Conformational Analysis. XVIII. 1,3-Dithianes. Conformational Preferences of Alkyl Substituents and the Chair–Boat Energy Difference[1,2]

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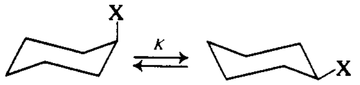
Abstract: Conformational preferences of alkyl substituents at various positions in the 1,3-dithiane system have been determined by acid-catalyzed equilibration of diastereoisomeric di- and trialkyldithianes. The results are supported by evidence from nuclear magnetic resonance spectroscopy. For alkyl groups at positions 2 and 4, free-energy differences ($-\Delta G°$ values) between equatorial and axial locations are of the same magnitude as in cyclohexane. In contrast, the preference of alkyl substituents at position 5 for the equatorial orientation is much less than in cyclohexane. The equatorial–axial free-energy differences (in kilocalories per mole) are Me-2, 1.77; Me-4, 1.69; Me-5, 1.04; Et-2, 1.54; Et-5, 0.77; *i*-Pr-2, 1.95; *i*-Pr-5, 0.85; *t*-Bu-2, $\geqslant 2.7$. The chair–skew boat enthalpy and entropy differences for 2,5-di-*t*-butyl-1,3-dithiane have been determined to be 3.42 kcal/mol and 5.3 cal/deg mol, respectively, by a study of the dependence of equilibrium upon temperature. The results are interpreted in terms of the known geometry of the 1,3-dithiane ring, the relative space requirement of sulfur compared with a methylene group and the known barrier to rotation about C–S bonds.

During the past several years, much effort has been devoted to studies of conformational equilibria (Scheme I) in alicyclic molecules with special emphasis on substituted cyclohexanes. A number of methods and techniques have been devised to measure the extent to which a particular substituent X prefers the equatorial over the axial orientation.[4] Such studies have provided $-\Delta G°$ values or "conformational energies" for a wide variety of groups[5] and have led to at least a qualitative understanding of the forces and interactions which determine conformation and reactivity in substituted cyclohexanes. Moreover, theoretical treatments of cycloalkanes have also progressed to the point where energy differences between various conformations of substituted cyclohexanes can be calculated using appropriate potential functions; such treatments provide values in reasonable agreement with experiment.[6–10]

Scheme I



$$-\Delta G° = RT \ln K$$

In contrast to the abundance of information in the cyclohexane area, there has been, until very recently, a paucity of data concerned with conformational preferences in heterocyclic systems, with the result that relatively little is known regarding the conformational consequences of introducing one or more heteroatoms into a six-membered ring.[4b,11] Such knowledge should be of very general interest since saturated heterocyclic compounds comprise a large segment of organic chemistry and are quite widespread in nature, *e.g.*, in alkaloids, carbohydrates, and plant growth regulators, among other compounds. Important questions to be answered are concerned with the effects of the variation in bond lengths, bond angles, and torsional barriers of heteroatoms on conformational preferences of substituents and on energy differences between chair and boat forms of heterocycles, and with the change in steric requirements introduced by replacing a methylene group by a heteroatom having one or more free electron pairs. This latter question has recently attracted considerable attention and controversy.[11–13] For these reasons, we have initiated a systematic investigation of conformational

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[1] Paper XVII: E. L. Eliel and C. A. Giza, *J. Org. Chem.*, **33**, 3754 (1968).

[2] Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1, 1968.

[3] National Science Foundation Postdoctoral Fellow, 1966–1967.

[4] For comprehensive reviews, see (a) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Division, John Wiley & Sons, Inc., New York, N. Y., 1965; (c) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965; (d) J. McKenna, "Conformational Analysis of Organic Compounds," The Royal Institute of Chemistry Lecture Series, No. 1, London, 1966; (e) for brief reviews of methods in conformational analysis, see E. L. Eliel, *Angew. Chem.*, **77**, 784 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965); E. L. Eliel, *Chimia*, **22**, 201 (1968).

[5] For a tabulation of known $-\Delta G°$ values and the methods used for their determination, see J. A. Hirsch in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience Division, John Wiley & Sons, Inc., New York, N. Y., 1967.

[6] F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956.

[7] (a) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **83**, 4537 (1961); (b) *ibid.*, **84**, 3355 (1962); (c) *ibid.*, **86**, 4854 (1964); (d) *ibid.*, **89**, 7036, 7043 (1967).

[8] (a) N. L. Allinger, M. A. Miller, F. A. VanCatledge, and J. A. Hirsch, *ibid.*, **89**, 4345 (1967); (b) N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tymenski, and F. A. VanCatledge, *ibid.*, **90**, 1199 (1968); see also ref 4b.

[9] K. B. Wiberg, *ibid.*, **87**, 1070 (1965).

[10] M. Bixon and S. Lifson, *Tetrahedron*, **23**, 769 (1967).

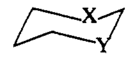
[11] For reviews of heterocyclic conformational analysis, see F. G. Riddell, *Quart. Rev.* (London), **21**, 364 (1967); C. Romers, C. Altona, H. R. Buys, and E. Havinga in "Topics in Stereochemistry," Vol. 4, Interscience Division, John Wiley & Sons, Inc., New York, N. Y., in press.

[12] (a) N. L. Allinger and J. C. Tai, *J. Amer. Chem. Soc.*, **87**, 1227 (1965); (b) N. L. Allinger, J. G. D. Carpenter, and F. M. Karkowski, *ibid.*, **87**, 1232 (1965); (c) J. B. Lambert, R. G. Keske, R. E. Cathcart, and A. P. Jovanovich, *ibid.*, **89**, 3761 (1967); (d) R. J. Bishop, L. E. Sutton, D. Dineen, A. Y. Jones, and A. R. Katritzky, *Proc. Chem. Soc.*, 257 (1964); (e) K. Brown, A. R. Katritzky, and A. J. Waring, *ibid.*, 257 (1964); (f) C. R. Johnson and D. McCants, *J. Amer. Chem. Soc.*, **86**, 2935 (1964); (g) N. L. Allinger, J. A. Hirsch, and M. A. Miller, *Tetrahedron Letters*, 3729 (1967); (h) M. J. T. Robinson, *ibid.*, 1153 (1968); (i) R. W. Baldock and A. R. Katritzky, *ibid.*, 1159 (1968); (j) H. Booth, *Chem. Commun.*, 802 (1968); (k) T. Masamune, *ibid.*, 244 (1968); (l) P. J. Buckley, C. C. Costain, and J. E. Parkin, *ibid.*, 668 (1968).

preferences in various heterocyclic systems, some results of which have been previously reported.[1,13a]

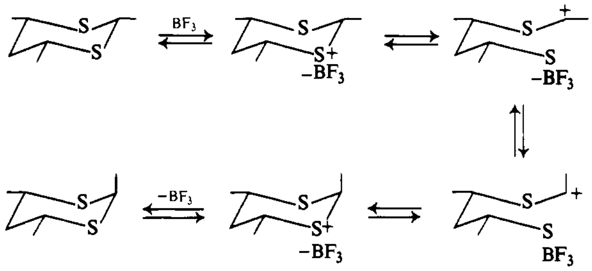
1,3-Diheterosubstituted cyclohexanes (Chart I) have been found to be almost ideally suited for studies of conformational equilibria in heterocyclic systems. Such compounds containing a variety of substituents located at different positions can usually be readily synthesized by standard procedures (*e.g.*, 1,3-dithianes are thioacetals, easily prepared from aldehydes and substituted 1,3-propanedithiols). Consequently, ΔG° values may often be determined for a particular group at all three nonequivalent sites (positions 2, 4, and 5) of the ring. Moreover, in cases where Y = X = O or S, acid-catalyzed equilibration of isomers occurs readily (since the compounds are acetals or thioacetals) thus permitting use of the reliable direct equilibrium method[4,13] of determining configurational preferences (Scheme II). Finally, the nmr spectra of this type of system can generally be analyzed without undue difficulty thus providing a convenient aid to configurational assignments and helping to establish conformational preferences of a particular isomer when two or more conformations are possible.

Chart I



X, Y=O, S, N

Scheme II



Recently, the conformational analysis of substituted 1,3-dioxanes (Chart I, X = Y = O) by equilibrium techniques was reported from our laboratories[13a] and, independently, by Riddell and Robinson.[13b] It was found that $-\Delta G^\circ$ values for 5 substituents were quite low (*e.g.*, 0.8 kcal/mol for methyl, 1.5 kcal/mol for *t*-butyl) while the corresponding values at positions 2 and 4 were much greater than those found in cyclohexane (*e.g.*, 2.9 kcal/mol for 4-methyl, *ca.* 3.6 kcal/mol for 2-methyl compared with about 1.7 kcal/mol for methyl in cyclohexane). It was concluded that the relatively short C–O bond length and possibly slight inward bending of the axial 2 substituent are primarily responsible for the high $-\Delta G^\circ$ values at positions 2 and 4 while the absence of *syn*-axial hydrogens possibly combined with ring flattening leads to the low values at position 5. This latter result was considered evidence that the steric requirement of O (with its axial lone pair of electrons) is less than that of CH. The conformational energies obtained for 2- and 4-methyl groups are in excellent agreement with those found in a recent thermochemical study of 1,3-dioxanes (for Me-4, $\Delta H^\circ = 2.9 \pm 0.5$ kcal/mol; for Me-2, $\Delta H^\circ = 4.1 \pm 0.7$ kcal/mol).[14]

The present work is concerned with conformational equilibrium studies of 1,3-dithiane ring system (Chart I, X = Y = S) substituted with various alkyl groups. There was, at the inception of the present study, only very meager information available concerning conformational aspects of 1,3-dithianes. Kalff and Romers have determined the solid-state geometry of 2-phenyl-1,3-dithiane by X-ray analysis[15] and barriers to ring inversion have been measured for 1,3-dithiane, 2,2-dimethyl- and 5,5-dimethyl-1,3-dithianes.[16] Several 2-aryl- and 2-aryl-2-alkyl-1,3-dithianes were studied by Kalff and Havinga using dipole moment and nmr spectroscopic measurements to determine conformational preferences.[17] In addition, the conformations of 5-hydroxy-1,3-dithiane[18a] and various 2-substituted 5-hydroxy- and 5-acetoxy-1,3-dithianes have been investigated by ir and nmr techniques.[18b] Recently, nmr coupling constants have been used to assess ring distortions in 4-*cis*,6-*cis*-dimethyl- and 4-*cis*,6-*trans*-dimethyl-2-*t*-butyl-1,3-dithianes (VII and VIII, respectively).[19] Important features of the 1,3-dithiane molecule include the facts that the C–C–C, C–C–S, and S–C–S angles (average 116°)[15] as well as the C–S–C angles (100°)[15,20] and C–S bond lengths (1.81 Å)[15,20] differ substantially from the corresponding C–C–C angles and C–C length in cyclohexane (111.5° and 1.54 Å, respectively).[21] Furthermore, similarly as in the 1,3-dioxanes, two of the axial hydrogens present in cyclohexanes are replaced by two lone pairs of electrons by introduction of the sulfur atoms.[22]

Results and Discussion

The dithianes used in the present study were prepared

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(13) (a) E. L. Eliel and Sr. M. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968); (b) F. G. Riddell and M. J. T. Robinson, *Tetrahedron*, **23**, 3417 (1967). References to other 1,3-dioxane work may be obtained from these papers.

(14) K. Pihlaja and J. Heikkila, *Acta Chem. Scand.*, **21**, 2390, 2430 (1967); K. Pihlaja and S. Luoma, *ibid.*, **22**, 2401 (1968).

(15) H. T. Kalff and C. Romers, *Acta Crystal.*, **20**, 490 (1966).

(16) H. Friebolin, S. Kabuss, W. Maier, and A. Lüttringhaus, *Tetrahedron Letters*, 683 (1962). The chair–chair interconversion barriers (in kilocalories per mol) were found to be 9.4 for 1,3-dithiane, 10.3 in 5,5-dimethyl-1,3-dithiane and 9.8 in 2,2-dimethyl-1,3-dithiane.

