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Crystal structures of two forms of a 2:1 cyclomaltohexaose (α-cyclodextrin)/4,4′-biphenyldicarboxylic acid inclusion complex

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Abstract

The inclusion complex of cyclomaltohexaose (α-cyclodextrin, α-CD)/4,4′-biphenyldicarboxylic acid (BPDC) was crystallized into two crystal forms; tetragonal, space group $P4_22_12$, $a=b=19.609(8)$ Å, $c=32.257(8)$ Å (Form 1), and orthorhombic, space group $P2_12_12$, $a=35.397(8)$ Å, $b=24.577(5)$ Å, $c=27.969(9)$ Å (Form 2). Both crystal structures were determined by the X-ray diffraction method. The results show that a guest BPDC was included in two α-CDs in the tail-to-tail orientation to form the 2:1 α-CD/BPDC inclusion complex, and that a BPDC interacts with another BPDC by guest–water–guest hydrogen bonds. In Form 1, the α-CDs are arranged in a continuous one-dimensional column structure, whereas in Form 2 they are arranged in a discontinuous array.

1. Introduction

Cyclomaltooligosaccharide cyclodextrins, (CDs) are cyclic oligosaccharides with α-1,4 linked six, seven, or eight glucose units forming truncated conical structures, having the primary hydroxyl groups at the narrow side (head) and the secondary hydroxyl groups at the wide side (tail), as shown in Fig. 1. CDs can form inclusion complexes with various guest molecules [1]. Recently, CDs have been widely studied not only as enzyme models but also as supermolecular assemblies to serve as molecular devices, such as the molecular tube [2–4]. The molecular tube was synthesized by using the formation of the one-dimensional column structure of CDs including polyethylene glycol as a guest molecule [3]. Such one-dimensional columns are found in the many crystal structures of the inclusion complexes of CDs [5]. In some of them, two CDs include a guest in the tail-to-tail orientation with the intermolecular hydrogen bonds between the secondary hydroxyl groups to form the 2:1 inclusion complex, and these complexes are stacked along one of the crystal axes to form a continuous one-dimensional column structure as shown in Fig. 1 [6,7]. This is favorable to generate guest–guest interactions, because guest molecules can approach each other between the primary hydroxyl groups of the 2:1 inclusion complexes. We selected 4,4′-biphenyldicarboxylic acid (BPDC) to generate guest–guest interactions, as shown in

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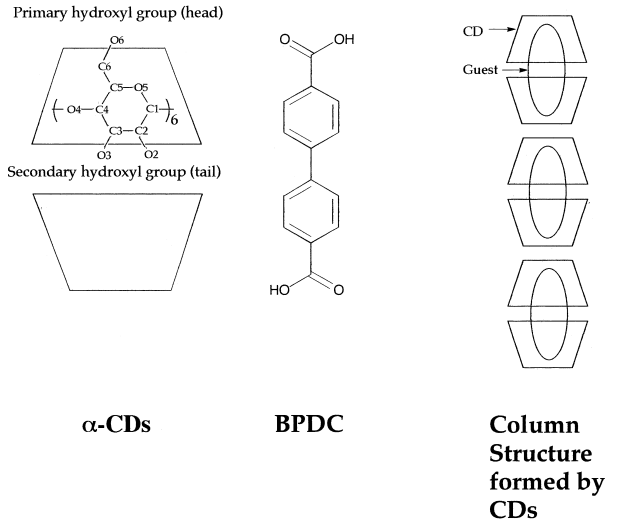

Fig. 1. A schematic diagram of α-CDs in the tail-to-tail orientation with the atomic numberings of a glucose unit (left), chemical structure of BPDC (center), and the one-dimensional column structure of CDs.

Fig. 1, and report here two crystal structures of the 2:1 α-CD/BPDC inclusion complex (Form 1 and Form 2) in which the guest–guest interactions are mediated by water molecules.

2. Experimental

Crystallization.—The Form 1 crystal of the 2:1 α-CD/BPDC inclusion complex was prepared by dissolving α-CD and BPDC in 2:1 molar ratio in water at 50 °C. By slow evaporation of this solution at 25 °C, suitable crystals for X-ray data collection were obtained. The Form 2 crystal was obtained by the same procedure, except by adding equimolar quantity of $CaCl_2$ with α-CD into the α-CD/BPDC solution 48 h later.

