

The Crystal Structure of Naproxen Sodium, (C₁₄H₁₃O₃Na), A Non-steroidal Antiinflammatory Agent

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Abstract □ The structure of the anti-inflammatory agent, naproxen sodium was determined by single crystal X-ray diffraction analysis. Crystal of the compound, which was recrystallized from methanol solution, is monoclinic, space group $P2_1$, with $a = 21.177(6)$, $b = 5.785(2)$, $c = 5.443(2)$ Å, $\beta = 91.41(3)^\circ$, and $Z = 2$. The calculated density is 1.346; the observed value is 1.35 g/cm³. The structure was solved by direct method. Block diagonal least-squares refinements based on 1093 reflections ($F \geq 3 \sigma(F)$) gave the final R value of 0.043. There are water molecules, which are thought to be absorbed during recrystallization, with the ratio of one water per one compound molecule in the crystal. The carboxyl group of the molecule is nearly perpendicular to the naphthalene ring. The molecules are arranged along with the screw axis, and stabilized by five O...Na type interactions. The molecule retains nearly same dimensions and similar conformation compared to its parent compound, naproxen, except for the torsion angles around C(5)-C(11) bond.

Keywords □ Naproxen sodium, antiinflammatory agent, X-ray diffraction, three-dimensional structure.

Naproxen sodium is a widely using non-steroidal antiinflammatory agent which inhibits prostaglandin biosynthesis, or more specifically the enzyme cyclooxygenase¹⁻³. The compound is a sodium salt of naproxen (Fig. 1). Its potency is nearly the same, but absorption is claimed to be more rapid compared to its parent compound, naproxen⁴.

The compound is an arylacetate derivative which consists of aromatic moiety and propionate side chain, and it has an asymmetric carbon at the side chain. In arylacetates with such moiety, only the S-conformer is known to have activities⁵. Though we did not determine the absolute configuration, we referred to the optical activities as described in USP XXI⁶.

It's an interesting subject to investigate and elucidate the molecular structures of related drug analogs. We have determined the three dimensional structures of the non-steroidal antiinflammatory agents⁷⁻¹⁰ including naproxen¹¹. This paper is an ac-

count of naproxen sodium and some structural comparisons with its parent compound to provide three dimensional structural data necessary for receptor modeling or new drug design¹²⁻¹⁵.

EXPERIMENTAL

A sample of naproxen sodium was kindly supplied by Chong Kun Dang Co. Ltd. We did not attempt to determine the absolute configuration of the compound. However, according to the provisions of USP XXI⁶, the compound was converted to its original acid form, naproxen, and then the optical activity was examined with digital polarimeter (JASCO DIP-360). It is dextrorotatory of $[\alpha]_D^{25} = +63.7(2)^\circ$, which agree to the S-conformer as determined by Riegl *et al.*, with stereochemical methods¹⁶.

The compound was recrystallized from methanol solution by slow evaporation at $18 \pm 1^\circ\text{C}$. Colorless transparent prisms were grown to suitable sizes. The density was measured by the flotation method on a mixture of carbon tetrachloride and cyclohexane.

Then a $0.4 \times 0.2 \times 0.1$ mm dimensioned crystal was mounted on an automatic four-circle diffractometer (Rigaku Denki Co. Ltd.) with graphite-monochromated CuK α radiations (30 kV, 100 mA). The lattice constants were determined from the least-squares

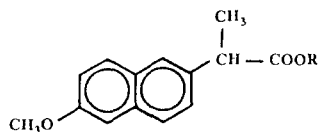


Fig. 1. R = H: Naproxen.

R = Na: Naproxen sodium.