(17) H. T. Kalff and E. Havinga, *Rec. Trav. Chim.*, **85**, 467 (1966). The $-\Delta G^\circ$ value for 2-*p*-chlorophenyl-1,3-dithiane was determined by dipole moment measurements, to be 1.7 ± 0.3 kcal/mol in favor of equatorial 2-*p*-chlorophenyl.

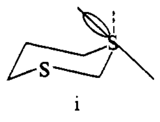
(18) (a) A. Lüttringhaus, S. Kabuss, H. Prinzbach, and F. Langenbucher, *Ann.*, **653**, 195 (1962). The conformation of 5-hydroxy-1,3-dithiane with axial OH was found to be favored over the equatorial form by 0.5 kcal/mol because of intramolecular hydrogen bonding. (b) R. J. Abraham and W. A. Thomas, *J. Chem. Soc.*, 335 (1965). The $-\Delta G^\circ$ value for 5-hydroxy was determined to be about −0.8 kcal/mol, in fair agreement with ref 18a. Likewise, the $-\Delta G^\circ$ value for 2-phenyl (*ca.* 1.7 kcal/mol) corresponded closely with that obtained for 2-*p*-chlorophenyl in ref 17.

(19) J. Gelan and M. Anteunis, *Bull. Soc. Chim. Belges*, **77**, 423 (1968).

(20) S. C. Abrahams, *Quart. Rev.* (London), **10**, 414 (1956).

(21) M. Davis and O. Hassel, *Acta Chem. Scand.*, **17**, 1181 (1963).

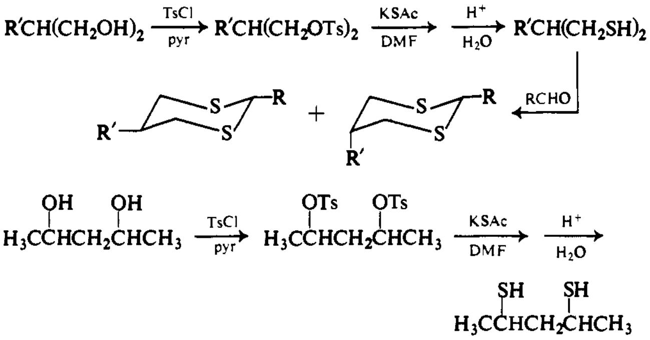
(22) Actually the lone pairs probably do not "occupy" strictly axial positions since the C–S–C angle (100°) suggests that hybridization of the sulfur bonds involves substantial p^3 character leaving one lone pair nearly in an s and the other nearly in a p orbital. The lone p pair would be perpendicular to the plane defined by C_1–S–C_4 thus pointing into the ring somewhat instead of having a typical axial direction (i).



i

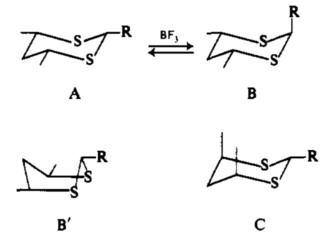
by acid-catalyzed condensation of substituted 1,3-propanedithiols with appropriate aldehydes. In most cases the required dithiols were synthesized from the corresponding diols by conversion to the ditosylates followed by displacement with thioacetate anion and hydrolysis (Scheme III). Isomers were separated by fractional crystallization and/or preparative glpc (see Experimental Section). Equilibration of the isomers was performed in chloroform solution using a catalytic amount of boron trifluoride etherate; in each case equilibrium was approached from both sides by using appropriate *cis*-rich and *trans*-rich mixtures. Equilibrated samples were analyzed by glpc to obtain equilibrium constants and from them, free-energy differences between isomers.

Scheme III



2-Alkyl Series. In order to investigate conformational preferences by the direct equilibrium method, models must be chosen which bias the compounds in such a way that essentially only one conformation exists for each isomer. In cyclohexyl compounds this criterion is met most satisfactorily in compounds having a *t*-butyl group located in position 4 with respect to the particular group studied; the bulky *t*-butyl group ($-\Delta G° > 4.9$ kcal/mol[23]) ensures conformational homogeneity and its distance from the substituent studied causes a minimum of disturbing steric and/or polar effects. The situation in 1,3-dithianes is different, however, in that $-\Delta G°$ for 5-*t*-butyl (located 1,4 to the 2-alkyl) may be substantially lower than 4.9 kcal/mol ($-\Delta G°_{5\text{-}t\text{-Bu}}$ in 1,3-dioxane is 1.4 kcal/mol[13a]) and thus biasing of isomers is not assured. We chose, therefore, to employ *cis*-4,6-dimethyl-2-alkyl-1,3-dithianes (Table I, structures A and B) since it appeared highly unlikely that conformation C with *syn*-axial methyls would be populated to a significant extent (except perhaps when R = *t*-butyl).[24]

Table I. Equilibria in 2-Alkyl-4,6-dimethyl-1,3-dithianes



R	*k*	$-\Delta G°$ kcal/mol[c] (69°)	*cis-cis*	*trans-trans*
CH_3	13.55[a]	1.77 ± 0.01	I	II
C_2H_5	9.61[b]	1.54 ± 0.01	III	IV
$(CH_3)_2CH$	17.71[a]	1.95 ± 0.02	V	VI
$(CH_3)_3C$	55.15[b]	2.72 ± 0.02	VII	VIII

[a] Corrected for the response ratio of isomers. [b] Not corrected, response ratio assumed to be unity. [c] Error is standard deviation.

Results obtained by equilibration of 2-alkyl-4,6-dimethyl-1,3-dithianes are presented in Table I. Interestingly, axial–equatorial free-energy differences ($-\Delta G°$) for 2-methyl (1.77 kcal/mol), 2-ethyl (1.54 kcal/mol), and 2-isopropyl (1.95 kcal/mol) were found to be of nearly the same magnitude as values observed[5] and calculated[8,25] for the corresponding substituents in cyclohexane (methyl, 1.7 kcal/mol; ethyl, 1.75 kcal/mol; and isopropyl, 2.15 kcal/mol);[26] the 2-methyl value is much smaller than that found in 1,3-dioxane (*ca.* 4 kcal/mol).[13a,14] The 2-*t*-butyl value (2.72 kcal/mol) appears anomalously low compared to that in cyclohexane (>4.9 kcal/mol;[23] calculated 5.4 kcal/mol[8b]) and will be discussed later.

The nmr spectra of the above compounds are consistent with the configurational and conformational assignments (Table II). Pertinent observations include the following. (1) The coupling constants between protons at positions 4, 5, and 6 (J_{AN} and J_{AM}) of the *cis-cis* and *trans-trans* isomers are, in all examples, consistent only with the assignment of axial $H_{4,6}$ ($J_{AN} =$ *ca.* 11–12 cps; $J_{AM} =$ *ca.* 2.3–3.4 cps) and therefore rule out conformations with *syn*-axial methyls at position 4 and 6 (*i.e.*, conformation C). This conclusion is supported by the nearly equivalent chemical shifts of the 4- and 6-methyl groups (71.5–76.5 cps) in all *cis-cis* and *trans-trans* isomers (and in *cis*-2-*t*-butyl-4-methyl-1,3-dithiane, XIII). In the *trans-cis* isomers, the axial 4-methyl groups

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[23] (a) N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **82**, 2393 (1960). (b) The minimum value of 4.9 kcal/mol at 25° is obtained from the data in ref 23a ($\Delta H° = 5.9$ kcal/mol, $\Delta S° = 4.9$ cal/deg mol) by offsetting the measured entropy difference between *cis*- and *trans*-1,3-di-*t*-butylcyclohexane by the trivial entropy of mixing of $R \ln 2 =$ 1.4 cal/deg mol expected from the fact that the *cis* isomer is *meso* and the *trans dl*. Thus $\Delta G°_{cor} = 5.9 - ((3.5 \times 298)/1000) = 4.9$ kcal/mol; since the *trans* isomer exists mainly in the twist form and only to a minor extent as a chair with axial *t*-butyl (ref 8b), the free energy of the axial *t*-butyl must be *more than* 4.9 kcal/mol above that of equatorial *t*-butyl. See also B. J. Armitage, G. W. Kenner, and M. J. T. Robinson, *Tetrahedron*, **20**, 747 (1964), especially p 763.

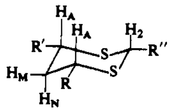
[24] (a) In cyclohexane the *syn*-axial methyl–methyl interaction is 3.7 kcal/mol and the total energy of the diaxial form of 1,3-dimethylcyclohexane above that of the diequatorial form is 3.7 + 1.7 = 5.4 kcal/mol. In 1,3-dioxane the value for $Me_{4\text{-ax}}$–$Me_{6\text{-ax}}$ is not known, but the $Me_{2\text{-ax}}$–$Me_{4\text{-ax}}$ interaction has recently been calculated (from thermochemical data) to be *ca.* 8.9 kcal/mol (total energy *ca.* 11.96 kcal/mol) (ref 24b). As will be seen later, axial interactions in 1,3-dithianes are generally similar to those in cyclohexane. In any case, the presence of significant amounts of conformation C should be evident from the $H_{4\text{-}5}$ coupling constants. (b) K. Pihlaja, *Acta Chem. Scand.*, **22**, 716 (1968)

[25] (a) N. L. Allinger and S. E. Hu, *J. Amer. Chem. Soc.*, **84**, 370 (1962); (b) N. L. Allinger and S. E. Hu, *J. Org. Chem.*, **27**, 3417 (1962).

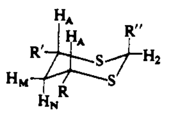
[26] Actually, the $-\Delta G°$ values found for groups in cyclohexane vary to a slight extent with the number and positions of other substituents on the ring. This is mainly due to slight ring distortions which affect enthalpy differences and/or to entropy of mixing or symmetry differences between isomers (ref 8a). More accurately, then, the 2-alkyl-4,6-dimethyl-1,3-dithiane values should be compared to corresponding values obtained for similarly substituted cyclohexanes. The enthalpy difference, $-\Delta H°$, between the 1,3,5-trimethylcyclohexanes is 2.11 kcal/mol,[27] slightly greater than the 1,3-dithiane value (1.77 kcal/mol). In this case comparison is made with $-\Delta H°$ since *cis,cis*-1,3,5-trimethylcyclohexane has a symmetry number of 3 ($\Delta S = 2.3$ cal/deg mol) while the corresponding dithianes are not symmetrical. Unfortunately, the values for ethyl and isopropyl are not known for trisubstituted cyclohexanes but are probably also slightly larger than those quoted above. For 1,3-disubstituted cyclohexanes, E. L. Eliel and T. J. Brett, *J. Amer. Chem. Soc.*, **87**, 5039 (1965), report Me, 1.75 kcal/mol; Et, 1.86 kcal/mol; *i*-Pr, 2.30 kcal/mol.

[27] C. J. Egan and W. C. Buss, *J. Phys. Chem.*, **63**, 1887 (1959).

