Predicting the Stability of Cyclic Disulfides by Molecular Modeling: "Effective Concentrations" in Thiol–Disulfide Interchange and the Design of Strongly Reducing Dithiols

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Abstract: We have tested molecular mechanics calculations at the level of MM2(85) for their capacity to rationalize relationships between structure and equilibrium constants for thiol–disulfide interchange reactions. With 20 α,ω-dithiols taken from the literature, equilibrium constants for thiol–disulfide interchange with 1,2-dithiane were calculated: $HSRSH + \overline{S(CH_2)_4S} \rightleftharpoons \overline{SRS} + HS(CH_2)_4SH$. The relation between experimental values of ΔG and calculated differences in strain energy was $\Delta G = 0.41\Delta SE + 0.5$ kJ/mol with a correlation coefficient of 0.93 (excluding one anomalous point). Results from molecular mechanics correlate well with experimental results, but they cannot give absolute values of energies. Results of molecular mechanics calculations are used to discuss the physical interpretation of the concept of "effective concentration" as it is used for the thiol–disulfide interchange reaction.

Introduction

We have studied two aspects of the relations between molecular structures and stabilities of α,ω-dithiols (HSRSH) and of cyclic disulfides ($\overline{SRS}$) derived from them by oxidation. First, we have explored the capacity of molecular mechanics to rationalize relative stabilities using equilibrium constants for thiol–disulfide interchange reactions as measures of these stabilities (eqs 1 and 2). Second, we applied these computational methods to the design of disulfides whose stability had not been determined.

$$HSRSH + \overline{SR'S} \rightleftharpoons \overline{SRS} + HSR'SH \qquad (1)$$

$$HSRSH + R''SSR'' \rightleftharpoons \overline{SRS} + 2R''SH \qquad (2)$$
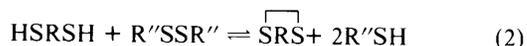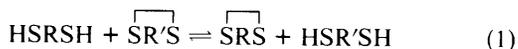
This work had four objectives. *First, we intended to evaluate the capability of molecular mechanics[1] to rationalize and predict equilibrium constants for thiol–disulfide interchange.* The absolute accuracy of the calculations was particularly relevant to their use in molecular design: Was their accuracy sufficient to give absolute values of energies, or only high enough to be useful in correlations? *Second, we wished to disentangle the various enthalpic contributions to these equilibria.* Estimating the importance of torsional strain in the C–S–S–C group of the disulfide relative to strain in other parts of the disulfide and in the thiol was important in interpreting the influence of structure on energy.

Third, we needed to evaluate the efficacy of molecular mechanics calculations as a guide to design and synthesis. We use thiol–disulfide interchange both as a model system for studies in physical-organic chemistry[2-6] and as a reaction useful in synthesis. A computational method that would increase the effectiveness of molecular design would improve the efficiency of both activities. *Fourth, we wished to understand the origin, utility, and significance of values of "effective concentration" (EC)[7,8] derived from measurements of equilibrium constants for thiol–disulfide interchange.[9]* The EC—a number characterizing the advantage in rate or equilibrium constant for an intramolecular reaction relative to a closely analogous intermolecular one—has come to be widely used in physical-organic chemistry and biochemistry

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Figure 1. The CSSC dihedral angle in a cyclic disulfide.

in discussions of conformation. The limitations of interpretations of the EC have not been clearly defined in general, and especially not for thiol–disulfide interchange.

A brief discussion of EC with respect to thiol–disulfide interchange provides a context for this work. Equations 3–7 are a starting point for interpretation of the EC in thiol–disulfide in-

$$\text{HSRSH} + \overline{\text{SR'S}} \xrightleftharpoons{K_{intra}} \overline{\text{SRS}} + \text{HSR'SH} \qquad (3)$$

$$2\text{R''SH} + \overline{\text{SR'S}} \xrightleftharpoons{K_{inter}} \text{R''SSR''} + \text{HSR'SH} \qquad (4)$$

$$\text{HSRSH} + \text{R''SSR''} \xrightleftharpoons{K = EC} \overline{\text{SRS}} + 2\text{R''SH} \qquad (5)$$

$$EC = \frac{K_{intra}}{K_{inter}} = \frac{[\overline{\text{SRS}}][\text{R''SH}]^2}{[\text{HSRSH}][\text{R''SSR''}]} \qquad (6)$$

$$[\text{R''SH}]\frac{[\text{R''SH}]}{[\text{R''SSR''}]} = EC\frac{[\text{HSRSH}]}{[\overline{\text{SRS}}]} \qquad (7)$$

terchange. For comparable intramolecular oxidation of a dithiol (HSRSH) (eq 3) and intermolecular oxidation of a thiol (R''SH) to disulfides with a common oxidant ($\overline{\text{SR'S}}$), the EC characterizing the dithiol is given by eq 6 (EC has units of concentration). For thiol–disulfide interchange, the EC is the equilibrium constant for the reaction given in eq 5, where the disulfide R''SSR'' is assumed to be strain-free. Equation 7 indicates that, for the intermolecular reaction to achieve the same fractional conversion of thiol to disulfide as is achieved in the intermolecular case, the concentration of the reacting monothiol (R''SH) would have to equal the EC. Since many reactions exist in which the EC is 10^6 to 10^{12} M,[7] intramolecularity can have a large effect on an equilibrium.

The concept of "effective concentration" is useful, stimulating, and easily interpreted physically, but it must be interpreted cautiously in thiol–disulfide interchange reactions, primarily because the enthalpy of the S–S bond depends strongly on the CSSC dihedral angle. "Concentration" is a scalar quantity that measures the number of reactive groups per unit volume, or equivalently, the average distance of reactive groups from one another. Concentration enters the expression for the free energy of reaction through its influence on entropy [$S \propto R \ln$ (concentration)]. The enthalpy of a disulfide bond (H_θ^{SS}, kJ/mol) is strongly influenced by the CSSC dihedral angle θ_{CSSC} (Figure 1), with an approximate functional form given by eq 8.[10] Thus, the

$$H_\theta^{SS} = 14.6 \cos (2\theta) + \cos (3\theta) + (H_{\theta=0}^{SS} - 15.6) \qquad (8)$$

$$\max(\Delta H_\theta^{SS}) = \max(H_\theta^{SS}) - \min(H_\theta^{SS}) = H_{\theta=0}^{SS} - H_{\theta=87.1}^{SS} = \\ -30.3 \qquad (9)$$

influence of torsional strain on the EC could be to decrease it by a factor of as much as $e^{-30.3/RT} = 2 \times 10^5$ M relative to the value at $\theta = 90°$ if $\theta = 0°$ (eq 9). The rigidity of the CSSC moiety also restricts the conformational flexibility of the remainder of the molecule and therefore increases the strain caused by other structural features. The magnitude of this possible contribution to EC for cyclic structures containing a disulfide unit is larger than it is for the all-carbon systems commonly studied: hydrocarbon derivatives normally have a much smaller dependence of

bond enthalpy on torsional angles around bonds to sp³ carbon.[11]

