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CRYSTAL STRUCTURES OF HEPTAKIS(2,6-DI-*O*-METHYL)-β-CYCLODEXTRIN COMPLEXES WITH *p*-IODOPHENOL AND *p*-NITROPHENOL

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Crystal structures of heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (dimethyl-β-CDx) complexes with *p*-iodophenol and *p*-nitrophenol were determined by the X-ray method. The dimethyl-β-CDx molecule is in the round shape, which is maintained by the intramolecular hydrogen bonds formed between adjacent 2,6-di-*O*-methylglucose residues. The guest molecules in both complexes are not included within the host cavity, but located in intermolecular spaces between dimethyl-β-CDx molecules. The host cavity includes three water molecules and a methoxyl group of adjacent dimethyl-β-CDx.

Chemical modifications of cyclodextrins have been extensively studied to improve complexing and catalytic abilities of these macrocyclic oligosaccharides.[1] X-Ray studies of several inclusion complexes of permethylated cyclodextrins have shown that the permethylation markedly changes the macrocyclic conformation of cyclodextrins and the geometrical feature of host-guest interaction.[2,3] On the other hand, only a few crystallographic data have been reported for heptakis(2,6-di-*O*-methyl)-β-cyclodextrin (abbreviated to dimethyl-β-CDx) and its host-guest complexes. Stezowski and his co-workers have shown that dimethyl-β-CDx forms an inclusion complex with 1-adamantanol.[4] In this paper, we briefly describe crystal structures of dimethyl-β-CDx complexes with *p*-iodophenol and *p*-nitrophenol (abbreviated to *p*-IPH and *p*-NPH, respectively) and demonstrate that these guest molecules are not included within the host macrocyclic ring in the crystalline state.

The dimethyl-β-CDx–*p*-IPH complex was crystallized at 50 °C by standing an aqueous solution of dimethyl-β-CDx, saturated with *p*-IPH. Crystals of the dimethyl-β-CDx–*p*-NPH complex were obtained at room temperature by the slow evaporation of an aqueous solution containing dimethyl-β-CDx and *p*-NPH in *ca.* 1:1 molar ratio. Lattice parameters and diffraction intensity data were measured on a Nicolet P3/F diffractometer with graphite-monochromated CuKα radiation. By using θ-2θ scan mode, 4045 (*p*-IPH complex) and 4670 (*p*-NPH complex) independent reflections with $|F_o| \geqq 3\sigma(F)$ were obtained up to 118° in 2θ. Crystal data were as follows: (1) *p*-IPH complex, $C_{56}H_{98}O_{35}\cdot C_6H_5OI\cdot 3H_2O$, F.W.=1605.4, orthorhombic, space group $P2_12_12_1$, Z=4, a=14.796(3), b=18.853(5), c=28.989(6) Å, V=8086(3) Å^3, D_x=1.319 g/cm^3; (2) *p*-NPH complex, $C_{56}H_{98}O_{35}\cdot C_6H_5O_3N\cdot 3H_2O$, F.W. = 1524.5,

orthorhombic, space group $P2_12_12_1$, Z=4, a=14.779(2), b=18.965(3), c=28.741(4) Å, V=8056(2) Å^3, D_x=1.257 g/cm^3. The crystal structure of the *p*-IPH complex was solved by the heavy atom method, combined with the phase refinement using the tangent formula, and refined by the block-diagonal least-squares method to the R-value of 0.12. A set of the dimethyl-β-CDx coordinates of the *p*-IPH complex was used to determine the structure of the isomorphous *p*-NPH complex, which was refined by the block-diagonal least-squares method to the R-value of 0.10.[5)]

