

## THREE-DIMENSIONAL STRUCTURES OF SUBSTITUTED DIPHENYL SULFIDES

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Three-dimensional crystal structures of a diphenyl sulfide skeleton from various compounds were confronted with computed conformational map. Diphenyl sulfide fragments, 31 in total, were retrieved from the Cambridge Structural Database and four fragments were taken from our measurements. Due to the symmetry of the fragment, the number of analyzed fragments rose to 140. The main features of geometrical behaviour of the fragment can be summarized as follows: If an endocyclic torsion angle of a phenyl ring deviates from  $0^\circ$ , the adjacent torsion angle is deformed in opposite direction by the same value keeping thus the phenyl ring planar. Repulsion of phenyl rings enlarges a C-S-C bonding angle in all fragments and bends aside the phenyl ring from a symmetrical attachment which has torsion around a S-C bond near  $0^\circ$ . Torsion angles around the S-C bonds correlate with each other keeping approximately perpendicular orientation of the phenyl rings. The correspondence between experimental values of torsion angles and low energy regions of the molecular mechanics conformational map suggests that possible gas-phase and crystal conformations of the diphenyl sulfide molecule are the same. *Ab initio* calculations fully confirmed results of molecular mechanics and — along with the crystal conformations — justify further usage of molecular mechanics in computational modelling of diphenyl sulfides.

In recent years, research of antidepressants has focused on compounds with specific mechanisms of action, particularly on those which affect the potentiation of 5-hydroxytryptamine (serotonin) transmission in nerves. The more specific mechanism of action of these compounds — “the second generation antidepressants” — bring about less side effects than do older tricyclic antidepressants<sup>1</sup>. Most of second generation antidepressants influence serotonergic nerve functions whereas noradrenaline functions are not affected.

Antidepressive properties were found in a group of aminoalkyldiphenyl sulfides<sup>2,3</sup>. These compounds show a high affinity to both <sup>3</sup>H imipramine and <sup>3</sup>H desipramine binding sites in the rat brain and inhibit the re-uptake of 5-hydroxytryptamine as well as of noradrenaline. Few of these compounds, however, are specific for the uptake inhibition of just one amine. The specific serotonin re-uptake inhibition is one of the aims in the design of the second generation antidepressants. Therefore, there is a necessity to find new diphenyl sulfide derivatives with more profitable pharmacological properties. In addition to the traditional (and up to now the most

successful) way to do so, an alternative approach based on ideas of quantitative structure–activity relationships becomes more important. For such an investigation of new, more specific inhibitors of serotonin re-uptake inhibitors with the diphenyl sulfide skeleton, we need to know as much as possible about their three-dimensional structures. In the present communication, we make the very first step in understanding of relationships between three-dimensional structures of diphenyl sulfides and their pharmacological activities by describing essential structural features of diphenyl sulfide molecules. The results published in the present paper were shown in a preliminary form earlier<sup>4</sup>. Seeking for general rules of geometrical behaviour of substituted diphenyl sulfides, precise molecular geometries are needed. We analyzed molecular structures experimentally determined by X-ray structure analysis and conformational properties of the diphenyl sulfide molecule were computed by molecular mechanics<sup>5</sup> and *ab initio* molecular orbital calculations.

The bulk of analyzed structures was retrieved from the Cambridge Structural Database<sup>6</sup> and four of them came from our diffraction experiments<sup>7–10</sup>. The use of this Data base for determination of mean molecular geometries and for identification of reaction pathways is well documented<sup>11–15</sup>. In the present paper, we give only a brief overview of employed methods.

The molecular mechanics and *ab initio* calculations were done in order to compare a computed potential energy surface with observed values of geometrical parameters. Differences would indicate changes of behaviour in crystal and gas phases, respectively.

The main aim of the present paper is, thus, the formulation of rules for geometrical behaviour of diphenyl sulfide skeleton. In particular, the following questions had to be answered: (i) which geometrical parameters are important describing the diphenyl sulfide geometry? (ii) What (statistical) relations can be found between them? (iii) Can these statistical phenomena be interpreted in terms of intramolecular interactions? Or are they only a side effect of non-randomness of crystal-packing forces? (iv) Is there a correspondence between experimental and computed values of torsion angles around the S—C bonds?

