Physical Chemistry

Quantum-chemical study of the molecular and electronic structure of 2,2'-dithiodi(2-methyl-2,3-dihydro-1,4-thiazino[2,3,4-*i*,*j*]quinolinium)

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Conformational isomerism of 2,2'-dithiodi(2-methyl-2,3-dihydro-1,4-thiazino[2,3,4-*i*,*j*]quinolinium) has been studied by semiempirical MNDO and AM1 methods. Six symmetrical and unsymmetrical stationary states have been found. Optimum intramolecular rotations around single bonds have been considered. The possibility of the inversion of the reaction centers in nucleophilic and electrophilic reactions depending on the conformational state of the molecule has been shown. The spatial structure of one of the conformers found is similar to that typical of (−)-cystine. The observed constancy of some geometric and electronic parameters makes it possible to study the principal physicochemical properties of dithiazinoquinolinium compounds by the most sophisticated *ab initio* methods using small model structures, which are constructed by taking into account the variability of other geometric parameters, as an example.

Key words: 2,2'-dithiodithiazinoquinolinium, quantum chemistry, conformation, geometric invariance.

Recently, previously unknown bisderivatives of 1,4-thiazinoquinolinium have been obtained.[1] This became possible owing to the development of a new approach to the synthesis of 1,4-thiazinoquinolinium salts.[2] One of the representatives of the dithiothiazinoquinolinium series, dithiodi(2-methyl-2,3-dihydro-1,4-thiazino[2,3,4-*i*,*j*]quinolinium chloride), which potentially exhibits a high structural mobility, occurs in the form of only one virtually symmetrical structure in the solid phase.[1] However, the NMR data are indicative of the presence of at least one spectroscopically distinguishable unsymmetrical conformer.[1] The aim of this work is to carry out a detailed analysis of characteristic features of new synthetic pathways associated with the possible existence of different stationary states of thiazinoquinolinium compounds.

Calculation procedure

We chose 2,2'-dithiodi(2-methyl-2,3-dihydro-1,4-thiazino[2,3,4-*i*,*j*]quinolinium chloride) (**1**), which is a recently synthesized representative of the thiazinoquinolinium series,[1] for the theoretical study; its molecular structure was established by X-ray structural analysis. The types of rotational isomerism and the mutual effect of the fragments of this compound may be typical of a wide range of structurally similar compounds.

† Deceased.

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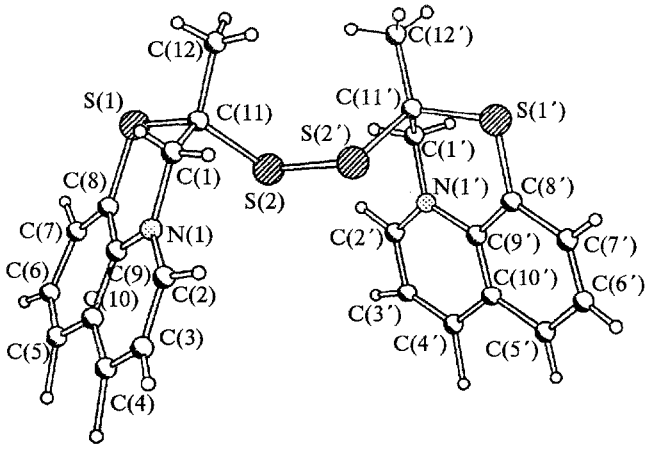


Fig. 1. Adopted atomic numbering scheme.

For the most part, adequate quantum-chemical methods and experimental results make it possible to obtain sufficiently reliable data on the relative stability of different conformers. Taking into account the rather large size of compound **1**, we have restricted ourselves to semiempirical methods.

The structure of **1** was studied by the MNDO method; the AM1 method was additionally used for the cases, in which nonbonded interactions greatly increase because of the steric effects. The atomic numbering scheme shown in Fig. 1 was used in calculations of the potential energy surface of intramolecular conformational rearrangements and in determination of stationary states of compound **1.**

The characteristic feature of both stationary and a number of other points on the potential energy surface that correspond to the optimum intramolecular transitions of molecule **1** is that (independently of the semiempirical method used) almost planar (within 0.02 Å) structures of quinolinium fragments correspond to these points; the deviation of the sulfur atom of the six-membered heterocycle from the plane N(1)C(9)C(8) (N(1′)C(9′)C(8′)) is no more than 0.05 Å. Therefore, the torsion angles ψ and $\varphi(\varphi')$, which characterize the relative rotation of two cyclic fragments of the molecule with respect to the S(2)—S(2′) bond and the central fragment (C(11)S(2)S(2′)C(11′)), respectively, and the inversion angle $\theta(\theta')$, which shows (taking into account the above-mentioned structural feature of the cyclic fragments) the deviation of the C(1)—C(11) (C(1′)—C(11′)) bond from the plane of the quinolinium fragment, are the major characteristics of intramolecular conformational rearrangements.