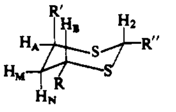
Table II. Chemical Shift and Coupling Constant Data for 2-Alkyl-4-methyl- and 2-Alkyl-4,6-dimethyl-1,3-dithianes



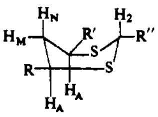
A, R = R′ = CH$_3$
4-*cis*-6-*cis*
E, R = H, R′ = CH$_3$
4-*cis*



B, R = R′ = CH$_3$
4-*trans*-6-*trans*
F, R = H, R′ = CH$_3$
4-*trans*



D, R = R′ = CH$_3$
4-*cis*-6-*trans*
G, R = H, R′ = CH$_3$
4-*trans*



B′, R = R′ = CH$_3$

Formula	R	R′	R″	$J_{H_4H_5}$		$-\nu_{CH_{3_{4,6}}}$	$-\nu_{H_2}$
				J_{AN}(4-a)	J_{AM}(4-e)		
			4-*cis*-6-*cis* Isomers (A)				
I	CH$_3$	CH$_3$	CH$_3$	11.3	2.3	74.8	248.0
III	CH$_3$	CH$_3$	C$_2$H$_5$	12.0	2.5	74.9	242.1
V	CH$_3$	CH$_3$	(CH$_3$)$_2$CH	11.2	2.6	76.6	243.5
VII	CH$_3$	CH$_3$	(CH$_3$)$_3$C	11.2^a (11.6)^b	2.4^a (2.3)^b	75.8	238.8
			4-*trans*-6-*trans* Isomers (B)				
II	CH$_3$	CH$_3$	CH$_3$	11.0	2.5	73.5	241.1
IV	CH$_3$	CH$_3$	C$_2$H$_5$	11.2	2.5	72.7	213.0
VI	CH$_3$	CH$_3$	(CH$_3$)$_2$CH	*Ca.* 11	*Ca.* 2.5	71.5	199.7
VIII	CH$_3$	CH$_3$	(CH$_3$)$_3$C	*Ca.* 11.2^a	*Ca.* 3.4^a	74.4	223.9
			4-*cis*-6-*trans* Isomers (D)				
IX	CH$_3$	CH$_3$	CH$_3$			72.3 (equatorial) 84.2 (axial)	263.0
X	CH$_3$	CH$_3$	C$_2$H$_5$			72.0 (equatorial) 88.2 (axial)	255.0
XI	CH$_3$	CH$_3$	(CH$_3$)$_2$CH			72.7 (equatorial) 87.8 (axial)	256.9
XII	CH$_3$	CH$_3$	(CH$_3$)$_3$C			72.3 (equatorial) 86.8 (axial)	253.3
			4-*cis* Isomers (E)				
XIII	CH$_3$	H	(CH$_3$)$_3$C			73.7	239.0
XV	CH$_3$	H	(CH$_3$)$_2$CH			73.9	244.5
XVII	CH$_3$	H	C$_2$H$_5$			73.9	243.8
XIX	CH$_3$	H	CH$_3$			73.3	249.0
			4-*trans* Isomers (F $\rightleftharpoons$ G)				
XIV	CH$_3$	H	(CH$_3$)$_3$C			86.2	246.5
XVI	CH$_3$	H	(CH$_3$)$_2$CH			81.5	230.4
XVIII	CH$_3$	H	C$_2$H$_5$			78.0	227.8
XX	CH$_3$	H	CH$_3$			82.4	250.5

[a] These J values along with the appropriate chemical shift data were used as computer input data to simulate the nmr spectra; the resulting plots were in very good agreement with the observed spectra. [b] Values from ref 19, determined by computer analysis.

appear at substantially lower field (84.2–88.2 cps). (2) The chemical shift difference observed for the 2-protons in any isomer pair suggest that they have different environments in the *cis-cis* and *trans-trans* isomers (*i.e.*, equatorial for *trans-trans*, axial for *cis-cis*). (3) In contrast to the situation in cyclohexanes, axial substituents attached to the ring, *e.g.*, H or CH$_3$ at position 2 (Tables II and III) and CH$_3$ at position 4 display shifts to lower field compared with their equatorial counterparts; this reversal has been observed previously[17] and attributed to deshielding of the axial group by the sulfur electron pairs.

The equilibration and nmr data for the 2-*t*-butyl-4,6-dimethyl isomers VII and VIII warrant further discussion. For VIII to exist in a chair conformation, either the 2-*t*-butyl or the 4,6-dimethyl groups must assume axial orientations; the other alternative is for the molecule to escape into a boat form. In view of the similarity between $-\Delta G°$ values of other 2 substituents in 1,3-dithiane and in cyclohexane, the observed value in the *t*-butyl case (2.72 kcal/mol) appears too small to accommodate either two *syn*-axial methyl groups (total interaction 5.4 kcal/mol in cyclohexane[24]) or an axial 2-*t*-butyl group (>4.9 kcal/mol in cyclohexane[23]). In addition, as previously discussed, the nmr spectra for VII and VIII are quite similar and incompatible with the assignment of axial 4 and 6 methyls in VIII. The evidence, therefore, appears to favor a boat conformation for the *trans-trans* compound VIII and, if so, the $-\Delta G°$ measured represents the free-energy difference between the chair and boat conformations in this particular example. Normally, the presence of a chair–boat equilibrium is reflected in a large entropy difference, $\Delta S°$, due to the increased flexibility of boat forms over chairs;[28] this can be determined through studies of equilibrium

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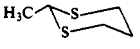
(28) Allinger and Freiberg[23a] have investigated the equilibrium constant of the 1,3-di-*t*-butylcyclohexanes as a function of temperature. From the high enthalpy and entropy differences, ($-\Delta H° = 5.6$ kcal/mol; $\Delta S = 4.9$ cal/deg mol) they concluded that the *trans* isomer exists as a flexible boat. If the *trans* isomer exists in the chair with an axial *t*-butyl, $-\Delta S°$ should be only about 1.4 cal/deg mol (the *trans* isomer is a *dl* pair). It may be noted that in this case the excess entropy of the boat form due to flexibility, is ~3.5 cal/deg mol. More recently, Allinger and coworkers[8b] have concluded from ir data that *trans*-1,3-di-*t*-butylcyclohexane actually is a mixture of chair– and twist–boat forms with the latter predominating.

Table III. Chemical Shifts of Axial and Equatorial 2-Methyl Groups in 1,3-Dithianes



XXI

	$\nu_{CH_3\text{-}2}$ (cps)		
Compd	Axial		Equatorial
I			89.4
II	111.4		
IX			89.7
XIX			89.0
XX		98.5[a]	
XXI			87.9

[a] Average shift.

as a function of temperature. Unfortunately, we have not been able as yet to complete such a study for compounds VII and VIII because of experimental difficulties and thus $-\Delta H°$ and $-\Delta S°$ remain unknown. However, there is some question as to whether such studies would be conclusive anyway since a large entropy of a boat introduced by high flexibility should also be accompanied by an averaging of the coupling constants between $H_{4,6}$ and H_5[29,30] (due to pseudorotation of the ring); this certainly does not occur, for J_{AN} (11.2 cps) and J_{AM} (3.4 cps) are quite different and indicative of a more rigid environment. This finding is compatible with a boat conformation for VIII only if it is more like a classical or "stiff" boat made rigid by steric requirements of the substituents. Indeed, an examination of a model shows that only one boat form (corresponding to B′, Table I) is free from serious alkyl–ring interactions. If it is true that VIII exists as a relatively nonflexible boat, then $\Delta S°$ is also probably much less than the *ca.* 3.5 eu expected by analogy with cyclohexane and the equilibrium *vs.* temperature study would not be conclusive. The question of chair–boat equilibria in 1,3-dithianes will be further discussed later.

The conclusion that $-\Delta G°$ values for 2-alkyl-1,3-dithianes are of the same magnitude as in cyclohexane is consistent with the similar ring-inversion barriers found for 2,2-dimethyl- and 5,5-dimethyl-1,3-dithiane, 1,3-dithiane, and cyclohexane, suggesting that no substantial ground-state compression exists.[16] Contrasted to this is the observation that the inversion barrier in 2,2-dimethyl-1,3-dioxane is considerably lower than the values for other 1,3-dioxanes[16,31] owing to ground-state compression introduced by an axial 2-methyl group; this is reflected in the large $-\Delta G°$ for this substituent (*ca.* 3.6–4.1 kcal/mol[13a,14]).

4-Alkyl Series. Various isomeric 2-alkyl-4-methyl-1,3-dithianes were prepared from 1,3-butanedithiol and appropriate aldehydes. As before, equilibration was effected by boron trifluoride in chloroform solution; the results are presented in Table IV. The $-\Delta G°$ value obtained for the 2-*t*-butyl-4-methyl isomers (XIII and XIV, 1.69 kcal/mol) indicates that the predominant conformation for XIV is that in which the 4-methyl group is axial (Table IV, G) and therefore the observed free-energy difference closely represents the conformational energy for a 4-methyl group in 1,3-dithiane. Clearly, conformation F (Table II) cannot contribute substantially since $-\Delta G°$ for the 2-*t*-butyl group is at least 2.7 kcal/mol. The nmr data for XIV support the assignment of conformation E (Table II). The chemical shift of the 4-methyl substituent (86.2 cps) is in the range observed for axial 4-methyl groups (84.2–88.2 cps; compounds IX–XII, Table II), whereas equatorial 4-methyl groups are found at somewhat higher field (71.5–76.6 cps, the signal of the equatorial 4-methyl group in XIII occurs at 73.7 cps).

The *trans* isomers of 2-methyl-, 2-ethyl-, and 2-isopropyl-4-methyl-1,3-dithianes (XX, XVIII, and XVI) should exist as mixtures of conformers G and F (Table II) and the resulting entropies of mixing are reflected in the lower $-\Delta G°$ values observed. Indeed, using the $-\Delta G°$ values measured for 4-methyl (1.69 kcal/mol), 2-methyl (1.77 kcal/mol), 2-ethyl (1.54 kcal/mol), and 2-isopropyl (1.95 kcal/mol) along with the appropriate entropy-of-mixing terms, the free-energy differences for 2,4-dimethyl-, 2-ethyl-4-methyl-, and 2-isopropyl-4-methyl-1,3-dithianes were calculated and found to agree well with measured values (see Table IV); this agreement shows that the $\Delta G°$ values in the 2-alkyl and 4-alkyl series are consistent and additive.

The nmr spectral data for the *trans* isomers XVI, XVIII, and XX are also indicative of conformational nonhomogeneity in that the chemical shifts of the 4-methyl groups for all three occur in a range intermediate between the normal shifts of axial and of equatorial 4-methyl substituents. Using 73.7 cps for the chemical shift of an equatorial 4-methyl group in XVI (the value from the *cis* isomer XV) and 86.2 cps for an axial 4-methyl group (the value from XIV), K_{equil} for conformations G and F is computed to be *ca.* 1.62 which corresponds to a free-energy difference between 2-isopropyl and 4-methyl of about 0.30 kcal/mol, in good agreement with the observed value of 0.26 (1.95–1.69) kcal/mol. A similar estimate for 2-ethyl *vs.* 4-methyl leads to a free-energy difference of −0.38 kcal/mol, in less good agreement with experiment (−0.15 kcal/mol); for 2-methyl *vs.* 4-methyl, the correspondence is even less good (*ca.* 0.55 calculated, 0.08 kcal/mol measured).[32]

Gelan and Anteunis[19] have investigated the relative populations of conformations H and I in *trans*-4,6-dimethyl-1,3-oxathiane (Scheme IV) by nmr and conclude

Scheme IV

H I

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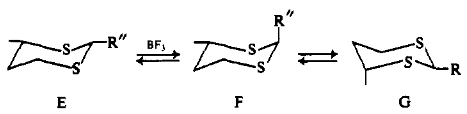
(29) H. Feltkamp, N. C. Franklin, M. Hanack, and K.-W. Heinz, *Tetrahedron Letters*, 3535 (1964).

(30) H. Booth and G. C. Gidley, *ibid.*, 1449 (1964).

(31) J. E. Anderson and J. C. D. Brand, *Trans. Faraday Soc.*, **62**, 39 (1966).

(32) However, if the nmr chemical shifts of 2-methyl groups (Table II) are used to compute k_{equil} and $\Delta\Delta G_{2\text{-Me}-4\text{-Me}}$ (111.4 cps for axial 2-methyl, 89.4 cps for equatorial methyl, and 98.6 cps found for XX), the value computed (0.21 kcal/mol) is much closer to that found (0.08 kcal/mol). It must be kept in mind that calculations of this type using chemical shifts obtained from differing models can at best be approximative, since the underlying assumption of constancy of chemical shift for corresponding groups in different compounds is not strictly valid, *cf.* E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, **90**, 682 (1968).

