

Conformational Preferences of Five-Membered Rings. Conformational Energy Calculations on Oxathiolanes

G. E. Wilson, Jr.

*Contribution from the Polytechnic Institute of New York,
Brooklyn, New York 11201. Received June 14, 1973*

Abstract: Conformational energy calculations have been carried out on 1,3-oxathiolane and 2-methyl-1,3-oxathiolane employing a 6-12 van der Waals potential for transannular interactions in the latter compound. The conformational energy minima for both oxathiolane and 2-methyl-1,3-oxathiolane are quite shallow, and the lowest energy transition states for pseudorotation are on the order of the energy for rotation of ethane (~ 3 kcal/mol). Thus, pseudorotation should be extremely rapid. For oxathiolane the minima represent very closely the enantiomeric envelope conformations (in Figure 6) in which the sulfur atom is β to the flap atom. For 2-methyl-1,3-oxathiolane the minimum exists at the ring conformation (2 in Figure 6) with both the sulfur and the methyl β to the flap atom and the methyl anti to it with respect to the ring plane. A secondary minimum 1 kcal above the preferred conformation occurs at a distorted envelope conformation similar to the former but with the oxygen atom β to the flap atom.

The conformational analysis of five-membered heterocyclic rings is complicated by a profusion of pseudorotamers of nearly equal conformational energy. Studies to date on such compounds¹ have provided little generally applicable predictive rules for conformations of substituted heterocycles. Work reported here indicates for the first time that such predictions are possible.

Considerable work has now been done on heterocycles with heteroatoms in the 1,3 positions because the isolated ethylene group in substituted derivatives gives rise to nmr spectra which can be solved for all the appropriate vicinal coupling constants.²⁻⁵ The coupling constants have then been utilized to deduce preferred conformations and to assess the average rotational angle of the ethylene group using the ratio of the trans to the cis vicinal coupling constant.⁴⁻⁶

Pasto³ clearly demonstrated that only two conformational minima exist for 2-methyl-1,3-oxathiolanes, and he found that the conformational free energy of the methyl group was 1.1 kcal/mol. The origin of this effect was attributed to a large 1,3-diaxial $\text{CH}_3\text{-H}$ interaction. Our studies on the nmr spectra of substituted 1,3-oxathiolanes indicated the presence of one highly preferred conformation (1 or 2), but our conclusions regarding the less populated pseudorotamers (3a or 4a) were not in agreement with 1,3-diaxial $\text{CH}_3\text{-H}$ interactions as the largest contributing factor to the conformational energy of the methyl group.

As a means to assess the validity of our conformational deductions about 1,3-oxathiolanes based on nmr spectra, we undertook conformational energy calculations of this ring system. The results support our previous conclusions and suggest predictive guidelines for assessing stable conformations of heterocyclic rings.

(1) For a review, see C. Romers, C. Altona, H. R. Buys, and E. Havinga, *Top. Stereochem.*, **4**, 39 (1969).

(2) G. E. Wilson, Jr., M. G. Huang, and F. A. Bovey, *J. Amer. Chem. Soc.*, **92**, 5907 (1970).

(3) D. J. Pasto, F. M. Klein, and T. W. Doyle, *J. Amer. Chem. Soc.*, **89**, 4368 (1967).

(4) G. E. Wilson, Jr., and T. J. Bazzone, *J. Amer. Chem. Soc.*, in press.

(5) L. A. Sternson, D. A. Coviello, and R. S. Egan, *J. Amer. Chem. Soc.*, **93**, 6529 (1971).

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

Torsional angles of five-membered rings are often characterized¹ by the relationship

$$\phi_j = \phi_{\max} \cos [1/2\Delta - j\delta]$$

$$j = 0, 1, 2, 3, 4$$

where ϕ_j is the torsional angle of bond $(j) - (j + 1)$, Δ is the phase angle of pseudorotation, and δ is the phase lag angle with a value of 144° . Unfortunately, for rings such as oxathiolanes with grossly unequal bond lengths and bond angles, this relationship breaks down. Lacking the advantages of symmetry for reducing the number of variables, we found it convenient to define conformations along the pseudorotation circuit by specifying two torsional angles and two bond angles. Utilizing molecular models, where bond angles are in accord with those normally encountered in five-membered rings, this notation provides for easy visualization of any conformation.

