DISULFIDE CONFORMATIONAL ANALYSIS

THE NATURE OF THE S–S ROTATION BARRIER[1]

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Abstract—Previous DNMR measurements for a series of bulky disulfides led to the conclusion that rotation about the S–S bond occurs preferentially through the *cis* transition state. To investigate this conclusion and to study the conformational properties of disulfides in general, we have applied Allinger's force field to a series of dialkyl disulfides generated by homologating dimethyl disulfide to di-t-butyl disulfide. The optimized ground state geometries evidence a gradual increase in the CS–CS dihedral angle from 83 to 114° and indicate that increased substituent bulk drives the disulfide system in the direction of the *trans* rotational maximum. Explicit calculation of barrier heights yields $\Delta E(trans) < \Delta E(cis)$ in every case. Furthermore the energy gap, $\Delta\Delta E(cis-trans)$, increases sharply as substituent size grows. This trend results from a rapid rise in the *cis* barrier and a small drop in the *trans* one. A rotation-inversion pathway is ruled out and it is concluded that disulfide conformational isomerization occurs by way of the *trans* transition state.

Torsion about the S–C bonds for several t-Bu substituted disulfides is considered. A strongly coupled alkyl-t-Bu rotation is observed computationally in accord with Nelander and Sunner's speculations concerning a "cogwheel" effect." $\Delta G\dagger$ trends for S–S rotation are discussed in connection with the latter.

Finally a $\Delta H(S–S)$ parameter is derived. Heats of formation and strain energies for dialkyl disulfides are calculated.

Geometry about the disulfide bond is a determining factor in protein structure.[2] In part this has stimulated the evaluation of both ground state structures and activation barriers for conformer interchange by experiment[3] and theory.[4] Recently Fraser *et al.* reported a variable temperature NMR study for a series of bulky acyclic disulfides.[5] The barrier to rotation about the S–S bond was found to increase from $\Delta G\dagger = 7.0$ to 8.8 kcal/mol with an increase in substituent size. The apparent steric rate retardation was interpreted in terms of a strong preference for the *cis* rotameric transition state over the *trans*.
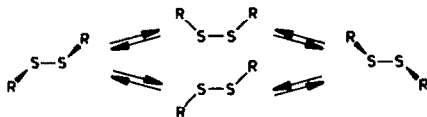
Although *cis/trans* barriers for simple, uncongested disulfides (e.g. HSSH and CH₃SSCH₃) have been computed at various levels of sophistication,[4] the *trans* energy maximum is consistently placed below the *cis*. None of the studies, however, have surveyed a range of sulfur substituents; and, more important, none have employed full geometry optimization along the potential energy surface. In order to shed some light on disulfide structural trends as a function of substituent bulk in general, and on the barrier question in particular, force field calculations employing the Allinger *et al.* prescription[4] have been performed for a series of acyclic alkyl disulfides.

Disulfide heats of formation and strain energies. In order to compare directly the homologous disulfides and their various rotameric forms, it was necessary to compute heats of formation and the associated strain energies. For this purpose we employ Allinger's formulation:[6–8]

$$E(strain) = \Delta H(steric) + \Delta H(conf) + \Delta H(tor) + \Sigma\Delta H(general) - \Sigma\Delta H(strainless).$$

The first four terms, less a partition function correction, correspond to the calculated heat of formation for a given molecule. $\Delta H(steric)$ is the molecular energy produced by the program, while $\Delta H(conf)$ and $\Delta H(tor)$ are corrections arising from the presence of other conformations and the existence of excited torsional states at 25°. The term $\Sigma\Delta H(general)$ is the sum of bond enthalpy and various substituent correction values. The final quantity, $\Sigma\Delta H(strainless)$, corresponds to the strainless heat of formation parameters derived from uncongested structures.

The previous efforts of Allinger and coworkers[4c] provide all the necessary S, C and H parameters with the exception of the heat of formation values for the S–S bond. The $\Delta H(S–S)$ parameter was obtained by a least-squares fit of the experimental heats of formation and the program generated value for six dialkyl disulfides (Table 1[9]): 8.9 kcal/mol. The resulting force field derived heats of formation are listed in Table 1. Agreement between the experimental and the calculated quantities is satisfactory, the average calculated error for the six compounds being 1.0 kcal/mol. This is to be compared with an average experimental error of 0.4 kcal/mol. The sec-Bu derivative deviates seriously from the general pattern, and without it the mean calculated error drops to 0.7 kcal/mol. In any case we can expect that on the average the predicted heats of formation of disulfides will be within a kcal/mol. In the present work the magnitude of the variance is not a limiting factor, however, since comparisons will be made for relatively large strain energy and $\Delta H(steric)$ differences and interpreted for their reflection of qualitative trends. Relative strain energies and $\Delta H(steric)$ are uninfluenced by the quality of the $\Delta H_f(calc)/\Delta H_f(exp)$ fit. The current disulfide parameters are therefore anticipated to provide a reliable overall perspective of disulfide energetics.

By assuming dimethyl disulfide to be strain free, a strainless disulfide contribution was obtained: $\Delta H(S–S,$ strainless$) = 2.1$ kcal/mol. The corresponding strain

Table 1. Heats of formation and strain energies for R-S-S-R, kcal/mol

R	θ[a]	torsion energy	conf. energy	ΔH		calcd -expt	expt[b] error	strain energy
				calcd	expt[b]			
Me	83.2	0.0	0.3	-6.32	-5.64	-0.68	±0.23	0.00
Et	84.1	0.2	0.9	-18.45	-17.7	-0.75	±0.25	0.06
n-Pr	84.1	0.6	1.5	-28.61	-27.88	-0.73	±0.25	0.07
n-Bu	84.7	1.3	2.1	-38.53	-37.69	-0.84	±0.62	0.02
s-Bu	84.7	0.5	1.5	-38.20	-40.69	2.49	±0.52	-2.03
t-Bu	113.8	0.0	0.3	-46.63	-47.13	0.50	±0.56	2.73

a. The CS-SC dihedral angle for the minimum energy conformation as derived by the force
field calculation.

b. J. D. Cox and G. Pilcher, "Thermochemistry of Organic and Organometallic Compounds,"
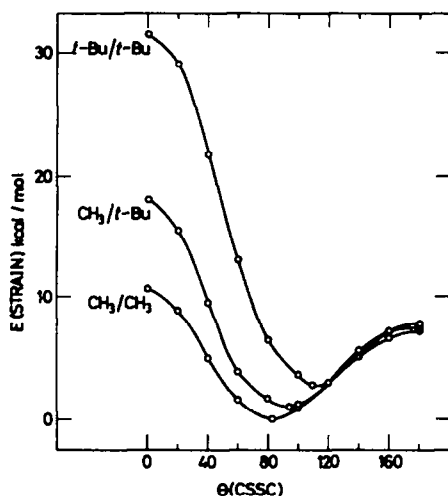Academic Press, New York, 1970.