Table I. Crystallographic data

Molecular formula: $C_{14}H_{13}O_3Na$	M.W. 252.24
Colorless transparent prism	Monoclinic
$a = 21.177(6) \text{ \AA}$	$b = 5.785(2) \text{ \AA}$
$c = 5.443(2) \text{ \AA}$	$\beta = 91.41(3)^\circ$
Volume of the unit cell: 666.61 \AA^3	$F(000) = 284$
$D_x = 1.346 \text{ g/cm}^3$	$D_m = 1.35 \text{ g/cm}^3$
Space group: $P2_1$	$Z = 2$
$CuK \alpha = 1.54178 \text{ \AA}$	$\mu (CuK \alpha) = 9.85 \text{ cm}^{-1}$

refinements of the angular values for 20 diffractometer-recorded reflections. Intensity data with range of $0 \leq H \leq 23$, $-6 \leq K \leq 0$, $-6 \leq L \leq 6$ were collected by ω - 2θ scan technique (scan speed $8^\circ/\text{min}$). Three standard reflections, (6 0 0), (3 -3 0), and (1 0 2) were monitored after every 100 reflections and showed no noticeable changes. Of all 1380 independent reflections, 278 reflections which had $F < 3 \sigma(F)$ were treated as unobserved. The reflections were corrected for usual Lorentz and polarization effects, but no absorption corrections were made. The space group was determined from systematic absences. The crystallographic data are listed in Table I.

The structure was solved by the multiresolution tangent refinement method with *SHELX 76* program¹⁷. *E* values larger than 1.2 were used for phase generation, and the solution was obtained from the set with the highest combined figure of merit. The *E* map revealed all the non-hydrogen atoms. But an unexpected peak, which was absent from naproxen sodium molecule, was found near to the sodium atom. It was separated by at least 2.27 \AA from other atoms. Because the integrated value of the electron density over an assumed volume for this peak amounted to about oxygen atom, it was supposed to be water molecule which was absorbed during evaporation procedure. Naproxen sodium is very hygroscopic.

We compared the calculated crystal densities with the observed one. The calculated densities from the diffractometer-measured lattice constants were 1.256 for one naproxen sodium molecule (anhydrated form), and 1.346 g/cm^3 for one naproxen sodium and one water molecules (hydrated form) in an asymmetric unit. The observed density by the flotation was 1.35 g/cm^3 , a close-fitting value to the hydrated form. And we also studied the elemental analysis (with Perkin-Elmer 240C Elemental Analyzer), and the infrared spectra (with Perkin-Elmer 1710 Infrared FT Spectrometer) of the crystal and the dried one, etc. The drying conditions of the compound (at vacuum, 105°C over 30 hrs.) were based on *USP XXI*¹⁶. The results of these studies are shown in Table II, and Fig. 2,

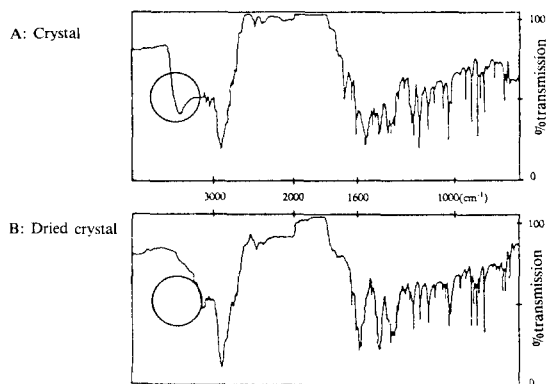


Fig. 2. Infrared spectra of naproxen sodium crystal (A) and its dried one (B). Notice the OH stretch peak near 3400 cm^{-1} in A, marked by a circle, which is not in B.

respectively. The infrared spectrum of the crystal revealed a broad peak near 3400 cm^{-1} which suggested the presence of OH bonds. There was no OH or NH bond in naproxen sodium. The elemental percentages of the crystal were closer to the values of the hydrated form. Anyway, all of the results indicate that the crystal includes water molecules with the ratio of one water per one compound molecule, whereas the dried materials do not.

Initial *R* value was 0.164. The structure was refined by full matrix least-squares procedure with isotropic temperature factors to the *R* value of 0.098. Further refinements with anisotropic temperature factors reduced *R* value to 0.070. A difference Fourier synthesis calculated at this stage revealed all the hydrogen atoms of naproxen sodium, but the hydrogens of the water molecule could not be correctly defined. Refinements by block diagonal least-squares procedure including hydrogen atoms for 1093 reflections ($F \geq 3 \sigma(F)$) produced the final *R* value of 0.043 (same with wR). The function minimized in the refinements 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. for the parameters are 0.052 and 0.181 for non-hydrogen atoms, and 0.055 and 0.161 for hydrogen atoms. The final difference Fourier calculation showed maximum electron density of 0.25 e/\AA^3 near to the oxygen of the water molecule where the undefined hydrogens seem to be vibrating around.

