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Selective modification of mono-*altro*-β-cyclodextrin: dependence of O-sulfonylation position on the shape of sulfonylating reactant

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Abstract—Mono-*altro*-β-cyclodextrin, which has 21 different hydroxyl groups, was selectively sulfonylated by 2-naphthalenesulfonyl chloride at the 2^A-OH of the altrose residue. By using 1-naphthalenesulfonyl chloride as reactant, the 3^G-OH of the neighboring glucose became available for selective sulfonylation, and the resulted sulfonate was proved to be a very important intermediate for introducing functionalities to the saccharide adjacent to the altroside of mono-*altro*-β-cyclodextrin that is capable of controlling the orientation of substrate.

Many artificial enzymes have been constructed from cyclodextrins (CDs) based on the chemical modifications.[1] Since the cavities of CDs are C_n symmetry, the CDs modified on primary side allow the substrates to rotate along the C_n symmetry axes in the CD-substrate complexes. As the result, the meeting between the substrate and the functional group attached on the CD rim is an accidental process instead of a well-controlled one. The situation is quite the same in the case of the secondary modified CDs. In this context, a refined artificial enzyme should be able to strictly control the substrate orientation and substantially ensure the reaction sites of the substrates to be located in the close vicinity of the catalytic site of the artificial enzyme with the conformation good for reaction to occur.

Mono-*altro*-β-CD has been prepared from β-CD through converting of one glucoside unit to altroside[2] and has very unique molecular recognition properties due to the distortion of the cavity: it can restrict the orientation of flat guests.[3,4] Therefore, the functionalization of mono-*altro*-β-CD becomes necessary in the purpose of constructing more sophisticated artificial enzymes. However functionalization or activation (e.g., sulfonylation) of a specific hydroxyl group seemed to be difficult, because mono-*altro*-β-CD has 21 different hydroxyl groups whose reactivities are similar to each other.

Recently, we have reported selective sulfonylation of one of the 21 different hydroxyl groups of mono-*altro*-β-CD with 2-naphthalenesulfonyl chloride (2-NsCl) in aqueous CH_3CN solution to give 2^A-*O*-(2-Ns)-mono-*altro*-β-CD.[5] The product seems to be an interesting precursor for further functionalization, especially for the preparation of an artificial enzyme partaking of the ability to restrict the rotation of substrate, although the direct substitution of the sulfonate group with appropriate proper nucleophiles still remains to be established.

The high regioselectivity of the sulfonylation on mono-*altro*-β-CD with 2-NsCl suggests that the chlorosulfonyl group is directed toward 2^A-OH by the restricted orientation of the naphthyl group in the cavity of mono-*altro*-β-CD. Subtle tuning of the guest orientation in the inclusion complex may provide a possibility for the reactant to selectively react with a different site of mono-*altro*-β-CD.

We report here that O-sulfonylation position of mono-*altro*-β-CD (Scheme 1) is indeed dependent on the shape of sulfonylating reactant and that the use of 1-naphthalenesulfonyl chloride makes the 3^G-*O*-sulfonate available (Table 1). Although its yield is somewhat low (8.6%), the 3^G-*O*-sulfonate is a very important compound because it is convertible into 2^G,3^G-alloepoxy-mono-*altro*-β-CD whose epoxy ring can easily react with

