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## Theoretical Study of Benzofused Thieno[3,2-*b*]furans in the reactions with electrophiles

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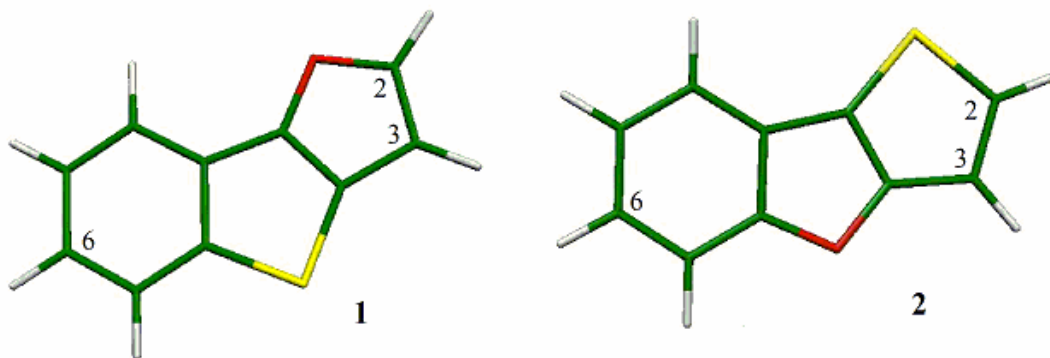
**Keywords:** Benzofused thieno[3,2-*b*]furans, electrophile, theoretical study, DFT.

### Abstract

Calculations of traditional HF and DFT based reactivity descriptors are reported for the benzofused thieno[3,2-*b*]furans in order to get insight into the factors determining the exact nature of its interactions with electrophiles. Global descriptors such as chemical potential, molecular hardness, electrophilicity, frontier molecular orbital energies and shapes, the condensed Fukui functions were determined and used to identify the differences in the stability and reactivity of heterocycles. In general calculated values lead to the conclusion that heterocyclic system in thieno[3,2-*b*]benzofuran is more aromatic and stable than in isomeric benzothieno[3,2-*b*]furan. Theoretical results are in complete agreement with the experimental results showing exceptional reactivity of C(2) atom for both isomers. The bond order uniformity analysis, local ionization energy and electrostatic potential energy maps revealed structural and reactivity differences of isomeric thieno[3,2-*b*]furans. Benzothieno[3,2-*b*]furan structurally could be analogues with molecule of aromatic benzothiophene substituted with C(2)-C(3) vinylic moiety. Contrary, calculated values for the of thieno[3,2-*b*]benzofuran shows delocalized  $\pi$ -electron surface that reports stable aromatic system between benzene ring and thiene heterocycle. This evidently point out wherefore the electrophilic substitution reaction for benzothieno[3,2-*b*]furan goes via addition-elimination mechanism at the C(2) position, and presumes possibility of aromatic electrophilic substitution mechanism scenario for thieno[3,2-*b*]benzofuran.

## Introduction

Benzofused five-membered heterocycles have been the subject of the sustainable interest [1]. They are useful reactants in the organic synthesis. There are many experimental results for benzothieno[3,2-*b*]furan **1** and thieno[3,2-*b*]benzofuran **2** showing different their stability and exclusively regioselective behaviour in the electrophilic substitution reactions [2, 3].



For example it was reported that 2-position of benzofused thieno[3,2-*b*]furans **1** and **2** are mostly reactive to attack of electrophilic reagents in the electrophilic substitution reactions such as chlorination, bromination [2, 3]. When the substitution is continued, the 6-position of heterocycles undergoes substitution reaction. The reactivity of heterocyclic compounds **1** and **2** under electrophilic substitution reactions conditions shows that the heterocyclic system in the compound **2** is more stable than in the compound **1** [2, 3].

Experimental and theoretical considerations on reaction mechanisms of benzofused heterocycles in the electrophilic substitution reactions point out a dual character in its reactivity [2-5]. One type of the reactions is the electrophilic substitution of benzofused thieno[3,2-*b*]furanes as an aromatic compound, resulting in the substitution of 2-hydrogen via the aromatic electrophilic substitution reaction mechanism. The other possibility of the reactivity is the electrophilic substitution reaction of benzofused thieno[3,2-*b*]furanes as an olefins undergoing electrophilic addition-elimination mechanism on the double C(2)-C(3) bond. Experimentally was shown that the mentioned halogenation for heterocycle **1** proceed by addition-elimination mechanism [2, 3].

Moreover, nowadays, computational chemistry methods offer a unique ability for the synthetic organic chemists to generate optimal geometry structures, and thought the structural and electronic properties of reactants and products make decisions as to which of the chemical transformations will occur in reactions. Here we will study the electrophilic substitution reactions with benzofused thieno[3,2-*b*]furans **1** and **2** using computational chemistry methods.

