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Note

Convenient preparation of monoacylated β-cyclodextrin (cyclomaltoheptaose) on the secondary hydroxyl side

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Torus shaped cyclomalto-oligosaccharides (cyclodextrins, CDs) contain 6, 7, 8 or more glucose units (named αCD, βCD, γCD, etc.) connected by α-1,4 linkages with the secondary hydroxyls of glucose C-2 and C-3 on their more open face and the primary hydroxyls of C-6 on the other. Their ability to accommodate a wide variety of organic molecules has permitted CDs to be used to construct efficient artificial enzymes, molecular recognition sensors and other functional models [1–6]. Recently, we have prepared a series of 6-*O*-acylated CD derivatives and found that this chromophoric modification was very useful as a spectrometry probe in clarifying discrimination in host–guest molecular recognition [6–8]. On the other hand, Inoue and Tong [7] have studied the photoisomerization of *cis*-cyclooctene in the presence of 6-*O*-benzoated CD derivatives as sensitizers, and found that its optical yield with 6-*O*-monobenzoyl-βCD was 5% higher than that with 6-*O*-monobenzoyl-αCD. Since the more open secondary hydroxyl side of CDs has been considered to be "the real business end" of the molecules [9,10], in this report we describe the convenient preparation of monoacylated βCD **1–6**. Each of the products has a chromophoric moiety located on the secondary hydroxyl side of βCD.

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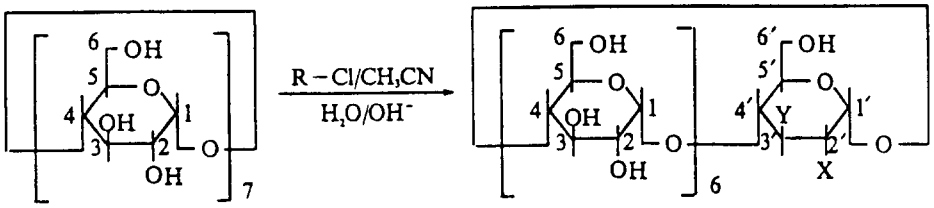

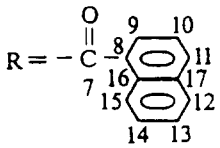

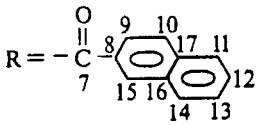

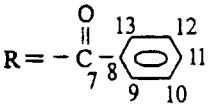

(1) X=OR, Y=OH (3) X=OR, Y=OH (5) X=OR, Y=OH

(2) X=OH, Y=OR (4) X=OH, Y=OR (6) X=OH, Y=OR

When an acetonitrile solution of acyl chloride was added dropwise into an alkaline aqueous solution of βCD with stirring, some inclusion compounds were formed as white suspended particles. After the reaction the solution was neutralized and filtered and silica gel TLC applied to analyse the formation of the products. The results suggested that the appropriate original pH value of the aqueous solution as well as the reaction time and reaction temperature might be determined by the reactivity of acyl chloride. In the preparation of **3** and **4**, the appropriate pH value was about 12.5. However, in the preparation of **1**, **2**, **5** and **6**, the appropriate pH value should be under 12. When the original pH value was about 12.5, no formation of **1**, **2**, **5** and **6** could be found by TLC. This direct acylation procedure on the secondary hydroxyl side of βCD, which may never have been reported before [11,12] may involve an inclusion complexation and a nucleophilic attack step.

