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Artificial enzyme activity from cyclodextrins with cyanohydrins on the secondary rim

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ABSTRACT

The synthesis of two per-O-methylated cyclodextrins with one or two α-hydroxypropionitrile groups attached to the secondary rim is described. The two new cyanohydrins are found to catalyse the hydrolysis of 4-nitrophenyl β-D-glucopyranoside in a buffer solution at pH 8.0 with a rate acceleration of up to 1770.

Enzymes are outstanding catalysts both in terms of efficiency[1] and selectivity, and are therefore potentially ideal catalysts in chemistry. Their ability to catalyse reactions in water under environmentally friendly conditions is also highly favourable. Yet, the practical use of enzyme catalysis is severely limited to reactions that occur naturally, or those that are very similar to biological reactions. Enzyme models or mimics that can perform enzyme catalysis on non-biological reactions or on different substrates are therefore highly desirable.

Chemzymes, or artificial enzymes, are small organic compounds that display enzyme catalysis, that is, the catalyst binds the substrate, converts it into the bound product and then releases it.[2] Cyclodextrin derivatives have proven to be some of the most successful artificial enzymes, but even among these molecules the number of successful catalysts, that actually display Michaelis–Menten kinetics, is quite small.[3] One of the problems with cyclodextrins is perceived to be a tendency to indiscriminate binding allowing guests to bind from both faces of the cavity and with opposite orientations (Fig. 1). O-methylation may be a solution to this problem as it is believed to essentially close the primary face to binding.[4] This is supported by crystallographic studies of complexes of permethylated and native cyclodextrins which show that they frequently bind guests in opposite orientations.[5]

Previously, we have shown that cyclodextrins with one or more cyanohydrins on the primary face catalysed glycoside hydrolysis.[6–9] The reaction followed Michaelis Menten catalysis and gave rate accelerations of up to 10,000, which was 10–100 times faster than a cyclodextrin with a carboxylic acid attached to the primary rim in the same position.[10] The proposed catalytic mechanism involves binding of the aryl group of the substrate in the cyclodextrin cavity with the glycoside extending from the primary phase (mode 1, Fig. 1), as this allows the cyanohydrin to function as a general acid catalyst protonating the exocyclic oxygen of the glycoside bond.[9] Nevertheless, 4-nitrophenyl glucoside can undoubtedly bind to β-cyclodextrin with the carbohydrate extending from either face (mode 1 or 2, Fig. 1), and it is therefore possible that a cyclodextrin with the cyanohydrin on the secondary face would be a better catalyst. In the present work, we have investigated this idea and devised a synthesis of two cyclodextrins with cyanohydrins on the secondary rim. To maximize the preference for substrate binding on the secondary face, we decided to prepare the O-methylated derivatives **1** and **2** (Fig. 2) that possess either one or two cyanohydrin groups.

The synthesis of the monocyanohydrin **1** started from the known 2-*O*-allyl-per-*O*-methyl-β-cyclodextrin (**3**) (Scheme 1).[11] This compound was prepared by $2^A,3^B$-di-desmethylation of permethylated β-cyclodextrin[12] followed by selective *O*-allylation of the 2^A-alcohol and remethylation of the 3^B-alcohol.

Subsequent dihydroxylation of the allyl group in **3** using osmium tetroxide and morpholine *N*-oxide (NMO) gave the diol **4** in 71% yield as a 1:1 mixture of diastereomers. Subsequent treatment of **4** with silica-supported sodium periodate,[13] a reagent suited to diol-cleavage in an organic solvent, gave the aldehyde **5** in 98% yield. Treatment of **5** with excess potassium cyanide and ammonium chloride in a 1:1:1 mixture of Et_2O, methanol and

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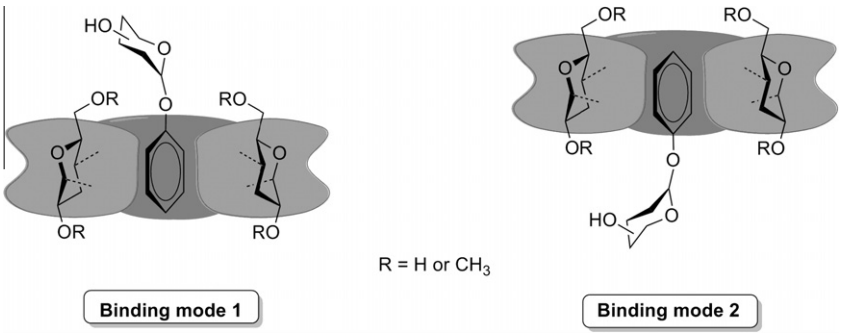


Figure 1. The two binding modes of a phenyl glycoside guest to a cyclodextrin.

