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Selective mono-*O*-sulfonylation of A,B-di-*altro*-β-cyclodextrin by utilizing restricted orientation of a guest-type sulfonylating reactant in the elliptically distorted cavity: the 2^A-*O*- and 3^G-*O*-2-naphthalenesulfonates as a versatile scaffold to prepare artificial enzymes with controlling substrate orientation

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Abstract—A,B-di-*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 and the 3^G-OH of the glucoside residue adjacent to the altroside residue. The latter sulfonate provides for the first time a possibility for the synthesis of functional cyclodextrins that have two altrose residues adjacent to the functionalized one (either of glucose type or of altrose type) to control the orientation of substrate.

Many artificial enzymes have been constructed through functionalization of cyclodextrins (CDs) whose cavities afford substrate (guest)-binding sites. [1] However, since the substrates are allowed to rotate in the CD cavities along their C_n symmetry axes, the substrates react only accidentally, except in well-designed cases, with the functional groups attached on the CD rims during the tour inside the cavities. In this context, it is of great challenge to prepare artificial receptors capable of restricting substrate orientation and then to functionalize them by introducing the desired number of desired functionalities into the desired positions.

Recently, mono-*altro*-β-CD, which was made from β-CD by converting one glucoside unit to altroside,[2] was demonstrated to form the elliptically distorted cavity and possess very unique molecular recognition properties. That is, upon binding a flat guest, it becomes more elliptical to better fit the geometry of guest and to restrict the guest orientation.[3] This flexibility of cavity, stemming from the conformational flexibility of the altroside unit, which is in an equilibrium among $^1C_4$, $^OH_2$, and $^4C_1$ conformers,[4] makes mono-*altro*-β-cyclodextrin a promising candidate building block for the construction of artificial receptors and so forth since the host–guest complexation with precisely defined geometry is the basis of many biological process such as enzymatic chemical reaction, information transfer and mass transportation. However, mono-*altro*-β-cyclodextrin contains no functionality other than OH groups and demonstrates only confined binding strength. Improvement of its binding ability and introduction of additional functionality depend undoubtedly on the methodological discovery of appropriate modification. More recently, the authors clarified that the elliptical cavity of mono-*altro*-β-CD could restrict the orientation of a guest-type sulfonylating reactant, 1-naphthalenesulfonyl chloride (1-NsCl) and direct the sulfonyl group to the 2^A-OH of the altroside residue and 3^G-OH of the glucoside residue to afford regioselectively the 2^A-*O*-sulfonate and 3^G-*O*-sulfonate. The latter compound was converted to 2^G,3^G-alloepoxy-mono-*altro*-β-CD **4** promising of regioselective functionalization of G residue adjacent to the unmodified altroside residue A.[5,6]

