Quantum-chemical study of possible structural transformations in 3-methylthio-3-phenyl-2-propenethial

V. A. Shagun, L. V. Timokhina, and G. M. Panova*

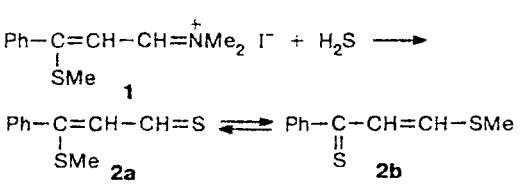
Irkutsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 1 ul. Favorskogo, 664033 Irkutsk, Russian Federation. Fax: 007 (395 2) 35 6046. E-mail: admin@irioch.irk.ru

The plausible formation of 3-methylthio-1-phenyl-2-propene-1-thione and 3-methylthio-3-phenyl-2-propenethial in the reaction of 3-methylthio-3-phenyl-2-propene-1-*N*,*N*-dimethyliminium iodide with hydrogen sulfide was shown in the framework of semiempirical AM1 and PM3 methods. In polar media, these products can be trimerized into four types of structures. The kind of trimer depends on the shift of the equilibrium in the 3-methylthio-3-phenyl-2-propenethial ⇌ 3-methylthio-1-phenyl-2-propene-1-thione mixture. Each of the four types of trimers is characterized by the presence of three nearly planar six-membered pseudo-chelate rings. The possibility of obtaining derivatives of 1,2-dithiolane (the basic fragment of lipoic acid) from the reaction products in nonpolar solvents was considered.

Key words: quantum-chemical calculations, AM1 and PM3 methods; conformation; 3-methylthio-3-phenyl-2-propenethial, trimerization, dithiolane, solvent polarity.

The interaction of 3-methylthio-3-phenyl-2-propene-1-*N*,*N*-dimethyliminium iodide (**1**) with hydrogen sulfide in anhydrous DMF at −60 °C proceeds with a loss of dimethylammonium iodide and the formation (*in situ*) of a mixture of 3-methylthio-3-phenyl-2-propenethial (**2a**) and 3-methylthio-1-phenyl-2-propene-1-thione (**2b**), in which product **2a** [1] is predominant (Scheme 1).

Scheme 1



The compound is rapidly transformed into a slightly colored stable trimer. Depending on the position of the equilibrium in the **2a** ⇌ **2b** mixture, the formation of four kinds of trimers **3a—d** is possible (Scheme 2).

To date, only trimer **3a** has been successfully isolated and studied.[1] Each of the four trimers **3a—d** has rich structural features for intramolecular conformational sigmatropic rearrangements to occur, finally leading to interesting tricyclic compounds in prototropic media. Phenyl substituents in compounds **3** play, to a certain extent, the role of a sterically shielding factor.

The mechanism of formation of compounds **2** and their plausible trimerization into structures **3a—d** has been little studied. This is mostly associated with difficulties of conducting experimental kinetic studies, since the interaction of compound **1** with hydrogen sulfide in the liquid phase can simultaneously proceed *via* several competing routes. Additionally, this reaction is extremely sensitive to temperature and microimpurities.[1] Hence, a quantum-chemical consideration of this reaction seems to be promising.

The main objective of this publication is to study intramolecular transformations of compounds **2a** and **2b** and the **2a** ⇌ **2b** equilibrium in the gaseous phase and in media of different polarities. The results were obtained within the framework of the semiempirical AM1[2,3] and PM3[4] approximations. Saddle points on the potential energy surface (PES) in calculations of transition states in the gaseous phase were determined using the only negative eigenvalue of the matrix of the second derivatives with respect to the geometric parameters. The solvent effect was estimated according to the procedure reported in Refs. 5—7 using two parameters determining properties of the solvent, dielectric permeability (ε) and an empirical constant (c) independent of the kind of atoms. All given quantum-chemical characteristics are referred to the AM1 method unless otherwise specified.

