These studies have established the reaction to be mechanistically at room temperature in aqueous solution and have prompted many to investigate the reversible cleavage and formation of strong, covalent S-S bonds. Interchange involves three steps (eq la-c): initial ionization of the thiol to thiolate anion, nucleophilic attack of the thiolate anion on a sulfur atom of the disulfide moiety, and elimination of the disulfide bond to reform the thiol.

A systematic search of a limited hemisphere of reciprocal space located a set of diffraction maxima with systematic absences corresponding to the unique monoclinic space group P2\(_1\)/a. Subsequent solution and refinement confirmed this choice.

The structure was solved by a combination of direct methods (MULTAN5) and Fourier techniques and refined by full-matrix least squares. Many of the hydrogen atom positions were visible in the difference Fourier phase on the non-hydrogen parameters. The positions of all hydrogens were calculated and placed in fixed idealized positions (d(C-H) = 0.95 Å) for the final cycles. The hydrogen atoms were assigned a thermal parameter of 1 + Biso of the carbon atom to which they were bound. The data were corrected for absorption for the final cycles of the refinement.

A final difference Fourier was essentially featureless, with the largest peak being 0.50 eÅ\(^{-1}\).

Acknowledgment. We thank Dr. D. M. Hoffman of Harvard University for helpful discussions and the National Science Foundation and the Wurling Computing Center for support. D.L.C. gratefully acknowledges the support of a General Electric Foundation fellowship for 1985–1986.

Registry No. W\(_{2}\)(np)\(_2\)(O\(_2\)CNMe\(_2\))\(_4\), 108603-67-4; W\(_2\)(np)\(_2\)(O\(_2\)CMe\(_2\))\(_2\) (S\(_2\)CNEt\(_2\))\(_2\), 110097-42-2; W\(_2\)(np)\(_2\)(O\(_2\)CMe\(_2\))\(_2\) (O\(_2\)CMe), 110116-42-2; W\(_2\)(np)\(_2\)(O\(_2\)CNMe\(_2\))\(_2\), 72286-53-4; W\(_2\)(np)\(_2\)(O\(_2\)CNMe\(_2\))\(_2\), 72286-52-0; W\(_2\)(np)\(_2\)(O\(_2\)CNMe\(_2\))\(_2\), 84913-56-4; W\(_2\)(np)\(_2\)(O\(_2\)CNMe\(_2\))\(_2\), 91549-49-4; W\(_2\)(np)\(_2\)(O\(_2\)CMe\(_2\))\(_2\) (S\(_2\)CNEt\(_2\))\(_2\), 110097-43-3; Na\(_2\)S\(_2\)CNEt\(_2\), 148-18-5; thioacetic acid, 507-09-5.

Supplementary Material Available: Anisotropic thermal parameters and a complete listing of bond distances and bond angles for the W\(_2\)(np)\(_2\)(O\(_2\)CMe\(_2\))\(_2\) (S\(_2\)CNEt\(_2\))\(_2\) molecule (4 pages); Fn and Fc values for the same compound (10 pages). Ordering information is given on any current masthead page.

Structure-Reactivity Relations for Thiol–Disulfide Interchange

Janette Houk and George M. Whitesides*

Contribution from the Departments of Chemistry, Harvard University, Cambridge, Massachusetts 02138, and Massachusetts Institute of Technology, Cambridge, Massachusetts 02139. Received February 5, 1987

Abstract: Equilibrium constants were determined for thiol–disulfide interchange between 36 di- and triethiols and the disulfides derived from either 2-mercaptoethanol or dithiothreitol. Reactions were conducted in methanol-d\(_6\)/aqueous buffer (pH 7) or methanol-d\(_6\) at 25 °C. The reactions were followed by NMR spectroscopy using either 3H NMR (22 °C, benzene-d\(_6\)) or 1H NMR (22 °C, benzene-d\(_6\)).

1H NMR (22 °C, benzene-d\(_6\)): δ 3.26 (s, O2CNMe\(_2\)), 3.03 (s, CH\(_2\)CMe\(_2\)). 2.85 (s, J\(_{\text{HH}}\) = 9.98 Hz, CH\(_2\)CMe\(_2\)) next to S). 2.32 (s, O2CNMe\(_2\)), 2.26 (s, CH\(_2\)CMe\(_2\) tran to OSCMe) (3.03 g, 0.44 mmol) was dissolved in CH\(_2\)Cl\(_2\) and then frozen in liquid N\(_2\). In a similar procedure a large excess of CO\(_2\) (1 atm) was reacted with W\(_2\)(np)\(_2\)(O\(_2\)CNMe\(_2\))\(_4\). A yellow powder (0.35 g, 92%).

Crystallographic Studies. General operating procedures and listings of programs have been previously published. Crystal data for W\(_2\)(np)\(_2\)(O\(_2\)CMe\(_2\))\(_2\) (S\(_2\)CNEt\(_2\))\(_2\) are given in Table VI. A suitable crystal was transferred to the goniostat by standard inert-atmosphere handling techniques employed by the IUMSC and cooled to -160 °C with a gas-flow cooling system.

The importance of the thiol–disulfide interchange reaction to biochemistry and the remarkable ability of this reaction to effect the reversible cleavage and formation of strong, covalent S-S bonds at room temperature in aqueous solution has prompted many studies of the physical-organic chemistry of this reaction. These studies have established the reaction to be mechanistically simple. Interchange involves three steps (eq la-c): initial ionization of the thiol to thiolate anion, nucleophilic attack of the thiolate anion on a sulfur atom of the disulfide moiety, and polymerization of the thiol to thiolate anion, nucleophilic attack of the thiolate anion on a sulfur atom of the disulfide moiety, and

(1) Supported by the National Institutes of Health, Grant GM 34411.
protonation of the product thiolate anion. All three steps are fully reversible. The nucleophilic attack appears to be an uncomplicated $S_2$ displacement that occurs along the axis of the sulfur–sulfur bond.\(^{18-20}\) For simple monothiols, both rate and equilibrium constants follow a Bronsted relation, but the factors that determine the position of equilibrium are more complicated.\(^{21}\) Oxidations of $\alpha,\omega$-dithiols by thiol–disulfide interchange under conditions leading to equilibrium mixtures of products generate cyclic monomeric disulfides, cyclic dimeric bis(disulfides), and oligomeric disulfides (eq 2).\(^{11}\) The yields of these products depend on the nature of $R$ and the concentrations of the dithiol and disulfide. Cyclic monomeric disulfides are the major products when the thiol groups are separated by three to six atoms. These thermodynamically stable cyclic monomers are strongly reducing relative to monothiols, reflecting the high effective concentration\(^{22-26}\) of cyclic monomeric disulfides. Qualitatively, we expect to be able to favor formation of cyclic bis(disulfides) by constraining the starting dithiols to geometries resembling those of the bis(disulfides) and by eliminating as many rotational degrees of freedom in the dithiols as possible.

