were recorded at different temperatures by UV measurements at 299 nm every 10 min. The program used to determine the decomposition rate constant was VA 04A (optimization of the parameter by minimization). The kinetics were also recorded by ^1H NMR (16 scans, C_6D_6).

Dehalogenation Measurements. Dilute (10^{-2} to 2.5×10^{-3} M) solutions of **4**, **5**, and **6** were irradiated for 320 h, 140 min, and 2 min, respectively. At regular time intervals, the tubes were opened, and the solution was evaporated at room temperature and redissolved in chloroform (0.1 mL). Quantitative measurements were made by gas chromatography, using acenaphthene (0.1 mL, 7.4×10^{-3}M) in chloroform as internal standard.

Quenching Experiments. *cis*-Piperylene (Fluka) and naphthalene (Merck) were used without purification. *cis*-Piperylene was diluted with cyclohexane and naphthalene was used in methanolic solution. Irradiations were performed at 300 nm. The relative concentrations of the quencher and the substrate were selected such that the quencher absorbed no more than 1% of the incident light. Solutions (2 mL) of 2-(4-halophenyl)-benzoxazole were added to solutions (2 mL) containing the quenchers and then deoxygenated by bubbling with argon. Irradiation times depended on both the compound and the quencher (see Table XI).

Dehalogenation yields were measured by VPC as described above. For the reaction of **4** with *cis*-piperylene, analysis by GC/MS of the mixture indicated the formation of a photoadduct (m/e M^+ = 297, 282, 229). Other products were detected corresponding to m/e M^+ = 297, 260, and 256, m/e M^+ = 399, 297, and 282, and m/e M^+ = 282 and 206, indicating that *cis*-piperylene is bonded to the carbon of the C=N double bond.

Sensitization by TEA. TEA (Prolabo) was used without further purification. Methanolic solutions of **4** (2 mL, 5.2×10^{-3} M) were added to solutions of TEA (2 mL, 3×10^{-2} to 1.5×10^{-1} M). The tubes were degassed and irradiated at 300 nm for 206 min. The analytical procedure was as described above.

Sensitization by Benzophenone. Benzophenone (Prolabo) was used without purification. Aliquots (4 mL) of a cyclohexane solution of 2-(4-halophenyl)benzoxazole (2 mL, 5×10^{-3} M) and benzophenone (2 mL, 2×10^{-2} M) in Pyrex tubes were deoxygenated as described. The tubes were irradiated at 350 nm on a "merry-go-round" sample holder immersed in an acetone bath to avoid irradiation at 300 nm. Irradiation times were 234 h for **4**, 145 min for **5**, and 2 min for **6**. The analytical procedure was as described above.

Viscosity Measurements. Kinematic viscosity was measured at 30 °C on a semiautomatic Schott-Geräte viscosimeter, model AVS/N.

Registry No. **1**, 51234-28-7; **2**, 833-50-1; **3**, 397-54-6; **4**, 1141-35-1; **5**, 3164-13-4; **6**, 33116-00-6; **8**, 99966-75-3; **9**, 99966-74-2; *cis*-piperylene, 1574-41-0; naphthalene, 91-20-3; triethylamine, 121-44-8.

Conformational Analysis. 46. Conformational Equilibria in 3-Hydroxy-, 3-Methoxy-, and 3-Acetoxythianes, Their Sulfoxides and Sulfones, and Some Corresponding 3-Methyl Homologues

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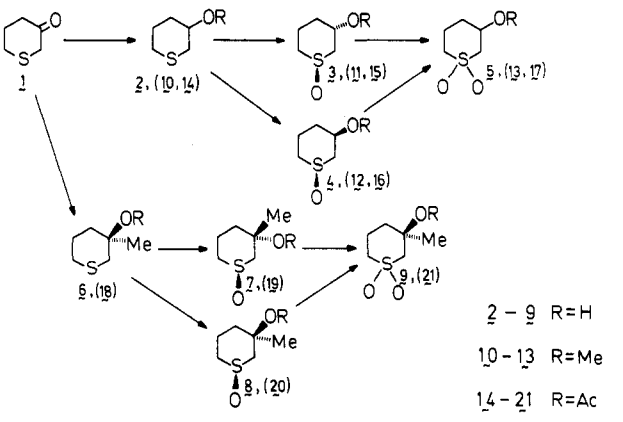
Conformational equilibria have been measured, by low-temperature carbon-13 and proton NMR spectroscopy, for 3-hydroxythiane, its two epimeric sulfoxides, and the corresponding sulfone and their methyl ethers and acetates, as well as the corresponding derivatives of 3-methyl-3-hydroxythiane and their acetates. Of particular note are large solvent and concentration effects on the conformational free energies, $\Delta G°_{a\rightleftharpoons e}$, especially in cases where intramolecular and intermolecular hydrogen bonding are competitive. Thus, in 3-hydroxythiane, $\Delta G°$ rises from −1.20 kcal/mol in 4 M CD_2Cl_2 to −0.22 kcal/mol in 0.0011 M CD_2Cl_2; for the corresponding cis sulfoxide the rise is from <−1.3 kcal/mol in 0.3 M CD_3OD to −1.0 kcal/mol in 2.8 M CD_2Cl_2 to >+1.3 kcal/mol in 0.0023 M CD_2Cl_2 and in the sulfone it is from <−1.3 kcal/mol in 0.3 M CD_3COCD_3 to −0.9 kcal/mol in 0.3 M CD_2Cl_2 to −0.16 kcal/mol in 0.002 M CD_2Cl_2.

In previous publications[1] we have reported on conformational equilibria in compounds of type MeS*CHR^{1}CHR^{2}OR^3 where S* = S, SO, or SO_2, R^1 and R^2 = alkyl or aryl, and R^3 = H, Me, or Ac. The technique used was proton NMR spectroscopy, specifically the evaluation of vicinal coupling constants by means of the Altona equation.[2] These studies gave valuable information as to the nature of the interactions between the heteroatomic functions; however, the results were quantitatively somewhat uncertain, especially in the sulfoxide and sulfone cases where the electronegativity values of the SO and SO_2 functions, required in the equation,[2] are not well-known.[1d] We have therefore now studied, and here report, conformational equilibria in the cyclic analogues shown in

Scheme I



(1) (a) Alcudia, F.; Brunet, E.; García Ruano, J. L.; Rodriguez, J. H.; Sánchez, F. *J. Chem. Res. Synop.* **1982**, 284; *J. Chem. Res. Miniprint* **1982**, 2826. (b) Brunet, E.; Garcia Ruano, J. L.; Hoyos, M. A.; Rodriguez, J. H.; Prados, P.; Alcudia, F. *Org. Magn. Reson.* **1983**, *21*, 643. (c) Brunet, E.; García Ruano, J. L.; Martinez, M. C.; Rodriguez, J. H.; Alcudia, F. *Tetrahedron* **1984**, *40*, 2023. (d) Brunet, E.; García Ruano, J. L.; Rodriguez, J. H.; Alcudia, F. *Tetrahedron* **1984**, *40*, 4433.

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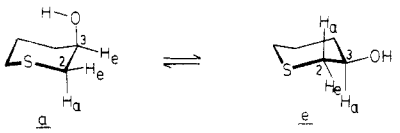
Table I. First-Order Coupling Constants (Hz) between the Protons in Positions 2 and 3 of 3-Hydroxythiane (2) and Derivatives 10 and 14 at 25 °C and Approximate Free Energies (kcal/mol, see text)

compd	concn (M)	solvent	$J_{2,3}$	$J_{2',3}$	$J_{2,2'}$	$\Delta G°$
2	neat		3.9	9.7	12.7	−1.03
	5	$CDCl_3$	3.9	9.4	12.9	−0.94
	2	$CDCl_3$	3.6	8.6	12.7	−0.50
	1	$CDCl_3$	3.2	8.2	12.9	−0.19
	0.01[a]	$CDCl_3$	3.1	7.7	13.1	−0.05
	0.001[a]	$CDCl_3$	2.8	7.7	13.0	−0.05
2	0.2	Me_2SO-d_6		9.6	12.4	−1.00
10	0.2	$CDCl_3$	3.7	9.7	12.8	−0.78
14	0.2	CD_2Cl_2	3.7	9.8	12.7	−0.82

[a] J_{HOCH} = 7.4 Hz. This coupling was not seen at the higher concentrations.

Scheme II



Scheme I. This is the first systematic study of 3-substituted thianes with polar substituents, previous investigations having been confined to thianes with nonpolar (methyl) substituents,[3] thianes with halo, alkoxy, and alkylthio substituents in position 2[4] in which the anomeric effect[5] is prominent, 3,3-dimethoxythiane sulfoxide,[6] and 3-chloro-, 3-bromo-, and 3-acetoxythiane[7] and its sulfone.[8]

Synthesis. 3-Thianone (1) was synthesized as previously described[9] and reduced to 2 with sodium borohydride. Oxidation of the sulfide to the sulfoxides (trans, 3; cis, 4) and sulfone 5 was effected with $NaIO_4$ or *m*-chloroperbenzoic acid (limited amount or excess, respectively) and the diastereomeric sulfoxides were separated by recrystallization and column chromatography. Tertiary alcohol 6 was obtained from 1 by treatment with methylmagnesium bromide and was similarly converted to sulfoxides 7 (trans) and 8 (cis) and to sulfone 9. The methyl ethers 10–13 and acetates 14–21 were obtained from the parent alcohols by standard procedures (see Experimental Section).

