Theoretical Study Regarding the Reactivity of 5-nitrofuran-2-carboxaldehyde Thiosemicarbazone

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The reactivity of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone and its copper (II) complex has been evaluated by means of computational chemistry techniques. The stability of the two tautomeric forms (thiol-thione) has been discussed; also, NBO analysis, in order to establish the stabilization interactions, has been performed. Geometric parameters of both ligand and complex and the Fukui functions for an electrophilic attack (f) have been computed.

Keywords: thiosemicarbazone, conformational analysis, NBO analysis

Metal complexes of various heterocyclic ligands play an important role in medicine, having antitumor, antiviral, and anti-inflammatory effects [1-3]. The general structure of a metal complex consists in a metallic atom (ion) surrounded by ligands – chemical species that show a strong electron-donor character [4]. In this regard, 5-nitrofuran-2-carboxaldehyde thiosemicarbazone, a ligand that forms with copper a metal complex with antiamoebic action [1], was investigated by means of the computational chemistry methods.

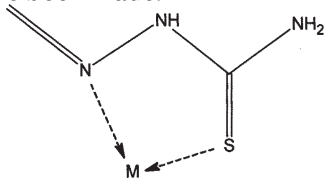
Literature survey reports a number of studies regarding the *ab initio* and DFT characterization of transition metal complexes and their corresponding ligands: DFT computations of metal complexes of cimetidine [14] and of the Schiff base of isatin [15], copper complexes of nicotinic carboxylic acids as superoxyde dismutase mimetics [5], theoretical evaluation of pKa of metal complexes in solution [16], characterization of the structure of vanadium complexes [17]. Most frequently encountered metals are copper, platin, nickel, vanadium, iron [4, 6-7], whereas the ligands consists in molecules that show a strong electron-donor character. One of the structures that have a number of applications within the metal complexes class is the thiosemicarbazone structure [8-13], where the N-N-S-N system has an efficient donor-electron character. According to Pelosi [8], an important role for the biologic activity of thiosemicarbazone complexes is played by the aromatic ring bound to the –NH-NH- group (which allow an extended conjugation of the system).

Experimental part

The compound that is investigated during the present study is 5-nitrofuran-2-carboxaldehyde thiosemicarbazone; its geometric parameters, the most stable conformer and reactivity centers have been investigated by means of computational chemistry methods. The reactivity study consists in computations of both Mulliken and natural atomic charges, the electron density and HOMO orbitals graphical representation and the calculation of the condensed Fukui functions (f) for an electrophilic attack [18].

$f_k^{\alpha} = \sum_{\mu \in k} \left| c_{\mu}^{\alpha} \right|^2$, α = HOMO orbital, with neglection of the overlap integral

Also, the structure of the Cu(II) complex with 5-nitrofuran-2-carboxaldehyde thiosemicarbazone is investigated; comparisons between the reactivity indices of the N-N-C-S atoms within the ligand and the complex have been made.



Scheme 1
Coorsination mode of thiosemicarbazone structures

Geometry optimization of both ligand and copper complex was performed with G09W program [19], at HF/6311G and LanL2DZ level of theory, respectively. The atomic charges and donor-acceptor interactions were calculated by means of NBO analysis (implemented in the Gaussian 09 suite). HOMO orbitals were visualized with GaussView 5.0, while AOMix 6.82 software [20,21] was employed for the charge decomposition analysis of the copper complex. The conformational analysis of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone was performed with Vega ZZ program [22].

Results and discussions

Thione-thiol tautomeric equilibrium

When the structure of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone is discussed, the existence of two tautomers -thione and thiol forms- must be taken into account.

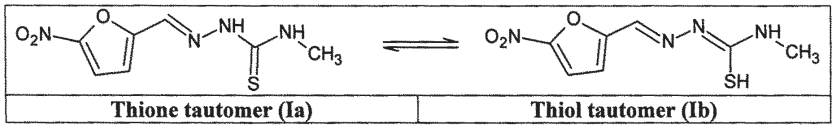


Fig. 1. Tautomeric forms of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone

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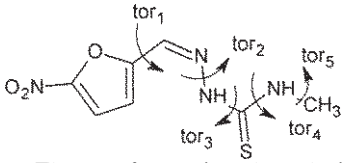
Stability computations must be performed, in order to determine which the most stable tautomeric form is. The computed heat of formation for the two compounds **Ia** (thione) and **Ib** (thiol) (gas phase calculations) show that the thione tautomer **Ia** is the most stable one (the difference between the enthalpies of formation is 26.6 kcal/mol in favor of the thione form of thiosemicarbazone derivative.