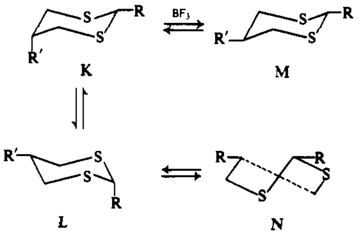
Table IV. Equilibria in 2-Alkyl-4-methyl-1,3-dithianes



R''	K^a	$-\Delta G°$, kcal/mol^b (°C)	$-\Delta G°$ calcd^c	*cis*	*trans*
$(CH_3)_3C$	11.94	1.69 ± 0.01 (69)		XIII	XIV
$(CH_3)_2CH$	11.66	1.45 ± 0.02 (25)	1.40	XV	XVI
C_2H_5	6.98	1.15 ± 0.02 (25)	1.20	XVII	XVIII
CH_3	8.37	1.26 ± 0.02 (25)	1.32	XIX	XX

[a] Corrected for response ratios of the isomers. [b] Error is standard deviation. [c] Calculated using $-\Delta G°$ values obtained from the trisubstituted dithianes (Table I) and from XIII-XIV and including the appropriate entropy of mixing terms.

Table V. Conformational Equilibrium Constants and Free-Energy Differences of 2,5-Dialkyl-1,3-dithianes



trans	*cis*	R	R'	K^a	$-\Delta G°$, kcal/mol^b (°C)
XXII	XXIII	$(CH_3)_3C$	CH_3	4.621	1.04 ± 0.01 (69)
XXIV	XXV	$(CH_3)_3C$	C_2H_5	3.109	0.77 ± 0.02 (69)
XXVI	XXVII	$(CH_3)_3C$	$(CH_3)_2CH$	3.507	0.85 ± 0.01 (69)
XXVIII	XXIX	$(CH_3)_3C$	$(CH_3)_3C$	22.67	1.85 ± 0.01 (25)
XXX	XXXI	$(CH_3)_2CH$	$(CH_3)_3C$	15.27	1.61 ± 0.01 (25)
XXXII	XXXIII	Phenyl	$(CH_3)_3C$	26.43	1.94 ± 0.02 (25)
XXXIV	XXXV	$(CH_3)_2CH$	$(CH_3)_2CH$	3.157	0.78 ± 0.01 (69)

[a] Corrected for response ratio of the isomers. [b] Error is standard deviation.

that H predominates to the extent of about 85%. The free-energy difference thus calculated (1.1 kcal/mol) agrees well with the value expected (1.2 kcal/mol) if the $-\Delta G°$ values for the methyl groups adjacent to O and adjacent to S are taken to be equal to the values found in 1,3-dioxane[13a] (2.9 kcal/mol) and 1,3-dithiane (1.69 kcal/mol) and conformational energies are assumed to be additive.

In summary, then, it appears that conformational energies of substituents at positions 2 and 4 of 1,3-dithiane (with the possible exception of 2-*t*-butyl), are similar to but slightly less than the corresponding values in cyclohexane. In order to rationalize this finding, a modified Dreiding model was constructed with the dimensions provided by X-ray analysis of 2-phenyl-1,3-dithiane.[15] The long C–S bonds (1.81 Å) and large C–C–C, C–C–S, and S–C–S angles (*ca.* 116°) produce a flattening of the dithiane ring which, however, is at least partially compensated for by the small (100°) C–S–C angles. As a result, the geometry of the ring is such that the *syn*-axial distances are only slightly greater than the corresponding distances in cyclohexane; thus, for 2-methyl-1,3-dithiane, the distance between the closest methyl hydrogen and the axial 4-hydrogen was measured in the model to be about the same as in methylcyclohexane.[33] This is at least semiquantitatively consistent with the experimental results.

5-Alkyl Series. In 5-substituted 1,3-dithianes, the situation is different from that in cyclohexane and that in the 2- and 4-substituted 1,3-dithianes in that no *syn*-axial hydrogens encumber an axial 5-alkyl group. In analogy with what has been found in 5-substituted 1,3-dioxanes[13] one might expect a resulting decrease in $-\Delta G°$ values if the steric requirement of S (with its axial electron pair) is less than that of CH.[34]

To bias the ring conformationally in the 5-alkyl series,

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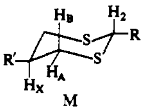
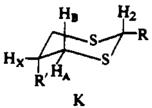
(33) We had planned to calculate the distance in question using the equations given by Hendrickson[7b] but in the attempt found that they are extremely sensitive to the exact bond and torsional angles (which are not precisely known). The numerical findings (which suggest that the distance is *shorter* in dithiane than in cyclohexane) are therefore probably not quantitatively significant.

(34) We are avoiding, in this paper, use of such terms as "size" or "steric requirement" in connection with electron pairs. Allinger and Tai[12a] have argued on theoretical grounds that the presence of an electron pair should in no way affect the bulk of a given atom and that considerations of interactions with the atom need not be concerned with the pair at all. In the present situation, we deal with the difference in repulsive van der Waals' interactions of an axial 5-alkyl substituent with the 3 carbon atom bearing an axial hydrogen as opposed to the corresponding interaction with a heteroatom (X, bearing unshared electron pairs) in the 3 position of the ring. Everything else being equal (and neglecting the electron pair), one would then predict that if X and C are of similar sizes, the interaction with X should be less than with CH and an axial 5-alkyl group would be more favored in the heterocyclic than in the carbocyclic compound. However, if the van der Waals' radius of X is large, the possibility exists that the alkyl–X repulsive interaction may be larger than the sum of alkyl–C and alkyl–*syn*-axial-H interactions in which case the axial orientation of the 5-alkyl group would be less favored in the heterocyclic ring. These effects may or may not have anything to do with a separate "space requirement" of the lone pair of electrons residing on X.

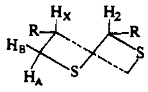
Table VI. Chemical Shift and Coupling Constant Data for 2,5-Dialkyl-1,3-dithianes



M
trans



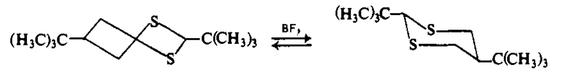
K
cis



N

Formula	R	R′	$J_{H_4H_5}$		$-\nu_{H_2}$	$-\nu_{2\text{-}t\text{-Bu}}$	$-\nu_{5\text{-}t\text{-Bu}}$
			J_{AX}	J_{BX}			
			trans Isomers (M)				
XXII	$(CH_3)_3C$	CH_3	4.0	9.2	234.7	67.8	
XXIV	$(CH_3)_3C$	C_2H_5	3.5	9.8	236.5	68.1	
XXVI	$(CH_3)_3C$	$(CH_3)_2CH$	4.2	9.8	235.9	68.2	
XXVIII	$(CH_3)_3C$	$(CH_3)_3C$	3.5	9.8	236.1	67.9	54.6
XXX	$(CH_3)_2CH$	$(CH_3)_3C$	*Ca.* 4	*Ca.* 10	240.1		55.5
XXXIV	$(CH_3)_2CH$	$(CH_3)_2CH$	. . .	. . .	239.0		
XXXII	Phenyl	$(CH_3)_3C$	. . .	. . .	309.5		54.6
			cis Isomers (K, L, or N)				
XXIII	$(CH_3)_3C$	CH_3	3.2	4.2	234.9	67.7	
XXV	$(CH_3)_3C$	C_2H_5	3.1	3.5	237.4	67.0	
XXVII	$(CH_3)_3C$	$(CH_3)_2CH$	Doublet; $(J_{AX} + J_{BX})/2 = 3.88$		239.4	66.6	
XXIX	$(CH_3)_3C$	$(CH_3)_3C$	Doublet; $(J_{AX} + J_{BX})/2 = 7.3$		236.2	65.0	55.0
XXXI	$(CH_3)_2CH$	$(CH_3)_3C$	. . .	. . .	201.6		55.3
XXXV	$(CH_3)_2CH$	$(CH_3)_2CH$	Doublet; $(J_{AX} + J_{BX})/2 = 4.24$		236.6		56.0
XXXIII	Phenyl	$(CH_3)_3C$	Doublet; $(J_{AX} + J_{BX})/2 = 6.86$		296.9		58.9
			2-Alkyl				
XXXVI	$(CH_3)_3C$	H			240.3	67.8	

Table VII. Equilibrium Data for 2,5-Di-*t*-butyl-1,3-dithiane as a Function of Temperature



Temp, °C	K^a	$-\Delta G°$, kcal/mol	$-\Delta H°$, kcal/mol^b	$-\Delta S$, cal/(deg mol)^b
25	22.10 ± 0.82	1.82 ± 0.02		
45	15.31 ± 0.29	1.72 ± 0.01		
69	10.51 ± 0.27	1.60 ± 0.02		
100	6.91 ± 0.22	1.43 ± 0.02	3.42 ± 0.01	5.33 ± 0.01

[a] Equilibrium constants are corrected for the response ratio of the isomers. [b] The errors given for $-\Delta H°$ and $-\Delta S°$ represent the statistical errors of the plot (determined by a computer) and are undoubtedly low since the errors in K_{eq} are not included.

a 2-*t*-butyl group seemed suitable because of its relatively large $-\Delta G$ value at this position, and since it had apparently served adequately as a "holding" group in the determination of the conformational energy of a 4-methyl group. Accordingly, appropriate 2-*t*-butyl-5-alkyl-1,3-dithiane isomers were prepared and equilibrated in the manner already described. In addition, several other isomeric pairs of 2,5-dialkyl-1,3-dithianes not having a *t*-butyl group at position 2 were studied. The pertinent equilibrium constants and conformational energy values are listed in Table V. It may readily be seen that in fact the $-\Delta G°$ values for 5-methyl, ethyl, and isopropyl (as well as *t*-butyl, but this appears to be a special case as discussed below) are substantially smaller than the corresponding values in cyclohexane or those at the 2 and 4 positions in 1,3-dithianes. Quantitatively, the observed values are (cyclohexane values[5] in parentheses): methyl, 1.04 (1.70); ethyl, 0.77 (1.75); isopropyl, 0.85 (2.15); *t*-butyl, 1.85 (>4.9). These values are quite similar to those found in 1,3-dioxanes[13] (5-Me, 0.80–0.97; 5-Et, 0.67–0.73; 5-*i*-Pr, 0.98; 5-*t*-Bu, 1.36–1.46) and are most readily explained on the assumption that sulfur, with an axial electron pair, has less space requirement than does methylene.[34]

In order to confirm the configurational assignments, the nmr spectra of the isomers were recorded (Table VI). The following points are of particular interest. (1) The chemical shifts of the 2-protons in all the 2-*t*-butyl-5-alkyl compounds are nearly equal (*i.e.*, <5 cps difference) suggesting that all the *t*-butyl groups at the 2 position have similar environments. This is consistent with the 2-*t*-butyl group remaining equatorial in all the compounds. (2) The $H_{4,5}$ coupling constants for the majority of the *cis* isomers (except XXIX, XXXIII, and possibly XXXI) are small, being in the approximate range $J_{ee} = 3.1$–3.2, $J_{ae} = 3.5$–4.2 cps where measurable. This is consistent only with the assignment of axial orientations to the substituents at positions 5.[35] The AB protons at position 4 in the *cis*-2-*t*-butyl-5-isopropyl compound (XXVII) were observed as a "deceptively simple" doublet, a situation which occurs when $\delta_{AB} \cong 0$ and the quantity $(J_{AX} - J_{BX})$ also approaches zero.[36] In such cases, the separation obtained is equal

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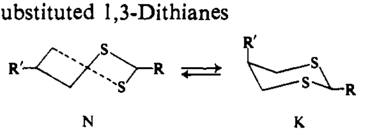
(35) Actually, as will be discussed later, the *cis*-2,5-dialkyl isomers contain about 15–20% flexible boat conformations so that the observed coupling constants are averages containing small contributions from the *J* values of the boats. However, this does not affect the argument that the predominant chair conformations have axial 5-alkyl groups.

