

## Sulfamethoxypyridazine의 결정 및 분자구조\*

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## The Crystal and Molecular Structures of Sulfamethoxypyridazine\*

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**요 약.** Sulfamethoxypyridazine,  $C_{11}H_{12}N_4O_3S$ 의 결정 및 분자구조를 X-선 사진 회절법으로 구명하였다. 결정구조는 직접법으로 탐혀 최소자승법으로 정밀화 하였으며 2615개의 회절 반점에 대한 최종  $R$  값은 0.085이었다. 비대칭단위내의 분자 두개 A와 B는 S-N(2) 결합에 대한 형태가 서로 다른 형태 이성질체를 이루며, N(2A)H...N(3B)와 N(2B)H...O(1A) 수소 결합으로 연결되어 있다. 벤젠과 피리다진 고리의 면들이 이루는 각은 분자 A에서는  $89^\circ$ , 분자 B에서는  $77^\circ$ 이다.

**ABSTRACT.** The crystal structure of sulfamethoxypyridazine has been solved by the direct method and refined by least squares methods from three-dimensional data collected by the multiple-film technique to a final residual of 8.5 %. Two molecules (A and B) in one asymmetric unit are different each other in the conformation about S-N(2) bond, and are linked together by N(2A)H...N(3B) and N(2B)H...O(1A) S hydrogen bonds. Benzene and pyridazine rings make the angles of  $89^\circ$  and  $77^\circ$  for molecules A and B respectively.

### INTRODUCTION

The analysis of X-ray crystal structures of sulfanilamide derivatives which usually have antibacterial activities has been undertaken by Professor C. H. Koo *et al.* Those are sulfapyridine<sup>1</sup>, sulfisoxazole<sup>2</sup>, sodium sulfisoxazole hexahydrate<sup>3</sup>, sulfaguanidine monohydrate<sup>4,5</sup>, sulfadiazine<sup>6</sup> and sulfadimethoxine<sup>7</sup>.

The crystal structure determination of sulfamethoxy pyridazine (N'-(6-methoxy-3-pyridazinyl)sulfanilamide) has been attempted to compare its molecular structure with those of other

previously determined structures, especially conformation of sulfanilamide group, conformation about S-N(2) bond and interplanar angle of two aromatic rings. It is also of interest to study the hydrogen bonding systems involving amino and imino hydrogens.

The molecular conformations of two crystallographically independent molecules in one asymmetric unit are also compared each other.

### EXPERIMENTAL

Transparent colorless crystals elongated along the  $a$  axis were obtained by slow evaporation of an acetone solution at room temperature.

Oscillation and Weissenberg photographs in-

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licated the monoclinic space group  $P2_1/C$ . Unit cell parameters were measured from the  $h0l$  and  $hk0$  Weissenberg photographs calibrated with superimposed NaCl powder pattern as a standard using  $\text{CuK}\alpha$  radiation. The crystal density was measured by the flotation method in a mixture of benzene and carbon tetrachloride. The crystal data are given in Table 1.

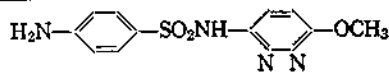
Intensity data were collected from equi-inclination Weissenberg photographs by use of multiple film method. The layers from  $0kl$  to  $7kl$  and from  $h0l$  to  $h1l$  were recorded. The approximate sizes of the crystals used for the data collection for the  $a$  and  $b$  axes were  $0.5 \times 0.3 \times 0.2$  mm and  $0.4 \times 0.2 \times 0.2$  mm respectively. The relative intensities were visually estimated by comparison with a calibrated density scale.

The intensities were corrected for spot-shape, Lorentz and polarization effects, and reduced to structure factors without corrections for absorption. The structure factors for various layers were placed on a common scale by correlating those of the equivalent reflections and then on an absolute scale by Wilson method<sup>8</sup>. A total of 2615 observed independent reflections were used in the structure analysis.

The structure was solved by MULTAN program<sup>9</sup> with reflections whose  $E$  values are greater than 1.30. The set with the best figure of merit revealed the positions of all 38 non-hydrogen atoms among the fifty highest peaks on Fourier map. Structure factors based on 38 atoms with 2615 reflections gave an initial  $R$  of 0.33.