Fig. 1. Plot of the strain energy for rotation about the S-S bond
(0→180°) for CH₃-SS-CH₃, CH₃-SS-t-Bu and t-Bu-SS-t-Bu.
The structure of each point was fully geometry optimized by the
force field method with the exception of the θ(CSSC) constraint.
At the *trans* barrier (180°) the relative energies are: t-Bu/t-Bu <
CH₃/t-Bu < CH₃/CH₃; cf. Table 3.

energies are given in Table 1. It is noteworthy that the
dialkyl disulfide structures with a dihedral angle (θ)
around 85° are found to be virtually without strain,
whereas the di-t-Bu derivative (θ = 114°) yields a strain
energy of 2.7 kcal/mol.

Disulfide ground states; θ(CSSC). Structural charac-
teristics for the series of dialkyl disulfides incremented
homologously from the dimethyl to the di-t-Bu derivative
are presented in Table 2. Throughout, the S-S bond
length is unaffected and the SS-CR dihedral angles
generally assume near ideal staggered values. However
both the CS-SC dihedral angles and the CSS bond angles
are predicted to increase along the series. The angles
θ(CSSC) are grouped into three sets. Those with a value
of 83-84° possess H atoms at positions 1 and 4 in
structure 1. A single Me group at either site results in
angles of 94-96°, while double Me substitution yields the
maximum θ values of 112-114°. Clearly an increased
steric repulsion arises by the introduction of substituents
at these locations.

The available experimental information, though
limited, is fully supportive. Dimethyl and methyl ethyl

disulfides sustain θ(CSSC) of 84-85°,[10] while angle
expansion to 110° for di-t-butyl disulfide has been
derived from dipole moments[11] and from PES and UV
measurements in conjunction with MO calculations.[12]
Structural information for other systems is lacking, but a
strong correlation between the first absorption band in
the UV and the disulfide dihedral angle exists.[3b,c] In
agreement the calculated dihedral angles of Me-SS-t-
Bu and the low energy conformations of Et-SS-t-Bu (G
and T) and i-Pr-SS-t-Bu (G) (see Table 2) all fall within
the 94-96° range, and each exhibits a long wavelength
λ_max between that of the dimethyl and the di-t-Bu spe-
cies.

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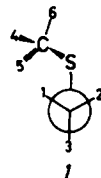
The CSS bond angles are calculated to open slightly
but progressively as Me-SS-Me is incremented with
Me groups again reflecting the steric demand indicated
by projection 1. This result was predicted by MO cal-
culations and suggested to contribute along with
θ(CSSC) increases to the observed blue shifts in the UV
observed upon increasing substituent bulk.[3b] If the
molecular mechanics calculation mirrors reality on this
point, it would appear that bond angle expansion in the
acyclic series is of relatively minor importance for the
UV spectra of bulky disulfides.

The significance of the large dihedral angle distortions
listed in Table 2 is appreciated by noting that the *release
of steric congestion drives the bulkier disulfides in the
direction of the* trans *transition state*. For example the
Me t-Bu system at the energy minimum of θ(CSSC) =
95.2° is calculated to be 0.8 kcal/mol more stable than at
the reduced angle of 80°. The corresponding gain for
t-Bu-SS-t-Bu (80→114°) is 3.6 kcal/mol. The situation is
depicted graphically in terms of strain energies in Fig. 1.
In general the disulfides with Me groups at either the 1 or
2 position of 1 experience an enhanced angle strain at the
lower dihedral angle which levels off at the minimum
energy value. The effect is explicitly reflected by a
harmonious reduction of 1-4° in each of the CSS bond
angles. The extremes of bond angle deformation are
found in the *cis* rotational transition states. We return to
this point below.

Although opening of the CSSC dihedral angle is in response to a total energy lowering, it is not without cost. The strain energies of Table 2 are indicative. At θ(CSSC)'s of 10–12° higher than those found for the simple, unstrained species, E(strain) amounts to 0.7–1.0 kcal/mol. At the $\Delta\theta = 30°$ upper limit of 113–114° the strain energy has risen to 2–3 kcal/mol and is attributable almost entirely to the unfavorable torsional contribution associated with the CSSC angle.

Disulfide rotational energy barriers. For dimethyl disulfide the Allinger force field is parameterized to yield a 7.0 kcal/mol *trans* energy barrier (θ(CSSC) = 180°) for rotation about the S–S bond.[4c] The *cis* barrier (θ(CSSC) = 0°) is thereby evaluated as 10.6 kcal/mol. The barrier characteristics of six additional structures are given in Table 3. In each case θ(CSSC) was fixed at 20° increments from 0 to 180° while all other parameters are allowed to relax to their minimum energy values. The most striking result is that the *trans* barrier lies below the *cis* value for every system examined, and that the difference between them increases sharply with increasing substituent size. Thus the barrier differential for Me–SS–Me, $\Delta\Delta E(cis\text{-}trans) = 3.6$ kcal/mol, rises to a maximum of 23.8 kcal/mol for t-Bu–SS–t-Bu. The increase in $\Delta\Delta E$ is a consequence of both a progressive small drop in the *trans* barrier and a large rise in the *cis* maximum (see Fig. 1).

