

# Binding Ability and Self-Assembly Behavior of Linear Polymeric Supramolecules Formed by Modified $\beta$ -Cyclodextrin

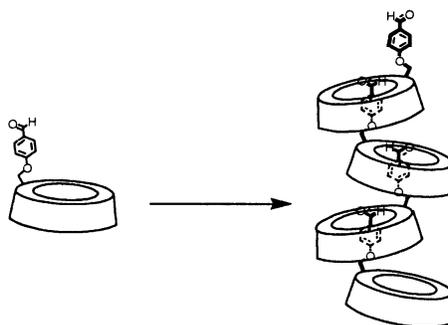
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## ABSTRACT



The binding ability and self-assembly behavior of molecular interpenetration by newly synthesized mono[6-*O*-(4-formyl-phenyl)- $\beta$ -cyclodextrin] has been investigated, revealing the formation mechanism of modified cyclodextrin from solution aggregation to solid linear polymeric supramolecules.

Investigations on molecular recognition and molecular self-assembly by native cyclodextrins and chemically modified cyclodextrins have gained extensive attention in recent years because of their potential in several areas of science and technology.<sup>1–3</sup> As a result, a lot of effort has been devoted to the conformation studies of chemically modified cyclodextrins in order to understand the mechanism of molecular recognition and molecular assembly by cyclodextrins and to obtain the more selective functional supramolecular systems. Most investigations on the conformations of chemically modified cyclodextrins in aqueous solution indicated that the chromatic substituents preferred to be self-included into the cavity of the parent cyclodextrin to form an intramolecular inclusion complex,<sup>4</sup> but heterodimerization (interaction between modified cyclodextrins with native

cyclodextrin),<sup>5</sup> homodimerization,<sup>6</sup> and the oligomeric supramolecular structure<sup>7</sup> have also been studied in aqueous solutions. However, some crystallographic studies of chemically modified cyclodextrins revealed that the substituents can be included into the cavities of the adjacent cyclodextrins to form a supramolecular helical column through intermolecular weak interactions.<sup>8</sup> Adamantane end-capped poly(ethylene oxide)s and  $\beta$ -cyclodextrin polymers are able to form large daisy chains by host–guest inclusion complex-

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ation.<sup>9</sup> Recent studies have also shown that cyclodextrins can form head-to-head channel structures<sup>10</sup> and head-to-tail chiral nanotubes.<sup>11</sup> However, to the best of our knowledge, there are no comparison studies for the inclusion complexation behavior of molecular interpenetration by modified  $\beta$ -cyclodextrin in solution and the solid state. Here, we investigated and compared the self-assembly behavior of molecular interpenetration by novel mono[6-*O*-(4-formyl-phenyl)]- $\beta$ -cyclodextrin (**1**) in both solution and the solid state. The binding constants and the thermodynamic parameters of the homodimerization of **1** and the heterodimerization of **1** with native cyclodextrin were measured by <sup>1</sup>H NMR and microcalorimetric titrations. These studies permit us to discuss the formation mechanism of modified cyclodextrin from solution aggregation to solid linear polymeric supramolecules.

Mono[6-*O*-(4-formyl-phenyl)]- $\beta$ -cyclodextrin (**1**) was synthesized by the reaction of mono[6-*O*-(*p*-toluenesulfonyl)]- $\beta$ -cyclodextrin with an excess of *p*-hydroxybenzaldehyde in DMF in the presence of K<sub>2</sub>CO<sub>3</sub>. After chromatographic purification over a Sephadex G-25 column, the residue obtained was recrystallized from water to give white solid **1**<sup>12</sup> in 30% yield. A small amount of **1** was dissolved in hot water to make a saturated solution, which was then cooled to room temperature. After removal of the precipitates by filtration, the resultant solution was kept at room temperature for 2 days. The crystal formed was collected along with its mother liquor for X-ray crystallographic analysis.