Equilibrium constants for thiol–disulfide interchange reactions have been determined by using a variety of analytical techniques: polarography,\(^{27}\) electrophoresis of $^{15}$S-labeled thiol,\(^{28}\) gas chromatography,\(^{29}\) ion-exchange chromatography,\(^{30}\) HPLC,\(^{31}\) enzymatic assay,\(^{32}\) and UV absorption of arenethiolate anion.\(^{33}\) We have employed an NMR method that minimizes the problems associated with manipulating dilute solutions of the air-sensitive thiols. Rabenstein et al. used a similar NMR method to determine equilibrium constants for the reaction of Captopril and penicillamine with oxidized glutathione.\(^{34}\)

\section*{Results and Discussion}

\subsection*{Synthesis of Thiols: General}

A wide range of thiol nucleophiles can be used to prepare thiols from the corresponding halides or tosylates.\(^{35-39}\) We used four such reagents routinely.

\subsection*{Synthesis of Thiols: Specific}

(43) This stability is the structural basis for the well-established ability of dihydrothreitol to act as a reducing agent for disulfides in biological systems and as a protective agent against protein autoxidation. Cleland, W. W. Biochemistry 1964, 3, 480–482.

---

\[ RSH + \overset{\text{mixed disulfide}}{\text{HS-R-SH}} \overset{\text{cyclic monomer}}{\text{R'SH}} \overset{\text{cyclic dimer}}{\text{S-R-S}} \overset{\text{oligomers}}{\text{S-R-S-SR'}} \]

in a process that forms an eight-membered ring by an intramolecular process. This reaction is concentration sensitive: At low concentration, the dimer forms; at high concentration the product is polymeric.\(^{11}\) Beyond these correlations of equilibrium constant with ring size for cyclic monomeric dithiols, the factors that influence the reduction potentials of dithiols are not known. We have studied these factors and report our results in this paper. We consider this study in part a problem in molecular design: Can we design dithiols that will form cyclic monomers, dimers, or polymers exclusively on oxidation under equilibrating conditions? What structural features must be built into a dithiol to make it strongly reducing, and can a structural parameter or parameters be identified that will enable us to predict the reducing ability of a dithiol based on its structure? We are most interested in reactions that form thermodynamically stable cyclic bis(disulfides), because these materials could form the basis for reversible coupling agents for use in biochemical systems and because they pose a more demanding problem for molecular design than do monomeric or polymeric disulfides. Qualitatively, we expect to be able to favor formation of cyclic bis(disulfides) by constraining the starting dithiols to geometries resembling those of the bis(disulfides) and by eliminating as many rotational degrees of freedom in the dithiols as possible.

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Results and Discussion

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\[ (\overset{\text{eq}}{\overset{\text{SH}}{\text{OH}}}) (\overset{\text{eq}}{\overset{\text{HS-SR}}{\text{OH}}}) (\overset{\text{eq}}{\overset{\text{HS-SR'}}{\text{OH}}}) \]

(3)
Sodium thioacetate in methanol proved the reagent of choice for displacement of primary bromides and tosylates or allylic chlorides. Conversion of the resulting thioacetate to product was effected with catalytic acid in methanol. Hydrolysis of many other thiol reagent intermediates required basic conditions that promoted oxidation of the thiol by adventitious oxygen. This reaction could be extended to sec-butyl centers if polar aprotic solvents were used. Reaction at still more hindered centers (neopentyl, sec-alkyl) were generally sluggish and gave poor yields.

**Disodium trithiocarbonate** was a very effective nucleophile for displacement at hindered centers. In the original literature description of the reagent, the intermediate monoalkyl sodium trithiocarbonate was treated with aqueous acid. This treatment liberates carbon disulfide and leaves the free thiol. In the preparation of 1,2- to 1,4-dithiols, however, one often obtains the cyclic 1,2- to 1,4-dialkyl trithiocarbonate. This product can be reduced (LiAlH₄, Zn–HCl) to give the corresponding dithiol. Unexpected products may arise if carbon disulfide is liberated during the displacement reaction.

**Thiourea** is especially useful in preparing benzylic thiols, despite the fairly harsh conditions that are required to hydrolyze the intermediate thiouronium salt (5 M NaOH in refluxing ethanol), yields of greater than 90% are often obtained.

**Potassium thioacetate** in a polar aprotic or complexing solvent, such as tetraethylene glycol, reacts at neopentyl and secondary centers. The intermediate thioacetate is reduced to thiol with LiAlH₄. These reactions proceed slowly and give poor to moderate yields but are otherwise straightforward. Compounds as hindered as 1,5-cyclohexanethiol were hydrolyzed with this reagent.

**Determination of Equilibrium Constants.** Reduction potentials for thiols were obtained by equilibration against 1 mM oxidized mercaptoethanol (MEₓ) or oxidized dithiothreitol (DTTₓ) at 25 °C. The reduction potentials of the two standards differ by 4 orders of magnitude (see below). This difference spans the range of equilibrium constant values observed for dithiols. Reactions were carried out in a 1:1 mixture of methanol-d₄ and phosphate buffer (pH 7.0, 50 mM) in D₂O. The reduced and oxidized forms of both ME and DTT are readily distinguished by integration of the appropriate NMR signals. Equilibrations were run under nitrogen in sealed 5-mm NMR tubes. The details of a typical equilibration are presented in the Experimental Section.

**Equilibrium Constant Expressions.** We have discussed the measurement and interpretation of equilibrium constants for thiol–disulfide interchange elsewhere. This analysis is complicated by two factors. First, both thiol and thiolate species may be present in appreciable concentration in solution. Measured equilibrium constants (K) may thus depend on the relative values of thiol pKₐ and solution pH in addition to the structures of the thiol and disulfide. We keep the solution pH constant in this work, and the values of equilibrium constant combine contributions from the structure and pKa of the equilibrating species. We have not separated effects from these two sources. In most cases, effects due to differences in pKₐ will be small; the acidity of simple aliphatic thiols is fairly insensitive to alkyl structure, and values of pKₐ of these compounds (9–10) are sufficiently larger than the solution pH (7.0) that little (ca. <1%) ionization to thiolate is expected. Second, the simplest type of equilibrium reaction to interpret—reduction of a symmetrical disulfide to a thiol with concomitant oxidation of the reducing thiol to a disulfide—is achieved only in two steps by way of an intermediate unsymmetrical disulfide. In the work reported here, we are concerned with four separate equilibrium situations. We outline the way in which we account for the presence of unsymmetrical disulfide separately for each case.

The standard disulfide DTTₓ was used only with thiols that form cyclic monomers on oxidation (eq 4a,b). The standard disulfide MEₓ was used with dithiols that form cyclic monomers (eq 5a,b), cyclic dimers (eq 6a–e), and higher oligomeric species (eq 7a–e).