The intramolecular 1,5-sigmatropic migration of the methyl group, which is a crucial act of **2a** ⇌ **2b** transformation, depends on the initial conformations of compounds **2a** and **2b**. As can be inferred from the

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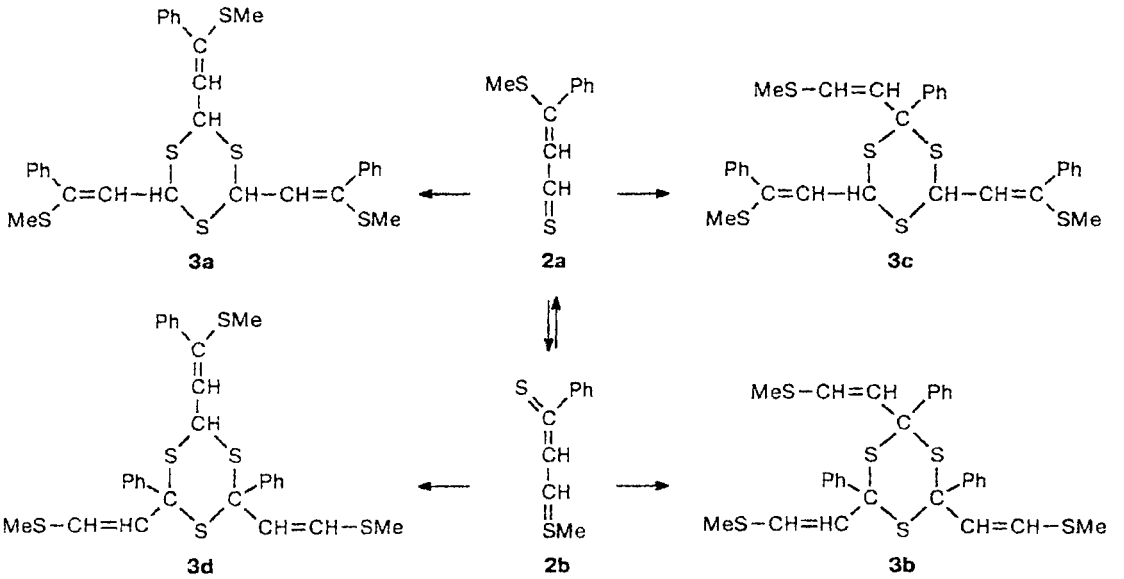
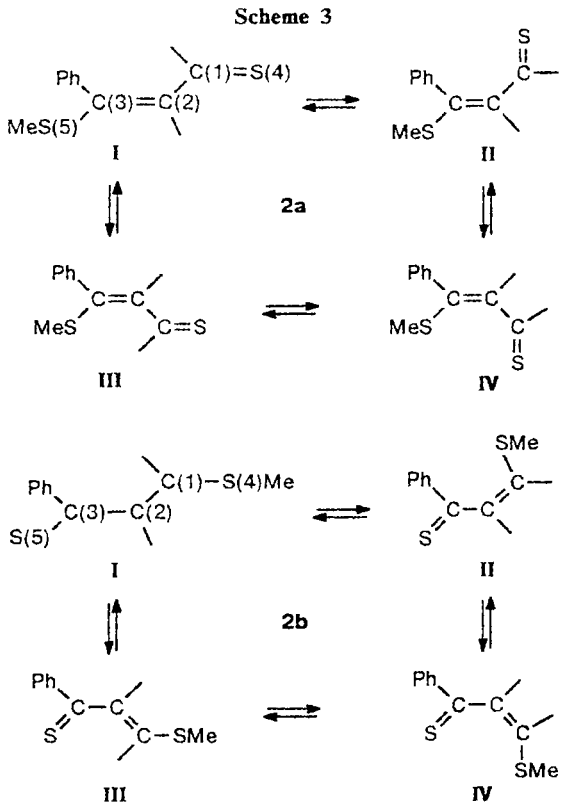
Scheme 2



results of the gas-phase quantum-chemical investigations, these compounds can exist in four stable conformations (Scheme 3).

