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Regioselective 2^A-2^D-Disulfonylations of Cyclodextrins for Practical Bifunctionalization on the Secondary Hydroxyl Face

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Abstract

A useful technique to bifunctionalize the secondary hydroxyl faces of cyclodextrins is described. Regioselective 2^A,2^D-disulfonylations of cyclodextrins were achieved by reacting cyclodextrins with a combination of a novel disulfonyl imidazole reagent and molecular sieves in *N*, *N*-dimethylformamide. The resulting disulfonates were converted to 2^A,3^A,2^D,3^D-dimannoepoxy-cyclodextrins and 3^A,3^D-diamino-3^A,3^D-dideoxy-($2^A S$,$3^A S$),($2^D S$,$3^D S$)-cyclodextrins, which contain two functional groups on the periphery of the molecules.

Introduction

Cyclodextrins (CDs), cyclic α-1,4-linked oligosaccharides, have optically active and hydrophobic cavities within their bucket-like structures, with primary hydroxyl groups at the C-6 positions and secondary hydroxyl groups at the C-2 and C-3 positions. The remarkable properties afforded by the CDs' cavity result in their functions as chiral host molecules or as transporters of hydrophobic molecules. In order to increase the functionality of these CDs, selective modifications of the primary and/or the secondary hydroxyl groups have been investigated, and a variety of sulfonylations of the hydroxyl group(s) have been extensively applied as effective functionalization methods [1]. However, specific positioning and degrees of sulfonylation are difficult to control due to the large number of the hydroxyl groups in the CD. Although several selective disulfonylations of two primary hydroxyl groups by bridging the CD molecules with disulfonyl chlorides have been developed to modify the primary hydroxyl face of CD [2], selective disulfonylation of the secondary hydroxyl face has proven to be more challenging. It has been reported that disulfonyl reactions of α- and β-CDs with *p*-toluenesulfonyl chloride afforded the regioisomeric 2^A,2^B-2^A,2^C-, and 2^A,2^D-disulfonates (the glucose units are designated with letters A through G, clockwise, as viewed from the primary hydroxyl face) [3]. Well-designed reactions of the CDs with sulfonyl imidazole reagents and molecular sieves in *N*, *N*-dimethylformamide (DMF) have been reported for regioselective monosulfonation of the C-2 hydroxyl group [4], and have proven to be especially useful since the mild non-alkaline reaction conditions do not induce the decomposition of the sulfonates, and since the reactions are independent of the sulfonyl group type. Recently, successful regioselective 2^A,2^B- and 2^A,2^C-disulfonylations using disulfonyl imidazole reagents and molecular sieves have been reported [5]. In this letter, a highly regioselective synthesis of 2^A,2^D-disulfonylated CDs is described to provide a useful method for the effective bifunctionalization of the secondary hydroxyl face on the A and D glucose units.

Materials and method

Materials

Powdered 4A molecular sieves, DMF, chlorosulfonic acid, imidazole, triethylamine, and 28% aqueous ammonia were purchased from Nacalai Tesque, Inc. (Kyoto, Japan). Powdered 4A molecular sieves were heated at 250–300 °C for 2 h. α-, β-, and γ-CDs were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan) and dried under vacuum at 120 °C for 12 h. D_2O and DMSO-d_6 were purchased from Aldrich Chemical Co. (St. Louis, MO, U.S.A.). 4,4′-Dibenzoylbiphenyl was prepared according to literature method [6].

HPLC analysis

HPLC analysis was carried out using a JASCO GULLIVER HPLC system equipped with a MD-910 three-dimensional UV-VIS detector. A Fuji Silysia Chromatorex-ODS DU0005MT column (4.6 mm × 150 mm) was used for the HPLC analysis.

Characterization of CD compounds

^{1}H and ^{13}C NMR spectra were recorded using a JEOL JNM-A500 spectrometer in D_2O or DMSO-d_6. ^{1}H and ^{13}C NMR chemical shifts were assigned on the basis of ^{1}H-^{1}H COSY, DEPT ^{13}C NMR, and ^{1}H-^{13}C COSY experiments. Chemical shift values are reported in δ (ppm) relative to DMSO

and coupling constants (J) are in Hz. MALDI-TOF-mass spectra (positive) were measured using a Kompact MALDI instrument (Shimadzu Corp., Japan). 2,5-Dihydroxybenzoic acid was used as matrix.

