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Refinement of the Structure of Naproxen, (+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid

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Abstract□The molecular structure of naproxen determined by X-ray diffraction technique was refined to the final R-value being 0.042. The compound was recrystallized from ethanol solution in monoclinic crystal system, space group $P2_1$, with $Z = 2$, $a = 13.375(5)$ Å, $b = 5.793(2)$ Å, $c = 7.914(3)$ Å, $\beta = 93.91(3)$ Å and $d_{obs} = 1.26$, $d_{calc} = 1.25$ g/cm^3. The structure was solved by direct method and refined by block diagonal least squares procedure for 747 reflections($F \geqq 6\sigma(F)$). The molecules are connected by two intermolecular OH--O type hydrogen bonds.

Keywords□Anti-inflammatory agent, Naproxen, X-ray diffraction, Direct method, Hydrogen bond.

(+)-6-Methoxy-α-methyl-2-naphthaleneacetic acid, Naproxen (Fig. 1) is a potent anti-inflammatory agent and believed to act through the inhibition of the enzyme cyclooxygenase involved in prostaglandin biosynthesis.[1-3] In non-steroidal anti-inflammatory agents containing an asymmetric carbon at the position α to the carboxyl group, their activities are known to reside mostly in the S-configuration isomer.[5,6]

We did not attempt to determine the absolute configuration of the titled compound. However it is dextrorotatory, and thus believed to be S-form isomer as determined by Riegl *et al.* with stereochemical methods[7].

It's an interesting subject to pharmaceutical scientists to investigate and elucidate the molecular structure of the related drug analogs in comparison with their physiological activities. We already presented the molecular structure of this compound briefly[8]. This paper deals with the precise three dimensional structural analysis of naproxen and comparison with those of related compounds.

EXPERIMENTAL

The compound was recrystallized from ethanol solution as colorless transparent plates. The space group was determined from Weissenberg photographs and the lattice constants were obtained from measurements on a computer-controlled four circle diffractometer with MoKα radiations.

The density was measured by the flotation method in a mixture of benzene and carbon tetrachloride. The crystallographic data are given in Table I. The optical rotation was mearsure on a digital polarimeter (JASCO DIP-360) in accordance with U.S.P. requirements[9]. The compound is dextrorotatory with $[\alpha]_D^{25} = +63.4(2)°$ confirming the S-isomer[7].

Three dimesional intensity data were collected on an automatic four circle diffractometer (Rigaku Denki Co. Ltd.) with Zr-filtered Mokα radiations. 1413 unique reflections ($\sin\theta/\lambda < 0.65$ Å^{-1}) were recorded by the ω-2θ scan technique (scan speed 2°/min.) from a crystal with dimensions of $0.01 \times 0.35 \times 0.55$ mm.

Lorentz and polarization corrections were applied to the data; absorption corrections were not considered($\mu = 0.51$cm^{-1}). Of all the 1413 independent reflections, 666 reflections which had $F < 6\sigma(F)$ were treated as unobserved.

The structure was solved by multisolution tangent refinement method with *SHELX 76* program[10]. A subsequent Fourier synthesis revealed all the seventeen non-hydrogen atoms.

The structure was refined by full-matrix least squares procedure first isotropically to R value of 0.115 and then anisotropically to R value of 0.092. A subsequent difference Fourier synthesis yielded the positions of all the hydrogen atoms. The block diagonal least squares procedure was adopted at this stage, and further refinements including hydrogen atoms produced the final R value of 0.042.

In the final cycle, the average and maximum

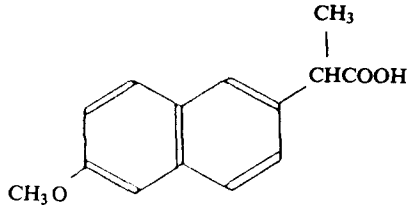

Fig. 1. Naproxen.

shift/e.s.d. ratio for the parameters are 0.038 and 0.156 for non-hydrogen atoms, and 0.056 and 0.213 for hydrogen atoms.

