

The F atom and the acetamide group are in *cis* position and the *tert*-butyl group is *trans* to the F atom.

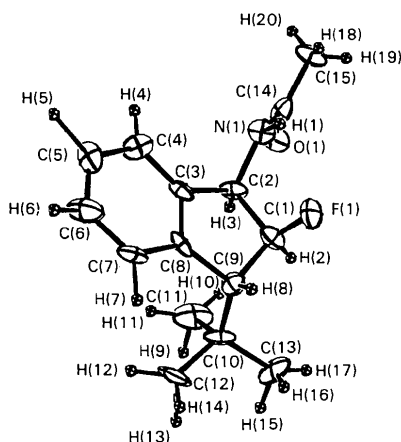


Fig. 1. 25% probability thermal ellipsoids for molecule (1) (H atoms are arbitrarily scaled).

Thus, this isomer is the major product of the electro-fluoroacetamidation process. Comparison of the ^1H and ^{19}F NMR spectra of *A* with those of the major isomer obtained in the same way from non-substituted indene has confirmed that in this latter case the major isomer is also *cis*.

Finally, as a structural feature we may note that the least-squares mean-plane calculations (deposited) involving the six C atoms of the phenyl ring show that C(2) and C(9) [C(17) and C(24) for molecule 2] lie in this plane while C(1) [C(16)] deviates by more than 0.4 Å.

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A Hydrated 1:1 Complex between Niflumic Acid and Ethanolamine,* $\text{C}_{13}\text{H}_8\text{F}_3\text{N}_2\text{O}_2^- \cdot \text{C}_2\text{H}_8\text{NO}^+ \cdot \text{H}_2\text{O}$

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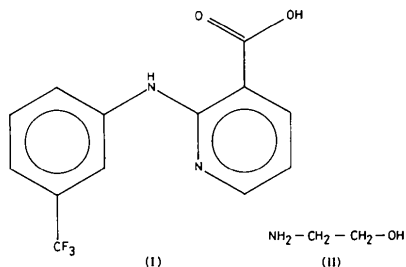
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Abstract. $M_r = 361.3$, triclinic, $P\bar{1}$, $a = 6.239$ (2), $b = 11.280$ (2), $c = 12.451$ (2) Å, $\alpha = 101.2$ (1), $\beta = 92.3$ (1), $\gamma = 99.9$ (1)°, $V = 844.123$ Å³, $Z = 2$, $D_x = 1.42$, $D_m = 1.42$ (1) Mg m⁻³, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu = 1.102$ mm⁻¹, $F(000) = 376$, $T = 293$ K. Final $R = 0.064$ for 2150 observed reflections. The niflumic acid anions consist essentially of three planar groupings, namely, two six-membered rings and a carboxylate group attached to one of them. The invariant common structural features observed in the crystal structures of fenamates, namely, the coplanarity of the carboxyl group and the six-membered ring bearing it, and the internal hydrogen bond between the carboxyl group and the imino N atom that bridges the two six-membered rings, are retained in the complex. The amino N atom is *gauche* with respect to the terminal hydroxyl group in the ethanolamine cation. The complexation between the two molecules is achieved through ionic and hydrogen-bonded interactions involving the carboxylate group in niflumic acid.

Introduction. Non-steroidal anti-inflammatory analgesics like salicylates, pyrazole derivatives and fenamates are believed to act through the inhibition of prostaglandin biosynthesis (Flower, 1974). We have been carrying out X-ray studies on analgetic pyrazole derivatives and fenamates, and their complexes in an attempt to understand their molecular geometry, the nature of the non-covalent interactions they are likely to be involved in, and the geometric and electronic consequences of such interactions (Singh & Vijayan, 1974, 1977; Krishna Murthy & Vijayan, 1981a). The crystal structures analysed include niflumic acid (Krishna Murthy & Vijayan, 1979), meclofenamic acid (Krishna Murthy & Vijayan, 1981b) and flufenamic acid (Krishna Murthy, Bhat & Vijayan, 1982). The crystal structures of mefenamic acid and a different form of flufenamic acid have been reported earlier (McConnell, 1973, 1976). Here we report the crystal structure of a 1:1 complex of niflumic acid (2-[3-(trifluoromethyl)phenyl]amino}-3-pyridinecarboxylic acid) (I) with ethanolamine (2-aminoethanol) (II). This represents the first structure determination of a complex involving an analgetic fenamate.

* Structural Studies of Analgesics and Their Interactions. X.



