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Unexpected regioselective debenzylation leading to modification of both rims of α-cyclodextrin

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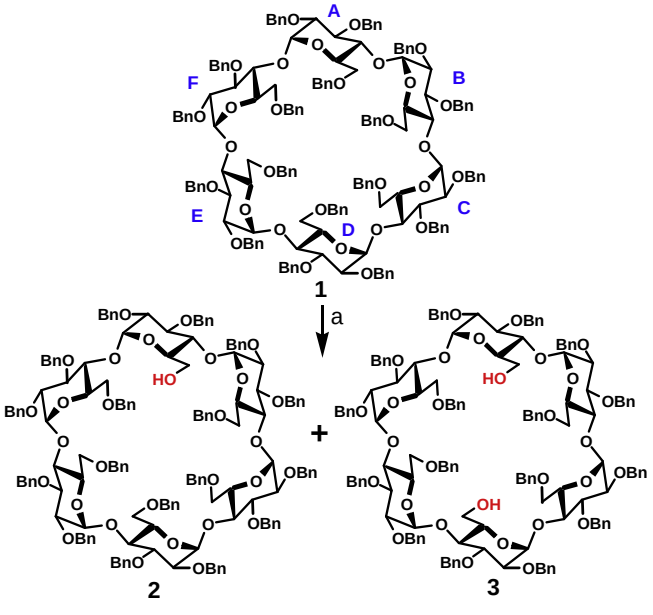
ABSTRACT

Diisobutylaluminum hydride-mediated debenzylation of perbenzylated α-cyclodextrin was investigated using modified conditions. It was found that the reaction proceeded much slower to allow a more controlled removal of benzyl groups. Prolonged reaction time led to the unprecedented observation that a cleavage of up to two benzyl groups can occur at the secondary rim in a highly regioselective manner.

Cyclodextrins (CDs)[1] are cyclic oligosaccharides consisting of 6–8 α-glucopyranosyl units. Because of their hydrophobic cavities, they have found great utilities in numerous applications such as drug carriers and food additives. Structurally modified CDs have further more potential because functional groups can be introduced to give CD molecules unusual properties.[2,3] Persubstitutions on all or different groups of hydroxyls such as those at C-6 or C-2 or C-3 are relatively straightforward[2] as methods are readily available. However, regioselective differentiation of hydroxyls of the same group is very challenging due to their identical chemical reactivities. Different methods have been reported in literature for multiple functionalizations of primary hydroxyl groups using bulky reagents,[4–7] by taking advantage of their steric hindrance, or using geometrically templated reagents.[8–13] An elegant strategy has been introduced by Sinaÿ's group[14] using diisobutylaluminum hydride (DIBAL-H) to regioselectively perform mono- and di-debenzylation from primary rim of perbenzylated CDs a few years ago. In the case of perbenzylated α-CD[15a] (**1**, Scheme 1), the second debenzylation was reported to occur in a remarkably regioselective manner to give a $6^{A},6^{D}$-O-didebenzylated compound **3** in high yields together with some mono-6-O-debenzylated intermediate **2**. Recently the mechanism of di-debenzylation has been studied thoroughly.[15] This method was later used by others to achieve various multiple functionalization of CDs in a stepwise fashion.[16,17]

In an ongoing project on CD chemistry in our laboratory we required mono- and disubstituted α-CD scaffolds and decided to use Sinaÿ's well-established method to prepare the desired compounds **2** and **3**. In the original procedure[14] the reaction was carried out in toluene using a solution of DIBAL-H in toluene. This reaction was reported to be dependent upon several variables like equivalents of DIBAL-H, concentration, temperature, and time to obtain compounds **2** and **3** in different ratios. We carried out the reaction slightly differently by using DIBAL-H in hexane as the reagent and still using toluene as the solvent, it was found that under the new conditions the debenzylations went much slower than it was reported. Using 30 equiv of DIBAL-H at 0.15 M concentration, we observed that ~85% of **1** remained even after 12 h at room temperature. This is in sharp contrast with the literature report that under similar conditions (30 equiv of DIBAL-H in toluene at 0.1 M concentration, room temperature), the reaction was 87%



Scheme 1. Regioselective mono/didebenzylations of perbenzylated α-CD.

