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Triclinic polymorph of sulfasalazine

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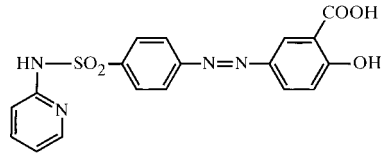
In this modification of the title compound, 5-{4-[(2-pyridylamino)sulfonyl]phenyldiazenyl}salicylic acid, $C_{18}H_{14}N_4O_5S$, the molecule is present in the amide tautomeric form. Two azo-bridged phenyl rings render the bulk of the molecule planar, with the carboxylic acid group at one terminal and the pyridylamino residue at the other. The repeating unit in the crystal is a centrosymmetric dimer containing two identical $R_2^2(8)$ hydrogen-bonded ring systems, each involving the carboxylic acid and pyridylamino moieties. Additional stabilization is due to an intramolecular hydrogen bond between the 2-hydroxyl group and the carbonyl O atom of the carboxylic acid group, as well as intermolecular π–π stacking.

Comment

Sulfasalazine (synonyms salazopyrine and salazosulfapyridine), (I), is a conjugate of 5-aminosalicylic acid and sulfapyridine possessing antibacterial properties which are useful in the treatment of ulcerative colitis and Crohn's disease (Merck Index, 1996). We are investigating the interaction between this drug and metal ions with a view to obtaining complexes with useful medicinal properties. The present analysis was undertaken to establish the molecular conformation of the uncomplexed drug. Van der Sluis & Spek (1990) reported difficulty in obtaining suitable single crystals of sulfasalazine but succeeded in isolating a pseudo-polymorph containing both *N*,*N*-dimethylformamide and water. The structure reported here is the first of a polymorph of sulfasalazine. An important structural feature of sulfonamides containing pyridine or pyrimidine residues is their ability to exist in different tautomeric forms, which is one factor contributing to their polymorphism (Byrn *et al.*, 1999).

The molecular structure and conformation of sulfasalazine are shown in Fig. 1. The bulk of the molecule, including the S atom, the C11–C16 phenyl ring, the azo bridge and the hydroxybenzoic acid moiety, is planar. An intramolecular O28—H28···O27 hydrogen bond fixes the orientation of the carboxylic acid group. Table 1 lists selected molecular parameters including the torsion angles defining the conformation from which the degree of coplanarity of the various residues can be gauged. Atom N7 (rather than the pyridine N1 atom) was found to be protonated, showing that the molecule is present in the amide tautomeric form with C2—N7 having



(I)

formal single-bond character (Table 1). This contrasts with the situation in the pseudo-polymorph reported by Van der Sluis & Spek (1990), where the two crystallographically independent sulfasalazine molecules both occur as the imide tautomers with N1 protonated and N7 deprotonated. In the latter case, the bonds equivalent to C2—N7 have double-bond character [1.349 (6) and 1.348 (7) Å] and the N—C═N—S chains adopt *trans*-planar configurations. The occurrence of the amide tautomer for sulfasalazine is also unexpected in light of previous studies which showed that all three polymorphic forms of sulfapyridine assume the imide form in the solid state (Bar & Bernstein, 1985). Apart from the differences in molecular parameters arising from tautomerism, other molecular parameters for the solvated and unsolvated forms of sulfasalazine are in close agreement.

In the conformation shown in Fig. 1, the molecule contains widely separated but complementary hydrogen-bonding moieties, namely the pyridinylamino grouping, N1═C2—N7—H7 and the carboxylic acid group. Consequently, two sulfasalazine molecules form a centrosymmetric dimer by head-to-tail hydrogen bonding which comprises two identical $R_2^2(8)$ systems (Bernstein *et al.*, 1995) including the intermolecular bonds N7—H7···O27^{i} and O26—H26···N1^{i} (Table 2). The formation of this dimer requires the drug to be in the amide tautomeric form since only this species permits the complementary hydrogen bonding observed. Within the dimer, the two coplanar azo-bridged phenyl-ring systems are offset from one another and there is no π–π stacking. However, as seen in Fig. 2, the outer faces of a dimer engage in π–π stacking with dimers translated along the *b* axis. Addi-

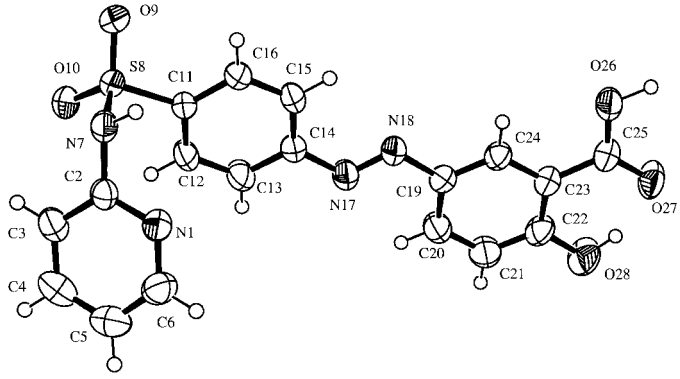


Figure 1
The structure of the sulfasalazine molecule showing 50% probability displacement ellipsoids and the atom-numbering scheme.

tional π–π stacking between the pyridine rings related by inversion at $\frac{1}{2},0,\frac{1}{2}$ stabilizes the crystal structure. For the first type of π–π stacking, the ring centroids are 3.885 (1) Å apart and the two perpendicular centroid–plane distances are 3.458 and 3.494 Å. For the second, the centroid–centroid distance is 3.680 (1) Å and the interplanar spacing is 3.410 Å. The dominant feature of the crystal packing is the location of the planar molecular residues parallel to and midway between the $(02\bar{2})$ planes. The powder X-ray diffraction pattern for this polymorph is accordingly dominated by the $(02\bar{2})$ reflection which occurs at $2\theta = 26.53^\circ$ corresponding to $d = 3.360$ Å.

