^{1}H NMR (22 °C, benzene-d_6): δ 3.26 (s, OSC*Me*), 3.03 (s, $^2J_{WH}$ = 8.54 Hz, CH_2CMe$_3$ next to S), 2.85 (s, $^2J_{WH}$ = 9.98 Hz, CH_2CMe$_3$ next to O), 2.32 (s, O$_2$C*Me*), 2.26 (s, O$_2$C*Me* trans to OSCMe) 1.49, 1.46 (s, CH$_2$C*Me*$_3$).

IR: 324 (m), 333 (m), 375 (w), 450 (w), 620 (w), 627 (w), 668 (ms), 680 (m), 907 (mw), 932 (w), 1018 (w), 1040 (w), 1088 (vs), 1175 (ms), 1202 (mw), 1236 (ms), 1349 (m), 1361 (ms), 1374 (ms), 1438 (vs), 1460 (s), 1492 (m) cm^{-1}.

W$_2$(np)$_2$(O$_2$CNMe$_2$)$_4$. In a Schlenk flask W$_2$(np)$_2$(NMe$_2$)$_4$ (0.30 g, 0.44 mmol) was dissolved in CH_2Cl_2 and then frozen in liquid N_2. A large excess (>4 equiv) of CO_2 was condensed into the flask. The solution was then slowly warmed to room temperature while the flask was connected to a Hg bubbler. The solvent was removed in vacuo to yield a yellow powder (0.35 g, 92%).

^{1}H NMR (22 °C, benzene-d_6): δ 2.66 (s, bridge O$_2$CN*Me*$_2$), 2.59 (s, chelate O$_2$CN*Me*$_2$), 2.46 (s, CH_2CMe$_3$), 1.23 (s, CH$_2$C*Me*$_3$).

IR: 212 (mw), 256 (m), 421 (m), 455 (m), 600 (mw), 615 (m), 651 (s), 669 (m), 696 (vw), 730 (ms), 748 (m), 769 (ms), 773 (ms), 778 (ms), 845 (mw), 872 (m), 995 (w), 1042 (m), 1060 (mw), 1091 (w), 1108 (vw), 1150 (vw), 1227 (m), 1268 (s, br), 1359 (m), 1410 (vs), 1500 (vs), 1570 (vw), 1610 (vs) cm^{-1}.

W$_2$Bz$_2$(O$_2$CNMe$_2$)$_4$. In a similar procedure a large excess of CO_2 was reacted with W$_2$Bz$_2$(NMe$_2$)$_4$.

^{1}H NMR (22 °C, benzene-d_6): δ 3.79 (s, CH_2Ph), 2.67, 2.28 s, O$_2$CN*Me*$_2$).

Crystallographic Studies. General operating procedures and listings of programs have been previously published.[23] Crystal data for W$_2$(np)$_2$(O$_2$CMe)$_2$(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.

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 (MULTAN78) and Fourier techniques and refined by full-matrix least squares. Many of the hydrogen atom positions were visible in a difference Fourier phased 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 + B_{iso} 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 e/Å^3.

Acknowledgment. We thank Dr. D. M. Hoffman of Harvard University for helpful discussions and the National Science Foundation and the Wrubel 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$_2$CMe)$_4$, 108603-67-4; W$_2$(np)$_2$(O$_2$CMe)$_2$(S$_2$CNEt$_2$)$_2$, 110097-42-2; W$_2$(np)$_2$(O$_2$CMe)$_3$(OSCMe), 110116-42-2; W$_2$(np)$_2$(NMe$_2$)$_4$, 72286-69-2; W$_2$(np)$_2$(O$_2$CNMe$_2$)$_4$, 72286-53-4; W$_2$Bz$_2$(NMe$_2$)$_4$, 82555-52-0; W$_2$Bz$_2$(O$_2$CNMe$_2$)$_4$, 84913-56-4; W$_2$(CH$_3$)$_2$(O$_2$CH)$_4$, 91549-49-4; W$_2$(CH$_3$)$_2$(O$_2$CNH$_2$)$_4$, 110097-43-3; NaS$_2$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)$_2$(S$_2$CNEt$_2$)$_2$ molecule (4 pages); F_o and F_c values for the same compound (10 pages). Ordering information is given on any current masthead page.

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Structure–Reactivity Relations for Thiol–Disulfide Interchange[1]

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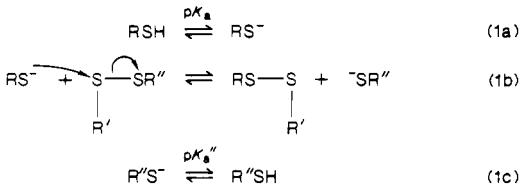
Abstract: Equilibrium constants were determined for thiol–disulfide interchange between 36 di- and trithiols and the disulfides derived from either 2-mercaptoethanol or dithiothreitol. Reactions were conducted in methanol-d_4/aqueous buffer (pH 7) or methanol-d_4 at 25 °C, using NMR spectroscopy to follow the reactions. These data were used to rank the dithiols in terms of reduction potential and to infer the structure of the disulfides formed from them on oxidation. There is a general correlation between the reducing ability of the dithiol and the size of the disulfide-containing ring formed on oxidation: dithiols that form six-membered rings are most strongly reducing (K = 10^3–10^5 M with respect to oxidized 2-mercaptoethanol); five- and seven-membered rings are approximately 1 order of magnitude less reducing. Compounds resembling 1,2-ethanedithiol form cyclic bis(disulfide) dimers in relatively dilute solutions (~1 mM) but polymerize at higher concentrations. Other classes of dithiols form polymers on oxidation.

The importance of the thiol–disulfide interchange reaction to biochemistry[2-8] 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[2-9] have prompted many studies of the physical-organic chemistry of this reaction.[10-17] These studies have established the reaction to be mechanistically simple. Interchange involves three steps (eq 1a–c): initial ionization of the thiol to thiolate anion, nucleophilic attack of the thiolate anion on a sulfur atom of the disulfide moiety, and



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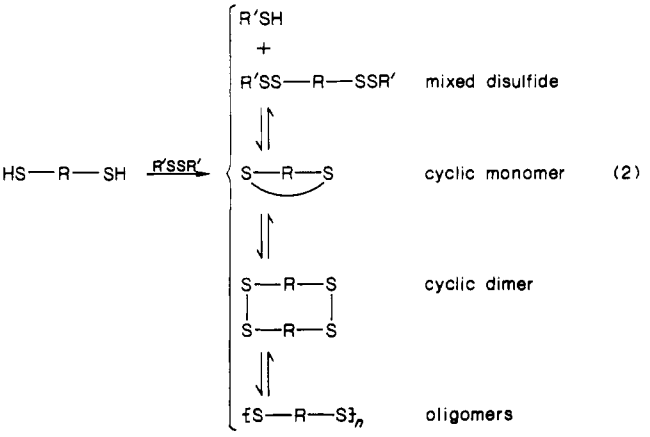
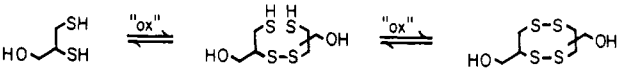
protonation of the product thiolate anion. All three steps are fully reversible. The nucleophilic attack appears to be an uncomplicated S_N2 displacement that occurs along the axis of the sulfur–sulfur bond.[18-20] For simple monothiols, both rate and equilibrium constants follow a Brønsted relation, but the factors that determine the position of equilibrium are more complicated.[21] Oxidations of α,ω-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



(2)

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 thiol groups in the intramolecular thiol–disulfide interchange step.[27] Their relative reducing potential is sensitive to the spacing between the thiols: 1,4-alkanedithiols that form strain-free six-membered 1,2-dithianes on oxidation are most strongly reducing. Rings larger than six members are less favored, presumably primarily for entropic reasons; rings smaller than six members are also less favored, probably for enthalpic reasons (ring strain). In dithiols separated by more than six atoms, the effective intramolecular concentration of thiol groups is sufficiently low that intermolecular oligomeric disulfide formation becomes competitive with cyclic monomer formation. The reducing potentials of dithiols that form oligomeric products are similar to those for monothiols.

