Crystal Structure of Antiinflammatory Sulindac

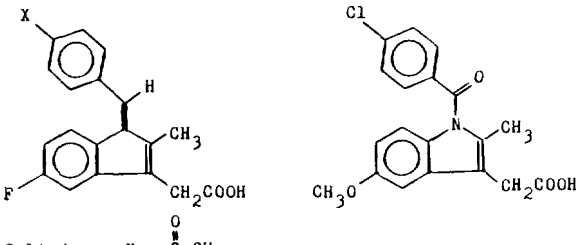
Chung Hoe Koo†, Sang Hern Kim and Wanchul Shin†

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151, Korea
(Received March 29, 1985)

The crystal structure of sulindac, $C_{20}H_{17}FO_3S$, one of the nonsteroid antiinflammatory agents, has been determined by the X-ray diffraction techniques using diffractometer data obtained by the ω-2θ scan technique with Cu K_α radiation from a crystal with space group symmetry Pbca and unit cell parameters $a = 8.166(1)$, $b = 18.291(8)$, $c = 23.245(10)$ Å. The structure was solved by direct methods and refined by full-matrix least-squares to a final R = 0.11 for the 1153 observed reflections. The carboxyl group is nearly perpendicular to the indenyl ring as observed in indomethacin. The dihedral angle between the indenyl and phenyl rings is 35° while the corresponding angle in indomethacin is 67°. Crystal packing consists of a hydrogen bond and partial ring stacking between the indenyl rings.

Introduction

Sulindac, (Z)-5-fluoro-2-methyl-1-[[4-(methylsulfinyl)-phenyl]methylene]-1H-indene-3-acetic acid, is one of the nonsteroid antiinflammatory drugs.[1,2] It is less than half as potent as widely used indomethacin, but is less toxic.[3] Sulindac is an inert compound *per se* and its biologically active form is the sulfide metabolite (see below) which is reversibly interconvertable with sulindac in the body.[4,5]



Sulindac : X = -S-CH3 (O)

Sulindac Sulfide : X = -S-CH3

Indomethacin

It is well known that prostaglandin and their metabolites are involved in the inflammatory processes and that many antiinflammatory drugs inhibit prostaglandin synthesis or more specifically the enzyme cyclooxygenase.[5,6] In an effort to elucidate the structure-activity relationships of this class of drugs, conformational studies of indomethacin and its analogs have been done and these studies led to the model for hypothetical synthetase binding site.[7-10] The minimum energy conformation of indomethacin calculated by quantum mechanical methods was found to be quite similar to its solid state conformation.[11] The present study has has been undertaken to compare the structure of sulindac with that of indomethacin.

Experimental

Needle crystals were grown from an ethanol solution of sulindac by slow evaporation at room temperature. Preliminary cell parameters were measured from oscillation and Weissenberg photographs and the space group was uniquely determined to be Pbca from the systematic absences. Accurate cell parameters were determined by least-squares refinement of the 2θ values for the 12 reflections centered on automated Rigaku four-circle diffractometer. The crystal data are as follows:

$C_{20}H_{17}FO_3S$; Mol. Wt. 356.4; F(000) = 1488

$a = 8.166(1)$, $b = 18.291(8)$, $c = 23.245(10)$ Å; $V = 3471.8$ Å^3

Space group Pbca; $Z = 8$; $\mu(CuK_\alpha) = 17.94$ cm^{-1}

$D_m = 1.36$ gcm^{-3} by flotation in CCl_4-*n*-butylacetic acid

$D_c = 1.362$ gcm^{-3}

Reflection data from a crystal with dimensions of $0.1 \times 0.2 \times 0.5$ mm were collected with graphite-monochromated Cu K_α radiation using ω-2θ scan technique over a range of $(1.2 + 0.5 \tan\theta)°$ in ω at a scan rate of 44°/min and a 10-s background count at each end of the scan range. Three stan-

