.9%), **4** (743 mg, 5.7%), and **5** (757 mg, 5.8%). R_f value of **2–5**, 0.40. FABMS of **2–5**, m/z 1605 ($M + H^+$). ^1H NMR (Me_2SO-d_6, aromatic protons) **2**, δ 7.72, 7.40; **3**, δ 7.74, 7.41; **4**, δ 7.72, 7.42; **5**, δ 7.43, 7.45.

Preparation of $3^A,6^A$-Anhydro-γ-cyclodextrin (6) and $3^A,6^A;3^X,6^X$-Dianhydro-γ-cyclodextrins (X = B–E) 7–10. A solution of 6-*O*-(*p*-tosyl)-γ-cyclodextrin (**1**) (1.5 g, 1.03 mmol) in 1 N NaOH (12 mL) was kept at 40 °C for 3.5 h. After neutralization, the mixture was applied chromatographed on a reversed-phase column (RP8, size B). After stepwise elution with water (800 mL), 1% aqueous methanol (300 mL), and 3% aqueous methanol (300 mL), elution with 7% aqueous methanol (1 L) was applied to give $3^A,6^A$-anhydro-γ-cyclodextrin (**6**) (817 mg, 61.8%). R_f value, 0.08. FABMS (m/z), 1274 ($M + H^+$).

6-Di-*O*-(*p*-tosyl)-γ-cyclodextrin **3** (400 mg, 0.249 mmol) was dissolved in 1 N NaOH (7 mL) and kept at 40 °C for 7 h. After neutralization, the mixture was dissolved in water (20 mL) and chromatographed on a reversed-phase column (RP8, size A). Elution of water (800 mL) gave 3,6-dianhydro-γ-cyclodextrin **8** (274 mg, 87.0%). Similarly, **2** (400 mg), **4** (400 mg), and **5** (400 mg) gave **7** (227 mg, 72.3%), **9** (196 mg, 62.5%), and **10** (239 mg, 76.1%), respectively. R_f value of **7–10**, 0.07. FABMS of **7–10**, m/z 1261 ($M + H^+$), 1283 ($M + Na^+$).

Taka Amylolyses of $3^A,6^A$-Anhydro-γ-cyclodextrin 6 and $3^A,6^A;3^X,6^X$-Dianhydro-γ-cyclodextrins (X = B–E) 7–10. A solution of $3^A,6^A$-anhydro-γ-cyclodextrin (**6**) (50 mg, 0.0454 mmol) and Taka amylase (amylase type IV, Sigma) (58 mg) in 0.2 M acetate buffer (pH 5.5) containing 0.01 M $CaCl_2$ was kept at 40 °C for 3 days. After deactivation of the enzyme by addition of 3 N NH_4OH followed by centrifugation, the supernatant was concentrated in vacuo to dryness and dissolved in water (35 mL). The solution was chromatographed on a reversed-phase column (RP18, size B). After elution with water (300 mL), gradient elution from water (100 mL) to 10% aqueous ethanol (100 mL) was applied to give 3″,6″-anhydomaltotetraose **11** (25 mg, 85.0%). R_f value, 0.13. FABMS, m/z 649 ($M + H^+$), 671 ($M + Na^+$), 687 ($M + K^+$).

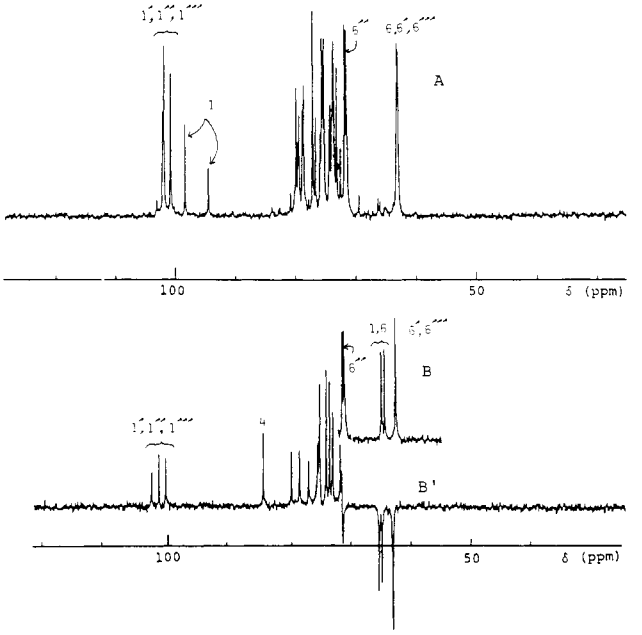

Figure 2. ^{13}C NMR spectrum of 3″,6″-anhydromaltotetraose (**11**) (A), ^{13}C NMR (B), and INEPT ^{13}C NMR (B′) spectra of its reduced compound (**15**) (B) in D_2O. The numbers for assignments represent the carbon numbers of **11** and **15**.

