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Molecular self-assembly behavior of mono[6-O-6-(4-carboxyl-phenyl)]-*β*-CD in solution and solid state

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Abstract

A novel modified cyclodextrin, mono[6-O-6-(4-carboxyl-phenyl)]-*β*-CD (**1**), has been synthesized by the reaction of mono[6-(*p*-toluenesulfonyl)]-*β*-CD with 4-hydroxybenzoate, and its molecular self-assembly behavior in both solution and solid state was studied by means of crystallography, NMR spectroscopy and microcalorimetry. The results indicate that the bezoic acid groups are successively penetrated intermolecularly into the adjacent *β*-CD cavities to form helical columnar supramolecules in the solid state. As compared with crystal, the similar self-assembly behavior of **1** in aqueous solution has also been confirmed by the ^{1}H ROESY spectroscopy. Thermodynamically, the formation of polymeric supramolecules by modified CD in aqueous solution is mainly driven by entropy changes.

Keywords: self-assembly, modified CD, crystal structure, supramolecules, thermodynamics.

Macrocyclic sugars called cyclodextrins (CDs) are composed of D-glucopyranose connected through α-1,4 glycosidic bonds. Possessing the hydrophobic cavity and the hydrophilic exterior, CD has been successfully employed in several areas of science and technology as an excellent model system for mimicking the substrate-specific interaction of enzymes[1]. In recent years, the investigations on nanoscale molecular aggregates constructed by native and modified CDs have attracted more and more attention for their potential application in nanostructured functional materials[2 — 5]. One of the current interests in this area is the linear polymeric supramolecules created by native and modified CDs through molecular assembly and self-assembly. Therefore, a lot of effort has been devoted to the studies on the conformation and the host-guest interaction in order to reveal the general rule of the molecular recognition and assembly[6 — 9]. The investigation on the conformations of mono-modified CDs indicates that the intramolecular or intermolecular inclusion complexes could be formed in aqueous solution[9]. On the other hand, the crystallographic studies show that mono-modified CDs crystallize in three types: self-inclusion, layer-type packing, and one-dimensional self-assembly[10]. The crystal structures of

molecular assembly further indicate that the formation of different self-assembly modes mainly depends on the geometric complementarily and/or spatial fit between the substituent and the CD cavity. We recently reported[11] that mono[6-O-(4-formyl-phenyl)]-*β*-CD firstly formed dimeric structures in aqueous solution and that is the key step for the formation of linear polymeric supramolecules. Herein, in order to further reveal the general role of molecular assembly formed by mono-functional CD, the binding behavior of the polymeric supramolecules constructed by a newly synthesized mono[6-O-6-(4-carboxyl-phenyl)]-*β*-CD (**1**) (Fig. 1) has been studied in both aqueous solution and solid state. The results obtained are helpful for understanding the interaction between different substituent and CD, which are considered to play the important role in constructing nanoscale supramolecular system.

1 Experimental

(i) Materials. *β*-CD of reagent grade was recrystallized twice from water and dried for 12 h in vacuo at 100ºC. Commercially available potassium carbonate (K_2CO_3) and 4-hydroxybenzoate were used without further purification. *N,N*-Dimethylformamide (DMF) was dried over calcium hydride for 2 d and then distilled under reduced pressure prior to use.

NMR spectra were performed on a Varian INVOA 300 spectrometer. Elemental analysis was performed on a Perkin-Elmer 2400C instrument. The X-ray intensity data of **1** were collected on a standard Siemens SMART CCD Area Detector System equipped with a normal-focus molybdenum-target X-ray tube (λ= 0.71073Å) operated at 2.0 kW(50 kV, 40 mA) and a graphite monochromator. An isothermal calorimeter (VP-ITC), purchased from Microcal Co. (Northampton, MA), was used for microcalorimetric experiments.

