

# The Crystal and Molecular Structures of 3-Methyl-5-amino-1,2-thiazole-sulfate

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The crystal and molecular structures of 3-methyl-5-aminoisothiazole  $\cdot \frac{1}{2} \text{H}_2\text{SO}_4$  have been determined at 121 K by X-ray crystallographic methods using 4837 reflections observed by counter methods. The crystals are monoclinic, space group  $C2/c$  with unit cell dimensions  $a = 7.417(2) \text{ \AA}$ ,  $b = 11.265(1) \text{ \AA}$ ,  $c = 15.929(1) \text{ \AA}$ ,  $\beta = 101.948(8)^\circ$ . The structure was refined to a conventional  $R$ -factor of 0.027. Estimated standard deviations are  $0.0005 \text{ \AA}$  and  $0.05^\circ$  in bond lengths and angles when hydrogen atoms are not involved. Bond lengths corrected for thermal motion are given.

Isothiazole derivatives represent a relatively new type of compound<sup>1</sup> and have attracted much interest, mostly because of the various biological activities they appear to have.<sup>2-5</sup> The isothiazole moiety has been studied by several authors employing X-ray crystallographic methods.<sup>6</sup> However, most studies have been performed on fused ring systems such as 1,2-benzisothiazole derivatives and only few on the free isothiazole ring.<sup>7,8</sup> Thus we present here an accurate X-ray crystallographic study of the protonized 5-amino-3-methylisothiazole molecule as found in crystals of the sulphate complex.

## EXPERIMENTAL

The general experimental procedure and conditions are given in the table below. Cell parameters were determined by a least squares fit to the diffractometer settings for 15 general reflections. The standard deviations in the measured intensities were calculated as  $\sigma(I) = |C_T + (0.02C_N)^2|^\dagger$  where  $C_T$  is the total number of counts and  $C_N$  is the scan count minus the background count. The intensity

data were corrected for Lorentz and polarization effects as well as for absorption effects. The variation in the intensities of the test reflections was less than 1.5% and no corrections were made on this basis.

Scattering factors used were those of Doyle and Turner<sup>9</sup> for the non-hydrogen atoms and of Stewart, Davidson and Simpson<sup>10</sup> for the hydrogen atoms. The density of the crystalline compound was measured by means of flotation. The conditions for reflection were found to be

$$hkl : h + k = 2n$$

$$0k0 : k = 2n$$

$$h0l : l = 2n$$

which indicates space group  $Cc$  or  $C2/c$ . The space group  $C2/c$  was chosen on the basis of  $N(z)$  statistics indicating a center of symmetry as well as on the density and cell volume indicating 8 asymmetric units in the cell.

### Experimental conditions.

Instrument	SYNTEX P1
Radiation	Graphite crystal monochromated MoK $\alpha$ $\lambda = 0.71069 \text{ \AA}$
Crystal dimensions/mm	$0.3 \times 0.25 \times 0.5$
Scanning mode	$\theta/2\theta$
Scan speed/ $^\circ \text{min}^{-1}$	2-4 depending on intensity
Scan range/ $^\circ$	$2\theta\alpha_1 - 0.8$ to $2\theta\alpha_2 + 1.4$ for $2.0 < 2\theta < 65.0$ $2\theta\alpha_1 - 0.8$ to $2\theta\alpha_2 + 1.0$ for $65.0 < 2\theta < 90.0$
Background counts	For 0.35 of scan time at scan limits
$2\theta$ range/ $^\circ$	$2.0 < 2\theta < 90.0$
Temperature/K	121
Number of reflections meas.	5355

Number of reflections $I > 2.5\sigma(I)$	4837
Number of test reflections	3
Number of reflections measured between test reflections	57
Absorption coefficient/mm <sup>-1</sup>	0.572
Trans min.	0.8507
Trans max.	0.9208

## CRYSTAL DATA

3-Methyl-5-amino-1,2-thiazol-sulfate, C<sub>4</sub>SN<sub>2</sub>-H<sub>7</sub>·½SO<sub>4</sub>, monoclinic;  $a = 7.417(2)$  Å,  $b = 11.265(1)$  Å,  $c = 15.929(1)$  Å,  $\beta = 101.948(8)^\circ$ ,  $V = 1302.0(1)$  Å<sup>3</sup>,  $M = 149.2$ , space group:  $C2/c$ ,  $Z = 8$ ,  $F(000) = 624$ ,  $D_x = 1.6$  g/cm<sup>3</sup>,  $D_o = 1.66$  g/cm<sup>3</sup>.

