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Regiospecific $2^A,2^C$-disulfonation of β-cyclodextrin

Katsunori Teranishi*

Faculty of Bioresources, Mie University, Kamihama 1515, Tsu, Mie 514-8507, Japan

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Abstract

The regiospecific $2^A,2^C$-disulfonation of β-cyclodextrin has been achieved by the reaction of β-cyclodextrin with 1,4-dibenzoylbenzene-3′,3″-disulfonyl imidazole and molecular sieves in DMF.

Keywords: β-cyclodextrin; regiospecificity; disulfonation.

Cyclodextrins are cyclic oligosaccharides consisting of six or more α-1,4-linked D-glucopyranose units, which possess primary hydroxyl groups at the C-6 positions and secondary hydroxyl groups at the C-2 and C-3 positions.[1] Because the cyclodextrins have a hydrophobic and optically active interior, they have been utilized as transporters of hydrophobic molecules and as miniature molecular mimics of enzymes. In order to enhance their ability as acceptors or artificial enzymes, regiospecific multifunctionalization techniques on the primary and secondary hydroxyl groups have been investigated. Several significant regiospecific disulfonations on the two primary hydroxyl groups have been developed to modify the primary face.[2] However, the regioselective bifunctionalization on the secondary face has proved more difficult to accomplish.[3] Published disulfonations on the two C-2 hydroxyl groups of α- and β-cyclodextrins afforded the regioisomeric $2^A,2^B$-, $2^A,2^C$-, and $2^A,2^D$-disulfonates (the glucose units are lettered A to F or G clockwise, viewed from the C-6 position) in extremely low yields, respectively.[4]

I have developed an interesting regiospecific monosulfonation on the C-2 hydroxyl groups of the cyclodextrins using a combination of sulfonyl imidazole and molecular sieves.[5] This sulfonyl reaction system is very useful, since the mild non-alkaline reaction conditions do not induce decomposition of the sulfonates, and the reaction occurs independently of the nature of the sulfonyl groups. Furthermore, I have recently shown that $2^A,2^B$-disulfonated α-,[6] β-,[6] and γ-cyclodextrins[7] can be exclusively regiospecifically prepared using benzophenone-3,3′-disulfonyl imidazole and molecular sieves in DMF. In this preliminary letter, to provide a useful method for the bifunctionalization on the A,C-secondary face of the cyclodextrins, I will show the highly regiospecific preparation of $2^A,2^C$-disulfonated β-cyclodextrin using 1,4-dibenzoylbenzene-3′,3″-disulfonyl imidazole (**1**) as a sulfonyl reagent (Scheme 1).

* Corresponding author. Tel: +81-59-231-9615; fax: +81-59-231-9684; e-mail: teranisi@bio.mie-u.ac.jp

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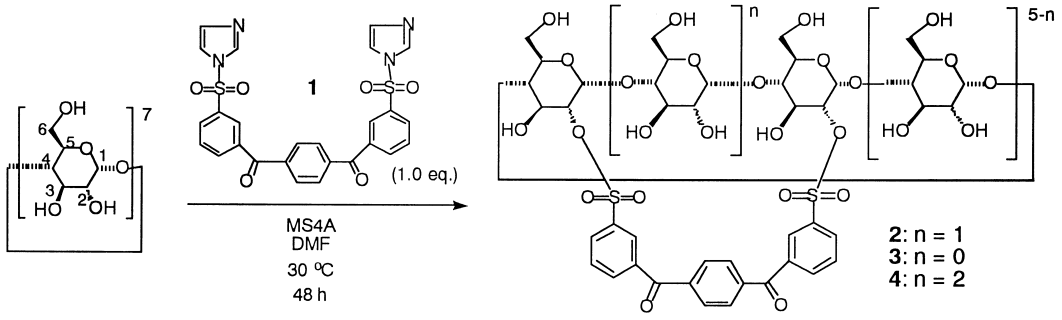

Scheme 1.

Compound **1** was easily prepared by the following procedure. A mixture of 1,4-dibenzoylbenzene (10 g) and chlorosulfonic acid (50 ml) was heated at 120°C for 24 h, and then the cooled reaction mixture was poured into ice (200 ml). The precipitate was filtered and washed with water, followed by crystallization from ethyl acetate and recrystallization from chloroform to give pure 1,4-dibenzoylbenzene-3′,3″-disulfonyl chloride (7.3 g). 1,4-Dibenzoylbenzene-3′,3″-disulfonyl chloride (6.2 g) was treated with imidazole (2.0 g) and triethylamine (4.2 ml) in chloroform (240 ml) at room temperature, and the reaction mixture was washed with water. The chloroform solution was evaporated to dryness, followed by crystallization from a mixture of chloroform and dichloromethane to give **1** (6.4 g).[8]