From the theoretical point of view, there are some kinetic, and quantum mechanics studies of the reactivity of benzofused heterocycles that reports the qualitative prediction of reactive sites of those compounds [5-7]. It was demonstrated [8, 9] that the B3LYP Density functional theory (DFT) is a reliable method for the calculation of geometries and energies of benzofused heterocycles. The optimized geometries and calculated electron density parameters

of benzodiazepines, benzothiophene, benzofuran were estimated in order to determine their reactivity in electrophilic substitution and Diels-Alder reactions [10-12]. Based on structural uniformity the relative aromaticity of the systems was predicted. From the theoretical results, the experimental stability of heterocycles was accurately described. The differences in the stability were explained in terms of aromaticity and delocalization of electron densities on  $\pi$  molecular orbitals. For the stable compounds, a high  $\pi$  molecular orbital delocalization established between two aromatic rings, which may not be presented in the less stable isomers.

It is evident that the aromaticity correlates with the thermodynamic stability of the system. There is also relationship between hardness and stability. Parr and Pearson [13-16] reported the principle of maximum hardness: a rule that molecules arrange themselves to be as hard as possible. DFT method provides definitions of important universal concepts of molecular structure and reactivity. It was developed [15, 16] an operational approximation for absolute hardness  $\eta$ :

$$\eta = \frac{1}{2}(I - A)$$

In the formula  $I$  is the vertical ionization energy and  $A$  stands for the vertical electron affinity. According to the Koopmans theorem, the hardness corresponds to the gap between the HOMO and LUMO orbitals. Hence, the principle of maximum hardness confirms the results that show that stability of aromatic hydrocarbons depends on HOMO-LUMO energy gap. The larger the HOMO-LUMO energy gap the harder molecule. The higher HOMO energy corresponds to the more reactive molecule in the reactions with electrophiles.

The electron affinity can also be used in combination with ionization energy to give electronic chemical potential  $\mu$  defined by Parr and Pearson [16] as the characteristic of electronegativity of molecules:

$$\mu = -\frac{1}{2}(I + A)$$

The global electrophilicity index  $\omega$  was introduced by Parr [17] and calculated using the electronic chemical potential  $\mu$  and chemical hardness  $\eta$ .

$$\omega = \frac{\mu^2}{2\eta}$$

According to the definition this index measures the propensity of a species to accept electrons. As Domingo et al [18] proposes the high nucleophilicity and electrophilicity of heterocycles corresponds to opposite extremes of the scale of global reactivity indexes. A good, more reactive, nucleophile is characterized by a lower value of  $\mu$ ,  $\omega$  and in opposite a good electrophile is characterized by a high value of  $\mu$ ,  $\omega$ .

The hard and soft acids and bases (HSAB) principle has been very useful to predict the reactivity of chemical systems. The HSAB principle has been used in a local sense in terms of density functional concepts such as Fukui function  $f(r)$  [19]. Fukui function  $f(r)$  is a

local reactivity descriptor that indicates the best way to change the number of electrons in a molecule. Hence it indicates the propensity of the electronic density to deform at a given position to accept or donate electrons [20]. The Fukui function is defined by Parr and Yang as [19, 21]:

$$f(r) = \left( \frac{\delta\mu}{\delta\nu(r)} \right)_N = \left( \frac{\delta\rho(r)}{\delta N} \right)_\nu$$

Where  $\mu$  is electronic chemical potential defined above,  $\nu$  is the external potential,  $\rho$  corresponds to the electronic density, and  $N$  is the total number of electrons of the system. The second formula for  $f(r)$ , written as  $[\delta\rho(r)/\delta N]_\nu$  shows that it is a quantity involving the electron density of the atom or molecule in its frontier valence regions. As  $\rho(r)$  is discontinuous function of  $N$ , three different types of  $f(r)$  can be defined:

for nucleophilic attack

$$f^+(r) = \left( \frac{\delta\rho(r)}{\delta N} \right)_\nu^+ = [\rho_{N+1} - \rho_N(r)] \quad (1)$$

for electrophilic attack

$$f^-(r) = \left( \frac{\delta\rho(r)}{\delta N} \right)_\nu^- = [\rho_N - \rho_{N-1}(r)] \quad (2)$$

for radical attack

$$f^0(r) = \left( \frac{\delta\rho(r)}{\delta N} \right)_\nu^0 = \frac{1}{2}[\rho_{N+1} - \rho_{N-1}(r)] \quad (3)$$

The problem of reactivity and aromaticity of benzofused heterocycles raises several questions. The matter of interest is involved in heterocyclic and aromatic chemistry. Surech and Gadre [22] characterized relationship between aromaticity of polycyclic benzenoid hydrocarbons and electrostatic potential topology. The use of molecular surfaces, based on the molecular electron density such as the molecular electrostatic potential (MEP) [23, 24] has a long tradition in the qualitative interpretation of chemical reactivity. The molecular electrostatic

potential gives a powerful description of molecular properties, such as strong non-covalent interactions, that are predominantly electrostatic in nature. However, much classical chemical reactivity depends on electron donor–acceptor interactions that are not encoded in the MEP.

