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CRYSTAL AND MOLECULAR STRUCTURE OF 2:2 (±)FLURBIPROFEN—β-CYCLODEXTRIN COMPLEX

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The crystal structure of β-cyclodextrin (β-CyD) complex with an antiinflammatory drug flurbiprofen (FP), 2-(2-fluoro-4-biphenylyl)propionic acid, was determined by the X-ray method. The complex crystallized in the space group P1, with unit cell dimensions a= 15.420(2), b= 15.490(2), c= 18.033(2) Å, α= 113.63(1)°, β= 99.36(1)°, and γ= 103.05(1)°. The structure was solved on the basis of the isomorphous structure of the *n*-propanol complex and refined to the R-value of 0.084. The two symmetry-independent β-CyD molecules are associated by intermolecular hydrogen-bonds between the secondary hydroxyl groups to form a head-to-head dimer. R- and S-isomers of FP are separately included in the two β-CyD cavities of the dimer, resulting in a 2:2 (guest:host) stoichiometry.

KEYWORDS——β-cyclodextrin; flurbiprofen; enantiomer; inclusion complex; X-ray analysis; crystal structure; dimeric structure

One of the important properties of cyclodextrins (CyDs) is their ability to form inclusion complexes with a variety of guest molecules, in which the guest molecules are included within the hydrophobic cavity of CyDs.[1)]

Flurbiprofen (FP), 2-(2-fluoro-4-biphenylyl)propionic acid, is a widely used antiinflammatory drug which is efficacious and safe in the treatment of rheumatoid arthritis.[2)] We have recently reported[3)] that FP forms an inclusion complex with β-CyD in water and in the solid state, and its absorption from the gastrointestinal and rectal tracts in rabbits are significantly enhanced by the CyD complexation. The present study deals with the X-ray crystallographic structure determination of the FP—β-CyD complex to gain insight into the detailed geometry of guest-host interaction in the solid state.

Single crystals of FP—β-CyD complex were prepared by slow cooling of a hot aqueous β-CyD solution saturated with racemic FP. The determination of the lattice parameters and the intensity measurements were carried out on a Nicolet P3/F diffractometer with graphite-monochromated Cu-K_α radiation. By using θ-2θ scan mode, 9472 independent reflections with $|F_o| \geq 3\sigma(F)$ were collected up to 120° in 2θ. No corrections were made for absorption and extinction. The crystal structure was determined on the basis of the isomorphous structure of *n*-propanol—β-CyD complex[4)] and refined by the block-diagonal least-squares method to the R-value of 0.084.

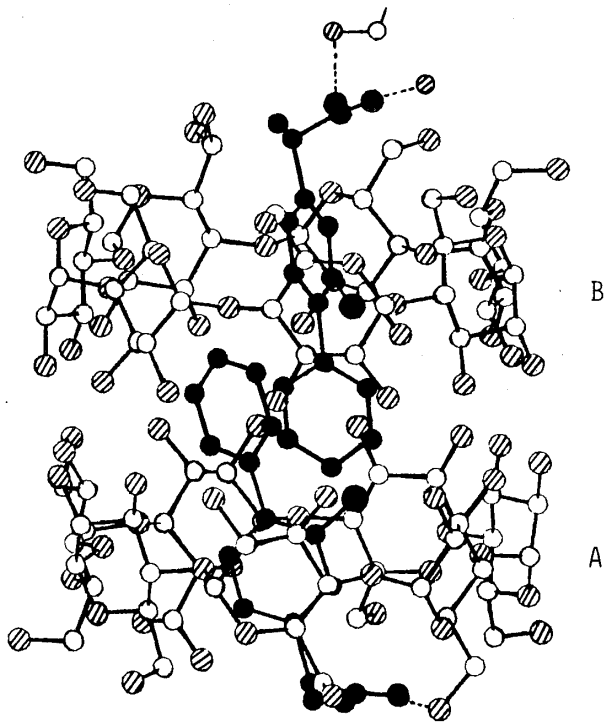

Fig. 1. Projection of the 2:2 (±)FP—β-CyD Complex
The atoms of FP are shaded. A water molecule and a primary hydroxyl group of the symmetry-operated β-CyD are shown hydrogen-bonded to the guest, indicated by broken lines. The circles in the β-CyD molecules represent oxygen(⊘) and carbon(o) atoms, respectively, and the circles(●) in FP molecules represent fluorine, oxygen and carbon atoms in order of decreasing size.

Crystal Data: $(C_{42}H_{70}O_{35}\cdot C_{15}H_{13}O_2F)_2\cdot 20H_2O$, F.W.= 3118.8, triclinic, space group P1 Z= 1, *a*= 15.420(2), *b*= 15.490(2), *c*= 18.033(2) Å, α= 113.63(1)°, β= 99.36(1)°, γ= 103.05(1)°, V= 3685.2 Å^3, D_x= 1.41 g·cm^{-3}, D_m= 1.42 g·cm^{-3} (flotation method: carbon tetrachloride—cyclohexane).

