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Regiospecifically Bifunctional Cyclodextrins Having Two Amino Groups on Secondary Hydroxyl Side

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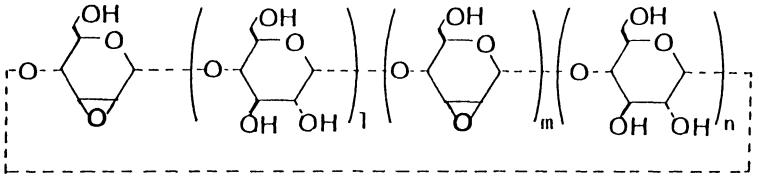
$3^A,3^X$-diamino-$3^A,3^X$-dideoxy-(2^AS),(2^XS),(3^AR),(3^XR)-α-cyclodextrins (X = B, X = C, and X = D) were prepared from the reactions of $2^A,3^A;2^X,3^X$-dianhydro-(2^AS),(2^XS)-α-cyclodextrins with aqueous ammonia.

Bifunctional cyclodextrins have attracted much attention since they are better (more sophisticated) artificial enzymes or receptors than monofunctional cyclodextrins.[1] These bifunctionalizations have been limited to the primary hydroxyl side of cyclodextrin, because regiospecific activation (sulfonylation) of the primary hydroxyl groups has been extensively studied to give the starting materials for the bifunctional cyclodextrins.[2]

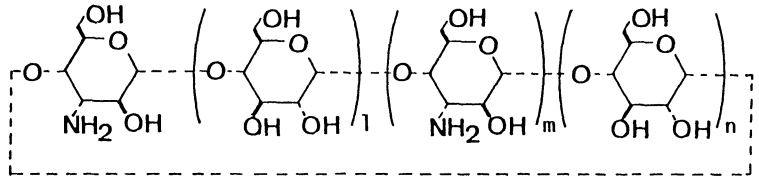
Since β-cyclodextrin having a pyridoxamine moiety on its secondary hydroxyl side showed quite different chiral recognition from that on its primary hydroxyl side in the transamination reaction,[3] it must be valuable to prepare cyclodextrin derivatives which have two functional groups at given positions on the secondary hydroxyl side. However, there has not been any study on regiospecific preparation of such cyclodextrin derivatives. The reason is that there has not existed any reliable method for regiospecific activation of two secondary hydroxyl groups.

Recently, we developed an effective method for specific preparation of 2-O-arenesulfonyl-[4-6] or $2^A,2^X$-di-O-(arenesulfonyl)-α-cyclodextrins (X = B, X = C, and X = D)[5] and their conversion to the corresponding mannoepoxides **1**a-d.[5] We describe here for the first time regiospecific preparation of α-cyclodextrin derivatives which have two amino groups on the secondary hydroxyl side. First, specific reaction of $2^A,3^A$-anhydro-(2^AS)-α-cyclodextrin **1**a with aqueous ammonia[7] and secondarily, its application to regiospecific diamination of the diepoxides **1**b-c are described in this report.

A solution of $2^A,3^A$-anhydro-(2^AS)-cyclodextrin **1**a (50 mg) in 28% aqueous



1a : l = 5, m = 0, n = 0
1b : l = 0, m = 1, n = 4
1c : l = 1, m = 1, n = 3
1d : l = 2, m = 1, n = 2



2a : l = 5, m = 0, n = 0
2b : l = 0, m = 1, n = 4
2c : l = 1, m = 1, n = 3
2d : l = 2, m = 1, n = 2