Keywords: Cyclodextrin; Altrose; Modification; Sulfonylation.
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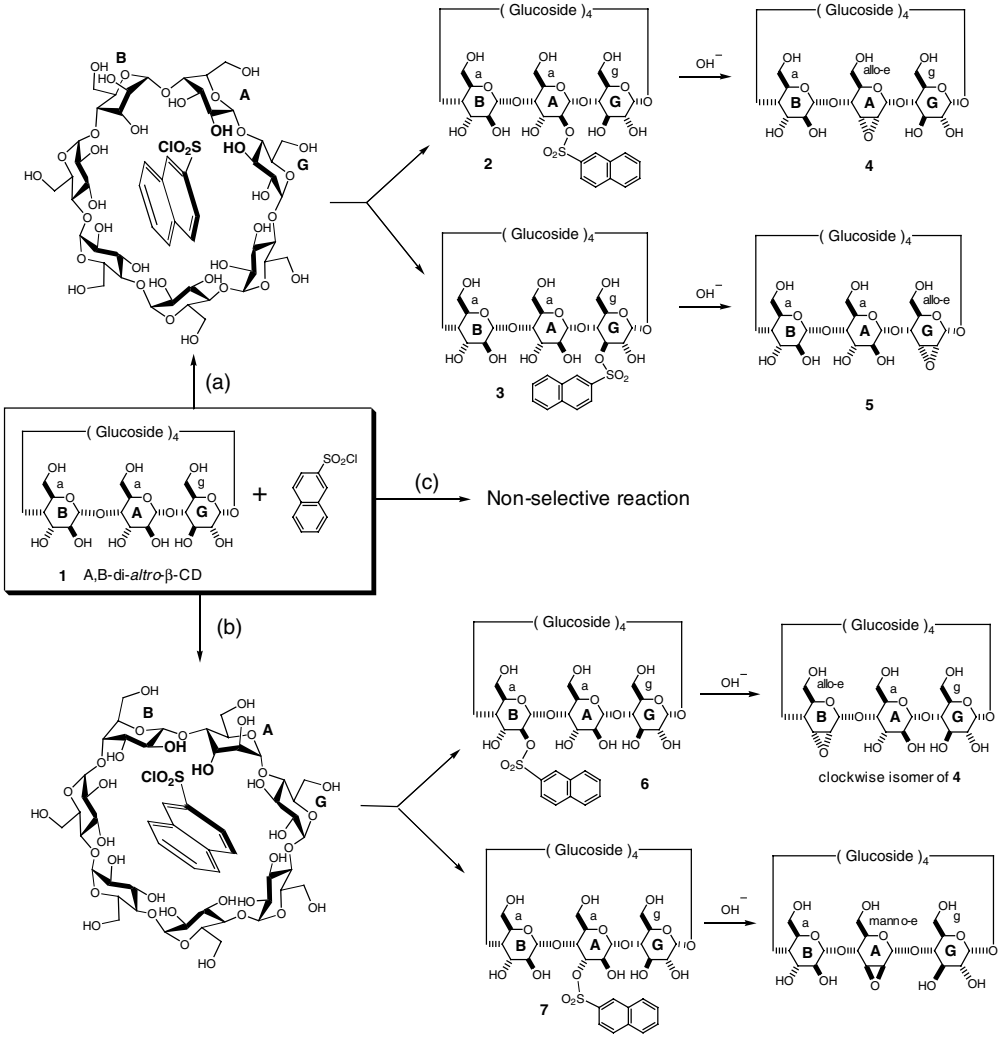
In this letter, we report the selective monosulfonylation of A,B-di-*altro*-β-CD **1**[7], which has two adjacent altroside residues. The sulfonylation reaction of **1** is supposed to be interesting at least in the following two aspects (Scheme 1). First, the reaction results will provide an approach to probe whether the macrocycle still adopts an elliptical shape as the mono-*altro*-β-CD does and, if it does, which of the two altroside residues is more important in determining the cavity shape. Second, the expected sulfonylation products can serve as very important intermediates for the syntheses of novel functional cyclodextrin derivatives that are otherwise inaccessible at present.

The sulfonylation reaction of **1** with 2-NsCl was carried out in aq CH_3CN and two isomeric monosulfonates of **1** were successfully isolated. The investigation on the regiochemistry of the two products indicated that they were sulfonates **2** and **3** (Scheme 1). The result implies that **1** is capable of restricting the orientation of the guest 2-NsCl and the cavity shape may be mainly governed by the altrose residue A rather than B. The sulfonates are easily convertible to the corresponding 2,3-alloepoxides **4** and **5**, which may readily react with appropriate nucleophiles to give functionalized mono-, di-, and tri-*altro*-β-CDs [8] that have desired functional groups on the specific positions and the distorted cavities to restrict the orientation of substrates.

Na_2HPO_4 (80 mg) was dissolved in 30% aq CH_3CN (50 mL) and the solution was adjusted to pH 12 with concd aq NaOH. To this phosphate solution (10 mL), A,B-di-*altro*-β-CD **1** (600 mg) was added and then powdered 2-NsCl (160 mg) 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. Ten minutes later, the mixture was neutralized with 0.1 M HCl and filtered. The filtrate was chromatographed on a reversed phase Lobar column



Scheme 1. Proposed reaction patterns of A,B-di-*altro*-β-cyclodextrin and 2-NsCl. (a) In the case that the altrose residue A predominates in determining the elliptical shape of the cavity, the sulfonyl group is expected to be delivered to the 2^A-OH (**2**) and 3^G-OH (**3**). (b) If the altrose residue B is more important in determining the cavity shape, selective sulfonylations of the 2^B-OH (**6**) and 3^A-OH (**7**) can be expected. (c) If the cavity does not restrict the orientation of the sulfonylation reagent, little regioselectivity can be expected. The marks, g, a, *allo*-e, and *manno*-e denote glucoside, altroside, 2,3-alloepoxide, and 2,3-mannoepoxide, respectively.