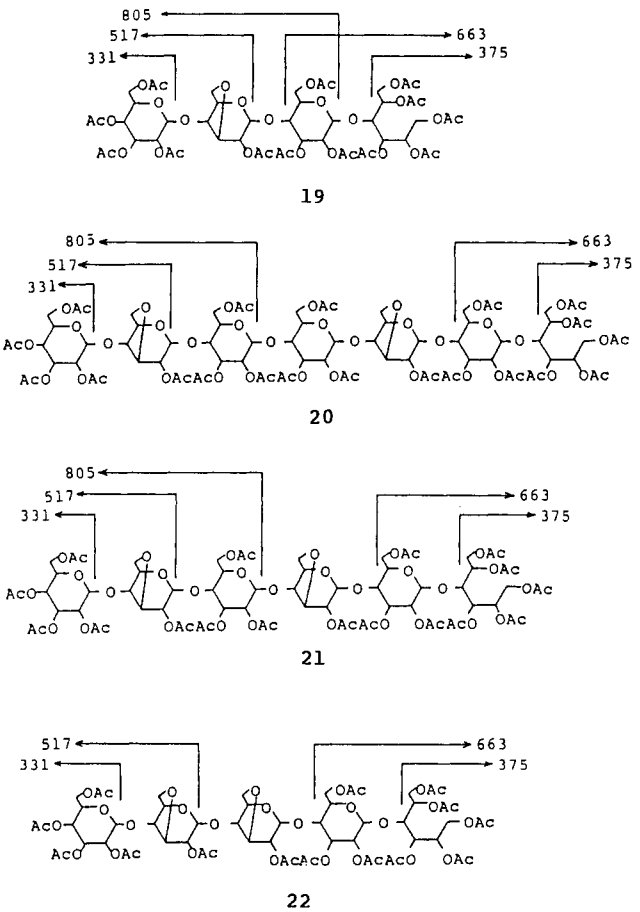

Figure 3. EIMS spectral fragmentation patterns of **19–22**.