Results

Oxathiolane rings possess nine degrees of freedom by virtue of the fact that they are rigid bodies. In order to reduce the number of variable parameters we have assumed fixed bond lengths identical with those observed in cholestan-4-one-3-spiro(2,5-oxathiolane).⁷ The use of fixed bond lengths is appropriate because of the large potential function associated with bond stretching and the relative constancy of interactions dictated by the rather narrow range of torsional angles allowed. Pseudorotation is not possible without some deviation of bond angles from normal values; thus, unable to reduce the variables further, we decided to operate with two bond angles and two torsional angles as variables and to map to derived energy minima on a two-dimensional surface with torsional angles as the variables. We allowed bond angle variations from 103° to 109° for θ_4 (Figure 1) and from 108° to 113° for θ_5 in order to bracket experimental values obtained from the oxathiolane ring of cholestan-4-one-3-spiro(2,5-oxathiolane).⁷ The HCH angles were maintained at 110° and the hydrogens were fixed to lie on a plane bisecting the XCY angle.

(7) A. Cooper and D. A. Norton, *J. Org. Chem.*, **33**, 3535 (1968).

In our calculations, programmed in Fortran for an IBM 360-50 computer, bond angles were incremented in 1° intervals. In all cases the minimum energy occurred within the set of available bond angles. Torsional angles were incremented at 3° intervals, but those areas physically unattainable within the allowable set of bond angles were omitted from the calculations. The minima of 2-methyl-1,3-oxathiolane were further refined by reducing the torsional angle increment to 0.6° and the bond angle increment to 0.5° .

To obtain the conformational energies, the formulation

$$E = E_\beta + E_\psi + E_{\text{vdw}}$$

was employed. For the bond angle deformation energies we assumed an elastic potential function

$$E_\beta = \frac{1}{2}k(\theta - \theta_0)^2$$

The zero-strain angles listed in Table I were obtained

Table I. Elastic Constants and Equilibrium Bond Angles for 1,3-Oxathiolanes

Angle	k , kcal/(mol rad ²)	Equilibrium angle, deg	Ref
θ_1	189	111.5	<i>a</i>
θ_2, θ_4	136	110	<i>b</i>
θ_3	136	100	<i>c, 8</i>
θ_5	136	112	<i>d</i>

^a R. G. Snyder and G. Zerbi, *Spectrochim. Acta, Part A*, **23** (2), 391 (1967); K. Kimura and M. Kubo, *J. Chem. Phys.*, **30**, 151 (1959). ^b R. G. Snyder and J. H. Schachtschneider, *Spectrochim. Acta*, **21**, 169 (1965); A. McL. Mathieson, *Acta Crystallogr.*, **5**, 332 (1962). ^c N. Kharasch, "Organic Sulfur Compounds," Vol. 1, Pergamon Press, New York, N. Y., 1961, p 542. ^d Values appropriate for an extended carbon chain were adopted for these constants: A. I. Kitaigorodskii, "Organic Chemical Crystallography," Consultants Bureau, New York, N. Y., 1961, Chapter 5.

from open chain compounds. The force constants chosen for the CCS and CSC angles were those previously adopted⁸ for conformational energy calculations of thiophane. The force constant for the CCO angle was assumed to be that for an extended carbon chain. Variation in the force constants may be expected to cause small shifts in the equilibrium position in analogy to the case of thiophane⁸ where variation of the CSC force constant from 90 to 180 kcal/(mole rad²) resulted in shifts of about 0.2° in the rotational angles for the conformational minimum. This minor dependence upon the bending force constant arises because of the relatively narrow limits placed upon these angles by the necessity to form a closed ring. They would certainly be small enough to leave intact the conformational conclusions drawn here. The internal potential energy function associated with torsional angles around the single bonds was assumed to be

$$E_\psi = \frac{1}{2}U_0(1 + \cos 3\psi)$$

where $\psi = 0^\circ$ for the cis conformation and $U_0 = 2.8$ kcal/mol⁹ for C-C bonds, 0.71 kcal/mol for C-S bonds,¹⁰ and 2.72 kcal/mol¹¹ for C-O bonds. The

(8) G. Allegra, G. E. Wilson, Jr., E. Benedetti, C. Pedone, and R. Albert, *J. Amer. Chem. Soc.*, **92**, 4002 (1970).

