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Conformational Analysis of 1,3-Oxathiane

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Abstract—Computer simulation of pathways of conformational isomerization of 1,3-oxathiane molecule carried out with the help of HF/6-31G(d), MP2.6-31G(d)/HF/6-31G(d), and PNE/3z quantum-chemical approximations showed that interconversion between the degenerate in energy *chair* conformers proceeds through seven independent pathways: directly and via six flexible forms. Potential energy surface contains eight minimum points including *chair* conformers and enantiomeric pairs of *twist* forms, and also five transition states, among them different modification of *semi-chair*, symmetric and unmmetrical *boat*. Molecular dynamics methods show that flexible forms at room temperature convert into one another and into the *chair* conformers.

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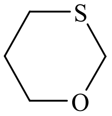
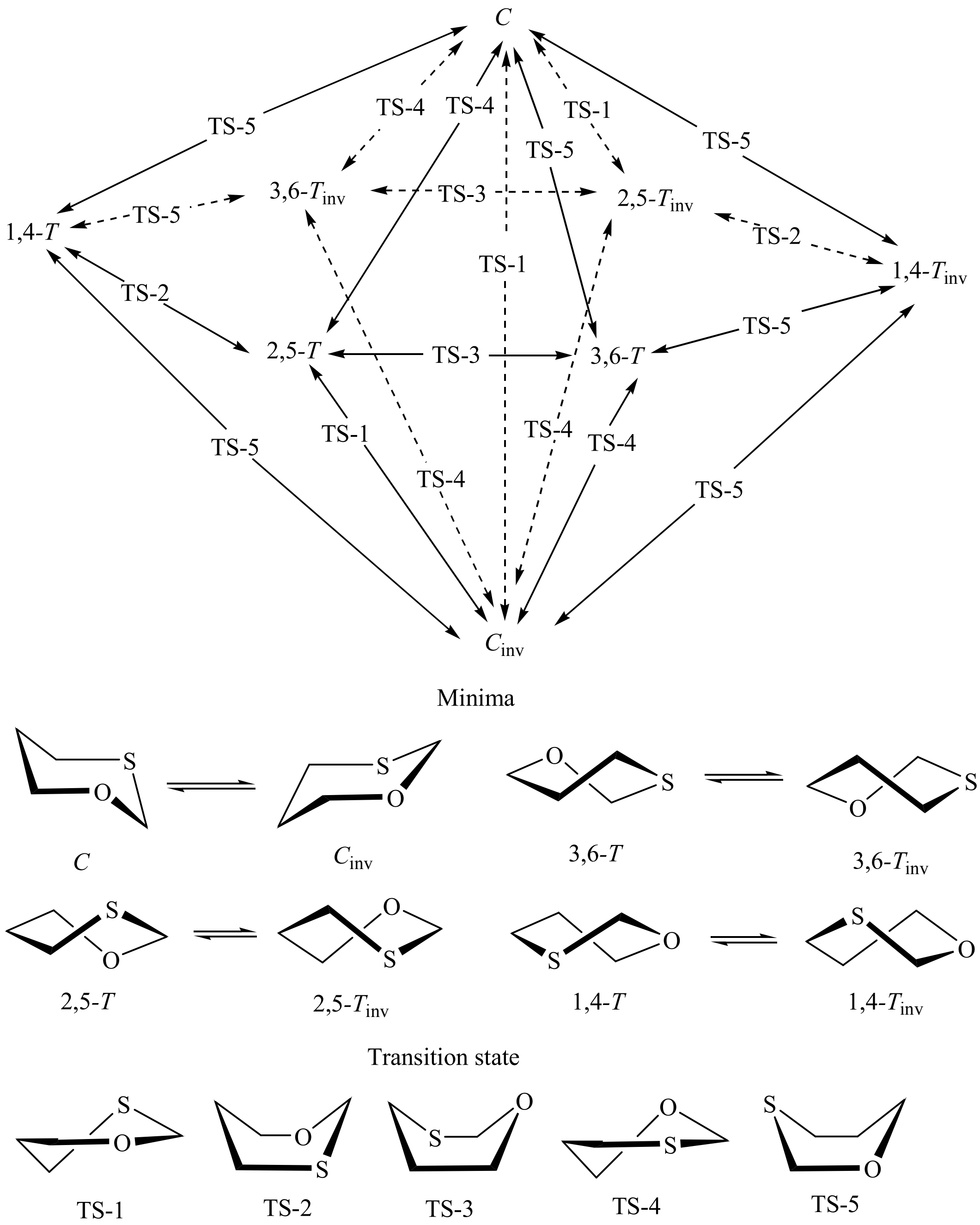
1,3-Oxathianes attract attention as valuable reagents used in fine organic synthesis [1–5]. Besides, these substances from the outset of stereochemical studies of saturated six-membered heterocycles were regaeded as convenient models for invest-tigation of the effect of heteroatom on the changes in the conformational characteristics of cyclohexane hetero-analogs [6–8]. According to NMR data the *chair* conformation is preferred for the majority of 1,3-oxathianes [6–19]. With the help of non-empiric quantum-chemical approximations the evaluation of stereoelectronic interactions was obtained and the presence of homoanomeric effects in the 1,3-oxathiane ring was established [20, 21]. But unlike cyclohexane [22], 1,3-dioxanes [22–32], and 1,3-dithiane [33, 34], pathways of conformational isomerization of 1,3-oxathiane molecules were not considered. In the majority of cases *"chair-chair*" inversion was postulated [6, 9–13], and in some cases the participation of flexible forms was suggested [14–16, 18]. In [35, 36] with the help of empiric and semiempiric methods the relative stability of *chair* conformers and *twist*-forms of unsubstituted as well as 5- and 2,2,5-substituted 1,3-oxathianes have been studied. At the same time it is known that the potential energy surfaces of substituted 1,3-heterocycles with different heteroatoms in the ring, for example, tetrahydro-1,3-oxazines, have a fairly large number of stationary points [37]. Recently it was shown by computer simulation that for 1,3-oxathianes the unusual direct *chair-chair* inversion takes place avoiding the intermediate flexible forms [38, 39]. Such direction of conformational isomerization is absent in the series of 1,3-dioxanes and 1,3-dithianes [24–34], but it is possible for 1,3-dioxa-2-sila- [40] and 2-germacyclohexanes [41]. In this study carried out by means of nonempiric HF/6-31G(d), MP2/6-31G(d)/HF/6-31G(d) approximations and density functional PBE/3z methods within the frame of HyperChem [42] and PRIRODA [43] complexes of programs all possible conforma-tional transformations of unsubstituted 1,3-oxathiane **I** were revealed.



