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Note

New cyclomaltoheptaose (β-cyclodextrin) derivative 2-*O*-(2-hydroxybutyl)cyclomaltoheptaose: preparation and its application for the separation of enantiomers of drugs by capillary electrophoresis

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Abstract—A new soluble cyclomaltoheptaose (cyclodextrin) derivative, 2-*O*-(2-hydroxybutyl)cyclomaltoheptaose [2-*O*-(2-hydroxybutyl)-β-cyclodextrin, 2-HB-β-CD], was prepared and studied as an efficient chiral selector in the separation of racemic mixtures of drugs by capillary electrophoresis (CE). Results showed that 2-HB-β-CD could provide higher separating capability than that of β-CD and the similarly substituted 2-HP-β-CD.

Keywords: 2-*O*-(2-Hydroxybutyl)cyclomaltoheptaose; 2-*O*-(2-Hydroxybutyl)-β-cyclodextrin; Capillary electrophoresis (CE); Chiral selector

Torus-shaped cyclomalto-oligosaccharides (cyclodextrins, CDs), which are cyclic oligosaccharides consisting of 6, 7, or 8-glucopyranose units (named α-, β-, and γ-CD, respectively) linked by α-(1→4) bonds have been widely used as host compounds in molecular recognition, for separation of enantiomers in racemic mixtures, and as enzyme models.[1,2] For constructing additional potential host models, research has focused on the regioselective functionalization of CDs, particularly on the more open secondary hydroxyl side of the molecules, 'the real business end' of CDs.[3,4] In this work, a new water-soluble β-CD derivative, 2-*O*-(2-hydroxybutyl)-β-cyclodextrin (2-HB-β-CD) was prepared with the intention of producing useful functional models with enhanced performance characteristics. Compared with 2-*O*-(2-hydroxypropyl)-β-CD (2-HP-β-CD), which has proved to be a potential functional model in chiral separation and in drug delivery, as well as a catalyst for organic reactions,[5–14] 2-HB-β-CD was found to be a more efficient chiral selector than the similarly substituted 2-HP-β-CD in the separation of racemic mixtures of drugs by capillary electrophoresis (CE).

It is generally recognized that a β-CD with a low degree of substitution cannot achieve appropriate solubility in water, and a β-CD with a high degree of substitution usually leads to a more complicated chiral environment, which results in less sensitivity in chiral selection. Therefore, in the design of a useful hydroxybutyled β-CD that might serve as a potential chiral selector, two 2-HB-β-CDs with different average degrees of substitution of about 3.0 and 4.0 were prepared (Scheme 1).

According to the elegant explanation of Ueno and Breslow,[15] the hydroxybutyl substituent position of the products (**2** and **3**) could be clearly indicated on the 2-OH of β-CD by the ^{13}C NMR spectrum, which showed a large downfield chemical shift for C-2 (73.76→78.58) and C-1 (101.9→103.5), and nearly no change in the chemical shift of C-6 of the unsubstituted glucose units. The degree of hydroxybutyl substitution of the products **2** and **3** could be determined by the ^{1}H NMR data based on the integral peak area ratio of H-10 to H-1, for the

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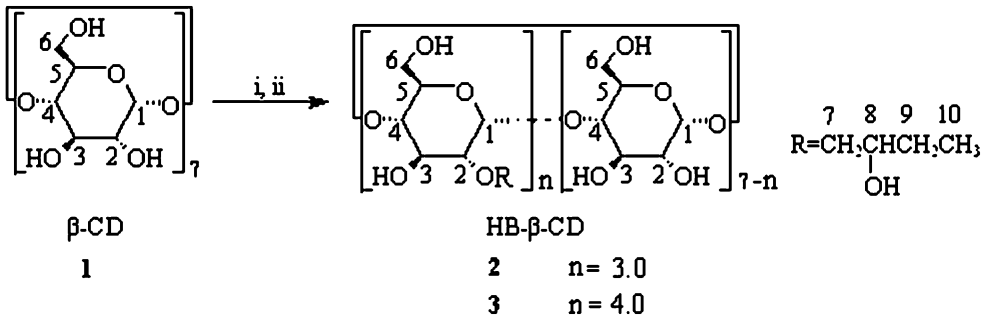

Scheme 1. (i) β-CD (6.6 g, 5.81 mmol), NaOH (100 mL, 0.375 mol L^{-1}), 1,2-butylene oxide (4.2 mL), rt, 15 h, (**2**, 40.8%); (ii) β-CD (6.6 g, 5.81 mmol), NaOH (100 mL, 0.375 mol L^{-1}), 1,2-butylene oxide (6.2 mL), rt, 15 h, (**3**, 44.6%).

signals of H-10 and H-1 are relatively separated from the others in the ^1H NMR spectrum. The average degrees of substitution (DS) of **2** and **3** were calculated to be approximately DS 3.0 and 4.0.