This study of the energetics of thiol–disulfide interchange is relevant to two distinct but overlapping areas of research: the biochemistry of the thiol–disulfide system and the use of this system as a model for molecular recognition and catalysis.[12-19] In biochemistry, thiol and disulfide groups serve as catalytic and structural groups in proteins, and thiol–disulfide interchange plays a role in a number of redox cycles and syntheses. In physical-organic chemistry, the thiol–disulfide interchange reaction is unique in its ability to break and reform strong (~ 270 kJ/mol), directional covalent bonds reversibly in water at room temperature, at a rate that one can vary over many orders of magnitude by controlling pH.[20]

A particular interest of ours is the design of dithiols that selectively form dimers on oxidation (eq 10).[2,4] This project in molecular recognition has proved challenging. The structurally

(10)

complex thiols of current interest in this project are difficult to synthesize. We hoped to improve the efficiency of the process extending from molecular design to synthesis by using molecular mechanics. Both as a preliminary step toward calculating energies of cyclic bis(disulfides) and as a guide to understanding the concept of EC, we have focused here on calculations of the energies of processes involving the formation of intramolecular disulfide bonds.

Calculations used the MM2(85) force field.[21] This field has been used successfully in a range of applications, including some involving cyclic disulfides.[22] All of our calculations were based on a standard equilibrium having 1,4-butanedithiol (BDT) as a reference dithiol (eq 11–13). The calculations assumed standard,

$$\text{HSRSH} + \overline{\text{S(CH}_2)_4\text{S}} \rightleftharpoons \overline{\text{SRS}} + \text{HS(CH}_2)_4\text{SH} \qquad (11)$$
$$\qquad\qquad \text{BDT}^{ox} \qquad\qquad\qquad\qquad \text{BDT}$$

$$K_{BDT} = \frac{[\overline{\text{SRS}}][\text{BDT}]}{[\text{HSRSH}][\text{BDT}^{ox}]} \qquad (12)$$

$$\Delta SE = SE(\overline{\text{SRS}}) + SE(\text{BDT}) - SE(\text{HSRSH}) - SE(\text{BDT}^{ox}) \qquad (13)$$

constant bond energies for unstrained bonds and then calculated the "steric energy" SE—that is, the sum of contributions to the energy from intramolecular strain. In certain cases, the bond

(11) For a C–C–C–C dihedral angle where all the carbons are sp³, H_θ^{CC} = 0.4 cos (θ) + 0.6 cos (2θ) + 1.3 cos (3θ) + ($H_{\theta=0}^{CC}$ – 2.3) (ref 10).

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Chart I. 1,2-Dithiolanes Examined in This Study

Chart II. 1,2-Dithianes Examined in This Study

energies may vary from their assumed standard values. Consider, for example, the reaction shown in eq 14. The S–H and S–S

bond energies appropriate for 2,2'-dimercaptobiphenyl and its disulfide may differ from the standard values applicable to BDT. The differences between S–H and S–S energies for the aromatic and aliphatic (BDT) systems will also compensate to some extent: *both* S–S and S–H bond energies for the aromatic redox pair will be less than the corresponding values for BDT^{ox} and BDT.

Methods

General. Steric energies and conformations of the compounds in this paper (Charts I–III) were calculated with Macromodel V2.0[23] with use of the MM2(85) parameter set.[21] We derived starting conformations by analogy to low-energy conformations of similar hydrocarbons[1] and by trial and error. The value of the steric energy used for each molecule was the minimum value obtained over the range of conformations explored. (The two best conformations of **53** had nearly identical energies; they were considered separately as **53bc** and **53tbc**.) The separate contributors to the steric energy (bond stretch, van der Waals, angle bend, torsion, stretch–bend, improper rotation, hydrogen bond, and electrical) for the conformation of lowest energy of each molecule were also analyzed to provide a more detailed understanding of the molecular interactions that determine stability.[1,21]

As a preliminary exercise, we calculated the shape of the torsional potentials for HSSH and CH$_3$SSCH$_3$. Figure 2 compares the results of these calculations with results from more detailed calculations.[24] The approximate agreement between these calculations indicates that parameters used in MM2 describe adequately the dependence of energy in the disulfide moiety on the CSSC (HSSH) dihedral angle.
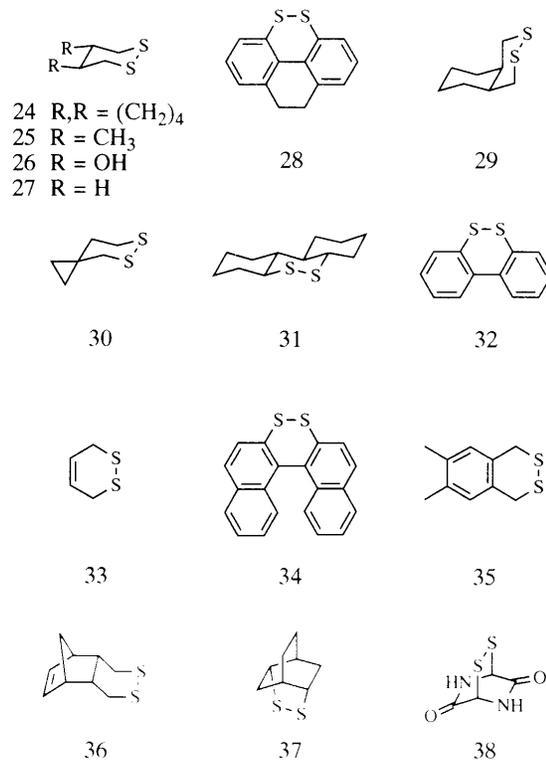
Chart III. 1,2-Dithiepanes and 1,2-Dithiocanes Examined in This Study
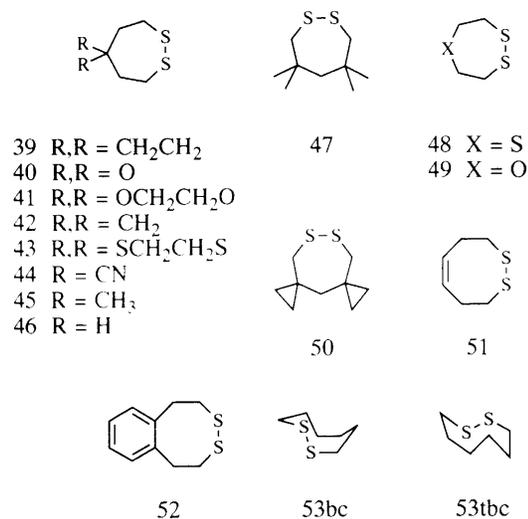
Why base interpretations on the change in steric energy (ΔSE) rather than some other parameter? We used the change in steric energy as the basis for this work without including terms from internal motion, solvation, or intermolecular hydrogen bonding. Calculation of steric energy has the virtues of simplicity and intellectual transparency. One can attempt to model the more complex properties, but doing so requires additional assumptions and greater computational effort. The enthalpy due to internal rotation about C–C bonds (about 1.5 kJ/mol each) is offset by the entropy of the conformational flexibility (a contribution to free energy that could be as high as $RT \ln 3 = 2.7$ kJ/mol per bond[25]). Additional terms for solvation and hydrogen bonding are difficult to estimate without making more complex models.[26] Because these approximations are imprecise and conflicting, we chose not to attempt to model the change in free energy for the thiol–disulfide interchange (eq 11) directly. Survey calculations carried out with more complex models did not yield better correlations with the experimental data than did the