to the average of the coupling constants (*i.e.*, $(J_{AX} + J_{BX})/2$) and therefore the small value observed (3.88 cps) is compatible only with relatively small values of both J_{AX} and J_{BX} (*i.e.*, *ca.* 3–4 cps); this once again indicates that H_5 in XXVII is equatorial and therefore the 5-isopropyl group is axial. A similar result is obtained for *cis*-2,5-diisopropyl-1,3-dithiane (XXXV). In this case, there is probably a small contribution from the other *cis* conformation (with 5-isopropyl equatorial) so that the average coupling observed is raised somewhat (to 4.24 cps) by contribution of a large (J_{aa}) coupling constant (see also ref 35). (3) The *cis*-2,5-di-*t*-butyl isomer appears to require special consideration. Again, the 4,6-proton region was observed as a "deceptively simple" doublet. However, the relatively large separation ($(J_{AX} + J_{BX})/2 = 7.3$ cps) demonstrates that at least one of the coupling constants is large; this is not consistent with a chair conformation in which proton 5 is equatorial (conformation K, Table V). The other possible chair conformation, corresponding to L in Table V, also seems to be ruled out since, in it, an axial *t*-butyl group would be placed at position 2, but the $-\Delta G°$ value observed (1.85 kcal/mol) is too small to accommodate axial *t*-butyl at this position ($-\Delta G°_{2\text{-}t\text{-Bu}} \geqslant 2.7$ kcal/mol). The observed average coupling is satisfactorily explained by a flexible boat conformation (N, Table V) in which the quantity $(J_{AX} + J_{BX})/2$ should be about 5–8 cps;[30] in such conformations the coupling constants (and chemical shifts) are averaged by pseudorotation of the ring so that J_{AX} approaches J_{BX} and $\nu_A \sim \nu_B$.[30] An examination of a model does in fact suggest that a 2,5-disubstituted dithiane boat is free to pseudorotate through several twist-boat forms without serious interactions involving the substituents; a similar conclusion was previously reached by Booth and Gidley[30] in a consideration of the twist-boat conformations of *cis*-4-*t*-butyl-1-phthalimidocyclohexane. In order to obtain additional support that the *cis* isomer XXIX exists in the twist-boat conformation, we have studied the equilibrium between XXVIII and XXIX as a function of temperature, since the increased flexibility of the twist-boat should be accompanied by a substantial increase in the entropy of the *cis* isomer. The results of this study (XXIX $\rightleftharpoons$ XXVIII) at four temperatures are shown in Table VII. A least-squares plot of log k_{equil} *vs.* $1/T$ gave the values, $-\Delta H° = 3.42 \pm 0.01$ kcal/mol and $-\Delta S° = 5.3 \pm 0.01$ cal/deg mol. The large entropy advantage of XXIX provides compelling evidence that this compound is indeed in the twist-boat conformation; the entropy difference found is similar to that in cyclohexane ($-\Delta S°_{c-b} = 3.5 \pm 1$ cal/deg mol)[23a,28] and in 1,3-dioxane ($-\Delta S_{c-b} = 3.9 \pm 0.5$ cal/deg mol).[24b] The chair–boat enthalpy difference (3.42 kcal/mol) is interesting, being appreciably lower than the values found for cyclohexane (*ca.* 4.7[37]–5.9[23a] kcal/mol) and 1,3-dioxane (6.8 ± 0.7 kcal/mol);[24b] this indicates that 1,3-dithiane can adopt the twist-boat conformation much more readily than either cyclohexane or 1,3-dioxane.

Table VIII. Temperature Variance of Coupling Constants for *cis*-2,5-Disubstituted 1,3-Dithianes



XXVII, R = *t*-butyl, R′ = isopropyl
XXXV, R = R′ = isopropyl

Temp, °C	J_{obsd}	k_{eq}[a]	k_{eq} calcd[b]
		XXII	
−100	6.26	139	
−81.5	6.46	31.3	
−48.5	6.76	14.0	23.3
−37.5	6.88	11.4	
−2	7.24	7.08	
41	7.76	4.39	4.37
59	8.08	3.47	
77	8.52	2.62	
102	8.80	2.23	
123	9.12	1.88	
152	9.64	1.44	1.47
		XXXV	
−95	6.28	104.0	
−81.5	6.52	25.3	
−67.5	6.80	13.0	
−48.5	7.16	7.75	
−37.5	7.20	7.40	
−2	7.80	4.25	
41	8.48	2.68	
59	8.72	2.33	
77	9.00	2.00	
102	9.16	1.84	
130	9.60	1.47	
152	9.80	1.33	
169	9.96	1.23	

[a] Equation ii, $(J_{AX} + J_{BX})_N = 14.60$ cps, $(J_{AX} + J_{BX})_K = 6.20$ cps. [b] Equation i, $\Delta H_{c-b} = 3.42$ kcal/mol, $-\Delta S_{c-b} = 5.33$ cal/deg mol. $-\Delta G_{5\text{-}i\text{-Pr}} = 0.85$ kcal/mol.

The relatively low chair–boat energy difference found for 2,5-di-*t*-butyl-1,3-dithiane ($-\Delta G°_{25} = 1.82$ and $-\Delta G°_{100} = 1.43$ kcal/mol) suggested the likelihood that other *cis*-2,5-dialkyl-1,3-dithianes would exist as equilibrium mixtures of chair and twist-boat forms (Table VIII, conformations K and N) and, furthermore, that the relative population of the two conformations should be temperature dependent. At low temperatures conformation K should predominate, but as the temperature is raised, the large entropy of the twist-boat should make itself felt leading to an increase in the contribution of N. The equilibrium constant K for the process is approximately given by the relationship

$$K = N_K/N_N = e^{-\Delta\Delta G_{K-N}/RT} \qquad \text{(i)}$$

where N_K and N_N are the mole fractions of conformations K and N and $\Delta\Delta G_{K-N} = \Delta G_K - \Delta G_N = \Delta G_K - (\Delta H°_{c-b} - T\Delta S°_{c-b})$ ΔG_K being the conformational energy of the R′ group at position 5 (i).

Thus, for the example of *cis*-5-isopropyl-2-*t*-butyl-1,3-dithiane (XXVII), $-\Delta G°$ for the chair conformation K may be approximated as the conformational energy of 5-isopropyl or 0.85 kcal/mol; likewise, $-\Delta G$ for N will be *ca.* $-\Delta H_{c-b} - T\Delta S_{c-b}$ $(3.42\text{–}5.3T)$. This predicts $k_{K/N}$ to range from *ca.* 156 at −100° to about 1.0 at 209°; above this temperature the twist-boat form predominates. Changes in the relative populations of

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(36) (a) J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. I, Pergamon Press, New York, N. Y., 1965, p 363; (b) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.* **39**, 216 (1961).

(37) H. van Bekkum, M. A. Hoefnagel, L. de Lavieter, A. van Veen P. E. Verkade, A. Wemmers, B. M. Wepster, J. H. Palm, L. Schafer, H. Dekker, C. Mosselman, and G. Somsen, *Rec. Trav. Chim.*, **87**, 1363 (1967).

Table IX. $-\Delta H°$ and $-\Delta S°$ Differences between Chair and Twist-Boat Conformations of Selected *cis*-2,5-Dialkyl-1,3-dithianes[a]

Compd	$-\Delta H°$, kcal/mol[b]	$-\Delta H°$ calcd, kcal/mol[c]	$-\Delta S°$, cal/deg mol[b]	$-\Delta S°$ calcd, cal/deg mol[d]
XXVII	2.37 ± 0.09	2.57	4.79 ± 0.48	5.3
XXXV	2.21 ± 0.17	2.64	4.93 ± 0.65	5.3

[a] Obtained from plot of data from Table VIII. [b] The errors indicated represent the statistical errors of the plots determined by computer and are low since errors in k_{equil} are not included. [c] Calculated for XXVII as $\Delta H_{\mathrm{c\text{-}b}} - (-\Delta H_{5\text{-}i\text{-}\mathrm{P.}}) = 3.42\text{–}0.85$ kcal/mole; for XXXV as $-\Delta H_{\mathrm{c\text{-}b}} - (-\Delta H_{2,5\text{-}dl\text{-}i\text{-}\mathrm{Pr}}) = 3.42\text{–}0.78$ kcal/mole since $\mathrm{XXXV_K}$ contains a small amount of the other chair conformation. [d] Taken as the value found for XXVIII–XXIX (Table VII).

K and N should, of course, be accompanied by a corresponding change in the nmr spectra of the compounds since the $H_{4,5}$ coupling constants for K and N are quite different (*i.e.*, both J_{AX} and J_{BX} for K are small, J_{AX} and J_{BX} for N are averaged and relatively large; see Table VI). The observed $H_{4,5}$ couplings will be weight-average values related to the amount of each conformation according to the equation

$$J_{\mathrm{AX}}(\mathrm{obsd}) = N_{\mathrm{K}}J_{\mathrm{AX}}(\mathrm{K}) + N_{\mathrm{N}}J_{\mathrm{AX}}(\mathrm{N})$$

$$J_{\mathrm{BX}}(\mathrm{obsd}) = N_{\mathrm{K}}J_{\mathrm{BX}}(\mathrm{K}) + N_{\mathrm{N}}J_{\mathrm{BX}}(\mathrm{N})$$

$$N_{\mathrm{K}} + N_{\mathrm{N}} = 1$$

which reduces to

$$k = N_{\mathrm{K}}/N_{\mathrm{N}} = \frac{(J_{\mathrm{AX}} + J_{\mathrm{BX}})_{\mathrm{N}} - (J_{\mathrm{AX}} + J_{\mathrm{BX}})_{\mathrm{obsd}}}{(J_{\mathrm{AX}} + J_{\mathrm{BX}})_{\mathrm{obsd}} - (J_{\mathrm{AX}} + J_{\mathrm{BX}})_{\mathrm{K}}} \qquad \text{(ii)}$$

Thus if $(J_{\mathrm{AX}} + J_{\mathrm{BX}})_{\mathrm{K}}$ and $(J_{\mathrm{AX}} + J_{\mathrm{BX}})_{\mathrm{N}}$ can be evaluated, the equilibrium constant K may be obtained from the observed J values. As discussed previously, the $H_{4,5}$ region of *cis* isomers XXVII and XXXV appear as "deceptively simple" doublets (see Table VI) in which the separation is equal to $(J_{\mathrm{AX}} + J_{\mathrm{BX}})/2$. These compounds, therefore, provide convenient cases to study since the desired sums of coupling constants $(J_{\mathrm{AX}} + J_{\mathrm{BX}})_{\mathrm{obsd}}$ can be obtained directly from the nmr spectra by inspection. Since at −100° the chair conformer K predominates overwhelmingly (*ca.* 99.4%), the observed coupling at this temperature will closely represent $(J_{\mathrm{AX}} + J_{\mathrm{BX}})_{\mathrm{K}}$; the value taken (6.20 cps) is corrected downward slightly from the experimental 6.26 to take into account the small amount of twist-boat present. For the twist-boat conformation N, the value $(J_{\mathrm{AX}}+J_{\mathrm{BX}})_{\mathrm{N}}$ used (*i.e.*, 14.60 cps) was that determined for XXIX since the coupling constants for the nearly identical twist-boats XXIX, XXXI, and XXXV are not expected to differ significantly. The nmr spectra for *cis*-XXVII and *cis*-XXXV were recorded in chloroform solution (or, below −37.5°, in CS_2) over a wide range of temperatures; the observed averaged coupling constants and the resulting k values (eq ii) are recorded in Table VIII. As expected, J_{obsd} increases and therefore k(K/N) decreases as the temperature rises; representative calculated values of k_{equil} (eq i) are also given in Table VIII. Agreement between k_{obsd} and k_{calcd} is quite good. The enthalpy and entropy differences between chair and twist-boat conformations K and N were obtained through plots of $\ln k_{\mathrm{equil}}$ *vs.* $1/T$; these results are presented in Table IX. The agreement with prediction is again very satisfactory and thus provides convincing supporting evidence for the presence of twist-boat conformations in the *cis* isomers of 2,5-disubstituted dithianes.