## CALCULATIONS

### *Database Search*

Structures containing a fragment of a general formula *I* (Fig. 1) were searched in the April 1988 version of the Cambridge Structural Database using a QUEST88 (ref.<sup>16</sup>) program. An interim run of QUEST88 excluded all diphenyl sulfide structures containing transition metals, Si, Sn, Ge, Sb, As, Se, and Te. The total number of identified structures was 29. The structure TOLSUL [(di-*p*-tolyl) sulfide] having *R* 0.22 was excluded. In a GSTAT88 (ref.<sup>16</sup>) program only symmetry-independent fragments

were looked for. Two found fragments of BAFPIH and four ones of HPTBZC were, however, manually identified as identical and thus only one fragment from each of these structures was considered. Thus, the total number of accepted fragments was 31. A list of compounds containing the fragment as given in Table I. The GSTAT88 program was used to compute all geometric parameters.

### Symmetry of the Fragment I

Respecting actual or possible symmetry of the fragment, raw data obtained from GSTAT88 had to be properly transformed. To handle bond lengths and angles is simple since transformed values are arithmetic means of symmetry-equivalent parameters. E.g., the valence bonds C2—C3, C2—C7, C8—C9, and C8—C13 as well as the valence angles C2—C3—C4, C2—C7—C6, C8—C9—C10, and C8—C13—C12 are equivalent. A proper treatment of other parameters is more complicated.

For symmetry considerations, the key parameters were  $\tau_1$  and  $\tau_2$  (for definition of parameters, see Fig. 1). In the beginning,  $\tau_1$  and  $\tau_2$  were corrected for nonplanarity of the phenyl rings:

$$\tau_i = \tau_i - (|\tau_i - \tau_i'| - 180^\circ)/2. \quad (1)$$

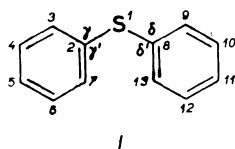


FIG. 1

Definition of geometrical parameters used for description of the diphenyl sulfide fragment:  $\Delta_1 \equiv \gamma - \gamma'$ ,  $\tau_1 \equiv \text{C2-S-C8-C9}$ ,  $\zeta_1 \equiv \text{S-C2-C3-C4}$ ,  $\omega_1 \equiv \text{C2-C3-C4-C5}$ ,  $\chi_1 \equiv \text{C3-C4-C5-C6}$ ,  $\Delta_2 \equiv \delta - \delta'$ ,  $\tau_2 \equiv \text{C8-S-C2-C3}$ ,  $\zeta_2 \equiv \text{S-C8-C9-C10}$ ,  $\omega_2 \equiv \text{C8-C9-C10-C11}$ ,  $\chi_2 \equiv \text{C9-C10-C11-C12}$ ,  $\varphi$  the oriented angle of the phenyl rings

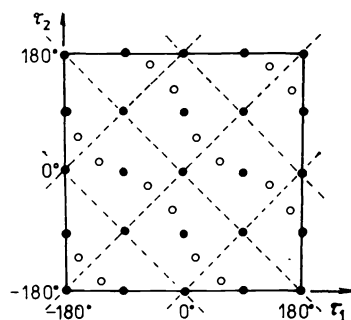


FIG. 2

The symmetry of the conformational map  $E = E(\tau_1; \tau_2)$  of the diphenyl sulfide. Equivalent positions (16 circles) are images of 16 isometric conformations of the molecule. Dashed lines are mirrors, black points are inversion centres

where  $i = 1, 2$  and  $\tau'_i$  is an "adjacent" torsion to  $\tau_i$ : for  $\tau_1 \equiv \text{C8—S1—C2—C3}$  is  $\tau'_1 \equiv \text{C8—S1—C2—C7}$ . Symmetric behaviour of  $\tau_1$  and  $\tau_2$  was studied by the

TABLE I

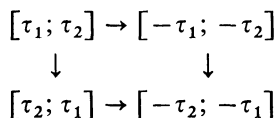
A list of reference codes and chemical names of compounds containing the diphenyl sulfide fragment

