

CRYSTAL STRUCTURES OF PERMETHYLATED α -CYCLODEXTRIN COMPLEXES
WITH L- AND D-MANDELIC ACIDSKazuaki HARATA,* Kaneto UEKAMA,[†] Masaki OTAGIRI,[†]
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The crystal structures of permethylated α -cyclodextrin complexes with L- and D-mandelic acids were determined by the X-ray method. The host molecule of the L-mandelic acid complex, having a *pseudo* two-fold symmetry, loosely includes the phenyl group, while the hydroxyl and carboxyl groups form hydrogen bonds with water molecules located outside the host cavity. D-Mandelic acid is tightly bound within the host cavity, forming a host-guest hydrogen bond.

Cyclodextrins form diastereoisomers by including optically active guests within the cavity of the macrocyclic ring. On this basis, complex formation of cyclodextrins has been employed as a method for resolution of racemic compounds.¹⁻³⁾ Permethylated cyclodextrins also form inclusion complexes with optically active guests. As permethylated cyclodextrin molecules are more distorted from the regular polygonal structure than the corresponding cyclodextrin molecules,^{4,5)} it is expected that the stereo-selectivity of permethylated cyclodextrins in the complex formation is higher than that of cyclodextrins. In this brief paper, we present crystal structures of permethylated α -cyclodextrin (abbreviated to methyl- α -CDx) complexes with L- and D-mandelic acids (abbreviated to L-MA and D-MA, respectively), and demonstrate the chiral recognition by the macrocyclic ring in the crystalline state.

Crystals of methyl- α -CDx complexes with L-MA and D-MA were obtained at 50 °C by standing aqueous solutions containing methyl- α -CDx and each isomer in *ca.* 1:1 molar ratio. Lattice parameters and diffraction intensities were measured on a Nicolet P3/F diffractometer with CuK α radiation. By using θ -2 θ scan mode, 4837 (L-MA complex) and 4925 (D-MA complex) independent reflections with $|F_o| \geq 3\sigma(F)$ were obtained up to 118° in 2 θ . Crystal data were as follows: (1) L-MA complex, C₅₄H₉₆O₃₀·C₈H₈O₃·3H₂O, F.W.=1431.5, monoclinic, space group P2₁, Z=2, $a=13.123(2)$, $b=23.187(4)$, $c=13.113(2)$ Å, $\beta=107.19(1)^\circ$, $V=3812(1)$ Å³, $D_x=1.247$ g·cm⁻³, (2) D-MA complex, C₅₄H₉₆O₃₀·C₈H₈O₃·2H₂O, F.W.=1413.5, monoclinic, space group P2₁, Z=2, $a=11.624(2)$, $b=23.739(4)$, $c=13.786(2)$ Å, $\beta=106.56(1)^\circ$, $V=3646(1)$ Å³, $D_x=1.289$ g·cm⁻³.

Both structures were solved by inspection of Patterson maps and the trial-and-error method combined with the rigid-body least-squares technique, and refined by the block-diagonal least-squares method to the final *R*-values of 0.087 for the L-MA complex and 0.055 for the D-MA complex.

Structures and numbering scheme of both complexes are shown in Fig. 1. The pyranose conformation of each tri-*O*-methylglucose residue does not significantly differ between the two complexes. The planarity of C(2), C(3), C(5), and O(5) atoms and that of C(1), C(4), O(4), and O(4') atoms of each residue are good; the maximum deviations of atoms from the plane are 0.05 Å for the former and 0.02 Å for the latter. The C(7)H₃O(2) methoxyl groups are directed outside the macrocyclic ring, while the C(8)H₃O(3) methoxyl groups turn toward the inside of the ring. The C(6)-O(6) bonds show two types of orientations, *gauche-gauche* (to C(5)-O(5) and C(5)-C(4) bonds) and *gauche-trans* (to C(5)-O(5) and C(5)-C(4) bonds). The C(6)-O(6) bonds in the G2 and G5 residues of the L-MA complex and those in the G4 and G6 residues of the D-MA complex are in the *gauche-gauche* conformation, and the other C(6)-O(6) bonds having the *gauche-trans* conformation. The C(9)H₃O(6) methoxyl groups, except for that of the G1 residue of the D-MA complex, are *trans* to the corresponding C(5)-C(6) bonds.