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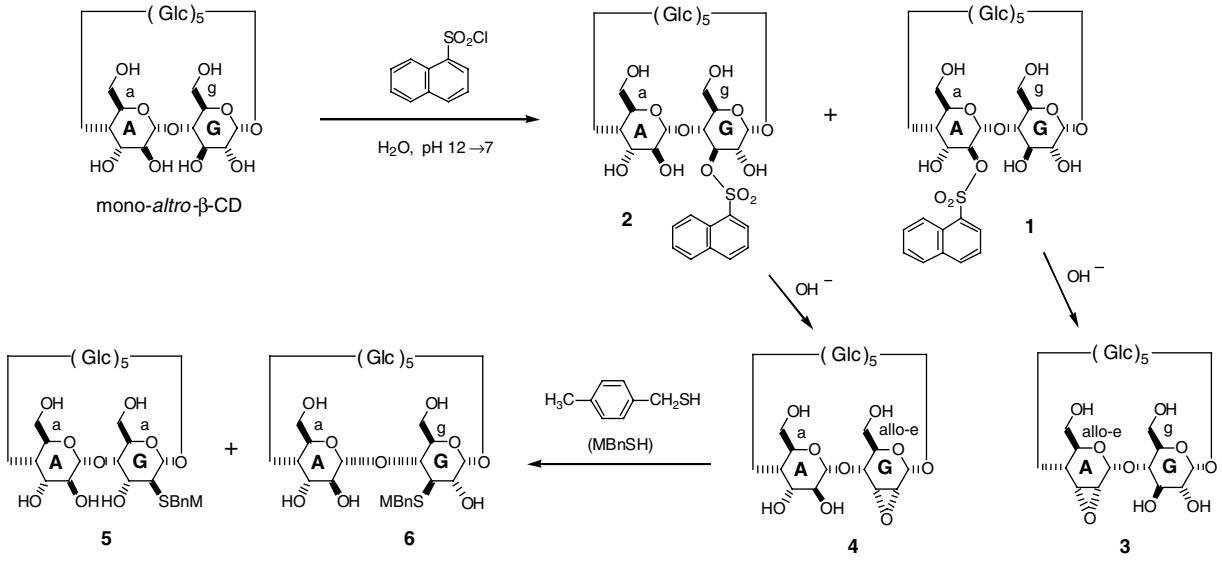

Scheme 1. Selective modification of mono-*altro*-β-cyclodextrin. The marks, g, a, and allo-e denote glucoside, altroside, and 2,3-alloepoxide, respectively.

Table 1. Dependency of O-sulfonylation position upon the shape of guest-type sulfonylating reactants

$ArSO_2Cl$	2^A-*O*-arenesulfonyl-mono-*altro*-β-CD	3^G-*O*-arenesulfonyl-mono-*altro*-β-CD
2-NsCl	25%	—
p-NBsCl	9.5%	0.43%
1-NsCl	11%	8.6%

Ns=naphthalenesulfonyl, NBs=nitrobenzenesulfonyl.

appropriate nucleophiles to give 3^G-functional-mono-*altro*-β-CD and 2^G-functional-A,G-di-*altro*-β-CD.[6] The latter two compounds may become sophisticated artificial enzymes, which have the distorted cavities to restrict the substrate orientation and the catalytic groups to be positioned closely to the substrate in the catalyst–substrate complexes.

Na_2HPO_4 (128 mg) was dissolved in 30% aqueous CH_3CN (80 mL) and the solution was adjusted to pH 12 with concd NaOH. To this phosphate solution, mono-*altro*-β-CD (1.4 g) was added and then a solution of 1-naphthalenesulfonyl chloride (0.7 g) in CH_3CN (5 mL) was poured in at one portion. The mixture was stirred vigorously and the pH of the mixture was allowed to decrease during the reaction in order to reduce the decomposition of sulfonate products in alkaline condition. Five minutes later, the mixture was diluted to 0.5 L with 5% aqueous ethanol and the insoluble materials were removed by filtration. Chromatography of the filtrate on a reversed-phase Lobar column (Rp-18, size C, eluted with 5% aqueous ethanol (1 L) and then with a gradient of 10% (1 L)–40% (1 L) aqueous ethanol) afforded two major products, **1** (179 mg, 11%) and **2** (140 mg, 8.6%).

After the solution of **2** (140 mg) in a saturated aqueous solution of $Ba(OH)_2$ (10 mL) was stirred at rt for 30 min, the reaction mixture was neutralized with 1 M H_2SO_4, diluted to 1 L with water, filtered, and chromatographed on anion-exchange resin (quaternary ammonium form) to give epoxide **4** (110 mg, 93%). Epoxide **3** (100 mg, 88%) was obtained from **1** (125 mg) by the similar method.[7]

A solution of epoxide **4** (85 mg), 4-methylphenylmethanethiol (128 μL), and Cs_2CO_3 (300 mg) in DMF (1 mL) was kept at 80 °C for 6 h. After 10 mL of water was added to dissolve the insolute, the mixture was neutralized with 0.1 M HCl, and washed with ether. The aqueous phase was diluted to 0.5 L with water, filtered, and chromatographed on reversed phase column (Rp-18, Size C) with a gradient elution from water (0.5 L) to 20% aqueous CH_3CN (0.5 L) to give two products, **5** (27 mg, 28%) and **6** (39 mg, 41%).

