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Regiospecific synthesis of $2^A,2^B$-disulfonated γ-cyclodextrin

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Abstract

A method for effective regiospecific preparation of $2^A,2^B$-disulfonated γ-cyclodextrin has been developed. Reaction of γ-cyclodextrin with benzophenone-3,3′-disulfonyl imidazole and molecular sieves in DMF yielded $2^A,2^B$-disulfonated γ-cyclodextrin with no $2^A,2^C$-, $2^A,2^D$-, $2^A,2^E$-, 3-, or 6-sulfonyl isomers.

Keywords: γ-cyclodextrin; regiospecificity; disulfonation.

Cyclodextrins consisting of many D-glucopyranose units have been studied and used practically, since their molecules contain hydrophobic and optically active cavities.[1] γ-Cyclodextrin, possessing eight D-glucopyranose units, has a larger cavity than α-cyclodextrin and β-cyclodextrin which are frequently used, and exhibits significant characteristics such as the inclusion of two molecular guests and molecular recognition as a molecular sensor.[2]

We have been studying the enhancement of chemiluminescence by covalently binding a chemiluminescent molecule to one cyclodextrin molecule. It has been shown that attachment at the secondary hydroxyl face of γ-cyclodextrin can greatly enhance chemiluminescence.[3] We were interested in investigating multifunctionalization at the secondary hydroxyl face of γ-cyclodextrin in order to construct a molecular system for even more effective enhancement.

Chemical modification of the primary and secondary hydroxyl faces of cyclodextrins has been investigated to increase the characteristic ability of cyclodextrins to recognize molecules. Up to now, several sulfonation processes on the primary or secondary hydroxyl group(s) of cyclodextrins have usually been adopted for the modification; several methods for regiospecific sulfonation have been developed.[4] Of these strategies, regiospecific sulfonation on the C-6 primary hydroxyl groups of γ-cyclodextrin has easily been done with sulfonyl chloride in pyridine.[2e,f,h,5] However, studies of regiospecific sulfonation on the secondary hydroxyl group of γ-cyclodextrin have demonstrated that this sulfonation is extremely difficult.[6] Only a few reports on the regiospecific monosulfonation on the C-2 secondary hydroxyl group have been published,[7] and there have been no reports on regiospecific disulfonation on the two C-2 hydroxyl groups, which should be useful for bifunctionalization at the secondary hydroxyl face of γ-

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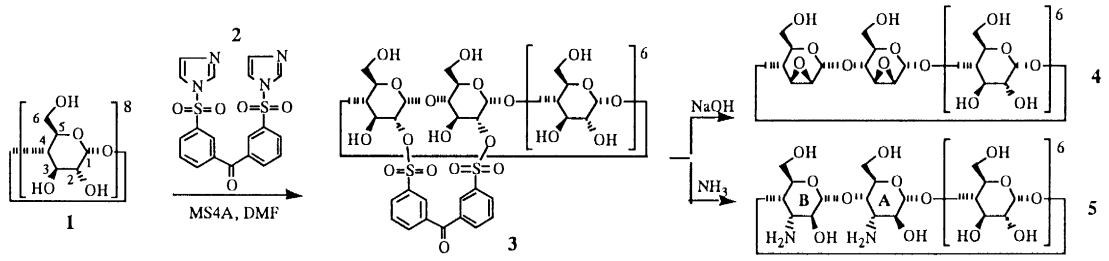
cyclodextrin. In this paper, we report successful regiospecific disulfonation on the two C-2 hydroxyl groups of glucose units A and B (the glucose units are lettered A to H), named 2^A,2^B-hydroxyl groups, of γ-cyclodextrin.