Another indicator of electrophilic attraction is provided by the local ionization energy potential map, an overlaying of the energy of electron removal (ionization) onto the electron density. Sjoberg et al and Politzer et al [25, 26] introduced the local ionization energy potential  $I(r)$ , defined as:

$$I(r) = \sum_i \frac{\rho_i(r)|\varepsilon_i|}{\rho(r)}$$

$\rho_i(r)$  is the electron density of the  $i$ -th molecular orbital (MO), and  $\varepsilon_i$  is its energy. Murray and Politzer et al [25-28] have discussed the properties of the local ionization energy in detail. It is clear that it describes the donor properties of the molecule directly.

Results reported by Clark et al [24] suggest that the local ionization energy can represent the visualization of reactivity properties of the aromatic substrate and the regioselectivity of the electrophilic substitution. The absolute reactivity can be judged from the values of the local ionization energy at the  $\pi$ -surface of the aromatic compound.

Our goal is to analyze aromaticity of the molecules **1** and **2** and to explain their stability and relative reactivity using MEP, local ionization energy surfaces and bond order characteristics as criteria of their aromaticity. For this purpose, DFT and ab-initio calculations were performed on these molecules. In terms of molecular surfaces based on electron density it is possible to explain the aromatic behavior of these compounds. Optimized structures, atomic charges, HOMO-LUMO gaps, Fukui functions, global hardness, electronegativity index are also reported to explain the experimental behavior of these systems.

Since these molecules play a fundamental role in many organic reactions, it is important to make theoretical studies of reactivity descriptors that could help to understand their chemical behavior. Experimentally, the chemical reactivity of those molecules is well known. The purpose of our work was to find reactivity descriptors that explains and confirms the experimental information. In the future for those classes of molecules with unknown reactivity, these parameters could help to understand and predict their behavior.

## Computational Details

Geometry optimizations for compounds **1** and **2** were performed at the HF and DFT level using the GAMESS package [29].

The geometries **1** and **2** were fully optimized at the DFT B3LYP level of theory with a 6-311G\* basis set and using ab-initio method with 6-311G\* basis set. The structures are minima on potential energy surface and their harmonic vibrational frequencies are positive. Visualization of

molecules at their optimized geometries was performed with MOLEKEL [30] program package and images of MEP and ionization potential surfaces was obtained using Spartan [31].

## Results and Discussions

### Geometry optimization and the analysis of properties

The geometries of optimized heterocycles **1** and **2** are shown in the figures 1 and 2. Figures 1, 2 also presents total energy of isomeric heterocycles **1** and **2** that confirms that structure **2** is more stable than isomeric structure **1**, the energy difference between isomers is 3,6 kcal/mol (calculated at the B3LYP 6-311G\* level).

