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Chemical Stability of Imidazole-Thiosemicarbazides in Solvents: NBO Studies and Theoretical Absorption Spectrum

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Abstract: This study of chemical stability in solvents was performed on four (4) molecules of a series of halogen-substituted imidazole-thiosemicarbazides (IT) using the TD-DFT method at the B3LYP/6-31+G (d, p) level. The solubility of the imidazole-thiosemicarbazides in solvents across the dipole moment revealed that the ITs have the lowest values of the dipole moment in cyclohexane, indicating that the ITs are more soluble in cyclohexane. This claim was confirmed by the assessment of the energy gap in the different solvents. Analysis of the effect of temperature on the stability of imidazole-thiosemicarbazides showed that temperature has no effect on the stability of the ITs studied. This observation could allow to fight effectively against the different bacteria and to control their storage conditions and also to establish their expiry dates. The NBO analysis and the study of the absorption spectrum were also carried out in order to show the hyperconjugative interactions and the delocalization of atomic charges. In this case, the stabilizing interactions involve the free pairs of nitrogen atoms N16 and N19 and the antibinding single bond are σ*(C18-S21). Analysis of the theoretical absorption spectrum showed that the absorption band representing cyclohexane is more intense for all the compounds studied. This is because cyclohexane better promotes the stabilization of substituted imidazole-thiosemicarbazides. Moreover, the maximum band corresponds to the electronic transition between the HOMO and the LUMO is due to an electron displacement from the LP (N) orbitals towards the σ*(CS) orbitals.

Keywords: Chemical Stability, TD-DFT, CPCM, HOMO-LUMO

1. Introduction

Toxoplasmosis is one of the most important parasitic diseases caused by the protozoan parasite *Toxoplasma gondii* in the world. This widespread disease mainly affects immunocompromised people and pregnant women [1]. *Toxoplasma gondii* is a ubiquitous organism capable of infecting a wide range of vertebrate hosts, including humans. Approximately one-third of the US population is estimated to be infected, with infection rates ranging from 10 to 90% elsewhere in the world. Although most infected individuals do not show signs of clinical disease, primary infection and pregnancy can result in severe birth defects [2, 3]. It is in this context that *Agata et al* [4, 5] have synthesized and tested halogen-substituted imidazole-thiosemicarbazides to control *Toxoplasma gondii* infection. Imidazole-thiosemicarbazides are convenient precursors that have been widely used in heterocyclic synthesis. These thiosemicarbazide derivatives are useful intermediates

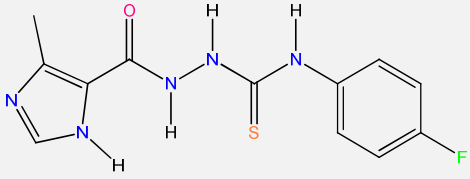
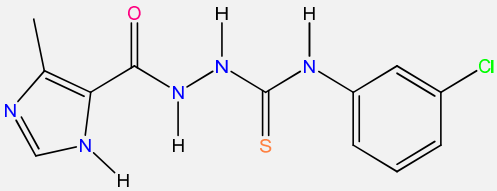
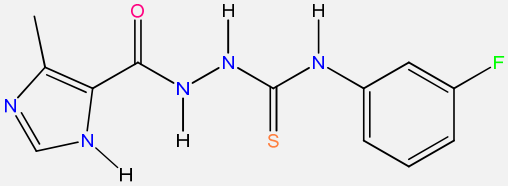
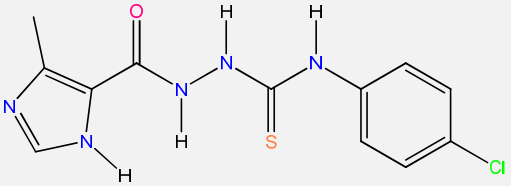
and subunits for the development of molecules of pharmaceutical or biological interest. An increased interest in thiosemicarbazide chemistry has developed in recent years. Indeed, these compounds and their derivatives have a broad spectrum of biological effects, including antibacterial [6], antifungal [7], anticonvulsant [8], antimicrobial [9], and antitumor [10]. The therapeutic properties are related to the conformation of the molecules and the interactions they can establish with each other. Knowledge of molecular conformation and interactions requires the determination of physico-chemical descriptors through theoretical chemistry. With the development of computational techniques and computational chemistry, quantum chemistry provides insight into the electronic structures of molecules and strongly propels the development of traditional experimental chemistry [11]. The aim of this work is to determine theoretically, on the one hand, the chemical stability of halogen-substituted imidazole-thiosemicarbazides in solvents and, on the other hand, to identify the sites of intramolecular interactions that stabilize the series of molecules studied by different methods of quantum chemistry.