## STRUCTURE DETERMINATION

The structure was solved by direct methods using the program assembly MULTAN,<sup>11</sup> the positions of all the non hydrogen atoms in the asymmetric unit being determined from subsequent Fourier analysis. The structure was refined by least squares methods to an  $R$ -factor of 0.10 using isotropic temperature factors. At this stage, the positions of all the hydrogen atoms were determined from a difference map and the structure refined to an  $R$ -factor of 0.0266 using anisotropic temperature factors for all the non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms. The figure of merit:  $s = [\Sigma W\Delta^2/(m-n)]^{1/2}$  for the final data was found

Table 2. Fractional atomic coordinates and isotropic thermal parameters for the hydrogen atoms. Estimated standard deviations in parentheses.

Atom	x	y	z	B
H 1	0.293(3)	0.432(2)	0.126(1)	3.9(2)
H 2	0.525(3)	0.610(2)	0.173(1)	4.1(3)
H 3	0.349(2)	0.682(2)	0.168(1)	3.9(3)
H 4	0.503(3)	0.728(2)	0.115(1)	4.5(3)
H 5	0.356(2)	0.672(1)	-0.047(1)	3.6(2)
H 6	0.207(2)	0.561(1)	-0.191(1)	3.7(2)
H 7	0.109(2)	0.451(1)	-0.181(1)	3.7(2)

to be 1.69. The positional parameters for the non-hydrogen atoms were corrected for librational effects according to the method of Schomaker and Trueblood.<sup>12</sup> The r.m.s. value of the  $\Delta U$ 's were found to be  $4.02 \times 10^{-4}$  Å<sup>2</sup> and  $2.92 \times 10^{-4}$  Å<sup>2</sup> for the isothiazole and sulfate moieties, respectively.

The final parameters are given in Tables 1 and 2. Tables of the observed and calculated structure factors are available from the authors.

## DESCRIPTION AND DISCUSSION

The labelling of the atoms is given in Fig. 1 whereas bond lengths and angles are given in Table 3. The S2-C3 bond length of 1.7352 Å is in good agreement with the mean value of such bond lengths as given in Ref. 6. The mean values of the N-S and N-C bonds are given to be 1.658(7) and 1.320(4) Å, respectively, whereas those distances in the present study are found to be 1.6828(5) and 1.3446(7) Å.

Table 1. Fractional atomic coordinates multiplied by 10<sup>5</sup> and thermal parameters multiplied by 10<sup>4</sup> for the non-hydrogen atoms in 3-methyl-5-amino-isothiazole-sulfate. The anisotropic temperature factor is given by  $\exp - 2\pi^2(U_{11}a^*h^2 + \dots + 2U_{12}a^*b^*hk + \dots)$ . Estimated standard deviations are given in parentheses.

