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Conformational Analysis of 5-Methyl- and 2,2,5-Trimethyl-1,3-dithianes

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Abstract—Conformational isomerization of 5-methyl- and 2,2,5-trimethyl-1,3-dithianes was studied using quantum-chemical HF/6-31G(d), HF/pVDZ, and PBE/3z approximations. The potential energy surface of molecules of both compounds is shown to contain the main minimum corresponding to the *equatorial chair* conformer *C*-5*e*. The calculated potential barriers of the conformational isomerization were found. Based on the experimental (^{1}H NMR) and theoretical vicinal coupling constants the ΔG^0 values were determined of the methyl group at the ring C^5 atom. The reasons for the distinctions between the values of this parameter from the ΔG^0, obtained by energy minimizations of the equatorial and axial chair conformers are discussed.

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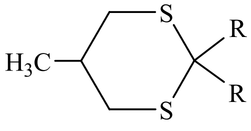
The interest in substituted 1,3-dithianes are due both to the peculiarities of their structure [1–11] and to their use as reagents in fine organic synthesis [12–19]. Earlier using ^{1}H and ^{13}C NMR spectroscopy it has been shown that the main minimum on the potential energy surface (PES) of 5-alkyl-1,3-dithianes is the *equatorial chair* conformer (C_e) [2, 3, 5–9]. Computer simulation applied to the conformational analysis of unsubstituted 1,3-dithiane has revealed the main conformer, the *chair* (*C*), and the local minima, 1,4-*twist* (1,4-*T*) and 2,5-*twist* (2,5-*T*), as well as transition states (TS): the *semi-chair*, symmetric *boat* and asymmetric *boat* conformations [20, 21]. In this paper conformational analysis is performed of the molecules of 5-methyl- (**I**) and 2,2,5-trimethyl-1,3-dithianes (**II**) using *ab initio* quantum chemical approximations HF/6-31G(d), HF/pVDZ, and PBE/3z within the HyperChem [22] and PRIRODA [23] software packages.

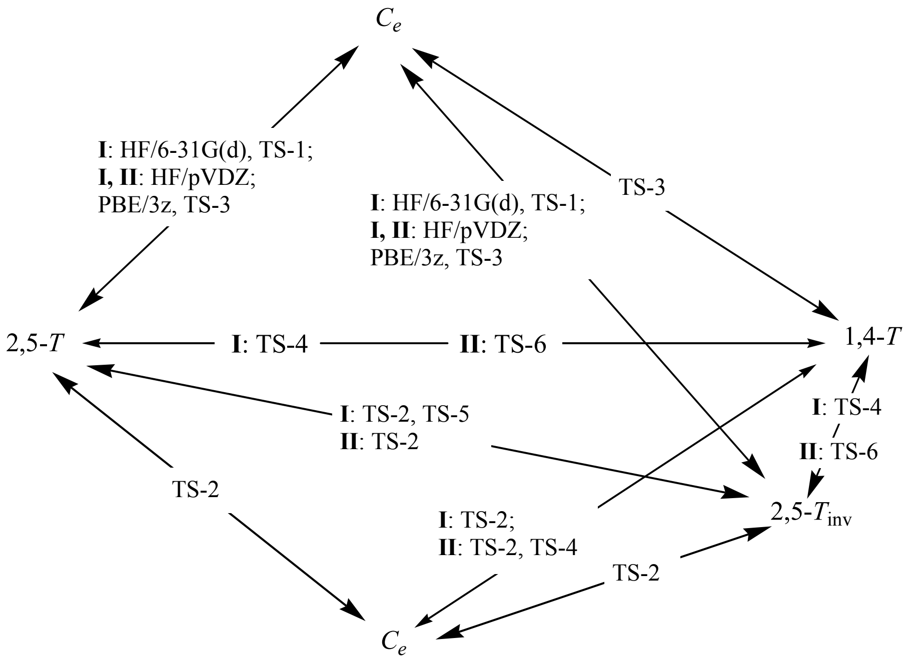


R = H (**I**), CH$_3$ (**II**).

