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Nonsteroidal Antiinflammatory Drugs. VI. The Crystal and Molecular Structure of (±)-(2*S**)-2-[4-((1*S**)-2-Oxocyclopentylmethyl)phenyl]-propionic Acid and Force-Field Calculations

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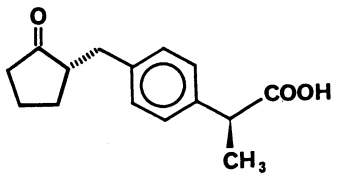
The crystal structure of the title compound was determined by X-ray diffraction techniques. The final *R* index was found to be 0.072 for 1187 reflections. The torsional angles of the 2-phenylpropionic acid moiety were comparable to those in other antiinflammatory arylpropionic acids. Force-field energy calculations suggested that the α-methyl substituent to the carboxyl group restricts the rotation of the benzene ring about the C_α-phenyl bond. This restricted conformation may be related to the antiinflammatory activity.

In the search for non-steroidal antiinflammatory drugs, a number of (cycloalkylmethyl)phenylacetic and -propionic acids have been synthesized.[1] Among them, 2-[4-(2-oxocyclopentylmethyl)phenyl]propionic acid (loxoprofen), exhibited particularly potent anti-inflamatory and analgesic activities.[2] This derivative is a mixture of two racemic diastereoisomers having melting points of 102 and 114 °C, respectively. The title compound **1** is the isomer of the lower melting



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point and structure analysis has established the relative configuration.

The potentiating effect of an α-(*S*)-methyl substituent to the carboxyl group has been observed for many antiinflammatory arylacetic acids.[3,4] On the other hand, the substitution of an (*R*)-methyl or two methyls results in manyfold reduction of activity.[5] This must be due to a steric effect at the enzyme surface. It is interesting to compare the conformation of (*S*)-2-phenylpropionic acids with those of phenylacetic and 2-methyl-2-phenylpropionic acids. The present paper deals with the crystal and molecular structure of **1** and the results of empirical force-field calculations for the related molecules based on the crystal structure of **1**.

Experimental

X-Ray Structure Determination of 1. Colorless prisms were grown by slow evaporation of an ether-hexane solution of **1** at room temperature. Diffraction experiments were performed with a crystal, 0.1×0.1×0.6 mm, on a Rigaku AFC-5 diffractometer; monochromated Cu $K\alpha$ radiation being used. The cell parameters were determined from the 2θ values of forty-four reflections in the range with $21° < 2\theta < 49°$. Space group was assigned from systematic absences. The crystal data are as follows; $C_{15}H_{18}O_3$, M_r=246.3, monoclinic, $I2/c$, a=18.276 (1), b=7.5164 (4), c=19.539 (2) Å, β=93.063 (2)°, V=2680.2 (2) Å^3, Z=8, D_c=1.22 g cm^{-3}, μ(Cu $K\alpha$)=6.9 cm^{-1}. An ω-2θ scanning mode was employed up to 2θ=130°. A total of 1842 reflections were measured, of which 1188 unique reflections with $F \geq 3\sigma(F)$ were used for the analysis. Three references measured every 100 reflections showed no significant variation in intensity. Correction was made for Lorentz and polarization factors, but not for absorption. The structure was solved by the direct method using MULTAN78,[6] and refined by the full-matrix least-squares method with anisotropic thermal parameters. Hydrogen atoms were located on a difference Fourier synthesis and their coordinates were refined with isotropic thermal parameters. One intense low-angle reflection (2,0,−4) seemed to suffer secondary extinction and excluded from the data set. The final refinement converged at R=0.072 and R_w=0.040. The weighting scheme was $w=1/\sigma^2(F)$. Atomic scattering factors were taken from Ref. 7. The final fractional coordinates and equivalent isotropic thermal parameters are given in Table 1.[8]

Table 1. Fractional Coordinates and Equivalent Isotropic Thermal Parameters, with e.s.d.'s in Parentheses

