

Structural Studies of Analgesics and Their Interactions.

VIII.* Rotational Isomerism and Disorder in the Crystal Structure of Meclofenamic Acid

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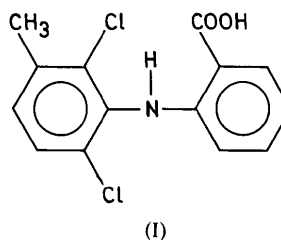
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Abstract

Meclofenamic acid, $C_{14}H_{11}Cl_2NO_2$, probably the most potent among analgesic fenamates, crystallizes in the triclinic space group $P\bar{1}$, with $a = 8.569(5)$, $b = 8.954(8)$, $c = 9.371(4)$ Å, $\alpha = 103.0(2)$, $\beta = 103.5(2)$, $\gamma = 92.4(2)^\circ$, $Z = 2$, $D_m = 1.43(4)$, $D_c = 1.41$ Mg m $^{-3}$. The structure was solved by direct methods and refined to $R = 0.135$ for 1062 observed reflections. The anthranilic acid moiety in the molecule is nearly planar and is nearly perpendicular to the 2,6-dichloro-3-methylphenyl group. The molecules, which exist as hydrogen-bonded dimers, have an internal hydrogen bond involving the imino and the carboxyl groups. The methyl group is disordered and occupies two positions with unequal occupancies. The disorder can be satisfactorily explained in terms of the rotational isomerism of the 2,6-dichloro-3-methylphenyl group about the bond which connects it to the anthranilic acid moiety and the observed occupancies on the basis of packing considerations.

Introduction

The X-ray analyses of three of the four well known anti-inflammatory analgesic fenamates have already been reported (McConnell, 1973, 1976; Krishna Murthy, Bhat & Vijayan, 1978; Krishna Murthy & Vijayan, 1979). We here report the crystal structure of the fourth and the most potent of this group of drugs, namely, 2-(2,6-dichloro-3-methylphenyl)aminobenzoic acid, generally known as meclofenamic acid (I), as part of a programme of X-ray studies on analgesics and their interactions. Meclofenamic acid is believed to act, like other anti-inflammatory analgesics, through the inhibition of prostaglandin biosynthesis (Flower, 1974).

**Experimental**

Chunky, slightly elongated crystals of the compound were crystallized from a solution in 95% ethanol using a sample supplied by Parke-Davis & Co., Pontypool, UK. The density was measured by flotation in aqueous potassium iodide solution. The diffraction patterns from the crystals were of poor quality. The photographs indicated a paucity of high-angle data and the spots were rather diffuse and streaky. Attempts at growing better crystals by changing the conditions of crystallization and solvents were to no avail.

The intensity data were collected on a CAD-4 diffractometer from a specimen of dimensions $0.3 \times 0.4 \times 0.6$ mm using graphite-monochromated Mo $K\alpha$ radiation up to a maximum Bragg angle of 22.5° . An $\omega/2\theta$ scan was employed for measuring intensities with a scan range varying between 0.78 and 0.97° depending upon the Bragg angle, and a scan speed ranging from 1.3 to $6.7^\circ \text{ min}^{-1}$ depending upon the intensity of the reflection. Two standard reflections were measured after every 75 reflections. The intensities of these standard reflections varied by less than 6% during data collection. Of the 2312 accessible reflections in the 22.5° sphere, 1062 observed reflections [$I > 3\sigma(I)$] were used for structure determination and refinement. The data were corrected for Lorentz and polarization factors but not for absorption ($\mu = 0.47 \text{ mm}^{-1}$ for Mo $K\alpha$).

Structure analysis

The solution of the structure was achieved by use of the program *MULTAN* (Germain, Main & Woolfson,

* Part VII: Krishna Murthy & Vijayan (1981).

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1971). Attempts at structure solution using normal E values as well as E values normalized separately in different $\sin \theta$ ranges and parity groups did not succeed. The statistical distribution of E values, however, invariably indicated the space group to be centrosymmetric and hence $P\bar{1}$. Attempts were therefore continued to solve the structure in this space group. The molecule was divided into three rigid groups (a phenyl ring with substituents, a second phenyl ring and the carboxyl group) and spherically averaged group scattering factors were calculated for each fragment. A *MULTAN* run using E values calculated from these group scattering factors readily yielded the structure.