The final atomic parameters are listed in Table III and IV, together with their estimated standard deviations. The observed and calculated structure factors are available upon request. All the calculation were carried out on *VAX-11/780* computer system at Seoul National University. The atomic scattering factors

Table II. The results of elemental analysis. The observed values of the crystal are similar to the calculated values of the hydrated form, while those of the dried one and raw sample are similar to the values of anhydrous form.

	E.A. results (%)			Calculated percentage (%) for	
	Crystal	Dried one	Raw sample	Anhydrous	Hydrated form
Carbon	62.9	67.3	67.0	66.7	62.2
Hydrogen	5.6	5.2	5.2	5.2	5.6

Table III. Fractional non-hydrogen atomic coordinates ($\times 10^4$) and thermal parameters ($\times 10^3$) with their e.s.d.'s in parentheses. The anisotropic temperature factors are in the form of

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

Atom	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
(in naproxen sodium)									
C(1)	1466 (2)	-619 (11)	5517 (10)	42 (3)	47 (3)	56 (3)	-4 (3)	-6 (2)	5 (3)
C(2)	1936 (2)	-1057 (9)	3759 (9)	36 (2)	40 (3)	49 (3)	1 (2)	-10 (2)	3 (2)
C(3)	2444 (2)	473 (10)	3366 (9)	42 (3)	38 (3)	62 (3)	-8 (3)	-6 (2)	0 (2)
C(4)	2891 (2)	14 (10)	1690 (9)	37 (3)	35 (3)	59 (3)	-3 (3)	-2 (2)	-2 (2)
C(5)	2877 (2)	-2051 (9)	274 (8)	40 (3)	36 (3)	41 (2)	3 (2)	-11 (2)	6 (2)
C(6)	2379 (2)	-3539 (9)	595 (9)	44 (3)	36 (3)	49 (3)	-5 (2)	-13 (2)	2 (2)
C(7)	1905 (2)	-3090 (11)	2289 (8)	37 (2)	41 (3)	49 (2)	4 (3)	-10 (2)	5 (3)
C(8)	1391 (2)	-4641 (11)	2658 (10)	48 (3)	44 (3)	64 (3)	-5 (3)	-8 (3)	-8 (3)
C(9)	941 (2)	-4186 (11)	4351 (10)	45 (3)	54 (4)	68 (4)	4 (3)	-3 (3)	-6 (3)
C(10)	984 (2)	-2150 (10)	5818 (9)	39 (3)	54 (4)	55 (3)	11 (3)	-5 (2)	2 (3)
C(11)	3399 (2)	-2487 (9)	-1537 (7)	42 (2)	42 (3)	37 (2)	2 (2)	-9 (2)	2 (2)
C(12)	4023 (2)	-2897 (11)	-64 (6)	39 (2)	46 (3)	27 (2)	4 (3)	-1 (2)	10 (3)
C(13)	3271 (3)	-4451 (12)	-3343 (10)	60 (4)	61 (4)	45 (3)	-13 (3)	-13 (3)	10 (3)
C(14)	535 (3)	24 (15)	9051 (13)	66 (4)	74 (5)	67 (4)	-1 (4)	5 (3)	8 (4)
O(1)	4343 (1)	-1102 (6)	528 (6)	45 (2)	39 (2)	51 (2)	-5 (2)	-5 (2)	-6 (2)
O(2)	4192 (2)	-4883 (7)	461 (6)	52 (2)	38 (2)	47 (2)	5 (2)	-12 (2)	13 (2)
O(3)	506 (2)	-1918 (8)	7433 (7)	47 (2)	72 (3)	67 (2)	-2 (2)	9 (2)	-5 (2)
Na	4681 (1)	2064 (5)	-1529 (3)	50 (1)	40 (1)	44 (1)	-2 (1)	-4 (1)	-3 (3)
(in water molecule)									
O(w)	4527 (2)	2013 (9)	-5677 (5)	104(3)	54 (2)	44 (2)	1 (3)	-15 (2)	14 (3)

were taken from "International Tables for X-ray Crystallography"¹⁸.