**DTTₓ**

\[
\text{DTT}^{+} + \text{HSRSSR} = \fbox{[HSC_{2}CH(OH)CH(OH)CH_{2}SSRSSR]} = \text{DTT} + \text{SRSSR}
\]  

(4a)

\[
K_{\text{DTT}} = [\text{DTT}] [\text{SRSSR}] / [\text{DTT}^{+}] [\text{HSRSSR}]
\]  

(4b)

\[
\text{ME}^{+} + \text{HSRSSR} = \text{HOCH}_{2} \text{CH}_{2} \text{SSRSSR} \rightarrow \text{SR} + 2 \text{ME}
\]  

(5a)

\[
K_{\text{ME}} = [\text{SRSSR}] [\text{ME}]^{2} / [\text{ME}^{+}] [\text{HSRSSR}]
\]  

(5b)

**MEₓ/cyclic dimer**

\[
\text{ME}^{+} + \text{HSRSSR} = \text{HOCH}_{2} \text{CH}_{2} \text{SSRSSR} + \text{ME}
\]  

(6a)

\[
\text{HSRSSRSH} + \text{ME} = \text{HSRSSRSSCH}_{2} \text{CH}_{2} \text{OH} + \text{ME}
\]  

(6b)

\[
\text{HSRSSRSSCH}_{2} \text{OH} = \text{SRSSRSS} + \text{ME}
\]  

(6c)

\[
K_{\text{ME}} = [\text{SRSSRSS}] [\text{ME}]^{+} / [\text{ME}^{+}] [\text{HSRSSR}]
\]  

(6d)

**MEₓ/oligomer**

\[
\text{HSRSSRSSCH}_{2} \text{OH} = \text{SRSSRSS} + \text{ME}
\]  

(6e)

\[
K_{\text{ME}} = [\text{SRSSRSS}] [\text{ME}]^{+} / [\text{ME}^{+}] [\text{HSRSSR}]
\]  

(6f)

The experimental procedure used measures directly only the ratio of oxidized and reduced ME or DTT. It does not identify the structures or concentrations of mixed disulfide species present. For the equilibria expressed in eq 4 and 5, the mixed disulfide will undergo facile intramolecular ring closure to give a stable cyclic monomer. The mixed species is assumed to exist only in low concentration as an intermediate between symmetric disulfides. The equilibrium can be accurately represented as in eq 4b or 5b. For the more complicated series of reactions occurring for cyclic dimer formation (eq 6), appreciable amounts of mixed disulfides may exist. Because we could not conveniently determine the concentration of these mixed species, we employed an approximate expression (eq 6e), in which only the concentrations of symmetric disulfide reactants and products appear; that is, we explicitly neglect any contribution from mixed disulfides. Values of
was necessary to determine an accurate equilibrium constant for gomers. Data obtained for cyclic monomeric disulfides from reaction with DTToX (eq 4b) to an equivalent form relative to ME (eq 5b), it one disulfide form was not the unambiguous product, i.e., a cyclic monomer on oxidation, trans-1,2-cyclohexanedithiol forms a cyclic dimer, and trans-2-butene-1,4-dithiol forms oligomeric species. Similar plots were established for all dithiols in which rings) and dithiols that could form either cyclic dimers or oligomers. Values of Equilibrium Constants. All values for equilibrium constants are reported vs ME° (eq 5b, 6e, and 7e). To convert data obtained for cyclic monomeric disulfides from reaction with DTT° (eq 4b) to an equivalent form relative to ME (eq 5b), it was necessary to determine an accurate equilibrium constant for thiol.

Table I. Equilibrium Constants for Dithiols Equilibrated with both Oxidized DTT and Oxidized ME

<table>
<thead>
<tr>
<th>thiol</th>
<th>$K_{MEO}$, M</th>
<th>$K_{DTT}$, M</th>
<th>$K_{MEO}/K_{DTT}$, M</th>
</tr>
</thead>
<tbody>
<tr>
<td>lipolic acid</td>
<td>3.5 (+1.0) $\times 10^2$</td>
<td>4.8 (+0.2) $\times 10^2$</td>
<td>7.3 $\times 10^0$</td>
</tr>
<tr>
<td>1,3-propanediol</td>
<td>1.2 (+0.5) $\times 10^3$</td>
<td>1.2 (+0.3) $\times 10^3$</td>
<td>1.0 $\times 10^0$</td>
</tr>
<tr>
<td>1,6-hexanediol</td>
<td>1.1 (+0.2) $\times 10^3$</td>
<td>1.1 $\times 10^3$</td>
<td>1 $\times 10^0$</td>
</tr>
</tbody>
</table>

* Average = 9.4 (+1.5) $\times 10^4$.

ME° vs DTT (eq 5b, SRS = DTT°, HSRSH = DTT). The establishment of an accurate value for this equilibrium constant is crucial before comparisons are possible between values of $K$ obtained with these two standard compounds. A direct measurement of the number would be difficult because ME and DTT differ substantially in reducing ability. For example, it would require a ca. 500 mM solution of ME to reduce 10% of a 1 mM solution of DTT°. A value of 9.4 (+1.5) $\times 10^4$ M was obtained indirectly by equilibrating both compounds against three dithiols of intermediate reducing ability (Table I).

Table II lists all compounds for which we have determined equilibrium constants. The reducing abilities of thiol are expressed as values of $K$ vs ME° and as standard potential ($E^0$) values. $E^0$ for each of the dithiols is related to the half-cell potential for the oxidized mercaptoethanol/mercaptoethanol couple (eq 8).

Table II also indicates whether the disulfide formed is a cyclic monomer, cyclic dimer, or oligomer, how many atoms the ring would contain if a cycle were formed, and whether the equilibration was carried out against ME° or DTT°.

The relative accuracy of these equilibrium constants deserves comment. The most accurate data were obtained for dithiols that are similar in reducing ability to the standard against which they were equilibrated. These compounds are those with values of $K$ greater than $\sim 10^3$ (equilibrated against DTT°) and those with values of $K$ less than $\sim 10$ (equilibrated against ME°). Equilibrium constants for dithiols having intermediate reducing ability are less accurate. These constants were determined (1) by equilibration with ME° in the presence of several equivalents of ME to make the solution more reductive or (2) by equilibration against DTT° using several equivalents of the dithiol. In both types of systems, the requirement for an excess in some component made it more difficult to detect the species generated or consumed in the thiol–disulfide interchange. The presence of mixed disulfides also complicated the determination of equilibrium constants for dithiols of intermediate reducing ability. The class of compounds having intermediate reducing ability included a few dithiols that formed cyclic monomeric disulfides and most 1,2-dithiols that formed cyclic bis(disulfide) dimers.

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$E^0$ vs ME° obtained with these two standard compounds. A direct measurement of the number would be difficult because ME and DTT differ substantially in reducing ability. For example, it would require a ca. 500 mM solution of ME to reduce 10% of a 1 mM solution of DTT°. A value of 9.4 (+1.5) $\times 10^4$ M was obtained indirectly by equilibrating both compounds against three dithiols of intermediate reducing ability (Table I).

