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Practicable regiospecific bifunctionalization on the secondary face of α- and β-cyclodextrins†

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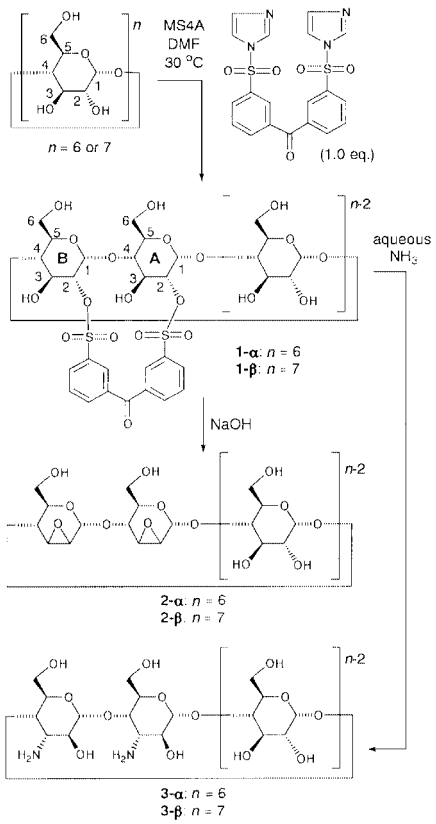
Practicable regiospecific bifunctionalization onto the A,B-secondary hydroxyl face of α- and β-cyclodextrins, such as diepoxidation and diamination, has been made possible by staple-disulfonation with benzophenone-3,3′-disulfonyl imidazole and molecular sieves in DMF.

Regiospecific multifunctionalization techniques on the primary and secondary hydroxyl groups of cyclodextrins have been investigated in order to enhance the ability of cyclodextrins to act as acceptors or artificial enzymes. Several significant regiospecific disulfonations on the primary hydroxyl groups have been developed to modify the primary face[1] and, as a result, some elegant bifunctional catalyses have been achieved.[2] However, regioselective bifunctionalization on the secondary face has proven more difficult to accomplish.[3] Hence, no absolutely regioselective bifunctionalizations have, as yet, been developed. Two reported disulfonations on two secondary hydroxyl groups of α-, and β-cyclodextrins were not absolutely regiospecific, but afforded mixtures of the regioisomeric $2^A,2^B$-, $2^A,2^C$-, and $2^A,2^D$-disulfonates in extremely low yields.[4] Additionally, inconvenient separation techniques were necessary to isolate the products. Accordingly, an investigation into the bifunctionalization of the secondary hydroxyl groups was undertaken and led to the development of a very useful and efficient method for the exclusively regiospecific preparation of $2^A,2^B$-disulfonates of α- and β-cyclodextrins, with no $2^A,2^C$- and $2^A,2^D$-disulfonate isomers. This preliminary communication details the new method and shows that the $2^A,2^B$-disulfonates are effectively converted to the corresponding A,B-dimannoepoxido and $3^A,3^B$-diamino compounds, useful for the functionalization of cyclodextrins.