(Rp-18, size C, eluted with a gradient of 5% (1000 mL)–25% (1000 mL) aq ethanol) to afford two major products, **2** (91 mg, 13%) and **3** (41 mg, 5.9%).

Both products gave the pseudo parent peak [M + Na^+] at *m/z* 1347 in their FAB MS spectra, indicating that they were regioisomers of the monosulfonates of **1**. Based on the NMR spectra of **2** and **3** as well as the epoxides **4** and **5** derived therefrom, **2** and **3** were determined to be 2^A-*O*- and 3^G-*O*-2-naphthalenesulfonates of A,B-di-*altro*-β-CD **1**, respectively.

The ^{13}C NMR spectrum of **2** indicated that 2^AC was subjected to strong induction effect and resonated at much lower field (δ 80.0) than the normal 2^XC, suggesting that this 2^AC bear the sulfonyl group. In agreement with this, significant downfield shift of 2^AH (δ 4.52) was observed. The assignment was further confirmed by the conversion of **2** to 2,3-epoxide **4** (88%) and subsequent comparison of ^1H and ^{13}C NMR spectra of **4** with those of the authentic compound.[5] The 2,3-epoxide **4** was identical with 2^A,3^A-alloepoxy-B-*altro*-β-CD and, therefore, **2** should be assigned to the 2^A-*O*-sulfonate of A,B-di-*altro*-β-CD.

Since the structure of **3** was difficult to be determined directly from the NMR spectra, **3** was also converted to epoxide **5**. The C signals at δ 57.1 (2^GC) and 54.1 (3^GC) were consistent with the 2,3-epoxide carbons [5] and the relatively large coupling constant $J_{1,2}$ = 3.2 Hz of 1^GH (δ 5.26) indicated the epoxide was a 2,3-*allo* type rather than a *manno* type (Fig. 1).[9] By ^1H,^1H- and ^1H, ^{13}C-COSY and HMBC NMR spectra, all H and C signals of the epoxy sugar unit as well as some other signals were assigned and the results were shown in Tables 1 and 2. The 4^GH signal (δ 4.12, dd, *J* = 1.9 and 9.5 Hz) of **5** was similar, both in terms of coupling constant and chemical shift, to the alloepoxide 4^AH of 2^A,3^A-alloepoxy-β-CD and 2^A,3^A-alloepoxy-B-*altro*-β-CD **4**. Thus G unit of **5** is a 2,3-alloepoxide and its precursor should be either the 2^B-*O*-sulfonylated altroside or the 3-*O*-sulfonylated glucoside of **1**.

Table 1. ^1H NMR chemical shift/ppm (coupling constant/Hz) of **5** in D_2O

Sugar unit	1H	2H	3H	4H	5H
G (epoxide)	5.26 (3.2)	3.76	3.67	4.12 (1.9, 9.5)	3.64
A (altroside)	4.88 (4.9)*[a]	3.76*[c]		3.92*[e]	4.18*[g]
B (altroside)	4.74 (3.8)*[b]	3.84*[d]		3.90*[f]	4.14*[h]
	4.98 (4.1)	3.47			
C∼F	4.98 (3.3)	3.54			
(glucoside)	5.02 (3.8)	3.55		3.48–3.56	
	5.05 (4.0)	3.57			

*These are similar to the corresponding values of A,B-di-*altro*-β-CD: [a]4.79 (4.5), [b]4.74 (4.5), [c]3.83, [d]3.82, [e]3.92, [f]3.90, [g]4.22, and [h]4.18, which are to be published elsewhere.

Table 2. ^{13}C NMR chemical shift/ppm of **5** in D_2O

Sugar unit	1C	2C	3C	4C	5C
G (epoxide)	95.3	57.1	54.1	72.8	69.1
A (altroside)	102.3	71.6	69.9	77.0	
B (altroside)	102.7	70.9	69.6	76.4	
C∼F (glucoside)	100.7, 100.7, 102.3, 102.6			79.6 (F), 81.1, 81.3, 81.4	