During the present study, the nomination "5-nitrofuran-2-carboxaldehyde thiosemicarbazone" will refer to the thione tautomer **Ia**.

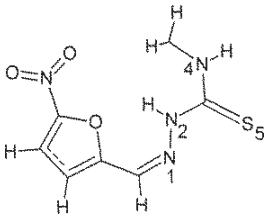
Conformational analysis of 5-nitrofuran-2-carbox-aldehyde thiosemicarbazone

Conformational analysis was performed in order to establish the most stable conformer of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone. It is well-known that the internal rotations around a σ-bond generate energetic barriers that are strongly influenced both by steric and electronic interactions. The structure of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone allows five torsions (scheme 2):



Scheme 2. Torsions within 5-nitrofuran-2-carboxaldehyde thiosemicarbazone

The conformational analysis was performed by taking into account all the five above-mentioned flexible torsions. The most stable structure has the following conformation:



Scheme 3. The most stable conformer of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone (Ia)

It may be observed that the dihedral angle N1-N2-C3-S5 has a value of 0°, which means a "bath"-type conformation of the four atoms that allow the N 1 and S5 atoms to establish coordinative bonds with the copper atom.

NBO analysis of the compound **Ia** has been performed in order to throw some light into the interactions that have led to the highest stability of this conformer. The results are presented in table 1.

Highest values have been obtained for the interactions between the lone pair of the N2 atom with π* C-N1 and π*C3-S5and the lone pair of N4 atom and π* C3-S5, respectively. It results that these stabilization energies are due to the hyperconjugation effect, established between the lone pairs of the two N atoms and the antibonding π*C3-S5. It has to be outlined the position of the furan ring to the thiosemicarbazone skeleton, position that allows the establishment of small donor-acceptor interactions between the lone pairs of the O atom within the ring and the N2-H bond (3.32 kcal/mol); also, the interaction between the LP of the O atom of the nitro group and the C6-N4 bond (16.62 kcal/mol).

Reactivity studies of the ligand behaviour of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone

The most important property of a ligand is the electron-donor capacity. In this regard, the conjugated N-N-S-N atoms play the central role and some reactivity descriptors –Mulliken and natural atomic charges, Fukui functions, electron density- will be computed and used for the evaluation of the four above-mentioned atoms.

Most negative values are obtained for the N4 atom and N2 atom of the thiosemicarbazone moiety, but the geometrical conformation favours the atoms N1 and S5 as electron donors.

It is well known that a metal complex results by the interactions between the occupied orbitals of the ligand and the unoccupied orbitals of the metal. In this regard, an estimation of the HOMO orbitals of the considered ligand, namely 5-nitrofuran-2-carboxaldehyde thiosemicarbazone, have been made.

The condensed Fukui functions f^-, computed for an electrophilick attack, offer a good estimation of the electron-donor capacity of the N-N-S-N atoms. The results are presented in table 3.

Highest value has been obtained for the sulfur, while amongst the N atoms similar values have been obtained for N2 and N4 atoms.

A graphical representation of the HOMO orbitals of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone is presented in figure 2 and leads to very similar conclusions. Highest localization is depicted for the S atom and for the two N atoms N2 and N4.

Geometric parameters and charge decomposition analysis of Cu(II) complex of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone

A copper(II) complex of type $LCuCl_2$, where L is 5-nitrofuran-2-carboxaldehyde thiosemicarbazone, has been investigated by means of computational chemistry techniques.

