the dotted lines 5, 7, 6, and 8 belong to the other isomer, $(AB)_2$. The exchange scheme is treated as the superposition of two simultaneous processes: (i) geometric isomerization between quartets, $(AB)_1 \rightleftharpoons (AB)_2$, *i.e.*, exchange between magnetic sites 1 and 5, 3 and 7, 2 and 6, and 4 and 8; and (ii) exchange of diastereotopic fluorines within an isomer, *i.e.*, in one isomer $(AB)_1 \rightleftharpoons (BA)_1$ exchanges magnetic sites 1 with 2, and 3 with 4, and in the other isomer, $(AB)_2 \rightleftharpoons (BA)_2$ exchanges lines 5 with 6 and 7 with 8. An 8 × 8 kinetic transfer matrix is then constructed in which each element contains terms which are exchange contributions from both processes, $[K_{mn}\,(ii)]/\tau + [K_{mn}\,(i)]/a\tau$, where K_{mn} is the kinetic exchange term for matrix element mn, i and ii refer to exchange processes described above, τ is the preexchange lifetime, and a is a variable which allows weighting of the two types of exchange. To take account of the coupling to X (*i.e.*, α and β spins of X), calculations are performed on two separate 8 × 8 matrices corresponding to the two spin states of X and are summed to give the complete line shape.

The low intensity outer portions of the low temperature ABX patterns were observable only for the *m*-difluoromethyltrityl cation. For the other cations, even though the outer lines were not observed, they were included in the line-shape calculations. J_{F-F} for these other cations could not be measured directly, but was reasonably approximated to be the same as in the former, 301.5 Hz.

The chemical shift nonequivalence between diastereotopic fluorines was observed to increase markedly with decreasing temperature at temperatures below coalescence (~1.1 Hz/deg). Fortunately the change was linear in temperature and chemical shifts at temperatures above coalescence could be obtained by extrapolation of the linear relationship.

Nuclear Magnetic Resonance Study of the Conformation of 1,3-Dithiolanes[1]

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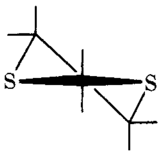
Contribution from the Department of Chemistry, University of Illinois at the Medical Center, Chicago, Illinois 60612, and Chemical Physics Section, Abbott Laboratories, North Chicago, Illinois 60064 *Received January 20, 1971*

Abstract: The AA′BB′ spin systems of the ring methylene protons of some 1,3-dithiolanes were analyzed. The geminal and vicinal coupling constants are reported and when compared to those previously reported for the corresponding 1,3-dioxolanes indicate that the sulfur hetero rings are more puckered than the oxygen isosteres. Application of the Lambert "*R*" factor determines approximate ring torsional angles for the 1,3-dithiolanes (±49°) and the corresponding 1,3-dioxolanes (±42°).

Since conformational analysis of five-membered heterocyclic rings by standard spectroscopic methods (nmr, Raman, and infrared) has been complicated and hampered by the facile interconversions which occur between the numerous nearly equienergy conformers, relatively limited information is available on this subject.[3,4] Although the conformations of 1,3-dioxolanes[5-14] and 1,3-oxathiolanes[15,16] have been examined by nmr spectroscopy, the only conformational data available for the 1,3-dithiolane system are based on the vibrational spectra of a series of 1,3-dithiolanes[17] and X-ray analysis of 2,2′-bis-1,3-dithiolane.[18] These data indicate that the 1,3-dithiolane ring exists preferentially in a C_2 "half-chair" (**1**) rather than a C_s "envelope" conformation (**2**).[19] However, Eliel[14] and Wilson[16] have since cautioned against considering one conformation as "preferred" and suggest a highly flexible five-membered ring with a large number of minimum energy conformations which are intermediate between the classical forms **1** and **2**. Eliel[14] further specifies that only the most bulky substituents show signs of specific steric interactions.



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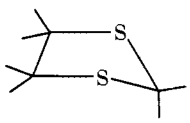

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Results

The nmr spectra of a series of 1,3-dithiolanes have been examined to define the ring geometry of this system. The magnitudes of the vicinal and geminal coupling constants of the C-4,5 methylene protons have been determined by iterative computer analysis. The nmr spectra of such ring systems are amenable to analysis since the sulfur atoms insulate the hydrogen atoms

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(1) Abstracted in part from the Ph.D. dissertation of L. A. Sternson, University of Illinois at the Medical Center, Chicago, Ill., 1970.

