

## The Crystal Structure of Methanesulfonanilide

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Methanesulfonanilide (MSA),  $C_6H_5-NH-SO_2CH_3$ , is closely related to a series of new compounds possessing interesting blood-pressure-control activity. This biological activity is thought to be due to the hydrogen of the phenyl-N-H portion of the molecules. A detailed study of MSA has been carried out to see whether it would be possible to reveal the complete stereochemistry around this nitrogen atom. The study has been highly successful in this respect. The crystals of MSA are monoclinic, space group  $P2_1/c$ , with  $a=9.203 \pm 0.007$ ,  $b=8.217 \pm 0.005$ ,  $c=11.026 \pm 0.006$  Å, and  $\beta=103.71 \pm 0.06^\circ$ . The unit cell contains four molecules. Three-dimensional intensity data were obtained with an automatic single-crystal diffractometer. The structure was solved by the direct method of Beurskens and refined by least-squares methods with anisotropic temperature factors. All hydrogen atoms were clearly revealed in a three-dimensional  $\Delta F$  difference synthesis. Pairs of MSA molecules form centrosymmetric dimers through a symmetrical pair of hydrogen bonds. The crystal structure is a three-dimensional packing of these dimeric molecules. The amine hydrogen clearly sticks out alone on one side of the plane of the phenyl group while the whole methylsulfone group is on the opposite side of the plane. The amine hydrogen of the monomer thus appears to be readily available to a receptor molecule during biological action. The molecule and, particularly, the phenyl ring vibrates and librates as a rigid body in the crystal.

### Introduction

The incorporation of the alkylsulfonamido group into the benzene ring of phenethanolamines provides a series of compounds possessing interesting blood-pressure-control activity (Larsen & Lish, 1964). Indeed, their intensity of action and biological profile are strikingly similar to those of certain well-known phenolic phenethanolamines, *e.g.* phenylephrine and epinephrine. In otherwise similarly constructed molecules the alkylsulfonamido group exhibits comparable acidity to that of the phenolic hydroxyl group. Then, assuming a trigonal arrangement around the nitrogen atom, it is suggested that the phenyl-N-H portion of the sulfonanilide can align itself, in relation to a receptor site, in a manner closely approximating the phenyl-O-H grouping both with respect to bond distances and bond angles. The stereochemistry of these molecules, particularly in the vicinity of the phenyl-N-H and phenyl-O-H portions, would thus be of extreme importance in formulating an explanation of their biological activity.

Following a suggestion of Larsen (1965) it was agreed that a study of the crystal structure and stereochemistry of methanesulfonanilide would be a useful start on this problem. Methanesulfonanilide has no value as a blood-pressure-control agent. However, it is a simple compound related to compounds with biological activity, and its study should reveal the possibility of locating the hydrogen atom on such sulfonamido groups directly from the X-ray diffraction data. If this hydrogen atom could be located, then most other aspects of the molecule's stereochemistry would probably also be forthcoming.

Although sulfones have been investigated, and sulfamic acid to some extent, there has been rather little study of sulfonamide groups. Trueblood & Mayer (1956) investigated sulfamide. More recently, O'Connor & Maslen (1965) have reported the crystal structure of  $\alpha$ -sulfanilamide, Alléaume & Decap (1965) have examined the structures of  $\beta$ - and  $\gamma$ -sulfanilamide, and O'Connell & Maslen (1967) have presented detailed findings on the  $\beta$  polymorph. In these three polymorphs the S-O, S-N, and S-C distances are very similar.

This paper reports the results of a detailed study of the crystal and molecular structure of methanesulfonanilide in which the complete stereochemistry of the molecule (in the crystal) has been revealed.

### Crystal data

Methanesulfonanilide (hereafter designated MSA)\*,  $C_6H_5-NH-SO_2CH_3$ , is a nicely crystalline solid, m.p.  $97.5-100.5^\circ$  (corr.). The material supplied had been recrystallized from a 50-50 vol. mixture of water and isopropyl alcohol, and directly yielded suitable crystals for study. The cell constants were determined from single-crystal diffractometer measurements of 10 moderately high-angle reflections ( $2\theta=20-52^\circ$ ) with Cu  $K\alpha$  (1.5418 Å) radiation. For these measurements the tube's line focus was used, rather than the spot focus, in order to minimize the contribution of the profile of the focal spot to the profile of the reflection and thereby improve the precision of measurement of

\* The author gratefully thanks Dr A. A. Larsen and the Mead Johnson Research Center, Evansville, Indiana, for the generous sample of methanesulfonanilide used in this study.

Table 1. Observed and calculated structure factors†

The data are separated into groups having common k & l values. The three columns of each group list values of h, 10F<sub>o</sub> and 10F<sub>c</sub> in that order. An asterisk indicates an unobserved reflection.

Table with multiple columns of data organized by k and l values. Each group contains three columns: h, 10F<sub>o</sub>, and 10F<sub>c</sub>. Groups are labeled with k and l values such as k=0, l=0; k=1, l=2; etc. Asterisks indicate unobserved reflections.

† Copying errors: 10F<sub>o</sub> for 022 should be 734 instead of 73; reflections 432, 555, 9-5-10, 175, and 415 should not be marked as unobserved. Also note that part of the data for h-6-12, all data for h-6-13 and h-7-1, and 078 are out of the regular order of the table and are to be found in the last three columns of the third page of the table.



Table 1 (cont.)