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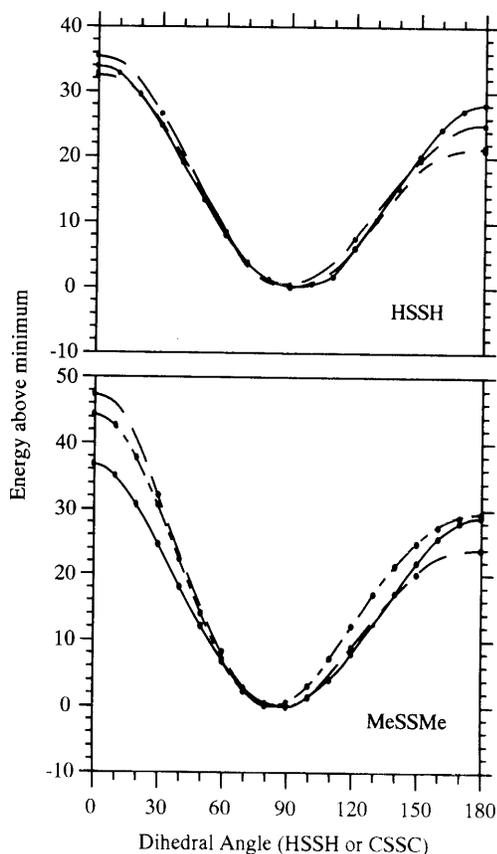
Figure 2. Relative energy (kJ/mol) of HSSH and MeSSMe as a function of the dihedral angle (HSSH or CSSC): (—) MM2(85) (this work); (--) 6-31G* (Aida); (--) SCF and MP2 (Marsden); (---) OPLS (Jorgensen).

Scheme I. Synthesis of Benzene-1,2-Diethanethiol (**52**[red])
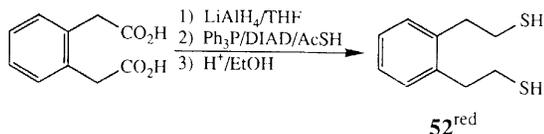
simpler calculations using only steric energies. Thus, instead of trying to create a theoretically correct model, we have developed a useful correlation between a well-defined quantity—the change in steric energy—and the experimentally derived change in free energy for thiol–disulfide interchange between the molecule of interest and BDT.

Results

Synthesis. The reduced form of **52**, benzene-1,2-diethanethiol, was prepared by standard procedures (Scheme I).[27]

Experimental Values of Equilibrium Constants. We have reported experimental values for equilibrium constants of thiol-disulfide interchange for a number of compounds previously.[2,3] The literature contains a mixture of values of equilibrium constants (with respect to 2-mercaptoethanol, K_{ME}; glutathione, K_{GSH}; and 1,4-dithiothreitol, K_{DTT}),[2,3] values of electrochemical half-cell potentials (usually at pH 7, $E^{\circ\prime}$),[28] and values of effective concentrations (EC).[9] All are useful in certain contexts. We used K_{BDT}, the equilibrium constant for the oxidation of the (fully protonated) dithiol of interest by 1,2-dithiane (BDT[ox]), because BDT and BDT[ox] are the simplest representatives of the class of compounds in which we are interested, and therefore, a suitable reference pair. There are few ambiguities in comparisons of values of K_{BDT}. Values of K_{BDT} can be derived easily from other equilibrium expressions by using eqs 15–19.[29] K_{ME} and K_{GSH}

$$K_{BDT} = \frac{K_{ME}}{4.0 \times 10^4 \text{ M}} \quad (15)$$

$$K_{BDT} = \frac{K_{GSH}}{1.3 \times 10^4 \text{ M}} \quad (16)$$

$$K_{BDT} = 2.4 K_{DTT} \quad (17)$$

$$K_{BDT} = \exp\left(\frac{-2F(E^{\circ\prime} + 0.345)}{RT}\right) \quad (18)$$

$$EC = K_{ME} \quad (19)$$

are defined by eq 6, with R″SH = 2-mercaptoethanol or glutathione. Values of EC are determined from eqs 6 and 7 and depend on choosing R″SH and HSRSH such that the thiols of these two compounds are as similar as possible in intrinsic reactivity (that is, in pK_a, structure close to the thiol group, etc.).

Determinations of new experimental values of K_{BDT} were carried out by measuring the concentrations of species in equilibrated mixtures directly by ^{1}H NMR spectroscopy.[2] Benzene-1,2-diethanethiol was equilibrated against BDT[ox] in dimethyl sulfoxide. The value of the standard free energy of the reaction, ΔG°_{BDT}, was obtained from K_{BDT} by using eq 20. Results of calculations

$$\Delta G^{\circ}_{BDT} = RT \ln (K_{BDT}) \quad (20)$$

and of experiments are summarized in Table I. This table also includes values of the van der Waals (vdW), angle bending (bend), and torsional strain (tors). The other contributors to the change in steric energy (bond stretching, stretch–bend interactions, improper rotation, hydrogen bonding, and electrical energy) are significantly smaller and have no consistent effect.

