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The Crystal Structure of Cinmetacin ($C_{21}H_{19}NO_4$), A Non-steroidal Antiinflammatory Agent

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Abstract □ The structure of cinmetacin was determined by single crystal X-ray diffraction analysis. The compound was recrystallized from a mixture of acetone and water in orthorhombic, space group $P2_12_12_1$, with $Z=4$, $a=35.681(8)$, $b=9.482(2)$, $c=5.071(1)$ Å, $D_x=1.352$ g/cm^3, and $D_m=1.35$ g/cm^3. The structure was solved by direct method and refined by least-squares procedure to the final R value of 0.036 for 1441 observed reflections ($F \geq 3\,\sigma(F)$). The carboxyl group of the molecule is nearly perpendicular to the indole ring. The dihedral angle between indole ring and phenyl group is 64.5°. The molecules are linked together via O(1)-H ---- O(3) hydrogen bonds, and arranged along 2-fold screw axis in the crystal. The intermolecular contacts are the normal van der Waals' forces.

Keywords □ non-steroidal antiinflammatory agent, cinmetacin, X-ray diffraction

Cinmetacin, 5-methoxy-2-methyl-1-(1-oxo-3-phenyl-2-propenyl)-1H-indole-3-acetic acid (Fig. 1) is a non-steroidal agent having antiinflammatory, antipyretic and analgesic activities.[1] The compound is classified as arylacetate analogues, one of the subclasses of non-steroidal antiinflammatory drugs,[2-4] and it is structurally very similar to indomethacin[5] and sulindac.[6]

It has been known that the enzyme cyclooxygenase is the target site where non-steroidal antiinflammatory agents interact,[2-4,7-9] and several models about their modes of interaction with receptor binding site were proposed independently.[10-12] But they have not been confirmed at the molecular level yet.

We have determined the three dimensional structures of the nonsteroidal antiinflammatory agents.[13-16] This paper is one of the structural studies to provide useful informations necessary for the receptor modeling or new drug design[17-19] of the nonsteroidal antiinflammatory agnts.

EXPERIMENTAL

Yellow prismatic crystals were grown by the slow evaporation method from a mixture of water and acetone at room temperature. The density was measured by the flotation method in a mixture of benzene and carbon tetrachloride. The lattice constants were determined from least-squares refinement of the 2θ values for the 20 reflections centered on an automatic four-circle diffractometer (Rigaku Denki Co. Ltd.) with Ni-filtered Cu$K\alpha$ radiations. The crystal data are listed in Table I.

Reflection data from a crystal with dimensions of $0.5 \times 0.2 \times 0.1$ mm were recorded by ω-2θ scan technique at a scan speed of 6°/min with range of $0 \leq h \leq 40$, $0 \leq k \leq 10$, and $0 \leq l \leq 5$. Three standard reflections, (511), (241) and (203) were monitored after each 100 data collections and showed no noticeable changes. Lorentz and polarization corrections were applied to the data; absorption corrections were not made. Of all 1568 independent reflections, 127 reflections which have $F<3$ (F)

Table I. Crystal data

5-Methoxy-2-methyl-1-(1-oxo-3-phenyl-2-propenyl)-1H-indole-3-acetic acid	
Molecular formula; $C_{21}H_{19}NO_4$	Mol. Wt. 349.39
Yellow transparent prism,	Orthorhombic
a = 35.681(8) Å	b = 9.482(2) Å
c = 5.071(1) Å	
Volume of unit cell;	1715.42 Å^3
D_x = 1.352 g/cm^3	D_m = 1.35 g/cm^3
Z = 4	Space group; $P2_12_12_1$
CuK = 1.54187 Å	
F(000) = 736	μ(Cu$K\alpha$) = 7.78 cm^{-1}

were treated as unobserved.

The structure was solved by direct method with *SHELX* 76[20] and *MULTAN* 84[21] programs. All the 26 nonhydrogen atoms are appeared on the first E-map calculated using the phase set with the highest reliability index, and the initial R value was 0.217. The structure was refined first isotropically to the R value of 0.107 by 4 cycles of full matrix least-squares procedure. Successive refinements with anisotropic temperature factors reduced the R value to 0.076. Difference Fourier synthesis calculated at this stage revealed all the hydrogen atoms of cinmetacin.

