Dedicated to G.A. Tolstikov on his 75th anniversary

Quantum-Chemical Study on the Mechanism of Formation of Geminal Hydroxy Thiols by Reaction of 1,3-Dihalopropan-2-ones with Hydrogen Sulfide

V. A. Shagun, L. G. Shagun, I. A. Dorofeev, I. A. Mikhailova, and M. G. Voronkov

Favorskii Irkutsk Institute of Chemistry, Siberian Division, Russian Academy of Sciences,
ul. Favorskogo 1, Irkutsk, 664033 Russia
*e-mail: shag@irioch.irk.ru*

Abstract—The reaction mechanism of 1,3-dihalopropan-2-ones with hydrogen sulfide in the presence of hydrogen chloride was studied in terms of the density functional theory. Unlike 1-halopropan-2-ones which give rise to 1-halo-2-sulfanylpropan-2-ols via preliminary enolization, 1,3-dihalopropan-2-ones preferentially undergo direct nucleophilic attack on the carbonyl group by hydrogen sulfide. The potential energy surface for rotational isomerism of 1,3-dihalopropane-2-thiones and 1,3-dihalo-2-sulfanylpropan-2-ols was analyzed, and their most stable rotamers were identified.

Our fundamental studies in the field of synthesis and transformations of thiones containing a halogen atom in the α-position [1], as well as of geminal dithiols derived therefrom [2], revealed their unique reactivity and wide prospects in using them in fine organic synthesis. By reactions of α-halo thiones and α-halo dithiols with various nucleophilic and electrophilic reagents we succeeded in purposefully obtaining a variety of heterocyclic systems, such as thiiranes [3], 1,4-dithianes [4], 1,3,5-trithianes [5], 2,3,5,6-tetrathianes [6], 2-sulfanyl-2-methyltetrahydro[1,4]thiazinoquinolinium halides [7], dithiiranes [8], 1,4-dithiines [9], and 1,3,4-thiadiazines [10], including those possessing biological activity. The ability of 1-halopropane-2-thiones to readily undergo homopolycondensation at 20°C to give polymeric products having paramagnetic, conducting, and photoconducting properties [11] underlies their possible application in the development of materials and coatings of practical importance. 1-Chloropropane-2,2-dithiol and 2-sulfanyl-2-methyltetrahydro[1,4]thiazinoquinolinium halides can be used as components for the design of pharmacological agents for neutralization of very stable and highly toxic alkylmercury cations [12]. The available data on the properties and transformations of α-halogenated thiones and geminal dithiols suggest that the synthesis and studies on the properties of compounds having two or three halogen atoms in the α-position with respect to C=S, C(SH)(OH), or C(SH)$_2$ moiety are expedient from the viewpoint of obtaining promising monomers and intermediate products for fine organic synthesis.

In the present work we analyzed the potential energy surfaces for rotational isomerism of 1,3-dihalopropane-2-thiones and 1,3-dihalo-2-sulfanylpropan-2-ols and the mechanism of formation of the latter by reaction of 1,3-dihalopropan-2-ones with hydrogen sulfide in the presence of hydrogen chloride (Scheme 1) in terms of the density functional theory (DFT). All calculations were performed using Gaussian 98 software package [13] with 6-311+G (3df) basis set and three-parameter B3LYP functional [14]. Full geometry optimization of molecular structures was continued up to a gradient value of 10^{-5} a.u./bohr. While analyzing flat areas of the potential energy surface, the gradient value was set at a level of 10^{-6} a.u./bohr. Stationary points were localized by analyzing Hessian eigen-

Scheme 1.

X = F, Cl, Br.
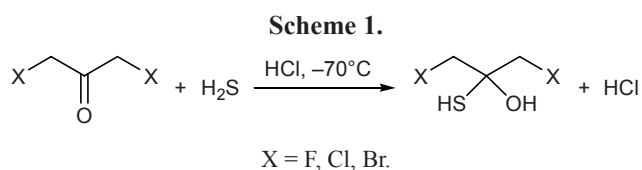
values. Transition states (TS) were identified by the linear synchronous transit-guided quasi-Newton method (QST2) [15]. Approximate transition state structure thus determined was then refined using the quadratic synchronous transit protocol (QST3) [15]. Analysis of vibration frequencies at saddle points was performed, and conformity of critical points to the gradient line connecting them was proved, by the internal reaction coordinate (IRC) technique. The energies of zero-point harmonic vibrations (ZPE) were calculated with the use of a calibration factor of 0.9806 [15].