2. Materials and Methods

2.1. Level of Computational Theory

The theoretical study of chemical stability was conducted based on NBO (Natural Bond Orbital) and TD-DFT analysis. Chemical stability, in the technical sense of the term used in chemistry, refers to the thermodynamic stability of a chemical system [12]. A chemical system is thermodynamically stable when it is at its lowest energy level, or in chemical equilibrium with its environment. The information provided by this study is of paramount importance. Indeed, this stability study makes it possible to verify the stability of pharmacoactive substances or medicinal products in a climatic environment (effect of temperature). The geometries of the molecules were optimized at the DFT calculation level with the B3LYP [13, 14] function in the 6-31+ G (d, p) base using Gaussian 09 software [15]. This Hybrid function gives better energies and is in agreement with the high-level ab initio methods [16, 17]. As for the split-valence and double-dzeta base (6-31G (d, p)), it is sufficiently extended and the consideration of polarization functions are important for the explanation of free doublets of heteroatoms. The global reactivity indices were obtained from the conceptual FFT model [18]. In this work, we were interested in two molecules of halogenated imidazole-thiosemicarbazides in order to study their chemical stability in solvents. The inhibitory structures, codes and concentrations of the studied imidazole-thiosemicarbazide series are presented in Table 1.

Table 1. *Structures and nomenclature of the imidazole-thiosemicarbazides studied and their inhibitory concentrations and codes.*

Structure and nomenclature	Codes	IC50 (µg/mL)
 *N*-(4-fluorophenyl)-2-(4-methyl-1*H*-imidazole-5-carbonyl)hydrazinecarbothioamide	IT 1	110.31
 *N*-(3-chlorophenyl)-2-(4-methyl-1*H*-imidazole-5-carbonyl)hydrazinecarbothioamide	IT2	25.70
 *N*-(3-fluorophenyl)-2-(4-methyl-1*H*-imidazole-5-carbonyl)hydrazinecarbothioamide	IT3	113.45
 *N*-(4-chlorophenyl)-2-(4-methyl-1*H*-imidazole-5-carbonyl)hydrazinecarbothioamide	IT4	73.37

2.2. Descriptors of the Conceptual DFT

To predict chemical reactivity, some theoretical descriptors related to conceptual DFT have been determined. In particular, the Lowest Vacuum Molecular Orbital Energy (E_{LUMO}). It provides information on the highest energy electrons, which are therefore the easiest to yield. It is related to the electron donor character of the molecule; a High Energy Value (HOMO) indicates the tendency of a molecule to give electrons to a suitable acceptor (molecule) with a low energy molecular orbital.

As for the energy of the Highest Occupied Molecular Orbital (E_{HOMO}), it indicates the electron acceptor character of the molecule. E_{HOMO} indicates the ability of a molecule to accept electrons, the lower the energy of the LUMO, the higher the probability that the molecule will accept electrons. The regioselectivity can therefore be studied qualitatively by examining the coefficients of the orbital boundaries: HOMO /LUMO. In addition, the energy gap ΔE between LUMO and HOMO is an important parameter that gauges the global reactivity towards an electron acceptor. In a family of molecules, this reactivity is all the greater the lower this value is. It should be noted that, the descriptors related to the molecular orbital boundaries have been calculated in a very simple way within the framework of the Koopmans approximation [19]. These different parameters are calculated from equations (1):

$$I = -E_{HOMO}$$

$$A = -E_{LUMO}$$

$$\Delta E = (E_{LUMO} - E_{HOMO}) \quad (1)$$

2.3. Dipole Moment

The dipole moment is the quantity that indicates the polarity of a molecule. This polarity is considered very important for many physicochemical properties. It is attributed an important role, for example, in the orientation of reactions and the solubility of solvents. Solubility can be determined by calculating the dipole moment. Indeed, the dipole moment indicates the stability of a molecule in water. Thus, a high dipole moment value will reflect low solubility in organic solvents and high solubility in water.