$k = 8, l = 3$	1 101 105 -1 112 116 0 24* 46 1 40 44 -1 25 30 2 25 -25 -2 22* 2 5 21* 32 4 23* 46 -4 23* 2 4 36 35 5 34 25 -5 35 -78 6 43 46 -6 23* 11 7 24* 1 -7 24* 8 8 25 -12 -8 25* 10 -9 27 27	1 45 41 -1 44 46 2 25* 32 -2 35 35 -3 24* 6 4 25* 9 -4 26* 4 5 27* 5 -5 25* -1 -6 28* 26 -7 27* 3 -8 28* 11	$k = 9, l = 3$	5 26* 12 -5 26* -45 -6 26* 32 -7 26* 18	$k = 9, l = 4$	0 67 73 1 27 24 -1 49 -66 2 65 69 -2 25* -43 3 101 111 -3 82 -71 4 24* 4 -5 31 -40 6 25* 43 -6 27* 33	$k = 9, l = 5$	0 24* -9 1 24* 11 -1 24* -35 2 24* 19 -2 23* 16 3 25* 36 -3 23* -2 4 23* -48 -4 24* -7 5 25* -22 -5 25* -19 6 25* 20 -6 25* 11	$k = 9, l = 6$	0 24* -4 1 41 -39 -1 24* 11 2 24* 21 -2 24* -14 -2 24* -2 -2 24* -2 3 25* -10 -3 25* -18 4 25* -1 5 24* -3	$k = 10, l = 2$	0 60 -53 1 24* -14 -1 47 -44 2 62 -61 5 53 44 -5 78 68 -6 56 52	$k = 10, l = 3$	1 25* -1 2 28 -5 3 58 -60	$k = 10, l = 4$	0 25* -15 1 34 -37 -1 57 -55 2 25* 32 -2 65 -60 3 24* -2 -3 24* -63 4 37 32 -4 34 31 -5 99 96 -6 49 43	$k = 10, l = 5$	0 27* -17 -1 25* -3 -1 25* 6 2 25* -11 -2 24* -2 3 25* 10 -3 25* -18 -4 25* -1 -5 26* 2	$k = 10, l = 6$	0 45 -38 1 25* -25 -1 58 -57 2 42 -44 -2 44 -44 -3 25* -4 -4 35 35 -5 68 65	$k = 6, l = 12$	5 36 -95 -5 62 53 6 34 35 -6 28 43 -7 26 85 -7 26 85 8 71 75 -8 90 -84 9 75 75 -9 33 -24 -10 25* -16	$k = 6, l = 13$	-1 25* -3 -2 25* -12 -3 25* -14 -4 25* 8	$k = 7, l = 0$	1 202 -203 2 237 -239 3 143 -134 4 128 -123 5 152 -149 6 24* 23 7 29* 2 8 128 125 9 26* 24 10 25* 17	$k = 7, l = 1$	0 24* 11 1 34 -33 -1 25* -13 2 28 23 -2 24* -8 3 27* -8 -3 26* -10 4 25* 1 -4 25* -11 -4 25* -11 -5 26* -3 -6 26* 5	$k = 7, l = 2$	0 25* -2 1 24* -5 -1 25* 6 -2 25* 2 -3 25* 18 4 83 83	$k = 7, l = 3$	0 55 -60 1 21* 3 -1 40 -41 2 39 28 -2 24 -7 -3 42 -37 4 83 83	$k = 7, l = 4$	0 67 -67 -1 96 -97 -1 179 180 2 169 -171 -2 107 -105 3 178 -172 -3 53 47 4 45 -43 -4 38 32 5 62 -62 -5 34 32 6 33 37 -6 22* -13 -7 79 77 -8 106 104 -8 85 -87 -9 52 -53 -10 29 -22	$k = 7, l = 5$	0 24* 24	$k = 7, l = 6$	0 24* 24	$k = 7, l = 7$	0 27* 3 1 54 -61 -1 46 -43 2 53 47 -2 45 -43 3 23 29 -3 23 16 4 36 31 -4 36 31 -5 30 29 -6 23 21 -7 66 62 -8 91 -85 -9 56 -56	$k = 7, l = 8$	0 28 26
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angles  $2\theta$  and  $\phi$ . These data were then used for a least-squares determination of the cell constants and their estimated standard deviations by an IBM 7090 program adapted from the University of Washington 'Param' refinement program. Reflections of all types were observed except  $h0l$  with  $l$  odd and  $0k0$  with  $k$  odd. The crystal data on MSA are summarized below:  $a = 9.2034 \pm 0.0073$ ,  $b = 8.2167 \pm 0.0051$ ,  $c = 11.0255 \pm 0.0059$  Å,  $\beta = 103.708 \pm 0.064^\circ$ . Goodness of fit is 2.39.  $Z = 4$ ,  $M.W. = 171.22$ ,  $D_x = 1.41$  g.cm $^{-3}$ ,  $D_m = 1.40$  g.cm $^{-3}$ . \* Monoclinic, space group  $P2_1/c$ ;  $F(000) = 360$ .

Determination of the structure

The structure has been determined with Mo  $K\alpha$  intensity data obtained on a General Electric-Datex automatic single-crystal diffractometer by the moving-crystal, moving-counter technique ( $\theta$ - $2\theta$  scan). The crystal used for the final intensity data measured approximately  $0.4 \times 0.2 \times 0.2$  mm. Attenuation of the beam for measuring the strong reflections was accomplished by inserting calibrated packs of thin niobium foils, the number of foils per pack varying from 3 to 10 as required. All reflections were initially measured

with one foil in the beam for monochromatizing action. Since the diffraction power of the crystal slowly diminished from exposure to the X-ray beam, three standard reflections were measured after each group of 25 reflection measurements to provide a correction factor for this effect as well as for long-range inconsistency of the direct beam. All reflections in the molybdenum sphere out to  $\sin \theta = 0.5$  were measured, at which point intensities were either indistinguishable from background, or barely measurable. The total number of independent reflections measured was 2362. Each intensity measurement involved a scan over the reflection peak, a background measurement at each end of the scan range, and a measurement of the peak height. Simultaneously the measurements were continuously monitored by preparing a recorder chart trace. The peak height measurement is used in the data-reduction program to indicate which reflection intensities were so strong as to exceed the linear range of the scintillation counter and associated circuitry. The program causes the angular setting data for such reflections to be punched out on a new card ready for the remeasurement. Reflections whose backgrounds were highly unsymmetrical, as evidenced from the recorder chart trace, were also remeasured. In this instance about 70 reflections required remeasurement because of high intensity or highly unsymmetrical back-

\* Density by helium displacement. Physical Measurements Laboratory, Mellon Institute.

grounds, and the remeasurement was done manually (semi-automatically).