All gas-phase conformers **I**—**IV** (**2a,b**), irrespective of the computational method used, are characterized by a nearly planar structure of the central S=C—C=C—S fragment (the out-of-plane deviations do not exceed 0.01 Å). The only exceptions are the sulfur atoms in conformer **IV**, which deviate 7—9° in the opposite directions from the plane of the central carbon fragment. For all conformations, the plane of the phenyl substituent is almost perpendicular to the plane of the molecular skeleton.

Scheme 3



The relative stability of rotamers **I**—**IV** of compounds **2a,b** and their main geometric parameters are listed in Table 1. Form **IV** with *cis*-positioned thione and thiol sulfur atoms is the most stable form for molecules **2a** and **2b**. The key feature of rotamers **IV** is the appreciably increased double bond character of the thiol sulfur atom (the bond length is 0.05—0.06 Å shorter than those in forms **I**—**III**) and the decreased double bond character of the thione sulfur atom (the bond lengthening by 0.03—0.04 Å); appreciable distortion of bond angles, which cause shortening of the interatomic S...S distance (Tables 1 and 2), and a corresponding

Table 1. Relative stabilities* (ΔE) of conformations **I**—**IV** of compounds **2a,b**

Compound	Conformer	ΔE/kcal mol^{-1}	
		AM1	PM3
2a	**I**	20.2	8.1
	II	25.0	13.4
	III	21.4	8.8
	IV	0.0	0.3
2b	**I**	19.6	9.3
	II	24.6	19.5
	III	19.3	6.8
	IV	0.1	0.0

* With respect to the energy of the most stable rotamer.

Table 2. Bond lengths in conformations I—IV of compounds **2a,b***

Compound	Conformer	Bond length/Å				
		C(1)—C(2)	C(2)—C(3)	C(3)—C_{ipso}(Ph)	C(1)—S(4)	C(3)—S(5)
2	**I**	1.439	1.356	1.463	1.536	1.691
		(1.445)	(1.352)	(1.470)	(1.568)	(1.757)
	II	1.436	1.354	1.461	1.536	1.698
		(1.441)	(1.353)	(1.466)	(1.570)	(1.763)
	III	1.440	1.356	1.466	1.535	1.691
		(1.447)	(1.353)	(1.473)	(1.567)	(1.759)
	IV	1.394	1.386	1.461	1.612	1.623
		(1.406)	(1.385)	(1.462)	(1.649)	(1.736)
2b	**I**	1.348	1.448	1.473	1.656	1.550
		(1.346)	(1.454)	(1.479)	(1.710)	(1.588)
	II	1.348	1.446	1.473	1.665	1.553
		(1.397)	(1.465)	(1.475)	(1.760)	(1.586)
	III	1.349	1.448	1.474	1.650	1.553
		(1.347)	(1.455)	(1.482)	(1.712)	(1.588)
	IV	1.387	1.405	1.461	1.625	1.611
		(1.375)	(1.418)	(1.465)	(1.721)	(1.655)

* Values obtained by the PM3 method are given in parentheses.

Table 3. Bond angles in conformations I—IV of compounds **2a,b***

Compound	Conformer	Bond angle/deg			
		C(1)—C(2)—C(3)	C(2)—C(3)—C_{ipso}(Ph)	C(2)—C(1)—S(4)	C(2)—C(1)—S(5)
2a	**I**	124.8	122.7	125.6	115.9
		(124.1)	(122.4)	(125.1)	(116.9)
	II	129.1	125.6	131.7	115.1
		(130.0)	(125.6)	(132.8)	(114.8)
	III	124.4	119.7	125.6	120.2
		(124.7)	(118.0)	(125.1)	(121.8)
	IV	118.7	119.2	119.5	115.4
		(116.9)	(121.7)	(115.1)	(113.6)
2b	**I**	124.9	116.3	129.9	121.3
		(124.3)	(116.1)	(129.8)	(121.2)
	II	128.3	117.7	126.2	120.8
		(132.9)	(119.4)	(132.4)	(119.1)
	III	123.1	113.2	130.5	125.0
		(122.8)	(111.7)	(129.7)	(125.8)
	IV	118.4	119.9	118.4	117.2
		(116.4)	(119.4)	(115.7)	(113.4)

* Values obtained by the PM3 method are given in parentheses.

equalization of the carbon C(2)—C(1) and C(2)—C(3) bonds was also observed.