NMR Spectra. Conformational Equilibria. Since, on the basis of earlier work,[1] it appeared that the conformational equilibria in the hydroxyl compounds (Scheme I, 2–9) might be concentration dependent, especially in nonpolar solvents, we examined the coupling constants of the carbinol [C(3)] proton in 2 with the adjacent protons at C(2) (which are well separated from the other protons) as a function of concentration. The results, displayed in Table I, show that the carbinol proton changes from a predominantly axial to a more equatorial conformation as the solution of 2 in $CDCl_3$ is made more dilute, i.e., the conformer with axial hydroxyl group becomes more prominent in this compound with dilution. It is also clear from Table I (last three entries) that a solution of 2 in Me_2SO as well as the methyl ether (10) and the acetate (14) of 2 have coupling constants corresponding to those of the most concentrated solution of 2 in $CDCl_3$ or of neat 2, i.e., the OR groups are largely equatorial in all these cases. The $\Delta G°$ values in Table I are based on the equation[10] $J = \Sigma n_i J_i$ with J_{2a3a} = 12.3 Hz, $J_{2e3a} = J_{2a3e}$ = 3.9 Hz, J_{2e3e} = 2.0 Hz (cf. Scheme II) derived from the Altona equation[2,1d] $n_e + n_a = 1$, $K = n_e/n_a$ and $\Delta G° = -RT \ln K$.

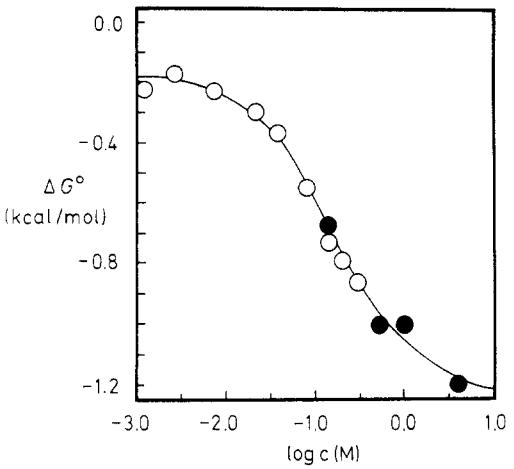


Figure 1. Plot of $\Delta G°$ (kcal/mol) vs. molar concentration for the conformational equilibrium of 2: open circles, ^1H data; filled circles, ^{13}C data.

The low-temperature C-13 spectra of 2–9 were therefore studied at various dilutions. The results for 2 are shown in Figure 1 (solid points), the chemical shifts (at the temperature indicated) for the two conformers (Scheme II) being tabulated in Table II. It is seen from Figure 1 that, at the lowest concentration at which usable C-13 spectra could be obtained (ca. 0.1 M), $\Delta G°$ has not yet come to a steady value. To reach lower concentrations, it was necessary to switch to the more sensitive proton NMR spectroscopy. This, in turn, made it necessary to synthesize 3-thianol-*2,2,4,4*-d_4 in order to simplify the proton spectrum. The tetradeuterated compound was readily obtained by exchanging 1 (Scheme I) with D_2O in base before reducing it to 2. Observation of the areas of the equatorial and axial carbinol protons (Scheme II) at low temperature made possible measurement of the n_e/n_a ratio down to concentrations of 10^{-3} M (Figure 1), at which concentration $\Delta G°$ comes to a plateau of −0.22 kcal/mol (at −90 °C). This is taken to be the conformational energy of hydroxyl in 3-thianol at high dilution (cf. Table III).

This value is in only semiquantitative agreement with that shown in Table I, presumably because of approximations (especially in regard to torsion angle) which must be made in applying the Altona equation.[2] Better agreement is obtained with the H–O–C–H coupling constant which is readily discerned in the low-temperature spectra of the tetradeuterated species (axial-OH conformer a, 11.1 Hz; equatorial conformer e, 4.5 Hz). The averaged coupling of 7.4 Hz seen in dilute solutions of 2 in $CDCl_3$ at room temperature (Table I, footnote) corresponds to a $\Delta G°$ of −0.14 kcal/mol at 25 °C. This limiting value is reached at a concentration of 10^{-2} M or even higher at room temperature whereas one has to dilute to 10^{-3} M to reach a plateau of $\Delta G°$ at −90 °C (Table III). The difference is presumably due to the general tendency of alcohols to

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Table II. Low-Temperature ^{13}C NMR Parameters of the Compounds Studied in This Work (See Scheme I)[a]

		chemical shifts (ppm)											
		OR equatorial						OR axial					
	solv[b]	C(2)	C(3)	C(4)	C(5)	C(6)	3-Me	C(2)	C(3)	C(4)	C(5)	C(6)	3-Me
2	A	37.2	71.5	34.6	25.1	27.2		34.7	66.3	32.1	20.5	28.1	
	B	34.2	68.5	34.0	26.7	27.5		35.2	61.3	30.8	20.4		
	C	35.4	69.2	35.4	27.4	28.7							
	D	35.9	70.3	35.9	28.3	29.6							
3	A	53.2	59.2	32.8	12.8	43.2		57.7	61.8	30.3	16.0	51.1	
	B	49.9	60.0	33.2	15.9	43.4		56.9	65.7	29.8	16.5	50.8	
	C	51.0	61.2	34.6	16.7	43.9							
	D	50.7	62.2	34.8	17.7	44.3		57.9	67.9	31.1	18.1	51.8	
4	A	60.2	67.0	32.8	20.6	50.2		50.7	54.0	30.3	8.2	44.1	
	B	58.1	64.1	32.3	17.3	49.8		44.4	65.5	30.9	9.0	44.2	
	C	58.6	65.2	33.5	18.0	50.0		44.6	67.5	31.8	9.9	44.2	
	D	58.4	65.8	33.8	18.7	50.4							
5	A	61.7	68.8	32.5	22.4	50.7		58.2	63.6	30.0	17.8	51.6	
	B	57.4	66.2	31.9	18.8	49.2			65.4	29.5	18.0	50.9	
	C	58.1	67.1	33.0	20.0	49.3							
	D	58.7	67.8	33.5	20.7	50.2							
6	A	42.7	71.6	40.1	18.6	27.3	17.5	43.3	72.0	40.7	20.3	27.4	22.8
	B	39.2	68.4	39.1	26.1	27.6	23.5	40.1	64.6	37.0	22.8	28.7	26.8
	C	40.1	68.4	40.3		27.2	23.4	40.1	65.0	38.1	24.2	28.0	27.1
	D	40.8	68.7	40.6	27.9	28.8	24.1	40.2	66.7	38.7	24.1	31.4	28.0
7	A	58.7	59.3	37.1	6.3	43.3	17.5	66.3	67.5	38.9	15.8	50.4	22.8
	B							61.4	70.6	35.6	17.6	50.1	30.3
	C							62.1	71.3	36.4	18.4	50.6	30.9
	D							62.0	72.6	36.9	19.1	51.0	30.9
8	A	65.7	67.1	38.3	14.1	50.3	17.5	59.3	64.7	38.9	8.0	43.4	22.8
	B	62.3	69.1	37.4	18.2	50.7	25.6	48.3	70.0	36.8	11.2	43.5	30.8
	C	62.5	70.9	38.1	18.8	50.9	26.0	48.4	71.0	37.6	12.1	43.5	31.4
	D	62.6	71.3	38.6	19.6	51.6	26.1	49.5	71.7	37.9	12.9	44.4	31.8
9	A	67.2	68.9	38.0	15.9	50.8	17.5	66.8	69.3	38.6	17.6	50.9	22.8
	B	61.0	70.1	36.9	18.6	49.7	24.4	58.6	70.1	35.4	18.6	49.7	29.7
	C	61.5	70.5	37.8	19.5	49.9	25.1	59.3	70.5	36.0	19.3	50.1	30.6
	D	62.2	71.6	38.6	20.2	51.0	25.5	60.3	71.6	36.7	20.2	51.3	31.5
10[c]	A	33.9	80.3	31.3	25.4	28.0		31.8	74.9	29.2	21.1	28.6	
	B	31.8	77.3	30.6	27.1	27.6			70.3	29.5	20.3	28.3	
	C	33.1	78.3	31.6	27.9	28.8			69.2		22.2		
11[c]	A	49.5	68.0	29.5	13.1	43.6		54.8	70.6	27.4	16.6	51.6	
	B	47.6	69.7	30.6	15.7	44.2			75.0	26.0	16.5	51.2	
	C	47.6	71.0	31.4	16.6	44.2		54.2	76.0	27.0	17.5	51.2	
	D	47.8	71.8	32.0	17.5	44.6		55.1	76.7	27.3	18.2	51.6	
12[c]	A	56.9	75.8	29.5	20.9	51.0		47.8	62.8	27.4	8.8	44.8	
	B	54.9	73.4	29.7	17.1	50.4							
	C	55.0	74.4	30.5	17.8	50.4							
13[c]	A	57.4	77.6	29.1	22.7	51.5		55.3	72.4	26.0	18.4	52.1	
	B	54.6	74.8	29.5	18.8	49.7							
	C	54.4	76.3	30.2	19.8	49.6							
14[d]	A	33.5	73.9	30.9	25.1	27.2		31.9	69.7	29.3	21.3	27.6	
	B	31.0	71.3	30.9	27.0	27.6							
	C	31.7	72.0	31.5	27.3	28.6							
15[d]	A	49.5	61.6	29.1	12.8	43.2		54.9	65.2	27.5	18.5		
	B	47.2	64.3	30.1	15.6	43.9		54.0	68.9	27.3	16.9	50.8	
	C	47.6	65.3	31.0	16.4	44.0		54.4	70.2	27.8	17.8	51.0	
16[d]	A	56.5	69.4	29.1	20.6	50.2		47.9	57.4	27.5	9.0	43.6	
	B	54.5	66.1	29.2	17.0	50.0							
	C	54.2	66.4	29.2	17.2	54.2							
17[d]	A	57.0	71.2	28.7	22.4	50.7		55.4	67.0	27.1	18.6	51.1	
	B	54.4	67.6	28.7	18.7	49.5							
	C	54.6	68.9	29.3	19.8	49.5							
18[d]	A	39.0	74.0	36.4	18.6	27.3	17.5	40.5	75.4	37.9	21.1	26.9	22.8
	B	36.5	80.5	35.7		27.7	19.3	36.7	75.7	34.5	22.3	26.8	25.4
	C	37.2	80.5	36.3		28.0	19.9	37.6	76.3	34.4	23.1	27.0	25.7
	D	38.3	82.1	37.3		29.0	20.4	38.8	79.7	35.3	24.1	28.0	26.2
19[d]	A	55.0	61.7	34.6	6.3	43.1	17.5	63.5	70.9	36.1	18.3	49.7	22.8
	B							57.2	80.7	34.6	17.2	50.0	24.9
	C							57.5	81.9	34.7	17.9	50.1	25.2
20[d]	A	62.0	69.5	34.6	14.1	50.1	17.5	56.5	63.1	36.1	8.8	42.9	22.8
	B	58.0	79.5	34.2	17.1	50.8	22.0	44.5	75.0	36.8	11.7	44.2	26.7
	C	58.6		34.9	17.9	51.0	22.4	44.8	76.1	37.4	12.5	44.4	27.3
	D	58.7	81.2	35.8	18.7	51.6	23.0	45.4	79.7	37.9	13.4	44.7	27.6
21[d]	A	62.5	71.3	34.2	15.9	50.8	17.5	64.0	72.7	35.7	18.4	50.4	22.8
	B	57.8		34.7	14.8		20.6	52.9	77.8	35.8	18.0	50.0	25.4
	D							53.9	80.2	37.1	20.0	51.0	26.3