The diffractometric intensities were converted to relative structure factors with an IBM 7090 data-reduction program\* which applied the Lorentz and polarization corrections and calculated the standard deviations of the  $F_o$ 's. The program decides whether a reflection is observed or unobserved by comparison of the net count ( $I$ ) to its standard deviation,  $\sigma_I$ . If  $I_{\text{obs}} \leq \text{CON} \times \sigma_I$ , where CON (for confidence limit) can be chosen by the user, the reflection is considered as unobserved. CON=2 was used here, equivalent to a confidence limit of 95%. Additional expressions in the program are:

$$I = \text{DD} \times f_m \times (C_T - t' C_B),$$

$$\sigma_I^2 = (C_T + t' C_B) \times (\text{DD} \times f_m)^2 + I^2 [D(m-1)^2 + E],$$

$$F_{hkl}^2 = I / Lp,$$

and

$$\sigma_F^2 = \frac{1}{4} \times \sigma_I^2 \times \frac{1}{LpI}.$$

Definitions:

DD = scaling factor with respect to the standard reflection.

$m$  = number of filters used.

$f_m$  = filter factor for  $m$  filters.

$C_T$  = total counts in a scan of  $t$  seconds duration.

$C_B$  = total counts per  $x$  seconds at background.

$t'$  =  $t/x$ .

$D$  = estimated relative error in the filter factor for one filter (typically 0.000025).

$E$  = estimated relative error in the stability of the instrument (typically 0.000025).

$L$  = Lorentz factor.

$p$  = polarization factor.

When the intensity data from the 2362 measured reflections were processed by this program, 801 were less than their confidence threshold values and were considered unobserved reflections on this statistical procedure, while 1561 were listed as observed. Later, in the course of the least-squares refinement, the  $F_c$ 's of 83 of the unobserved reflections calculated greater than their  $F_o$ 's. These 83 reflections were then treated by the least-squares program as observed reflections and contributed to the refinement of the parameters. No correction was made for absorption ( $\mu R = 0.085$  for  $R = 0.025$  cm) or extinction.

Preliminary scale and temperature factors were derived from a Wilson plot. The structure factors were then reduced to normalized structure factors,  $E$ 's. The program of Beurskens (1963) (see also Kim, 1964), based on the  $\Sigma_2$  relation (Sayre, 1952; Hauptman & Karle, 1953), yielded two solutions, one of which gave the correct set of signs to 202 reflections.

\* This program was adapted by Robert F. Stewart from an older one prepared by Gordon S. Smith and Patricia B. Isaacs. It has the option to punch cards in either 'X-RAY 63' format or 'Shiono SFI' (1620) format.

The usual  $R$  index based on the signs of the 202 reflections started at 0.348 and four cycles of least-squares refinement (isotropic temperature factors) reduced it to 0.154. When a total of 720 reflections were used  $R$  increased to 0.269, but six cycles of refinement reduced it to 0.170.

At this time it was recognized that rather large discrepancies still persisted between  $F_o$  and  $F_c$  for certain prominent reflections. Also it had been discovered that extraneous electrical effects within the X-ray laboratory and neighboring laboratories were causing unexpected errors in measuring intensities. When these difficulties had been overcome enough intensities were remeasured to give a set of good precision. Then with all 1561 observed  $F$ 's, and anisotropic temperature factors, the  $R$  value dropped to 0.076 in four cycles of refinement. A three-dimensional difference Fourier synthesis at this point yielded the positions of the 9 hydrogen atoms in the molecule. Introduction of the hydrogen parameters with  $B = 4.00$  for each hydrogen atom reduced  $R$  to 0.070. With the hydrogen parameters and their  $B$ 's held constant and the heavy atom parameters and anisotropic  $B_{ij}$ 's varied, two more cycles of refinement lowered  $R$  to 0.054. Following this two cycles of refinement were carried out on the hydrogen coordinates and  $B$ 's, with the heavy atom parameters fixed. This concluded the refinement with a final  $R$  of 0.052 and a weighted  $R_w = [\Sigma w(F_o - kF_c)^2 / \Sigma wF_o^2]^{1/2} = 0.038$ , based on observed reflections only. If the three very strong reflections 002,  $\bar{1}12$ , and 020 are assumed to suffer from extinction, since their  $F_c$  has always calculated somewhat larger than their  $F_o$ ,  $R$  drops to 0.050 when they are omitted. The value of the quantity  $[\Sigma w(\Delta F^2)^2 / (n-p)]^{1/2}$  - the goodness of fit - is 2.5. This value is somewhat larger than the expected value 1.0, possibly as a result of unknown systematic errors, or the model not being a perfect one.

In the refinement above the residual minimized was  $\Sigma w(|F_o| - k|F_c|)^2$ . The overall scale factor  $k$  was refined at each cycle. The refinement of the non-hydrogen atoms in the last cycle showed an average shift/standard error for 99 positional and temperature parameters of 0.30 with a maximum shift in any parameter of 0.0003. Hydrogen atom refinement was terminated after two cycles with an average shift/standard error for 36 parameters of 0.37. The maximum shift of a hydrogen atom positional coordinate was 0.003 and of a  $B$  was 0.38. The weight  $w$  of each observation  $F_o$  was taken as  $w = 1/\sigma^2(F_o)$  where  $\sigma$  is the standard deviation described earlier. For most of the calculations in this study the IBM 7090 computer with the integrated system of programs known as 'X-ray 63' was used.\*

\* This Laboratory expresses its thanks and appreciation to Lyle H. Jensen, University of Washington, for providing the X-RAY 63 programs, to James H. Stewart, University of Maryland, for assistance in installing the system, and finally to Robert F. Stewart of this Laboratory for initiating the use of the system at Mellon Institute and patiently assisting members in its use.

The least-squares refinements were carried out with the X-ray 63 version of the Busing, Martin & Levy (1962) full-matrix program.