As shown in Fig. 1, the dimethyl-β-CDx molecule in both complexes is in the round shape, similar to that of β-cyclodextrin.[6)] The C(6)-O(6) bonds show two types of orientations; a *gauche-gauche* conformation is found in the G1, G2, G3, and G7 residues, while the C(6)-O(6) bonds in the G4, G5, and G6 residues show a *gauche-trans* conformation. Most of the O(2)-C(7) and O(6)-C(8) bonds are *trans* to the C(2)-C(3) and C(5)-C(6) bonds, respectively. The seven O(4) atoms form a slightly distorted heptagon. The radius of the heptagon, which is measured from the center of gravity of the seven O(4) atoms to each individual O(4) atom, is in the ranges 4.85-5.22 Å (*p*-IPH complex) and 4.92-5.16 Å (*p*-NPH complex); the average values, 5.04 and 5.06 Å, respectively, are in good agreement with the corresponding value (5.02 Å) of β-cyclodextrin.[6)] Distances between O(2) and O(3') of the adjacent 2,6-di-*O*-methylglucose residue are in the ranges 2.73-3.10 Å (*p*-IPH complex) and 2.80-3.04 Å (*p*-NPH complex). These values indicate that the O(3')H hydroxyl group is hydrogen-bonded to the O(2) oxygen atom. The root-mean-square deviations of O(4) atoms from the least-squares plane through the seven O(4) atoms are 0.110 Å (*p*-IPH complex) and 0.093 Å (*p*-NPH complex), showing good planarity of the O(4) heptagon. The tilt-angle of each 2,6-di-*O*-methylglucose residue, which is defined as the angle made by the O(4) plane and the plane through C(1), C(4), O(4), and O(4') atoms of each residue, is in the ranges

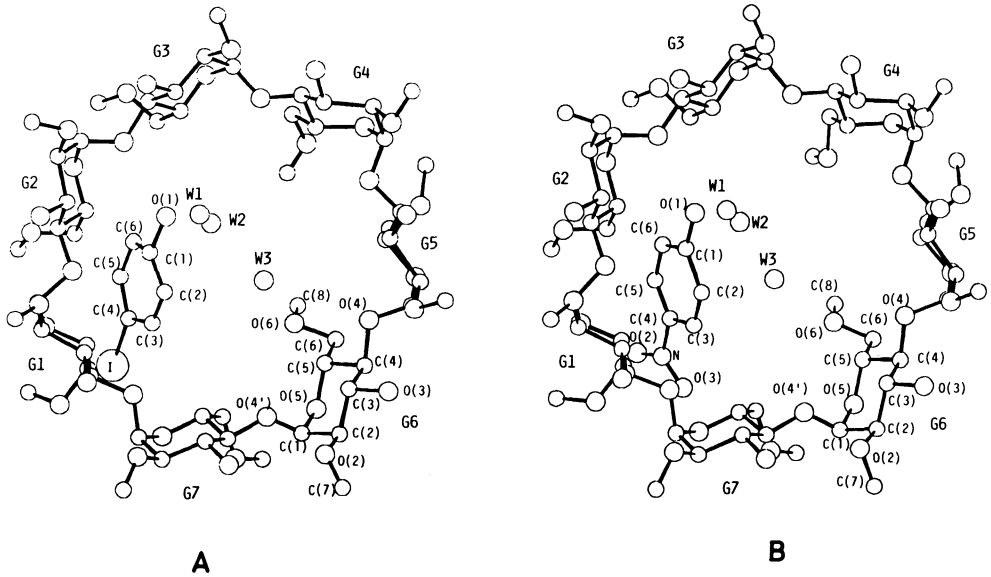

Fig. 1. Structures of dimethyl-β-CDx complexes with *p*-IPH (A) and *p*-NPH (B).

5.6-24.4° (*p*-IPH complex) and 2.2-24.7° (*p*-NPH complex); the respective average values, 15.0° and 14.2°, are somewhat larger than that (11.4°) of β-cyclodextrin.[6] These geometrical data indicate that the macrocyclic conformation of dimethyl-β-CDx is similar to that of β-cyclodextrin, but quite different from that of permethylated β-cyclodextrin.[3] The macrocyclic ring of permethylated β-cyclodextrin is remarkably distorted because of the steric hindrance involving methyl groups attached to O(3) atoms and the incapability of forming intramolecular hydrogen bonds; the tilt-angle of 2,3,6-tri-*O*-methylglucose residue is in the range from -16.3° to 43.0°. In the dimethyl-β-CDx complexes, however, the $O(2)C(7)H_3$ and $O(6)C(8)H_3$ methoxyl groups are oriented outside the macrocyclic ring so that these methoxyl groups cause no steric hindrance between adjacent 2,6-di-*O*-methylglucose residues. Moreover, the intramolecular O(2)···H-O(3') hydrogen bonds may maintain the round shape of the macrocyclic ring, as observed in β-cyclodextrin.[6]