Use of strongly compulsory activation of the C-2 hydroxyl group, such as the formation of metal alkoxide or alkyltin alkoxide, appears to be difficult to apply to effective 2^A,2^B-disulfonation, since the activation reagents cannot selectively activate the 2^A- and 2^B-hydroxyl groups, as shown in studies for α-, and β-cyclodextrins.[8] Also, the use of these methods poses other serious problems, including decomposition of produced sulfonates, isolation from other isomers, and scale-limited separation. We have developed an effective method of regiospecific monosulfonation on the C-2 hydroxyl group of cyclodextrins by utilizing sulfonyl imidazole and molecular sieves.[7b,9] This sulfonation can occur under temperate conditions without compulsory activation of the C-2 hydroxyl group. Thus, development of only suitable sulfonyl reagent(s) can enable the 2^A,2^B-disulfonation of γ-cyclodextrin. Our studies led us to develop a methodology for complete regiospecific synthesis and effective separation of the 2^A,2^B-disulfonated γ-cyclodextrin. We designed benzophenone-3,3′-disulfonyl imidazole as the 2^A,2^B-disulfonyl reagent, in which the distance between the two reacting sites at the *Z*-oid type is 6.0 Å.[10] This distance is suitable for the distance between the oxygen atoms on the 2^A- and 2^B-hydroxyl groups.[11]

In our experiment, 20 g of dried γ-cyclodextrin (**1**) dissolved in DMF (400 mL) was treated with benzophenone-3,3′-disulfonyl imidazole (**2**) (6.8 g), which was prepared from benzophenone-3,3′-disulfonyl chloride,[12] imidazole, and triethylamine, using the procedure of Berlin et al.,[13] and freshly activated powder molecular sieves 4A (20 g) at 30°C for 20 h (see Scheme 1). The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. Warm 20% aqueous MeOH (400 mL) was added to the residue and an insoluble solid containing a small amount of target compound 2^A,2^B-disulfonated γ-cyclodextrin **3** and excessively sulfonated γ-cyclodextrins was removed by filtration. The filtrate was subjected to a simple open reverse-phase column chromatography (Fuji Silisia Chromatorex-ODS DM1020T gel, 50×180 mm). Elution with water and 10% aqueous MeOH removed unreacted **1**. Then, stepwise gradient elution to 50% aqueous MeOH gave pure **3** in a 30% yield. No other mono- or disulfonate isomers such as 2^A,2^C-, 2^A,2^D-, 2^A,2^E-, 3-, and 6-sulfonate(s) resulting from the reaction were observed by HPLC analysis of the reaction mixture and ^{1}H NMR measurement of products.



Scheme 1.

The structure of **3** was determined by ^{1}H NMR, H–H COSY, ^{13}C NMR, H–C COSY, and DEPT techniques, a FABMS spectrum, and further conversions. The ^{1}H NMR spectrum (Fig. 1) of **3** in DMSO-d_6 and the FABMS spectrum showed that one γ-cyclodextrin molecule was sulfonated by one benzophenone-3,3′-disulfonyl molecule. The ^{1}H NMR spectrum assigned by the H–H COSY technique exhibits an appreciable downfield-shift of the H-1, H-2, and H-3 protons of the two glucose units. In particular, the chemical shifts of the H-2 protons show a larger downfield-shift than do the H-3 protons. The ^{13}C NMR spectrum assigned by the H–C COSY showed an upfield-shift of the C-1 and C-3 carbons and a downfield-shift of the C-2 carbons of the two glucose units.[14] The treatment of **3** with aqueous NaOH at 37°C for 1.5 h followed by open reverse-phase column chromatography yielded di-2,3-manno-

epoxide γ-cyclodextrin **4** in an 89% yield. The ^{1}H NMR spectrum of **4** in D_2O showed two downfield-shifted singlet peaks of the H-1 protons at δ 5.18 and δ 5.24. The ^{13}C NMR spectrum showed four peaks at δ 50.23, δ 50.57, δ 55.20 and δ 55.24 as epoxide carbons, indicating that **4** is di-2,3-manno-epoxide γ-cyclodextrin, as shown in Scheme 1.[15] These results indicate that the two sulfonyl groups of the benzophenone-3,3′-disulfonyl molecule are located at the C-2 oxygen of the two glucose units.[16] However, the regiospecific relationships, named 2^{A},2^{B},2^{A},2^{C},2^{A},2^{D}, or 2^{A},2^{E}, could not be determined by these techniques. One of the NMR techniques, the ROESY technique, in which an NOE afforded by the short distance between the H-1 proton of a glucose unit and the H-4 proton of the adjacent glucose unit can be observed, is effective for the sequence analysis of the glucose units.[17] For compounds **3** and **4**, the regiospecific relationships could not be determined by the ROESY technique, because all H-4 protons could not be differently assigned.