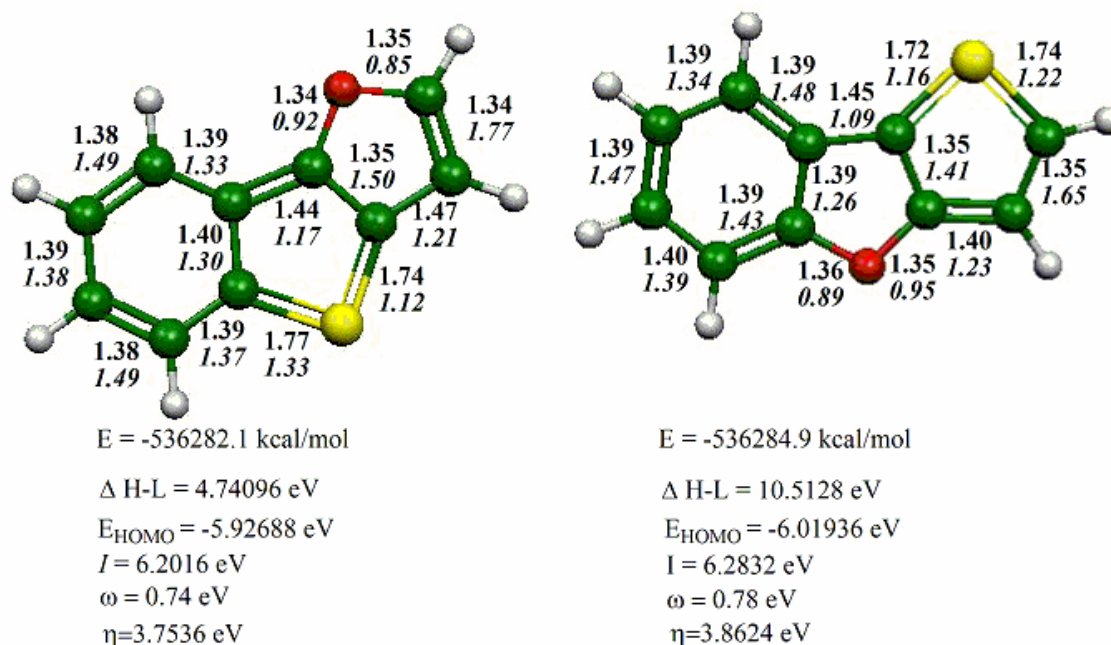


Figure 1. Optimized geometries HF/ 6-311G\* of heterocycles **1** and **2** and calculated  $E$  - total energy,  $I$  - ionization potential,  $\eta$  - molecular hardness,  $\omega$  - electrophilicity,  $\Delta H-L$  - frontier molecular orbital energy gap, bond length in Å and bond order (italic).

This agrees with experimental results that established a high reactivity for **1** and a greater stability of **2**. The calculated ionization energies  $I$ , global hardness index  $\eta$  and HOMO-LUMO energy gaps ( $\Delta$  H-L) for benzofused heterocycles **1** and **2** are also reported in figures 1, 2. For more stable heterocycle **2** the HOMO-LUMO energy gap and hardness index  $\eta$  is larger. This confirms the previous results that claim that the stability of aromatic hydrocarbons depends on HOMO-LUMO gap. The principle of maximum hardness represents that the system would be more stable if the global hardness, related to HOMO-LUMO gap, is a maximum. As shown in figures 1, 2 the HOMO-LUMO gap correlate well with the expected stability of molecules.

The calculated values of global reactivity index  $\omega$  show the nucleophilicity power of heterocycles. We obtained lower  $\omega$  value for heterocycle **1** that explain better propensity of **1** to be involved in the reactions with electrophiles than for heterocycle **2**.

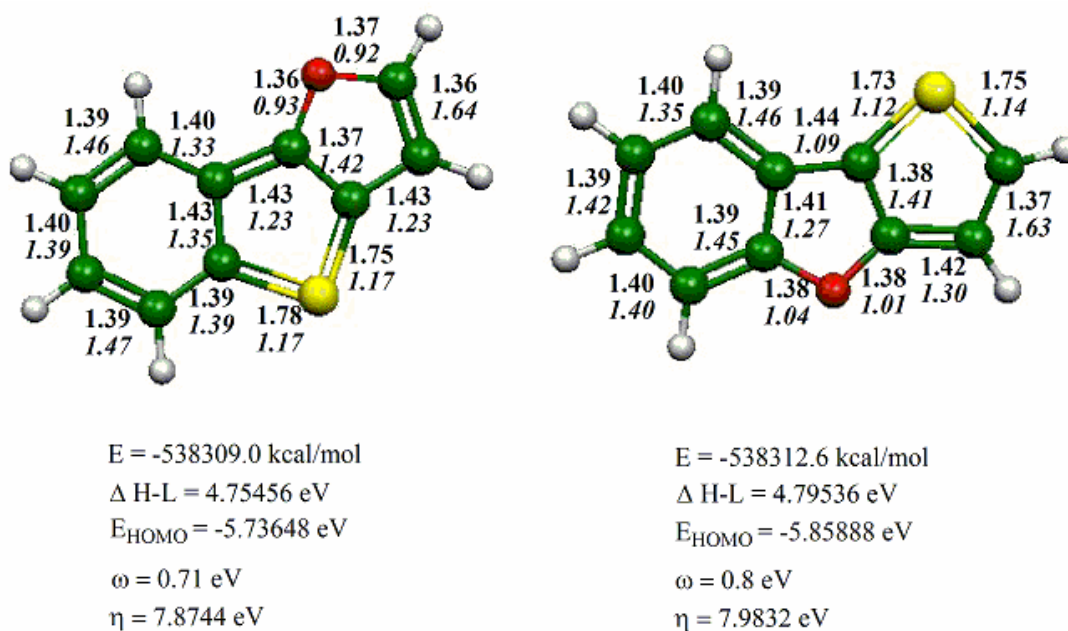


Figure 2. Optimized geometries of heterocycles **1** and **2** using B3LYP functional and 6-311G\* basis set and calculated  $E$  - total energy,  $\eta$  - molecular hardness,  $\omega$  - electrophilicity,  $\Delta$  H-L - frontier molecular orbital energy gap, bond length in Å and bond order ( italic).