Atom	x	y	z	U <sub>11</sub>	U <sub>22</sub>	U <sub>33</sub>	U <sub>12</sub>	U <sub>13</sub>	U <sub>23</sub>
S2	17450(0)	40066(1)	-1094(0)	169(1)	118(1)	170(0)	17(0)	65(0)	-36(0)
N2	27766(2)	47357(1)	7812(1)	195(1)	209(1)	128(0)	43(0)	42(0)	45(0)
C1	31505(8)	60671(5)	-2459(4)	144(2)	132(2)	129(2)	3(2)	26(2)	-1(2)
C2	34675(8)	57927(6)	6218(3)	139(2)	195(3)	123(1)	37(2)	21(2)	-9(2)
C3	21590(6)	51714(4)	-7517(3)	133(2)	119(1)	119(1)	9(1)	31(1)	10(1)
N1	15478(6)	51471(4)	-15989(3)	215(2)	168(2)	118(1)	-34(1)	17(1)	0(1)
C4	44219(6)	65413(4)	13509(3)	186(1)	328(0)	161(1)	43(1)	0(1)	-81(1)
S1	50000	28289(5)	25000	135(1)	90(2)	119(1)	0(1)	32(1)	0(1)
O1	48419(6)	20958(4)	32432(3)	285(1)	269(1)	383(1)	116(1)	191(1)	224(1)
O2	33418(8)	35905(6)	22796(4)	357(2)	434(3)	175(1)	270(2)	117(1)	133(2)

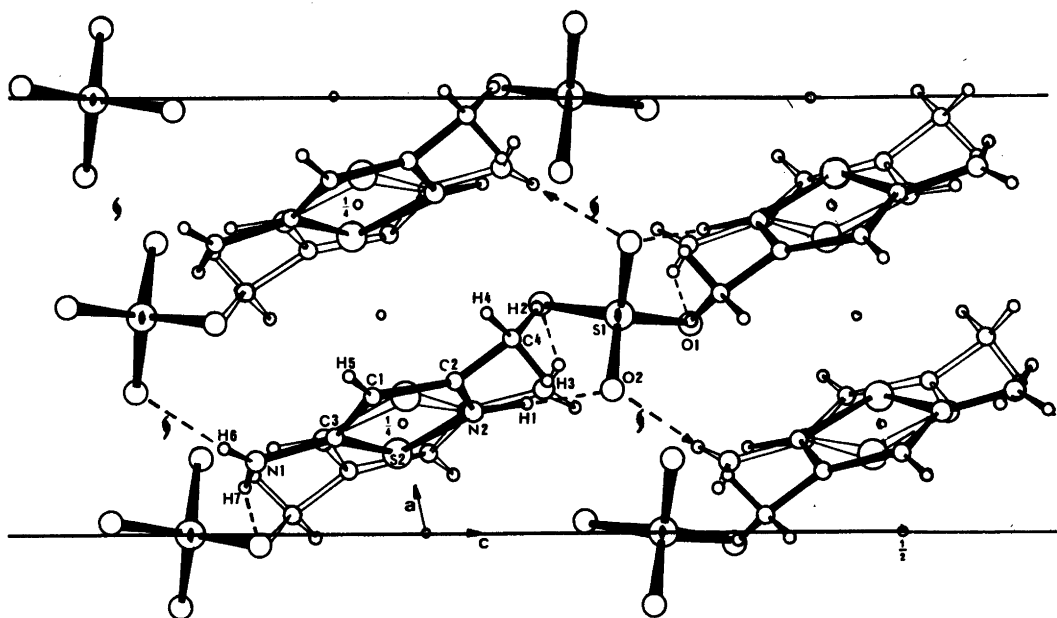


Fig. 1. Molecular packing in the crystals of 3-methyl-5-aminoisothiazole-sulfate as seen down the *b*-axis.

These elongations as well as the double bond character of the C3–N1 bond (1.3349(6) Å) are in accordance with the protonization of the N2-atom:

Table 3. Bond lengths and angles in 3-methyl-5-amino-isothiazole-sulfate. Estimated standard deviations given in parentheses.