The observed and calculated structure factors are listed in Table 1. The fractional atomic coordinates, the atomic thermal parameters (anisotropic for the heavy atoms, isotropic for the hydrogen atoms), and the estimated standard deviations of each are presented in Tables 2 and 3. The atomic scattering factors used were those of Dawson (1960) for sulfur; those of *International Tables for X-ray Crystallography*, Vol. III, p.202, for nitrogen and oxygen; those of Berghuis, Haanappel, Potters, Loopstra, MacGillavry & Veenendaal (1955) for carbon; and those of Stewart, Davidson & Simpson (1965) for hydrogen. The estimated standard deviations of the parameters were calculated from the sum of the residuals and the diagonal terms of the inverse matrix of the least-squares normal equations. Correction for the anomalous dispersion of the sulfur was found to make only an insignificant difference in the  $F_c$ 's and  $R$ .

A final three-dimensional  $F_o - F_c$  synthesis in which the hydrogen contributions were omitted from the  $F_c$ 's yielded the composite projection of the hydrogen atoms shown in Fig.1. In this synthesis the nine hydrogen atoms were the nine highest peaks with electron concentrations of 0.45 to 0.65  $e.\text{\AA}^{-3}$ . No other concentrations of electron density greater than 0.3  $e.\text{\AA}^{-3}$  were

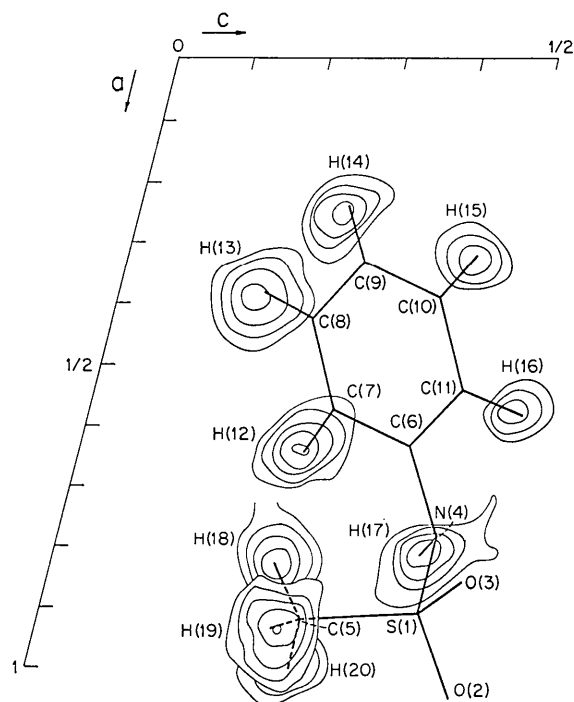


Fig. 1. Composite [010] projection of the hydrogen atoms of a molecule prepared from a three-dimensional  $F_o - F_c$  synthesis. The contours are drawn at intervals of 0.1  $e.\text{\AA}^{-3}$  beginning with 0.2  $e.\text{\AA}^{-3}$ . Values of  $F_c$  used had the contributions of the hydrogen atoms omitted. Final positions of the hydrogen atoms and of the rest of the molecule are superposed.

Table 2. Fractional atomic coordinates ( $\times 10^4$ ) and their estimated standard deviations,  $\sigma$

	$x$	$y$	$z$
S(1)	9096 (1)	2518 (1)	4994 (0)
O(2)	0492 (2)	1825 (2)	5675 (1)
O(3)	8579 (2)	3976 (2)	5452 (1)
N(4)	7843 (2)	1107 (2)	4982 (2)
C(5)	9208 (2)	2840 (3)	3453 (2)
C(6)	6313 (2)	1376 (2)	4330 (2)
C(7)	5736 (2)	0589 (3)	3224 (2)
C(8)	4249 (3)	0806 (3)	2626 (2)
C(9)	3337 (3)	1810 (3)	3124 (3)
C(10)	3916 (2)	2857 (3)	4230 (2)
C(11)	5411 (2)	2385 (3)	4848 (2)
H(12)	6441 (18)	9878 (21)	2939 (15)
H(13)	3822 (20)	0217 (24)	1894 (16)
H(14)	2408 (18)	1956 (21)	2697 (15)
H(15)	3226 (17)	3279 (20)	4568 (15)
H(16)	5836 (20)	2894 (22)	5701 (17)
H(17)	8164 (17)	0259 (22)	4815 (14)
H(18)	8273 (22)	3185 (25)	2933 (17)
H(19)	9355 (22)	1796 (24)	3106 (16)
H(20)	10013 (22)	3637 (25)	3459 (17)

observed. Another three-dimensional  $F_o - F_c$  synthesis (all atoms included) was prepared to observe the background. Only rarely did the background exceed  $\pm 0.2 e.\text{\AA}^{-3}$ . No positive area exceeded 0.3  $e.\text{\AA}^{-3}$ . Several negative areas in the vicinity of the sulfur atom reached a value of  $-0.5 e.\text{\AA}^{-3}$ .

#### Discussion of the molecular structure

Bond distances and bond angles within the MSA molecule are presented in Fig.2. These values were calculated by the X-RAY-63 BONDLA program which takes account of the standard deviations of both the lattice constants and the atomic parameters. The average standard deviation for bonds to the sulfur atom is  $\pm 0.002 \text{\AA}$ , for C-C and N-C bonds it is  $\pm 0.003 \text{\AA}$ , and for C-H or N-H it is  $\pm 0.018 \text{\AA}$ . The angles at the sulfur atom have  $\sigma = \pm 0.1^\circ$ ; the inner angles of the benzene ring have an average  $\sigma = \pm 0.2^\circ$ ; the external C-C-H angles of the benzene ring have an average  $\sigma = \pm 1.1^\circ$ ; the H-C-H angles of the methyl group have an average  $\sigma = \pm 1.7^\circ$ , and the S-C-H angles have  $\sigma = \pm 1.2^\circ$ .