The figures 1, 2 also show bond lengths and bond order (italic) values of optimized heterocycles **1** and **2**. One can see that optimized geometries of heterocycles **1** and **2** represent planar structures with n- $\pi$  conjugated bond systems arising due to sulfur and oxygen lone pair electron conjugation with  $\pi$  system. According to the bond order uniformity approach the ring systems that have the most uniform bond order distributions are the most stable ones [32]. This can be estimated by the bond order deviations from an average bond order; i.e for delocalized system of benzene that contains 6  $\pi$  electrons over 6 carbons average bond order is 1.5. According to our computational study, the structure of heterocycle **2** produces more uniform (more aromatic) ring system. While the less uniform ring system is the heterocycle **1**. For heterocycle **1** we observed aromaticity system disarrangement caused by weakening of C-O bond in the furane ring of molecule. The C(2)-O(1) bond order (0.9) of heterocycle **1** is up to 0.3 weaker comparing to appropriate C(2)-S(1) bond order (1.2) in the molecule **2**. Therefore using bond order uniformity approach we can suggest that heterocycle **1** structurally could be analogues with molecule of aromatic benzothiophene substituted with vinylic moiety (C(2)-C(3) bond), while heterocycle **2** can be considered as a stable aromatic system of thiophene and phenoxy rings.

Further we made an attempt to compare results of bond order uniformity analysis with results of molecular surfaces, based on the molecular electron density analysis. The visualized results of MEP energy and local ionization energy surfaces are shown in Figures 3, 4.

The presented MEP surface, an overlaying of the electrostatic potential (the attraction or repulsion of a positive charge for a molecule) is valuable for describing overall molecular charge distribution as well as anticipating sites of electrophilic addition. The red color represent negatively charged areas of surface (i.e. those areas where accepting an electrophile is most favorable).

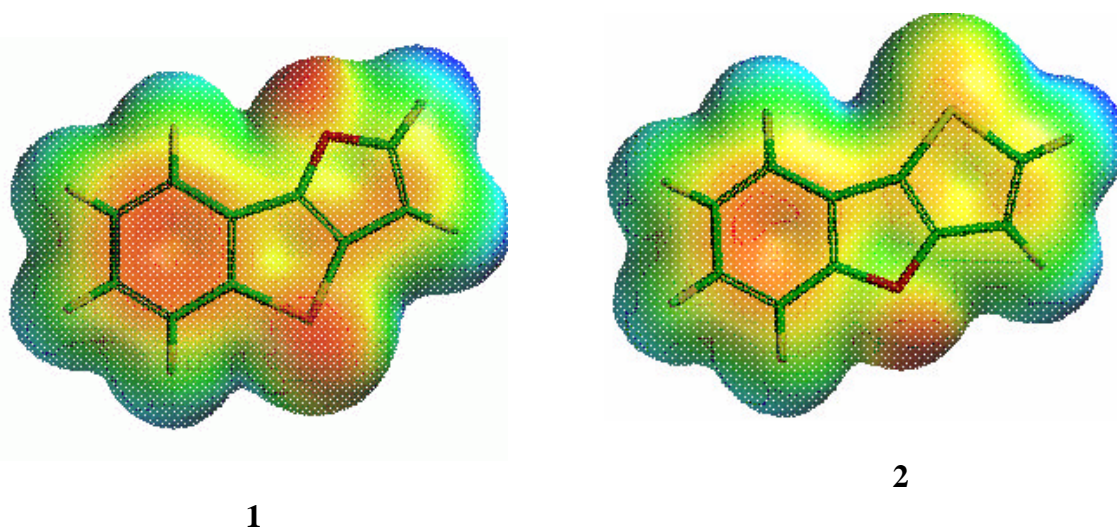


Figure 3. Calculated electrostatic potential surfaces on the molecular surfaces of heterocycles **1** and **2**. Color ranges, in kcal/mol: from red -25.5 to blue +32.5. B3LYP functional and 6-311G\* basis set



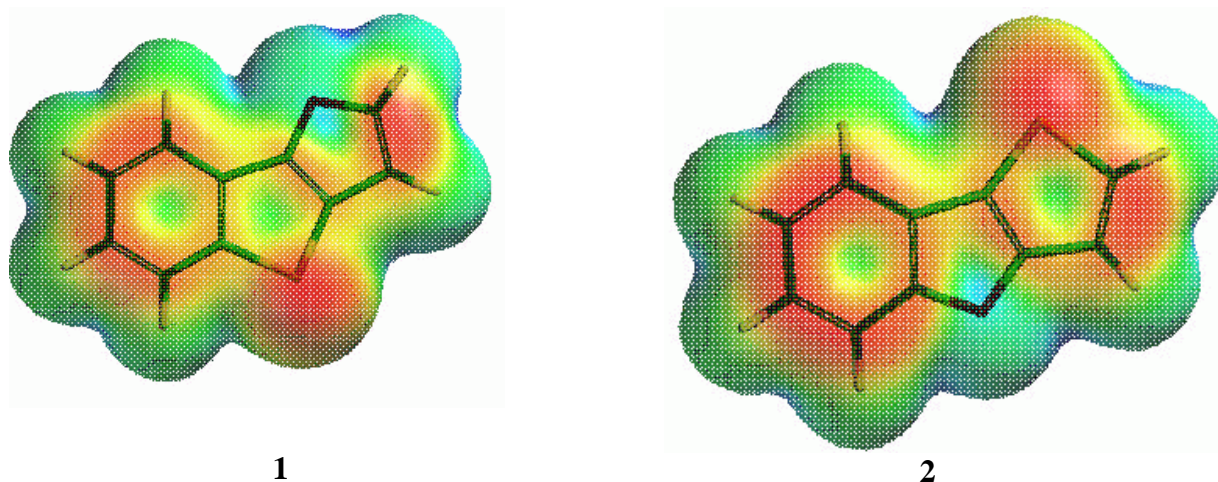


Figure 4. Calculated local ionization energy surfaces on the molecular surfaces of heterocycles **1** and **2**. Color ranges, in kcal/mol: from red -0.5 to blue +20.5. B3LYP functional and 6-311G\* basis set