The crystals<sup>13</sup> of **1** were orthorhombic with the space group *P*2(1)2(1)2(1), *Z* = 4 and the unit cell parameters *a* = 13.204 Å, *b* = 19.146 Å, and *c* = 28.835 Å. In the structure, the

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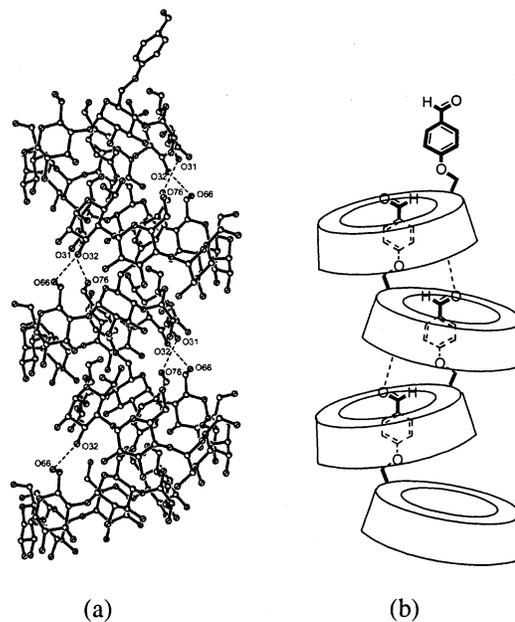
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(12) Data for **1**: <sup>1</sup>H NMR (D<sub>2</sub>O, TMS)  $\delta$  9.9 (s, H), 7.3–8.1 (m, 4H), 5.2 (m, 7H), 3.6–4.2 (m, 42H); UV-vis (H<sub>2</sub>O)  $\lambda_{\text{max}}$  ( $\epsilon$ ) = 283 nm (1.45 × 10<sup>4</sup> dm<sup>3</sup> mol<sup>-1</sup> cm<sup>-1</sup>). Anal. Calcd for C<sub>49</sub>H<sub>74</sub>O<sub>36</sub>·6H<sub>2</sub>O: C, 43.69; H, 6.43. Found: C, 43.87; H, 6.38.

(13) 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 (Mo K $\alpha$  radiation  $\lambda$  = 0.71073 Å) operated at 2.0 kW (50 kV, 40 mA) and a graphite monochromator. Data were collected to  $2\theta_{\text{max}}$  = 50.06°. Crystal data for **1**: C<sub>49</sub>H<sub>80</sub>O<sub>40</sub>, *M* = 1309.13; crystal size = 0.30 × 0.20 × 0.15 mm; orthorhombic; space group *P*2(1)2(1)2(1); *a* = 13.204(5) Å, *b* = 19.146(7) Å, *c* = 28.835(12) Å; *V* = 7290(5) Å<sup>3</sup>; *Z* = 4; *D<sub>m</sub>* = 1.193 g/cm<sup>3</sup>; absorption coefficient = 0.105 mm<sup>-1</sup>; *T* = 293 K. Reflections collected, 30 174; independent reflections, 12 876 (*R*(int) = 0.2146). The structure was solved by using the direct method and refined employing full-matrix least squares on *F*<sup>2</sup> = 1.016 (Siemens, SHELXTL, version 5.04). Data/restraints/parameters = 12 876/0/803. Final *R* indices [*I* > 2 $\sigma$ (*I*)] *R*<sub>1</sub> = 0.1416, *wR*<sub>2</sub> = 0.3217, *R* indices (all data), *R*<sub>1</sub> = 0.2946, *wR*<sub>2</sub> = 0.4211, largest difference peaks and holes = 1.005 and -0.695 e/Å<sup>3</sup>. The final *R* value was not particularly precise because of the background arising from the aqueous solution and the glass tube as well as slow airslaking.

original skeleton of cyclodextrin moiety with an approximate 7-fold axis and a round shape is not significantly changed with the introduction of the substituent group. The benzaldehyde group of **1** is located just above the GIU(7) glucose residues, and the dihedral angle of the aromatic ring and the  $\beta$ -cyclodextrin ring is 126.1°, which enhances the formation of a one-dimensional columnar superstructure. As shown in Figure 1, the aromatic group in **1** is deeply included into the