The product was further characterized by ^{13}C NMR spectroscopy. Usually, arylation of a hydroxyl group of CDs leads to a downfield chemical shift of the carbon carrying the hydroxyl (α-carbon), but a smaller upfield chemical shift of β-carbon and a still smaller shift of γ-carbon [13]. The ^{13}C NMR spectra of **1**, **3** and **5** show one small peak around 74 ppm corresponding to a downfield chemical shift of C-2′ and one small peak around 98.5 ppm corresponding to an upfield chemical shift of C-1′. The ^{13}C NMR spectra of **2**, **4** and **6** showed one small peak around 75 ppm corresponding to a downfield chemical shift of C-3′ and one small peak around 101.5 ppm corresponding to a smaller upfield chemical shift of C-1′. Furthermore, compared with C-6 substituted CD derivatives, none of the products show a clear change in the chemical shift of C-6′. The ^{13}C NMR spectra of **3** and **4** as examples are shown in Fig. 1.

1. Experimental

Commercially available βCD was recrystallized from water and dried at 120°C for 4 h. Acyl chloride agents were used without further purification. ^{1}H NMR and ^{13}C NMR

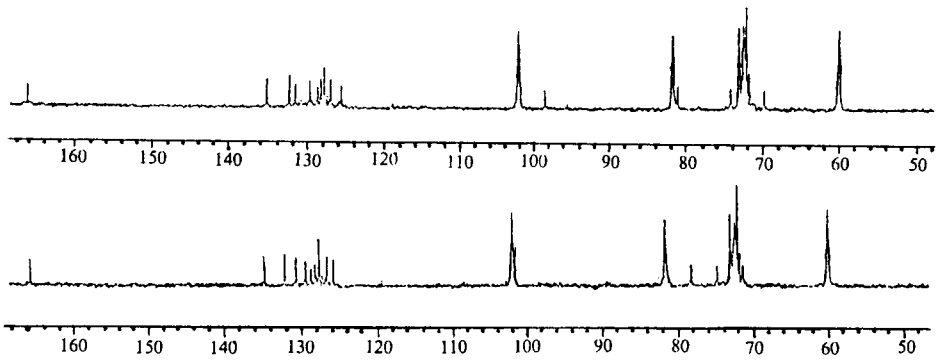

Fig. 1. ^{13}C NMR spectra of **3** and **4** in DMSO-d_6 (ppm; Me_4Si used as an internal reference): **3** above, **4** below.

spectra were recorded on AM-400 spectrometer (ppm; Me_4Si used as an internal reference in DMSO-d_6). TLC was run with 0.2 mm precoated silica gel plates, elution solvent was n-PrOH–$CH_3COOC_2H_5$–H_2O (4:3:2 by volume).

2- and 3-O-Mono-α-naphthoyl-βCD (**1** *and* **2**).—1.3 g α-Naphthoyl chloride in 100 mL CH_3CN was added within 5 min to 400 mL alkaline aqueous solution (adjusted by 0.2 g NaOH) of 6.5 g βCD at 5°C under stirring. After 10 min, the reaction solution was neutralized and filtered. The filtrate was concentrated to about 10 mL in vacuo, and the residue was treated with 500 mL CH_3COCH_3 to obtain products **1** and **2** as mixed precipitate with βCD. Finally, a silica gel column chromatography ($\Phi 3 \times 100$ cm) was applied, using *n*-PrOH–$CH_3COOC_2H_5$–H_2O (4:3:2 by volume) as an eluent and TLC as a monitor of the products, to furnish pure products **1** and **2**. A mixture of some dinaphthoated isomers as the major by-products was also got by a yield of 2%.

1: 10% yield; $R_f = 0.41$; δ_H: 8.80 (d, 1 H, H-9), 8.40–8.45 (d, 1 H, H-11), 8.15–8.19 (d, 1 H, H-12), 8.00–8.05 (d, 1 H, H-15), 7.54–7.65 (m, 3 H, H-10,13,14), 5.70–5.80 (br, O(2)H, O(3)H), 5.30 (s, 1 H, H-1′), 4.85 (s, 7 H, H-1), 4.45–4.60 (br, O(6)H), 3.82 (d, 1 H, H-2′), 3.25–3.78 (m, 40 H, H-2,4,6,5,3), 3.12 (s, 1 H, H-3′); δ_C: 167.05 (C-7), 133.32, 131.40, 130.90, 127.90, 126.60, 126.10, 126.05, 125.85, 125.05 (C-8 ~ 17), 101.93 (C-1), 98.40 (C-1′), 81.57 (C-4), 80.90 (C-4′), 74.05 (C-2′), 72.96 (C-3), 72.35 (C-2), 72.05 (C-5), 71.05 (C-5′), 69.85 (C-3′), 59.86 (C-6). Anal. Calcd for $C_{53}H_{76}O_{36} \cdot 4H_2O$: C, 46.77; H, 6.22. Found: C, 46.99; H, 6.34.