Correlation of Theoretical and Experimental Values of Energies. Our calculated values of ΔSE correlate roughly linearly with the experimental values of ΔG°_{BDT} for the thiol–disulfide equilibrium reaction in eq 11 for 20 cyclic disulfides previously examined experimentally[2] (Figure 3). The best correlation line is given by eq 21, with a standard deviation of 2.8 kJ/mol. The sign of

$$\Delta G^{\circ}_{BDT} = 0.41 \Delta SE + 0.5 \text{ kJ/mol} \quad (21)$$

the slope supports the theoretical relationship between ΔG°_{BDT} and ΔSE. One point (**36**) diverges noticeably from the line and is not considered in the linear fit. Compound **36** is a six-membered disulfide ring in a boat conformation with $\theta_{CSSC} \sim 0°$. Some feature of this geometry of the disulfide moiety may be responsible for the difference between theory and experiment, since the MM2 calculations differ most from more detailed calculations at $\theta = 0°$. In addition, a recent paper by Allinger introducing the MM3 force field[30] suggests that MM2 calculations on norbornane and its derivatives are less accurate than similar calculations on other types of structures. When compound **36** is included in the set of data, the correlation coefficient for the data in Figure 3 is 0.86; without **36**, the correlation coefficient is 0.93.

Equation 21 carries two qualitative messages. First, theory and experiment correlate: The slope of the line has a positive sign and the correlation coefficient is reasonably high. Second, theory systematically overestimates the influence of the collection of contributions lumped together in the steric energy ΔSE to the change in free energy experienced by the reactants: $\Delta G \propto 0.4 \Delta SE$.

Can we rationalize this slope? Why does ΔG not equal ΔSE, as would be expected for a perfect theory? We do not know. Although it is straightforward to list several enthalpic terms—rotation, vibration, and solvation—that are not included in ΔSE, it is not clear why they should correlate with ΔSE. We have been unable to change the slope or increase the correlation by including other terms.

Although we have not been able to interpret the correlation between ΔG and ΔSE in a satisfying way, the correlation justifies the use of this technique as a tool for design. We used the linear

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Table I. Calculated Changes in the Overall Steric Energy and Its Components, Experimental $\Delta G°$ and K, and Predicted $\Delta G°_{BDT}$ and K_{BDT} for Reactions Forming Cyclic Disulfides According to Equation 11

compd	ring size	ΔSE	theoretical		experimental		ΔSE (vdW)	ΔSE (bend)	ΔSE (tors)
			$\Delta G°_{BDT}$	K_{BDT}	$\Delta G°_{BDT}$	K_{BDT}			
1	5	−24.6	−9.5	4.8×10^1			−8.0	−1.8	−14.9
2	5	−22.7	−8.8	3.5×10^1			−9.9	1.1	−14.3
3	5	−19.4	−7.4	2.0×10^1			−16.6	−4.9	5.5
24	6	−16.2	−6.1	1.2×10^1	−7.3	2.0×10^1	−6.6	−4.5	−3.2
28	6	−14.7	−5.5	9.2			0.5	−8.2	−4.5
39	7	−14.5	−5.4	8.9			−5.8	−5.0	−1.2
40	7	−14.2	−5.3	8.5			−0.9	−0.5	9.6
4	5	−14.1	−5.3	8.5			−15.2	−12.4	14.7
25	6	−13.8	−5.1	7.9			−4.6	−2.7	−5.8
26	6	−12.1	−4.4	6.0	−2.1	2.4	−1.5	−3.7	−2.6
29	6	−9.6	−3.4	3.9	−5.4	8.8	−3.3	−1.6	−3.4
5	5	−7.7	−2.7	2.9			−11.3	−12.7	16.0
30	6	−3.3	−0.8	1.4			−0.2	−2.8	0.6
31	6	−2.5	−0.5	1.2			1.3	−4.8	0.2
41	7	−1.6	−0.1	1.0			2.2	7.5	−1.6
32	6	−1.1	0.1	9.6×10^{-1}			5.1	−5.4	−1.0
42	7	−0.3	0.4	8.4×10^{-1}			−7.0	−3.6	8.2
27	6	0.0	0.6	8.0×10^{-1}	0.0	1.0	0.0	0.0	0.0
43	7	0.4	0.7	7.5×10^{-1}			2.5	12.7	−0.2
51	8	0.7	0.8	7.1×10^{-1}			3.1	3.4	−3.5
47	7	1.4	1.1	6.3×10^{-1}			−1.8	8.5	−3.0
52	8	2.4	1.5	5.4×10^{-1}	0.4	8.4×10^{-1}	3.2	4.5	−8.8
6	5	3.5	2.0	4.5×10^{-1}			−3.5	6.1	15.9
44	7	3.9	2.1	4.2×10^{-1}			0.6	11.0	3.7
33	6	4.1	2.2	4.1×10^{-1}	1.4	5.8×10^{-1}	3.2	2.9	−4.9
48	7	5.6	2.8	3.2×10^{-1}	6.0	8.8×10^{-2}	2.7	8.3	−0.8
34	6	9.1	4.3	1.8×10^{-1}			7.3	−3.8	5.2
45	7	9.7	4.5	1.6×10^{-1}	4.2	1.8×10^{-1}	1.7	9.9	−1.1
16	5	9.8	4.6	1.6×10^{-1}			−8.8	−0.8	21.9
17	5	10.1	4.7	1.5×10^{-1}			−6.9	6.8	6.5
35	6	10.2	4.7	1.5×10^{-1}	3.4	2.5×10^{-1}	4.0	6.8	−4.5
7	5	12.0	5.5	1.1×10^{-1}	5.6	1.1×10^{-1}	−10.3	−3.8	25.6
50	7	12.2	5.6	1.1×10^{-1}			9.4	0.9	2.9
8	5	12.3	5.6	1.0×10^{-1}			−7.1	−2.4	27.6
9	5	13.3	6.0	8.8×10^{-2}	7.5	4.8×10^{-2}	−10.0	−2.5	25.1
18	5	13.5	6.1	8.5×10^{-2}			−7.9	−2.3	28.0
10	5	14.8	6.6	6.9×10^{-2}			−7.4	−1.1	26.8
11	5	14.9	6.7	6.7×10^{-2}	8.1	3.8×10^{-2}	−7.4	−5.0	26.7
19	5	15.0	6.7	6.6×10^{-2}			−8.9	−0.3	23.0
46	7	16.1	7.2	5.5×10^{-2}	7.5	4.8×10^{-2}	4.4	7.8	4.5
12	5	16.1	7.2	5.5×10^{-2}	7.1	5.8×10^{-2}	−8.6	−0.2	24.2
13	5	16.3	7.2	5.3×10^{-2}	10.2	1.6×10^{-2}	−5.7	2.4	18.3
20	5	19.5	8.5	3.1×10^{-2}	4.8	1.4×10^{-1}	−6.8	0.1	26.7
21	5	19.7	8.6	3.0×10^{-2}			−8.0	−0.5	27.6
36	6	21.9	9.5	2.1×10^{-2}	0.4	8.5×10^{-1}	1.4	18.5	0.5
14	5	22.6	9.8	1.9×10^{-2}	8.7	3.0×10^{-2}	−4.5	0.7	27.0
22	5	22.9	9.9	1.8×10^{-2}			−4.2	6.3	22.9
53bc	8	26.8	11.5	9.3×10^{-3}	14.6	2.8×10^{-3}	5.4	14.8	7.1
53tbc	8	27.1	11.7	8.9×10^{-3}			7.2	9.5	10.4
15	5	29.8	12.8	5.7×10^{-3}	11.7	8.8×10^{-3}	−3.9	3.8	23.7
23	5	34.6	14.7	2.6×10^{-3}			−0.1	13.7	21.3
37	6	34.7	14.8	2.5×10^{-3}			15.3	−0.2	17.6
38	6	36.1	15.3	2.0×10^{-3}			10.0	−9.6	15.6

