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# CONFORMATIONAL ANALYSIS—CXVII

## METHYL ETHYL DISULFIDE. MOLECULAR MECHANICS AND MOLECULAR ORBITAL CALCULATIONS[1]

N. L. ALLINGER,* J. KAO and H-M. CHANG
Department of Chemistry, University of Georgia, Athens, GA 30602, U.S.A.

and

D. B. BOYD
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46206, U.S.A.

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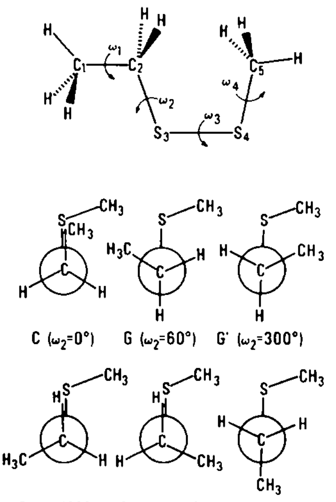
**Abstract**—The conformation of methyl ethyl disulfide was investigated by molecular mechanics calculations using a recently developed force field for sulfur-containing alkanes. The results indicate that in the gas phase the molecule exists predominantly in two conformations, both with the CS–SC dihedral angle *gauche* (84°), and the SS–CC dihedral angle either *gauche* (72°) or *trans* (179°), and the methyl protons staggered. *Ab initio* molecular orbital calculations using an STO-3G basis set were employed to corroborate that these two conformations are of roughly equal stability, and that the next most stable conformation (by 0.6 kcal/mole) has the SS–CC dihedral angle *gauche* (295°) with the terminal methyls proximal. In contrast to earlier CNDO/2 (*spd*) predictions, the SS–CC *cis* conformer is the least stable, and no sizable attractive S···H–C nonbonded interactions are discerned. Reasons for this are traced to a failure of the CNDO/2 method, which is especially serious when *d* orbitals are included in the basis set (*spd*) and the rigid rotor approximation is used. The present results are found to be consistent with recent electron diffraction, IR, Raman spectroscopic and X-ray diffraction data. The conformation of diethyl disulfide was also investigated by molecular mechanics calculations, and again *gauche* and *trans* SS–CC arrangements are predicted to be preferred.

## INTRODUCTION

A CNDO/2 (*spd*) molecular orbital (MO) study was recently reported by Scheraga *et al.* regarding the preferred conformations of methyl ethyl disulfide.[2] The equilibrium CS–SC dihedral angle (Fig. 1) was found at about 90°, which is typical of disulfides.[2-12] The surprising result of the CNDO/2 (*spd*) calculations was that methyl ethyl disulfide is most stable with a 0° SS–CC dihedral angle. Such a conformational preference would be in sharp contrast to those seen for the *n*-alkanes,[13] which are ordinarily gauche (60° ± 30°) or anti (180° ± 30°). It was concluded[2] that the *cisoid* conformation in methyl ethyl disulfide and other sulfur-containing hydrocarbons† is more stable than might be anticipated because of some unidentified, attractive interaction between a sulfur atom and C-H units when they are separated by three covalent bonds. A non-committal name, 1,4-carbon–sulfur interaction was adopted.[2] With an optimal CS–SC dihedral angle of 90°, the SS–CC trans (T) conformer was calculated by the CNDO/2 (*spd*) method to be 2–4 kcal/mole less stable than the *cis* (C). The *gauche* (G,G′) and *skew* (S,S′) conformers (Fig. 1) were even less stable than the T conformer. It was further concluded[2] that because of the known tendency of CNDO/2 to underestimate repulsive potentials, the stability of the *cis* conformation was probably overestimated, and at the energy minimum the molecule could be slightly twisted away from the 0° dihedral angle obtained calculationally. Sabin[14] earlier showed that CNDO/2 (*spd*) theory performs poorly in treatments of the S···H–S hydrogen bond, and, in fact, he explicitly warned of difficulties in applying this method to hydrogen-bonded systems involving second-row atoms in general. Sabin suspected the fault lay in the *d* orbital parameterization. The nature of the CNDO/2 shortcoming was that the stabilization to be derived from S···H–S interactions was overestimated by factors between 30 and 400 compared to *ab initio* MO calculations.[14]

Obviously, in the case of S···H–C interactions there will be less ionic bonding than in the usual H-bond, and Scheraga *et al.*[2] carefully avoided referring to the S···H–C



C (ω2=0°) G (ω2=60°) G′ (ω2=300°)
S (ω2=120°) S′ (ω2=240°) T (ω2=180°)

Fig. 1. Structures and numbering system for methyl ethyl disulfide. Newman projections of the SS–CC conforms look down the $S_2$–$C_3$ axis. The *cis* and *trans* SS–CC conformers for rotation about this axis are labeled C and T, respectively. There are two *gauche* (G and G′) and two skew (S and S′) conformers possible.