2.4. NBO (Natural Bond Orbital)

The NBO (Natural Bond Orbital) analysis shows the interaction between donor NBO (filled or binding NBO) and acceptor NBO (empty or anti-binding NBO). It also provides an effective method for the study of intra- and intermolecular interactions [20]. This analysis is performed by examining all possible interactions between filled and empty Lewis-type NBOs and estimating their energy by the second order perturbation theory [21]. The stabilization energy E2 [21] associated with the electron delocalization between the electron donor NBO (i) and the electron acceptor NBO (j) is evaluated according to the equation below.

$$E_2 = \Delta E(ij) = q_i \frac{(F(ij))^2}{\varepsilon_j - \varepsilon_i} = q_i \frac{F_{ij}^2}{\Delta\varepsilon} \quad (2)$$

Fij is an element of the Fock matrix, q_i represents the occupation of the donor orbital, εi and εj are the energies of the acceptor and donor NBO orbitals respectively. The permitted electronic transitions [22] within a molecule are shown in Figure 1.

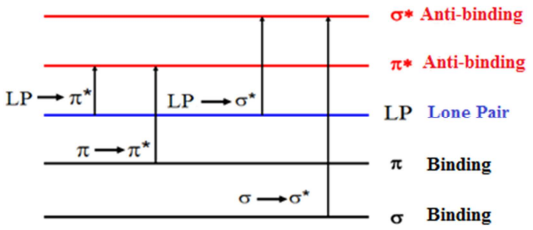


Figure 1. *Representation of the different types of electronic transitions allowed.*

2.5. Theoretical Absorption Spectra

The absorption spectrum is the amount of light absorbed by a compound as a function of wavelength. Molecules with a UV-visible absorption spectrum are those that absorb photons whose energy corresponds to wavelengths in the range (100 nm <λ<800 nm). When molecules absorb UV-Visible photons, the energy of the valence electrons increases. The absorption phenomenon in the UV-Visible region is related to variations in the molecular energy of electron transitions [23].

3. Results and Discussion

3.1. Solubility of Imidazole-Thiosemicarbazides in Solvents

The theoretical values of the dipole moment of the compounds IT1, IT2, IT3 and IT4 in the three solvents are given in Table 2. It should be noted that the three solvents selected are: A protic polar solvent (water), an aprotic polar solvent (Dimethylsulfoxide, (DMSO)), and an aprotic apolar solvent (cyclohexane). In addition, there are no significant differences in structure and energy when using similar solvents [24].

Table 2. *Theoretical values of the dipole moment in the solvents of the compounds IT1, IT2, IT3 and IT4 at calculation level TD-DFT B3LYP/6-31+G(d,p).*

MOLECULES	μ(D)
Water	
IT1	5.60
IT2	6.792
IT3	6.737
IT4	5.678
DMSO	
IT1	5.576
IT2	6.763
IT3	6.709
IT4	5.653
Cyclohexane	
IT1	4.470

MOLECULES	μ(D)
IT2	5.449
IT3	5.452
IT4	4.538

The results of the table of studied compounds show that we record the lowest values of dipole moments for the molecules IT1, IT2, IT3 and IT4 respectively of 4,470 D, 5,449 D 5,452 D and 4,538 D in cyclohexane. These low values indicate that these molecules are more soluble in cyclohexane and therefore more stable in this solvent. As imidazole-thiosemicarbazide molecules are synthesized in DMSO, a synthesis in cyclohexane could further improve the properties of these compounds.

3.2. Effect of Temperature on Imidazole-Thiosemicarbazides

ITs were synthesized by *Agata et al* [4, 5] at temperatures between 204°C and 230°C. The same authors tested these compounds on bacteria such as: Mesophilic (37°C), Thermophilic (45°C<T<70°C), Hyperthermophilic (T>80°C), Psychrophilic (0°C<T<15°C), Psychrotropic (0°C<T<37°C). As imidazole-thiosemicarbazides are molecules used against bacteria, they should therefore maintain their stability at various temperatures, in order to fight effectively against different bacteria and to control storage conditions and expiry date of IT.

The compounds IT1, IT2, IT3 and IT4 have been optimized at different temperatures in order to observe the variation of the energy gap. These data are listed in Table 3.