(2) (a) Present address: Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 60064. (b) Abbott Laboratories.

(3) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, Chapter 2.

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(15) D. J. Pasto, F. M. Klein, and T. W. Doyle, *ibid.*, **89**, 4368 (1967).

(16) G. E. Wilson, Jr., M. G. Huang, and F. A. Bovey, *ibid.*, **92**, 5907 (1970).

(17) H. Fuhrer and H H. Gunthard, *Helv. Chim. Acta*, 45, 2036 (1962).

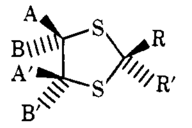
(18) L. B. Brahde, *Acta Chem. Scand.*, **8**, 1145 (1954).

(19) For convenience, only a single representative conformation of **1** and **2** from each of the 10 possible conformers in the pseudorotation circuit is shown, and no attempt is made to imply that these are the "preferred" conformations of each type.

Table I. Nmr Parameters of Some 1,3-Dithiolanes

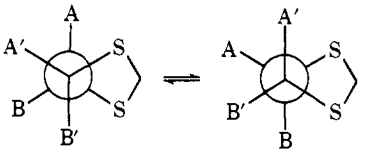
R	R′	Chemical shifts, ppm, δ: H_A,$H_{A'}$	H_B,$H_{B'}$	Other	J_{gem}, Hz	J_{cis}, Hz	J_{trans}, Hz	Other, Hz	RMS error
H	H	3.11	3.11	2-CH_2 = 3.81		5.30	6.39	$J_{^{13}C,H}$ = 142.64	0.052
CH_3	CH_3	3.32	3.32	2-CH_3 = 1.76		5.32	6.56	$J_{^{13}C,H}$ = 142.04	0.100
CH_3	H	3.25	3.15	2-CH_3 = 1.59 2-CH = 4.52	−11.32	5.49	6.62	$J_{CH_3,H}$ = 6.5	0.000
Ph	H	3.42	3.27	2-CH = 5.52	−11.25	5.21	6.55		0.009
Ph	CH_3	3.37	3.26	2-CH_3 = 2.08	−11.20	5.71	6.49		0.016

on C-2 from those on C-4 and C-5 which thus comprises an AA′BB′ spin system consisting of two pairs of enantiotopic nuclei (*cf.* **3**).



3

Three different coupling constants can be determined from the AA′BB′ spectra—J_{cis} ($J_{AA'}$ = $J_{BB'}$),[20] J_{trans} ($J_{AB'}$ = $J_{A'B}$), and J_{gem} (J_{AB} = $J_{A'B'}$). The equality $J_{AB'}$ = $J_{A'B}$ = J_{trans}, etc., is the consequence of rapid interconversion between two equally populated families of enantiomeric pseudorotamers, **4** and **5**, of the nonplanar ring. Since pseudolibration takes place in such systems, each form, **4** and **5**, represents the average of a range of conformations of similar energies.[14]



4 **5**

Although the C-4 and C-5 methylene protons of 1,3-dithiolane and its 2,2-symmetrically disubstituted derivatives are enantiotopic and therefore isochronous, the couplings between these protons can be determined from the carbon-13 satellites of the singlet resonance.[21]

The chemical shifts and coupling constants determined for a series of 1,3-dithiolanes are collected in Table I. The coupling constants previously reported for the analogous 1,3-dioxolanes are presented in Table II.

Table II. Coupling Constants of Some 1,3-Dioxolanes

R	R′	J_{gem}, Hz	J_{cis}, Hz	J_{trans}, Hz	Reference
H	H		7.3	6.0	*a, b*
CH_3	CH_3		6.3	6.3	*a*
CH_3	H	−7.68	7.20	6.06	*c, d*
Ph	H	−7.26	7.16	6.19	*c*
Ph	CH_3	−7.50	7.22	6.20	*c*

[a] See ref 5. [b] See ref 19. [c] See ref 9. [d] See ref 10.

Discussion

Chemical Shifts. Abraham[11] in his analysis of the spectrum of 2-methyl-1,3-dioxolane assigned the low-field resonances to protons cis to the 2-methyl group on the basis of the known deshielding effect arising from 1,3-diaxial methyl interactions.[22a,b] A contemporary analysis by Anteunis,[8,10] which has since been corrected[14] and withdrawn,[23] postulated a shielding effect for a 2-*cis*-methyl group. The chemical shift assignments for 1,3-dithiolanes collected in Table I are made by analogy with the paramagnetic shift observed in 1,3-dioxolanes.