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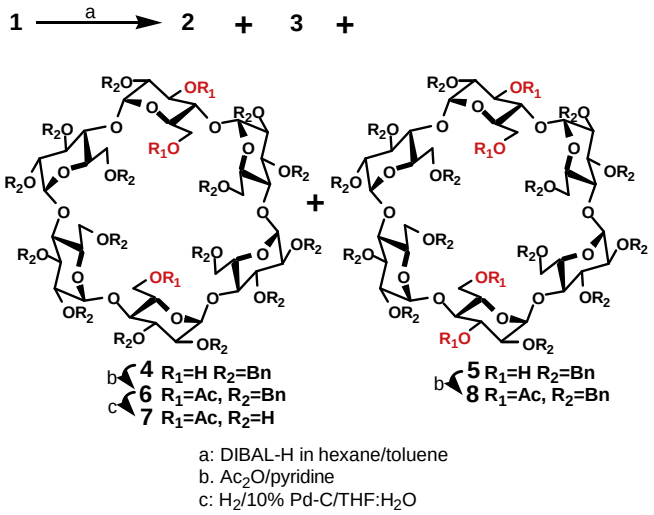
Table 1
DIBAL-H mediated stepwise debenzylation results

	Conditions[a]	1	2	3	4	5
1	30 equiv, 0.15 M, rt, 12 h	85%	10%			
2	30 equiv, 0.15 M, 50 °C, 12 h	5%	60%	20%		
3	50 equiv, 0.15 M, 50 °C, 20 h		48%	24%		
4	40 equiv, 0.9 M, 50 °C, 12 h		50%	30%		
5	40 equiv, 0.9 M, 50 °C, 24 h		15%	50%	8%	Trace
6	40 equiv, 0.9 M, 50 °C, 48 h			35%	16%	6%
7	40 equiv, 0.9 M, 50 °C, 96 h			5%	32%	10%

[a] In all conditions reported, DIBAL-H in hexane (1.4 M) was used.



Scheme 2. Stepwise debenzylations of perbenzylated α-CD.

completed in just 2 h. In our case, the desired compound **2** was isolated in ~10% yield while there was practically no didebenzylated **3** formed.

The slower reaction course in fact gave us advantage to investigate the reaction because it provides us with opportunities to perform the stepwise debenzylations in a more controlled manner (Table 1). In order to push the reaction to proceed further, we heated the reaction to 50 °C and after 12 h, we were able to isolate **2** in 60% yield and the $6^A,6^D$-O-didebenzylated **3** in 20% yield; however, we still recovered ~5% of **1** (entry 2). By carrying out the reaction for longer period (20 h) and using 50 equiv of DIBAL-H, we observed that (entry 3) the starting material **1** was completely consumed, similar yields of **2** and **3** were isolated but in the mean time, some more polar spots started to form as seen from TLC, indicating further debenzylations. By subjecting the reaction to less equivalents of DIBAL-H but at a higher concentration (0.9 M), **2** and **3** were obtained in 50% and 30% yields, respectively, after 12 h at 50 °C (entry 4); however, when gradually prolonging the reaction time under the same conditions, we observed (entries 5–7) the formation of two more polar compounds **4** and **5** (Scheme 2) which became majorities (entry 7) when we continued the reaction for 4 days at 50 °C and were isolated in 32% (**4**) and 10% (**5**) yields (Table 1). Other minor products were also formed but could not be isolated in pure forms. Subjecting the reaction for more than 4 days did not improve the yields of compounds **4** and **5**, leading to the formation of mixtures of further debenzylated products.