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†These include the dialkyl sulfides and disulfides in Ref. 2 and apparently also diaryl disulfides. For example, in Ref. 11, the preferred conformation of diphenyl disulfide is predicted by CNDO/2 (*spd*) to have a CS–SC dihedral angle of 90° and SS–CC dihedral angles of 0°.

interactions as H-bonds. These workers also recognized that CNDO/2 (*spd*) could overestimate the strength of the 1,4 carbon–sulfur interaction, but they did not mention by how much. They cited estimates of S···H–C bond enthalpies being in the range 1–2 kcal/mole and larger than O···H–C or N···H–C values.[15] Such estimates are larger than the 0.4–0.7 kcal/mole values for the S···H–S stabilization energies obtained from the *ab initio* calculations on $H_2S$ dimers.[14] Even if a stabilization energy of 1 or 2 kcal/mole could be derived from an intramolecular S···H–C interaction, this might not be enough to overcome the energy of eclipsing bonds necessary to achieve the requisite C conformation of the disulfide. But if this stabilization energy were overestimated by an order of magnitude, for example, then a 2–4 kcal/mole apparent (but unreal) preference for the C conformers is easily conceivable. Therefore, one cannot help but question the reliability of the CNDO/2 (*spd*) predictions.

A consequence of the tendency† of the CNDO/2 (*spd*) method to overestimate the attractive part of the S···H–C interaction potential with respect to the repulsive part is that nonbonded contact S···C distances of 2.5–3.0 Å occur in the predicted equilibrium C conformations of some of the thiaalkanes.[2] These distances seem short indeed. Space-filling molecular models of the CPK type[17] suggest that severe steric overlaps occur in the C conformations of the thiaalkanes. The situation is partially ameliorated, if, as Scheraga *et al.* recommend,[2] the S···C van der Waals contact distance is revised downward from 3.85 to 3.40 Å. It is interesting to notice that the cited X-ray data[2] on the *aliphatic* disulfides show the close S···C contacts generally occur *without* SS–CC dihedral angles near 0°, and in fact, the dihedral angles prefer to be in the gauche region. X-ray diffraction data[2] do support the existence of rather small SS-CC dihedral angles in crystalline *aryl* disulfides. These structures display large SSC bond angles and long S–C bond lengths, however. The situation here seems to be that the near coplanarity comes about because it allows effective delocalization of the lone pair of electrons in a sulfur 3*p* orbital into the aromatic ring. The relatively long $C_{Ar}$–S bonds in the near-coplanar compounds have been interpreted[2] as indicating relatively unimportant $C_{Ar}$–S conjugation, since the increased bond orders should yield shorter bonds. Steric repulsions will tend to stretch the bond, however, and the interpretation of the outcome of these effects on the bond lengths is ambiguous. The opening out of the bond angles, however, seems to be a clear indication of repulsion. We will therefore limit our consideration to *alkyl* disulfides in assessing the inherent characteristics of a 1,4 carbon–sulfur interaction.

In this paper we will examine the conformation of one of the simplest thiaalkanes claimed[2] to manifest the 1,4 carbon–sulfur interaction, namely, methyl ethyl disulfide. Later in the paper, diethyl disulfide will be briefly discussed also. We have employed computational methods of established reliability for structural predictions. Owing to the ordinary nature of the conformational information obtained, we believe that any novel S···H–C interactions are too small to appreciably affect the relative populations of the SS–CC rotamers of these molecules in the gas phase. We will not probe here the question of the directionality of sulfur lone-pairs[7,18] and how that might affect nonbonded contacts of sulfur.‡

Experimental investigations on methyl ethyl disulfide have only partially succeeded in establishing the relative conformer populations. Gas phase electron diffraction data[21] indicate that (a) *more than one conformer is present* at room temperature, (b) the trans conformer is present to a substantial extent (at least 36%), (c) the gauche conformer constitutes the remaining fraction if the trans form is present in the 36–45 percent range, (d) the relative amounts of the C, G, G′, S and S′ conformers (Fig. 1) cannot be determined uniquely in the least squares fits. Early Raman and IR spectra of methyl ethyl disulfide were interpreted[22,23] as though the gauche forms were about 0.9 kcal/mole more stable than the T form in the liquid state and only the gauche are present in the solid state. The G and G′ conformers were not distinguished in the vibrational studies, and the amounts of S, S′ and C conformers were not mentioned.[22,23] After this paper had been submitted for publication there became available to us the results of temperature dependent Raman spectral studies,[24] which were interpreted as indicating the coexistence of three conformers derived from rotation about the SS–CC bond. Two of these were similar in energy, and the third was less stable by about 0.3–0.8 kcal/mole. It was concluded that the latter was not the *trans* form.[24]