The MSA molecule in Fig.2(a) and (b) is presented as the orthographic projection on the plane of its benzene ring. It is seen that the hexagonal benzene ring is only very slightly distorted. The ring C-C distances do vary from 1.367 to 1.393  $\text{\AA}$  with  $3\sigma = 0.009 \text{\AA}$ . Hence, some of the differences in the C-C distances could be significant. Their average value is 1.380  $\pm 0.003 \text{\AA}$  (uncorrected for thermal motion), a value slightly lower than the average aromatic C-C bond distance found in many compounds, 1.394  $\pm 0.005 \text{\AA}$  (Sutton, 1965), 1.380–1.385  $\text{\AA}$  (Brown, 1966). Likewise the deviations of the inner angles of the benzene ring from  $120^\circ$  are only very slightly greater than  $3\sigma = 0.6^\circ$ , and the significance of their deviations is somewhat questionable.

The eight C-H distances in the molecule vary from 0.88 to 1.02 Å with the average 0.965 Å, a value in good agreement with that observed in other recent work, 0.963 Å in 5-ethyl-6-methyluracil (Reeke & Marsh, 1966) and  $0.99 \pm 0.05$  Å in androsterone (High & Kraut, 1966). The single N-H distance is 0.80 Å, and is somewhat shorter than the average value, 0.95 Å, observed in 2-aminoethylphosphonic acid (Okaya, 1966) and the average value 0.895 Å found in 5-ethyl-6-methyluracil (Reeke & Marsh, 1966). Exterior C-C-H angles around the benzene ring and H-C-H and S-C-H angles in the methyl group are completely satisfactory and as expected.

The C-N distance in the anilide group is  $1.438 \pm 0.003$  Å, to be compared with  $1.43 \pm 0.01$  Å reported for acetanilide (Sutton, 1965). It is to be noted that

the MSA C-N bond is essentially a pure single bond. Its LCAO-MO double bond order  $p$  is only 0.13 as calculated from Coulson's (1939) C-C formula modified by Liquori & Vacigo (1956) for the C-N bond:

$$B = S - \frac{S - D}{1 + 0.6625(1 - p)/p}$$

where

$B$  = the observed C-N bond distance, here = 1.438 Å,  
 $S$  = the pure C-N single bond distance = 1.472 Å,  
 $D$  = the pure C=N double bond distance = 1.287 Å. }  
 (Pauling, 1960)

Around the sulfur atom the arrangement is only slightly distorted from regular tetrahedral. The various

Table 3. Thermal parameters\* of the atoms and their estimated standard deviations,  $\sigma$

$B_{ij}$  values are in Å<sup>2</sup>. Hydrogen atoms were treated as isotropic.

	$B_{11}$	$B_{22}$	$B_{33}$	$B_{12}$	$B_{13}$	$B_{23}$
S(1)	2.56 (2)	3.31 (2)	3.18 (2)	-0.07 (2)	0.41 (1)	-0.25 (3)
O(2)	3.01 (7)	5.08 (9)	4.75 (8)	0.47 (6)	-0.46 (6)	-0.22 (7)
O(3)	4.03 (7)	3.69 (8)	5.66 (8)	-0.26 (6)	1.66 (6)	-1.51 (7)
N(4)	3.13 (8)	2.56 (8)	4.46 (9)	0.26 (7)	0.46 (7)	0.54 (7)
C(5)	4.27 (11)	5.79 (16)	3.88 (10)	-1.06 (10)	1.29 (8)	-0.20 (10)
C(6)	2.79 (9)	2.63 (10)	3.44 (10)	-0.28 (8)	0.57 (7)	0.49 (8)
C(7)	3.75 (10)	3.82 (12)	4.40 (11)	-0.63 (9)	1.05 (9)	-0.59 (10)
C(8)	4.57 (12)	5.57 (15)	3.54 (11)	-2.14 (12)	0.20 (9)	0.06 (12)
C(9)	2.95 (10)	5.90 (15)	5.31 (14)	-0.60 (10)	0.09 (10)	2.21 (12)
C(10)	3.38 (10)	5.16 (13)	5.80 (12)	0.79 (11)	1.60 (9)	0.97 (13)
C(11)	3.49 (9)	4.52 (12)	3.78 (9)	-0.17 (11)	1.14 (7)	0.07 (11)
H(12)	4.82 (43)					
H(13)	6.36 (50)					
H(14)	4.35 (43)					
H(15)	4.02 (41)					
H(16)	5.61 (49)					
H(17)	4.81 (44)					
H(18)	6.49 (51)					
H(19)	5.93 (48)					
H(20)	6.87 (52)					

\* For the heavy atoms the expression is:  $\exp[-\frac{1}{3}(h^2a^*2B_{11} + \dots + 2klb^*c^*B_{23})]$ .

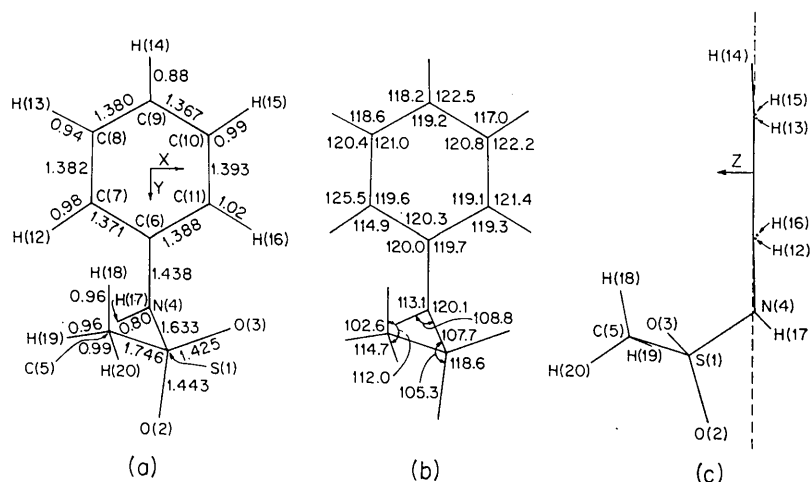


Fig. 2. Orthographic projection of the MSA molecule onto the plane of the benzene ring: (a) Observed bond distances (Å), and molecular axial system chosen. Positive  $Z$  is perpendicular to the plane of the ring and directed downward. (b) Observed bond angles ( $^{\circ}$ ). (c) Orthographic projection of the molecule edge-on to the plane of the benzene ring in the direction of positive  $X$ .

bond distances observed are best compared with those recently reported in the various polymorphs of sulfanilamide (Table 4).