A mixture of β-cyclodextrin (2.0 g, 1.76 mmol), which was dried under vacuum at 120°C for 12 h, **1** (0.96 g, 1.76 mmol), and freshly activated powder 4 Å molecular sieves (6.0 g) in *N*,*N*-dimethylformamide (DMF; 118 ml) was stirred at 30°C for 48 h. The HPLC analysis of the reaction mixture showed that 2^{A},2^{C}-disulfonated β-cyclodextrin **2** was highly regiospecifically afforded in 24% yield, and 2^{A},2^{B}- and 2^{A},2^{D}-disulfonated β-cyclodextrins (**3** and **4**) were given as minor disulfonates in 3.1% and 1.0% yields, respectively,[9] whereas 6-sulfonate(s) and 3-sulfonate(s) resulting from the reaction were not observed by HPLC analysis. Then, the molecular sieves were removed by filtration and the filtrate was concentrated under reduced pressure. DMF (4 ml) was added to dissolve the residue and subsequently water (100 ml) was added to the solution. The solution was subjected to a simple open reverse-phase column chromatography (20mm×150mm, Fuji Silisia Chromatorex-ODS DM1020T gel). Elution with water and subsequently water:MeOH (9:1) removed unreacted cyclodextrin (recovered in 30% yield). Next, stepwise gradient elution with water:MeOH (65:35) could satisfactorily give the pure fractions of **2**, which were then concentrated to give **2** in 18% yield. The impure fractions of **2** contaminated with the other disulfonate isomers **3** and **4** were applied on a reverse-phase HPLC chromatography to give disulfonates **2**–**4** in 1.0, 1.3, and 0.2% yields, respectively.[10]

The structural assignments of **2**–**4** were performed by ^{1}H NMR, H–H COSY, ^{13}C NMR, H–C COSY, and FABMS spectra, and by subsequent epoxidation.[11] The ^{1}H NMR spectra assigned by the H–H COSY NMR experiments exhibit an appreciable downfield shift of the H-1, H-2, and H-3 protons of the two glucose units of **2**–**4** (see Fig. 1). In particular, the chemical shifts of the H-2 protons show a larger downfield shift than do the H-3 protons. These NMR data indicate that the disulfonation onto two C-2 hydroxyl groups was performed by a single 1,4-dibenzoylbenzene-3′,3″-disulfonyl molecule, whereas the regiochemistry of **2**–**4** could not be determined. For the desired compound **2**,[12] the ^{13}C NMR peaks at 79.61 and 80.48 ppm for C-2 carbons of the substituted glucose units are largely shifted downfield from the other C-2 peaks, and the ^{13}C