The observation that a solution of BAL (2,3-dimercapto-1-propanol) is much more strongly reducing than a solution of a monothiol containing an equal concentration of thiol groups has led to the conclusion that BAL forms a cyclic bis(disulfide).[11] The initial formation of the half-oxidized dimer of BAL requires an intermolecular step (eq 3), but the second disulfide bond is formed



(3)

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.

Equilibrium constants for thiol–disulfide interchange reactions have been determined by using a variety of analytical techniques: polarography,[28] electrophoresis of ^{35}S-labeled thiol,[29] gas chromatography,[30] ion-exchange chromatography,[31] HPLC,[32] enzymatic assay,[11] 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]

Results and Discussion

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.

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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,[40] 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.[41] This product can be reduced ($LiAlH_4$, Zn–HCl) to give the corresponding dithiol. Unexpected products may arise if carbon disulfide is liberated during the displacement reaction.[41] We encountered two such instances: Reaction of *cis*-1,2-bis(*O*-tosyl)cyclohexane with Na_2CS_3 gave exclusively *trans*-1,2-cyclohexanedithiol, and reaction of *cis*-1,2-bis(*O*-tosylmethyl)cyclohexane with Na_2CS_3 gave *cis*-octahydrobenzo[*c*]thiophene. *cis*-Octahydrobenzo[*c*]thiophene is also obtained when *cis*-1,2-bis(bromomethyl)cyclohexane is treated with thiourea.[43]

Thiourea is especially useful in preparing benzylic thiols.[44-46] 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 thiocyanate in a polar aprotic or complexing solvent, such as tetraethylene glycol, reacts at neopentyl and secondary centers.[47] The intermediate thiocyanates are reduced to thiols with $LiAlH_4$. These reactions proceed slowly and give poor to moderate yields but are otherwise straightforward. Compounds as hindered as 1,3,5-cyclohexanetrithiol have been prepared with this reagent.[48]

Determination of Equilibrium Constants. Reduction potentials for thiols were obtained by equilibration against 1 mM oxidized mercaptoethanol (ME^{ox}) or oxidized dithiothreitol (DTT^{ox}) 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-d_4 and phosphate buffer (pH 7.0, 50 mM) in D_2O. 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.[11] 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 pK_a 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 pK_a of the equilibrating species. We have not separated effects from these two sources. In most cases, effects due to differences in pK_a will be small; the acidity of simple aliphatic thiols is fairly insensitive to alkyl structure,[29] and values of pK_a 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 DTT^{ox} was used only with thiols that form cyclic monomers on oxidation (eq 4a,b). The standard disulfide ME^{ox} was used with dithiols that form cyclic monomers (eq 5a,b), cyclic dimers (eq 6a–e), and higher oligomeric species (eq 7a–e).

DTT^{ox}

$$DTT^{ox} + HSRSH \rightleftharpoons [HSCH_2CH(OH)CH(OH)CH_2SSRSH] \rightleftharpoons DTT + \overbrace{SRS} \quad (4a)$$

$$K_{DTT} = [DTT][\overbrace{SRS}]/[DTT^{ox}][HSRSH] \quad (4b)$$

$$ME^{ox} + HSRSH \rightleftharpoons HOCH_2CH_2SSRSH \rightarrow \overbrace{SRS} + 2ME \quad (5a)$$

$$K_{ME} = [\overbrace{SRS}][ME]^2/[ME^{ox}][HSRSH] \quad (5b)$$

ME^{ox}/cyclic dimer

$$ME^{ox} + HSRSH \rightleftharpoons HOCH_2CH_2SSRSH + ME \quad (6a)$$

$$HOCH_2CH_2SSRSH + HSRSH \rightleftharpoons HSRSSRSH + ME \quad (6b)$$

$$HSRSSRSH + ME^{ox} \rightleftharpoons HSRSSRSSCH_2CH_2OH + ME \quad (6c)$$

$$HSRSSRSSCH_2CH_2OH \rightleftharpoons \overbrace{SRSSRS} + ME \quad (6d)$$

$$K_{ME} = [\overbrace{SRSSRS}][ME]^4/[ME^{ox}]^2[HSRSH]^2 \quad (6e)$$

ME^{ox}/oligomer

$$HSRSH = 2R'SH \quad (7a)$$

$$ME^{ox} + R'SH \rightleftharpoons HOCH_2CH_2SSR' + ME \quad (7b)$$

$$HOCH_2CH_2SSR' + R''SH \rightleftharpoons R'SSR'' + ME \quad (7c)$$

(R'' = some $HS(SRS)_nSH$ oligomer)

$$K_{ME} = [R'SSR''][ME]^2/[R'SH]^2[ME^{ox}] \quad (7d)$$

(R'SH = 2HSRSH)

$$K_{ME} = [RSSR][ME]^2/[ME^{ox}][2(HSRSH)]^2 \quad (7e)$$

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

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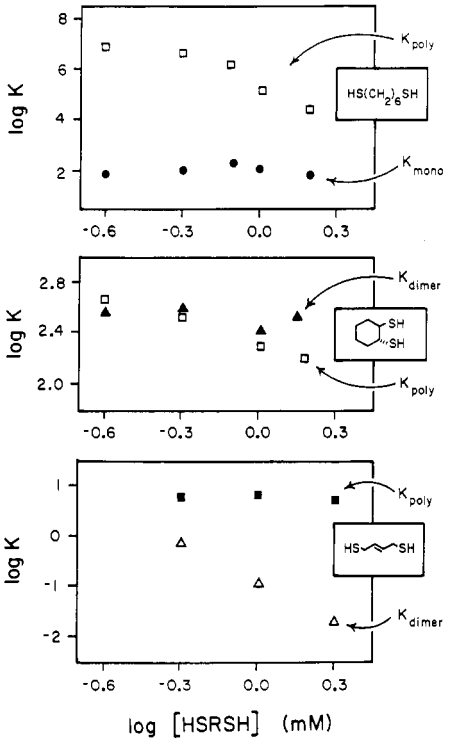

Figure 1. Plots of log K as a function of the concentration of reducing thiol. K values are calculated on the assumption that oxidation of the dithiols (HSRSH) yields (●) cyclic monomeric disulfides (K_{mono}, eq 5), (▲) cyclic dimeric disulfides (K_{dimer}, eq 6), or (■) polymeric disulfides (K_{poly}, eq 7). K_{mono} and K_{dimer} have units of M, and K_{poly} is dimensionless. Equilibrations were carried out in 1:1 methanol/0.1 M phosphate buffer at 25 ± 1 °C under nitrogen. Data are shown for 1,6-hexanedithiol, *trans*-1,2-cyclohexanedithiol, and *trans*-2-butene-1,4-dithiol.

equilibrium constants obtained by this procedure may not be highly accurate; they do, however, serve to compare relative reducing abilities for thiols.

The equilibrium expression for oligomer formation (eq 7e) assumes that all SH groups present in solution are equally reactive in each thiol–disulfide interchange. Thiol groups of the α,ω-dithiol react completely independently. R′SH and R″SH are thus arbitrary SH groups in the reaction mixture derived either from the original dithiol or from some oligomeric species. In all cases of oligomer formation, equilibrium constant values are near unity. One molecule of ME and one molecule of R″SH are required for the formation of each molecule of mixed disulfide. This equivalence reduces the terms in [ME] and [R″SH] in eq 7e by equivalent amounts. Since both terms are raised to the same power there will be no net change in K_{ME}. Values of equilibrium constants for oligomers are thus accurately expressed by eq 7e.

The various equilibria represented in eq 4–7 can be differentiated by constructing plots of equilibrium constant vs concentration of starting thiol. Values of K should be invariant to changes in this concentration if the correct expression for the equilibrium constant is applied.[11] Representative plots of log K vs the concentration of starting α,ω-dithiol are shown in Figure 1. These data lead to the following conclusions: 1,6-hexanedithiol forms 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 one disulfide form was not the unambiguous product, i.e., α,ω-dithiols that are capable of intramolecular disulfide formation but are weakly reducing (those forming 5-, 8-, 9-, and 10-membered rings) and dithiols that could form either cyclic dimers or oligomers.

