Host–Guest Systems

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Easy Access to Modified Cyclodextrins by an Intramolecular Radical Approach**

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Abstract: *A simple method to modify the primary face of cyclodextrins (CDs) is described. The 6^{I}-O-yl radical of α-, β-, and γ-CDs regioselectively abstracts the $H5^{II}$, located in the adjacent* D*-glucose unit, by an intramolecular 1,8-hydrogen-atom-transfer reaction through a geometrically restricted nine-membered transition state to give a stable 1,3,5-trioxocane ring. The reaction has been extended to the 1,4-diols of α- and β-CD to give the corresponding bis(trioxocane)s. The C_2-symmetric bis(trioxocane) corresponding to the α-CD is a stable crystalline solid whose structure was confirmed by X-ray diffraction analysis. The calculated geometric parameters confirm that the primary face is severely distorted toward a narrower elliptical shape for this rim.*

The design of nanosystems as novel drug carrier systems which allow controlled release is currently a topic of great relevance in medical research for the treatment of a wide variety of diseases, including cancer therapy.[1] In this regard, cyclodextrins (CDs) are of interest as nanocarriers because of their ability to encapsulate biomolecules.[2] These naturally occurring macrocyclic oligosaccharides, composed of 1,4-α-linked glucose units, are conical in shape and have an internal cavity creating a hydrophobic microenvironment, whereas the outside is hydrophilic because of the presence of hydroxy groups.[3] These properties are responsible for their aqueous solubility and ability to form host–guest or inclusion complexes with a wide range of molecules, thus making them one of the most important supramolecular host families. These features illustrate the potential utility of CDs as drug- and gene-delivery vehicles,[4] enzyme mimics,[5] or catalysts,[6] among others.

Native CDs are rarely well-suited to pharmaceutical applications, so modification is necessary to tune their chemophysical properties for enhancing their solubility, changing the cavity size, or improving their complexing ability. By taking advantage of the different accessibility and reactivity of the hydroxy groups, efficient and selective chemical modifications have been carried out by allowing, for instance, the grafting of substituents at different positions to access amphiphilic CDs,[7] and hence fascinating molecular architectures.[8] It is also worth mentioning that there are synthetic reports describing significant changes in the shape of the cavity by altering the conformation of glucose residues.[9] Despite the great deal of methodologies employed, radical processes are practically unknown in these macromolecules because in simple carbohydrates they mostly involve the anomeric position, which is committed in the cyclic CD structure.[10] In fact, we have found a single example in the literature concerning intermolecular radical attack on CDs and it is based on EPR experiments with reactive-oxygen-centered free radicals generated in aqueous solutions.[11]

As part of our ongoing research program on radical chemistry in carbohydrates, we have recently described a novel 1,8-hydrogen-atom-transfer reaction (1,8-HAT) between the two pyranose units in Hex*p*-(1→4)-Hex*p* disaccharide systems through a nine-membered transition state (TS).[12] The process is initiated by a primary 6^{I}-*O*-yl radical (**A**), generated under oxidative conditions, which regioselectively abstracts the hydrogen atom at $C5^{II}$ to give a C5 radical (**B**; Scheme 1). Then, after a one-electron oxidation, **B** collapses into the 1,3,5-trioxocane **D** via an oxacarbenium ion intermediate (**C**). Alternatively, **A** may abstract the $H1^{II}$ through a seven-membered TS to generate a C1 radical (**E**) which finally stabilizes via the oxacarbenium (**F**) to give the spiro-orthoester **G**. We have demonstrated that this regioselectivity is not only dependent on the configuration of the four chiral centers implicated in the cyclization step ($C5^{II}$, $C1^{II}$, $C4^{I}$, and $C5^{I}$), but also on the conformations of the glycosidic ($\Phi = H1^{II}\text{-}C1^{II}\text{-}O4^{I}\text{-}C4^{I}$) and aglyconic ($\Psi = C1^{II}\text{-}O4^{I}\text{-}C4^{I}\text{-}H4^{I}$) bonds.