The least-squares best plane through the six carbon atoms of the benzene ring was calculated by the

X-RAY-63 program according to the method of Schomaker, Waser, Marsh & Bergman (1959). The equation for this plane is

$$0.38062x + 0.77722y - 0.57698z = 0.33465$$

Table 4. Comparison of bonds to the tetrahedral sulfur atom

Bond	MSA (this study)	$\alpha$ -Sulfanilamide (O'Connor & Maslen, 1965)	$\beta$ -Sulfanilamide (O'Connell & Maslen, 1967)	$\gamma$ -Sulfanilamide (Alléaume & Decap, 1965)
S-O(2)	1.443	1.47 Å	1.454 ± 0.0017 Å	1.452 ± 0.014 Å
S-O(3)	1.425	1.41	1.448 ± 0.0014	1.438 ± 0.019
S-N(4)	1.633	1.61	1.620 ± 0.0016	1.666 ± 0.015
S-C(5)	1.746	1.74	1.750 ± 0.0018	1.739 ± 0.014

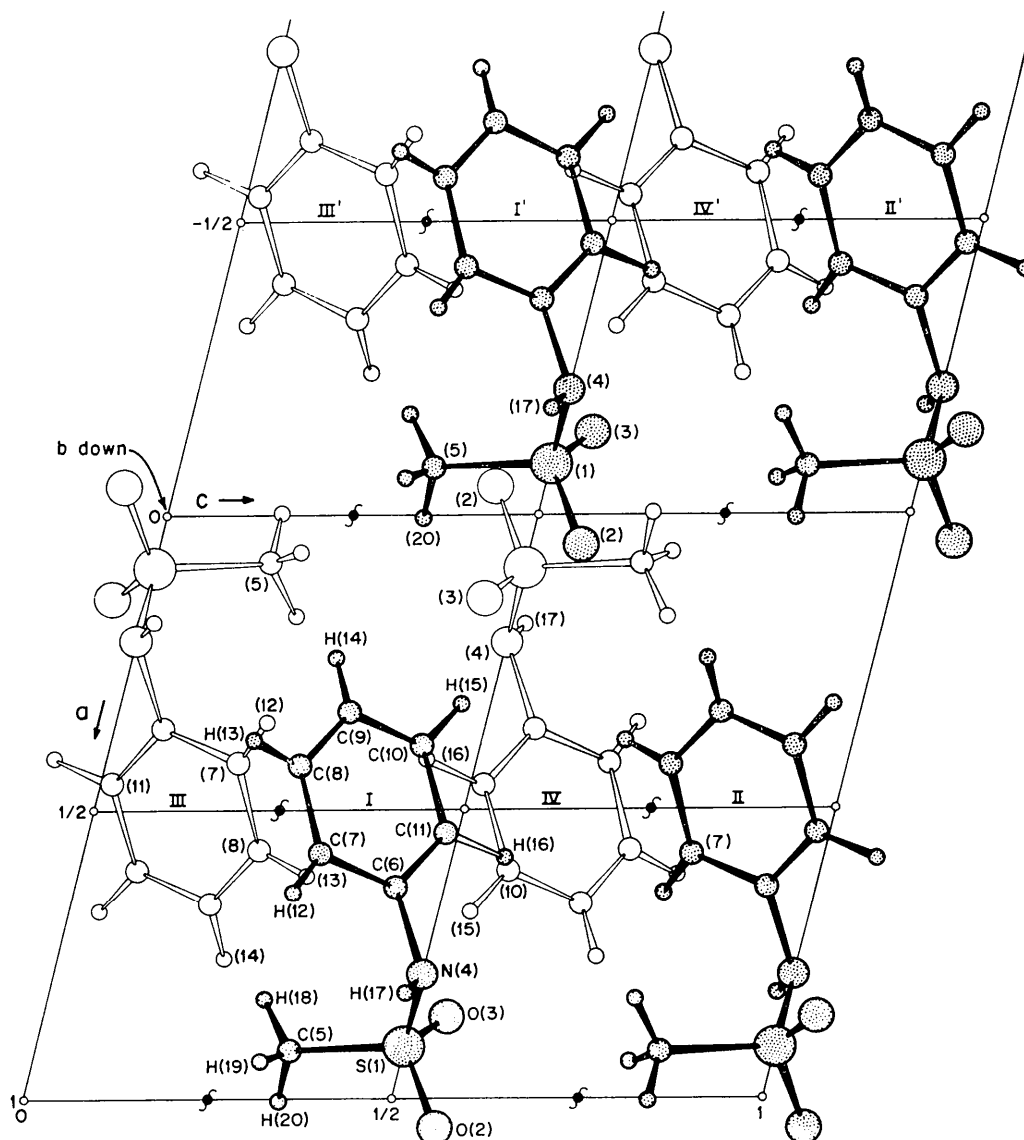


Fig. 3. Projection of the structure onto the (010) plane. Heavily outlined molecules are related by the glide plane at  $y=0.75$ . Lightly outlined molecules are related by the glide plane at  $y=0.25$ . Projections of the screw axes and symmetry centers are shown. Atoms of the asymmetric unit (molecule I) have been identified by chemical symbol and number. Selected atoms in other molecules are given their corresponding numbers as an aid in identifying the intermolecular distances discussed in the text.



in which  $x$ ,  $y$ , and  $z$  are the atomic coordinates in Å units referred to the crystallographic axes, and 0.33465 is the distance from the plane to the origin in Å units. The standard deviation of the atoms defining the plane from the plane is  $\sigma = 0.0016$  Å. The perpendicular distances of the various atoms from this plane are as follows:

C(6)	0.0009 Å	H(12)	-0.025 Å
C(7)	0.0002	H(13)	-0.062
C(8)	-0.0019	H(14)	0.042
C(9)	0.0026	H(15)	-0.017
C(10)	-0.0015	H(16)	-0.069
C(11)	-0.0003	H(17)	-0.372
S(1)	1.2831	H(18)	2.732
O(2)	0.8957	H(19)	2.114
O(3)	1.7416	H(20)	3.295
N(4)	-0.0495		
C(5)	2.5082		