Recently, an interesting regiospecific monosulfonation on the secondary hydroxyl groups of cyclodextrins using a combination of sulfonyl imidazole and molecular sieves has been reported,[5] although the mechanism of the sulfonation is not yet clear. This method is extremely encouraging in practical cyclodextrin chemistry because the mild non-alkaline reaction conditions do not induce decomposition of the sulfonates. Furthermore, the reaction occurs independently of the nature of the sulfonyl groups. In this study, the use of benzophenone-3,3′-disulfonyl imidazole,† easily prepared from benzophenone-3,3′-disulfonyl chloride, imidazole and triethylamine,[6] as a $2^A,2^B$-disulfonation 'stapling' reagent (see Scheme 1) has been investigated. A mixture of α- or β-cyclodextrin (0.01 mol), benzophenone-3,3′-disulfonyl imidazole (0.01 mol), and freshly activated powdered molecular sieves 4 Å (10 g) in *N*,*N*-dimethylformamide (DMF) (200 ml) was stirred at 30 °C for 20 h. The molecular sieves were removed by filtration and the filtrate concentrated under reduced pressure. Warm 20% aqueous MeOH (400 ml) was added to the residue and the insoluble solid, containing a small amount of **1-α** or **1-β** and more complex sulfonated cyclodextrins, was removed by filtration. The filtrate was passed through a simple open reverse-phase chromatography column (50 × 120 mm, Fuji Silisia Chromatorex-ODS DM1020T). Elution with water and 10% aqueous MeOH removed the remaining unreacted cyclodextrin. Stepwise gradient elution to 50% aqueous MeOH gave pure 'staple-$2^A,2^B$-disulfonate' **1-α** and **1-β** in 30 and 33% yields, respectively. No other mono- or disulfonate isomers, such as staple-$2^A,2^C$-disulfonates, staple-$2^A,2^D$-disulfonates, 6-sulfonates or 3-sulfonates, resulting from the reaction were observed by HPLC analysis of the reaction mixture and ^{1}H NMR spectroscopy on the reaction products. The structural assignments of **1-α** and **1-β** were made from ^{1}H NMR, H–H COSY, ROESY, HOHAHA, ^{13}C NMR, H–C COSY, and FAB-MS spectra,† and by further derivatisations. The FAB-MS spectra of **1-α** and **1-β** indicated that the disulfonation of each cyclodextrin molecule was performed by a single benzophenone-3,3′-disulfonyl molecule. The ^{1}H NMR spectra, assigned from the H–H COSY experiments, exhibit an appreciable downfield shift of the resonances due to the H-1, H-2 and H-3 protons of the two glucose units of **1-α** and **1-β**, as shown in Fig. 1. 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 spectra, assigned from the H–C COSY experiments, show an upfield shift of the C-1 and C-3 carbon resonances and a downfield shift of the C-2 carbon peaks of the two glucose units of **1-α** and **1-β**. These data show that the two sulfonyl groups of



Scheme 1

† Electronic supplementary information (ESI) available: spectroscopic data. See http://www.rsc.org/suppdata/cc/b0/b002445g/

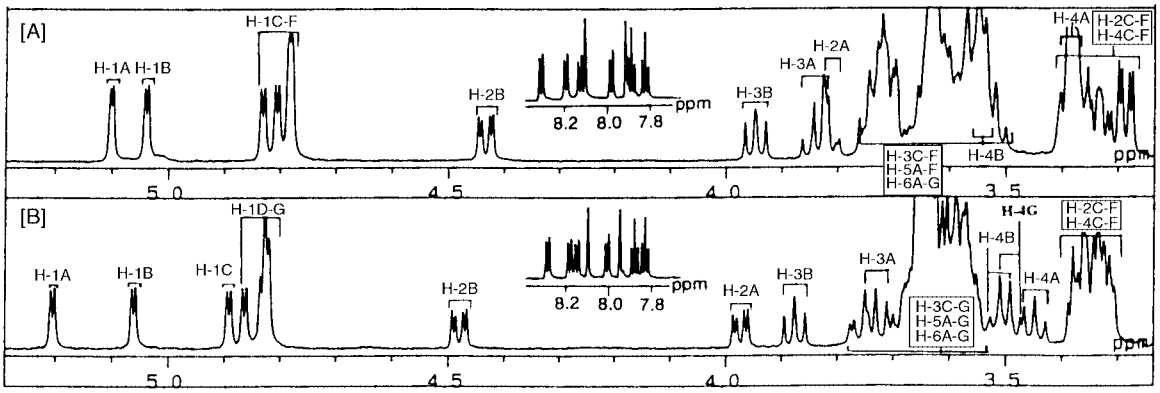


Fig. 1 [A] ^{1}H NMR spectrum of **1-α** [500 MHz, DMSO-d_6 containing 5% D_2O, 60 °C, ref. DMSO (δ 2.49)]. [B] ^{1}H NMR spectrum of **1-β** [500 MHz, DMSO-d_6 containing 5% D_2O, 80 °C, ref. DMSO (δ 2.49)]. The assigned signals are numbered according to the usual convention, shown in Scheme 1, and the glucose units are lettered A to F or G. The letters A and B refer to the sulfonated glucose units.