[a] The chemical shift for the C=O group of the acetoxy derivatives is not included in this table because this peak was not measured at low temperature since the spectral window was reduced to 100 ppm in order to get better digital resolution (see Experimental Section). Nevertheless, these compounds showed a peak in the range 170–171 ppm at room temperature. [b] A = calculated (see text); B = CD_2Cl_2; C = acetone-d_6; D = CD_3OD. [c] These compounds showed a peak at 55–56 ppm corresponding to the OCH_3 group. [d] These compounds showed a peak at 20–22 ppm corresponding to the $OCOCH_3$ group.

associate more strongly at lower temperatures[11] where translational entropy factors—which work against association—have less effect on $\Delta G°$.[12]

The methyl ether **10** and acetate **14** of alcohol **2** cannot, of course, engage in intermolecular hydrogen bonding, and one might therefore have anticipated that their $\Delta G°$ values (Scheme II, OMe or OAc instead of OH) would be close to those of the alcohol **2** at high dilution. As seen in Table III, this is not the case; $\Delta G°$ for the methoxy compound is −1.08 kcal/mol (CD_2Cl_2) and that for the acetoxy compound less than −1.3 kcal/mol (the equilibrium corresponding to Scheme II is too one-sided to measure). Thus there is a factor in **2** which favors the axial conformation more than it is favored in **10** and **14**. It appears that this factor is intramolecular hydrogen bonding, as evidenced by the very high H–O–C–H coupling constant (11.1 Hz) in the axial conformer (Scheme II, a) compared to the equatorial one (Scheme II, e, 4.5 Hz). This indicates that the hydroxyl group in conformer a turns inward to form a hydrogen bond with sulfur and thus becomes nearly antiperiplanar to the carbinol hydrogen. In contrast, in the equatorial conformer e, three staggered conformations are possible for OH, one antiperiplanar and the other two synclinal to CH, and the coupling constant is averaged to a much lower value than that in conformer a. If the difference of the $\Delta G°$ values of OCH_3 (−1.08) and OH (−0.22 kcal/mol)[16] is taken as a measure of the strength of the intramolecular OH···S hydrogen bond, this is calculated to be 0.9 kcal/mol.[17,19]

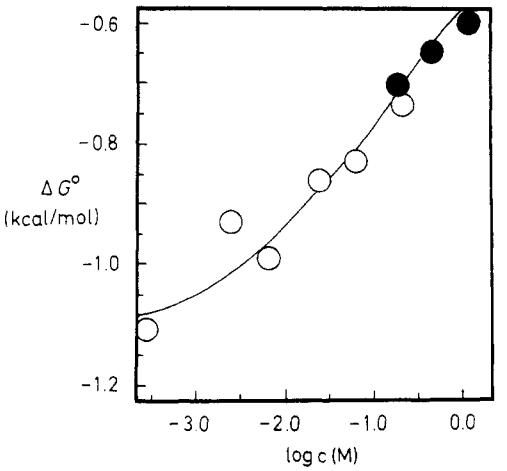


Figure 2. Plot of $\Delta G°$ (kcal/mol) vs. molar concentration for the conformational equilibrium of **3**: open circles, ^1H data; filled circles, ^{13}C data.

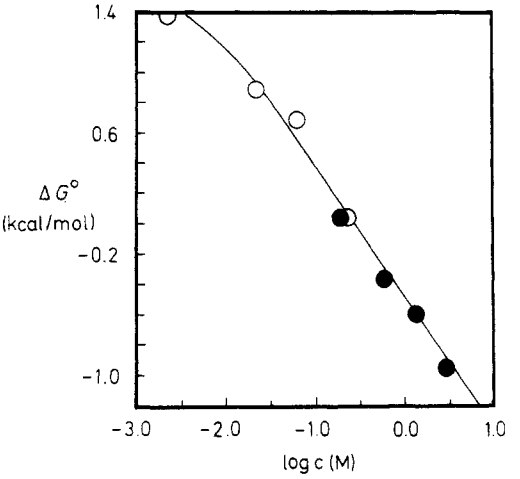


Figure 3. Plot of $\Delta G°$ (kcal/mol) vs. molar concentration for the conformational equilibrium of **4**: open circles, ^1H data; filled circles, ^{13}C data.

The $-\Delta G°$ values for MeO (1.08) and AcO (>1.3 kcal/mol) in a 3-substituted thiane in a solvent of low polarity such as CD_2Cl_2 are substantially larger than those in cyclohexane (0.58[18] and 0.79[20] kcal/mol, respectively). We ascribe this to unfavorable (polar) interactions between the ring sulfur and the exocyclic axial OR group.

Whether this interaction is strictly dipole–dipole repulsion (a similar effect is seen in 5-methoxy-1,3-dioxane[21]) or whether it includes a "gauche-repulsive" effect[22,23] is not certain. The fact that $\Delta G°$ is more, rather than less, negative for 3-methoxythiane (**10**, Scheme I) in acetone-d_6 as compared to CD_2Cl_2 (Table III) might be taken as evidence *against* a purely dipolar repulsion (which should

(11) Pimentel and McClennan (Pimentel, G. C.; McClennan, A. L. "The Hydrogen Bond"; W. H. Freeman & Co.: San Francisco, CA, 1960.) indicate $\Delta H°$ = −2 to −7 kcal/mol, $\Delta S°$ = −10 to −24 G for intermolecular OH···O hydrogen bonds. (Note that for $\Delta H°$ = −4000 cal/mol, $\Delta S°$ = −16 G, K_{assoc} = 0.26 at 300 K, but 23 at 180 K, i.e., at a given concentration, the degree of association is nearly 100 times as great at 180 K than at 300 K.

(12) This argument may explain the discrepant values for $\Delta G°_{OH(a=e)}$ for cyclohexanol in nonpolar solvents obtained by chemical equilibrium at temperatures somewhat above ambient on one hand[13] and by low-temperature NMR spectroscopy[14] on the other. Under the conditions of the NMR experiment, association is apparently unavoidable, and $\Delta G°_{OH}$ values of −0.9 to −1.2 kcal/mol have been measured in various (including nonpolar) solvents.[14] The chemical measurement at the much higher temperature,[13] on the other hand, gives a value of −0.6 kcal/mol which is probably closer to that of cyclohexanol monomer; even under these conditions the equatorial and axial model alcohols (*trans*- and *cis*-4-*tert*-butylcyclohexanol) were found to be slightly associated.[13] It is of interest that molecular mechanics (MM2[15]) calculations—which, of course, refer to unassociated cyclohexanol—give a predicted value of −0.57 kcal/mol in excellent agreement with that determined chemically in a 79–155 °C temperature range. On the other hand, the NMR value is much closer to that (−0.95 kcal/mol) determined chemically in isopropyl alcohol solvent, where there is extensive dative and acceptor hydrogen bonding between cyclohexanol and the solvent. Although we also measured values for $\Delta G°$ of −0.93 kcal/mol by ^1H NMR for cyclohexanol-2,2,6,6-d_4 at −80 °C even in 10^{-3} M solution in CS_2, the value changed to −0.83 ± 0.01 kcal/mol in THF-d_8. This value is close to that (−0.77 kcal/mol) measured chemically[13] at much higher temperatures in 1,2-dimethoxyethane; apparently the intermolecular hydrogen bond is supplanted by a solute-to-solvent hydrogen bond in ether solvents. When methanol-d_4 (which provides a solvent-to-solute hydrogen bond) is added to the TFA-d_8 as a cosolvent, $\Delta G°$ goes back to −0.99 kcal/mol, a value close to that of presumably self-associated cyclohexanol.

(13) Eliel, E. L.; Gilbert, E. C. *J. Am. Chem. Soc.* **1969**, *91*, 5487.

(14) (a) Bushweller, C. H.; Beach, J. A.; O'Neil, J. W.; Rao, G. U. *J. Org. Chem.* **1970**, *35*, 2086. (b) Moulines, J.; Bats, J.-P.; Petraud, M. *Tetrahedron Lett.* **1972**, 2971. (c) Subbotin, O. A.; Sergeyev, N. *J. Chem. Soc., Chem. Commun.* **1976**, 141. (d) Pehk, T.; Kooskoroa, H.; Lippmaa, E. *Org. Mag. Reson.* **1976**, *8*, 5. (e) Subbotin, O. A.; Sergeyev, N. M.; Chlopkov, V. N.; Nikishova, N. G.; Bundel', Yu. G. *Ibid.* **1980**, *13*, 259. See also ref 20.