In general, the nonplanar structure of the heterocycle cannot be unambiguously characterized by this angle because, in the general case, the nonplanarity reflects two independent actions: the parallel shift and the angular displacement of the C(1)—C(11) (C(1′)—C(11′)) bond with respect to the remaining part of the cyclic fragment. Therefore, we take the parameters $d_1(d'_1)$ and $d_{11}(d'_{11})$ that describe deviations of the C(1) (C(1′)) and C(11) (C(11′)) atoms from the plane of the heterocycle as the main measure of its nonplanar deformations. In this case, the positive sign indicates that the angular deformation of the cyclic subsystem causes this subsystem and the quinoline fragment to approach each other, whereas the negative sign is indicative of the fact that these fragments move apart.

The conformation of molecule **1** with the planar central fragment and *cis* orientations of the C(11) and C(11′) atoms was taken as the origin (ψ = 0°, $\varphi(\varphi')$ = 0°); in this case, the bisector of the C(1)C(11)S(1) (C(1′)C(11′)S(1′)) angle is located in the plane S(2′)S(2)C(11) (S(2)S(2′)C(11′)) and is *trans* oriented with respect to the S(2′)—S(2) (S(2)—S(2′)) bond. The clockwise rotation about the axis directed from the central fragment toward the substituent was taken to be positive ($\varphi > 0$).

The study of the potential energy surface was generally carried out with the step of 10—15°. Near the stationary states, the step was decreased. All bond lengths and bond angles, except for the C—H bonds of the quinolinium fragment (1.08 Å), were optimized. Calculated quantum-chemical characteristics of the compound studied were obtained by the MNDO method unless otherwise stated.

Results and Discussion

The optimized geometric parameters of the most stable conformer and the experimental X-ray structural data for the solid phase are given in Table 1. Of the stationary states of compound **1**, which will be analyzed below, the most stable state corresponds to the isolated molecule (**1a**), the structure of which is close to that observed in the solid state. The quantum-chemical models constructed with the use of the MNDO and AM1 methods are structurally similar although the central and cyclic fragments of molecule **1a** obtained by the AM1 method are more planar, being more flattened, than those observed in the solid phase (see Table 1). As for other geometric parameters of compound **1a** obtained by the MNDO and AM1 methods, their values as a whole differ only slightly. Primarily, the bonds, in which the sulfur atom is involved, are shortened (by ~0.01—0.02 Å) and most of the other bonds are longer (within 0.01—0.03 Å), when they are calculated by the MNDO method compared to those calculated by the AM1 method.

The analysis of the stationary states and the structural forms on the potential energy surface that correspond to the optimum conformational transitions, demonstrated that these geometric characteristics can be arbitrarily divided into two groups. The first group consists of the structural parameters of compound **1** that are almost independent of the position on the potential energy surface. In this group, the maximum changes in the bond lengths Δd and in the bond angles $\Delta\omega$ in any point on the potential energy surface are no more than 0.020 Å and 3.0°, respectively compared to the optimum values for conformer **1a** (see Table 1). The parameters of the second group depend on the position on the potential energy surface and allows for rather substantial variations (Δd — 0.14 Å, $\Delta\omega$ — 8.0°) primarily of the following bonds: S(2)—S(2′), S(2)—C(11) (S(2′)—C(11′)), S(1)—C(11) (S(1′)—C(11′)), and N(1)—C(1) (N(1′)—C(1′)).