In a disaccharide with an arrangement of α-D-Glc*p*-(1→4)-β-D-Glc*p* (β-maltose) the 6^{I}-*O*-yl radical exclusively abstracts the $H5^{II}$ to give a trioxocane ring in a stable boat-chair conformation.[12a] In the TS involved in the 1,8-HAT, the glycosidic bond adopts an *exo-syn* conformation with torsion angles ($\Phi = -32.7$, $\Psi = -37.3°$) leading to an ideal distance of 3.1 Å between the alkoxyl radical and the $H5^{II}$, which can

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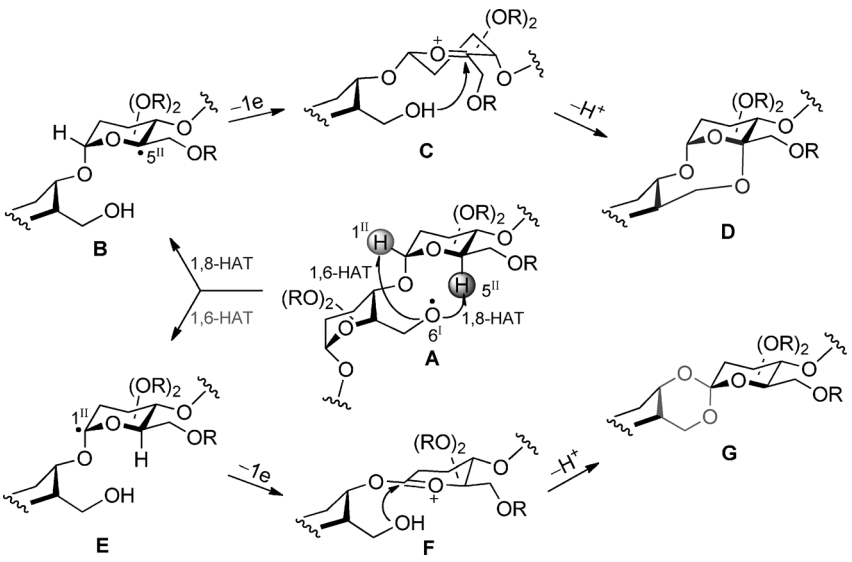


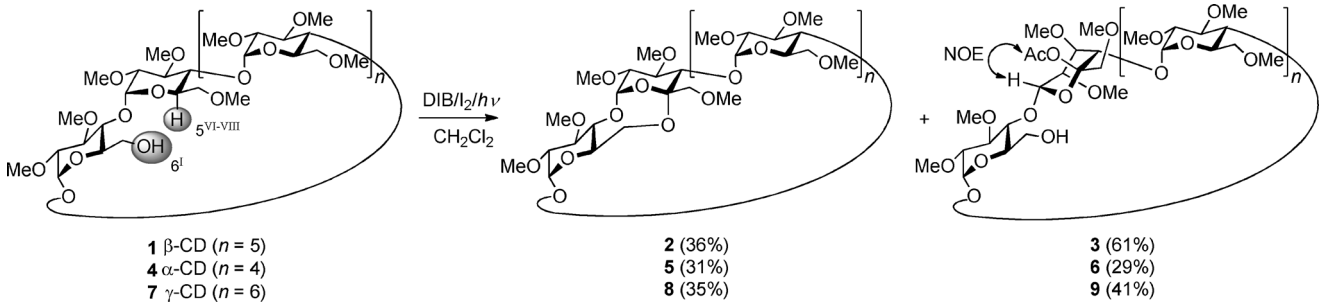
Scheme 1. HAT reactions in Hex*p*-(1→4)-Hex*p* systems.

potentially be abstracted. We wondered whether this radical methodology might be suitably deployed for remote functionalization in more complex carbohydrate systems such as CDs where the D-glucose units are linked in a similar fashion (cyclo-[α-D-Glc*p*-(1→4)]$_n$). Preliminary observations made on the X-ray structure of permethylated β-CD show that the macrocyclic ring has sufficient inter-residue flexibility to permit the glycosidic and aglyconic bonds adopt an *exo-syn* conformation with values of Φ and Ψ similar to those of β-maltose.[13] The analogous situation is obtained over a minimized structure of permethylated β-CD and therefore, we anticipated that the 1,8-HAT process between two vicinal units could take place with high regioselectivity.[14] If this strategy succeeded, it could provide facile access to modified CDs on their primary face, CDs which are difficult to obtain by conventional methods, and which could show significant deformations in their cavities.