Another indicator of electrophilic attraction is provided by the local ionization potential energy surface, an overlaying of the energy of electron removal (ionization) onto the electron density. The low (red) values of the local ionization energy indicate high reactivity to electrophilic substitution.

The differences in reactivity of heterocycles **1** and **2** can be judged from the values of electrostatic potential and local ionization energy surfaces presented in Figures 3, 4. For heterocycle **1** the lowest local ionization energy values and negatively charged electrostatic potential values are found on benzothiophene and on the C(2)-C(3) carbons of furane ring. While magnitude values on C(2)-C(3) carbons higher than that on benzene ring. This evidently point out wherefore the electrophilic substitution reaction for **1** undergoes via addition-elimination mechanism at the C(2) position.

Contrary the electrostatic potential and local ionization energies surfaces for the of heterocycle **2** shows delocalized  $\pi$ -electron surface that reports stable aromatic system between benzene ring and thiophene heterocycle. This result suggests the presumable possibility of aromatic electrophilic substitution mechanism scenario in the halogenation reactions of heterocycle **2**. Therefore, for exact identification of reaction mechanism it would be of interest to calculate potential energy surface of more probable reaction pathways.

## Molecular orbitals analysis

The frontier molecular orbital pictures of the both molecules **1**, **2** under study are shown in Figure 5. We present only the HOMO, HOMO-1 and LUMO. The energy difference between the HOMO and HOMO-1 for **1** is smaller than for **2**.

For the heterocycles **1** and **2** the  $\pi$  molecular orbital delocalization exists between benzene thiophene and benzene furane rings accordingly as shown in HOMO shapes. For both molecules is greatest extension value of HOMO observed on C(2) atom. Moreover for **1** the HOMO-1 is delocalized on C(2)-C(3) bond while for **2** the HOMO-1 shape located on C(3) atom. With this molecular orbital analysis the relative reactivity can be explained. The  $\pi$  molecular orbital delocalization agrees well with the reactivity behavior of heterocyclic rings. The greatest extension value of HOMO shape on C(2) atom suggest exceptional reactivity of this atom in the electrophilic reactions. Furthermore the HOMO-1 delocalization on C(2)-C(3) bond in case **1** compatible with addition-elimination mechanism version.

## Reactivity parameters for benzofused heterocycles

Reactivity indexes derived from DFT and ab-initio calculations have been successfully applied in describing and understanding of chemical reactivity. As outlined in the Introduction it is possible to define atomic reactivity indexes, such as the condensed Fukui functions for given atom in a molecule. For electrophilic addition or substitution reactions that occur with benzofused heterocycles **1** and **2** condensed Fukui functions is obtained according to Eq.2 .

In the Figure 6 the absolute values for condensed Fukui function for electrophilic attack are shown for relevant atoms in heterocyclic compounds. For **1** and **2** the largest of value belong to C(2) atom in the furan and thiophene rings accordingly. This means that C(2) atom should be mostly reactive site towards an electrophilic attack of molecule. The Mulliken charge population analysis in the Figure 7 shows the contrary situation. The negative charge increase in molecule represents the attraction of relevant sites of molecule in reactions with electrophiles. Figure 7 shows the highest negative charge on C(3) atom of heterocycle **1**. So Mulliken charge and Fukui indexes values for **1** suggest expectation that electrophilic reaction could occur with C(2) and C(3) atoms via three-membered cyclic intermediate. For heterocycle **2** the increase of negative charge and highest Fukui function values observed on C(2) atom. It is compatible with experimental results showing that C(2) site of molecule proceeds directly by an electrophilic mechanism.