(9) K. S. Pitzer and W. E. Donath, *J. Amer. Chem. Soc.*, **81**, 3213 (1959).

(10) R. W. Kilb, *J. Chem. Phys.*, **23**, 1736 (1955).

(11) P. H. Kasai and R. J. Meyers, *J. Chem. Phys.*, **30**, 1096 (1959).

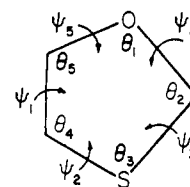


Figure 1. Bond angles and torsional angles in 1,3-oxathiolanes.

van der Waals energy was neglected for 1,3-oxathiolane in view of the large distances involved; however, 6-12 potentials

$$E_{\text{vdw}} = Ar^{-12} - Br^{-6}$$

were assumed for the CH₃-H interactions of 2-methyl-1,3-oxathiolane with $A = 185,540$ and $B = 345.6$.¹² For H-H interactions¹² we assumed $A = 4809$ and $B = 49.29$. The coefficients were obtained assuming a van der Waals radius for hydrogen of 1.2 Å. Because of the small variations possible in the angle between the dipoles involving sulfur and oxygen, we elected to ignore contributions of dipole-dipole interactions to the conformational energies.

The conformational energy maps for 1,3-oxathiolane and 2-methyl-1,3-oxathiolane pseudorotation (Figures 2 and 3 and Table II) were obtained by selecting the

Table II. Bond Angles (θ , deg) and Rotational Angles (ψ , deg) of 1,3-Oxathiolanes

Angle	A	B ^a	C ^b	D ^c
ψ_1	38	-39.0	38.0	34.3
ψ_2	-16	22.8	-16.6	-13.5
ψ_3		2.3	-8.1	-10.4
ψ_4		-21.3	33.0	34.0
ψ_5		40.9	-48.0	-46.3
θ_1		112.9	111.0	112.0
θ_2		107.5	106.4	106.0
θ_3		91.8	91.9	91.9
θ_4	104	103.5	104.0	105.2
θ_5	108	109.0	108.0	107.8

^a +1 kcal minimum of conformational energy map. ^b Minimum energy of conformational energy map. ^c Reference 8.

minimum energy for each dihedral angle (ψ_1, ψ_2) (Figure 1) combination from the set of energies for bond angle (θ_4, θ_5) combinations. Figures 4 and 5 show the variations of θ_4 and θ_5 on the pseudorotation minimum energy surface for 2-methyl-1,3-oxathiolane.

Discussion

The conformational energy minima for both oxathiolane and 2-methyl-1,3-oxathiolane are quite shallow allowing for a great deal of pseudolibration. Indeed, maximum torsional distortions of about 10° for both ψ_1 and ψ_2 along the pseudorotation pathway can occur before the energy increases by 0.5 kcal/mol.

(12) M. Goodman and G. C.-C. Niu, *Macromolecules*, **1**, 223 (1968).