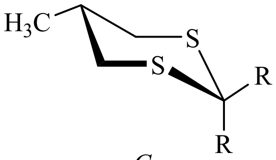
As known [24], the conformational analysis involves a study of the minima on the PES and the transition barriers between them. We found that, like in unsubstituted 1,3-dithiane [20, 21], the PES of compounds **I** and **II** contains five minima: the *equatorial chair* and *axial chair* conformers (C_e, C_a), as well as flexible conformers, 1,4-*T* and two enantiomeric forms of 2,5-*T*. The overall picture of the conformational transitions in this case corresponds to a trigonal bipyramid.

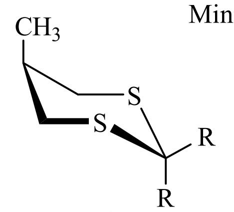
Note that all the used approximations show only one of the two possible 1,4-*T* forms, with pseudo-equatorial methyl group at the C^{5}atom of the ring. In the course of the geometry optimization and energy minimization the alternative conformer is irreversibly converted into 2,5-*T* form.

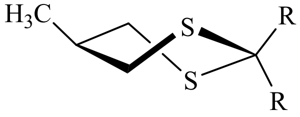
Analysis of the calculated parameters of the conformational equilibria of studied 1,3-dithianes (Table 1) shows that the difference in the energy of C_e and C_a forms (ΔH) is 1.2–1.5 kcal mol^{-1}, except for the case of HF/pVDZ approximation. Accordingly, the value of ΔG^0 for the $C_e \leftrightarrow C_a$ equilibrium is equal to 1.3–1.4 kcal mol^{-1} (PBE/3z). However, the calculated value of ΔH for similar conformers of 5-methyl-1,3-dioxane in the framework of the HF/6-31G(d) does not exceed 0.6 kcal mol^{-1} [25] . The large value of this parameter for compounds **I** and **II** is difficult to explain by steric interactions of the axial methyl group at the C^5 atom with the heteroatomic ring fragment, because an increase in the C–S bond length compared with C–O, should, conversely, reduce the ΔH and ΔG^0

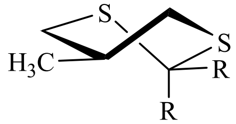


Minima

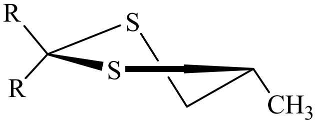

C_e

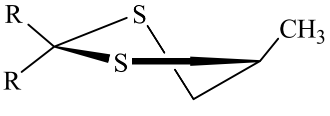

C_a


2,5-T


1,4-T

Transition state


TS-1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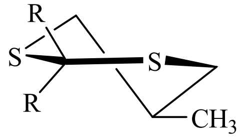
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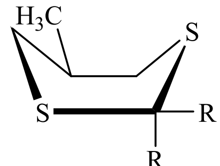
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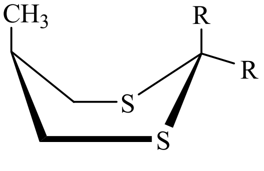
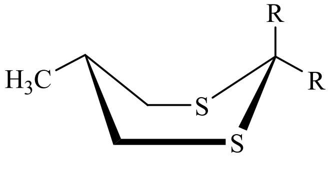
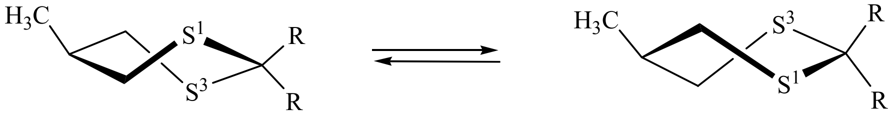

