Highly Shape-Selective, Biomimetic, and Efficient Deprotection of Carbonyl Compounds Masked as Ethylene Acetals or Dioxolanes Produced from 1,2-Ethanediol

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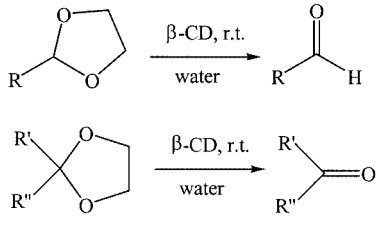
A simple, mild, efficient, and organic solvent-free biochemical approach for the deprotection of carbonyl compounds protected as 1,3-dioxolanes through the use of cyclodextrins as catalysts has been developed.

Introduction

Selective protection and deprotection of carbonyl groups can be of great importance in the course of a total organic synthesis.[1−4] Of the various protecting groups for carbonyl groups, the protection of carbonyl compounds as their acetals and ketals has found wide application in the multistep synthesis of organic molecules.[5−18] The hydrolysis of acetals and ketals to regenerate their corresponding carbonyl compounds is also of interest to synthetic organic chemists. Recently, considerable interest has been focused on mild, selective methods for acetal and ketal deprotection.[19−38] Most of the general methods used for the cleavage of acetals and ketals involve a variety of catalyst systems, such as bismuth triflate/THF/H_2O,[19] $KMnO_4$ supported on alumina,[32] decaborane/THF/H_2O,[20] pyridinium poly(hydrogen fluoride)/CH_3CN,[23] bismuth nitrate pentahydrate/CH_2Cl_2,[24] ceric ammonium nitrate/CH_3CN/borate/HCl,[26] or (trimethylsilyl)bis(fluorosulfuryl)imide/CH_2Cl_2.[27] Although many mild methods used for deprotection of acetals and ketals have been developed, some of the reported methods for deprotection of the such species still suffered from one or more disadvantages, such as low product yields, high cost or toxicity of the reagents, long reaction times, elevated temperatures, and tedious workups. In view of these limitations of the existing procedures, a totally new, mild, economical, and safe approach under neutral conditions with water as solvent was recently developed,[39] based on the use of commercially available, biomimetic, naturally occurring catalysts: cyclodextrins (CDs). Aromatic acetals were deprotected to regenerate the corresponding aldehydes by use of β-CD in water at 50 °C. In our earlier research, we had also discovered this biomimetic approach for deprotection of aromatic acetals by use of β-CD under mild reaction conditions. Furthermore, the corresponding ethylene acetals and dioxolanes produced through protection with 1,2-ethanediol can be smoothly deprotected to generate the corresponding aldehydes and ketones; surprisingly, some of these deprotections can be accomplished even at room temperature.

Results and Discussion

Efficient CD-catalyzed deprotection of ethylene acetals and dioxolanes was achieved here with the use of water as the only solvent (Scheme 1). These reactions do not need any other additive, and many deprotection reactions can even be performed at room temperature.



Scheme 1

The experimental procedure is extremely simple. The reactions were performed by dissolving CDs in water, fol-

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Table 1. Deprotection of **1** with different CDs

Entry[a]	Catalyst	Catalyst mass (mmol)	Conv. (%)	Yield (%)[b]
1	β-CD	1	100	> 99
2	β-CD	0.5	87	87
3	β-CD	0.1	34	34
4	α-CD	1	< 0.5	< 0.5
5	γ-CD	1	< 0.5	< 0.5
6	−	−	0	0

[a] Reaction conditions: **1** (2 mmol), water (25 mL), 2.5 h, room temp. (no reflux), Ar. [b] Yield of product was determined by GC-MS with a DB-1 (25m) column by use of an internal standard. In all cases, product was exclusively obtained.

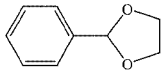
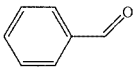
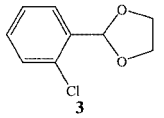
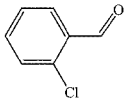
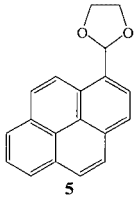
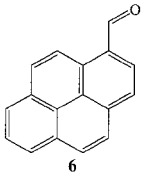
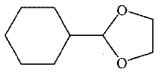
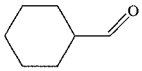
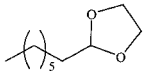
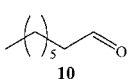
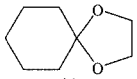
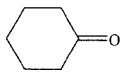
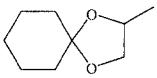
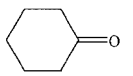
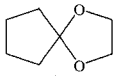
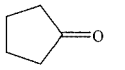
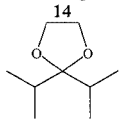
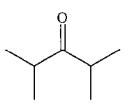
lowed by the addition of acetals or ketals while stirring. Firstly, using deprotection of **1** as the typical reaction, three species of CDs were evaluated as shown in Table 1.

