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Crystal and Molecular Structure of Sulfadimethoxine, Polymorph III

Crystal structure of sulfadimethoxine, $C_{12}H_{14}N_4O_4S$, has been determined and refined to an R-value of 0.043 using direct methods. It crystallizes in the triclinic space group $P\bar{1}$ with a = 7.946(1), b = 9.330(1), c = 10.407(1)Å, α = 93.46(1), β = 95.43(1), γ = 114.62(1)° and Z = 2. The dihedral angle between the two six - membered rings of the molecule is 77.6(8)°. Molecule adopts a gauche conformation about S8-N11 bond with torsional angle of 60.0(2)°. The structure is mainly stable due to strong hydrogen bonds, amino nitrogen plays the role of donor in two different intermolecular hydrogen bonds where sulfonyl oxygen and pyrimidine nitrogen act as acceptor.

Keywords: X-ray diffraction, polymorph, sulfonamide

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1. Introduction

Polymorphism is the ability of a compound to crystallize in different forms. The pharmaceutical property of a molecule is very much an involved function of its structure and since the only variable parameter in the case of polymorphs is their three-dimensional structure, the polymorphic form of a molecule provides an unique opportunity to study the structure – property relationship.4-p-aminobenzenesulfonamido – 2,6-dimethoxypyrimidine (INN : sulfadimethoxine(1)) is a well known member of antimicrobial sulfonamide family. Crystallographic data of polymorph I and polymorph II are already reported in literature (PATEL et al.; NARULA et al.). To investigate the influence of different crystallographic environment on molecular structure and hence on its action, we report here the crystal and molecular structure of polymorph III of sulfadimethoxine.

2. Experimental

Pure powder (99.99%) of sulfadimethoxine has been procured from Sigma, India. Diamond shaped transparent and pretty good crystals of the title compound have been grown at room temperature from the mixture of ethyl acetate and methanol under control evaporation. Crystal data are : molecular formula $C_{12}H_{14}N_4O_4S$, molecular weight 310.33 Da, a = 7.946(1), b = 9.330(1), c = 10.407(1) Å α = 93.46(1), β = 95.43(1), γ = 114.621(1)°, V = 693.99(13) Å^3, ρ_{mea} = 1.475 and ρ_{cal} = 1.48 Mg m^{-3} . It crystallizes in triclinic system in space group $P\bar{1}$ with Z = 2. Density is measured using floatation method in a mixture of benzene and carbon tetrachloride. Intensity data of 2438 unique reflections are collected on CAD-4 diffractometer using ω-2θ scan technique with CuKα radiation. Data are corrected for

Lorentz, polarization and absorption effects. SHELX-97 programme package (SHELDRICK) was used to solve and refine the structure. All the hydrogen atoms were located from difference Fourier map. Non-hydrogen atoms were refined anisotropically and all the hydrogens were included in the refinement cycle keeping the distances, to the atoms to which they are attached, fixed. (riding model). Final R indices [I > 2σ(I)] are $R_1 = 0.043$ and $wR_2 = 0.148$ for 1840 reflections and the goodness of fit S is 1.596.

3. Results and discussion

Atomic co-ordinates of non-hydrogen atoms with their equivalent isotropic thermal parameters are presented in the Table 1. Selected bond distances and angles involving non-hydrogen atoms are summarized in Table 2.

Table 1: Fractional co-ordinates ($\times 10^4$) and equivalent isotropic displacement parameters($Å^2 \times 10^4$) of non-hydrogen atoms

Atom	x	y	z	$U (eq) = 1/3$ $(U_{11}+U_{22}+U_{33})$
C1	3238(15)	2881(17)	1544(11)	35(4)
C2	4250(3)	4464(18)	2043(13)	45(4)
C3	6110(2)	5200(2)	1923(13)	47(4)
C4	7010(3)	4387(19)	1342(11)	38(3)
C5	5980(3)	2806(19)	862(12)	42(4
C6	4140(3)	2070(2)	965(11)	41(4)
N7	8860(2)	5130(2)	1227(13)	56(4)
S8	867(4)	1958(3)	1640(3)	43(2)
O9	445(15)	2842(10)	2614(7)	53(3)
O10	-186(10)	1618(12)	374(9)	52(3)
N11	451(15)	182(13)	2066(14)	40(3)
C12	1247(16)	-140(2)	3214(17)	34(4)
C13	2077(18)	940(2)	4289(19)	38(4)
C14	2806(19)	430(2)	5314(19)	40(4)
N15	2715(15)	-1030(2)	5277(16)	41(4)
C16	1870(2)	-2000(2)	4210(2)	36(4)
N17	1121(15)	-1622(19)	3170(17)	39(3)
O18	3655(12)	1427(11)	6368(12)	56(3)
C19	4300(3)	820(2)	7477(17)	62(4)
O20	1747(11)	-3467(14)	4094(8)	62(5)
C21	2480(3)	-3970(2)	5221(17)	57(3)

