CHEMISTRY LETTERS, pp. 1549 - 1552, 1984.

CRYSTAL STRUCTURES OF PERMETHYLATED β-CYCLODEXTRIN COMPLEXES WITH *R*-(-)- AND *S*-(+)-FLURBIPROFEN

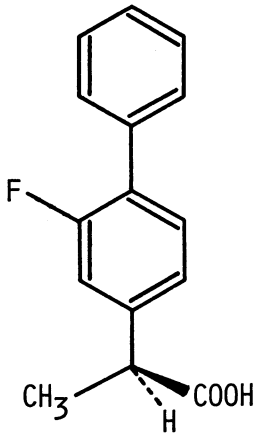
Kazuaki HARATA,* Fumitoshi HIRAYAMA,† Teruko IMAI,†
Kaneto UEKAMA,† and Masaki OTAGIRI†

Research Institute for Polymers and Textiles, 1-1-4 Yatabe-Higashi, Tsukuba, Ibaraki 305

†*Faculty of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto 862*

Crystal structures of permethylated β-cyclodextrin complexes with *R*-(-)- and *S*-(+)-flurbiprofen have been determined by the X-ray method. Host molecules in both complexes are markedly distorted from the regular heptagonal structure, and include the phenyl group of the guest. The carboxyl group of the *R*-isomer forms a hydrogen bond with a water molecule, while the *S*-isomer is hydrogen-bonded to an oxygen atom of the adjacent host molecule.

β-Cyclodextrin forms crystalline inclusion complexes with flurbiprofen, an anti-inflammatory drug. Previously, we have determined the crystal structures of β-cyclodextrin complexes with racemic flurbiprofen[1] and *S*-(+)-flurbiprofen.[2] Although cyclodextrins are optically active compounds, their chiral selectivity in the complex formation with optically active guests seems to be small, as shown in the β-cyclodextrin complex with racemic flurbiprofen and the α-cyclodextrin complex with racemic 1-phenylethanol.[3] On the other hand, permethylated α-cyclodextrin has been shown to form the complexes with D- and L-mandelic acid with different inclusion geometries to each other.[4] Since the cavity of permethylated cyclodextrins is less symmetrical than that of cyclodextrins, it can be expected that the permethylated cyclodextrins have more ability to recognize chiral guests than cyclodextrins. In this brief paper, we present crystal structures of permethylated β-cyclodextrin (1) complexes with *R*-(-)-flurbiprofen (2) and *S*-(+)-flurbiprofen (3).



3

Crystals of both complexes were obtained at 50 °C by standing aqueous solutions containing 1 and each guest 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, 3525 (complex with 2) and 5419 (complex with 3) reflections with $|F_o| \geq 3\sigma(F)$ were collected up to 118° in 2θ. No corrections were made for absorption or extinction effect. Crystal data were as follows: (1) the complex with 2, $C_{63}H_{112}O_{35}\cdot C_{15}H_{13}O_2F\cdot H_2O$,

F.W.=1691.8, orthorhombic, space group $P2_12_12_1$, Z=4, a=15.092(2), b=21.714(3), c=28.269(4) Å, V=9264(2) Å^3, D_x=1.213 g·cm^{-3}; (2) the complex with 3, $C_{63}H_{112}O_{35}\cdot C_{15}H_{13}O_2F$, F.W.=1673.8, orthorhombic, space group $P2_12_12_1$, Z=4, a=15.271(2), b=21.451(3), c=27.895(3) Å, V=9137(2) Å^3, D_x=1.217 g·cm^{-3}. The crystal structures of both complexes were determined by using a set of coordinates of 1 of the isomorphous *p*-iodophenol complex,[5] and refined by the block-diagonal least-squares method to the *R*-value of 0.10 (the complex with 2) and 0.089 (the complex with 3).