It is strikingly surprising to find out that **1** was efficiently deprotected into **2** through the use of β-CD as a catalyst, while little deprotection was achieved in the cases both of α-CD and of γ-CD (Entries 1, 4 and 5). It might be concluded that the deprotection with CD as a catalyst is highly shape-selective, owing to the different interior cavity sizes of these CDs. A similar conclusion could also be arrived at in the following discussion. With regard to the mass of β-CD, use of more β-CD accelerated the reaction rate (Entries 1−3). No deprotection was observed when **1** was stirred in water in the absence of β-CD, indicating that the presence of CD is necessary to cause deprotection (Entry 6).

In view of the efficient deprotection of **1**, the deprotection for various ethylene acetals and dioxolanes was investigated and the results are shown as Table 2.

Aromatic ethylene acetals underwent smooth deprotection (Entries 1 and 3). However, polycyclic aromatic aldehyde-derived **5** could not be deprotected to give **6**. The lack of deprotection (Entry 4) might be accounted for, on the basis of fundamental computation, by the steric volume of **5** being too large to enter into the hydrophobic cavity of β-CD during the reaction. The acetal derived from cyclohexanecarbaldehydes rather than aromatic aldehydes, (i.e., **7**) suffered from low reactivity towards its deprotection (Entry 5). The bulk of the cyclohexyl group, with chair and boat conformations occupying more space than an aromatic group, might explain the low reactivity towards deprotection for the small hydrophobic cavity of β-CD as a microreactor for deprotection. It was also verified that the existence of other groups on the aromatic group sharply decreased the reactivity, by comparison of the deprotection of **1** with that of **3**, in which deprotection of **1** could be performed at room temperature while a reaction temperature of 60 °C was necessary for smooth deprotection of **3** (Entries 1 and 3). When **9** was heated to 60 °C for 12 h, no **10** was formed and the starting material was recovered unchanged. The lack of deprotection of ethylene acetals derived from aliphatic aldehydes might be one reason, as also reported elsewhere;[19,24] another reason might be the steric structure of β-CD, as discussed later. It is noteworthy that the use of

Table 2. Hydrolysis of various ethylene acetal and dioxolane protecting groups to regenerate the corresponding carbonyl compounds[a]

Entry	Substrate	Product	Time (h)	Conv. (%)[b]	Yield (%)[b,c]
1[d]			2.5	100	> 99 (91)
	1	**2**			
2[d,e]	20 mmol scale		8	100	> 99 (94)
3[d,f,g]			6	99	99
	3	**4**			
4[d,f,g]			12	NR	NR
	5	**6**			
5[f]			96	33	33
	7	**8**			
6[f]			12	NR	NR
	9	**10**			
7[f]			2.5	100	> 99 (92)
	11	**12**			
8			26	94	94 (85)
9[f,g]			46	100	> 99
	13	**12**			
10			16	100	98
	14	**15**			
11[f]			25	NR	NR
	16	**17**			

[a] Reaction conditions: β-CD (1 mmol), substrate (2 mmol), water (25 mL), room temp., no reflux. [b] Conversion and yield were determined by GC, GC-MS or LC by use of an internal standard. In all cases, product was exclusively obtained. [c] Values in parentheses are isolated yields. [d] Protected by Ar to prevent from further oxidation. [e] Large scale: substrate (20 mmol). [f] Reaction temperature (60 °C). [g] Substrate (1 mmol).

inert gas such as Ar is necessary for the hydrolysis of aromatic ethylene acetals. Otherwise, the deprotected products such as **2** could easily be further oxidized to the corresponding carboxylic acids, owing to the presence of oxygen.