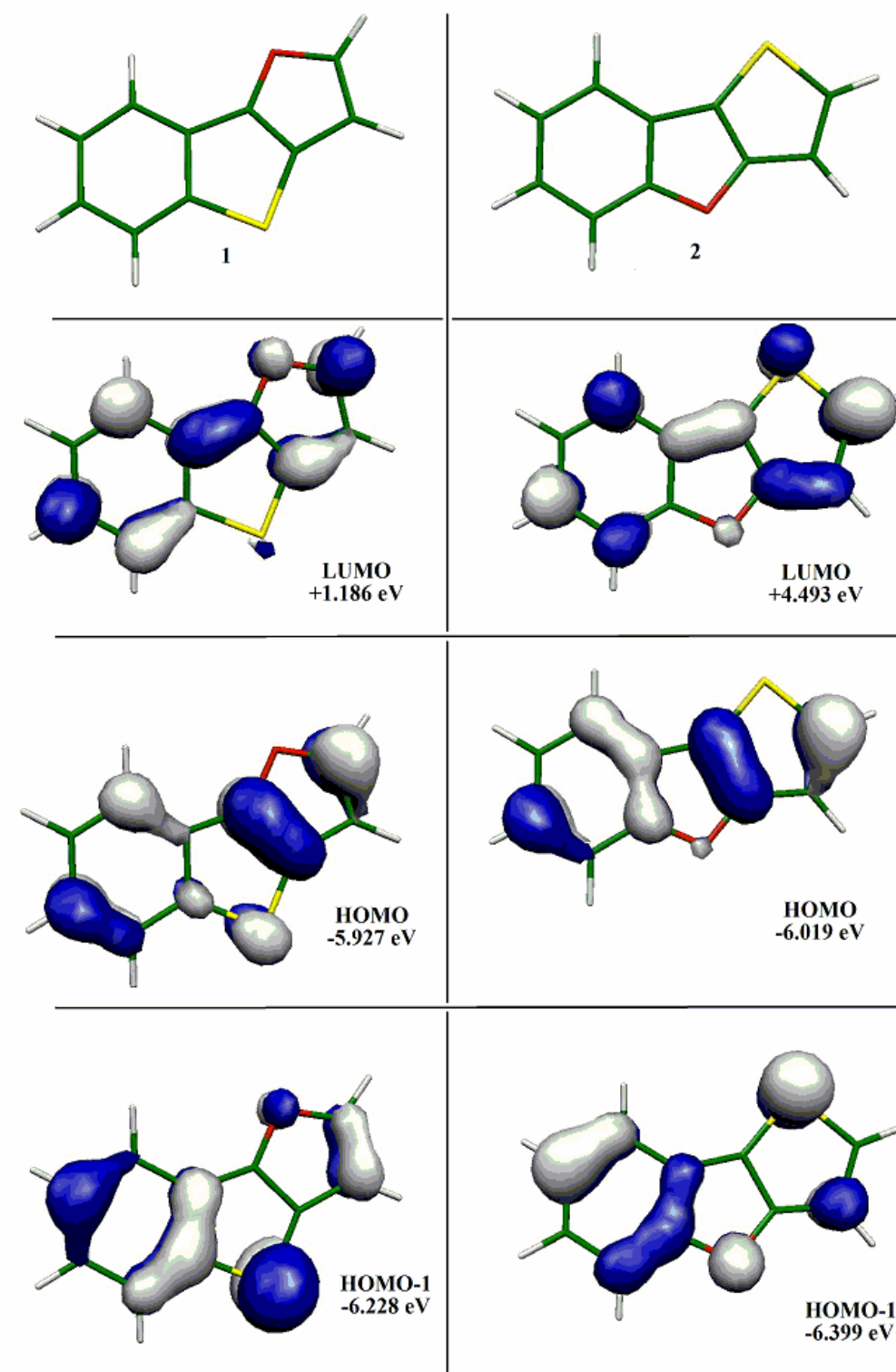


Figure 5. HOMO, HOMO-1, LUMO orbitals for heterocycles **1** and **2** calculated using B3LYP functional and 6-311G\* basis set.

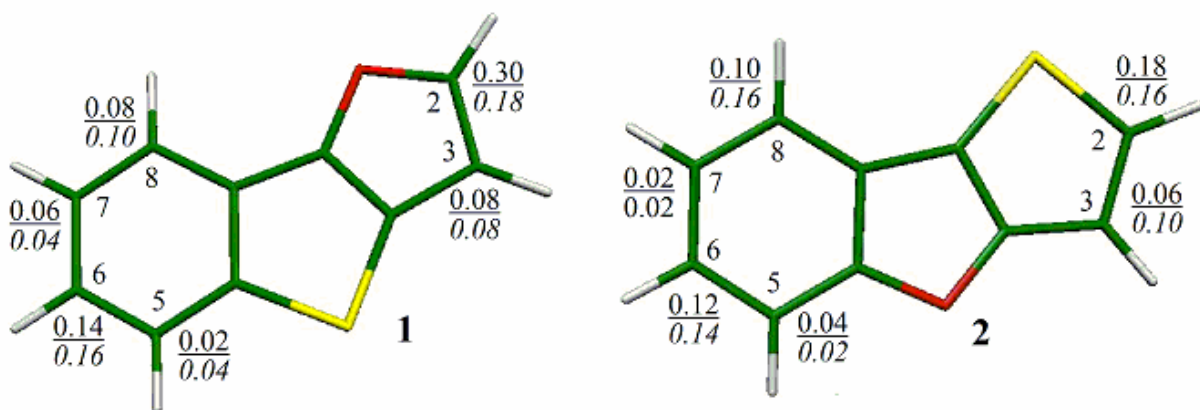


Figure 6. Calculated Fukui functions for electrophilic attack at the atoms for the heterocycles **1** and **2**. UHF/6-311G\* (italic) and B3LYP/6-311G\*

