were calibrated by using methanol, and integration of peak areas due to individual conformers in I, IX, X, and VII was carried out at least four times at each temperature. Equilibrium constants reported are average values of four to six determinations.

**Acknowledgment.** We are grateful to Dr. James G. Colson Hooker Chemical Corp., for running a number of 100-mHz spectra for us and to the National Science Foundation for generous financial support.

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# Analysis of the Nuclear Magnetic Resonance Spectra of 2-Substituted 1,3-Oxathiolanes. Determination of the Conformation of the Oxathiolane Ring System and the Conformational Free Energy Values for the 2-Alkyl Substituents

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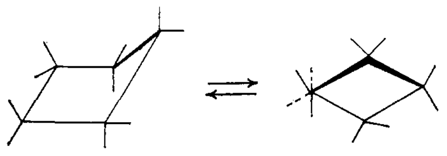
**Abstract:** The hydrogen magnetic resonance spectra of a number of 2-mono- and 2,2-disubstituted 1,3-oxathiolanes were analyzed by computer techniques to determine the chemical shifts and coupling constants of the $C_4$ and $C_5$ hydrogens. The nmr data were employed to predict the conformation of the oxathiolane ring system, to calculate the long-range shielding effects of alkyl and aryl groups in the 2 position, and to calculate the conformational free energy values for substituents in the 2 position. It is concluded that the conformation of the oxathiolane ring system most compatible with the nmr data is a slightly distorted envelope conformation with the oxygen atom at the "flap" position. Pseudo-rotation does not appear to be present in this ring system. The following $-\Delta G$ values (kcal/mole) were calculated for substituents in the 2 position: methyl, 1.13; ethyl, 1.16; isopropyl, 2.01; and phenyl, 1.87. It is also concluded that axial and pseudo-axial ring hydrogens in five-membered ring systems appear at higher field, except in cases involving long-range shielding effects, and that the chemical shifts of ring hydrogens are a better indicator of conformation than are just coupling constants. A review of the few examples of conformational analysis of heterocyclic five-membered ring systems is made with suggested alternatives for the conformations of the hydroxyprolines.

The study of the conformation of substituted five-membered rings is an area in which relatively little research has been devoted compared to the vast amount of work expended on cyclohexyl systems.[2]

The five-membered ring has been described as existing in a puckered conformation,[3] the puckering moving freely about the ring (pseudo-rotation). Two puckered forms may be written for cyclopentane, the $C_s$[3] or envelope[4] form **1a** and $C_2$[3] or half-chair[4] form **1b**, the interconversion apparently involving no substantial change in potential energy.[5] In monosubstituted cyclopentanes, the envelope form would appear to be favored in which the substituent is in the pseudo-equatorial position of the "flap" carbon. This would tend to relieve eclipsing between the substituent and the hydrogens on the adjacent carbon atoms. Calculation indicates this conformation to be more stable by 0.9 kcal/mole[6] whereas a value of 0.75 kcal/mole is suggested by entropy measurements.[7]



**1a** **1b**

The determination of the conformation of substituted cyclopentanes by the general methods used in dealing with cyclohexyl systems (infrared, nmr, and chemical methods) is hindered by the numerous possible conformations available with relatively low energy barriers to interconversion. Further difficulties arise in the analysis of the spectral and chemical data in terms of the conformation of the ring, the orientation of the substituent, and the various ring hydrogens, and, in the use of nmr techniques, the dihedral angular relationships between vicinal pairs of closely similar hydrogens in the rapidly interconverting systems.

These problems partially disappear in the rigid polycyclic molecules and in more highly substituted systems. Brutcher and Leopold[8] have assigned conformations of the D ring in a number of steroids by X-ray techniques. In more highly substituted systems the number

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[1] (a) National Science Foundation Predoctoral Fellow, 1963–1965, Lubrizol Fellow, 1965–1966; (b) McKenna Fellow, 1964–1966.

[2] (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 Publishers, Inc., New York, N. Y., 1965.

[3] J. E. Kilpatrick, K. S. Pitzer, and R. Spitzer, *J. Am. Chem. Soc.*, **69**, 2483 (1947).

[4] F. V. Brutchner, Jr., T. Roberts, S. J. Barr, and N. Pearson, *ibid.*, **81**, 4915 (1959).

[5] Reference 2a, p 249.

[6] K. S. Pitzer and W. E. Donath, *J. Am. Chem. Soc.*, **81**, 3213 (1959); *cf.* J. P. McCullough, R. E. Pennington, J. C. Smith, I. A. Hossenlopp, and G. Waddington, *ibid.*, **81**, 5880 (1959).

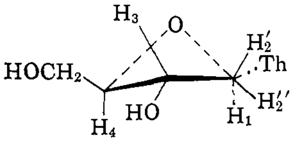
[7] J. E. Kilpatrick, H. G. Werner, C. W. Beckett, K. S. Pitzer, and F. D. Rossini, *J. Res. Natl. Bur. Std.*, **39**, 523 (1947).

[8] F. V. Brutcher and E. J. Leopold, *J. Am. Chem. Soc.*, **88**, 3156 (1966).

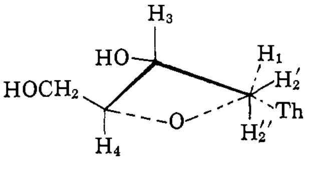
of chemically similar hydrogens is reduced and differences in chemical shifts are induced by the substituents thus facilitating analysis by nmr techniques. However, the introduction of a number of substituents may produce long-range shielding effects which may not allow an unambiguous assignment of pseudo-axial and -equatorial hydrogens based on chemical shift data, and one must then rely on the values of the coupling constants to derive dihedral angles to arrive at the conformation of the compound. The use of coupling constant data to determine dihedral angles, and hence the conformation, may lead to erroneous assignments of conformation.

Conformational studies involving five-membered heterocyclics by nmr techniques are simplified in that the heteroatom produces differences in the chemical shifts of the hydrogens attached to the different ring carbon atoms without generally producing unsymmetrical long-range shielding effects.