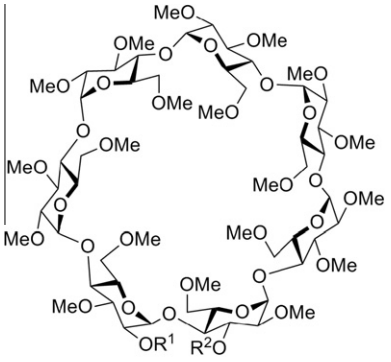
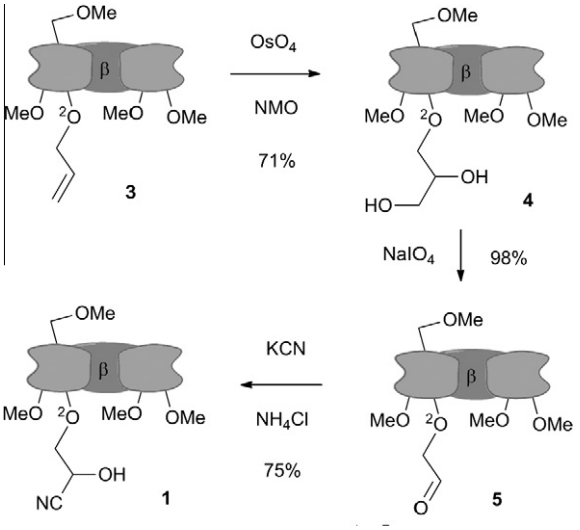


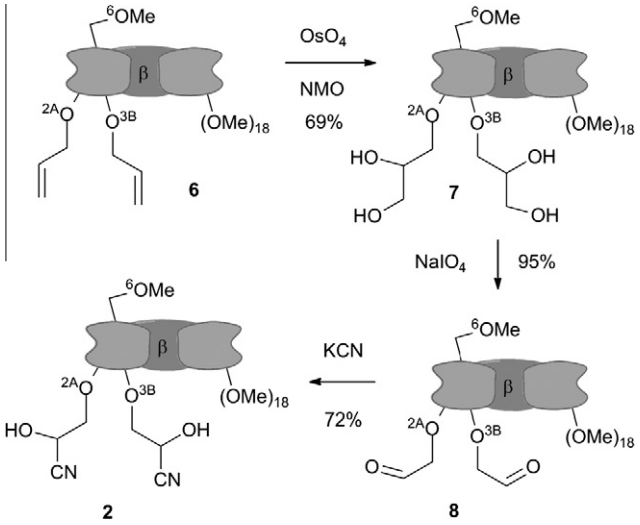
Figure 2. Target compounds **1** and **2**.



Scheme 1. Synthesis of monocyanohydrin **1**.

water gave the cyanohydrin **1** in 75% yield as a 2:1 mixture of diastereoisomers.

Similarly the dicyanohydrin **2** was prepared from the diallyl derivative **6**[11] (Scheme 2), the latter being obtained by diallylation of $2^A,3^B$-di-desmethyl-per-O-methylated β-cyclodextrin. Dihydroxylation of **6** with OsO_4/NMO gave the tetrol **7** in 69% yield as a mixture of four diastereomers. Reaction of **7** with silica-supported periodate in dichloromethane gave the dialdehyde **8** in 95% yield. Finally, treatment of **8** with KCN/NH_4Cl in water/MeOH/Et_2O



Scheme 2. Synthesis of dicyanohydrin **2**.

(1:1:1) gave dicyanohydrin **2** in 72% yield. This compound was a mixture of four diastereomers (at the cyanohydrin stereocentres).

Compounds **1** and **2** were investigated as catalysts for the hydrolysis of the 4-nitrophenyl glucopyranoside **9** (Fig. 3). Both **1** and **2** showed excellent catalysis of this reaction: adding 0.15–0.4 mM of the modified cyclodextrin to a concentration of 1.5–24 mM of the substrate **9** in phosphate buffer increased the rate of hydrolysis 2–4 times. By determining the rate at different substrate concentrations and using the Michaelis–Menten equation the kinetic parameters shown in Table 1 were obtained. For substrate **9** the k_{cat} values of **1** and **2** were over 100 times higher than that of the methylated cyclodextrin **13** (Fig. 4) that has the cyanohydrin group attached to the primary face (Table 1 and Table

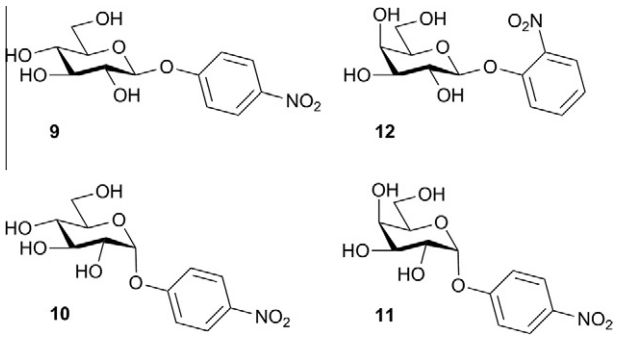


Figure 3. Substrates **9**–**12**.