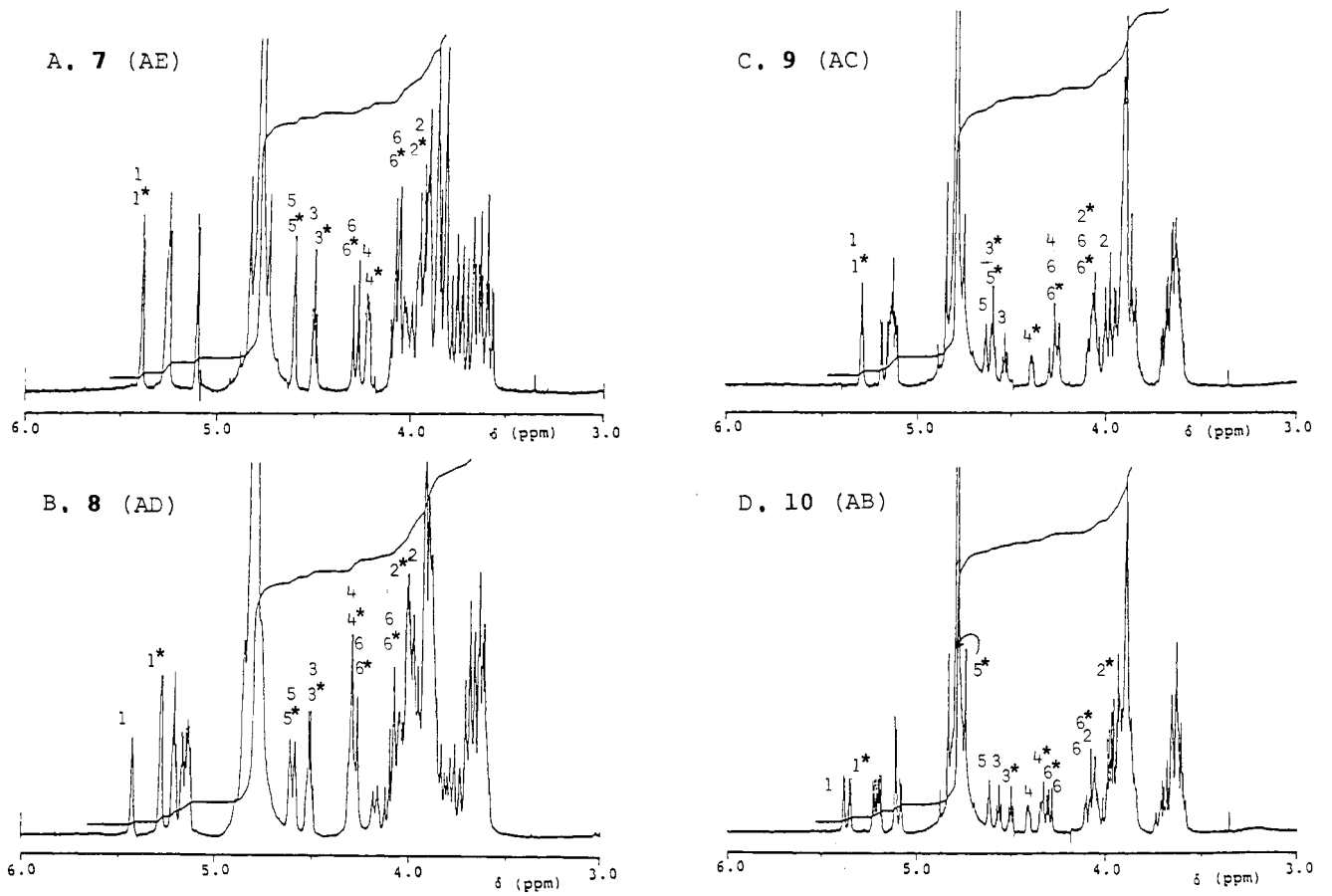

Figure 4. ^{1}H NMR spectra of $3^A,6^A;3^X,6^X$-dianhydro-γ-cyclodextrins in D_2O. **7**, A; **8**, B; **9**, C; **10**, D. The numbers for assignments represent the carbon numbers in two 3,6-anhydroglucose units.

A solution of dianhydro-γ-cyclodextrin **8** (40 mg, 0.0313 mmol) and Taka amylase (40 mg) in acetate buffer was kept at 40 °C for 2 days. After the workup procedures described above, the mixture was chromatographed on a reversed-phase column (RP18, size B). After elution of water (200 mL), gradient elution from water (200 mL) to methanol (200 mL) gave 3''''',6''''';3'',6''-dianhydroheptaose **12** (32 mg, 90.3%). Similarly, dianhydro-γ-cyclodextrins **7**, **9**, and **10** (40 mg, 0.0317 mmol) gave **11** (39 mg, 94.8%), **13** (26 mg, 85.2%), and **14** (18 mg, 71.6%), respectively. R_f value of **12–14**, 0.11. FABMS, m/z **12**, 1117 (M + H$^+$); **13**, 955 (M + H$^+$), 977 (M + Na$^+$); **14**, 793 (M + H$^+$), 815 (M + Na$^+$).

$NaBH_4$ Reduction of 3'',6''-Anhydromaltotetraose 11 and Dianhydromaltooligosaccharides 12–14. A solution of 3'',6''-anhydromaltotetraose **11** (70 mg, 0.108 mmol) in 1% aqueous $NaBH_4$ (25 mL) was kept at room temperature for 6 h. After neutralization, the solution was chromatographed on a reversed-phase column (RP18, size B). After elution with water (300 mL), gradient elution from water (200 mL) to 20% aqueous ethanol (200 mL) was applied to give the reduced sugar **15** (55 mg, 71.1%). R_f value, 0.11. FABMS, m/z 651 (M + H$^+$).

