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**ENERGY PROPERTIES AND STRUCTURE
OF 2- AND 8-ALLYLTHIOQUINOLINE
COMPLEXES WITH IODINE**

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The study focuses on the energy and quantum topological properties of substituted 2- and 8-allylthioquinoline complexes with iodine, which are assumed to correspond to prereaction states in the iodocyclization reaction leading to the formation of thiazolo- and thiazinoquinoline systems. The structures of the complexes and the corresponding atomic interactions are modeled considering the different conformational states of allyl-substituted quinolinethiols (thioquinolines). The energy values are analyzed for the interactions between the iodine molecule and different donor centers of the substituted quinoline system: the nitrogen heteroatom, sulfur, and π -system of the allyl group. It is shown that the formation of stable complexes with the nitrogen of the quinoline ring is complicated by steric hindrances posed by the S-allyl group at positions 2 and 8 of the quinoline system, which in turn contributes to the convergence of the cyclization centers.

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INTRODUCTION

Allyl-substituted compounds of 2- and 8-thioquinoline actively participate in the halocyclization reaction with excess iodine [1-3] to form polyiodides of the cyclic derivatives of thiazolo- and thiazinoquinoline systems. The carbon atom of the allyl group and the nitrogen atom in the quinoline heterocycle are the main cyclization reaction centers. Such a reaction may be preceded with molecular iodine complexes. The ability of molecular iodine to form complexes with heterocyclic and, in particular, substituted quinoline systems was reported in [4, 5]. A D...I-I halogen bond (D is a center acting as an electron donor) is formed in these systems. We follow the terminology of [6-8], according to which the halogen bond is a non-covalent interaction involving a halogen as an electron acceptor.

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Analysis of rotational spectra has given a large amount of experimental data on the geometry and properties of gas-phase charge-transfer complexes involving halogen molecules [7]. The function of electron donors (Lewis bases) in these complexes is performed by ammonia, water, hydrogen cyanide, hydrogen sulfide, ethylene, etc. molecules [8-11]. The quadratic force constants of the bonds suggest that, provided that the acceptor molecule is unchanged, the strength of the halogen bond decreases with decreasing nucleophilicity or basicity of the donor, i.e., $N > O > S > C=C$, and the values of charge transfer, e.g., to the iodine atoms in the $D...I-Cl$ series, must be consistent with the sequence of change in the ionization energy of the donor base D : $NH_3 > H_2S > C_2H_4$ [12].

The structures of 2- and 8-allylthioquinolines are characterized by the presence of several electron-donor centers in each molecule. There is potential to form a complex with the iodine molecule in four centers, which include the nitrogen atom in the heterocycle, the sulfur atom in the substituent, and the π -system of the allyl fragment or the aromatic quinoline ring. It is natural to assume that the most stable complexes are those with the $N...I$ halogen bond and the least stable ones are those with the $C^{Allyl}...I$ allyl group. However, the $N-C$ and $C-I$ covalent bonds, which are observed experimentally in the cyclization products, indicate that the reaction states whereby iodine directly reacts with the carbon atom of the allyl group must be formed on the reaction pathway. At least, such interactions should not interfere the convergence of heteroatom with the carbon atom.

The aim of this work is to find out why complexation involving the strongest electron donor center in the system, the nitrogen atom of the quinoline ring, does not prevent the further development of the iodocyclization stage. We also analyze the electronic and energy properties of the complexes formed by the iodine atom with different donor centers to find out how complexation involving different donor centers of allylthioquinolines affects the conformational states of the allyl group and, consequently, the relative position of the cyclization reaction centers.