Molecules of 1 in both complexes are markedly distorted from the regular heptagonal symmetry, as shown in Fig. 1. Although shapes of 1 in the complexes with 2 and 3 are similar to each other, a difference is observed in the orientation of the C(6)-O(6) bond in the G7 residue; a *gauche-gauche* conformation is observed in the complex with 2, while the C(6)-O(6) bond in the complex with 3 shows a *gauche-trans* conformation. The seven O(4) atoms of 1, which are arranged to form a distorted heptagon, are coplanar within the maximum deviations, 0.659 Å (the complex with 2) and 0.599 Å (the complex with 3), from their least-squares

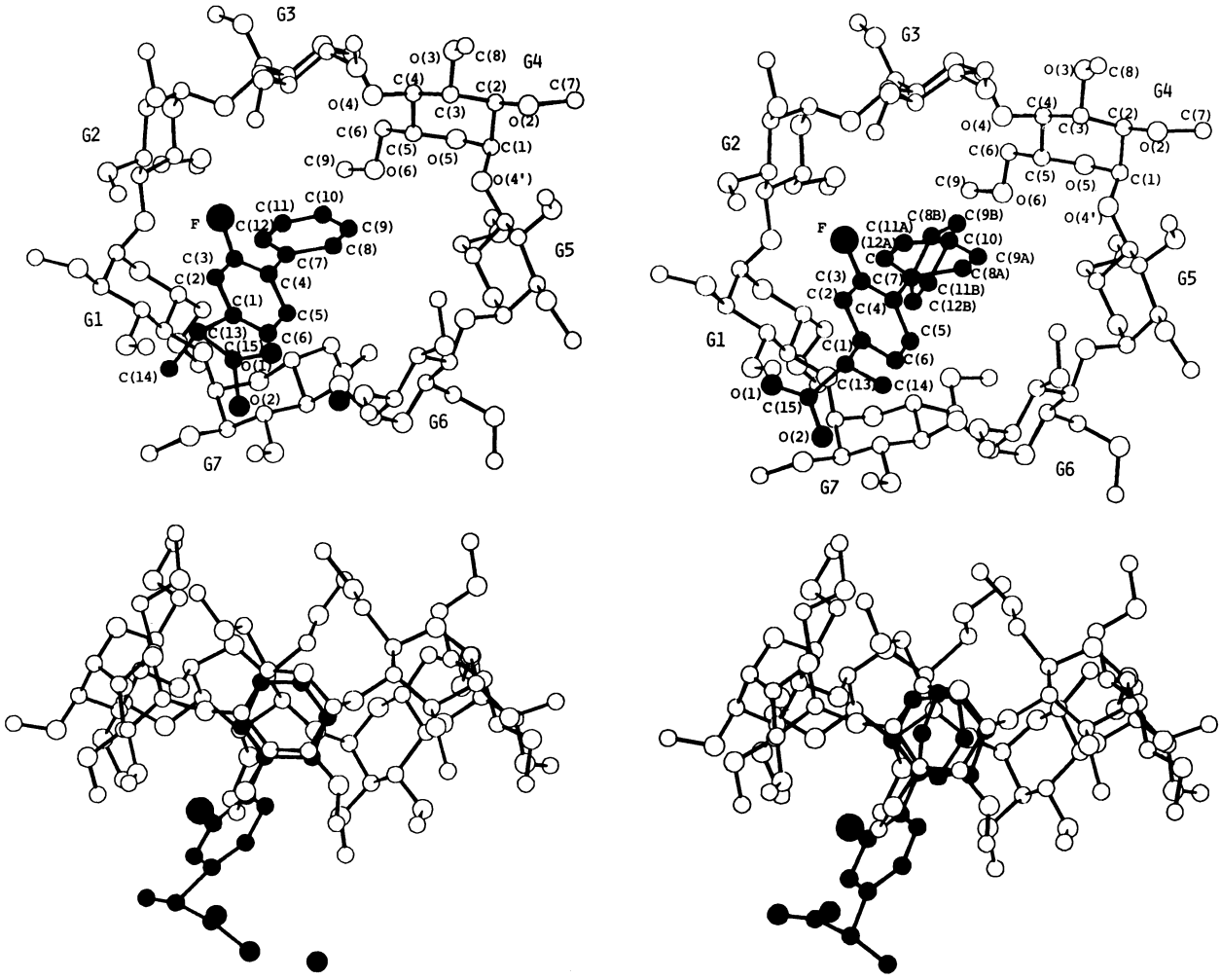


Fig. 1. Inclusion features of the complexes with 2 (left) and 3 (right). The guest and water molecules are shown by full circles.