RESULTS AND DISCUSSION

The atomic numbering scheme, bond lengths and angles are shown in Fig. 3. The stereoscopic ORTEP¹⁹ drawing of the naproxen sodium molecule is presented in Fig. 4. All the values are within the chemically reasonable range compared to those of other related compounds^{7-11, 20-28}.

The naphthalene ring and carboxyl group are

planar. The equations of the least-squares planes of these regions of the molecule, and the deviations of individual atoms from these planes are collected in Table V. The compound has three single bonds. Fig. 5 shows torsion angles around these bonds. The methoxy group is nearly coplanar to the naphthalene ring, and the C(10)-O(3) bond is shorter than the O(3)-C(14) in length despite they are both single bonds. This is presumably due to the effective overlap of the unbonded electron lobe of oxygen atom with the π cloud of the ring as pointed out earlier²⁹. It was also observed in the structures with similar moiety^{9,11,20}.

Table IV. Fractional hydrogen atomic coordinates and thermal parameters ($\times 10^3$) with their e.s.d.'s in parentheses. The isotropic temperature factors are in the form of $\exp(-8\pi^2 U \sin^2 \theta / \lambda^2)$

Atom	Bonded to	x/a	y/b	z/c	U
(in naproxen sodium)					
H (1)	C (1)	151 (3)	69 (12)	653 (10)	76 (21)
H (3)	C (3)	245 (2)	209 (13)	442 (8)	68 (15)
H (4)	C (4)	325 (2)	106 (8)	130 (7)	33 (11)
H (6)	C (6)	236 (3)	-477 (12)	-33 (9)	66 (18)
H (8)	C (8)	140 (3)	-601 (10)	166(10)	71 (18)
H (9)	C (9)	53 (2)	-537 (11)	472 (9)	75 (17)
H (11)	C (11)	350 (2)	-93 (9)	-267 (9)	56 (15)
H (13-1)	C (13)	364 (2)	-464 (8)	-451 (7)	31 (11)
H (13-2)	C (13)	326 (2)	-599 (10)	-260 (9)	48 (14)
H (13-3)	C (13)	286 (3)	-415 (11)	-414 (9)	83 (19)
H (14-1)	C (14)	14 (3)	-78 (13)	1052 (12)	95 (21)
H (14-2)	C (14)	96 (3)	-17 (14)	1017 (11)	97 (22)
H (14-3)	C (14)	48 (4)	130 (19)	824 (15)	148 (42)
(in water molecule)					
H (w-1)	O (w)		not found		
H (w-2)	O (w)		not found		