α-Halopropan-2-ones XCH$_2$C(O)Me in solution and in the gas phase (X = F) exist as mixtures of *cis* and *trans* rotameres [16–18], as well as *cis* and *gauche* rotamers (X = Cl, Br, I) [19]. The predominant structure for fluoroacetone is *trans*, while *gauche* rotamer is the most thermodynamically stable for the other α-haloacetones [20].

cis   *trans*   *gauche*
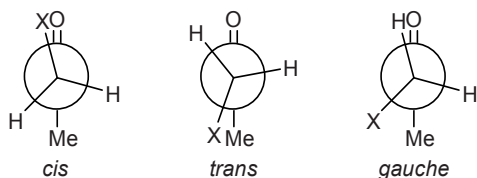
Theoretical [B3LYP/6-311++G(2*df*,2*p*)] and spectral (IR) study of 1,3-difluoropropan-2-one (**Ia**), 1,3-dichloropropan-2-one (**Ib**), and 1,3-dibromopropan-2-one (**Ic**) showed that introduction of similar halogen atoms into positions *1* and *3* increases the number of nondegenerate stationary states on the potential energy surface for rotational transformations [21]. Regardless

of the aggregate state and solvent polarity, 1,3-difluoroacetone (**Ia**) exists mainly as *cis-trans* conformer **C**. Dichloroacetone **Ib** in the gas phase has *gauche-gauche'* structure **E**, while solvent stabilizes rotamer **C**. Structure **E** is also the most stable for dibromo derivative **IIc** in weakly polar solvents and in the gas phase, while polar solvents shift the equilibrium toward *cis-gauche* rotamer **B** [21].
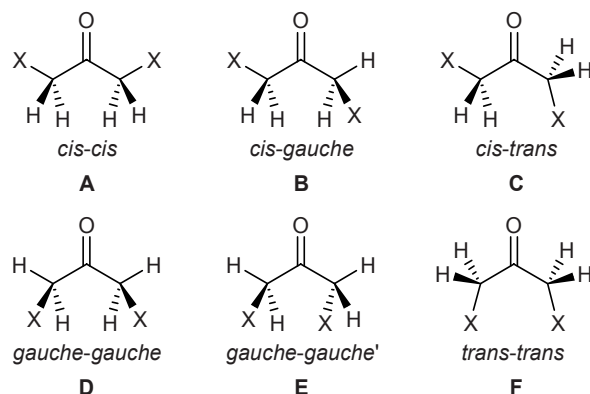
The principal structural parameters of the most stable rotamers of **Ia**–**Ic** and **IIa**–**IIc** are given in Fig. 1, and Table 1 contains their electronic parameters. The potential energy surface for rotational transformations of fluoro ketone **Ia** does not change to an appreciable extent. 1-Fluoropropane-2-thione (**IIa**) is most stable as rotamers **C**, **E**, and **A**; their thermodynamic stability varies within 11.9 kJ/mol (Table 1). The corresponding energy interval for compound **Ia** is slightly broader, 13.8 kJ/mol [21]. Like ketones **Ib** and **Ic**, structure **E** with *gauche-gauche'* orientation of the halogen atoms
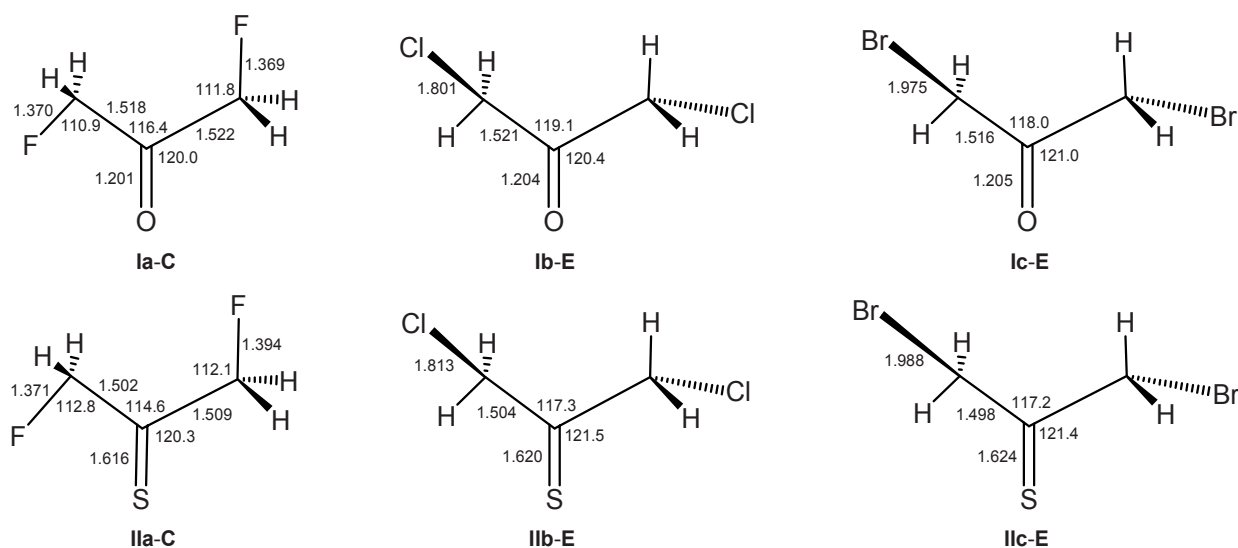

