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The Solvent-Independent Structure of Piroxicam

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피록시캄의 용매 비의존 결정구조

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The three-dimensional structures of piroxicam crystallized from two different solvents, toluene and toluene/hexane mixture respectively, are proved identical: $C_{15}H_{13}N_3O_4S$, M = 331.35, monoclinic, a = 7.128(1), b = 15.146(2), c = 13.956(2) Å, β = 97.33(1)°, V = 1494.37Å^3, Dx = 1.472 g/cm^3, Z = 4, space group $P2_1/c$, Mo Kα(λ = 0.71073 Å), F(000) = 688, T = 295 K, R = 0.0611 for 1993 unique observed reflections. The thiazine ring exhibits a half chair conformation. An amide group is involved in an intramolecular hydrogen bond to the hydroxy group, O(17)-H(17)···O(15)Å. The molecule is planar within 2 Å with the interplanar angle 127.9(4)° between pyridine and benzene rings. A molecular chain parallel to [011] is formed by two intermolecular hydrogen bonds N(16)-H(6)···O(11) and C(6)-H(6)···O(11), and the molecular chains are held together by van der Waals forces.

Keywords— piroxicam, crystal form, solvent-independent structure, toluene, toluene/hexane, x-ray diffractometry

Many organic compounds have been reported to exist in more than a single crystalline form, and differences in crystalline form have been described in terms of the thermodynamic properties such as heats of solution, the entropy and enthalpy change in going from one form to another. Of biopharmaceutical interest is the difference in solubility commonly exhibited by crystal modifications. Enhanced therapeutic activity may be achieved with the use of the higher energetic form[1-5]. Piroxicam, 4-hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide, nonsteroidal anti-inflammatory agent, is an example of water-insoluble drugs[6-7]. *In vitro* absorption of the drug from a solid dosage form is thus expected to be dissolution rate limited. It has been published to exist in more than four crystalline forms in piroxicam depending upon solvents[8]. Our interest in pursuing studies is to compare the differences of molecular structure of each crystal prepared from different solvents by X-ray diffraction method. In this paper, however, it has been elucidated that two crystals of piroxicam obtained from two different solvents, toluene and toluene/hexane mixture, had the identical structure in spite of their different colours.

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EXPERIMENTAL

Piroxicam was dissolved in toluene and toluene/hexane (1:1) respectively and then cooled on ice bath. The resulting precipitates were dried at 50 °C. Each crystal had different colour; white (from toluene) and yellow (from toluene/hexane). The infrared spectra of the both crystals were recorded on a Perkin-Elmer 783 infrared spectrophotometer. The 3400 cm^{-1} band is due to an N-H stretching vibration, and the 1300 and 1100cm^{-1} bands have been assigned to asymmetrical and symmetrical SO_2 stretching vibrations. perkin-Elmer DSC-4, equipped with a standard cell, was employed to detect transition and melting temperature of the crystals of piroxicam.

In all determinations the heating rate was 10 °C /min, range 10 μV, pressure gauge 2kg/cm^2, chart speed 1 mm/sec. The thermograms of the crystals gave an essentially straight base line with a single peak corresponding to fusion at 202 °. As shown in Figs. 1 and 2, the infrared spectra and the DSC thermogram patterns of the both crystals were identical.

The same space group $P2_1/c$ of the crystals was determined from Weissenberg photographs recorded with Cu Kα radiation, where a quick adjustment method for crystal oscillation photograph described by Suh, *et al.*[9] was employed. The cell dimensions given in the abstract were obtained by least-squares fit of diffracting positions of 20 reflections (10.42 ° < θ < 15.63 °) on an Enraf-Nonius CAD-4 diffractometer using graphite monochromatized Mo Kα radiation. Intensity data were collected using w-20 scan over w-scan angle ($0.8 + 0.34 \times \tan\ \theta$) from a crystal of dimension $0.2 \times 0.16 \times 0.25$ mm mounted in random orientation. One standard reflection (4-1-4) had maximum 3.9% variation during data collection, thus no decay correction was applied. Data were, however, corrected for Lorentz and polarization effects, but not absorption effect. A same process was used for data collection and data reduction in