Table 3. *Values of the energy gaps ΔE (eV) and the different temperatures of the molecules IT1, IT2, IT3 and IT4 at calculation level TD-DFT B3LYP/6-31+G(d,p).*

Temperature (KELVIN)	E(HOMO) eV	E(LUMO) eV	ΔE (eV)
IT1			
150	-6.380	-1.636	4.744
200	-6.380	-1.636	4.744
250	-6.380	-1.636	4.744
300	-6.380	-1.636	4.744
350	-6.380	-1.636	4.744
400	-6.380	-1.636	4.744
450	-6.380	-1.636	4.744
IT2			
150	-6.434	-1.738	4.696
200	-6.434	-1.738	4.696
250	-6.434	-1.738	4.696
300	-6.434	-1.738	4.696
350	-6.434	-1.738	4.696
400	-6.434	-1.738	4.696
450	-6.434	-1.738	4.696
IT3			
150	-6.416	-1.738	4.678
200	-6.416	-1.738	4.678
250	-6.416	-1.738	4.678
300	-6.416	-1.738	4.678
350	-6.416	-1.738	4.678
400	-6.416	-1.738	4.678
450	-6.416	-1.738	4.678
IT4			
150	-6.370	-1.728	4.643
200	-6.370	-1.728	4.643
250	-6.370	-1.728	4.643
300	-6.370	-1.728	4.643
350	-6.370	-1.728	4.643
400	-6.370	-1.728	4.643
450	-6.370	-1.728	4.643

The analysis of Table 3 shows that for different temperatures taken, the energy gap hardly varies (ΔE=4.744 eV for IT 1, ΔE=4.696 eV for IT2, ΔE=4.678 eV for IT3 and ΔE=4.643 eV for IT4). We can say that temperature has no effect on the stability of the different compounds studied. Therefore these results could allow a good understanding of the efficacy and give a good control of the storage conditions and the expiry date of the imidazole-thiosemicarbazide molecules.

3.3. Chemical Stability of Solvents on Imidazole-Thiosemicarbazides

In order to evaluate the influence of the environment on TTIs, calculations were made by optimizing the four compounds in water, DMSO and cyclohexane. All optimization and frequency calculations were performed at TD-DFT/6-31+G (d, p). The results of these calculations are shown in Table 4.

Table 4. *Energy gap values of IT 1, IT 2, IT 3 and IT 4 compounds in vacuum, water, DMSO and cyclohexane at TD-DFT/6-31+G level (d, p).*

Compounds	E(HOMO) eV	E(LUMO) eV	ΔE eV
Vide			
IT1	-6.380	-1.636	4.744
IT2	-6.434	-1.738	4.696
IT 3	-6.416	-1.738	4.678
IT 4	-6.370	-1.728	4.643
Eau			
IT 1	-6.310	-1.627	4.683
IT 2	-6.361	-1.723	4.639
IT 3	-6.332	-1.723	4.609
IT 4	-6.286	-1.698	4.588
DMSO			
IT 1	-6.311	-1.627	4.684
IT 2	-6.362	-1.723	4.639
IT 3	-6.333	-1.723	4.610
IT 4	-6.287	-1.698	4.588
Cyclohexane			
IT 1	-6.353	-1.632	4.721
IT 2	-6.406	-1.730	4.676
IT 3	-6.381	-1.729	4.651
IT 4	-6.334	-1.715	4.620

Analysis of the data in Table 4 shows that compound IT 1 has the highest energy gap values compared to compounds IT 2, IT 3 and IT 4 regardless of the solvent. On the other hand, vacuum and cyclohexane better stabilize TTIs. The order of decreasing stability of IT in the different media is as follows: Vacuum > Cyclohexane > DMSO > Water.

This result is in line with that obtained in the evaluation of the solubility of TTIs in solvents from the dipole moments.

3.4. NBO Analysis of Imidazole-Thiosemicarbazides

NBO (Natural Bond Orbital) analysis was used to explain

the intra and intermolecular interactions of the most stable ITs. The results of the second order disturbance energies of the Fock matrix by the NBO method were obtained by applying the TD-DFT method at level B3LYP / 6-31 + G (d, p). These results are reported in Table 5.

Table 5. *Second order interaction energy (E2. kcal/mol) between donor orbitals(i) and acceptors(j) of IT 1, IT 2, IT 3 and IT 4 compounds in vacuum, water, DMSO and cyclohexane at B3LYP/6-31+ G(d, p).*

