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Research Article

Stability and Reactivity of Two Benzimidazole Hydrazide-Hydrazone Compounds: A Theoretical Study by DFT Method

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Abstract

This work contributes to theoretical chemistry's knowledge of benzimidazole-hydrazide-hydrazone. Indeed, hydrazides-hydrazones-benzimidazoles have shown anticancer, antibacterial, antiparasitic activities, and many other activities. A benzimidazole-hydrazide-hydrazone compound can exhibit four conformers: E/Z synperiplanar (Esp, Zsp) and E/Z antiperiplanar (Eap, Zap). Studies have indicated that the prevalence of these compounds is attributed to their stability and their tendency to readily bind to DNA. A theoretical study with advanced methods would make it possible to evaluate the stability of benzimidazole-hydrazide-hydrazone conformers. Therefore, we carried out this theoretical study on the conformers of two benzimidazoles-hydrazides-hydrazones denoted C_1 and C_2 wich differ by the presence of fluorine atom in the structure of C_2. Specifically, we analyze the stability and the reactivity of the compounds based on the dipole moment, Gibbs free energy, HOMO and LUMO energies and UV-visible. For this purpose, calculations were performed in gas phase and DMSO using DFT and TD-DFT methods at the B3LYP/6-311+G(d, p) level theory. The dipole moment values show that Zap conformer is the most polar for both compounds. The Gibbs free energy indicate that Esp conformer emerges as the most stable for both compounds in both phases. The energy gap (E_{LUMO}-E_{HOMO}) and TD-DFT results suggest that Esp conformer is the most reactive conformer for the two compounds.

Keywords

Benzimidazole, Hydrazide-Hydrazone, Stability, B3LYP

1. Introduction

Heterocyclic compounds are the most widely used organic compounds in medicinal chemistry [1-5]. They exhibit various properties depending on the nature of the heteroatom.

Nitrogen heterocycles stand out as crucial components in pharmaceutical products owing to the wide array of their biological activities [1-3]. In endeavors to enhance these

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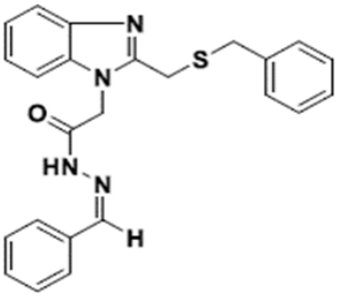
activities, synthetic chemists have integrated benzimidazoles [4-6] and Hydrazides-hydrazones [7-9] to design new derivatives known as benzimidazoles-hydrazides-hydrazones [10-14]. These compounds have demonstrated activities such as anticancer [12], antibacterial [13] and various other properties [14]. Their structure is characterized by the N-acylhydrazone skeleton C(O) N N=C<. This scaffold is an encompasses amide (C(O)-NH) and imine (N=C) functional groups, giving rise to four conformers: E Synperiplanar (Esp), E Antiperiplanar (Eap), Z Synperiplanar (Zsp) and Z Antiperiplanar (Zap) [15, 16]. Furthermore, research has shown that the prevalence of nitrogen heterocycles can be attributed to their stability and their tendency to readily bind to deoxyribonucleic acid (DNA) through hydrogen bonding [17]. Therefore, it appeared crucial for us to investigate the stability of the conformers of two benzimidazoles-hydrazides-hydrazones among those which were synthesized by ACHI and collaborators [18]. This will enable the establishment of a reactivity hierarchy among these conformers.

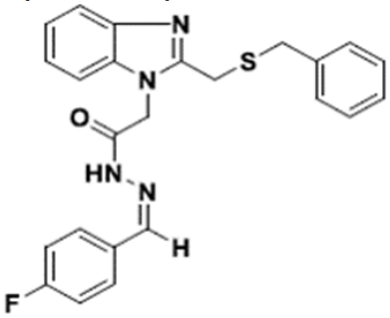
Specifically, we initially ascertain the dipole moment of the conformers, followed by evaluating their stability based on the Gibbs free energy. Finally, we evaluate the reactivity of the conformers from the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energies and the UV-visible absorptions.