Comparison of the NMR spectra of **5** with those of **1** revealed that the two altroside residues sustained in **5** since similar chemical shift pattern of the altrosides of **1** were also recognized in the spectra of **5** (Table 1). Among the several signals of the altrosides of **5**, 5^AH and 5^BH signals had most distinguishable chemical shifts and coupling patterns, which were characteristic of altrosidic 5H.[2,7] Therefore, the origin of the 2,3-alloepoxide is not 2-*O*-sulfonyl-altroside but 3-*O*-sulfonyl glucoside. In order to clarify the relation between the altrosides and the sulfonyl glucoside, HMBC experiments were carried out. The HMBC spectra (Fig. 1) demonstrated clear correlation of 1^AH (δ 4.88, $J_{1,2}$ = 4.9 Hz) to 4C (δ

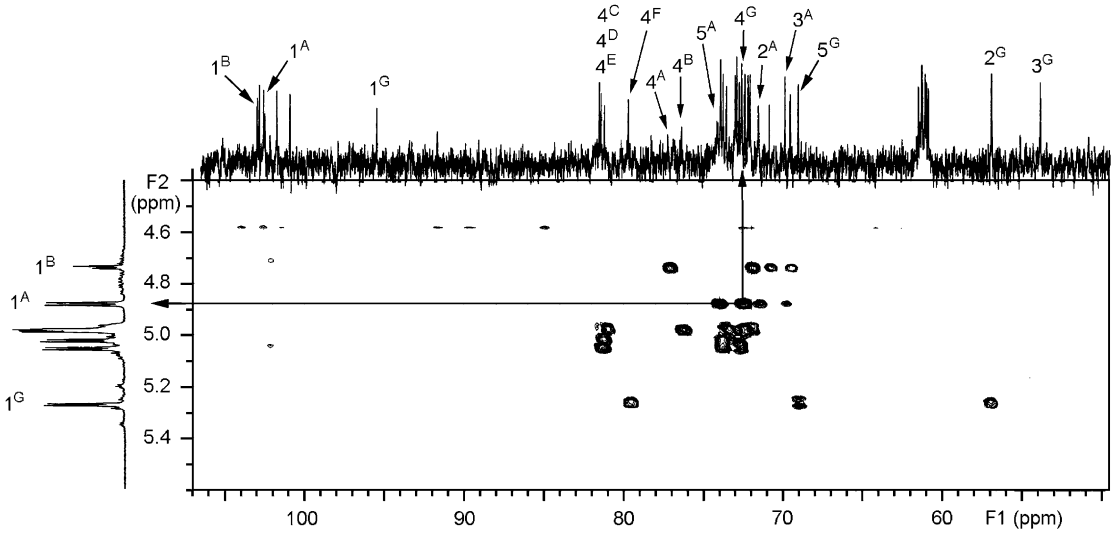


Figure 1. Partial HMBC spectrum of alloepoxide **5** in D_2O.

72.8) of the alloepoxide residue. This observation indicated that alloepoxide residue is adjacent to A sugar unit (altroside). Therefore, **5** is identical to 2^{G},3^{G}-alloepoxy-A,B-di-*altro*-β-CD and **3** should be the 3^{G}-*O*-sulfonate of A,B-di-*altro*-β-CD.

The secondary hydroxyls, 2-OH of A (altroside) unit and 3-OH of G (glucoside) unit are reactive sites, but those of B (altroside) unit and C∼F (glucoside) are not reactive, demonstrating that the sulfonylation reaction is neither controlled by the intrinsic reactivity of hydroxyls nor occurs outside the cavity. The spatially close proximity of reactive 2^{A}-OH and 3^{G}-OH indicates that the reaction occurred in the cavity, which restricts the orientation of 2-NsCl to direct the chlorosulfonyl group between A and G units. And it suggests that A unit, one of two altroside units, mainly determines the oval shape of cavity responsible to the selectivity. It is worthy of note that the 2^{A}-*O*-sulfonate of **1** leading to **4** was obtained as the major product since the another precursor of **4**, the 3^{G}-*O*-sulfonate of mono-*altro*-β-CD, had been available as the minor product in the reaction of mono-*altro*-β-CD with 1-NsCl.

Epoxides **4** and **5** are important starting materials for preparing unique artificial enzymes since the alloepoxide can react with desired nucleophiles to give 3-functionalized glucoside and 2-functionalized altroside. Thus, these artificial enzymes have functional groups on the specific positions and distorted cavities with restriction of substrate orientation.

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