Fig. 1. Molecular structures and principal geometric parameters (bond lengths, Å, and bond angles, deg) of the most stable rotamers of ketones **Ia**–**Ic** and thiones **IIa**–**IIc**, calculated at the B3LYP/6-311+G(3*df*) level.

Table 1. Total energies (E_{tot}), energies of zero-point harmonic vibrations (ZPE), relative energies (ΔE), imaginary or least harmonic frequencies (iw/ω), dipole moments (μ), and dihedral angles (θ_1, θ_2) for ketones **Ia–Ic** and thiones **IIa–IIc**, calculated at the B3LYP/6-311+G(3df) level

| Structure no.	$-E_{tot}$,[a] a.u.	ZPE,[b] a.u.	ΔE,[c] kJ/mol	iw/ω, cm^{-1}	μ,[c] D	θ_1,[d] deg	θ_2,[d] deg
Ia-C	391.75271	0.06825	–	77	2.65 (2.66)	0.0	180.0
Ib-E	1112.46621	0.06581	0.0	34	0.61 (0.64)	54.5	54.2
Ib-C	1112.46505	0.06573	2.8 (3.0)	47	2.33 (2.35)	1.0	179.7
Ic-E	5340.30872	0.06475	0.0	30	1.47 (1.43)	73.0	73.0
Ic-B	5340.30556	0.06426	7.0 (8.4)	30	3.31 (3.30)	74.5	174.8
IIa-C	714.70955	0.06608	0.0	41	2.07	0.0	180.0
IIa-E	714.70846	0.06645	3.8	74	0.61	42.3	42.3
IIa-A	714.70504	0.06609	11.9	73	3.70	170.3	170.3
IIb-E	1435.42307	0.06386	0.0	25	0.01	60.8	60.8
IIb-B	1435.41955	0.06314	7.3	37	1.96	46.3	168.6
IIb-A	1435.41548	0.06280	17.1	49	3.17	173.3	173.0
IIc-E	5663.26585	0.06273	0.0	27	0.48	69.2	69.2
IIa-B	5663.26033	0.06206	12.7	28	2.49	71.5	177.4
IIa-A	5663.25526	0.06161	24.8	26	2.93	165.0	164.8

[a] 1 a.u. = 2622 kJ/mol.
[b] Calculated with a correction factor of 0.9806.
[c] In parentheses are given the data of [21].
[d] θ_1 is the dihedral angle X^{1}CCC, and θ_2 is the dihedral angle CCCX^2.

(Fig. 1) is the most stable for chloro and bromo thiones **IIb** and **IIc**. The depth of the corresponding potential well relative to those for the nearest rotamers increases with rise in the halogen atom number (Table 1). Judging by the calculated dipole moments (Table 1), which reflect the degree of charge separation in isomers **IIa–IIc**, the population of the *cis-cis* rotamers of **IIa** and **IIc** and *cis-gauche* rotamer of **IIb** should increase in going to condensed phase.

According to the calculations performed at the B3LYP/LANL2DZ level, reactions of α-haloacetones with hydrogen sulfide involve intermediate formation of the corresponding enol [20], while hydrogen chloride mediates the enolization process (Scheme 2). Here, the rate-determining stage is the reaction of hydrogen sulfide with the active enol form. Its activation energy is 230.3, 232.5, 237.7, and 241.1 kJ/mol for
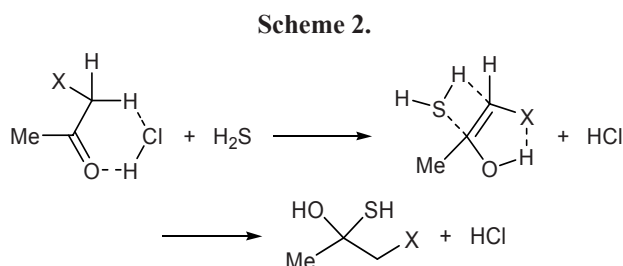
fluoro, chloro, bromo, and iodo derivatives, respectively. Direct attack on the substrate by hydrogen sulfide molecule with formation of a four-center transition state is less favorable by about 80–90 kJ/mol [20].
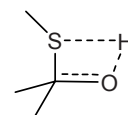

The resulting hydroxy thiol is capable of undergoing HCl-promoted intramolecular autoprotonation and elimination of either water molecule to give the corresponding thione (Scheme 3) or hydrogen sulfide to give the initial ketone (Scheme 4), depending on the rotational state of the hydroxy thiol.