X-ray analyses.—Form 1. $C_{36}H_{60}O_{30}/0.5(C_{14}H_{10}O_4)/9.5H_2O$, M = 1265.10, tetragonal, space group $P4_22_12$, ($a = b = 19.609(8)$ Å, $c = 32.257(8)$ Å, $V = 12403(8)$ Å^3, $Z = 8$, $Dc = 1.37$. Diffraction data up to $2\theta = 120°$C were collected by a Rigaku AFC5R diffractometer on a Rigaku rotating anode X-ray generator with graphite monochromated CuKα radiation using the ω-scan mode. The initial phase angles were determined by the isomorphous replacement method, using the coordinates of α-CDs of the crystal structure of the $(\alpha\text{-CD})_2/Cd_{0.5}/I_5/27H_2O$ inclusion complex [8]. Guest and water molecules were located on a difference Fourier map. The atoms of α-CD and BPDC were refined anisotropically, and atoms of solvent molecules were refined isotropically. Hydrogen atoms except hydroxyl hydrogens were introduced by geometrical calculations and were not refined. The structure was refined to an *R*-factor = 0.107 by a full matrix least-squares method using program SHELX97 [9], based on 1557 reflections out of 5289 [Io > 3σ(Io)], 761 parameters and 868 geometrical restraints.

Form 2. $4(C_{36}H_{60}O_{30})/2(C_{14}H_{10}O_4)/28H_2O$, M = 4880.25, orthorhombic, space group $P2_12_12$, $a = 35.397(8)$ Å, $b = 24.577(5)$ Å, $c = 27.969(9)$ Å, $V = 24332(11)$ Å^3, $Z = 4$, $Dc = 1.36$. Diffraction data up to $2\theta = 120°$ using the $2\theta/\omega$-scan mode were collected by the same procedure as that of Form 1. The initial phase angles were determined by the molecular replacement method using the program X-PLOR [10]. From the cell volume, it is expected that two of the 2:1 α-CD/BPDC inclusion complex exist in an asymmetric unit. Two α-CDs in the tail-to-tail orientation (host structure) were extracted from Form 1 and used as an initial model. Cross rotation function showed that the molecular 6-fold rotation axis of the host structure was coincident with the crystallographic α-axis, suggesting that both host structures in the asymmetric unit were in similar orientations. Three-dimensional translation search for the two hosts gave a solution with an *R*-factor of 0.48 for 280 reflections. The structure was refined to an *R*-factor of 0.34 by the rigid-body least-squares method using rigid-body protocol of X-PLOR [10]; each glucose residue was fixed throughout the refinement. After several cycles of refinement using the positional protocol of X-PLOR [10], guest and water molecules were located on the difference Fourier maps. The structure was refined by a block diagonal matrix least-squares method using the program, SHELX97 [9], because of small number of observed reflections relative to the number of parameters. Solvent molecules and hydrogen atoms were treated in the same manner as in Form 1. Final *R*-factor reached 0.101 based on 3830 reflections out of 16471 [Io > 2σ(Io)], 2920 parameters and 7117 geometrical restraints.

Atomic coordinates, bond distances and angles, and thermal parameters of Forms 1 and 2, have been deposited at the Cambridge Crystallographic Data Centre.[1]

[1]Tables of atomic coordinates, bond lengths, and bond angles have been deposited with the Cambridge Crystallographic Data Centre. These tables may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

3. Results and discussion

Form 1.—Two α-CD molecules are arranged in the tail-to-tail orientation and connected by intermolecular hydrogen bonds between their secondary hydroxyl groups. A BPDC is included in the center of this dimer. The resulting complex forms a one-dimensional column structure, as shown in Fig. 2 [11]. Since the crystallographic 4_2 axis along the *c*-axis passes through the center of the complex, two half α-CDs (Mol-A and Mol-B), and half a BPDC comprise the asymmetric unit. There are two water molecules, OW1 and symmetry mate OW1′ between adjacent BPDCs. Both water molecules hydrogen bond with the carboxyl groups of BPDCs and the primary hydroxyl groups of the α-CDs. There is no direct hydrogen bond between primary hydroxyl groups, but there are 12 hydrogen bonds between secondary hydroxyl groups, as shown in Fig. 2.