ammonia (1 mL) was kept at 60 °C for 24 h[8] and concentrated in vacuo to give a product **2a** (48 mg, 98%). The silica gel TLC which was developed with H_2O/$CH_3CO_2C_2H_5$/n-C_3H_7OH (5/7/7 v/v/v) showed one spot at R_f 0.13 and complete disappearance of the starting material (R_f 0.16). The spot staining with ninhydrin followed by that with a sugar-detection reagent[9] showed that **2a** was an aminosugar. By treatment with 2,4-dinitrofluorobenzene, **2a** was converted to the 2,4-dinitroaniline derivative whose reverse-phase HPLC demonstrated that the reaction of **1a** with ammonia gave only one product. The fast-atom-bombardment mass spectrum of **2a** showed the corresponding molecular ions at m/z 972 ($M + H^+$) and 994 ($M + Na^+$). The ^1H NMR and ^{13}C NMR spectra are shown in Fig. 1 (A and A'), where the absorptions of the aminosugar part was assigned with the aid of the COSY ^1H NMR spectrum. The COSY spectrum demonstrated that **2a** was 3^A-amino-3^A-deoxy-(2^AS),(3^AR)-α-cyclodextrin. The $^1H,^1H$-coupling constants of the altrosamine moiety of **2a**, $J_{1,2}$ (6.9 Hz), $J_{2,3}$ (10.5 Hz), and $J_{3,4}$ (3.7 Hz) showed that the altrosamine moiety had a $^1C_4$ conformation.[10]

Similarly, $3^A,3^X$-diamino-$3^A,3^X$-dideoxy-(2^AS),(2^XS),(3^AR),(3^XR)-α-cyclodextrins **2b** (X = B, 65.9 mg, 85%), **2c** (X = C, 55.6 mg, 77%), and **2d** (X = D, 27.2 mg, 82%) were prepared from the corresponding dimannoepoxides **1b** (75 mg), **1c** (70 mg), and **1d** (32 mg), respectively.[11] Their fast-atom-bombardment mass spectra and ^{13}C NMR and ^1H NMR spectra (Fig. 1) confirmed their structures. While the NMR spectra of **2b** and **2c** (Fig. 1, B, B', C, and C') demonstrate that two altrosamine moieties in **2b** or **2c** are spectrally different from one another, the spectra of **2d** (Fig. 1, D and D') shows two equivalent altrosamine moieties reconfirming that **2d** is a symmetric compound, i. e. the A,D isomer. A $^1C_4$ conformation of each altrosamine moiety in **2d** is deduced from the coupling constants $J_{1,2}$ (7.0 Hz), $J_{2,3}$ (11.4 Hz), and $J_{3,4}$ (2.2 Hz) of equivalent two H-1's and two H-3's.[10] The cyclodextrin derivative **2b** ($J_{1,2}$ = 5.9 and 7.3 Hz, $J_{2,3}$ = 10.3 and 10.4 Hz, and $J_{3,4}$ = 2.9 and 2.8 Hz) or **2c** ($J_{1,2}$ = 5.5 Hz and 5.5 Hz, $J_{2,3}$ = 10.1 and 9.3 Hz, and $J_{3,4}$ = 3.5 and 3.9 Hz) possesses nonequivalent

altrosamine moieties which have also $^1C_4$ conformations.[10]