No.	Code	Chemical name
1	AMPPSM	N-(3-dimethylamino-propyl)-2-amino-2'-chlorodiphenyl sulfide
2	APCDPS	2-(N-(3-dimethylamino)-propyl)amino-2',4-dichloro-diphenyl sulfide
3	APPSMA	N-(3-dimethylamino-propyl)-2-amino-4-chloro-diphenyl sulfide
4	BAFPIH	1,4-bis(phenylthio)benzene
5-6	BPTHNB	2,4-bis(phenylthio)nitrobenzene
7	CULFAQ10	methyl-2-(2-nitrophenylthio) benzoate
8	CULFIY10	2-(2-nitrophenylthio)phenyl acetate
9	DABMOI	2,2'-thio-bis(4-methyl-6-t-butylphenol)
10-11	DAKGAX	2-nitro-1,3-bis(phenylthio)-benzene
12	DAPHSD	4,4'-diamino-diphenyl sulfide
13	DEKDIG	2,2'-dinitrodiphenyl sulfide
14	DMOPHS	bis(3,4-dimethoxyphenyl) sulfide
15	DOTOLS	2,2'-dimethyldiphenyl sulfide
16	DTFNPS	bis(2,5,6-trifluoro-4-nitrophenyl) sulfide
17	EAPSOX	N-(3-diethylaminopropyl)-2-methylamino-4-chlorodiphenyl sulfide
18	FATZAB	methyl-2-(4-nitrophenylthio) benzoate
19	FATZEF	2-diazoacetyl-4'-nitrodiphenyl sulfide
20	FIHBED	4-amino-4'-nitrodiphenyl sulfide
21-22	FIVREH	2-(methyldiethylammoniummethylthio)-4-( <i>p</i> -phenylthiophenyl)-3 <i>H</i> -1,5-benzodiazepine
23	HPTBZC	hexakis(phenylthio)benzene-carbon tetrachloride clathrate
24	MAMPHS10	4-dimethylaminodiphenyl sulfide
25	METBZB10	dimethyl-2,2'-thiodibenzoate
26	NMADPS	4-nitro-4'-dimethylaminodiphenyl sulfide
27-28	NOPHTE01	2,4-dinitrodiphenyl sulfide
29	NTPXMB10	2-(4'-carbomethoxy-2'-nitrothiophenyl)-1,3,5-trimethylbenzene
30	PNDPHS	4-nitro-diphenyl sulfide
31	PSEAOX	3-(3-chloro-6-phenylthio-phenylamino)-propyldiethylammonium oxalate

Dunitz method<sup>17</sup> considering both phenyl rings as rigid regular hexagons. The symmetry of a conformational map  $E = E(\tau_1; \tau_2)$  is *cm*m (Fig. 2). All  $\tau_i$  values were thus transformed into an interval of  $\tau_i \in \langle -90^\circ; 90^\circ \rangle$ :

$$\begin{aligned} \tau_i < -90^\circ : \tau_i &\rightarrow \tau_i + 180^\circ \\ \tau_i < 90^\circ : \tau_i &\rightarrow \tau_i - 180^\circ \end{aligned} \quad (2)$$

and then we generated all symmetry equivalent positions of points  $[\tau_1; \tau_2]$  in the map (Scheme 1).



SCHEME 1

The total number of analyzed fragments is thus four times the number of identified fragments.

Transformations of  $\tau_1$  or  $\tau_2$  necessitate transformations of other parameters. When transforming one of  $\tau_i$  from the interval  $\langle -180^\circ; -90^\circ \rangle$  or  $\langle 90^\circ; 180^\circ \rangle$  to  $\langle -90^\circ; 90^\circ \rangle$ , the following holds:

$$\begin{aligned} \varphi &\rightarrow 180^\circ - \varphi \\ \Delta_1 &\rightarrow -\Delta_1 \\ \zeta_1 \equiv \text{S1—C2—C3—C4} &\rightarrow \zeta_1 \equiv \text{S1—C2—C7—C6} \\ \omega_1 \equiv \text{C2—C3—C4—C5} &\rightarrow \omega_1 \equiv \text{C2—C7—C6—C5} \\ \chi_1 \equiv \text{C3—C4—C5—C6} &\rightarrow \chi_1 \equiv \text{C7—C6—C5—C4} \end{aligned} \quad (3)$$

Similar transformations were performed with  $\varphi$ ,  $\Delta_2$ ,  $\zeta_2$ ,  $\omega_2$ , and  $\chi_2$  if  $\tau_2$  was transformed. It follows from Eq. (3) that if both  $\tau_1$  and  $\tau_2$  were transformed,  $\varphi$  did not change  $[180 - (180 - \varphi) = \varphi]$ .