Further refinenments by block diagonal least-squares procedure including hydrogen atoms converged the R value to 0.036 and wR to 0.034 for 1441 observed reflections (where $wR = [\Sigma w(|F_o|-|F_c|)^2/\Sigma wF_o^2]^{1/2}$). The function minimized in the refinement was $w(|F_o|-|F_c|)^2$. where $w = 1/\sigma^2(F)$. In the final cycle, the average and maximum shift/e.s.d. ratio for parameters of nonhydrogen atoms and hydrogen atoms were 0.032 and 0.475, 0.054 and 0.971, respectively.

All the calculations were carried out on VAX-11/780 computer system at Seoul National University. The atomic scattering factors were taken from "*International Tables for X-ray Crystallography*"[22].

RESULTS AND DISCUSSION

The final atomic coordinates and temperature

Table II. Final positional ($\times 10^4$) and thermal ($\times 10^3$) parameters with their estimated standard deviations in parentheses. The anisotropic temperature factors are expressed in the form of

$$exp\{-2\pi^2(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + U_{33}c^{*2}l^2 + 2U_{12}a^*b^*hk + 2U_{13}a^*c^*hl + 2U_{23}b^*c^*kl)\}$$

Atom	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	3687(1)	8881(3)	-505(7)	40(2)	33(2)	43(2)	2(2)	6(2)	-10(1)
C(2)	3381(1)	9512(3)	562(7)	40(2)	31(2)	41(2)	2(2)	-7(2)	-4(1)
C(3)	3227(1)	8606(3)	2559(7)	39(2)	29(2)	40(2)	-1(2)	-5(2)	-3(1)
C(4)	2930(1)	8760(3)	4313(7)	40(2)	33(2)	44(2)	-3(2)	-7(2)	0(1)
C(5)	2852(1)	7685(3)	6056(6)	38(2)	42(2)	36(2)	-3(2)	-3(2)	-3(1)
C(6)	3071(1)	6452(3)	6105(7)	49(2)	34(2)	39(2)	5(2)	-2(2)	-6(2)
C(7)	3370(1)	6290(3)	4371(7)	43(2)	33(2)	44(2)	1(2)	-5(2)	-1(1)
C(8)	3444(1)	7361(3)	2604(7)	39(2)	28(2)	41(2)	-1(2)	-1(2)	-2(1)
C(9)	3982(1)	6461(3)	26(7)	44(2)	37(2)	52(2)	-5(2)	-1(2)	1(1)
C(10)	4337(1)	6828(3)	-1294(7)	43(2)	36(2)	55(2)	2(2)	2(2)	-3(2)
C(11)	4487(1)	5943(3)	-2997(7)	49(2)	38(2)	55(2)	-1(2)	3(2)	0(2)
C(12)	4848(1)	6081(3)	-4375(7)	45(2)	39(2)	46(2)	4(2)	1(2)	5(1)
C(13)	4930(1)	5153(4)	-6390(8)	61(2)	54(2)	55(2)	-4(2)	1(2)	0(2)
C(14)	5265(1)	5240(4)	-7763(9)	67(2)	74(3)	51(2)	-6(2)	12(2)	10(2)
C(15)	5525(1)	6262(4)	-7116(8)	53(2)	71(3)	59(2)	8(3)	6(2)	8(2)
C(16)	5449(4)	7179(4)	-5083(9)	48(2)	50(2)	77(3)	5(2)	3(2)	0(2)
C(17)	5115(1)	7107(4)	-3700(8)	50(2)	48(2)	64(2)	-3(2)	4(2)	4(2)
C(18)	3223(1)	10910(3)	-306(8)	44(2)	34(2)	50(2)	6(2)	-4(2)	-2(2)
C(19)	3406(1)	12156(3)	996(8)	45(2)	35(2)	52(2)	6(2)	5(2)	4(2)
C(20)	2441(1)	6773(4)	9399(9)	61(2)	58(2)	53(2)	5(2)	13(2)	-7(2)
C(21)	3918(1)	9401(4)	-2736(8)	51(2)	42(2)	47(2)	6(2)	2(2)	-7(2)
N	3736(1)	7537(2)	747(6)	39(1)	30(1)	45(2)	1(1)	-1(1)	-2(1)
O(1)	3350(1)	13329(3)	-384(7)	101(2)	36(1)	79(2)	17(2)	-23(2)	-12(1)
O(2)	3574(1)	12145(3)	3040(6)	93(2)	46(1)	64(2)	2(2)	-30(2)	-3(1)
O(3)	3910(1)	5241(2)	621(6)	58(1)	31(1)	90(2)	4(2)	20(2)	1(1)
O(4)	2557(1)	7914(2)	7741(5)	51(1)	50(1)	48(1)	5(1)	9(1)	5(1)