## METHODS

The computational methods that we have used are a molecular mechanics method and an *ab initio* quantum mechanical MO method. The molecular mechanics method has been described previously[13] and has been parameterized recently for thiaalkanes and polysulfides.[12,19] Previous applications[12,19] of this method have demonstrated its ability to predict not only conformational energies, but also bond lengths, bond angles, and dihedral angles in good agreement with experiment. Thus we have the opportunity to compare later in this paper the geometrical parameters of methyl ethyl disulfide from the electron diffraction study[21] with our values. No special 1,4 interaction between carbon and sulfur (other than the normal van der Waals interaction) was considered in the parameterization of the force field. If such parameterization is required to match experimental facts, then we could not expect the calculations to reproduce these facts. Conversely, if the calculations do reproduce the experimental facts, then we have evidence for the lack of any special 1,4 interaction. (Note that we use the expression *evidence for*, not *proof for*, because the facts chosen may not have been appropriate for demonstration of the effect.)

With regard to the molecular mechanics method, it is interesting to note that this method predicted[12] that the chair conformation of cyclohexasulfur $S_6$ is the most stable conformation, and a barrier of 29.9 kcal/mole separates it from the boat form which is 19.7 kcal/mole less

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†The fairly well known characteristic of CNDO/2 theory to predict equilibrium nonbonded contact distances to be too short is also evident in the study of N-methylpyridinium chloride (Ref. 16 and D. B. Boyd, unpublished work). The latter work showed that in optimizing the position of a chloride ion in the plane perpendicular to and bisecting the pyridinium ring through N, the Cl atom prefers a location over the center of the ring and only 1.3–1.4 Å above it. The CNDO/2D charge distribution is unusual at this abnormal geometry with the Mulliken net atomic charge on Cl almost neutral (−0.03 e) and the Cl···N Mulliken overlap population slightly bonding (0.07 e). According to these calculations this geometry with Cl···N 1.7 Å and Cl···C ortho 1.85 Å is more stable than the geometry with Cl 3.3 Å perpendicularly above the nitrogen by the huge amount of 184 kcal/mole.

‡As explained in Ref. 19, S atoms are approximated as being spherical in the present molecular mechanics calculations, although refinements, such as those used in treating oxygen lone-pairs (Ref. 20), may be instituted if proved to be necessary.

stable. Recent CNDO/2 calculations[25] gave lower estimates: the barrier was calculated at 23 kcal/mole and the boat form appeared to be only 4 kcal/mole less stable than the chair. Here again the CNDO/2 results seem to be exhibiting too little nonbonded repulsion. The molecular mechanics method has also been used to study $S_8$. An equilibrium geometry is predicted where the molecule has $D_{4d}$ symmetry and S–S bond lengths of 2.02 Å, SSS bond angles of 107.2°, and SS–SS dihedral angles of 99.7°. These are in good agreement with experimental X-ray diffraction data.[26,27] The previously calculated chair conformational preference of thiane[19] was corroborated by a recent microwave study.[28]

Another calculational method used in the present work is the *ab initio* STO-3G MO method.[29,30] This method has proven useful in structural studies of ethane,[30] acetone,[31] $S_8$,[27] and numerous other molecules.[30] The minimum basis set is expected to give fairly reliable structural predictions without augmenting it with *d* functions.[14,32] The input geometries used for the *ab initio* calculations were the optimized structures from the molecular mechanics calculations. We used the STO-3G basis set because its small size permits treatment of a molecule as large as methyl ethyl disulfide, but we concede that the calculated conformational energies so-obtained may be only semiquantitatively correct. The numbers from the molecular mechanics results are expected to be more accurate. The *ab initio* method does have one important advantage, however. Namely, this MO method should be able to expose any unexpected electronic effects in a 1,4 carbon-sulfur interaction without having to be parameterized for this type of potential.

We also will discuss CNDO/2 MO calculations using standard parameters[33] both with (*spd*) and without (*sp*) sulfur 3*d* atomic orbitals in the basis set.