Compounds	Donors (i)	Acceptors (j)	E_j-E_i (u.a)	F_{ij} (u.a)	E_2 (kcal/mol)
void					
IT 1	π(C1-N10)	π*(C2-C3)	0.33	0.084	24.51
	LP(1)N19	σ*(C18-S21)	0.2	0.108	64.69
	LP(1)N11	π*(C1-N10)	0.27	0.108	52.57
	LP(2)O13	σ*(C12-N14)	0.71	0.117	23.47
IT 2	π(C1-N10)	π*(C2-C3)	0.33	0.084	24.59
	LP(1)N16	σ*(C18-S21)	0.23	0.111	60.32
	LP(1)N11	π*(C1-N10)	0.27	0.108	52.58
	LP(2)O13	σ*(C12-N14)	0.71	0.117	23.53
IT 3	π(C1-N10)	π*(C2-C3)	0.33	0.084	24.57
	LP(1)N11	π*(C1-N10)	0.27	0.108	52.58
	LP(1)N16	σ*(C18-S21)	0.23	0.112	60.77
	LP(2)O13	σ*(C12-N14)	0.71	0.118	23.55
IT 4	π(C1-N10)	π*(C2-C3)	0.33	0.084	24.57
	LP(1)N11	π*(C1-N10)	0.27	0.108	52.58
	LP(1)N19	σ*(C18-S21)	0.20	0.106	61.96
	LP(2)O13	σ*(C12-N14)	0.71	0.117	23.52
water					
IT 1	π(C1-N10)	π*(C2-C3)	0.33	0.085	24.54
	LP(1)N11	π*(C1-N10)	0.26	0.109	55.49
	LP(2)O13	σ*(C12-N14)	0.72	0.117	23,3
	LP(3)F31	π*(C26-C28)	0.44	0.085	17.55
IT 2	π(C2-C3)	π*(C12-O13)	0.27	0.075	24.36
	LP(1)N11	π*(C1-N10)	0.26	0.109	55.51
	LP(2)O13	σ*(C12-N14)	0.72	0.117	23.36
	LP(3)Cl32	π*(C23-C25)	0.33	0.061	11.77
IT 3	π(C1-N10)	π*(C2-C3)	0.33	0.085	24.60
	LP(1)N11	π*(C1-N10)	0.26	0.109	55.51
	LP(2)N14	π*(C12-O13)	0.30	0.111	49.05
	LP(2)O13	σ*(C12-N14)	0.72	0.117	23.38
IT 4	π(C1-N10)	π*(C2-C3)	0.33	0.085	24.59
	LP(1)N11	π*(C1-N10)	0.26	0.109	55.51
	LP(2)N14	π*(C12-O13)	0.30	0.111	48.62
	LP(2)O13	σ*(C12-N14)	0.72	0.117	23.35
DMSO					
IT 1	π(C2-C3)	π*(C12-O13)	0.27	0.075	24.19
	LP(1)N11	π*(C1-N10)	0.26	0.109	55.46
	LP(2)O13	σ*(C12-N14)	0.72	0.117	23.3
	LP(3)F31	π*(C26-C28)	0.44	0.085	17.56
IT 2	π(C2-C3)	π*(C12-O13)	0.27	0.075	24.36
	LP(1)N11	π*(C1-N10)	0.26	0.109	55.48
	LP(2)O13	σ*(C12-N14)	0.72	0.117	23.36
	LP(3)Cl32	π*(C23-C25)	0.33	0.061	11.78
IT 3	π(C2-C3)	π*(C2-C3)	0.33	0.085	24.60
	LP(1)N11	π*(C1-N10)	0.26	0.109	55.48
	LP(2)O13	σ*(C12-N14)	0.72	0.117	23.39
	LP(1)N19	σ*(C22-C24)	0.29	0.080	26.63
IT 4	π(C2-C3)	π*(C2-C3)	0.33	0.085	24.59
	LP(1)N11	π*(C1-N10)	0.26	0.109	55.48
	LP(2)O13	σ*(C12-N14)	0.72	0.117	23.36
	LP(1)N19	π*(C2-C3)	0.29	0.074	23.74
Cyclohexane					
IT 1	π(C1-N10)	π*(C2-C3)	0.33	0.085	24.56
	LP(1)N19	σ*(C18-S21)	0.2	0.109	67.77
	LP(1)N11	π*(C1-N10)	0.27	0.109	53.89
	LP(2)O13	σ*(C12-N14)	0.72	0.117	23.38
IT 2	π(C1-N10)	π*(C2-C3)	0.33	0.085	24.63
	LP(1)N19	σ*(C18-S21)	0.2	0.105	62.38
	LP(1)N11	π*(C1-N10)	0.27	0.109	53.91

Compounds	Donors (i)	Acceptors (j)	E_j-E_i (u.a)	F_{ij} (u.a)	E_2 (kcal/mol)
IT 3	LP(2)O13	σ*(C12-N14)	0.71	0.117	23.44
	π(C1-N10)	π*(C2-C3)	0,27	0.085	24.62
	LP(1)N11	π*(C1-N10)	0.27	0.109	53.90
	LP(1)N16	σ*(C18-S21)	0.23	0.112	62.16
IT 4	LP(2)O13	σ*(C12-N14)	0.72	0.117	23.46
	π(C1-N10)	π*(C2-C3)	0.33	0.085	24.61
	LP(1)N11	π*(C1-N10)	0.27	0.109	53.90
	LP(1)N19	σ*(C18-S21)	0.20	0.107	64.85
	LP(2)O13	σ*(C12-N14)	0.72	0.117	23.43