TABLE 1: Positional (× 10^4) and Thermal (× 10^3) Parameters for Sulindac*

Atom	X	Y	Z	U_{eq}†
C(1)	5367(21)	4345(9)	2705(8)	56
C(2)	5182(21)	4306(10)	3330(9)	58
C(3)	5684(20)	4939(10)	3569(7)	53
C(4)	6906(26)	6135(9)	3159(8)	67
C(5)	7386(23)	6454(11)	2639(10)	71
C(6)	7331(22)	6135(10)	2114(8)	66
C(7)	6655(21)	5417(10)	2095(8)	58
C(8)	6088(19)	5069(9)	2587(7)	52
C(9)	6209(20)	5432(10)	3122(7)	50
C(10)	4892(22)	3806(9)	2363(7)	58
C(11)	4850(21)	3721(9)	1740(8)	56
C(12)	4532(20)	4276(9)	1348(8)	53
C(13)	4592(21)	4160(10)	765(8)	63
C(14)	4889(21)	3480(10)	547(8)	61
C(15)	5182(24)	2875(10)	926(8)	71
C(16)	5160(24)	3010(10)	1500(8)	72
C(17)	4564(26)	3661(11)	3650(9)	81
C(18)	5744(23)	5138(10)	4193(7)	59
C(19)	4274(30)	5598(11)	4372(7)	66
O(1)	2864(19)	5221(7)	4329(5)	85
O(2)	4317(21)	6201(8)	4576(7)	110
F	7995(18)	7151(6)	2685(5)	116
S	4763(9)	3331(4)	−201(3)	111
O(3)	4844(14)	4073(6)	−486(5)	84
C(20)	6530(24)	2940(13)	−317(9)	119

*Estimated standard deviation in parentheses is for the least significant figure. †$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}\, a_i^* a_j^* (a_i, a_j)$

dard reflections were monitored after every 50 reflections and showed no noticeable changes. Of all 1933 independent reflections in the range of $2\theta<100°$, 780 which had $F<3\ \sigma(F)$ were treated as unobserved.

The structure was solved by direct methods using the program SHELX.[12] All of the nonhydrogen atoms were located in an E map calculated using the phase set with the highest reliability index. Successive refinements of the structure were carried out with considerable difficulties mainly due to poor intensity data resulting from the very weak diffracting power of the crystal. After anisotropic full-matrix least-squares refinements for the nonhydrogen atoms which led the R value to 0.14, positions of the hydrogen atoms were either found in the difference map or generated geometrically with the idealized bond lengths (1.08 Å) and angles. These were included in the subsequent structure factor calculation and not refined. The final refinement converged the R value ($R=\Sigma||Fo|-|Fc||/\Sigma|Fo|$) to 0.11 for the 1153 observed reflections. The function minimized in the refinement was $\omega(|F_o|-|F_c|)^2$ where $\omega=k/(\sigma^2(F)+gF^2)$. k and g were refined to 5.35 and 0.002, respectively, in the last cycle of refinement. The final atomic parameters are listed in Table 1.*

Results and Discussion

The atomic numbering scheme, bond distances and angles are presented in Figure 1. The stereoscopic ORTEP[13] drawing of the sulindac molecule is presented in Figure 2. Although critical evaluation of the molecular dimensions are somewhat meaningless due to limited quality of the data, none of them are deviated quite from the chemically reasonable values. For example, the endocyclic angle at C(5), 126°, is considerably larger than the normal hexagonal angle of 120°, which is a characteristically observed phenomemon when the electron-withdrawing functional group is substituted in the benzene ring.[14] Although the C(10) atom bridging the two rings maintains an sp^2 hybridization, the electrons are localized only on the C(1)–C(10) bond so that the phenyl ring can be rotated in order to relieve the steric hindrance between the two rings, specifically the C(7) and C(12) atoms. Accordingly the C(1)–C(10)–C(11) angle is widened to 133(1)°. The geometry around the sulfur atom in the methylsulfinyl moiety is not planar but pyramidal, similar to that in dimethylsulfoxide.[15] The S–C(20) bond is rotated by −58° from the phenyl ring and the S–O(3) bond by 20°. The indenyl and phenyl rings are planar within experimental errors, with the estimated standard deviations of 0.04 and 0.02Å, respectively.

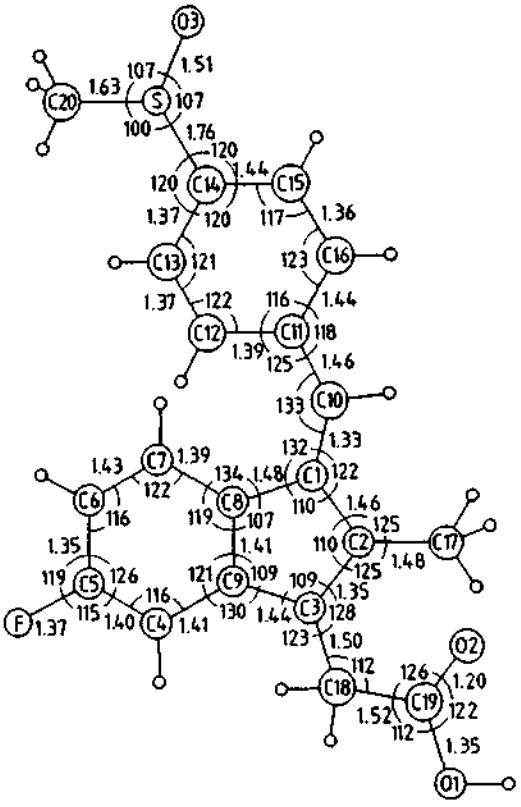


Figure 1. Schematic representation of the sulindac molecule showing the atomic numbering scheme, the bond distances (Å), and the bond angles (°). The esd's for bonds range from 0.01 to 0.03 and those for the bond angles range from 1 to 2.