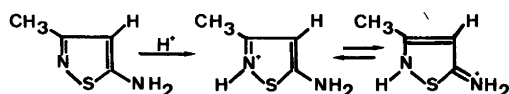
Bond lengths (Å)

	Uncorr.	Corrected
S2–N2	1.6802	1.6828(5)
S2–C3	1.7300	1.7352(4)
N2–C2	1.3413	1.3446(7)
C1–C2	1.3879	1.3916(6)
C1–C3	1.4010	1.4030(6)
C2–C4	1.4902	1.4924(7)
C3–N1	1.3319	1.3349(6)
S1–O1	1.4679	1.4839(4)
S1–O2	1.4809	1.5030(4)
N2–H1	0.88(2)	
C1–H5	0.90(2)	
N1–H6	0.86(2)	
N1–H7	0.83(2)	
C4–H2	0.91(2)	
C4–H3	0.99(2)	
C4–H4	1.03(2)	

Table 3. Continued.

Bond angles (°)

O1–S1–O2	109.07(4)	S2–N2–H1	115(1)
O1–S1–O11	110.99(5)	C2–N2–H1	130(1)
O1–S1–O22	109.36(3)	C2–C1–H5	125(1)
O2–S1–O22	108.96(6)	C3–C1–H5	123(1)
C3–S2–N2	91.36(3)	C2–C4–H2	110(1)
S2–N2–C2	113.46(3)	C2–C4–H3	108(1)
N2–C2–C1	113.26(4)	C2–C4–H4	112(1)
C2–C1–C3	111.84(4)	H2–C4–H3	106(2)
C1–C3–S2	110.02(3)	H2–C4–H4	112(2)
C2–C3–N1	121.31(3)	H3–C4–H4	108(2)
N2–C2–C4	119.50(5)	C3–N1–H6	118(1)
C1–C2–C4	127.22(5)	C3–N1–H7	117(1)
C1–C3–N1	128.67(4)	H6–N1–H7	118(2)



The effect of the protonation on the N2 atom is furthermore apparent in the increase in the angle at N2 as well as the decrease in the neighbouring angles at S2 and C2. In general the situation may be compared to that in the crystal structure of 2-

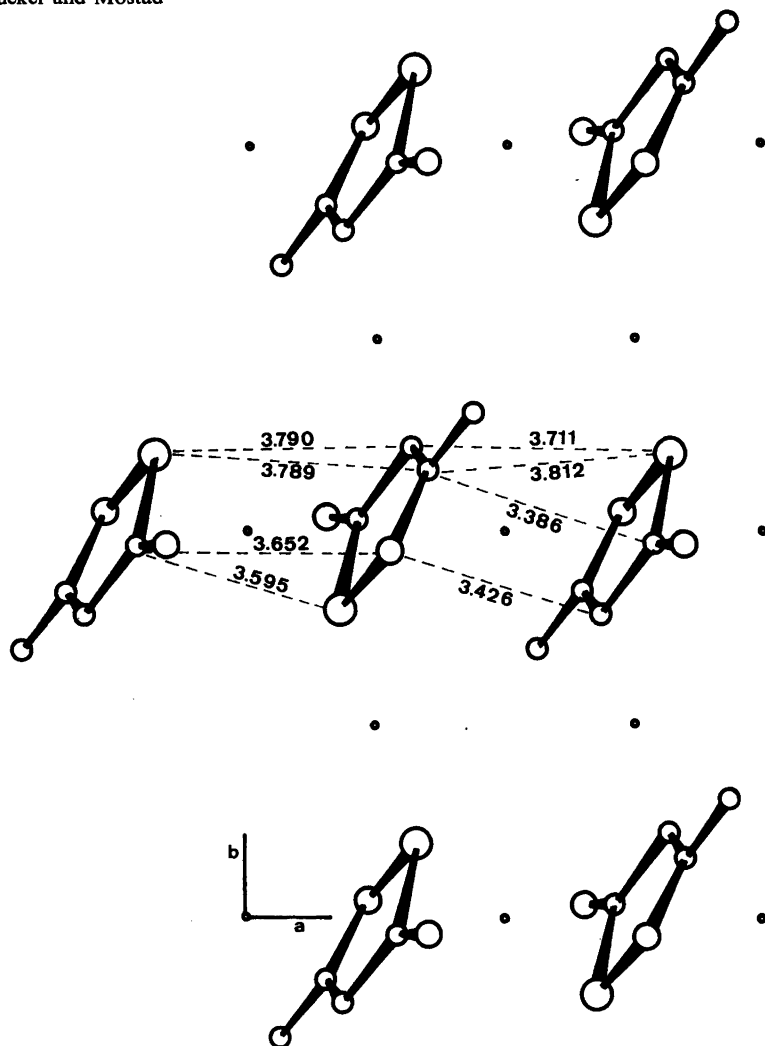


Fig. 2. Stacking of the 3-methyl-5-amino-isothiazole rings in crystals of the sulfate complex as seen down the *c*-axis.