I

It is established that degenerate in energy *chair* C and C_{inv} invertomers correspond to the main minimum point on the potential energy surface of oxathiaformal **I**. At the same time $C \leftrightarrow C_{\text{inv}}$ isomerization may proceed directly as well as through the 1,4-*twist* (1,4-*T*), 2,5-*twist* (2,5-*T*), and 3,6-*twist* (3,6-*T*) flexible forms existing as the invert enanthiomer pairs.

All flexible forms located in the equatorial plain of the presumable hexagonal bipyramide also take part in equilibrium with one another. These directions of conformational isomerization are listed separately to simplify the general scheme: $1,4\text{-}T \leftrightarrow \text{TS-3} \leftrightarrow 1,4\text{-}T_{\text{inv}}$;



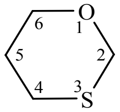
1,4-*T* ↔ TS-2 ↔ 3,6-*T*; 1,4-*T* ↔ TS-2 ↔ 2,5-T_{inv}; 2,5-*T* ↔ TS-5 ↔ 1,4-T_{inv}; 2,5-*T* ↔ TS-5 ↔ 3,6-T_{inv}; 2,5-*T* ↔ TS-1 ↔ 2,5-T_{inv}; 3,6-*T* ↔ TS-5 ↔ 2,5-T_{inv}; 3,6-*T* ↔ TS-1 ↔ 3,6-T_{inv}; 1,4-T_{inv} ↔ TS-2 ↔ 3,6-T_{inv}.

Calculated geometrical parameters of forms corresponding to minimum points and the transition states on the potential energy surface of oxathiane **I** (Table 1) show that the largest deviations of bond lengths and bond angles in the heteroatomic fragment of the ring to the larger (+) as well as to the lower (–) side from the values calculated for the *chair* conformer (Δ*C*) are characteristic of the C–S bonds as well as of the OCS and SCS bond angles of TS-1, TS-3, and TS-4 forms. Then follow *twist*-conformers of minimum points. Note that the results of calculation of the parameters under consideration of *chair* conformer in the HF/6-31G(d) approximation agree on the whole better with the results of X-ray measurements [44]. Values of calculated torsion angles (Table 2) confirm the previously established conclusion on the significant flattening of the thioether fragment of the ring as compared to the ether one [8, 13–17, 35, 36]. At the same time PRE/3z method more correctly represents the values of dihedral angles of molecule as shows the comparison with the experimental data [44].