*Tables for the observed and calculated structure factors, the atomic coordinates for hydrogen atoms and the least-Squares planes are available as supplementary materials from the author upon request.

The stereoscopic PLUTO[16] packing drawing of the crystal structure is presented in Figure 3. The molecules are arranged to form wrinkled sheets perpendicular to the a axis. Between these sheets there are partial ring stacking interactions. These occur between the indenyl rings of the two molecules related by the a glide plane symmetry. The closest contacts are listed in Table 2. The indenyl ring also makes a close contact with the phenyl ring but there are no stacking interactions between these two rings. There is only one kind of intermolecular hydrogen bond in the structure. The hydrogen bond from carboxyl O(1) to sulfinyl O(3) interconnects the molecular sheets. Besdie these interactions, there are only weak van der Waals interactions be-

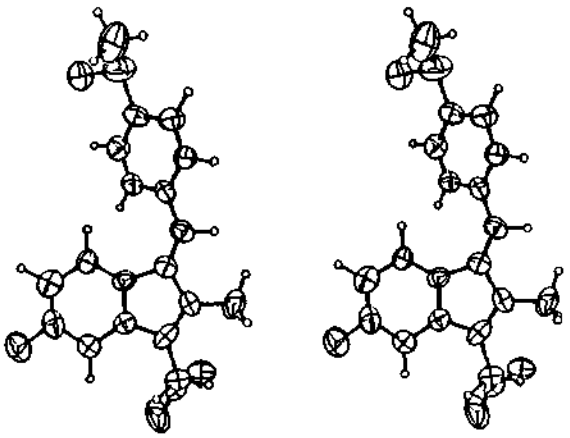


Figure 2. Stereoscopic view of the sulindac molecule

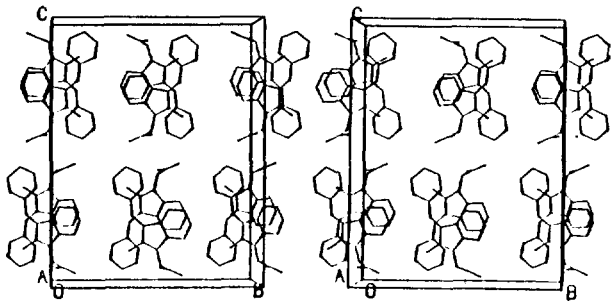


Figure 3. Stereoscopic packing diagram for sulindac.

TABLE 2: Hydrogen Bond and Close Contacts in Sulindac

D H	A	DA(Å)	HA(Å)	<DHA(°)
O(1)-H···O(3)[a]		2.60(2)	1.78(2)	148(2)
C(3)	C(12)[b]	3.37(2)		
C(6)	C(9)[b]	3.46(3)		

Symmetry code : (a) 0.5-x, 1-y, 0.5+z (b) 0.5+x, y, 0.5-z

TABLE 3: Comparison of Torsion and Dihedral Angles in Sulindac and Indomethacin

	Sulindac	Indomethacin
Torsion Angle (°)		
τ_1: C(1) - C(10) - C(11) - C(16)	145	-144.2
τ_2: C(2) - C(1) - C(10) - C(11)	176	
C(2) - N(1) - C(10) - C(11)		-151.1
τ_3: C(2) - C(3) - C(18) - C(19)	-99	-99.9
τ_4: C(3) - C(18) - C(19) - O(1)	65	-146.7
Diheral Angle (°)		
Phenyl-indene (indole)	35	66.8
Carboxyl-indene (indole)	70	92.9

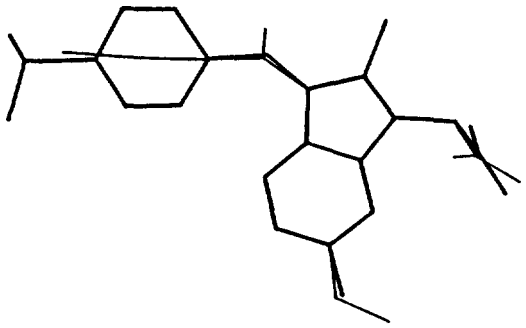


Figure 4. Least-squares fitted molecules of sulindac (heavy lines) and indomethacin (light lines) according to the procedure of Nyburg.[20]

tween the molecules. Very weak intermolecular interactions seem to result in poor diffracting power of the crystals.