fit from Figure 3 to predict ΔG for the equilibration reactions of a variety of disulfides (Table I). The experimental value of $\Delta G°_{BDT}$ for **52** differs from the predicted value by only 1.1 kJ/mol, less than half of the standard deviation (Figure 3).

Analysis of Theoretical Models

Molecular mechanics calculations provide both an empirically useful measure of stability and information about the molecular interactions that determine it. Three components of the change in steric energy calculated by MM2 vary significantly from structure to structure and seem largely to determine ΔSE: bending strain between two adjacent bonds (ΔSE(bend) in Table I), torsional strain from rotations about a bond between atoms (ΔSE(tors)), and van der Waals forces between nonbonded atoms that are not bonded to the same atom (ΔSE(vdW)) (Figure 4). Analysis of the results of these calculations shows certain trends in the stability of cyclic disulfides.

Five-Membered Rings. The most favorable effect in the formation of 1,2-dithiolanes (five-membered rings) from 1,3-dithiols

arises from the relief of steric interactions in the open dithiol. The sulfur atoms press against β-substituents or γ-carbon atoms in thiols or unconstrained disulfides. In the dithiolane, the sulfur atoms are pulled away from those groups and toward each other instead (Figure 5). The small size of the ring constrains the CSSC dihedral angle to a value less than 35°. This CSSC torsional strain lowers the stability of these disulfides by 8.4 kJ/mol relative to fully relaxed disulfides ($\theta_{CSSC} = 90°$ [31]). In rings this strained, MM2 reproduces known values of θ_{CSSC} poorly: lipoic acid has a dihedral angle of 35° in the crystal,[32] but MM2 calculations give a minimum in energy at a value close to 0°. Despite the stabilizing effect of steric relief, the unfavorable dihedral angle of the CSSC group makes typical 1,2-dithiolanes less stable and

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(32) Stroud, R. M.; Carlisle, C. H. *Acta Crystallogr.* **1972**, *B28*, 304–307.
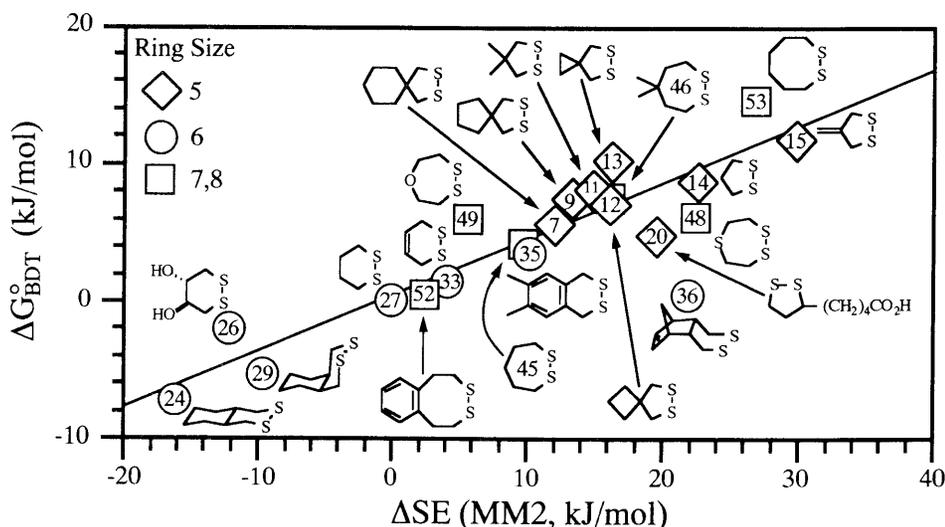
Figure 3. Experimental $\Delta G°_{BDT}$ of the reaction in eq 1 plotted as a function of ΔSE. Compound **27** is the reference disulfide: ΔG, $\Delta SE = 0$.

more easily reduced than 1,2-dithianes.

In especially crowded 1,3-dithiols, steric strain may result in molecular deformation (Figure 6). In the reduced forms of compounds **1, 2,** and **3,** the nonbonded sulfur atoms are so close together that the aromatic rings must twist to accommodate them: the calculated change in torsional strain ($-35.5, -33.0,$ and -13.4 kJ/mol of change, respectively) comes almost entirely from the release of that twisting in going from the dithiols to the corresponding disulfides. In reduced **4** and **5,** calculations indicate that the sulfur–sulfur repulsion in the dithiol forces the CCC bond angles on the α- and β-carbons to distort (12.5 kJ/mol in bending strain). Strain in reduced **2, 3, 4,** and **5** manifests itself in van der Waals repulsions as well. Increasing the dihedral angle to decrease the torsional strain in **17** ($\theta_{CSSC} = 35°$ in our calculation) achieves only modest results due to the intrinsic strain caused by including a large twist in a small ring.