Decomposition of total force field energies into separate contributions can be a risky procedure, since a differently balanced force field may well lead to a somewhat different energy partition.[13] With this reservation in mind, we note that the variation in the *cis* barrier height as a function of Me substitution may be rationalized within the boundaries of the present force field by recognizing that its energy is composed of essentially two components: torsional and angle bending terms. The 10.6 kcal/mol relative energy content of the
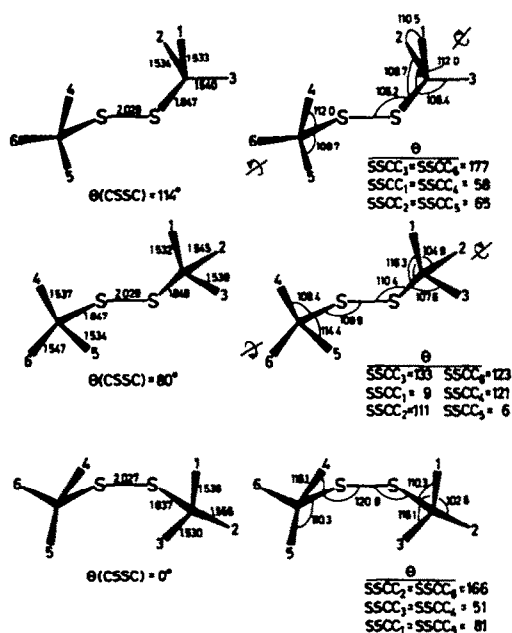

$$\frac{\theta}{SSCC_2 = SSCC_6 = 177}$$
$$SSCC_1 = SSCC_4 = 58$$
$$SSCC_2 = SSCC_5 = 65$$

θ(CSSC) = 114°

θ(CSSC) = 80°

$$\frac{\theta}{SSCC_2 = 123 \quad SSCC_6 = 123}$$
$$SSCC_1 = 9 \quad SSCC_4 = 121$$
$$SSCC_2 = 111 \quad SSCC_5 = 6$$

θ(CSSC) = 0°

$$\frac{\theta}{SSCC_2 = SSCC_6 = 166}$$
$$SSCC_3 = SSCC_4 = 51$$
$$SSCC_1 = SSCC_5 = 81$$

Fig. 2. Fully optimized force field geometries for t-Bu–SS–t-Bu as it passes from the energy minimum (θ(CSSC) = 114°) through $\theta = 80°$ to the *cis* transition state ($\theta = 0°$). The structures in the left column list bond lengths (Å), while those on the right display bond angles (deg). Dihedral angles are given below the latter. The arrows accompanying the upper right structures indicate the direction of rotation of the two *t*-Bu groups as the CS–SC dihedral angle is compressed from 114 to 0°.

cis transition state for Me–SS–Me contains 82 and 12% of the latter two contributions respectively. The corresponding quantities for Me–SS–t-Bu, i-Pr–SS–t-Bu (G) and t-Bu–SS–t-Bu are 51/39, 46/43 and 26/62% respec-

Table 2. Some bond lengths, bond angles and energies from the molecular geometries of selected dialkyl disulfides fully geometry optimized by the Molecular Mechanics method (lengths, Å; angles, deg; E, kcal/mol)

1	2	3	4	5	6	conformer[a]	θCSSC	θSSC1	θSSC4	∠SSC(123)	∠SSC(456)	rSS	E_{rel}	E_{strain}
H	H	H	H	H	H		83.2	62.6	62.8	103.7	103.7	2.030		0.00
H	H	CH$_3$	H	H	H		83.6	59.2	62.0	104.1	103.8	2.030		0.07
H	CH$_3$	CH$_3$	H	H	H	G	83.4	51.9	63.8	104.4	103.8	2.030	0.0	0.25
CH$_3$	CH$_3$	H	H	H	H	T	94.4	59.7	62.4	105.5	104.2	2.029	0.4	0.68
CH$_3$	H	CH$_3$	H	H	H	G'	96.0	61.2	59.4	105.3	104.1	2.029	0.7	0.96
CH$_3$	CH$_3$	CH$_3$	H	H	H		95.2	57.7	63.5	106.1	104.2	2.029		0.90
CH$_3$	CH$_3$	CH$_3$	H	CH$_3$	H	G	94.2	57.1	54.0	106.2	104.7	2.029	0.0	0.77
CH$_3$	CH$_3$	CH$_3$	H	H	CH$_3$	T	95.8	58.4	57.4	106.1	104.4	2.029	0.1	0.88
CH$_3$	CH$_3$	CH$_3$	CH$_3$	H	H	G'	112.6	60.9	68.9	106.2	105.1	2.029	1.6	2.38
CH$_3$	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$	G	94.8	57.2	46.6	106.0	105.0	2.029	0.0	0.94
CH$_3$	CH$_3$	CH$_3$	CH$_3$	CH$_3$	H	T	112.8	57.6	61.7	106.2	105.7	2.029	1.6	2.58
CH$_3$	CH$_3$	CH$_3$	CH$_3$	H	CH$_3$	G'	113.3	57.9	59.9	106.1	105.5	2.029	1.8	2.77
CH$_3$	CH$_3$	CH$_3$	CH$_3$	CH$_3$	CH$_3$		113.8	57.7	57.7	106.2	106.2	2.029		2.73

a) For Newman projections of the conformations see Figure 4.

tively. Thus as bulkier substituents are introduced into the disulfide, the Allinger method posits that the *cis* barrier changes from one dominated by torsional strain to one dominated by angle bending strain. As indicated by Table 3 the *cis* torsional component is nearly constant (± 1 kcal/mol), while the bending term rises by 16.7 kcal/mol. Indeed linear relationships between $\Delta\Delta E(cis)$, $\Delta E(bend)$ and $E(strain)$ obtain. Structurally the energy variations are matched by the widening of the CSS bond angle from 107.4° (MeSSMe) to 120.8° (t-Bu–SS–t-Bu).

In contrast to the steeply increasing disulfide *cis* rotation barrier dependent on substituent bulk, the energy of the *trans* maximum decreases slightly by 2.0 kcal/mol from Me–SS–Me to t-Bu–SS–t-Bu. This is a direct consequence of the fact that the *gauche* disulfide ground states experience an increase in strain with increased methyl substitution. Comparison of $E(strain)$ in Table 2 with $E(barrier)$-*trans* in Table 3 reveals the very close parallel and quantitatively underlines the result above that increased disulfide homologation causes a geometric and an energetic shift for a given system in the direction of the *trans* barrier (Fig. 1). Unlike the *cis* rotation maximum, the *trans* value is made up of an unfavorable torsional energy alone in accord with intuitive ideas concerning the role of steric effects. It is noteworthy that the *trans* quantities $E(barrier)$ and $\Delta E(torsion)$ (Table 3) are virtually identical.