To test the viability of the radical process, we initiated our investigations by preparing $2^{I–VII}$,$3^{I–VII}$,$6^{II–VII}$-icosa-*O*-methyl-β-CD (**1**)[15] according to a three-step literature procedure, where all the hydroxy groups, with the exception of a primary one, are transformed into methyl ethers. Such protecting groups usually lead to an increase in solubility both in water and in organic solvents (Scheme 2).[16] Excitingly, when we treated **1** with (diacetoxyiodo)benzene (DIB) (2.2 equiv) and I_2 (1 equiv) under irradiation with visible light at 30 °C, it was found that the reaction proceeded very fast, with complete consumption of the starting material after 30 minutes, to give two main products in near quantitative overall yield: the expected trioxocane derivative **2** (36 %) together with the acetate **3** (61 %) as the major compound. A minor side reaction involving a competitive intermolecular addition of external nucleophilic acetate ion coming from the reagent to the oxacarbenium ions has also occasionally been observed in disaccharide systems.[12a,14] If we decreased the temperature or the equivalents of DIB or I_2, the reaction became slower and did not go to completion. However, when we increased the reaction time or the amount of DIB and I_2, the **2** was obtained in 60 % yield as the only product.

The NMR data of **2** clearly indicate that oxidation has taken place at $C5^{VII}$. Accordingly, the presence of seven anomeric carbon atoms in the range of $\delta_C = 96.97–99.39$ ppm and the HMBC correlation of the $H1^{VII}$ proton signal at $\delta_H = 5.06$ ppm with the $C5^{VII}$ quaternary carbon atom ($\delta_C = 101.04$ ppm) confirm the formation of the trioxocane moiety. Moreover, all D-glucopyranose units are in $^4C_1$ chair conformations as can be deduced from the values of the coupling constants of the anomeric hydrogen atoms ($J_{1,2} \approx 3.6$ Hz).

In contrast, the acetate group at $C5^{VII}$ of **3** could be clearly established by two-dimensional (2D) HSQC and HMBC experiments, whereas the observed deshielding of the ring hydrogen atoms in this unit VII and the values of their coupling constants ($J_{1,2} = 1.9$, $J_{2,3} = 2.5$, $J_{3,4} = 1.9$ Hz), determined on the basis of one-dimensional (1D) TOCSY experiments, deviate considerably from those of the normal $^4C_1$ chair and were more consistent with a $^1C_4$ chair conformation. The stereochemistry of the quaternary $C5^{VII}$ was tentatively assigned as *R* on the basis of an NOE interaction between $H1^{VII}$ and the methyl of the acetate group. These results suggest that the nucleophilic attack of the acetate proceeded with inversion of configuration at $C5^{VII}$ and consequently the original α-D-glucopyranose unit has been transformed into



1 β-CD (*n* = 5)
4 α-CD (*n* = 4)
7 γ-CD (*n* = 6)

2 (36%)
5 (31%)
8 (35%)

3 (61%)
6 (29%)
9 (41%)

Scheme 2. 1,8-HAT for the 6^I-ol-α-CD **1**, 6^I-ol-β-CD **4**, and 6^I-ol-γ-CD **7**. DIB = (diacetoxyiodo)benzene.