Table I. Crystallographic data

(+)-6-Methoxy-α-Methyl-2-Naphthaleneacetic acid	
Molecula formula; $C_{14}H_{14}O_3$	Mol. wt. 230.26
Colorless transparent plate,	Monoclinic
$a = 13.375(5)$ Å	$b = 5.793(2)$ Å
$c = 7.914(3)$ Å	$\beta = 93.91(3)°$
Volume of the unit cell	611.7(3) Å^3
$d_{obs} = 1.26$ g/cm^3	$d_{calc} = 1.25$ g/cm^3
$Z = 2$	Space group; $P2_1$

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

RESULTS AND DISCUSSION

The final atomic coordinates and temperature factors are listed in Table II and Table III. The stereoscopic view of the molecule drawn by *ORTEP*[29] is presented in Fig. 2. The observed and calculated structure factors for naproxen are given in Table IV.

The bond lengths and angles are shown in Fig. 3. These are in agreement with those of *d*-6-chloro-5-cyclohexylindan-1-carboxylic acid (*d*-TAI-284)[6], sulindac[12], 3-indolylacetic acid[13], flurbiprofen[14], indomethacin[15], (+)-(2R, α S)-2-isopropyl-α-methyl-5-indanacetic acid[16], (±)-(2SR)-2-{4-[1SR, 2RS)-2-hydroxycyclopentylmethyl] phenyl}propionic acid[17], alclofenac[18], [2-phenyl-4-(*p*-chlorophenyl)-5-thiazolyl]acetic acid[19], ibuprofen[20], cyclohexyl-4-naphthalene-1-propionic acid[21], [4-(Benzyloxy)phenyl]acetic acid[22], niflumic acid[23]. The bond lengths around the ring-acetate moiety,

Table II. Final positional ($\times 10^4$) and thermal ($\times 10^3$) parameters with their 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	x/c	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	7349(4)	5053(11)	2857(8)	51(4)	30(4)	52(4)	8(3)	-7(3)	15(3)
C2	7558(4)	7066(12)	1929(7)	43(3)	34(4)	35(3)	-5(3)	-1(2)	0(3)
C3	6801(4)	8606(13)	1524(7)	49(3)	32(4)	36(3)	0(3)	1(3)	-7(3)
C4	4991(5)	9639(12)	1452(7)	60(4)	29(4)	43(3)	0(3)	-4(3)	7(3)
C5	4037(5)	9087(14)	1745(8)	45(4)	53(5)	51(4)	4(4)	-2(3)	15(4)
C6	3820(5)	6968(14)	2574(7)	50(4)	57(5)	34(3)	-14(4)	7(3)	8(4)
C7	4586(4)	5516(14)	3150(7)	55(4)	46(4)	32(3)	4(3)	8(3)	1(4)
C8	6396(4)	4585(13)	3298(7)	50(4)	32(4)	49(4)	10(3)	4(3)	1(4)
C9	8620(4)	7553(11)	1380(7)	49(3)	48(4)	42(3)	5(3)	4(3)	3(3)
C10	9295(4)	8168(12)	2964(7)	34(3)	63(4)	55(3)	5(4)	-1(3)	-5(3)
C11	9042(6)	5501(15)	412(10)	63(5)	64(5)	70(5)	-14(4)	22(4)	4(4)
C12	2532(7)	4527(22)	3530(12)	60(5)	82(7)	81(7)	2(6)	13(5)	-6(6)
C13	5805(4)	8156(12)	1951(6)	52(4)	39(4)	23(3)	-3(3)	-1(2)	2(3)
C14	5594(4)	6079(11)	2837(7)	43(4)	36(4)	34(3)	-2(3)	-1(3)	1(3)
O1	9748(4)	6753(10)	3822(6)	87(3)	77(3)	90(3)	17(3)	-38(3)	13(3)
O2	9279(4)	0369(9)	3280(6)	74(3)	56(3)	60(3)	-5(3)	-15(2)	-2(3)
O3	2812(3)	6589(11)	2731(6)	49(3)	71(4)	70(3)	5(3)	12(2)	6(3)