E(2) means the energy of hyper-conjugative interactions (stabilization energy in kcal/mol), Energy difference (a.u.) between the donor and acceptor NBO orbitals i and j, F (i, j) is the Fock matrix between orbitals i and j (a.u.), π: binding double bond; π*: antibinding double bond; LP: free electron pair; σ: single bond; σ*: antibinding single bond.

Table 5 shows the highest values of intramolecular interactions that stabilize each molecule studied. Analysis of the Fock matrix second-order perturbation theory in the different solvents shows that the strong conjugations for molecules IT1, IT2, IT3 and IT4 take place respectively between the orbitals LP(N) and σ*(CS), LP(N) and π*(CN), LP(O) and σ*(CN), π(CN) and π*(CC), LP(F) and π*(CC), π(CC) and π*(CO). These interactions result in Intramolecular Charge Transfer (ICT) creating the stabilization of the different molecular systems.

In vacuum, the highest values of the stabilization energy of the compounds IT1, IT2, IT3, and IT4 correspond to the interaction between free electron pairs (LP) of the nitrogen atoms N16 and N19, and the antibinding single bond σ*(C18-S21). This result is nearly consistent in cyclohexane, where the stabilizing interaction takes place between the free electron pairs LP(N19) or LP(N16) and σ*(C18-S21). Furthermore, the transition corresponds to this electron shift from the LP(N19) or LP(N16) orbitals to the σ*(C18-S21) orbitals with stabilizing energies ranging from 60.32 to 67.77 kcal.mol-1 in vacuum and cyclohexane.

Concerning DMSO solvents and water, the high stabilization energy values are observed only for the interaction between LP(N11) and the antibinding double bond π*(C1-N10). At the end of our analysis, IT1, IT2, IT3 and IT4 being more stable in vacuum and cyclohexane, we retain that the interactions which stabilize our compounds are due to the LP of the nitrogen atoms N16 and N19, and the antibinding single bond σ*(C18-S21) Figure 2.

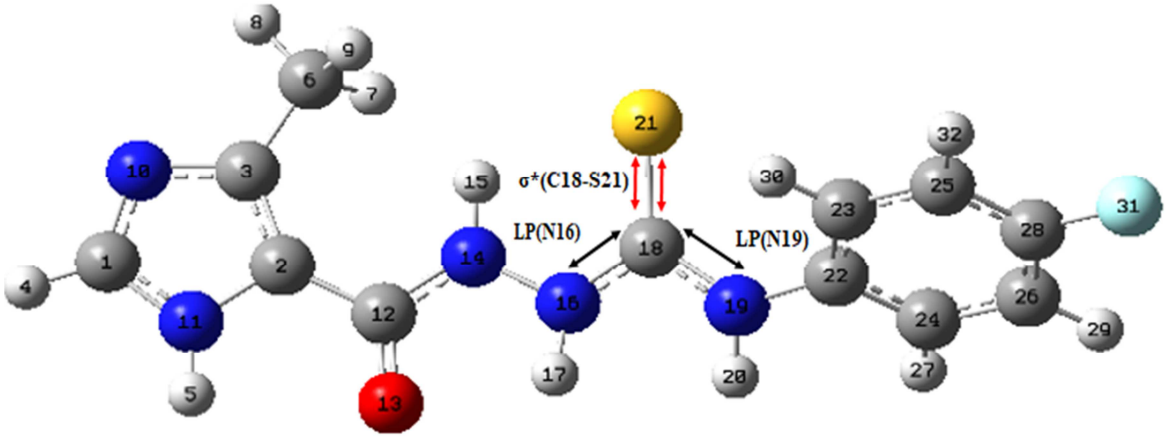


Figure 2. *Illustration of the Lone Pair interactions of the N16 and N19 nitrogen atoms and the single antibinding bond σ*(C18-S21). that stabilize imidazole-thiosemicarbazides.*

3.5. TD-DFT Analysis of the Absorption Spectrum of Imidazole-Thiosemicarbazides

The theoretical absorption spectra of the ITS nucleus and its derivatives IT1, IT2, IT3 and IT4 were calculated in vacuum, water, Dimethylsulfoxide (DMSO), and cyclohexane. The maximum values of excitation energy (ΔEexcit), wavelength (λ), and oscillator strength f for each compound are listed in Table 6.