CALCULATIONS

The geometry of charge-transfer complexes with molecular iodine for 2-allylthioquinoline and 8-allylthioquinoline was modeled by the following procedure. First, we used the Balloon algorithm [13] to search for conformational states with the least total energy for isolated molecules of 2- and 8-allylthioquinoline compounds. The most probable conformational states were selected using the Conformers program [14]. The resulting geometrical parameters of each of the conformers were optimized by quantum chemical methods described below. Then, we chose the conformer with the lowest energy to build the structures of complexes with I_2 using the three potential donor centers. We assumed that these complexes may include $N...I$, $S...I$, and $C^{Allyl}...I$ halogen bonds. The iodine molecule was put at a distance equal to the sum of the van der Waals radii so as to simulate the orientation of the undivided electron pair of the donor atom to the area with decreased electron density concentration in the valence shells of the iodine atom. Thus, we followed the main principles [15] of geometrical structures with halogen bonds. The following approach was used to optimize the geometry of the structures and calculate the wave functions: the Kohn–Sham method with the B3LYP functional and 6-311G** basis set in the Firefly program [16]. During the optimization process, we controlled for the absence of imaginary frequencies in the structures corresponding to the stationary points. Examples of the resulting molecular complexes with a halogen bond formed by different donor centers are shown in Fig. 1.

The energy of the interaction between the substituted quinoline (acting as an electron donor) molecule and iodine molecule in the complex was estimated by the formula

$$E_{inter} = E_{Q...I-I} - (E_Q + E_{I-I}) - \Delta E_{CP}. \quad (1)$$

Here $E_{Q...I-I}$ is the energy of the complex; E_Q and E_{I-I} are energies of isolated molecules of substituted quinolines and iodine, respectively; and ΔE_{CP} is a compensatory correction for the superposition error of the basis set [17]. The calculated interaction energy values for triples of the most stable structures are given in the Table 1.

The next step was to analyze the resulting wave functions within the quantum theory of atoms in molecules (QTAIM) [18, 19]. The bond paths along which electron density is at a maximum relative to any other line connecting pairs

