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Note

An investigation of the inclusion complex of β-cyclodextrin with *p*-nitrobenzoic acid in the solid state

Zhi Fan,* Chun-Hua Diao, Min-Jie Guo, Rong-Juan Du, Yuan-Fang Song, Zuo-Liang Jing and Ming Yu

College of Sciences, Tianjin University of Science and Technology, Tianjin 300222, PR China

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Abstract—The weak inclusion complex of cyclomaltoheptaose (β-cyclodextrin, βCD) with *p*-nitrobenzoic acid was investigated in the solid state. Crystallography shows that two βCD molecules co-crystallize with two *p*-nitrobenzoic acids and 28.5 water molecules $[2(C_{42}H_{70}O_{35})\cdot 2(C_7H_5NO_4)\cdot 28.5H_2O]$ in the triclinic system.

Keywords: β-Cyclodextrin; Cyclomaltoheptaose inclusion complex; Crystal structure; *p*-Nitrobenzoic acid

Cyclomaltooligosaccharides (cyclodextrins, CDs) are known to include a variety of apolar guest molecules in their macrocyclic structure.[1–13] To get further insight into the mechanism that governs the formation of inclusion complexes, we prepared such complex **1** with cyclomaltoheptaose (β-cyclodextrin, βCD) and *p*-nitrobenzoic acid (pNBA) and investigated it by X-ray crystallography.

The crystal data, experimental and refinement parameters of **1** are shown in Table 1. A numbering scheme for βCD and the guest molecule is shown in Figure 1.

In the crystal structure, two βCD molecules are linked through hydrogen-bonds producing a barrel-like structure inside of which a pair of guest molecules is accommodated, as shown in Figure 2. All glucose residues are in the $^4C_1$ conformation. No disordered atom has been found in the host molecule. The primary hydroxyl groups having a *gauche–gauche* orientation point outward the cavity, except for atoms O63 and O66, which have *gauche–trans* orientation and point inside the cavity. The sevenfold symmetry of the βCD molecule appears to be well maintained. This is reflected in the O4(n)···O4($n-1$) distances [average 4.36 and 4.37 Å] and O4($n+1$)···O4(n)···O4($n-1$) angles [128.6°]. The latter is equal to the angle of the regular heptagon (128.5714…°). However, the deformation of the macrocycle, if compared with the conformation typical of uncomplexed βCD, can be described through a heptagon defined by the O4 atoms bridging the seven glucopyranose units (average values for uncomplexed βCD: radius of the O4 heptagon is 5.04 Å, values ranging between 4.86 and 5.18 Å, O4(n)···O4($n-1$) distances are 4.31 Å, values ranging between 4.20 and 4.50 Å).[14] The guest molecule, located in the cavity of βCD, interacts with the macrocyclic host and this causes the deformation in the βCD ring: (the radius of the O4 heptagon is 5.02 and 5.03 Å, values ranging between 4.85 and 5.21 Å, O4(n)···O4($n-1$) distances are 4.36 and 4.37 Å, values ranging between 4.23 and 4.53 Å). On the other hand, the deviations of the O4 atoms from their optimum planes are 0.020 and 0.023 Å, respectively, which is small compared with the 'empty' βCD (0.028 Å).[15] In other words, the heptagon of the βCD molecule is better maintained in the inclusion complex than in the 'empty' βCD because of the presence of the guest molecule.

As can be seen in Figure 2, both *p*-NBA molecules are placed in the central cavities of βCD molecules. The two

* Corresponding author. Tel.: +86 22 60600808; fax: +86 22 23001002; e-mail: zhifan@tust.edu.cn

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Table 1. Crystal data, experimental and refinement parameters for **1**

	Crystal **1**
Molecular formula	$C_{49}H_{103.5}N_1O_{53.25}$
M_r (g mol^{-1})	1558.83
Crystal system	Triclinic
Space group	*P*1
Z	2
a (Å)	15.260(2)
b (Å)	15.4342(19)
c (Å)	17.950(2)
α (°)	99.2040(10)
β (°)	113.150(2)
γ (°)	103.272(2)
V (Å^3)	3632.6(8)
ρ_{calcd} (g cm^{-3})	1.425
F(000)	1661
Absorption coefficient (mm^{-1})	0.131
Crystal size (mm)	0.18 × 0.16 × 0.14
Range scanned θ (°)	1.41 to 25.00
Index range	$-18 \leqslant h \leqslant 18$, $-18 \leqslant k \leqslant 18$, $-21 \leqslant l \leqslant 21$
Data/restraints/parameters	10,329/102/856
Final *R* indices [$I > 2\sigma(I)$]	0.0887
R indices (all data)	$R_1 = 0.0922$, $wR_2 = 0.2634$
Largest diff. peak and hole (e Å^{-3})	1.292 and −0.821