Experimental. Crystals of the complex grown by slow evaporation of a solution in slightly aqueous methanol of the components in molar proportion. D_m measured by flotation in benzene/carbon tetrachloride. Crystal of approximate dimensions $0.9 \times 0.5 \times 0.3$ mm. Computer-controlled CAD-4 diffractometer, ω - 2θ scan to a maximum Bragg angle of 60° , graphite-monochromated Cu $K\alpha$ radiation. 20 reflections in θ range 11.9 to 44.7° used for measuring lattice parameters. Intensities not corrected for absorption. h 0–6, k –12–12, l –13–13. Two standard reflections (011, 111) showed 4 and 5% variation in intensity respectively. 2284 unique reflections measured, 2150 having $I > 3\sigma(I)$ used in refinement. $R_{\text{int}} = 0.008$ for 00 l and 0 k 0 reflections (symmetry equivalents measured only for these reflections). Structure solved by direct-methods program *MULTAN* (Germain, Main & Woolfson, 1971) followed by Fourier techniques.

The non-H atoms were refined anisotropically and the H atoms, located from a difference Fourier map with the aid of geometrical considerations, isotropically on F using the block-diagonal structure-factor least-squares method to an R value of 0.096. A difference Fourier map computed at this stage contained three residual peaks, each nearly midway between two F atoms in the trifluoromethyl group, thereby indicating possible rotational disorder in this group. Another difference Fourier map phased on all the atoms other than the F atoms was then computed. The main features in this map could be readily explained in terms of two sets of positions for the three F atoms, generated by a rotation about the bond that connects the trifluoromethyl group to the phenyl ring. The occupancies of the two sets of positions were estimated to be 0.667 and 0.333 from peak heights. The fact that the equivalent isotropic temperature factors (Hamilton, 1959) of the atoms in the two sets of positions had comparable values when refinement converged indicated that the assignment of occupancy factors was essentially correct. Refinement converged at $R = 0.064$, $R_w = 0.122$, $S = 1.0217$, when all least-squares shifts were less than corresponding standard deviations (max. $\Delta/\sigma = 0.87$). Weighting scheme employed in final cycles had the form $1/(a + bF_o + cF_o^2)$ with $a = 0.776$, $b = 0.255$ and $c = 0.004$. $\Delta\rho = -0.37$ – 0.24 e \AA^{-3} . Secondary extinction correction not used. Form factors for non-H atoms taken from Cromer & Waber (1965), those for H from

Stewart, Davidson & Simpson (1965). Computations performed on a DEC-1090 computer.

Discussion. The final atomic parameters of the non-H atoms are given in Table 1.*

Unlike in the crystal structures of uncomplexed fenamates, the carboxyl group in the niflumic acid molecule in the present structure is deprotonated and hence negatively charged. The amino group in the ethanolamine molecule is protonated and positively charged. The geometry of the niflumic acid and ethanolamine molecules, and their interactions among themselves as well as with water molecules are illustrated in Fig. 1. The anions in the structure, like those of the other fenamates, consist essentially of three planar groupings, namely, the two six-membered rings and a carboxylate group attached to one of them. Three torsion angles, given in Table 2 along with that necessary to define the conformation of the ethanolamine molecule, are therefore sufficient to describe the molecular conformation of niflumic acid. The carboxylate group and the six-membered ring bearing it are nearly coplanar, the angle between the two planes being 12.9° , whereas the two six-membered rings are

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, and bond lengths and angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38643 (17 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Final positional coordinates ($\times 10^4$) and equivalent isotropic temperature factors (Hamilton, 1959) of non-H atoms with e.s.d.'s in parentheses

	x	y	z	$B_{\text{eq}}(\text{\AA}^2)$
C(1)	8615 (9)	5384 (5)	7941 (4)	3.0 (2)
C(2)	9276 (9)	4370 (5)	8298 (4)	3.1 (2)
C(3)	11276 (9)	4567 (6)	8862 (5)	3.5 (2)
C(4)	12593 (10)	5718 (6)	9084 (5)	3.6 (2)
C(5)	11806 (10)	6663 (6)	8745 (5)	3.7 (2)
N(6)	9848 (9)	6516 (5)	8194 (4)	3.6 (2)
C(7)	7818 (10)	3128 (6)	8135 (5)	3.4 (2)
O(1)	5829 (7)	3025 (4)	7822 (4)	4.6 (2)
O(2)	8609 (8)	2246 (4)	8349 (4)	4.8 (2)
N(1)	6646 (8)	5243 (4)	7361 (4)	3.3 (2)
C(8)	5937 (9)	5940 (5)	6654 (4)	2.9 (2)
C(9)	7281 (9)	6856 (5)	6271 (5)	3.2 (2)
C(10)	6435 (10)	7415 (5)	5482 (5)	3.5 (2)
C(11)	4279 (11)	7097 (6)	5098 (5)	3.9 (2)
C(12)	2900 (10)	6222 (6)	5509 (5)	3.6 (2)
C(13)	3731 (9)	5626 (6)	6264 (5)	3.2 (2)
C(14)	7929 (12)	8339 (7)	5035 (6)	4.9 (3)
F(1)	8345 (16)	7908 (10)	4015 (7)	9.3 (4)
F(2)	7145 (18)	9302 (9)	4989 (11)	10.4 (6)
F(3)	9906 (12)	8660 (8)	5503 (7)	7.2 (3)
F'(1)	8434 (34)	9424 (17)	5802 (14)	9.1 (8)
F'(2)	7143 (29)	8759 (16)	4290 (14)	8.3 (8)
F'(3)	9646 (39)	8048 (26)	4748 (31)	13.9 (17)
N(21)	2517 (8)	1418 (5)	8457 (4)	3.8 (2)
C(22)	2292 (13)	94 (7)	7973 (7)	5.3 (3)
C(23)	4395 (14)	–210 (7)	7581 (6)	5.0 (3)
O(24)	6050 (8)	120 (5)	8446 (6)	5.8 (2)
W(25)	7264 (10)	–1718 (5)	9288 (4)	5.7 (2)