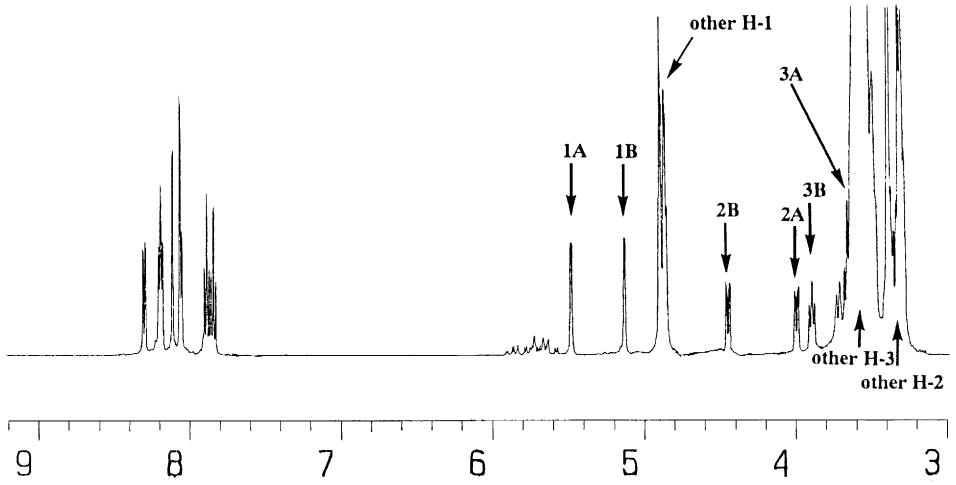


Fig. 1. ^{1}H NMR spectrum of **3** (500 MHz, DMSO-d_6 containing 5% D_2O, 30°C, ref, DMSO: δ 2.49). The assigned signals are numbered according to the usual convention shown in Scheme 1 and the letters, A and B, refer to the sulfonated glucose units

The treatment of **3** with aqueous 28% NH_3 at 37°C for 5 days followed by ion-exchange chromatography on Sephadex CM-25 yielded diamino γ-cyclodextrin **5** in an 88% yield. The ^{1}H and ^{13}C NMR spectra assigned by the H–H COSY and H–C COSY techniques, and the FABMS spectrum of **5** indicated that the structure is 3,3′-diamino-3,3′-dideoxy-(2*S*),(2′*R*),(3*R*),(3′*R*)-γ-cyclodextrin.[18] The ROESY spectrum of **5** showed that the H-1 proton of aminoglucose unit B (see Scheme 1) had a cross peak with the H-4 proton of aminoglucose unit A, indicating that the two aminoglucose units adjoin. Therefore, the structure of **3** converted to **5** is 2^{A},2^{B}-disulfonated γ-cyclodextrin, as shown in Scheme 1.

In summary, we have described the complete regiospecific synthesis of 2^{A},2^{B}-disulfonated γ-cyclodextrin, which is useful for bifunctionalization at the secondary hydroxyl face of γ-cyclodextrin.