The paramagnetic shift caused by 2-phenyl substituents observed by Anteunis[9,10] is also observed in the spectra of 2-phenyl-1,3-dithiolanes (Table I) and the magnitude of the shift is larger than for alkyl groups. The anisotropic effect of the aromatic ring on trans protons is also significant.

Coupling Constants. The magnitude of the geminal and vicinal coupling constants obtained from the spectra of 1,3-dithiolanes (Table I) when contrasted with the analogous couplings reported for 1,3-dioxolanes (Table II) establish the conformational differences between these systems.

Geminal Coupling Constants. In 1,3-dioxolanes, the geminal couplings range from −7.3 to −7.7 Hz while in 1,3-dithiolanes, the range is between −11.2 and −11.3 Hz.

Two factors affecting J_{gem} in CH_2 groups α to heteroatoms are inductive removal of electrons and the conformationally dependent back donation of the lone-pair electrons into the CH_2 antisymmetric molecular orbital.[24] Sternhell and others[25] have attempted to separate conformational and inductive effects by studying geminal couplings in methyl ethers and thioethers, compounds in which free rotation averages conformational effects. They find geminal couplings decrease from −10.6 to −11.9 Hz when sulfur is substituted for oxygen. Since the relative decrease in J_{gem} in 1,3-dithiolanes as contrasted to 1,3-dioxolanes is larger than can be attributed simply to electronegativity effects, the conformational effect must be significant.

Cahill and others[24] report that the most positive geminal couplings are those in which lone-pair electrons eclipse the adjacent CH bonds, while those with more negative values exist in more puckered conformations.

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[20] A referee has pointed out that since R ≠ R′, protons A and B (and likewise A′ and B′) are diastereotopic and therefore the equality of $J_{AA'}$ = $J_{BB'}$ does not necessarily follow. An analysis of the nmr spectra of the compounds, however, indicates that the equality does, in fact, exist (*vide infra*).

[21] N. Sheppard and J. J. Turner, *Proc. Roy. Soc., Ser. A*, **252**, 566 (1959).

[22] (a) R. J. Abraham and J. S. E. Holker, *J. Chem. Soc.*, 806 (1963); (b) E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Lett.*, 735 (1962).

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[24] R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **25**, 4681 (1969).

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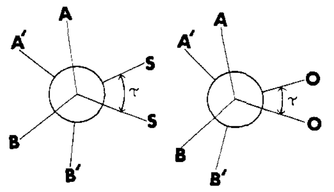
Therefore, the observed decrease in J_{gem} of 1,3-dithiolanes compared to those previously reported for analogous 1,3-dioxolanes offers evidence that 1,3-dithiolanes are more puckered. Such increased puckering will result in an increase in the ring torsional angles (τ) of the 1,3-dithiolanes (**6**) relative to their oxygen isosteres (**7**) (Figure 1).

Since the maximum torsional angle of the C_s and C_2 forms of carbocyclic five-membered rings are nearly equal[4] (±48° and ±46°, respectively) a conformational difference of this type in the heterocyclic compounds is probably too small to be detected by changes in geminal couplings.

The C–CH$_2$–C angle of the methylene group is also known to influence the magnitude of geminal couplings, but this is assumed to be more important in nonheterocyclic fragments.[26,27] The magnitude of J_{gem} becomes more positive as the angle becomes smaller. The O–CH$_2$–C and S–CH$_2$–C angles have been determined from X-ray analyses of 2,2′-bis-1,3-dioxolane and 2,2′-bis-1,3-dithiolane and found to be 111° and 102°, respectively,[4] which indicates that this factor is not responsible for the decrease of J_{gem}.

Vicinal Coupling Constants. In apparent opposition to the extended Karplus rule,[28] with reference to the effect of electronegative substituents, J_{cis} of 1,3-dithiolanes (Table I) is smaller than that of the corresponding 1,3-dioxolane (Table II). On the basis of ionic perturbation effects alone it would be anticipated that since oxygen is more electronegative than sulfur, the oxygen-containing compounds should have a smaller vicinal coupling than the corresponding sulfur-containing compounds. In a recent investigation, however, Pachler[29] has concluded from molecular orbital calculations that an *increase* in coupling with increased electronegativity is predicted for certain conformations. Therefore, since the differences between the vicinal couplings observed in 1,3-dioxolanes and 1,3-dithiolanes are functions of both electronegativity and conformational effects, the former is anticipated to be minor when compared with the conformational effect (*vide infra*).