Synthesis of disulfonyl reagent **3**

A mixture of 4,4′-dibenzoylbiphenyl (18 g), hydrazine monohydrate (25 ml), potassium hydroxide (28 g), and triethyenglycol (180 ml) was heated at 140 °C for 2 h, and then heated at 200 °C for 5 h. The reaction mixture was cooled, crashed ice (about 500 g) and chloroform (500 ml) were added, and aqueous conc. HCl was added to the mixture. The mixture was extracted with chloroform. The organic extracts were washed with water (300 ml) two times, dried over anhydrous Na_2SO_4, and evaporated to dryness. The residue was chromatographed on silica-gel column (dichloromethane: hexane, 1:2) followed by crystarization from a mixture of dichloromethane – hexane to give 4,4′-dibenzylbiphenyl (12.5 g, 75% yield).

Chlorosulfonic acid (16 ml) was added at 0 °C to 4,4′-dibenzylbiphenyl (8.0 g) and the mixture was maintained at 0 °C for 4 h, periodically stirred, followed by the addition of a second portion of chlorosulfonic acid (16 ml) at 0 °C. The mixture was maintained at 0 °C for 2 h, then poured over crashed ice (about 300 g). The precipitate was filtered, washed with cold water, and then dried under reduced pressure. The crude product was treated with imidazole (4.0 g) and triethylamine (8.0 ml) in dichloromethane (120 ml) at room temperature for 30 min. The reaction mixture was subjected on silica gel column chromatography and eluted with a mixture of dichloromethane – ethyl acetate (2:1), subsequently dichloromethane – ethyl acetate (1.5:1) to yield the crude product (5.9 g). This product was further purified by crystallization from chloroform to give pure reagent **3** (3.1 g, 20% yield on the basis of 4,4′-dibenzylbiphenyl). Analytical data for **3**; colorless needles, m.p. 143–145 °C. ^{1}H NMR δ ($CDCl_3$, 20 °C): 4.14 (4H, s), 7.10 (2H, s), 7.31 (2H,s), 7.39 (4H, d, $J = 7.9$ Hz), 7.39 (2H, d, $J = 7.9$ Hz), 7.60 (2H, s), 7.70 (2H, d, $J = 7.9$ Hz), 7.90 (4H, d, $J = 7.9$ Hz), and 8.02 (2H, s).

General procedure for reactions of CDs with disulfonyl reagent **3**

Freshly activated powdered 4A molecular sieves (200% w/w, on the basis of CD) was added to a solution (8.8 mmol/l) of CD in DMF, followed by the addition of disulfonyl imidazole **3** (2.9 mmol/l). The mixture was stirred at 30 °C for 5 days. The reaction was monitored using HPLC analysis. When the sulfonyl reagent was determined to be exhausted, HPLC analysis of the reaction mixture confirmed the yields of sulfonyl CDs by comparison with pure sulfonyl CDs. After removing the molecular sieves by filtration, the filtrate was concentrated under reduced pressure, and then the residue was subjected to preparative open reversed-phase column chromatography (15 mm × 120 mm; elution: H_2O to 35:65 CH_3CN—H_2O). The fractions containing the disulfonyl CDs were concentrated.

Preparation of $2^A,3^A,2^D,3^D$*-dimannoepoxy-CDs*

Aqueous NaOH (1 mol/l) solution was added to a solution of $2^A,2^D$-disulfonyl CDs in a mixture of water and MeOH and the reaction was carried out at 20–30 °C for 4–30 h, followed by open column chromatography on silica gel (CH_3CN, CH_3CN/water (6:1), CH_3CN-water (6:2)), yielded dimannoepoxy-CDs in 83–93% yields.

Preparation of $3^A,3^A$*-diamino-*$3^A,3^D$*-dideoxy-(*$2^AS,3^AS$*),(*$2^DS,3^DS$*)-CDs*