To exemplify the structural changes which are predicted to occur for disulfide rotation within the force field framework, Fig. 2 indicates bond length, bond angle and dihedral angle values for di-t-butyl disulfide at three different dihedral angles: 114 (min), 80 and 0°. The structural parameters other than $\theta(CSSC)$ are identical for the *trans*, the energy optimized *gauche* form and intermediate geometries. Thus the staggered t-Bu groups found for $\theta = 114°$ are retained upon passage through the *trans* transition state.

By contrast, a major structural reorganization occurs

Fig. 3. Potential energy minima (3 and 5) and maxima (4 and 6) for rotation about the C–S bond (S–C(C₁C₂C₃)) in di-*tert*-butyl disulfide. Each number within the structures (1–6) corresponds to a CH₃ group. The Newman projections look down the C–S bond axis. In structures 4 and 6 the SS–CC₁ and SS–CC₂ dihedral angles respectively are 20°. Parenthetical values beneath each structure refer to the CS–SC dihedral angle; those beside C₄, refer to the SS–CC₄ dihedral angle.

when t-Bu–SS–t-Bu traverses the *cis* saddle point. In addition to the CSS bond angle expansion mentioned above, the most dramatic changes are associated with torsion about the C–S bond and angle deformation around methyls 1, 4 and 5 in 1. As $\theta(CSSC)$ is reduced from the *gauche* value to 80° each originally staggered t-Bu group rotates into a near eclipsed conformation in order to reduce repulsive interactions between Me's 1 and 4. The t-Bu moiety in S–C(1,2,3) rotates clockwise when viewed down the C–S axis, whereas S–C(4,5,6) turns counterclockwise when considered analogously (Fig. 2). The SCC_1 and SCC_5 bond angles simultaneously widen by 4–5°. From $\theta(CSSC) = 80$ to 0° the S–C(1,2,3) unit continues its original clockwise journey, but the S–C(4,5,6) fragment is predicted to reverse direction. The mutual clockwise twisting of both t-Bu groups for $\theta < 80°$ leads to the C_2 *cis* structure depicted in Fig. 2. The unsymmetrical relation between C_1 and C_3 (likewise C_4 and C_5) as well as the exaggerated SSC, SCC_1 and SCC_4 angles indicate the considerable strain experienced by the structure ($E(strain) = 31.5$ kcal/mol).[14] Bond length changes also accompany the travel from *gauche* to *cis*, in particular the shrinkage of rC–S by 0.01 Å and the reduction of certain C–H bonds on carbons 1, 2, 4 and 5. Finally both bond angle ($\angle$HCH) and dihedral angle ($\angle$HCCS) distortions are evident in the t-Bu groups and found to be most severe for Me's 1 and 4. The t-Bu-SS-t-Bu case illustrates the extremes of geometric perturbation for the structures given in Table 3. Thus rotation of dimethyl disulfide through 0° is predicted to lead to a C_{2v} *cis* form in which the Me groups are staggered. Addition of Me's causes the motions described for the t-Bu system to commence for methyl ethyl disulfide and to be magnified gradually until the t-Bu limit is reached.

In summary the calculations suggest that the *trans* barrier lies considerably lower than the *cis* maximum ($\Delta E(cis-trans) = 3$-24 kcal/mol) and that the gap between them increases sharply as a function of substituent bulk. The behavior of $\Delta E(cis-trans)$ is a consequence of a rapid rise in the *cis* barrier and a small drop in the *trans*. These quantitative changes in turn arise from angle bending strain occasioned by alkyl-alkyl steric repulsion and from a rise in the ground state energy of the heavily substituted disulfides respectively.

The possibility exists that disulfide rotation is mediated by a rotation-inversion pathway thereby avoiding both the *cis* and the *trans* transition states. This mechanism has been rejected by Kessler and Rundel[3c] for diaryl disulfides on the basis that inversion at sulfur in diaryl sulfides requires a barrier of at least 15 kcal/mol.[16] The calculated *cis* barriers and SSC bond angles of Table 3 are in agreement. The single structural parameter restricted in these calculations was $\theta(CSSC)$; symmetry across the S–S bond was not assumed. Thus unequal distortion around the SSC angles was permitted. Although a slight asymmetry is evident for the unsymmetrical disulfides at $\theta(CSSC) = 0°$, the force field maintains bond angle equality across the rotational potential energy surface and prefers a genuine *cis* orientation at the transition state. An explicit test of the sulfur inversion route was conducted by carrying out a CNDO/B[17] MO SCF calculation of dimethyl disulfide with one SSC bond angle fixed at 180°, the other optimized to 114°. An energy barrier of 28 kcal/mol relative to the *gauche* ground state is obtained. The corresponding *cis* and *trans* energy maxima lie at 5.5 and 4.0 kcal/mol respectively.[3b] Thus both experiment and
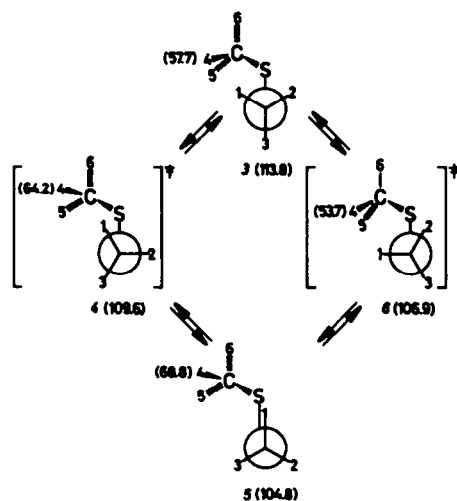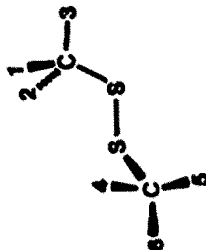
Table 3. Force field calculated energy barriers, energy barrier components and CSS bond angles for rotation about the S–S bond in selected dialkyl disulfides (E, kcal/mol; angles, deg)