(15) Allinger, N. L.; Chang, S. H.-M.; Glaser, D. H.; Hönig, H. *Isr. J. Chem.* **1980**, *20*, 51. Allinger, N. L.; Yuh, Y. H. *QCPE* **1980**, *11*, 395.

(16) This value is in good agreement with that, −0.4 kcal/mol, found by Lüttringhaus et al. (Lüttringhaus, A.; Kabuss, S.; Prinzbach, H.; Langenbucher, F. *Liebig Ann. Chem.* **1962**, *653*, 195.) from infrared studies on the approximative assumption that bands due to unbonded and intramolecularly bonded OH have the same extinction coefficient.

(17) The $-\Delta G°$ values for OH[13] and OMe[18] (in cyclohexanol and its methyl ether) are nearly the same, 0.6 kcal/mol. We shall therefore assume that, except for the hydrogen bond, the two values would also be the same in **2** and **10** (Scheme I).

(18) Höfner, D.; Lesko, S. A.; Binsch, G. *Org. Magn. Reson.* **1978**, *11*, 179.

(19) This conclusion differs from that tentatively reached by Aaron and Ferguson (Aaron, H. S.; Ferguson, C. P. *Tetrahedron* **1974**, *30*, 803.) that the hydrogen-bond strength calculated from ref 16 is zero. This calculation disregards the unfavorable polar interaction of axial OH as compared to equatorial with ring-S. The observed[16] difference in the IR spectrum of **2** between OH-free and OH-bonded bands of 93 cm^{-1} is now in reasonable agreement with the strength of the hydrogen bond.

(20) Schneider, H.-J.; Hoppen, V. *J. Org. Chem.* **1978**, *43*, 3866.

(21) Eliel, E. L.; Hofer, O. *J. Am. Chem. Soc.* **1973**, *95*, 8041.

(22) Zefirov, N. S.; Gurvich, L. G.; Shaskov, A. S.; Krimer, M. Z.; Vorob'eva, E. A. *Tetrahedron* **1976**, *32*, 1211.

(23) Eliel, E. L.; Juaristi, E. *J. Am. Chem. Soc.* **1978**, *100*, 6114.

Table III. Conformational Free Energy (kcal/mol) for the Equilibrium of the Compounds Studied in This Work (See Scheme I)

compd	solv[a] (conc[b])	signals[c] measured	$K[OR_a]/[OR_e]$	$-\Delta G°$ (T, K)[d]
2	A (4)	1	0.04	−1.20
	A (0.0011)	2[e]	0.55 ± 0.05	−0.22 ± 0.03 (183)
	B		<0.03	<−1.3
	C		0.03 ± 0.01	−1.31 ± 0.08
3	A (1.17)	5	0.21 ± 0.03	−0.60 ± 0.05
	A (0.0003)	1[e]	0.07 ± 0.01	−1.05 ± 0.07
	B		<0.03	<−1.3
	C	3	0.12 ± 0.01	−0.82 ± 0.03
4	A (2.8)	5	0.085 ± 0.009	−0.95 ± 0.04 (183)
	A (0.0023)	1[e]	>32.3	>1.3 (183)
	B	5	0.19 ± 0.02	−0.61 ± 0.04 (183)
	C		<0.03	<−1.3
5	A (2.0)		<0.03	<−1.3
	A (0.002)	1[e]	0.65 ± 0.05	−0.16 ± 0.03
	B		<0.03	<−1.3
	C		<0.03	<−1.3
6	A (4.5)	1	1.10	0.04
	A (0.59)[f]	3	8.85 ± 1.16	0.83 ± 0.05
	B	3	0.76 ± 0.07	−0.10 ± 0.04
	C	3	0.69 ± 0.10	−0.15 ± 0.06
7	A (0.1)		>32.3	>1.3
	B		>32.3	>1.3
	C		>32.3	>1.3
8	A (1.0)	2	22.7 ± 3.8	1.19 ± 0.07
	B	4	8.5 ± 2.2	0.83 ± 0.12
	C	5	1.4 ± 0.3	0.12 ± 0.08
9	A (1.5)	3	6.03 ± 0.49	0.69 ± 0.03
	A (0.4)		>32.3	>1.3
	B	3	1.68 ± 0.05	0.20 ± 0.01
	C	3	2.68 ± 0.24	0.37 ± 0.03
10	A	4	0.04 ± 0.01	−1.08 ± 0.08 (173)
	B	2	0.038 ± 0.003	−1.19 ± 0.03 (183)
11	A	3	0.41 ± 0.03	−0.33 ± 0.04 (183)
	B	4	0.22 ± 0.02	−0.59 ± 0.03
	C	4	0.35 ± 0.03	−0.39 ± 0.03
12	A		<0.03	<−1.3
	B		<0.03	<−1.3
13	A		<0.03	<−1.3
	B		<0.03	<−1.3
14	A		<0.03	<−1.3
	B		<0.03	<−1.3
15	A	4	0.21 ± 0.04	−0.57 ± 0.06 (183)
	B	5	0.057 ± 0.014	−1.11 ± 0.10
16	A		<0.03	<−1.3
	B		<0.03	<−1.3
17	A		<0.03	<−1.3
	B		<0.03	<−1.3
18	A	3	2.89 ± 0.08	0.41 ± 0.02
	B	5	5.24 ± 0.59	0.64 ± 0.05
	C	4	4.59 ± 0.03	0.58 ± 0.01
19	A		>32.3	>1.3
	B		>32.3	>1.3
20	A	4	2.86 ± 0.14	0.38 ± 0.02 (183)
	B	4	10.07 ± 1.73	0.84 ± 0.06 (183)
	C	2	12.5 ± 0.3	0.97 ± 0.02
21	A	3	33.7 ± 1.6	1.28 ± 0.02 (183)
	C		>32.3	>1.3

[a] Solvent A is CD_2Cl_2; B, acetone-d_6; C, CD_3OD. [b] 0.1–0.5 M unless otherwise stated. [c] Number of signal pairs in the ^{13}C NMR spectrum used to evaluate K. [d] $OR_e \rightleftharpoons OR_a$ in kcal/mol at 193 K unless otherwise indicated. [e] By ^1H NMR. [f] $\Delta G° > 1.3$ at lower concentration.

be attenuated in the more polar solvent acetone); similar observations had previously been made in the case of 5-methoxy-1,3-dithiane.[23,24]

Before discussing the sulfoxides **3** and **4** and their derivatives, we must address their configurational assignment, which was accomplished on the basis of C-13 and proton chemical shifts. In Table II are listed the low-temperature C-13 shifts for both conformers of **3** and of **4**. A comparison is made in the table with shifts calculated by parametric addition, the shift parameters to be added being derived from the spectra of various cyclohexanols[14d,20,25] and of the conformers of thiane sulfoxide.[26] In a semiquantitative way it is seen that the cis isomer **4**—which exists as a diequatorial and diaxial conformer at low temperature—presents the sets of lowest (e,e conformer) and highest field shifts (a,a conformer), this being particularly notable in the shifts of C(3) and C(5) which would be subject to a γ-axial effect from an axial sulfoxide function. In contrast, the trans isomer **3**, which exists as

(24) Somewhat surprisingly, the $\Delta G°$ values for 3-methoxythiane and 5-methoxy-1,3-dithiane are almost the same.

(25) Stothers, J. B. "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972.

(26) Lambert, J. B.; Netzel, D. A.; Sun, H.-N.; Lilianstrom, K. K. *J. Am. Chem. Soc.* **1976**, *98*, 3778.

a,e or e,a conformations, shows intermediate shifts notably at C(3) and C(5). Proton spectroscopy is particularly useful in identifying the trans isomer **3**. In this isomer one of the $J_{2,3}$ coupling constants, clearly discerned, amounts to 9.4 Hz, indicating that the major conformer has axial carbinol-H, hence equatorial OH. At the same time the difference in chemical shift of the protons at C(6)—which are little affected by the distant hydroxyl—is only 0.32 ppm (δ_e 2.88 ppm, δ_a 2.56 ppm); such a small difference suggests an axial disposition of the sulfoxide oxygen.[27,28]

Low-temperature NMR examination of the trans isomer **3** (Figure 2 and Table III) was relatively uneventful. The isomer with equatorial OH predominates under all conditions, as one might have expected from the tendency of OH to be predominantly equatorial[13] and that of SO to be predominantly axial.[27] There is a slight concentration dependence of $\Delta G°$ in CD_2Cl_2 (Figure 2), the value varying from −0.60 kcal/mol at high concentration to −1.05 kcal/mol at the highest dilution. This trend is the opposite from that seen in cyclohexanol and probably implies that intermolecular hydrogen bonding (at 1.17 M concentration) is of the S–O···H–O type (rather than O–H···O–H) and that it is therefore favored when some appreciable fraction of the molecules exists with equatorial SO (and hence axial OH). The equilibrium is also shifted toward equatorial SO in CD_3OD where the hydrogen bond is presumably from the solvent to the SO of the solute. In dilute solution (3×10^{-4} M) in CD_2Cl_2, ($\Delta G° = -1.05$ kcal/mol), equatorial OH is more favored; $\Delta G°$ differs only slightly from the value of −0.8 kcal/mol which would correspond to additivity between the equatorial preference of OH (0.6 kcal/mol)[13] and the axial preference of SO (0.2 kcal/mol).[27] In acetone, which is a hydrogen-bond acceptor but not a donor (in contrast to methanol), equatorial OH is favored even more.