Values of Equilibrium Constants. All values for equilibrium constants are reported vs ME^{ox} (eq 5b, 6e, and 7e). To convert data obtained for cyclic monomeric disulfides from reaction with DTT^{ox} (eq 4b) to an equivalent form relative to ME (eq 5b), it was necessary to determine an accurate equilibrium constant for

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

thiol	$K_{ME^{ox}}$, M	$K_{DTT^{ox}}$	$K_{ME^{ox}}/K_{DTT^{ox}}$,[a] M
lipoic acid	3.5 (±1.0) × 10^3	4.8 (±0.2) × 10^{-2}	7.3 × 10^4
1,3-propanedithiol	1.2 (±0.5) × 10^3	1.2 (±0.3) × 10^{-2}	1.0 × 10^5
1,6-hexanedithiol	1.1 (±0.2) × 10^2	1 × 10^{-3}	1 × 10^5

[a] Average = 9.4 (±1.5) × 10^4.

ME^{ox} vs DTT (eq 5b, $\overline{SRS}$ = DTT^{ox}, 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^{ox}. A value of 9.4 (±1.5) × 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 thiols are expressed as values of K vs ME^{ox} and as standard potential ($E°$) values. $E°$ for each of the dithiols is related to the half-cell potential for the oxidized mercaptoethanol/mercaptoethanol couple (eq 8). Certain of these values of K (eq 5b and 6e) have units

$$2e^- + ME^{ox} + 2H^+ \xrightarrow[25\ °C,\ pH\ 7.0]{E'° = -0.207\ V\ vs\ SHE} ME \qquad (8)$$

M; others (eq 7e) are dimensionless. Direct comparison between the two is not possible, but qualitative comparison is possible by assuming a reference concentration (eq 1 or 10 M) for the ME. We have taken an $E'°$ value for ME/ME^{ox} of –0.207 V to remain consistent with $E'°$ values reported in earlier thiol–disulfide equilibration studies.[49] Half-cell potentials for other thiols are linked to the value of the ME/ME^{ox} couple by

$$E'°_{RSH} - E'°_{ME} = -(RT/nF)\ \ln K_{ME} \qquad (9)$$

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^{ox} or DTT^{ox}.

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 ~10^3 (equilibrated against DTT^{ox}) and those with values of K less than ~10 (equilibrated against ME^{ox}). Equilibrium constants for dithiols having intermediate reducing ability are less accurate. These constants were determined (1) by equilibration with ME^{ox} in the presence of several equivalents of ME to make the solution more reductive or (2) by equilibration against DTT^{ox} 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.

Thiols **16**, **30**, and **32** were equilibrated in methanol-d_4/0.02 mM sodium methoxide rather than in the standard methanol/aqueous buffer solution to increase their solubilities. The base concentration in methanol was chosen to make the data as easily comparable to those in methanol buffer as possible. As discussed previously, equilibrium constants for thiol–disulfide interchange that are *not* corrected for ionization of thiol to thiolate can best be compared if the ratio of thiol to thiolate is constant. Roughly

(49) An $E'°$ value of –0.207 V for the ME/ME^{ox} couple was determined indirectly by utilizing a lipoamide/lipoamide dehydrogenase, $^-NAD^+/NADH$ enzymatic assay. This method is described in detail in ref 11.

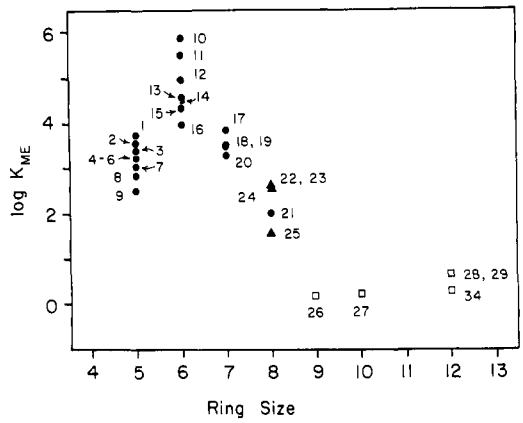

Figure 2. Plot of log K vs the size of the ring formed upon oxidation for the reduction of ME^{ox} or DTT^{ox} by dithiols. K values are calculated on the assumption that oxidation of dithiols yields (●) cyclic monomeric disulfides (K_{mono}, eq 5), (▲) cyclic dimeric disulfides (K_{dimer}, eq 6), or (□) polymeric disulfides (K_{poly}, eq 7). K_{mono} and K_{dimer} have units of M, and K_{poly} is dimensionless. Compounds **30–33**, **35**, and **36** would form rings with size >13; all form polymers.

1% of an alkanethiol in the methanol/buffer system is ionized to thiolate. Sodium methoxide (0.02 mM) reacts quantitatively with 1 mM dithiol (i.e. 2 mM "SH") to give ca. 1% alkanethiolate in methanol containing no added aqueous buffer. Equilibrations performed in methanol/buffer and methanol/0.02 mM methoxide under the two above sets of conditions should thus be comparable. This assumption was verified by determining several alkanedithiol reduction potentials using both solvent systems. K values did not differ by greater than 20% in any case. Arenethiols in Table II were also equilibrated in methanol/methoxide.

Dependence of Equilibrium Constant on Ring Size. Figure 2 illustrates the variation of K_{ME} with the size of the hypothetical ring that might form on formation of disulfide bonds. Previously established trends are reemphasized in this plot:[11] The maximum equilibrium advantage is observed for dithiols capable of forming six-membered rings. The relatively lower stability of five-membered rings can be attributed to enthalpic effects and the relatively lower stability of seven-membered and larger rings to entropic terms. We believe that 1,2-dithiols form eight-membered ring bis(disulfides). Intramolecular disulfide formation is unfavorable relative to formation of polymers and oligomers for rings that would contain more than eight atoms. The relative free energy of monomers, dimers, and polymers obviously depends on concentration; we can favor monomers and dimers relative to polymers by lowering the concentration of organic disulfides in solution.

1,3-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[50,65] 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 strain in the dithiolane ring. Figure 3 is a plot of log K vs the C_1–C_2–C_3 angle (θ) for substituted 1,3-propanedithiols: in general, thiols become less reducing as this angle increases. The sources of values used for θ[51,52,95] 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 based on the hybridization of the C_2 carbon. This correlation provides an example supporting the hypothesis developed by Thorpe and Ingold[54] 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

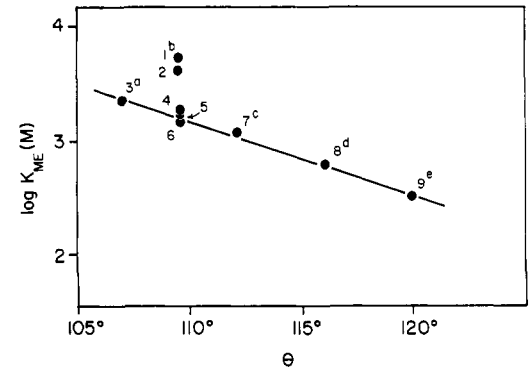

Figure 3. Plot of log K vs estimated values of the C_1–C_2–C_3 angle (θ) of substituted 1,3-propanedithiols. The values of K assume that oxidation of these dithiols yields cyclic monomeric disulfides. Dithiols were equilibrated against DTT^{ox}. Values of θ were obtained from the following sources: (a) the X-ray crystal structure value for the H–C–H angle in cyclobutane;[52] (b) θ is assumed to be 109.5° for tetrasubstituted compounds; (c) θ = 112° for the H–C–H angle in propane;[95] (d) the X-ray crystal structure value for the H–C–H angle in cyclopropane;[51] (e) θ is assumed to be 120° based on sp^2 hybridization at the C_2 carbon.

angles. If the angle between two of the substituents deviated from 109.5° because of incorporation into a ring, the angle between the two remaining groups would be altered by way of compensation. Similarly, if two of the four substituents were more bulky than the others, an angular deformation would occur in such a manner as to allow the most efficient utilization of the space available. Schleyer has established a similar correlation between C_1–C_2–C_3 angle and the strength of intramolecular hydrogen bond formation (as determined by IR) that occurs in 2-substituted 1,3-propanediols.[55]

1,1-Bis(mercaptomethyl)cyclohexane (**2**) and lipoic acid (**1**) are better reducing agents than predicted from estimated C–C–C bond angles alone. A CPK model of 1,1-bis(mercaptomethyl)-cyclohexane suggests significant eclipsing interactions between the sulfur of the axial thiomethyl group and the axial C_3 and C_5 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. Lipoic acid is a 1,3-propanedithiol substituted at C_1. All of the other dithiols in Figure 2 are substituted at C_2. This difference is reflected in the fact that the reducing ability of lipoic 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 rings[56–59] 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.[51] 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-CH_2 group in 1,5-pentanedithiol with oxygen or sulfur increases the equilibrium constant of the

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(60) Dale, J. *Tetrahedron* **1974**, *30*, 1683–1694.