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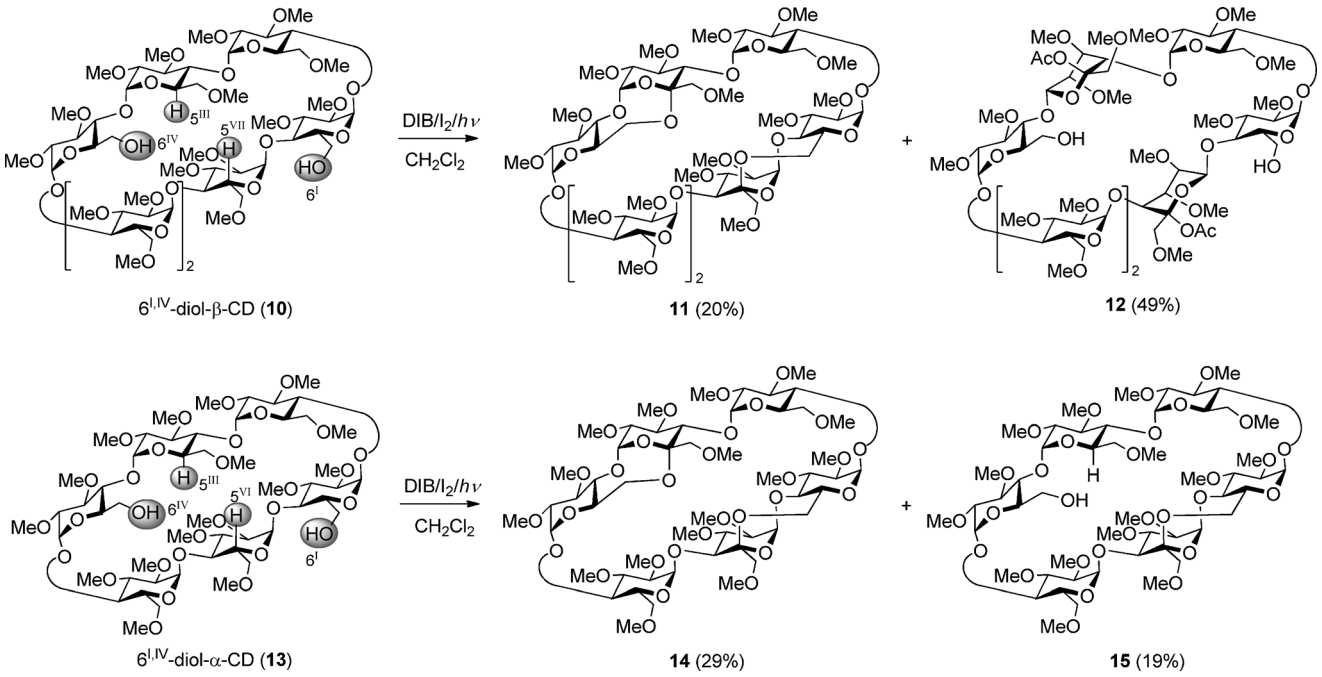

Scheme 3. 1,8-HAT for the $6^{I,IV}$-diol-β-CD **10** and $6^{I,IV}$-diol-α-CD **13**.

a β-L-idopyranose adopting a $^1C_4$ chair conformation. It is evident that both products are formed by the same $C5^{VII}$ radical intermediate, promoted by the alkoxyl radical, through an intramolecular 1,8-HAT process. No products functionalized at $C1^{VII}$ by the alternative 1,6-HAT reaction were detected. As far as we know, the presence of a sugar unit with a structure of β-L-idopyranose as part of a β-CD ring has no literature precedent.

Encouraged by these preliminary results, we decided to extend the reaction to the monoalcohols derived from the α-CD **4**[17] and the γ-CD **7**,[18] which were prepared following the same procedure used for the 6^I-ol-β-CD derivative. Pleasingly, both compounds behaved in an analogous manner to that of the β-CD derivative, albeit generating the corresponding trioxocane derivatives **5** and **8** and acetates **6** and **9**, in somewhat lower overall yields (Scheme 2). We soon realized that **6** and **9** were undergoing complete hydrolysis during the standard purification process, thus giving exclusively the trioxocane derivatives **5** and **8**, respectively, and this is most likely responsible for the lower yield observed. Notwithstanding, the pure acetates **6** and **9** were obtained by avoiding the typical aqueous workup, and after careful flash-column chromatography using silica gel scraped from commercial coated TLC plates (see the Supporting Information). In contrast, the trioxocane derivatives are stable for extended periods of time at room temperature.

The structures and conformations of **6** and **9** were analogously confirmed by 1D TOCSY and 2D HSQC and HMBC experiments. Of particular relevance are the differences observed in the conformation of unit VI of **6** by changing the solvent from $CDCl_3$ to C_6D_6. Thus, in $CDCl_3$ small coupling constants were noted in the 1D TOCSY experiment for all the vicinal ring protons ($J_{1,2}=2.8$, $J_{2,3}=3.2$, $J_{3,4}=2.8$ Hz), thus suggesting a predominant $^1C_4$ chair conformation, while in C_6D_6 these values ($J_{1,2}=3.5$, $J_{2,3}=8.5$, $J_{3,4}=7.9$ Hz) preferentially point to a $^4C_1$ conformation. These observations are in contrast with the acetates derived from the β-CD **3** and γ-CD **9**, which show the same $^1C_4$ conformation in both solvents.