The crystal structure of the *p*-NPH complex is shown in Fig. 2. Dimethyl-β-CDx molecules, the plane of which makes an angle of 24.7° with the crystallographic a axis, are arranged along the two-fold screw axis parallel to the a axis, forming a zigzag pattern in the crystal. It should be noted that the guest *p*-NPH molecule is not included within the host cavity, but located in an intermolecular space between dimethyl-β-CDx molecules. Such a kind of host-guest relationship has not been previously found in cyclodextrin and permethylated

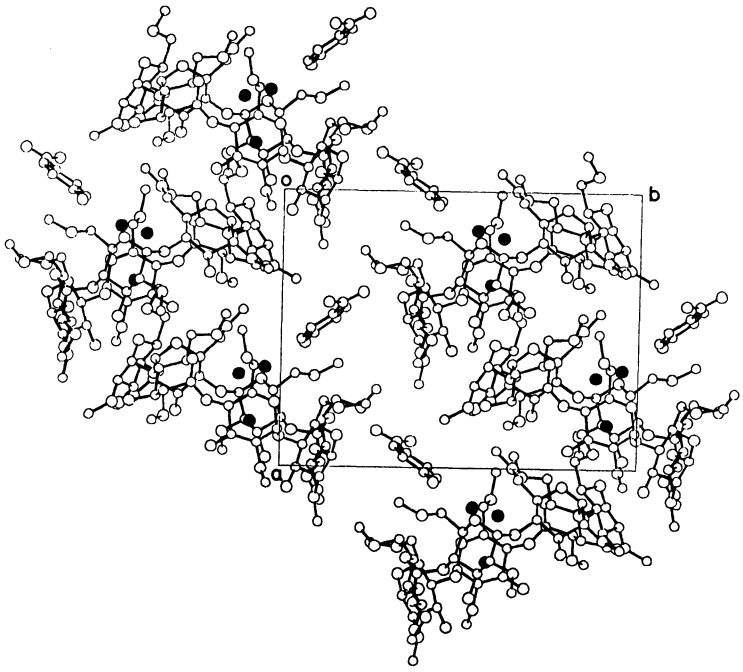

Fig. 2. The crystal structure of the *p*-NPH complex viewed along the c axis. Water molecules are shown by full circles. Molecules, related *via* two-fold screw axis parallel to the c axis, are not shown because of the clarity of representation.

cyclodextrin complexes, in which guest molecules are included within the host cavity. In the present dimethyl-β-CDx complexes, the host cavity includes three water molecules linked to each other by the W1···W2···W3 hydrogen bonds. The O(6)C(8)H_3 methoxyl group of the G5 residue is inserted into the cavity of the adjacent dimethyl-β-CDx, which is related *via* two-fold screw axis parallel to the a axis. The included O(6) atom of the G5 residue forms the hydrogen bond with the W1 water molecule. The hydroxyl group of *p*-NPH is located near the O(6) side of the dimethyl-β-CDx ring, forming the hydrogen bond with the W2 water molecule. The W3 water molecule is hydrogen-bonded to the O(6) atom of the G6 residue.

Circular dichroism spectra of the *p*-NPH complex in aqueous solutions have strongly suggested that the *p*-NPH molecule is included within the host cavity in a manner similar to that of the β-cyclodextrin–*p*-NPH complex.[7] Since the complex can be formed in solution by replacing the included water molecules with the guest molecule, it is plausible to speculate that the complex formation occurs as follows, if we assume that the guest molecule is inserted into the host cavity from the O(6) side. The guest molecule forms hydrogen bonds with included water molecules, which may be in an "activated state"[8] and located in a manner similar to that found in the crystalline state. Then, the guest molecule is pulled into the host cavity, pushing out the water molecules into bulk water. Accordingly, the host-guest geometry found in the present crystal structures may exhibit an intermediate state in the complexation reaction.

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