Disorder

The positions of the non-H atoms were refined, first isotropically and then anisotropically, using the block-diagonal structure-factor least-squares (SFLS) method, to an R value of 0.155. A difference Fourier map computed at this stage contained a solitary peak as the only significant positive feature. This peak could be readily explained on the basis of the disorder postulated in Fig. 1. The disorder involves a rotation by 180° of the 2,6-dichloro-3-methylphenyl group about N(1)–C(8). The peak strengths in a difference Fourier map phased on atoms other than those in the methyl group indicated the occupancy factors of C(14) and C(14'), and hence of isomer (I) and isomer (II), to be 0.65 and 0.35. The two atoms were assigned these occupancy factors in further calculations. Anisotropic refinement of the non-H atoms converged at $R = 0.147$. The equivalent isotropic temperature factors (Hamilton, 1959) of C(14) and C(14') were comparable indicating

thereby that the assignment of occupancy factors was essentially correct. Difference Fourier maps and trial calculations showed that the disorder was confined, within the limits of accuracy, to the methyl group. SFLS calculations were also carried out in the space group $P1$, but the results indicated the space group to be $P\bar{1}$.

At this stage, the positions of all the H atoms except those belonging to the methyl groups were fixed from geometrical considerations. These atoms were assigned the equivalent isotropic thermal parameters of the heavier atoms to which they were attached. In the subsequent calculations, the H atoms were included in the structure-factor calculations, but their positional and thermal parameters were not refined. The positional and anisotropic thermal parameters of the non-H atoms were refined further in three SFLS cycles. The refinement was terminated at $R = 0.135$ when all the least-squares shifts had become smaller than the corresponding standard deviations. The weighting scheme used in the final cycles had the form $1/(a + bF_o + cF_o^2)$ with $a = 3.0$, $b = 0.5$ and $c = 0.03$. The form factors were taken from *International Tables for X-ray Crystallography* (1974). The final coordinates and equivalent isotropic temperature factors of the non-H atoms are given in Table 1.*

* Lists of structure factors, anisotropic thermal parameters and H atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35914 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

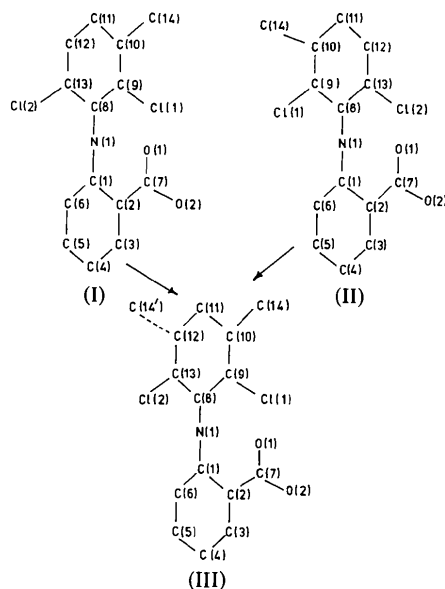


Fig. 1. Explanation of disorder in the crystal structure. (I) isomer (I); (II) isomer (II); (III) observed structure.

Table 1. Final positional coordinates ($\times 10^3$) and equivalent isotropic temperature factors of the non-H atoms with e.s.d.'s in parentheses

$$B_{\text{eq}} = \frac{4}{3} \sum_i \sum_j b_{ij} a_i \cdot a_j$$

| | x | y | z | B_{eq} (\AA^2) |
|--------|----------|----------|---------|------------------------------------|
| C(1) | 415 (3) | 239 (2) | 315 (2) | 3 (1) |
| C(2) | 529 (3) | 354 (3) | 308 (3) | 4 (1) |
| C(3) | 660 (3) | 405 (3) | 431 (3) | 4 (1) |
| C(4) | 685 (4) | 350 (3) | 555 (4) | 6 (2) |
| C(5) | 571 (4) | 236 (3) | 565 (3) | 5 (1) |
| C(6) | 436 (3) | 185 (3) | 440 (3) | 4 (1) |
| C(7) | 512 (3) | 418 (3) | 172 (3) | 4 (1) |
| O(1) | 401 (2) | 380 (2) | 62 (2) | 5 (1) |
| O(2) | 633 (2) | 519 (2) | 184 (2) | 5 (1) |
| N(1) | 279 (3) | 185 (2) | 196 (3) | 4 (1) |
| C(8) | 170 (3) | 64 (3) | 193 (3) | 5 (2) |
| C(9) | 44 (4) | 84 (4) | 258 (3) | 5 (2) |
| C(10) | -65 (4) | -44 (5) | 253 (3) | 6 (2) |
| C(11) | -38 (4) | -186 (4) | 174 (4) | 7 (2) |
| C(12) | 79 (5) | -211 (4) | 105 (4) | 7 (2) |
| C(13) | 182 (4) | -84 (3) | 116 (3) | 5 (2) |
| C(14) | -207 (7) | -33 (7) | 319 (7) | 8 (3) |
| C(14') | 52 (16) | -360 (9) | 47 (15) | 10 (6) |
| Cl(1) | 20 (1) | 267 (1) | 349 (2) | 9 (1) |
| Cl(2) | 342 (1) | -118 (1) | 34 (1) | 9 (1) |