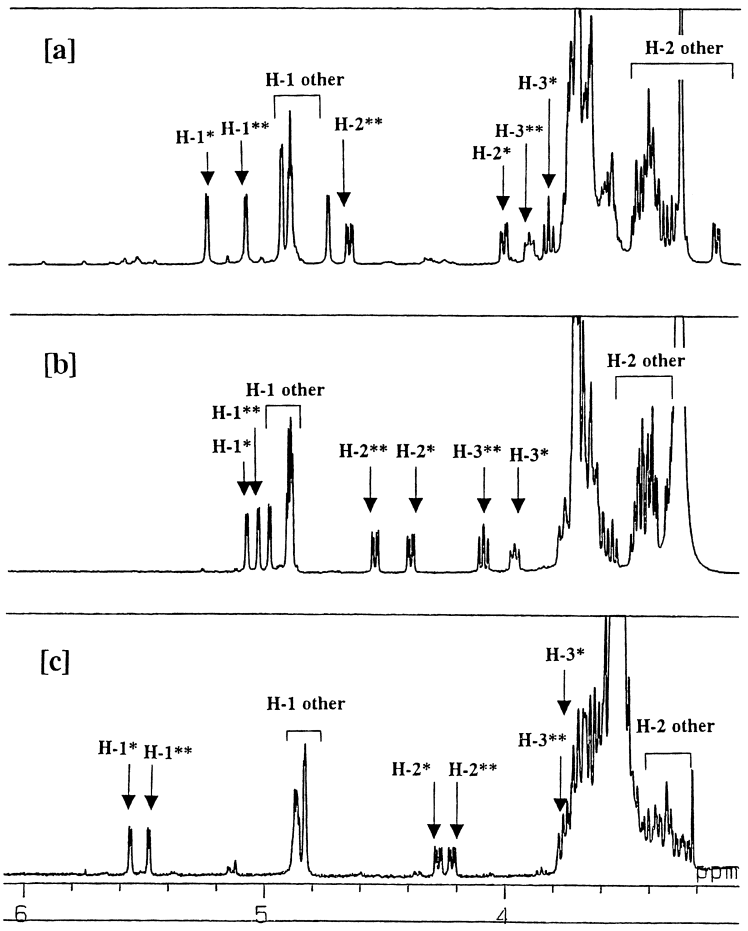

Figure 1. Partial ^{1}H NMR spectra of **2**–**4** (500 MHz, DMSO-d_6 containing 5% D_2O, ref. DMSO: δ 2.49). The assigned signals are numbered according to the usual convention shown in Scheme 1, and the symbols * and ** refer to the sulfonated glucose units. [a] Compound **2** (at 80°C). [b] Compound **3** (at 80°C). [c] Compound **4** (at 40°C)

NMR peaks for C-1 and C-3 carbons of the substituted glucose units are shifted upfield in a small way from the other C-1 and C-3 peaks, supporting the notion that the sulfonation was at the two C-2 hydroxyl groups. Then, the treatment of **2**–**4** with NaOH (5 equiv.) in water or a mixture of water and MeOH at 20°C for 3 h followed by open column chromatography on silica gel eluting with CH_3CN and then CH_3CN:water (6:1), and finally CH_3CN:water (6:2), afforded the corresponding pure di-2,3-manno-epoxides in 90, 71, and 76% yields, respectively. Their ^{1}H NMR spectra were seen to be identical with authentic published A,C-, A,B-, and A,D-di-2,3-manno-epoxides' spectra.[4b] Hence, these disulfonates **2**–**4** were assigned to $2^A,2^C$-, $2^A,2^B$-, and $2^A,2^D$-isomers, respectively.

In summary, this study described a preparatively useful method for the regiospecific $2^A,2^C$-disulfonation and A,C-epoxidation of β-cyclodextrin using the combination of 1,4-dibenzoylbenzene-3′,3″-disulfonyl imidazole and molecular sieves.

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8. Analytical data for **1**: colorless needles, mp 175–177°C. ^{1}H NMR δ ($CDCl_3$, 20°C): 7.14 (2H, s), 7.35 (2H, s), 7.78 (2H, t, $J=7.9$ Hz), 7.86 (4H, s), 8.05 (2H, s), 8.13 (2H, d, $J=7.9$ Hz), 8.20 (2H, d, $J=7.9$ Hz), and 8.40 (2H, s). UV λ_{max} (CH_3CN) 267 nm, ε 30,900. FABMS m/z: 547 (M+1).
9. A gradient elution with water to water:CH_3CN (80:20) in 10 min, to water:CH_3CN (70:30) in 20 min, and to water:CH_3CN (45:55) in 10 min was applied using a COSMOSIL packed column 5C18-MS (4.6 mm×150 mm, Nacalai Tesque).
10. A gradient elution with water:CH_3CN (80:20) to water:CH_3CN (75:25) in 30 min, to water:CH_3CN (70:30) in 45 min was applied using a COSMOSIL packed column 5C18-MS (20mm×250mm, Nacalai Tesque).
11. One of the NMR techniques, a 2D ROESY technique, could not be applied for compounds **2–4**, because H-4 protons of the sulfonated glucose units and those of adjoining glucose units could not be assigned unequivocally.
12. Data for **2**. ^{13}C NMR δ (80°C, DMSO-d_6 containing 5% D_2O, ref. DMSO: δ 39.50, the symbols * and ** refer to the sulfonated glucose units): 58.85 (C-6), 59.29 (C-6), 59.77 (C-6), 59.97 (C-6), 60.05 (C-6), 60.11 (C-6), 60.46 (C-6), 68.50, (C-3*) 69.31 (C-3**), 71.80-73.47 (C-2, 3, 5), 78.57 (C-4), 79.61 (C-2**), 79.90 (C-4), 80.48 (C-2*), 80.60 (C-4), 81.11 (C-4), 81.65 (C-4), 81.75 (C-4), 81.81 (C-4), 97.87 (C-1**), 99.10 (C-1*), 100.32 (C-1), 101.26 (C-1), 101.55 (C-1), 101.60 (C-1), 101.78 (C-1), 128.16 (ArC), 128.58 (ArC), 128.99 (ArC), 129.52 (ArC), 129.67 (ArC), 130.05 (ArC), 130.79 (ArC), 131.03 (ArC), 133.45 (ArC), 133.54 (ArC), 135.72 (ArC), 137.40 (ArC), 137.80 (ArC), 139.34 (ArC), 139.72 (ArC), 140.44 (ArC), 194.82 (C=O), 195.42 (C=O). UV λ_{max} (water) 269 nm, ε 24,400. FABMS *m*/*z*: 1545 (M+1).