1	2	3	4	5	6	E(barrier)			E(strain)		ΔE(bend)		ΔE(torsion)		bond angles(cis)	
						trans	cis	gs	trans	cis	trans	cis	trans	cis	SSC(123)	SSC(456)
H	H	H	H	H	H	7.0	10.6	-0.05	7.0	10.6	-0.02	1.2	6.9	8.6	107.4	107.4
H	CH$_3$	CH$_3$	H	H	H	7.1	12.2	0.15	7.2	12.3	-0.04	2.1	7.0	8.9	109.3	108.9
CH$_3$	CH$_3$	CH$_3$	H	H	H	6.6	17.2	0.84	7.4	18.0	-0.25	6.7	6.4	8.8	114.8	111.9
CH$_3$	CH$_3$	CH$_3$	H	H	CH$_3$(T)[a]	6.6	17.7	0.85	7.5	18.5	-0.22	6.6	6.4	8.9	115.2	112.2
CH$_3$	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$(G)[a]	6.7	19.6	0.86	7.6	20.4	-0.13	8.3	6.4	9.0	116.3	113.5
CH$_3$	CH$_3$	CH$_3$	H	CH$_3$	CH$_3$(G')[a]	4.9	26.3	2.7	7.6	28.9	-0.68	16.4	4.8	7.7	118.7	118.9
CH$_3$	CH$_3$	CH$_3$	CH$_3$	CH$_3$	CH$_3$	5.0	28.8	2.7	7.7	31.5	-0.48	27.9	4.7	7.4	120.8	120.8

a) For Newman projections of the conformations see Figure 4.

theory render inversion at disulfide sulfur an unlikely isomerization pathway.

The question of a trans *vs a* cis *S–S torsional barrier in dialkyl disulfides.* The computational sketch described above is at odds with Fraser *et al.*'s interpretation of $\Delta G\dagger$ measurements for the isomerization of bulky disulfides, PhCH$_2$–SS–R, in which a preferred *cis* barrier was postulated.[5] The experimental effect is small ($\Delta\Delta G\dagger =$ 1.8 kcal/mol for carbon substituted disulfides) and its analysis complicated by the possible operation of a superimposed inductive effect. Both inversion[18a,19] and rotation[18b,19] barriers in other systems are known to be raised when electron withdrawing substituents are placed on the isomerizing center.

Fraser *et al.* have estimated the relative sizes of R groups in PhCH$_2$–SS–R as follows: C(Ph$_3$) > CCl$_3$ > CMe$_3$ > C$_6$Cl$_5$ > C$_6$F$_5$ > Ph > CH$_2$Ph > CF$_3$.[5] If this ordering is correct, the advanced positions of the trihalomethyl groups in the sequence of $\Delta G\dagger$'s can be attributed to the inductive effect: ($\Delta G\dagger$) CCl$_3$ > CPh$_3$ > CF$_3$ = C$_6$Cl$_5$ = C$_6$F$_5$ = Ph = CMe$_3$ > CH$_2$Ph. The observation that the mono-aryl cases exhibit a $\Delta G\dagger$ coincident with that of t-Bu might suggest that the phenyl sp^2 carbon is also operating as an electronegative unit, but the effect does not extend to β-CX (X = F, Cl). It would likewise seem to imply that if a steric rate retardation is responsible for the $\Delta G\dagger$ changes, the flat phenyl ring is able to rotate in such a way as to mediate the effect of β-CX substituents (X = H, F, Cl) on S–S rotation. Kessler and Rundel's findings that similarly substituted diaryl disulfides influence the C–S but not the S–S barrier are in accord.[3e,20] Of the remaining substituents CPh$_3$ falls in the $\Delta G\dagger$ sequence as expected for a large, polar group. A clearcut separation of steric and inductive factors for the latter is not obvious.

The only R moieties which might unambiguously reflect the existence of a steric effect on disulfide rotation are t-Bu and CH$_2$Ph with $\Delta G\dagger = 7.0$ and 7.8 kcal/mol respectively. Are the latter numbers in fact different? For the complete series, R: CH$_2$Ph → CCl$_3$, the increasing tendency of $\Delta G\dagger$ (7.0 → 9.4 kcal/mol) cannot be questioned. However the differences between adjacent members may well be swamped out by experimental error. A straightforward consideration of the latter[21] allows the conclusion that the $\Delta G\dagger$'s for PhCH$_2$–SS–R (R = CMe$_3$ and CH$_2$Ph) are probably indistinguishable, and therefore that there is no definitive experimental evidence for the operation of steric retardation to disulfide S–S rotation.

The values of $\Delta G\dagger$ (7–8 kcal/mol) for the latter two substances are, however, certainly indicative of the energy requirement for dialkyl disulfide rotation. Although we have not applied the force field method explicitly to these species, the E(barrier) results of Table 3 are entirely consistent with rotation through the *trans* transition state (6–7 kcal/mol) but incompatible with a *cis* maximum (12–20 kcal/mol). The possibility remains that highly accurate measurements on dialkyl disulfide rotation will reveal small $\Delta G\dagger$ variations as a function of structure. In this event, entropy effects can be expected to exert themselves.

The "Cogwheel effect". The influence of entropy on the conformational properties of dialkyl disulfides has been investigated by Sunner *et al.* in another connection, namely the equilibrium constant dependence of the disulfide interchange reaction.[22,23]

$$R_1\text{–SS–}R_1 + R_2\text{–SS–}R_2 \rightleftharpoons 2R_1\text{–SS–}R_2.$$

For R$_1$, R$_2 \neq$ t-Bu, K ranges from 4–6 favoring the unsymmetrical disulfide. When R$_1$ = t-Bu and R$_2$ = Et, n-Bu, n-Pr or i-Pr the equilibrium constant was found to be K = 15–27. An extreme value of K = 43 is exhibited by R$_1$ = Me, R$_2$ = t-Bu. The driving force for the disproportionation was shown to be entropy. Its drastic increase for cases involving t-Bu groups was interpreted as arising from t-Bu coupled rotation in t-Bu–SS–t-Bu. Nelander and Sunner have termed the synchronized S–CMe$_3$ rotations the "cogwheel effect".[23] The large contributions of ΔS when the di-t-Bu species is employed as one of the disulfide pairs was associated with the restoration of free rotation in the unsymmetrical disulfide.