In our opinion, the behavior of the C(1)—C(11) (C(1′)—C(11′)) bond is unexpected; in spite of its high

Table 1. Calculated bond lengths and bond angles in the most stable symmetrical conformer and the data of X-ray structural analysis of compound **1**

Bond	d/Å			Angle	ω/deg		
	MNDO	AM1	Experiment		MNDO	AM1	Experiment
S(2)—S(2′)	2.09	2.11	2.05	C(8)—S(1)—C(11)	106.7	103.5	100.4
S(2)—C(11)	1.78	1.80	1.84	C(11)—S(2)—S(2′)	108.4	107.9	106.2
S(1)—C(8)	1.74	1.76	1.73	C(1)—N(1)—C(2)	119.0	118.6	117.1
S(1)—C(11)	1.77	1.78	1.80	C(1)—N(1)—C(9)	119.6	121.8	122.1
N(1)—C(1)	1.46	1.45	1.50	N(1)—C(1)—C(11)	114.5	115.1	112.3
N(1)—C(2)	1.39	1.36	1.35	N(1)—C(2)—C(3)	120.3	120.1	121.5
N(1)—C(9)	1.40	1.39	1.41	C(2)—C(3)—C(4)	122.1	122.6	121.4
C(1)—C(11)	1.49	1.49	1.52	C(5)—C(6)—C(7)	121.6	121.2	120.0
C(2)—C(3)	1.36	1.35	1.35	C(6)—C(7)—C(8)	124.2	123.4	122.5
C(3)—C(4)	1.38	1.37	1.36	S(1)—C(8)—C(7)	115.4	117.8	116.8
C(5)—C(6)	1.37	1.36	1.35	S(1)—C(8)—C(9)	124.3	123.9	126.1
C(6)—C(7)	1.41	1.40	1.40	N(1)—C(9)—C(10)	117.1	118.7	117.9
C(7)—C(8)	1.40	1.39	1.39	S(1)—C(11)—S(2)	105.2	106.0	103.4
C(8)—C(9)	1.41	1.41	1.41	S(1)—C(11)—C(1)	114.1	113.5	112.2
C(9)—C(10)	1.41	1.40	1.42	S(2)—C(11)—C(1)	113.2	114.2	112.0
C(11)—C(12)	1.56	1.53	1.55	C(2)—C(11)—C(12)	114.6	112.9	113.6
d_1	−0.223	−0.117	−0.192	ψ	60.7	54.6	68.6
d_{11}	0.512	0.411	0.542	S(2′)—S(2)—C(11)—C(12)*	−13.4	−9.2	−20.8
				φ	−21.7	−17.3	−35.2

* See text for description of the origin and the direction of rotation.

lability in molecule **1**, this bond virtually retains its length irrespective of its spatial orientation with respect to the quinoline fragment, whereas most bonds that are in direct contact with the C(1)—C(11) (C(1′)—C(11′)) bond undergo substantial changes. All other carbon—carbon bonds also remain virtually unchanged. Among the bond angles, the angles that have the C(11) (C(11′)) atom in the apex as well as the S(2′)—S(2)—C(11) (S(2)—S(2′)—C(11′)) and C(11)—C(1)—N(1) (C(11′)—C(1′)—N(1′)) angles, vary more substantially.

Variable structural characteristics and relative energies of the most stable conformers (**a—e**) of compound **1** are given in Table 2. The character of internal rotations in molecule **1** about the S(2)—S(2′), S(2)—C(11) (S(2′)—C(11′)), and C(11)—C(12) (C(11′)—C(12′)) bonds is determined primarily by the gear effect (see, for example, Ref. 3), because the corresponding fragments obviously cannot independently change their orientation in space and can rotate within certain limits only simultaneously. Apparently, this factor causes the appearance of a large number of stationary states on the potential energy surface and exert a substantial effect on the activation parameters of the internal transitions between the stable forms.

Thus, the analysis of decomposition from the total energy demonstrated that ~60 % of the internal rotation barrier about the S(2)—C(11) bond with the fixed torsion angles of the S(2′)—R′ fragment is determined by its two-center components corresponding to nonbonded interactions of the hydrogen atoms of the methyl group and the quinoline fragment, which cause a substantial distortion of their geometry (for example, the deformation of the S(2)C(11)C(12) (S(2′)C(11′)C(12′)) angle is as large as 10°). The internal rotation barrier calculated in the MNDO approximation is 0.57 eV. The AM1 method gives a similar value (0.61 eV).

Conformational isomers listed in Table 2 may be arbitrarily divided into two groups according to the configuration of the central dithiazine fragment: **1d—f** are *trans* conformers with the flattened central fragment (the deviation of the C(11) (C(11′)) atom from the plane is no more than 10° (**1e**)); **1a—c** are *cis* conformers with a highly nonplanar central fragment, which adopts a nearly orthogonal configuration for form **1c** (see Table 2). Each group contains one unsymmetrical conformer (**1b** and **1e**). As for the cyclic fragments, the maximum nonplanar distortions are observed in the series of structures **1c**, **1a**, and **1e**, whereas the minimum deformations are observed in conformers **1b** and **1f** (see Table 2).