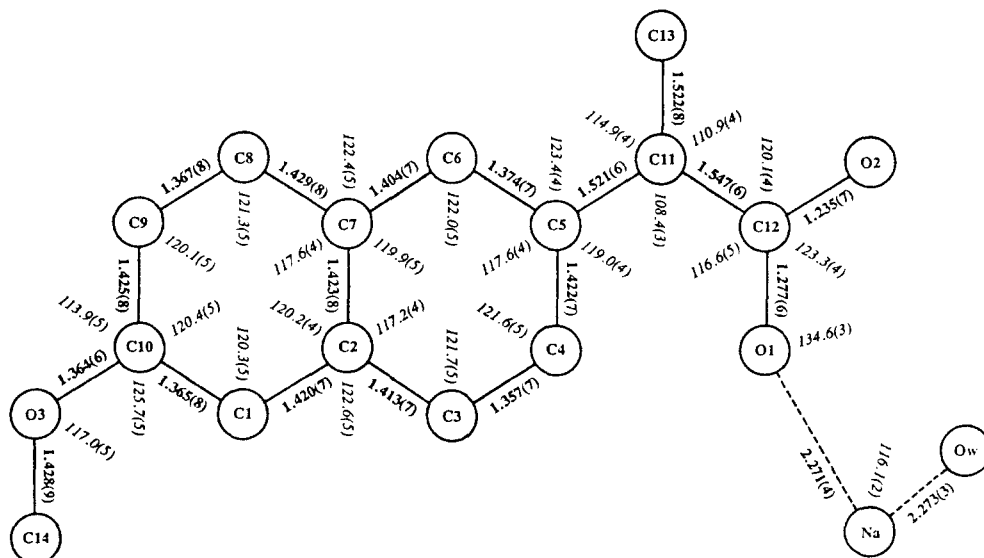


Fig. 3. Bond lengths (Å) and angles ($^\circ$) of naproxen sodium with their e.s.d.'s in parentheses.

The carboxyl group is nearly perpendicular to the naphthalene ring. This seems to be a common feature of arylacetates^{7-11, 20-28}.

Fig. 6 shows the stereoscopic molecular packing

in the crystal. The molecules are arranged along with the screw axis, and they are stabilized by five O...Na type interactions between sodium ion and electronegative oxygens (four from carboxyl groups, and

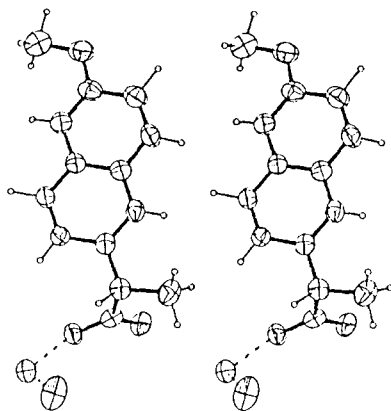


Fig. 4. The stereoscopic view of naproxen sodium molecule. The thermal ellipsoids are drawn at the 50% probability level.

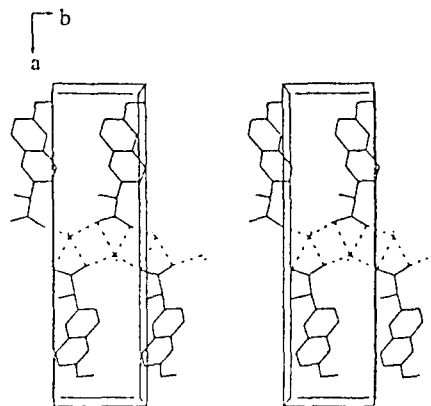


Fig. 6. The stereoscopic packing diagram for naproxen sodium. The broken lines indicate O...Na type interactions.

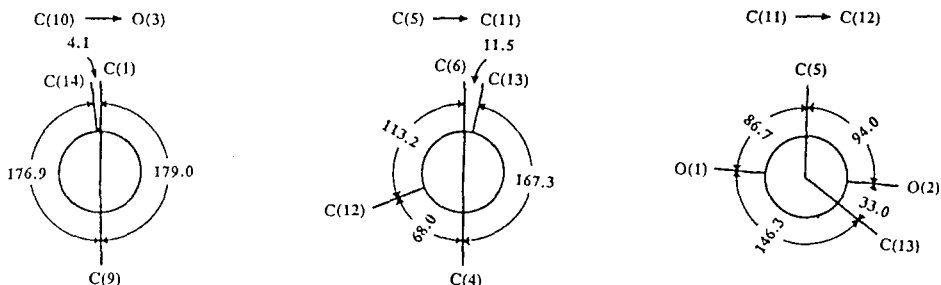


Fig. 5. Newman projections of the atoms around three single bonds.

Table V. The equations of the least-squares planes of the naphthalene ring and carboxyl group, and the deviations of individual atoms from these planes (Å). The dihedral angle between these planes is 107.4°.