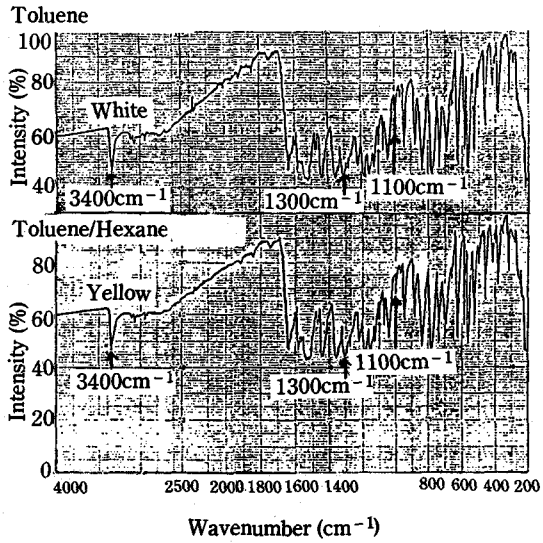

Figure 1—Infrared spectra of crystal forms of piroxicam crystals.

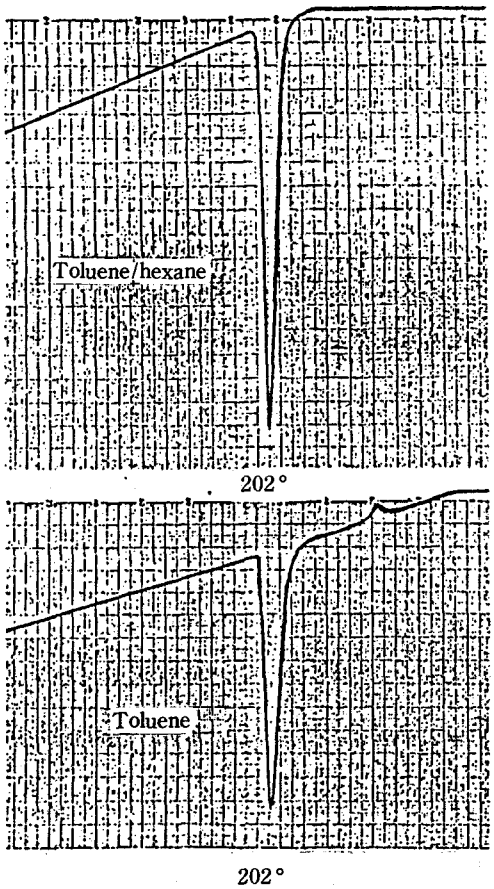

Figure 2—DSC Thermograms of piroxicam crystals.

Table I—*The Comparision of Crystallographic Data of Yellow and White Piroxicams.*

Unit cell	Yellow	White
a	7.122(1)	7.128(1)Å
b	15.127(2)	15.146(2)Å
c	13.946(2)	13.956(2)Å
β	97.29(1)	97.33(1)°
V	1490.2817	1494.3658Å^3

Atom	Code	Yellow	White
S1	X	.5535	.5533
	Y	.4035	.4034
	Z	.0986	.0986
C4	X	.3913	.3937
	Y	.2274	.2279
	Z	.0533	.0535
C7	X	.6820	.6799
	Y	.2581	.2580
	Z	.3394	.3388
C10	X	.4983	.4969
	Y	.2359	.2358
	Z	.1515	.1510
C13	X	.1800	.1794
	Y	.4211	.4210
	Z	.0880	.0886
N16	X	.1647	.1651
	Y	.3643	.3639
	Z	-.1430	-.1429
C2′	X	.0691	.0689
	Y	.3744	.3749
	Z	-.2382	-.2374
C5′	X	-.1190	-.1087
	Y	.4144	.4137
	Z	-.4152	-.4158
N2	X	.3411	.3416
	Y	.3863	.3860
	Z	.0397	.0405
C5	X	.5177	.5186
	Y	.1637	.1639
	Z	.2145	.2151
C8	X	.6617	.6611
	Y	.3309	.3306
	Z	.2774	.2768
O11	X	.5512	.5510
	Y	.4863	.4863
	Z	.1470	.1466
C14	X	.2151	.2170
	Y	.2871	.2877
	Z	-.0953	-.0945
O17	X	.3742	.3741
	Y	.1442	.1446
	Z	.0193	.0185
C3′	X	.0250	.0257
	Y	.3044	.3045
	Z	-.3014	-.3016
C6′	X	-.0585	-.0593
	Y	.4778	.4780
	Z	-.3471	-.3467
C3	X	.3180	.3196
	Y	.2983	.2986
	Z	.0023	.0016
C6	X	.6098	.6098
	Y	.1753	.1761
	Z	.3080	.3074
C9	X	.5706	.5716
	Y	.3176	.3178
	Z	.1827	.1838
O12	X	.6889	.6883
	Y	.3886	.3889
	Z	.0336	.0336
O15	X	.1775	.1780
	Y	.2120	.2124
	Z	-.1280	-.1285
N1′	X	.0299	0.291
	Y	.4587	.4591
	Z	-.2568	-.2569
C4′	X	-.0656	-.0661
	Y	.3250	.3256
	Z	-.3948	-.3927

both structures.