In the ^{1}H NMR spectra of compound **4**[18] (Fig. 1) it was difficult to determine the number of benzyl groups removed. However, after we performed an acetylation (→**6**), we observed in the ^{1}H NMR of **6** three singlets at 2.01, 2.10, and 2.11 ppm, indicating that compound **4** had triple debenzylations; more interestingly, we found a proton signal at 5.80 ppm which appeared as a doublet of doublets with large coupling constant (J = 9.9, 9.9 Hz), indicating that it is one of the H-3 protons of the glucopyranosyl units. Clearly the debenzylation went to the secondary face of α-CD. Due to the interference from the numerous benzyl groups, 2D NMR experiments did not help to conclude the structure. Therefore, a complete debenzylation was performed under catalytic hydrogenolysis to give **7**. The ^{1}H 2D TOCSY experiment of **7** (Fig. 2) unambiguously revealed that the O-3 debenzylation occurred at one of the glucopyranosyl units which had a prior O-6 debenzylation as correlation peaks were observed to the same anomeric proton for both the downfield shifted H-3 and a pair of H-6 protons which are also downfield shifted (4.66 and 4.36). This confirms that compound **4** was $3^A,6^A,6^D$-tri-O-debenzylated.

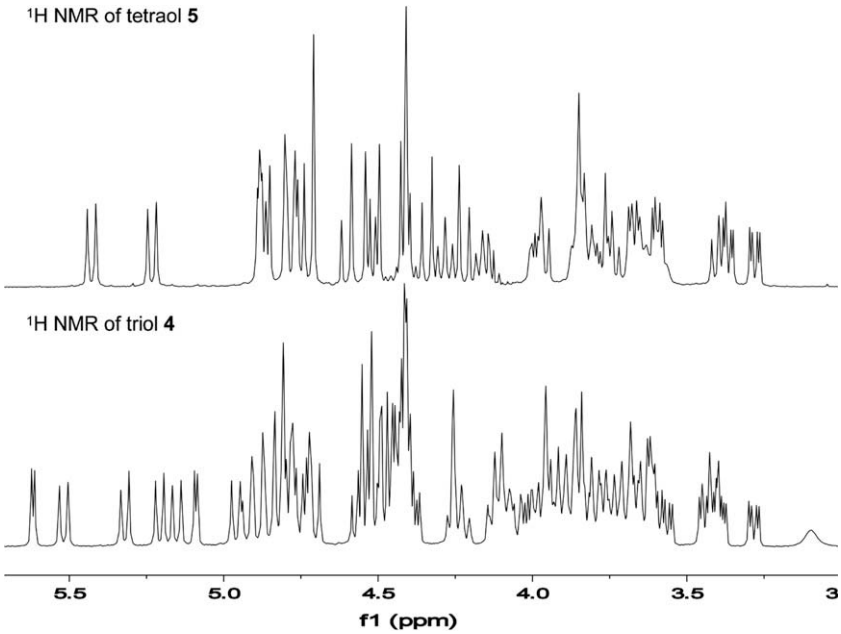


Figure 1. 1D ^{1}H of compounds **4** and **5** in $CDCl_3$ (400 MHz).