The structure was refined by standard least squares method. After six cycles of block-diagonal least squares refinements, the Fourier and difference Fourier syntheses were made to assign four nitrogen atoms in two pyridazine rings, and to locate hydrogen atoms. The atomic species of N(3), N(4), C(8) and C(9) could be readily discerned from comparison of the electron densities. The atoms that had the higher electron densities were assigned as N(3) and N(4) according to the method suggested by Stout and Jensen.<sup>10</sup> The positions of the hydrogen atoms except H(N1) were located on the successive difference Fourier maps; they were included in the further refinements with fixed temperature factors equal to that of atom to which they were attached. Refinements were continued by several cycles of the full-matrix least squares using anisotropic structure factor calculations, and gave  $R$  value of 0.085 for all 2615 observed reflections with Hughes weighting scheme<sup>11</sup>. The scattering factors for the sulfur, oxygen, carbon and nitrogen atoms were taken from Cromer and Waber<sup>12</sup> and those for hydrogen atom were assigned by Stewart, Davidson and Simposon.<sup>13</sup> Table 2 gives the final positional and thermal parameters of atoms\*.

Table 1. The crystal data of sulfamethoxypyridazine. Sulfamethoxypyridazine,  $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_3\text{S}$ , M. W. = 280.32.



Unit cell parameters :

$a = 8.70$  (2) Å

$b = 11.08$  (4)

$c = 26.64$  (4)

$\beta = 100.5$  (8)°

Space group :  $P2_1/C$

$Z = 8$

Density : calculated value ;  $1.47 \text{ g} \cdot \text{cm}^{-3}$

measured value : 1.41

## RESULTS AND DISCUSSION

The molecular conformation of two independent molecules are depicted in Fig. 1 with atomic numbering. Two molecules are contained in each asymmetric unit and distinguished by

\* Observed and calculated structure factors can be obtained from the authors.

Table 2. Final positional and thermal parameters for sulfamethoxypyridazine. The positional parameters are given as fractional coordinates ( $\times 10^4$  for the non-hydrogen atoms and  $\times 10^2$  for hydrogen atoms with the variances of atomic positions ( $\times 10^4 \text{ \AA}$ )). The anisotropic thermal parameters ( $\times 10^4$ ) are defined as  $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$ . For each atom, the parameters are given on the first line for A and on the second for B molecule respectively.

	<i>x</i>	<i>y</i>	<i>z</i>	$\sigma$		<i>x</i>	<i>y</i>	<i>z</i>	$\sigma$
S	7395	3156	4345	18	C ( 8)	7343	197	5615	88
	9159	1736	2785	17		9950	-849	3312	86
O ( 1)	7968	3065	3875	53	C ( 9)	6918	-192	5557	74
	9268	3001	2826	53		9863	-1894	3531	106
O ( 2)	8235	3913	4720	53	C (10)	6248	685	5826	88
	10167	1096	2521	58		9234	-1956	3978	78
O ( 3)	5858	327	6267	57	C (11)	5212	1247	6556	133
	9205	-3009	4200	60		8471	-3051	4649	110
N ( 1)	844	4725	3850	76	H (N1)	8	54	41	
	2693	348	1962	79		20	4	22	
N ( 2)	7466	1766	4532	60	H (N2)	78	11	44	
	9543	1326	3385	58		93	16	36	
N ( 3)	6398	2169	5253	74	H (C2)	48	21	38	
	8824	52	3953	57		81	0	20	
N ( 4)	5992	1762	5685	57	H (C3)	23	27	36	
	8776	-1017	4182	62		53	-7	18	
C ( 1)	5441	3584	4218	62	H (C5)	31	57	45	
	7247	1335	2540	66		36	21	56	
C ( 2)	7344	2836	3926	71	H (C6)	57	53	45	
	6949	441	2193	76		64	25	29	
C ( 3)	2806	3258	3812	77	H (C8)	79	-3	48	
	5422	126	2000	97		104	-1	30	
C ( 4)	2365	4355	3987	72	H (C9)	72	-9	58	
	4193	662	2160	75		101	-26	33	
C ( 5)	3497	5036	4276	77	H (C11)	63	16	67	
	4487	1568	2516	84		85	-39	48	
C ( 6)	5002	4650	4393	72	H' (C11)	51	5	68	
	6020	1888	2716	80		72	-30	43	
C ( 7)	7044	1409	4986	57	H'' (C11)	40	17	63	
	9435	151	3544	68		88	-23	49	