In turn, several stable conformations determined by the inversion of the cyclic fragments of the molecule and the rotation of the methyl groups about the C(11)—C(12) (C(11′)—C(12′)) bonds correspond to each stationary state observed (**1a—f**). The inversion structures, which are less stable than conformations **1a,b,d—f** (by 0.16, 0.15 (0.18), 0.07, 0.10 (0.12), and 0.12 eV, respectively) correspond to all forms listed in Table 2 except for **1c**. For **1c**, no stable inversion form was observed, which is attributable to strong nonbonded interactions between the terminal hydrogen atoms of the quinoline fragments.

Let us consider two possible mechanisms of inversion of six-membered heterocycles. The first mechanism is

Table 2. Variable structural characteristics (d/Å, ω/deg) of the conformers and their relative energies (eV)

Conformer	Angle								
	C(11)—S(2)—S(2′)	N(1)—C(1)—C(11)	S(1)—C(11)—S(2)	S(1)—C(11)—C(1)	S(2)—C(11)—C(1)	S(2)—C(11)—C(12)	ψ	φ	S(1′)—S(2)—C(11)—C(12)
1a	108.4	114.5	105.2	114.1	113.2	114.6	60.7	−21.7	−13.4
1b*	109.2 (117.1)	114.8 (114.6)	104.8 (104.2)	113.9 (114.6)	114.3 (114.4)	114.1 (111.4)	17.3	−12.1 (176.8)	4.1 (162.4)
1c	114.8	112.8	106.9	117.6	112.7	110.8	89.6	−36.4	16.3
1d	107.6	115.2	103.1	114.0	114.8	113.2	180.0	−2.3	2.1
1e*	108.9 (111.4)	114.2 (114.4)	104.9 (104.7)	114.7 (114.9)	113.4 (113.5)	115.0 (114.2)	170.2	9.3 (−4.2)	5.6 (168.9)
1f	113.3	113.9	103.9	115.3	114.5	116.6	174.6	7.2	4.2

	Bond				d_1	d_{11}	ΔE/eV
	S(2)—S(2′)	S(2)—C(11)	S(1)—C(11)	N(1)—C(1)			
1a	2.09	1.78	1.77	1.46	−0.223	0.512	0.0
1b*	2.12	1.79 (1.80)	1.76 (1.74)	1.49 (1.48)	−0.113 (−0.092)	0.411 (0.317)	0.34
1c	2.04	1.82	1.82	1.52	−0.267	0.612	0.56
1d	2.02	1.73	1.74	1.46	−0.034	0.117	0.17
1e*	2.14	1.75 (1.77)	1.77 (1.75)	1.49 (1.48)	−0.204 (−0.180)	0.464 (0.381)	0.46
1f	2.13	1.76	1.75	1.44	−0.087	0.287	0.23

* Unsymmetrical form.

asynchronous, *i.e.*, involves the angular displacement of the planar quinoline fragment attended by entering of the C(1) (C(1′)) or C(11) (C(11′)) atom the plane of the heterocycle and its subsequent displacement to another half-space with respect to this fragment. As a result, the whole C(1)—C(11) (C(1′)—C(11′)) bond is in the single half-space in the region of the transition state of the inversion of the heterocycle. The obtained activation barriers of these inversion transitions are 0.27, 0.25 (0.27), 0.11, 0.15 (0.16), and 0.18 eV for **1a,b,d—f**, respectively.

The second mechanism of inversion of the six-membered heterocycle may be determined as synchronous. This mechanism is characterized by an almost planar* transition state, *i.e.*, assuming an angular deformation of the heterocycle, in which the C(1) (C(1′)) and C(11) (C(11′)) atoms pass through the plane of the quinoline fragment almost simultaneously. Activation barriers of the synchronous mechanism of inversion of the heterocycle are 0.21, 0.22 (0.20), 0.12, 0.13 (0.13), and 0.18 eV for forms **1a,b,d—f**, respectively.