Discussion

Molecular geometry

The bond lengths and angles in the molecule are listed in Table 2. No discussion about them is attempted here in view of their high standard deviations. A perspective view of the molecule is shown in Fig. 2. The molecule essentially consists of three planar groupings, namely the 2,6-dichloro-3-methylphenyl group, the phenyl ring bearing the carboxyl group and the carboxyl group itself. The last two are coplanar with an inclination with respect to each other of 1° . The first two are, however, nearly perpendicular to each other, the angle between the plane normals being 81° , presumably due to the steric interactions involving the two Cl atoms. The three-atom plane, made up of C(1), N(1) and C(8), is inclined with respect to the phenyl ring bearing the carboxyl group at an angle of 6° whereas it makes an angle of 85° with the other phenyl ring.

Hydrogen bonding, crystal structure and rotational isomerism

The crystal structure of meclofenamic acid is shown in Fig. 3. There are two crystallographically independent hydrogen bonds in the structure, the parameters of which are given in Table 3. As in the case of other

Table 3. *Hydrogen-bond parameters*

| | |
|---------------------------------|------------|
| N(1)···O(1) | 2.68 (3) Å |
| O(2)···O(1) ^a | 2.62 (3) |
| O(1)···N(1)—H(N1) | 34° |
| O(1) ^a ···O(2)—H(O2) | 0 |

Symmetry code: (a) $1 - x, 1 - y, -z$.

fenamates, the molecules exist as hydrogen-bonded dimers. The intramolecular hydrogen bond with the imino group as the donor and the carboxyl group as the acceptor is also a feature common to all fenamates.

As noted earlier, the two six-membered rings in the molecule are nearly perpendicular to each other. Thus the intramolecular environments of C(14) [the methyl carbon in isomer (I)] and C(14') [the methyl carbon in isomer (II)] are nearly the same. The observed population difference between the two isomers could

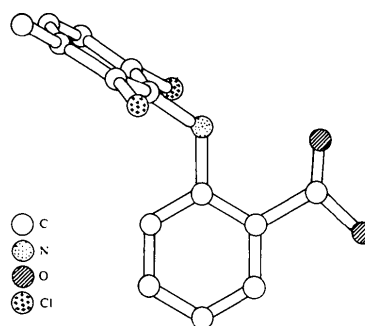


Fig. 2. A perspective view of the molecule as seen along the plane normal of the anthranilic acid moiety.

Table 2. *Bond lengths (Å) and angles (°) with e.s.d.'s in parentheses*

| | | | |
|--------------------|-----------|--------------------|----------|
| C(1)—C(2) | 1.42 (3) | C(1)—C(6) | 1.34 (3) |
| C(1)—N(1) | 1.39 (3) | C(2)—C(3) | 1.38 (4) |
| C(2)—C(7) | 1.49 (4) | C(3)—C(4) | 1.34 (4) |
| C(4)—C(5) | 1.41 (4) | C(5)—C(6) | 1.41 (4) |
| C(7)—O(1) | 1.20 (3) | C(7)—O(2) | 1.32 (3) |
| N(1)—C(8) | 1.39 (4) | C(8)—C(9) | 1.36 (4) |
| C(9)—C(10) | 1.44 (5) | C(9)—Cl(1) | 1.72 (4) |
| C(10)—C(11) | 1.38 (5) | C(10)—C(14) | 1.48 (7) |
| C(11)—C(12) | 1.31 (6) | C(12)—C(13) | 1.39 (5) |
| C(12)—C(14') | 1.31 (10) | C(13)—Cl(2) | 1.72 (3) |
| C(13)—C(8) | 1.37 (4) | | |
| C(2)—C(1)—C(6) | 119 (2) | C(2)—C(1)—N(1) | 121 (2) |
| C(6)—C(1)—N(1) | 120 (2) | C(1)—C(2)—C(3) | 118 (2) |
| C(1)—C(2)—C(7) | 121 (2) | C(3)—C(2)—C(7) | 121 (2) |
| C(2)—C(3)—C(4) | 124 (3) | C(3)—C(4)—C(5) | 119 (3) |
| C(4)—C(5)—C(6) | 118 (3) | C(1)—C(6)—C(5) | 123 (2) |
| C(2)—C(7)—O(1) | 124 (2) | C(2)—C(7)—O(2) | 113 (2) |
| O(1)—C(7)—O(2) | 123 (3) | C(1)—N(1)—C(8) | 123 (2) |
| N(1)—C(8)—C(9) | 123 (3) | N(1)—C(8)—C(13) | 121 (3) |
| C(9)—C(8)—C(13) | 117 (3) | C(8)—C(9)—C(10) | 121 (3) |
| C(8)—C(9)—Cl(1) | 118 (2) | C(10)—C(9)—Cl(1) | 120 (3) |
| C(9)—C(10)—C(11) | 116 (3) | C(9)—C(10)—C(14) | 125 (4) |
| C(11)—C(10)—C(14) | 119 (4) | C(10)—C(11)—C(12) | 125 (4) |
| C(11)—C(12)—C(13) | 116 (3) | C(11)—C(12)—C(14') | 102 (6) |
| C(13)—C(12)—C(14') | 142 (6) | C(8)—C(13)—C(12) | 125 (3) |
| C(8)—C(13)—Cl(2) | 119 (2) | C(12)—C(13)—Cl(2) | 116 (2) |

