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Disordered Crystal Structure of Diflunisal ($C_{13}H_8F_2O_3$)

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디플루니살의 불균일 결정구조

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The crystal structure of diflunisal, 2′,4′-difluoro-4-hydroxy-3-biphenyl-carboxylic acid, was determined by single crystal X-ray diffraction technique. The compound was recrystallized from a mixture of acetone and water in monoclinic, space group C2/c, with a = 34.666(6), b = 3.743(1), c = 20.737(4) Å, β= 110.57(2)°, and Z = 8. The calculated density is 1.324 g/cm^3. The structure was solved by the direct method and refined by full matrix least-squares procedure to the final R value of 0.045 for 1299 observed reflections. It was found that the molecules in the crystal are partially disordered, that is, the two equivalent conformers (180° rotated ones through C(1)-C(7)) are packed alternatively without regular symmetry or sequence. The two phenyl rings of the biphenyl group is tilted to each other by the dihedral angle of 43.3°. The carboxyl group at the salicylic moiety is just coplanar to the phenyl ring, and the planarity of this salicylic moiety is stabilized by an intramolecular hydrogen bond of O(3)-H(O3)···O(2). The molecules are dimerized through the intermolecular hydrogen bonds at the carboxyl group in the crystal.

Keywords—Diflunisal, Antiinflammatory, Crystal structure, Disorder, X-ray diffraction, Hydrogen bond

Diflunisal (Fig. 1) is a widely using non-steroidal antiinflammatory drug(NSAID), related structurally to drugs such as salicylic acid, aspirin, and fendosal. The compound is four times more potent and much less irritating than aspirin, and it is a moderately active reversible cyclooxygenase inhibitor with minimal platelet inhibitory effect at therapeutic dose.[1]

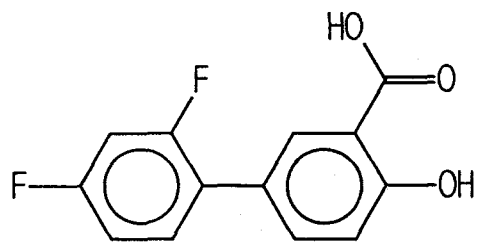

Figure 1—Diflunisal.

NSAIDs inhibit prostaglandin biosynthesis, or more specifically the enzyme cyclooxygenase.[2-3] As an attempt to understand the mode of interaction of the drug molecules to the target enzyme, we have dete/rmined the 3D structures of some NSAIDs.[4-12] And in this paper, we are reporting the structure of the titled compound to provide precise and useful informations necessary for the understanding and designing of a more useful NSAID.

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Table I — *Descriptors for the Experimental Procedure*

CRYSTAL DATA	
$C_{13}H_8F_2O_3$	MoKα radiation
M_r=250.20	λ=0.7107Å
Monoclinic	Cell parameters from 25 reflections
C2/c	θ=3.8-9.4°
a=34.666(6) Å	μ=0.074 mm^{-1}
b=3.743(1)Å	T=293°K
c=20.737(1)Å	Colorless prism
β=110.57(2)°	0.30×0.15×0.10 mm
V=2519.4(4)$Å^3$	
Z=8	
D_x=1.324 g/cm^3	
D_m=1.33 g/cm^3	by flotation in CCl_4 and benzene solution
DATA COLLECTION	
Enraf-Nonius CAD-4 diffractometer	R_{int}=0.035
ω2θ scans	θ_{max}=25.0°
Absorption correction: none	h=0->40
	k=0->4
	l=-24->23
4433 measured reflections	3 standard reflections frequency:60 min intensity decay:none
2221 independent reflections	
1299 observed reflections [F>3σ(F)]	
REFINEMENT	
Refinement on F	Unit weights applied
R=0.045	$(\Delta/\sigma)_{max}$ = 0.001
ωR=0.061	$\Delta\rho_{max}$ = 0.313 $e/Å^3$
S=2.347	$\Delta\rho_{min}$= -0.132 $e/Å^3$
1299 reflections	Extinction correction:none
200 paramenters	Atomic scattering factors
All H-atom parameters refined	from International Tables for X-ray Crystallography

EXPERIMENTAL

Colorless prismatic crystals were grown by the slow evaporation from a mixture of acetone and water at room temperature. A crystal of suitable size was mounted on an Enraf-Nonius CAD4 diffractometer. Lattice parameters were obtained by angular positions of randomly-obtained diffraction spots, and intensity data within range of $\theta \leq 25°$(MoKα) were collected using the informations obtained previously. The significant descriptors explaining the experimental procedure in detail are summerized in Table I.