	$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$		$\beta_{11}$	$\beta_{22}$	$\beta_{33}$	$\beta_{12}$	$\beta_{13}$	$\beta_{23}$	
S	122	41	9	3	4	1		N (2)	189	40	12	16	9	5
	125	72	11	-10	8	- 0			148	47	10	- 2	2	- 5
O (1)	147	80	12	11	17	5		N (3)	200	92	10	19	11	3
	176	94	14	-22	10	0			152	52	12	11	10	4
O (2)	159	71	14	- 3	-10	- 5		N (4)	247	74	11	- 2	16	- 1
	128	150	15	9	15	- 1			155	66	14	9	9	- 0
O (3)	348	79	15	- 9	26	8		C (1)	146	27	9	11	6	- 3
	263	78	21	24	3	- 2			128	65	10	- 7	6	- 4
N (1)	148	78	26	- 5	14	4		C (2)	138	53	10	-13	3	- 1
	146	125	19	-13	3	-10			148	90	13	- 0	8	-14

C (3)	153	56	16	-24	1	5		112	87	11	-1	1	-3
	145	171	17	0	9	-22	C (8)	220	52	15	13	15	9
C (4)	133	49	12	3	9	9		236	76	11	23	6	-2
	153	75	12	3	1	-6	C (9)	274	76	11	-3	20	4
C (5)	167	85	15	8	13	-17		237	110	20	36	15	-5
	163	70	19	-2	8	5	C (10)	235	44	9	-23	4	-3
C (6)	184	51	11	18	-0	-7		171	68	15	24	0	-1
	143	85	15	-2	5	-8	C (11)	435	134	17	8	49	-2
C (7)	178	13	13	5	2	-1		197	110	22	7	13	10

Table 3. Least square best planes in sulfamethoxypyridazine. Plane constants with respect to orthogonal axes.  $L$ ,  $M$ ,  $N$  are direction cosines of the normal in  $LX+MY+NZ-D=0$ , where  $W$ ,  $Y$ ,  $X$  are in Å.

	Distance from best plane (Å)		Plane constant	
	A	B	A	B
Benzene ring plane				
C (1)	-0.01	-0.02		
C (2)	0.01	0.01		
C (3)	-0.01	-0.00		
C (4)	0.00	0.01	L = -0.352	-0.099
C (5)	-0.01	-0.00	M = -0.439	-0.674
C (6)	0.01	0.01	N = 0.827	0.732
S	-0.10	-0.01	D = 6.174	3.238
N (1)	-0.04	-0.01		
Pyridazine ring plane				
C (7)	-0.00	0.02		
C (8)	-0.00	-0.00		
C (9)	0.00	-0.00	L = 0.825	0.828
C (10)	0.00	-0.01	M = 0.255	0.136
N (3)	0.01	-0.02	N = 0.504	0.543
N (4)	-0.01	0.02	D = 9.648	10.007
N (2)	-0.01	0.17		
O (3)	0.03	0.02		

labelling them A and B. The bond lengths and angles are given in Fig. 2. The standard deviations of bond lengths and angles involving sulfur atom have average values of  $\pm 0.006$  Å and  $\pm 0.3^\circ$  respectively. The average standard deviations of bond lengths and angles are  $\pm 0.01$  Å and  $\pm 0.6^\circ$  respectively, and are not shown separately.

Two benzene rings are planar within experimental error (see Table 3.). The S and N(1) atoms of A molecule are slightly out of the

benzene plane. The C-C bond lengths in the benzene rings vary from 1.35 to 1.40 Å with a mean value of 1.37 Å. The C(4)-N(1) bond lengths of 1.37 Å for A molecule and 1.36 Å for B molecule, which are significantly shorter than the corresponding normal single bond length of 1.44 Å and in good agreement with the values reported in sulfanilamides<sup>14-17</sup>, show an appreciable amount of double bond character.