plane. The radius of the O(4) 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 4.63-5.25 Å (the complex with 2) and 4.70-5.23 Å (the complex with 3). The corresponding average values, 5.00 and 5.01 Å, are in good agreement with that found in the *p*-iodophenol complex. The average distances between O(2) and O(3') of adjacent residue, 3.44 Å (the complex with 2) and 3.43 Å (the complex with 3), are significantly larger than that found in β-cyclodextrin (2.80 Å).[1] Such large O(2)···O(3) distances of 1, being also observed in the *p*-iodophenol complex, may be ascribed to the steric hindrance involving methyl groups bonded to O(3) atoms and the incapability of forming intramolecular O(2)···O(3') hydrogen bonds.[5] The tilt-angle of each 2,3,6-tri-*O*-methylglucose residue, which is defined as the angle made by the plane through seven O(4) atoms and the plane through C(1), C(4), O(4) and O(4') atoms of each residue, is in the ranges from -12.9° to 43.8° (the complex with 2) and from -14.3° to 43.3° (the complex with 3). The G4 residue is most sharply inclined with the O(6) side nearer to the center of the macrocyclic ring. The G3 and G6 residues, having negative tilt-angles, are so inclined that their O(2), O(3) sides come nearer to each other. The similarity in the macrocyclic conformation of 1 found in the present complexes and the *p*-iodophenol complex indicates that the conformation of the host molecule is little affected by the guest molecule. On the other hand, in the permethylated α-cyclodextrin complexes with D- and L-mandelic acid, the host molecule recognizes the chirality of the guest molecule and changes its macrocyclic conformation.[4]

The guest molecules of 2 and 3 are inserted into the cavity of 1 from the O(2), O(3) side. The host molecule includes only the phenyl group in both complexes, because the O(6) side is too narrow to accommodate the guest molecule. When these inclusion features are compared with those of the β-cyclodextrin complexes,[1,2] it should be noted that the guest molecules of the complexes of 1 are located in the upside down orientation with respect to the host molecule. The biphenyl moiety of 2 is twisted by an angle of 54.7° around the *C(4)-C(7)* bond. The phenyl group of 3 is statistically disordered with the occupancy factor of 0.5 each. The phenyl group, containing *C(8A)*, *C(9A)*, *C(11A)*, and *C(12A)* atoms is in the same orientation as the phenyl group of 2, making of an angle of 51.1° with the fluorophenylene group. The other phenyl group of 3 is rotated around the axis through *C(7)* and *C(10)* atoms to the opposite side, and makes an angle of 60.3° with the fluorophenylene group. These values of the biphenyl angle are similar to that of uncomplexed racemic flurbiprofen (54.4°),[6] but larger than those (37.4° and 34.8°) found in the β-cyclodextrin–racemic flurbiprofen complex.[1] The carboxyl groups of 2 and 3 in the complexes of 1 are oriented in the same direction as that found in the uncomplexed flurbiprofen, but in the β-cyclodextrin complexes, the carboxyl group is rotated by about 180° around the *C(1)-C(13)* bond of flurbiprofen. These conformational differences in the guest molecules suggest that the guest molecules are bound in the cavity of 1 more loosely than in the β-cyclodextrin cavity, and therefore, the conformation of flurbiprofen is less affected by the complex formation with 1.