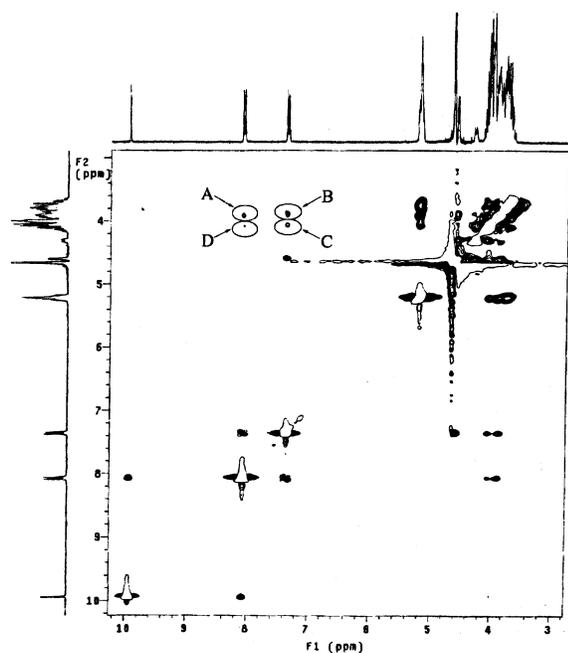
**Figure 1.** Stereodrawing of the stacking structure of **1**. Hydrogen bonds between cyclodextrin molecules are shown:  $d_{[\text{H31B}\cdots\text{O76}]} = 1.980$  Å,  $\Phi_{[\text{O31-H31B}\cdots\text{O76}]} = 176.9^\circ$ ;  $d_{[\text{H32B}\cdots\text{O66}]} = 2.005$  Å,  $\Phi_{[\text{O32-H32B}\cdots\text{O66}]} = 179.7^\circ$ . The column is located on a 2-fold screw axis. (a) Helical columnar structure of **1**. (b) Schematic representation of packing of **1**.

hydrophobic cavity of an adjacent cyclodextrin from the secondary hydroxyl side to make an angle of 116.3°. Interestingly, the aldehyde group attached to the benzene ring not only protrudes from the primary hydroxy side but also further interacts with the secondary hydroxyl of O3(GIU1)H in the third  $\beta$ -cyclodextrin by hydrogen bonding, forming an analogous rotaxane structure. Expanding the structural feature to the whole helical columnar superstructure, every cyclodextrin residue is regarded as both “wheel” and “stopper”. However, the “wheels” in the analogous rotaxane structure do not freely rotate along their axes, due to hydrogen bonding interaction between adjacent cyclodextrin molecules. On the other hand, these hydrogen bonds fix the relative position of the tethering cyclodextrin units, and they play an important role in stabilizing the helical columnar superstructure.

Compared with the previous report, the simple penetration of monosubstituted  $\beta$ -cyclodextrins,<sup>8</sup> mono[6-*O*-(4-formyl-phenyl)]- $\beta$ -cyclodextrin, gives rise to an unusual supramolecular self-assembly column tethered by four hydrogen

bonds between the penetrating cyclodextrin molecules. It is noted that the position and orientation of the benzaldehyde groups penetrated intermolecularly into the adjacent cyclodextrin cavities can be regulated by the hydrogen-bonding interactions. Furthermore, the helical columns associating with each other through hydrogen-bonding interactions along the *a* and *b* axes further extend to a more sophisticated level.