In broad terms relevant to molecular design, we conclude that in five-membered rings, destabilizing the reduced form is generally the best approach to stable disulfides.

Six-Membered Rings. 1,2-Dithianes adopt a chair conformation with a CSSC dihedral angle of 58–66°. Despite the torsional strain associated with that twist (6–9 kJ/mol), 1,2-dithianes are generally the most stable of the cyclic disulfides. The separate components of the steric energy change for the equilibration with an acyclic disulfide, 2-mercaptoethanol, are all close to zero. Like cyclohexanes, 1,2-dithianes are nearly strain free.

Although the compounds in this class have similar enthalpy terms for each interaction, classes of structures consistently above and below the average can be identified. A double bond in the ring introduces van der Waals and bending strain in compounds **32–35.** Compound **36** suffers similarly because the carbons of the dithiane moiety are confined to a plane by the rigidity of the norbornene skeleton. On the other hand, relative strain in saturated rings can be reduced by adding gauche interactions to the dithiol (Figure 7). Unsubstituted 1,2-dithiane (**27,** BDT^{ox}) has three gauche interactions about C–C bonds in the ring; reduced **27,** BDT, has none in its fully extended form. Compounds **25** and **26** have four such gauche interactions in the dithiane moiety; however, the corresponding dithiols also have four. Compound **28** is an exceptional case: the dithiol is destabilized relative to other dithiols not so much by the torsional restriction imposed by the bridging ethylene group as by the bending strain transmitted to the ring containing the bridge by the proximity of the thiols.

Larger Rings. We calculate that 1,2-dithiepanes (seven-membered rings) have the same conformation—a twist-chair—as their carbocyclic analogues.[33] CSSC dihedral angles in these molecules are calculated to be close to ideal (81–89°). 1,2-Dithiocanes

(eight-membered rings) can adopt boat–chair, twist–boat–chair (+0.2 kJ/mol), or crown (+3.5 kJ/mol) conformations, with slightly larger dihedral angles (about 100°) (Figure 8). Rings of this size suffer strain because the angles between bonds in the ring are generally wider than ideal. In addition, the conformations available to these rings do not allow complete staggering of substituents: van der Waals strain results.

Functional groups that increase the angle between bonds stabilize the disulfide by relaxing bending strain. It is clear from Figure 4 that compounds **39, 40, 42, 50, 51,** and **52,** which have these groups, have significantly less bending strain than the other compounds of these ring sizes, which do not. Steric crowding (van der Waals repulsion) destabilizes **50.** In 1,2-dithiepanes, increasing angles between bonds reduces θ_{CSSC}, increasing torsional strain; the spirocyclopropyl derivative, **39,** strikes the best balance between the two forces. The double bond in the eight-membered rings of compounds **51** and **52** contributes over 12 kJ/mol to their stability relative to 1,2-dithiocane (**53**). This double bond increases bond angles in the ring, freezes the C_2–C_3–C_4–C_5 dihedral angle at approximately 0°, decreases torsional strain about the C–C bonds, and removes unfavorable cross-ring van der Waals repulsions (Figure 9).

Conclusions

Conformational Analysis of Cyclic Disulfides by Using Molecular Mechanics. The molecular mechanics method used here is not sufficiently accurate to calculate absolute values for equilibrium constants of thiol–disulfide interchange reactions, but it does yield energies that correlate usefully with experimental data. It is clearly a successful aid to molecular design. In particular, it successfully predicted the high stability of **52** relative to **53,** a similar disulfide without a double bond.

These calculations have also identified a number of energetically important characteristics of conformations of cyclic disulfides. There is only a single important low-energy conformation for five-, six-, and seven-membered rings, although eight-membered rings have three. A θ_{CSSC} of 90° contributes about 28 kJ/mol of the stability to a disulfide relative to one of 0°. Trans-extended conformations of dithiols can be destabilized by adding β-substituents. In larger rings, bond-angle strain can be relieved by adding double bonds or creating spirocyclopropyl junctions. The dithiol can be destabilized relative to the disulfide by placing the sulfurs so close together that they experience strong van der Waals repulsion when not bonded to each other.

These considerations provide a set of working rules that are clearly useful in molecular design. They also provide a semi-quantitative basis for rationalizing the conformations of dithiols and of the cyclic disulfides derived from them.

Effective Concentration. For thiol–disulfide interchange, the EC is another name for a particular equilibrium constant: that

(33) Joshua, A. V.; Scott, J. R.; Sondhi, S. M.; Ball, R. G.; Lown, J. W. *J. Org. Chem.* **1987,** *52,* 2447–2451.
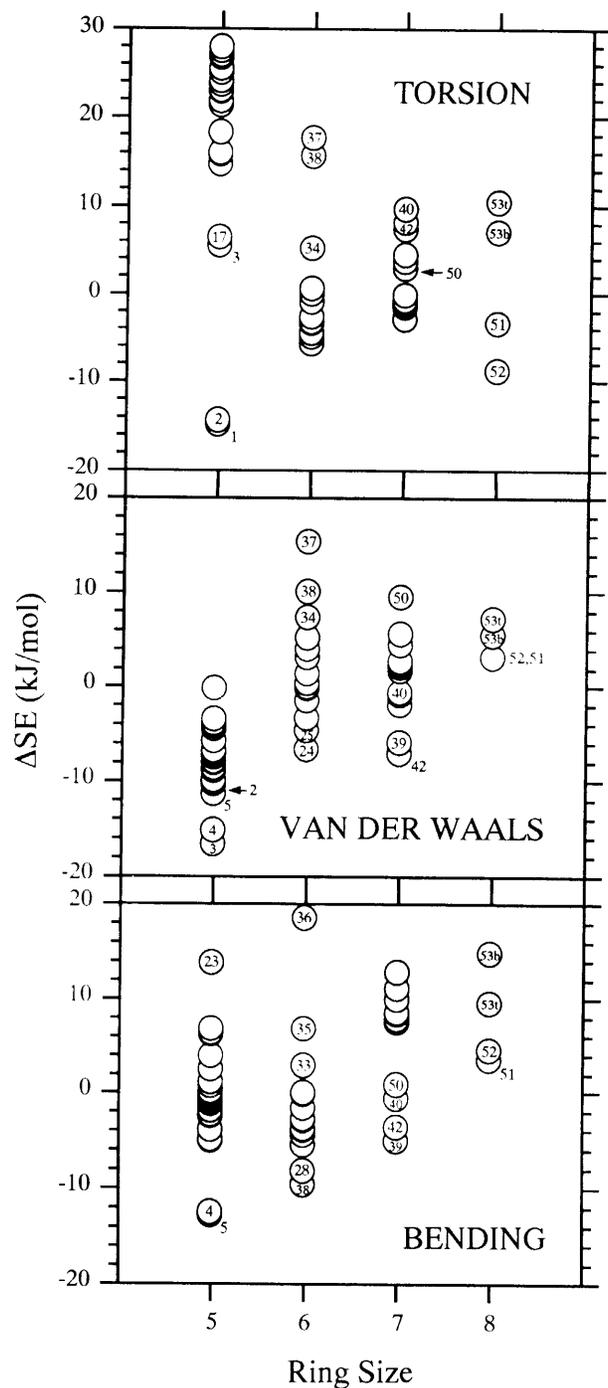
Figure 4. Changes in torsional strain, van der Waals energy, and bending strain for eq 11 as a function of the size of the ring $\overline{SRS}$.
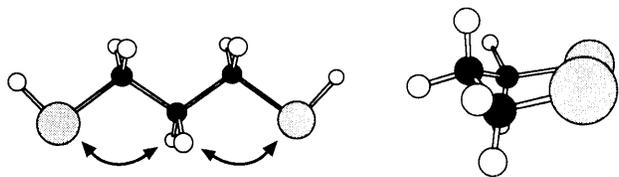
Figure 5. Van der Waals interactions in 1,3-propanedithiol and 1,2-dithiolane.