The structure was solved by the direct method with MULTAN84.[13] However, the electron density of 2′-fluorine atom was too low, and an unexpected peak whose density was nearly the same as the previous one was found at the counterpart of the ring. In other words, two half-fluorine atoms were appeared at both of the equivalent sites of the ring on the E-map. The phenyls in the biphenyl group can be rotated, and it is possible that the two equivalent conformers (180° rotated ones) may be packed as one after another. So it could be thought that the molecules in the crystal are partially disordered as explained, or the current centered symmetry (C2/c) is correct for the remaining structure, but is wrong for the flourine atom only.

To check the possible error due to centrosymmetry, we reduced the C-centered monoclinic cell to a primitive triclinic one (a=3.744, b=17.433, c=20.737Å, α=110.44, β=89.99, γ=96.22°), and attempted to solve the structure without any symmetry (P1). However, the result was exactly equivalent to the solution with C2/c. The E-map showed that all the four molecules in the asymmetric unit have the same half-flourines at the both sides of the rings. So the structure was assumed to be partially disordered, and the cell and space group were reconstructed to the previous C-centered ones. The two half-flourines were named as F(2) and F(3), respectively.

The structure was refined by full matrix least squares procedure with SHELX76.[14] At first, the site occupation factors of F(2) and F(3) were allowed to be refined with various initial value pairs (i.e. 0.3 & 0.7, 0.7 & 0.3, 0.4 & 0.6,...), but they were always converged to 0.534 and 0.502. So we fixed the both values as 0.5, and the refinement was re-performed. The final R value was 0.045 with unit weight (wR=0.061). All the calculations were done on a microVAX

Table II — *Fractional Atomic Coordinates and Equivalent Isotropic Displacement Parameters(Å²).*
$U_{eq} = (1/3)\sum_i\sum_j U_{ij}\, a_i^*\, a_i^*\, \mathbf{a}_i \cdot \mathbf{a}_j$

Atom	s.o.f.	x	y	z	U_{eq}
F(1)	1.0	.5427(1)	.2321(12)	.0154(1)	.094(2)
F(2)	0.5	.5200(2)	.5119(18)	.2179(3)	.065(2)
F(3)	0.5	.6480(2)	.0215(19)	.2235(3)	.069(3)
O(1)	1.0	.7168(1)	.6566(14)	.4114(2)	.072(2)
O(2)	1.0	.7100(1)	.5814(13)	.5132(2)	.074(2)
O(3)	1.0	.6413(1)	.3149(14)	.5181(2)	.076(2)
C(1)	1.0	.6007(1)	.2715(14)	.3042(2)	.048(2)
C(2)	1.0	.6394(2)	.3998(15)	.3406(2)	.051(2)
C(3)	1.0	.6543(1)	.4176(15)	.4126(2)	.049(2)
C(4)	1.0	.6295(2)	.3039(16)	.4485(2)	.055(2)
C(5)	1.0	.5899(2)	.1761(17)	.4124(3)	.058(2)
C(6)	1.0	.5764(2)	.1601((16)	.3415(3)	.054(2)
C(7)	1.0	.5851(1)	.2584(14)	.2279(2)	.049(2)
C(8)	1.0	.6093(1)	.1399(16)	.1915(3)	.055(2)
C(9)	1.0	.5952(2)	.1326(19)	.1204(3)	.067(3)
C(10)	1.0	.5564(2)	.2416(17)	.0854(3)	.063(2)
C(11)	1.0	.5307(2)	.3594(19)	.1175(3)	.061(2)
C(12)	1.0	.5456(1)	.3678(16)	.1886(2)	.054(2)
C(13)	1.0	.6958(2)	.5581(16)	.4497(3)	.058(2)

3100 and a personal computer. The atomic scattering factors were taken from "International Tables for X-ray Crystallography".[15]

RESULTS AND DISCUSSION

The final atomic coordinates and equivalent isotropic temperature factors are listed in Table II. The list of structure factors, anisotropic displacement parameters, hydrogen atomic coordinates and complete geometry is available uponrequest.