Table II. Equilibrium Constants for Thiol–Disulfide Interchange[a]

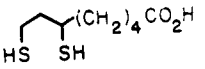
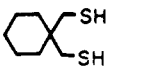
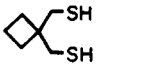
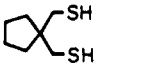
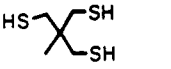
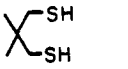
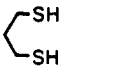
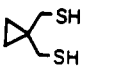
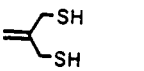
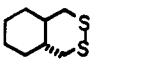
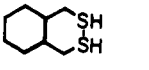
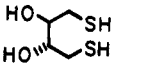
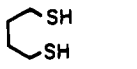
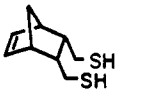
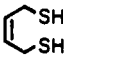
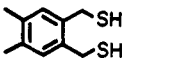
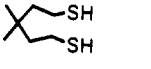
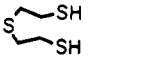
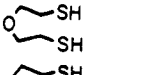
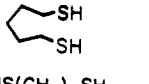
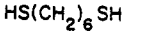
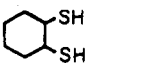
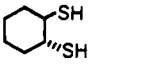
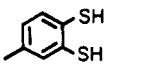
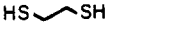
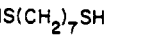
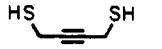
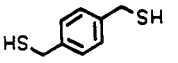
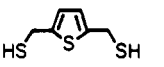
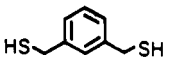
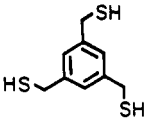
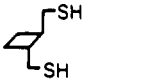
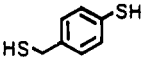
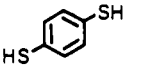
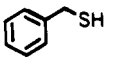
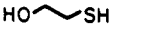
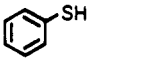
compd	ring size	structure	disulfide form[d]	$K_{ME^{ox}}$[e]	E'°,[f] V	equilib against
1	5		CM	5.7×10^3	−0.32	ME, DTT
2	5		CM	4.2×10^3	−0.32	DTT
3	5		CM	2.3×10^3	−0.31	DTT
4	5		CM	1.9×10^3	−0.31	DTT
5	5		CM	1.6×10^3	−0.30	DTT
6	5		CM	1.5×10^3	−0.30	DTT
7	5		CM	1.2×10^3	−0.30	ME, DTT
8	5		CM	6.5×10^2	−0.29	DTT
9	5		CM	3.5×10^2	−0.28	DTT
10	6		CM	7.8×10^5	−0.38	DTT
11	6		CM	3.5×10^5	−0.37	DTT
12	6		CM	9.4×10^4	−0.36	*g*
13	6		CM	4.0×10^4	−0.345	DTT
14	6		CM	3.4×10^4	−0.34	DTT
15	6		CM	2.3×10^4	−0.34	DTT
16	6		CM	1.0×10^{4b}	−0.33	DTT
17	7		CM	7.2×10^3	−0.32	DTT
18	7		CM	3.5×10^3	−0.31	DTT
19	7		CM	3.2×10^3	−0.31	DTT
20	7		CM	1.9×10^3	−0.31	DTT
21	8		CM	1.1×10^2	−0.27	ME, DTT
22	8		CD	4.0×10^2	−0.29	ME
23	8		CD	3.8×10^2	−0.285	ME
24	8		CD	3.2×10^{2b}	−0.28	ME
22 + **23** (1:1)	8		CD	3.0×10^2	−0.28	ME
25	8		CD	3.5×10^1	−0.255	ME
26	9		P	1.4	−0.21	ME

Table II (Continued)

compd	ring size	structure	disulfide form[d]	$K_{ME^{ox}}$[e]	$E'°$,[f] V	equilib against
27	10	$HS(CH_2)_8SH$	P	1.7	−0.22	ME
28			P	4.8	−0.23	ME
29			P	4.0	−0.23	ME
30			P	3.4[b]	−0.225	ME
31			P	3.1	−0.22	ME
32			P	3.0[b]	−0.22	ME
33			P	2.8[c]	−0.22	ME
34			P	1.8	−0.22	ME
35			P	1.3[b]	−0.21	ME
36			P	0.20[b]	−0.19	ME
37			M	2.6	−0.22	ME
38		$CH_3(CH_2)_6SH$	M	1.1	−0.21	ME
39			M	1.0	−0.207	ME
40			M	0.31[b]	−0.19	ME

[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_2O, 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] $K_{ME^{ox}}$ has units of M for **1–25** and is dimensionless for **26–40**. [f] $E°$ (V) values vs standard hydrogen electrode at pH 7.0 and 25 °C. [g] See Table I.

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 *intra*molecular disulfide bond formation by locating the two thiol groups beyond bonding distance. The more challenging problem is to favor *inter*molecular 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 (σ) (that is, the number of internal bond rotations) 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 α,ω-*n*-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_7. For 1 mM solutions of C_7 and longer dithiols (σ = 6), intermolecular disulfide formation becomes competitive with intramolecular cyclization and equilibrium constants are similar to those for monothiols.

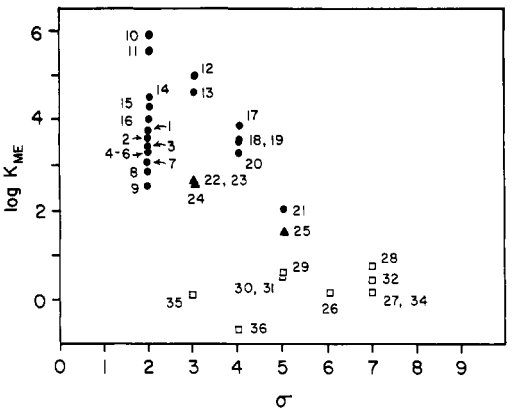


Figure 4. Plot of log K vs the degrees of freedom that must be frozen for ring closure to occur (σ). K values are calculated on the assumption that oxidation of dithiols yields (●) cyclic monomeric disulfides (K_{mono}, eq 5), (▲) cyclic dimeric disulfides (K_{dimer}, eq 6), or (□) polymeric disulfides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

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

(61) Page, M. I.; Jencks, W. P. *Proc. Natl. Acad. Sci. U.S.A.* **1971**, *68*, 1678. Page, M. I. *Chem. Soc. Rev.* **1973**, *2*, 295–323.

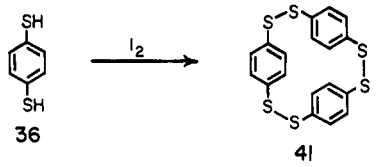
are included in this plot for completeness; we have, however, already noted that a model based solely on rotational entropy fails to rationalize reduction potentials for these compounds and that enthalpic factors (primarily ring strain) are important for these substances.

Restricting rotation around single bonds by incorporating them into rings or by converting them to double bonds makes it possible to decrease σ. 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**).[62] 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 ~90°.[50]

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 CH_2SH moieties of 1,2-ethanedithiol 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-ethanedithiol: 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.