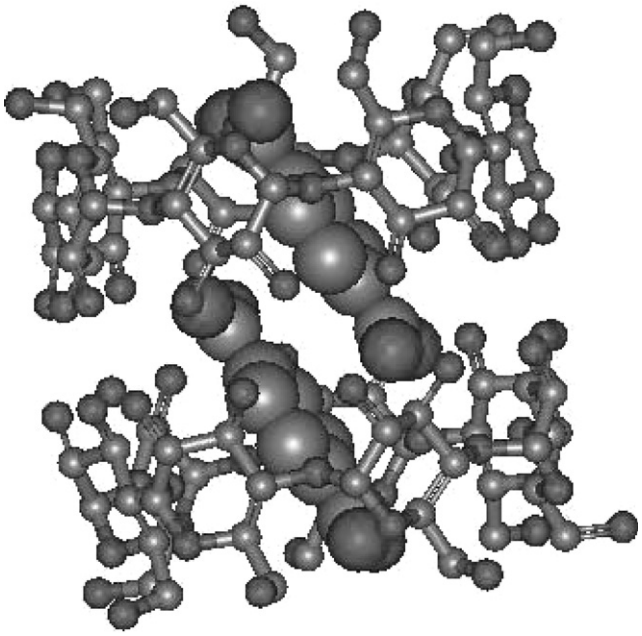

Figure 2. Stereoscopic view of the βCD dimer with the guest molecules inside the cavity.

aromatic rings of *p*-NBA are shifted from the O4 plane centers to the primary sides of βCD by 1.331 and 1.642 Å, respectively. The two rings are inclined by 64.4° and 62.2° with respect to the O4 plane, which show that the guest is tilted to occupy most of the available space in the cavity. It should be noted that the majority of the guest molecules of the βCD inclusion complexes include a hydrophobic moiety and a polar group, found as a rule in the region of the primary hydroxyl groups or protruding from it. In this inclusion complex, however, a carboxyl group is maintained by hydrogen bonding to the four surrounding hydroxyl groups and six water molecules, while the nitro group protruding from the region of the second hydroxyl groups, is located in the interface of the secondary hydroxyl groups of the two adjacent βCD and does not form hydrogen bond with the hydroxyl groups, as shown in Figure 3.

Crystal structures of the βCD inclusion complexes are classified into three types according to the host–guest interactions. In the present inclusion complex, as shown in Figure 3, the two βCD molecules are arranged in a brickwork pattern to form a layer-type structure. Adja-

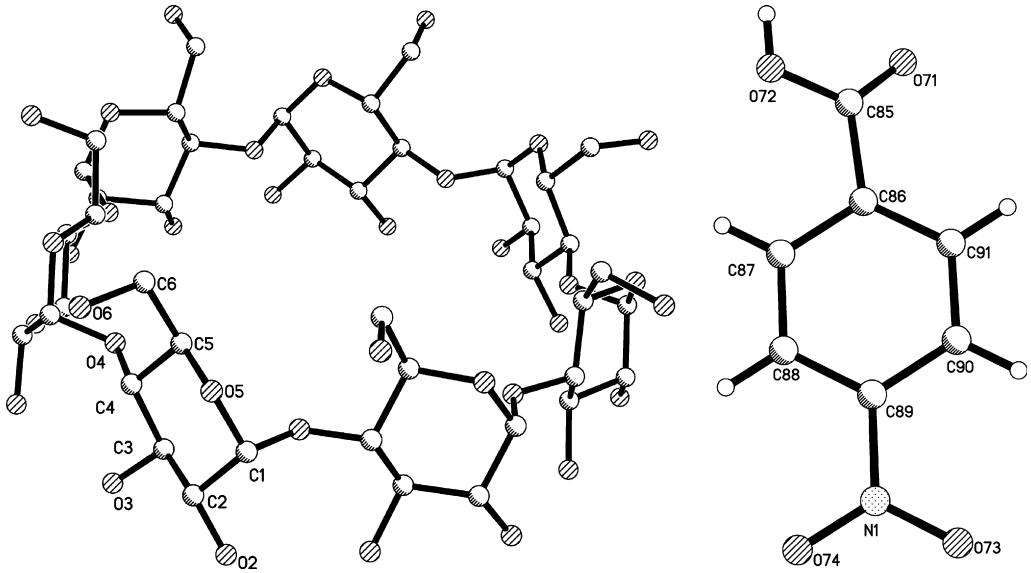

Figure 1. Diagram showing βCD and *p*-nitrobenzoic acid molecules and the numbering scheme.