2: 17% yield; $R_f = 0.36$; δ_H: 8.79–8.81 (d, 1 H, H-9), 8.20–8.23 (d, 1 H, H-11), 8.11–8.14 (d, 1 H, H-12), 7.96–8.00 (d, 1 H, H-15), 7.58–7.69 (m, 3 H, H-10,13,14), 5.71–5.78 (br, O(2)H, O(3)H), 5.0 (s, 1 H, H-1′), 4.80–4.90 (s, 7 H, H-1), 4.50–4.62 (br, O(6)H), 4.2 (d, 1 H, H-3′), 3.25–3.78 (m, 40 H, H-2,4,6,5,3), 3.18 (s, 1 H, H-2′); δ_C: 166.90 (C-7), 133.22, 132.12, 130.60, 129.87, 128.52, 128.24, 127.26, 125.99, 124.80 (C-8 ~ 17), 101.93 (C-1), 101.51 (C-1′), 81.57 (C-4), 78.04 (C-4′), 74.82 (C-3′), 72.96 (C-3), 72.35 (C-2), 72.05 (C-5), 71.79 (C-5′), 71.50 (C-2′), 59.86 (C-6). Anal. Calcd for $C_{53}H_{76}O_{36} \cdot 6H_2O$: C, 45.56; H, 6.35. Found: C, 45.27; H, 6.09.

2- and 3-O-mono-β-naphthoyl-βCD (**3** *and* **4**).—β-Naphthoyl chloride (1.3 g) in 100 mL CH_3CN was added within 15 min to 400 mL alkaline aqueous solution

(adjusted by 1.2 g NaOH) of 6.5 g βCD under stirring. After 40 min, the reaction solution was neutralized and filtered. The filtrate was treated similiarly to that of **1** and **2** to get pure **3** and **4**, accompanied by 2% yield of dinaphthoated isomers as the major by-products.

3: 15% yield; $R_f = 0.35$; δ_H: 8.79 (s, 1 H, H-15), 8.10 (d, 1 H, H-9), 7.90–8.05 (d, 3 H, H-10, 11, 14), 7.60–7.64 (m, 2 H, H-12,13), 5.64–5.85 (br, O(2)H, O(3)H), 5.26 (s, 1 H, H-1′), 4.72–4.84 (m, 7 H, H-1), 4.42–4.56 (br, O(6)H), 4.20 (m, 1 H, H-2′), 3.22–3.70 (m, 40 H, H-2,4,6,5,3), 3.18 (d, 1 H, H-3′); δ_C: 166.12 (C-7), 135.10, 132.11, 131.33, 129.33, 128.51, 127.97, 127.64, 126.82, 125.50 (C-8 ~ 17), 102.0 (C-1), 98.32 (C-1′), 81.62 (C-4), 81.03 (C-4′), 74.08 (C-2′), 73.04 (C-3), 72.41 (C-2), 72.09 (C-5), 71.74 (C-5′), 69.73 (C-3′), 59.95 (C-6). Anal. Calcd for $C_{53}H_{76}O_{36} \cdot 4H_2O$: C, 46.77; H, 6.22. Found: C, 46.81; H, 6.08.

