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APPLICABILITY OF EMPIRICAL AND SEMIEMPIRICAL CALCULATION METHODS FOR CONFORMATIONAL ANALYSIS OF 1,3-OCTATHIANES

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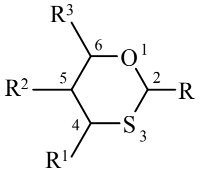
We have analyzed the advantages and disadvantages of using empirical and semiempirical approximations in calculations of the optimal geometry and energy of conformational conversions of molecules in the 1,3-oxathiane series.

Keywords: 1,3-oxathiane, conformational analysis.

The distinguishing features of the stereochemistry of 1,3-oxathianes compared with 1,3-dioxanes and 1,3-dithianes are connected with differences in the geometry of the ether and thioether moieties of the ring and the increase in the number of possible discrete conformers as a result of flexible forms [1-5]. However, a theoretical estimate of the relative stability of such forms so far has been limited to calculation of the energy of the chair and one of the twist conformations within various CNDO modifications [6, 7]. Accordingly, with the aim of searching for proper approaches to conformational analysis of cyclic thioacetals, this work has been devoted to the study of the applicability of empirical (MM+) and individual semiempirical methods (HyperChem 5.02 software [8]) to calculation of the optimal geometry and energy of conformational conversions of molecules in the 1,3-oxathiane series **1-11**).



1 R = p-$O_2NC_6H_4$; **2**, **4–6** R = H; **3**, **7** R = Me; **8** R = Et; **9** R = *n*-Pr; **10** R = *i*-Pr;
11 R = Ph, **1–3**, **5–11** R^1 = H, **4** R^1 = Me; **1–4**, **6** R^2 = H; **5**, **7–11** R^2 = Me;
1–5, **7–11** R^3 = H, **6** R^3 = Me

From comparison of data for calculation of bond lengths and also bond angles and torsional angles for 2-*p*-nitrophenyl-1,3-oxathiane (**1**) with the results of X-ray diffraction measurements [9], it follows that the most satisfactory agreement with experiment (the smallest value of ΣΔ) is given by the AM1 method (Table 1). In this case, the calculated data support flattening of the thioether moiety of the ring compared with its ether part.

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TABLE 1. Calculated and Experimental Geometric Parameters of the 2-*p*-Nitrophenyl-1,3-oxathiane Molecule **1**

Parameters	X-ray [9]	MM+	Δ, %*	AM1	Δ, %*	PM3	Δ, %*
1–2	0.138	0.142	2.9	0.142	2.9	0.142	2.9
2–3	0.181	0.180	0.6	0.181	0.0	0.187	3.3
3–4	0.179	0.180	0.6	0.177	1.1	0.182	1.7
1–6	0.143	0.142	0.7	0.143	0.0	0.141	1.4
ΣΔ, %	0.0	4.8		4.0		9.3	
1–2–3	111.5	110.4	1.0	113.6	1.9	115.2	3.3
2–3–4	96.5	108.0	11.9	100.3	3.9	99.5	3.1
6–1–2	113.0	113.1	0.1	113.2	0.2	114.2	1.1
ΣΔ, %	0.0	13.0		6.0		7.5	
1–2–3–4	-57	-46	19.3	-48	15.8	-43	24.6
2–3–4–5	54	44	18.5	46	14.8	43	20.4
3–4–5–6	-60	-55	8.3	-57	5.0	-57	5.0
4–5–6–1	61	69	13.1	64	4.9	66	8.2
5–6–1–2	-65	-70	7.7	-66	1.5	-66	1.5
6–1–2–3	66	58	12.1	61	7.6	57	13.6
ΣΔ, %	0.0	79.0		49.6		73.3	
ΣΣΔ, %	0.0	96.8		59.6		90.1	

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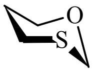
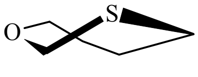
* Δ, % = (|*A* calc – *A* exp|/(A exp) × 100%, where *A* is the parameter under consideration. The bond lengths are given in nm, and the bond angles and torsional angles are given in degrees.