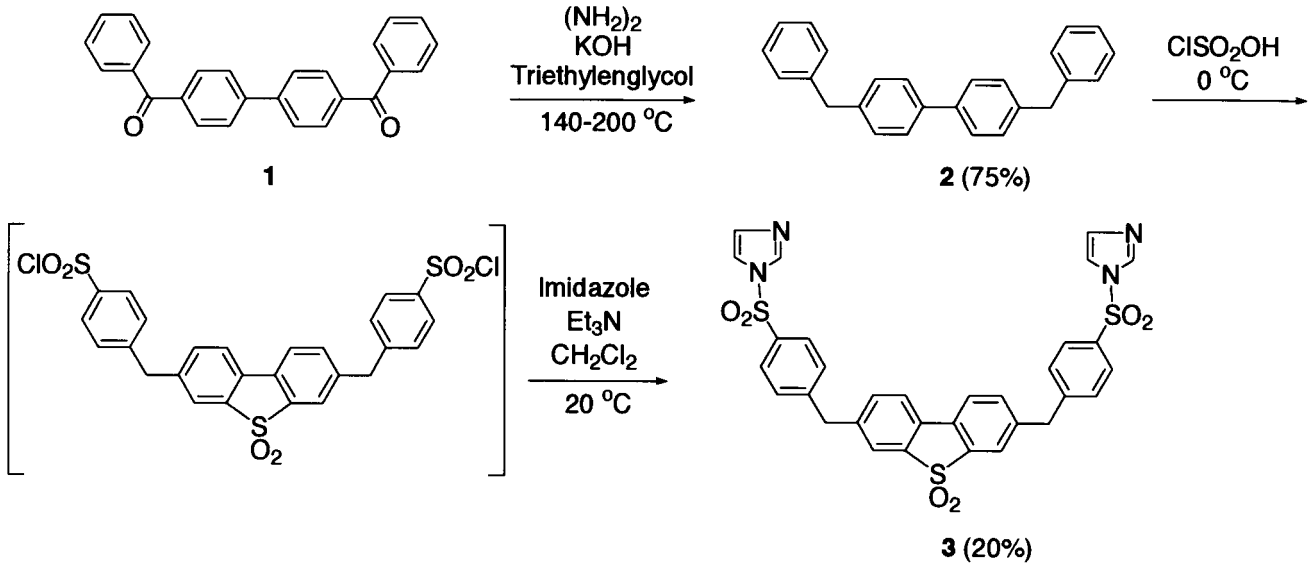
Treatment of $2^A,2^D$-disulfonyl CDs with 28% aqueous NH_3 solution and MeOH at 40 °C for 10 days, followed by ion-exchange column chromatography (Sephadex-CM C-25), yielded $3^A,3^D$-diamino-$3^A,3^D$-dideoxy-($2^AS,3^AS$),($2^DS,3^DS$)-CDs in 87–90% yields.

Results and discussion

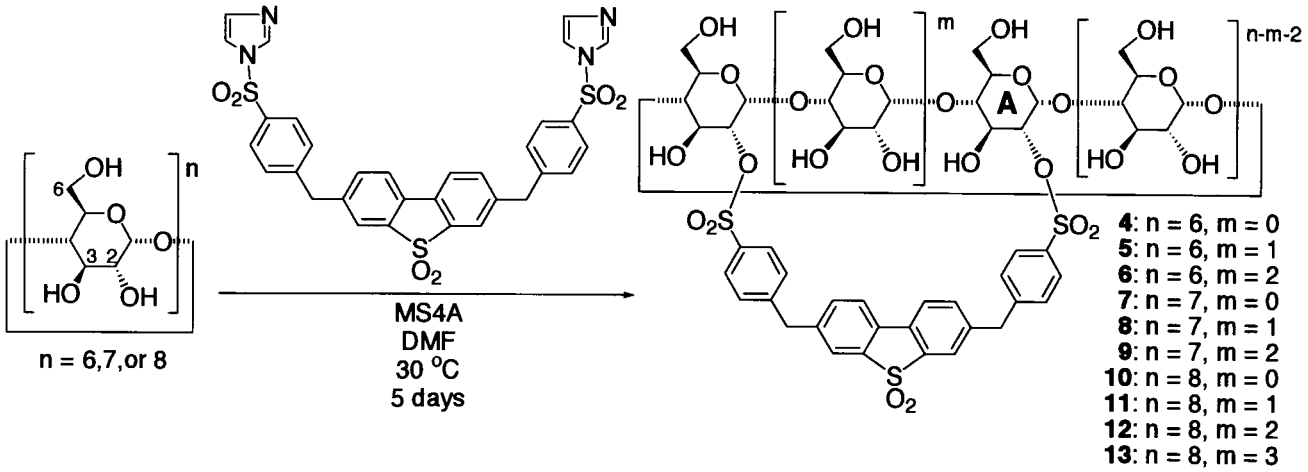
A novel disulfonyl imidazole reagent **3** was readily synthesized as shown in Scheme 1. Treatment of 4,4′-dibenzylbiphenyl, which was prepared by Wolff–Kishner reduction of 4,4′-dibenzoylbiphenyl [6], with chlorosulfonic acid, followed by reaction with imidazole afforded **3**. The efficiency of chlorosulfonylation was found to be very sensitive to the amount of chlorosulfonic acid; when a large amount of chlorosulfonic acid was used at the start of the reaction, the yield was markedly decreased. Thus, the initial amount of chlorosulfonic acid should be minimized.