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14. ^{13}C NMR of **3** δ (30°C, DMSO-d_6 containing 5% D_2O, chemical shift of DMSO is δ 39.50): 59.2–60.2, 68.42 (C-3 of sulfonated glucose unit A), 69.00 (C-3 of sulfonated glucose unit B), 71.74–73.37, 77.70, 78.08 (C-2 of sulfonated glucose unit B), 79.56, 80.38–81.09, 81.09 (C-2 of sulfonated glucose unit A), 97.49 (C-1 of sulfonated glucose unit A), 98.02 (C-1 of sulfonated glucose unit B), 100.93, 101.32, 101.55, 101.74, 101.74, 101.74, 128.48, 129.93, 129.96, 130.23, 131.30, 131.58, 133.34, 133.73, 136.05, 136.83, 137.76, 138.52, 194.54. FABMS *m/z* 1603 [M+1].
15. ^{1}H NMR of **4** δ (24°C, D_2O): 3.33 (1H, br., H-2 of anhydroglucose unit), 3.36 (1H, br., H-2 of anhydroglucose unit), 3.4–3.9 (majority, H of cyclodextrin), 4.9–5.1 (6H, m, H-1 of glucose unit), 5.18 (1H, br.s, H-1 of anhydroglucose unit), 5.24 (1H, br.s, H-1 of anhydroglucose unit). ^{13}C NMR of **4** δ (24°C, D_2O): 50.23 (C-2 of anhydroglucose unit), 50.57 (C-2 of anhydroglucose unit), 55.20 (C-3 of anhydroglucose unit), 55.24 (C-3 of anhydroglucose unit), 60.87, 61.02, 61.49, 69.31, 69.80, 69.88, 71.88, 72.34, 72.42, 72.52, 72.93, 73.09, 73.19, 73.44, 73.72, 79.59, 80.25, 80.46, 80.66, 81.04, 81.09, 96.45 (C-1 of anhydroglucose unit), 97.85 (C-1 of anhydroglucose unit), 100.52, 101.70, 101.88, 101.95, 102.24, 102.31. FABMS *m/z* 1261 [M+1].
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18. ^{1}H NMR of **5** δ (50°C, DMSO-d_6 containing 5% D_2O, chemical shift of DMSO is δ 2.49): 2.78 (1H, dd, *J*=4.3, 8.6 Hz, H-3 of aminoglucose unit B), 2.85 (1H, dd, *J*=3.7, 7.3 Hz, H-3 of aminoglucose unit A), 3.2–3.7 (majority, H of cyclodextrin), 3.72 (1H, m, H-4 of aminoglucose unit B), 3.75 (1H, m, H-4 of aminoglucose unit A), 3.77 (1H, m, H-5 of aminoglucose unit B), 3.92 (1H, m, H-5 of aminoglucose unit A), 4.49 (1H, d, *J*=4.9 Hz, H-1 of aminoglucose unit B), 4.59 (1H, d, *J*=4.3 Hz, H-1 of aminoglucose unit A), 4.79 (1H, d, *J*=3.7 Hz, H-1 of glucose unit), 4.83 (2H, m, H-1 of glucose unit), 4.86 (1H, d, *J*=3.7 Hz, H-1 of glucose unit), 4.92 (1H, d, *J*=3.7 Hz, H-1 of glucose unit), 4.95 (1H, d, *J*=3.7 Hz, H-1 of glucose unit). ^{13}C NMR of **5** δ (50°C, DMSO-d_6 containing 5% D_2O, chemical shift of DMSO is δ 39.50): 51.97 (C-3 of aminoglucose unit A), 52.20 (C-3 of aminoglucose unit B), 59.70–60.74, 70.77, 71.09, 71.93–73.03, 73.72, 75.55, 76.94, 78.51, 79.87, 80.33, 81.06, 81.39, 81.53, 100.58, 101.13, 101.39, 101.57, 101.85, 102.03, 102.77 (C-1 of aminoglucose unit A), 103.17 (C-1 of aminoglucose unit B). FABMS *m/z* 1295 [M+1]. 2^A,2^B-Diamino-2^A,2^B-dideoxy α-cyclodextrin was reported in the following paper: Fujita, K.; Egashira, Y.; Imoto, T.; Fujioka, T.; Mihashi, K.; Tahara, T.; Koga, T. *Chem. Lett.* **1989**, 429–432.