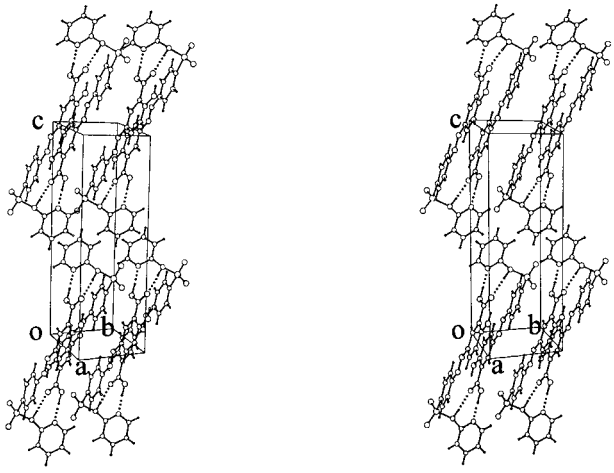


Figure 2
Stereoview of the crystal packing showing the hydrogen-bonded dimers.

Experimental

Sulfasalazine was obtained from the Laboratory of A. C. HELCOR, Baia-Mare, Romania. Recrystallization from ethanol (50 mg dissolved in 10 ml ethanol) yielded clusters from which single crystals were excized. Elemental analysis gave C 53.9, H 3.5, N 13.7, S 7.8%; calculated 54.3, 3.5, 14.1, 8.1%. It was established by X-ray photographic methods that the same polymorphic form of sulfasalazine precipitated in a failed attempt to produce a copper complex by refluxing ethanolic solutions of copper(II) chloride and sulfasalazine in a 1:1 molar ratio for 24 h.

Crystal data

$C_{18}H_{14}N_4O_5S$
$M_r = 398.39$
Triclinic, $P\bar{1}$
$a = 7.017$ (1) Å
$b = 7.307$ (1) Å
$c = 18.091$ (1) Å
$\alpha = 94.673$ (3)°
$\beta = 92.059$ (3)°
$\gamma = 106.633$ (3)°
$V = 884.11$ (18) Å^3
$Z = 2$
$D_x = 1.497$ Mg m^{-3}
$D_m = 1.48$ Mg m^{-3}
D_m measured by flotation in aqueous KI
Mo $K\alpha$ radiation
Cell parameters from 7652 reflections
$\theta = 2.26$–27.75°
$\mu = 0.224$ mm^{-1}
$T = 298$ (2) K
Prism, orange
0.35 × 0.20 × 0.14 mm

Data collection

Nonius KappaCCD diffractometer
1.2° φ and ω scans
7652 measured reflections
4046 independent reflections
3021 reflections with $I > 2\sigma(I)$
$R_{int} = 0.018$
$\theta_{max} = 27.75^\circ$
$h = -9 \rightarrow 9$
$k = -8 \rightarrow 9$
$l = -23 \rightarrow 22$
Intensity decay: negligible

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.043$
$wR(F^2) = 0.113$
$S = 1.032$
4046 reflections
262 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.0484P)^2 + 0.1794P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.30$ e Å^{-3}
$\Delta\rho_{min} = -0.32$ e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.340 (2)	S8—C11	1.7637 (17)
C2—N7	1.425 (2)	N17—N18	1.249 (2)
N7—S8	1.6539 (16)	C22—O28	1.344 (2)
N1—C2—N7	115.71 (15)	C15—C14—N17	125.35 (15)
C3—C2—N7	121.78 (15)	N18—N17—C14	115.06 (15)
C2—N7—S8	117.45 (12)	N17—N18—C19	113.37 (15)
N7—S8—C11	104.87 (7)	C20—C19—N18	123.61 (16)
N1—C2—N7—S8	107.13 (16)	C15—C14—N17—N18	0.2 (3)
C2—N7—S8—C11	−61.00 (13)	C14—N17—N18—C19	178.99 (14)
N7—S8—C11—C12	86.38 (16)	N17—N18—C19—C20	−0.4 (3)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N7—H7···O27^{i}	0.99 (2)	1.97 (2)	2.9472 (19)	170 (2)
O26—H26···N1^{i}	1.00 (2)	1.62 (2)	2.623 (2)	173.3 (18)
O28—H28···O27	0.91 (3)	1.76 (3)	2.604 (2)	154 (3)

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

All H atoms were located and were placed in idealized positions in a riding model, except for H26 and H28 which refined freely and H7 which was included with a distance restraint of 1.000 Å (s.u. 0.005 Å).

Data collection: *COLLECT* (Nonius, 2000); cell refinement and data reduction: *DENZO-SMN* (Otwinowski & Minor, 1997); structure solution: *SHELXS*97 (Sheldrick, 1990); structure refinement: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ZORTEP* (Zsolnai & Pritzkow, 1994).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1126). Services for accessing these data are described at the back of the journal.

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