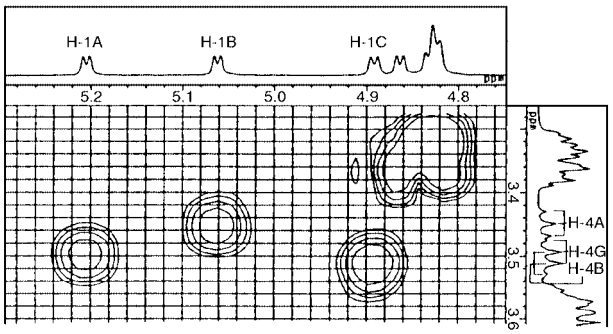


Fig. 2 Partial 2D ROESY NMR spectrum of **1-β** [500 MHz, DMSO-d_6 containing 5% D_2O, 80 °C, ref. DMSO (δ 2.49)].

the benzophenone-3,3′-disulfonyl molecule are located at the C-2 oxygen of the two glucose units. The regiochemistry of the disulfonyl groups of **1-β** was determined using a 2D ROESY NMR experiment (Fig. 2), whereas for **1-α**, this could not be done because the H-4 protons of the sulfonated glucose units and those of adjoining glucose units could not be assigned definitely (see Fig. 1[A]). The 2D ROESY NMR spectrum of **1-β** shows that the H-1B proton of one sulfonated glucose unit has a cross peak with the H-4A proton of another sulfonated glucose unit, indicating that the two units adjoin. Therefore, the structure of **1-β** is 2^A,2^B-disulfonated β-cyclodextrin, as shown in Scheme 1. Treatment of **1-α** and **1-β** with 0.1 mol l^{-1} aqueous NaOH (10 equiv.) at 20 °C for 1 h followed by simple open reverse-phase column chromatography afforded the corresponding pure di-2,3-manno-epoxides **2-α** and **2-β** in 87 and 90% yields, respectively. Their ^{1}H and ^{13}C NMR spectra were seen to be identical with published spectra for authentic A,B-di-2,3-mannoepoxides.[4] Hence **1-α** was assigned as 2^A,2^B-disulfonated α-cyclodextrin, as shown in Scheme 1, and furthermore, the structure of **1-β** was reconfirmed as 2^A,2^B-disulfonated β-cyclodextrin.

The conversion of the hydroxyl groups of cyclodextrins to amino groups is one of the important techniques for the modification of cyclodextrins. Hence, the transformation of 2-mono- or di-*O*-sulfonylcyclodextrins to 3-amino-3-deoxy-2(*S*),(3*R*)-cyclodextrins *via* 2,3-mannoepoxidocyclodextrins has been investigated.[7] However, a straightforward method for absolutely regiospecific A,B-diamination on the secondary face has never been reported.

Investigation into selective A,B-diamination on the secondary face showed that the staple-A,B-disulfonates prepared in the present study were very useful substrates for diamination. The treatment of **1-α** and **1-β** in 28% aqueous NH_3 at 37 °C for 5 days, followed by ion-exchange column chromatography (Sephadex CM-25) efficiently yielded the corresponding pure 3^A,3^B-diamino-3^A,3^B-dideoxy-(2*S*),(3*R*)-cyclodextrins **3-α** and **3-β** in 86 and 84% yields, respectively. The ^{1}H and ^{13}C NMR spectra of **3-α** were seen to be thoroughly identical with authentic published spectra[7b] and the structure of **3-β** was confirmed by ^{1}H and ^{13}C NMR and FAB mass spectroscopies (ESI†).

Studies on the scope and limitations of the present strategy for the absolutely regiospecific disulfonation are currently in progress.

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