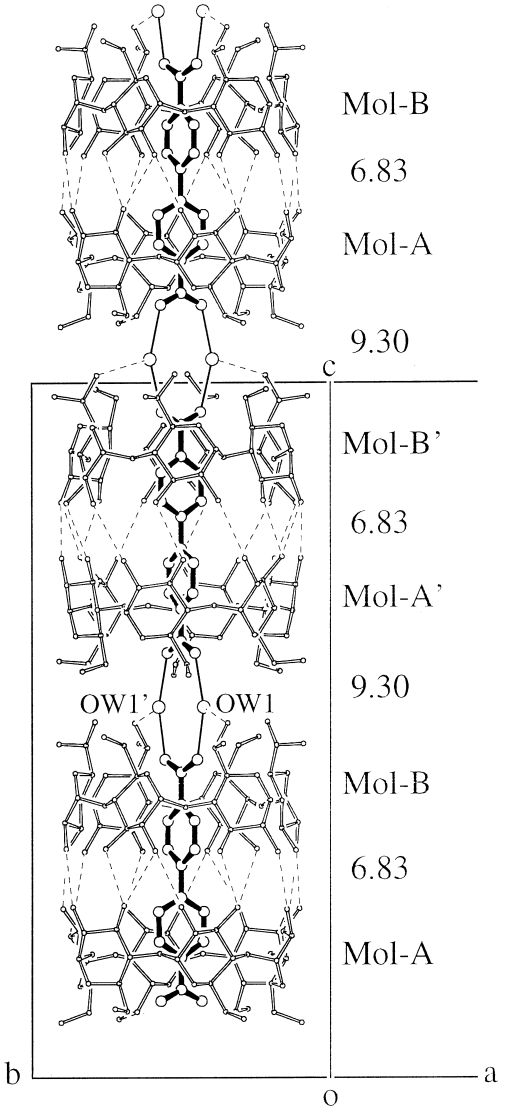

Fig. 2. One-dimensional column structure of the α-CD/BPCD inclusion complex in the Form 1 with a unit cell, viewed from the diagonal of the *ab* plane. The CDs and BPDCs are shown by open and solid bonds, respectively. The crystallographic 4_2 axis passes through the center of the column. The guest–water–guest hydrogen bonds are indicated by thin lines, and other hydrogen bonds (less than 3.1 Å) are represented by dotted lines. For clarity, water molecules are not shown except those between BPDCs. The distances (Å) between the O-4 atom planes are also indicated.

Each α-CD is distorted to an ellipsoid shape, induced by a planar structure of a phenyl ring of BPDC, as shown in Fig. 3. The angle between two phenyl rings is 85°.

Since the six O–4 atoms of each α-CD are in a plane within 0.04 Å, the center of the plane can be defined as the center of the α-CD. The distances between Mol A and Mol B (between their centers) and between Mol B and Mol A′ are 6.83, 9.30 Å, respectively. The corresponding distances in the isomorphous crystal structure of $(\alpha\text{-CD})_2/Cd_{0.5}/I_5/27H_2O$ inclusion complex are 6.66 and 8.78 Å, showing that the inclusion of a BPDC affects the distance between the primary hydroxyl groups rather than the distance between the secondary hydroxyl groups. Six hydrogen bonds between primary hydroxyl groups, in addition to the 12 hydrogen bonds between secondary hydroxyl groups as in Form 1, were reported in the crystal structure of the $(\alpha\text{-CD})_2/Cd_{0.5}/I_5/27H_2O$ inclusion complex [8]. Primary hydroxyl groups of α-CD/BPDC inclusion complex do not form hydrogen bonds with hydroxyl groups of another α-CD nor with the carboxyl groups of BPDC; however, they do form hydrogen bonds with solvent water molecules. In Fig. 2, only the water molecules between BPDCs are shown, but those between the primary hydroxyl groups of α-CDs are not shown for clarity. The absence of intermolecular hydrogen bonds between primary hydroxyl groups in the α-CD/BPDC inclusion complex is perhaps due to the guest–water–guest hydrogen bonds. The distance between the carboxyl oxygen atoms of BPDCs is 4.95 Å. If Mol B and Mol A′ approach each other to the distance of 8.78 Å as in the $\alpha\text{-(CD)}_2/Cd_{0.5}/I_5/27H_2O$ inclusion complex, the distance between the carboxyl oxygen atoms of BPDCs should be 4.43 Å [4.95−(9.3−8.78)], which is unusually long for direct hydrogen bonds. To obtain direct hydrogen bonds (less than 3.1 Å) between BPDCs, Mol-B and Mol-A′ should