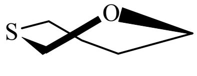
The global minimum on the potential energy surface (PES) for the molecule of unsubstituted 1,3-oxathiane (**2**) and also the *cis* and *trans* isomers of the 2,5-dimethyl analog **7** corresponds to the chair conformer C (*e* indicates an equatorial orientation of the substituents, *a* indicates an axial orientation). In addition, we also observe local minima corresponding to the 1,4-, 3,6-, and 2,5-twist forms (1,4-T, 3,6-T, and 2,5-T).



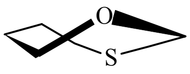
C



1,4-T



3,6-T



2,5-T

The rest of the theoretically possible conformers (various modifications of the half-chair and the asymmetric boat [10]) were not considered, since they are realized only when certain endocyclic torsional angles are fixed, and for this reason are strictly speaking not the true minima but rather correspond to points on the ascending part of the curve representing the two-dimensional cross-section of the potential energy surface. According to the data in Table 2, within the MNDO, AM1, and PM3 methods, all the flexible forms of the molecule for unsubstituted oxathiane **2** are degenerate with respect to energy, while MINDO/3 does not distinguish between any of the four conformers. For the *cis* and *trans* isomers of compound **7** considered in the MM+, AM1, and PM3 approximations, the local minimum closest to the main minimum corresponds to the 3,6-T form. In this case, we must note the trend (also typical for 1,3-dioxanes [10]) toward a decrease in the energy differences (Δ*E*) between the chair and the flexible conformations for the *cis*-**7** molecules. Considering that the Δ*E* between the chair and the twist forms for a number of methyl-substituted 1,3-oxathianes is 5.0-5.5 kcal/mol according to NMR data [2, 4], we should note that only the MM+ results agree satisfactorily with experiment.

TABLE 2. Relative Energies of Conformers of Compounds **2** and **7**, kcal/mol

Conformer	MM+	CNDO	INDO	MINDO/3	MNDO	AM1	PM3
2C	0	0	0	0	0	0	0
3,6-T	4.4	0.7	0.7	0	1.2	1.9	2.2
1,4-T	5.8	0.7	0.7	0	1.2	1.9	2.2
2,5-T	5.2	1.7	1.1	0	1.2	1.9	2.3
7, *cis-*							
C 2e5a	0	—	—	—	—	0	0
1,4-T*	5.3	—	—	—	—	1.1	*[2]
3,6-T*	3.7	—	—	—	—	0.4	0.6
2,5-T*	4.6	—	—	—	—	0.9	0.7
7, *trans-*							
C 2e5a	0	—	—	—	—	0	0
1,4-T	6.9	—	—	—	—	3.0	2.5
3,6-T	5.9	—	—	—	—	1.9	1.1
2,5-T	5.1	—	—	—	—	2.9	3.0

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* Only conformers with pseudoequatorial orientation of substituents were considered.

*[2] Is converted to the chair during minimization.

Most of the calculation methods used lead to unsatisfactory values for the conformational energy of the methyl group in different positions of the 1,3-oxathiane ring, defined as the difference between the energies of the corresponding *Ca* and *Ce* forms (Table 3).

According to PM3 and CNDO, the axial conformers of the molecules for the individual compounds are even more stable than the equatorial forms (negative values of Δ*E*). Relative agreement with experiment may be claimed only in the case of Δ*E* for $C_{(5)}$–CH_3 (MM+, INDO, and to some extent MNDO data). Most likely, most of the methods used do not fully take into account the energy of intramolecular nonbonding interactions, which is also responsible for the substantial errors in determination of the calculated energy Δ*G*°. Accordingly, it was of interest to estimate the given quantity for the 5-methyl analog of **5** by an independent method, using the

TABLE 3. Conformational Energies of Methyl Substituents in Different Positions of the 1,3-Octathiane Ring, kcal/mol