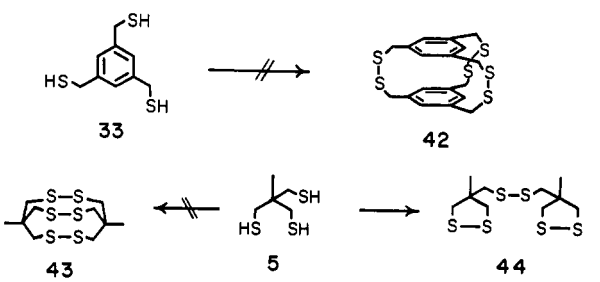
Oxidation of **36** with iodine using high-dilution techniques affords **41** (eq 10).[63] We determined an equilibrium constant



36 41 (10)

for reaction of **36** with ME^{ox} 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 σ 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 $K \simeq 0.2$ indicates that oxidation of **36** is not exceptionally favorable thermodynamically. Studies of cyclic bis(disulfides) derived from several thiols 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.[64]

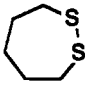
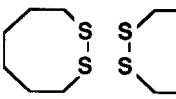
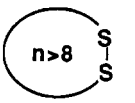
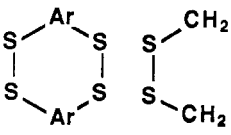
Adding a third disulfide unit to an existing dithiol might increase energetic terms enough to favor dimerization. Trithiols **33** and **5** were equilibrated with ME^{ox} in the hope of obtaining tris(disulfides) **42** and **43** (eq 11). Trithiol **33** was weakly reducing,



33 42 43 5 44 (11)

(62) 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.
(63) Wong, D. T.; Marvel, C. S. *J. Polym. Sci.* **1976**, *14*, 1637–1644.
(64) Houk, J.; Whitesides, G. M., unpublished.

Table III. Stability of Cyclic Disulfides with respect to Ring-Opening Polymerization

structural type	stability
	stable in concentrated solutions and as pure liquids
	not stable in concentrated solutions; stable in more dilute (<0.01 M) solutions; may be kinetically stable as solids
	
	
	polymerize; may be kinetically stable as solids
	

and only polymeric disulfide products were obtained. Trithiol **5** was moderately 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,[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-Dithiacyclohexanes. 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.[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 H_2S_2 ($\angle HSSH \simeq 98° \rightarrow \angle HSSH = 0°$) has been estimated theoretically to be ~7.5 kcal/mol.[65] Assuming a cos θ dependence of energy on dihedral angle, this barrier would ~5 kcal/mol for a change in ∠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 ∠CSSC of close to 60°) and **16** (which probably has a significant residual pucker to its ring and might still have ∠CSSC ~20°) is ~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-Dithiacyclopentanes are entropically favored, but enthalpically disfavored by the CSSC dihedral angle. If we extrapolate the data for eight-, seven-, and six-membered rings

(65) Dixon, D. A.; Zeroka, D.; Wendoloski, J. J.; Wasserman, Z. R. *J. Phys. Chem.* **1985**, *89*, 5334–5336.

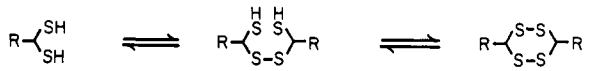
(Figure 2) to an anticipated value for five-membered rings of log $K_{ME} \sim 6$, the difference between this value and that observed, log $K_{ME} \simeq 3$, corresponds to $\Delta E \simeq 4$ kcal/mol. This value is again compatible with the assumption that torsional strain in the CSSC group is important 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-Tetrathiacyclooctanes. 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., $\Delta G \simeq 1.4$ 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 do so. 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 tetrathiane **47** is formed. By analogy, the precursor of this species would be a *gem*-dithiol **45**. Several compounds of structure **45**[66–68]



45 **46** **47**

and **47**[68,69] 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.[68,70] The NMR spectrum of this compound in either degassed D_2O or degassed benzene containing a catalytic amount of the base tetramethylguanidine became uninterpretably 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 number of disulfide moieties from two to three or four.

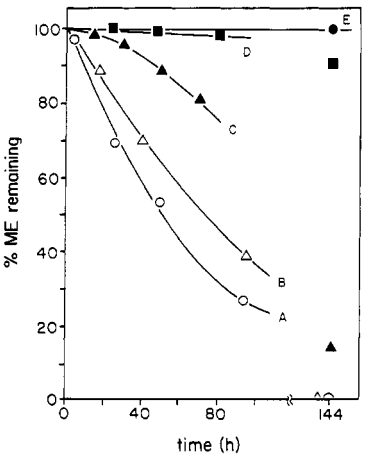


Figure 5. Rate of air oxidation of mercaptoethanol solutions in NMR tubes sealed in different ways. Solutions are initially 20 mM mercaptoethanol in methanol-d_4/aqueous buffer. NMR tubes were sealed in the following manner: curve A, conventional plastic NMR tube cap; curve B, screw-capped NMR tube fitted 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.

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 α,α'-dithiodurene (4,5-bis(mercaptomethyl)-*o*-xylene) was obtained from Lancaster Synthesis Ltd. Deuteriated 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 before use. 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. Deuteriated phosphate buffer (0.1 M, pH 7) was prepared by dissolving 85% phosphoric acid-d_3 (0.303 g, 2.5 mmol) in 99.5% deuterium oxide (D_2O) (20 mL). The pH of the solution was adjusted to 7.0 with 5 M sodium deuterioxide in D_2O, and the final solution volume was brought to 25 mL with D_2O. 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/deuteriated phosphate buffer were monitored for conversion of ME to ME^{ox}. 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 reseal 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

(66) Paquer, D.; Vazeux, M. *Tetrahedron Lett.* **1978**, *27*, 2411–2412.
(67) Adolfsson, L.; Andersson, R.; Olsson, K. *Chem. Scr.* **1980**, *16*, 122–129.
(68) Jentzsch, J.; Fabian, J.; Mayer, R. *Schwefel-Heterocyclen, (VIII)* **1962**, *95*, 1764–1766.
(69) Lalancette, J. M.; Freche, A.; Brindle, J. R.; Laliberte, M. *Synthesis* **1972**, 526–532. Lalancette, J. M.; Freche, A. *Can. J. Chem.* **1970**, *48*, 2366–2371.
(70) Fournier, C.; Lemarie, B.; Brallion, B.; Paquer, D.; Vazeux, M. *Org. Magn. Reson.* **1977**, *10*, 20–22.

(71) Purging with a slow nitrogen stream (3–4 bubbles/s) was found to effectively degas solutions without causing appreciable solvent evaporation. This method can be used as an acceptable alternative to degassing by the freeze–pump–thaw method. See: White, I.; Goddard, W. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1984**, *106*, 3461–3474.

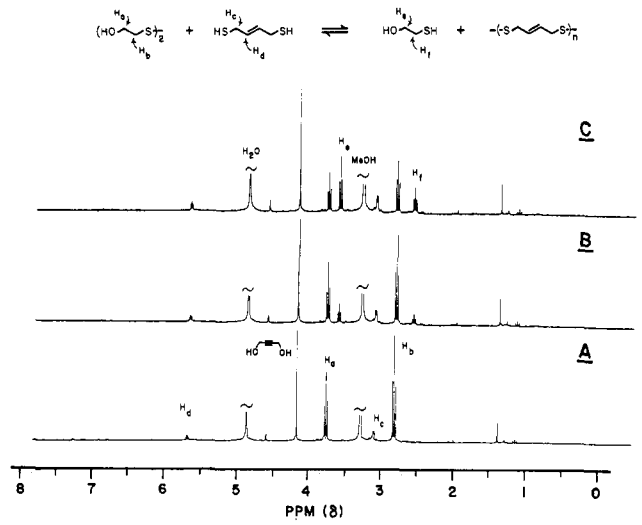


Figure 6. Reaction of ME^{ox} with *trans*-2-butene-1,4-dithiol as monitored by ^1H NMR. Solution is initially 1 mM ME^{ox}, 1 mM *trans*-2-butene-1,4-dithiol, and 0.5 mM 2-butyne-1,4-diol (internal standard) in 1:1 methanol-d_4/aqueous buffer (0.1 M phosphate, pH 7). Spectra shown correspond to an equilibration: (A) at the start of the experiment (t = 0); (B) during the equilibration (t = 12 h); (C) at final equilibrium.