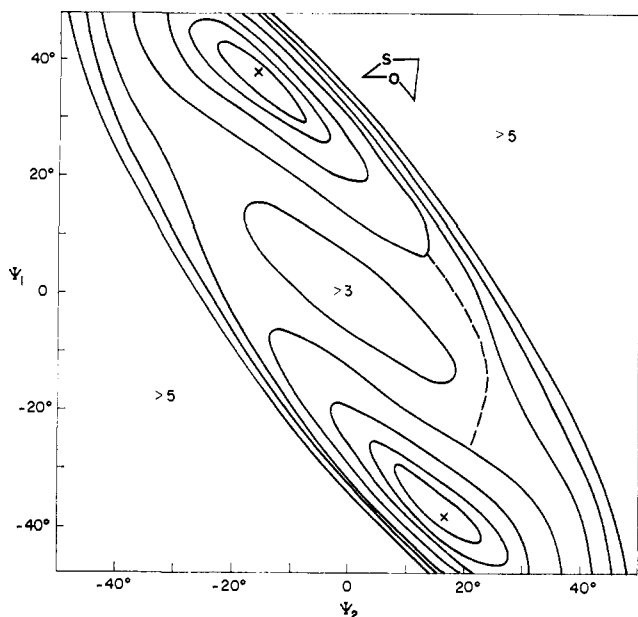


Figure 2. Conformational energy map for 1,3-oxathiolane. The minima are indicated by crosses and energy contour lines are drawn at 0.5, 1.0, 1.5, 2.0, and 3.0 kcal. The lowest energy pathway for pseudorotation is shown by the dashed line.

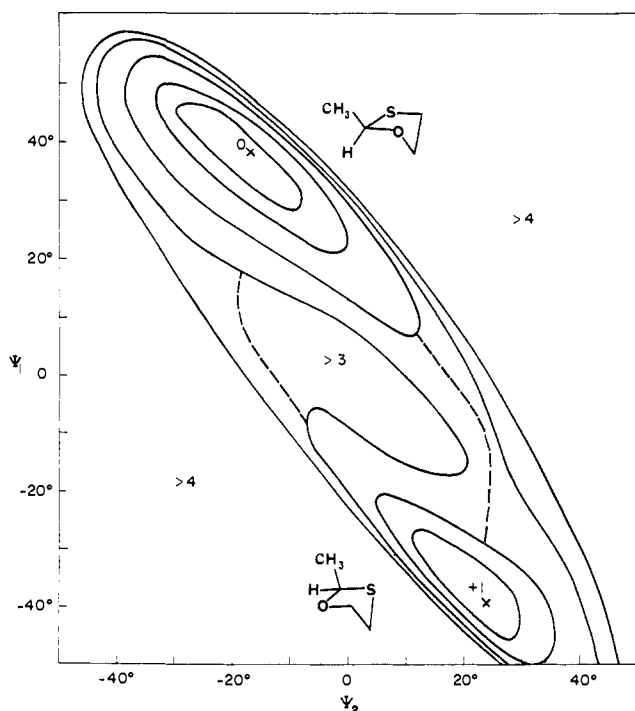


Figure 3. Conformational energy map for 2-methyl-1,3-oxathiolane. Minima are indicated by crosses and their relative energy in kilocalories is shown. Energy contour lines are drawn at 0.5, 1.0, 1.5, 2.0, and 3.0 kcal. The lowest energy pathways for pseudorotation are shown by dashed lines.

The transition states for pseudorotation of both 1,3-oxathiolane and 2-methyl-1,3-oxathiolane occur when $\psi_1 = 0^\circ$ indicating a large contribution from eclipsing the ethylene unit. For the 2-methyl derivative, the larger barrier to pseudorotation reflects the forcing of the endo methyl group into the ethylene unit. When the methyl group is exo, the transition state energy is calculated to be essentially the same as that for oxathiolane itself.