Table 6. *Excitation energies ΔEexcit(eV), wavelengths λ (in nm), oscillator strength f and electronic transitions of the core absorption maxima of IT and its derivatives calculated at B3LYP/6-31+G (d, p) in vacuum, water, DMSO and cyclohexane.*

Compounds	ΔE_{excit}(eV)	λ(nm)	*f*	Electronic Transition	Contribution
vacuum					
IT 1	4.199	295.308	0.680	HOMO ⟶ LUMO	57%
IT 2	4.138	299.661	0.709	HOMO ⟶ LUMO	65%
IT 3	4.123	300.701	0.736	HOMO ⟶ LUMO	67%

Compounds	ΔE_{excit}(eV)	λ(nm)	*f*	Electronic Transition	Contribution
IT 4	4.107	301.879	0.790	HOMO ⟶ LUMO	62%
water					
IT 1	4.108	301.813	0.656	HOMO ⟶ LUMO	52%
IT 2	4.031	307.617	0.788	HOMO ⟶ LUMO	63%
IT 3	4.010	309.182	0.780	HOMO ⟶ LUMO	61%
IT 4	4.025	308.006	0.652	HOMO ⟶ LUMO	49%
DMSO					
IT 1	4.099	302.446	0.653	HOMO ⟶ LUMO	51%
IT 2	4.021	308.328	0.790	HOMO ⟶ LUMO	62%
IT 3	4.001	309.900	0.775	HOMO ⟶ LUMO	60%
IT 4	4.018	308.589	0.638	HOMO ⟶ LUMO	47%
Cyclohexane					
IT 1	4.109	301.718	0.791	HOMO ⟶ LUMO	58%
IT 2	4.043	306.666	0.855	HOMO ⟶ LUMO	66%
IT 3	4.024	308.144	0.880	HOMO ⟶ LUMO	67%
IT 4	4.021	308.313	0.891	HOMO ⟶ LUMO	60%

Analysis of the data in Table 6 shows that the imidazole-thiosemicarbazides studied exhibit oscillator strength values with high contributions in vacuum and cyclohexane compared to other media. A high oscillator strength value reflects an intense absorption band [25] in the theoretical absorption spectrum. Figure 3 shows the different absorption spectra obtained from Table 6.