As a consequence of generation of equivalent positions in the conformational map  $E = E(\tau_1; \tau_2)$ , an original set of other parameters had to be transformed, too. For inversion on the map ( $[\tau_1; \tau_2] \rightarrow [-\tau_1; -\tau_2]$ ), the following transformations were used:

$$\begin{aligned} \varphi, \Delta_i &\dots \text{ no change} \\ \zeta_i &\rightarrow 360 - \zeta_i \\ \omega_i &\rightarrow 360 - \omega_i \\ \chi_i &\rightarrow 360 - \chi_i \end{aligned} \quad (4)$$

and for reflection  $[\tau_1; \tau_2] \rightarrow [\tau_2; \tau_1]$ :

$$\begin{aligned} \varphi & \dots \text{no change} \\ \Delta_1 & \rightarrow \Delta_2 ; \quad \text{and vice versa} \\ \zeta_1 & \rightarrow \zeta_2 ; \quad \text{and vice versa} \\ \omega_1 & \rightarrow \omega_2 ; \quad \text{and vice versa} \\ \chi_1 & \rightarrow \chi_2 ; \quad \text{and vice versa .} \end{aligned} \tag{5}$$

### *Statistical Treatment of Data*

Basic statistical descriptions of all the symmetrized internal coordinates of the fragment were computed. Parameters with potentially interesting distributions were studied in greater detail. Only standard statistical methods were used; arithmetic means and their e.s.d., deviations from normality of distributions, linear regression analysis, histograms (frequency diagrams), and scattergrams.

All the studied data was collected to a data matrix. The rows of the data matrix consist of parameter values for a particular fragment and its columns are composed from values of a particular parameter in all fragments. Each fragment appeared four times in the data matrix. The number of analyzed diphenyl sulfide fragments was therefore 140 (31 fragment from the database and four from our experiments times 4).

### *Molecular Mechanics Calculations*

We used the MMPMI program<sup>18</sup> modified for IBM-PC computers<sup>19</sup>. Some parameters needed for description of bond and torsion angles are missing in the program. The assigned values of the missing parameters are listed in Table II. The conformational map  $E = E(\tau_1; \tau_2)$  was computed in fixed points  $[\tau_1; \tau_2]$  changing  $\tau_1$  from  $-90^\circ$  to  $0^\circ$  and  $\tau_2$  from  $-90^\circ$  to  $90^\circ$  in steps of  $15^\circ$  by the dihedral driver option of the program. All other geometrical coordinates of the diphenyl sulfide were optimized in all points of the map. The other half of the map was obtained by application of symmetry operations of the plane group *cmm*.

### *Ab initio Calculations*

To verify results of molecular mechanics, an *ab initio* calculation was performed for five points of the  $\tau_1$ - $\tau_2$  conformational map employing the minimal STO-3G basis set<sup>20</sup>. A diphenyl sulfide geometry for these calculations was taken from the energetically lowest molecular mechanics geometry.

## RESULTS AND DISCUSSION

*Description of Diphenyl Sulfide Geometries*

All distributions of symmetrized bond lengths are unimodal. The mean value of a S—C bond length is 1.775 Å with the estimated standard deviation (e.s.d.) 0.013 Å. "Aromatic" bond lengths in FIVREH have extrema 1.30 Å and 1.48 Å. These distances are not bond lengths in an aromatic system and they could be an artefact of X-ray structure refinement in the noncentrosymmetric space group  $P2_1$  instead of the centrosymmetric one. Regardless of FIVREH values, other aromatic bond lengths keep within expected values. Not any one of the bond lengths was studied in further detail.

All distributions of symmetrized bond angles are unimodal. A slight indication of bimodal distribution of a C—S—C bond angle was ruled out by plotting it against other parameters but no interpretable dependencies might be seen. The mean value of the C—S—C angle is 103.2° with the e.s.d. 1.5° and minimal and maximal values 99.7° and 105.8°. Only parameters  $\Delta_1$  and  $\Delta_2$  were subjected to subsequent analysis. Their distribution significantly differs from the normal one (Fig. 3) with the mean value 1.3° and e.s.d. 1.8°.