Table III. Fractional coordinates and thermal factors of hydrogen atoms($\times 10^3$). The isotropic temperature factors are expressed in the form of $exp(-8\pi^2 U\sin^2\theta/\lambda^2)$

Atom	x/a	y/b	z/c	U
H(C4)	278(1)	963(3)	427(7)	43(9)
H(C6)	302(1)	573(3)	742(6)	34(8)
H(C7)	353(1)	540(3)	458(7)	44(9)
H(C10)	445(1)	768(3)	-78(7)	44(9)
H(C11)	434(1)	506(3)	-361(6)	46(9)
H(C13)	473(9)	441(3)	-697(8)	61(10)
H(C14)	532(1)	453(4)	-933(9)	88(13)
H(C15)	577(1)	630(4)	-835(8)	87(13)
H(C16)	561(1)	796(4)	-475(8)	72(12)
H(C17)	506(1)	772(3)	-212(7)	46(9)
H(C18-1)	324(1)	1099(4)	-243(8)	60(10)
H(C18-2)	295(1)	1094(3)	6(7)	49(9)
H(C20-1)	236(1)	587(4)	825(8)	76(13)
H(C20-2)	265(1)	650(4)	1082(8)	72(12)
H(C20-3)	223(1)	707(4)	1025(8)	67(13)
H(C21-1)	395(1)	874(4)	-418(7)	54(10)
H(C21-2)	417(1)	971(4)	-221(8)	65(11)
H(C21-3)	381(1)	1020(4)	-357(8)	58(11)
H(O1)	351(2)	1385(7)	-66(16)	224(36)

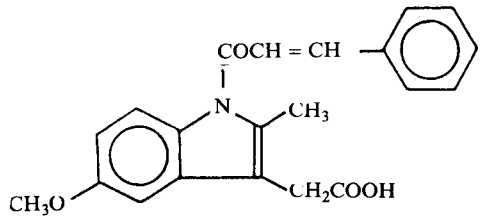

Fig. 1. Cinmetacin.

factors are listed in Table II and III. The observed and calculated structure factors are available upon request.

The atomic numbering scheme, bond lengths and angles are presented in Fig. 2. None of the molecular dimensions are deviated largely from the chemically reasonable values. The stereoscopic view of the molecule drawn by *ORTEP*[23] is shown in Fig. 3. Phenyl group and indole ring are connected by three carbon atoms compared to one carbon in indomethacin and sulindac. Although all the three carbons are sp^2-hybrid, the electrons are localized mainly on the C(10)-C(11) bond so that the remaining bonds can be rotated in order to relieve the steric strains. For example, the bond distance of the N-C(9), 1.396Å (in the case of indomethacin, 1.416 Å) is considerably longer than the value of an amide bond, about 1.32 Å[24], and the torsion angle of C(8)-N-C(9)-O(3) is 13.8°. Newman projections of