## RESULTS AND DISCUSSION

Looking first at our results from the molecular mechanics calculations on methyl ethyl disulfide, we calculate that G, T and G′ forms belong to local energy minima, with G and T forms being almost equally stable and more stable than the G′ form by about 0.7 kcal/mole, while S, S′ and C forms are rotational transition states. The calculations are summarized in Table 1. The calculated potential curve is depicted in Fig. 2. Note that the curve is rather soft between G′ (optimized SS–CC dihedral angle 295°) and G conformations since the maximum barrier is only about 1 kcal/mole. The calculated and experimental[21] geometries corresponding to form G (shown in Table 2) are in quite satisfactory agreement with each other. Structural parameters for the T conformer are not greatly changed from the G values, except, of course, for the SS–CC dihedral angle.

These calculations support neither the idea that there is a nonbonded 1,4-attraction between the S atom and the Me group, nor the idea that the C form is the most stable. Rather, there is a calculated repulsion in the C form, which is largely relieved by opening the SCC and SSC bond angles,† so that both the sulfur and carbon move away from each other, resulting in an optimized minimum $S\cdots H$ contact distance of 2.96 Å. Note that this distance is reasonable with respect to a $S\cdots C$ contact distance near 3.40 Å, since the $S\cdots H$–C contacts are not in general colinear. Although according to the force field the final interactions between the methyl group and the S atom are slightly attractive in some of the optimized geometries, nonbonded repulsions are the *cause* of the bond angle bending. In general, one would expect the resultant 1,4-interactions to be weakly attractive or repulsive depending on the final geometry and the nature of the dialkyl sulfide or disulfide in question.

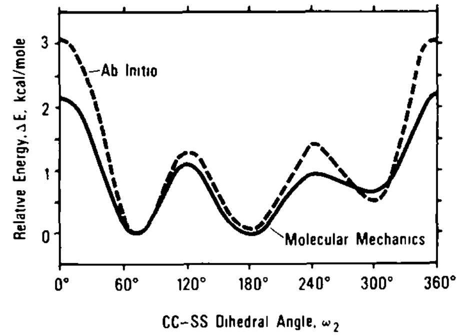

Fig. 2. Potential energy curves for rotation about the SS–CC bond of methyl ethyl disulfide. The solid curve shows the energy obtained with full geometry optimization according to the molecular mechanics method. The dashed curve was obtained from the *ab initio* STO-3G MO method using the optimized geometries from molecular mechanics at the dihedral angles corresponding to maxima and minima of the solid curve. Energies for each curve are relative to those for the most stable conformer (G) (see Ref. 40).

As described earlier,[34] our force field indicates that the repulsive interactions between *vicinal*-2,3-hydrogens of butane are mainly responsible for the relative instability of gauche conformations with respect to the anti. Whether or not this corresponds to physical reality is not yet known, but this is the interpretation which follows from our force field. A similar explanation has been successfully employed in interpreting the equatorial preference of a substituent on a cyclohexane ring.[34,35] An analogous situation is found in methyl ethyl disulfide. The sulfur atom $S_4$ in the T conformer is squeezed between two vicinal hydrogens, whereas there is only one corresponding repulsion plus one attenuated 1,4-nonbonded $C\cdots S$ interaction in the G form. The energy difference calculated between the G and T forms depends mainly on how much steric energy can be relieved versus the increase in energy from other deformations.

As can be seen in Table 1, the trend in the relative stabilities of the methyl ethyl disulfide conformers from the molecular mechanics results are in strikingly good agreement with the *ab initio* results. Both the molecular mechanics potential curve and the *ab initio* one (based on the six points obtained in each case) are displayed in Fig. 2. The curves have similar shapes and match quite well in most regions.[40]

Both of our calculational procedures show that the relative populations of the SS–CC rotamers of methyl ethyl disulfide (gas phase) are in the order $G \approx T > G' > S, S' > C$. This order is consistent with the conclusions from the electron diffraction study.[21] It is also in agreement with the recent temperature dependent Raman spectral data[24] which show three relatively stable rotamers about the S–C bond. While Yokozeki and Bauer[21] refer to

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†The SCC bond angle opens to 116.4° in C and 112.5° in G′ compared to 109–110° for the T and G conformers of Table 2. The SSC bond angles are less affected by conformational changes with only the $S_2S_3C_4$ angle opening to 107.0° in C and 105.1° in G′. CCH bond angles are not especially sensitive to conformational changes.