Equations: Plane A (naphthalene ring)

$$0.5250 X - 0.4855 Y + 0.6990 Z = 3.8536$$

Plane B (carboxyl group)

$$0.5129 X - 0.0608 Y - 0.8563 Z = 4.5057$$

Deviations	Atom	From plane A	plane B	Atom	From plane A	plane B
	C (1)*	-0.010	5.500	C (11)**	-0.050	-0.001
	C (2)*	0.001	4.143	C (12)**	-1.409	0.004
	C (3)*	0.013	3.459	C (13)	0.214	-0.785
	C (4)*	0.013	2.165	C (14)	-0.113	8.205
	C (5)*	-0.023	1.438	O (1)**	-1.483	-0.001
	C (6)*	-0.008	2.078	O (2)**	-2.351	-0.001
	C (7)*	0.012	3.410	O (3)	-0.022	7.403
	C (8)*	0.012	4.088	Na	-0.200	-1.229
	C (9)*	0.007	5.393	-		
	C (10)*	-0.016	6.112	O (w)	1.505	-3.025

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

** : Atoms used for the plane B.

Table VI. Comparisons of the structure of naproxen sodium to that of naproxen.

1. Mean differences (Å) of the corresponding bond lengths in the				
	naphthalene moiety	:	0.009	
	methoxy group	:	0.015	
	propionate side chain	:	0.021	
	hole molecule	:	0.013	
List of differences (Å) greater than 3 (e.s.d. of that length)				
	C(12)-O(1)	:	0.023	
	C(12)-O(2)	:	0.033	
2. Mean differences (°) of the corresponding interatomic angles in the				
	naphthalene moiety	:	0.6	
	methoxy group	:	0.4	
	propionate side chain	:	2.5	
	hole molecule	:	1.2	
List of differences (°) greater than 3 (e.s.d. of that angle)				
	C(4)-C(5)-C(6)	:	1.6	
	C(4)-C(5)-C(11)	:	2.1	
	C(6)-C(5)-C(11)	:	3.7	
	C(5)-C(11)-C(13)	:	2.9	
	C(11)-C(12)-O(1)	:	5.0	
	C(11)-C(12)-O(2)	:	3.2	
	O(1)-C(12)-O(2)	:	1.8	
3. Typical torsion angles (°) around three single bonds				
	C(1)-C(10)-O(3)-C(14)	:	naproxen	naproxen sodium
		:	346.3	355.9
	C(6)-C(5)-C(11)-C(12)	:	108.9	246.8
	C(5)-C(11)-C(12)-O(2)	:	88.7	94.0
4. Dihedral angles (°) between				
	two benzenes of naphthalene	:	naproxen	naproxen sodium
		:	6.7	1.1
	naphthalene and carboxyl group	:	111.6	107.4
5. Stabilization forces in packing				
	naproxen:		hydrogen bonds	
	naproxen sodium :		O...Na type interactions	

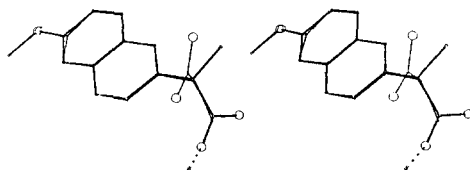


Fig. 7. The superimposed stereoview of naproxen sodium (heavy line) and naproxen (light line) according to the procedure of Nyburg³⁰. The oxygens are designated by different size of spheres for the ease in observation.

one from water). The shortest distance of these interactions is 2.271 Å between Na and O(1), and the longest one is 2.690 Å between Na and O(2) at (1 - x, 0.5 + y, - z). Other intermolecular contacts appear to be the normal *van der Waals'* interactions.

The structure of the subject molecule was compared to that of its parent compound, naproxen, whose structure we had already published ($R = 0.042$)¹¹. The comparisons of the corresponding interatomic dimensions and the conformational parameters were summarized in Table VI. The superimposed stereoview of the compounds according to the proce-

cedure of Nyburg³⁰ was presented in Fig. 7. The bond lengths and the interatomic angles for the corresponding atoms were found to be nearly the same, especially in the naphthalene moiety. The maximum differences were observed in the carboxyl group, which may be due to the changed degree of electronic resonance of the group. As mentioned previously, three single bonds can be rotated. The torsion angles around two bonds retain nearly similar values, however those around the C(5)-C(11) bond have been changed by about 138°. It may be due to the different stabilizations in packing between the compounds. Though the C(5)-C(11) bond has been rotated in naproxen sodium, the dihedral angles between the naphthalene ring and carboxyl group are very similar. Both crystal share the same $P2_1$ space group, while their packing patterns are somewhat different according to their stabilizations.

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