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RESEARCH ARTICLE

Convenient Preparation of Mono-2 or Mono-3-*O*-benzoyl-*β*-cyclodextrin Dependent the Solvent Equilibrium

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Abstract: A new and convenient method is presented for the preparation of mono-2 or mono-3-*O*-benzoyl-*β*-cyclodextrin by direct benzoylation of *β*-cyclodextrin on the secondary hydroxyl face using *N*-benzoylimidazole in carbonate buffer solution. These processes involved the solvent-dependent equilibriums of isomerization to improve the yields. Among the common solvents (*N*,*N*-dimethylformamide, dimethyl sulfoxide, and H_2O), dimethyl sulfoxide is the most advantageous for preparing mono-2-*O*-benzoyl-*β*-cyclodextrin, and H_2O is the most advantageous for preparing mono-3-*O*-benzoyl-*β*-cyclodextrin.

Keywords: Cyclodextrin, Benzoylation, Isomerization, Equilibrium

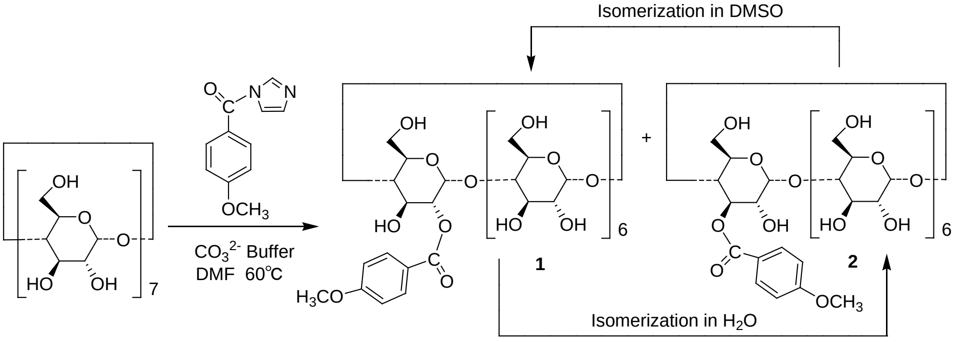
Introduction

Cyclodextrins (CDs), well-known macrocyclic oligosaccharides, have hollow truncated cones capable of forming inclusion complexes with a variety of organic molecules in aqueous solution. CDs have attracted widespread interest for building supramolecular structures, and their derivatives have evolved into a versatile class of host molecules with applications in enzyme mimics, molecular recognition, drug delivery and chiral discrimination[1-4], *etc*.

In recent years, selective benzoylation of the C-6 hydroxyl groups has been extensively studied, and the obtained mono-6-*O*-benzoyl-*β*-CDs have been used as novel supramolecular photosensitizing hosts in photochirogenesis[5-11]. Since the more open secondary hydroxyl face of CDs is stated to be catalytically very important[12-15], benzoylations of this face are believed to produce valuable derivatives for asymmetry catalysis. However only very few examples are known of the introduction of a single benzoyl group at the secondary face of CDs, because of the competitive reaction of the primary face and purification of the synthesized cyclodextrin derivatives[16]. Hao *et al*. monobenzoylated *β*-CD on the secondary face with acyl chloride in alkaline acetonitrile solution, a method which used a toxic solvent and a highly reactive reagent. Moreover, those isolated yields were relatively low[17]. Herein, we describe a new and convenient method for the preparation of mono 2- or mono-3-*O*-benzoyl-*β*-CD by the solvent-dependent equilibrium of isomerization in good yields (Scheme 1).