While studying the mechanism of formation of geminal hydroxy thiols from 1,3-dihalopropan-2-ones, as starting structures we used the most stable rotamers,
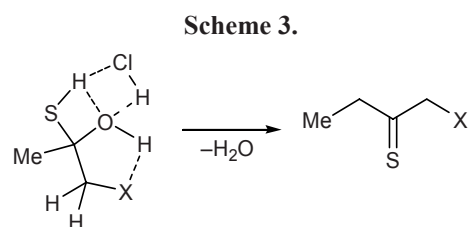
Scheme 2.

Scheme 3.

Scheme 4.
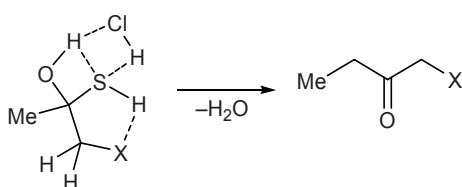
Ia-C, **Ib-E**, and **Ic-E** (Fig. 1). The optimal structures of trimolecular systems (**Ia–Ic**)–HCl–H₂S were determined, and their thermodynamic stabilities were esti-

mated as the difference between the total energy of the complex and the sum of the energies of particular components (**Ia–Ic**, HCl, and H₂S). It was found that the stability weakly depends on the halogen nature: it slightly increases with rise in the halogen atom number (28.1, 31.3, and 39.6 kJ/mol for X = F, Cl, and Br, respectively). Figure 2 shows the calculated structures of the molecular systems **Ia**·HCl·H₂S, **Ib**·HCl·H₂S, and **Ic**·HCl·H₂S (principal interatomic distances are given).
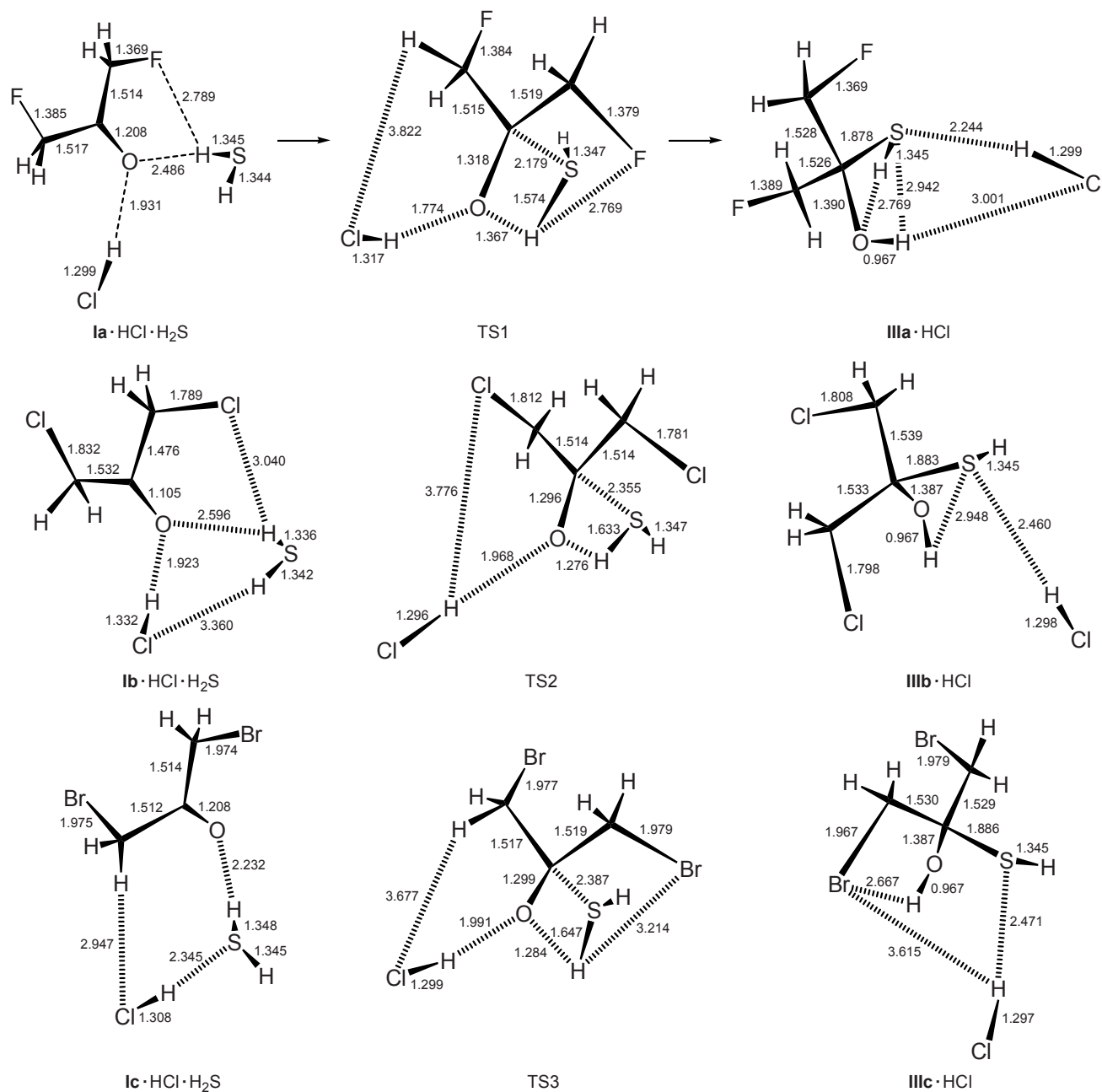