A much more dramatic result is obtained with the cis sulfoxide **4**.[29] Here (cf. Figure 3 and Table III) $\Delta G°$ in CD_2Cl_2 varies from −0.95 kcal/mol at 2.8 M to more than +1.3 kcal/mol at 2.3×10^{-3} M,[30] i.e., there is a change in $\Delta G°$ over the concentration range investigated of 2.25 kcal/mol corresponding to a change in equilibrium from $K \simeq 12$ in favor of the equatorial conformer to essentially total predominance of the axial one. A reasonable explanation is to assume that in concentrated solution hydrogen bonding is largely *inter*molecular and of the S–O···H–O type; this kind of bonding is optimal when both functions are equatorial and the energy gained by the intermolecular hydrogen bond forces them to be in that position. At high dilution, on the other hand, where association is inhibited by entropic considerations, the molecule is stabilized by an *intra*molecular hydrogen bond which forces it into the diaxial conformation. The plot of $\Delta G°$ vs. concentration (Figure 3) does not come to a plateau at either end, showing that the 2.25-kcal/mol range in $\Delta G°$ is imposed merely by the limitations of our measurements; the true range between infinite and infinitesimal substrate concentration would be considerably larger. In methanol-d_4, in fact, the diaxial isomer of **4** is no longer seen ($\Delta G°$ < −1.3 kcal/mol); hydrogen bonding from the solvent to the sulfoxide forces the latter into the equatorial position. An intermediate situation is seen in acetone-d_6 which can

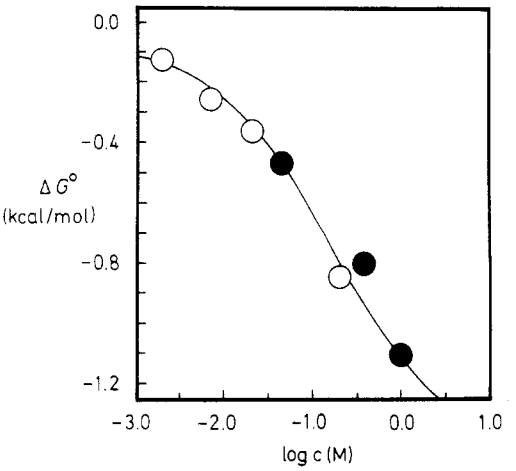
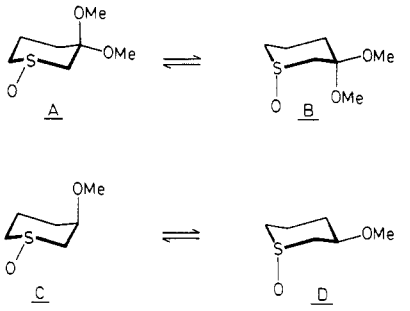


Figure 4. Plot of $\Delta G°$ (kcal/mol) vs. molar concentration for the conformational equilibrium of **5**: open circles, ^1H data; filled circles, ^{13}C data.

Scheme III



interact only with the OH function: this solvent does force the molecule into a predominantly diequatorial conformation (i.e., it breaks the intramolecular hydrogen bond) but it does so less than self-association and much less than CD_3OD (cf. Table III).

The sulfone **5** (Figure 4 and Table III) behaves similarly to the cis sulfoxide **4**, but somewhat less so. At the highest concentration in CD_2Cl_2 (2.0 M) the hydroxyl is entirely equatorial ($\Delta G° < -1.3$ kcal/mol), suggesting strong intermolecular hydrogen bonding. ($\Delta G°$ has not yet come to a plateau but higher concentratons cannot be investigated, both because of solubility problems and because a further increase in the equatorial conformer population cannot be fathomed experimentally.) At the lowest concentration studied (2×10^{-3} M) the diequatorial conformation is still preferred but $\Delta G°$ is now only −0.16 kcal/mol, indicating that hydrogen bonding to the less polar (compared to SO) sulfone function is too weak to force even a majority of the molecules into the axial conformation. In fact, there seems to be almost a stand-off between hydrogen bonding (which would favor OH_{ax}) and steric and dipolar O/O repulsion (which would favor OH_{eq}).[31] Under these circumstances it is understandable

(27) Lambert, J. B.; Keske, R. G. *J. Org. Chem.* **1966**, *31*, 3429.
(28) Equatorial SO induces a large shift difference (0.87 ppm) between adjacent axial and equatorial protons (see ref 27).
(29) For a preliminary report, see: Eliel, E. L.; Brunet, E. *Tetrahedron Lett.* **1985**, *26*, 3421.
(30) Lower concentrations were not investigated because already at 0.0023 M the diequatorial conformer could no longer be detected in the ^1H NMR spectrum.
(31) One can estimate the RO:OS syn-axial interaction in the *cis*-sulfoxide/methyl ether **12** (and, implicitly, in the sulfone methyl ether **13** and the corresponding acetates **16** and **17**) as follows: Anteunis[6] has measured a $\Delta G°$ value of 1.2 kcal/mol in $CHCl_2F$ for the ketal sulfoxide **22** (Scheme III). whereas we measure −0.33 kcal/mol in CD_2Cl_2 for ether sulfoxide **11**. If we assume, arbitrarily, that structures A and C in Scheme III are isoenergetic (A = C), then, energywise, B–A = 1.2 kcal/mol; D–C = −0.33 kcal/mol; (B–A) − (D–C) = B–D = 1.53 kcal/mol. The interaction in D is that of an axial sulfoxide, −0.2 kcal/mol;[27] hence B − (−0.2) = 1.53 or B = 1.33 kcal/mol. If the SO:H *syn*-diaxial interaction is taken to be −0.1 kcal/mol[27] and the OMe:H = 0.3 kcal/mol,[18] the SO:OMe interaction is 1.13 kcal/mol. It is therefore not surprisingly that in the *cis*-sulfoxide series (**12**, **16**) and the sulfone series (**13**, **17**) the axial isomer is shunned in the absence of intramolecular hydrogen bonding.

Table IV. Conformational Free Energy (kcal/mol) for the Equilibrium of the Indicated Compounds

compd	solv[a] (concn)[b]	signals[c] measured	$K[OR_a]/[OR_e]$	$\Delta G°$ (T, K)[d]
1-methylcyclohexanol	A	3	1.82 ± 0.33	0.23 ± 0.07 (200)
	A (0.01)	3	2.90 ± 0.30	0.41 ± 0.04
	B	3	3.70 ± 0.38	0.50 ± 0.04
	C	3	2.78 ± 0.25	0.39 ± 0.04
1-acetoxy-1-methylcyclohexane	A	2	6.69 ± 0.55	0.73 ± 0.04
	B	2	8.44 ± 0.56	0.82 ± 0.03

[a] Solvent A is CD_2Cl_2; B, acetone-d_6; C, CD_3OD. [b] 0.1–0.5 M unless otherwise stated. [c] Number of signal pairs in the ^{13}C NMR spectrum used to evaulate K. [d] 193 K unless otherwise indicated.

that not only a hydrogen donor/acceptor solvent (CD_3OD) but even a pure acceptor solvent (CD_3COCD_3) can force the equilibrium completely back to the equatorial side (Table III). However, even in the methyl ether **13** and the acetate **17** equilibrium is entirely on the equatorial side, showing that the equatorial isomer is by far the predominant one in the absence of hydrogen bonding as well and that the partial shift of the alcohol **5** toward the axial side in 0.002 M solution in CD_2Cl_2 must, in fact, be due to intramolecular (albeit weak) hydrogen bonding. The same argument applies to the cis sulfoxide ether **12** and acetate **16**.[31] In both, the conformational equilibrium is entirely on the diequatorial side. In contrast, the methyl ether **11** and acetate **15** of the trans alcohol **3** show more evenly balanced conformational equilibria, with the equatorial isomer favored in both cases, more so in the case of the acetate than that of the ether, and with some solvent effect in methanol-d_4, which, for reasons already explained, biasses the equilibrium toward the conformer with equatorial sulfoxide.

Alcohols **6–9** and their acetates **18–21** were investigated with the hope that the geminal methyl group might act as a "counterpoise" in cases where the equilibria discussed above were quite one-sided. It was anticipated that the results might be only semiquantitatively meaningful since the $\Delta G°$ values of geminal substituents tend not to be additive.[32] In the present work it was confirmed (cf. Table IV) that $\Delta G°$ ($OH_a \rightleftharpoons OH_e$) for 1-methylcyclohexanol is in the 0.2–0.5-kcal/mol range[14e] whereas the calculated value is 0.7–1.1 kcal/mol. (For 1-methylcyclohexyl acetate the observed value of 0.7–0.8 kcal/mol compares better with the calculated 0.9 kcal/mol.) An additional complications is introduced in that the $-\Delta G°$ value for methyl in 3-methylthiane sulfoxide is not known (it is, however, probably close to the value of 1.4 kcal/mol measured for 3-methylthiane[3]) and that nothing is known, a priori about the SO/Me syn-axial interaction which comes into play in one of the conformers of trans sulfoxide **7** and of sulfone **9**; the same applies to the SO/OAc interaction in **19** and **21**.[31]

In the few cases where comparisons are possible, the values of $\Delta G°$ calculated on the assumption of geminal additivity are sometimes close to the observed ones and other times not. Thus for **6** in concentrated solution one calculates +0.2 kcal/mol ($OH_a \rightleftharpoons OH_e$) whereas the experimental value is +0.04 kcal/mol; in dilute solution one calculates +1.2 kcal/mol and finds +0.83 kcal/mol (the latter value would probably increase somewhat in more dilute solution). Agreement is less good for the corresponding acetate **18** where one calculates a value of 0 or greater but finds values in the −0.4 to −0.6 kcal/mol range. For the cis sulfoxides **8** and **20** one calculates the following values compared to the ones found (in parentheses): **8**, concentrated CD_2Cl_2 +0.45 (+1.19); acetone-d_6, +0.8 (+0.83); CD_3OD, ≤0 (+0.12); **20**, ≤0 (0.4–1.0) kcal/mol.