A solution of dianhydromaltooligosaccharide **12** (20 mg, 0.0179 mmol) in 1% aqueous $NaBH_4$ (4.3 mLe) was kept at room temperature for 15 h. After neutralization, the solution was chromatographed on a reversed-phase column (RP18, size B). After elution with water (200 mL), gradient elution from water (200 mL) to 20% aqueous methanol (200 mL) was applied to give the reduced sugar **16** (19 mg, 92.3%). Similarly, **17** (9 mg, 58.4%) and **18** (11 mg, 87.3%) were obtained. R_f value of **16–18**, 0.11. FABMS, m/z **16**, 1141 (M + Na$^+$); **17**, 957 (M + H$^+$), 979 (M + Na$^+$); **18**, 817 (M + Na$^+$).

Acetylation of Reduced Sugars 15–18. A solution of **15** (5 mg) and acetic anhydride (0.25 mL) in pyridine (0.25 mL) was allowed to stand at room temperature for 2 days and concentrated by evaporation of voltatile materials together with a stream of nitrogen. After dry chloroform (0.5 mL) was added to the residue, the evaporation was repeated. The residue **19** was directly analyzed by FDMS and EIMS spectra. R_f value ($CHCl_3$/EtOH, 20/1), 0.41. FDMS, m/z 1197 (M + H$^+$).

Similarly, peracetates **20–22** were obtained from **12–14**, respectively, and analyzed directly by EIMS spectra. R_f value ($CHCl_3$/EtOH, 20/1), **20**, 0.23; **21**, 0.23; **22**, 0.30.

Results and Discussion

Preparation and Isolation of $6^A,6^X$-Di-O-(p-tosyl)-γ-cyclodextrins. 6-O-(p-Tosyl)-γ-cyclodextrin (**1**) and a regioisomeric mixture of 6-O-ditosyl-γ-cyclodextrins **2–5** were prepared by the reaction of γ-cyclodextrin with p-tosyl chloride in pyridine by monitoring the progress of the reaction with TLC and regulating the amount of the sulfonyl chloride. The products were separated from the mixture by reversed-phase column chromatography with a gradient elution of water–ethanol. ^{1}H NMR and FABMS spectra of **2–5** demonstrated that **2–5** were disulfonates.

Preparation of $3^A,6^A$-Anhydro-γ-cyclodextrin from 6-O-(p-Tosyl)-γ-cyclodextrin and Its Taka Amyloysis. In order to obtain information concerning an enzymatic hydrolysis pattern of $3^A,6^A$-anhydro-γ-cyclodextrin by Taka amylase, this anhydro derivative **6** was prepared by the reaction of **1** with 1 N NaOH. Its FABMS spectrum showed the correct molecular ion at m/z 1279 (M + H$^+$). Its ^{1}H NMR and ^{13}C NMR spectra (Figure 1) were very similar to those of $3^A,6^A$-anhydro-β-cyclodextrin and methyl 3,6-anhydro-α-D-glucoside reported before,[5] demonstrating that **6** was $3^A,6^A$-anhydro-γ-cyclodextrin. The proton absorption of the 3,6-anhydroglucose unit in its ^{1}H NMR spectrum were assigned as shown in Figure 1A with the aid of the COSY ^{1}H NMR spectrum.