4: 10% yield; $R_f = 0.30$; δ_H: 8.60 (s, 1 H, H-15), 8.08 (d, 1 H, H-9), 7.90–8.05 (d, 3 H, H-10,11,14), 7.60–7.64 (m, 2 H, H-12,13), 5.65–5.85 (br, O(2)H, O(3)H), 4.97 (s, 1 H, H-1′), 4.72–4.85 (m, 7 H, H-1), 4.45–4.55 (br, O(6)H), 3.85 (m, 1 H, H-3′), 3.23–3.70 (m, 40 H, H-2,4,6,5,3), 3.05 (d, 1 H, H-2′); δ_C: 165.72 (C-7), 134.80, 132.09, 130.51, 120.31, 128.67, 128.06, 127.61, 126.58, 125.73 (C-8 ~ 17), 101.97 (C-1), 101.68 (C-1′), 81.70 (C-4), 78.27 (C-4′), 74.55 (C-3′), 72.94 (C-3), 72.67 (C-2), 72.36 (C-5), 72.06 (C-5′), 71.72 (C-2′), 59.90 (C-6). Anal. Calcd for $C_{53}H_{76}O_{36} \cdot 2H_2O$: C, 48.04; H, 6.08. Found: C, 48.38; H, 5.94.

2- and 3-O-mono-benzoyl-βCD (**5** *and* **6**).—Benzoyl chloride (1.0 g) in 100 mL CH_3CN was added within 5 min to 400 mL alkaline aq solution (adjusted by 0.2 g NaOH) of 6.5 g βCD under stirring. After another 5 min, the reaction solution was neutralized and treated similarly to that described above to obtain pure products **5** and **6**, as well as about 2% yield of dibenzoated isomers.

5: 8% yield; $R_f = 0.37$; δ_H: 7.96–8.60 (d, 2 H, H-9,13), 7.60–7.62 (d, 1 H, H-11), 7.48–7.51 (t, 2 H, H-10,12), 5.76–5.81 (br, O(2)H, O(3)H), 5.37 (d, 1 H, H-1′), 4.88–4.94 (m, 7 H, H-1), 4.56–4.68 (br, O(6)H), 4.12 (d, 1 H, H-2′), 3.22–3.68 (m, 40 H, H-2, 4,6,5,3), 3.19 (d, 1 H, H-3′); δ_C: 165.92 (C-7), 133.07 (C-8), 131.26 (C-11), 129.40 (C-9, 13), 128.12 (C-10, 12), 101.98 (C-1), 98.29 (C-1′), 81.64 (C-4), 80.99 (C-4′), 73.89 (C-2′), 72.99 (C-3), 72.63 (C-2), 72.05 (C-5), 71.12 (C-5′), 69.62 (C-3′), 59.94 (C-6). Anal. Calcd for $C_{49}H_{74}O_{36} \cdot 5H_2O$: C, 44.28; H, 6.37. Found: C, 44.06; H, 6.07.

6: 16% yield; $R_f = 0.32$; δ_H: 7.93–7.96 (d, 2 H, H-9,13), 7.52–7.57 (d, 1 H, H-11), 7.44–7.48 (t, 2 H, H-10,12), 5.68–5.77 (br, O(2)H, O(3)H), 4.93 (d, 1 H, H-1′), 4.75–4.81 (m, 7 H, H-1) 4.48–4.56 (br, O(6)H), 3.85 (d, 1 H, H-3′), 3.22–3.62 (m, 40 H, H-2, 4,6,5,3), 3.08 (d, 1 H, H-2′); δ_C: 165.66 (C-7), 132.30 (C-8), 131.62 (C-11), 129.49 (C-9,13), 128.13 (C-10,12), 101.76 (C-1), 101.62 (C-1′), 81.62 (C-4), 78.23 (C-4′), 74.73 (C-3′), 72.63 (C-3), 72.39 (C-2), 72.04 (C-5), 71.71 (C-5′), 71.03 (C-2′), 59.94 (C-6). Anal. Calcd for $C_{49}H_{74}O_{36} \cdot 5H_2O$: C, 44.28; H, 6.37. Found: C, 44.12; H, 6.03.

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