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Selective sulfonylation of one of the 21 different hydroxyl groups of mono-*altro*-β-cyclodextrin

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Abstract—Mono-*altro*-β-cyclodextrin, which has 21 different hydroxyl groups, has been selectively sulfonylated at the 2-OH of the altrose residue.

β-Cyclodextrin (β-CD) is well known to have a C_7 symmetrical rigid structure that allows a lock-key type binding to a variety of guests and leaves considerable freedom for the bound guest to rotate along the axis of the CD cavity.[1–3] On the other hand, mono-*altro*-β-CD **1** (MA-β-CD), which is derived from β-CD by converting one glucose unit to altrose, no longer has C_7 symmetry.[4] It not only has the necessary flexibility to ensure a guest-induced fit in binding a suitable guest, but demonstrates the ability to restrict the free rotation of the bound guest as well,[5,6] which is similar chemistry to that employed by natural enzymes in their substrate binding. In this respect, MA-β-CD turns out to be of special significance and may provide a preferable hydrophobic pocket in developing artificial receptors and enzyme mimics. However, like β-CD itself, MA-β-CD contains no functionality other than OH groups and demonstrates only confined binding strength.[7] Improvement of its binding ability and introduction of additional functionality stand undoubtedly in the need of appropriate modification. The first step towards this modification needs the selective activation of one or more hydroxyl groups.[8] Considering that all the 21 hydroxyl groups of MA-β-CD are different from each other, sulfonylation of one hydroxyl group will theoretically generate 21 regio-isomers versus the three theoretical isomers in the case of β-CD! It is a great challenge to control the reaction to occur in a highly selective manner. In this paper, we describe our first successful investigation into this subject.

By using phosphate buffer (pH 12) as reaction medium, MA-β-CD **1** readily reacts with 2-naphthalenesulfonyl chloride and causes a pH drop to neutral.[9] The reaction solution gave a very simple HPLC chromatogram in which only one main peak appeared in the region of mono-sulfonates of **1** (Fig. 1a). Reversed-phase column chromatography of the reaction mixture afforded one mono-sulfonylation product (in 25% yield) with no other mono-sulfonates being obtained. NMR spectra (for ^{13}C NMR, cf. Fig. 2) confirmed that the isolated product was a single sulfonate rather than a mixture.

The ^1H NMR spectrum[9] of the product can hardly afford a clue to the determination of modified position because of its very high sensitivity to the ring current effect of aromatics. ^{13}C NMR spectrum, on the other hand, is much less sensitive to the ring current effect, and enables us to examine the inductive effect of the sulfonate group. Since the sulfonylation of a OH group is well known to exercise a strong inductive effect on the α-carbon and usually causes this carbon to be notably shifted downfield, DEPT experiments were first displayed to verify whether the sulfonylation took place

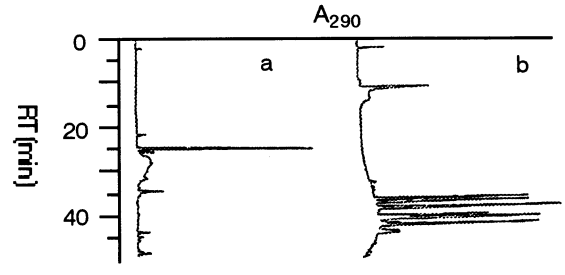

Figure 1. HPLC chromatograms of sulfonylation mixture of (a) MA-β-CD and (b) MA-α-CD. TSK-gel ODS-80™ column and a gradient elution of 0–40% aq. CH_3CN were applied.