Comparison of the data for the trans sulfoxides **7** and **19** suggests that the Me/SO/H syn-axial interaction is over 2 kcal/mol,[33] since the introduction of the geminal methyl group changes equilibria which are sometimes substantially on the side of equatorial OH or OAc to equilibria which are entirely on the side of axial OH or OAc (and hence equatorial Me so as to avoid the syn-axial interaction with the methyl group). It is of interest to apply this finding to the sulfones **9** and **21** since equilibria for the lower homologues **5** and **17** are entirely on the side of equatorial OH or OAc (except for OH in very dilute CD_2Cl_2 solution). The geminal methyl substituent reverses this situation and suggests that the equatorial preference of OH in concentrated CD_2Cl_2 or CD_3COCD_3 amounts to approximately 2 kcal/mol whereas that for the corresponding acetate (where no intermolecular hydrogen bonding is possible for equatorial OR) amounts to only 1.3 kcal/mol.

Discussion

Calculations. The most important conclusion from this work is that the competition between intramolecular and intermolecular hydrogen bonding may lead to a substantial change in conformational equilibrium in a nonpolar solvent with concentration (cf. compounds **2–5** and **10**), in addition to the usual change observed when the solvent is changed into a more polar one, especially when the latter is a hydrogen donor or acceptor.[13] In some cases the change is quite dramatic (cf. compound **4**[29]), shifting the equilibrium from one almost entirely on the equatorial-OH side to one in which the OH is almost entirely axial. It is once again confirmed that the O/S: gauche interaction is more repulsive than O/CH[22,23,34] (cf. compounds **10**, **14**, **18**), whereas RO/SO (compound **11**) is less repulsive (however, this is not true for AcO/SO, perhaps because the acetyl substituent diminishes the negative charge on oxygen and thereby the O/SO attraction; cf. compound **15**). The SO:O syn-axial interaction seen in sulfones **5**, **13**, **17** is evidently large and forces these compounds into the equatorial conformation unless there is a strong intramolecular hydrogen bond stabilizing the syn-axial OH··OS arrangement (compounds **4** and **5** in dilute solution); the CH_3:SO syn-axial interaction in compounds **7**, **19**, **9**, and **21** is even larger, amounting to an estimated 2.4 kcal/mol, approximately.[33]

In order to gain a better understanding of the factors involved in the interactions studied experimentally, we carried out MM2[15] calculations for a number of the compounds above and GAUSSIAN-80 ab initio calculations[35] for some of them, using the geometry optimized by MM2. The

(32) Eliel, E. L.; Enanoza, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 8072.

(33) MM2 calculations[15] performed for *cis*-3-methylthiane *S*-oxide and the corresponding sulfone predict values of 2.0 and 2.4 kcal/mol, respectively, for the Me/SO/H *syn*-axial interaction.

(34) Kaloustian, M. K.; Dennis, N.; Mager, S.; Evans, S. A.; Alcudia, F.; Eliel, E. L. *J. Am. Chem. Soc.* **1976**, *98*, 956.

(35) Binkley, J. S.; Whiteside, R. A.; Krishnan, R.; Seeger, R.; DeFrees, D. J.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. *QCPE* **1981**, *13*, 406.

Table V. Calculated (MM2[15] and GAUSSIAN-80[35]) and Experimental Energy ($\Delta G°$) Differences between the Two Chair Conformations of the Indicated Compounds (kcal/mol)

compd	$\Delta G°$	ΔE (MM2)[h]	ΔE (GAUSSIAN 80)[a]			
			STO-3G	STO-3G*	STO-4G	STO-4G*
cyclohexanol	−0.60[b]	−0.56				
methoxycyclohexane	−0.60[c]	−0.56				
acetoxycyclohexane	−0.80[d]	−0.44				
thiane *S*-oxide	0.18[e]	0.17				
trans-3-methylthiane *S*-oxide		−1.12				
3-methylthiane	−1.40[f]	−1.44				
3-hydroxythiane (**2**)	−0.22[g]	−1.24	−0.09	0.19	−0.01	0.27
3-methoxythiane (**10**)	−1.08[g]	−1.05				
3-acetoxythiane (**14**)	<−1.3[g]	−0.42				
cis-3-hydroxythiane *S*-oxide (**4**)	>1.3[g]	0.48	1.68	1.12	1.83	1.33
cis-3-methoxythiane *S*-oxide (**12**)	<−1.3[g]	2.20				
trans-3-hydroxythiane *S*-oxide	−0.92[g]	−1.11				
3-hydroxythiane *S,S*-dioxide (**5**)	−0.28[g]	−1.69	0.27	0.09		

[a] Calculations made for the indicated basis sets. [b] Reference 12. [c] Reference 18. [d] Reference 20. [e] Reference 27. [f] Reference 3. [g] This work. [h] 1977 version.

Table VI. Room-Temperature ^{13}C NMR Parameters of the Compounds Studied in This Work (See Scheme I)

compd (solvent)[a]	chemical shifts (ppm)							
	C(2)	C(3)	C(4)	C(5)	C(6)	3-Me	Me	CO
2	34.6	67.2	33.9	26.3	27.2			
3	53.1	62.4	33.6	16.6	46.5			
4 (CD_3OD)	57.6	66.5	34.0	17.6	50.5			
5	57.5	66.8	32.3	19.2	50.9			
6	41.4	65.2	38.2	24.0	28.8	27.7		
7	62.0	71.0	37.4	17.8	50.6	30.8		
8	50.3	69.7	37.3	11.8	44.6	30.8		
9	60.0	70.3	36.8	19.2	50.6	29.7		
10 (acetone-d_6)	33.0	78.3	32.4	28.4	28.4		55.6	
11 (CD_2Cl_2)	47.9	72.6	30.9	17.0	51.6		56.5	
12	55.7	74.1	30.4	17.3	51.0		56.3	
13	55.5	75.4	29.9	19.1	50.5		56.2	
14	31.9	70.8	31.5	27.2	27.7		21.0	169.9
15 (acetone-d_6)	50.4	66.7	31.3	17.1	46.7		21.0	170.0
16	54.8	67.5	30.3	17.0	50.7		20.9	169.9
17	55.6	69.4	29.9	20.2	51.0		20.8	169.9
18	37.5	78.0	36.4	24.4	27.9	24.2	22.4	170.3
19	57.6	80.7	35.2	17.1	50.0	25.4	21.4	169.3
20	51.6	77.0	36.3	14.3	47.5	25.6	21.8	170.3
21	55.4	78.6	36.5	18.7	51.0	25.6	21.9	170.4

[a] Solvent is $CDCl_3$ unless otherwise indicated (0.5–2 M concentration range).

results are shown in Table V. It is of interest that the MM2 calculation gives results in reasonable agreement with the experimental findings in most cases *except* those in which intramolecular hydrogen bonding plays an important role (compounds **2**, **4**, **5**). With these three compounds MM2 predicts equatorial preferences for OH which are over 1 kcal/mol larger than the observed ones.[36] Yet the GAUSSIAN-80 calculations for these same compounds are in reasonable agreement with experimental data. It thus appears that MM2 (which handles hydrogen bonding as a simple electrostatic interaction) does not take the strength of the hydrogen bond sufficiently into account, perhaps because there are other aspects to hydrogen bonding than electrostatics. In contrast, the ab initio calculations does seem to account for the entire hydrogen-bond energy.

Experimental Section

^1H (250 MHz) and ^{13}C NMR (62.87 MHz) spectra were recorded on a Bruker WM-250 instrument (coupled to an ASPECT 2000 computer) equipped with 5-mm duel $^1H/^{13}C$ probe operated in pulsed FT mode and locked on solvent deuterium. Low-temperature spectra were recorded with a Bruker B-VT 1000 temperature controller and temperature values are expected to be within ±3 K. The ^{13}C spectral parameters were set depending on the particular compound and concentration to get a reasonable S/N ratio in order to accurately integrate the signals. We observed no appreciable changes in peak area ratios over a wide range of conditions (30° to 90° pulse angle and 0.08 to 0.65 s acquisition time) in a model compound in which the equilibrium was rather biassed toward one conformer. Typical conditions are as follows: 6.3 KHz (100 ppm) spectral width, 60° pulse angle (9 μs pulse width), 0.16–0.32 s acquisition time with transforming 8K data points with 4–6K zero-filling. For area measurements portions of the spectra were expanded, the individual peaks electronically integrated, and the ratio of the peaks of the integral tracings taken as peak area ratios. ^2H NMR (38.38 MHz) spectra were recorded on the same instrument by using a 10-mm BB probe without lock.

Boiling and melting points were uncorrected. Microanalyses were performed by M-H-W Laboratories. High-resolution mass spectra were recorded by Triangle Laboratories.

3-Hydroxythiacyclohexane (2). To a cold solution of 10 g (86 mmol) of 3-oxothiacyclohexane[9] in 100 mL of ethanol was added 3.28 g (86 mmol) of sodium borohydride in small portions. The reaction mixture was stirred for 2 h and the solvent removed. The residue was treated with 20 mL of water and extracted with chloroform. Standard workup of the extracts and distillation of the resulting oil yielded 9 g (88%) of **1**, bp 45–47 °C (0.4 mm) (lit.[9] bp 114–118 °C (24 mm)): IR (film) 3350, 2920, 2840, 1030, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52 (m, 1 H), 1.79 (m, 2 H), 2.06 (m, 1 H), 2.19 (d, 1 H, J = 7.4 Hz), 2.48 (m, 2 H), 2.55 (m, 1 H), 2.82 (m, 1 H), 3.91 (m, 1 H).