The FAB-MS spectra of both products **1** and **2** gave m/z 1347 as the pseudo parent peak $[M+Na^+]$ to show that they were the mono-sulfonates of mono-*altro*-β-CD. Their structures were determined via their chemical transformation to epoxides **3** and **4**.

The FAB-MS spectra of **3** and **4** showed the parent ion at m/z 1117 $(M+H^+)$. The comparison of ^1H and ^{13}C NMR spectra demonstrated that **3** is the known compound, 2,3-alloepoxy-β-CD and therefore **1** is 2^A-*O*-(1-naphthalenesulfonyl)-mono-*altro*-β-CD.

The ^1H and ^{13}C NMR spectra of **4** are shown in Figure 1. The signals of 2^GC (δ 57.2) and 3^GC (δ 54.4) were the typical epoxy C-signals and correlated to the 1^GH signal of the lowest chemical shift. The $J_{1,2} = 3.93$ Hz of this 1^GH indicated the epoxide was a 2,3-allo-type.[9] In addition, the 4^GH signal (δ 4.1, dd, $J = 1.9$ and 9.5 Hz) was characteristic to the alloepoxide 4H in terms of coupling constant and chemical shift compared with

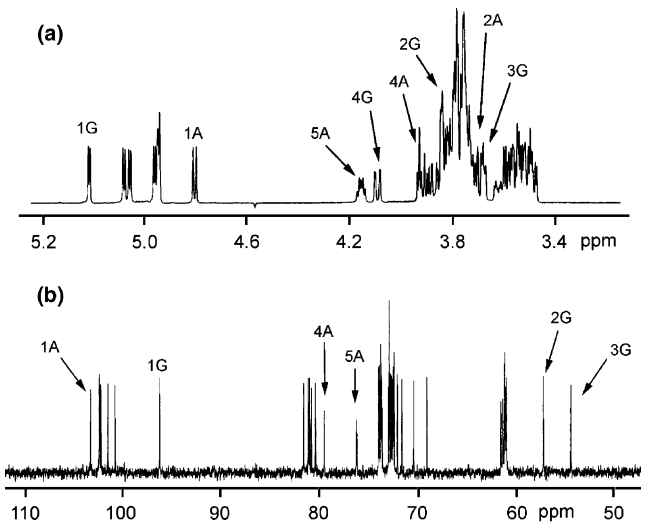

Figure 1. 500 MHz ^{1}H NMR (a) and 125 MHz ^{13}C NMR (b) spectra of **4** in D_2O.

other H signals. These observations imply that the sulfonyl sugar unit in **2** was the 3-*O*-sulfonyl glucoside.

Among the seven 1Hs in **4**, the one resonating at δ 4.81 showed much larger $J_{1,2}$ (6.3 Hz) than the others. We tentatively assign this proton to 1^{A}H of altroside since $J_{1,2}$ values of α-altrosides vary in an extended range from 1.9 to 7.5 Hz,[3,8] which is in sharp contrast to the nearly constant values (3.4–4.2 Hz) of α-glucosides. The HMBC spectrum showed 4^{G}H and 1^{A}H were correlated to 1^{A}C and 4^{G}C, respectively, indicating A sugar unit (altroside) to be adjacent to the G sugar unit (glucoside) with 1^{A}C–*O*–4^{G}C linkage as shown in Scheme 1. Therefore, **4** can be assigned to 2^{G},3^{G}-alloepoxy-mono-*altro*-β-CD and **2** should be assigned to the 2^{G}-*O*-sulfonate of mono-*altro*-β-CD.

