Direct Regioselective Esterification at *O*-2 of β -Cyclodextrin and Hydrolysis by Neighboring-group Participation

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Received 06 January 2010; Accepted 01 March 2011

Abstract: A simple and efficient strategy for direct regioselective esterification at *O*-2 of β -cyclodextrin was developed by using the combination of *N,N'*-carbonyldiimidazole and carbonate buffer in 1,4-dioxane, which does not require large amounts of polar organic solvents such as *DMF*, toxic solvents such as *CH₃CN*, or flammable bases such as *NaH*. Moreover, their hydrolyses by neighboring-group participation were observed. Mono-2-tosyl- β -cyclodextrin was liable to epoxidation, while mono-2-(*p*-methylbenzoyl)- β -cyclodextrin liable to isomerization. They had different mechanisms of hydrolysis.

Keywords: β -Cyclodextrin, Regioselective esterification, Neighboring-group participation, Hydrolysis.

Introduction

Cyclodextrins (CDs) are well-known macrocyclic compounds consisting of six or more α -1,4-linked D-glucopyranose units, which possess the secondary C-2 and C-3 hydroxyl groups on their more open face and the primary C-6 hydroxyl groups on the other face. Owing to their hydrophobic and optically active interior, now, derivatives of CDs have evolved into a versatile class of host molecules with applications in artificial enzymes and biomimetic materials¹⁻⁴.

Of the three types of hydroxyl groups present in β -CD, those at the 6-position are the most basic and often most nucleophilic, those at the 2-position are the most acidic, and those at the 3-position are the most inaccessible. Thus, under normal circumstances, an electrophilic reagent attacks the 6-position, and it is important to recognize that more reactive reagents will attack the hydroxyl groups less selectively. Selective introduction of functional groups to β -CD has been extensively studied for the primary hydroxyl face⁵, but less well for the secondary hydroxyl face. The most commonly used method for selective introduction of one functional group at the secondary face is via activation of one hydroxyl group by sulfonylation⁶. Only very few examples are known of the introduction of a single

functional group at the secondary face of CDs without prior sulfonylation. Ding Rong and Valerian T. D'Souza functionalized the C-2 OH by deprotonation with *NaH* in *DMF* and subsequent reaction with an electrophilic reagent⁷, this method needs the use of strong alkali as reactant and requires polar organic solvent. Hao Ai You et al. monoacylated β -CD on the secondary hydroxyl face with acyl chloride in alkaline acetonitrile solution⁸, which uses the toxic solvent and highly reactive reagent. To our knowledge, this reaction gave a mixture of C-2, C-3, and C-6 positions. Herein, the authors describe a simple and efficient method for direct regioselective esterification at *O*-2 of β -CD, and report their hydrolyses by neighboring-group participation (Scheme 1, 2).

Experimental

Preparative HPLC separations were carried out with a Perkin-Elmer Series 200 HPLC system with UV/Vis detector using ZORBAX SB-C18 column (10 mm $\times$ 250 mm). NMR spectra were recorded on Bruker AM-600 (¹H 600MHz and ¹³C 150 MHz) in *DMSO-d*₆ solutions with *TMS* (tetramethylsilane) as standard. The ESI-MS experiments were performed using a ThermoQuest Finnigan LCQ^{DECA} system equipped with an ESI source (ThermoQuest LC/MS Division, San Jose, CA, USA). 0.2 *M* carbonate buffer (*pH* 9.9) was prepared by mixing equal volumes of 0.2 *M* sodium carbonate and 0.2 *M* sodium bicarbonate. All other chemicals were of commercial grade without further purification.

General Experimental Procedure

To a solution of 2.65 mmol aromatic acid in 20 cm³ anhydrous 1,4-dioxane, 1.2 equivalents of *N,N'*-carbonyldiimidazole (CDI) were added at room temperature. After stirred for 2 h, 1.76 mmol β -CD and 20 cm³ of 0.2 *M* carbonate buffer (*pH* 9.9) were added. The reaction mixture was heated at 50 °C for 1 h. Then the mixture was neutralized with 1 *N HCl*, evaporated *in vacuo* to a volume of *ca.* 5 cm³, and 300 cm³ acetone was added to precipitate cyclodextrin derivatives. The crude products were subjected to an open reversed-phase column or preparative column of HPLC.

Scheme 1

Scheme 2

Mono-2-tosyl-β-CD (**1**)

The crude product of **1** was subjected to an open reversed-phase column eluted with *H*₂*O*-*MeOH*, the eluent composition was gradually changed (*MeOH*-*H*₂*O*, 0-10%-20%-30%) until the pure product was eluted. The residue obtained after removal of the solvent was triturated with acetone, filtered, washed with acetone, and dried. Thus, the pure **1** was obtained in 31% yield (0.71 g).

¹H and ¹³C NMR spectra were identical with the authentic mono-2-tosyl-β-CD reported in Reference⁹.