As a result of this distortion of the geometry that caused equalization of the characters of the double and ordinary bonds, considerable redistributions of the charges in the central fragments of the molecules (including the methyl group) are observed (Table 2). A rather sharp increase in the polarity of the S—CH_3 bond in rotamers **IV** makes this form close to the ionic form. This indicates that the **2a** $\rightleftharpoons$ **2b** transition most likely occurs through rotamers **IV**, which is also confirmed by the quantum-chemical model. Thus, the activation energy of transition **2b** → **2a** with the initial and final steady states **IV** is equal to 39.9 kcal mol^{-1}, while an

Table 4. Charge distributions in the central fragments of rotational forms I—IV of compounds **2a,b**

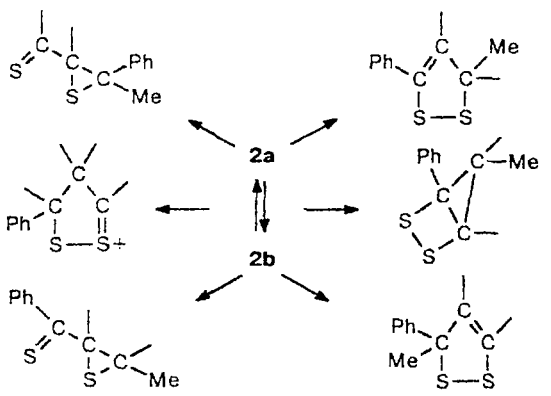
Compound	Form	*q*					
		C(1)	C(2)	C(3)	S(4)	S(5)	C(Me)
2a	**I**	−0.167	−0.194	−0.179	−0.009	0.274	−0.373
	II	−0.159	−0.205	−0.147	−0.009	0.255	−0.368
	III	−0.176	−0.190	−0.183	−0.003	0.269	−0.370
	IV	−0.231	−0.196	−0.269	−0.081	0.710	−0.562
2b	**I**	−0.259	−0.221	−0.053	0.314	−0.018	−0.387
	II	−0.301	−0.197	−0.059	0.335	−0.020	−0.396
	III	−0.295	−0.230	−0.046	0.334	−0.038	−0.392
	IV	−0.406	−0.191	−0.125	0.716	−0.079	−0.571

activation energy of 64.8 kcal mol^{-1} corresponds to an analogous transformation with participation of conformers **III**.

Such behavior of compounds **2a** and **2b** in the gaseous phase suggests that 1,4-sigmatropic rearrangement of form **IV** with the subsequent formation of highly reactive 1,2-dithiolane[8] (or a stable dithiolinium cation[9] in the case of elimination of the methyl group) can in principle occur. It should be noted that according to the data of the PM3 approximation, the corresponding 1,2-dithiolane in the gas phase is ~4.5 kcal mol^{-1} more stable than rotamer **IV**. The AM1 method also indicates a higher relative stability of the former, however, only by 1.5 kcal mol^{-1}. The activation barrier of the 1,4-sigmatropic migration of the methyl group is equal to 47.8 kcal mol^{-1}.

Thus, production of very interesting compounds, 1,2-dithiolanes (which are a basic fragment of lipoic acid), from 3-methylthio-3-phenyl-2-propenethial **2a** and 3-methylthio-1-phenyl-2-propene-1-thione **2b** is possible in the gaseous phase and, perhaps, in nonpolar solvents. Two important biochemical processes involving a thiol-disulfide system, electron transfer and the generation of high-energy thioester bonds,[10,11] are related to this acid. Therefore, production of compounds **2** with appropriate substituents can result in a new method for the synthesis of lipoic acid. The possibility of obtaining thiiranes from compounds **2** can not also be ruled out. 1,2-Sigmatropic rearrangement of the methyl group (Scheme 4) is able to initiate this process.