Atom	10^4x	10^4y	10^4z	B_{eq}/Å^2
O(1)	569(2)	6680(6)	3408(2)	6.3(2)
C(2)	612(3)	8134(9)	3665(3)	4.1(2)
C(3)	−27(4)	9319(11)	3829(5)	6.2(3)
C(4)	286(4)	11067(10)	4047(4)	5.3(2)
C(5)	1065(4)	10655(9)	4328(4)	4.6(2)
C(6)	1317(3)	9097(8)	3895(3)	3.5(2)
C(7)	1900(3)	7824(9)	4220(3)	3.4(2)
C(8)	1725(3)	7174(7)	4923(2)	2.9(2)
C(9)	2049(3)	7969(8)	5503(3)	3.6(2)
C(10)	1877(3)	7448(8)	6157(3)	3.6(2)
C(11)	1377(3)	6101(7)	6241(2)	2.6(2)
C(12)	1056(3)	5261(7)	5667(3)	3.2(2)
C(13)	1236(3)	5807(7)	5010(3)	3.0(2)
C(14)	1179(3)	5483(7)	6960(3)	3.0(2)
C(15)	1116(4)	6989(10)	7469(3)	5.0(2)
C(16)	1769(3)	4158(8)	7212(3)	3.0(2)
O(17)	2303(2)	4602(4)	7559(2)	3.9(1)
O(17)	1639(2)	2530(6)	7004(2)	3.7(1)

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Force-Field Calculations. The force-field calculations were performed on the model compounds of (*S*)-2-phenylpropionic acid which was constructed based on the crystal structure of **1**, using the MM2′ program.[9] The two torsional angles of τ_1 and τ_2, which correspond to C(10)-C(11)-C(14)-C(16) and C(11)-C(14)-C(16)-O(17) of **1**, were simultaneously varied at intervals of 10 degrees and the conformational energy map for double rotation was calculated. In order to evaluate the effect of the α-methyl group, conformation energy calculations for the two model compounds of phenylacetic acid and 2-methyl-2-phenylpropionic acid which have no and two methyl groups, respectively, were also performed in the same manner as for (*S*)-2-phenylpropionic acid.

Results and Discussion

The Crystal and Molecular Structure of 1. The atom labelling and the thermal ellipsoids are shown in Fig. 1. This racemate crystal of mp 102°C contains molecules with (S, S) and (R, R) configurations. Bond lengths and angles are all normal within the limits of experimental error.

The torsional angles of τ_1[C(12)-C(11)-C(14)-C(16)] and τ_2[C(11)-C(14)-C(16)-O(17)] of the propionic acid side chain are 95.5 (6) and 93.5 (6)°, respectively. These values are compatible with those of other antiinflammatory drugs; 96.4 and 89.3° in ibuprofen,[10] 107.7 and 77.3° in flurbiprofen,[11] 111.7 and 90.2° in naproxen.[12] The torsional angles of other 2-phenylpropionic acids such as 2-(2-isopropyl-5-indanyl)propionic acid (IPIP)[13] and the four racemic diasteroisomers of 2-[4-(2-hydroxycyclopentylmethyl)phenyl]propionic acid (HOPP)[14-16] are listed in Table 2. The corresponding angles of phenylacetic and 2-methyl-2-phenylpropionic acids[17-21] are also included in Table 2. As shown in Table 2, τ_1 and τ_2 of the 2-phenylpropionic acid are localized around angles of 110 and 90°, respectively, with a few exceptions. The corresponding angles for the phenylacetic acid side chain, on the other hand, are 24.4—112.6° and −128.6—25.7°. Therefore, the α-methyl group of the 2-phenylpropionic acid moiety restricts the conformation of this moiety, which should be related to the antiinflammatory activity.