Mono-2-(*p*-methylbenzoyl)-β-CD (**2**)

On the preparative column with the elution of 20% aqueous *MeOH*, **2** was resolved, collected, and lyophilized. Yield 12% (0.27 g); ESI-MS: *m/z* 1275 ([*M*+*Na*]⁺); ¹H NMR (600MHz, *DMSO*-*d*₆): δ = 7.95 (d, 2H), 7.28(d, 2H), 5.90-5.52(m, 14H), 4.95-4.72(m, 7H), 4.60-4.32(m,7H), 3.85(br,1H), 3.78-3.22(m, 40H), 2.36(s, 3H); ¹³C NMR (150MHz, *DMSO*-*d*₆): δ = 166.1, 143.2, 130.2, 129.8, 129.0, 102.4, 102.3, 102.1, 98.7(C-1'), 82.1, 81.8, 81.7, 74.2, 73.4, 72.8, 72.5, 72.2, 71.8, 60.6, 60.5, 60.3, 21.7.

Results and Discussion

In our work, the authors found that carbonate buffer (*pH* 9.9) can efficiently activate the C-2 OH of β-CD in a 1:1 mixture of 1,4-dioxane-water, and regioselectively promote reactions at the 2-position. *N,N'*-carbonyldiimidazole is a useful, general carboxylic acid activating reagent¹⁰, and the only byproducts are carbon dioxide and imidazole (*pKa* = 6.80) which, being a relatively weak base, are unlikely to cause the distinct change of *pH* value of the reaction system. Therefore, mono-2-tosyl-β-CD (**1**) and mono-2-(*p*-methylbenzoyl)-β-CD (**2**) were prepared in a simple, two-step sequence via a one-pot reaction. In the first step,

based on TLC analysis, the reactions between aromatic acids and *N,N'*-carbonyldiimidazole were quantitative in 1,4-dioxane within 2 h at room temperature. In the second step, the couplings of acyls to the *O*-2 of β -CD were accomplished in the carbonate buffer at 50 °C for 1 h.

In the preliminary hydrolytic experiment of **1** (Figure 1), initially, the positive ion mode ESI-MS spectrum exhibited only one molecular ion $[M+Na]^+$ at m/z 1311. After 1 h at 60 °C in 20% aqueous *MeOH*, three peaks were observed at m/z 1311, 1157, and 1139 which was the molecular ion of mono-2,3-mannoepoxy- β -CD. This result is consistent with that of ^{13}C NMR spectra. As shown in Figure 2, the time-based 150 MHz ^{13}C NMR spectra demonstrated the presence of the epoxide carbons at δ 49.1 and 54.0 ppm¹¹. Therefore, it is important to note that **1** was partly transformed into its corresponding mono-2,3-mannoepoxy- β -CD with loss of *TsOH*.

Figure 1. ESI (+) mass spectra in the positive ion mode for (A) **1** initially; (B) **1** h after heated at 60°C for **1**.

Figure 2. The time-based 600 MHz ^{13}C NMR spectra for (A) **1** initially; (B) **1** h after heated at 60°C for **1**. The numbers indicate the peak assignments.

For **2** (Figure 3), initially, the positive ion mode ESI-MS spectrum exhibited only one molecular ion $[\text{M}+\text{Na}]^+$ at m/z 1275. After 1 h at 60°C in 20% aqueous *MeOH*, two peaks were observed at m/z 1275 and 1157. However, as shown in Figure 4, the time-based 150 MHz ^{13}C NMR spectra demonstrated a new chemical shift at δ 78.5 ppm, which indicated the *p*-methylbenzoyl group was attached to *O*-3 of β -CD, according to explanations by Breslow⁹. Therefore, it is important to recognize that **2** was partly isomerized to its corresponding mono-3-(*p*-methylbenzoyl)- β -CD.

Figure 3. ESI (+) mass spectra in the positive ion mode for (A) **2** initially; (B) **1** h after heated at 60°C for **2**.

Based on the above facts, ester hydrolyses by neighboring-group participation were observed. For **1**, the *O*-3 of β -CD attacked the C-2, which resulted in epoxidation; whereas for **2**, the *O*-3 attacked the carbon of carbonyl group of benzoyl group, which resulted in isomerization. They had different hydrolytic reaction mechanisms. Consequently, a systematic study on the kinetics models of hydrolysis is in progress.

Figure 4. The time-based 600 MHz ^{13}C NMR spectra for (A) **2** initially; (B) 1 h after heated at 60°C for **2**. The numbers indicate the peak assignments.

Conclusions

A simple and efficient method for direct regioselective esterification at *O*-2 of β -CD was developed by using the combination of *N,N'*-carbonyldiimidazole and carbonate buffer in 1,4-dioxane, which does not require large amounts of polar organic solvents such as *DMF*, toxic solvents such as CH_3CN , or flammable bases such as *NaH*. In addition, their hydrolyses by neighboring-group participation were observed. In the preliminary experiments of hydrolysis, mono-2-tosyl- β -CD was liable to epoxidation, and mono-2-(*p*-methylbenzoyl)- β -CD liable to isomerization. They had different hydrolytic reaction mechanisms. The neighboring-group participation proves the more open secondary hydroxyl face of CDs is catalytically very important.

Acknowledgements

Financial support from the Natural Science Foundation of Ningxia Medical University (No. XT201001) is gratefully acknowledged.

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