Products **5** and **6** were structurally determined as follows.[10] The FAB-MS spectra of both products gave m/z 1277 as the pseudo parent peak [M+Na$^+$] to show that they were the addition reaction products of 4-methylphenylmethanethiol to **4**. The assignment of NMR spectra of **5** based on ^{1}H–^{1}H and ^{13}C–^{1}H COSY experiments indicated that the most upfield shifted carbon (δ 47.5) was a 2C and thereon the thio group of **5** is attached. Considering the stereochemistry of ring-opening reaction of the epoxide, the attack of thiolate anion to 2C of the alloepoxy ring of **4** should generate an altroside unit. The ^{1}H–^{1}H coupling constants, $J_{1,2} = 5.5$ Hz and $J_{2,3} = 9.6$ Hz of the modified residue suggested that this residue be predominantly in $^{0}S_2$ conformation, which is supposed to equilibrate with $^{1}C_4$, and $^{4}C_1$.[3] Consequently, the structure of **5** is determined to be 2^{G}-deoxy-2^{G}-(4-methylphenylmethanethio)-A,G-di-*altro*-β-CD. Similarly, a sugar residue of **6** possessed 3H and 3C with upfield shifted chemical shifts, δ 2.84 and 52.0, respectively, indicating the attack of thiolate anion to 3C of the alloepoxy ring of **4** to afford 3-deoxy-3-(4-methylphenylmethanethio)glucoside. The coupling constants, $J_{1,2}$ (ca. 3.5 Hz), $J_{2,3}$ (10.7 Hz), and $J_{3,4}$ (10.7 Hz), confirms that the modified sugar residue is a glucopyranoside with $^{4}C_1$ conformation. Thus **6** is assigned as 3^{G}-deoxy-3^{G}-(4-methylphenylmethanethio)-A-mono-*altro*-β-CD.

Apart from 1-NsCl, 2-NsCl, and *p*-nitrobenzenesulfonyl chloride were also reacted on mono-*altro*-β-CD and the results are summarized in Table 1. As the data indicated, 2-NsCl only sulfonylated the 2^{A}OH of altroside residue while both the other two reagents reacted on the 3^{G}OH of glucoside residue in addition to the 2^{A}OH. All the other hydroxyl groups, both primary and secondary ones, remained unaffected during the reaction. These results strongly suggest that the reaction selectivity should not be controlled by the intrinsical nucleophilicity of the various hydroxyls but by the geometry of the CD-reactant complex. Based on the fact that only the closely situated 2^{A}OH and 3^{G}OH are susceptible to the attack of the sulfonyl chloride, it can be deduced that inclusion of 2-NsCl in the CD cavity occurred prior to the reaction, most likely with the sulfonyl chloride group being located close to 2^{A}OH and 3^{G}OH.[5]

Since the alloepoxide can normally react with desired nucleophiles to give 3-functionalized glucoside and 2-functionalized altroside,[6] epoxide **4** is important as a starting material for preparing unique artificial enzymes in which an altroside adjoins the functional sugar residue to distort the cavity and thus restrict the substrate orientation. To ensure this expectation, the reaction of **4** with 4-methylphenylmethanethiol was carried out, as an example, to afford the compounds **5** and **6**, whose reduction generates SH functionalities on 2^{G}C of A,G-di-*altro*-β-CD and 3^{G}C of A-mono-*altro*-β-CD, respectively. These studies are in progress.

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10. Compound **5**: ^{1}H NMR (500 MHz, in DMSO-d_6, TMS int.), δ 7.27 (d, $J = 8.0$ Hz, 2H), 7.10 (d, $J = 8.0$ Hz, 2H), 5.13 (d, $J = 5.5$ Hz, 1H), 4.86 (d, $J = 3.8$ Hz, 1H), 4.83–4.73 (m, 4H), 4.57 (d, $J = 3.1$ Hz, 1H), 3.89–3.22 (m, 43H), 2.84 (dd, $J = \sim 10.9$, 5.5 Hz, 1H), 2.29 (s, 3H); Compound **6**: ^{1}H NMR (500 MHz, in DMSO-d_6, TMS int.), δ 7.26 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 4.87 (d, $J = 3.6$ Hz, 1H), 4.85–4.74 (m, 5H), 4.70 (d, $J = 5.2$ Hz, 1H), 4.00 (d, $J = 12$ Hz, 1H), 3.88 (d, $J = 12$ Hz, 1H), 3.88–3.85 (m, 2H), 3.76 (dd, $J = \sim 4.7$, ~ 4.3 Hz, 1H), 3.67–3.31 (m, 38H), 2.84 (t, $J = \sim 10.7$ Hz, 1H), 2.29 (s, 3H).