Scheme 4



It should be noted that the activation barriers to rotational transformations of compounds **2a** (25.6, 10.9, 8.4, and 27.6 kcal mol^{-1} for transitions **II** → **IV**, **III** → **IV**, **I** → **II**, and **I** → **III**, respectively) and **2b** (6.1, 26.8, 9.8, and 28.3 kcal mol^{-1} for the same transitions) show that the found stable forms should be spectroscopically discernible.

Calculations of the relative stability of conformers **2** taking into account the simulated effect of solvents of different polarities (ε = 10; 20) to a certain extent level the results and reveal a tendency for the sequence of stabilities of forms **I**—**IV** to change as the polarity of the medium increases. At ε = 10, this sequence is little changed: from **IV**—**I**—**III**—**II** (Table 1) to **IV**—**III**—**I**—**II** (with relative energies of rotamers of 0.0, 10.9, 17.5, and 22.6 kcal mol^{-1}, respectively) for compound **2a**, and from **IV**—**III**—**I**—**II** to **IV**—**I**—**III**—**II** (with corresponding energies of 0.0, 9.6, 15.3, and 20.8 kcal mol^{-1}, respectively) for compound **2b**. The energy gap between rotamer **IV** and the form closest in stability is nearly halved (see Table 1).

The results obtained by the PM3 method are characterized by the same order in the stability of the conformers as that obtained by the AM1 method; however, the energy gap between the two most stable forms nearly disappears (0.4 and 1.2 kcal mol^{-1} in favor of rotamer **IV** of compounds **2a** and **2b**, respectively). An increase in the polarity of the simulated solvent from ε = 10 to ε = 20 results in the following change in the sequence of the relative stabilities of conformations **I**—**IV**: **III**—**IV**—**I**—**II** (0.0, 3.2, 3.7, and 14.8 kcal mol^{-1}, respectively) for compound **2a**, and **I**—**IV**—**III**—**II** (0.0, 2.8, 5.6, and 18.2 kcal mol^{-1}, respectively) for compound **2b**. Thus, the solvent effect manifests itself not only in decreasing the differences in the stability of conformers, but also in changing the most reactive form.

To obtain elementary information on the channels of trimerization of compounds **2a,b**, we considered all plausible schemes of the reaction:

$$j\ \mathbf{2a}_i + (3 - j)\ \mathbf{2b}_i \rightarrow 3\ (l) + \Delta H_l^j,$$

where j is the number of allowed combinations taking the values 3, 2, 1, and 0, while parameter l maps this set one-to-one onto structures **3a**, **3c**, **3d**, and **3b**, and i is the rotational form of the systems **2a** and **2b**.

Analysis of the obtained ΔH_l^j values allowed us to select the trimerization routes that are the most probable according to the model given:

$$3 \cdot \mathbf{2a}_3 \rightarrow \mathbf{3a} + 107.3 \text{ kcal mol}^{-1},$$

$$3 \cdot \mathbf{2b}_1 \rightarrow \mathbf{3b} + 103.7 \text{ kcal mol}^{-1},$$

$$2 \cdot \mathbf{2a}_3 + 1 \cdot \mathbf{2b}_1 \rightarrow \mathbf{3c} + 86.5 \text{ kcal mol}^{-1},$$

$$1 \cdot \mathbf{2a}_3 + 2 \cdot \mathbf{2b}_1 \rightarrow \mathbf{3d} + 78.5 \text{ kcal mol}^{-1}.$$

Of course, similar consideration of the reaction channels says nothing about the reaction mechanisms; nevertheless, it gives a basic idea of the most probable rotational forms participating in trimerization.

As noted above, trimers **3a—c** are extremely mobile conformationally; this results in the appearance of a large number of local minima on the PES of configurational transformations. However, several common features are inherent in the most stable states of all considered compounds **3a—d**. The central six-membered fragment has a chair shape; each of the three sulfur atoms of

this cycle is bonded by a weak hydrogen S...H—C—S bond to the substituent of the adjacent atom, so that a nearly planar six-membered pseudo-chelate ring is formed. The interatomic S...H distance is 2.7—2.9 Å. The phenyl substituents tend to become perpendicular to the plane of the pseudo-chelate cycle.

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