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Acta Cryst. (1982). B38, 315–317

Structure of a New Crystal Form of 2-[[3-(Trifluoromethyl)phenyl]amino]benzoic Acid (Flufenamic Acid)*

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(Received 26 March 1981; accepted 18 June 1981)

Abstract. $C_{14}H_{10}F_3NO_2$, $P2_1/c$, $a = 12.523$ (4), $b = 7.868$ (6), $c = 12.874$ (3) Å, $\beta = 95.2$ (2)°, $D_m = 1.47$ (4), $D_c = 1.47$ Mg m⁻³, $Z = 4$. Final $R = 0.074$ for 2255 observed reflections. The carboxyl group and the phenyl ring bearing the carboxyl group are nearly coplanar whereas the two phenyl rings are inclined with respect to each other at 52.8°. The difference between the two polymorphs of flufenamic acid lies in the geometrical disposition of the [3-(trifluoromethyl)-phenyl]amino moiety with respect to the benzoic acid moiety. As in other fenamate structures, the carboxyl group and the imino N atom are connected through an intramolecular hydrogen bond; also, pairs of centrosymmetrically related molecules are connected through hydrogen bonds involving carboxyl groups.

Introduction. Fenamates are a series of recently developed anti-inflammatory analgesics. They are believed to act, like other drugs possessing similar pharmacological properties, through the inhibition of prostaglandin biosynthesis (Flower, 1974). The crystal structures of all the four important members of this family of drugs, namely flufenamic acid, mefenamic acid, niflumic acid and meclofenamic acid, have already been reported (McConnell, 1973, 1976; Krishna Murthy & Vijayan, 1979, 1981). Flufenamic acid is, however, known to exhibit polymorphism in the crystalline state (Kuhnert-Brandstatter, Borka &

Friedrich-Sander, 1974) and we have been successful in growing a new crystal form of this compound.

Crystals of the new form of flufenamic acid were grown by slow evaporation of a solution in 95% ethanol using a sample of the compound supplied by Parke-Davis & Co., Pontypool, UK. The intensity data were collected on a CAD-4 four-circle diffractometer

Table 1. *Coordinates ($\times 10^4$) and equivalent isotropic thermal parameters (Hamilton, 1959) of the non-H atoms with e.s.d.'s in parentheses*

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> (Å ²)
C(1)	3202 (5)	7246 (7)	2338 (5)	3.3 (2)
C(2)	3901 (5)	7806 (7)	3201 (5)	3.4 (2)
C(3)	4185 (5)	9527 (8)	3276 (5)	3.8 (2)
C(4)	3799 (6)	10694 (8)	2538 (6)	4.4 (3)
C(5)	3119 (6)	10146 (8)	1704 (6)	4.4 (3)
C(6)	2821 (5)	8466 (8)	1597 (5)	4.1 (3)
N(1)	2905 (5)	5564 (7)	2253 (5)	4.3 (2)
C(7)	4326 (5)	6619 (8)	4009 (5)	3.7 (2)
O(1)	4084 (4)	5101 (6)	4042 (4)	4.7 (2)
O(2)	5019 (5)	7293 (6)	4726 (4)	5.1 (2)
C(8)	2235 (5)	4814 (7)	1447 (5)	3.5 (2)
C(9)	1398 (5)	3805 (7)	1716 (4)	3.3 (2)
C(10)	750 (5)	2980 (7)	954 (5)	3.6 (2)
C(11)	918 (6)	3164 (10)	-86 (5)	4.6 (3)
C(12)	1761 (7)	4152 (10)	-348 (5)	5.2 (3)
C(13)	2421 (6)	4964 (9)	404 (5)	4.5 (3)
C(14)	-119 (6)	1846 (9)	1279 (6)	4.7 (3)
F(1)	-862 (5)	1487 (10)	523 (5)	9.2 (4)
F(2)	-619 (6)	2475 (9)	2035 (6)	10.8 (4)
F(3)	249 (5)	335 (7)	1574 (6)	8.8 (3)

* Structural Studies of Analgesics and Their Interactions. IX.