Parameters of conformational equilibrium ΔH, ΔG^0 (Table 3) show that 2,5-*T* and 3,6-*T* forms are close to one another by energy. The most labile of the conformers corresponding to minimum points on the potential energy surface within the frames of all the calculated approximations is the 1,4-*T* (1,4-T_{inv}) form. This peculiarity typical also for non-substituted [23, 24], 2-, 5-, and 2,5-disubstituted 1,3-dioxanes [25–29], non-substituted 1,3-dithiane [33, 34], 1,3,2-dioxathian-2,2-dioxide [45], complexes of 2-methyl- and 2,5-dimethyl-1,3,2-dioxaborinanes with hydroxyl anions [46, 47] is probably the most general characteristic of the conformational properties of symmetrically substituted six-membered 1,3- and 1,3,2-heterocyclic compounds. Besides, all conformational *chair*-flexible form transformations are characterized by positive changes in entropy ΔS which is observed also for 1,3-dioxane [23] and 1,3-dithiane [33].

The established transition states including two *semichair* forms (TS-1 and TS-4) and also slightly distorted symmetric (TS-2) and unsymmetrical (TS-3 and TS-5) *boats* were previously found in 1,3-dioxane [23–29] and 1,3-dithiane [33,34]. The maximum value of the calculated activation barrier ($\Delta G^{\neq}$) is 11.2 kcal mol^{-1} (PBE/3z, TS-1) exceeding the data of low-temperature NMR experiment (9.3 kcal mol^{-1}) [48]. This circumstance confirms the results of the studies presented which show that the conformational transformation $C \leftrightarrow C_{\text{inv}}$ may occur directly as well as through the *twist*-conformers. The contribution of the latter pathways including less energy rich forms TS-4 and TS-5 as the transition states should decrease the total $\Delta G^{\neq}$ value as compared to TS-1 barrier. Note also that the negative values of activation entropy ($\Delta S^{\neq}$) show the increased sensitivity of all transition states to the sterical demands of the system. In the absence of

Table 1. Bond lengths and bond angles of forms corresponding to the minimum points and transition states on the potential energy surface of 1,3-oxathiane **I**



Method of calculation	Form	Bond length (Å)				Bond angle (deg)		
		C^6–O^1	C^2–O^1	C^2–S^3	C^4–S^3	$C^6O^1C^2$	$O^1C^2S^3$	$C^2S^3C^4$
HF/6-31G(d)	*C*	1.403	1.386	1.817	1.819	114.5	113.2	96.4
	2,5-*T*	1.406	1.387	1.840	1.818	114.8	112.5	96.4
	3,6-*T*	1.407	1.384	1.832	1.825	114.9	111.3	97.1
	1,4-*T*	1.409	1.389	1.814	1.832	117.6	114.2	98.0
	TS-1	1.413	1.389	1.807	1.810	125.7	115.7	93.1
	TS-2	1.411	1.385	1.818	1.833	118.0	113.9	98.6
	TS-3	1.405	1.383	1.845	1.819	114.9	111.9	97.2
	TS-4	1.403	1.380	1.845	1.837	114.3	114.4	104.5
	TS-5	1.404	1.399	1.813	1.820	118.8	114.8	96.3
	Δ*C* (+)	**0.010**	**0.003**	**0.028**	**0.018**	**4.3**	**2.6**	**8.1**
	(–)	**0**	**0.007**	**0.010**	**0.009**	**0**	**1.9**	**3.3**
PBE/3z	*C*	1.436	1.411	1.844	1.839	111.7	114.1	94.9
	2,5-*T*	1.440	1.410	1.875	1.836	112.0	113.1	94.9
	3,6-*T*	1.443	1.406	1.867	1.846	111.9	111.8	95.8
	1,4-*T*	1.446	1.417	1.836	1.855	114.1	114.3	96.4
	TS-1	1.448	1.408	1.833	1.831	119.6	115.1	90.6
	TS-2	1.450	1.408	1.846	1.856	114.6	114.2	97.2
	TS-3	1.439	1.403	1.885	1.836	112.1	112.4	95.7
	TS-4	1.438	1.401	1.881	1.858	111.2	115.0	103.5
	TS-5	1.435	1.434	1.827	1.839	115.6	115.2	94.0
	Δ*C* (+)	**0.014**	**0.023**	**0.041**	**0.019**	**8.0**	**1.2**	**8.6**
	(–)	**0.001**	**0.008**	**0.017**	**0.008**	**0.4**	**2.2**	**4.4**
Experimental data [44]	*C*	1.430	1.380	1.810	1.790	113.0	111.5	96.5