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$$2e^- + ME^0 + 2H^+ \rightarrow E^{0\text{RSH} - E^{0\text{ME}}} \text{ vs SHE} \quad 25^\circ C, pH 7.0$$ ME° to remain consistent with $E^{0\text{RSH} - E^{0\text{ME}}}$ values reported in earlier thiol–disulfide equilibration studies. Half-cell potentials for other thiol are linked to the value of the ME°/ME° couple by

1.6-hexanediol forms a cyclic dimer, and trans-1,2-cyclohexanediol forms oligomeric species. Similar plots were established for all dithiols in which one disulfide form was not the unambiguous product, i.e., the cyclic di-
with size

Figure

This assumption was verified by determining several alkanedithiol disulfides were also equilibrated in methanol/methoxide. Concentration; we can favor monomers and dimers relative to polymers. Differences in size can be attributed to enthalpic effects and the relatively lower stability of five-membered rings. The relatively lower stability of seven-membered and larger rings to entropy. Some substituted 1,3-propanedithiols: in general, thiols become less favored CSSC dihedral angle of -90° in this ring system. The interaction is minimized when the sulfur has been rotated away from the ring. This conformation places the two thiol groups in close proximity of each other and is the conformation required for formation of a disulfide bond. Lipic acid is a 1,3-propanedithiol substituted at C3. All of the other dithiols in Figure 2 are substituted at C2. This difference is reflected in the fact that the reducing ability of lipic acid is larger than predicted.

1.5-Dithiols: Influence of gem-Dimethyl and Oxygen Substitution in Equilibrium Constants. Substituting two methyl groups for hydrogen atoms at a methylene carbon enhances the rate of formation of small- and medium-sized rings8-26 and is attributed in part to the reduction in the number of energetically accessible rotamers in the open-chain dimethyl precursor relative to the nonsubstituted open chain. The equilibrium constant for 3,3-dimethyl-1,5-pentanedithiol (17) shows a small gem-dimethyl effect: it is 3.8 times more reducing than 1,5-pentanedithiol. The ease with which ring closure occurs may also be influenced by replacing methylene groups with oxygen or other heteroatoms.45 Bond opposition forces and transannular interactions are less unfavorable for CH-::O interactions than the corresponding CH-::CH interactions.60 The greater the strain in the cyclic product, the greater the effect of introduction of an oxygen atom will be. Replacement of the 3-CH2 group in 1,5-pentanedithiol with oxygen or sulfur increases the equilibrium constant of the

Figure 3. Plot of log K vs estimated values of the C1-C2-C3 angle (θ) of substituted 1,3-propanedithiols. The values of θ assume that oxidation of these dithiols yields cyclic monomeric disulfides. Dithiols were equilibrated against DTT. Values of θ were obtained from the following sources: (a) the X-ray crystal structure value for the H-C-H angle in cyclobutane;62 (b) θ is assumed to be 109.5° for tetrasubstituted compounds; (c) θ = 112° for the H-C-H angle in propane;60 (d) the X-ray crystal structure value for the H-C-H angle in cyclopropane;61 θ is assumed to be 112° based on sp2 hybridization at the C2 carbon.

1,1-Bis(mercaptopmethyl)cyclohexane (2) and lipic acid (1) are better reducing agents than predicted from estimated C-C-C bond angles alone. A CPK model of 1,1-bis(mercaptopmethyl)cyclohexane suggests significant eclipsing interactions between the sulfur of the axial thiomethyl group and the axial C2 and C3 ring protons. The interaction is minimized when the sulfur has been rotated away from the ring. This conformation places the two thiol groups in close proximity of each other and is the conformation required for formation of a disulfide bond. Lipic acid is a 1,3-propanedithiol substituted at C3. All of the other dithiols in Figure 2 are substituted at C2. This difference is reflected in the fact that the reducing ability of lipic acid is larger than predicted.

1.5-Dithiols: Influence of Ring Strain on Equilibrium Constant. 1.3-Dithiols are oxidized to five-membered ring 1,2-dithiolanes. It is not possible to obtain the theoretically exaggerated and experimentally favored CSSC dihedral angle of ~90° in this ring system. The range of values of equilibrium constant obtained for 1,3-dithiols can be attributed to differences in the angle in the dithiolane ring. Figure 3 is a plot of log K vs the C1-C2-C3 angle (θ) for substituted 1,3-propanedithiols: in general, thiols become less reducing as this angle increases. The sources of values used for θ53,93 are summarized in the caption of the figure and are either X-ray crystal structure values of H-C-H angles for nonsubstituted compounds or approximate values of the hybridization of the C2 carbon. This correlation provides an example supporting the hypothesis developed by Thorpe and Ingold52 in the early 1900s in their attempt to explain the gem-dialkyl effect. This hypothesis includes the assertion that only tetrasubstituted carbon atoms having four equivalent substituents possess exactly tetrahedral

### Table II. Equilibrium Constants for Thiol–Disulfide Interchange

<table>
<thead>
<tr>
<th>compd</th>
<th>ring size</th>
<th>structure</th>
<th>disulfide form$^a$</th>
<th>$K_{MEn}^{c}$</th>
<th>$E^{n+/V}$</th>
<th>equilib against</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td><img src="image" alt="Structure" /></td>
<td>CM</td>
<td>$5.7 \times 10^3$</td>
<td>$-0.32$</td>
<td>ME, DTT</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td><img src="image" alt="Structure" /></td>
<td>CM</td>
<td>$4.2 \times 10^3$</td>
<td>$-0.32$</td>
<td>DTT</td>
</tr>
<tr>
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<td>5</td>
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<td>CM</td>
<td>$2.3 \times 10^3$</td>
<td>$-0.31$</td>
<td>DTT</td>
</tr>
<tr>
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<td>5</td>
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<td>$1.9 \times 10^3$</td>
<td>$-0.31$</td>
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</tr>
<tr>
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<td>5</td>
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<tr>
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<td>5</td>
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<td>CM</td>
<td>$1.5 \times 10^3$</td>
<td>$-0.30$</td>
<td>DTT</td>
</tr>
<tr>
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### Table II (Continued)

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$^a$Equilibrations were carried out at 25 °C, in a 1:1 mixture of methanol-d$_4$/phosphate buffer (50 mM, pH 7.0) in D$_2$O, unless otherwise noted.

$^b$Equilibrations were carried out in methanol-d$_4$ with 0.02 mM sodium methoxide added.

$^c$Equilibrations were carried out in benzene-d$_6$ with 0.02 mM tetramethylguanidine added.

$^d$CM = cyclic monomer, CD = cyclic dimer, P = polymer, and M = monomer. $^e$K$_{\text{MEOX}}$ has units of M for 1–25 and is dimensionless for 26–40. $^f$E$^\circ$ (V) values vs standard hydrogen electrode at pH 7.0 and 25 °C.