(ii) Synthesis of mono[6-O-(4-carboxyl-phenyl)]-*β*-CD (**1**). 4-Hydroxybenzoate (0.28 g, 2 mmol) was dissolved in DMF (10 mL), to which anhydrous K_2CO_3 (0.56 g, 4 mmol) was added. The mixture was stirred at room temperature for 2 h , then mono[6-(*p*-toluenesul-fonyl)]-*β*-CD (1.9 g, 1.5 mmol) in dry DMF (20 mL) was added dropwise into the solution with stirring under nitrogen and heated to 80° for 24 h. The resultant solution was evaporated under a reduced pressure to give a yellow powder, which was dissolved in a minimum amount of hot water and then the solution was poured into acetone (200 mL). The crude product was purified on a column of Sephadex G-25, then was hydrolyzed in the presence of hydrochloric acid and dried in vacuo to give a pure sample **1** (yield: 18%). ^{1}HNMR (D_2O, TMS, ppm):δ 3.4 - 4.0 (m, 42 H); 4.9 - 5.0 (m, 7 H); 6.8 - 6.9 (d, 2 H); 7.7 - 7.8 (d, 2 H). UV-vis (H_2O) λ_{max} (ε) = 249 nm (7.1×10^3 $dm^3 \cdot mol^{-1} \cdot cm^{-1}$). Anal. Calcd for $C_{49}H_{74}O_{37}\cdot 8H_2O$: C, 42.06; H, 6.48. Found: C, 42.02; H, 6.34.

(iii) Crystal preparation. Crystals of the compound **1** were obtained from aqueous water (pH = 1.0). A small amount of the compound was dissolved in hot water to make a saturated solution, which was set at pH = 1.0 by HCl and then cooled to room temperature.

After removing the precipitates by filtration, the resultant solution was kept at room temperature for several weeks. The crystal formed was collected along with its mother liquor for X-ray crystallographic analysis.

(iv) Microcalorimetric experiment. The microcalorimetric titrations[12] were performed at the atmospheric pressure and 25 °C in aqueous solution. In each run, a solution of *β*-CD (13.6 mmol/L) in the 0.250 mL syringe was sequentially injected into an aqueous solution of **1** (0.13 mmol/L) in the sample cell (1.4227 mL volume). Each titration experiment was composed of 25 successive injections (10 μL per injection). Control experiment was performed to determine the heat of dilution by injecting a *β*-CD aqueous solution into a pure aqueous solution, containing no **1**. The dilution enthalpy was subtracted from the apparent enthalpy obtained in each titration run, and the net reaction enthalpy was analyzed by using the "one set of binding sites" model. The thermodynamic parameters obtained indicate that the substituent group is included into another *β*-CD cavity to form the dimer[11].

2 Results and discussion

(i) The molecular self-assembly behavior of **1** in the solid state. The crystals of **1** were orthorhormbic with the space group P2(1)2(1)2(1), empirical formula: $C_{49}H_{89.5}ClO_{44.25}$; M = 1422.16; a = 1.3866(5) nm, b = 1.5367(6) nm, c = 2.9744(7) nm, V = 6.338(3) nm^3; Z = 4; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0625, wR_2 = 0.1673.

In the molecular structure, every glucose residue has $^4C_1$ chair conformation, seven glycosidic oxygen atoms O(4) are coplanar within 0.00514 nm. Although introducing the substituent groups into the CD rings, the original skeleton of every *β*-CD rings has an approximate 7-fold axis and maintains the round shape of the macrocycle, which may be due to the intramolecular hydrogen bonds formed between adjacent glucose units. The benzoic acid group of **1** is located just above the GIU(1) glucose residue and the dihedral angle of the aromatic ring and the *β*-CD ring is 50.3°. The substituent attached to CD extends outside the CD ring and stretches straight along the side wall of the CD, facilitating the formation of head-to- tail helical columnar superstructure.

As shown in Fig. 2, the molecules are arranged along a 2-fold screw axis to form a head-to-tail linear polymeric supramolecule in which the substituent groups successively penetrate into the adjacent *β*-CD cavities from the secondary side. Interestingly, as compared with the previous reported CD derivatives, mono[6-O-(4-formyl - phenyl)]-*β*-CD [11] and mono(6-anilino-6-deoxy)-*β*-CD[13], compound **1** bears a carboxyl group in the *para* position of the aromatic ring to form the intermolecular hydrogen bonds, which can control the position and orientation of the substituent group in the CD cavity to some extent. It can also be seen that, along with the aromatic ring insetting into an

