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Does the Abnormal Ring Opening of Cyclodextrin-2,3-epoxide Have Generality?

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Abstract Na_2S has been found to attack the C2 of β-cyclodextrin mannoepoxide **1** more easily than various other nucleophiles, and with the subsequent CD-2-S^- only the abnormal ring opening of **1** has been observed.

Keywords: Cyclodextrin, Sugar-epoxide, Cyclodextrin Dimer.

The nucleophilic ring opening of cyclodextrin 2,3-mannoepoxides **1** [1,2] is believed to give exclusively the functional CDs with the functional groups at the C3 of an altroside residue. Since its establishment [1], most of the CD derivatives functionalized at C3 were synthesized by this method. However, the altroside residue distorts the CD cavity and decreases their binding ability towards normal guests [3,4] or even makes them lose their catalytic ability [5]. A generally applicable method is needed to make the secondary functional CDs without distorting their cavity. We found that, in addition to the main reaction at the C3, imidazole can also attack the C2 of the epoxide **1** to regenerate the glucoside structure keeping the CD cavity undistorted [6]. Is this abnormal reaction just an exception [2] or does it have generality? Our recent findings show that various sulfur- or nitrogen-containing nucleophiles can attack the C2 of **1**, just as imidazole does. The reaction of **1** with Na_2S is somewhat astonishing. The intermediate CD-2-S^- **3** predominantly accesses the C2 giving the dimer 2,2'-CD-S-CD **5** in a considerably high yield. Here we report this abnormal reaction.

A degassed mixture of **1** [1] (0.26 mmol) and Na_2S (0.12 mmol) in 5 ml DMF was stirred at 85 °C in a nitrogen atmosphere for 8 d. After the evaporation of solvent, the residue was chromatographed on a reverse-phase column. A gradient elution from H_2O to 40% *aq.* MeOH gave two CD dimers **4** (30%) and **5** (13%). FAB-MS spectra showed the expected M^+ peak at *m/z* 2267.8 and $[M+Na]^+$ peak at *m/z* 2289.5 for both **4** and **5**.

^1H- and ^{13}C NMR spectra showed the symmetric nature for both **4** and **5**. Compound **4** gave a highly resolved ^1H-NMR spectrum in which seven doublet signals can be unambiguously derived for the H1 protons. The signals related to the functional residues are the mostly shifted, and have the basic pattern of the altroside residue in the *altro*-CD [7]. The altroside structure with a predominant conformation of $^1C_4$ is also supported by the coupling

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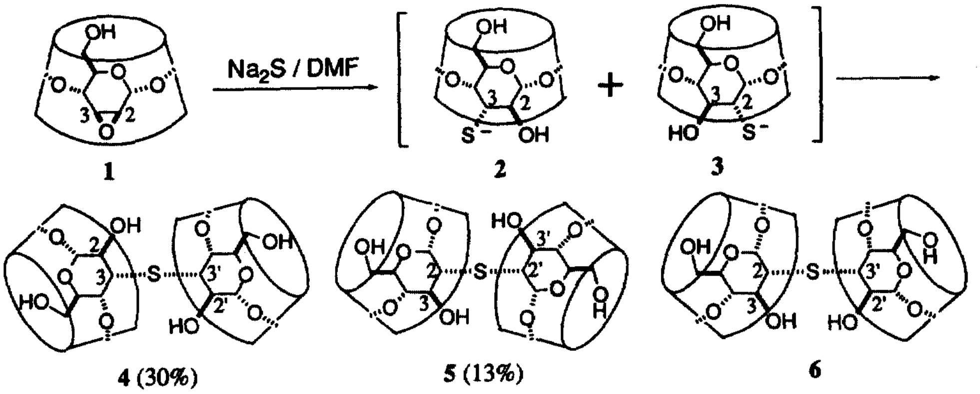

constants ($J_{1,2}$ = 7.2 Hz, $J_{2,3}$ = 11.4 Hz and $J_{3,4}$ = 3.2 Hz). The upfield shift of H3 to 3.24 ppm indicates the attachment of sulfur at C3, which is confirmed by the large upfield shift (to 51.9 ppm) of this C3. Both the ^{1}H- and ^{13}C NMR spectra of **5** are quite similar to those of β-CD. No significant shifts from the normal signals present except the peak at 51.0 ppm for the sulfur-bearing carbon C2.

The abnormal ring opening of **1** indeed has some generality. Various nucleophiles do access the C2 of **1**, leading to the formation of undistorted CD derivatives with the functional groups at the C2 [8]. However, this reaction at the C2 occurs only in a trivial extent, and the ratio of distorted product to the undistorted one is around 15 or even much higher. Based on these results, a major product **4** and a minor one **6** were expected from the reaction of **1** with Na_2S, while the homo-dimer **5** should be negligible. In fact, the unexpected dimer **5** was isolated in 13% yield. The product ratio of **4** to **5** implies that S^{2-} can accesses the C2 of **1** much more easily than other nucleophiles. What is surprising is that the crossed dimer **6** was not observed though both the homo-dimers **4** and **5** were obtained in considerably good yields. This result suggests that the C2 of **1** is the only accessible reaction site for the CD-2-S^- **3**, and CD-3-S^- **2** can only attack the C3. The ring opening of **1** requires the nucleophile to approach the reaction sites from inside the CD cavity, which may prevent the bulky CD thiolates from accessing certain reaction site.

In conclusion we have shown that the abnormal ring opening of CD mannoepoxide has generality, and by choosing suitable nucleophile it is possible to reverse the reaction selectivity and eventually lead to the selective synthesis of the undistorted secondary functional CDs.

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