inclined with respect to each other at 32.2° . As in the structures of uncomplexed fenamates, the imino N atom bridging the two six-membered rings and the carboxylate group are connected through an internal $N-H \cdots O$ hydrogen bond. Thus, it is interesting to note that the invariant structural features of the fenamates observed in their crystal structures, namely, the coplanarity of the carboxyl group and the six-membered ring bearing it, and the internal hydrogen bond between the carboxyl group and the imino group, are retained in the complex.

The central C—C bond in the ethanolamine molecule is of the sp^3-sp^3 type and the molecule assumes a *gauche* conformation. The conformation permits the two functional groups to interact simultaneously with the carboxylate group of a niflumic acid molecule.

The crystal structure of the complex, shown in Fig. 2, is stabilized by ionic interactions between the carboxylate group of niflumic acid and the amino group of

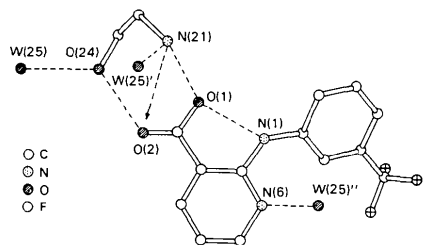


Fig. 1. A perspective view of the complex. The broken lines indicate hydrogen bonds. The minor disordered component of the trifluoromethyl group is not shown.

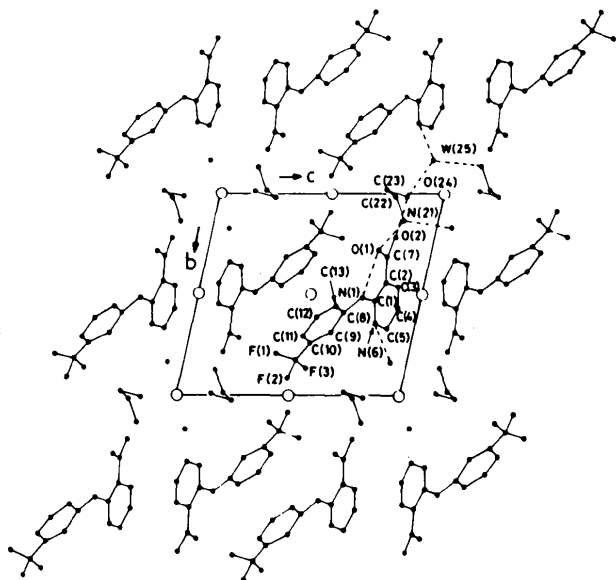


Fig. 2. Crystal structure of the complex. The broken lines indicate hydrogen bonds. The minor disordered component of the trifluoromethyl group is not shown.

Table 2. Torsion angles that define the conformation of niflumic acid and ethanolamine, and hydrogen-bond parameters

The standard deviations are given in parentheses.