Table 1. Calculated relative energies (kcal/mole)

| Molecule | Molecular Mechanics | Ab initio STO-3G | CNDO/2 (spd) | CNDO/2 (sp) |
|---|---|---|---|---|
| Methyl ethyl disulfide | | | | |
| G | 0.00 | 0.00[a] | 0.68 | 0.91 |
| T | 0.01 | 0.06 | 0.00 | 0.00 |
| G' | 0.68 | 0.58 | 1.57 | 0.95 |
| S' | 0.94 | 1.38 | 1.42 | 1.45 |
| S | 1.13 | 1.26 | 1.45 | 1.33 |
| C | 2.12 | 3.06 | 1.28 | 1.53 |
| C[b] | 11.67 | 9.02 | -2.08 | 3.81 |
| G[b] | 0.60 | - | 0.14 | 1.27 |
| Diethyl disulfide | | | | |
| GG | 0.00 | | | |
| GT | 0.01 | | | |
| TT | 0.04 | | | |
| GG' | 0.61 | | | |
| G'G' | 2.25 | | | |

[a] Total energy of this conformer is -903.2392 a.u. (1 a.u. = 627.54 kcal/mole).

[b] These conformations were obtained by a rigid rotation from the optimized trans conformation All other conformations were allowed to relax in all degrees of freedom, except for dihedral angle in the case of eclipsed conformations.

Table 2. Geometries of methyl ethyl disulfide

| Bond Length (A) or Angle (Deg) | Calcd.[a] G | Calcd.[a] T | Exptl.[b] G |
|---|---|---|---|
| $(C-S)_{av}$ | 1.821 | 1.822 | 1.817 ± 0.004 |
| S-S | 2.030 | 2.030 | 2.031 ± 0.003 |
| C-C | 1.529 | 1.530 | 1.540 ± 0.007 |
| C-C-S | 110.3 | 108.9 | 112.4 ± 1.6 |
| $(S-S-C)_{av}$ | 104.0 | 103.7 | 103.2 ± 0.3 |
| C-S-S-C | 83.5 | 83.5 | 84.4 ± 6.9 |
| C-C-S-S | 72.1 | 178.8 | 66.8 ± 7.6 |

[a] Methyl group hydrogens are staggered (i.e., one HC-SS or HC-CS dihedral angle is near 180° and the other two are about 120° away from this). Optimized C-H bond lengths are near 1.10 Å, and other optimized bond angles are 110.3-112.0° (CCH), 104.7-108.4° $(S_3C_2H)$, and 107.3-110.7° $(S_4C_5H)$.

[b] Ref. 21. The dihedral angles given are presumably sensitive to assumptions made regarding the conformational composition.

the Raman data[24] as showing rotamer populations in the order G > T > G', Scheraga *et al.*[24] did not make that claim, but concluded that there are two nearly equally stable rotamers (they did not specify which ones) and a third rotamer which is about 0.3–0.8 kcal/mole less stable than the other two. They did conclude the least stable conformer was not trans. Even though their CNDO/2 (*spd*) calculations[2] on this molecule showed only two stable rotamers and populations in the order C > T, they were encouraged by their MO results to describe the third conformer as C. In Sugeta's earlier Raman work,[23] one rotamer, presumed to be T, was estimated to be about 0.9 kcal/mole less stable than a second rotamer, presumed to be G.

What emerges from our calculations is that there are three stable rotamers as Scheraga *et al.* find, and that the rotamer estimated to be 0.3–0.9 kcal/mole less stable is G'. Note in Table 1 that the relative energy of G', 0.7 kcal/mole, is exactly in the range of the experimental estimates. Thus, G, T, and G' are all relatively stable, whereas C is not. Hence our calculations are apparently in good agreement with the published data up until early 1976, although not with all of the conclusions drawn from those data (see below).

A detailed analysis of the STO-3G charge distribution of methyl ethyl disulfide reveals that there is no significant intramolecular H-bonding, nor is there any significant variation of electrostatic interactions among conformations. The calculated Mulliken net charges on both S atoms are slightly positive, whereas the charge on the methyl carbon C of the Et group is negative. Note that these net charges on carbon and sulfur are opposite to those obtained from the CNDO/2 (*spd*) method,[2] which gives negative charges on sulfur and a slightly positive charge on the carbon. The *ab initio* positive charges that we calculate on the methyl sulfur ($S_4$, Fig. 1) are, respectively, +0.060, +0.060, +0.059 and +0.065 for T, G, G′ and C forms, and charges calculated on the carbon atom C-1 are −0.171, −0.173, −0.176 and −0.175, respectively. Hence, it is expected that a slightly more attractive electrostatic interaction among these atoms will be found in the C form rather than the T form, although the variation of the electrostatic energy among conformers should be pretty small. Most of this attractive electrostatic interaction would be balanced out by the repulsion between the sulfur and the slightly positively charged hydrogens on the C-1 atom, which became even more positive in the C conformer. The *ab initio* charge distribution does show that the C-1 Me group hydrogens have more positive net atomic charges (+0.059 to +0.066) in the C conformer than in the other conformers (+0.056 to +0.063).