Table 2: Selected bond lengths (Å) and bond angles (º) involving non – hydrogen atoms

$C_1 – S_8$	1.730(12)	C14 – O18	1.331(15)
C4 – N 7	1.364(15)	N15 - C16	1.319(17)
S8 – O9	1.419(8)	C16 – N17	1.321(16)
S8 – O10	1.434(8)	C16 – O20	1.327(14)
S8 – N11	1.646(11)	O20 – C21	1.448(14)

C12 – N17	1.338(15)	O18 – C19	1.443(15)
C13 - N15	1.332(16)		
C2 – C1 – S8	119.5(14)	S8 – N11 – C12	125.9(13)
C6 – C1– S8	120.9(13)	N11 – C12 – C13	123.8(15)
C1 – S8 – O9	108.5(7)	C13 – C12 – N17	122.3(16)
C1 – S8 – O10	110.7(5)	C13 – C14 – N15	122.3(16)
C1 – S8 – N11	106.1(6)	C14 – N15 – C16	117.7(17)
O9 – S8 – O10	117.9(6)	N15 – C16 – N17	124.5(18)
O9 – S8 – N11	110.0(5)	C14 – O18 – C19	117.9(14)
O10 – S8 – N11	103.1(7)	C16 – O20 – C21	116.8(14)

Table 3: Torsional Angles, hydrogen bond parameters, interatomic distances less than 3.5 A° and symmetry codes

a. Torsional Angles

	PolyIII	PolyI	Sulfamonomethoxine	
			MolA	MolB
O9–S8–N11–C12	-57.1(9)	-56(1)	177.5(2)	171.5(3)
O10–S8–N11–C12	176.4(8)	-	-50.5(3)	42.3(3)
C1–S8–N11–C12	60.0(10)	-	67.3(3)	−74.1(3)
C2–C1–S8–N11	-137.7(10)	44(1)	46.8(3)	91.1(3)
C6–C1–S8–N11	-1.0(16)	42(1)	-134.9(2)	−91.7(3)

b. Hydrogen bond parameters s

D – H ...A	D...A Å	D–H Å	H....A Å	∠D – H – A (°)
N7 – H71…..O9a	3.24(2)	0.91	2.71	117.3
N7 – H72…..N17a	3.25(2)	0.82	2.44	171.3
N11 – H11….O10b	3.00(2)	0.87	2.15	142.3

c. van der Waal distances (Å)

N7 – N7c	3.32(2)
N7 – O10b	3.39(3)
O9 – O20d	3.38(1)
O10 – N11e	2.84(2)
O10 – O10e	2.96(2)
O20 – C21f	3.39(2)

d. Symmetry codes

a	1+x	y	z
b	1-x	1-y	z
c	2-x	1-y	z
d	x	1+y	z
e	-x	-y	-z
f	-x	-1-y	1-z

Three different polymorphs of sulfadimethoxine have been grown from different solutions.

Polymorph I with space group P$\bar{1}$ was crystallized from aqueous ethyl alcohol, Polymorph II with space group P1 (two independent molecules per unit cell) from a mixture of acetone and ethyl alcohol whereas the present compound, polymorph III, was crystallized from a mixture of ethyl acetate and methanol.