The conformation of several highly substituted five-membered heterocyclic systems has been inferred from nmr data. Lemieux[9] has derived the conformations of thymidine (**2**) and the anomer of thymidine (**3**) from nmr coupling constant data. We will simply note here that $H_2'$ is pseudo-axial in both **2** and **3** and appears at higher field than $H_2''$.



**2**

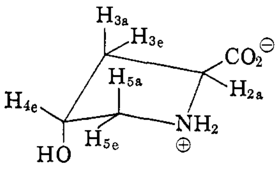


**3**

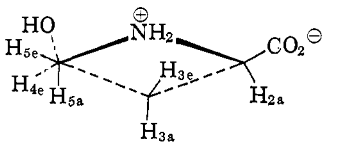
Chemical Shifts, Hz[10]

| | 2 | 3 |
|---|---|---|
| $H_1$ | −380 | −378.3 |
| $H_2'$ | −152 | −174 |
| $H_2''$ | −145 | −137 |
| $H_3$ | −274.5 | −275 |
| $H_4$ | −246 | −270 |

Abraham and McLauchlan[11] have analyzed the nmr spectra of *trans*-4-hydroxy-L-proline (**4**) and *cis*-4-hydroxy-L-proline (**5**). From the assigned coupling constants they have suggested that **4** exists mainly in an " 'envelope' conformation in which $C_4$ is out of the plane containing the other four nuclei . . . so that the hydroxyl group goes into a pseudo-axial position." (We have indicated the pseudo-equatorial and pseudo-axial nature of the ring hydrogens in their proposed conformations.) Similar considerations suggested that **5** "is puckered so that the hydroxyl becomes axial" and that "the conformation of the molecule is probably not the simple 'envelope' conformation." The observed long-range coupling between $H_{3e}$ and $H_{5e}$ in both molecules requires these hydrogens to be pseudo-equatorial thus giving the depicted conformations for **4** and **5**. It is interesting to note that in **4** the pseudo-axial hydrogen $H_{3a}$ appears at higher field than its pseudo-equatorial counterpart $H_{3e}$, whereas pseudo-axial $H_{5a}$ appears at lower field than $H_{5e}$. The reverse is true with **5**, the pseudo-axial hydrogen $H_{3a}$ appearing at lower field than $H_{3e}$ with $H_{5a}$ appearing at higher field than $H_{5e}$.



**4**

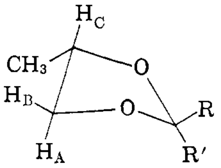


**5**

Chemical shift data, τ

| | 4 | 5 |
|---|---|---|
| $H_{2a}$ | 5.83 | 5.96 |
| $H_{3a}$ | 8.05 | 7.69 |
| $H_{3e}$ | 7.79 | 7.95 |
| $H_{4e}$ | 5.52 | 5.60 |
| $H_{5a}$ | 6.69 | 6.81 |
| $H_{5e}$ | 6.83 | 6.75 |

Anteunis and Alderweireldt have recorded the nmr spectra of various substituted 1,3-dioxolanes. The pseudo-axial hydrogen of **6**, $H_A$ appears at higher field than the pseudo-equatorial hydrogen $H_B$ in 2,2,4-trimethyl-1,3-dioxolane (**6**) ($R = R' = CH_3$) (0.61 ppm), *trans*-2,4-dimethyl-1,3-dioxolane (**6**) ($R = CH_3$, $R' = H$) (0.46 ppm), and *cis*-2,4-dimethyl-1,3-dioxolane (**6**) ($R = H_1$, $R' = CH_3$) (0.74 ppm).[12] This difference in chemical shifts has been attributed to shielding of $H_A$ by the adjacent *cis*-methyl group.[10] However, the estimated $\Delta\delta_{AB}$ due to shielding by the adjacent C–C bond of 0.30 ppm[13] is considerably smaller than the $\Delta\delta_{BA}$'s observed with the substituted 1,3-dioxolanes indicating a possible further contribution from other sources. These authors also observed that the introduction of an alkyl group *cis* to a $C_4$ or $C_5$ hydrogen results in an upfield shift with essentially no effect on the *trans*-hydrogens on $C_4$ and $C_5$.



**6**

Alderweireldt and Anteunis have also recorded the nmr spectra of a series of 2-mono- and 2,2-disubstituted 1,3-dioxolanes. Analysis of the $A_2B_2$ system of the $C_4$ and $C_5$ hydrogens gave a value for $\Delta\delta_{AB}$ for 2-methyl-1,3-dioxolane of 7.9 Hz (all values quoted are for 1 *M* solutions in carbon tetrachloride), this value decreasing to 3.24 Hz for 2-*t*-butyl-1,3-dioxolane at 56.4 MHz.[14] The coupling constants $J_{gem}$, $J_{trans}$, and $J_{cis}$ ranged from −7.49 to −7.66, 5.97 to 6.11, and approximately 7 Hz, respectively, for the 2-alkyl substituted 1,3-dioxolanes. These data were interpreted as representing a puckered conformation in which rapid pseudorotation was involved in the conformational equilibrium **6a** $\rightleftarrows$ **6b** so that time-averaged chemical shifts and coupling constants are observed.[14]

The availability of a number of 2-mono- and 2,2-disubstituted 1,3-oxathiolanes, prepared for an unrelated

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[9] R. U. Lemieux, *Can. J. Chem.*, **39**, 116 (1961).

[10] Derived from the spectra of **2** and **3** presented in ref 7.

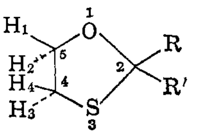
[11] R. J. Abraham and K. A. McLauchlan, *Mol. Phys.*, **5**, 195 (1962).

[12] M. Anteunis and F. Alderweireldt, *Bull. Soc. Chim. Belges*, **73**, 889 (1964).

[13] F. Alderweireldt and M. Anteunis, *ibid.*, **73**, 285 (1964).

[14] F. Alderweireldt and M. Anteunis, *ibid.*, **74**, 488 (1965).