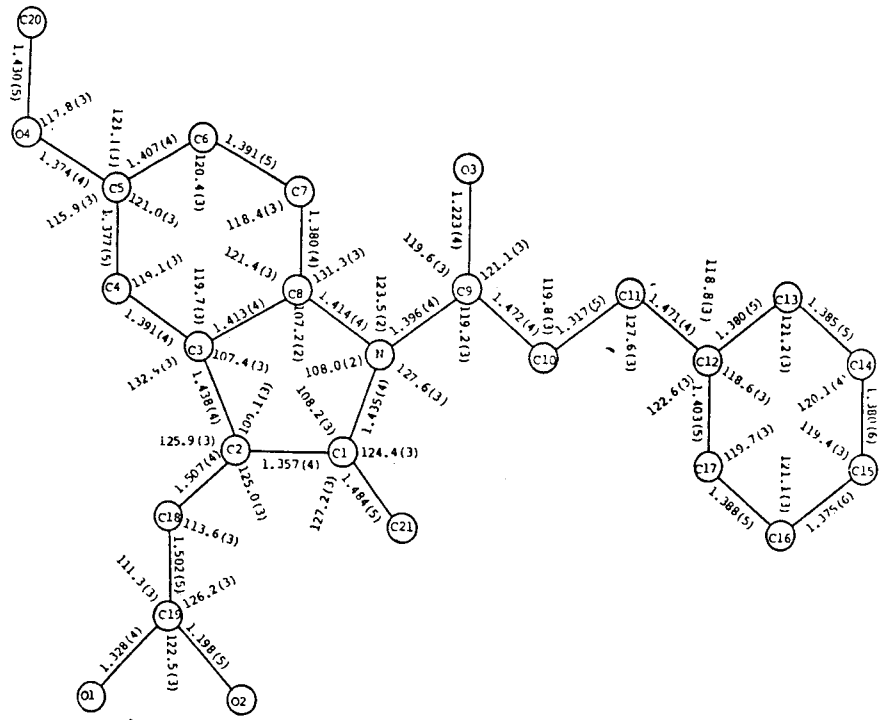

Fig. 2. Bond lengths(Å) and angles(°) of Cinmetacin with their estimated standard deviations in parentheses.

atoms around four single bonds are shown in Fig. 4.

The indole and the phenyl rings are planar within experimental errors. The equations of least-squares planes of indole, phenyl rings and the deviations of individual atoms from these planes are listed in the Table IV. The dihedral angle between the planes is 64.5°, while the corresponding values in indomethacin and sulindac are 67° and 35°, respectively. The methoxy group shows a tendency to be coplanar with the plane of indole ring. The torsion angle of C(6)-C(5)-O(4)-C(20) is 7.6°. This may be due to the effective overlapping of remaining orbitals of oxygen with the π system of the ring. And the bond length of C(5)-O(4) is somewhat shortened to 1.374 Å. Similiar effects are observed in the case of related compounds[7,14,16] which have methoxyaryl moiety. As proposed in the receptor models,[10-12], the ring-carboxyl moiety is supposed to be important for the antiinflammatory activities of the compounds. The carboxyl group is nearly perpendicular to the planar region of the ring with dihedral angle of 84.7°. This seems to be a common feature of arylacetate analogues.[5,6,13-16,25-34] Indole ring is constituted of two rings which are five and six membered, respectively. The dihdral angle be-

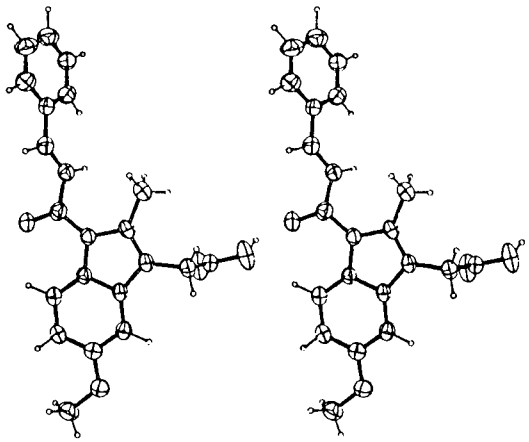

Fig. 3. The stereoscopic view of the cinmetacin molecule. The thermal ellipsoids are drawn at the 50% probability level.