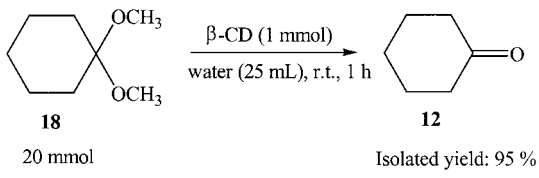
Similar reaction characteristics can be found in the cases of dioxolanes protected by use of 1,2-ethanediol, except the lower activities owing to the presence of cyclohexyl group (Entries 7−10). Reaction temperature is a key factor for the deprotection; the use of elevated reaction temperature sharply increased the level of deprotection (Entries 7 and 8). From the above discussion, use of CD as a catalyst for deprotection of carbonyl compounds masked as ethylene

acetals and dioxolanes produced from 1,2-ethanediol is highly dependent on molecular shape and the deprotection mechanism is different from other reported catalyst systems. The steric factor is the most important, if the hydrophobic cavity of CD is regarded as the microreactor for deprotection. The highly shape-selective and catalytic nature of this system makes some substrates particularly efficient for large-scale synthesis. The effective large-scale utilization of this system is demonstrated by the successful deprotection of **1** (Entry 2).

To obtain some mechanistic insights of the CD-catalyzed deprotection, special conformations of CDs should be a key factor. In general, biotransformations are a useful and complementary tool for preparative organic chemistry. In the course of a biotransformation, the chemo-, regio-, and stereoselective transformation of a substrate often takes place under mild and ecologically compatible conditions. CDs, which are cyclic oligosaccharides with toroidal hydrophobic cavities, exert microenvironmental effects giving rise to selective reactions. They catalyze reactions involving supramolecular catalysis through reversible formation of host-guest complex with substrates by non-covalent bonding, as seen in enzymes. This complexation depends on the size, shape, and hydrophobicity of the guest molecule. Thus, biochemical-like selectivity for shape and substrate with reactions performed in water will be superior to chemical selectivity. The role of CD appears to be to activate the −O− group by hydrogen bonding, thus facilitating its cleavage in the presence of water by acid-base catalysis.

The above discussion might easily explain the greater ease of deprotection of carbonyl compounds masked as acetals derived from aromatic aldehydes than of those derived from cyclohexanecarbaldehydes. The existence of other groups in the substrate might retard the host-guest complex intermediate formation by hydrogen bonding, owing to steric factors. The lack of reaction in the attempted deprotection of **9** might be attributable to the long aliphatic chain, and thus the impossibility of formation of an intermediate by hydrogen bonding, owing to the long distance between the −O− group of **1** and the −OH group of CD.

In view of the proposed mechanism, we now also speculated that dimethyl acetals or ketals might also be deprotected successfully, owing to their similar structures and −O− groups. Compound **18** was used to verify this supposition, and highly efficient conversion was found as shown in Scheme 2.



Scheme 2

Conclusion

In conclusion, a simple, mild, efficient, and biochemical procedure for the deprotective hydrolysis of carbonyl compounds masked as ethylene acetals and dioxolanes produced from 1,2-ethanediol has been developed, through the use of CD as a catalyst to regenerate their corresponding carbonyl compounds. This biomimetic methodology is the first of its kind to be applied for the cleavage of ethylene acetals and dioxolanes under neutral conditions with water as solvent in the presence of CDs. These biomimetic reactions can be effectively conducted in water as the sole solvent under neutral conditions without generating any toxic waste products. In addition, the use of water as solvent, the readily commercial availability of the catalyst, the high yields of the products, the easy workup, low costs, and the safety of the catalyst are other advantages of this method, making this procedure a useful and attractive addition to the currently available methods. In addition, this deprotection methodology is highly shape-selective, owing to the conformations of CDs.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively, with a JLN AL-400 spectrometer. Chemical shifts were reported in parts per million (ppm, δ) relative to Me_4Si (δ = 0.00 ppm). IR spectra were recorded with an FT-IR spectrometer (JASCO FT/IR-410) and reported in wavenumbers (cm^{-1}). GC-MS analyses were performed with a Shimadzu GCMS-QP5050A GC-mass spectrometer. α-CD, β-CD, γ-CD, and solvents were purchased from WAKO Co. and solvents were further purified before use. Other chemicals are commercially available (from Aldrich Co. or WAKO Co.), unless otherwise indicated, and were used as received. Commercially unavailable substrates were synthesized by known methods and analyzed by ^{1}H NMR, ^{13}C NMR, FT-IR and MS.