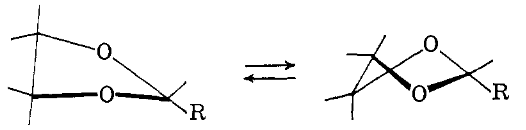
**Table I.** Calculated Chemical Shifts and Coupling Constants for 2-Mono- and 2,2-Disubstituted Oxathiolanes[a,b]



| Compd | R | R′ | $\delta_{H_1}$ | $\delta_{H_2}$ | $\delta_{H_3}$ | $\delta_{H_4}$ | $J_{12}$ | $J_{13}$ | $J_{14}$ | $J_{23}$ | $J_{24}$ | $J_{34}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **8** | *t*-Bu | H | 259.79 | 218.60 | 174.19 | 168.55 | −9.03 | 2.21 | 5.77 | 5.02 | 9.92 | −9.76 |
| **9** | *i*-Pr | H | 258.55 | 222.51 | 176.29 | 173.53 | −8.96 | 2.41 | 6.46 | 5.53 | 9.69 | −9.80 |
| **10** | Et | H | 254.98 | 221.71 | 177.76 | 173.75 | −8.99 | 4.40 | 4.96 | 6.13 | 8.05 | −9.95 |
| **11** | Me | H | 254.88 | 221.46 | 178.67 | 178.75 | −9.09 | 4.67 | 4.69 | 7.23 | 7.21 | −9.43 |
| **12** | H | H | 234.76 | 234.76 | 174.67 | 174.67 | ... | 6.12 | 5.58 | 5.58 | 6.12 | ... |
| **13** | $C_6H_5$ | H | 258.02 | 224.47 | 183.12 | 177.62 | −8.57 | 6.44 | 3.20 | 9.39 | 5.26 | −10.01 |
| **14** | *t*-Bu | Me | 254.88 | 234.98 | 175.51 | 167.83 | −9.06 | 3.21 | 5.35 | 4.38 | 9.63 | −9.86 |
| **15** | *i*-Pr | Me | 248.53 | 239.04 | 176.92 | 171.79 | −9.19 | 3.98 | 6.02 | 5.45 | 7.93 | −9.71 |
| **16** | Et | Me | 246.53 | 241.82 | 178.15 | 177.08 | −9.40 | 4.08 | 6.47 | 6.02 | 7.18 | −9.86 |
| **17** | Me | Me | 243.96 | 243.96 | 180.49 | 180.49 | ... | 5.88 | 5.39 | 5.39 | 5.88 | ... |
| **18** | $C_6H_5$ | Me | 251.29 | 229.48 | 184.18 | 174.79 | −9.25 | 6.23 | 4.47 | 6.95 | 6.35 | −9.18 |
| **19** | $C_6H_5CH_2$ | Me | 239.41 | 236.78 | 171.02 | 162.45 | −9.79 | 4.56 | 5.45 | 5.67 | 6.70 | −10.78 |
| **20** | $C_6H_5CH_2CH_2$ | Me | 244.46 | 238.06 | 175.33 | 174.15 | −8.94 | 5.92 | 4.71 | 6.51 | 6.17 | −11.24 |
| **21** | Et | Et | 242.15 | 242.15 | 173.29 | 173.29 | ... | 5.95 | 5.51 | 5.51 | 5.95 | ... |
| **22** | *i*-Pr | *i*-Pr | 244.78 | 244.78 | 170.36 | 170.36 | ... | 6.05 | 5.66 | 5.66 | 6.05 | ... |

[a] The chemical shifts are given in −Hz relative to internal tetramethylsilane at 60.0 MHz with the coupling constants given in Hz. The average deviation of the calculated line positions with respect to the observed line positions averaged less than 0.25 Hz, except with R = *i*-Pr, R′ = H, and R = $C_6H_5$, R′ = H, with an average of 24 to 33 transition assignments per compound. The number of iterations employed for each compound was sufficient to reduce the rms error in the chemical shifts to less than 0.01 Hz, except for hydrogens 3 and 4 in (R = $CH_3$, R′ = H), (R = Et, R′ = $CH_3$), and (R = $C_6H_5CH_2CH_2$, R′ = $CH_3$) in which the chemical shifts of $H_3$ and $H_4$ are very similar, and the rms error in the coupling constants generally much less than 0.7 Hz except in (R = $CH_3$, R′ = H), (R = Et, R′ = $CH_3$), and (R = $C_6H_5CH_2CH_2$, R′ = $CH_3$). [b] The method of preparation and the physical properties of the compounds appearing in this table may be found in ref 15.

investigation,[15] offered us the opportunity to investigate the conformational equilibria of these systems using nmr techniques.



**6a** **6b**

## Discussion

The nmr spectra of the $C_4$ and $C_5$ hydrogens of the 2-substituted 1,3-oxathiolanes varied from a typical AMXY pattern for the 2-*t*-butyl-1,3-oxathiolane to an ABXY system for 2-benzyl-2-methyl-1,3-oxathiolane to an AA′–XX′ system for the parent unsubstituted system or symmetrically 2,2-disubstituted 1,3-oxathiolanes. As the spectra were too complex for simple first-order analyses, the chemical shifts and coupling constants were determined by computer techniques employing the iterative program of Swalen and Reilly.[16] The calculated parameters are recorded in Table I. The spectra were recorded in 20–25% solutions in carbon tetrachloride with internal tetramethylsilane as standard on a Varian HR-60 spectrometer. The observed line positions, except in cases of severely overlapping peaks, were readily measured to the nearest 0.1 Hz and were reproducible to ±0.1 Hz.