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
C1H	783(3)	402(10)	312(5)	27(14)
C3H	694(4)	988(12)	87(7)	55(19)
C4H	513(4)	1108(10)	95(6)	35(16)
C5H	348(3)	993(10)	129(6)	34(14)
C7H	444(3)	411(10)	374(6)	29(15)
C8H	626(3)	320(10)	389(6)	31(14)
C9H	860(3)	892(8)	61(5)	28(12)
C11H1	969(4)	581(11)	-1(8)	73(21)
C11H2	855(4)	519(13)	-60(7)	96(24)
C11H3	913(4)	410(13)	108(7)	74(22)
C12H1	188(5)	1431(14)	349(7)	68(23)
C12H2	275(6)	311(17)	306(11)	115(35)
C12H3	279(5)	1420(16)	473(9)	108(30)
O1H	1046(5)	567(13)	586(8)	76(25)

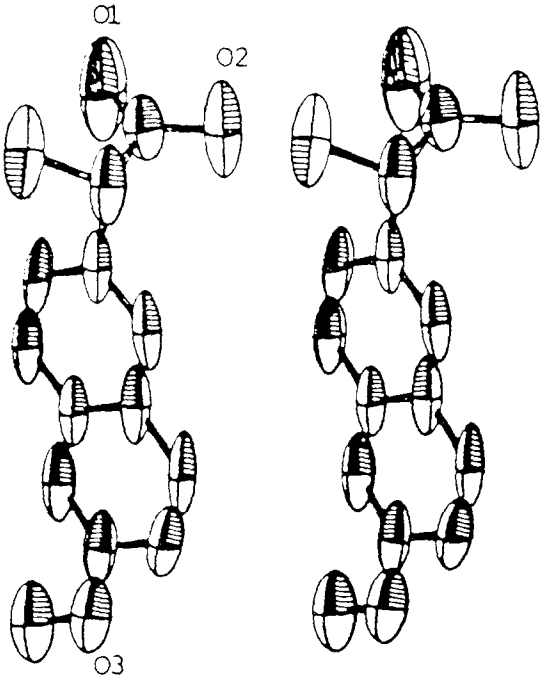

Fig. 2. The stereoscopic view of the molecule drawn by *ORTEP*.

which is commonly believed to be important for anti-inflammatory activity in three independently proposed receptor models by Scherrer[24], Shen[25] and Appleton[26] are compared in Table V.

As shown, the two carbon-oxygen bonds of the carboxyl group show distinct double or single bond character in their lengths. In naproxen, as in the case of the related compounds, the inner angles of the naphthalene ring have some deviations from 120° along with their substitution positions as reported by Domenicano *et al.*[27,28].

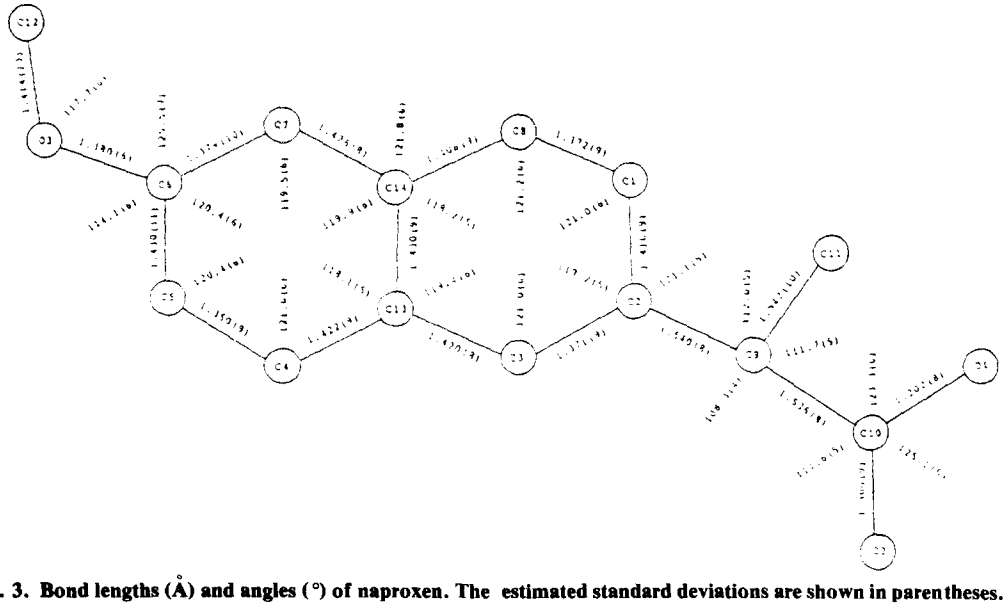

Fig. 3. Bond lengths (Å) and angles (°) of naproxen. The estimated standard deviations are shown in parentheses.