Typical Procedure for the Hydrolysis of Ethylene Acetal and Dioxolane Protecting Groups Formed from 1,2-Ethanediol: β-CD (1 mmol) was dissolved in water (25 mL) at room temperature, and the substrate (2 mmol) was added with stirring. When the reaction was complete, the mixture was extracted with ethyl acetate (2 × 30 mL) and dried with anhydrous sodium sulfate, and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography with ethyl acetate/hexane (3:7) as eluent. Products were characterized by GC, LC, or GC-MS and compared with authentic samples.

Large-Scale Hydrolysis of Ethylene Acetal and Dioxolane Protecting Groups Formed from 1,2-Ethanediol: β-CD (1 mmol) was dissolved in water (25 mL) at room temperature, and the substrate (20 mmol) was added with stirring. When the reaction was complete, the mixture was extracted with ethyl acetate (2 × 30 mL) and dried with anhydrous sodium sulfate, and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography with ethyl acetate/hexane (3:7) as eluent. Products were characterized by GC, LC, or GC-MS and compared with authentic samples.

General Procedure for the Preparation of Ethylene Acetals and Dioxolanes:[11] A mixture of carbonyl compound (10 mmol), ethane-

1,2-diol (15 mmol), Ti-montmorillonite (0.3 g), and toluene (20 mL) was heated at reflux under Dean−Stark conditions. After 2 h, the Ti-montmorillonite was separated by filtration. The organic layer was concentrated under vacuum distillation and subjected to column chromatography on Florisil® with a mixture of *n*-hexane and ethyl acetate (9:1), which afforded pure ethylene acetals and dioxolanes.

Preparation of 1-Pyrenecarboxaldehyde Ethylene Acetal (5) (Table 2, Entry 4): A mixture of **6** (6 mmol), ethane-1,2-diol (10 mmol), Ti-montmorillonite (0.2 g), and toluene (20 mL) was heated at reflux under Dean−Stark conditions. After 3 h, the Ti-montmorillonite was separated by filtration. The organic layer was concentrated under vacuum distillation and light yellow crystals were obtained. Recrystallization from ethanol, followed by vacuum distillation, provided pure **5** (1.48 g, 90%). Light yellow crystals. ^{1}H NMR: δ = 4.20−4.31 (m, 4 H), 6.76 (s, 1 H), 7.98−8.47 (m, 9 H) ppm. ^{13}C NMR: δ = 131.88, 130.58, 128.92, 127.73, 127.31, 125.87, 125.28, 124.48, 123.36, 123.06, 102.28, 65.52 ppm. MS (EI, 70 eV): *m/z* (%) = 274 (24.87), 243 (1.29), 229 (11.41), 215 (11.15), 202 (100).

Data for 2-Cyclohexyl-1,3-dioxolane (7) (Table 2, Entry 5): The preparation conditions were the same as above, providing 0.86 g of pure **7** (92%). Colorless, oily compound. ^{1}H NMR: δ = 1.04−1.29 (m, 10 H), 1.77 (dt, *J* = 10.50, *J* = 3.17 Hz, 1 H), 3.82−3.85 (m, 2 H), 3.91−3.94 (m, 2 H), 4.59 (d, *J* = 4.88 Hz, 1 H) ppm. ^{13}C NMR: δ = 107.59, 64.91, 41.78, 27.37, 26.47, 25.80 ppm. IR (neat): $\tilde{\nu}$ = 2928, 2853, 1451, 1400, 1153, 1132, 1075 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 156 (0.29), 155 (0.82),126 (0.15), 96 (0.53), 83 (1.02), 73 (100).

Data for 2-Heptyl-1,3-dioxolane (9) (Table 2, Entry 6): The preparation conditions were the same as above, providing 1.01 g of pure **9** (91%). Colorless, oily compound. ^{1}H NMR: δ = 0.88 (t, *J* = 6.84 Hz, 3 H), 1.23−1.34 (m, 8 H), 1.37−1.45 (m, 2 H), 1.64 (dt, *J* = 15.14, *J* = 8.79, 2 H), 3.82−3.86 (m, 2 H), 3.94−3.98 (m, 2 H), 4.84 (t, *J* = 4.88 Hz, 1 H) ppm. ^{13}C NMR: δ = 104.71, 64.81, 34.03, 31.78, 29.62, 29.30, 24.20, 22.71, 14.14 ppm. IR (neat): $\tilde{\nu}$ = 2928, 2854, 2763, 1467, 1409, 1144, 1037 cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 171 (3.03), 99 (1.72), 74 (8.00), 73 (100), 55 (7.38), 45 (35.31).

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