Our assignment of the chemical shifts is based on the following line of reasoning. It was assumed that the 2-*t*-butyl-1,3-oxathiolane would be a highly conformationally biased system, an assumption which will be shown to be valid in the discussion of conformational free energy values of groups in the 2 position, in which the *cis*-5-hydrogen (closest to the 2 position) would prefer to be pseudo-equatorial for steric reasons thus requiring the *trans*-5-hydrogen to be pseudo-axial. By analogy with the fact that equatorial hydrogens in cyclohexyl systems are known to appear at lower field than their axial counterparts,[17] the resonance at −259.79 Hz was assigned to the pseudo-equatorial *cis*-5-hydrogen, hereafter designated as $H_1$, and the resonance at −218.60 Hz was assigned to the pseudo-axial *trans*-5-hydrogen,[18] hereafter designated as $H_2$. Inspection of a Dreiding model of the system gives support to our assignment. The assignment of the *cis*- and *trans*-4-hydrogens in 2-*t*-butyl-1,3-oxathiolane was based primarily on the coupling constant data and consideration of the dihedral angles as indicated by the Dreiding model of the system. The resonance at −174.19 Hz is assigned to the *trans*-4-hydrogen ($H_3$) and the resonance at −168.55 is assigned to the *cis*-4-hydrogen ($H_4$).

The Dreiding model indicates that the 1,3-oxathiolane ring should exist predominantly as a very slightly distorted envelope conformation with the oxygen as

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(15) E. L. Eliel and T. Doyle, *J. Org. Chem.*, in press; T. Doyle, Ph.D. Dissertation, University of Notre Dame, 1967.

(16) J. D. Swalen and C. A. Reilly, *J. Chem. Phys.*, 37, 21 (1962).

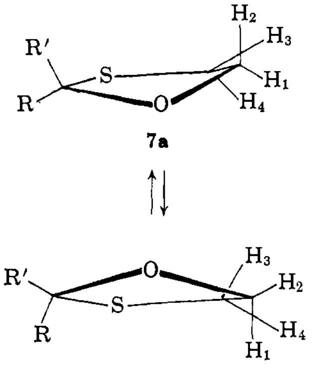
(17) R. U. Lemieux, R. K. Kullnig, J. H. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(18) The difference in the chemical shifts of the equatorial and axial hydrogens in cyclohexyl systems has been attributed to ring bond ($C_2$–$C_3$) diamagnetic anisotropy,[19] leading to a shielding of the axial hydrogen. The extension of this phenomenon to the oxathiolane system as the basis for the assignment of the chemical shifts of $H_1$ and $H_2$ would appear at first to be ill-founded. The two systems represent two quite distinctly different conformations, the cyclohexyl system, a chair conformation and the oxathiolane system, an envelope conformation, in which the distances, angles, and ring atoms involved in the shielding of the axial and equatorial hydrogens are quite different. Despite these differences, it is observed that the axial hydrogen on $C_5$ does in fact appear at higher field than the pseudo-equatorial hydrogen on $C_5$ in the 1,3-oxathiolane system (distinction between the $C_4$ hydrogens is rather tenuous due to the near identity of position as indicated by a Dreiding model of the system).

(19) See L. M. Jackman, "Application of NMR Spectroscopy in Organic Chemistry," Pergamon Press Inc., London, England, 1959, Chapter 7.

the "flap" atom (see Figure 1). Carbon atoms 2, 4, and 5 and the sulfur atom appear to be distorted only a few degrees (~11°) from a planar arrangement. The dihedral angles and the angles made by the carbon–hydrogen bonds relative to a plane perpendicular (A) to the $C_2$–S–$C_4$–$C_5$ plane as observed down the axis of the $C_4$–$C_5$ bond are indicated beside a drawing of the model in Figure 1. The coupling constants are in reasonable agreement with what would be expected from the Karplus relationship.[20] The model demonstrates readily the axial nature of $H_2$ and R′ and the equatorial nature of $H_1$ and R. However, $H_3$ and $H_4$ form nearly the same angle with respect to the A plane thus resulting in similar chemical shifts, the small difference probably being due to long-range shielding by the ring oxygen. Other possible conformations for the 1,3-oxathiolane system do not correlate as well with experimental data. The model also suggests that pseudo-rotation is not occurring. This is consistent with the nmr data and an earlier suggestion that tetrahydrothiophene is a *restricted pseudo-rotator*,[21] a property which might be expected to remain in the 1,3-oxathiolane system.[22]

In the parent 1,3-oxathiolane (**12**) system the two conformations **7a** and **7b** (R = R′ = H) will be of equal energy and rapidly interconverting (relative to the nmr time scale). The conversion of **7a** to **7b** results in $\delta_{H_1} = \delta_{H_2}$ and $\delta_{H_3} = \delta_{H_4}$ thus giving rise to a time-averaged AA′–XX′ ($H_1H_2$–$H_3H_4$) system. When R becomes more sterically demanding than R′, conformer **7a** will become more favorable than **7b** whence $\delta_{H_1} \neq \delta_{H_2}$ and $\delta_{H_3} \neq \delta_{H_4}$. Since again the rate of interconversion of **7a** and **7b** is faster than the rate of observation, $H_1$, $H_2$, $H_3$, and $H_4$ will appear as time-averaged signals, $H_1$ and $H_2$ appearing intermediate in position with respect to the chemical shifts of these hydrogens in **7a** and **7b** and the same being true for $H_3$ and $H_4$. The position of the resonance signals for the hydrogens will, of course, depend on the relative contributions of conformations **7a** and **7b** and is the basis for calculating conformational free energies differences by nmr techniques.[23]



**7a**

**7b**

In addition to affecting the chemical shifts of $H_1$, $H_2$, $H_3$, and $H_4$, the **7a** ⇄ **7b** equilibrium will result in distinct changes in the various coupling constants due to the changes in the various dihedral angles. The $H_1$–$C_5$–$C_4$–$H_3$ dihedral angle increases from approximately 91 to 148° and the $H_2$–$C_5$–$C_4$–$H_4$ dihedral angle decreases from 148 to 91° in the **7a** to **7b** interconversion. In the parent 1,3-oxathiolane (**12**) system, or any symmetrically 2,2-disubstituted system in which **7a** and **7b** contribute equally, the coupling constants $J_{13}$ and $J_{24}$ should equal $(J_{13} + J_{24})/2$ of the conformationally biased 2-*t*-butyl-1,3-oxathiolane (**8**). Inspection of the data in Table I reveals that such is true, $(J_{13} + J_{24})/2$ being 6.06 Hz compared to 5.89 Hz for the parent system (**12**) and 5.80, 5.80, and 5.99 Hz for the 2,2-dimethyl- (**17**), 2,2-diethyl- (**21**), and 2,2-diisopropyl-1,3-oxathiolanes (**22**), respectively. In going from **7a** to **7b** the $H_1$–$C_5$–$C_4$–$H_4$ and $H_2$–$C_5$–$C_4$–$H_3$ dihedral angles remain essentially the same and thus $J_{14}$ and $J_{23}$ should, and do, remain reasonably constant except for the 2-phenyl- (**13**) and 2-methyl-2-phenyl- (**18**) cases (these will be discussed in greater detail later). The trends in both the chemical shifts and coupling constants are therefore completely compatible with the adopted model.