adjacent CD cavity, the carboxyl group pierces through the adjacent *β*-CD cavity to form the hydrogen bonds with the third CD by H_2O and Cl^- ($d_{O37A\cdots O38A}$ = 0.2568 nm, $d_{O38A\cdots Cl1A}$ = 0.3135 nm, $d_{Cl1A\cdots O7B}$ = 0.3074 nm).This hydrogen bond strengthens the interaction between the penetrating group and the *β*-CD cavity, resulting in the formation of another hydrogen bond between the glucosyl O atom and one of the aromatic hydrogens ($d_{C48A-H48\cdots O21C}$ = 0.2530 nm). These two independent hydrogen-bonding interactions fix the position and orientation of the substituent of **1** in the linear polymeric supramolecular. Comparison of the present results with the previous reports[10,11,13] shows that these crystals all possess the similar helical columnar suprastructures with a 2-fold axis. However, the self-assembly of mono(6- anilino-6-deoxy)-*β*-CD was stabilized by van der Waals interactions between host-guest[13], while mono[6-O-(4-formyl-phenyl)]-*β*-CD was stabilized not only by van der Waals interactions but also by the intermolecular hydrogen-bonding between the formyl group and CD[11]. Whereas in present study, due to the introducing the carboxyl group and Cl^-, hydrogen-bonding interactions become the main force for controlling the position and orientation of the penetrating group at the center of the *β*-CD cavity.

On the other hand, the strong hydrogen-bonded network formed by the hydroxyl group of the CD and intervening water not only stabilizes the linear polymeric supramolecules but also associates the columns with each other to further extend them to a more sophicticated level, as shown in Fig. 3.

(ii) The molecular self-assembly behavior of **1** in solution. It is well known that the NOE cross-peaks between the protons that are closer than 0.4 nm in space will be observed in ROESY spectrum and the relative intensities of these cross-peaks depend on the spaces between the corresponding protons. The height and the diameter of the *β*-CD cavity are about 0.79 ± 0.01 nm and 0.60 - 0.65 nm, respectively. Therefore, while the substituent group is included into the *β*-CD cavity, the NOE correlations between the protons of the substituent group and the protons of the *β*-CD cavity (H-3 and H-5) will be measured. On the other hand, according to the relative intensity of these cross-peaks[14], it is possible to estimate the orientation of the substituent group within the *β*-CD cavity. In order to compare the self-assembly behavior of compound **1** in aqueous solution and the solid state, ^{1}H ROESY (Rotating Frame Nuclear Overhauser Effect Spectroscopy) experiments have been performed on a Varian INVOA 300 spectrometer. As shown in Fig. 4, the ROESY spectrum of **1** exhibits clear NOE cross-peaks between the H-5 and H-3 protons of *β*-CD and aromatic protons in compound **1** (peaks A, B, C, D), demonstrating that the aromatic ring in **1** is deeply included into the *β*-CD cavity. Further information about the orientation of aromatic ring in the cavity of *β*-CD may be reasonably deduced according to the relative intensity of these cross-peaks. It can be clearly seen that the correlations between the *meta* protons (H^m) of the aromatic group and H-5 (peak A) and the cross-peaks between H^m and H-3 protons (peak B) are of the similar intensities, which implies that the aromatic ring

should be located longitudinally in the cavity of the β-CD. On the other hand, the correlations between the *ortho* protons (H^o) and H-5 (peak C) are weaker than that of between the H^o and H-3 (peak D), while the correlations between H^m and H-5 (peaks A) are stronger than that of between H^o and H-5 (peak C), showing that the aromatic substituent must be intermolecularly included into the hydrophobic cavity of another β-CD from the secondary side, just like the case in crystal, as can be seen from Fig. 5.

(iii) The binding ability of the dimerization and heterodimerization of **1**. In order to study the mechanism of the polymeric supramolecules by self-assembly of modified β-CD, self-aggregation constant (K_a) and the heterodimerization binding constant (K_s) and the thermodynamic parameters (ΔH^o and ΔS^o) of heterodimerization were measured in aqueous solution. The self-aggregation constant (K_a = 280 M^{-1}) of **1** was obtained by means of NMR titration[11] (Fig. 6), which is almost consistent with the heterodimerization binding constant (K_s = 240 M^{-1}) of **1** with native CD determined by isothermal titration calo- rimetry (ITC), implying the same binding ability of the heterodimerization and the dimerization.

These observations indicate that the dimerization and heterodimerization of modified β-CD possess the similar binding mode, that is, the substituent group appended to β-CD penetrated into the cavity of the partner β-CD from the secondary side to form a head-to-tail structures. Therefore, the thermodynamic parameters obtained upon the inclusion complexation of **1** with β-CD could be used to describe the self-assembly behavior of **1**. Thermodynamically, the penetration of the substituent group in **1** into β-CD cavity to form aggregates in aqueous solution is driven by favorable entropy changes ($T\Delta S$ = (7.63 ± 0.58) $kJ \cdot mol^{-1}$) with a negative enthalpy contribution (ΔH = −5.95 ± 0.42 $kJ \cdot mol^{-1}$), indicating that the molecular self- assembly is mostly attributed to the extensive desolvation effects and van der Waals interactions.