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

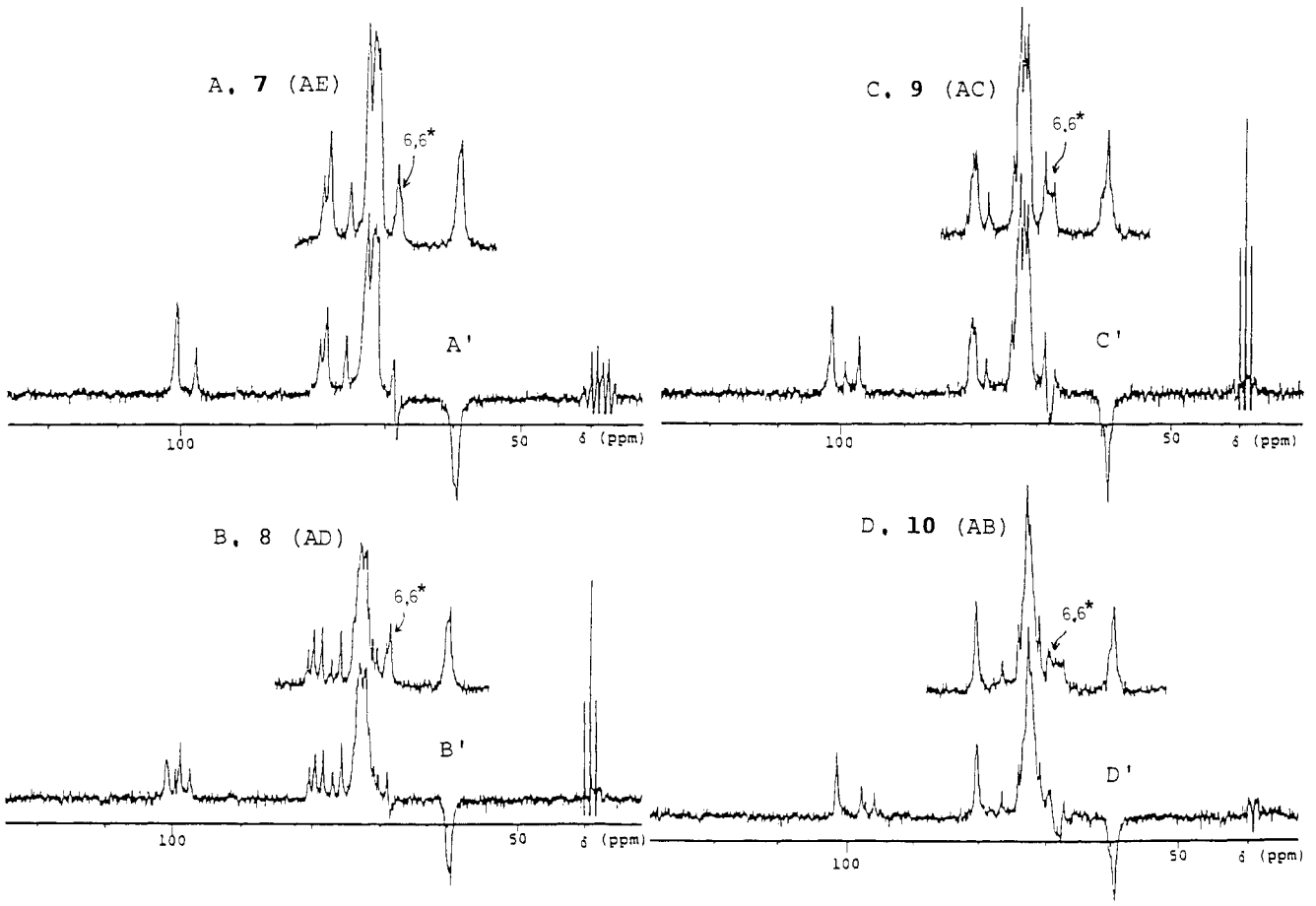

Figure 5. ^{13}C NMR (A–D) and INEPT ^{13}C NMR (A′–D′) spectra of $3^A,6^A;3^X,6^X$-dianhydro-γ-cyclodextrins. **7**, A and A′; **8**, B and B′; **9**, C and C′; **10**, D and D′ in Me_2SO-d_6. The numbers for assignments represent the carbon numbers in two 3,6-anhydroglucose units.

The 3,6-anhydro-γ-cyclodextrin **6** was enzymatically hydrolyzed by Taka amylase. The mixture was chromatographed by use of a reversed-phase column with a gradient elution of water–ethanol to give 3″,6″-anhydromaltotetraose **11** (85.0%) whose FABMS spectrum showed the correct molecular ion at m/z 649 ($M + H^+$). The position of 3,6-anhydroglucose unit in **11** was determined as shown in Scheme I. The anhydro tetraose **11** was reduced with aqueous $NaBH_4$ to give **15**. The conversion was confirmed by its FABMS spectrum and ^{13}C NMR spectra of **11** and **15** (Figure 2). Complete acetylation of **15** (5 mg) with pyridine–acetic anhydride gave **19**, whose FDMS spectrum showed the correct molecular ion at m/z 1197 ($M + H^+$). The fragmentation pattern of the EIMS spectrum of **19** clarified the position of the 3,6-anhydroglucose unit as shown in Figure 4.

In conclusion, $3^A,6^A$-anhydro-γ-cyclodextrin which was easily prepared from 6-*O*-(*p*-tosyl)-γ-cyclodextrin was hydrolyzed by Taka amylase to give 3″,6″-anhydromaltotetraose exclusively. From this hydrolytic pattern, we could expect that Taka amylolysis was applicable to the structure determination of $6^A,6^X$-di-*O*-(*p*-tosyl)-γ-cyclodextrins after the conversion to $3^A,6^A;3^X,6^X$-dianhydro-γ-cyclodextrins as shown in Scheme I.