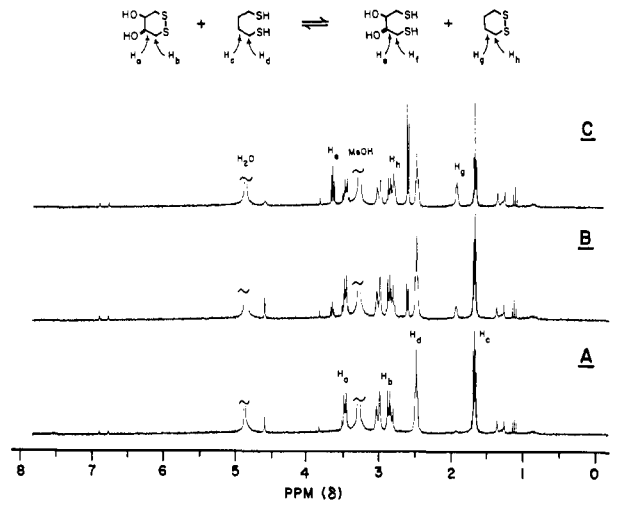


Figure 7. Reaction of DTT^{ox} with 1,4-butanedithiol as monitored by ^1H NMR. Solution is initially 1 mM DTT^{ox} and 1 mM 1,4-butanedithiol in 1:1 methanol-d_4/aqueous buffer (0.1 M phosphate, pH 7). Spectra shown correspond to an equilibration: (A) at the start of the experiment; (B) during the equilibration; (C) at final equilibrium.

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 ME^{ox} was used as the standard disulfide and one in which DTT^{ox} 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 ME^{ox}. Standard solutions containing 1 mM ME^{ox}, 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 D_2O and flushed with nitrogen were added via syringe under a static nitrogen head 0.092 M 2-butyne-1,4-diol in degassed methanol-d_4 (27.3 μL) and 0.85 M ME^{ox} in degassed D_2O (27.0 μL). A 1:1 mixture of deuteriated phosphate buffer and degassed methanol-d_4 was added to the flask to bring the total solution volume to 5 mL. To a 5-mm screw-cap NMR tube that had been dried at 110 °C and flushed with nitrogen were added via syringe under a static nitrogen atmosphere the ME^{ox} standard solution (0.7 mL) and 0.0917 M *trans*-2-butene-1,4-dithiol in methanol-d_4 (7.6 μL, 1 equiv relative to ME^{ox}). Reaction tubes were allowed to equilibrate for 12 h under 1–2 psi of nitrogen. The course of the reaction as monitored by ^1H NMR is shown in Figure 6. The methylene peak of 2-butyne-1,4-diol occurring at 4.23 ppm was used as an internal standard. Peaks corresponding to disulfide species formed from *trans*-2-butene-1,4-dithiol do not differ in chemical shift from peaks assigned to the dithiol.

Equilibrations with DTT^{ox}. To a 2-mL crimp-cap vial that had been rinsed with D_2O, dried at 110 °C, and flushed with nitrogen were added DTT^{ox} (15.4 mg, 0.1 mmol), 1,4-butanedithiol (12.2 mg, 0.1 mmol), and 1.4 mL of degassed methanol-d_4. To a 5-mm NMR tube that had been dried at 110 °C and flushed with nitrogen were added via syringe under a static nitrogen head an aliquot of the above solution (9.8 μL) and a 1:1 mixture of deuteriated phosphate buffer and degassed methanol-d_4 (0.7 mL). The nitrogen inlet to the NMR tube was closed. The bottom 5-cm portion of the tube was cooled to −78 °C in liquid nitrogen to create a slight vacuum, and the tube was flame sealed. The course of the reaction was monitored by ^1H NMR. Figure 7 shows spectra of DDT^{ox} and 1,4-butanedithiol at the start of an equilibration, during the equilibration, and at final equilibrium. The α-hydroxy methylene peak of DTT^{ox} occurring as a multiplet at 3.55 ppm and that of DTT occurring at 3.7 ppm were used to determine the relative amounts of oxidized and reduced DTT present at equilibrium.

Freshly prepared thiol solutions were used in all equilibrations. Possible oxygen contamination of deuteriated phosphate buffer or methanol-d_4 was tested by running a blank experiment with every set of equilibrations. A tube containing only the solvent mixture and ME (1 mM) was prepared in the same manner as equilibration tubes, and an NMR spectra of the blank solution was taken at the end of the equilibration time to check for the formation of ME^{ox}.

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[98] and equilibration of DTT with 1,2-dithiane both gave equilibrium constant values within 10% of K^{-1} 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-cyclobutanedithiol (20.4 mg, 0.17 mmol)[68] in degassed benzene-d_6 (1.0 mL) 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-d_6; tube 2, benzene-d_6 containing 0.1 mM tetramethylguanidine as a base; tube 3, a 1:1 mixture of deuteriated phosphate buffer/methanol-d_4. 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, 2.4, 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 the dianion of diethyl malonate gave diethyl 1,1-cyclohexanedicarboxylate[72] in 30% yield; bp 82–90 °C at 1 Torr (lit.[72] bp 119–130 °C at 16 Torr). Reduction of the diester with $LiAlH_4$ gave 1,1-bis(hydroxymethyl)cyclohexane in 89% yield; mp 93–96 °C (lit.[73] mp 95–97.5 °C). The diol was allowed to react with mesyl chloride to give the dimesylate, which on treatment with potassium thiocyanate followed by reduction with $LiAlH_4$ gave 1,1-bis(mercaptomethyl)cyclohexane[47] (45% from the diol). Distillation (70–75 °C at 0.1 Torr, lit.[47] bp 140 °C at 13 mm) afforded the product as a colorless liquid: ^1H NMR ($CDCl_3$) δ 2.4 (d, 4 H), 1.7 (m, 6 H), 1.4 (m, 4 H), 1.2 (t, 2 H); IR (neat) 2940, 2860, 2560, 1430, 1290 cm^{-1}.

1,1-Bis(mercaptomethyl)cyclobutane (3). A solution of 1,1-cyclobutanedicarboxylic acid (15 g, 0.10 mol) in THF (110 mL) was added dropwise with stirring to a refluxing solution of $LiAlH_4$ (18 g, 0.474 mol) in THF (450 mL). The reaction mixture was refluxed for 12 h under nitrogen and then cooled to 0 °C, and excess hydride was destroyed by cautious addition of a 1 M solution of NaOH (78 mL). The solution was stirred at room temperature for 1–2 h, during which time the initially gray slurry separated into a clear solution and a granular white precipitate. The reaction mixture was filtered and THF was removed from solution at reduced pressure to give 10.6 g (88%) of 1,1-bis(hydroxymethyl)cyclobutane as a clear oil; ^1H NMR ($CDCl_3$) δ 4.06 (br s, 2 H), 3.55 (s, 4 H), 1.8 (m, 2 H), 1.67 (t, 4 H).

Toluenesulfonyl chloride (45.5 g, 0.24 mol) was added batchwise to a stirred solution of crude 1,1-bis(hydroxymethyl)cyclobutane (10.6 g,

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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 give 30 g (77%) of 1,1-bis(*O*-tosylmethyl)cyclobutane as fluffy white flakes: mp 92–93 °C (lit.[74] mp 96.5 °C); ^{1}H NMR ($CDCl_3$) δ 7.7 (d, 2 H), 7.4 (d, 2 H), 3.4 (s, 4 H), 2.4 (s, 3 H), 1.8 (m, 2 H), 1.75 (m, 4 H).

A 33% aqueous solution of disodium trithiocarbonate[40] (66 mL, 0.14 mol) was added dropwise to 1,1-bis(*O*-tosylmethyl)cyclobutane (20 g, 0.047 mol) in DMF (100 mL). 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 ($MgSO_4$), and the solvent was removed at reduced pressure to give 7 g of an amber oil. This oil was taken into dry THF (70 mL) and added dropwise to a stirred suspension of $LiAlH_4$ (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 ditosylate) of an amber oil. Kugelrohr distillation (45–50 °C at 0.4 Torr) afforded **3** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.78 (d, 4 H), 1.7–1.9 (m, 6 H), 1.13 (t, 2 H); IR (neat) 3000–2900, 2560, 1420, 1270 cm^{-1}; exact mass calcd for $C_6H_{12}S_2$ (M^+) *m/e* 148.0380, found 148.0364.

1,1-Bis(mercaptomethyl)cyclopentane (4) was prepared in five steps in analogy to **2**. Reaction of 1,4-dibromobutane with the dianion of diethyl malonate gave diethyl 1,1-cyclopentanedicarboxylate in 45% yield; bp 78–84 °C at 1 Torr (lit.[72] bp 115 °C at 16 Torr). Reduction of the diester with $LiAlH_4$ gave 1,1-bis(hydroxymethyl)cyclopentane in 85% yield; mp 91–93 °C (lit.[75] mp 93.5 °C). The diol was reacted with mesyl chloride and then with potassium thiocyanate followed by $LiAlH_4$ reduction to give **4** in 55% yield. The crude dithiol was distilled (76–79 °C at 0.5 Torr, lit.[47] bp 123 °C at 14 Torr) to give a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.7 (d, 4 H), 1.6 (m, 8 H), 1.1 (t, 2 H); IR (neat) 2940, 2860, 2560, 1440, 1280 cm^{-1}.