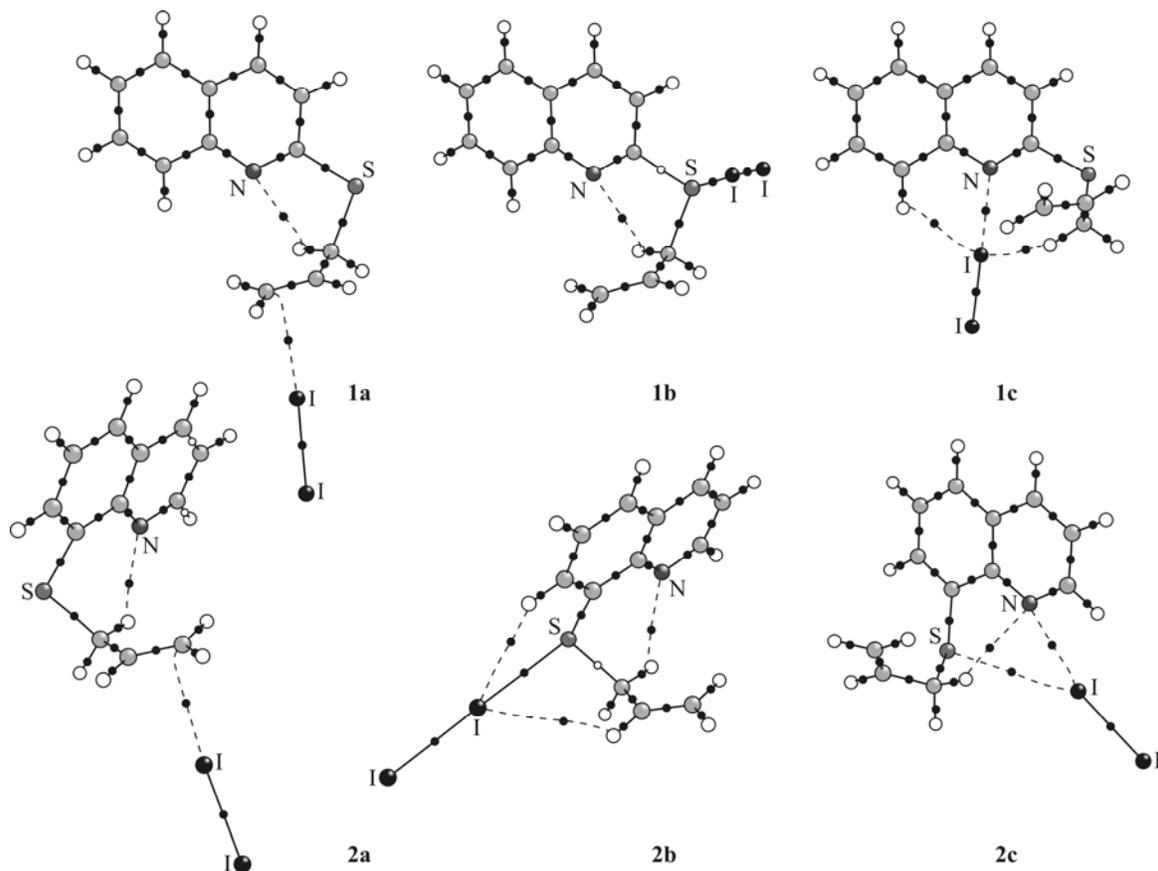


Fig. 1. Bond paths and critical points of electron density in 2-allylthioquinoline (**1a-1c**) and 8-allylthioquinoline (**2a-2c**) complexes with molecular iodine. The halogen bonds are dashed.

of nuclei were built in the AIMALL program [20]. The existence of bond paths in electron density is confirmed experimentally [21]; this gives a reasonable method to identify and characterize all types of atomic interactions occurring in the chemical compounds [22]. At the bonds critical points through which the bond paths go, including the bonds corresponding to the non-covalent interactions D...I, I...H, and N...H, we calculated the values of electron density ρ_b , which characterize the strength of these interactions.

RESULTS AND DISCUSSION

Compared with the approaches focused on searching for a single conformer with the lowest energy, genetic algorithms used to construct conformational state ensembles, including the algorithm used in this study [13], have indisputable advantages [23]. They allow a quick search for conformers in structures with multiple degrees of freedom for rotations causing a change in several dihedral angles simultaneously. This technique is best suited for the assessment of the relative energies of S-allyl-substituted quinoline conformers, which have three dihedral angles defining the orientation of the S-allyl group with respect to the quinoline ring.

The geometry of the most stable conformational states of 2- and 8-allylthioquinolines was already discussed in [24]. The two conformers with the lowest energy of both 2- and 8-substituted thioquinoline have similar absolute values of dihedral angles defining the orientation of the allyl group with respect to the quinoline ring. However, these conformers can differ in the relative orientation of the terminal ethylene group. One can also observe degeneration of the conformer sets, which is associated with the mirror orientation of the substituent relative to the quinoline ring plane. Note that the cyclization reaction takes place without any signs of stereodifferentiation during its way and leads to the formation of a racemic product.

The optimization of the geometry of substituted quinoline complexes with N...I, S...I, and C^{Allyl}...I halogen bonds by the B3LYP/6-311G** method does not lead to any significant change in the orientation of the S-allyl substituent in the complexes, compared with the substituted quinoline molecule in an isolated state. The sample average value of the mean-square displacement of atomic coordinates due to complexation is RMSD = 0.66 Å. At the same time, the average value of the change in the dihedral angles defining the orientation of the allyl group with respect to the quinoline ring is 13° or less. The maximum change in the value of the dihedral angle $\varphi(\text{N-C-S-C})$, 35°, is observed for the 2-allylthioquinoline complex with the C^{Allyl}...I halogen bond. In these conformation states, the cyclization reaction centers in the structure are drawn together by, on average, 3.5±0.1 Å for 2-allylthioquinoline and 4.0±0.2 Å for 8-allylthioquinoline.