The *ab initio* charge distributions are not consistent with a picture of S···H–C hydrogen bonding. What occurs in the usual hydrogen-bonded systems according to STO-3G MO calculations[36] is that the hydrogen donor and acceptor atoms become more negative and the hydrogen itself becomes more positive in the dimer compared to the separated monomers. As noted above, the methyl carbon C-1 becomes quite (but not the most) negative in the C conformer. The sulfur S-4 is most positive in the C conformer, so the S···H–C interaction has induced a shift in electron density away from, rather than toward, the sulfur.

The Mulliken population analysis also provides some insights into the bonding relationships among conformations. In cases of the G and T forms, the overlap populations between the S-4 sulfur and the C-1 Me group atoms are negligible (0.000) and indicative of the absence of significant bonding and antibonding covalent interactions. This is consistent with molecular mechanics calculations which show no appreciable interactions (less than 0.2 kcal/mole) of a 1,4 type. Furthermore, according to the molecular mechanics calculations the C form is more crowded and has larger interactions between the S atom and the Me group (about 0.6 kcal/mole). Indeed, the overlap population between the sulfur and the Me group in the C form is slightly negative, −0.003 (essentially from the C, S atom-pair overlap), and indicative of a slight antibonding interaction.

Both experimental and theoretical studies have shown that intermolecular S···H–S hydrogen bonds do exist in a variety of systems.[14,37] However, the interaction is quite weak with a stabilization energy of no more than about 2 kcal/mole.[14,37] Still smaller stabilization energies are anticipated for S···H–C interactions, especially since at no time during rotation about the S–C bond are the C–H bond and the S atom colinear in methyl ethyl disulfide. Hence, it seems unlikely both on the basis of the charge distributions discussed above and on the basis of these latter considerations that any appreciable amount of S···H–C hydrogen bond interaction can be said to exist in the dialkyl disulfides.

The CNDO/2 (*spd*) calculations reported by Scheraga *et al.*[2] included *d* orbitals. Our *ab initio* calculations did not. One might ask if the exclusion of *d* orbitals here is in part responsible for the large differences in the results of the calculations. We are not able at this time to include *d* orbitals in our *ab initio* calculations. However, we were able to investigate the matter by comparing CNDO/2 calculations which included *d* orbitals (*spd*) with those excluding them (*sp*). Both sets of calculations used our molecular mechanics geometries. The results are summarized in Table 1. It is important to point out that the calculated energies depend markedly on whether relaxed geometries are used, or rigid rotation is assumed. If one used the relaxed molecular mechanics geometries, which are believed to be near the true geometries, then the CNDO/2 results are not too bad, and they do not depend very much on whether *d* orbitals are included or not. However, if one uses a rigid rotation, then the energies are strongly dependent on whether *d* orbitals are included (see Table 1). In this case, inclusion of the *d* orbitals gives populations in the order C > T, whereas excluding them gives T > C as obtained with the molecular mechanics and *ab initio* calculations.† Of course, any calculational method should have the energy minimized with respect to the geometry. The CNDO/2 (*spd*) results are thus really very poor, although one would not know this if one looks at only the results for conformations generated by rigid rotation.

Diethyl disulfide is another interesting molecule we can consider here. Based on our methyl ethyl disulfide results, the larger molecule can in principle exist in six distinct conformations which may be designated as TT, TG, TG′, GG, GG′ and G′G′ according to the configuration of the two SS–CC chains. Implicit in these designations is the fact that the CS–SC dihedral angle will be between 80° and 90° as usual. One may expect that the conformations having the G′ arrangement ought to have higher energies than those with only G or T arrangements, and G′G′ will be of still higher energy. Scott *et al.*[38] assumed, quite reasonably, that consideration of only the TT, GG and TG conformers should suffice in interpreting the vibrational spectra of this molecule. They reported that the spectra of this molecule indicate the presence of *two* conformations, and they argued at first[38] in favor of the TT form as being the more stable isomer, but later[22] they concluded that GG is the most stable with TG the second contributing form. By the study of the temperature dependence of Raman spectra, Sugeta reported that the GG isomer is more stable than the TG isomer by 0.6 ± 0.2 kcal/mole in the liquid state and only the GG form is observed in the solid state.[23] These vibrational spectral studies are thus consistent with each other, although the assignment of conformations is not unequivocal.

