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X-RAY CRYSTALLOGRAPHIC DETERMINATION OF THE ABSOLUTE CONFIGURATION OF (+)FLURBIPROFEN UTILIZING β-CYCLODEXTRIN COMPLEXATION

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The crystal structure of the β-cyclodextrin (β-CyD) complex with an optically active antiinflammatory drug (+)flurbiprofen (FP), 2-(2-fluoro-4-biphenylyl)propionic acid, was determined by the X-ray method, in the hope of establishing the absolute configuration of the chiral guest molecule. The complex crystallized in a space group P1, with unit cell dimensions a= 15.446(2), b= 15.513(2), c= 18.107(2) Å, α= 113.52(1)°, β= 99.32(1)°, and γ= 102.89(1)°. The structure was solved on the basis of the isomorphous structure of the n-propanol complex and refined by the block-diagonal least-squares method to the R-value of 0.095. It was confirmed that the chirality at an asymmetric carbon atom of (+)FP is the S-configuration.

KEYWORDS——β-cyclodextrin; (+)flurbiprofen; chirality; absolute configuration; X-ray analysis; inclusion complex; crystal structure

Flurbiprofen (FP), 2-(2-fluoro-4-biphenylyl)propionic acid, is an optically active antiinflammatory drug with potent antirheumatic activity.[1] Greig and Griffin have reported[2] that the (+)enantiomer of FP is about 30-fold more active than the racemic FP in antagonizing various agonists such as slow reacting substances in anaphylaxis (SRS-A). However, the absolute configuration of (+)FP has not been assigned on the basis of X-ray crystallography.[3] Although the absolute configuration of chiral compounds is usually determined by using the anomalous dispersion effects of heavy atoms for X-ray radiation,[4] this method requires the existence of some heavy atom in a molecule and/or more accurate measurements of X-ray reflection intensities.

β-Cyclodextrin (β-CyD), cyclic oligosaccharide, is known to form inclusion complexes with a variety of guest molecules.[5] Since β-CyD is a chiral macromolecule consisting of the seven optically active glucose units, the chirality of the included guest molecule can be determined on the basis of the absolute configuration of β-CyD by solving the crystal structure of the inclusion complex. Thus the present study deals with the X-ray crystallographic structure analysis of the (+)FP—β-CyD complex to demonstrate the usefulness of inclusion complexation in determining the absolute configuration of the chiral guest molecule.

Single crystals of (+)FP—β-CyD complex were prepared by slowly cooling a hot β-CyD solution saturated with (+)FP ($[\alpha]_D^{22}$ = +45.6° in ethanol). Lattice parameters and reflection intensities were measured on a Nicolet P3/F diffractometer with graphite-monochromated Cu-K_α radiation. By using the θ-2θ scan mode, 9639 independent reflections with $|F_o| \geq 3\sigma(F)$ were obtained up to 117° in 2θ. The crystal structure was deduced on the basis of the isomorphous structure of *n*-propanol—β-CyD complex,[6] and refined by the block-diagonal least-squares method to the R-value of 0.095. Crystal data were as follows : $(C_{42}H_{70}O_{35}\cdot C_{15}H_{13}O_2F)_2\cdot 21H_2O$, F.W.= 3136.8, triclinic, space group P1, z= 1, *a*= 15.446(2), *b*= 15.513(2), *c*= 18.107(2) Å, α= 113.52(1)°, β= 99.32(1)°, γ= 102.89(1)°, V= 3721.9(7) Å^3, D_x= 1.40 g·cm^{-3}, D_m= 1.41 g·cm^{-3} (flotation method : carbon tetrachloride—cyclohexane).

The molecular structure of the (+)FP—β-CyD complex is shown in Fig. 1. The two β-CyD molecules are associated through intermolecular hydrogen-bonds with their secondary hydroxyl groups to form a head-to-head dimer, in which two (+)FP are included. The chirality at an asymmetric carbon atom of the included (+)FP molecule is assignable to the S-configuration, as depicted in Fig. 2. It is interesting that the molecular geometry of the (+)FP—β-CyD complex is nearly the same as that of the racemic (±)FP—β-CyD complex reported previously.[7] In both

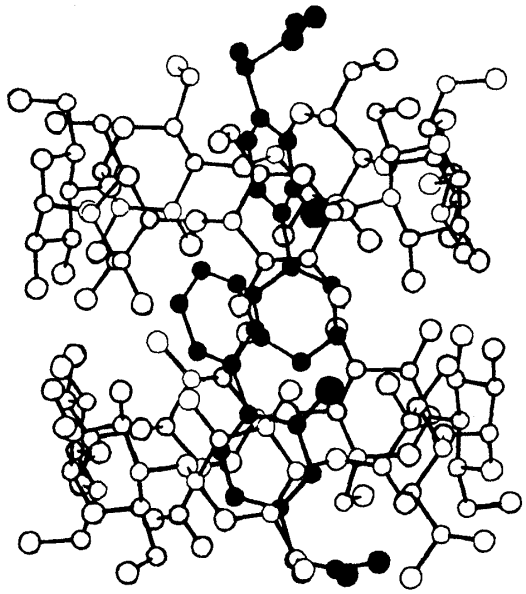

Fig. 1. Projection of the 2:2 (+)FP—β-CyD Complex
The atoms of FP are drawn with shading, and the circles represent fluorine, oxygen and carbon atoms in order of decreasing size.

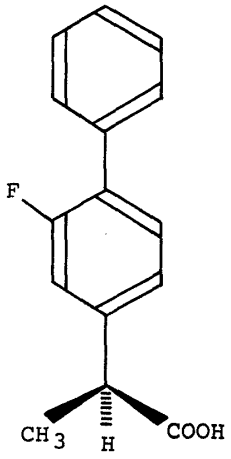

Fig. 2. Schematic Drawing for the Configuration of the Propionic Portion of the (+)FP Molecule

β-CyD complexes, however, slight structural differences between the (+)FP complex and (±)FP complex are noted in the orientation of the primary hydroxyl groups of β-CyD and in the distribution of the waters of crystallization. The detailed structure of the (+)FP complex will be reported elsewhere.

The present result indicates that the CyD complexation is particularly useful for the determination of the absolute configuration of the chiral guest molecule. Moreover, this method may be applicable even to the liquid chiral molecule because of the crystallization as a solid inclusion complex.[8)]

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