TS-5


TS-6


2,5-T 2,5-T_{inv}

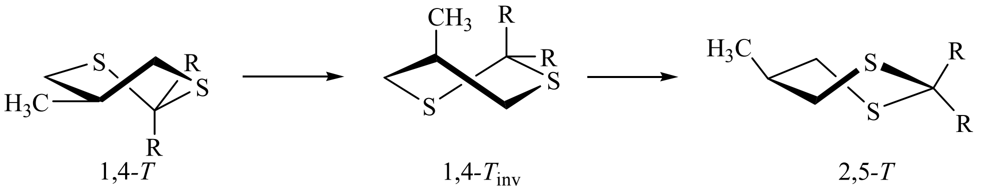

1,4-T 1,4-T_{inv} 2,5-T

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

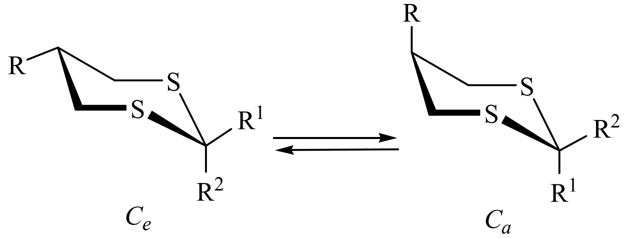
Comp. no.	Conformer or transition state	HF/6-31G(d)	HF/pVDZ	PBE/3z			
		0 K	0 K	0 K	298 K		
		ΔH ($\Delta H^{\neq}$)	ΔH ($\Delta H^{\neq}$)	ΔH ($\Delta H^{\neq}$)	ΔH ($\Delta H^{\neq}$)	ΔG^0 ($\Delta G^{\neq}$)	ΔS ($\Delta S^{\neq}$)
I	C_e	0	0	0	0	0	0
	C_a	1.5	0.7	1.3	1.3	1.4	–0.3
	2,5-*T*	4.3	3.9	4.0	4.1	3.7	1.3
	1,4-*T*	4.8	4.9	4.7	4.8	4.5	1.1
	TS-1	(10.6)	–	(10.1)	(9.8)	(10.1)	(–1.2)
	TS-2	(11.9)	(11.7)	(11.0)	(10.5)	(11.2)	(–2.3)
	TS-3	(9.9)	(10.2)	(10.1)	(9.9)	(9.8)	(0.2)
	TS-4	(5.9)	(5.9)	(5.4)	(4.9)	(5.8)	(–3.0)
	TS-5	(9.3)	(9.2)	(9.0)	(8.6)	(9.4)	(–2.5)
II	C_e	0	0	0	0	0	0
	C_a	1.5	0.7	1.2	1.2	1.3	–0.5
	2,5-*T*	3.1	2.5	2.3	2.2	2.0	0.7
	1,4-*T*	5.0	4.9	4.5	4.5	4.2	1.0
	TS-2	(11.9)	(11.4)	(10.5)	(10.1)	(10.7)	(–1.9)
	TS-3	(9.9)	(9.7)	(9.0)	(8.7)	(8.3)	(1.3)
	TS-4	(5.4)	(5.2)	(4.5)	(4.0)	(5.1)	(–3.8)
	TS-6	(7.9)	(8.2)	(7.5)	(7.2)	(7.9)	(–2.4)

for the alkyl group at the C^5 atom in 1,3-dithianes [2, 3, 6]. A possible reason for the large difference in energy of the C_e and C_a is the existence of notable stereoelectronic interactions in 1,3-dithiane ring, causing, in particular, the lengthening of the equatorial C^5–H bond [26]. According to the energy of these interactions in the HF/6-31G(d) and PBE/3z approximations probably leads to additional stabilization of the C_e conformer and/or destabilization of the C_a structure. At the same time the values of ΔH of the flexible forms 2,5-*T* and 1,4-*T* are less than those calculated for the 5-methyl-1,3-dioxane by HF/6-31G(d): 4.6 and 5.8 kcal mol^{-1}, respectively [25]. This is consistent with the experimental data: the *twist* conformers are present in the equilibrium of 1,3-dithianes in higher concentrations than in 1,3-dioxanes [1].

We should also note the relatively small contribution of the entropy component ΔS to the value of ΔG^0 of the conformational equilibrium between the minima on the PES (Table 1).