be close to 7.45 Å [9.3−(4.95−3.1)], but they cannot approach than 8.78 Å found in the α-$(CD)_2$/$Cd_{0.5}/I_5/27H_2O$ inclusion complex, because of the direct hydrogen bonds between the primary hydroxyl groups of the α-CDs. Guest molecules slightly longer than BPDC are required for direct hydrogen bonds between them.

Form 2.—In Form 1, if a sufficient quantity of the cations exits, OW1 and OW1′ are thought to be replaced by a cation. So, preparation of the crystals of the α-CD/BPDC/Ca^{2+} inclusion complex has been examined by adding $CaCl_2$. A Ca^{2+} ion was expected between the carboxyl groups of BPDCs; however, Ca^{2+} and Cl^- ions could not be located in the difference Fourier map, because there were no distinct peaks of electron density among solvent molecules. Hence, ions were not included in the structure refinement. However, ionic strength of $CaCl_2$ affects the molecular packing of the α-CD/BPDC inclusion complex to give Form 2.

As shown in Fig. 4, there are four α-CDs (Mol-A, Mol-B, Mol-C and Mol-D) and two BPDCs in the asymmetric unit. Each set of two α-CD molecules (Mol-A and Mol-B, or Mol-C and Mol-D) is arranged in a tail-to-tail orientation with intermolecular hydrogen bonds between secondary hydroxyl groups and include a BPDC, all arranged in the same manner as Form 1.

In Form 2, the 2:1 complexes of α-CD and BPDC do not form the continuous one-dimensional column, but form just the short column composed of four α-CDs (Mol-A, Mol-B, Mol-A′ and

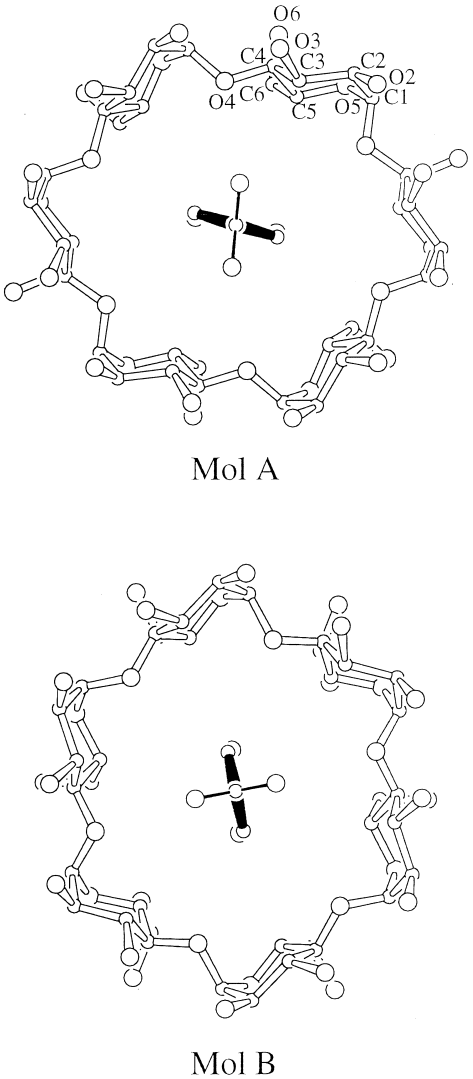

Fig. 3. The structures of Mol-A and Mol-B viewed along the *c*-axis. The CDs and BPDCs are shown by open and solid bonds, respectively. The included moieties of BPDC by CDs are shown by relatively thick bonds. Atomic numberings of a glucose unit are indicated.