For all halogen bonds with iodine in complexes **1-3**, the quantum topological analysis of electron density (ED) shows the presence of bond critical points in the bond paths corresponding to the D...I interactions, where D = N, S, C. For the strongest halogen bond in complex **3** of unsubstituted quinoline with iodine, the ED value in the bond critical point $\rho_b(\text{N...I})$ is 0.034 au. For the weakest halogen bond found in our study, $\rho_b(\text{C...I}) = 0.016$ au. In all the cases whereby the halogen bond with the iodine atom is formed with the carbon or sulfur atom, the complexes also have, in addition to this bond, the intramolecular hydrogen bond N...H with one of the hydrogen atoms in the methylene group of the allyl substituent. These hydrogen bonds stabilize the conformation in which the cyclization reaction centers are close together. The range of changes in the values of $\rho_b(\text{N...H})$ in these structures is 0.009-0.014 au.

The interaction energies E_{inter} of substituted quinolines with iodine for complexes formed with different donor centers differ significantly (Table 1). The highest interaction energy is observed for complex **3** of unsubstituted quinoline with iodine. Lower interaction energies are found for complexes **1b** and **2b** with the S...I halogen bond, where the sulfur atom is the donor center. It can be assumed that the possibility of formation of **1b** and **2b** must affect the kinetic characteristics of the redox reaction stage, which is responsible for the formation of iodide anions. This explains the need to use excess iodine in the reaction [25].

In the substituted quinoline complexes containing the N...I halogen bond, the interaction energy is higher than in those where iodine interacts with sulfur. The likely reason why the N...I interactions observed in substituted quinolines are significantly weaker than those in unsubstituted quinolines is that, in their most beneficial conformational states stabilized by the N...H hydrogen bond, 2- and 8-allylthioquinolines have a shielded nitrogen heteroatom. As a result of this shielding, the iodine molecule cannot approach the quinoline ring heteroatom closely enough to form a strong N...I halogen bond. The angle between the I-I bond and the normal to the quinoline ring plane in these complexes is much less than 90°, and the internuclear distance N...I is, on average, larger by 0.3 Å than the corresponding distance in the unsubstituted quinoline complex. Thus, the low probability of formation of a strong complex with the nitrogen atom for 2- and 8-allylthioquinolines is well consistent with the experimental data [25], which indicate that, in the observed conditions, the possibility of complexation does not prevent the nitrogen atom from participating in the formation of a new covalent bond with the carbon atom of the allyl group.

The complexes with the C^{Allyl}...I halogen bond have the lowest interaction energy (Table 1). However, the formation of pre-reaction complexes with the allyl group is confirmed by the presence of products with the C-I covalent bond, which are observed in experiments [1-3]. Moreover, the C^{Allyl}...I halogen bond can be formed with any substituted quinoline conformers, including those in which the main reaction centers (the nitrogen atom and the carbon atom in the allyl group) are close together. The geometric characteristics illustrating the orthogonal orientation of the iodine molecule with respect to the plane of the ethylene system give no specific clues as to which one of the carbon atom participates in the halogen bond. At the same time, the pattern of the electron density bridges (i.e., bond paths) for the interactions involving the ethylene system of the allyl group (Fig. 2) provides decisive evidence that the halogen bond is formed between iodine and the terminal carbon atom of the allyl group.

In some cases, the bond critical points of ED are observed for the weak non-covalent interactions I...H between iodine atoms and the hydrogen atoms of the allyl group. The value of $\rho_b(\text{I...H})$ for these interactions does not exceed

TABLE 1. Interaction Energies and Electron Density at Bond Critical Points in the Complexes of Allylsubstituted 2- and 8-Thioquinolines with Molecular Iodine