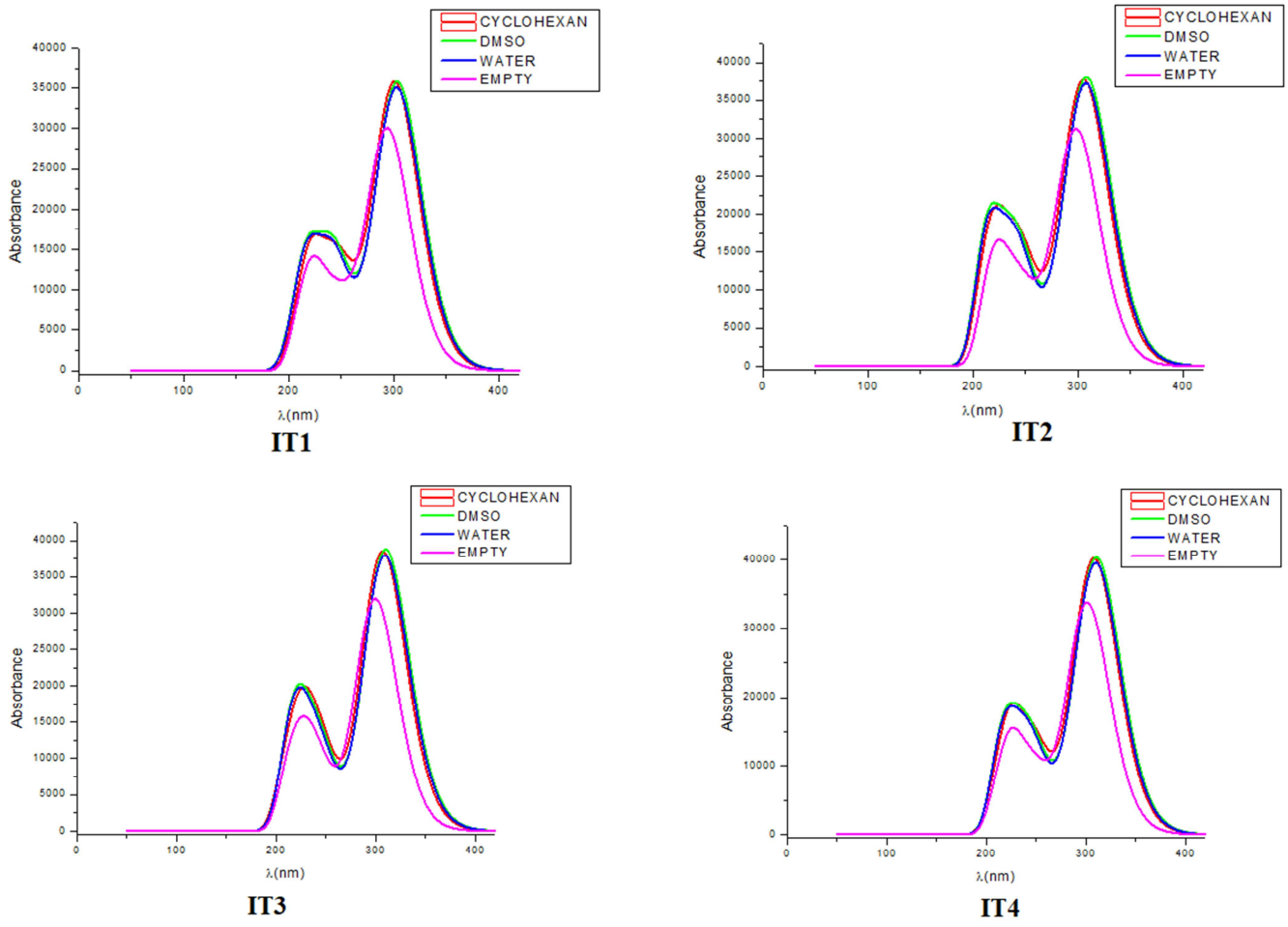


Figure 3. *Comparison of the theoretical absorption spectra of the IT nucleus and its most stable derivatives determined by TD-DFT in vacuum, water, DMSO and cyclohexane.*

The study of the absorption spectrum of the compounds in the different solvents used shows that they are generally observed in the ultraviolet (100-400 nm), which is consistent with the literature [4]. The spectra show the same pattern and each of the spectra have 2 absorption bands regardless of the medium (Figure 3). The theoretical absorption spectrum shows that the absorption band representing cyclohexane is more intense for all the compounds studied. This is due to the fact that cyclohexane better promotes IT stabilization. The maximum band corresponds to the electronic transition

between HOMO and LUMO. This transition corresponds to an electron shift from the LP(N) orbitals to the σ*(CS) orbitals.

4. Conclusion

In order to know the chemical stability of newly synthesized imidazole-thiosemicarbazides, a study was carried out using TD-DFT and NBO (Natural Bond Orbital). These studies allowed us to evaluate the solubility and dipole moment of imidazole-thiosemicarbazides in the solvents which are water, DMSO and cyclohexane. At this level we note that the ITs have the lowest values of the dipole moment in cyclohexane. This result indicates that the ITs are more soluble in cyclohexane. The imidazole-thiosemicarbazides studied were optimized at different temperatures in order to fight effectively against the different bacteria and to control their storage conditions and also to establish their expiry dates. At this level, there is no effect on the stability parameter considered (ΔE: energy gap). In order to evaluate the stability of IT in solvents. The studied halogenated imidazole-thiosemicarbazides were optimized in three solvents, in order to see how their stability evolved in the medium. This analysis shows that cyclohexane stabilizes all the compounds studied. The NBO analysis revealed that the interactions that stabilize these compounds are due to the LPs of the nitrogen atoms N16 and N19, and the single antibinding bond σ*(C18-S21). The excitation energies, maximum wavelengths, oscillator strength and electronic transitions of each compound were determined using the TD-DFT method. From these data we concluded that the absorption spectrum of all these compounds is observed in the ultraviolet ($100 < \lambda < 400$ nm) and that the absorption band of cyclohexane for each molecule is more intense due to the stabilizing effect of cyclohexane. The intramolecular electronic transitions that stabilize these compounds are from HOMO to LUMO. This transition corresponds to an electron shift from the LP(N19) or LP(N16) orbitals to the σ*(C18-S21) orbitals with stabilization energies ranging from 60.32 to 67.77 $kcal.mol^{-1}$ in vacuum and cyclohexane. Halogen-substituted imidazole-thiosemicarbazides (IT) are more stable and more soluble in aprotic apolar solvents such as cyclohexane.

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