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Regiochemical Correlation between 6-O-Sulfonylated Cyclodextrins and 3-O-Sulfonylated Cyclodextrins via 3,6-Anhydrocyclodextrins

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(3R)-2,3-Anhydrocyclodextrins which were prepared from 3-O-sulfonylcyclodextrins were treated with aqueous alkali to give 3,6-anhydrocyclodextrins, which were prepared by the reaction of 6-O-sulfonylcyclodextrins with aqueous alkali. This regiochemical correlation was applicable to regioisomer determination of 3-O-disulfonylcyclodextrins on the basis of the regiochemistry of 6-O-disulfonates.

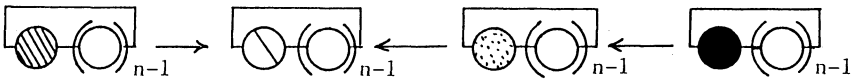
In order to determine regiochemical structures of 6-O-polysulfonylcyclodextrins, we developed the extended Körner method[1] and the Taka amylase hydrolysis method followed by analysis of the products,[2a-d] the substituted linear oligosaccharides. Since the latter method produces 6'-sulfonylmaltose from a 6-O-monosulfonylcyclodextrin, it is useful only for the structure determination of $6^A,6^B$-O-disulfonylcyclodextrins and the related compounds which have the sulfonyl groups on the glucose units adjacent to one another. Only one method for the regiochemical structure determination of isomeric 2-O- or 3-O-disulfonylcyclodextrins is the Taka amylase hydrolysis.[2d-f] Since this method

gives 2"-O-sulfonylmaltotriose or 3'-O-sulfonylmaltotriose (and 3"-sulfonylmaltotetraose in some cases) from 2-O- or 3-O-monosulfonylcyclodextrin, respectively, this method is applicable not only to the A,B-isomers but also to the A,C- and A,D-isomers. Although this enzymatic method seems to be widely applicable to the isomer determination of 2-O- or 3-O-polysubstituted cyclodextrins, there is a serious defect that the polysubstituted cyclodextrins, even disubstituted cyclodextrins, are too slowly hydrolyzed by Taka amylase to be practically used. Therefore, novel and appropriate method should be established for regioisomer determination of polysubstituted cyclodextrins. In this report, we describe a new method which correlates regioisomers of 6-O-polysulfonylated cyclodextrins with those of 3-O-poly-sulfonylated cyclodextrins via regiosomeric poly-3,6-anhydrocyclodextrins (Scheme 1). This implies that regiochemistry of 3-O-polysulfonylcyclodextrins can be determined if 6-O-polysulfonylcyclodextrins are structurally determined by appropriate method such as the extended Körner method.

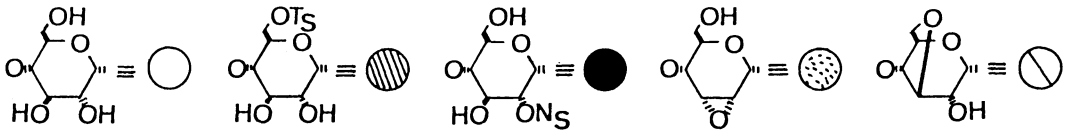
6-O-Tosyl-α-cyclodextrin (**1**a) was converted to $3^{A},6^{A}$-anhydro-α-cyclodextrin (**2**a) in 57.7% yield by treatment with aqueous NaOH (1 mol dm^{-3}) similarly to the 6-O-tosyl-β-cyclodextrin case (**1**b, **2**b) reported before by us.[3]

A solution of $(3^{A}R)$-$2^{A},3^{A}$-anhydro-α-cyclodextrin **3**a (50 mg) in 4% aqueous $Ba(OH)_2$ (1 mL) was kept at 100 °C for 48 h in a sealed tube and was neutralized with dilute H_2SO_4. The solution was filtered, concentrated in vacuo and applied on a reverse-phase column (Merck Lobar column LiChroprep Rp18). After eluting with water (300 mL), a gradient elution of 5% aqueous MeOH (500 mL) was applied to give **2**a (35.0 mg, 70.0%).[4] The product **2**a was identified by comparing its ^{13}C NMR (67.5 MHz) and ^{1}H NMR (270 MHz) spectra and its HPLC retention time with those of the authentic specimens. The epoxide was easily prepared by the reaction of 3-O-(β-naphthylsulfonyl)-α-cyclodextrin **4**a under a milder condition (25 °C, 5 h)[2d,f] than that employed in the reaction of **3**a. Therefore, it is possible to convert the 3-O-sulfonate **4**a to the 3,6-anhydrocyclodextrin **2**a directly under the reaction condition employed in the reaction of **3**a.[4] As shown above, 3-O-sulfonylated cyclodextrins can be correlated with 6-O-sulfonylated cyclodextrins via $3^{A},6^{A}$-anhydrocyclodextrins.[5] Before the applicability of this correlation method was tested, conversions of $6^{A},6^{X}$-O-disulfonyl-α-cyclodextrin **5**a-**7**a (X = B, C, or D)[1] and $6^{A},6^{X}$-O-disulfonyl-β-cyclodextrin **5**b-**7**b (X = B, C,