The host macrocyclic ring of the L-MA complex has a *pseudo* two-fold symmetry. The diagonal distances of the hexagon, composed of the six O(4) oxygen atoms, are 8.45-8.73 Å. On the other hand, the methyl- α -CDx ring of the D-MA complex is more elliptically distorted from the round structure, as indicated by the diagonal distances of the O(4) hexagon, 8.08-9.08 Å. The planarity of these O(4) hexagon is fairly good; the maximum deviations of O(4) atom from the plane are 0.27 Å in the L-MA complex and 0.20 Å in the D-MA complex. The distances between O(2) and O(3') of the adjacent tri-*O*-methylglucose residue, 3.30-3.46 Å in the L-MA complex and 3.20-3.55 Å in the D-MA complex, are larger than those of α -cyclodextrin because of the steric hindrance involving C(8)H₃ methyl groups and the incapability of forming intramolecular O(2)···O(3') hydrogen bonds which hold the O(2)···O(3')

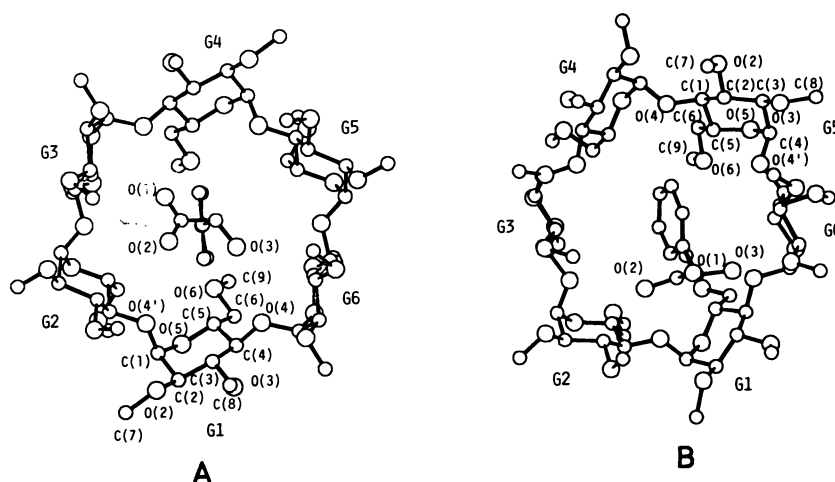


Fig. 1. Structure and numbering scheme of the methyl- α -CDx complexes with L-MA (A) and D-MA (B).

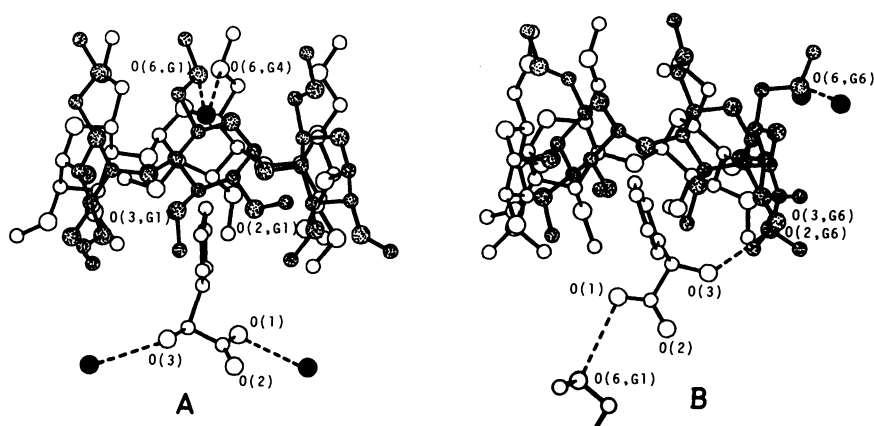


Fig. 2. Host-guest interaction in the methyl- α -CDx complexes with L-MA (A) and D-MA (B). Water molecules are shown by full circles. Broken lines indicate hydrogen bonds. The G1, G2, and G6 residues in the L-MA complex and the G4, G5, and G6 residues in the D-MA complex are shaded.

distances mostly within the range 2.7-3.0 Å in α -cyclodextrin.⁶⁾ The C(8)H₃ methyl groups are located at a position nearly equidistant from adjacent two O(2) oxygen atoms; the average O(2)···C(8) and C(8)···O(2') distances are 3.37 and 3.36 Å, respectively, in the L-MA complex, and the corresponding values in the D-MA complex being 3.30 and 3.38 Å, respectively.