Torsion angles  $\zeta_i$ ,  $\omega_i$ , and  $\chi_i$  have unimodal distributions (for their definition, see Fig. 1). All  $\chi_i$  and  $\omega_i$  values lie within the range  $\langle -6^\circ; 6^\circ \rangle$  (the mean values and their e.s.d.'s being for  $\chi_i$  0.0°, 1.5°, and for  $\omega_i$  0.0°, 1.6°). Deformations of phenyl rings from planarity thus exceed accuracy of refinement of torsion angles and have to be considered as significant. The histogram of  $\zeta_i$  has much broader distribution in the range of  $\langle 170.5^\circ; 189.5^\circ \rangle$  which suggests that relatively large deviations of the S atom from the mean plane of the phenyl rings are allowed (the greatest distance

TABLE II

Parameters of the molecular force field added to the original set<sup>19</sup>. These parameters lead to energies in kcal mol<sup>-1</sup> (1 kcal mol<sup>-1</sup> = 4.184 kJ mol<sup>-1</sup>)

Atom types	$V_1$	$V_2$	$V_3$
C( $sp^2$ )-S-C( $sp^2$ )-C( $sp^2$ )	-1.8	1.8	1.2
S-C( $sp^2$ )-C( $sp^2$ )-C( $sp^2$ )	2.0	15.0	2.0
S-C( $sp^2$ )-C( $sp^2$ )-H	-2.0	15.0	2.0
	$K_s$	$\alpha_0$	
S-C( $sp^2$ )-C( $sp^2$ )	0.70	120.0	

is 0.261 Å for EAPSOX, the mean is 0.00 Å; e.s.d. 0.02 Å). The mean value of  $\zeta_i$  is 180.0°, its e.s.d. 3.8°. The histogram of the dihedral angle  $\varphi$  (Fig. 4) shows a flat distribution between 61° and 117° with a broad maximum near 90° (the mean 93°; e.s.d. 13°).

The distribution of torsion angles  $\tau_1$  and  $\tau_2$  (Fig. 5) suggests presence of at least two clusters around 0° and 90°. A scattergram of these two angles (see Fig. 6) shows their more complex behaviour. There are two bands of experimental points which are separated by a broad forbidden area. Each band is made up of two bridged clusters. The clusters have centroids at points of inversion symmetry (see the symmetry of the conformational map, Fig. 2). The pattern of  $[\tau_1; \tau_2]$  points will be discussed later in connection with the molecular mechanics calculation.\*

For subsequent analysis, the data matrix had to be split into two submatrices containing the fragment parameters from the upper band and the lower band of  $\tau_2$ - $\tau_1$  dependence. All statistical results that follow were obtained by analyzing the "upper" submatrix which contains the data on the 70 fragments contributing to the upper band in Fig. 6.

In other scattergrams, linear dependence of  $\omega_1$  on  $\chi_1$  (or  $\omega_2$  on  $\chi_2$ ) is significant (see Fig. 7):

$$\omega_1 = -0.75\chi_1 - 0.29 \quad (6)$$

$$N = 70; \quad s = 1.07; \quad r = 0.715; \quad F = 70.9.$$

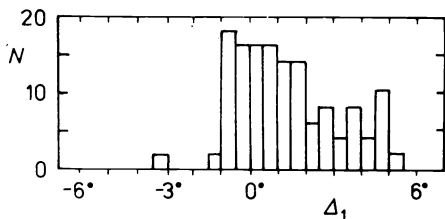


FIG. 3

Histogram of the parameter  $\Delta_1$  (or  $\Delta_2$ )

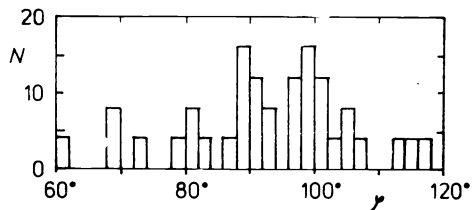


FIG. 4

Histogram of the dihedral angle  $\varphi$

\* Linear correlation between  $\tau_2$  and  $\tau_1$  showed a relatively tight correlation inside the bands. For the upper band the following holds:

$$\tau_2 = -0.904\tau_1 + 82.1$$

$$N = 70; \quad s = 15.8; \quad r = -0.904; \quad F = 305.4,$$

where  $N$  is a number of correlated points,  $s$  is an estimated standard deviation of estimation,  $r$  is a correlation coefficient,  $F = r^2(N - 2)/(1 - r^2)$ . As will be shown later, this equation has physical meaning despite its statistical irregularity.