In all previously examined 2-substituted 1,3-dioxolanes (Table II), J_{cis} was significantly larger than J_{trans}.[5-14] In contrast, in the 1,3-dithiolanes (Table I), the opposite trend is observed and J_{trans} is greater than J_{cis}. On the basis of the Karplus relationship,[28] J_{cis} is maximal when the vicinal protons are eclipsed. As the dihedral angle between the cis vicinal protons increases (a result of increased ring puckering) a concomitant decrease in coupling is observed. Similarly, increased ring puckering will cause an increase in J_{trans}, although the relative increase of J_{trans} will be smaller than the relative decrease of J_{cis}. The difference in the relative change is expected since increased ring puckering will cause the coupling of both sets of cis vicinal protons to simultaneously and equally increase, but the coupling between one set of trans vicinal protons increases while the other decreases. An overall increase in J_{trans} is observed when the two changes are time-averaged since the slope of the Karplus curve is greater between 90° and 180° than between 90° and 0° (*cf.* Figure 1).



6 **7**

Figure 1. Ring torsional angles of 1,3-dithiolanes (**6**) and 1,3-dioxolanes (**7**).

The observed changes in the relative magnitude of the vicinal couplings in the 1,3-dithiolanes are thus in complete agreement with the proposed increase in ring puckering (torsional angle).

Torsional Angle Determination. Although several attempts have been made to use the magnitudes of vicinal coupling constants (absolute value or difference) to estimate the ring torsional angle in 1,3-dioxolanes, no completely successful method has been reported.[6,11,12] Lambert[30] has observed that the ratio of $J_{\text{trans}}/J_{\text{cis}}$, defined as "*R*," for CH$_2$CH$_2$ moieties, in nonaromatic six-membered ring systems may be used in successfully predicting molecular ring shape. High values indicate puckered forms, while lower values indicate a flatter, more planar geometry. The Lambert "*R*" factors determined for a series of 1,3-dioxolanes and 1,3-dithiolanes (Table III) also indicate that the sulfur-containing ring is significantly more puckered than its oxygen isostere. Buys[31,32] has used this criterion and a modified Karplus equation for the calculation of the ring torsional angle, τ, with eq 1 and found excellent agreement with values determined by X-ray analysis.

$$\text{"}R\text{"} = (3 - 2\cos^2\tau)\,4\cos^2\tau \qquad (1)$$

The application of this equation to the nmr data obtained from the 1,3-dithiolanes gives values of approximately ±49° for the torsional angle (Table III).

Table III. Calculated Ring Torsional Angles (τ)

		1,3-Dioxolanes		1,3-Dithiolanes	
R	R′	"*R*"[a]	τ, deg	"*R*"[a]	τ, deg
H	H	0.822	41	1.206	49
CH$_3$	CH$_3$	1.000	45	1.233	48
CH$_3$	H	0.842	42	1.206	49
Ph	H	0.865	42	1.257	50
Ph	CH$_3$	0.859	42	1.137	48

[a] Lambert "*R*" factor.[29]

Similar calculations for the analogous 1,3-dioxolanes using the reported vicinal couplings give values of approximately ±42° (Table III), indicating that the sulfur hetero ring is approximately ±7° more puckered.

Tabacik[33] has pointed out that calculations of specific torsional angles from coupling constants in

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(26) R. C. Cookson, J. J. Frankel, J. Hudec, and T. A. Crabb, *Tetrahedron Suppl.*, 7, 335 (1966).

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(30) J. B. Lambert, *J. Amer. Chem. Soc.*, **89**, 1836 (1967).

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(32) (a) N. de Wolf and H. R. Buys, *Tetrahedron Lett.*, 511 (1970); (b) H. R. Buys and E. L. Eliel, *ibid.*, 2779 (1970); (c) H. R. Buys and H. J. Geise, *ibid.*, 2991 (1970).

(33) V. Tabacik, *ibid.*, 555, 561 (1968).

five-membered rings should be viewed with caution. Therefore, the τ values calculated for both the 1,3-dioxolanes and the 1,3-dithiolanes are presented only to establish general differences between the two ring systems and not to establish accurate values for the respective torsional angles. Nevertheless, it is interesting to note that the values obtained from the vicinal coupling constants are in good agreement with the maximum torsional angles obtained by X-ray analysis of 2,2′-bis-1,3-dioxolane (±31°) and 2,2′-bis-1,3-dithiolane (±45°).[3]

These results do not, however, give unambiguous evidence of the conformational form, C_2 or C_s, since the maximum torsional angles of both forms are nearly identical.