Preparation of $3^A,6^A;3^X,6^X$-Dianhydro-γ-cyclodextrins from $6^A,6^X$-Di-*O*-(*p*-tosyl)-γ-cyclodextrins and Their Taka Amyloylses. The disulfonates **2–5** gave the corresponding di-3,6-anhydro-γ-cyclodextrins **7**, **8**, **9**, and **10**, respectively, according to the method described above. The FABMS spectra of **7–10** showed the correct molecular ions at m/z 1261 ($M + H^+$) and 1283 ($M + Na^+$). The ^1H NMR (Figure 4) and ^{13}C NMR (Figure 5) spectra also demonstrated the presence of two 3,6-anhydroglucose units in **7–10**. These observations reconfirmed that **2–5** were 6-*O*-disulfonates. The assignment of the 3,6-anhydroglucose units in Figure 4 was carried out by the COSY ^1H NMR spectra. The ^1H NMR spectra strongly suggested that **7** was a symmetric compound and therefore $3^A,6^A;3^E,6^E$-dianhydro-γ-cyclodextrin. Simplicity of the ^{13}C NMR (Figure 5A) also supported this suggestion.

Taka amylolyses of **7–10** produced oligosaccharides **11** (94.8%), **12** (90.3%), **13** (85.2%), and **14** (71.6%), respectively. The FABMS spectra demonstrated that **11–14** were 3,6-anhydromaltotetraose, di-3,6-anhydromaltoheptaose, di-3,6-anhydromaltohexaose, and di-3,6-anhydromaltopentaose, respectively. The oligosaccharides **11–14** were reduced with $NaBH_4$ to give **15**, **16**, **17**, and **18**, whose FABMS spectra showed the corresponding correct molecular ions. They were completely acetylated with pyridine–acetic anhydride to give **19–22**, whose EIMS spectra demonstrated the position of a 3,6-anhydroglucose unit as shown in Figure 3. The EIMS spectrum fragmentation patterns of **20–22** do not seem to clarify the position of another 3,6-anhydroglucose unit. But, since the original oligosaccharides **16–18** were determined to be di-3,6-anhydromaltoheptaose, di-3,6-anhydromaltohexaose, and di-3,6-anhydromaltopentaose, respectively, by their FABMS spectra, **17** and **18** should be assigned to 3‴,6‴;3″,6″-dianhydromaltohexaose and 3‴,6‴;3″,6″-dianhydromaltopentaose, respectively, and therefore **16** should be assigned to 3⁗,6⁗;3″,6″-dianhydromaltohexaose. These Taka amylolysis products revealed that **2–5** were $6^A,6^E$, $6^A,6^D$, $6^A,6^C$, and $6^A,6^B$ isomers, respectively.

The present results showed that the enzymatic cleavage patterns of the dianhydrocyclodextrins **7–10** were understandable by superimpositions of patterns of two monoanhydrocyclodextrins. Since Taka amylolysis patterns of $6^A,6^X$-di-*O*-sulfonyl-α- or -β-cyclodextrins[1c,d,f] and $2^A,3^A;2^X,3^X$-dianhydro-α- or -β-cyclodextrins[6] were also understandable by "superimposition", the Taka amylolysis method may be widely applicable to structure determination of polysustituted cyclodextrins or oligosaccharides, after an appropriate chemical conversion, if necessary. In the present study, all 6-O-disulfonylated γ-cyclodextrins and 3,6-dianhydro-γ-cyclodextrins were isolated as pure materials and structurally assigned. These disulfonated γ-cyclodextrins will serve as the starting materials for the synthesis of unique enzyme mimics with binding of two substrates in the active site. The 3,6-dianhydro-γ-cyclodextrins have unique cavity shapes which are different from one another and from that of γ-cyclodextrin itself and are expected to show unique molecular recognition. Also, the present study shows that the Taka amylolysis is an effective synthetic method for linear maltooligosaccharides containing 3,6-anhydroglucose units at specific positions.