Fig. 2. Structures and geometric parameters (interatomic distances, Å) of stationary and transition states of molecular systems involved in reactions (**Ia–Ic**)·HCl·H₂S → (**IIIa–IIIc**)·HCl, calculated at the B3LYP/6-311+G(3*df*) level.

Table 2. Total energies (E_{tot}), energies of zero-point harmonic vibrations (ZPE), relative energies (ΔE), imaginary or least harmonic frequencies (iw/ω), dipole moments (μ), and dihedral angles (θ_1, θ_2) for complexes (**IIa–IIc**)·H$_2$S·HCl, transition states TS1–TS3, and structures (**IIIa–IIIc**)·HCl, calculated at the B3LYP/6-311+G(3df) level[a]

Structure no.	$-E_{tot}$, a.u.	ZPE, a.u.	ΔE, kJ/mol	iw/ω, cm^{-1}	μ, D	θ_1, deg	θ_2, deg
IIa·H$_2$S·HCl	1252.02083	0.09875	7.4	37	3.99	0.0	180.0
TS1	1251.95469	0.09804	179.0	i746	4.56	70.0	168.2
IIIa·HCl	1252.02410	0.09920	0.0	26	2.83	57.5	174.6
IIb·H$_2$S·HCl	1972.73555	0.09711	1.7	31	4.36	4.9	178.0
TS2	1972.66533	0.09617	183.4	i655	4.56	70.0	168.2
IIIb·HCl	1972.73707	0.09798	0.0	13	2.62	61.0	176.0
IIc·H$_2$S·HCl	6200.58122	0.08994	1.3	11	2.38	−75.5	75.9
TS3	6200.50622	0.08603	187.6	i542	4.11	46.2	165.3
IIIc·HCl	6200.58236	0.09059	0.0	12	2.47	61.7	176.6

[a] See notes to Table 1.