SOLUTION

The direct method (MULTAN)[10] gave the coordinates of sulfur atom including several carbon atoms, and the coordinate of sulfur atom was confirmed by the Patterson method[11] for both structures. A difference Fourier map, evaluated with observed F_o values phased on these atoms, showed all the coordinates of the rest non-hydro-

Table II—*Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters ($\times 10^4 Å^2$) of White Piroxicam.*

Atom	x	y	z	U
S1	5532(1)	4035(1)	986(1)	301
N2	3411(4)	3862(2)	407(2)	301
C3	3194(5)	2984(2)	22(3)	302
C4	3928(5)	2275(2)	539(3)	322
C5	5194(6)	1649(3)	2154(3)	390
C6	6098(6)	1764(3)	3068(3)	457
C7	6794(7)	2585(3)	3384(3)	461
C8	6594(6)	3295(3)	2768(3)	407
C9	5718(5)	3176(2)	1833(3)	310
C10	4966(5)	2360(2)	1510(3)	309
O11	5515(4)	4862(2)	1470(2)	431
O12	6881(4)	3891(2)	331(2)	421
C13	1808(6)	4207(3)	875(3)	433
C14	2164(5)	2874(3)	-949(3)	346
O15	1774(4)	2128(2)	-1283(2)	467
N16	1640(4)	3629(2)	-1434(2)	340
O17	3749(4)	1445(2)	197(2)	472
N1′	296(6)	4587(3)	-2570(3)	498
C2′	690(5)	3750(3)	-2376(3)	353
C3′	256(6)	3057(3)	-3018(3)	434
C4′	-659(6)	3268(4)	-3922(3)	515
C5′	-1074(7)	4128(4)	-4149(3)	639
C6′	-589(8)	4765(4)	-3462(4)	610
H5	4695(52)	1150(24)	1923(26)	181
H6	6246(57)	1224(27)	3483(31)	492
H7	7412(73)	2664(37)	4060(38)	694
H8	7178(66)	3797(30)	2906(34)	516
H1 31	432(74)	4029(36)	440(38)	749
H1 32	1960(68)	4805(33)	1021(35)	575
H1 33	1760(83)	3930(39)	1541(42)	1078
H16	1944(72)	4071(34)	-1153(35)	614
H17	3037(72)	1513(38)	-369(37)	700
H3′	400(63)	2391(31)	-2782(33)	511
H4′	-1080(68)	2829(34)	-4299(36)	717
H5′	-1631(79)	4326(37)	-4752(38)	787
H6′	-841(80)	5365(39)	-3462(42)	952

gen atoms. When all the atoms were refined anisotropically, the R values for the yellow and white crystals were 8.68 and 7.91%, respectively. As

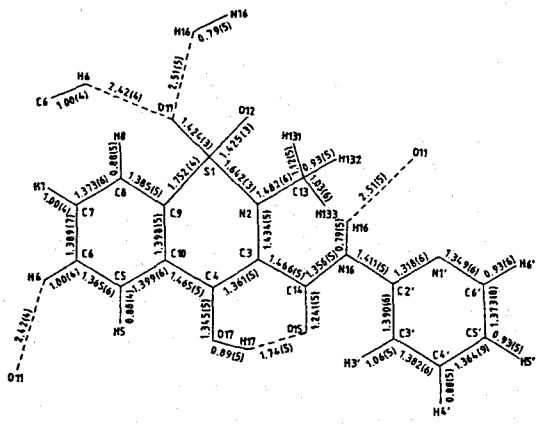

Figure 3—Bond lengths(Å) and the atom numbering scheme in the title compound, with e.s.d.'s in parentheses. Broken lines denote hydrogen bonds.

shown in Table I, thir coordinates were identical and their ORTEP[12] drawings also confirmed the same conformation. Therefore the further calculation was conducted only on the white crystal. Thirteen hydrogen atoms could be located clearly from several difference Fourier maps. The final refinement with anisotropic temperature factor(U_{ij}) for all non-H atoms and isotropic one for H atoms gave R = 6.11% and R_w = 6.98% for 1993 reflections [$F_o > 3\sigma(F_o)$]. Function minimized was $w = 1.5435/[\sigma^2(F_o) + 0.006093/F_o^2]$. The least-squares refinements were carried out with the SHELX system[11] and all calculations were performed on MV-10000 computer at Chungnam National University.