from a specimen of dimensions $1.0 \times 0.6 \times 0.4$ mm using graphite-monochromated Mo $K\alpha$ radiation up to a Bragg angle of 30° . Of the 3695 reflections in this range 2255 had $I > 3\sigma(I)$ and were used for structure solution and refinement. The structure was solved by direct methods using *MULTAN* (Germain, Main & Woolfson, 1971) and refined using a block-diagonal least-squares program originally written by R. Shiono to an R factor of 0.074. The heavy atoms were refined with anisotropic thermal parameters whereas the H atoms were given isotropic thermal parameters. The weighting scheme used in the final refinement cycles had the form $1/(a + bF_o + cF_o^2)$ with $a = 1.0$, $b = 0.4$ and $c = 0.01$. The form factors of the non-H atoms were taken from Cromer & Waber (1965) and those of the H atoms from Stewart, Davidson & Simpson (1965). The final coordinates of the non-H atoms are given in Table 1.*

Discussion. The bond lengths and angles in the structure, given in Fig. 1, do not merit special comment. The dihedral angles which define the conformation of the molecule are given in Table 2. As in the case of the other fenamates, the geometry of the molecule can be described in terms of three planar groupings, namely the six-membered ring bearing the carboxyl group (phenyl ring 1), the carboxyl group and the other phenyl ring (phenyl ring 2). The first two are nearly coplanar with an angle of 3.8° between the plane normals, a feature observed in all fenamate structures. The two phenyl rings are oriented with respect to each other at 52.8° .

In contrast to the other polymorph of flufenamic acid (McConnell, 1973) but in common with the other fenamate structures (McConnell, 1976; Krishna Murthy & Vijayan, 1979, 1981), the dihedral angle C(2)–C(1)–N(1)–C(8) in this structure is close to 180° implying that the plane of the atoms C(1), N(1), C(8) is nearly coplanar with that of phenyl ring 1. This angle is $-145.5(3)$ in the other polymorph. The other difference between the two polymorphs pertains to the geometrical disposition of the trifluoromethyl group. The angle between the two phenyl rings in the present case is 52.8° , a value comparable to the corresponding angle of 43.0° in the other polymorph. However, phenyl ring 2 is rotated by an angle of around 180° about the N(1)–C(8) bond in the present case compared to that in the other polymorph such that the carboxyl group and the trifluoromethyl group point towards the same side in the former whereas the two groups point towards opposite sides in the latter.

* Lists of structure factors, thermal parameters and H-atom parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36223 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Fig. 2 shows the crystal structure as viewed down the b axis. There exists a pair of symmetry-related intermolecular O–H...O hydrogen bonds, spanning an inversion centre, involving carboxyl groups, leading

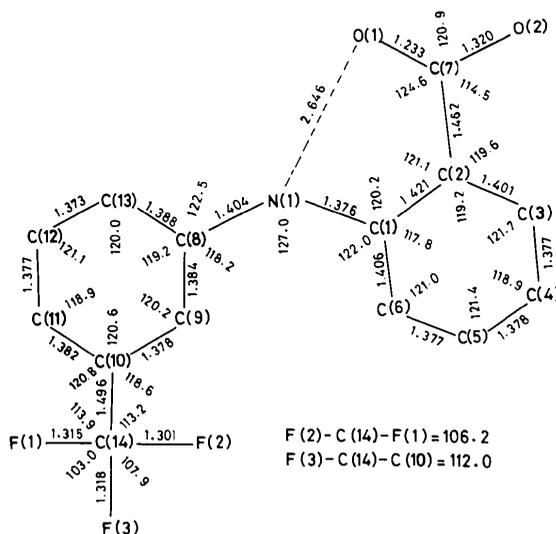


Fig. 1. Bond lengths (Å) and angles ($^\circ$) involving non-H atoms. The average standard deviations in bond lengths and angles are 0.009 Å and 0.6° respectively.

Table 2. Dihedral angles ($^\circ$) and hydrogen-bond lengths (Å)

The primed atoms are related to the unprimed atoms by
 $1 - x, 1 - y, 1 - z$.