It has been noted that the relative orientations of the phenyl ring, the carboxyl group and the indenyl (indole in case of indomethacin) ring may very well play an important role in the chemistry of these arylacetic acid antiinflammatory drugs.[17] The effectiveness of indomethacin is usually attributed to the fact that, although different in detail, the overall conformation of receptor bound arachidonic acid can resemble the conformation of indomethacin either calculated by quantum mechanical methods[2,18] or determined by crystallographic methods[11]. The comparison of the conformations of indomethacin and sulindac is summarized in Table 3. The utmost common features in the two structures is that the carboxyl group is nearly perpendicular to the central ring (see τ_3 in Table 3). 3-Indolylacetic acid[19] also assume a same conformation and this relative orientation may in fact be a structural characteristic among arylacetic acids. It is also consistent with the prediction for the bioactive conformation studied by quantum mechanical methods.[8] Beside this orientation of the carboxyl group, there are relatively large conformational differences between the two compounds as shown in Figure 4, except the fact that the phenyl ring is tilted with respect to the central ring. However, the present structure of sulindac seems to support the general ideas about the structural characteristics of the arylacetic acid antiinflammatory drugs and thus the rather crude model for the fatty acid substrate binding site of prostaglandin synthetase.

Acknowledgement. We thank Dr. S. W. Suh for his valuable dicular to the central ring (see τ_3 in Table 3). 3-indolylacetic discussion. This research was supported by a research greant (No. ED-83-307) from the Ministry of Education.

References

(1) T. Y. Shen, *J. Med. Chem.*, **24**, 1 (1981).
(2) T. Y. Shen and C. A. Winter, *Adv. Drug Res.*, **12**, 89-245 (1977).
(3) R. N. Brogden, R. C. Heel, T. M. Speight, and G. S. Avery, *Drugs*, **16**, 97-114 (1978).
(4) D. E. Duggan, K. F. Hooke, E. A. Risley, T. Y. Shen, and C. G. Van Arman, *J. Pharmacol. Exp. Ther.*, **201**, 8 (1977).
(5) J. R. Vane, *Nature (London), New Biol.*, **231**, 232-234 (1971).
(6) R. W. Egan, P. H. Gale, and F. A. Kuehl, Jr., *J. Biol. Chem.*, **254**, 3295-3302 (1979).
(7) P. Gund and T Y. Shen, *J. Med. Chem.*, **20**, 1146-1152 (1977).
(8) G. Dive, C. L. Lapier, and G. Leroy, *Bull. Soc. Chim. Belg.*, **86**, 73 (1977).
(9) P. Gund and N. P. Jensen, "Quantitative Structure-Activity Relationships of Drugs," J. G. Topliss, Ed., p. 285, Academic Press, New York, 1983.
(10) R. A. Scherrer, "Antiinflammatory Agents: Chemistry and Pharmacology," R. A. Scherrer and M. W. Whitehouse, Eds., Vol. 1, p. 29, Academic Press, New York, 1974.
(11) T. J. Kistenmacher and R. E. Marsh, *J. Am. Chem. Soc.*, **94**, 1340 (1972).
(12) G. M. Sheldrick, SHELX. Program for crystal structure determination, Univ. Chem. Lab., Cambridge, England, 1976.
(13) C. K. Johnson, ORTEP. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, 1965.
(14) A. Domenicano and A. Vaciago, *Acta Cryst.*, **B31**, 221 (1975).
(15) R. Thomas, C. B. Shoemaker and K. Eriks, *Acta Cryst.*, **21**, 12 (1966).
(16) W. D. S. Motherwell and W. Clegg, PLUTO. Program for plotting molecular and crystal structures. Univ. Chem. Lab., Cambridge, England, 1978.
(17) T. Y. Shen, *Top. Med. Chem.*, **1**, 29 (1967).
(18) F. Salvetti, A. Buttinoni, R. Ceserani, and C. Tosi, *Eur. J. Med. Chem. Chim. Ther.*, **16**, 81 (1981).
(19) *I. L. Karle, K. Britts, and P. Gum, Acta Cryst.*, **17**, 496 (1964).
(20) S. C. Nyburgh, *Acta Cryst.*, **B30**, 251 (1974).