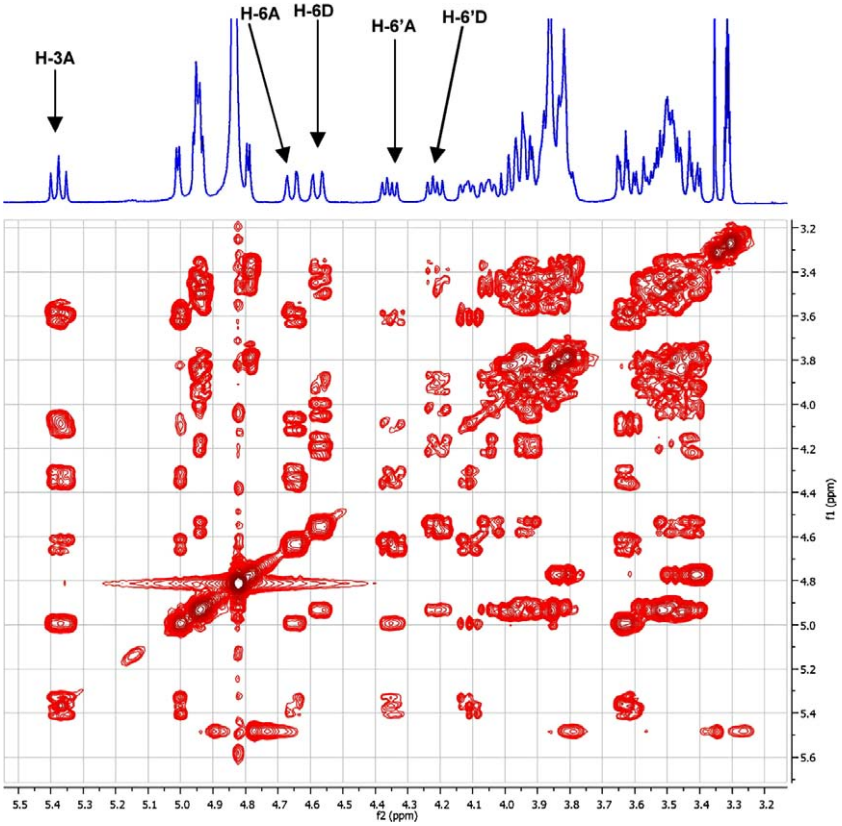


Figure 2. A subset of 2D TOCSY spectra of **7** in CD_3OD (400 MHz).

For the more polar compound **5**[18], both its ^1H (Fig. 1) and ^{13}C NMR spectra appeared much simpler than **4**; a C2 symmetry seemed to be present in the molecule. To confirm the structure of **5**, it was acetylated to give compound **8** in quantitative yield.

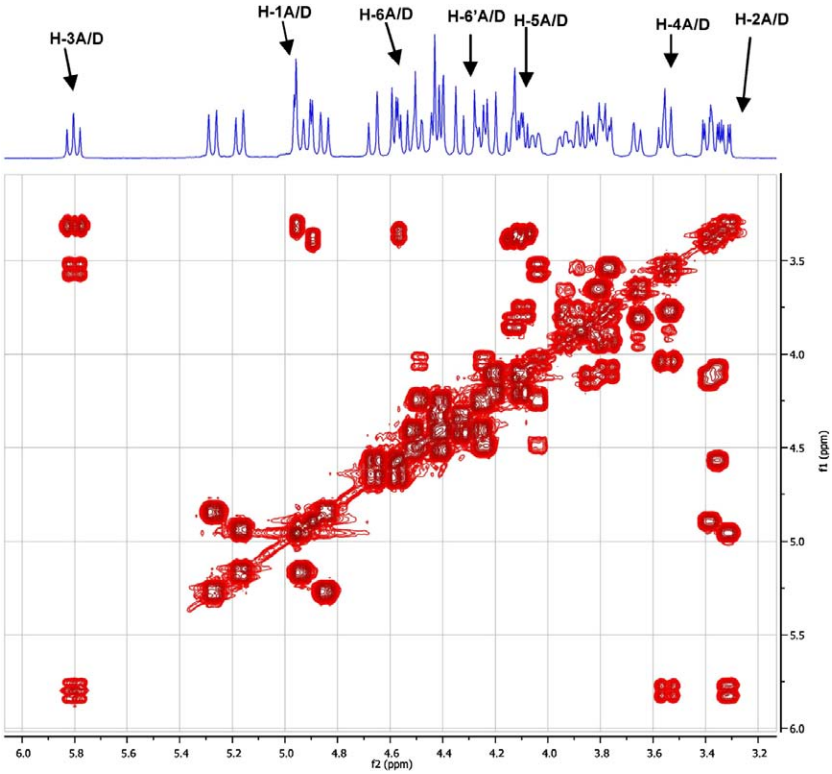


Figure 3. A subset of 2D COSY spectra of **8** in $CDCl_3$ (400 MHz).

In the ^{1}H NMR spectrum of **8**, it shows integration of aromatic protons as half (35) than the expected (70) and two sets of acetate peaks and also one set of H-3 at 5.8 ppm with large coupling constants (dd, J = 9.9, 9.9 Hz) indicating that compound **8** has a C2 symmetry which is consistent with the observed structural feature for **5**. The observation of only one set of downfield shifted H-3 and two sets of acetate protons in **5** indicates that a tetra-O-debenzylation took place; the third and fourth debenzylations regioselectively went to the same positions (O-3's of A and D units) at the secondary face. Both the COSY (Fig. 3) and TOCSY experiments of **8** confirmed that the third and fourth debenzylations occurred at the O-3 positions of glucopyranosyl units which had a prior O-6-debenzylation. These indicate that the original compound **5** was 3^A,6^A,3^D,6^D-tetradebenzylated.