Equation (6) shows a tendency to compensate deviations from planar *cis*-arrangement of one torsion angle by deformation of the second angle in the opposite direction. By this way, atoms of phenyl rings keep nearer to their mean plane.

The scattergram of  $\Delta_1$  and  $\tau_1$  (or  $\Delta_2$  and  $\tau_2$ ) in Fig. 8 was interpreted as follows: Deviations of a line defined by the S and C2 atoms from the axis of the angle C2—C2—C7 are not the same for structures with the  $\tau_1$  torsion near  $0^\circ$  and near  $90^\circ$ . For  $\tau_1$  near  $0^\circ$ ,  $\Delta_1$  has more positive values and for  $\tau_1$  near  $90^\circ$ ,  $\Delta_1$  is closer to the zero value. This qualitative relation is supported by a weak correlation of both parameters explaining only 25% of variance. This statement was interpreted as follows. A steric repulsion between the phenyl rings relieves not only by opening the

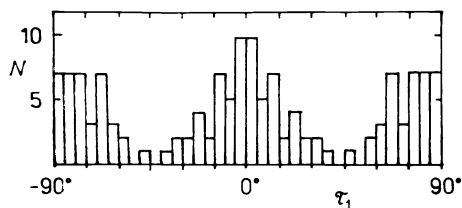


FIG. 5  
Histogram of the torsion angle  $\tau_1$  (or  $\tau_2$ )

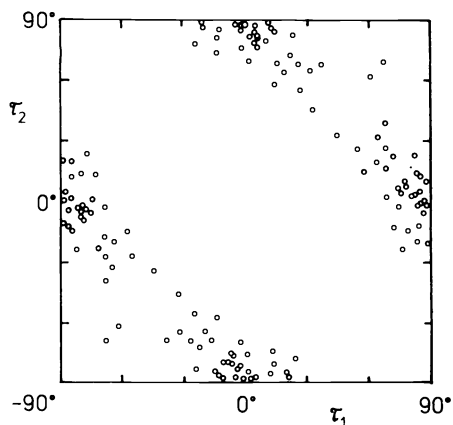


FIG. 6  
Scattergram of the torsion angles  $\tau_1$  versus  $\tau_2$

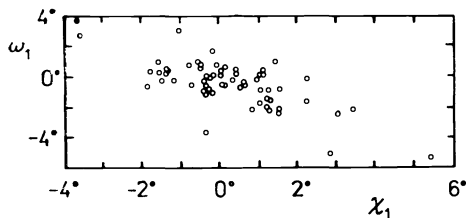


FIG. 7  
Scattergram of the torsion angles  $\chi_1$  versus  $\omega_1$

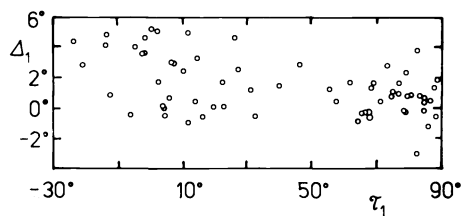


FIG. 8  
Scattergram of the torsion angle  $\tau_1$  versus  $\Delta_1$

C2—S—C8 angle but also by bending aside the phenyl ring having  $\tau_i$  near  $0^\circ$ . In this connection, it may be of interest that no correlation or any other interpretable dependence might be found between the values of the valence angle C2—C—C8 and that of the torsion angle  $\tau_1$  (or  $\tau_2$ ) because the repulsion between the rings is approximately the same in all studied fragments. This repulsion thus causes a non-specific widening of the C2—S—C8 angle from its non-strained value of  $98^\circ$ . However, if we want to study the repulsion as a function of torsion around the S—C bond, we have to use a parameter symmetrically related to  $\tau_1$  or  $\tau_2$ .

A scattergram of  $\zeta_1$  versus  $\tau_1$  (or  $\zeta_2$  versus  $\tau_2$ , Fig. 9) can be described as follows. Scatter of  $\zeta_1$  values is larger for points near  $\tau_1 = 90^\circ$  than for points near  $\tau_1 = 0^\circ$ . In other words, sulfur atoms lie nearer to a plane of those phenyl rings which have smaller torsion angles around the S—C bond.

No systematic connection between a phenyl ring substitution (Table I) and the geometrical behaviour was detected.