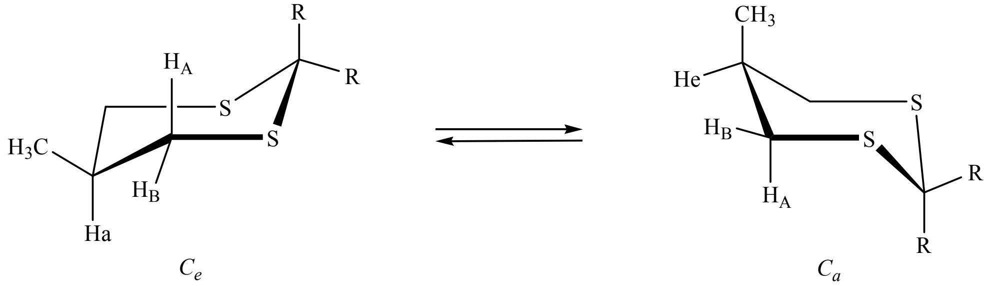
The identified transition states: three *semi-chair* forms (TS-1 to TS-3) and asymmetric (TS-4) and symmetric (TS-5, TS-6) *boats* are similar to those found previously for unsubstituted 1,3-dithiane [20, 21]. In the course of conformational transformations the forms TS-1–TS-5 are realized for compound **I** and forms TS-2–TS-4 and TS-6 for compound **II,** through the forms TS-2 to TS-4 and TS-6. Some conformational transformations can go through two maxima. Thus, in the case of dithiane **I** the conformational transition 2,5-*T* ↔ 2,5-T_{inv} is realized through the TS-2 and TS-5, and the isomerization C_a ↔ 1,4-*T* of dithiane **II** through TS-2 and TS-4. The maximum value of the calculated activation barrier ($\Delta G^{\neq}$, TS-2 structure) is 11.4 kcal mol^{-1} for the compound **I** and 10.7 kcal mol^{-1} for dithiane **II** (method PBE/3z, Table 1). These values are close to the experimental value of $\Delta G^{\neq}$ for unsubstituted 1,3-dithiane (10.4 kcal mol^{-1} [27]). We should also note the negative values of activation entropy $\Delta S^{\neq}$ for the majority of transiton states (Table 1), indicating their more compact nature compared with the conformers corresponding to the minima on the PES, and increased sensitivity of the system to the steric requirements.

The method of configuration isomerization leads to noticeable differences in the estimates of experimental



R	R^1	R^2	ΔG^0 (kcal mol^{-1})
CH$_3$	CH$_3$	H	0.52±0.03 [3]
CH$_3$	*t*-C$_4$H$_9$	H	1.04±0.01 [5]
CH$_3$	*i*-C$_3$H$_7$	CH$_3$	0.02±0.01 [2]
C$_2$H$_5$	*i*-C$_3$H$_7$	H	0.77±0.01 [3]
C$_2$H$_5$	*i*-C$_3$H$_7$	CH$_3$	0.02± 0.01 [2]

Table 2. Evaluation of ΔG^0 (kcal mol^{-1}) of *chair–chair* inversion of 1,3-dithianes **I** and **II**



Comp. no.	Method	Torsion angles				Spin–spin coupling constants, Hz				N	$-\Delta G^0$
		φ_{Aa}	φ_{Ba}	φ_{Ae}	φ_{Be}	J_{Aa}	J_{Ba}	J_{Ae}	J_{Be}		
I	6-31G(d)	178.5	63.7	54.3	63.3	11.6	3.6	2.6	3.6	0.7	0.5
	PBE/3z	177.5	63.8	55.6	63.2	11.6	3.6	2.4	3.6	0.7	0.5
II	6-31G(d)	179.7	62.8	53.0	64.4	11.5	3.7	2.8	3.5	0.6	0.2
	PBE/3z	175.0	66.3	50.6	67.4	11.7	3.2	3.1	3.1	0.6	0.2

Experimental spin–spin coupling constants, Hz: **I**, $^3J_{AX}$ 9.0 Hz, $^3J_{BX}$ 3.3 Hz [7]; **II**, $^3J_{AX}$ 7.6 Hz, $^3J_{BX}$ 4.1 Hz [2].

ΔG^0 for the CH$_3$ group at the atom C^5 in 1,3-dithianes that essentially depends on the degree of substitution and the nature of the substituents at the ring C^2 atom.