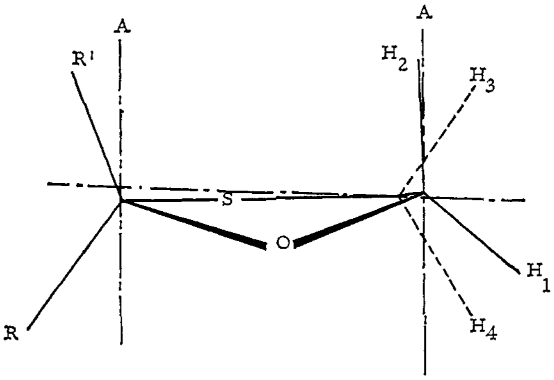


Figure 1. Drawing of a Dreiding model of the 1,3-oxathiolane system. The dihedral angles and observed coupling constants are: $\angle_{13}$, 91°, $J$ = 2.21 Hz; $\angle_{14}$, 25°, $J$ = 5.77 Hz; $\angle_{23}$, 33°, $J$ = 5.02 Hz; and $\angle_{24}$, 148°, $J$ = 9.92 Hz. The A-plane CH bond angles are: $\angle_{A1}$, 58°; $\angle_{A2}$, −2°; $\angle_{A3}$, 31°; $\angle_{A4}$, 33°; $\angle_{AR}$, 44°; and $\angle_{AR}$ 18°.

In order that chemical shift data be used to calculate conformational free energy values, the time-averaged chemical shift of the nuclei exchanging positions must be constant. Inspection of the data for the 2-monoalkyl-substituted 1,3-oxathiolanes reveals that the time-averaged chemical shifts of $H_1$ and $H_2$[24] do not remain constant.

The introduction of an alkyl group in the 2-pseudo-equatorial position results in a change in the averaged chemical shifts of $H_1$ and $H_2$ from −234.76 Hz in 1,3-oxathiolane (**12**) to −239.20 Hz in 2-*t*-butyl-1,3-oxathiolane (**8**). The change in the $H_1$–$H_2$ averaged shifts would appear to be due to long-range deshielding of both $H_1$ and $H_2$ by the pseudo-equatorial alkyl group as indicated by calculations derived by use of the McConnell equation.[25] The use of this equation predicts a deshielding of $H_1$ and $H_2$ by 2.0 and 4.8 Hz, respec-

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(20) M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).

(21) W. N. Hubbard, H. L. Finke, D. W. Scott, J. P. McCullough, C. Katz, M. E. Cross, J. G. Messerly, R. E. Pennington, and G. Waddington, *ibid.*, 74, 6025 (1952).

(22) Attempts are being made to determine the conformation of 1,3-oxathiolane by microwave spectroscopy with Professor L. Pierce of our department.

(23) E. L. Eliel, *Chem. Ind.* (London), 568 (1959).

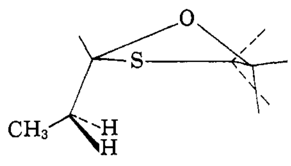
(24) The chemical shift data for $H_3$ and $H_4$ are not useful for the calculation of conformational free energy values because the shifts are quite similar, thus introducing a large uncertainty in the calculations, and also there are much larger variations in the $H_3$–$H_4$ average with change in substituent than in the case of the $H_1$–$H_2$ average.

(25) H. M. McConnell, *J. Chem. Phys.*, 27, 226 (1957).

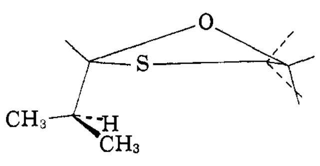
tively, for an averaged deshielding of 3.4 Hz compared to an observed 4.4 Hz.[26]

The averaged $H_1$–$H_2$ chemical shifts for the 2-isopropyl- (**9**), 2-ethyl- (**10**), and 2-methyl- (**11**) 1,3-oxathiolanes differ slightly from the 2-*t*-butyl derivative **8**. These slight changes can be explained readily by long-range shielding effects of the 2-pseudo-axial alkyl groups which are present in 3–12% as conformer **7b**. A more dramatic demonstration of this effect is shown by the data for 2-*t*-butyl-2-methyl-1,3-oxathiolane in which the methyl group is essentially constrained to the pseudo-axial orientation. Comparison of the chemical shifts of $H_1$ and $H_2$ in **8** and **14** reveals that the introduction of the pseudo-axial methyl group in the 2 position results in a *shielding* of $H_1$ by 4.91 Hz and a *deshielding* of $H_2$ by 16.38 Hz. Similar long-range shielding effects by alkyl groups in the cyclohexyl system have been reported by Eliel and coworkers, the sign of the shifts being dependent on the position and orientation of the alkyl group with respect to the hydrogen being observed.[27] Calculation of the expected shifts by use of the McConnell equation predicts a *shielding* of both $H_1$ and $H_2$, $H_1$ by 1.5 Hz and $H_2$ by 4.7 Hz. The use of the McConnell equation does not correctly predict the shielding effect on $H_2$. Similar instances have been noted with substituted cyclohexyl systems.[27] The unexpectedly large deshielding may be due to steric compression[28] in that the closest approach of the hydrogens of the pseudo-axial methyl group to $H_2$ is approximately 2.2 A as indicated by Drieding models. A similar effect is evident with the 2,2-dimethyl-1,3-oxathiolane (**17**); however, the averaged $H_1$–$H_2$ shift for this compound is 0.97 Hz less than for **14** indicating a smaller deshielding contribution to $H_2$ by the pseudo-axial methyl group in **17** than in **14**. This is as expected in that the *gem*-dialkyl distortion in the dimethyl case should be less than in the *t*-butylmethyl case reducing the steric compression. If we apportion the shielding effects in the 2,2-dimethyl compound **17** to the same extent as in the 2-*t*-butyl-2-methyl compound **14** we calculate that the pseudo-axial methyl in **17** shields $H_1$ by 4.4 Hz and deshields $H_2$ by 14.8 Hz.