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**Figure 4.** Plot of log $K$ vs the degrees of freedom that must be frozen for ring closure to occur ($\sigma$). $K$ values are calculated on the assumption that oxidation of dithiols yields (1) cyclic monomeric disulfides ($K_{\text{MEOX}}$, eq 5), (2) cyclic dimeric disulfides ($K_{\text{dimers}}$, eq 6), or (2) polymeric disulfides ($K_{\text{poly}}$, eq 7). $K_{\text{MEOX}}$ and $K_{\text{dimers}}$ have units of M, and $K_{\text{poly}}$ is dimensionless. Values for $\sigma$ are calculated for the half-oxidized dimer of compounds that should form cyclic dimeric disulfides.

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resulting dithiols 18 and 19 by 1.7 and 1.9 times, respectively.

**Dependence of Equilibrium Constant on Degrees of Conformational Freedom in the Dithiol.** We are most interested in dithiols that form cyclic bis(disulfide) dimers upon equilibration. It is straightforward to block intramolecular disulfide bond formation by locating the two thiol groups beyond bonding distance. The more challenging problem is to favor intermolecular dimer formation relative to intermolecular polymerization. Since formation of medium-sized rings is usually enthalpically unfavored, the best strategy seemed to be to maximize the entropic advantage of dimer formation relative to polymerization. Initial attempts at designing such compounds and at rationalizing the data in Table I were based on a model that counted the degrees of freedom lost in forming the cyclic dimers. The number of rotational degrees of freedom ($\sigma$) that must be frozen for ring closure to occur is a useful concept that is often used to describe the contribution of entropy to ring-closure reactions.$^{56,61}$ For the simple C$_4$ and higher a,$\omega$-alkanedithiols, the number of degrees of freedom possessed by the molecule is directly related to ring size. Addition of each methylene unit adds one degree of rotational freedom. The entropic contribution of a rotor is roughly 4.5 eu,$^{56}$ which corresponds at room temperature to a change in equilibrium constant of approximately 10. This change is approximately that observed experimentally as methylene groups are added in the series C$_4$–C$_5$. For 1 mM solutions of C$_5$ and longer dithiols ($\sigma = 6$), intermolecular disulfide formation becomes competitive with intramolecular cyclization and equilibrium constants are similar to those for monothiols.

Figure 4 shows a plot of log $K$ vs $\sigma$ for the thiols listed in Table II. Values of $\sigma$ are calculated for the half-oxidized dimers (HSRSSSRSH) of compounds that are expected to form cyclic dimers on complete oxidation. Data for the 1,3-propanedithiols

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are included in this plot for completeness; we have, however, already noted that a model based solely on rotational entropy fails to rationalize reduction potentials for these compounds and that enthalpic factors (primarily ring strain) are important for these substances.

Restricting rotation around single bonds by incorporating them into rings or by converting them to double bonds makes it possible to decrease $\sigma$. Compounds 10 and 11 are more strongly reducing than the parent compound 13 by roughly the predicted factor of 10. The trans compound 10 has a slightly larger value of $K$ than the cis compound (11). Compounds 14, 15, and 16, which also have $\sigma = 2$, are significantly less reducing than expected by analogy with other compounds capable of forming six-membered rings. We speculate that the rigid structure of each of these compounds forces the CSSC dihedral angle to be close to 0° in the cyclic disulfide. This value is far from the optimal angle of $\sim 90°$.

The 1,2-dithiols form moderately stable eight-membered-ring bis(disulfides). Limiting internal rotation increases the reduction potential of these compounds also. Compound 22, compound 23, and a 1:1 mixture of compounds 22 and 23 are more strongly reducing than reference compound 25.

Compounds 29, 30, and 31 are structurally related to 1,2-ethanedithiol by the formal separation of the two CH₂SH moieties of 1,2-ethanediyl by rigid spacer groups. Although these spacers introduce no additional degrees of freedom, cyclic dimers are not formed, and compounds 29, 30, and 31 are weakly reducing. Dithiol 35 has even fewer degrees of rotational freedom than 1,2-ethanethiol: its unsymmetric half-oxidized dimer requires only three degrees of freedom to be frozen for ring closure. It is not, however, significantly more reducing than a monothiol.

Oxidation of 36 with iodine using high-dilution techniques affords 41 (eq 10). We determined an equilibrium constant

$$
36 \xrightarrow{I_2} 41
$$

for reaction of 36 with ME\textsuperscript{64} to establish if this tris(disulfide) is merely the kinetically formed product of oxidation or whether it is a thermodynamically favorable structure. The value of $\sigma$ for the two-thirds-oxidized trimer of 36 (HSArSSArSSArSH) is 4, which is the same value as for the formation of a seven-membered ring. An equilibrium constant value of $K \approx 0.2$ indicates that oxidation of 36 is not exceptionally favorable thermodynamically. Studies of cyclic bis(disulfides) derived from several thiolates including 22, 23, 28, 32, and 33 by kinetic oxidation with iodine established that none of these structures were thermodynamically stable with respect to polymer in neat liquid form.

Adding a third disulfide unit to an existing dithiol might increase energetic terms enough to favor dimerization. Trithiols 33 and 5 were equilibrated with ME\textsuperscript{64} in the hope of obtaining tris(disulfides) 42 and 43 (eq 11). Trithiol 33 was weakly reducing, and only polymeric disulfide products were obtained. Trithiol 5 was more strongly reducing, and we infer that it forms one intramolecular and one intermolecular disulfide bond (44). We note that molecular models suggest that both 42 and 43 are seriously strained, and it is not surprising that these substances do not form.

Conclusions

On the basis of the data in Table II, Figure 2, and a separate publication discussing stabilities,\textsuperscript{64} we classify cyclic disulfides into three groups based on reduction potential and on stability toward ring-opening polymerization (Table III). This classification is a broad generalization: substitution in each class of cyclic disulfides can decrease the stability of that class.

(i) 1,2-Dithiacyclopentanes. Dithiols having the two SH groups separated by four carbon atoms are strongly reducing; the corresponding six-membered cyclic disulfides are the most stable we have examined. Within this group, $K_{ME}$ varies by a factor of 78 (from 10 to 16). The less stable compounds are only marginally stable: the cyclic disulfide from 16, for example, polymerizes as a melt in the presence of methanethiolate.\textsuperscript{64} We believe the difference in stability between compounds such as 10 and 11 and 15 and 16 reflects torsional strain: the latter compounds are constrained to have C-S-S-C dihedral angles close to 0°; the latter are probably close to 60°. The cis barrier to rotation in H₂S₂ (2HSSH $\rightarrow$ 2HSSH = 0°) has been estimated theoretically to be $\sim 7.5$ kcal/mol.\textsuperscript{65} Assuming a cos $\theta$ dependence of energy on dihedral angle, this barrier would $\sim 5$ kcal/mol for a change in $\angle$CSSC from 60° to 0°. The change in energy corresponding to the difference in the values of $K_{ME}$ for compounds 10 (which we assume to have a value for $\angle$CSSC of close to 60°) and 16 (which probably has a significant residual pucker to its ring and might still have $\angle$CSSC $\sim 20°$) is $\sim 2.5$ kcal/mol. These values of energy are sufficiently close qualitatively to suggest that much of the spread in $K_{ME}$ for six-membered disulfides can be rationalized on the basis of the CSSC dihedral angle.