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Fig. 1.

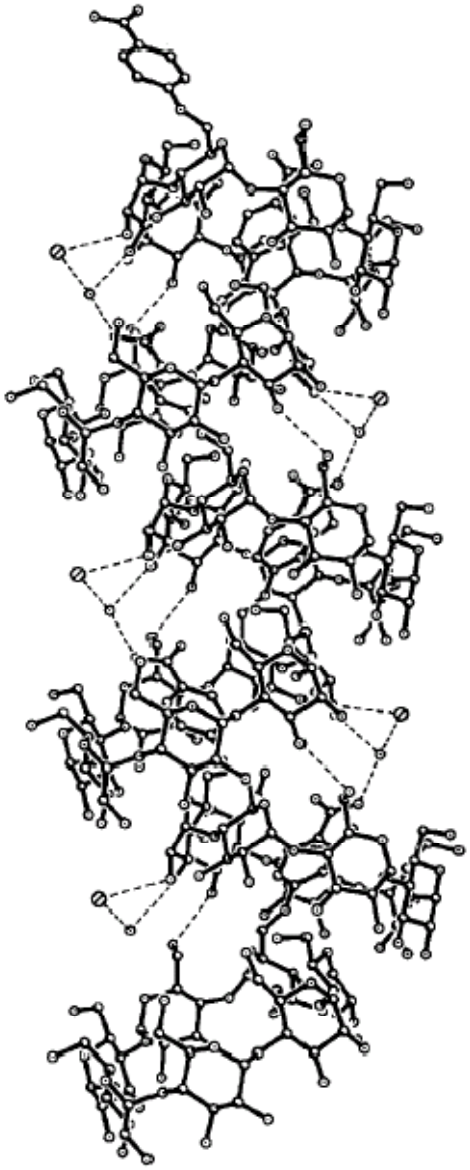


Fig. 2.

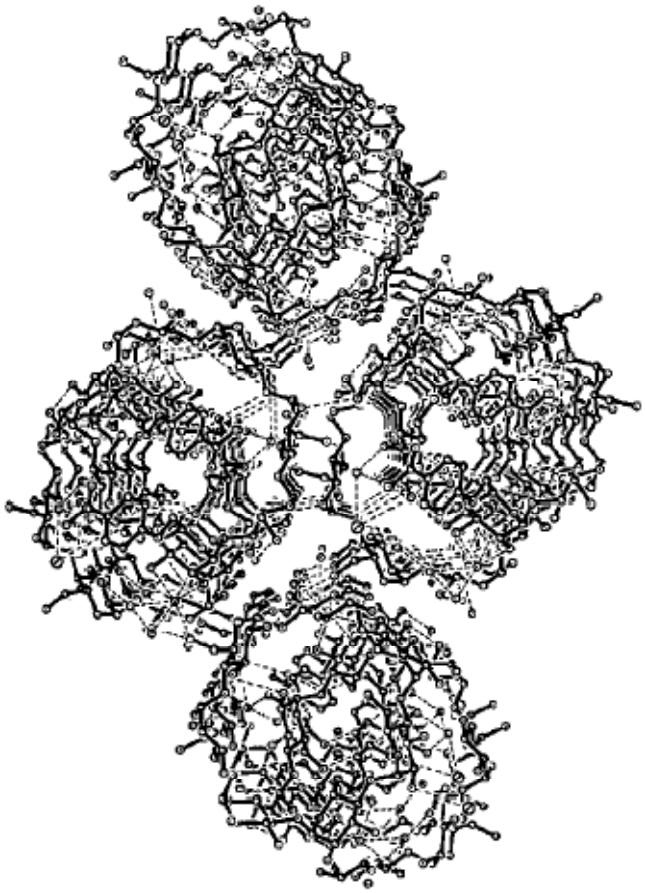
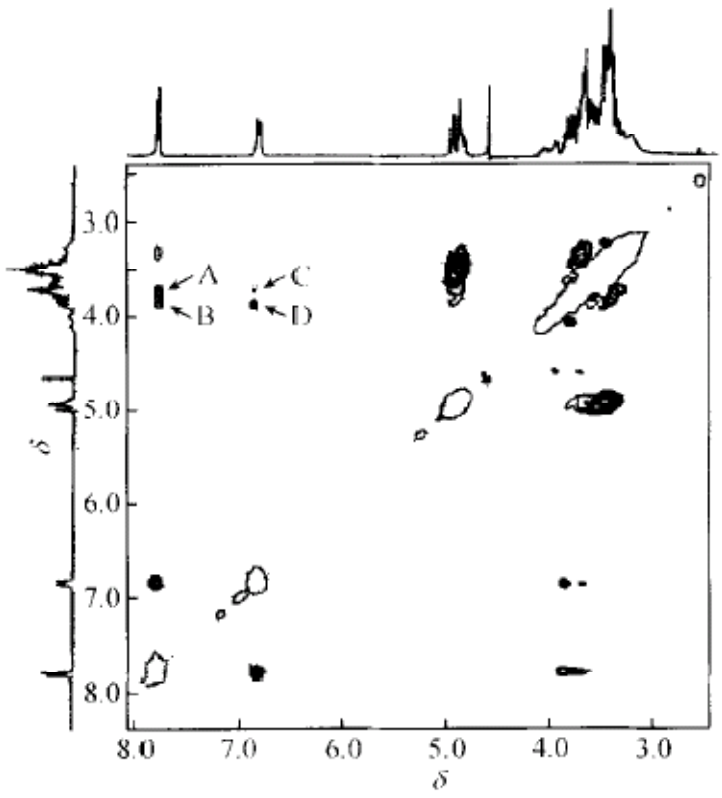