The atomic numbering scheme and a perspective view of the molecule drawn by ORTEPII[16] is shown in Fig. 2. All of the molecular dimensions are in the reasonable range, and some selected geometric parameters are collected in Table III.

The two phenyl rings in the biphenyl are tilted to each other by the dihedral angle of 43.3°, indicating the existence of steric repulsion between fluorine and hydrogens of neighboring

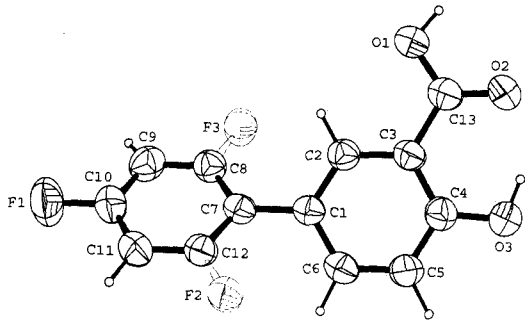

Figure 2 — A perspective view of the molecule drawn by ORTEP with the atomic numbering scheme. The displacement ellipsoids are drawn at the 50% probability level. H atoms are drown as small circles of arbitratry radii. Notice the half-occupeied fluorine atoms designated by light lines.

ring. The carboxyl group at the salicylic moiety is just coplanar to phenyl ring within the experimental errors (dihedral angle: 0.5°). This planarity of the salicylic moiety is stabilized by an intramolecular hydrogen bond between the phenolic OH and carboxylic oxygen (H(O3)···O(2): 1.83(7)Å, ∠O(3)-H(O3)···O(2): 148(6)°).

The stereoscopic molecular packing is presented in Fig. 3. In the crystal, the molec-

Table II — *Selected Geometric Parameters(Å, °).*

F(1)—C(10)	1.359(6)	O(1)—C(13)	1.305(6)
F(2)—C(12)	1.350(7)	O(2)—C(13)	1.237(6)
F(3)—C(8)	1.346(7)	O(3)—C(4)	1.356(6)
C(1)—C(7)	1.482(60	C(3)—C(13)	1.471(7)
C(11)-C(12)-F(2)	115.4(5)	C(4)-C(3)-C(13)	120.4(4)
C(1)-C(7)-C(12)	122.2(5)	O(1)-C(13)-O(2)	122.0(5)
C(2)-C(1)-C(7)-C(8)	43.8(6)		
O(1)-C(13)-C(3)-C(2)	0.7(6)		

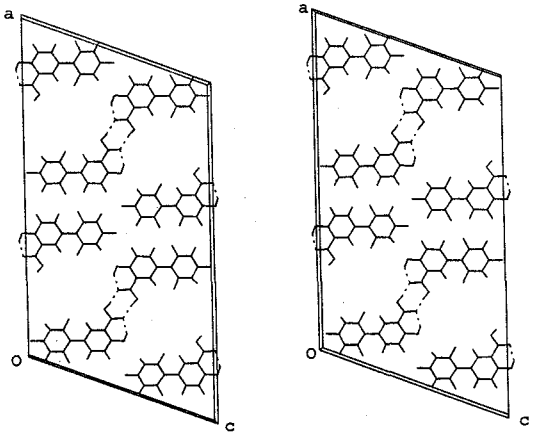

Figure 3. Crystal packing for difluisal viewing down along the b-axis. The broken lines indicate OH···O type intramolecular and intermolecular hydrogen bonds.

ules are dimerized through the intermolecular hydrogen bonds between the carboxyl groups. The distance between O(1) and O′(2) at (1.5-x, 1.5-y, 1-z) is 2.655(6)Å (H(O1)···O′(2): 1.80(7)Å, ∠O(1)-H(O1)···O′(2): 170(7)°). An intermolecular contact somewhat shorter than van der Waals′ distance was found between F(2) and F′(3) at (1.0-x, y, 0.5-z) (2.24(1)Å, cf. sum of van der Waals′ radii for two fluorines: 2.70Å17)). However the disordered fluorine atoms will exist alternatively at these half-occupied positions, and this intermolecular strain will not be in effect in the real crystal. The other interatomic distances are in the range of normal van der Waals′ contacts.

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