(ii) 1,2-Dithiacyclohexanes. Cyclic disulfides are entropically favored, but enthalpically disfavored by the CSSC dihedral angle. If we extrapolate the data for eight-, seven-, and six-membered rings

| Table III. Stability of Cyclic Disulfides with respect to Ring-Opening Polymerization |
|-----------------------------------|------------------|------------------|
| structural type                  | stable           | not stable        |
|                                  | in concentrated  | in more dilute (<0.01 M) |
|                                  | solutions and as pure liquids | solutions; may be kinetically stable as solids |

\textsuperscript{64} This fact is consistent with the analogous all-carbon system: trans-decalin is 3 kcal more stable than cis-decalin. Carey, F. A.; Sundberg, R. J., Advanced Organic Chemistry; Plenum: New York, 1977; p 91.
Thiol–Disulfide Interchange

(Figure 2) to an anticipated value for five-membered rings of log $K_{ME} \approx 6$, the difference between this value and that observed for $\log K_{ME} \approx 3$, corresponds to $\Delta G \approx 4$ kcal/mol. This value is again compatible with the assumption that torsional strain in the CSSC group is important in determining the stabilities of these compounds.

(iii) 1,2-Dithiacycloheptanes and -cyclooctanes. These rings should be sufficiently flexible that CSSC torsional strain is relatively unimportant, but other types of strain associated with medium rings may be important. In any event, they are still slightly more favorable than the corresponding polymers in solutions having 0.01–0.1 M concentrations but polymerize in concentrated solutions or as liquids.

(iv) 1,2,5,6-Tetra(thiacyclooctanes). These substances are the only ones we have identified that form dimeric bis(disulfides) of any significant equilibrium stability. Freezing one degree of rotational freedom (e.g., 22 or 23 vs 25) per monomer (or two per dimeric unit) contributes approximately a factor of 10 (i.e., $\Delta G \approx 1.4$ kcal/mol) to $K_{ME}$. Further efforts to build bis- or tris(disulfides) that are thermodynamically stable entities in solution must, we believe, start with these types of structures.

(v) Others. A surprising number of dithiols do not form even moderately stable bis(disulfides) at the concentrations used in these studies (although we assume that at least certain of these would be favored relative to polymer in more dilute solutions, since dimeric species are always preferable to polymeric species when translational entropy is dominant). For example, compounds 31, 32, 34, and 35 all appear to form relatively strain-free dimeric bis(disulfides) from examination of models, and all require freezing only small numbers of degrees of rotational freedom to so do. These species, together with 28, 29, and 30 (which do appear strained in models), make clear the fact that small unfavorable enthalpic contributions in a true equilibrium system can easily shift the balance from dimer to polymer.

Overall, perhaps the most surprising feature of this work is its demonstration of the substantial difficulty of building dithiols that will spontaneously dimerize on oxidation rather than polymerize. Comparison of the several systems examined here suggests that the most energetically favorable reaction capable of forming a cyclic bis(disulfide) should be one in which a six-membered ring tetrahane 47 is formed. By analogy, the precursor of this species would be a gem-dithiol 45. Several compounds of structure 456-68 and 479,69 are known and are relatively stable in nonaqueous media. Unfortunately, they are unstable to the basic conditions required for thiol–disulfide interchange. In this work, we briefly explored the oxidation of 1,1-cyclobutanedithiol.68 The NMR spectrum of this compound in either degassed D$_2$O or degassed benzene containing a catalytic amount of the base tetramethylguanidine became uninterpretable complex within a few hours of sample preparation as peaks corresponding to the dithiol disappeared and other peaks emerged.

We conclude that no simple alkane- or arenedithiol prefers the dimeric bis(disulfide) structure relative to a polymeric structure in concentrated solutions under conditions of thermodynamic equilibrium. To achieve such structures, it will be necessary to add additional features to aid dimerization energetically (e.g., hydrogen bonds or hydrophobic interactions) or to increase the

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Figure 5. Rate of air oxidation of mercaptoethanol solutions in NMR tubes sealed in different ways. Solutions are initially 20 mM mercaptoethanol in methanol-d$_4$/aqueous buffer. NMR tubes were sealed in the following manner: curve A, conventional plastic NMR tube cap; curve B, screw-capped NMR tube fitted with flat, Teflon-faced, silicone septum; curve C, screw-capped NMR tube fitted with thick, molded silicone septum; curve D, screw-capped NMR tube fitted with thick, molded silicone septum, maintained under positive inert gas pressure; curve E, flame-sealed NMR tube.

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number of disulfide moieties from two to three or four.

We note the relevance of these studies to the question of the role of cystine disulfide groups in maintaining the tertiary structure of polypeptides. Intramolecular formation of a disulfide link appears to be favored only if the participating thiol groups are relatively exactly aligned. Thus, a long polypeptide loop closed by a cystine moiety (e.g., vasopressin) is unlikely to hold such a structure under equilibrating conditions unless the secondary interactions among the peptide groups favor it: the large-ring cyclic disulfide is not intrinsically a highly stable structure.

Experimental Section

General. All reactions and measurements were carried out under a nitrogen or an argon atmosphere. 1,2-Dithiane was obtained from Columbia Organic Chemicals, and $\alpha,\alpha'$-dithiodihurene (4,5-bis(mercapto-methyl))-o-xylene) was obtained from Lancaster Synthesis Ltd. Deuterated solvents and other chemicals were obtained from Aldrich Chemical Co. Commercially obtained thiols were recrystallized or distilled under nitrogen before use. Tetrahydrofuran (THF) was distilled from disodium benzophenone dianion under an argon atmosphere. Rast molecular weights were determined by using benzophenone. Melting points are uncorrected. Values of pH were measured with a Radiometer PH M62 pH meter.

Thiol Equilibrations. General. Deuterated phosphate buffer (0.1 M, pH 7) was prepared by dissolving 85% phosphoric acid-d$_2$ (0.503 g, 2.5 mmol) in 99.5% deuterium oxide (D$_2$O) (20 mL). The pH of the solution was adjusted to 7.0 with 5 M sodium deuterioxide in D$_2$O, and the final solution volume was brought to 25 mL with D$_2$O. The solution was transferred to a 25-mL crimp-cap vial, and nitrogen was bubbled through it for 6 h.71 This solution was stored under nitrogen.