The *2,2,4,4-d*$_4$ derivative **2′** was obtained by refluxing 3-oxothiacyclohexane[9] for 2 h in a 40-fold molar excess of D_2O con-

(36) MM2 predicts the OH to point almost exactly at the center of the chair rater than at the S, SO, and SO_2 function.

taining a catalytic amount of anhydrous potassium carbonate. Extraction with chloroform and standard workup afforded crude 3-oxothiacyclohexane-*2,2,4,4-d*$_4$ which was reduced with sodium borohydride as described above: bp 110–111 °C (18 mm); IR (film) 3370, 2920, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.73 (m, 1 H), 2.03 (m, 1 H), 2.43 (m, 3 H), 3.79 (s br, 1 H); ^{2}H NMR ($CHCl_3$) δ 1.28 (1 H), 1.75 (1 H), 2.39 (1 H), 2.62 (1 H).

The *O*-methyl derivative **10** was prepared by successively treating **2** with sodium hydride and methyl iodide following standard procedures: yield 74% after distillation (Kugelrohr): bp 76–77 °C (18 mm); IR (film) 2930 and 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (m, 1 H), 1.75 (m, 1 H), 2.10 (m, 2 H), 2.42 (m, 3 H), 2.83 (m, 1 H), 3.35 (m, 1 H), 3.38 (s, 3 H).

The acetyl derivative **14**, obtained from **2** and acetic anhydride in pyridine following standard procedures, was purified by distillation (Kugelrohr): yield 91%, bp 75–80 °C (0.9 mm); IR (film) 2950, 1740, 1240, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (m, 1 H), 1.90 (m, 2 H), 2.04 (s, 3 H), 2.13 (m, 1 H), 2.50 (m, 2 H), 2.58 (m, 1 H), 2.75 (m, 1 H), 4.88 (m, 1 H).

3-Hydroxythiacyclohexane *S*-Oxide (3, 4). To a solution of 2 g (17 mmol) of **2** in 20 mL of water was added slowly a saturated solution of 3.6 g (17 mmol) of sodium metaperiodate in water at 0–5 °C. The reaction mixture was stirred overnight at room temperature and the solvent removed. The residue was extracted several times with hot ethyl acetate and the solvent evaporated, yielding 2.1 g (92%) of a mixture of the two possible diastereomers (2.4:1 ratio by ^{13}C NMR) of the sulfoxide. The major isomer was designated **3** and crystallized from ethyl acetate (mp 101–102 °C). The minor isomer (**4**) obtained from the mother liquors was purified by flash chromatography[37] on silica gel [chloroform–methanol (14:1)] and did not crystallize in our hands. IR **3** (Nujol): 3310, 1065, 1000 cm^{-1}. IR **4** (film): 3400, 1050, 1005 cm^{-1}. ^{1}H NMR **3** ($CDCl_3$): δ 1.54 (m, 1 H), 2.02 (m, 2 H), 2.37 (m, 1 H), 2.56 (m, 2 H), 2.88 (m, 1 H), 3.16 (m, 1 H), 3.52 (d, 1 H, J = 4.2 Hz), 4.38 (m, 1 H). ^{1}H NMR **4** (CD_3OD, 4.3%): δ 1.37–1.69 (m, 2 H), 1.95 (m, 1 H), 2.20 (m, 1 H), 2.55–2.68 (m, 2 H), 3.29–3.36 (m, 1 H, overlaid by solvent), 3.51 (d of m, 1 H, J_d = 11.4 Hz), 3.80 (t of t, 1 H), 4.61 (s, ca. 1 H, OH). *Note:* In $CDCl_3$ and CD_2Cl_2 the spectrum of **4** is extremely concentration dependent because of the strong concentration dependence of the **4(e,e)**/**4(a,a)** equilibrium (see text) and the large difference in chemical shift of some of the signals in **4(e,e)** and **4(a,a)** (cf. Table II).

The 2,2,4,4-*d*$_4$ derivatives **3′** and **4′** were obtained from **2′** following the procedure described for the undeuterated species, mp (**3**) 95–97 °C; **4** did not crystallize. IR **3** (Nujol): 3330, 1150, 1110, 1065, 1032, 1020, 1003 cm^{-1}. IR **4** (film): 3360, 1150, 1030 cm^{-1}. ^{1}H NMR **3** (CD_2Cl_2): δ 1.97 (m, 1 H), 2.28 (m, 1 H), 2.52 (m, 1 H), 2.81 (m, 1 H), 4.39 (s, br, 1 H). ^{1}H NMR **4** (CD_2Cl_2): δ 1.62 (m, 1 H), 2.49 (m, 1 H), 2.62 8 (m, 1 H), 2.93 (m, 1 H), 4.08 (d, 1 H, J = 8.7 Hz), 4.75 (d, 1 H, J = 8.7 Hz). ^{2}H NMR **3** ($CHCl_3$/$CDCl_3$): 1.50 (1 H), 2.00 (1 H), 2.55 (1 H), 3.13 (1 H). ^{1}H NMR **4** ($CHCl_3$/$CDCl_3$): 1.77 (1 H), 2.02 (1 H), 2.59 (1 H), 3.26 (1 H).

The *O*-methyl derivatives **11** and **12** were obtained by phase-transfer methylation of **3** and **4**, respectively, following the procedure described by Merz.[38] Compound **3** gave **11** quantitatively but, under the same conditions, **4** yielded a (6:1) mixture of **12** (major product) and starting material, separated by flash chromatography[37] on silica gel [ethyl acetate–methanol (4:1)]. Neither **11** nor **12** crystallized in our hands. IR **11** (film): 1080 and 995 cm^{-1}. IR **12** (film): 1085 and 1000 cm^{-1}. ^{1}H NMR **11** ($CDCl_3$): δ 1.52 (m, 1 H), 2.00 (m, 2 H), 2.28 (m, 1 H), 2.60 (m, 2 H), 2.83 (m, 1 H), 3.13 (m, 1 H), 3.36 (s, 3 H), 3.94 (m, 1 H). ^{1}H NMR **12** ($CDCl_3$): δ 1.35 (m, 1 H), 1.52 (m, 1 H), 2.10 (m, 2 H), 2.50 (m, 2 H), 3.30 (m, 2 H), 3.38 (s, 3 H), 3.65 (m, 1 H). MS, *m/e* **11** 148 (44), 117 (27), 85 (100), 67 (42); **12** 148 (97), 117 (51), 85 (100), 67 (66). Exact mass calcd for $C_6H_{12}O_2S$ M^+, 148.06, found (**11**) 148.06, (**12**) 148.06.

The acetyl derivatives **15** and **16** were obtained from **3** and **4**, respectively, by treatment with acetic anhydride in pyridine following standard procedures and were purified by recrystallization from ethyl ether, mp (**15**) 80–81 °C, (**16**) 58–65 °C. IR **15** (Nujol): 1735, 1255, 1033, 1012 cm^{-1}. IR **16** (Nujol): 1740, 1260, 1040, 1022 cm^{-1}. ^{1}H NMR **15** ($CDCl_3$): δ 1.62 (m, 1 H), 1.96 (m, 2 H), 2.02 (s, 3 H), 2.38 (m, 1 H), 2.64 (m, 2 H), 2.82 (m, 1 H), 3.09 (m, 1 H), 5.38 (m, 1 H). ^{1}H NMR ($CDCl_3$): δ 1.51 (m, 1 H), 1.62 (m, 1 H), 1.96 (m, 1 H), 2.04 (s, 3 H), 2.15 (m, 1 H), 2.51 (m, 1 H), 2.62 (m, 1 H), 3.27 (m, 1 H), 3.49 (m, 1 H), 4.85 (m, 1 H). Anal. Calcd for $C_7H_{12}O_3S$: C, 47.71; H, 6.86. Found: (**15**) C, 47.79, H, 6.81; (**16**) C, 47.84, H, 6.99.

3-Hydroxythiacyclohexane *S,S*-Dioxide (5). To a solution of 0.5 g (4.2 mmol) of **2** in 25 mL chloroform was added 1.72 g (8.4 mmol) of *m*-chloroperoxybenzoic acid in small portions at 0–5 °C. The reaction mixture was stirred for 2 h at room temperature and concentrated to half of its volume, and the precipitated *m*-chlorobenzoic acid was filtered. Following solvent removal 0.4 g (63%) of the sulfone **5** was obtained after purification by flash chromatography[37] on silica gel (ethyl acetate): mp 82–86 °C (lit.[9] mp 94–95 °C); IR (Nujol) 3455, 3350, 1315, 1290, 1280, 1245, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61 (m, 1 H), 1.95 (m, 2 H), 2.20 (m, 1 H), 2.80 (s, br, 1 H), 2.95 (m, 2 H), 2.97 (m, 1 H), 3.29 (m, 1 H), 4.22 (m, 1 H).

The 2,2,4,4-*d*$_4$ derivative **5′** was obtained from **2′** following the same procedure as for **5**, mp 84–87 °C: IR (Nujol) 3400, 1320, 1285, 1150, 1135 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.01 (m, 1 H), 2.26 (m, 1 H), 2.78 (d, 1 H, J = 7.6 Hz), 2.96 (m, 2 H), 4.30 (d, 1 H, J = 7.6 Hz); ^{2}H NMR ($CHCl_3$/$CDCl_3$) δ 1.63 (1 H), 1.95 (1 H), 3.00 (1 H), 3.29 (1 H).