In order to explore the nature of the C–S torsional motions for t-Bu–SS–t-Bu and related disulfides and to examine its impact on the S–S rotation, we have carried out a force field analysis of the geometric and energetic consequences of rotation about the S–CMe$_3$ bond for R–SS–CMe$_3$, R = Me, i-Pr (G and G') t-Bu. Starting with the ground state staggered conformation of 1, the t-Bu group was incremented by 20° in both the clockwise and the counterclockwise directions until the eclipsed structures 2 and 2' were realized. Apart from the fixed dihedral angles θ(SSCC$_1$) and θ(SSCC$_2$), all geometric
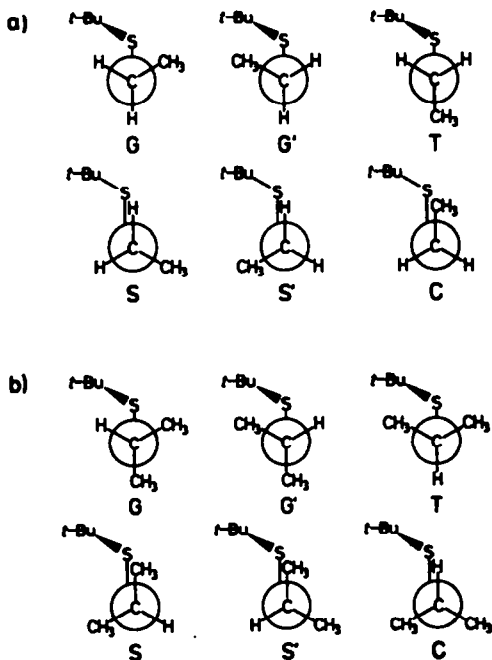

Fig. 4. Structures for (a) ethyl *tert*-butyl disulfide and (b) 2-propyl *tert*-butyl disulfide. The Newman projections look down the C–S axis. The *cis* and *trans* SS–CC conformers are labeled C and T respectively; the two *gauche* and *skew* forms G/G' and S/S' respectively.
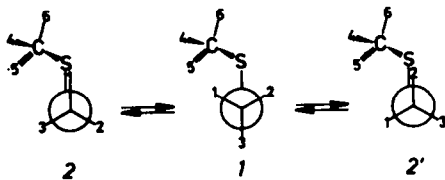
Table 4. Force field results for the clockwise and counterclockwise rotation about S–C(CH$_3$)$_3$ from the ground states of R–SS–t-Bu: R = CH$_3$; i-Pr and t-Bu (angles, deg; E, kcal/mol)

4	5	6	θ_{SSCC_1}[a]	θ_{CSSC}	θ_{SSC4}	θ_{SSC5}	E_{rel}	4	5	6	θ_{SSCC_2}[a]	θ_{CSSC}	θ_{SSC4}	θ_{SSC5}	E_{rel}
H	H	H	58.0	95.4	60.8	60.8	0.0	H	H	H	64.4	95.4	60.8	60.8	0.0
			40	93.6	68.4	54.3	0.48				40	90.9	76.6	47.0	0.55
			20	94.7	62.1	59.5	1.42				20	85.0	68.2	54.2	0.67
			0	90.1	56.6	64.7	1.29				0	90.1	56.6	64.7	1.79
CH$_3$	H	CH$_3$(G')[b]	57.9	113.3	59.9	59.5	0.0	CH$_3$	H	CH$_3$	64.5	113.3	59.9	59.5	0.0
			40	112.1	62.5	57.1	0.40				40	113.0	63.3	56.4	0.60
			29	111.4	64.5	55.1	0.78				20	107.6	55.8	63.9	1.02
			20	109.8	65.2	54.3	0.86				0	104.8	68.8	54.1	0.64
			0	104.8	68.8	54.1	0.64								
H	CH$_3$	CH$_3$(G)[b]	57.2	94.8	72.8	46.6	0.0	H	CH$_3$	CH$_3$	65.2	94.8	72.8	46.6	0.0
			40	94.4	70.0	49.5	0.56				40	95.2	70.6	48.9	0.71
			20	93.5	79.3	39.9	1.34				20	85.8	67.2	52.6	0.74
			0	89.2	75.0	44.3	1.17				0	89.2	75.0	44.3	1.17
CH$_3$	CH$_3$	CH$_3$	57.7	113.8	57.7	64.7	0.0	CH$_3$	CH$_3$	CH$_3$	64.7	113.8	57.7	64.7	0.0
			40	111.7	60.2	62.3	0.41				40	112.5	61.6	61.0	0.61
			20	109.6	64.2	58.3	1.00				20	106.9	53.7	68.7	0.86
			0	104.8	68.8	54.1	0.82				0	104.8	68.8	54.1	0.82

a) With the exception of the 0-40° values of θ_{SSCC_1} and θ_{SSCC_2} all geometric parameters have been fully optimized.
b) For Newman projections of the G and G' conformers see Figure 4.

parameters were fully energy optimized. The most important results are given in Table 4.

Several interesting features are described by the calculations, all of which reflect the operation of coupled alkyl rotation even in the methyl t-Bu system. We exemplify the situation with di-t-Bu disulfide. At the equilibrium geometry (θ(CSSC) = 114°) the t-Bu groups assume a nearly staggered arrangement (θ(SSCC) = 58, 65, 177°). It should be recalled that the expanded CSSC dihedral angle is the result of steric interaction between Me's 1 and 4 in 3. (Fig. 3). Rotation of one t-Bu group (S–C(1,2,3)) clockwise to θ(SSCC$_1$) = 20° produces an energy maximum, 4, in which the dihedral angle about the S–S bond has *dropped* by 4°. Simultaneously the opposite t-Bu group (S–C(4,5,6)) rotates in the same direction to minimize C$_1$–C$_4$ repulsion; i.e. θ(SSCC$_4$): 58→64°. Further torsion to the eclipsed conformation 5, an energy minimum, causes further reduction in θ(CSSC) to 105° and additional readjustment about S–C(4,5,6); θ(SSCC$_4$) = 69°. The finding that 4 represents the torsional transition state and 5 a genuine conformation can be interpreted as a trade-off between bond length compression and a combined relief of S–S torsional strain and van der Waals repulsion at C$_1$ and C$_4$. In the eclipsed conformation 5 the energy gain associated with the latter simply outweighs the energy loss occasioned by the former.