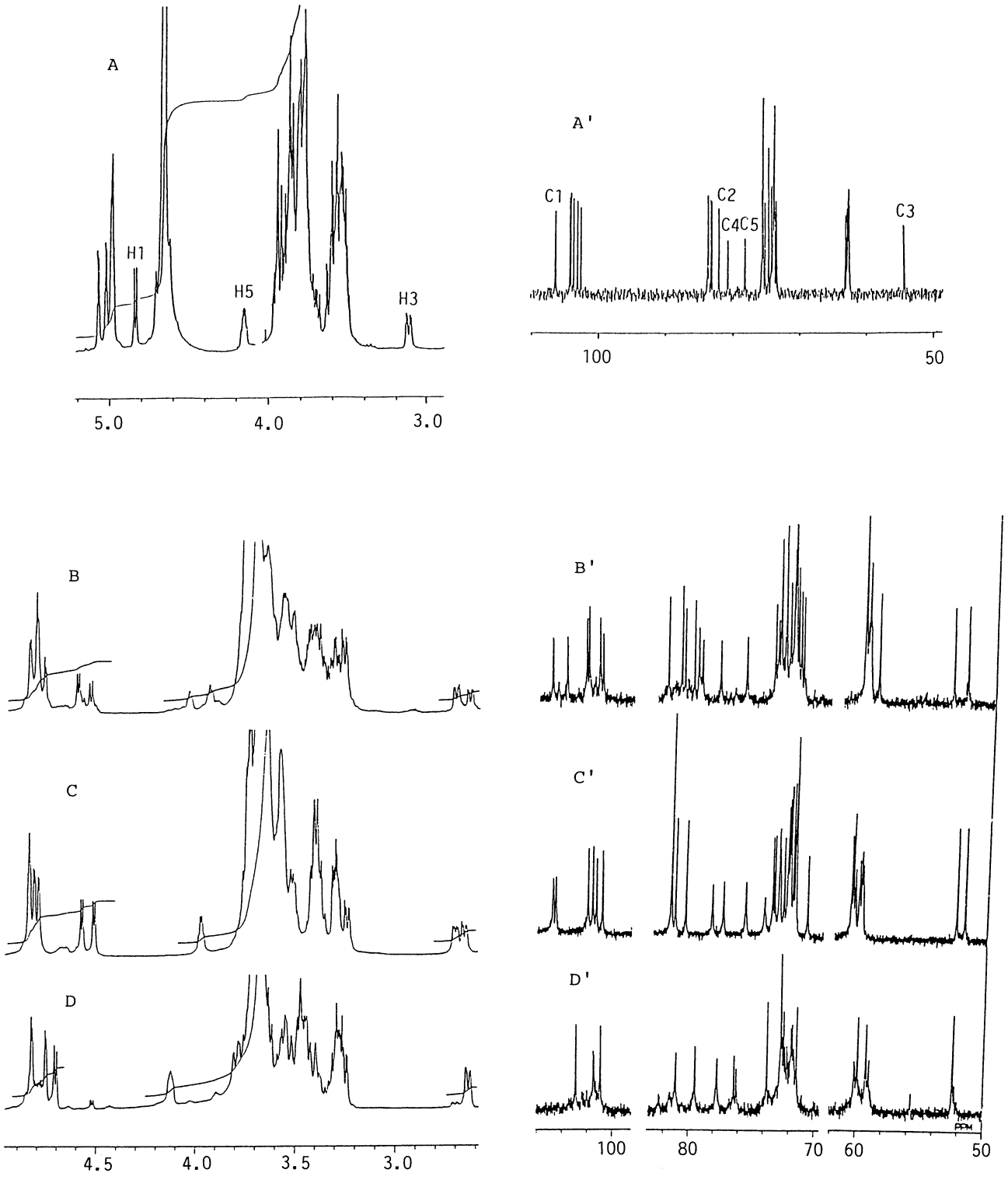


Fig. 1. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra of 2a (A and A') in D_2O and ^1H NMR (500 MHz) and ^{13} NMR (125 MHz) of 2b (B and B'), 2c (C and C'), and 2d (D and D') in Me_2SO-d_6-D_2O.

These cyclic diaminooligosaccharides will be starting materials for some artificial enzymes or receptors which need two functional groups at the given positions.

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7) Preparation of a similar compound (β-cyclodextrin analogue) to **2**a has been reported. T. Murakami, K. Harata, and S. Morimoto, Chem. Lett., 1988, 553. We had already represented the results, which we described in this report, at the 52nd National Meeting of the Chemical Society of Japan, Tokyo, April 3, 1986, Abstr. II, 3Q36, p. 1157.

8) Ammonia gas was frequently bubbled into the solution to make up for the lost.

9) 0.1% solution of 1,3-dihydroxynaphthalene in $C_2H_5OH/H_2O/H_2SO_4$ (200/157/43 v/v/v)

10) Since a glucose unit which is a component of the cyclodextrin have been known to possess a $^4C_1$ conformation, introduction of the $^1C_4$ conformer into the cyclodextrin shown in this case must be interesting with respect to deformation of the cyclodextrin macrocyclic ring.

11) In these cases, the products **2**b-d were purified through ion-exchange column chromatography (Dowex 50W-X-8, 10 mm x 100 mm) with elution of water (65 mL) followed by gradient elution from water (200 mL) to 5% aqueous ammonia (200 mL). Before such a purification, the yields of **2**b-d were 97%, 95%, and 93%, respectively.

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