Table IV. Observed and calculated structure factors for naproxen.

Table V. Comparison of bond lengths of carboxyl-ring moeity with those of related compounds. The compounds are arranged in the order of decreasing e.s.d., and the bond designation was like as naproxen. I, *d*-TAI-284; II, sulindac; III, 3-indolylacetic acid; IV, flurbiprofen;; V, indomethacin; VI, (+)-(2R, α S)-2-isopropyl-α-methyl-5-indanacetic acid; VII, (±)-(2SR)-2-{4-(1RS, 2RS)-2-hydroxycyclopentylmethyl]phenyl}propionic acid; VIII, alclofenac, IX, [2-phenyl-4-(*p*-chlorophenyl)-5-thiazolyl] acetic acid; X, ibuprofen; XI, cyclohexyl-4-naphthalene-1-propionic acid; XII, [4-(benzyloxy)phenyl]acetic acid.

***: Another one of the two independent molecules.**

Compound	C2-C9	C9-C10	C10-O1	C10-O2
I	1.53	1.47	1.31	1.27
*	1.55	1.39	1.30	1.23
II	1.50	1.52	1.35	1.20
III	1.514	1.495	1.298	1.223
IV	1.552	1.515	1.288	1.206
V	1.493	1.501	1.299	1.212
VI	1.545	1.512	1.299	1.245
*	1.523	1.523	1.295	1.227
VII	1.532	1.518	1.326	1.204
*	1.532	1.508	1.314	1.311
VIII	1.471	1.576	1.248	1.177
IX	1.495	1.504	1.291	1.220
X	1.525	1.509	1.305	1.221
XI	1.503	1.514	1.308	1.217
XII	1.508	1.502	1.273	1.237
*	1.509	1.499	1.258	1.252
naproxen	1.540	1.536	1.300	1.202

Fig. 4 shows the torsion angles of the atoms around three bonds in crystalline state of naproxen. Because the torsion angles around these rotatable single bonds are somewhat different from other non-steroidal anti-inflammatory drugs, and vary with compounds according to their molecular interacting conditions in the crystalline state, the comparison of the torsion angles were not considered.

Naphthalene ring and carboxyl group are planar. Table VI shows the equations of the least-squares planes of the two groups and the deviations of the individual atoms from these planes. As shown, the methoxy group is nearly coplanar with the naphthalene ring as indomethacin[15].

Table VI. The equations of the least square planes of naphthalene ring and carboxyl group and the deviations of individual atoms from these planes(Å).

***: Atoms used for the calculation of plane A, **: Atoms for plane B.**

Equation of plane A (naphthalene ring)

0.0740 X + 0.4831 Y + 0.8724 Z = -4.1279

plane B (carboxyl group)

0.8210 X + 0.1209 Y - 0.5580 Z = -9.3297

Deviations	Atom	from plane A	from plane B
	C1*	0.030	2.292
	C2*	0.082	1.471
	C3*	0.003	1.998
	C4*	-0.058	3.879
	C5*	-0.009	5.107
	C6*	0.173	5.799
	C7*	-0.027	5.436
	C8*	-0.046	3.585
	C9**	0.216	0.005
	C10**	-1.108	-0.012
	C11	1.412	-0.784
	C12	0.193	7.944
	C13*	-0.065	3.330
	C14*	-0.070	4.137
	O1**	-1.344	0.006
	O2**	-1.939	0.005
	O3	0.135	7.105

The naproxen molecules are connected by intermolecular OH--O type hydrogen bonds between the two oxygen atoms of the carboxyl group as shown in Fig. 5; the distance of this hydrogen bond is 2.681 Å. The intermolecular contacts between adjacent molecules are the normal van der Waals interactions.