Rotation of the t-Bu group in 3 (S–C(1,2,3)) in the counterclockwise sense leads to a second energy maximum, 6, at θ(SSCC$_2$) = 20°. The CSSC dihedral angle falls by 7° and the second t-Bu group (S–C(4,5,6)) readjusts in the same direction; θ(SSCC$_4$): 58→54°. Both motions are slightly larger than those accompanied by 3→4 and reflect a relaxed steric interaction between C$_1$ and C$_4$. Nonetheless, as above, the unfavorable van der
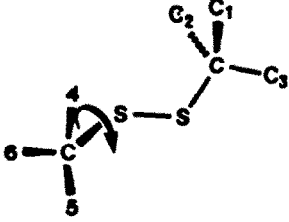
Waals and CSSC dihedral angle effects contribute to a total energy higher than the eclipsed form 5.

The conformational portrait elaborated for t-Bu–SS–t-Bu (3–6) is very similar for the other bulky disulfides in Table 4. The S–S dihedral angle closes upon rotation of the t-Bu group away from the low energy minimum; with the exception of Me–SS–t-Bu there are two rotational transition states; and finally none of the energy maxima are coincident with the fully eclipsed t-Bu group and the S–S bond.

In order to complete our examination of the "cogwheel" effect" in bulky disulfides, torsion about the S–C(4,5,6) bond for ethyl-t-butyl and i-propyl-t-butyl disulfides has likewise been investigated. The results are presented in Table 5. Although the potential energy surfaces are considerably less symmetrical than those for S–CMe$_3$ rotation, no essential new points emerge. Certain clearcut differences are evident, however. The G conformations (Fig. 4) are lowest in energy in each case, the G' and T forms representing less stable conformers. Except for S (Et–t-Bu) and S' (i-Pr–t-Bu) transition states between energy minima are not the eclipsed rotamers, but skewed by 20° as found for 4 and 6. The reasons are precisely the same as those developed above. Furthermore, except where an energy maximum is flanked by a G conformer, θ(CSSC, transition state) drops relative to θ(CSSC, ground state). Again the rationale given for S–CMe$_3$ rotation is applicable here.

Unlike S–CMe$_3$ torsion the eclipsed forms here (Et: S', C'; i-Pr: C, S; Fig. 4) are not found in potential wells but on the energy slopes between transition states and ground states. The asymmetry of the torsional potential is responsible. For S–CMe$_3$ motion both maxima 4 and 6 involve a destabilizing Me–Me interaction (C$_1$...C$_4$). The eclipsed form is trapped in-between. The lack of Me

Table 5. Force field results for the rotation about S–C(4,5,6) for R-SS-t-Bu; R = Et and i-Pr (angles, deg; E, kcal/mol)

4	5	6	rotamer[a]	θCSSC	θSSC6	θSSC4	θSSC5	θSSC1	θSSC2	E_{rel}
H	CH$_3$	H	G	94.2	169.6	54.0	70.0	57.1	65.4	0.0
			S	89.4	117.6	0.0	122.1	58.2	64.2	0.64
H	H	CH$_3$	T	95.8	57.4	60.2	179.1	58.4	64.0	0.12
			S'	87.5	0.0	114.3	126.6	78.1	45.2	0.96
				105.1	20.0	133.4	107.4	53.5	68.9	1.96
H$_3$	H	H	G'	112.6	56.1	170.0	68.8	60.9	61.6	1.61
				108.5	100.0	148.1	25.7	63.3	59.3	2.62
			C	102.4	123.2	123.3	0.0	65.5	57.0	2.19
J	CH$_3$	CH$_3$	G	94.8	163.9	46.6	72.8	57.2	65.2	0.0
			C	98.6	122.2	0.0	115.4	49.3	73.1	1.61
				110.8	96.7	24.3	140.0	65.2	57.2	2.34
H$_3$	H	CH$_3$	G'	113.3	59.9	59.5	175.4	57.9	64.5	1.83
				107.8	18.6	100.0	145.1	63.4	59.0	2.74
			S	103.2	0.0	117.6	128.0	68.7	54.1	2.34
H$_3$	CH$_3$	H	T	112.8	61.7	178.6	66.0	57.6	64.9	1.65
				110.9	104.2	140.0	22.9	62.1	60.3	2.88
			S'	103.6	126.6	118.3	0.0	61.9	60.4	2.47

a) For Newman projections of the rotameric forms see Figure 4.

groups in Et and i-Pr in the present cases causes one rotamer of either the 4 or the 6 type to be avoided. For example for i-propyl-t-butyl disulfide rotation from G to G' requires passage through transition state 8. Structure 7 does not incorporate the Me–Me interaction of 4 and therefore there is a smooth uphill climb from G to 8 (see Table 5).

7   8
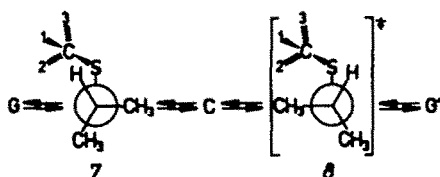
Most important the "cogwheel effect" is manifested in the Et and i-Pr systems of Table 5. The S–C(4,5,6) rotation causes θ(CSSC) to vary from 90–113°. Simultaneously SS–CMe$_3$ dihedral angles remain fairly close to the staggered values except near the S' (Et) and C (i-Pr) forms. Here they run from 45 to 78°.

Thus we conclude that the experimentally based "cogwheel effect" is accurately depicted by the present calculations but that its operation, though gradually muted, extends to the lower homologs of t-Bu–SS–t-Bu as well. In Me–SS–Me the effect has disappeared. Neither rotation about S–S nor C–S involves transmission of information from one Me to the other.

ΔG† Variation and substituent size. Insofar as S–S rotation barriers are concerned, any trend in ΔG† as a function of structure will result from a balance of ΔH† and ΔS†. These in turn will reflect the combined action

of disulfide internal degrees of freedom, substrate-solvent interaction and solvent cage reorganization.[24] Internal molecular motions can be analyzed in a relatively straightforward fashion. The molecular mechanics calculations predict ΔH† (trans) to fall slightly with increasing substituent bulk (Table 3, Fig. 1). The ΔS† (trans) contribution is expressed by the magnitude of the "cogwheel effect" and should reach its maximum positive value in the bulkiest cases leading to a drop in ΔG†. Thus both ΔH† and ΔS† arising from intramolecular motion during trans disulfide rotation can be expected to respond to steric effects in a mutually reinforcing manner and cause a reduction in ΔG†. The energy differences may be small, however, and the trend reversed by the intervention of solvent.[25]

REFERENCES

[1] Organo-Sulfur Mechanisms—9. For Part 8 see L. Carlsen and J. P. Snyder, J. Org. Chem. 43, 2216 (1978).