The cyclopentanone ring adopts a half-chair form with the equatorial hydroxyl and methylphenyl groups, in which the C (4) and C (5) atoms are dis-

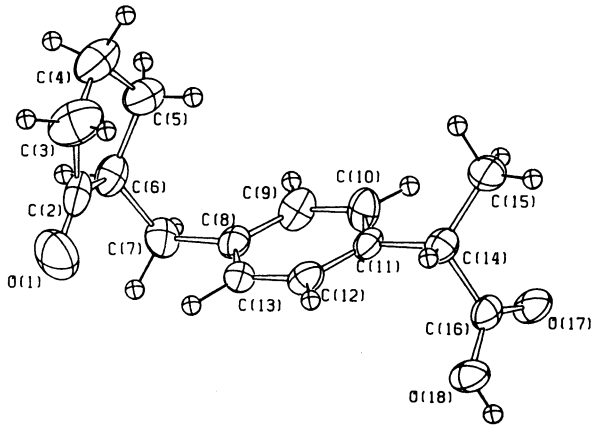

Fig. 1. ORTEP plot of the title compound with thermal ellipsoids at the 50% probability level.

Table 2. Torsional Angles (θ/°) of τ_1 and τ_2

Compound[a]	τ_1	τ_2	Reference
2-Phenylpropionic acid			
Present compound	95.5	93.5	this work
Ibuprofen	96.4	89.3	10)
Flurbiprofen	107.7	77.3	11)
Naproxen	111.7	90.2	12)
IPIP molecule (I)	79.7	102.2	13)
IPIP molecule (II)	119.3	−109.7	13)
HOPP SRS-isomer	108.3	84.0	14)
HOPP SRR-isomer (I)	114.7	94.9	15)
HOPP SRR-isomer (II)	162.6	96.2	15)
HOPP SSR-isomer	122.0	126.5	16)
HOPP SSS-isomer	116.2	95.3	14)
Phenylacetic acid			
EOIA	101.5	25.7	17)
HIPA	24.4	−128.6	18)
BZPA molecule (I)	85.8	−98.4	19)
BZPA molecule (II)	38.2	−90.7	19)
PMPA	112.6	7.7	20)
2-Methyl-2-phenylpropionic acid			
IPIMP	144.4	110.0	21)

a) IPIP; 2-(2-isopropyl-5-indanyl)propionic acid, HOPP; 2-[4-(2-hydroxycyclopentylmethyl)phenyl]propionic acid, EOIA; (2-ethoxy-5-indanyl)acetic acid, HIPA; (*E*)-4-[2-(hydroxyimino)cyclopentylmethyl]phenylacetic acid, BZPA; 4-(benzyloxy)phenylacetic acid, PMPA; 4-(phenoxymethyl)phenylacetic acid, IPIMP; (2-isopropyl-5-indanyl)-2-methylpropionic acid.

placed by −0.22 (9) and 0.30 (9) Å from the plane through C (3), C (2) and C (6). The torsional angles of C(2)-C(6)-C(7)-C(8) and C(5)-C(6)-C(7)-C(8) are −72.5 (7) and 49.2 (8)°, respectively.

The molecules form centrosymmetric dimers by the hydrogen-bonds between the carboxyl groups. The O (18) atom donates a hydrogen to O(17^{i}) [(i) 1/2−x, 1/2−y, 3/2−z]; the hydrogen bond distance being 2.619 (5) Å.

Force-Field Calculations. The conformational energy map for double rotation, τ_1 and τ_2, of the acetic acid residue in phenylacetic acid is given in Fig. 2. The map is cyclic with a period of 180° in τ_1 owing to the two-fold rotation symmetry of the benzene ring and also the two-fold rotation axis at τ_1=180°, τ_2=180° owing to the two equivalent hydrogen atoms at the α-carbon of acetic acid, resulting in four global minima A, A′, A″, and A‴. The rotation around the C_α-phenyl bond is somewhat hindered by a barrier of 5.0 kJ mol^{-1} (between A and A′), whereas the rotation barrier between the global minima A and A″ is only 2.9 kJ mol^{-1}. The values of τ_1 and τ_2 in the crystals of phenylacetic acids, which are plotted by the symbol X in Fig. 2, scatter owing to the low energy barriers. It is suggested that the side chain of acetic acid is freely rotated about the C_α-phenyl and C_α-COOH bonds.