Analysis of the chemical shift data for the 2,2-diethyl- and 2,2-diisopropyl-1,3-oxathiolanes (**21** and **22**) reveals similar long-range shielding effects produced by pseudo-axial ethyl and isopropyl groups. It should be noted, however, that the effect of the ethyl group is slightly less than that produced by the methyl whereas the effect by the isopropyl leads to an average value higher than the methyl group. This could appear to be rationalized on the basis of considering rotational conformer preferences of the pseudo-axial groups as pictured in **23** and **24**. The expected conformation for pseudo-axial 2-ethyl-1,3-oxathiolane is as shown in **23** in which steric compression should approximate that for the pseudo-axial methyl group; however, the long-range shielding of the additional methyl group would be expected to lead to a small shielding contribution toward both $H_1$ and $H_2$ resulting in a slightly less deshielded $H_1$–$H_2$ averaged value. Such is not true in the case of the pseudo-axial 2-isopropyl-1,3-oxathiolane illustrated as **24**. All rotational conformations of **24** produce a substantially greater steric compression and hence a greater deshielding of $H_1$. By apportioning the long-range shielding and deshielding effects for the pseudo-axial 2-ethyl and 2-isopropyl groups in a similar fashion as for the pseudo-axial methyl group (see above) we calculate that pseudo-axial 2-ethyl and 2-isopropyl groups *shield* $H_1$ by 3.6 and 4.8 Hz, respectively, and *deshield* $H_2$ by 11.9 and 16.4 Hz. If we use these values, and the conformational populations calculated later in this paper, to correct for the contributions of **7b** ($R = CH_3$, Et, *i*-Pr, and $R' = H$) to the $H_1$–$H_2$ averaged shifts, we arrive at averaged shifts for $H_1$ and $H_2$ of −238.83, −238.82, and −240.71 Hz, respectively. These values are in better agreement with the averaged $H_1$–$H_2$ shift in 2-*t*-butyl-1,3-oxathiolane and are probably within the limits of experimental errors.[29]



**23**



**24**

A similar trend in the averaged $H_1$–$H_2$ shifts is noted in the series 2-*t*-butyl-2-methyl- (**14**, −244.93 Hz), 2-isopropyl-2-methyl- (**15**, −243.78 Hz), 2-ethyl-2-methyl- (**16**, −244.18 Hz), and 2,2-dimethyl-1,3-oxathiolane (**17**, −243.96 Hz).

Introduction of an alkyl group in the 2 position also affects the chemical shift of $H_3$ and $H_4$; however, here the effect is a function of the type of alkyl group. A similar trend is apparent in the 2,2-dialkyl derivatives. It is not immediately apparent what the rather consistent changes are due to. Calculations employing the McConnell equation predict that the pseudo-equatorial alkyl groups should *deshield* both $H_3$ and $H_4$, and that the pseudo-axial alkyl groups should *shield* $H_3$ and *deshield* $H_4$. Further speculation does not seem warranted.

A final observation should be made concerning the parameters for the 2-phenyl- and 2-phenyl-2-methyl-1,3-oxathiolanes (**13** and **18**). Employing the assignment of chemical shifts and estimated coupling constants comparable to the 2-alkyl derivatives at the beginning of the iterative sequence led to a final inversion of $J_{13}$ and $J_{14}$ and of $J_{23}$ and $J_{24}$ (see **13** and **18** in Table I). The values calculated for $J_{14}$ and $J_{23}$ are more in line with what would be expected for $J_{13}$ and $J_{24}$. The only rational explanation is that the chemical shifts of $H_3$ and $H_4$ are reversed, the reversal being due apparently to long-range deshielding of $H_4$ thus also reversing $J_{14}$ and $J_{13}$, and $J_{23}$ and $J_{24}$. This is accommodated if the conformation of 2-phenyl-1,3-oxathiolane (**13**) is as shown in **25** in which the plane of the benzene ring bisects the OCS angle such that $H_4$

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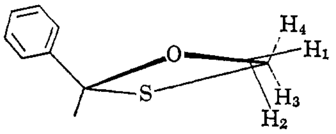
[26] The long-range shielding effects of the 2-pseudo-equatorial alkyl groups do not appear to vary greatly with the nature and size of the alkyl group, the effects, if any, being negligible or within the limits of detection. The slight changes observed in the $H_1$–$H_2$ averaged chemical shifts are attributed more readily to shielding effects by pseudo-axial alkyl groups as discussed in the following paragraph.

[27] E. L. Eliel, M. H. Gianni, Th. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, 741 (1962).

[28] S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Am. Chem. Soc.*, 87, 5247 (1965).

[29] Slight errors are introduced in making these corrections in that the long-range shielding and deshielding values are derived from *gem*-dialkyl derivatives which would be expected to display larger values for these shifts due to the *gem*-dialkyl distortions. These errors are not believed to be serious in that the results of the calculations are not extremely sensitive to small changes in these values.

lies in the plane of the benzene ring. These effects are not evident in 2-benzyl-2-methyl- (**19**) and 2-β-phen-



**25**

ethyl-2-methyl-1,3-oxathiolane (**20**). The benzene ring in **25** does not appear to affect greatly the chemical shift of $H_1$,[30] but appears to deshield $H_2$ in both **13** and **18**.