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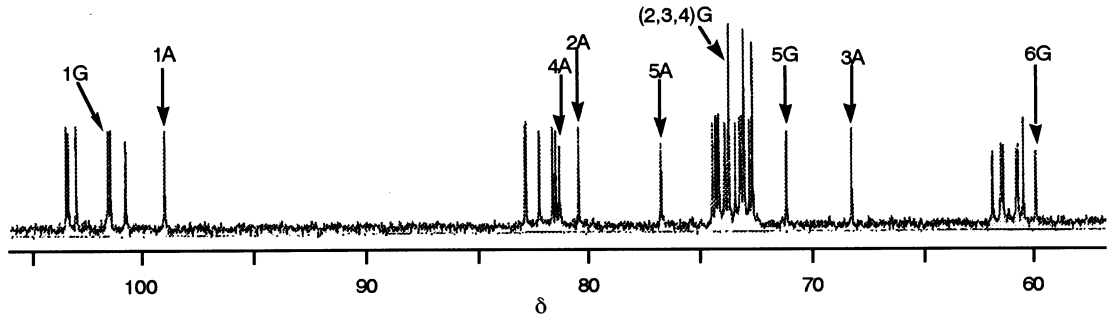
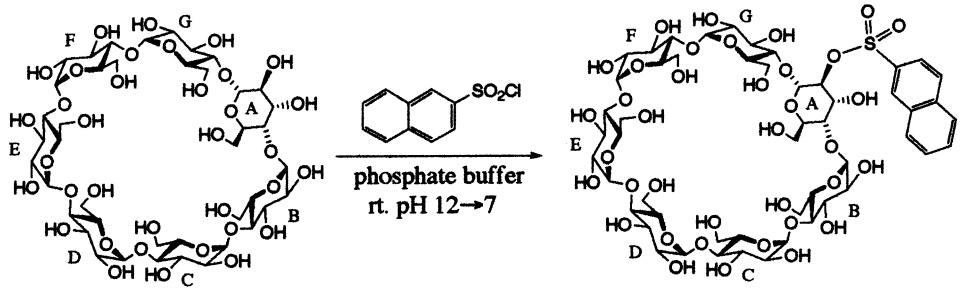


Figure 2. ^{13}C NMR spectrum of MA-β-CD sulfonate **2** in D_2O, assigned based on 1D TOCSY, 2D COSY, HSQC, HMBC and NOE experiments. The sugar residues are labeled clockwise A–G on viewing from the primary hydroxyl side, starting from the altrose residue (cf. Scheme 1). The numbers denote the intra-residue positions of carbon atoms. (Only the sugar part is shown.)

Table 1. Chemical shifts (ppm) of C1–C4 carbons of MA-β-CD **1** and its sulfonate **2**

	Altrose residue A				glucose residues B–G			
	C1	C2	C3	C4	C1	C2	C3	C4
MA-β-CD **1**[a]	104.2	~72	70.7	79.9	101.9–102.6	72.0–74.0	73.7–74.0	81.3–81.9
Sulfonate product **2**	99.1	80.4	68.1	81.2	100.8–103.5	72.5–74.3	71.0–74.3	81.4–82.8[b]

[a] Data were extracted from Ref. 4.
[b] The signal relating to the C4 carbon of pyranose G was found at δ 73.6.



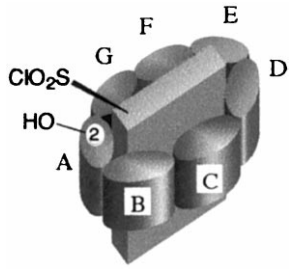
1 **2**

Scheme 1.

on the primary face or not. The result indicated that the sulfonyl group was not attached onto the primary face since the DEPT spectra demonstrated all seven methylene carbons in the region of δ 59.9–61.8. 2D ^1H–^1H COSY and 1D TOCSY spectra of the product were then thoroughly examined, and seven sets of intra-residue H1–H4 protons were extracted out therefrom. With these proton chemical shifts in hand, the corresponding intra-residue shift patterns of C1–C4 carbons were extracted out from the HSQC and HMBC spectra, and the results are listed in Table 1. As it is clearly shown in Table 1, the C2 of the altrose residue is significantly shifted downfield ($\Delta\delta \sim 8.4$), and both the adjacent carbons C1 and C3 are moderately shifted upfield. For all the glucose residues, only the C4 in the vicinity of the C1 of the altrose residue is significantly shifted upfield, while the rest of all C1–C4 carbons basically resonate within the corresponding normal regions.[10] These facts strongly suggest that the C2–OH group of the altrose residue (*altro*-2-OH) is sulfonylated. That is, the reaction in Scheme 1 occurred, and the isolated product has the structure of sulfonate **2**.