Bond distances and angles of the six-membered benzene ring are normal. The S=O distances (1.419(8) and 1.434(8) A^{o}) are within the range observed for other sulfonamides (GIUSEPPETTI et al.; BETTINETTI et al.). The C1-S8 distance of 1.730(12) A^{o} is significantly shorter than that reported in literature 1.758 Å (ALLEN et al.).The C4-N7 distance of 1.364(15) A^{o} is shorter than that normally observed in other sulfonamides: the distance is 1.41(2) A^{o} in sulfadiazine(JOSHI et al.) , 1.389(3) Å in Na-Sulfadimidine (PATEL U. H.), 1.39(2) A^{o} in sulfamoxole (HARIDAS et al.). These shortening of C1-S8, C4-N7 bonds are not entirely due to extension of delocalized electrons from the conjugated ring. The molecule as a whole looks much more folded, stacking constraint may be forcing the molecule to attain the folded shape and thus bringing the terminal methoxy groups close to each other, giving a coil shape at this end. Dimensions of pyrimidine ring are normal. However, the angles at C14 and C16, where methoxy groups are attached are quite large, the angles are C12-C14-N15 = 122.3(16)^{o} and N15-C16-N17 = 124.3(18)^{o}.
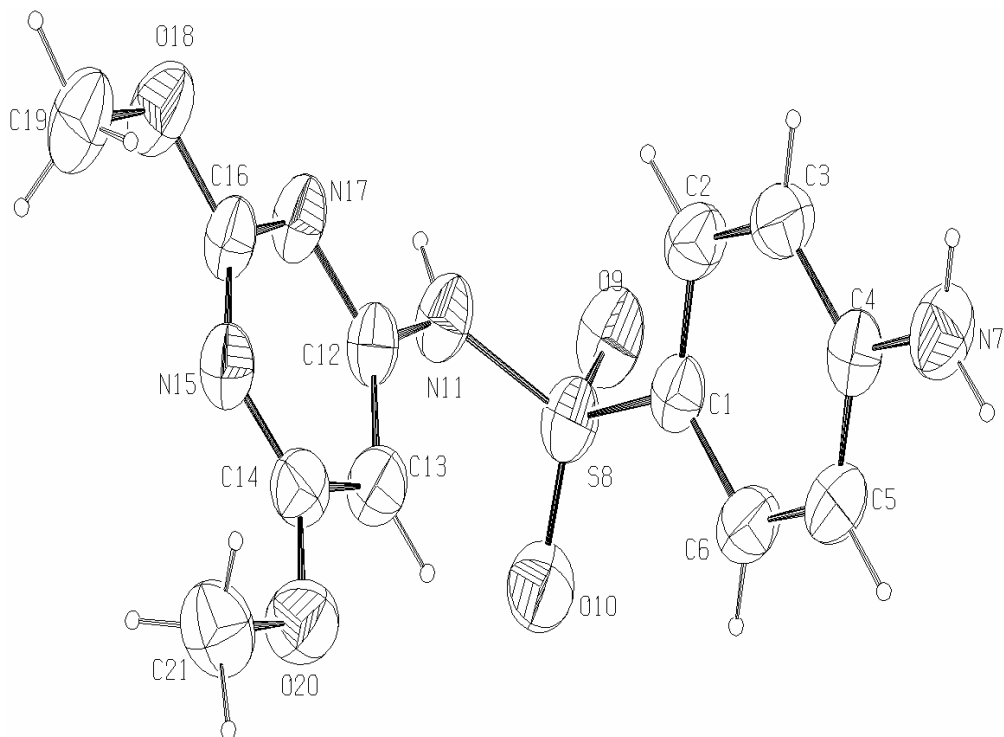

Fig. 1: Molecular structure of the title compound

Molecular dimension of all the three polymorphs are in general good agreement among one another but there are few significant differences observed which might be due to somewhat different intermolecular interaction in the three polymorphs. Coordination geometry around Sulfur is as usual a distorted tetrahedron in all three polymorphs. The orientation of the benzene ring plane with respect to that of the pyrimidine ring plane is nearly the same in all