The remarkably good planarity of the six-carbon ring is at once evident. The positions of the hydrogen atoms are not known with much precision but the ring hydrogen atoms, H(12) to H(16), are essentially coplanar with the carbon atoms. Fig. 2(c) is an orthographic projection of the MSA molecule as viewed edge-on to the plane of the benzene ring. It spectacularly shows the distribution of the atoms relative to the least-squares plane of the ring. Of greatest interest to this study is the fact that the amine hydrogen, H(17), clearly sticks out alone on one side of the plane while the whole methylsulfone group is on the opposite side of the plane. Evidently, as long as the molecule keeps the stereochemistry observed in the crystal, this acidic hydrogen, or the whole phenyl-N-H portion of the molecule, would appear to be readily available to a receptor molecule.

The plane through atoms C(6), H(17), and S(1) was calculated to complete the picture of the geometry about the N(4) atom. The equation of this plane is

$$-0.29647x + 0.03110y + 0.99764z = 3.0749.$$

The nitrogen atom, N(4), is 0.293 Å out of this plane. Thus the nitrogen atom is at the apex of a very low and somewhat distorted trigonal pyramid.

### Molecular packing

The molecular packing within the crystal cell is depicted in Fig. 3. Two MSA molecules (for instance, I' and IV) form a centrosymmetric dimer through a symmetrical pair of N-H...O hydrogen bonds, I'(4)-I'(17)...IV(2) and IV(4)-IV(17)...I'(2). These N-H...O bonds, of length 3.03 Å, are typical hydrogen bonds of the type X-NH...O-S where the nitrogen is covalently bonded to another atom X (carbon in MSA), and the oxygen is bonded to sulfur. The angle C-N...O is 119.5°. Fuller (1959) reports the average value of the X-N...O angle for a planar trigonal nitrogen atom to be 119 ± 15°, and for NH<sub>3</sub><sup>+</sup> donor

groups the angle becomes 108 ± 12°. The angle at the hydrogen atom, N-H...O, is 167.7°. The bond distance, 3.03 Å, is to be compared with 3.02 Å reported in sulfamide (Trueblood & Mayer, 1956), with values, 2.94-3.17 Å, observed in  $\alpha$ -sulfanilamide (O'Connor & Maslen, 1965), with values, 3.03-3.12 Å, observed in  $\beta$ -sulfanilamide (O'Connell & Maslen, 1967), and values, 2.96-3.24 Å, in  $\gamma$ -sulfanilamide (Alléaume & Decap, 1965). After this investigation had been completed it was learned that infrared and other studies indicate this same symmetrical hydrogen-bonded dimerization of MSA also occurs in solution (Malewski & König, 1964).

Except for the hydrogen bonds in the dimeric molecules, all contacts between molecules are of the van der Waals type, and are always in the expected range. Contacts between the benzene rings of neighboring molecules (Fig. 3) involve CH of one molecule and CH of another. The smallest such C...C distance observed is II(7)...III(11), 3.56 Å, and other values range upward to well over 4 Å. Because of the tilt of the molecules about the glide planes, distances that appear short on the projection are often highly deceptive. For instance, I(8)...III(7) is 4.04 Å and I(7)...III(8) is 4.39 Å, whereas I(10)...III(7) is only 3.73 Å and III(8)...IV(10) is only 3.91 Å. The van der Waals radius of a CH group is expected to lie somewhere between the half thickness of the aromatic molecule, 1.70 Å, and the radius of CH<sub>3</sub> and CH<sub>2</sub> groups, estimated to be about 2.0 Å (Pauling, 1960).

There are occasional contacts between hydrogen of the CH groups and oxygen and nitrogen atoms. These, likewise, are satisfactory. For example, the shortest observed are I(3)...IV(15), 2.80 Å, expected value, > 2.60 Å, and I(14)...IV(4), 3.64 Å, expected value, > 2.70 Å.

The packing and contacts around the methyl sulfone groups are interesting. A CH<sub>3</sub>...O contact distance should be greater than about 3.4 Å (Pauling, 1960). Observed CH<sub>3</sub>...O distances are: III(5)...IV(2), 3.55 Å; and III(5)...IV(3), 3.55 Å. The CH<sub>3</sub>...CH<sub>3</sub> distance, I'(5)...III(5), is about 4.98 Å, expected, > 4.00 Å. In the dimeric molecule the O...O distance, I'(2)...IV(2), is 3.33 Å, and the O...O distance, I'(3)...IV(3), between dimeric molecules is 3.45 Å. Both are well above the sum of the van der Waals radii, 2.80 Å. The two shortest S...O intermolecular distances are well above the expected minimum value of 3.25 Å. The I'(1)...IV(2) distance in the dimer is 3.68 Å, and the I'(1)...IV(3) distance between dimers is 3.67 Å. The methyl hydrogen to oxygen distance, I'(20)...IV(3), is 2.50 Å, which is a trifle under the expected 2.60 Å.

### Analysis of thermal motion

With the higher quality intensity and thermal data now available and the greater refinement of structures now possible, there is increased interest in an analysis of

the thermal motions of the atoms and molecules in crystal structures. In Table 3 the anisotropic thermal parameters were listed as  $B_{ij}$ 's, which from their magnitude provide a general idea of the motions of the individual atoms. It is the purpose now to analyze the anisotropic thermal motions of the heavy atoms in MSA in terms of possible rigid-body motions of the molecules, or parts of molecules, by the method of Cruickshank (1956*a*). The considerations set forth by Scheringer (1966) for the transformation of tensors in oblique crystallographic systems have also been taken into account.