[2] H. E. Van Wart and H. A. Scheraga, J. Phys. Chem. 80, 1812, 1823 (1976); E. Bastian and R. B. Martin, Ibid. 77, 1129 (1973); H. Sugeta, A. Go and T. Miyazawa, Bull. Chem. Soc. Jpn. 46, 3407 (1973); and refs therein.

[3a] For a recent review of structure studies see P. H. Laur, Steric Aspects of Sulfur Chemistry in Sulfur in Organic and Inorganic Chemistry (Edited by A. Senning), Vol. 3, p. 91. Marcel Dek-

ker, New York (1972): UV, CD and PE studies: cf. [b]J. P. Snyder and L. Carlsen, J. Am. Chem. Soc. 99, 2931 (1977); [c]D. B. Boyd, Ibid. 94, 8799 (1972) and refs therein; [d]raman, IR: see Ref. 2; [e]NMR: H. Kessler and W. Rundel, Chem. Ber. 101, 3350 (1968) and Ref. 5.

[4]Quantum mechanical calculations: [a]D. B. Boyd, J. Phys. Chem. 78, 1554 (1974); H. E. Van Wart, L. L. Shipman and H. A. Scheraga, Ibid., 78, 1848 (1974); L. A. Eslava, J. B. Putnam and L. Pedersen, Int. J. Peptide Protein Res. 11, 149 (1978); P. H. Blustin. Theoret. Chim. Acta Berl 48, 1 (1978); Refs. 3b, c and citations given; [b]N. L. Allinger, J. Kao, H.-M. Chang and D. B. Boyd, Tetrahedron 32, 2867 (1976); Force field calculations: [c]N. L. Allinger, M. J. Hickey and J. Kao, J. Am. Chem. Soc. 98, 2741 (1976) and Ref. 4b.

[5]R. R. Fraser, G. Boussard, J. K. Saunders, J. B. Lambert and C. E. Mixan, J. Am. Chem. Soc. 93, 3822 (1971).

[6]N. L. Allinger, Adv. Phys. Org. Chem. (Edited by V. Gold and D. Bethell) Vol. 13, p. 1. Academic Press, New York (1976) and Ref. 4c.

[7]N. L. Allinger, M. T. Tribble, M. A. Miller and D. H. Wertz, J. Am. Chem. Soc. 93, 1637 (1971).

[8]N. L. Allinger and M. J. Hickey, Ibid. 97, 5167 (1975).

[9]We are grateful to Professor Allinger who suggested the values of $\Delta H(conf)$ and $\Delta H(tor)$ given in Table 1.

[10]D. Sutter, H. Driezler and H. D. Rudolph, Z. Naturforsch. A 20, 1676 (1965); B. Beagley and K. T. McAloon, Trans. Faraday Soc. 67, 3216 (1971); A. Yokozeki and S. H. Bauer, J. Phys. Chem. 80, 618 (1976).

[11]B. Nelander, Acta Chem. Scand. 23, 2127 (1969).

[12]H. Bock and G. Wagner, Angew. Chem. 84, 119 (1972): Int. Ed. Engl. 11, 150 (1972); G. Wagner and H. Bock, Chem. Ber. 107, 68 (1974); A. D. Baker, M. Brisk and M. Gellender, J. Electron Spectrosc. Relat. Phenom. 3, 227 (1974); Ref. 3b.

[13]E. M. Engler, J. D. Andose and P. von R. Schleyer, J. Am. Chem. Soc. 95, 8006 (1973).

[14]The C_2 symmetry of the cis transition state structure in Fig. 2 is reminiscent of the Allinger and Sprague result for cis-butene-2.[15] It may, therefore, be an artifact of the hard H···H potential incorporated in the version of the force field we have employed (MM1-73). For a comparative discussion of the cis-butene problem, see: D. N. White and M. J. Bovill, J. Chem. Soc. Perkin II, 1610 (1977); for Allinger's resolution, see: N. L. Allinger, J. Am. Chem. Soc. 99, 8127 (1977).

[15]N. L. Allinger and J. T. Sprague, Ibid. 94, 5734 (1972).

[16]H. Kessler, A. Riecker and W. Rundel, Chem. Commun. 475 (1968).

[17]R. J. Boyd and M. A. Whitehead, J. Chem. Soc. Dalton Trans. 73, 78, 82 (1972).

[18]N. D. Epiotis, W. R. Cherry, S. Shaik, R. L. Yates and F. Bernardi, Topics in Current Chem. 70 (1977): [a]pp. 140–146; [b]pp. 190–193.

[19]A. Veillard, Quantum Mechanics of Molecular Conformations (Edited by B. Pullman), pp. 1–115. Wiley New York (1976).

[20]Several tetra-ortho substituted diphenyldisulfides have been examined by DNMR.[3a] The S–S rotation barriers for small to medium sized groups, R = H, Me, Et, and i-Pr, are low ($\Delta G\dagger(-100°) < 9.7$ kcal/mol), although S–C torsional barriers for R = Et and i-Pr are $\Delta G\dagger = 11.7$ (−55°) and 12.8 (−27°) kcal/mol respectively. However when a very bulky substituent is attached, R = t-Bu, S–S rotation is costly by comparison: $\Delta G\dagger(39°) = 15.7$ kcal/mol.

[21]The $\Delta G\dagger$ error margin, the probable error, has been given as ±0.3 kcal/mol corresponding to a 50% confidence interval. A more realistic analysis of the accuracy of the measurements would raise the magnitude of the error by a factor of at least two or three.

[22]L. Haraldson, C. J. Olander, S. Sunner and E. Varde, Acta Chem. Scand. 14, 1509 (1960).

[23]B. Nelander and S. Sunner, J. Am. Chem. Soc. 94, 3576 (1972).

[24]W. P. Jencks, Catalysis in Chemistry and Enzymology, pp. 605–614. McGraw-Hill, New York (1969).

[25]The measurements of Fraser et al.[5] might fulfill these conditions (PhCH_2–SS–R: R = CH_2Ph and CMe_3, $\Delta H\dagger = 6.6$ and 6.8 ±0.7 kcal/mol, $\Delta S\dagger = -2.6$ and −6.7 ±3.5 e.u. respectively), but the magnitude of the errors permits no decision.