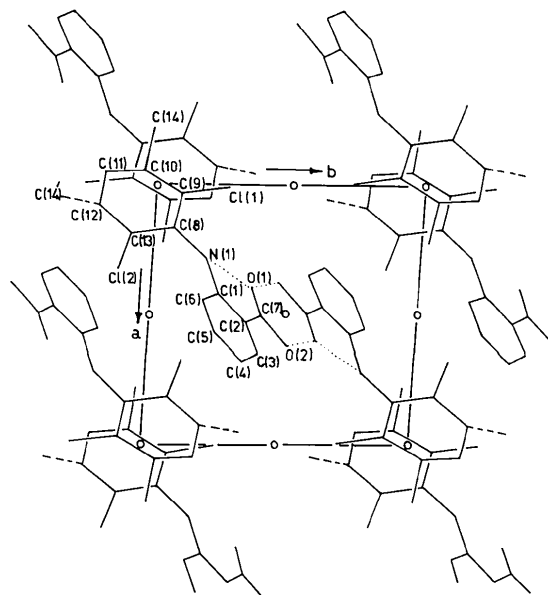


Fig. 3. Crystal structure as viewed along the *c* axis. Dotted lines represent hydrogen bonds.

not hence be explained in terms of differences in intramolecular interactions. Therefore, it was suspected that the explanation for the population difference might be in the differences in intermolecular interactions.

An examination of intermolecular contact distances revealed that a distance of 2.5 (1) Å between C(14') and its centrosymmetric partner (or its translational equivalent) is shorter than the least permissible C—C contact distance. C(14), on the other hand, is not involved in any undesirable steric contact. This meant that isomer (II) and its centrosymmetric equivalent could not be simultaneously present in the same unit cell whereas isomer (I) and its centrosymmetric equivalent could be.

In the light of the above observation, the observed occupancy factors of isomer (I) and isomer (II) could be readily explained in the following manner. The atoms other than those belonging to the methyl group have a well ordered centrosymmetric arrangement (within the limits of detection using the available diffraction data) in the crystal. The methyl group can now be attached either to C(10) (I) or to C(12) (II). As indicated earlier, both the isomers have nearly equal intrinsic probabilities of occurrence. However, in a given unit cell, both the molecules cannot be of isomer (II) on account of the short contact referred to earlier. If the two molecular sites in each cell are denoted by *A* and *B*, the possible ways in which the two isomers could be located are the following.

| Site <i>A</i> | Site <i>B</i> | |
|---------------|---------------|--------------------|
| Isomer (I) | Isomer (I) | Component <i>A</i> |
| Isomer (I) | Isomer (II) | Component <i>B</i> |
| Isomer (II) | Isomer (I) | Component <i>C</i> |

Among the three possible arrangements, only the first one is perfectly centrosymmetric. The other two are

centrosymmetric only as far as the atoms other than those in the methyl group are concerned. Thus a third of the total number of unit cells in the crystal are centrosymmetric while the remaining two-thirds are only nearly so. However, when the electron density is averaged over all the cells, as happens in a diffraction experiment, a centrosymmetric cell with disordered positions for the methyl group is obtained. As the three possible arrangements in each cell have equal probabilities of occurrence, C(14) and C(14') are expected to have occupancies of $\frac{2}{3}$ and $\frac{1}{3}$ respectively. The expected occupancy factors are in close agreement with the corresponding observed values of 0.65 and 0.35.

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