The ring protons have been shown to be significantly more staggered in the sulfur isosteres than in their oxygen analogs, and therefore the 1,3-dithiolane ring is more puckered than the 1,3-dioxolane.

The increased size of the sulfur atom and the increased C–S bond lengths result in a smaller 1,3-transannular alkyl proton interaction between C-2 substituents and the ethylene bridge protons in the case of 1,3-dithiolanes than with the corresponding 1,3-dioxolanes.[5,34] As indicated by Dreiding models, it can be anticipated that the tendency of the ring to flatten in order to decrease syn-axial repulsion is less for the 1,3-dithiolanes than their oxygen counterpart, thus contributing to the observed differences in coupling values and corresponding conformational changes.

Experimental Section

Nmr spectra were determined with Varian Associates HA-100 and HR-220 spectrometers with approximately 5% solutions in CCl_4. Chemical shifts of all compounds are reported in parts per million (δ) and were measured from internal TMS. The coupling constants, expressed in hertz, were determined under standard conditions except for those of 1,3-dithiolane and 2,2-dimethyl-1,3-dithiolane which were determined from neat samples.

The AA′BB′ spectra were calculated using LAOCN3[35] and were simulated with a Calcomp plotter using NMRPL.[36] Initial parameters were chosen from those previously reported for 2-alkyl-1,3-dioxolanes[16] and 2-alkoxy-1,3-dioxolanes.[12] Iterations were performed using several different starting parameters and always minimized to the same solution which, when plotted, was indistinguishable from the experimental spectra. Analysis of AA′BB′ spectra yields four sets of mathematically correct solutions,[37] and since not physically meaningful solutions have been encountered in the analysis of the spectra of 1,3-oxathiolanes,[15,16] the spectrum of 2-methyl-2-phenyl-1,3-dithiolane was obtained at both 100 and 220 MHz.[38] The coupling constants determined at both field strengths are identical as are the field-dependent expressions of the chemical shift differences when changed by the proper factor. This clearly indicates that the minimized solution is physically significant.[39]

The 1,3-dithiolanes were prepared by the method of Coffin, *et al.*,[40] and their physical properties were in satisfactory agreement with literature values.[41,42] All compounds were homogeneous by the criterion of thin-layer chromatography.

Acknowledgments. The assistance and helpful advice of Dr. M. I. Levenberg and Mr. W. C. Bass (Abbott Laboratories) and Dr. C. L. Bell (University of Illinois at the Medical Center) is thankfully acknowledged. Stimulating discussions with Dr. Peter Beak (University of Illinois), Dr. J. Tadanier (Abbott Laboratories), Dr. A. J. Perkins (University of Illinois at the Medical Center), and Dr. M. M. Mertes (University of Kansas) were appreciated. The facilities at the University of Kansas were generously made available (to L. A. S.) for the completion of part of the synthetic work.

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Long-Range Hydrogen–Fluorine Spin–Spin Coupling. Further Support for the "Through-Space" (Direct) Mechanism

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Abstract: Hydrogen–fluorine long-range coupling is studied in a novel class of 2-substituted-3-trifluoromethylquinoxalines, their 1-oxides, and 1,4-dioxides. It is shown that $J_{\text{H–F}}$ is susceptible to changes in hydrogen–fluorine internuclear distances. This effect is explained by the through-space mechanism.

The nature of long-range fluorine–flourine and fluorine–hydrogen spin–spin couplings has been a controversial issue for some time. Early investigators found that the coupling constant increased with decreasing internuclear distance[2a] and suggested that coupling occurred through space. However, systems with long-range couplings were soon found in which the

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(2) (a) L. Petrakis and C. H. Sederholm, *J. Chem. Phys.*, **35**, 1243 (1961); (b) D. R. Davis, R. P. Lutz, and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 246 (1961); (c) M. Takahashi and J. D. Roberts, *ibid.*, **84**, 2935 (1962); (d) S. Ng and C. H. Sederholm, *J. Chem. Phys.*, 40, 2090 (1964); (e) A. H. Lewin, *J. Amer. Chem. Soc.*, **86**, 2203 (1964); (f) J. Burdon, *Tetrahedron*, **21**, 1101 (1965).