To assess the versatility and scope of this methodology we investigated the feasibility of applying the same procedure to the 1,4-diols of β- and α-CD to determine whether the two hydroxy groups can participate in two 1,8-HAT reactions simultaneously. The reaction of the $6^{I,IV}$-diol-β-CD derivative **10**[15a] with DIB (3 equiv) and I_2 (1.7 equiv) afforded four products in good overall yield: the bis(trioxocane) compound **11** (20%), bis(acetyl) derivative **12** as the major product (49%), and a mixture of monotrioxocane-monoacetyl derivatives (14%, see the Supporting Information) which could be transformed into **11** after treatment with iodine (Scheme 3). The NMR characteristics of **12** clearly indicate that the introduction of both acetates in the corresponding D-glucose units III and VII has taken place with inversion of configuration at C5. Accordingly, the deshielding of the hydrogen atoms of these units and their small coupling constants ($J\approx1.9$–2.5 Hz) confirmed the presence of two β-L-idopyranose units, both in $^1C_4$ chair conformations. Moreover, the NOE experiments show an interaction between $H1^{VII}$ or $H1^{III}$ and the respective methyl groups of the acetate, thus tentatively establishing the absolute configuration at $C5^{VII}$ and $C5^{III}$ as *R*.

Finally, we carried out the reaction with the $6^{I,IV}$-diol-α-CD derivative **13**.[17,19] The bis- and mono-trioxocanes, **14** and **15**, respectively, were the only compounds obtained in the reaction, and no product from the incorporation of acetate in the molecule was detected, thus revealing the greater steric hindrance in this hexamer (Scheme 3). The structures of both products were determined by 1D and 2D NMR experiments.

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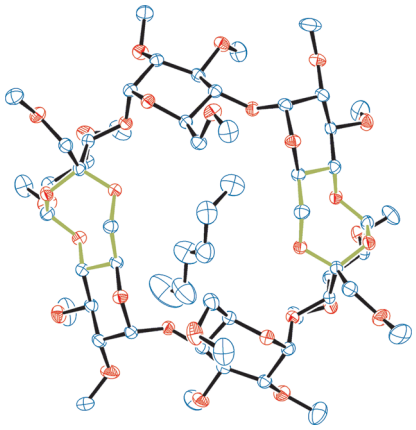

Figure 1. X-ray crystal structure of **14**. C blue, O red, H atoms not shown. Thermal ellipsoids drawn at 50% probability.

Furthermore, **14** is a stable crystalline solid whose structure was unambiguously confirmed by X-ray crystallographic analysis, thus showing two 1,3,5-trioxocane rings in boat-chair conformations with a guest *n*-hexane molecule in the CD cavity (Figure 1).[20] As expected, the NMR spectra are consistent with the C_2 symmetry of the proposed structure.

The comparison of the geometrical parameters of **14** with those of the related permethylated α-CD[21] shows that the presence of the two 1,3,5-trioxocane rings does not significantly alter the secondary face of the molecule (see Tables S2 and S3 in the Supporting Information). Thus, for instance, the distances and angles between the six interglycosidic oxygen atoms ($O4^n$), as well as the radii of the gravity center of the hexagon formed by these $O4^n$ oxygen atoms are quite similar in both X-ray structures. The trioxocane rings do not seem to affect the $^4C_1$ chair geometries of the six glucose units, as shown with the Cremer–Pople puckering parameters which describe slightly distorted chairs similar to those found in the permethylated α-CD.[22] The most significant differences are observed in the tilt angles made by the $O4^n$ mean plane and the mean planes through the glucose units principally in residues II and V adjacent to the trioxocane rings. However, the trioxocane rings severely distort the primary face of the molecule. This distortion is clearly observed when comparing the geometrical parameters of the irregular hexagon comprising the side-chain carbon atoms ($C6^n$), which points toward a much narrower elliptical shape for this rim (see Tables S2 and S3).

In summary, the remote C–H functionalization initiated by 6-*O*-yl radicals proceeds with complete regioselectivity in α-, β-, and γ-cyclodextrin models because of very suitable geometrical requirements which favor the TS of an intramolecular 1,8-HAT process between two contiguous units of the macromolecule. To the best of our knowledge, this is the first time that a radical approach is applied to access modified CDs with significant deformations on the primary face. The mild reaction conditions and high efficiency are the key features of this procedure with potential synthetic and pharmaceutical applications. The possibility to apply this methodology not only to monoalcohols but also to 1,4-diols and carry out two 1,8-HAT processes simultaneously, opens the way to generating more complex CD systems. Work in this sense is now in progress and will be reported in due course.

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