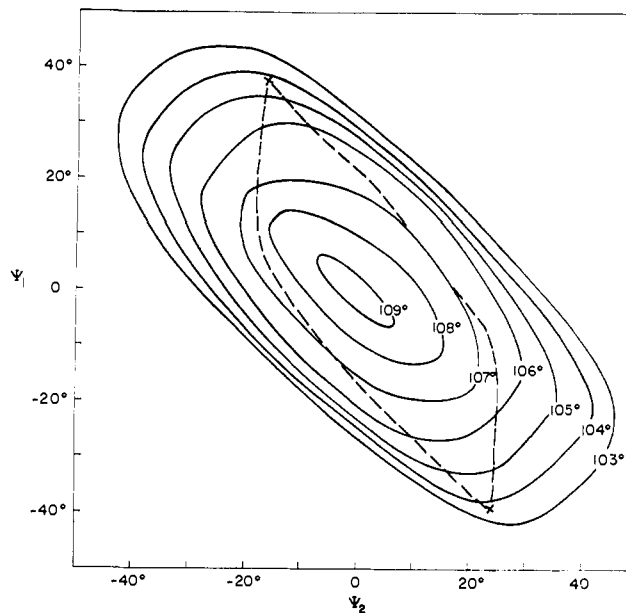


Figure 4. Plot of θ_4 which provides the minimum energy (dashed line) as a function of ψ_1 and ψ_2 for 2-methyl-1,3-oxathiolane.

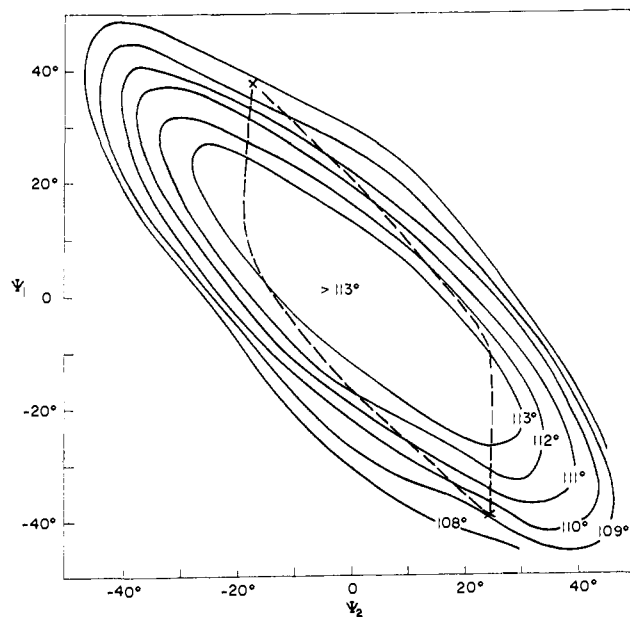


Figure 5. Plot of θ_5 which provides the minimum energy (dashed line) as a function of ψ_1 and ψ_2 for 2-methyl-1,3-oxathiolane.

It is interesting that no local minima were observed along the pseudorotation circuit. This may be a reflection of the crudeness of the approximations or the size of the increments for the bond angles and torsional angles.

For oxathiolane the minima represent very closely the enantiomeric envelope conformations (in Figure 6) in which the sulfur atom is β to the flap atom. For 2-methyl-1,3-oxathiolane the minimum exists at the ring conformation (2 in Figure 6) with both the sulfur and the methyl β to the flap atom and the methyl anti to it with respect to the ring plane. A secondary minimum for the 2-methyl derivative 1 kcal above the preferred conformation occurs at a distorted envelope conformation similar to the former, but with the oxygen atom β to the flap atom. As alternatives to the envelope con-

formations, which we find convenient for working models, the half-chair, C_s -type conformations with C-4 or C-5 and one heteroatom lying above and below the plane defined by the remaining three atoms are essentially equivalent (± 0.2 kcal) energetically to the corresponding envelopes.

It is interesting that the minimized bond angles and dihedral angles for 2-methyl-1,3-oxathiolane agree within ± 1.2 and $\pm 4^\circ$, respectively (Table II), with those for the steroidal oxathiolane determined by Cooper and Norton.⁷ Also, the existence of only two discrete minima 1 kcal apart for the 2-methyl compound agrees with the finding of two preferred pseudorotamers and with the conformational free energy of the methyl group in oxathiolanes as previously determined by Pasto and coworkers.³

We may clearly identify three factors which control the conformational population of the oxathiolanes. Most important of these is the minimization of transannular van der Waals interactions of the substituents at C-2 with the methylene units at the 4 and 5 positions. Second in importance is minimization of torsional energies achieved by maintaining a heteroatom not bearing a proton or other group β to the flap atom in the nearly planar portion of the ring. Finally, of approximately equal importance is maximization of group staggering by having one carbon atom of an ethylene unit at the flap position. These minima are simul-