aminopyrimidine·HCl.<sup>13</sup> The sum of the internal angles in the ring is 539.95° as compared to 540° in a planar pentagon. However, a least squares plane through the four ring atoms S2, N2, C2 and C1 indicates a significant envelope form. The atomic deviations from the least squares plane are given in Table 4. The asymmetry in the external angles at N2, C2 and C3 may well be explained by intramolecular non-bonded interactions. Thus the distances between the pairs of hydrogen atoms H1–H2, H1–H3, H4–H5 and H5–H6 are all close to 2.7 Å.

The conformation about the C2–C4 bond is such as to bring the H4 atom only slightly out of the ring

Table 4. Atomic deviations from a least squares plane through atoms S2, N2, C1 and C2.

Atom	Å
S2	–0.0011
N2	0.0052
C1	0.0037
C2	–0.0067
C3	0.0383
C4	–0.0014
N1	0.1088
H6	–0.137
H7	0.025

Table 5. Geometry in the hydrogen bonding system in crystals of 3-methyl-5-amino-isothiazole-sulfate.

D	H	A		D...A	H...A	$\angle \text{D-H}\cdots\text{A}$	$\angle \text{H}\cdots\text{A-S}$
N1	H7	O1	$(-\frac{1}{2}+x, \frac{1}{2}-y, -\frac{1}{2}+z)$	2.7991(6)	2.03(2)	153(2)	110.5(5)
N1	H6	O2	$(x, 1-y, -\frac{1}{2}+z)$	2.8094(6)	1.95(2)	170(2)	126.0(5)
N2	H1	O2	$(x, y, z)$	2.6483(6)	1.77(2)	175(2)	117.1(6)

plane, the C1-C2-C4-H4 angle being  $-8^\circ$ . Similarly, both the hydrogen atoms H6 and H7 are close to the ring plane. As may be seen from Table 4, the N1 atom is somewhat above the ring plane due to the slight envelope form of the ring. Nor is the aminogroup strictly planar as the N1 atom is situated 0.14(1) Å above a least square plane through the atoms C3-H6-H7. The two torsional angles S2-C3-N1-H6 and S2-C3-N1-H7 are found to be  $-160(1)$  and  $-9(1)^\circ$ , respectively.

Also in the sulfate ion there are significant variations in bond lengths and angles. The longest S-O bond is 1.5030 Å and involves the O2 atom which is engaged in two hydrogen bonds, whereas the shortest S-O distances of 1.4839 Å is to the oxygen atom O1 which is engaged in only one hydrogen bond. Finally the angle between the two short bonds (O1-S1-O11) is  $110.99^\circ$  as compared to the angle between the two long bonds (O2-S1-O22) of  $108.96^\circ$ .

The packing of the ions in the crystal as seen down the *b*-axis is depicted in Fig. 1 where also the hydrogen bonding is indicated. The geometry of the hydrogen bonding is given in Table 5.

Each isothiazole molecule is hydrogen bonded to three sulfate ions which in turn are connected to six different isothiazole moieties through such bonds. The crystals display a layered structure with all sulfate ions lying in planes containing the screw and rotation axes and the isothiazole molecules situated between these planes in stacked pairs related by the centers of symmetry; the shortest distance being 3.386 Å (C2-C3). The distance between the two ring planes is found to be 3.35 Å. The stacking of the rings in these layers is depicted in Fig. 2 where some of the distances are also indicated.

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