The above assignment was confirmed by converting the sulfonate to its corresponding 2,3-epoxide. It is documented that the 2- or 3-sulfonylated glucoside of CDs undergoes intra-molecular substitution of the sulfonate to generate 2,3-manno or alloepoxide.[8,11–13] Was the sulfonate group located on a glucose unit, intra-molecular substitution would generate an epoxide together with the altrose residue sustained. Actually, treatment of **2** with saturated $Ba(OH)_2$ solution gave the known β-CD 2,3-alloepoxide[14] without the altrose residue remaining, which strongly supports the proposed structure.

It is clear that the *altro*-2-OH is preferentially peaked from the many different OH groups of MA-β-CD, and its sulfonylation predominates greatly in the reaction. The native β-CD was regiospecifically sulfonylated at the 3-OH groups by the same reagent under similar reaction condition.[15,16] Why is MA-β-CD predomi-



Scheme 2. Pre-inclusion locates the sulfonyl group in the close vicinity to the *altro*-2-OH (view from the secondary hydroxyl side): the cylinders denote pyranosides while the plate represents naphthalene ring.

nantly sulfonylated at its *altro*-2-OH rather than the glucose 3-OH or any other OH groups? A reasonable explanation relies on a possible formation of inclusion complex prior to sulfonylation. In the preceding papers,[5,6] it has been elucidated that MA-β-CD has an elliptic cavity and can localize 2-naphthalene sulfonate guest in a preferred orientation by arranging the 1-9-8 or 4-10-5 rim of the guest towards between the altrose unit A and its adjacent glucoside B. Taking into consideration the possible pre-localization of the naphthalene moiety in the elliptic cavity of MA-β-CD (Scheme 2), it is not too surprising that the *altro*-2-OH gets access to the sulfonyl group much easier than any other OH groups. When 1-naphthalenesulfonyl chloride or mesitylenesulfonyl chloride was used instead of 2-naphthalenesulfonyl chloride, many small peaks appeared in the HPLC chromatogram and similar work-up procedure afforded the altro-2-sulfonate only in 10% yields. Moreover, when MA-α-CD, which has a cavity too small to accommodate the naphthalene moiety, was treated with 2-naphthalenesulfonyl chloride under the same condition, no obvious selectivity was observed (Fig. 1b). These results indicated that a possible difference in the inherent reactivity between the *altro*-2-OH and other OH groups could hardly account for the regio-selectivity.

In conclusion, we have succeeded in activating the altro-2-OH versus the 20 other OH groups of MA-β-CD, and reasoned that the high selectivity probably results from the pre-inclusion of the sulfonylating reagent into the cavity of MA-β-CD.