Contrary to our expectations, the optimal gradient channel for the formation of hydroxy thiols was that involving no intermediate enol forms of dihalo ketones **Ia–Ic**. It was direct nucleophilic attack by hydrogen sulfide molecule on the carbonyl group. Unlike analogous reaction of monohalo derivatives, 1,3-dihalo-2-sulfanylpropan-2-ols are formed from 1,3-dihalopropan-2-ones in one step. Hydrogen chloride molecule reacts at the carbonyl group; as a result, the order of the C=O bond decreases, favoring addition of proton
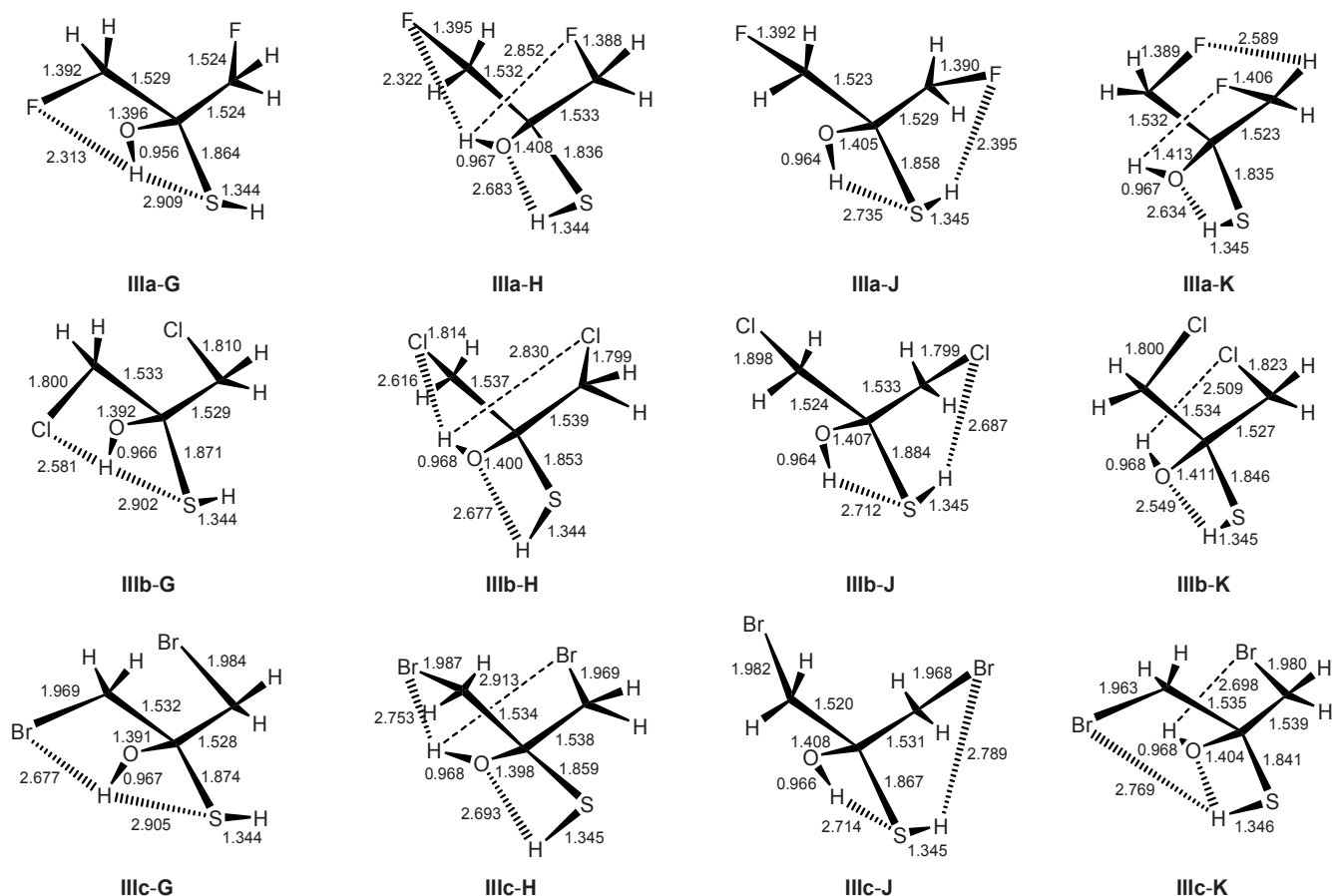

Fig. 3. Molecular structures and principal geometric parameters (interatomic distances, Å) of the most stable rotamers of compounds **IIIa–IIIc**, calculated at the B3LYP/6-311+G(3df) level.

Table 3. Total energies (E_{tot}), energies of zero-point harmonic vibrations (ZPE), relative energies (ΔE), imaginary or least harmonic frequencies (iw/ω), dipole moments (μ), and dihedral angles (θ_1, θ_2) for the most stable rotational states of 1,3-dihalo-2-sulfanylpropan-2-ols **IIIa–IIIc**, calculated at the B3LYP/6-311+G(3df) level[a]

Structure no.	$-E_{tot}$, a.u.	ZPE, a.u.	ΔE, kJ/mol	iw/ω, cm^{-1}	μ, D	θ_1, deg	θ_2, deg
IIIa-G	791.18470	0.09082	0.0	96	1.24	−172.1	57.8
IIIa-H	791.18057	0.09031	9.5	42	1.78	63.4	9.5
IIIa-J	791.18360	0.09081	2.9	98	1.77	−55.0	62.9
IIIa-K	791.18328	0.09068	3.4	85	1.40	−67.1	60.5
IIIb-G	1511.89583	0.08771	0.0	79	1.23	−175.2	61.0
IIIb-H	1511.88948	0.08706	15.0	23	1.79	79.3	73.1
IIIb-J	1511.89433	0.08776	4.1	70	1.98	−56.3	58.3
IIIb-K	1511.89488	0.08754	2.0	65	1.35	−60.2	65.0
IIIc-G	5739.73573	0.08637	0.0	61	1.24	−175.9	61.7
IIIc-H	5739.72843	0.08573	17.5	24	1.78	77.4	17.5
IIIc-J	5739.73391	0.08641	4.9	49	2.02	−56.6	57.7
IIIc-K	5739.73475	0.08592	1.4	70	1.87	−179.5	68.0

[a] See notes to Table 1.

from hydrogen sulfide molecule at the π-orbital of the oxygen atom. No dissociation of the S–H bond occurs along the gradient path connecting the initial molecular system and transition state, i.e. the reaction involves no ionic species. The enrgies of activation for the systems including structures **Ia–Ic** were estimated at 179.0, 183.4, and 187.6 kJ/mol, respectively (Table 2); these values are lower by about 50 kJ/mol than the activation barrier to the formation of geminal hydroxy thiols from monohaloacetones [20].