It is not sufficient to elucidate the conformations in aqueous solution by crystal structures. To obtain detailed information about the solution structure of mono[6-*O*-(4-formyl-phenyl)- $\beta$ -cyclodextrin],  $^1\text{H}$  NOESY experiments<sup>14</sup> have been performed on a Varian Mercury VX300 spectrometer. As shown in Figure 2, the NOESY spectrum of **1**



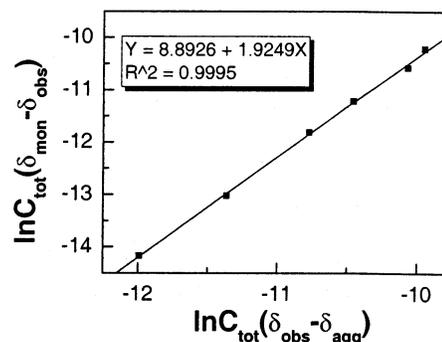
**Figure 2.**  $^1\text{H}$  NOESY spectrum (300 MHz) of **1** ( $[\mathbf{1}] = 1.0 \times 10^{-4}$  M) in  $\text{D}_2\text{O}$  at 298 K with a mixing time of 600 ms.

exhibits clear NOE cross-peaks between the H5 and H3 (weak) of cyclodextrin and aromatic protons of benzaldehyde group in compound **1** (peaks A–D), which demonstrate that the aromatic ring in **1** is deeply included into the cavity of cyclodextrin. Further information about the orientation of the aromatic ring in the cavity of the cyclodextrin moiety may be reasonably deduced according to the relative intensity of these cross-peaks. As illustrated in Figure 2, the clear and similar correlations between H5 and the *meta* protons (peaks A) or *ortho* protons (peaks B) in the benzaldehyde group imply that the aromatic ring should be located longitudinally near to H5, while the correlation between H3 and the *meta* protons (peaks D) are weaker than that between H3 and the *ortho* protons (peaks C), which indicates that the *meta* protons in the aromatic ring must be further away from H3

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than *ortho* protons. These results show that the aromatic substituent must be intermolecularly included into the hydrophobic cavity of another cyclodextrin from the secondary hydroxyl side. Therefore, the formation of the linear polymeric supramolecules of **1** in the solid state is a natural process.

It is very significant to reveal the stability of aggregation in solution, because it involves not only the formation of the certain structure in solid but also how to design versatile building units for supramolecular self-assembly. To investigate the binding ability of **1** by NMR, the sample was dissolved in  $\text{D}_2\text{O}$ , and  $^1\text{H}$  NMR measurements were carried out over a concentration range between  $1.0 \times 10^{-4}$  and  $1.22 \times 10^{-3}$  M, which spans the practical limits of NMR detection at the low concentration end to those dictated by the solubility of **1** at the high end. The effective binding constant *K* and the aggregation number *n* were calculated to be  $345 \text{ M}^{-1}$  and 1.9, respectively (Figure 3),<sup>15</sup> indicating that mono[6-



**Figure 3.** Plot from  $^1\text{H}$  NMR data of **1** as a function of total concentration to determine the aggregation equilibrium constant and aggregation number.

*O*-(4-formyl-phenyl)- $\beta$ -cyclodextrin molecules form dimers in the determined concentration range, which further reveals the general rule of the formed dimers in the self-assembly process of modified cyclodextrins.<sup>6a,b</sup> The dimerization is the first step for the formation of higher head-to-tail linear polymeric supramolecules.

Interestingly, the heterodimerization binding constant ( $K_S = 316 \text{ M}^{-1}$ ) of **1** with native cyclodextrin measured by isothermal titration calorimetry (ITC) is consistent with that by the NMR titration, suggesting the same binding properties between the heterodimerization and the dimerization. Therefore, the thermodynamic parameters obtained upon the inclusion complexation of **1** with native cyclodextrin by ITC can be used to describe the aggregation of **1**. Thermodynamically, the penetration of the benzaldehyde group in