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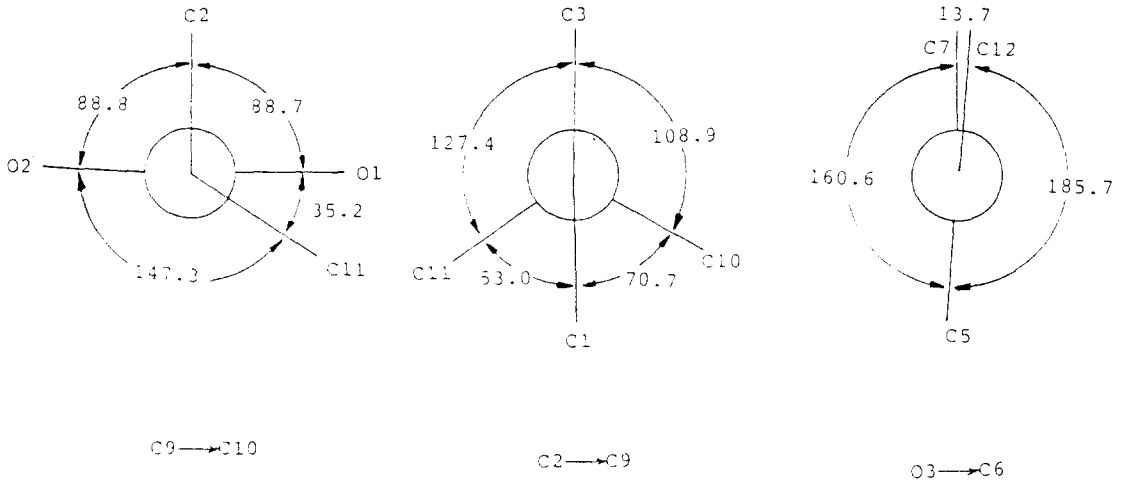

Fig. 4. Newman projections of atoms around three bonds.

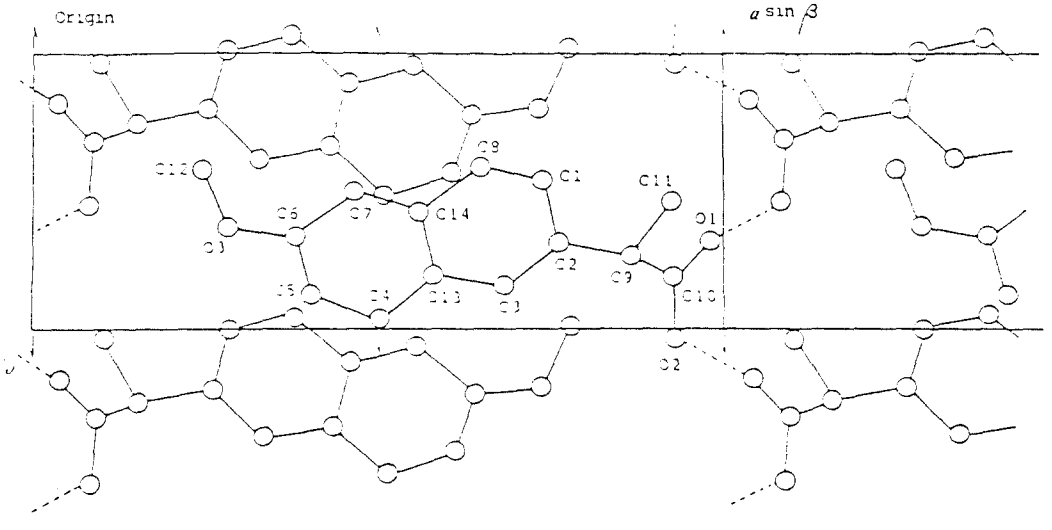

Fig. 5. Molecular packing of naproxen projected along *c*-axis. The broken lines indicate OH--O type hydrogen bonds.

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