On the other hand, the conformational behavior of the molecules of dithianes **I** and **II** can be quite correctly described as a binary equilibrium between alternative *chair* forms, as they correspond to the main and adjacent to it minima, and the concentrations of other conformers are rather low. Hence, it becomes possible to estimate the ΔG^0 of the $C_e \leftrightarrow C_a$ conversion by an independent method, using the experimental ($^3J_{AX}$, $^3J_{BX}$) and theoretical (J_{Aa}, J_{Ba}, J_{Ae}, J_{Be}) vicinal spin-spin coupling constants for the conformers C_e and C_a and their relative contents N and 1–N, respectively [28]:

$$^3J_{AX} + {}^3J_{BX} = N\,(J_{Aa}+J_{Ba}) + (1-N)(J_{Ae}+J_{Be}),$$

$$\Delta G^0 = -RT\ln\,[N/(1-N)].$$

In turn, the theoretical coupling constants can be determined with the modified Karplus equation [29], using torsion angles (φ) between the protons in the conformers involved in the binary equilibrium. These angles were calculated by HF/6–31G(d) and PBE/3z methods, the results of calculation of the optimum geometry by the HF/pVDZ method are almost identical to those of HF/6-31G(d) calculation.

The data listed in Table 2 show that about 70% of the molecules of **I** and 60% of **II** exist as a C_e conformer. The value of ΔG^0 of the chair-chair inversion of dithiane **I** coincides with the experimentally observed for 2,5-dimethyl-1,3-dithiane [3]. For the dithiane **II** (ketal) they are naturally reduced. The values of ΔG^0 calculated (Table 1) and found from the spin-spin coupling constants (Table 2) are significantly different. This is due to the above noted inadequate accounting for the stereoelectronic interactions in the 1,3-dithiane ring, and the influence of the environment. The data on the configurational isomerization were obtained for solutions in CHCl$_3$ [2, 3, 5], while NMR spectra were recorded for solutions in CCl$_4$, C$_6$H$_6$, and C$_6$H$_5$NO$_2$ [2, 3]. We suggest that a good agreement of the method of spin-spin coupling and the data on the configurational isomerization evidences the adequacy in general of the calculated and actual geometric characteristics of molecules **I** and **II**. At the same time, the overestimation of the calculated value of ΔG^0 (Table 1) shows that the correct assessment in the case of 1,3-dithianes in further calculations is connected with the use of continuous or discrete models for the specific solvents.

The results obtained indicate that relatively high conformational flexibility of 1,3-dithianes is defined by both nonbonding interactions in the heteroatomic ring fragment and by stereoelectronic effects typical for this class of compounds.

EXPERIMENTAL

Compounds **I** and **II** has been described in [2, 7]. The routes of interconversion and values of barriers are found with the HyperChem [22] and PRIRODA [23] softwares. Belonging of the PES stationary points to the minima was confirmed by the absence of imaginary frequencies in the corresponding Hessian matrix, belonging to the transitional state, by the presence of one imaginary frequency. The applicability of computational methods to determination of the value of free conformational energy of the substituents in the saturated 1,3-heterocycles has been discussed in [30] by the examples of 1,3-dioxanes. The modified Karplus equation has the form [29]:

$$^{3}J_{\mathrm{HH}} = P_1\cos^2\varphi + P_2\cos\varphi + P_3 + \Sigma\Delta\chi_i[P_4 + P_5\cos^2(\xi_i\varphi + P_6|\Delta\chi_i|)].$$

Here $\Delta\chi_i$ is the difference in electronegativity between substituents in the corresponding ethane fragment and hydrogen, φ is the calculated torsion angle between the interacting protons, ξ_i takes the values ±1 depending on the orientation of substituents at the carbon atoms of ethane fragment, and P_1–P_6 are the parameters depending on the degree of substitution at this fragment. In the solving the P_1–P_6 values were used for the fragment with three substituents: $P_1 = 13.22$, $P_2 = -0.99$, $P_3 = 0$, $P_4 = 0.87$, $P_5 = -2.46$, $P_6 = 9.19°$, as well as numerical data on electronegativity from [31].

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