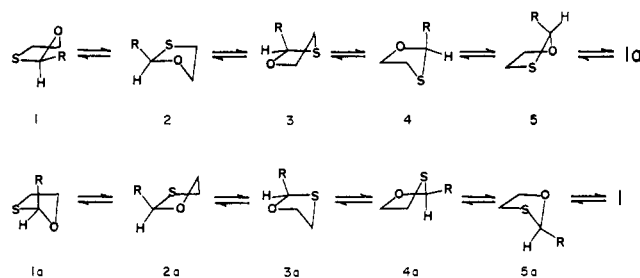


Figure 6. Envelope conformations of the pseudorotamers of 1,3-oxathiolanes.

taneously achieved in the oxathiolanes by allowing a substituent at the 2 position to adopt a position β to the flap atom and anti to it with respect to the ring plane.

In a number of other studies on heterocycles containing sulfur, the thiophane ring,⁸ 1,3-thiazolidines,⁴ and 1,3-dithiolanes⁵ these principles may be seen to apply. We suggest that they may, indeed, be quite general, and we are pursuing efforts to extend our capability of predicting preferred geometry to other systems and other substitution patterns.

Acknowledgment. Numerous discussions with Professor G. Allegra of the University of Trieste and Drs. E. Benedetti and C. Pedone are gratefully acknowledged, as is the assistance of the staff of the Polytechnic Institute of New York computer center.

Oxyphosphorane Models for Displacement Reactions of Pyrophosphates

Fausto Ramirez,*^{1a,b} Yu Fen Chaw,^{1b} James F. Marecek,^{1b} and Ivar Ugi^{1c}

Contribution from the Department of Chemistry, State University of New York, Stony Brook, New York 11790, and the Organisch-Chemisches Laboratorium, Technische Universität, München, West Germany. Received August 10, 1973

Abstract: The reactions of hexafluorobiacyl, $\text{CF}_3\text{COCOCF}_3$, with mixed anhydrides of phosphorous and phosphoric acids, $(\text{RO})_2\text{POP}(\text{O})(\text{OC}_2\text{H}_5)_2$ ($\text{R} = \text{CH}_3, \text{C}_2\text{H}_5$), give relatively stable 4,5-bis(trifluoromethyl)-2,2-dialkoxy-2-diethylphosphato-2,2-dihydro-1,3,2-dioxaphospholenes. These compounds are oxyphosphorane models of the hypothetical intermediates derived from the addition of nucleophiles to the phosphorus of pyrophosphates, such as ADP and ATP.

Numerous publications have described the synthesis and the molecular structure of oxyphosphoranes, *i.e.*, of P(5) compounds² having at least one phosphorus-oxygen bond.^{3,4} The existence of the relatively stable trigonal bipyramidal oxyphosphoranes has provided increasing support for the hypothesis that metastable

oxyphosphoranes are intermediates in displacement reactions of P(4) compounds.^{2,5-10} When applied to the biochemically important pyrophosphates, *e.g.*, ADP² and ATP,² these concepts lead to oxyphosphoranes of the type shown in Scheme I.

Due to the occurrence of relatively rapid PI^2 ,¹¹ in

(1) (a) This research was supported by the Cancer Institute of the U. S. Public Health Service (Grant CA-04769) and by the National Science Foundation (Grant GP-23018); (b) State University of New York; (c) Technische Universität.

(2) The following abbreviations will be used in this paper: P(3), P(4), P(5) = three-, four-, and five-coordinate phosphorus; ADP = adenosine 5'-diphosphate; ATP = adenosine 5'-triphosphate; PI = permutational isomerization of trigonal bipyramidal P(5) compounds.

(3) (a) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968); (b) F. Ramirez, *Bull. Soc. Chim. Fr.*, 3491 (1970); (c) F. Ramirez and I. Ugi, *Advan. Phys. Org. Chem.*, **9**, 25 (1971).

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(7) G. Kamai and G. M. Usacheva, *Russ. Chem. Rev.*, **35**, 601 (1966).

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