The geometric parameters of the complex are presented in table below; for comparison, the bond length values of

Table 1
STABILIZATION ENERGIES OF THE MOST STABLE CONFORMER OF **Ia**

Donor-acceptor interactions	E2 (kcal/mol)
LP N2 – π* C-N1	**48.52**
LP N2 – π* C3-S5	**95.68**
LP S5 - σ* N2-C3	18.17
LP S5 - σ* C3-N4	12.62
LP N4 - π* C3-S5	**131.2**

Table 2
MULLIKEN AND NATURAL ATOMIC CHARGES OF 5-NITROFURAN-2-CARBOXALDEHYDE THIOSEMICARBAZONE (HF/6311G)

Ligand	Mulliken charges	Natural charges
C3	0.104	-0.009
N1	-0.082	-0.134
N1	-0.695	-0.506
S5	-0.147	-0.350
N4	-0.777	-0.654

Table 3
CONDENSED FUKUI FUNCTIONS (f-) COMPUTED AT B3LYP/6311G LEVEL OF THEORY

Atoms	f-
N1	0.014
N2	0.105
S5	0.410
N4	0.104

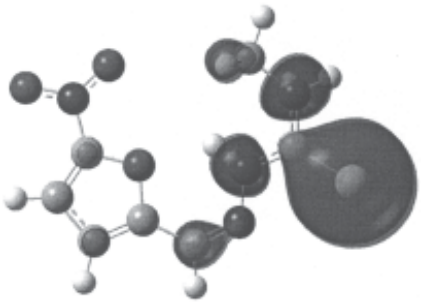
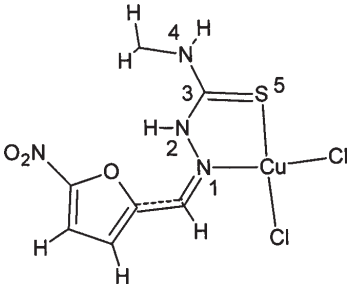


Fig. 2. Graphical representation of the HOMO orbitals of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone



Scheme 4. Structure of $LCuCl_2$ complex, where L is 5-nitrofuran-2-carboxaldehyde thiosemicarbazone

Bond length (Angstrom)

Bond	Complex	Ligand
N1-N2	1.403	1.348
N2-C3	1.338	1.363
C3-S5	1.794	1.721
S5-Cu	2.281	-
N1-Cu	2.010	-

Table 4
GEOMETRIC PARAMETERS OF $LCuCl_2$ COMPLEX AND LIGAND L

Mulliken charges

Atoms	Complex	Ligand
S5	0.193	-0.040
N1	-0.524	0.182
N2	-0.373	-0.468

Table 5
MULLIKEN ATOMIC CHARGES OF N-N-S ATOMS (HF/LanL2DZ)

the ligand are mentioned in parenthesis. The same numbering –as used in scheme 3- is employed.

Along with the complex formation, N1-N2 and S5-C3 become larger with 0.06 A, while a shortening of N2-C3 bond with 0.025A.

The Mulliken charges, computed for N-N-S atoms involved in the formation of the LCuCl2 complex, are calculated (LanL2DZ basis set for both complex and ligand).

Positive charge of the S atom within the complex show that the electron transfer from S atom to the metal (in our case, copper) has occurred. Instead, the nitrogen atom N1 which has a less electronegative character that the vicinal N2 atom within the ligand, shows an augmented electronegativity within the $LCuCl_2$ complex.

The electron-donor ability of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone was also outlined by means of charge decomposition analysis performed for the two fragments (L and $CuCl_2$) of the complex. It resulted a value of 0.865 electrons of the net charge of donation (from fragment L to fragment $CuCl_2$).

Conclusions

The reactivity of a thiosemicarbazone derivative with biologic activity was investigated by means of computational chemistry techniques. Conformational analysis led to the obtaining of the most stable conformer of 5-nitrofuran-2-carboxaldehyde thiosemicarbazone, while evaluation of the tautomeric equilibrium thione-thiol showed that the thione tautomer is the most stable one. Reactivity studies have been carried out, involving NBO analysis and condensed Fukui functions computations, in order to assess the electron-donor capacity of the thiosemicarbazone derivative as ligand. The results concluded that the S atom showed a higher electron-donor character that the nitrogen N1 atom.

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