Experimental

Analytical and preparative HPLC column chromatographies were done using a Perkin-Elmer Series 200 HPLC system equipped with a UV/Vis detector. A Kromasil 100-10-C18 column (4.6 mm×250 mm) was used for the analytical HPLC, and a ZORBAX SB-C18 column (10 mm×250 mm) was used for the preparative HPLC. NMR spectra were recorded on Bruker AM-600 spectrometer (^{1}H 600 MHz and ^{13}C 150 MHz) in DMSO-d_6 solutions with tetramethylsilane as standard. The ESI-MS experiments were performed using a Thermo Quest Finnigan LCQ^{DECA} system equipped with an ESI source (ThermoQuest LC/MS Division, San Jose, CA, USA). Carbonate buffer (0.2 M, pH 9.9) was prepared by mixing equal volumes of 0.2 M sodium carbonate and 0.2 M sodium bicarbonate. *N*-Benzoylimidazole was prepared according to the reference[18]. All other chemicals were of commercial grade and used without further purification.



Scheme 1

General experimental procedure

To a stirred solution of 2 g *β*-CD with one molar equiv. of *N*-(*p*-methoxybenzoyl) imidazole in DMF (60 cm^3), carbonate buffer (12 cm^3, 0.2 M, pH 9.9) was added. After heated at 60 °C for 2 h, the reaction mixture was neutralized with 1 M HCl, evaporated *in vacuo* to a volume of ca. 5 cm^3, and acetone (300 cm^3)was added to precipitate the cyclodextrin derivatives. The crude products were isolated by an open RP-18 column using H_2O-MeOH (10%-20%-30%) as eluents. Thus, a mixture of **1** and **2** was obtained.

*Mono-2-O-(p-methoxybenzoyl)-β-CD (**1**, $C_{50}H_{76}O_{37}$)*

The mixture of **1** and **2** was dissolved in DMSO (4 cm^3), heated at 50 °C for 1 h and concentrated *in vacuo*. Then the residue was dissolved in 20% aqueous MeOH (70 cm^3) and purified by preparative HPLC using 20% aqueous MeOH as eluent. The fractions containing **2** were evaporated *in vacuo*, dissolved in DMSO (2 cm^3), heated at 50 °C for 1 h and concentrated *in vacuo*. Then the residue was dissolved in 20% aqueous MeOH (30 cm^3), and purified by preparative HPLC using 20% aqueous MeOH as eluent. The processes were carried out three times, and all the fractions containing **1** were combined and lyophilized to give the pure **1**. Yield 32% (0.72 g); ESI-MS: *m/z* = 1,291 ([M+Na]$^+$); ^{1}H NMR (600 MHz, DMSO-d_6): δ = 3.20-3.74(m, 39H), 3.77(t, 1H), 3.83(s, 3H), 3.88(br, 1H), 4.39-4.70(m, 7H), 4.75-4.86(m, 6H), 4.90(d, 1H), 5.16(d, 1H), 5.39(t, 1H), 5.50-6.00 (m, 12H), 7.01(d, 2H), 8.03(d, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 55.9, 60.6, 70.1, 71.5, 72.2, 72.6, 72.8, 73.0, 73.5, 74.9, 81.1, 81.8, 82.0, 98.8(C-1′), 102.0, 102.3, 102.4, 114.1, 123.8, 132.3, 162.9, 166.0.

Mono-3-O-(p-methoxybenzoyl)-β-CD (***2***, *$C_{50}H_{76}O_{37}$*)

The mixture of **1** and **2** was dissolved in H_2O (50 cm^3), heated at 50 °C for 1 h and concentrated *in vacuo*. Then the residue was dissolved in 20% aqueous MeOH (70 cm^3) and purified by preparative HPLC using 20% aqueous MeOH as eluent. The fractions containing **1** were evaporated *in vacuo*, dissolved in H_2O (20 cm^3), heated at 50 °C for 1 h and concentrated *in vacuo*. Then the residue was dissolved in 20% aqueous MeOH (20 cm^3) and purified by preparative HPLC using 20% aqueous MeOH as eluent. The processes were carried out twice and all the fractions containing **2** were combined and lyophilized to give the pure **2**. Yield 35% (0.79 g); ESI-MS: m/z = 1,291 ($[M+Na]^+$); ^1H NMR (600 MHz, DMSO-d_6): δ = 3.20-3.75(m, 39H), 3.76(t, 1H), 3.82(s, 3H), 3.89(br, 1H), 4.38-4.61(m, 7H), 4.74-4.87(m, 6H), 4.94(d, 1H), 5.34(t, 1H), 5.39(br, 1H), 5.48-6.08 (m, 12H), 7.00(d, 2H), 7.91(d, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ = 55.8, 60.4, 71.5, 71.9, 72.2, 72.5, 72.8, 73.1, 73.4, 75.0, 78.6(C-4′), 81.8, 82.0, 82.1, 102.1, 102.3, 102.4, 113.9, 122.5, 131.9, 162.8, 165.8.