**Calculation of Conformational Free Energy Differences of Alkyl Groups in the 2 Position of 1,3-Oxathiolane.** 2-*t*-Butyl-1,3-oxathiolane should represent a conformationally biased system based by analogy with substituted cyclohexane chemistry.[31] One must be concerned, however, with the fact that conformational steric interactions in the more planar 1,3-oxathiolane system might be less than that observed in the chair conformation of cyclohexane and that 2-*t*-butyl-1,3-oxathiolane might thus not be essentially completely conformationally homogeneous. Employing the general method of calculation of conformational free energy differences from nmr data, the conformational free energy difference for the 2-methyl substituent in the 1,3-oxathiolane system, based on the assumption that the 2-*t*-butyl-1,3-oxathiolane is conformationally homogeneous and that the chemical shifts of $H_1$ and $H_2$ for this system represent the extreme values for the chemical shifts of $H_1$ and $H_2$, is found to be −1.21 kcal/mole, or approximately 71% of the value (−1.7 kcal/mole[31]) for the methyl substituent in cyclohexyl systems. Assuming that the $-\Delta G$ value for the 2-*t*-butyl group in the 1,3-oxathiolane system is also 71% of the value for the *t*-butyl group in the cyclohexyl system leads to a predicted minimum conformational free energy difference of −2.9 kcal/mole for the 2-*t*-butyl group in this system. This value corresponds to >99.2% of the more favorable conformation **7a** (R = *t*-Bu, R′ = H), and hence the chemical shifts for $H_1$ and $H_2$ in **8** are characteristic of the extreme values for the chemical shifts of $H_1$ and $H_2$.

In previous portions of this paper it was demonstrated that the pseudo-axial alkyl substituents give rise to long-range shielding of $H_1$ and deshielding of $H_2$, the magnitudes of these shifts being a function of the alkyl group. In order to calculate the conformational free energy differences of the alkyl groups in the 2 position of the 1,3-oxathiolane system, appropriate corrections should be made in the observed values of $H_1$ for these compounds in Table I.[32] One must first estimate the approximate conformational populations in order that the corrections applied are in accordance with the contribution of **7b**. This was done by using the data of Table I indicating that the population of **7b** was *ca.* 0.12, 0.12, and 0.03 for R = $CH_3$, Et, and *i*-Pr, respectively. The corrected and uncorrected values for the conformational free energy differences for alkyl groups in the 2 position of the 1,3-oxathiolane system are contained in Table II (only a single correction sequence was required for each compound). The differences between the corrected and uncorrected values are quite small and within the estimated experimental error of ±0.1 kcal/mole.

**Table II.** Conformational Free Energy Differences for Alkyl Groups in the 2 Position of 1,3-Oxathiolane[a]

| 2-Monoalkyl derivatives | | |
|---|---|---|
| R | $-\Delta G$, kcal/mole[b] | $-\Delta G$, kcal/mole[c] |
| Methyl | 1.13 | 1.21 |
| Ethyl | 1.16 | 1.22 |
| Isopropyl | 2.01 | 2.09 |
| Phenyl | *d* | 1.87 |

| 2,2-Dialkyl derivatives | | | |
|---|---|---|---|
| R | R′ | $\Delta(-\Delta G)$, kcal/mole[e] | $\Delta(-\Delta G)$, kcal/mole[f] |
| Ethyl | Methyl | 0.19 | 0.20 |
| Isopropyl | Methyl | 0.28 | 0.46 |
| Phenyl | Methyl | *c* | 0.91 |

[a] Estimated precision ±0.06 kcal/mole. [b] Corrected for long-range shielding effects by the 2-pseudo-axial alkyl group on $H_1$. [c] Uncorrected value. [d] No correction could be made as the long-range shielding constants for a 2-pseudo-axial phenyl were not available. [e] Corrected values based on $H_1$ in **7a** (R = *t*-Bu, R′ = H). [f] Uncorrected values based on $H_1$ in **7a** (R = *t*-Bu, R′ = $CH_3$).

It is interesting to compare the $-\Delta G$ value for methyl in the 2 position of 1,3-oxathiolane with similar values in the cyclohexane and cyclopentane systems. In the 1,3-oxathiolane system the steric interaction would appear to be primarily between the pseudo-axial methyl group and the axial $H_2$, or a single $CH_3$–H interaction. The $-\Delta G$ value for methyl in the cyclohexyl system arises from two diaxial $CH_3$–H equivalent to 0.85 kcal/mole for each interaction. The considerably larger value in the 1,3-oxathiolane system indicates a much more severe interaction and is consistent with the model chosen and the interpretation of the nmr data. The $-\Delta G$ value for methyl in the cyclopentane system is 0.75 kcal/mole and indicates a considerably smaller interaction consistent with the proposed conformation for methylcyclopentane.[33]

The nmr data for the 2,2-dialkyl-1,3-oxathiolanes may be used to calculate the differences in the conformational free energy difference for alkyl groups. These calculations have been made after correcting the chemical shift of $H_1$ for the pseudo-axial shielding contributions by each alkyl group. The $\Delta(-\Delta G)$ values determined for the 2,2-dialkyl systems give an indication of the steric deformation occurring in these *gem*-dialkyl derivatives.

## Conclusion

The present data, along with the earlier data reviewed at the beginning of this article, indicate that the appearance of pseudo-axial hydrogens at higher field than pseudo-equatorial hydrogens is a general trend in substituted five-membered heterocyclic rings, and

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(30) The calculation of $-\Delta G$ for $C_6H_5$ based on the chemical shift of $H_1$ in this system (see section on conformational free energy values for alkyl groups in the 1,3-oxathiolane system) gives a value consistent with the $-\Delta G$ values calculated for the alkyl groups.

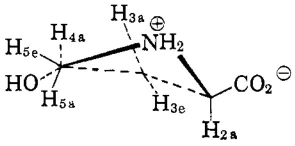
(31) E. L. Eliel, *Angew. Chem. Intern. Ed. Engl.*, **4**, 761 (1965).