As the halogen atom number increases, the heat effect tends to zero (Table 2). Therefore, a dynamic equilibrium between the ketone, hydroxy thiol, and thione is possible. Elimination of hydrogen sulfide or water from hydroxy thiol is largely determined by its rotational state and is related to the ability of the hy-

droxy or sulfanyl group to abstract proton from each other. Analysis of the potential energy surfaces for rotational isomerism of hydroxy thiols **IIIa–IIIc** revealed their most stable rotamers. The structures and principal geometric parameters of four most low-lying states of **IIIa–IIIc** are shown in Fig. 3.

The relative stability range broadens from 9.5 to 17.5 kJ/mol in going from fluoro to bromo derivatives (Table 3). Unlike rotamers **I** and **II** (Table 1), the polarity of molecules **IIIa–IIIc** changes insignificantly, the maximal variation not exceeding 0.54, 0.75, and 0.78 D, respectively; therefore, no essential redistribution in the population of different states might be expected for condensed phase.

As follows from the character of intramolecular interaction between the hydroxy and sulfanyl groups in
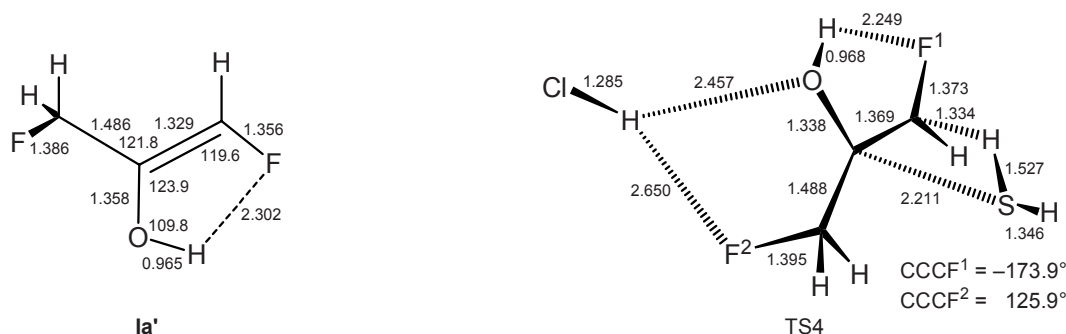

Fig. 4. Molecular structures and principal geometric parameters (interatomic distances, Å, and bond and dihedral angles, deg) of the enol form of ketone **Ia** (**Ia′**) and transition state TS4, calculated at the B3LYP/6-311+G(3df) level.

IIIa–IIIc (Fig. 3), elimination of hydrogen sulfide with formation of initial dihaloacetone is favorable from rotational states **G** and **J** (regardless of the halogen nature), while structures **H** and **K** are the most probable precursors of dihalopropanethiones. The most stable rotamers of compound **IIIa** are **G** and **J** (Table 3). Therefore, rise in temperature could displace the reaction equilibrium toward the corresponding ketone. The most stable structures of molecules **IIIb** and **IIIc** are rotamers **G** and **K**. In these cases, the formation of ketone or thione is almost equally probable.

The path of formation of hydroxy thiol through activation of intermediate enol was analyzed only for 1,3-difluoropropan-2-one (**Ia**). The structure of isolated enol form **Ia′** was calculated (the activation barrier to ketone–enol transformation was not estimated, for this step is not rate-determining). The optimized structure of enol **Ia′** is represented by a five-membered pseudocoordination ring including one of the halogen atoms, which stabilizes the system (Fig. 4). The second fluorine atom is oriented almost orthogonally to the five-membered ring ($\theta = 110.2°$). Unlike α-fluoroacetone whose enolization reduces the stability by 59 kJ/mol, the enol form of **Ia** is less stable than the ketone form by only 34.8 kJ/mol. The gradient channel connecting molecular system **Ia′**·HCl·H$_2$S and product **IIIa**·HCl through transition state TS4 (Fig. 4) is characterized by an activation barrier of 208.5 kJ/mol; taking into account the initial gain in energy (34.8 kJ× mol^{-1}), this value considerably exceeds the energy of TS1 (Table 2).