the three polymorphs: 77.6° in I,, 79.3 and 77.4° in molecule A and molecule B, respectively in II and 77.6(8)° in polymorph III. The methoxy group planes C14-O18-C19 and C16-O20-C21 are inclined at 5.1 and 3.5° in I, 3.8 and 13.3° in molecule A and 2.0 and 15.0° in molecule B of II respectively, and 2.8(2) and 1.4(3)° in III with the pyrimidine ring plane. Both the six-membered rings are planar in three polymorphs.
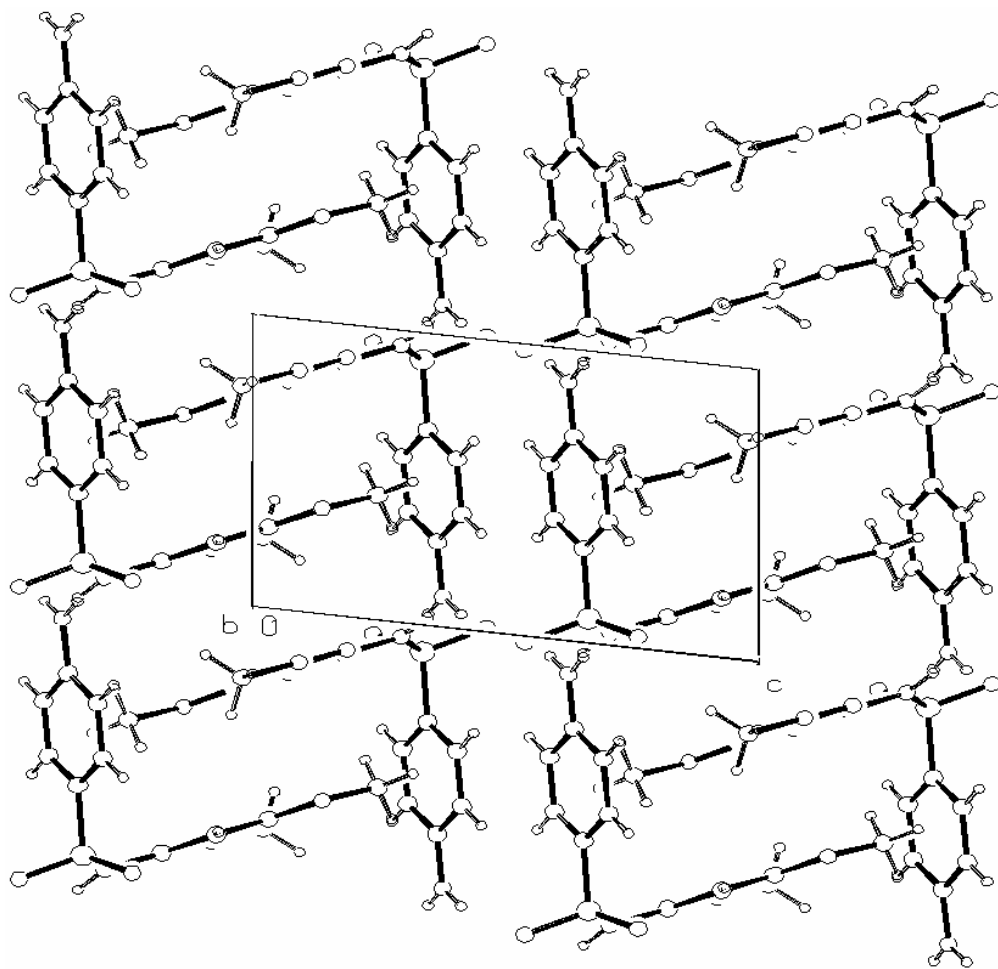

Fig. 2: Crystal packing down b-axis

The displacements of the methoxy oxygen O18 and O20 from the plane of pyrimidine ring are 0.03 and –0.01 Å in I, in case of II the displacement is on the same side by -0.027(8) and –0.014(8) Å for molecule A and –0.062(8) and –0.119(8) Å for molecule B and those for polymorph III are 0.0009(35) Å and -0.019(4) Å respectively. Few significant torsional angles, which define the conformation of the molecule about C1-S8 and S8-N11 bonds are listed in Table 3a. The values in the square bracket are those of I and molecule A and B of sulfamonomethoxine respectively (PATEL H.R.), a very similar compound where only one methoxy group is attached at pyrimidine ring. Comparison of the torsional angles of I with

those of III (having different crystallographic environment) and with sulfamonomethoxine (a slight different chemical environment), reveal that even a minor change in the structure i.e. the conformation of a molecule can affect considerably the intermolecular interaction.

4. Molecular Packing

Figure 1 is the ORTEP (JONSHON C. K.) diagram of the molecule and crystal packing of polymorph III as seen along b axis is given in Figure 2. Hydrogen bonding interaction and few short van der Waal contact distances are presented in Table 3b. Crystal packing and hydrogen bonding scheme for the two polymorphs I and III are similar whereas the interaction in II is quite different. In case of I and III, amino nitrogen N7 forms two hydrogen bonds with sulfonyl oxygen O9 and pyrimidine nitrogen N17 of the symmetry-related molecule respectively and in an other interaction imino nitrogen N11 interacts with sulfonyl oxygen O10. Though the number and the nature of hydrogen bonds are quite same in I and III but the hydrogen bond interaction in III is comparatively stronger resulting a stronger packing.

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