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Molecular binding thermodynamics of spherical guests by β-cyclodextrins bearing aromatic substituents

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ABSTRACT

The molecular binding behaviors of two β-cyclodextrin (β-CD) derivatives bearing 1,2,3-triazole moieties, i.e. mono-6-deoxy-6-{4-(8-oxymethylquinolino)[1,2,3]triazolyl}-β-CD (**1**) and mono-6-deoxy-6-{4-(8-oxymethylnaphthol)[1,2,3]triazolyl}-β-CD (**3**), and their analogs without 1,2,3-triazole moieties, i.e. mono-6-deoxy-6-(8-oxymethylquinolino)-β-CD (**2**) and mono-6-deoxy-6-(8-oxymethylnaphthol)-β-CD (**4**) toward spherical guests (±)-borneol and (±)-camphor were investigated to elucidate how substituent moiety of host affects the binding abilities by 2D NMR as well as microcalorimetric titrations in aqueous phosphate buffer solution (pH 7.20) at 298.15 K. The binding modes of host–guest interactions obtained from 2D NMR displayed that host CDs without triazole moieties gave better induce-fit efficiency between hosts and guests, leading to stronger binding abilities. Thermodynamically, the inclusion complexation was driven by enthalpy with the stoichiometry of 1:1. Another factor contributed to the enhanced binding abilities was the enthalpy gain with the smaller entropy loss.

1. Introduction

Cyclodextrins (CDs) are cyclic oligosaccharides, formed from α-1,4 glucosidic bonds of a number of glucose units. Due to their hydrophilic outer surface and hydrophobic inner cavity, they offer the advantage of encapsulating various organic guests within their hydrophobic cavities to form host–guests complexes through the contribution of many intermolecular weak interactions, such as van der Waals, hydrophobic, hydrogen-bonding, dipole–dipole, and electrostatic interactions [1–4]. Moreover, introduction of diverse substituents may alter both the physicochemical properties of the CDs and the binding ability between CDs and guest molecules [5–7]. Therefore, great efforts have been put into designing and developing of novel CD derivatives. In addition, "click chemistry" [8] was widely studied in various fields, particularly in designing new molecules and macromolecules under very mild reaction conditions and high yield [9,10]. In the present work, we synthesized a series of quinoline- and naphthol-modified β-CD derivatives with and without triazole moieties (Fig. 2), and investigated their binding behaviors toward (±)-borneol and (±)-camphor (Fig. 1), which are bicyclic terpenoids possessing the advantages of biological functions such as antibacterial, antispasmodic, choleretic, and tranquilizing effects [11]. It was our special interest to examined the effects of different conformation on binding abilities of β-CD derivatives from the viewpoints of binding geometry and binding thermodynamics.

2. Experimental

2.1. Materials

All chemicals were used as reagent grade unless noted. β-CD was recrystallized twice from water and dried in vacuo at for 24 h. Camphor and borneol enantiomers were commercially available and used as received. Phosphate buffer solution of pH 7.20 (I = 0.1 M, 3% DMSO) was used for ITC experiments. Mono[6-*O*-(*p*-toluenesulfonyl)]-β-CD (6-OTs-β-CD) **7** was prepared by the reaction of native β-CD with *p*-toluenesulfonyl chloride in NaOH aqueous solution in ca. 10% yield [12]. 6-Deoxy-6-azido-β-CD **8** was prepared according to the literature procedure [13]. Crude DMF was stirring in CaH_2 for three days and then distilled under reduced pressure prior to use.

2.2. Synthesis of 8-propargyloxynaphthalene (**6**)

A mixture of 1-naphthol **5** (2.4 g, 0.015 mol), K_2CO_3 (6.2 g, 0.045 mol) and propargyl bromide (80%, w/w solution in toluene, 3.6 mL, 0.045 mol) in 40 mL of acetone was refluxed overnight. Insoluble precipitates were removed by filtration, and the filtrate was evaporated in vacuo. The residue was dissolved in CH_2Cl_2

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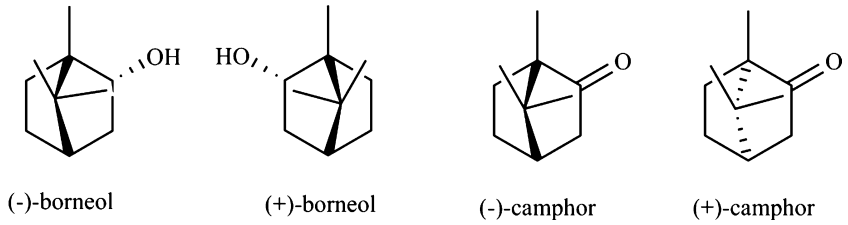

Fig. 1. Structures of guest molecules.

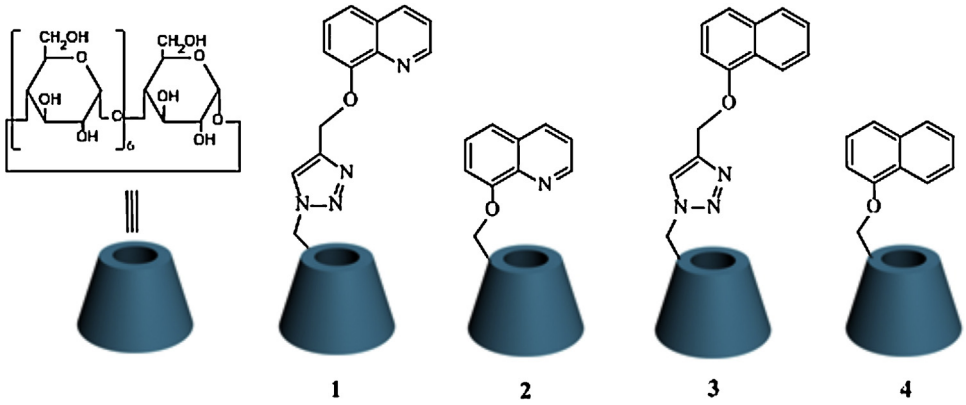

Fig. 2. Structures of host molecules.