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†The CNDO/2 (*spd*) results are also rather poor for rotational barriers about the S–$CH_3$ bond of methyl ethyl disulfide. This method gives a barrier height of only about 0.1 kcal/mole, whereas the force field calculations and the *ab initio* and CNDO/2 (*sp*) MO calculations all give a barrier of about 1.6 kcal/mole. The latter figure is in excellent agreement with experimental and earlier MO results on the S–$CH_3$ rotational barrier in dimethyl disulfide (Ref. 4).

Our calculations on diethyl disulfide (Table 1) predict relative populations of the three most stable conformers is in the order GG ≈ GT ≈ TT, qualitatively consistent with the experimental deductions. However, the molecular mechanics calculations give much smaller energy differences than those deduced experimentally.[23] Our conclusion is that all three conformations have similar energies and co-exist in nearly equal proportions in fluid phases, and hence, do not contribute temperature dependence to the vibrational spectra. Rather, the higher energy conformer detected spectroscopically is the GG′. One also notes in Table 1 that the relative conformational energies of diethyl disulfide are very nearly additive from the corresponding values in methyl ethyl disulfide. Thus, the GG′ form lies about 0.6 kcal/mole above the GG. The CC form is very high in energy and is just a transition state on the potential energy surface. By way of contrast, CNDO/2 (*spd*) predicted[2] the CC form of diethyl disulfide to be most stable.

Before concluding, it is worthwhile to insert here some remarks about additional Raman spectral studies[39] which came into our hands after our present paper had been accepted for publication. These studies were aimed at finding cisoid SS–CC arrangements in molecules more complex than methyl ethyl and diethyl disulfide, and at assigning the S–S stretching frequency which might be associated with those arrangements. Van Wart and Scheraga complied[39] X-ray crystallographic data for these compounds and also presented interesting histograms showing the frequency of observation of various SS–CC and CS–SC dihedral angles in the cystine residues of eight proteins. The X-ray determined dihedral angles have an uncertainty of 20–30°. The SS–CC histogram shows that the most frequently occurring values are at or on the high side of the *gauche* region 50–100°. Second most frequent are values in the trans region, and a third peak is seen in the low *gauche* region 20–30°. To these data could be added X-ray determined dihedral angles for smaller, but still complex, disulfides also summarized by these authors.[2,39] Either with or without these additions, by far the most common SS–CC dihedral angles are at or on the high side of the *gauche* region. Note that the most stable conformers of our model disulfides, methyl ethyl and diethyl disulfide, have SS–CC dihedral angles in this region too. The occurrence of SS–CC dihedral angles in the trans region is also understandable in terms of the potential energy curve we obtain. Structures observed to have SS–CC dihedral angles in the low gauche region contrast with the lack of a corresponding minimum in our energy curves (Fig. 2). In fact, the curves seem too steep for even a shoulder to be expected in the 20–30° region. Whereas one cannot expect the data from gas and condensed phases to be exactly comparable, the crystallographic data suggest to us that the S–C rotational potential is soft enough for the SS–CC conformation to be easily compromised at the expense of other structural constraints in the molecules. Our calculations show that the conformational energy of methyl ethyl disulfide hardly rises above 1 kcal/mole all the way from 30° to 330° SS–CC dihedral angle. In contrast to the broad peaks in the SS–CC histogram,[39] the histogram for the CS–SC dihedral angles in proteins shows a distinct and sharp peak near 90°. This finding is consistent with the 7–11 kcal/mole calculated for the CS–SC rotational barriers in model disulfides.[4,9,12] Thus, most of an imposed deformation will show up in the S–C rotational isomers, not the S–S isomers, Van Wart and Scheraga state[39] that the reason for not observing a low gauche SS–CC conformer in the simple model disulfides in X-ray studies is that it is less stable than the other forms. While we agree such a structure is less stable, our conclusions differ from those of Van Wart and Scheraga[39] in that we do not find a stable conformation in the cisoid region (their "A" conformer) in simple molecules in the gas phase. To the extent that such conconformations exist under more constrained conditions of phase or structure, we suspect that they result from outside forces (van der Waals, etc), not from the inherent torsional potential function of the SS–CC bonding arrangement.