The energy surface of 2-phenylpropionic acid as a function of τ_1 and τ_2 is shown in Fig. 3. Because of the two-fold rotation symmetry of the benzene ring, the map is cyclic with a period of 180° in τ_1, resulting in two global minima A and A′. Local minima B and B′ are 5.9 kJ mol^{-1} higher in energy. The rotation around the C_α-phenyl bond is somewhat hindered by a barrier of 11.3 kJ mol^{-1} (between A and A′), whereas the rotation barrier between the global minimum A and local minimum B is 8.4 kJ mol^{-1}. These values are appreciably higher than those of 5.0 and 2.9 kJ mol^{-1} in 2-phenylacetic acid; 2-phenylpropionic acid has more tendency to take the definite conformation than phenylacetic acid. Smeyer et al.[22] have reported that 2-(4-isobutylphenyl)propionic acid (ibuprofen) presents a preferred conformation with torsional angle τ_1 between 90 and 120°, or between 270 and 300° from CNDO/2 molecular orbital calculations. These coincide with the present global minimum A or A′.

The τ_1 and τ_2 torsional angles in the crystals of some derivatives of 2-phenylpropionic acid are given in Table 2 and plotted by the small circles in Fig. 3. In contrast with phenylacetic acid, these are crowded around τ_1=110° and τ_2=90°, which slightly deviates from the point A. This fact, combined with the higher rotation barrier of the side chain in 2-phenylpropionic acid, indicates that the α-methyl substituent to the carboxyl group restricts rotations about the C_α-phenyl and C_α-COOH bonds. The potentiating effect of α-(*S*)-methyl substituent in many antiinflammatory arylacetic acids may be related to such restricted conformation of propionic acid.

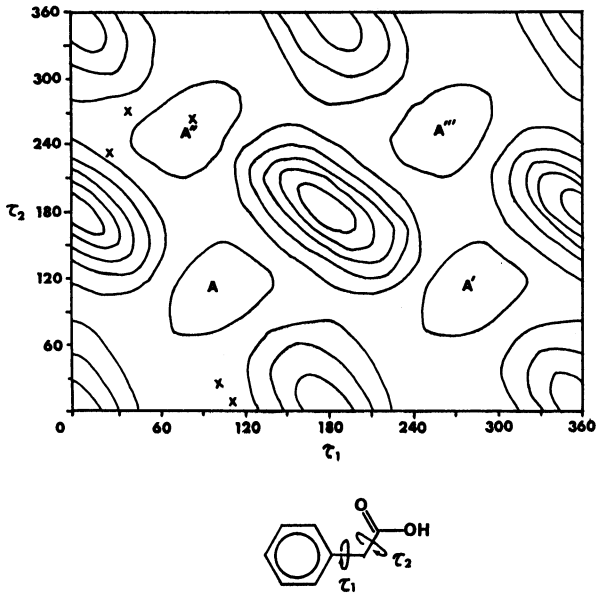

Fig. 2. The conformational energy map for the acetic acid residue in phenylacetic acid by MM2′ calculations. Isobars are drawn at 4.2 kJ mol^{-1} intervals. Four global minimum energy points are A, A′, A″, and A‴. The observed point in the crystal of phenylacetic acids are denoted by the symbol x.