(100 mL), and the organic layer was extracted with 1 M HCl solution (2× 50 mL) and brine. The yellow solution was dried under reduced pressure and further purified by flash column chromatography using PE/CH_2Cl_2 (10:1, v:v) as eluent to give the product as a colorless oil with a yield of 79% (R_f = 0.4). ^{1}H NMR (400 MHz, $CDCl_3$, TMS, ppm): δ = 2.55 (t, J = 2.4 Hz, 1H; H of CH≡C—), 4.91 (d, J = 2.4 Hz, 2H; H of CH≡C—CH_2—), 6.95 (d, J = 7.6, 1H; H of naphthalene), 7.39 (t, J = 8.0 Hz, 1H; H of naphthalene), 7.45–7.53 (m, 3H; H of naphthalene), 7.81 (dd, J = 6.2, 3.2 Hz, 1H; H of naphthalene), 8.32–8.24 (m, 1H; H of naphthalene). Anal. Calcd. for $C_{13}H_{10}O$: C, 85.69%; H, 5.53%. Found: C, 85.40%; H, 5.73%. EI-MS: 182 $[M+H]^+$.

2.3. Synthesis of mono-6-deoxy-6-{4-(8-oxymethylnaphthol) [1,2,3]triazolyl}-β-CD (3)

8-Propargyloxynaphthalene **6** (328 mg, 1.80 mmol) in 15 mL of THF was added to a solution of $CuSO_4 \cdot 5H_2O$ (600 mg, 2.40 mmol) and mono-6-deoxyl-6-azido-β-CD **8** (1.39 g, 1.20 mmol) in 35 mL of water. The mixture was kept at 50 °C for 10 min, and then sodium ascorbate (1.42 g, 7.20 mmol) was added. The color of the mixture turned orange immediately. Then, the mixture was heated at 50 °C under an atmosphere of N_2 overnight. After cooled to room temperature, insoluble precipitates were removed by filtration, and the filtrate was evaporated in vacuo. The residue was dissolved in a small amount of water, and washed with 300 mL of acetone for at least three times. After separation by column chromatography (silica gel) using n-PrOH:H_2O:$NH_3 \cdot H_2O$ (6:3:1, v:v:v) as eluent, **3** was obtained as a white solid with a yield of 70% (R_f = 0.4). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ = 3.65 (dd, J = 40.2, 19.4 Hz, 24H; C2-6 H of β-CD), 4.54 (dd, J = 41.9, 20.9 Hz, 6H; O-6 H of β-CD), 4.96–4.78 (m, 7H; C-1 H of β-CD), 5.30 (s, 2H; H of —CH_2—), 5.97–5.62 (m, 14H; O-2, 3 H of β-CD), 7.19 (d, J = 7.7 Hz, 1H; H of naphthalene), 7.55–7.41 (m, 4H; H of naphthalene), 7.87 (d, J = 8.2 Hz, 1H; H of naphthalene), 8.11 (d, J = 8.0 Hz, 1H; H of naphthalene), 8.28 (s, 1H; H of triazole). Anal. Calcd. for $C_{55}H_{79}N_3O_{35} \cdot 2H_2O$: C, 47.93%; H, 6.07%; N, 3.05%. Found: C, 47.90%; H, 6.27%; N, 3.12%. ESI-MS: 1364 $[M+H]^+$.

2.4. Synthesis of mono-6-deoxy-6-(8-oxymethylnaphthol)-β-CD (4)

Anhydrous K_2CO_3 (0.47 g, 3.0 mmol) was added to a solution of 8-hydronaphthalene (516 mg, 3.0 mmol) in dry DMF (12 mL). The mixture was stirred for 2 h at room temperature under nitrogen. Then, 6-OTs-β-CD **7** (1.9 g, 1.5 mmol) in dry DMF (20 mL) was

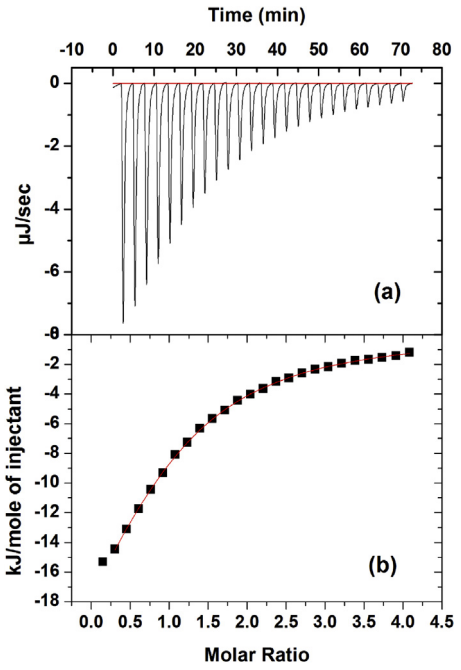

Fig. 3. Microcalorimetric titration of host **1** with (−)-borneol in phosphate buffer solution (pH = 7.20, I = 0.1 M, 3% DMSO) at 298.15 K. (a) Raw data for sequential 25 injections (10 μL/injection) of (−)-borneol solution (2.00 mM) into host **1** solution (0.094 mM). (b) Apparent reaction heat obtained from the integration of the calorimetric traces.