Equilibration experiments were carried out in 5-mm NMR tubes. Oxygen was excluded either by sealing tubes under nitrogen or by using screw-cap tubes with replaceable open-top caps and septa, maintained under nitrogen. Figure 5 demonstrates the effectiveness of these methods in protecting solutions of thiols against autoxidation. Solutions of ME (20 mM) in 50/50 methanol-d$_4$/deuterated phosphate buffer were monitored for conversion of ME to ME$_2$. Flame-sealed tubes maintain oxygen-free conditions indefinitely (curve E). Capped NMR tubes (curve A) and screw-cap tubes fitted with flat, Teflon-faced silicone septa (Aldrich catalog no. Z11,410-3) (curve B) work poorly. Thicker, molded silicone septa (Aldrich catalog no. Z10,148-6) hold pressure and seal well if solutions are introduced through the septa via syringe. The molded septa perform somewhat better than flat septa when no inert gas pressure is maintained over the solution (curve C). When a positive nitrogen
pressure of 1-2 psi is maintained over solutions sealed with molded septa (curve D), oxygen exclusion performance is comparable to that of flame-sealed tubes over a 2-3-day period.

The following sections describe two representative equilibration experiments, one in which ME9 was used as the standard disulfide and one in which DTT was used. Reaction solutions were equilibrated at 25 °C, and the probe of the NMR spectrometer was thermostated at 25 ± 1 °C. All equilibrium constant values represent an averaged value of at least two runs.

Equilibrations with ME9. Standard solutions containing 1 mM ME9, 0.5 mM 2-butyne-1,4-diol, and from 0 to 100 mM ME (depending on the reducing ability of the thiol to be equilibrated) were prepared as follows: To a 10 mL volumetric Schlenk flask that had been rinsed with D2O and flushed with nitrogen were added via syringe under a static nitrogen atmosphere the ME9 standard. Peaks corresponding to disulfide species formed from trans-2-butyne-1,4-diol occurring at 4.23 ppm was used as an internal standard. Peaks of DTT occurring at 3.7 ppm were used to determine the relative amounts of oxidized and reduced DTT present at equilibrium. Spectra shown correspond to an equilibration: (A) at the start of the experiment (t = 0); (B) during the equilibration (t = 12 h); (C) at final equilibrium.

Check for Reversibility in Equilibration Experiments. In order to establish that the reaction conditions used are truly equilibrating, one must demonstrate that the same position of equilibrium is reached starting with either set of a thiol-disulfide pair. Equilibration of ME with the cyclic bis(disulfide) dimer of 1,3-bis(mercaptomethyl)benzene and equilibration of DTT with 1,2-dithiane both gave equilibrium constant values within 10% of K, for the reaction proceeding in the usual direction.

Gem-Dithiol Stability to Equilibrating Conditions. A 0.17 M stock solution of 1,1-cyclobutanedithiol was prepared by dissolving 1,1-cyclobutanethiol (20.4 mg, 0.17 mmol) in degassed benzene-d6 under a nitrogen atmosphere. To three 5-mm NMR tubes that had been dried at 110 °C and flushed with nitrogen were added via syringe an aliquot of the above stock solution (41 μL) and 0.66 mL of the following degassed solvents: tube 1, benzene-d6; tube 2, benzene-d6 containing 0.1 mM tetramethylguanidine as a base; tube 3, a 1:1 mixture of deuterated phosphate buffer/methanol-d4. The tubes were cooled in liquid nitrogen and flame sealed. NMR spectra of the solutions were taken immediately and then once an hour for 6 h. The spectrum of 1,1-cyclobutanedithiol in tube 1 remained unchanged. The spectrum of 1,1-cyclobutanedithiol in tubes 2 and 3 became unintelligible within a few hours as peaks due to the dithiol disappeared and new peaks (complex multiplets at 2.2, 2.5, and 2.8-3.0 ppm) emerged.

1,1-Bis(mercaptomethyl)cyclohexane (2) was prepared in five steps according to literature procedures. Reaction of 1,5-dibromopentane with Me2NCS followed by treatment of the cyclic bis(disulfide) dimer of 1,3-bis(mercaptomethyl)benzene and equilibration of DTT with 1,2-dithiane both gave equilibrium constant values within 10% of K, for the reaction proceeding in the usual direction.


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8 7 6 5 4 3 2 1 0

Figure 6. Reaction of ME9 with trans-2-buten e-1,4-dithiol as monitored by 'H NMR. Solution is initially 1 mM ME9, 1 mM trans-2-buten e-1,4-dithiol, and 0.5 mM 2-butyne-1,4-diol (internal standard) in 1:1 methanol-d4/aqueous buffer (0.1 M phosphate, pH 7). Spectra shown correspond to an equilibration: (A) at the start of the experiment (t = 0); (B) during the equilibration (t = 12 h); (C) at final equilibrium.

Figure 7. Reaction of DTT with 1,4-butanedithiol as monitored by 'H NMR. Solution is initially 1 mM DTT and 1 mM 1,4-butanedithiol in 1:1 methanol-d4/aqueous buffer (0.1 M phosphate, pH 7). Spectra shown correspond to an equilibration: (A) at the start of the experiment; (B) during the equilibration; (C) at final equilibrium.
0.10 mol) in dry pyridine (70 mL) at 0 °C. The solution was stored at 0 °C for 3 days, during which time a large precipitate of pyridine hydrochloride formed. The reaction mixture was poured into 300 mL of cold 1 M hydrochloric acid. A yellow solid formed after the solution was stirred for several minutes. The solid was collected by filtration, washed with several portions of distilled water, and recrystallized from hot methanol to yield 2-(thioacetyl) (97%) of 1-bis-(o-tosylmethy1)cyclobutane. The reaction mixture was refluxed overnight, during which time the initially deep red solution turned clear yellow-green. Heating was discontinued and 10% sulfuric acid (100 mL) was added. This cloudy solution was reduced in volume to 60 mL, washed with additional water (4 × 100 mL), and dried (MgSO₄), and the solvent was removed at reduced pressure to give 7 g of yellow oil. This oil was taken into dry THF (70 mL) and added dropwise to a stirred suspension of LiAlH₄ (2.1 g, 0.055 mol) in THF (50 mL) at room temperature. After stirring for 6 h, the solution was cooled to 0 °C and excess hydride was destroyed by addition of 1 M sodium hydroxide (8.4 mL). The solution was filtered to remove aluminum salts, and the solvent was removed at reduced pressure to give 2.6 g (37% from the distosylate) of an amber oil. Kugelrohr distillation (45–50 °C at 0.4 Torr) afforded 3 as a colorless liquid: 'H NMR (CDCl₃) δ 2.78 (d, 4 H, 1.7–1.9 (m, 4 H), 1.6 (1, 2 H); IR (neat) 3000–2900, 2560, 1420, 1270 cm⁻¹; exact mass calcd for C₆H₁₀S₂ (M⁺) m/e 148.0380, found 148.0364.