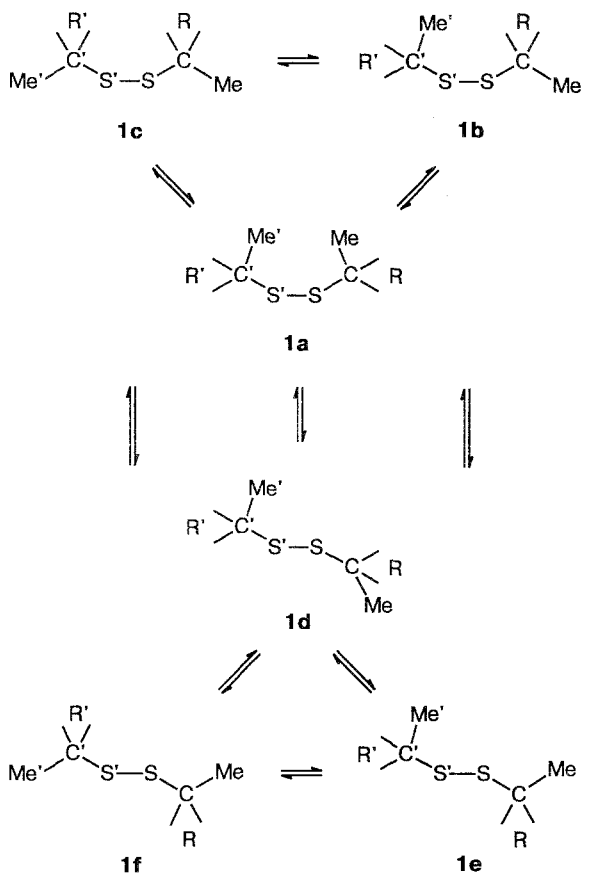
* The cyclic fragments do not become absolutely planar because both mechanisms of inversion do not exclude deviations of other atoms from the plane of the six-membered cycle, which are no more than 0.05 Å.

The results obtained point to the fact that the synchronous mechanism of inversion is preferential for structures **1a,b** and, to a smaller extent, for **1e**. For conformers **1d** and **1f**, both mechanisms of inversion are possible. All other local minima, which are located near the determined stationary states and associated mainly with the internal rotation of methyl groups, correspond to transitions with very low activation barriers between energetically similar (<0.15 eV), *i.e.*, spectroscopically indistinguishable, forms; therefore, these forms were not considered in this work.

The major conformers of compound **1** and the energetically most probable pathways of intramolecular rotations about the C—S bonds are shown in Scheme 1. If the structural "mobility" of the fragments is considered as an energy "response" ΔE of molecule **1** to variations of the angles ψ, φ(φ′), and θ(θ′) near the optimum values ($|\psi_{opt} - \psi| < 30°$, $|\varphi_{opt}(\varphi'_{opt}) - \varphi(\varphi')| < 20°$), the analysis of the relationship between this "mobility" and the conformational state may point to the starting directions of the preferred pathways of intramolecular rearrangements. Forms **1a—c** (ΔE = 0.08 to 10 eV) are more rigid than forms **1d—f** (ΔE = 0.03 to 0.05 eV) with respect to the angle ψ. Symmetrical structures **1d,f** (ΔE = 0.09 to 0.12 eV) and unsymmetrical conformer **1e** (ΔE = 0.11 (0.05) eV) are less sensitive to variations of the angle φ(φ′). For forms **1a—c**, ΔE is within 0.15—

0.20 eV. The relative "mobility" with respect to θ(θ′) can be judged from the analysis of the above-mentioned mechanisms of inversions of six-membered heterocycles.

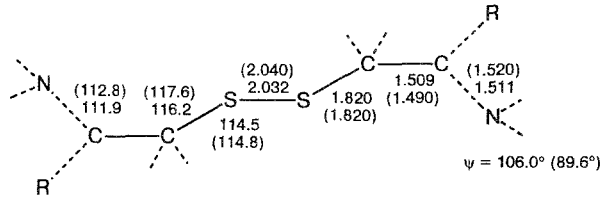
Scheme 1



The optimum ways of internal rotations, which are shown in Scheme 1, are arbitrarily divided into two groups. Transitions, for which one of the torsion angles (ψ or φ(φ′)) is the principal coordinate, whereas other angles are treated as variable parameters (although sometimes their variations are rather large (see Table 2)), can be placed into the first group. Transitions **1b—1e**, **1c—1f**, and **1d—1a** (the principal coordinate is ψ) and **1d—1e**, **1b—1a**, **1f—1e**, and **1c—1b** (the principal coordinate is φ(φ′)) belong to this group. None of the above-mentioned transitions involves inversions of six-membered heterocycles, and only planar distortions occur in these cases (see $d_1(d'_1)$ and $d_{11}(d'_{11})$, Table 2). Activation barriers E_a are 0.22, 0.44, 0.32, 0.50, 0.27, 0.36, and 0.29 eV for transitions **1d—1e**, **1b—1a**, **1f—1e**, **1c—1b**, **1b—1e**, **1c—1f**, and **1d—1a**, respectively.