Crystal structures of both complexes are illustrated in Fig. 2. Molecules of 1 are stacked in a head-to-tail mode to form a column structure parallel to

the crystallographic b axis. The crystal of the complex with 2 contains a water molecule, which forms hydrogen bonds with the carboxyl group of 2 and the O(6) atom of the G7 residue. This O(6)···water hydrogen bond may be responsible for the orientation of the C(6)-O(6) bond of the G7 residue, since the *gauche-gauche* conformation is preferable in forming the hydrogen bond with water. On the other hand, the corresponding O(6) atom of the complex with 3 forms no hydrogen bond. The carboxyl group of 3 protrudes outside the column of 1, and forms a hydrogen bond with an O(3) atom of the adjacent host molecule, as shown by dotted lines in Fig. 2. These differences in the crystal structures suggest a possibility of resolving racemic flurbiprofen by utilizing the complexation with 1. We are attempting to apply permethylated cyclodextrins for the resolution of racemic compounds.

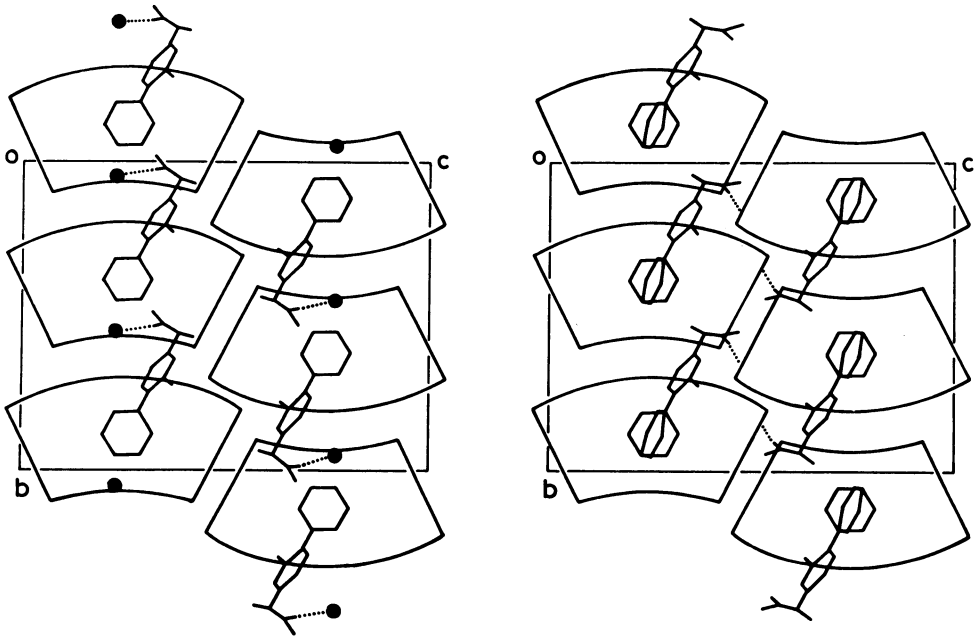


Fig. 2. Schematic drawings of the crystal structures of the complexes with 2 (left) and 3 (right). Water molecules are shown by full circles. Dotted lines indicate hydrogen bonds.

References

1) K. Uekama, F. Hirayama, T. Imai, M. Otagiri, and K. Harata, Chem. Pharm. Bull., 31, 3363 (1983).
2) K. Uekama, F. Hirayama, T. Imai, M. Otagiri, and K. Harata, Chem. Pharm. Bull., 32, 1662 (1984).
3) K. Harata, Bull. Chem. Soc. Jpn., 55, 1367 (1982).
4) K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, Chem. Lett., 1983, 1807.
5) K. Harata, K. Uekama, M. Otagiri, and F. Hirayama, Bull. Chem. Soc. Jpn., 56, 1732 (1983).
6) J. L. Flippen and R. D. Gilardi, Acta Crystallogr., Sect. B, 31, 926 (1975).

(Received June 30, 1984)