In both complexes, two tri-*O*-methylglucose residues, G3 and G6, are almost perpendicular to the plane through six O(4) atoms, while the other residues incline to make their O(6) side nearer to the molecular axis of methyl- α -CDx, which is the axis through the center of gravity of the six O(4) atoms and perpendicular to the O(4) plane. The tilt-angle of these residues, which is defined as an angle made by the O(4) plane and the plane through C(1), C(4), O(4), and O(4') of each residue, is the range 18.7-35.9° in the L-MA complex and 23.0-29.3° in the D-MA complex. The G1 and G4 residues of the L-MA complex incline to make the tilt-angles of 35.9° and 34.6°, respectively, which are larger than values previously found in other methyl- α -CDx complexes. These two residues are held by the O(6,G1)···water···O(6,G4) hydrogen-bond bridge, as shown in Fig. 2A.

The phenyl group of L-MA, which is inserted into the methyl- α -CDx cavity from the O(2), O(3) side of methyl- α -CDx, is located on the *pseudo* two-fold axis of methyl- α -CDx. The vacant space near the O(6) side is filled with a water molecule. The hydroxyacetic acid moiety of L-MA protrudes outside the methyl- α -CDx cavity, forming hydrogen bonds with two water molecules (Fig. 2A). The phenyl group of D-MA is more deeply inserted into the host cavity (Fig. 2B) than that of L-MA, and sandwiched by the G3 and G6 residues. The phenyl plane is not parallel to the molecular axis of methyl- α -CDx, but makes an angle of 70.5° with the O(4) plane. The hydroxyl group of D-MA is hydrogen-bonded to the O(2) oxygen atom of the O(6) residue. The carboxyl group, protruding from the O(2), O(3) side of the methyl- α -CDx ring, forms the hydrogen bond with the O(6,G1) oxygen atom of the adjacent methyl- α -CDx molecule. The C(9,G1)H₃O(6,G1) methoxyl group is oriented

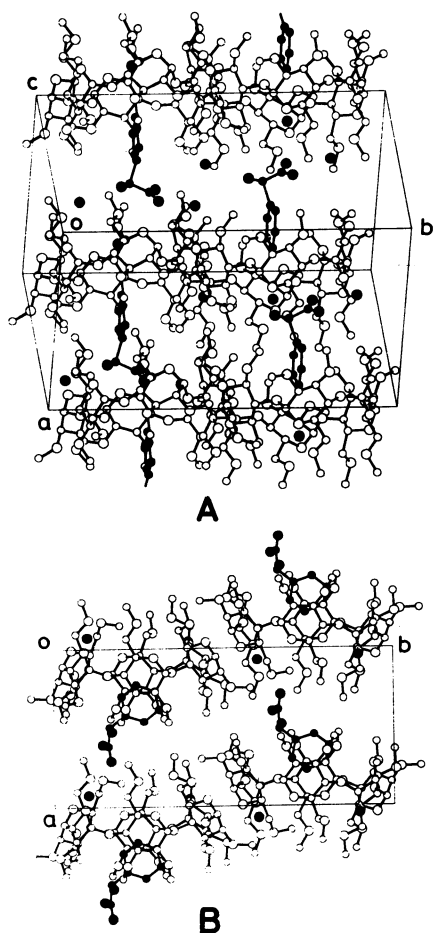


Fig. 3. Projections of the crystal structures of the methyl- α -CDx complexes with L-MA (A) and D-MA (B). Atoms in the guest and water molecules are shown by full circles.

so that the methyl group caps the narrower side of the cavity. Therefore, the D-MA molecule is more tightly bound within the methyl- α -CDx cavity by means of the host-guest hydrogen bond and van der Waals force. Moreover, comparison of the two structures suggests that the complex formation with D-MA induces the conformational change of the host molecule to accommodate the guest molecule more suitably within the cavity. On the other hand, the shallow inclusion of the L-MA molecule may be ascribed to the followings: (1) the formation of the host-guest hydrogen bond is sterically hindered, and (2) the hydrogen-bond formation of L-MA with water molecules prevents the phenyl group from penetrating deeply into the macrocyclic ring.

The crystal structures of both complexes are shown in Fig. 3. The crystal of the L-MA complex is built up of molecular layers parallel to the $[1\ 0\ \bar{1}]$ plane. The hydroxyacetic acid moiety of L-MA is located in the intermolecular space between methyl- α -CDx molecules of the adjacent layer. The methyl- α -CDx molecules in the D-MA complex are stacked along the a axis, with which the O(4) plane makes an angle of 72.5° , forming a channel-type structure. The D-MA molecule is enclosed within the methyl- α -CDx column. Two water molecules are located outside the methyl- α -CDx ring, and form hydrogen bonds with oxygen atoms of methyl- α -CDx.

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