Separation of enantiomers by capillary electrophoresis (CE) has attracted much attention for its high efficiency, small sample requirement, low cost, simplicity, and flexibility. CE with a background electrolyte containing modified CDs as the chiral selector has been widely used in the operating mode of CE[16–18] for resolving enantiomers. When 2-HB-β-CD was used as a chiral selector in CE, it was found that the enantiomers of anisodamine, promethazine, adrenaline, verapamil, and salbutamol could be separated effectively under the optimum conditions (50 mmol L^{-1} H_3PO_4–NaH_2PO_4 (pH 2.5), 5 mmol L^{-1} 2-HB-β-CD). The most suitable pH (pH 2.5) for the separation of the drug enantiomers might be related to the nitrogen-containing ring systems of the drugs, which could cause enhanced complexation of the drugs with CDs by inhibiting of the electroosmotic flow under acidic conditions.

2-HB-β-CD (**2** and **3**) was found to be the most effective chiral selector compared with β-CD and 2-HP-β-CD (average DS 4.0) (Figs. 1, 2 and Table 1). The

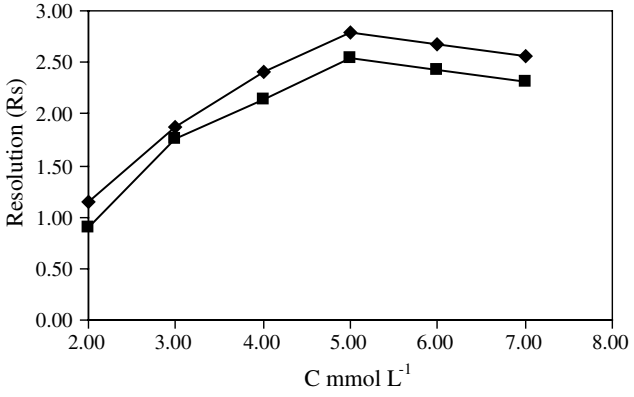

Figure 1. Concentration effect of 2-HB-β-CD (**2**) on the resolution (Rs) (◆) anisodamin (■) promethazine. Sample concentration: 100 μg mL^{-1}; buffer: phosphate 50 mmol L^{-1} (pH 2.5); Applied voltage: 15 kV; Rs: Resolution of the enantiomers; *C* (mmol L^{-1}): Concentration of 2-HB-β-CD (**2**).

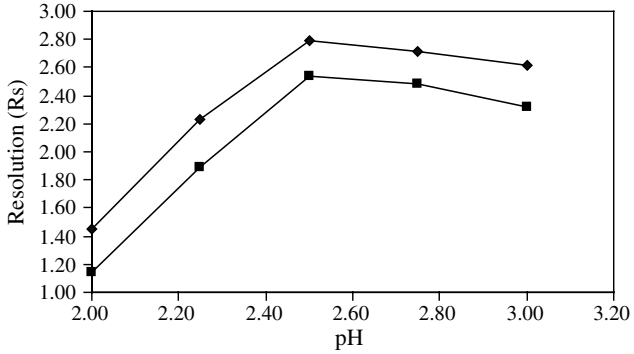

Figure 2. pH effect of the phosphate buffer on the resolution (Rs) (◆) anisodamin (■) promethazine. Sample concentration: 100 μg mL^{-1}; 2-HB-β-CD (**2**) concentration: 5 mmol L^{-1}; Applied voltage: 15 kV; Rs: Resolution of the enantiomers; pH: pH of the phosphate buffer.

Table 1. The separation of racemic drugs by CE using β-CD derivatives as chiral selectors[a]

Pharmaceutical	Resolution (Rs)			
	β-CD	2-HB-β-CD	2-HB-β-CD	2-HP-β-CD[b]
	(**1**)	(**2**)	(**3**)	—
Anisodamin	1.05	2.79	2.32	1.35
Promethazine	2.10	2.54	2.48	2.24
Adrenaline	0	3.05	0.78	0
Verapamil	0	1.59	1.21	0
Salbutamol	0	1.76	1.32	0

[a] Conditions: Capillary: fused silica, 45 cm total length, 36 cm effective length, 75 μm inner diameter; Sample concentration: 100 μg mL^{-1}; Buffer: phosphate 50 mmol L^{-1} (pH 2.5); Chiral selector concentration: β-CD, 2-HP-β-CD, 2-HB-β-CD 5 mmol L^{-1}, respectively; Applied voltage: 15 kV; capillary temperature: 25 °C. Rs = resolution of the enantiomers.