Bonding around the sulfur atom is distorted from the ideal tetrahedral. The bond lengths



Fig. 1. ORTEP stereoscopic pair showing the molecular configuration of the sulfamethoxypyridazine with atomic numbering.

around the sulfur atom agree with the value reported in the related compounds.

The C(7)-N(2) bond lengths of 1.382 Å for A and 1.377 Å for B molecule indicate double bond character. Those double bond characters seem to be due to the conjugation of  $P_z$  electron on the nitrogen atom with the  $\pi$ -system of the pyridazine ring.

The six-membered pyridazine rings are almost planar (Table 3) and show the aromatic character. The N-N bond lengths of two molecules are same as 1.34 Å and are of the same order as the

length of similar bond in other pyridazine ring compound, e. g. 1.36 Å found by Cuckla and Smith<sup>18</sup> in 6-amido-3-pyridazone. The N-C bond lengths range from 1.26 to 1.30 Å, which are close to the mean value between N-C double bond length of 1.21 Å in isocyanic acid<sup>19</sup> and hybrid N-C bond length of 1.37 Å in pyridine<sup>20</sup>. Similar N-C bond lengths have been found in 2-amino-4,6-dichloropyrimidine<sup>21</sup> and 4-amino-2,6-dichloropyrimidine.<sup>22</sup> The C(8)-C(9) bond lengths are significantly shorter than C(7)-C(8) and C(9)-C(10) bond lengths in both molecules.



Fig. 2. Bond lengths and angles of sulfamethoxyridazine. (a) bond lengths (Å), (b) valence angles (°).

forms with different direction; Torsion angles are  $-66.6^\circ$  for

A and 58.5° for B molecule respectively. The benzene and pyridazine ring planes make the angle of 89.2° for A and 77.0° for B molecule respectively. The conformational angles of C(1)-S-N(2)-C(7) in related compounds are compared in Table 5.

Table 4. Selected torsion angles ( $^{\circ}$ ) in sulfamethoxypyridazine.

	A	B
C (2)-C (1)-S-O (1)	62.8	140.2
C (2)-C (1)-S-O (2)	-169.0	6.7
C (2)-C (1)-S-N (2)	-46.4	-109.3
C (6)-C (1)-S-O (1)	-115.7	-43.0
C (6)-C (1)-S-O (2)	12.5	-176.5
C (6)-C (1)-S-N (2)	135.1	67.6
C (1)-S-N (2)-C (7)	-66.6	58.5
S-N (2)-C (7)-C (8)	-173.3	42.4
S-N (2)-C (7)-N (3)	7.7	-139.4
N (4)-C (10)-O (3)-C (11)	-2.0	6.7
C (9)-C (10)-O (3)-C (11)	178.0	-177.0

Table 5. Comparison of the conformational angle of C (1)-S-N (2)-C (7) and the angle between two aromatic rings in related compounds.

	conformational angle about S-N (2) bond	angle between two aromatic rings
Sulfamethoxypyridazine		
A	-67	89
B	59	77
Sulfapyridine	-71	84
Sulfaguanidine monohydrate	-76	—
Sulfadiazine	77	76
Sulfadimethoxine	-61	78
Sulfisoxazole	54	69
Sodium sulfisoxazole hexahydrate	73	60
Sulfathiazole*		
IA <sup>23</sup>	**	101
IB	**	99
II <sup>24</sup>	80	90
IIIA <sup>23</sup>	78	92
IIIB	76	100

\* The thiazole ring is not aromatic. \*\*The calculation of conformational angle from the reported coordinates does not give any proper value.

with the angles between the two aromatic planar rings in these compounds. As shown in Table 5, the molecules in these compounds maintain *gauche* forms with torsion angles in the range

of  $54^{\circ}$  to  $80^{\circ}$  and two rings are almost perpendicular to each other with mean interplanar angle of  $85^{\circ}$ . These differences of the conformation and interplanar angles may be attributed to different hydrogen bonding schemes and different molecular environments in these compounds.