O(2)–C(7)–C(2)–C(1)	175.8 (6)
C(2)–C(1)–N(1)–C(8)	–179.2 (6)
C(1)–N(1)–C(8)–C(9)	–130.1 (7)

N(1)...O(1)	2.646 (7)	O(2)...O(1')	2.647 (7)
O(1)...H(N1)	2.0 (1)	O(1')...H(O2)	1.8 (1)

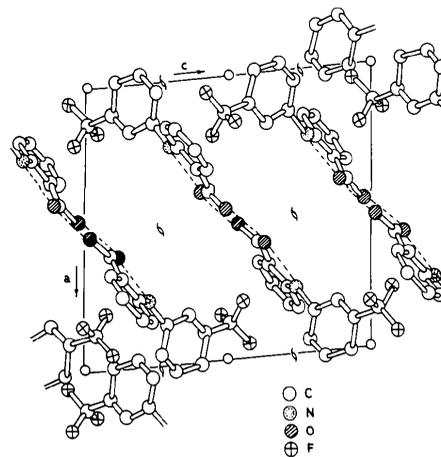


Fig. 2. The crystal structure as viewed along the b axis. The dashed lines indicate hydrogen bonds.

to hydrogen-bonded dimers. This is a feature observed in all fenamate structures. The structure also contains, in common with other fenamates, an intramolecular hydrogen bond between the carbonyl group of the carboxyl acid moiety and the imino group that bridges the two six-membered rings. The parameters for both the hydrogen bonds are listed in Table 2.

The authors thank Parke-Davis & Co., Pontypool, UK, for a free gift of the sample used in this investigation. Financial support from the University Grants Commission, India, is acknowledged.

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Acta Cryst. (1982). **B38**, 317–319

Structure of 2*H*,2'*H*-Octafluorobiphenyl*

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(Received 29 April 1981; accepted 18 June 1981)

Abstract. C₁₂H₂F₈, orthorhombic, *Pbca*, *a* = 21.710 (5), *b* = 7.545 (5), *c* = 12.79 (1) Å, *Z* = 8, λ(Cu *Kα*) = 1.5418 Å, μ = 2.00 mm⁻¹. *R* = 0.045 for 1078 observed reflexions with *I* > 3σ(*I*). The dihedral angle between the rings is 54.7 (4)° and the inter-ring bond length is 1.491 (5) Å (uncorrected for thermal libration).

Introduction. The inter-ring bond length and dihedral angle in perfluorobiphenyl (Gleason & Britton, 1976) are virtually unaffected by 2-substitution with hydrogen (Hamor & Hamor, 1978*a*). This analysis investigates the effect on these two parameters of 2,2'-disubstitution with hydrogen and is the second in a series of studies on the correlation between inter-ring bond length and dihedral angle in substituted perfluoropolyphenyls.

The compound was prepared by the method of Cohen & Massey (1966). Colourless crystals were obtained from ethanol and the selected crystal (1.1 × 0.3 × 0.15 mm) was mounted in a sealed Lindemann-glass capillary.

The intensities and cell dimensions were obtained from a Stoe Stadi-2 two-circle diffractometer by an ω scan with graphite-monochromated Cu *Kα* radiation. Of 1539 reflexions, measured out to a maximum 2θ of 135°, 1078 had *I* > 3σ(*I*) and were classed as observed. Corrections were applied for Lp but not for absorption or extinction.

The structure was solved by direct methods with *MULTAN* (Germain, Main & Woolfson, 1971). It was refined by full-matrix least squares using the XRAY system (1972) to a conventional *R* of 0.045. Anisotropic temperature factors were used for C and F, but the H atoms were placed in calculated positions and not refined. Calculated shifts were <0.1σ in the final cycle of refinement with 1252 contributing reflexions. The weighting scheme used was *w* = 1 for *F_o* ≤ 30 and *w* = (30/*F_o*)² for *F_o* > 30. Scattering factors were those of Cromer & Mann (1968) for C and F and of Stewart, Davidson & Simpson (1965) for H.†

†Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36224 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

* Structures of Substituted Perfluoropolyphenyls. II.