The *O*-methyl derivative **13** was obtained by treatment of 0.23 g (1.7 mmol) of **10** in 10 mL of water with 0.73 g (3.4 mmol) of sodium metaperiodate at 0–5 °C. The mixture was stirred overnight at room temperature, the solvent was removed, and the solid mass was extracted with ethyl acetate, yielding 0.28 g of crude **7**. The methoxy sulfone was purified by flash chromatography[37] on silica gel [ethyl acetate–hexane (2:1)] and recrystallized from ethyl ether: mp 62–63 °C; IR (Nujol) 1315, 1290, 1140, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.37 (m, 1 H), 1.88 (m, 1 H), 2.13 (m, 2 H), 2.88 (m, 3 H), 3.35 (s, 3 H), 3.39 (m, 1 H), 3.64 (m, 1 H). Anal. Calcd for $C_6H_{12}O_3S$: C, 43.88; H, 7.37. Found: C, 44.26; H, 7.29.

The acetyl derivative **17** was obtained by oxidation of **14** with 2 equiv of sodium metaperiodate and purified by recrystallization from ethyl ether: mp 133.5–134.5 °C; IR (Nujol) 1740, 1305, 1290, 1260, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (m, 1 H), 2.00 (m, 1 H), 2.05 (s, 3 H), 2.15 (m, 2 H), 2.95 (m, 3 H), 3.36 (m, 1 H), 5.09 (m, 1 H). Anal. Calcd for $C_7H_{12}O_4S$: C, 43.73, H, 6.29. Found: C, 43.79, H, 6.40.

3-Hydroxy-3-methylthiacyclohexane (6). To a solution of 1.16 g (10 mmol) of 3-oxothiacyclohexane in 10 mL of anhydrous ethyl ether was added 14 mL of a 2.9 N solution of methylmagnesium bromide in ethyl ether (40 mmol) under N_2 at 0 °C. The mixture was stirred 10 min; 20 mL of water was then added cautiously. Standard workup of the mixture and distillation of the product afforded 0.90 g (68%) of **10**: bp 45–47 °C (0.5 mm); IR (film) 3400, 2900, 930, 905, 865 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.37 (m, 1 H), 1.68 (m, 1 H), 1.89 (m, 2 H), 2.45 (m, 3 H), 2.72 (d, 1 H, J = 13.4 Hz), 3.19 (s, 1 H).

The acetyl derivative **18** was obtained by treatment of 0.50 g of **10** with 2 mL of acetic anhydride and a catalytic amount of 4-(dimethylamino)piridine at 70 °C for 10 h. The mixture was cooled and poured into 10 mL of water. The aqueous solution was carefully neutralized with sodium bicarbonate and extracted several times with chloroform. Standard workup of the extracts and flash chromatography[37] on silica gel [ethyl acetate–hexane (1:9)] yielded 0.27 g of product: IR (film) 1730, 1370, 1230, 1075, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 3 H), 1.56 (m, 1 H), 1.90 (m, 3 H), 2.03 (s, 3 H), 2.48 (m, 2 H), 2.69 (d, 1 H, J = 13.7 Hz), 3.20 (ddd, 1 H, J = 14.14, 13.7 Hz).

3-Hydroxy-3-methylthiacyclohexane *S*-Oxide (7, 8). A solution of 0.5 g (3.8 mmol) of **6** in 50 mL of water was treated with 0.75 g (3.8 mmol) of potassium metaperiodate at 0–5 °C and stirred at room temperature for 24 h. The solvent was removed and the residue extracted several times with ethyl acetate, yielding 0.53 g (95%) of a mixture of the two diastereomers **7** and **8** (ratio 2:1 by ^{13}C NMR). The isomers were separated by flash chromatography[37] on silica gel [chloroform–methanol (12:1)]; mp (**7**) 80.5–81.5 °C; (**8**) 61–65 °C. IR **7** (Nujol): 3330, 1205, 1115, 1085, 990, 940 cm^{-1}. IR **8** (Nujol): 3340, 1235, 1080, 970, 930 cm^{-1}. ^{1}H

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NMR 7 ($CDCl_3$): δ 1.37 (s, 3 H), 1.49 (m, 1 H), 1.69 (m, 1 H), 2.00 (m, 2 H), 2.48 (m, 1 H), 2.53 (d, 1 H, J = 12.3 Hz), 3.30 (m, 1 H), 3.38 (ddd, 1 H, J's = 2.3, 2.3, 12.3 Hz), 3.42 (s, br, 1 H). ^{1}H NMR 8 ($CDCl_3$): δ 1.22 (s, 3 H), 1.56 (m, 1 H), 1.84 (m, 1 H), 1.92 (m, 1 H), 2.03 (s, br, 1 H), 2.26 (d, 1 H, J = 14.3 Hz), 2.41 (m, 1 H), 2.68 (m, 1 H), 3.10 (m, 2 H). Anal. Calcd for $C_6H_{12}O_2S$: C, 48.62, H, 8.16. Found: C, 48.73, H, 8.32 (mixture of diastereomers).

The acetyl derivative **19** was obtained by treatment of 0.14 g of **7** with 1 mL of acetic anhydride and a catalytic amount of 4-(dimethylamino)pyridine at 65 °C for 90 min. The mixture was cooled and poured into 2 mL of water. The solution was carefully neutralized with sodium carbonate and repeatedly extracted with chloroform. Workup of the extracts and purification of the crude product by flash chromatography[37] on silica gel [chloroform–methanol (80:1)] gave **19**: IR (film) 1730, 1230, 1080, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40 (m, 1 H), 1.52 (s, 3 H), 1.80 (m, 2 H), 1.90 (s, 3 H), 2.11 (m, 1 H), 2.46 (m, 1 H), 2.51 (d, 1 H, J = 12.8 Hz), 3.22 (m, 1 H), 3.93 (ddd, 1 H, J = 2.4, 2.4, 12.6 Hz); MS, m/e 190 (9), 172 (15), 130 (100), 113 (22), 101 (57), 81 (100), 69 (51). Exact mass calcd for $C_8H_{14}O_3S$ M^+, 190.067, found 190.064.

The acetyl derivative **20** was obtained from **8** following the same procedure described for **19**. The resulting crude acetoxy sulfoxide was purified by flash chromatography[37] on silica gel [chloroform–methanol (100:1)]: IR (film) 1730, 1240, 1185, 1015 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 3 H), 1.72 (m, 2 H), 2.01 (s, 3 H), 2.02 (m, 1 H), 2.48 (m, 1 H), 2.83 (m, 2 H), 2.92 (d, 1 H, J = 13.5 Hz), 3.70 (d, 1 H, J = 13.5 Hz); MS, m/e 190 (43), 130 (65), 113 (18), 101 (15), 81 (100), 69 (31). Exact mass calcd for $C_8H_{14}O_3S$ M^+, 190.067, found 190.063.

3-Hydroxy-3-methylthiacyclohexane *S*,*S*-Dioxide (9). A solution of 0.5 g (3.8 mmol) of **6** in 20 mL of water was treated at 5–10 °C with 1.62 g (7.6 mmol) of sodium metaperiodate and stirred at room temperature overnight. The solvent was removed and the residue extracted several times with ethyl acetate, yielding 0.45 g (73%) of **9** which was purified by recrystallization from ethyl acetate–ethyl ether: mp 79–79.5 °C; IR (Nujol) 3480, 1315, 1265, 1200, 1185, 1145, 1115, 1000, 940, 915, 865 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 3 H), 1.51 (m, 1 H), 1.88 (m, 1 H), 2.09 (m, 1 H), 2.28 (m, 1 H), 3.05 (m, 1 H), 4.05 (s, 1 H).

The acetyl derivative **21** was obtained by oxidation of **6** with 2 equiv of sodium metaperiodate and was purified by recrystallization from ethyl acetate–ethyl ether: mp 130–131 °C; IR (Nujol) 1730, 1230, 1140, 1100, 1020, 950, 865 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.53 (m, 1 H), 1.61 (s, 3 H), 2.00 (m, 2 H), 2.04 (s, 3 H), 2.36 (m, 1 H), 2.95 (m, 2 H), 2.99 (d, 1 H, J = 15.3 Hz), 4.16 (ddd, 1 H, J = 1.8, 3.4, 14.8 Hz). Anal. Calcd for $C_8H_{14}O_4S$: C, 46.59, H, 6.84. Found: C, 46.85, H, 7.07.

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Synthetic Studies Relating to the Structure of Senoxydene. A Sequential Annulation Approach to Angular Triquinane Construction Capable of Varied Tetramethyl Substitution Patterns

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A totally stereocontrolled route to the sesquiterpene known as senoxydene is described. The key phases of the synthesis involve a thermal ene reaction to set stereochemistry while constructing the diquinane segment and a vinylsilane-mediated annulation to elaborate the third, unsaturated five-membered ring. Our findings have disclosed that the natural product has been incorrectly formulated. In an attempt to broaden the scope of this methodology while simultaneously assessing ^{1}H NMR spectral parameters of this group of triquinanes, the positional isomers **20** and **21** were also prepared. The synthetic schemes paralleled that developed earlier. Neither **20** nor **21** proved to be senoxydene. The proton magnetic resonance spectra of all known angular triquinanes are tabulated and discussed as appropriate. The ordering of chemical shifts for natural senoxydene shows them to be atypical for this class of compounds. Close agreement is, however, noted with $\Delta^{9,12}$-capnellene, suggesting that senoxydene may be a linear triquinane. A definitive reinvestigation of its structure is in order.

The tricyclo[6.3.0.0^{1,5}]undecane or angular triquinane sesquiterpenes have figured prominently in the recent explosive growth of polycyclopentanoid natural-product chemistry.[1] Their isolation from a variety of sources has fostered considerable speculation concerning their biosynthesis.[2] Additionally, their unusual structural features have prompted many synthetic studies intent on the expedient multiple fusion of five-membered rings and the setting of relative stereochemistry, particularly at adjacent quaternary centers. To date, efforts culminating in the successful total synthesis of isocomene (**1**),[3] β-isocomene

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