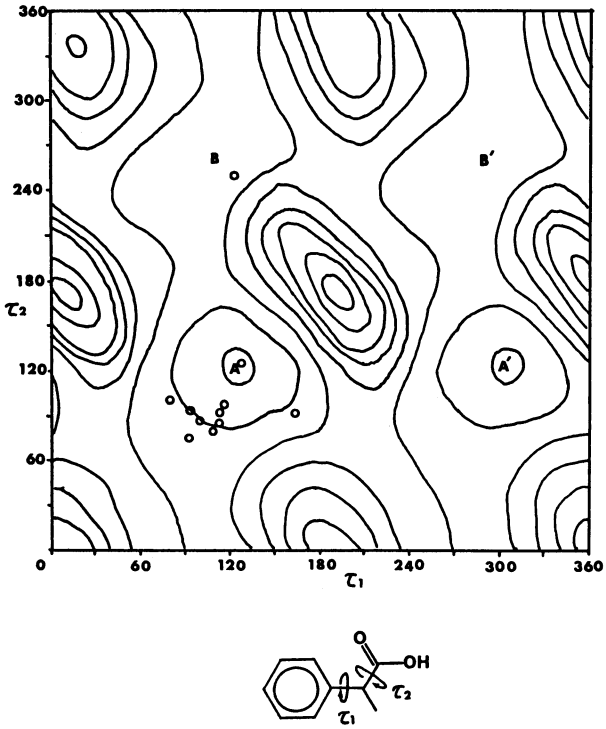

Fig. 3. The conformational energy map for double rotation of the propionic acid residue in 2-phenylpropionic acid by MM2′ calculations. Contours are drawn at 4.2 kJ mol^{-1} intervals. The global minimum points are A and A′ and local ones are B and B′. The observed crystal conformations of 2-phenylpropionic acids are plotted by the small circles.

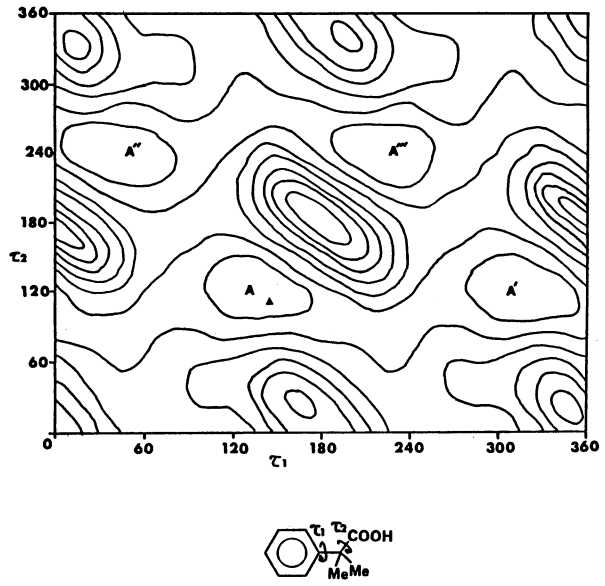

Fig. 4. MM2′ calculated rotational energy surface for the side chain of 2-methyl-2-phenylpropionic acid. Contours are drawn at 4.2 kJ mol^{-1} intervals. The global minimum points are A, A′, A″, and A‴. The observed point of 2-methylpropionic acids in the crystal is denoted by the symbol ▲.