(6) (a) Fujita, K.; Tahara, T.; Nagamura, S.; Imoto, T.; Koga, T. *J. Org. Chem.* **1987**, *52*, 636. (b) Fujita, K.; Tahara, T.; Imoto; Koga, T. *J. Am. Chem. Soc.* **1986**, *108*, 2030. (c) Fujita, K.; Nagamura, S.; Tahara, T.; Imoto, T.; Koga, T. *Ibid.* **1985**, *107*, 3233.

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Diastereoselective Alkylation Guided by Electrophile–Nucleophile π-Interactions

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Alkylation of the enolate **1a** obtained from the (*R*)-camphor imine of *tert*-butyl glycinate with a variety of alkylating agents gives products whose trends in diastereomeric excesses appear to correlate with π electron density and steric effects in the electrophile. Secondary allylic or benzylic halides undergo efficient double chiral induction. Anion **1a** undergoes smooth Michael additions with no chiral discrimination, but aldol condensations cannot be achieved.

Enantioselective alkylation reactions are the subject of current intense investigation. A recent comprehensive review[2] summarizes much of the currently available information. An especially active area is the asymmetric alkylation of derivatized glycine using a variety of reaction types[3–6] to provide higher amino acids of known configuration and high optical purity. Recently we reported[7] the results of a study designed to examine the use of camphor as a chiral auxilliary in such alkylations. The specific reaction probed was the alkylation of the (*R*)-camphor imine of *tert*-butyl glycinate (**1**). The diastereomeric excesses (de) of the products showed several distinct trends. For primary alkylating agents that do not have an adjacent π-system, increasing steric bulk increased the de values to a maximum of ca. 50% (R = *i*-Bu or Bu) while significantly higher values were observed for halides which contained a π-system attached to the reacting center (allylic and benzylic halides). The latter observation was true even though the steric requirements of the R group in these alkylating agents were, in many examples, significantly less than the saturated cases. In all instances, attack from the *re* face (opposite side from camphor C8) was favored and the products were shown to be those of kinetic control. It is worth noting that **1a** can be classified as a type of azallyl anion[8] that has not received the study accorded the more usual type derived from enamines.

On the basis of these results, a conceptual model for the alkylation process was developed (Figure 1)[7] that included the following points. Imine **1**, which appears to be stereochemically homogeneous from its ^1H and ^{13}C NMR spectra and presumably exists in the *E* configuration, affords an enolate (**1a**) on treatment with LDA. In accord

(1) (a) Taken in part from the Ph.D. Dissertation of R. K. Leavitt, University of Windsor, 1986. (b) Taken in part from the Ph.D. Dissertation of P. Mishra, University of Windsor, 1985. (c) Holder, Natural Sciences and Engineering Research Council of Canada Predoctoral Fellowship, 1981–85. (d) Taken in part from the undergraduate research report of K. C. Cassidy, 1987.

(2) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 1.

(3) (a) For some leading references, see ref 8. (b) Seebach, D.; Wasmuth, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *21*, 654.

(4) Pd(0)-catalyzed alkylation: Genet, J. P.; Ferroud, S.; Juge, S.; Montes, J. R. *Tetrahedron Lett.* **1986**, *27*, 4573.

(5) (a) Enolate alkylations: Seebach, D.; Miller, D. D.; Muller, S.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 949. Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Ibid.* **1985**, *68*, 144. Naef, R.; Seebach, D. *Ibid* **1985**, *68*, 135 and refererences therein. Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. (b) Electrophilic glycinates: Sinclair, P. J.; Zhair, D.; Reibenzpies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103. O'Donnell, M. J.; Falmange, J. B. *Tetrahedron Lett.* **1985**, *26*, 699. O'Donnell, M. J.; Falmange, J. B. *J. Chem. Soc., Chem. Commun.* **1985**, 1168. O'Donnell, M. J.; Bennett, W. B.; Polt, R. L. *Tetrahedron Lett.* **1985**, *26*, 695.

(6) Oppolzer, W.; Pedrosa, R.; Moretti, R. *Tetrahedron Lett.* **1986**, *27*, 831. Ikegami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3403. Bajgrowicz, J. A.; Cossec, B.; Pigiere, C.; Jaquier, R.; Villafont, P. *Tetrahedron Lett.* **1983**, *24*, 3721.

(7) McIntosh, J. M.; Mishra, P. *Can. J. Chem.* **1985**, *64*, 726.

(8) Bergbreiter, D. E.; Newcomb, M. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 2, p 243.

0022-3263/88/1953-1947$01.50/0