DISCUSSION

The refined atomic coordinates and thermal parameters are given in Table II. The atomic bond lengths with atomic numbering scheme are shown in Fig. 3, and Fig. 4 shows the valence angles. The steroview of a molecule is presented in Fig. 5.

The bond lengths in the pyridine ring range from 1.318(6) to 1.390(6) Å with the mean value 1.363 Å which is very similar to the value in the pyridine ring of tris(2-pyridyl) phosphine[13]. The

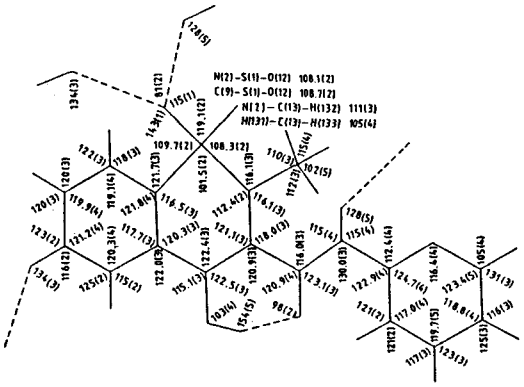

Figure 4—Valene angles(°) in the title compound, with e.s.d.'s in parentheses. Broken lines denote hydrogen bonds.

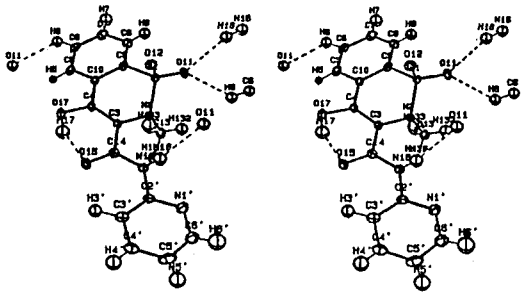

Figure 5—Stereodrawing of a molecule. Broken lines denote hydrogen bonds.

mean bond length 1.385Å in the benzene ring attached to thiazine ring is close to sp^2 hybrid bond length 1.390Å and its mean valence angle is 120°.

AS shown in Figs. 3 and 4, the bond lengths S(1) – N(2) = 1.642(3), S(1) – C(9) = 1.752(4). S(1) – O(11) = 1.424(3), S(1) – O(12) = 1.425(3)Å and the valence angles of sulfonamide group agree very well with those found in methyl 4-hydroxy-2-methyl 2H – 1, 2-benzothiazine-3-carboxylate 1,1-dioxide[14]. C(14) – O(15) = 1.241(5) and C(4) – O(17) = 1.345(5)Å indicate single and double bonds, respectively.

Table III shows the planarities. The atoms in pyridine ring are almost coplanar and within < 0.008 Å from the least-squares plane. N(16) is displaced by 0.020(6)Å from this plane. S(1) and C(4) atoms are deivated only – 0.089(6) and 0.070(7) Å from the best plane through the benzene ring, while N(2) and C(3) atoms are displaced by 0.751(7) and 0.423(8) Å to the same direction from the same plane. Consequently the thiazine ring has a half chair conformation. One molecule is planar within 2 Å with the interplanar angle 127.9(4)° between pyridine and benzene rings. The molecular planarity is reflected in the values of the torsion angles of C(2') – N(16) – C(14) –

Table III—*Least-Squares Planes and the Deviation (Å) of Individual Atom from These Planes.*

Atoms in plane	Atoms out of plane	Distance in Å from best plane	Plane constant
Benzene			
C(5)		.001(3)	P(1) = – 5.58(2)
C(6)		– .007(3)	P(2) = 2.89(2)
C(7)		.003(4)	P(3) = 5.07(3)
C(8)		.008(3)	D = – 1.33(1)
C(9)		– .012(3)	
C(10)		.008(3)	
	S(1)	– .089(6)	
	C(4)	.070(7)	
	N(2)	.751(7)	
	C(3)	.423(8)	
Pyridine			
N(1')		– .002(3)	P(1) = 6.39(1)
C(2')		.001(3)	P(2) = 1.58(3)
C(3')		.002(3)	P(3) = – 6.04(3)
C(4')		– .004(3)	D = 2.47(1)
C(5')		.0043(4)	
C(6')		– .000(5)	
	N(16)	.020(6)	
S(1), C(4), C(9), C(10) plane			
S(1)		.0010(1)	P(1) = 5.09(1)
C(4)		– .012(1)	P(2) = – 3.36(1)
C(9)		– .021(3)	P(3) = – 4.78(4)
C(10)		.024(3)	D = 0.99(1)
	N(2)	– .774(5)	
	C(3)	– .376(7)	

The equation of the plane is expressed in the form P1*X + P2*Y + P3*Z = D, where X,Y and Z are fractional coordinates measured along a, b and c axes, respectively.