With the information concerning the 1,3-dithiane chair-boat enthalpy and entropy differences in hand, we are now in a position to consider further the conformation of 4-*trans*,6-*trans*-dimethyl-2-*t*-butyl-1,3-dithiane (VIII). If the reasonable assumption is made that $-\Delta H°_{\mathrm{c-b}}$ is approximately the same for 2,5-di-*t*-butyl- (3.4 kcal/mol) and 2-*t*-butyl-4,6-dimethyldithianes, then the high free-energy difference between VII and VIII (2.7 kcal/mol) precludes the existence of VIII as a flexible boat having a large entropy (~5 eu); as discussed previously, the nmr data are also not in accord with a flexible boat conformation. On the other hand, a relatively nonflexible or "stiff" boat form (low entropy) for VIII is accommodated nicely by both the equilibrium and nmr information; the free-energy difference is lowered relatively little from $-\Delta H°_{\mathrm{c-b}}$ suggesting a small entropy difference between VII and VIII and the $H_{4,5}$ coupling constants of VIII are quite distinct and different, indicating very-little averging of hydrogen orientations (*i.e.*, pseudorotation does not play an important part).[38] If this supposition regarding the conformation of VIII is accepted, the entropy of VIII required to give the observed $-\Delta G°$ value (2.72 kcal/mol) can be estimated as approximately 2 cal/deg mol $(2.72 - \Delta H°_{\mathrm{c-b}}/342)$ — over 3 cal/deg mol less than that of the flexible-boat XXIX as a result of steric constraints in 2,4,6-trisubstituted dithiane boats.

The thermodynamic and nmr data (Tables V and VI) suggest that two other compounds studied, namely *cis*-2-isopropyl- and *cis*-2-phenyl-2-*t*-butyl-1,3-dithiane (XXXI and XXXIII, respectively) exist as mixtures containing substantial or even predominating amounts of twist-boat forms. In XXXI, the conformational energy of 2-isopropyl (1.95 kcal/mol) is high enough to suggest that the twist-boat form should be present to the extent of about 55% at room temperature. Calculation of the expected free-energy difference between XXX and XXXI using $-\Delta H°_{\mathrm{c-b}} = 3.42$ kcal/mol, $\Delta S°_{\mathrm{c-b}} = 5.3$ eu, and the approximation $-\Delta H°_{2\text{-}i\text{-}\mathrm{Pr}} = -\Delta G°_{2\text{-}i\text{-}\mathrm{Pr}}$ (1.95 kcal/mol) gives $-\Delta G° =$ *ca.* 1.57 kcal/mol,[39] in very good agreement with the experimental value (1.61 kcal/mol). Unfortunately the nmr spectrum of XXXI is quite complex and we were unable to extract J values. In the nmr spectrum of XXXIII, the 4,6-proton region appeared as a "deceptively simple" doublet having a separation of 6.86 cps $((J_{\mathrm{AX}} + J_{\mathrm{BX}})/2)$, reminiscent of XXIX and suggestive of a twist-boat conformation for XXXIII. In this case the interpretation is complicated by the fact

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(38) It should be pointed out that the argument against VIII possessing a high entropy does not depend upon the actual conformation. Even if VIII exists in some other form (such as a deformed chair with axial 2-*t*-butyl), the large $-\Delta G°$ value indicates that the boat conformation is low in entropy; otherwise the compound would certainly exist as a flexible boat and the free-energy difference between VII and VIII would be much smaller (*i.e.*, about 1.6 kcal/mol at 69°). Of course, this does not hold if $-\Delta H°_{\mathrm{c-b}}$ (VII–VIII) is much larger than $-\Delta H°_{\mathrm{c-b}}$ (XXVIII–XXIX), but we can see no reason why this should be so.

Table X. Chair–Boat Interconversion

	$\Delta G°_{25}$, kcal/mol	$\Delta H°$, kcal/mol	$\Delta S°$,[b] cal/deg mol	Ref
Cyclohexane	4.9	5.9[a]	3.5	23a, 24
1,3-Dioxane	5.6	6.8	3.9	24b
1,3-Dithiane	1.8	3.4	5.3	This work

[a] Reference 37 reports 4.7 kcal/mol for 1,4-di-*t*-butylcyclohexane; the value in the table is for the 1,3-di-*t*-butyl isomer. [b] The differences in $\Delta S°$ may be artifacts, since in cyclohexane and dioxane 1,3- (or 2,4-) substituted derivatives were studied rather than 1,4- (or 2,5-) substituted ones; as explained later in the text, substituents in positions 3 and 5 increase the stiffness of the boat.

that the other conformation (chair, with equatorial 5-*t*-butyl) can also conceivably give a "deceptively simple" spectrum with the observed separation although this appears unlikely since the requirement that $(J_{AX} - J_{BX})/J_{AB} = 0$ is probably not met. If the conformational energy of 2-phenyl in 1,3-dithiane is close to the value in cyclohexane (*i.e.*, 2–3 kcal/mol[5]), the twist-boat should be the predominant conformation as suggested by the nmr data. A comparison of the thermodynamic parameters of chair–boat transformation in cyclohexane, 1,3-dioxane, and 1,3-dithiane may be of interest and is shown in Table X.

It may be of interest to speculate on the trends in ΔH. The instability of the twist-boat in cyclohexane is due largely to torsional strain (calculated[7a] 5.1 kcal/mol) but to some extent also to nonbonded interactions (calculated 0.6 kcal/mol). In dioxane, the torsional strain might be expected to be about the same as or slightly less than in cyclohexane (compare the barriers in dimethyl ether, 2.72 kcal/mol,[40a] and propane, 3.3 kcal/mol)[40b] but the nonbonded interaction should be more severe because the ring is appreciably tighter, due to the smaller C–O distance compared with C–C. In the dithiane skew boat, on the other hand, the nonbonded interaction might be expected to be slightly less (larger ring!) and the torsional interactions would be expected to be considerably less (compare the propane barrier, 3.3 kcal/mol[40b] with the dimethyl sulfide barrier, 2.13 kcal/mol[40c]) with a resulting over-all drop in ΔH.

Conclusions

The main conclusions reached with respect to the conformational analysis of 1,3-dithianes in this work are as follows. (1) Alkyl substituents other than *t*-butyl in the 2 and 4 positions have conformational energies, $-\Delta G°$, similar to those of corresponding groups in cyclohexane,[41] and considerably smaller than those of similar groups in 1,3-dioxane. (2) Alkyl groups other than *t*-butyl in the 5 position have conformational energies similar to those in 1,3-dioxanes and considerably smaller than corresponding energies in cyclohexane. (3) $\Delta H°$ for the chair–boat interconversion in 1,3-dithiane is considerably smaller (3.4 kcal/mol) than the corresponding value in cyclohexane (5.9 kcal/mol) or 1,3-dioxane (6.8 kcal/mol). As a result, *cis*-2,5-di-*t*-butyl-1,3-dithiane exists largely as a twist-boat form and the twist-boat conformation contributes appreciably at elevated temperatures in the case of other *cis*-2,5-dialkyl-1,3-thianes. 2-*t*-Butyl-*trans*-4,*trans*-6-dimethyl-1,3-dithiane appears to exist as a relatively stiff boat.

The observed conformations are interpreted in terms of ring size (1–3), steric requirements of S (plus electron pairs) compared with CH_2 or O (plus electron pairs) (2), and the torsional barriers of C–S as compared with C–C and C–O bonds (3).

Experimental Section

Nmr spectra were recorded by Mr. Donald Schifferl or Mrs. Robert Hutchins on a Varian A-60A instrument as 15–25% solutions in deuteriochloroform; chemical shifts are reported in counts per second downfield from tetramethylsilane at 60 Mcps. Infrared spectra were recorded on a Perkin-Elmer Infracord or Perkin-Elmer Model 457 grating instrument. Elemental analyses were performed by Midwest Microlab, Indianapolis, Ind., or M-H-W Laboratories, Garden City, Mich. Preparative gas chromatographic separations were effected on a Wilkins (Varian) Aerograph Model A-700 instrument or a Varian Aerograph Model 1521B instrument using $^3/_8$-in. aluminum columns of varying lengths. Analytical gas–liquid chromatographic analyses were carried out on an F & M Instrument and Research Inc. Model 810-29 instrument equipped with dual thermal conductivity detectors coupled with a 1-mV Honeywell Elektronik Model 15 recorder equipped with a disk integrator.

Preparation of Materials. 2,4-Pentanediol (*meso* and *dl* Isomers). Utilizing the procedure of Pritchard and Vollmer,[42] 2,4-pentanedione was reduced with sodium borohydride to a mixture of *meso*- and *dl*-2,4-pentanediols in 84% yield. Conversion into the cyclic sulfides with thionyl chloride followed by separation by fractionation through a Nester–Faust Teflon spinning-band column afforded 140.0 g (48.6%) of *meso*-4,6-dimethyltrimethylene sulfite [bp 74° (12 mm), $n^{0}\text{D}$ 1.4409 (lit.[42] bp 73° (12 mm), $n^{20}\text{D}$ 1.4403)] and 83.6 g (29%) of *dl*-4,6-dimethyltrimethylene sulfite [bp 80–82° (12 mm), $n^{20}\text{D}$ 1.4490 (lit.[42] bp 82° (12 mm), $n^{20}\text{D}$ 1.4472)]. Hydrolysis[42] gave 93% of *meso*-2,4-pentanediol [bp 50–52° (0.05 mm), $n^{20}\text{D}$ 1.4325 (lit.[42] bp 73° (3 mm), $n^{20}\text{D}$ 1.4327)] and 92.7% of racemic 2,4-pentanediol [bp 58° (0.10 mm), $n^{20}\text{D}$ 1.4374 (lit.[42] bp 74° (3 mm), $n^{20}\text{D}$ 1.4378)].

***meso*-2,4-Pentanediol Ditosylate.** A solution of *p*-toluenesulfonyl chloride (33.4 g, 0.176 mol) in 50 ml of dry pyridine was cooled to 0° and *meso*-2,4-pentanediol (9.0 g, 0.0865 mol) in 30 ml of dry pyridine was added. The solution was kept at 0° for 40 hr and poured into a mixture of 250 g of cracked ice, 100 ml of concentrated hydrochloric acid, and 50 ml of water. The resulting solid was extracted out with three 150-ml portions of methylene chloride. The organic solution was washed twice with 100 ml of 10% hydrochloric acid, twice with 100 ml of water, and dried. Removal of solvent under reduced pressure afforded 33.0 g (92.8%) of white, solid ditosylate. Five recrystallizations from hexane–ethyl acetate gave colorless prisms, mp 135.5–136°.

Anal. Calcd for $C_{19}H_{24}O_6S_2$: C, 55.32; H, 5.86. Found: C, 55.23; H, 5.77.

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(39) From $N_{\text{boat}}/N_{\text{chair}} = e^{\Delta S_{\text{c-b}}/R}\, e^{-\Delta\Delta H(\text{2-i-Pr})_{(\text{c-b})}/RT}$ – ΔH(XXXIII–XXXII) = $N_{\text{boat}}H_{\text{boat}} + N_{\text{chair}}H_{\text{chair}}$: $\Delta S°$ (XXXIII–XXXII) = $N_{\text{boat}}(\Delta S_{\text{c-b}}) + R(N_{\text{c}} \ln N_{\text{c}} + N_{\text{b}} \ln N_{\text{b}})$; $\Delta G = \Delta H - T\Delta S$. The assumption that $\Delta G°$(*i*-Pr) = $\Delta H°$(*i*-Pr) made here and also in the calculation in Table VIII seems unjustified at first sight since an axial isopropyl generally has fewer rotameric conformations available than an equatorial one and thus possesses lesser entropy. However, the error so committed is probably partly compensated by the similar assumption that in the K $\rightleftarrows$ N equilibrium (Table VIII) the various rotameric conformations of the isopropyl group do not contribute to the entropy difference either.

(40) (a) U. Blakis, P. H. Kasai, and R. J. Myers, *J. Chem. Phys.*, **38**, 2753 (1963); (b) K. S. Pitzer, *ibid.*, **12**, 310 (1944); (c) L. Pierce and M. Hayashi, *ibid.*, **35**, 479 (1961).

(41) Unlike in cyclohexane where the trend of $-\Delta G°$ is *i*-Pr > Et > Me, we find that both in the 2 and 5 positions of 1,3-dithiane Et < Me (a similar trend was found in the 5 position of 1,3-dioxane) and in the 2 position of 1,3-dithiane *i*-Pr < Me. The only suggestion we can offer to explain this reversal is that the additional methyl groups of the ethyl and isopropyl groups interact sterically (with ring atoms) to a greater extent in the equatorial position of the heterocycles than in the axial position.