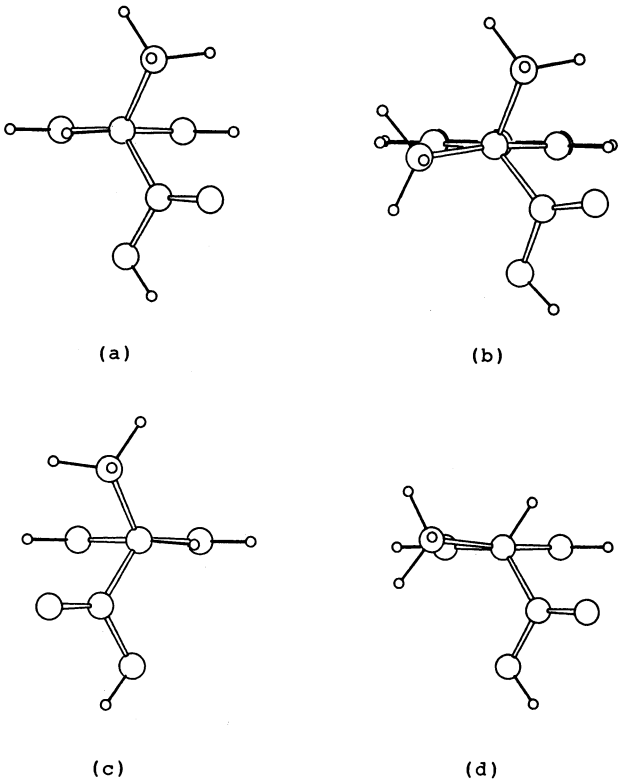

Fig. 5. Perspective projections along the C_α-phenyl axis. (a) The global minimum energy conformation of (*S*)-2-phenylpropionic acid. (b) The global minimum energy conformation of 2-methyl-2-phenylpropionic acid. (c) The global minimum energy conformation of (*R*)-2-phenylpropionic acid. (d) The conformation of (*R*)-2-phenylpropionic acid with torsional angles of τ_1=120° and τ_2=120° corresponding to the global minimum energy conformation of the (S)-isomer.

In order to evaluate the effect of one more methyl group, empirical force-field energy calculations have been performed for 2-methyl-2-phenylpropionic acid. The conformational energy map for double rotation of the 2-methyl-2-phenylpropionic acid is given in Fig. 4. This energy surface map has the four global minima A, A′, A″, and A‴, as in phenylacetic acid. The rotation barriers between the global minima A and A′ and between A″ and A‴ are 7.1 and 9.2 kJ mol^{-1}, respectively. The former is lower by 4.2 kJ mol^{-1} than that in 2-phenylpropionic acid and the latter is higher by 0.8 kJ mol^{-1}. The conformation analysis of 2-methyl-2-phenylpropionic acid has been performed by CNDO/2 molecular orbital calculations.[22] Its results show that the τ_1 torsional angle in the preferred conformation is around 0 or 180° which is different from the global minimum points indicated by the MM2′ calculations. The values of τ_1 and τ_2 in crystals of 2-(2-isopropyl-5-indanyl)-2-methylpropionic acid (IPIMP) are plotted by the symbol ▲ in Fig. 4, close to the global minimum A. It is noted that the bulkier the α-substituent to the carboxyl group is, the larger the value of τ_1 for the global minimum; the τ_1 valules of phenylacetic acid, 2-phenylpropionic acid, and 2-methyl-2-phenylpropionic acid being 100, 120, and 130°, respectively.

The most stable conformations of (*S*)-2-phenylpropionic acid and 2-methyl-2-phenylpropionic acid projected along the C_α-phenyl axis are shown in Fig. 5. For the former the α-hydrogen atom lies in the phenyl plane and one of the two methyl groups of the latter is also located approximately on the phenyl plane. On the other hand, (*R*)-2-phenylpropionic acid presents a preferred conformation with τ_1=60° and τ_2=−120°, which is a mirror image of the structure of the (S)-isomer at the global minimum as shown in Fig. 5. These differences in the torsional angles of the global minimum energy conformation of (*R*)-2-phenylpropionic acids may contribute to the lowering of the antiinflammatory activity of the (R)-isomer. However, in the crystal of the antiinflammatory agent, (*S*)-6-chloro-5-cyclohexyl-1-indancarboxylic acid (clidanac), where the carboxyl group is constrained by attachment to a five-membered ring, the τ_1 torsional angle has been found[23] to be 61.8°, compatible with the value of 60° in the global minimum energy conformation of the (R)-isomer molecule. Therefore, conformations with a τ_1 torsional angle of 60° should be able to exhibit some antiinflammatory activity.

The conformation of the (R)-isomer (τ_1=120° and τ_2=120°) corresponding to the preferred conformation of the (S)-isomer is higher by 7.5 kJ mol^{-1} in energy than the global minimum and the projection is also given in Fig. 5. In this conformation (τ_1=120°), not the α-hydrogen atom but the α-methyl group is approximately in the phenyl ring plane just as 2-

methyl-2-phenylpropionic acid. These projecting methyl groups of both compounds, (*R*)-2-phenylpropionic acid and 2-methyl-2-phenylpropionic acid, may point into the receptor site to prevent binding, giving rise to the manyfold reduction in antiinflammatory activity.

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