The mechanistic origin of the regioselectivity in the tri- and tetra-debenzylations of α-CD is still unknown. Considering the first and second debenzylations occurred at the O-6 positions of the A and D rings, and within the same glucopyranosyl units, the O-3 and O-6 positions are located at the same face of the pyranose ring, we hypothesized that there might be an intramolecular coordination to the O-3 by aluminum that was attached to the O-6 after the first and second debenzylations; the coordination activated the O-benzyl linkage, making it prone to be attacked by another molecule of DIBAL-H, thus leading to the preferential removal of the benzyl groups at O-3 position of the glucopyranosyl unit which had a prior O-6 debenzylation. We are currently carrying out a more detailed study on the debenzylation mechanism.

This is the first report that debenzylation of perbenzylated α-CD has occurred at both rims of α-CD and in a regioselective fashion. The one-pot reaction progresses from primary face to secondary face giving a new triol (32%) and a symmetric tetraol (10%) which were unable to obtain previously. These well-defined structures should allow easy access to uniquely modified CD derivatives requiring simultaneous modifications at both faces. Currently we are investigating the stepwise debenzylations of other CD structures and also exploring the utilities of these novel compounds with unique topology.

Acknowledgments

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18. *General method for debenzylations*: To a solution of perbenzylated α-cyclodextrin[15a] in toluene, was added 40 equiv of DIBAL-H (1.4 M solution in hexane) with stirring under argon atmosphere at room temperature. Reaction is then carried out according to the conditions reported in Table 1. The reaction was then quenched by pouring the reaction mixture into ice-cold water and the mixture was diluted with EtOAc (50 mL). After filtering through Celite, water was added to the filtrate and the organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel. Selected data for **4**:.R_f = 0.45 (6:4 hexane/ethyl acetate) $[\alpha]_D^{25}$: +42.2° (*c* 0.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.07 (m, 75H, Aromatic), 5.62 (d, J = 4.0 Hz, 1H, H-1), 5.52 (d, J = 11.0 Hz, 1H, PhCH), 5.32 (d, J = 10.6 Hz, 1H, PhCH), 5.21 (d, J = 10.8 Hz, 1H, PhCH), 5.15 (d, J = 11.2 Hz, 1H, PhCH), 5.09 (d, J = 3.8 Hz, 1H, H-1), 5.01–4.67 (m, 13H, 4 × H-1, 9 × PhCH), 4.59–4.36 (m, 17H, 17 × PhCH), 4.29–4.19 (m, 2H), 4.16–3.53 (m, 30H), 3.48–3.36 (m, 4H), 3.28 (dd, J = 3.5, 9.9 Hz, 1H, H-2), 3.10 (br s, 1H, OH), 2.76 (br s, 1H, OH). ESI-MS *m/z* 2345 $[M+Na]^+$. Selected data for **5**:.R_f = 0.25 (6:4 hexane/ethyl acetate) $[\alpha]_D^{25}$: +50.8° (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.06 (m, 35H, aromatic), 5.44 (d, J = 11.2 Hz, 1H, PhCH), 5.24 (d, J = 11.2 Hz, 1H, PhCH), 4.94–4.84 (m, 3H, 2 × PhCH+H-1), 4.83–4.70 (m, 4H, 2 × PhCH, H-1), 4.61 (d, J = 13.0 Hz, 1H, PhCH), 4.53 (m, 2H, PhCH), 4.46–4.38 (m, 3H, PhCH), 4.35 (d, J = 13.0 Hz, 1H, PhCH), 4.29 (dd, J = 9.33, 9.70 Hz, 1H, H-3), 4.23 (d, J = 13.0 Hz, 1H, PhCH), 4.17 (dd, J = 9.16, 8.56 Hz, 1H, H-3), 4.04–3.94 (m, 2H, H-3, H-6), 3.90–3.72 (m, 6H, 3 × H-5, 2 × H-4, 1 × H-6), 3.71–3.56 (m, 5H, 4 × H-6, 1 × H-2), 3.45–3.35 (m, 2H, H-4, H-2), 3.29 (dd, J = 3.4, 10.0 Hz, 1H, H-2). ESI-MS *m/z* 2233 $[M+H]^+$.