[b] A gift of Huantai Xinda Co. Ltd., P.R.C. Avg. DS = 4.0.

enantiomers of adrenaline, verapamil, and salbutamol showed no separation when using β-CD and 2-HP-β-CD (average DS 4.0) as the chiral selector. These results might be related to the relatively linear structures of the molecules of the three drugs. In comparison with the other two drugs, adrenaline, verapamil, and salbutamol showed obvious stronger complexation with **2** than that with β-CD, 2-HP-β-CD and **3**. The enantioselectivity for

drug isomers in CE was also influenced by the degree of substitution of 2-HB-β-CD. The chiral selectivity of **2** with a low degree of substitution (DS ~3.0) was more sensitive than that of **3** with a relatively high degree of substitution (DS ~4.0). This might be related to a more complicated interior chiral environment of 2-HB-β-CD with relatively high degree of substitution than that with low degree of substitution.

1. Experimental

1.1. General methods

Commercial cyclomaltoheptaose (β-CD) was recrystallized from water and dried at 100 °C in vacuum (2 torr) for 4 h. 2-HP-β-CD (average DS 4.0) was a gift of Huantai Xinda Co. Ltd, P. R. China. 1,2-Butylene oxide, acetone, 2-propanol, sodium hydroxide, and other reagents were of A.R. grade and used without further purification. NMR spectra were recorded on Bruker Avance-600 and -400 spectrometers. Capillary electrophoresis (CE) was run on an ACS-2000 capillary electrophoresis system (Beijing Cai-Lu Scientific Apparatus Co. Ltd. China). The combustion analysis was recorded on a Perkin–Elmer 2400(II) elemental analyzer.

1.2. 2-*O*-(2-Hydroxybutyl)cyclomaltoheptaose (2)

β-CD (6.6 g, 5.81 mmol) was dissolved in a solution of NaOH (100 mL, 0.375 mol L^{-1}). Then 1,2-butylene oxide (4.2 mL) was added dropwise in 50 min at 0 °C under stirring. The mixture was stirred for a further 15 h at room temperature. Hydrochloric acid was used to adjust the pH of reaction solution to pH 7.0. TLC on silica gel showed the formation of the product **2** (R_f 0.61 for **2**, R_f 0.42 for **1**; developing agent, 5:2:2 2-PrOH–EtOAc–H_2O). The solvent was vaporated in vacuum, and the residue was dried in vacuum for 10 h at 80 °C. The mixture was further purified by silica gel chromatography (eluent, 6:1:1 2-PrOH–EtOAc–H_2O) to furnish 3.2 g of **2** as white powder (yield, 40.8%). ^{1}H NMR (D_2O, 600 MHz): δ 5.18–5.33 (m, 7H, H-1, H-1′), 4.12–3.70 (m, ~51H, H-2, H-2′, H-3, H-3′, H-4, H-4′, H-5, H-5′, H-6, H-6′, H-7, H-8), 1.58 (m, 6H, H-9), 1.05 (t, 9H, H-10); ^{13}C NMR (D_2O, 150 MHz): δ 103.50 (C-1), 101.90 (C-1′), 82.89 (C-4), 82.64 (C-4′), 78.58 (C-2′), 74. 84 (C-7), 74.05 (C-3), 73.76 (C-2), 73.56 (C-5), 73.33 (C-8), 62.02 (C-6), 31.97 (C-9), 10.70 (C-10). Anal. Calcd for $C_{54}H_{94}O_{38}\cdot 8H_2O$: C, 43.37; H, 7.36. Found: C, 43.17; H, 7.29.

1.3. 2-*O*-(2-Hydroxybutyl)cyclomaltoheptaose (3)

According to the preparation of **2**, 6.2 mL of 1,2-butylene oxide was used instead of 4.2 mL, and 3.5 g of **3** could be prepared (yield, 44.6%). R_f 0.63 (developing agent, 5:2:2 2-PrOH–EtOAc–H_2O). ^{1}H NMR (D_2O, 400 MHz): δ 5.05–5.22 (m, 7H, H-1, H-1′), 3.95–3.56 (m, ~54H, H-2, H-2′, H-3, H-3′, H-4, H-4′, H-5, H-5′, H-6, H-6′, H-7, H-8), 1.50 (m, 8H, H-9), 0.92 (t, 12H, H-10). ^{13}C NMR (D_2O, 150 MHz): δ 102.82 (C-1), 101.80 (C-1′), 82.74 (C-4), 82.57 (C-4′), 78.52 (C-2′), 74.78 (C-7), 74.01 (C-3), 73.62 (C-2), 73.47 (C-5), 73.19 (C-8), 61.92 (C-6), 31.84 (C-9), 10.06 (C-10). Anal. Calcd for $C_{58}H_{102}O_{39}\cdot 7H_2O$: C, 44.96; H, 7.49. Found: C, 44.76; H, 7.32.

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