Table IV. The equations of the least-square planes of phenyl ring and indole ring, and the deviations of individual atoms from the planes(Å)

Equations: Plane A (Phenyl ring)

$0.4205\ X - 0.6302\ Y + 0.6527\ Z = 2.2066$

Plane B (Indole ring)

$0.6011\ X + 0.4206\ Y + 0.6795\ Z = 11.2541$

Dihedral angle between these planes; 64.5°

Deviations from;	Plane A	Plane B		Plane A	Plane B
C(1)**	2.149	-0.022	C(2)**	2.631	0.015
C(3)**	1.631	0.020	C(4)**	1.618	-0.009
C(5)**	0.516	-0.014	C(6)**	-0.567	-0.010
C(7)**	-0.538	0.011	C(8)**	0.576	0.034
C(9)	0.084	0.126	C(10)	0.208	-0.325
C(11)	0.018	0.232	C(12)*	0.015	-0.062
C(13)*	0.003	0.826	C(14)*	0.007	0.546
C(15)*	0.014	-0.641	C(16)*	0.003	-1.550
C(17)*	0.004	-1.275	C(18)	3.992	0.096
C(19)	4.032	-1.241	C(20)	-0.520	0.078
C(21)	2.851	0.044	N**	0.858	-0.023
O(1)	5.272	-1.116	O(2)	3.096	-2.302
O(3)	-0.734	0.563	O(4)	0.537	-0.053

*;Atoms used for the calculation of equation of the plane A.

**; Atoms used for the plane B.

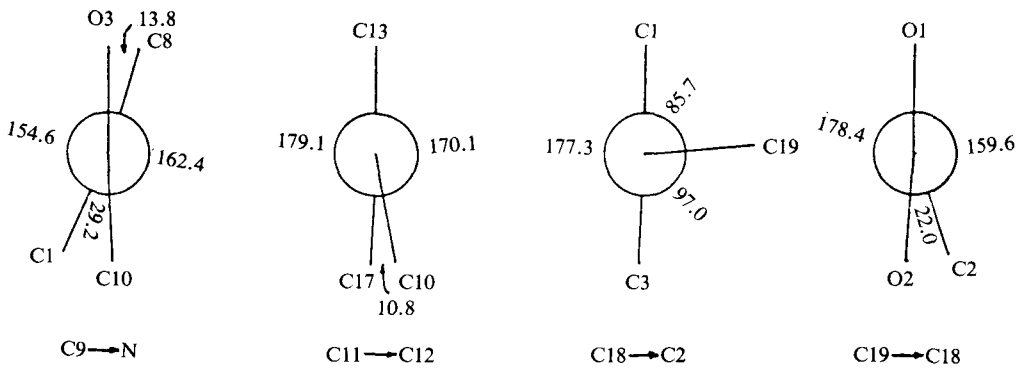

Fig. 4. Newman projections of atoms around four bonds.

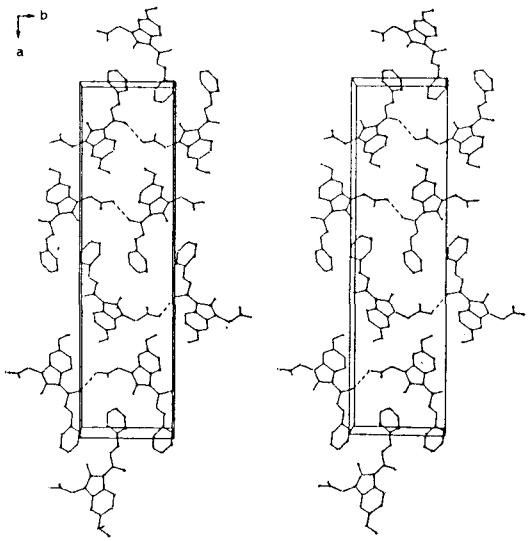

Fig. 5. Stereoscopic packing diagram for cinmetacin. The broken lines indicate OH···O type hydrogen bonds.

tween these rings is 2.39°.

The stereoscopic molecular packing is presented in Fig. 5. The molecules in the crystal are related by 2-fold screw axis, and stabilized by intermolecular hydrogen bonds between carboxyl O(1) and carbonyl O(3) of a neighboring molecule at (x, y-1, z). The distance of O(1)-H···O(3) hydrogen bond is 2.744 Å. The interatomic contacts are normal van der Waals' forces. The shortest distance of the nonhydrogen atoms between neighbouring molecules is 3.357 Å (C(15) to O(2) at (1-x, y-1/2, 1/2-z)).

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