Table 2. Torsion angles of *chair* conformer of 1,3-oxathiane **I**

Method of calculation	Torsion angle, deg					
	OC^2SC^4	$C^2SC^4C^5$	$SC^4C^5C^6$	$C^4C^5C^6O$	$C^5C^6OC^2$	C^6OC^2S
HF/6-31G(d)	–55	50	–57	60	–65	66
PBE/3z	–57	52	–59	61	–64	67
Experimental data [44]	–57	54	–60	61	–65	66

Table 3. Parameters of conformational equilibrium of 1,3-oxathiane **I** (ΔH, ΔG^0, $\Delta H^{\#}$, $\Delta G^{\neq}$ in kcal mol^{-1}, ΔS and $\Delta S^{\neq}$ in cal mol^{-1} K^{-1})

Conformer or TS	HF/6-31G(d)	MP2/6-31G(d)//HF/6-31G(d)	PBE/3z			
	0 K	0 K	0 K	298 K		
	ΔH ($\Delta H^{\neq}$)	ΔH ($\Delta H^{\neq}$)	ΔH ($\Delta H^{\neq}$)	ΔH ($\Delta H^{\neq}$)	ΔG^0 ($\Delta G^{\neq}$)	ΔS ($\Delta S^{\neq}$)
C	0	0	0	0	0	0
2,5-*T*	4.9	5.0	5.0	5.2	4.7	1.6
1,4-*T*	6.1	6.5	5.7	5.9	5.3	2.0
3,6-*T*	4.6	4.9	5.1	5.3	4.8	1.6
TS-1	(12.3)	(13.4)	(11.3)	(11.1)	(11.2)	(–0.2)
TS-2	(6.2)	(7.0)	(5.9)	(5.6)	(6.2)	(–2.1)
TS-3	(5.5)	(5.9)	(5.8)	(5.4)	(6.0)	(–2.0)
TS-4	(8.9)	(10.4)	(9.1)	(8.9)	(9.1)	(–0.4)
TS-5	(7.4)	(7.7)	(6.8)	(6.6)	(6.9)	(–1.3)

substituents this means that the other interactions bring to the fore, in particular, the orbital interactions, due to more significant spatial demands of or-bitals of *p*-electron pairs of sulfur heteroatoms [49].

Using of the molecular dynamics method for simulation the conformational behavior of compound under study at room temperature (HyperChem, 295–300 K) we showed that *twist*-forms transform into one another with the period 3–6 ps. Hence, in the course of 6 ps the isomerization 1,4-*T* ↔ 3,6-*T* ↔ 2,5-*T* was observed. 2,5-*T* Form within 3 ps transforms into 3,6-*T twist*-conformer, and the latter, into the *chair* one. At the same time the *chair* conformer proper studied as the starting form at this temperature undergoes only relatively small distortions and does not transform into the flexible forms.

The results obtained demonstrate the increased conformational flexibility of 1,3-oxathiane molecules as compared to 1,3-dioxane due to the increase in length of C–S bonds as compared to C–O ones, flattening of thioether part of the ring, and the effect of stereoelectronic interactions in the hetero-atomic fragment of the ring.

EXPERIMENTAL

Conformational isomerization of *chair* to flexible forms was carried out by optimization of molecular geometry of compound under study at the variation of the intracyclic torsion angles OCCC, SCCC, SCOC, or OCSC within the limits of ±60°. Under these conditions direct *chair-chair* inversion was observed only while varying OCCC angle from –60° to 60° (or vice versa) in the course of preliminary calculations by means of semi-empiric PM3, MNDO, or ZINDO/1 (HyperChem) methods. This effect was revealed also while using semi-empiric RM1 approximation, but in this case the limits of variation of OCCC torsion angle must be increased to ±75°–80°. The other pathways of interconversion were established within the frame of HF/6-31G(d) and PBE/3z methods with the help of procedure of search for the transition states using the HyperChem [42] and PRIRODA [43] software. The assignment of stationary points of the potential energy surface to the maximum points was confirmed by presence of one imaginary frequency, and to the minimum points, by the absence of imaginary frequencies in corresponding Hessians. Thermal conformational transformations were studied by molecular dynamics method [HyperChem, HF/6-31G(d)] in the course of integration of the equations of movement at constant temperature. Sequence of temperature regime included heating from the initial (295 K) to the desired temperature (300 K), maintaining at 300 K, and cooling to 295 K. Period of each of three stages was 2 ps. Total time necessary for modeling of isomerization of one conformer in the course of 6 ps within the frames of chosen basis of calculation varied from 140 to 150 h.

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