Fig. 3.



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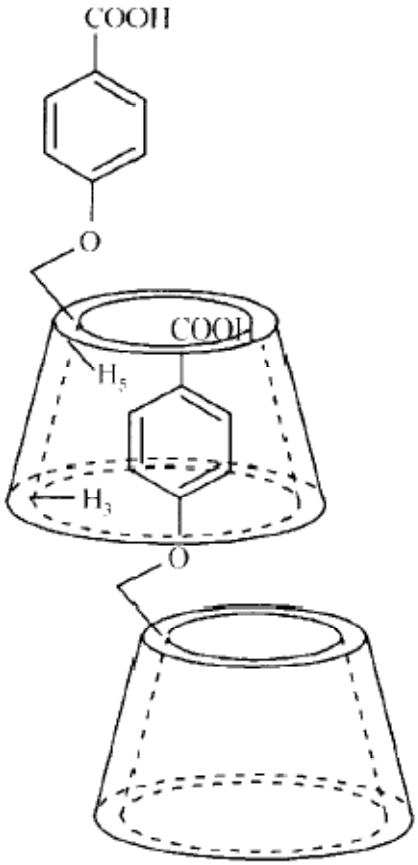

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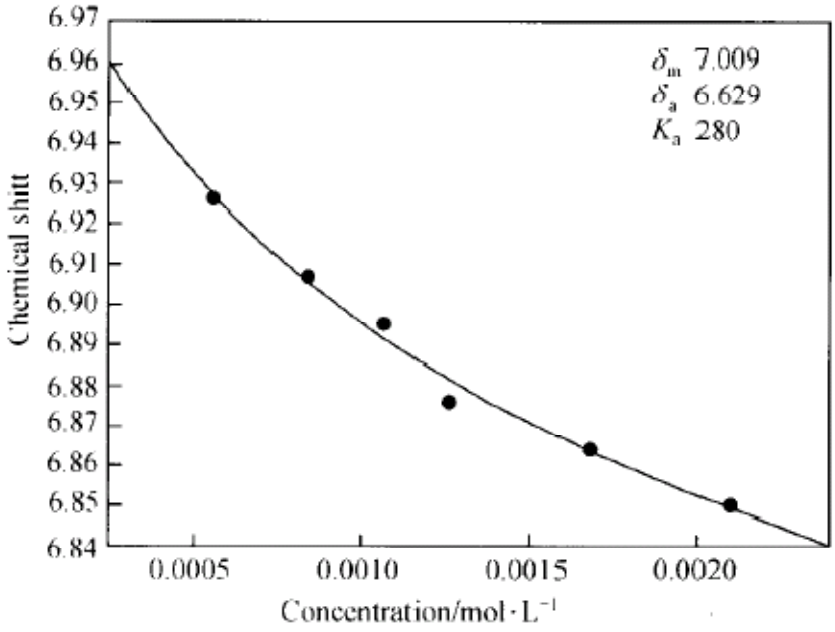
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Concentration/mol·L^{-1}

Fig. 6.