Table IV—*Torsion Angle(°) with e.s.d.'s in Parentheses.*

S(1)-N(2)-C(3)-C(4)	40.8(4)	C(3)-N(2)-S(1)-O(12)	59.0(3)
N(2)-C(3)-C(4)-O(17)	- 179.9(3)	C(4)-C(3)-N(2)-C(13)	- 96.2(4)
N(2)-C(3)-C(4)-C(10)	0.3(6)	C(14)-C(3)-N(2)-C(13)	84.1(4)
C(3)-C(4)-C(10)-C(9)	- 18.7(6)	S(1)-N(2)-C(3)-C(14)	- 138.9(3)
C(3)-C(4)-C(10)-C(5)	159.3(4)	N(2)-C(3)-C(14)-O(15)	- 173.0(3)
C(4)-C(10)-C(9)-S(1)	- 5.6(5)	N(2)-C(3)-C(14)-N(16)	5.4(5)
C(4)-C(10)-C(9)-C(8)	175.5(4)	C(3)-C(14)-N(16)-C(2')	178.2(4)
C(10)-C(9)-S(1)-N(2)	39.2(3)	C(14)-N(16)-C(2')-N(1')	175.1(4)
C(3)-N(2)-S(1)-O(11)	- 170.7(3)	C(3)-N(2)-S(1)-C(9)	- 55.3(3)

Table V—*Dimensions of Possible Hydrogen Bonds.*

D-H··· A	D-H	H···A	D···A	/DHA	Symmertry operation on A
O(17)-H(17)···O(15)	0.89(5)	1.74(5)	2.564(4)	154(5)	(X,Y.Z)
C(6)-H(6)···O(11)	1.00(4)	2.42(4)	3.198(5)	134(3)	(1 - X, - 0.5 + Y, 0.5 + Z)
N(16)-H(16)···O(11)	0.79(5)	2.51(5)	3.060(4)	128(5)	(1 - X, 1 - Y, - Z)

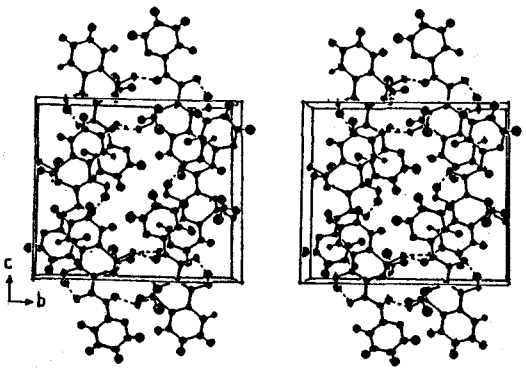

Figure 6—Stereoview of the unit cell packing. Broken lines denote hydrogen bonds.

C(3)[178.2(4)°] and N(16) - C(14) - C(3) - C(4) [- 174.3(3)°] (Table IV) as well as their valene angles. There is one intramolecular hydrogen bond; O(17) - H(17)...O(15) with O(17) - O(15) = 2.564(4)Å. O(11) atom, as an acceptor, in sulfonyl radical appears to form two intermolecular hydrogen bonds to carboxamide N(16) atom[1 - x, 1 - y, - z] and benzene C(6) atom[1 - x, 1 - y, 0.5 + z]. Table V shows the distances and angles related to hydrogen bonds. These C - H···O interactions are within the limits specified by Taylor, *et al.*[15] as well as by Rust, *et al.*[16] These hydrogen-bonding networks form infinite molecular chain parallel to [011] and the chains related by a center of symmetry are held together by van der Waals forces with H(6)-O(12), 2.57(A) A, being the shortest. This value is out of limit for hydrogen bond[15]. The stereoview of the molecular packing is displayed in Fig. 6. In conclusion, the structure of piroxicam described here is completely identical with the previously reported one by Prodic, *et al.*,[17] except for the missing of an intermolecular hydrogen bond C(6)-H(6)···O(11).

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