Complex	Structure No.	Interaction energy, E_{inter} , kcal/mol	Interaction or bond	Internuclear distance R , Å	ρ_b , au
2-Allylthioquinoline·I ₂ (C ₁₂ NH ₁₁ S·I ₂)	1a	-3.37	C...I	3.177	0.016
			N...H	2.444	0.014
			I-I	2.780	0.064
	1b	-5.68	S...I	3.110	0.026
			N...H	2.431	0.014
			I-I	2.811	0.061
	1c	-4.25	N...I	2.921	0.023
			I...H	3.064	0.008
			I...H	3.147	0.007
8-Allylthioquinoline I ₂ (C ₁₂ NH ₁₁ S·I ₂)	2a	-3.46	I-I	2.780	0.065
			C...I	3.170	0.016
			N...H	2.436	0.013
	2b	-7.03	I-I	2.780	0.064
			S...I	3.091	0.027
			I...H	3.129	0.007
			I...H	3.441	0.005
			N...H	2.532	0.011
	2c	-4.64	I-I	2.822	0.060
N...I			3.048	0.018	
I...S			3.758	0.008	
Quinoline·I ₂ (C ₁₀ NH ₇ ·I ₂)	3	-8.70	N...H	2.640	0.009
			I-I	2.776	0.065
			N...I	2.712	0.034
			I...H	3.112	0.007
			I-I	2.811	0.062

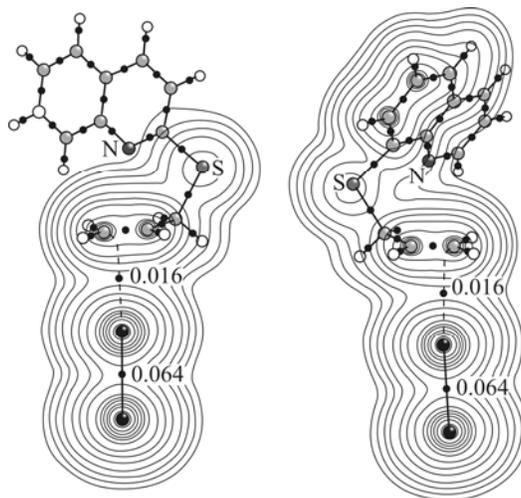


Fig. 2. Contour maps of electron density with a minimum value of 0.001 au in the planes defined by the coordinates of the atoms C=C^{Allyl}...I in complexes **1a** and **2a** and the bond paths (dashed) corresponding to the C^{Allyl}...I halogen bonds. The electron density values at the saddle critical points of the halogen bonds are indicated.

0.008 au. Moreover, in complex **2c**, in addition to the N...I halogen bond, which is weakened due to steric hindrances posed by the allyl group, the iodine atom is involved in the interaction with the neighboring sulfur atom; $\rho_b(I...S) = 0.008$ au. The geometric parameters of this contact do not provide sufficient evidence to classify it as a halogen bond. Additional studies are needed to investigate the properties of electron density in the area of these interactions to find out whether they are synergistic with respect to the observed stronger halogen bond. In the case of **2c**, the interaction energy is more negative than in the geometric isomer complex **1c** with a single halogen bond N...I. However, the interactions in complex **2b** with the S...I halogen bond remain the strongest among substituted quinolines.

Thus, the range of changes in E_{inter} that is observed in the studied complexes with halogen bonds formed by molecular iodine is -3.46 kcal/mol to -8.70 kcal/mol. Note that the differences in the interaction energies for geometric isomers such as 2- and 8-allylthioquinolines are quite small in the identified stable conformations in comparison with the differences defined by the properties and accessibility of the donor center.

CONCLUSIONS

The complexes of molecular iodine with 2- and 8-allylthioquinolines, where the ethylene π -system acts as a donor center in the formation of the halogen bond, are observed to have a bond path in the electron density between the iodine atom and the terminal carbon atom of the allyl group, which indicates the presence of a bonding interaction between these atoms. The assumption that such a complex is formed as a prereaction state is consistent with the data on the formation of a new covalent C–I bond in the iodocyclization products observed in the experiment.

The energy and geometric properties of the complexes formed by molecular iodine with the heteroatom of the quinoline ring show that the N...I interactions in these complexes are weakened due to steric hindrances posed by the S-allyl group in positions 2 and 8 and, hence, cannot interfere with the iodocyclization reaction.

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