## CONCLUSIONS

The present calculations on methyl ethyl disulfide using molecular mechanical and quantum mechanical methods of proven utility give conformational and structural information in satisfactory agreement with each other and with recent experimental electron diffraction, infrared, and, except perhaps for one or two questionable points, Raman spectroscopic results. Moreover, the calculations provide information where the experiments have been inconclusive or unrevealing. Both types of calculational methods indicate that in the gas phase the trans and one of the *gauche* SS–CC conformers of methyl ethyl disulfide are of nearly equal stability, and the second *gauche* form (G′) is the next most stable. The 2–3 kcal/mole energy cost to force methyl ethyl disulfide into a *cisoid* structure with short intramolecular S · · · H–C contacts means that this form will not be frequently encountered. Similar conformational preferences are seen in calculations on diethyl disulfide, and are expected to carry over to related thiaalkanes. We should emphasize that our results apply most directly to the isolated SS–CC moiety. When it occurs in complex molecules or proteins (as part of cystine), then structural constraints may be imposed on it by the rest of the molecule or neighboring molecules. These constraints, such as crystal packing forces, solution effects, resonance effects, or ring systems, may twist the SS–CC moiety away from one of the preferred conformations we find. Condensed-phase data obtained in the vibrational and X-ray diffraction studies seem to be understandable in terms of the softness of the calculated rotational potential energy curve between the gauche and trans conformers.

Our results are not incompatible with the existence of close S···H–C nonbonded contacts. Our calculations do not show them to be especially attractive. Although conceivably the S···H–C interactions could be slightly stabilizing, the force field and *ab initio* calculations show that the net result of eclipsing the SS–CC moiety is to make the cisoid conformers of methyl ethyl disulfide 2–3 kcal/mole less stable than the equilibrium gauche conformer. Thus, close S···H–C contacts of this sort appear to cost more energy than can be derived from them. Structural constraints seem to be necessary to make up the energy deficit. X-ray crystallographic data[2,39] also support this conclusion in terms of the non-occurrence of *cis* SS–CC dihedral angles in the simple dialkyl disulfides, the low frequency of occurrence of small SS–CC dihedral angles in the more complex disulfides, and in the form of bent bond angles and stretched bond lengths in structures where they do occur.

While very useful in stimulating the accumulation of valuable Raman and X-ray data, earlier CNDO/2 (*spd*) calculations[2] appear to have given spurious conformational predictions on the model thiaalkanes because of this method's overestimation of nonbonded S···H–C attractions with respect to the overlap repulsions. The problem is present to some degree without *d* orbitals in the basis set, but becomes especially evident when they are present. How much this problem could be alleviated with suitable reparameterization and how much is inherent in the theory is not known. Scheraga *et al.*[2,24,39] pointed out the possibility that their CNDO/2 (*spd*) predictions might yield conclusions which were contrary to fact, and we concur.

Finally, some comments regarding the discrepancies between our conclusions and those[24] of Van Wart and Scheraga appears to be in order. Their spectral interpretations and our calculations agree that there are two methyl ethyl disulfide conformers of equal stability, G and T, and there is a third conformer which is several tenths of a kilocalorie less stable. The only disagreement is that we believe this third conformer to be G′ and they believe that it is "A". Since they see only three conformations spectroscopically, the G′ conformer is not specifically accounted for by them. Their spectroscopic arguments seem reasonable, and might be convincing in the absence of the theoretical calculations reported herein. The possibility of the misassignment of spectral bands always exists, of course. On the other hand, the *ab initio* calculations are not infallible either. The use of a larger basis set and a more thorough exploration of the energy surface in question would be desirable, but this is currently an economic impossibility for us. Since the postulated 1,4 carbon-sulfur interaction does not, at least so far, stand up to theoretical scrutiny we do not believe that its existence has been convincingly demonstrated.

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[40] A referee has asked that we express these potential curves in terms of Fourier series, and compare them. While this could be done, we feel that it would be misleading. It is not possible to fit these curves very well with only $V_1$, $V_2$ and $V_3$ terms in the series. The reason is mainly that there is a large steric effect at $\omega = 0°$ (which is not "Fourier-like") superimposed on the inherent "torsional potential". Five (or more) term series expansions will fit the observed curves well, but they cannot be given any simple physical interpretation. The relative energies at $\omega = 0°$ differ significantly in the *ab initio* and molecular mechanics calculations, and this is probably due in part to the fact that the energy is minimized for the molecular mechanics calculations (an approximate $r_a$ or $r_g$ structure), and then those structures are used for the *ab initio* calculations (where the $r_e$ structures are wanted). In generating the rotational curves the errors should approximately cancel, but the structures are likely to differ most where the steric energy is largest, and the *ab initio* energy would then be higher at this point due to the structure corresponding to a less-well minimized energy. This trend of the exaggeration of energy changes with conformation may be anticipated when *ab initio* and molecular mechanics calculations are compared in this way. The small basis set used also introduces some uncertainty.