Method	**3**, $C_{(2)}$	**4**, $C_{(4)}$	**5**, $C_{(5)}$*	**7**, $C_{(5)}$*	**8**, $C_{(5)}$*	**9**, $C_{(5)}$*	**10**, $C_{(5)}$*	**11**, $C_{(5)}$*	**6**, $C_{(6)}$
MM+	1.8	0.7	0.8	0.7	0.6	0.6	0.8	0.6	2.5
CNDO	1.2	0.2	-0.2	-0.2	-0.3	-0.3	-0.2	-0.3	0.4
INDO	2.1	0.0	0.9	0.7	0.7	0.7	0.7	0.7	0.8
MINDO/3*[2]	1.0	0.9	0.2	0.2	0.2	0.2	0.2	0.3	2.8
MNDO	1.2	0.6	0.5	0.5	0.6	0.6	0.5	0.6	1.4
AM1	0.0	0.7	1.6	1.6	1.5	1.6	1.7	1.6	0.4
PM3	-1.2	0.0	1.6	1.6	1.5	1.5	1.4	1.4	-0.4
Exp Δ*G*° [2, 11, 12]	3.3	1.6	0.7						2.6

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* Δ*E* = *E C* 2*e*5*a* – *E C* 2*e*5*e*.

*[2] Axial $C_{(2)}$ and $C_{(4)}$ conformers are distorted toward one of the flexible forms during optimization within this method.

calculated vicinal spin–spin coupling constants obtained on the basis of torsional angles φ between the corresponding protons (optimal geometry data from MM+, AM1, and PM3) through a modified Karplus equation [13] and electronegativities [14], and also using an equation relating the weighted mean and standard spin–spin coupling constants [15].

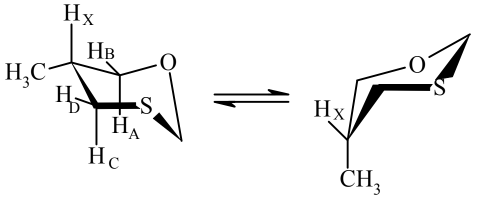
$$^{3}J_{AX} + {}^{3}J_{BX} + {}^{3}J_{CX} + {}^{3}J_{DX} = N\,(J_{aa1} + J_{aa2} + J_{ae1} + J_{ae2}) + (1 - N)\,(J_{ea1} + J_{ea2} + J_{ee1} + J_{ee2}),$$

where N is the fraction of the equatorial conformer.

As the standard values on the right-hand side of the equation, we used the calculated constants for the forms *C 5e* and *C 5a*, and the weighted mean values (the experimental values) were the spin—spin coupling constants from the spectrum of compound **5** [16]. The results (Table 4) suggest good agreement of the value obtained for ΔG° with data from the configuration isomerization method (0.7 kcal/mole [12]) and support the absence of appreciable amounts of other forms besides *Ce* and *Ca* participating in the conformational equilibrium of molecules of formula **5**.

On the whole, we may say that the MM+, PM3, and especially AM1 methods lead to rather reliable data on the optimal geometry and results of determination of ΔG° based on it, but except for MM+ and in some cases INDO and MNDO, are not suitable (as is the case for the rest of the semiempirical approximations used) for direct calculation of the energy of conformational conversions of 1,3-oxathiane molecules.

TABLE 4. Angles Between Vicinal Protons, Spin–Spin Coupling Constants, and Conformational Equilibrium Parameters for Molecules of Compound **5** at 298 K



C **5e** (N) C **5a** (1 – N)

Method, conformer	φ, degrees				spin–spin coupling constant, Hz					
	φ_{AX}	φ_{BX}	φ_{CX}	φ_{DX}	$^{3}J_{AX}$	$^{3}J_{BX}$	$^{3}J_{CX}$	$^{3}J_{DX}$	N	ΔG°, kcal/mol*
MM+,										
Ce	176.5	65.3	175.5	55.7	11.3	3.0	12.6	4.6		
Ca	60.1	57.5	51.5	67.6	3.5	3.9	5.2	3.0	0.78	0.74
AM1,										
Ce	177.7	60.4	176.2	56.9	11.4	3.5	12.6	4.4	0.76	0.67
Ca	55.0	66.5	47.2	71.7	4.2	2.8	5.9	2.6		
PM3,										
Ce	179.1	59.8	173.6	56.7	11.4	3.6	12.5	4.4	0.75	0.64
Ca	53.1	67.6	44.4	72.1	4.5	2.7	6.3	2.6		

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* ΔG° = -RTln(N/1–N), ΔG° av = 0.68 kcal/mol.

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