Transitions **1c—1a** and **1f—1d** (the principal coordinates are φ and φ′) with E_a 0.72 and 0.31 eV, respectively, belong to the second group. Transition **1c—1a** occurs through disrotatory synchronous rotation of substituents about the S(2)—C(11) and S(2′)—C(11′) bonds. The conrotatory mechanism is unfavorable (by 0.48 eV) because of strong nonbonded interactions between cyclic fragments and involves the inversion of six-membered heterocycles. Transition **1f—1d** (E_a = 0.32 eV) is conrotatory; however, in this case, the synchronous disrotatory mechanism is quite competitive (E_a = 0.38 eV). The activation barriers determined and the data on relative stability of conformers (see Table 2) point to the fact that all these forms may be spectroscopically distinguishable.

The analysis of the spatial structures of the varying framework of conformers of compound **1** points to a striking similarity of structure **1c** to the central skeleton of amino acid (−)-cystine.[4] The maximum differences in structural parameters of the skeleton of **1c** (see values in the parentheses) and of (−)-cystine are no more than 0.03 Å and 1.5° for bond lengths and bond angles, respectively. Characteristically, in both cases, the CSSC fragment has a virtually orthogonal structure. In our opinion, this manifestation of the fundamental laws of the living nature in synthetic chemistry calls for more detailed studies, which we planned to perform in the future.



The analysis of the electron (π+σ) redistribution and the behavior of the highest occupied molecular orbitals in relation to the conformational state also makes it possible to set off arbitrarily invariant and varying fragments in molecule **1**. Thus, variations of the electron density relative to the most stable conformation, which were estimated as

$$\Delta\rho = \left|\sum_{i=1}^{N} \rho_i^a\right| - \left|\sum_{i=1}^{N} \rho_i^j\right|,$$

where ρ_i^j is the electron density on the atom i in the conformer j (**1b—f**), are 1.34 (1.21), 1.62 (1.30), 0.56 (0.52), 0.94 (0.85), and 0.82 (0.76), respectively. The S(2), S(2′), C(11), C(11′), S(1), S(1′), C(1), C(1′), N(1), and N(1′) atoms account for ~90 % of all changes Δρ (the total values are given in parentheses).

The major characteristic feature of the electron redistribution in relation to the conformational state of compound **1** reflects the occupancy of one of the sulfur atoms of the disulfide bridge. In conformer **1e**, the effective charge on the S(2) atom becomes positive (0.038, −0.117 on S(2′)). This may results in the change of the reaction center in charge-controlled reactions (for examples of such inversions in disulfide bridges see Ref. 5).

Therefore, the major variations of the electron distribution in relation to the conformational state affect virtually the same fragments of the molecule, the geometry of which changes (see Table 2). The highest occupied MOs behave in a similar manner. Predominantly MOs localized on the S(2), S(2′), C(11), C(11′), S(1), S(1′), C(1), C(1′), N(1), and N(1′) atoms undergo more substantial changes compared to the MOs localized on geometrically invariant fragments of the molecule.

Note only one characteristic feature of the behavior of two highest occupied MOs, which manifests itself in transitions between form **1e** and other conformers. Thus, the highest MOs that are localized on varying fragments with the energies of −9.87 eV (S(2), C(11),...) and −10.26 eV (S(1), C(1), C(11),...) are inverted upon transition **1a—1e** and have energies −9.96 eV (S(1), C(1), C(11),...) and −10.18 eV (S(2), C(11),...). Similar to the charge redistribution (see above), this may also lead to the change of reaction centers but in orbital-controlled reactions.

A more sophisticated analysis of the reactivity of compound **1** can be performed with the use of the obtained data on the invariance of intramolecular geometric and electronic characteristics. As a result, it is possible to construct small model structures, which account for the principal characteristic features of disulfides of the thiazinoquinolinium series and to calculate their physicochemical properties by the developed *ab initio* methods.

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