O(2)—C(7)—C(2)—C(1)	171.3 (6)°	C(1)—N(1)—C(8)—C(9)	10.0 (10)°
C(2)—C(1)—N(1)—C(8)	−157.7 (6)	N(21)—C(22)—C(23)—O(24)	58.1 (9)
N(1)⋯O(1 ^l)	2.644 (8) Å	H(N1)—N(1)⋯O(1)	25 (5)°
N(21)⋯O(1 ^l)	2.752 (7)	H1(N21)—N(21)⋯O(1)	8 (4)
N(21)⋯W(25 ^h)	2.757 (8)	H2(N21)—N(21)⋯W(25)	9 (8)
N(21)⋯O(2 ^h)	2.765 (8)	H3(N21)—N(21)⋯O(2)	11 (4)
O(24)⋯O(2 ^h)	2.669 (7)	H(O24)—O(24)⋯O(2)	7 (6)
W(25)⋯O(24 ^h)	2.700 (9)	H2(W25)—W(25)⋯O(24)	15 (6)
W(25)⋯N(6 ^h)	2.941 (8)	H1(W25)—W(25)⋯N(6)	16 (5)

Symmetry code: (i) x, y, z ; (ii) $1-x, y, 2-z$; (iii) $x-1, y, z$; (iv) $x, y-1, z$.

ethanolamine, and hydrogen bonds. The parameters of the hydrogen bonds are given in Table 2. In the crystal structures of uncomplexed fenamates (Krishna Murthy & Vijayan, 1979, 1981*b*; Krishna Murthy, Bhat & Vijayan, 1982; McConnell, 1973, 1976), the molecules form centrosymmetric dimers, hydrogen-bonded through the carboxyl groups. In the present structure, however, a specific interaction exists, involving two nearly parallel hydrogen bonds, between the carboxylate group of niflumic acid and ethanolamine. The topology of this interaction is similar to the type *A* and type *B* interactions involving the guanidyl group (Salunke & Vijayan, 1981). Each ethanolamine molecule is, in addition, hydrogen-bonded, through its amino group, to the carboxylate group of another niflumic acid molecule related by an *a* translation to the one with which it forms the specific interaction. The amino group of ethanolamine is involved as a donor in a third hydrogen bond with a water molecule whereas the hydroxyl group accepts a proton in a hydrogen bond with a symmetry-related water molecule. The lone water molecule in the structure is also involved in a hydrogen bond as a donor, with the pyridine-ring N atom.

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Combined X-ray and Neutron Study of 1,1,2,2-Ethanetetracarbonitrile, C₆H₂N₄, at 158 K

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Abstract. $M_r = 130.11$. X-ray: monoclinic, $P2_1/n$, $a = 7.367$ (1), $b = 5.705$ (1), $c = 7.780$ (1) Å, $\beta = 95.02$ (1)°, $V = 325.8$ Å³, $Z = 2$, $D_x = 1.327$ g cm⁻³, $T = 158$ K, $\text{Mo } K\alpha$, $\lambda = 0.7107$ Å, $\mu = 0.99$ cm⁻¹, $F(000) = 132$. In order to explain the lengthening observed in the central bond of a number of symmetrically substituted ethanes, an analysis of the charge density of the title compound has been undertaken. The structure was redetermined at 158 K from neutron and X-ray diffraction data and refined to $R_w = 1.4$ and 2.8% respectively. $X-N$ and $X-X$ deformation maps show a weak density in the region of the central bond. A least-squares refinement including atomic charges was performed on the X-ray data and indicates two negatively charged C atoms at the ends of the central bond.

Introduction. This analysis of charge density in 1,1,2,2-ethanetetracarbonitrile (Fig. 1a) is part of a structural study of dehydro dimers corresponding to the formula $(R_1R_2R_3C)_2$. The structures of some of these dimers presented in Fig. 1 have been elucidated by X-ray diffraction at room temperature (Parfonry, Tinant, Declercq & Van Meerssche, 1982). We observed a significantly stretched central bond ($d \approx 1.59$ Å) for molecules like (b) and (c) (Tinant, Arte, Parfonry, Declercq, Germain & Van Meerssche, 1982) while the

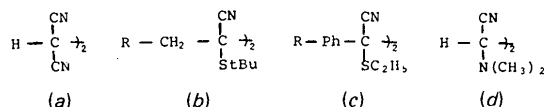


Fig. 1. Examples of dimers related to this study and whose structures have been determined by X-ray diffraction.

expected distance of 1.54 Å was found for molecule (d). A partial explanation of the bond lengthening in (b) and (c) can be found in the work of Rüchardt & Beckhaus (1980). They established quantitative correlations between steric strain, thermal stability and central bond lengths in a series of substituted alkanes. In ethane-tetracarbonitrile steric strain seems to be low and does not appear to explain the long bond length (1.561 Å) observed at room temperature. Moreover, *ab initio* calculations performed by Leroy, Wilante, Peeters & Khalil (1981) determine a central length of 1.584 Å. Electronic effects should be important and an experimental study of the charge density deformation must be of prime interest for the interpretation of the observed effects.

Experimental. Crystals grown by slow evaporation of a 3:2 solution of benzene and ethyl acetate. D_m not measured. Details of the data collections are summarized in Table 1.