1,1-Bis(mercaptoethyl)cyclohexane (11) cis-1,1-Bis(o-tosylmethyl)cyclohexane was prepared in 87% yield from 1,1-Bis(o-tosylmethy1)cyclohexane and toluenesulfonyl chloride. Recrystallization from hot methanol afforded white flakes, mp 83.5–85 °C (lit. mp 84–85 °C). The distosylate (16 g, 0.035 mol) was added to a solution of thioacetate (7.6 mL, 0.1 M) and sodium methoxide (5.73 g, 0.11 mol) in DMF (50 mL) that had been purified with nitrogen. The reaction mixture was refluxed at 100 °C for 4.5 h, and the reaction was quenched with 100 mL of water. The product was extracted with chloroform (300 mL). The organic layer was washed with water (6 × 160 mL) and dried (MgSO₄), and the solvent was removed at reduced pressure to give 8 g (87%) of the bis(thioacetate) of 11 as an amber oil. This oil was taken into a solution of methanol (50 mL) and hydrochloric acid (0.01 mol) that had been purged with nitrogen. After 4 h of stirring at reflux under nitrogen, methanol and methyl acetate were removed at reduced pressure, leaving 4.7 g (76%) of amber liquid. Kugelrohr distillation (80–85 °C at 1 Torr) afforded 11 as a colorless liquid: 'H NMR (CDCl₃) δ 2.4 (m, 4 H), 1.8 (m, 2 H), 1.3–1.6 (m, 6 H), 1.2 (t, 2 H); IR (neat) 2920, 2830, 2560, 1450, 1340 cm⁻¹.

2,2-Dimethyl-1,3-propanedithiol (6) was prepared in 30% yield from 2,2-dimethyl-1,3-dibromopropane and sodium thioacetate by the same procedure described for the preparation of 3. Distillation (42–44 °C at 2 Torr; lit. 57 °C at 17 Torr) afforded 6 as a colorless liquid: 'H NMR (CDCl₃) δ 3.75 (t, 4 H), 2.45 (s, 6 H), 1.5 (t, 2 H), 0.95 (s, 6 H); IR (neat) 3085, 3010, 2980, 2880, 2560, 1460, 1430, 1280 cm⁻¹.

1,1-Bis(mercaptoethyl)cyclohexane (8) was prepared in four steps from 3,3-dimethylglutaric acid following the general procedures described for the synthesis of 3. Reaction of the ditosylate with potassium thiocyanate (62% yield) followed by Kugelrohr distillation (bp 57–61 °C at 1 Torr) afforded dithiol 14 as a colorless liquid: 'H NMR (CDCl₃) δ 6.0 (s, 2 H), 2.75 (s, 2 H), 2.5 (m, 4 H), 2.55–2.35 (m, 2 H), 1.35 (m, 2 H), 1.25 (t, 2 H); IR (neat) 2920, 2830, 2560, 1450, 1340 cm⁻¹.

2-Butene-1,4-dithiol (15) was prepared in 70% yield from cis-1,1-dichloro-2-butanethiol and thiocarbamic acid by the procedure described for the synthesis of 9. Distillation (bp 30 °C at 1 Torr; lit. 87 °C at 20 Torr) afforded 15 as a colorless liquid: 'H NMR (CDCl₃) δ 5.6 (t, 2 H), 3.2 (t, 4 H), 1.5 (t, 2 H); IR (neat) 3030, 2960, 2930, 2860, 2560, 1650, 1440 cm⁻¹.

3,3-Dimethyl-1,5-pentanedithiol (17) was prepared in three steps from 3,3-dimethylglutaric acid following the general procedures described for the synthesis of 3. Reaction of the diol with LiAlH₄ afforded 1,1-bis(2-hydroxyethyl)cyclopentane in 80% yield; mp 79–81 °C (lit. mp 79–82 °C). The corresponding di-tosylate was prepared in 80% yield; mp 87–89 °C (lit. mp 90–91 °C). Reaction of the di-tosylate with potassium thiocyanate (62% yield) followed by Kugelrohr distillation (bp 57–61 °C at 1 Torr) afforded dithiol 14 as a colorless liquid: 'H NMR (CDCl₃) δ 6.0 (s, 2 H), 2.75 (s, 2 H), 2.5 (m, 4 H), 2.55–2.35 (m, 2 H), 1.35 (m, 2 H), 1.25 (t, 2 H); IR (neat) 2920, 2830, 2560, 1450, 1340 cm⁻¹.

2-Cyclohexanedithiol (22) was treated with toluenesulfonyl chloride to give cis-1,2-Bis(oi-tosyl)methylcyclohexane in 85% yield. Recrystallization from hot methanol gave small white platelets, mp 128–130 °C (lit. mp 128–130 °C). Dithiol 22 was...
prepared from the dithiolate by a modified literature procedure.\(^{41}\) Potassium thiocyanate (56 g, 0.55 mol) was dissolved in diethylene glycol (60 mL) at 100 °C. The dithiol (12.0 g, 0.028 mol) was added in one portion and the solution stirred at 100 °C for 3 days. The reaction mixture was poured into water (100 mL) and extracted with chloroform (1 × 80 mL and 2 × 40 mL). The organic fractions were combined, washed with water (2 × 50 mL) and dried (MgSO\(_4\)), and the solvent was removed to give 4.5 g of a dark orange oil. The oil was dissolved in THF (30 mL) and added dropwise to a stirred solution of LiAlH\(_4\) (4.5 g, 0.119 mol) in THF. The reaction mixture was refluxed overnight under a static nitrogen head. Heating was discontinued and excess hydride was decomposed by cautious addition of 1 M HCl (30 mL) at 0 °C. The resulting sticky gray precipitate was separated by filtration, leaving a cloudy solution. The volume of this solution was reduced to 10 mL and taken up into water (50 mL) and chloroform (20 mL). The organic layer was washed with water (2 × 20 mL) and dried (MgSO\(_4\)), and the solvent was removed to give 2.3 g (55%) of slightly yellow liquid.

1,2-Cyclohexanediol (23) was prepared in two steps following literature procedures. Treatment of cyclohexene oxide with carbon disulfide and potassium hydroxide afforded trans-1,2-cyclohexanediol trithiocarbonate as a yellow solid in 88% yield; mp 167–169 °C (lit.\(^{76}\) mp 169 °C). The ditosylate (12.0 g, 0.028 mol) was added in one portion and the solution stirred at 100 °C for 3 days. The reaction mixture was not necessary. Acidification of the intermediate bis(sodium hydroxymethyl)cyclobutane in 50% yield. Tosylation of the diol proceeded in analogy to \(\text{a.a}'\)-dibromo-m-xylene in analogy to \(\text{a.a}'\)-dibromo-m-xylene and sodium methanethiolate\(^{91}\) in 73% yield. Distillation (50-53 °C at 2 Torr, IR (KBr) 2860, 2560, 1460, 1280 cm\(^{-1}\)).

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