Figure 6. Sulfur–sulfur repulsion in two unusual 1,3-dithiols: naphthalene-1,8-dithiol and bicyclo[3.3.0]octane-2,8-dithiol.
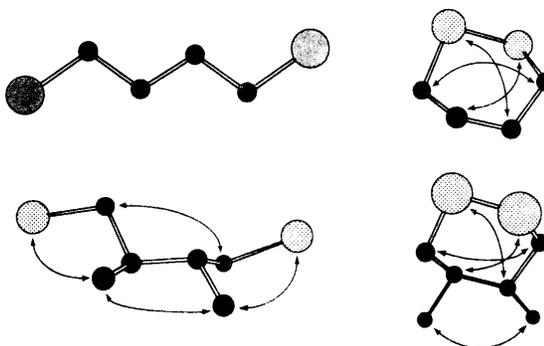
Figure 7. Gauche interactions in 27^{red} (BDT), 25^{red}, **27** (BDT^{ox}), and **25**.

| 7-membered ring | 8-membered ring | 8-membered ring |
| twist-chair | boat-chair | twist-boat-chair |
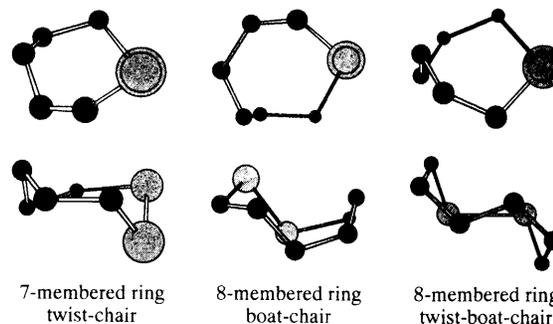
Figure 8. Low-energy conformations of **46** (1,2-dithiepane) and **53** (1,2-dithiocane).
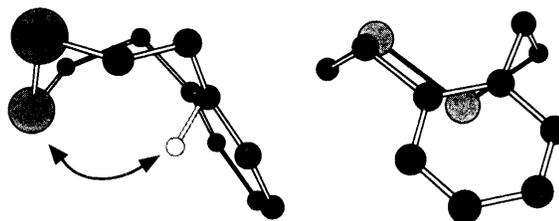
Figure 9. The most stable conformation of **52**. In **53**, hydrogen atoms of methylene units project into the crease of the molecule (relative position in light gray) and experience van der Waals repulsion. These hydrogen atoms and unfavorable interactions have been eliminated in **51** and **52**.

between a dithiol capable of forming a cyclic disulfide on oxidation and a strain-free dialkyl disulfide that yields 2 equiv of thiol on reduction (eqs 3–7). Since the EC is an equilibrium constant, how helpful is it to interpret it as a concentration? In particular, does EC (or $K_{R''SH}$, eqs 5 and 6) correlate well or poorly with the central idea that connects "concentration" to "reactivity": that is, the average proximity of the reacting centers? Because the

thiol–disulfide interchange reaction is mechanistically simple, and because molecular mechanics calculations are able to disentangle at least semiquantitatively the factors contributing to differences in energy, we are able to set some limits on the extent to which EC and "proximity" coincide.

The equilibrium constant is a ratio of concentrations because translational entropy depends on concentration. The change in entropy for intramolecular reactions comes not from translational entropy but from conformational entropy, which correlates *loosely* with distance. Ring strain, an enthalpic contribution that is not necessarily correlated to distance, will also affect the free energy change of the reaction. In the absence of conformational entropy and strain enthalpy, the EC will be around 10^8 M.[7] A loss of

conformational entropy or an increase in strain will decrease the EC; a decrease in strain will increase it.

The largest single enthalpic contributor to the equilibrium constant in reactions involving transformation of HSRSH to $\overline{SRS}$ is probably θ_{CSSC}. Since the torsional strain can range from 0 (at 90°) to 30 kJ/mol (at 0° or 180°), this factor is able to decrease the EC by a multiplicative factor of as much as 10^{-5}. This contribution will tend to make the EC *smaller* than a true measure of conformational entropy. It is also possible to have the EC *larger* than would be expected based on entropy. Unfavorable interactions in the reduced (HSRSH) species that are relieved on oxidation to the disulfide ($\overline{SRS}$) fall in this category. It is difficult to set a limit on this type of interaction, but the release of steric energy on oxidizing 1,1-bis(mercaptomethyl)cyclohexane to **7** provides an example. This release multiplies a measure of concentration based on proximity (cf. **14**) by a factor of 6.

In these small molecules, the enthalpic contribution of ring strain to ΔG strongly outweighs the contribution of conformational entropy. First, ΔSE correlates well with ΔG; survey calculations that included entropy terms had no better correlation. Second, the stability of rings does not uniformly decrease with ring size as one would expect on the basis of proximity of sulfur atoms in the dithiols. In the reduced form of **45**, the sulfur atoms are 8.0 Å apart; in the reduced form of **15**, they are only 3.7 Å apart. Compound **45** is nonetheless more stable relative to its dithiol than **15** is by a factor of 30.