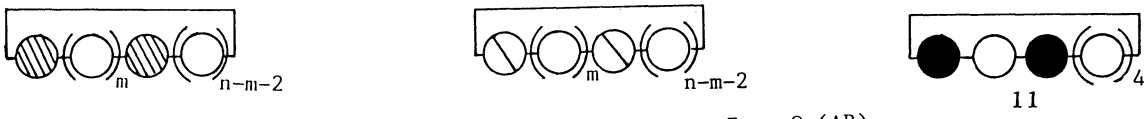
or D)[2a] to the corresponding $3^A,6^A;3^X,6^X$-dianhydrocyclodextrins **8**a,b-**10**a,b were successfully carried out. ^{1}H NMR spectra of **10**a and **10**b which was obtained from **7**a and **7**b, respectively, were shown in Fig. 1 as examples. The proton absorptions of the 3,6-anhydroglucose units were assigned as shown in Fig. 1 with the aid of COSY ^{1}H NMR spectra. Simplicity of the spectrum (Fig. 1A) of **10**a demonstrates that **10**a is a symmetric compound i.e. $3^A,6^A;3^D,6^D$-dianhydro-α-cyclodextrin, which reconfirms the structure determination carried out before by us. Since there is not such a symmetry in the disubstituted β-cyclodextrin, two 3,6-anhydroglucose units in **10**b show absorptions different from one another as shown in Fig. 1B. To test the usefulness of the correlation method, $(3^AR,3^CR)$-$2^A,3^A;2^C,3^C$-dianhydro-β-cyclodextrin **12** (100 mg) which was easily obtained from



1a; n=6, 1b; n=7 2a; n=6, 2b; n=7 3a; n=6, 3b; n=7 4a; n=6, 4b; n=7



Ts ; p-toluenesulfonyl Ns ; β-naphthylsulfonyl



5a; n=6, m=0 (AB) 5b; n=7, m=0 (AB) 8a; n=6, m=0 (AB) 8b; n=7, m=0 (AB)
6a; n=6, m=1 (AC) 6b; n=7, m=1 (AC) 9a; n=6, m=1 (AC) 9b; n=7, m=1 (AC)
7a; n=6, m=2 (AD) 7b; n=7, m=2 (AD) 10a; n=6, m=2 (AC) 10b; n=7, m=2 (AD)

11

12

Scheme 1.

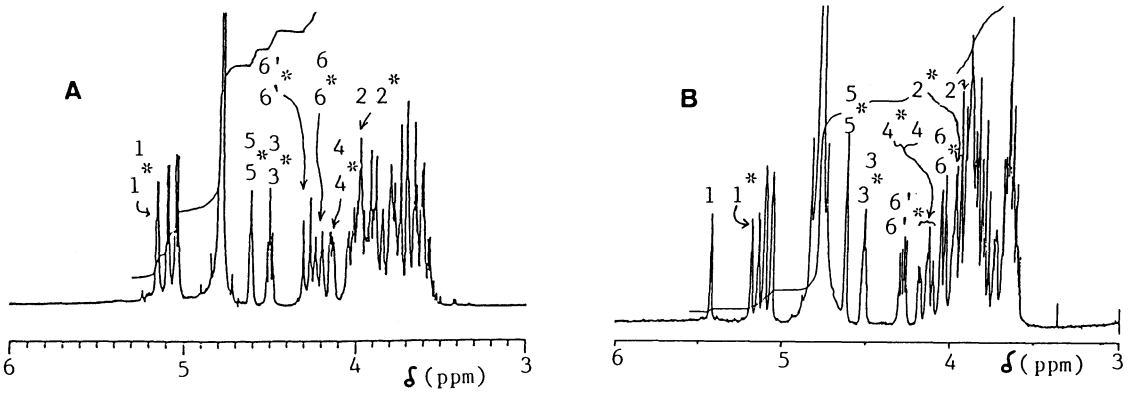


Fig. 1. ^{1}H NMR spectra of $3^A,6^A;3^D,6^D$-dianhydro-α-cyclodextrin **10**a (A, 270 MHz) and $3^A,6^A;3^D,6^D$-dianhydro-β-cyclodextrin **10**b (B, 400 MHz) in D_2O.

the corresponding disulfonate **11** was successfully converted to $3^{A},6^{A};3^{C},6^{C}$-dianhydro- -cyclodextrin **9**b (73.8 mg, 73.8%) by the procedure similar to that described in the conversion of the monosulfonate **3**b. The product **9**b was identified by comparing its ^{13}C and ^{1}H NMR spectra and its HPLC retention time with those of the product **9**b obtained from $6^{A},6^{C}$-di(tosyl)-β-cyclodextrin **6**b. In conclusion, this correlation method via 3,6-anhydrocyclodextrins is expected to be useful to determine the regiochemistry of 3-O-polysulfonylated cyclodextrins. This method will be applicable to regiochemical determination of 3-O-trisulfonylated β-cyclodextrin[2f] which has not been structurally determined and also, to more difficult regiochemical problem, determination of isomeric 3-O,6-O-disulfonylated cyclodextrins. These applications will be reported in the near future. Also, it should be noted that the regioisomeric 3,6-anhydrocyclodextrins **8**a,b-**10**a,b have unique cavity shapes which are different from one another and from that of cyclodextrins themselves and are expected to show unique molecular recognition.

References

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4) The analysis of the products by HPLC demonstrated that the reaction proceeded nearly quantitatively.

5) A similar conversion of methyl 2,3-anhydro-α-D-allopyranoside to methyl 3,6-anhydro-α-D-glucopyranoside was reported. A. B. Foster, M. Stacey, and S. V. Vardheim, Acta Chem. Scand., 12, 1819 (1958).

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