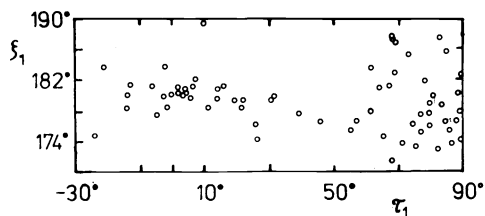


FIG. 9  
Scattergram of the torsion angles  $\tau_1$  versus  $\zeta_1$

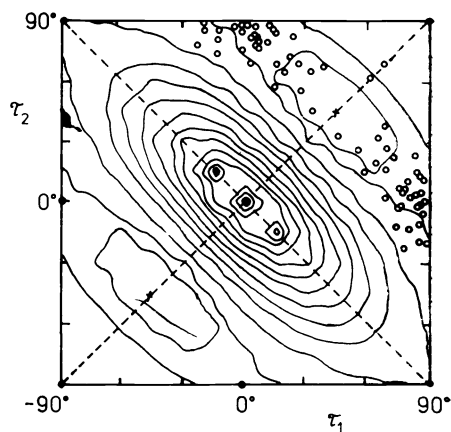


FIG.10  
The conformational map  $E = E(\tau_1; \tau_2)$  of the diphenyl sulfide molecule. Curves of constant enthalpy of formation ( $\Delta H^f$ ) are plotted in heights of 3, 5, 10, ..., 65 kJ mol $^{-1}$  above the minimum. The minimal value of  $\Delta H^f$  is 43.9 kJ mol $^{-1}$  and is indicated by a cross. Circles are images of the experimental points  $[\tau_1; \tau_2]$ . The symmetry operations of the map are drawn, too

*Molecular Mechanics and ab initio Calculation*

The conformational map of the fragment computed by molecular mechanics can be seen in Fig. 10. Valleys of low enthalpies are parallel to the lines:

$$\tau_2 = -\tau_1 + 90 - 180n, \quad (7)$$

where  $n$  is an integer and angles are in degrees. Saddle points joining two valleys are in points  $[90^\circ; 90^\circ]$  (modulo  $180^\circ$ ) and have enthalpy  $10.5 \text{ kJ mol}^{-1}$  above the minimum. An amount of 20% of experimental points are projected to regions with enthalpy lower than  $3 \text{ kJ mol}^{-1}$  above the minimum, 80% are lower than  $5 \text{ kJ mol}^{-1}$  and no point climbs higher than  $9 \text{ kJ mol}^{-1}$  above the minimum. Such a correspondence between the experimental  $[\tau_1; \tau_2]$  points and low energy valleys is rather surprising and shows that available conformational space of the free diphenyl sulfide molecule is not restricted and even not markedly deformed by passing from the gas to the crystal state.

Comparison of *ab initio* results with molecular mechanics ones is given in Table III and shows very similar results of both methods. Very good agreement between both computational methods (Table III) as well as between molecular mechanics and crystal conformations (Fig. 10) justify further usage of molecular mechanics for prediction of possible conformations of diphenyl sulfides. A high rapidity of molecular mechanics calculations will allow modelling of diphenyl sulfide molecules of practical importance.

The experimental points cumulate near inversion center  $[0^\circ; 90^\circ]$  (modulo  $180^\circ$ ) of the conformational map and not in the lowest part of the map around the point  $[45^\circ; 45^\circ]$  (modulo  $180^\circ$ ). This is the main, even when not essential, difference between the map and the experimental points. Considering that energetical dif-

TABLE III

Comparison of molecular mechanics and *ab initio* calculations of the diphenyl sulfide. The differences from the respective minimal energy are given in  $\text{kJ mol}^{-1}$

$\tau_1$	$\tau_2$	Molecular mechanics	<i>Ab initio</i>
45	45	0.00	0.00
30	60	1.00	0.73
0	90	3.81	3.79
60	60	4.27	4.37
90	90	10.29	10.51

ferences inside the valleys are small (lower than say  $5 \text{ kJ mol}^{-1}$ ), this may be either a coincidence or an influence of crystal packing forces. In the latter case, it is not quite clear why crystal packing should prefer "inversion" conformations with  $\tau_1 = 0^\circ$  and  $\tau_2 = 90^\circ$  and exclude "reflection" conformations with  $\tau_1 = \tau_2 = 45^\circ$ . To attribute the excess of the "inversion" conformations to an influence of entropy seems to be premature without much more detailed thermodynamic considerations of the diphenyl sulfide fragment.

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