1,1,1-Tris(mercaptomethyl)ethane (5) was prepared in 78% yield from 1,1,1-tris(*O*-tosylmethyl)ethane and disodium trithiocarbonate followed by Zn amalgam/HCl reduction using a literature procedure.[41] The crude product was distilled (70 °C at 4 Torr, lit.[41] bp 114 °C at 18 Torr) to provide **5** as a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 3.7 (d, 6 H), 1.6 (s, 3 H), 1.2 (t, 3 H); IR (neat) 2980, 2920, 2880, 2560, 1460, 1420, 1380, 1290 cm^{-1}.

2,2-Dimethyl-1,3-propanedithiol (6) was prepared in 30% yield from 2,2-dimethyl-1,3-dibromopropane and sodium trithiocarbonate by the same procedure as described for the preparation of **3**. Distillation (42–44 °C at 2 Torr, lit.[77] bp 72 °C at 12 Torr) afforded **6** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.45 (d, 4 H), 1.1 (t, 2 H), 0.95 (s, 6 H); IR (neat) 2980, 2920, 2880, 2560, 1470, 1420, 1380, 1360 cm^{-1}.

1,1-Bis(mercaptomethyl)cyclopropane (8) was prepared in four steps in 31% overall yield from 1,1-cyclopropanedicarboxylic acid by the same procedure as described for the synthesis of **3**. The crude dithiol was distilled (Kugelrohr, 45–50 °C at 1 Torr) to give a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.8 (d, 4 H), 1.1 (t, 2 H), 0.4 (s, 4 H); IR (neat) 3085, 3010, 2980, 2880, 2560, 1430, 1280 cm^{-1}; exact mass calcd for $C_5H_{10}S_2$ (M^+) *m/e* 134.02239, found 134.02229.

2-(Mercaptomethyl)-1-propene-3-thiol (9). 3-Chloro-2-(chloromethyl)-1-propene (10 g, 0.08 mol) was added dropwise to a degassed solution of sodium thioacetate (0.2 mol, from 14 mL of thiolacetic acid and 4.5 g of sodium) in methanol (300 mL). The reaction mixture was heated for 5 h under nitrogen. Concentrated hydrochloric acid (21 mL, 0.21 mol) was added, and the solution was refluxed for an additional 4 h. Methanol and methyl acetate were removed at reduced pressure, leaving precipitated sodium chloride, a small amount of water, and a yellow oil. The oil was taken up in methylene chloride (25 mL) and washed with 0.1 M hydrochloric acid (2 × 20 mL) and water (2 × 20 mL). The organic fraction was dried ($MgSO_4$) and the solvent removed at reduced pressure to give 6.8 g (72%) of yellow liquid. Distillation (44–46 °C at 0.3 Torr, lit.[78] bp 65–66 °C at 13 Torr) afforded the product as a colorless, foul-smelling liquid: ^{1}H NMR ($CDCl_3$) δ 5.0 (s, 2 H), 3.35 (d, 4 H), 1.45 (t, 2 H); IR (neat) 2090, 2970, 2930, 2560, 1700, 1650, 1440 cm^{-1}.

***trans*-1,2-Bis(mercaptomethyl)cyclohexane (10).** *trans*-1,2-Bis(*O*-tosylmethyl)cyclohexane[79] was treated with disodium trithiocarbonate by the same procedure as in the preparation of **3**. The product was obtained in 71% yield and purified by Kugelrohr distillation (90 °C at 2.5 Torr, lit.[80] bp 73–75 °C at 2.5 Torr): ^{1}H NMR ($CDCl_3$) δ 2.5 (m, 4 H), 1.8–1.6 (m, 2 H), 1.2–1.0 (m, 8 H), 1.1 (t, 2 H); IR (neat) 2930, 2860, 2560, 1450, 1315 cm^{-1}.

***cis*-1,2-Bis(mercaptomethyl)cyclohexane (11).** *cis*-1,2-Bis(*O*-tosylmethyl)cyclohexane was prepared in 87% yield *cis*-1,2-bis(hydroxymethyl)cyclohexane and toluenesulfonyl chloride. Recrystallization from hot methanol afforded white flakes, mp 83.5–85 °C (lit.[81] mp 84–85 °C). The ditosylate (16 g, 0.035 mol) was added to a solution of thiolacetic acid (7.6 mL, 0.11 mol) and sodium methoxide (5.73 g, 0.11 mol) in DMF (50 mL) that had been purged with nitrogen. The reaction mixture was stirred under nitrogen at 80 °C for 12 h. Water (150 mL) was added and the solution was extracted with chloroform (150 mL). The organic layer was washed with water (6 × 160 mL) and dried ($MgSO_4$), 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, lit.[82] bp 138–142 °C at 12.5 Torr) afforded **11** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.4 (m, 4 H), 1.8 (m, 2 H), 1.3–1.6 (m, 6 H), 1.3 (t, 2 H), 1.2–1.4 (m, 2 H); IR (neat) 2930, 2860, 2560, 1450, 1320 cm^{-1}.

***endo*-2,3-Bis(mercaptomethyl)-*cis*-5-norbornene (14)** was prepared in three steps from *cis*-5-norbornene-*endo*-2,3-dicarboxylic acid following the procedures described for the synthesis of **3**. Reduction of the diacid with $LiAlH_4$ afforded *endo*-2,3-bis(hydroxymethyl)-*cis*-5-norbornene in 80% yield; mp 79–81 °C (lit. mp[83] 79–82 °C). The corresponding ditosylate was prepared in 80% yield; mp 87–89 °C (lit.[84] mp 90–91 °C). 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: ^{1}H NMR ($CDCl_3$) 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), 1.2 (t, 2 H); IR (neat) 2980, 2880, 2560, 1450, 1340 cm^{-1}.

***cis*-2-Butene-1,4-dithiol (15)** was prepared in 70% yield from *cis*-1,4-dichloro-2-butene and thiolacetic acid by the procedure described for the synthesis of **9**. Distillation (bp 30 °C at 0.1 Torr, lit.[85] bp 80–81 °C at 11 Torr) afforded **15** as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 5.6 (t, 2 H), 3.21 (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**. Reduction of the diacid gave 3,3-dimethyl-1,5-pentanediol in 55% yield: ^{1}H NMR ($CDCl_3$) δ 3.75 (t, 4 H), 2.45 (br s, 2 H), 1.5 (t, 4 H), 0.95 (s, 6 H). Tosylation of the diol followed by recrystallization from hot methanol gave 3,3-dimethyl-1,5-bis(*O*-tosyl)-pentane in 73% yield: mp 55.5–57 °C; ^{1}H NMR ($CDCl_3$) δ 7.9 (d, 4 H), 7.4 (d, 4 H), 4.15 (t, 4 H), 2.55 (s, 6 H), 1.65 (t, 4 H), 0.95 (s, 6 H). Treatment of the ditosylate with sodium thioacetate using the same procedure as described for the synthesis of **9** afforded **17** in 56% yield. Kugelrohr distillation (50–55 °C at 0.1 Torr) gave the product as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.4 (m, 4 H), 1.5 (m, 4 H), 1.3 (t, 2 H), 0.95 (s, 6 H); IR (neat) 2960, 2910, 2880, 2560, 1470, 1380, 1340 cm^{-1}; exact mass calcd for $C_7H_{16}S_2$ (M^+) *m/e* 164.06934, found 164.06986.