A mixture of β-CD (8.8 mmol/l), **3** (2.9 mmol/l), and freshly activated powder 4A molecular sieves in DMF was stirred at 30 °C for 5 days and monitored by HPLC analysis. When the sulfonyl reagent **3** was determined to be exhausted, HPLC analysis of the mixture confirmed that $2^A,2^C$-disulfonate (Scheme 2, **8**) and $2^A,2^D$-disulfonate (Scheme 2, **9**) were afforded in 3.5% and 53% yields, based on **3**, respectively. However, $2^A,2^B$-disulfonate (Scheme 2, **7**), 6-, and 3-sulfonate(s) were not detected by HPLC analysis of the reaction mixture nor by NMR analysis of the isolated products. After removing the molecular sieves by filtration, the filtrate was concentrated under reduced pressure. Purification of products in the residue was carried out by chromatography using a simple open reverse-phase column to yield unreacted β-CD (57% yield), **8** (1.7% yield, based on **3**), and **9** (42% yield, based on **3**). In this reaction, the amount of β-CD used should be threefold than that of **3** to avoid multisulfonylation. Moreover, low concentration of CD successfully afforded desired disulfonylation, because production of CD-dimer could be decreased.

Disulfonates **8** and **9** were fully characterized by ^{1}H and ^{13}C NMR spectroscopy, MALDI-TOF-MS, and subsequent derivative reactions. Both the MALDI-TOF-MS spectra of disulfonates **8** and **9** exhibited molecular ions $[M + Na]^+$ at *m/z* 1677.3. Peak integrations of the ^{1}H NMR spectra and the MALDI-TOF-MS spectra indicate that the disulfonation on one CD molecule was executed by a single molecule of



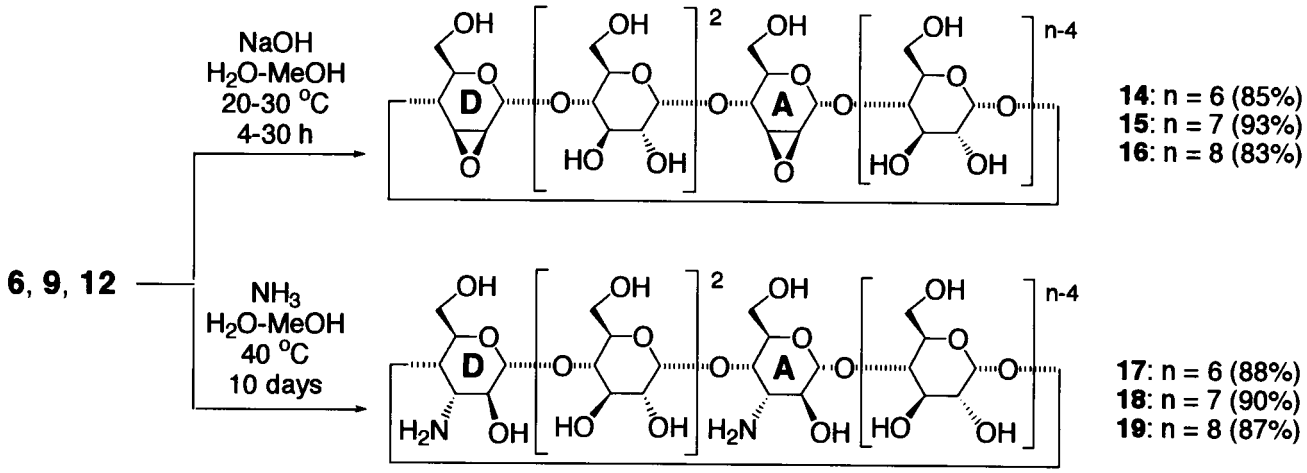
Scheme 1. Synthesis of a novel disulfonul imidazole reagent **3**.



Scheme 2. Disulfonylations of CDs with **3**.