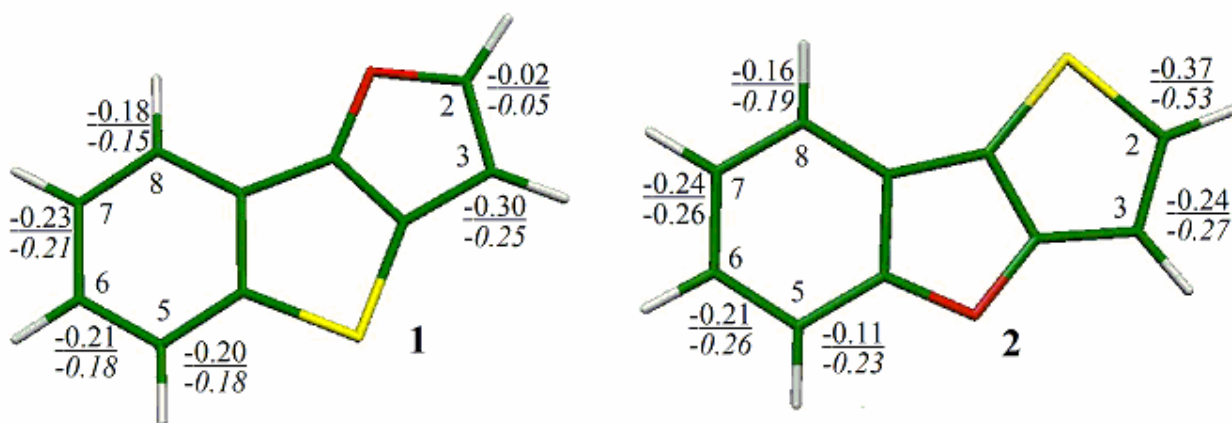


Figure 7. Calculated Mulliken population analysis for the heterocycles **1** and **2** at the particular atoms. UHF/6-311G\* (italic) and B3LYP/6-311G\*

## Conclusions

A theoretical study of the stability and reactivity was carried out at the density functional theory and ab-initio calculation level for the structures of benzofused isomeric thieno[3,2-*b*]furans. Global descriptors such as chemical potential ( $\mu$ ), ionization energy ( $I$ ), molecular hardness ( $\eta$ ), electrophilicity ( $\omega$ ), frontier molecular orbital (HOMO-LUMO) energy gap, local ionization energy and electrostatic potential energy surfaces were determined and used to identify the differences in the reactivity of heterocycles.

In general calculated values of  $\mu$ ,  $I$ ,  $\eta$ ,  $\omega$  lead to the conclusion that heterocyclic system in thieno[3,2-*b*]benzofuran is more aromatic and stable than in isomeric heterocycle. This result concurs with the experimental information concerning the reactivity and stability of the systems.

The bond order uniformity, local ionization energy and electrostatic potential energy surfaces analysis also suggest structural and reactivity differences of isomeric thieno[3,2-*b*]furans. Benzothieno[3,2-*b*]furan structurally could be analogues with molecule of aromatic benzothiophene substituted with C(2)-C(3) vinylic moiety. This evidently point out wherefore the electrophilic substitution reaction for benzothieno[3,2-*b*]furan goes via addition-elimination mechanism at the C(2) position. Contrary the bond order, electrostatic potential and local ionization energy surfaces values for the of thieno[3,2-*b*]benzofuran shows delocalized  $\pi$ -electron surface that reports stable aromatic system between benzene ring and thiophene heterocycle. This result suggests the presumable possibility of aromatic electrophilic substitution mechanism scenario for thieno[3,2-*b*]benzofuran. For better understanding of reaction mechanism it would be of interest to calculate potential energy surface of more probable reaction pathways on electrophilic substitution of thieno[3,2-*b*]benzofuran.

For the isomeric benzofused thieno[3,2-*b*]furans there is  $\pi$  molecular orbital delocalization between benzene and thiophene, also between benzene and furan rings. Moreover for **1** the highest occupied molecular orbital is delocalized on C(2)-C(3) bond while for **2** the shape located on C(3) atom. The calculated values for condensed Fukui function for electrophilic attack shows the largest value belong to C(2) atom for both heterocycles. Theoretical results from the molecular orbital analysis and Fukui function reactivity indexes are in complete agreement with the observed reactivity of these compounds showing exceptional reactivity of C(2) atom for both isomers.

In general theoretical results from the reactivity indexes are in complete agreement with observed reactivity of these compounds.

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