(32) The conformational equilibrium constants were calculated using the chemical shift data for $H_1$ in the various systems. Calculations employing the chemical data for $H_2$ gave essentially identical results for the $-\Delta G$ values.

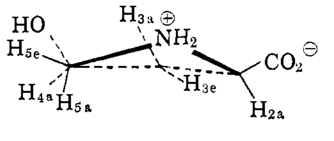
(33) See ref 2a, pp 250–251.

in fact may be a more accurate indicator of the conformation of cyclic compounds than just relying on coupling constants.[34,35] The data on the thymidines and substituted 1,3-dioxolanes are consistent with this general trend.

As pointed out earlier in this article the nmr data of the assigned conformations for the *cis*- and *trans*-3-hydroxy-L-prolines do not conform to this general trend. Conformation **4a** would seem more appropriate for *trans*-3-hydroxy-L-proline in which the orientation of the $C_5$ hydrogens is reversed compared to that of the same hydrogens in **4** and now conforms to the observed trend of pseudo-axial hydrogens appearing at higher field than pseudo-equatorial hydrogens. The assigned coupling constants are compatible with conformation **4a** with the possible exception of the long-range $J_{35}$ coupling constant. In **4a** both the hydroxyl and carboxylate groups are pseudo-equatorial.



**4a**



**5a**

Conformation **5a** would appear to satisfy both the chemical shift and coupling constant data. Conformation **5a** is nearly an "envelope" conformation in which both hydroxyl and carboxylate are pseudo-equatorial. This conformation is more in keeping with the proposed conformation of *cis*-1,3-dimethylcyclopentane.[36]

**Acknowledgment**. The authors wish to thank Professors Ernest L. Eliel and Gerhard Binsch of our department and Dr. G. Edwin Wilson of the Polytechnic Institute of Brooklyn for helpful discussions, and the Computing Center of the University of Notre Dame for providing the computing time.

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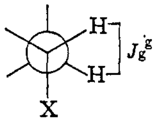
(34) It has been shown recently that the axial hydrogens in *cis*-3-isopropylcyclobutyl amine and alcohol appear at higher field than do the equatorial hydrogens in *trans*-3-isopropylcyclobutylamine and alcohol [I. Lillian and R. A. Doughty, *J. Am. Chem. Soc.*, **89**, 155 (1967)].

(35) The use of the Karplus relationship to determine HCCH dihedral angles should be used in only a qualitative manner [M. Karplus, *ibid.*, **85**, 2870 (1963)], particularly in complex systems. The vicinal coupling constants vary widely as a function of the substituents on the two carbon atoms and the HCC bond angles as well as the HCCH dihedral angle [for a recent review of coupling constants see A. A. Bothner-By, *Advan. Magnetic Resonance*, **1**, 201 (1965)]. One would also expect the vicinal coupling constants to be a function of the XCCH dihedral angle [G. M. Whitesides, J. P. Sevenair, and R. W. Goetz, *J. Am. Chem. Soc.*, **89**, 1135 (1967)], *e.g.*, the vicinal coupling constant $J_g{}^t$ in fragment i may not be equal to $J_g{}^g$ in fragment ii even though the HCCH dihedral angles may be the same. The conversion of one conformation of a substituted five-membered ring to an alternate conformation may well transform $J_g{}^g \rightarrow J_g{}^t$, or *vice versa*, as actually happens in **4** → **4a**, thus inducing changes in coupling constants that will not be indicated by the Karplus relationship. $J_g{}^g$ and $J_g{}^t$ may vary by as much as a factor of 3 (Whitesides, *et al.*).



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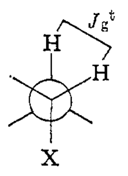

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(36) Reference 2a, p 250.

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# Benzene-Photosensitized Transformations of the Four Geometrical Isomers of 1,5,9-Cyclododecatriene

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*Contribution No. 1486 from the Department of Chemistry, Indiana University, Bloomington, Indiana 47401.*

*Received March 16, 1967*

**Abstract:** The sensitized photochemical reactions of the four isomeric 1,5,9-cyclododecatrienes in benzene solution have been examined. The predominant process is simple *cis–trans* isomerization of the olefinic bonds which transforms each of the isomers into the same photostationary mixture of all four trienes. In addition, there is an irreversible isomerization to a material identified as *endo,endo*-2,6-divinyl-*cis*-bicyclo[3.3.0]octane. The details of these photochemical reactions are discussed.

This paper is concerned with the photochemical reactions of the isomeric 1,5,9-cyclododecatrienes (I–IV), a set of medium-ring compounds with three formally isolated double bonds.[1] Among the numerous possibilities for phototransformation of this interesting system, we considered the following as most likely: (1) photo-Cope rearrangement of the 1,5-hexadiene units present in the starting material,[2] (2) cycloaddition of two of the olefinic groups to produce a tricyclic cyclobutane species, (3) some more extensive type of "cycloaddition" involving all three of the double bonds.

A recent review article[4] concerned with intramolecular photocycloadditions of nonconjugated olefins reveals very little work on medium-ring compounds with the exception of 1,5-cyclooctadiene. This material can be converted to tricyclo[3.3.0.0$^{2,6}$]octane by mercury

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(1) H. Breil, P. Heimbach, M. Kroner, H. Muller, and G. Wilke, *Makromol. Chem.*, **69**, 18 (1963).

(2) For example, see R. C. Cookson, V. N. Gogte, J. Hudec, and N. A. Mirza, *Tetrahedron Letters*, 3955 (1965). Such photorearrangements are not common however, and, in fact, are predicted not to be favorable as concerted reactions by Woodward–Hoffmann considerations.[3]

(3) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, **87**, 395, 2511 (1965); R. Hoffmann and R. B. Woodward, *ibid.*, **87**, 4389 (1965).

(4) W. L. Dilling, *Chem. Rev.*, **66**, 373 (1966). See also J. Dale and C. Moussebois, *J. Chem. Soc.* (*C*), 264 (1966).