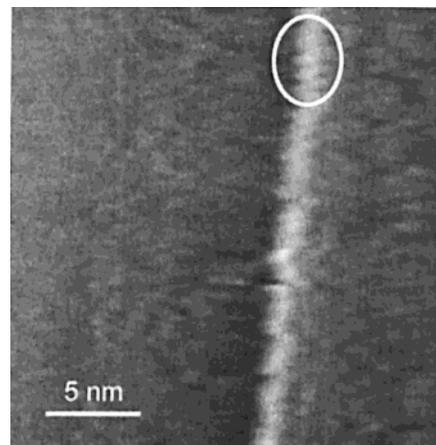
(15) A 1.22 mM solution of **1** in  $\text{D}_2\text{O}$  was sequentially diluted to a final concentration of 0.10 mM, and the chemical shift of the *meta* proton in aromatic ring was monitored. The observed shifts ( $\delta_{\text{obs}}$ ) were fit to the equation  $\ln[C_{\text{tot}}(\delta_{\text{mon}} - \delta_{\text{obs}})] = n \ln[C_{\text{tot}}(\delta_{\text{obs}} - \delta_{\text{agg}})] + \ln K + \ln(n) - (n - 1) \ln(\delta_{\text{mon}} - \delta_{\text{agg}})$ , where  $C_{\text{tot}}$  corresponds to the total concentration of **1**;  $\delta_{\text{mon}}$  and  $\delta_{\text{agg}}$  are the extrapolated values of the monomer and aggregate, respectively; and *K* and *n* are calculated from the plot of  $\ln[C_{\text{tot}}(\delta_{\text{mon}} - \delta_{\text{obs}})]$  vs  $\ln[C_{\text{tot}}(\delta_{\text{obs}} - \delta_{\text{agg}})]$ .

**1** into the cyclodextrin cavity to form the assembly in aqueous solution is driven by a favorable entropy change ( $T\Delta S = 11.63 \pm 0.01$  kJ/mol) with a minor negative enthalpy contribution ( $\Delta H = -2.63 \pm 0.12$  kJ/mol), to give a moderate binding constant. This study helps the understanding of the thermodynamic origin in the process of the molecular assembly.

To obtain further experimental information about the structure of the supramolecular assembly, STM (scanning tunneling microscopy) experiments<sup>16</sup> were performed to characterize the structure. The aqueous solution of samples were prepared in the concentration of  $10^{-5}$  M and dripped onto a fresh, highly ordered pyrolytic graphite (HOPG) surface at room temperature, and then the samples were dried in a vacuum for 30 min. Regularly aligned cyclodextrin units were clearly observed on the graphitic surface, as shown in Figure 4. From the image, we can obtain the detailed size according to the proportion shown in the figure. The length and width of each white dot are about 1.4 and 0.7 nm, respectively, which are consistent with the actual value of the diameter ( $1.54 \pm 0.04$  nm) and the height ( $0.79 \pm 0.01$  nm) of  $\beta$ -cyclodextrin. We conclude that one white dot corresponds to one cyclodextrin unit. Interestingly, the molecules are arranged distinctly in a herringbone fashion on a HOPG substrate (ellipse part) forming nanometer-sized wire-shaped aggregates such as compound **1** does in crystals.

In summary, we have compared the self-assembly behaviors of linear polymeric supramolecules formed by modified  $\beta$ -cyclodextrin **1** in both solution and the solid state to reveal the general rule of formation of the dimer. The binding constants and the thermodynamic parameters obtained in this study open new doors for investigation of the thermodynamic origin of molecular aggregation. The formation mechanisms of dimerization and/or heterodimerization of modified cyclodextrin allow further understanding of molecular recognition and self-assembly behavior in supramolecular chemistry,

(16) STM experiment was performed by using DS-89S with a W tip and with a sample bias voltage of +300 mV and a tunneling current of 2.10 nA.



**Figure 4.** STM image of supramolecular assembly of **1**.

and they indicate further promise for applications in designing novel functional assembly.

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**Supporting Information Available:** Tables of atomic coordinates, bond lengths and angles, and anisotropic displacement parameters for **1**; figures of the molecular structure and image of molecular stacking of **1**; ITC titration data; and the <sup>1</sup>H NMR titration experiments and the principle of the detailed calculation. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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