***cis*-1,2-Cyclohexanedithiol (22).** *cis*-1,2-Cyclohexanediol[86] was treated with toluenesulfonyl chloride to give *cis*-1,2-bis(*O*-tosyl)cyclohexane in 85% yield. Recrystallization from hot methanol gave small white platelets, mp 128–130 °C (lit.[87] mp 128–130 °C). Dithiol **22** was

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prepared from the ditosylate by a modified literature procedure.[48] Potassium thiocyanate (56 g, 0.55 mol) was dissolved in diethylene glycol (60 mL) at 100 °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 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 (50 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. Kugelrohr distillation (65–70 °C at 1.5 Torr, lit.[88] bp 48–51 °C at 0.2 Torr) gave **22** as a colorless liquid: ^1H NMR ($CDCl_3$) δ 3.21 (m, 2 H), 1.84 (m, 4 H), 1.77 (d, 2 H), 1.62 (m, 2 H), 1.34 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 44.4, 32.8, 22.7; IR (neat) 2940, 2860, 2560, 1450 cm^{-1}.

***trans*-1,2-Cyclohexanedithiol (23)** was prepared in two steps following literature procedures. Treatment of cyclohexene oxide with carbon disulfide and potassium hydroxide afforded *trans*-1,2-cyclohexyl trithiocarbonate as a yellow solid in 88% yield; mp 167–169 °C (lit.[76] mp 169 °C). Reduction of the trithiocarbonate with $LiAlH_4$ afforded **23** in 79% yield. The product was distilled (40–45 °C at 0.5 Torr, lit.[89] bp 104–106 °C at 18–19 Torr) to give a colorless liquid: ^1H NMR ($CDCl_3$) δ 2.6 (m, 2 H), 2.05 (m, 2 H), 1.95 (d, 2 H), 1.6 (m, 2 H), 1.1–1.35 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 47.9, 36.6, 26.1; IR (neat) 2940, 2860, 2560, 1450 cm^{-1}.

1,7-Heptanedithiol (26) was prepared in 95% yield from 1,7-dibromoheptane and sodium thioacetate by the procedure described for the synthesis of **9**. Kugelrohr distillation (80–85 °C at 0.1 Torr (lit.[96] bp 127 °C at 14 Torr) afforded **26** as a colorless liquid: ^1H NMR ($CDCl_3$) δ 2.5 (m, 4 H), 1.6 (q, 4 H), 1.35 (m, 6 H), 1.31 (t, 2 H); IR (neat) 2940, 2860, 2560, 1460, 1280 cm^{-1}.

***trans*-2-Butene-1,4-dithiol (28)** was prepared in analogy to **9** from *trans*-1,4-dichlorobutene in 78% yield. Distillation (50–53 °C at 2 Torr, lit.[85] bp 81–82 °C at 11 Torr) afforded the product as a slightly yellow, foul-smelling liquid: ^1H NMR ($CDCl_3$) δ 5.6 (m, 2 H), 3.0 (m, 4 H), 1.35 (t, 2 H); IR (neat) 3040, 2930, 2830, 2560, 1670, 1430 cm^{-1}.

1,4-Butynedithiol (29) was prepared in analogy to **9** from 1,4-dichloro-2-butyne in 75% yield. Kugelrohr distillation (45–50 °C at 1 Torr) afforded the dithiol as a pale yellow, foul-smelling liquid (*extensive polymerization occurs if this compound is heated above 100 °C*); ^1H NMR ($CDCl_3$) δ 3.3 (d, 4 H), 2.0 (t, 2 H).

1,4-Bis(mercaptomethyl)benzene (30). α,α'-Dibromo-*p*-xylene (10 g, 0.038 mol) was combined with thiourea (7.5 g, 0.075 mol) in ethanol (100 mL). The reaction mixture was stirred for 5 h and the solvent was removed at reduced pressure, leaving the bis(thiouronium) salt as a white solid. A solution of sodium hydroxide (6 g, 0.15 mol) in degassed water (100 mL) was added and the solution was refluxed for 4 h. The reaction mixture was cooled to 0 °C and acidified to pH 2 with 6 N hydrochloric acid. The solution was extracted with chloroform (2 × 40 mL). The chloroform fractions were combined and dried ($MgSO_4$), and the solvent was removed to give 6 g (90%) of the dithiol as a slightly yellow solid. Kugelrohr distillation (76–80 °C at 1.5 Torr) afforded **30** as a white solid: mp 46 °C (lit.[90] mp 46–47 °C); ^1H NMR ($CDCl_3$) δ 7.2 (s, 4 H), 3.8 (d, 4 H), 1.8 (t, 2 H).

2,5-Bis(mercaptomethyl)thiophene (31) was prepared in analogy to **9** from 2,5-bis(chloromethyl)thiophene[91] in 50% yield. Kugelrohr distillation (90–95 °C at 1 Torr) afforded the product as a colorless liquid with spectral properties consistent with those previously reported:[91] ^1H NMR ($CDCl_3$) δ 6.75 (m, 2 H), 2.9 (d, 4 H), 1.95 (t, 2 H).

1,3-Bis(mercaptomethyl)benzene (32) was prepared in 96% yield from α,α'-dibromo-*m*-xylene in analogy to **30**. Kugelrohr distillation (80–84 °C at 1 Torr, lit.[92] bp 157–158 °C at 15 Torr) afforded **32** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.2 (m, 4 H), 3.7 (d, 4 H), 1.75 (t, 2 H); IR (neat) 3060, 3030, 2970, 2940, 2860, 2560, 1610, 1590, 1490, 1450 cm^{-1}.

1,3,5-Tris(mercaptomethyl)benzene (33). Trimethyl 1,3,5-benzenetricarboxylate was reduced with $LiAlH_4$ in THF to give 1,3,5-tris(hydroxymethyl)benzene in 50% yield. Recrystallization from hot ethyl acetate gave white needles, mp 77–78 °C (lit. mp[93] 77 °C). This triol, on treatment with phosphorus tribromide in ether[93] gave 1,3,5-tris(bromomethyl)benzene in 95% yield as white needles, mp 92–93 °C (lit.[93] mp 93 °C). Reaction of the tribromide with thiourea gave **33** in 58% yield. Kugelrohr distillation (90–95 °C at 1 Torr, lit.[94] bp 177 °C at 1 mm) afforded the trithiol as a colorless oil: ^1H NMR ($CDCl_3$) δ 6.9 (s, 3 H), 3.3 (d, 4 H), 1.5 (t, 3 H); IR (neat) 3020, 2980, 2940, 2860, 2560, 1720, 1610, 1450, 1250 cm^{-1}.

***trans*-1,2-Bis(mercaptomethyl)cyclobutane (34)** was prepared in three steps in analogy to **3** from dimethyl *trans*-1,2-cyclobutanedicarboxylate. The diester was reduced with $LiAlH_4$ in THF to give *trans*-1,2-bis(hydroxymethyl)cyclobutane in 50% yield. Tosylation of the diol proceeded in 69% yield to give *trans*-1,2-bis(*O*-tosylmethyl)cyclobutane as a viscous liquid.[68] Reaction of the ditosylate with disodium trithiocarbonate was carried out as described in the synthesis of **3** except that $LiAlH_4$ reduction was not necessary. Acidification of the intermediate bis(sodium trithiocarbonate) liberated carbon disulfide and gave **34** directly in 69% yield. Kugelrohr distillation (46–50 °C at 0.5 Torr) afforded the product as a colorless liquid: ^1H NMR ($CDCl_3$) δ 2.7 (m, 4 H), 2.15 (m, 4 H), 1.6 (m, 2 H), 1.3 (t, 2 H); IR (neat) 2980, 2920, 2870, 2560, 1440, 1430 cm^{-1}; exact mass calcd for $C_6H_{12}S_2$ (M^+) *m/e* 148.03804, found 148.03807.

1,4-Benzenedithiol (36) was prepared following a literature procedure from 1,4-dichlorobenzene and sodium methanethiolate[77] in 73% yield. Recrystallization from ethanol afforded the product as a colorless solid: mp 97–99 °C (lit.[97] mp 97–99 °C); ^1H NMR ($CDCl_3$) δ 7.0 (s, 4 H), 3.4 (s, 2 H).

1,1-Cyclobutanedithiol was prepared from cyclobutanone and hydrogen sulfide in 53% yield following a literature procedure.[68,70] The crude product was distilled (51 °C at 5 Torr) to give a colorless liquid: ^1H NMR ($CDCl_3$) δ 2.8 (s, 2 H), 2.5 (t, 4 H), 2.05 (q, 2 H); IR (neat) 2940–3000, 2870, 2550, 1440 cm^{-1}.

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