3. Spectral assignments of disulfonates **8** and **9** were performed using ^{1}H-^{1}H COSY. The ^{1}H NMR spectra showed an appreciable downfield-shifts of the H-2 and H-3 protons of the two glucose units of **8** and **9**, respectively. In particular, the H-2 protons showed a larger downfield-shift than the H-3 protons. The ^{13}C NMR spectra assigned from ^{1}H-^{13}C COSY and DEPT experiments demonstrated an upfield shift of the C-1 and C-3 carbon peaks and a downfield shift of the C-2 carbon peaks of the two glucose units of **8** and **9**. These ^{1}H and ^{13}C NMR data, which do not conflict with the known shift effect of C-2 sulfonates [7], indicate that the two sulfonyl groups are located at the C-2 oxygen of the two glucose units. Although the regiochemistry of the disulfonyl groups of **9** could not be determine from NMR experiments, that of **8** was readily assigned using 2D ROESY NMR. In the 2D ROESY NMR spectrum of **8**, cross peaks were observed between a H-4A proton of the sulfonylated glucose unit A and the H-1B proton of the unsulfonylated glucose unit B and between the H-4B proton of the unit B and the H-1C proton of the sulfonylated glucose unit C; therefore, the structure of **8** was determined as 2^{A},2^{C}-disulfonate. Treatment of **9** with NaOH in a mixture of water and MeOH at 30 °C for 30 h, followed by open column chromatography on silica gel, yielded dimannoepoxy-β-CD **15** in 93% yield. ^{1}H and ^{13}C NMR spectra for **15** were in agreement with the published spectra for 2^{A},3^{A},2^{D},3^{D}-dimannoepoxy-β-CD [3b], suggesting that the structure of **9** is 2^{A},2^{D}-disulfonylated β-CD.

Disulfonylations of α- and γ-CDs were carried out similar to that of β-CD, resulting in 2^{A},2^{D}-regioselective disulfonylation as shown in Table 1. For α-CD, although high 2^{A},2^{D}-regioselectivity was afforded, yield of 2^{A},2^{D}-disulfonate **6** was remarkably lower than those of 2^{A},2^{D}-disulfonyl-β-CDs **9** and 2^{A},2^{D}-disulfonyl-γ-CDs **12**, and production of CD-dimer, in which sulfonation on C-2 hydroxyl groups of two CD molecules was executed by a single molecule of **3**, was increased. These results indicate that a distance between two reacting sites of **3** should be suitable for distances between the oxygen atoms on the 2^{A}- and 2^{D}-hydroxyl groups of β- and γ-CDs molecules, not for that of α-CD molecule.



Scheme 3. Preparation of $2^A,3^A,2^D,3^D$-dimanoepoxy-CDs and $3^A,3^D$-diamino-$3^A,3^D$-dideoxy-($2^A S$,$3A^A S$), ($2^D S$,$3^D S$)-CDs.

Table 1. Disulfonylation of CDs with disulfonyl imidazole reagent **3**[a]

CD	HPLC and isolated yields of disulfonylated CDs[b]			
	$2^A,2^B$	$2^A,2^C$	$2^A,2^D$	$2^A,2^E$
α-CD	[**4**] 0	[**5**] 3.8 (2.1)	[**6**] 16 (11)	–
β-CD	[**7**] 0	[**8**] 3.5 (1.7)	[**9**] 53 (43)	–
γ-CD	[**10**] 0	[**11**] 4.0 (1.1)	[**12**] 37 (21)	[**13**] 8.0 (2.4)

[a] Reactions were carried out using CDs (8.8 mmol/l), disulfonyl imidazole reagent **3** (2.9 mmol/l), and powdered activated 4A molecular sieves (200% w/w on the basis of CDs) in DMF at 30 °C for 5 days.
[b] Compound numbers are shown in brackets. HPLC and isolated yields were determined on the basis of disulfonyl imidazole reagent **3**. HPLC yields were determined on the basis of pure sulfonyl CDs. Isolated yields are shown in parentheses.

One of several functionalization of CDs is introduction of amino group(s) onto the rim of CD molecules. Treatment of **6**, **9**, and **12** with 28% aqueous NH_3 and MeOH at 40 °C for 10 days, followed by ion-exchange column chromatography, readily yielded $3^A,3^D$-diamino-$3^A,3^D$-dideoxy-($2^A S$,$3^A S$),($2^D S$,$3^D S$)-CDs **17–19** in 87–90% yields.

Conclusion

Reactions of CDs with a new disulfonyl imidazole reagent **3** in DMF in the presence of molecular sieves regioselectively afforded $2^A,2^D$-disulfonyl CDs, in particular the reaction yield and regioselectivity for β-CD were excellent. The resulting $2^A,2^D$-disulfonyl CDs were satisfactory converted to $2^A,3^A,2^D,3^D$-dimannoepoxy-CDs and $3^A,3^D$-diamino-$3^A,3^D$-dideoxy-($2^A S$,$3^A S$),($2^D S$,$3^D S$)-CDs, which contain two functional groups on the periphery of the molecules. The procedures for the production and purification of bifunctionalized CDs described herein are simple and useful, and consequently these procedures can be further utilized toward the controlled derivation of CDs, thus overcoming the main difficulties associated with regioselectivity, efficiency, and isolation techniques.

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