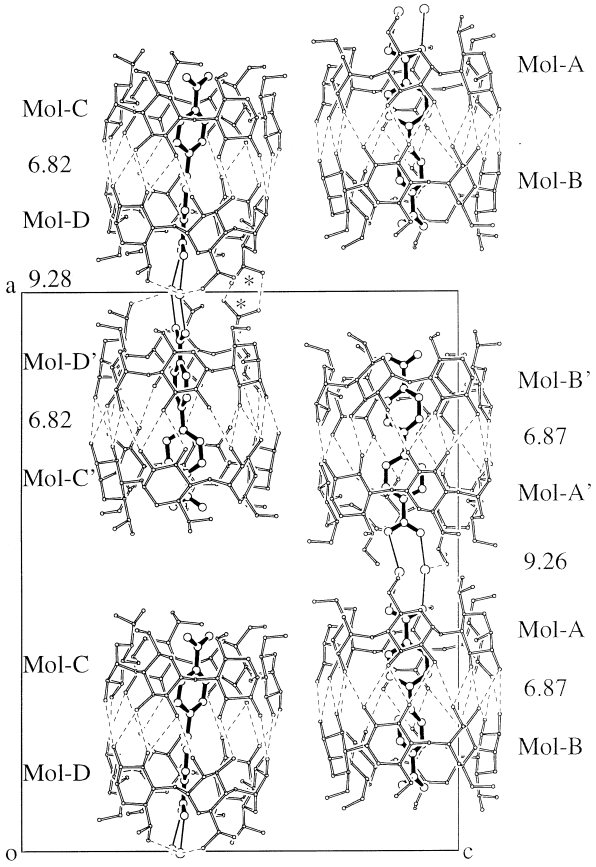

Fig. 4. The crystal structure of Form 2 with a unit cell, viewed from the *b*-axis. The CDs and BPDCs are represented by open and solid bonds, respectively. The guest–water–guest hydrogen bonds are indicated by thin lines, and other hydrogen bonds (less than 3.1 Å) are represented by dotted lines. The distances (Å) between the O-4 atom planes are indicated. The primary hydroxyl groups forming direct intermolecular hydrogen bonds are indicated by (*).

Mol-B′, or, Mol-C, Mol-D, Mol-C′ and Mol-D′) and two BPDCs. The space between these columns is occupied by highly disordered solvent molecules (water molecules and ions), as shown in Fig. 4. This discontinuous column structure seems to be caused by $CaCl_2$.

The distances between α-CDs are 6.87 Å (Mol-A and Mol-B), 9.26 Å (Mol-A and Mol-A′), 6.82 Å (Mol-C and Mol-D) and 9.28 Å (Mol-D and Mol-D′), as indicated in Fig. 4, are similar to those in Form 1. There are two water molecules between BPDCs, and they form hydrogen bonds with carboxyl oxygen atoms of BPDCs and primary hydroxyl groups of α-CDs, as in Form 1. However, in the column formed by Mol-C, Mol-D, Mol-D′, Mol-C′, the direct intermolecular hydrogen bonds are between the primary hydroxyl groups that are disordered in two positions as indicated by (*) in Fig. 4. This is because this complex has a large kink at its center relative to others. The kinks of the column, defined as the angle between the molecular axes of BPDCs (the axes giving the minimum moment of inertia), is 7.8° in the complex of Mol-C and Mol-D, 2.2° in the complex of Mol-A and Mol-B in Form 2, and 0° in the complex in Form 1.

An ellipsoid shape distortion induced by BPDC is found in each α-CD as Form 1. The angles between two phenyl rings of BPDC are 51° in the complex of Mol-A and Mol-B, and 44° in the complex of Mol-C and Mol-D, suggesting that the structural difference of BPDC between Forms 1 and 2 is only marginal.

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