The structure of the FP—β-CyD complex is shown in Fig. 1. All D-glycosyl residues are in the C_1 chair conformation and the secondary hydroxyl groups form intramolecular O(2)---O(3) hydrogen bonds (2.70∼2.86 Å) with the adjacent glucose unit to fix the β-CyD molecule in a round shape. The two-independent β-CyD molecules, A and B in Fig. 1, are coupled through intermolecular hydrogen bonds with their secondary hydroxyl ends facing each other to form a head-to-head dimer.[5] In one of the β-CyD molecules (A in Fig. 1), five of the primary hydroxyl groups point away from the cavity [(-)*gauche* orientation],[1] one of them points towards the cavity [(+)*gauche* orientation], and the seventh hydroxyl group is statistically disordered, showing (+) and (-)*gauche* orientaions. In the case of the other β-CyD molecule (B in Fig. 1), however, six of the primary groups are in the (-)*gauche* orientation and only one of the primary hydroxyl groups is disordered in the (+) and (-)*gauche* orientations. All twenty water molecules are located outside the β-CyD dimer, forming a hydrogen-bond network in the crystal.

It is interesting to note that R- and S-isomers of FP molecule, shown fully shaded in Fig. 1, are independently located in the A and B cavities of β-CyD, respectively. The fluorobenzene moiety of FP molecule lies in the middle of each β-CyD annulus, while the phenyl group protrudes from the secondary hydroxyl side and is partly inserted into the other β-CyD cavity. The polar substituent of FP molecule, the carboxyl group, is located at the primary hydroxyl end of β-CyD and is hydrogen-bonded to a primary hydroxyl group (2.83 Å) in the complex with R-isomer. It is also hydrogen-bonded to

a neighbouring water molecule (2.66 Å) and a primary hydroxyl group of the symmetry-operated (x, -1+y, -1+z) β-CyD molecule (2.95 Å) in the complex with S-isomer. A close contact is found between the fluorine atom of FP and a glycosidic oxygen atom of the β-CyD molecule (3.12 Å), indicating that the FP molecule is fixed in the β-CyD cavity through the hydrogen-bonding and van der Waals contact.[6] It is also noted that the conformation of FP[7] is significantly different from that of the complexed one, probably because the FP molecule is tightly fitted to the β-CyD cavity. For example, the angles between the two benzene planes [C(1)∼C(6) and C(7)∼C(12)] in the biphenyl moiety (see Fig. 2) are 37.4° and 34.8° in the R- and S-isomers, respectively, while the corresponding angle in the uncomplexed FP molecule is 54.4°. Moreover, the propionic acid moiety in both isomers is *ca.* 180° rotated around the C(4)-C(13) bond by the complexation with β-CyD.

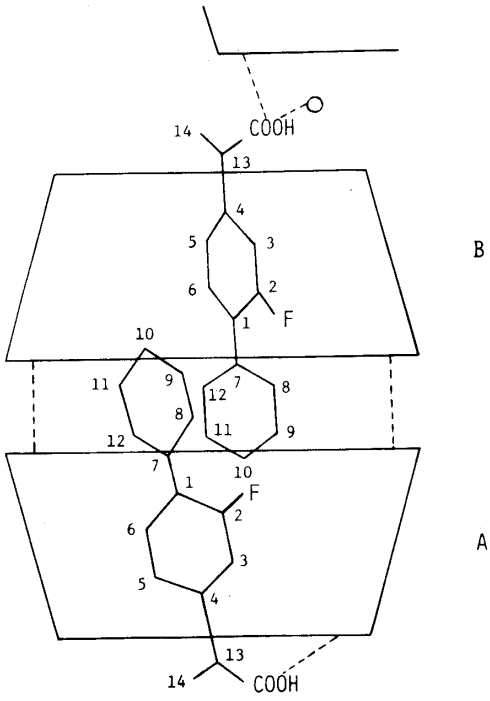

Fig. 2. Schematic Drawing of the 2:2 (±)FP—β-CyD Complex
R- and S-isomers of FP are included in the A and B cavities of β-CyD, respectively. The circle and the dashed lines indicate water molecule and hydrogen-bonds, respectively.

Although the hydrophobic interaction between the phenyl groups of two FP molecules may play an important role for dimer formation in the aqueous solution, such an interaction may not be worthy of consideration in the solid state, as seen in Fig. 1. According to the above observations, the dimeric structure of (±)FP—β-CyD complex is schematically illustrated in Fig. 2. The structure of the complex described here lends great support to the inclusion mode reported previously.[3] In contrast to β-CyD, we have recently found[8] that S-isomer of FP is stereoselectively included in the cavity of heptakis(2,3,6-tri-O-methyl)-β-CyD, showing a head-to-tail type channel structure. The full X-ray crystallographic study of this complex is under way.

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