(42) J. G. Pritchard and R. L. Vollmer, *J. Org. Chem.*, **28**, 1545 (1963).

meso-2,4-Pentanedithiol. A solution of *meso*-2,4-pentanediol ditosylate (36.6 g, 0.089 mol) and potassium thioacetate (21 g, 0.184 mol) in 200 ml of dimethylformamide was refluxed for 51 hr and poured into 700 ml of degassed water. The mixture was extracted with three 200-ml portions of chloroform, the organic solution was washed twice with 100 ml of water, and dried. Solvent was removed under reduced pressure and the resulting oil was stirred at room temperature with a mixture of 200 ml of 95% ethanol, 25.0 g of zinc amalgam, and 30 ml of concentrated hydrochloric acid for 40 min and then poured into 700 ml of degassed water. The yellow oil which separated was extracted out with three 100-ml portions of chloroform. The organic solution was washed twice with 100 ml of degassed water and dried. Solvent was removed at atmospheric pressure and the residue was distilled to afford a small forerun (1.9 g) followed by 4.70 g (38.9%) of *meso*-2,4-pentanedithiol [bp 48–54° (2.8 mm), n^{25}D 1.5018 (lit.[42] bp 74.5° (12 mm), n^{25}D 1.5052)].[43] Analysis of the product by glpc (QF-1 on Chromosorb W column, 130°) indicated the presence of only *ca.* 3% *dl*-2,4-pentanedithiol.

Racemic 2,4-Pentanediol Ditosylate. In an analogous manner as described for the *meso* isomer, *dl*-2,4-pentanediol was converted into the ditosylate in 88% yield. Five recrystallizations from methanol afforded the analytical sample (mp 91–92°).

Anal. Calcd for $C_{19}H_{24}S_2O_6$: C, 55.32; H, 5.86. Found: C, 55.18; H, 5.81.

Racemic 2,4-Pentanedithiol. In the manner described for the *meso* isomer, *dl*-2,4-pentane ditosylate was converted into the corresponding dithiol in 19% yield [bp 54–58° (8 mm), lit.[43] 65° (11 mm)].

1,3-Butanedithiol. A mixture of 1,3-dibromobutane (34.5 g, 0.160 mol), thiourea (32.0 g, 0.422 mol), and 23 ml of water was refluxed under nitrogen for 3 hr, cooled, and sodium hydroxide (20.0 g, 0.50 mol) in 100 ml of water was added. After refluxing for 2 hr, the solution was cooled and the layers were separated. The aqueous phase was extracted twice with 100-ml portions of ether and the combined organic solutions were dried. Solvent was removed under diminished pressure and the residue was combined with 100 ml of 95% ethanol, 10 g of zinc amalgam, and 6 ml of concentrated hydrochloric acid. After stirring at room temperature for 2 hr, the solution was decanted into 350 ml of degassed water and the resulting mixture was extracted with three 100-ml portions of ether. The ether solution was dried and the solvent was removed at atmospheric pressure. Distillation of the residue yielded 13.2 g (67.8%) of colorless product: bp 64–67° (10 mm), n^{20}D 1.5208. The analytical sample was purified by preparative glpc using a QF-1 on Chromosorb W column at 128°.

Anal. Calcd for $C_4H_{10}S_2$: C, 39.30; H, 8.25. Found: C, 39.42; H, 8.32.

2-Methyl-1,3-propanediol Ditosylate. Diethyl methylmalonate was reduced with lithium aluminum hydride according to the general procedure given by Eliel and Knoeber.[13a] The product (59%) had bp 61–67° (0.025 mm), n^{20}D 1.4444 (lit.[44] bp 83.5–84° (3 mm), n^{20}D 1.4430). Conversion into the ditosylate was accomplished in a similar manner as described for 2,4-pentanediol. The product (93.6%) was recrystallized five times from 95% methanol to afford colorless prisms, mp 83–84°.

Anal. Calcd for $C_{18}H_{22}S_2O_6$: C, 54.25; H, 5.57. Found: C, 54.77; H, 5.82.

2-Methyl-1,3-propanedithiol. A solution of 2-methyl-1,3-propanediol ditosylate (35.0 g, 0.080 mol) and potassium thioacetate (20.1 g, 0.176 mol) in 200 ml of dry dimethylformamide was refluxed for 25 hr, cooled and poured into 700 ml of degassed water. The mixture was extracted with three 150-ml portions of chloroform, the organic solution was washed twice with 150 ml of water and dried. Solvent was distilled at atmospheric pressure and the dark residue was combined with 200 ml of ethanol, 25 g of zinc amalgam, and 30 ml of concentrated hydrochloric acid. After stirring at room temperature for 1.3 hr, the colorless solution was decanted into 800 ml of degassed water. The layers were separated and the aqueous phase was extracted twice with 150 ml of ether. The organic solutions were combined, washed twice with 100 ml of water, and dried. Solvent was removed at atmospheric pressure and the residue was distilled *in vacuo* to afford 6.76 g (69%) of colorless product: bp 37–39° (2.5 mm), n^{20}D 1.5217. The product was characterized as the bis(2,4-dinitrophenyl) thioether obtained as yellow crystals by repeated crystallization from ethyl acetate, mp 134.5–135°.

Anal. Calcd for $C_{16}H_{14}N_4S_2O_8$: C, 42.29; H, 3.11. Found: C, 42.47; H, 3.31.

2-Ethyl-1,3-propanediol Ditosylate. Diethyl ethyl malonate was reduced to the corresponding diol in 74% yield with lithium aluminum hydride.[13a] The product obtained had bp 70–74° (0.12–0.20 mm), n^{20}D 1.4478 (lit.[43] bp 83–86° (1–2 mm), n^{20}D 1.4471). Using the same procedure described for the preparation of 2,4-pentanediol ditoslyate, 2-ethyl-1,3-propanediol was converted into the corresponding ditosylate in 91% yield. Five recrystallizations from 95% methanol afforded the analytical sample as colorless prisms, mp 63.5–64.5°.

Anal. Calcd for $C_{19}H_{24}O_6S_2$: C, 55.32; H, 5.86. Found: C, 55.45; H, 5.83.

2-Ethyl-1,3-propanedithiol. Using the same procedure described for the preparation of 2-methyl-1,3-propanedithiol, 2-ethyl-1,3-propane ditosylate was converted into the corresponding dithiol in 62% yield: bp 59–62° (3 mm), n^{25}D 1.5154. The analytical sample was purified by preparative glpc using a QF-1 on Chromosorb column at 102°.

Anal. Calcd for $C_5H_{12}S_2$: C, 44.07; H, 8.87. Found: C, 44.53; H, 8.96.

2-*t*-Butyl-1,3-propanediol Ditosylate. Diethyl isopropylidenemalonate[45] was converted into diethyl *t*-butylmalonate with methyl magnesium iodide and cuprous chloride in the manner previously described[13a,46] in 89.6% yield. The product had bp 60–61° (0.7 mm), n^{20}D 1.4250 (lit.[47] bp 78–83° (1.6 mm), n^{20}D 1.4250). Reduction[13a] with lithium aluminum hydride afforded 2-*t*-butyl-1,3-propanediol in 71% yield. Recrystallization from ether–Skellysolve F gave colorless needles, mp 57–58° (lit.[48] mp 58–59°). Conversion into the ditosylate was accomplished in 83% yield using the procedure described for 2,4-pentanediol. Six recrystallizations from hexane–ethyl acetate afforded colorless prisms, mp 86.5–87.5°.

Anal. Calcd for $C_{21}H_{28}O_6S_2$: C, 57.25; H, 6.41. Found: C, 57.38; H, 6.50.

2-*t*-Butyl-1,3-propanedithiol. Treatment of 2-*t*-butyl-1,3-propanediol ditosylate with potassium thioacetate in the manner previously described for 2-methyl-1,3-propanedithiol afforded the corresponding *t*-butyldithiol in 80% yield, bp 40° (0.04 mm). The analytical sample was purified by preparative glpc using a QF-1 on Chromosorb W column at 128°.

Anal. Calcd for $C_7H_{16}S_2$: C, 51.16; H, 9.81. Found: C, 51.52; H, 9.72.

2-Isopropyl-1,3-propanediol Ditosylate. Diethyl isopropylmalonate was prepared by hydrogenation of diethyl isopropylidenemalonate over Pd–C in the manner described by Eliel and Knoeber.[13a] The product (95%) had bp 72–74° (2.3 mm), n^{20}D 1.4190 (lit.[49] bp 74–76° (3 mm), n^{22}D 1.4186). Reduction with lithium aluminum hydride[13a] afforded 2-isopropyl-1,3-propanediol (84%): bp 72–74° (0.35–0.50 mm), n^{20}D 1.4509 (lit.[50] bp 148–148.5° (18 mm), n^{20}D 1.4505). Conversion into the ditosylate was carried out as before in 91.5% yield. Five recrystallizations from 95% methanol afforded the analytical sample, mp 45–46°.

Anal. Calcd for $C_{20}H_{26}O_6S_2$: C, 56.32; H, 6.14. Found: C, 56.74; H, 6.21.

2-Isopropyl-1,3-propanedithiol. 2-Isopropyl-1,3-propanediol ditosylate was allowed to react with potassium thioacetate in the previously described manner to obtain the corresponding dithiol in 69.5% yield: bp 47–52° (0.90 mm), n^{25}D 1.5102.

Anal. Calcd for $C_6H_{14}S_2$: C, 47.95; H, 9.39. Found: C, 48.22; H, 9.29.

1,3-Dithiane Isomers. General Procedure. The preparation of substituted 1,3-dithiane isomers was accomplished by refluxing a solution of the appropriate dithiol, the desired aldehyde, and a few crystals of *p*-toluenesulfonic acid in benzene (10–20 ml/g of dithiol) for 2–5 hr using a Dean–Stark apparatus to collect water. For higher molecular weight aldehydes, equal molar amounts of

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Table XI. Data for 1,3-Dithiane Isomers