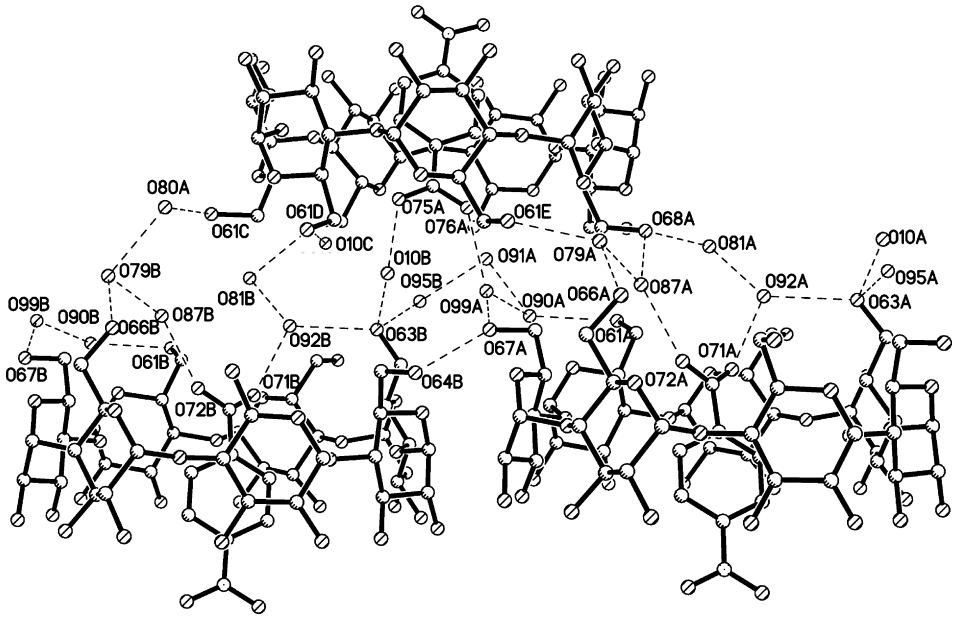

Figure 3. The layer-type molecular packing structure of the inclusion complex **1**. Intermolecular hydrogen bond interactions are drawn by dotted lines.

cent layers are shifted by half a molecule. As a result, the primary hydroxyl sides are open to the intermolecular space of the adjacent layer. The interspace between the adjacent layers is filled with water molecules. It should be noted that the water molecules filled in the layer interspace participate in interactions with a carboxyl group to form 13 hydrogen-bonds (ranging between 2.56 and 2.84 Å), typically bridging hydroxyl groups of βCD molecules of the next layer, which could not only determine the position and orientation of the guest, but also contribute to the stabilization of the layer-type structure. So these hydrogen-bonding characteristics exhibited by the water molecules seem to be a crucial factor in determining the guest position and orientation.

In conclusion, the inclusion behavior of βCD with *p*-NBA was studied in the solid state. In the crystal structure, the *p*-NBA molecules prefer to occupy most of the available space in the cavity, and prefer to protrude with their polar COOH and NO_2 groups at hydroxyl groups sides. On the other hand, the *p*-NBA molecules are maintained in positions to form hydrogen bonds with carboxyl groups and the surrounding hydroxyl groups; water molecules further stabilize the layer structure. This system is of interest as a model for the study of weak binding interactions.

1. Experimental

1.1. General methods

Elemental analyses was performed on a Perkin–Elmer 2400C instrument. ^{1}H NMR spectra were recorded in D_2O on a Varian Mercury VX300 spectrometer. The X-ray intensity data were collected on a Saturn-70 Rigaku CCD Area Detector System equipped with a microfocus molybdenum target of Micro-Max-007 rotating anode (Mo Kα radiation $\lambda = 0.71073$ Å) operated at 50 kV and 16 mA and a confocal monochromator. During data collection, no intensity decay was observed. Data collection, reduction, and absorption correction were performed by program CRYSTALCLEAR.[16] The structure was eventually solved employing SHELXD.[17] Atom co-ordinates and anisotropic thermal parameters were refined for all non-hydrogen atoms using conjugate gradient least squares in the initial stages, and finally full-matrix least squares on F^2 with the SHELXL97 program.[18] All hydrogen atoms were introduced in idealized positions, those belonging to water molecules were not introduced. *p*-NBA was purchased from Tianjin Chemical Reagent Plant and used without further purification. Reagent grade βCD (from Shanghai Reagent works) was recrystallized twice from water and dried under diminished pressure at 95 °C for 24 h prior to use.

Synthesis of complex **1**. The EtOH soln of *p*-NBA (1 mmol, 20 mL) was added dropwise to an aq soln of βCD (1 mmol, 40 mL) and stirred at 70 °C for 6 h. Then the soln was cooled to room temperature, and the precipitate was obtained by slow evaporation of the soln. The crude product was recrystallized from water to give white solid **1** in 65% yield. Data for **1**: ^{1}H NMR (D_2O, 300 ppm) δ 8.10–8.14 (d, 2H), 7.91–7.95 (d, 2H), 4.86–4.88 (m, 7H), 3.35–3.77 (m, 42H). Anal. Calcd for $C_{49}H_{75}NO_{39}{\cdot}14H_2O$: C, 37.86; H, 6.68, N, 0.06. Found: C, 37.89; H, 6.64, N, 0.02.

Crystals of **1** were obtained from the aq soln. A small amount of **1** was dissolved in hot water to make a satu-

rated soln, which was then cooled to room temperature. After removal of the precipitate by filtration, the resultant soln was kept at room temperature for 1 week. The crystals formed were collected from the mother liquor for X-ray crystallographic analysis.

Supplementary data

Complete crystallographic data for compounds **1** have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 635474. Copies may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033, deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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