The crystal structure of sulfamethoxypyridazine is shown in Fig. 4. All amino and imino hydrogen atoms are involved in six hydrogen bonds as all donors with distances in the range of 2.82 to 3.21 Å (see Fig. 3). Both N(1) atoms of the amino groups of A and B molecules participate in four hydrogen bonds with oxygen atoms; N(1A)H...O(1A)a, N(1A)H...O(3B)b, N(1B)H...O(1B)c and N(1B)H...O(2B)a. The molecules A and B are connected each other through two strong hydrogen bonds involving imino hydrogen atoms, one is N(2A)H...N(3B) with N...N distance of 2.84 Å and the other N(2B)H...O(1A) with N...O distance of 2.82 Å. The oxygen atom O(1A) is thus bonded to two different hydrogen bonds with N(1A) and N(2B) respectively. Atoms O(2A), O(3A), N(3A),

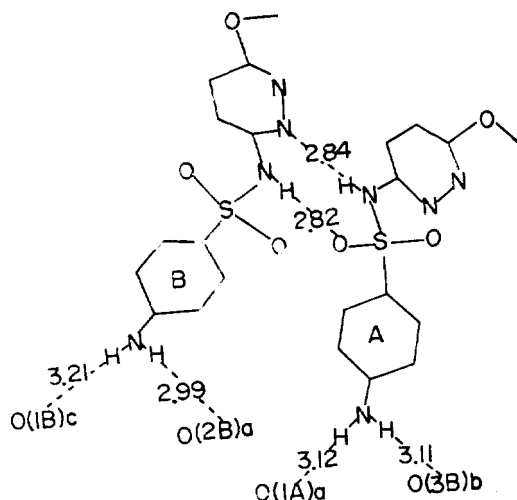


Fig. 3. The hydrogen bonding in sulfamethoxypyridazine. symmetry code: (a)  $x-1, y, z$ ; (b)  $x-1, y-1, z$ ; (c)  $-x+1, y-0.5, -z+0.5$ .

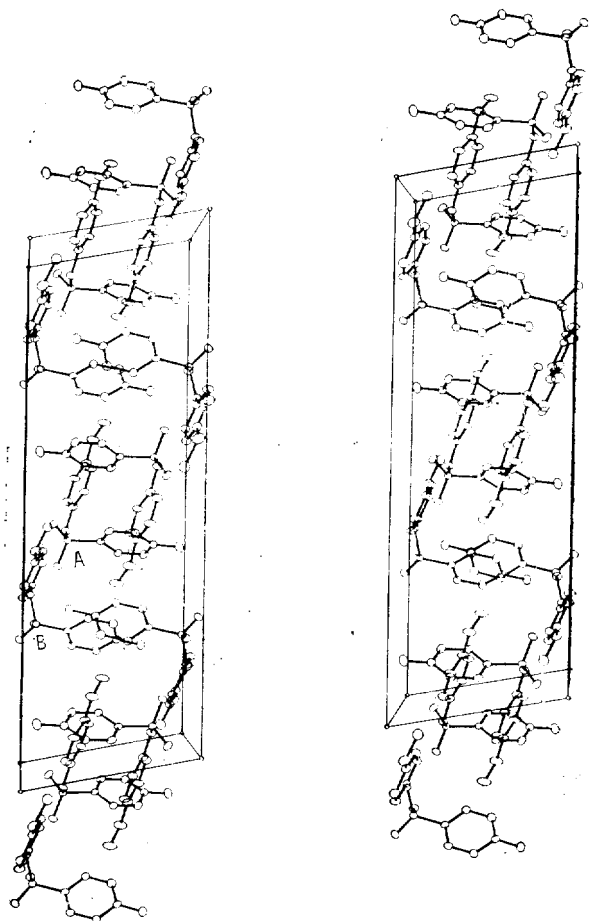


Fig. 4. The crystal structure of sulfamethoxypyridazine, origin in the remote lower right corner,  $a$  pointing to the left,  $c$  up and  $b$  forward. The reference molecules (Table 2) are indicated.

N(4A) and N(4B) do not take part in any hydrogen bonds.

Apart from the hydrogen bonds, the molecules are held together by the van der Waals interactions. There are 28 intermolecular atomic distances less than 3.5 Å.

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