REFERENCES

1. Voronkov, M.G., Shagun, L.G., and Shagun, V.A., *Russ. J. Org. Chem.*, 2003, vol. 39, p. 905.

2. Voronkov, M., Shagun, L., Ermolyuk, L., and Timokhina, L., *Sulfur Chem.*, 2004, vol. 25, p. 131.

3. Shagun, L.G., Usov, V.A., Voronkov, M.G., Usova, T.L., and Il'icheva, L.K., *Zh. Org. Khim.*, 1989, vol. 25, p. 878.

4. Usov, V.A., Shagun, L.G., Belskii, V.K., and Usova, T.L., *Sulfur Lett.*, 1992, vol. 14, p. 145.

5. Shagun, L.G., Usova, T.L., Voronkov, M.G., Usov, V.A., Romanenko, L.S., and Efremova, G.G., *Zh. Org. Khim.*, 1990, vol. 26, p. 2029.

6. Shagun, L.G., Ermolyuk, L.P., Sarapulova, G.I., and Voronkov, M.G., *Russ. J. Org. Chem.*, 2004, vol. 40, p. 766.

7. Usov, V.A., Shagun, L.G., Belskii, V.K., Usova, T.L., Perkovskaya, L.M., and Voronkov, M.G., *Sulfur Lett.*, 1995, vol. 18, p. 281.

8. Shagun, L.G., Timokhina, L.V., Voronkov, M.G., Dorofeev, I.A., Usova, T.L., Sarapulova, G.I., and Klyba, L.V., *Russ. J. Org. Chem.*, 1996, vol. 32, p. 1823.

9. Shagun, L.G., Ermolyuk, L.P., Dorofeev, I.A., Il'icheva, L.N., and Voronkov, M.G., *Khim. Geterotsikl. Soedin.*, 2004, p. 1400.

10. Shagun, L.G., Ermolyuk, L.P., Dorofeev, I.A., Sarapulova, G.I., and Voronkov, M.G., *Khim. Geterotsikl. Soedin.*, 2005, p. 1112.

11. Shagun, L.G., Dabizha, O.N., Voronkov, M.G., Myachina, G.F., Sarapulova, G.I., Vakul'skaya, T.I., Protasova, L.E., and Panov, A.M., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2000, p. 330.

12. Shagun, V.A., Smirnov, V.I., Shagun, L.G., Shevchenko, S.G., and Frolov, Yu.L., *Zh. Strukt. Khim.*, 2006, p. 847.

13. Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., Zakrzewski, V.G., Montgomery, J.A., Stratmann, R.E., Burant, J.C., Dapprich, S., Millam, J.M., Daniels, A.D., Kudin, K.N., Strain, M.C., Farkas, O., Tomasi, J., Barone, V., Cossi, M., Mennucci, B., Pomelli, C., Adamo, C., Clifford, S., Ochterski, J., Petersson, G.A., Ayala, P.Y., Cui, Q., Morokuma, K., Malick, D.R., Rabuck, A.D., Raghavachari, K., Foresman, J.B., Cioslowski, J., Ortiz, J.V., Stefanov, B.B., Liu, G., Liashenko, A., Piskorz, P., Komaromi, I., Gomperts, R., Martin, R.L., Fox, D.J., Keith, T., Al-Laham, M.A., Peng, C.Y., Nanayakkara, A., Gonzalez, C., Challacombe, M., Gill, P.M.W., Johnson, B.G., Chen, W., Wong, M.W., Andres, J.L., Head-Gordon, M., Replogle, E.S., and Pople, J.A., *Gaussian 98. Rev. A.6*, Pittsburgh: Gaussian, 1998.

14. Becke, A.D., *J. Chem. Phys.*, 1993, vol. 98, p. 5648; Lee, C., Yang, W., and Parr, R.G., *Phys. Rev. B*, 1988, vol. 37, p. 785; Miehlich, B., Savin, A., Stoll, H., and Preuss, H., *Chem. Phys. Lett.*, 1989, vol. 157, p. 200.

15. Scott, A.P. and Radom, L., *J. Phys. Chem.*, 1996, vol. 100, p. 16 502.

16. Abraham, R.J., Jones, A.D., Warne, M.A., Rittner, R., and Tormena, C.F., *J. Chem. Soc., Perkin Trans. 2*, 1996, p. 533.

17. Abraham, R.J., Tormena, C.F., and Rittner, R., *J. Chem. Soc., Perkin Trans. 2*, 1999, p. 1663.

18. Tormena, C.F., Rittner, R., and Abraham, R.J., *J. Phys. Org. Chem.*, 2002, vol. 15, p. 211.

19. Olivato, P.R. and Rittner, R., *Rev. Heteroatom Chem.*, 1996, vol. 15, p. 115.

20. Shagun, V.A., Shagun, L.G., and Voronkov, M.G., *Russ. J. Gen. Chem.*, 2004, vol. 74, p. 594.

21. Tormena, C.F., Freitas, M.P., Rittner, R., and Abraham, R.J., *J. Phys. Chem.*, 2004, vol. 108, p. 5161.