Results and Discussion

In previous work, we reported the acyl migration between the C-2 and C-3 hydroxyl groups of *β*-CD in the form of short communications[19]. During our studies of the solvent effects on the equilibrium of acyl migration, three solvents (*N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO) and H_2O), which can well dissolve the mon-benzoate of *β*-CD, were used, and the processes were monitored using the analytical HPLC. When the equilibriums of acyl migration were established at 50 °C for 1 h, the ratios between **2** and **1** approached 2.8:1 in H_2O, 1:1 in DMSO and 1.3:1 in DMF (Figure 1).

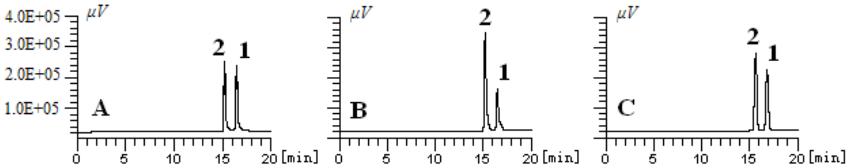


Figure 1. HPLC analysis of the equilibrim mixture of **1** and **2** in DMSO (a), H_2O (b) and DMF (c) at 50 °C for 1 h. Detection was done at 255 nm wavelength. Gradient elution was done from 10:90 to 40:60 MeOH–H_2O for 20 min, to 100:0 MeOH–H_2O for 20 min; flow rate of 0.8 mL/min. Compound numbers are presented corresponding peaks.

On the basis of the above facts, DMSO appeared to be optimal for preparing the mono-2 isomer (**1**) and H_2O is the most advantageous for preparing the mono-3 isomer (**2**). Therefore, **1** was obtained in 32% yield by the equilibrium of isomerization in DMSO three times and **2** was obtained in 35% yield by the equilibrium of isomerization in H_2O twice. On the other hand, it has to be noted that the mono-2 and mono-3 isomers must be lyophilized, due to the acyl migration between the C-2 and C-3 hydroxyl groups.

The structures of **1** and **2** were characterized by ESI-MS and NMR spectra. their ESI-MS spectra exhibited the molecular ion $[M+Na]^+$ at m/z = 1,291. ^{13}C NMR spectroscopy is an effective technique for the analysis of cyclic oligosaccharides. As elegantly explain by Breslow[20], usually, arylation of a hydroxyl group of CDs leads to a downfield chemical shift of the carbon carrying the hydroxyl (*α*-carbon), but a small upfield chemical shift of *β*-carbon and a still smaller shift of *γ*-carbon. In the ^{13}C NMR spectra of **1** and **2**, the peak at δ = 98.8 ppm (C-1′) clearly indicates that the benzoyl substituent is at the 2-position of *β*-CD, and the peak at δ = 78.6 ppm (C-4′) indicates that the benzoyl substituent is at the 3-position.

Conclusion

A new and convenient method was developed for the preparation of mono-2 or mono-3-*O*-(*p*-methoxybenzoyl)-*β*-CD by direct benzoylation of *β*-CD on the secondary hydroxyl face using *N*-(*p*-methoxybenzoyl)imidazole in carbonate buffer solution. These processes involved the solvent-dependent equilibriums of isomerization to improve the yields. Among the common solvents (DMF, DMSO and H_2O), DMSO is the most advantageous for preparing mono-2 isomer and H_2O is the most advantageous for preparing mono-3 isomer. This benzoylation method can be highly useful for the preparation of other benzoates of *β*-CD as macrocyclic host molecules.

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