The calculations were done with a program DIAGUS for the IBM 7090 computer written by R.F. Stewart of Mellon Institute. This program uses Patterson's (1952) orthogonal unit vector system  $\mathbf{E}$  for the basic calculations. First the anisotropic thermal parameters are diagonalized to provide the principal values of the  $B_{ii}$ 's and their direction angles relative to a chosen right-handed Cartesian coordinate system  $\mathbf{X}, \mathbf{Y}, \mathbf{Z}$  related in a natural way to the molecule [Fig. 2(*a*), (*c*)]. The program then continues with a rigid-body analysis and computes the elements of the librational tensor  $\omega$  about the center of mass and the elements of the translational tensor  $\mathbf{T}$ . These computations are carried out first with reference to the  $\mathbf{E}$  vector system, and then transformed to the molecular Cartesian  $\mathbf{X}, \mathbf{Y}, \mathbf{Z}$  system. These molecular axes of reference [Fig. 2(*a*), (*c*)] are defined in the following manner. The unit normal to the least-squares plane of the benzene ring was taken

as positive  $\mathbf{Z}$ . The direction C(9) to C(6) was used to define a vector  $\mathbf{Y}'$ . Vector relations  $\mathbf{X} = \mathbf{Y}' \times \mathbf{Z}$  and  $\mathbf{Y} = \mathbf{Z} \times \mathbf{X}$  then complete the description and definition of the axial system.

Application of the rigid-body analysis to the thermal motions of the eleven heavy atoms of the MSA molecule demonstrated that the MSA molecule does indeed vibrate as a unit. Table 5 presents the r.m.s. amplitudes of the translational motion and angular libration corresponding to the three principal axes of the  $\mathbf{T}$  and  $\omega$  ellipsoids, respectively, and the orientation of these axes relative to the molecular axes,  $\mathbf{X}, \mathbf{Y}, \mathbf{Z}$ . It is seen that the molecule's translational vibrations are essentially isotropic, whereas its librations are rather anisotropic. Application of the rigid-body analysis to the benzene ring only of the molecule (Table 5) is apparently somewhat more appropriate, as evidenced by the improved goodness of fit, 2.7, as against 7.0 for the entire MSA molecule. The program used weights based on the variances of the thermal parameters. The ring exhibits essentially the same isotropic translational vibration as the whole molecule, but its librations are more anisotropic. The principal axes of the  $\omega$  tensors for the whole molecule and the ring have essentially the same orientation relative to the molecular axes,  $\mathbf{X}, \mathbf{Y}, \mathbf{Z}$ . The maximum librational motion of both the MSA molecule as a whole and of its benzene ring is approximately a  $7^\circ$  oscillation about the  $\omega_2$  axis of the  $\omega$  tensor. This axis lies almost in the  $\mathbf{YZ}$  plane and makes an angle of  $\sim 25^\circ$  with positive  $\mathbf{Y}$ . This is essentially a torsional

Table 5. Principal values of the  $\mathbf{T}$  and  $\omega$  tensors for the MSA molecule and its benzene ring relative to the orthogonal molecular axis system  $\mathbf{X}, \mathbf{Y}, \mathbf{Z}$

	R.M.S. amplitude of translation	Direction angles with respect to $\mathbf{X}, \mathbf{Y},$ and $\mathbf{Z}$			R.M.S. amplitude of oscillation	Direction angles with respect to $\mathbf{X}, \mathbf{Y},$ and $\mathbf{Z}$		
MSA molecule	0.168 (19) Å	155.4°	79.7°	112.1°	2.55 (10)°	152.7°	74.4°	111.8°
	0.197 (22)	112.1	88.0	22.2	6.59 (13)	85.6	27.6	62.8
	0.183 (41)	79.7	10.6	88.0	3.66 (16)	63.2	67.8	143.9
Goodness of fit is 7.0								
Benzene ring	0.168 (10)	80.6	95.7	11.1	1.50 (3)	163.4	79.9	103.0
	0.199 (87)	33.2	57.3	94.9	7.30 (11)	85.8	24.2	66.2
	0.195 (97)	121.5	33.3	80.1	3.97 (7)	74.0	68.3	152.5
Goodness of fit is 2.7								

Table 6. Observed and calculated  $U_{ij}$  and their standard deviations for the atoms of the benzene ring with respect to the orthogonal vector system  $\mathbf{E}$

	$U_{11}$		$U_{22}$		$U_{33}$		$U_{12}$		$U_{13}$		$U_{23}$	
	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.	obs.	calc.
C(6)	357 (12)	392	333 (13)	330	443 (13)	408	-43 (10)	-32	-21 (10)	-2	69 (9)	62
C(7)	471 (14)	514	484 (15)	495	555 (15)	535	-73 (12)	-103	12 (12)	-32	-66 (10)	-67
C(8)	603 (16)	545	705 (18)	750	474 (15)	529	-278 (15)	-223	-104 (13)	-105	43 (11)	73
C(9)	395 (14)	414	747 (19)	730	708 (18)	654	-109 (13)	-116	-116 (13)	-87	296 (11)	297
C(10)	409 (13)	388	653 (17)	671	722 (17)	740	89 (14)	40	72 (12)	42	113 (11)	105
C(11)	434 (12)	399	572 (15)	533	470 (12)	491	-24 (14)	5	38 (10)	55	12 (9)	7

(in  $10^{-4}$  Å<sup>2</sup>)

wobble of the molecule about the direction from the ring center to atom S(1). It seems evident from Fig. 3 that the hydrogen bond scheme in the dimeric molecule more readily permits the maximum oscillations to occur about  $\omega_2$  rather than about either of the other two  $\omega$  tensor axes.

Table 6 provides a comparison of the observed mean square amplitudes of vibration,  $U_{ij}$ 's, of the carbon atoms constituting the benzene ring, their standard deviations, and the values calculated from the rigid-body model. It is seen that the agreement is completely satisfactory.  $U_{ij}$  data for the remaining atoms of the molecule are comparable. These quantities and their standard deviations, of course, are affected by errors (not taken into account) due to absorption and extinction. Cruickshank (1965*b*) has shown that the errors in bond lengths due to rotational oscillations of molecules may be calculated. These corrections in a molecule such as MSA would be expected to increase the bond lengths of Fig. 2(a) and Table 4 by approximately 0.005–0.008 Å.

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