1,3-Dithiane	No.	Yield, % (% of mixture)[c]	Preparative glpc column (°C)[a]	Mp, °C	Ir,[b] μ	Calcd, % C	Calcd, % H	Found, % C	Found, % H
2-*cis*-4-*cis*-6-Me$_3$	I	79 (88)	A (100)		6.86, 7.26, 8.05, 8.37 9.70, 13.75	51.80	8.69	51.89	8.58
2-*trans*-4-*trans*-6-Me$_3$	II	79 (12)	A (100)	64–65.5	6.91, 7.25, 7.95, 8.67 9.70	51.80	8.69	51.75	8.62
2-*cis*-4-*trans*-6-Me$_3$	IX		A (100)		6.90, 7.27, 7.99, 8.40 9.39	51.80	8.69	52.01	8.55
4-*cis*-6-*cis*-Me$_2$-2-Et	III	98 (92)	A (125)		6.89, 7.29, 8.01, 9.70 12.17	54.59	9.15	54.20	9.12
4-*trans*-6-*trans*-Me$_2$-2-Et	IV	98 (12)	A (125)		6.88, 7.25, 7.99, 8.67 9.7, 12.3	54.59	9.15	54.60	9.25
4-*cis*-6-*trans*-Me$_2$-2-Et	X		A (125)			54.59	9.15	54.16	9.00
4-*cis*-6-*cis*-Me$_2$-2-*i*-Pr	V	75 (92.5)	A (142)		6.85, 7.28, 7.94, 8.20 12.65	56.78	9.53	56.62	9.42
4-*trans*-6-*trans*-Me$_2$-2-*i*-Pr	VI	75 (7.5)	A (142)		6.91, 7.27, 8.00, 8.65 9.72, 12.7	56.78	9.53	56.83	9.48
4-*cis*-6-*trans*-Me$_2$-2-*i*-Pr	XI		A (142)		6.87, 7.25, 8.03, 8.41 12.85	56.78	9.53	56.86	9.64
4-*cis*-6-*cis*-Me$_2$-2-*t*-Bu	VII	48 (92)	A (150)		6.84, 7.29, 7.97, 8.40 8.62, 9.64, 12.46	58.76	9.86	59.02	9.75
4-*trans*-6-*trans*-Me$_2$-2-*t*-Bu	VIII	48 (8)	A (150)	32–33		58.76	9.86	58.78	9.80
cis-2,4-Me$_2$	XIX	96.5 (80)	B (172)		6.92, 7.07, 7.28, 7.48 8.35	48.60	8.16	48.88	8.13
trans-2,4-Me$_2$	XX	96.5 (20)	B (172)		6.88, 7.05, 7.27, 9.5	48.60	8.16	48.67	8.28
cis-2-Et-4-Me	XVII	98 (80)	B (170)		6.85, 7.03, 7.90, 8.40	51.80	8.69	51.76	8.63
trans-2-Et-4-te	XVIII	98 (20)	B (170)		6.88, 7.04, 7.26, 7.95 12.35	51.80	8.69	51.77	8.73
cis-2-*i*-Pr-4-Me	XV	93 (82)	A (130)		6.89, 7.08, 7.31, 7.96 8.49, 12.83	54.49	9.15	54.51	9.07
trans-2-i-Pr-4-Me	XVI	93 (18)	A (130)		6.93, 7.26	54.49	9.15	54.10	8.97
cis-2-*t*-Bu-4-Me	XIII	80	A (135)	46.5–47.5	6.86, 7.34, 7.96, 8.08 12.10	56.78	9.53	57.09	9.53
trans-2-*t*-Bu-4-Me	XIV	80	A (135)	31–33		56.78	9.53	57.42	9.49
cis-2-*t*-Bu-5-Me	XXIII	75 (*ca.* 50)	A (134)	62–63	6.88, 7.29, 7.35, 7.53 8.49, 12.85	65.78	9.53	56.68	9.48
trans-2-*t*-Bu-5-Me	XXII	75 (*ca.* 50)	A (134)		6.89, 7.32, 8.09, 8.44 12.67	56.78	9.53	57.00	9.58
trans-2-*t*-Bu-5-Et	XXIV	99 (*ca.* 50)	A (126)		6.85, 7.32, 8.12, 8.48 12.41	58.76	9.86	58.73	9.80
cis-2-*t*-Bu-5-Et	XXV	99 (*ca.* 50)	A (126)		6.85, 7.33, 8.14, 8.51 12.39	58.76	9.86	58.95	9.91
trans-2-*t*-Bu-5-*i*-Pr	XXVI	83.5 (*ca.* 50)	A (135)	81.5–83	6.84, 7.00, 7.32, 7.35 7.69, 8.14, 12.89	60.49	10.15	60.57	10.14
cis-2-*t*-Bu-5-*i*-Pr	XXVII	83.5 (*ca.* 50)	A (135)	44–45	6.80, 6.86, 6.98, 7.30 7.79, 8.50, 12.85	60.49	10.15	60.63	10.05
trans-2,5-*t*-Bu$_2$	XXVIII	95	C (210)	143.5–144.5		62.00	10.41	62.00	10.40
cis-2,5-*t*-Bu$_2$	XXIX	95	C (210)	41–43		62.00	10.41	61.99	10.34
trans-2-*i*-Pr-5-*t*-Bu	XXX	100 (60)	D (210)	59–60		60.49	10.15	60.57	10.02
cis-2-*i*-Pr-5-*t*-Bu	XXXI	100 (40)	D (210)	34–35.5	6.80, 7.14, 7.30, 8.10 12.7	60.49	10.15	60.65	9.98
trans-2-Ph-5-*t*-Bu	XXXII	99	C (220)	126.5–127		66.61	7.99	66.87	8.17
cis-2-Ph-5-*t*-Bu	XXXIII	99	C (220)	67–68		66.61	7.99	66.83	8.15
trans-2,5-*i*-Pr$_2$	XXXIV	98 (60)	A (150)	39.5–40	6.86, 7.23, 7.33	58.76	9.86	59.20	9.75
cis-2,5-*i*-Pr$_2$	XXXV	98 (40)	A (150)		6.88, 7.02, 7.26, 7.35 7.81, 8.43, 12.38	58.76	9.86	59.15	9.77

[a] The preparative glpc column packings are coded as follows: column A, 20 ft × $^3/_8$ in. 20–33% QF-1 on Chromosorb W; column B, 30 ft × $^3/_8$ in. 20% Carbowax 20M on Chromosorb W; column C, 10 ft × $^3/_8$ in. 20% Carbowax 20M on Chromosorb W; column D, 20 ft × $^3/_8$ in. 20% Carbowax 20M on Chromosorb W. [b] Major ir bands above 6 μ. Liquids were determined neat, solids were determined in KBr pellets or neat (melt) if low melting. [c] Per cent of given isomer in reaction mixture.

the dithiol and aldehyde were found to be sufficient, but the use of 1.5–3 mol excess of volatile aldehydes is recommended. Upon completion of the reaction, the benzene solutions were washed twice with 5% aqueous sodium hydroxide, once with water, and dried. Solvent was then removed under reduced pressure and the remaining mixture of isomers was either distilled at reduced pressure or recrystallized. Separation of isomers was accomplished by preparative glpc and/or fractional crystallization as indicated for each case. The above procedure is illustrated for the preparation and separation of the two isomers of 2,4-dimethyl-1,3-dithiane and 2,5-di-*t*-butyl-1,3-dithianes. Pertinent data for other compounds are presented in Table XI.

2,4-Dimethyl-1,3-dithiane. A solution of 1,3-butanedithiol (2.0 g, 16.4 mmol), acetaldehyde (1.0 g, 22.8 mmol), and a few crystals of *p*-toluenesulfonic acid in 30 ml of benzene was refluxed for 3 hr during which time water was removed using a Dean–Stark separator. The solution was cooled, washed twice with 10 ml of 5% aqueous sodium hydroxide, once with 20 ml of water, and dried. Removal of solvent under reduced pressure afforded a colorless oil which was vacuum distilled in a short-path molecular distillation apparatus to obtain 2.35 g (96.5%) of 2,4-dimethyl-1,3-dithiane isomers. Separation of the isomers was accomplished by preparative glpc using a 30-ft 20% Carbowax 20M on Chromosorb W column at 172°. The relative amounts of *cis* and *trans* isomers

Table XII. Equilibration and Analysis of Substituted 1,3-Dithianes

Dithiane isomers	Anal. glpc column (°C)[a]	Response ratio	K_{equil}	$-\Delta G°$, kcal/mol[b] (°C)
2,4-Dimethyl	B (150)	0.997 ± 0.002	8.3670	1.26 ± 0.01 (25)
2-Ethyl-4-methyl	B (150)	1.020 ± 0.003	6.9788	1.15 ± 0.02 (25)
2-Isopropyl-4-methyl	C (138)	0.988 ± 0.006	11.6558	1.45 ± 0.02 (25)
2-*t*-Butyl-5-methyl	C (145)	0.995 ± 0.009	11.935	1.69 ± 0.01 (69)
2,4,6-Trimethyl	C (130)	1.027 ± 0.016	1.3550	1.77 ± 0.01 (69)
2-Ethyl-4,6-dimethyl	C (139)	*c*	9.607	1.54 ± 0.01 (69)
2-Isopropyl-4,6-dimethyl	C (150)	0.939 ± 0.005	17.705	1.95 ± 0.02 (69)
2-*t*-Butyl-4,6-dimethyl	C (140)	*c*	55.152	2.72 ± 0.02 (69)
2-*t*-Butyl-5-methyl	C (145)	1.066 ± 0.003	4.6211	1.04 ± 0.01 (69)
2-*t*-Butyl-5-ethyl	C (150)	1.033 ± 0.002	3.109	0.77 ± 0.02 (69)
2-*t*-Butyl-5-isopropyl	C (150)	0.991 ± 0.012	3.5071	0.85 ± 0.01 (69)
2,5-Di-*t*-butyl	A (175)	1.003 ± 0.006	22.671	1.85 ± 0.01 (25)
2-Isopropyl-5-*t*-butyl	A (175)	1.008 ± 0.005	15.268	1.61 ± 0.01 (25)
2-Phenyl-5-*t*-butyl	A (220)	0.964 ± 0.008	26.432	1.94 ± 0.02 (25)
2,5-Diisopropyl	C (150)	0.998 ± 0.009	3.1569	0.78 ± 0.01 (69)

[a] The glpc columns used for equilibrium determinations are coded as follows: column A, 9 ft × $^1/_8$ in. 20% Carbowax 20M on $^{45}/_{60}$ Chromosorb W; column B, 21 ft × $^1/_8$ in. 20% Carbowax 20M on $^{45}/_{60}$ Chromosorb W; column C, 20 ft × $^1/_8$ in. 25% QF-1 on $^{45}/_{60}$ Chromosorb W. [b] The error is reported as standard deviation; an additional small error in $-\Delta G°$ introduced by the error in the response ratio has been neglected. [c] Not determined; asssumed to be unity.

were 80 and 20%, respectively, with the *cis* compound eluted first. The analytical data are provided in Table XI.

2,5-Di-*t*-butyl-1,3-dithiane. From 2-*t*-butyl-1,3-propanedithiol (3.28 g, 0.020 mol) and pivaldehyde (1.72 g, 0.020 mol) was obtained 4.42 g (95%) of 2,5-di-*t*-butyl-1,3-dithiane isomers. The crude solid mixture of isomers was recrystallized four times from hexane (methanol also works well) to afford the *trans* isomer as shimmering plates, mp 143.5–144.5°. Sublimation gave the analytical sample (Table X). Repeated concentration and crystallization of the mother liquor afforded additional crops of the *trans* compound. The residue remaining after crystallization was analyzed by glpc (10-ft 20% Carbowax 20M on Chromosorb W column, 210°) and found to contain less than 5% of the *trans* isomer. The *cis* isomer was isolated by preparative glpc using the above column and temperature. Sublimation of the resulting solid afforded the analytical sample, mp 41–43°.

Equilibration of Dithiane Isomers. General Procedure. For each pair of stereoisomeric 1,3-dithianes, two samples were prepared for equilibration using appropriate *cis*- and *trans*-rich mixtures so as to approach equilibrium from both sides. The samples were prepared by dissolving the appropriate mixture (usually 50–200 mg) in spectroscopic grade chloroform (*ca.* 200–750 m), adding a catalytic amount of boron trifluoride etherate (1 or 2 small drops; *ca.* 6–12 × 10^{-2} mmol of boron trifluoride) and sealing the solution in a small glass vial. The samples were kept at room temperature (*ca.* 25°) or, more often, in a constant-temperature bath kept at 69°. Equilibrium was reached much faster at the higher temperature. Periodically, 100–250-ml aliquots were removed, extracted twice with 5% aqueous sodium bicarbonate, once with water, dried, and analyzed by glpc. The glpc columns and conditions employed varied and are indicated for each case in Table XII. Equilibrium was considered reached when the same and reproducible area ratios were obtained from both the initial *cis*-rich and *trans*-rich samples. With the exception of two cases, area response ratios were obtained by glpc analysis of isomer mixtures having known weight compositions. Using the appropriate response ratio, the isomer ratio in the equilibrated sample was determined by correcting the measured area ratio. The pertinent data are presented in Table XII.

Entropy Determination. Equilibria were established in the usual manner at 25.0, 45.0, 69.0, and 100.0° using thermostat-controlled baths to maintain the temperatures. The respective equilibrium constants measured were K_{25} = 22.095 ± 0.824, K_{45} = 15.310 ± 0.285, K_{69} = 10.505 ± 0.270, and K_{100} = 6.911 ± 0.219 (all constants corrected for glpc response ratio). A computer program was used to draw a least-squares plot of these data to obtain $-\Delta H°$ = 3.42 ± 0.01 kcal/mol, $-\Delta S°$ = 5.33 ± 0.01 cal/deg mol. The errors given are the statistical errors of the plot.

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