Thus, we conclude that the EC in thiol–disulfide interchange can differ significantly from a measure of conformational entropy, which is itself only partially a measure of distance. The EC is a useful measure of *reactivity* (as it should be, since it is an equilibrium constant); it is more complicated to interpret it as a measure of conformation, and the EC is probably only useful as a measure of proximity when other data allow independent estimates of terms—conformational entropy (flexibility), strain from an unfavorable θ_{CSSC}, or terms destabilizing the dithiol relative to the disulfide—that could be large.

The EC remains a qualitatively appealing concept. Its principal virtue is that, by phrasing an equilibrium constant as a concentration, it provides a reference state that is immediately understandable. To say that the equilibrium constant K is 10^6 M for a reaction is colorless. To say the effective concentration EC is 10^6 M (correctly) focuses attention on an energetically favorable reaction. Ideally, the EC compares an intramolecular process with an intermolecular model having similar changes in bond energies and allows large effects due to conformation to be identified. To the extent that the energetics of the two processes are different, the comparison is difficult to interpret.

It is interesting that the reciprocal use of the EC to characterize *unfavorable* intramolecular reactions has not caught on. An EC of 10^{-6} M is a number that is as readily interpreted mechanistically as an EC of 10^6 M, but it is less successful in capturing attention.

Experimental Section

General. Chemicals were obtained from Aldrich Chemical Co. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Diethyl ether was dried over $MgSO_4$. Other compounds were not purified before use. All reactions were done under an argon atmosphere. NMR spectra were taken on a Bruker AM-500.

Calculations. Steric energies and conformations were calculated and minimized by Macromodel V2.0[23] with the MM2(85) parameter set.[21] The energy of each structure was minimized by the block-diagonal

Newton–Raphson method until the root mean square of the derivatives of energy with respect to each Cartesian coordinate was less than 10 $J \cdot \text{Å}^{-1} \cdot \text{mol}^{-1}$. The default dielectric constant of 1.0 was used. The calculations were performed on a DEC VAX 11/780 with a floating point processor running VMS 4.6.

Measurement of K_{BDT}. A solution of benzene-1,2-diethanethiol (**52**[red]) and BDT[ox] (5 to 20 mg each) in deuterated dimethyl sulfoxide (4.2 mL) was degassed by bubbling argon through it for 30 min. Sodium deuteroxide (10 mM in D_2O) was added by syringe to bring the total base concentration to 1–5% of the thiol concentration. An aliquot of this solution was transferred by cannula into an argon-filled 5-mm NMR tube equipped with a rubber septum stopper. The top of the tube was sealed immediately with paraffin wax. The concentrations of the four species in solution (**52**[red], **52**, BDT, and BDT[ox]) were measured by integrating the ^1H NMR signal for each compound and normalizing the total BDT concentration ([BDT] + [BDT[ox]]) to its initial value. K_{BDT} was calculated from the concentrations with use of eq 12.

Benzene-1,2-diethanethiol (52[red]) was made in three steps following standard procedures. A solution of benzene-1,2-diacetic acid (4.85 g, 25.0 mmol) in THF (150 mL) was added dropwise over 40 min to a slurry of $LiAlH_4$ (1.93 g, 50.9 mmol) in THF (100 mL) at 0 °C. After 12 h at 25 °C, the reaction mixture was cooled back down to 0 °C and water (100 mL) was added to it dropwise over 40 min. The reaction mixture was saturated with potassium carbonate and separated. The aqueous phase was extracted with two 50-mL portions of THF. The combined organic layer was washed with concentrated aqueous $NaHCO_3$ (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered, and concentrated to give 3.85 g of crude benzene-1,2-diethanol (23.2 mmol, 93%) as a brown oil: ^1H NMR ($CDCl_3$) δ 7.17 (s, 4 H), 3.79 (t, J = 6.9 Hz, 4 H), 2.94 (br s, 2 H), 2.89 (t, J = 6.9 Hz, 4 H).

The alcohol was converted to the thioacetate by Volante's method.[27] A solution of diisopropyl azodicarboxylate (11.8 mL, 60 mmol) in diethyl ether (50 mL) was added over 10 min to a solution of triphenylphosphine (15.74 g, 60 mmol) in diethyl ether (100 mL) at 0 °C. A large quantity of hard white precipitate formed. A solution of thiolacetic acid (4.3 mL, 60 mmol) and benzene-1,2-diethanol (3.85 g, 23.2 mmol) in diethyl ether (100 mL) was added over 15 min at 0 °C. The precipitate broke up, but the solution remained cloudy. After 26 h at 25 °C, the reaction mixture was washed with water (200 mL), concentrated aqueous $NaHCO_3$ (200 mL), and brine (200 mL). It was dried over $MgSO_4$, filtered, and concentrated to give a damp yellow and white solid. The crude product was taken up in hexane (100 mL) and water (100 mL). The mixture was filtered and separated. The organic phase was washed with water (100 mL), concentrated aqueous $NaHCO_3$ (100 mL), and brine (100 mL). It was dried over $MgSO_4$, filtered, and concentrated to give a beige solid. Recrystallization from methanol afforded 2.9 g of 1,2-bis(2-acetylthioethyl)benzene (10 mmol, 45%) as a slightly yellow powder: ^1H NMR ($CDCl_3$) δ 7.20 (s, 4 H), 3.05 (m, 4 H), 2.95 (m, 4 H), 2.35 (s, 6 H); methanol contamination, δ 3.48 (s), 1.53 (s).

The powder was taken up in ethanol (50 mL). Acetyl chloride (0.5 mL) was added to the reaction mixture. The solution was stirred at reflux for 13 h. The reaction mixture was concentrated to give 1.5 g of **52**[red] as a yellow oil: ^1H NMR ($CDCl_3$) δ 7.18 (s, 4 H), 3.01 (t, 4 H), 2.75 (q, 4 H), 1.44 (t, 2 H).

The 4-nitrobenzoyl derivative was made to further identify the compound: mp 133–135 °C. ^1H NMR ($CDCl_3$) δ 8.29 (dm, J = 8.9 Hz, 4 H), 8.10 (dm, J = 8.9 Hz, 4 H), 7.30 (m, 2 H), 7.26 (m, 2 H), 3.36 (br m, 4 H), 3.11 (br t, 4 H). Anal. Calcd for $C_{24}H_{20}N_2O_6S_2$: C, 58.0; H, 4.0; N, 5.6. Found: C, 57.9; H, 3.9; N, 5.5.