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References

1. In *Comprehensive Supramolecular Chemistry*, Atwood, J. L.; Davies, J. E.; MacNicol, D. D.; Vogtle, F., Eds. Cyclodextrins. Pergamon Elsevier: Oxford, UK, 1996; Vol. 3.
2. Behr, J. P.; Lehn, J. M. *J. Am. Chem. Soc.* **1976**, *98*, 1743–1747.
3. Kuroda, Y.; Yamada, M.; Tabushi, I. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1409–1415.
4. Fujita, K.; Ohta, K.; Ikegami, Y.; Shimada, H.; Tahara, T.; Nogami, Y.; Koga, T.; Saito, K.; Nakajima, T. *Tetrahedron Lett.* **1994**, *35*, 9577–9580.
5. Fujita, K.; Chen, W.-H.; Yuan, D.-Q.; Nogami, Y.; Koga, T.; Fujioka, T.; Mihashi, K.; Immel, S.; Lichtenthaler, F. *Tetrahedron: Asymmetry* **1999**, *10*, 1689–1696.
6. Chen, W.-H.; Fukudome, M.; Yuan, D.-Q.; Fujioka, T.; Mihashi, K.; Fujita, K. *Chem. Commun.* **2000**, 541–542.
7. Fujita, K.; Okabe, Y.; Ohta, K.; Yamamura, H.; Tahara, T.; Nogami, Y.; Koga, T. *Tetrahedron Lett.* **1996**, *37*, 1825–1828.
8. Methods for selective modification of native CDs have been well established and were reviewed recently: Khan, A. R.; Forgo, P.; Stine, K. J.; D'Souza, V. T. *Chem. Rev.* **1998**, *98*, 1977–1996.
9. For a typical procedure, Na_2HPO_4 (225 mg) was dissolved in water (5.1 ml), and the solution was adjusted to pH 12. To the resultant phosphate solution, MA-β-CD (600 mg, 0.53 mmol) was added and then powdered 2-naphthalenesulfonyl chloride (1.8 g, 7.9 mmol) was poured in at one portion. The pH of the reaction mixture was allowed to decrease during the reaction in order to reduce the decomposition of sulfonate product in alkaline solution. Three hours later, the reaction mixture reached a neutral pH and the insolutes were then removed by filtration. Chromatography of the filtrate on a reversed-phase Lobar column (Rp-18, size C, eluted with a gradient of 0–60% aq. CH_3CN) afforded the only sulfonate **2** in 25% yield. The ^1H NMR spectrum of **2** clearly exhibited seven doublets for the anomeric protons: δ 4.83 (1A, *J* 7.0), 5.02 (1B, *J* 4.0), 5.25 (1C, *J* 4.0), 5.17 (1D, *J* 3.5), 5.14 (1E, *J* 3.5), 5.10 (1F, *J* 3.5), 4.65 (1G, *J* 3.5). The pyranose G is fully under a strong shielding effect and all its signals jumped out of the normal region up to the very high field: 3.19 (2G, dd, *J* 3.5 and 9.5), 2.91 (3G, t, *J* 9.5), 2.97 (4G, t, *J* 9.5), 1.55 (5G, br d, *J* 9.5), 2.76 (6G, dd, *J* 2 and 12.5), 2.82 (6G′, dd, *J* 3.5 and 12.5). All other sugar protons resonate in the region of δ 3.4–4.4.
10. For a review on the NMR study of CDs, see: Schneider, H.-J.; Hacket, F.; Rüdiger, V. *Chem. Rev.* **1998**, *98*, 1755–1785.
11. Breslow, R.; Czarnik, A. W. *J. Am. Chem. Soc.* **1983**, *105*, 1390–1391.
12. Fujita, K.; Nagamura, S.; Imoto, T.; Tahara, T.; Koga, T. *J. Am. Chem. Soc.* **1985**, *107*, 3233–3235.
13. Fujita, K.; Nagamura, S.; Imoto, T. *Tetrahedron Lett.* **1984**, *25*, 5673–5676.
14. The sulfonate **2** (0.15 g) was dissolved in saturated $Ba(OH)_2$ solution (15 ml) and stirred at rt for 10 min. The solution was neutralized with 2N sulfuric acid and then chromatographed on a reversed-phase Lobar column (Rp-18, size B, eluted with a gradient of 0–30% aq. CH_3CN), affording β-CD 2,3-alloepoxide in 80% yield.
15. Fujita, K.; Tahara, T.; Imoto, T.; Koga, T. *J. Am. Chem. Soc.* **1986**, *108*, 2030–2034.
16. Fujita, K.; Tahara, T.; Yamamura, H.; Imoto, T.; Koga, T.; Fujioka, T.; Mihashi, K. *J. Org. Chem.* **1990**, *55*, 877–880.