2. Materials and Methods

Our study focuses on two benzimidazole-hydrazide-hydrazone compounds named C_1 and C_2. their names according to international union of pure and applied chemistry (IUPAC) nomenclature were also given. These compounds are illustrated in Figure 1. They differ in that a hydrogen atom in C_1 is substituted with a fluorine atom in C_2.



C_1: N-benzylidene-2-(2-((benzylthio)methyl)-1H-benzo[d]imidazol-1-yl)acetohydrazide



C_2 : *N*-(4-fluorobenzylidene)-2-(2-((benzylthio)methyl)-1*H*-benzo[*d*]imidazol-1-yl)acetohydrazide

Figure 1. *Benzimidazoles-hydrazides-hydrazones.*

Each compound presents four conformers. The conformers of compound C_1 are depicted in Figure 2.

Initially, the geometries of these conformers were optimized using the density functional theory (DFT) method with the B3LYP functional, associated with the 6-31G(d,p) basis set [19, 20]. This method is implemented in the GAUSSIAN-09 program [21]. The calculations were carried out in the gas phase and solution. Solution calculations are were performed using Tomasi's conductor-like polarizable continuum model (CPCM) in Dimethylsulfoxide (DMSO) [22]. Furthermore, the Time-Dependent Density Functional Theory(TD-DFT) was employed to conduct spectral studies of the conformers of the two benzimidazoles-hydrazides-hydrazones in gas phase [23, 24]. The results obtained are as follows.

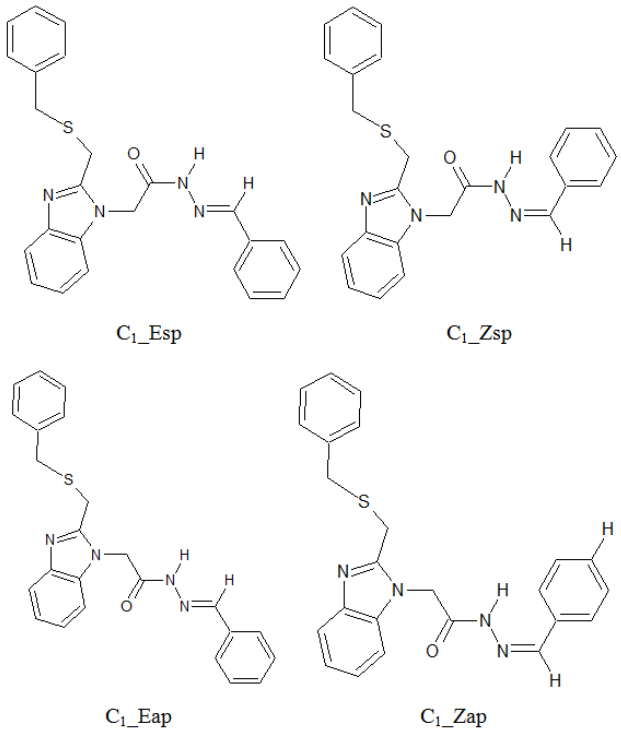


Figure 2. *C_1 conformers.*

3. Results and Discussion

3.1. Dipole Moments

The dipole moment serves to characterize the charge distribution within a molecule. Understanding this distribution is fundamental to the comprehension of the molecule's electronic properties, geometry, and interactions with other particles [25].

Table 1 contains the dipole moments of the eight conformers of the two benzimidazole-hydrazide-hydrazone compounds, calculated at the B3LYP/6-31G(d,p) level. In the gas phase, the dipole moment values range between 3.21 and 6.91 D, indicating that all studied conformers exhibit polarity. The Zsp conformer stands out as the most polar in both compounds, with values of 6.91 D for C_1 and 6.04 D for C_2. Consequently, halogenation reduces the polarity of benzimidazole-hydrazide-hydrazone compounds.

Transitioning into DMSO, the dipole moment increases for all conformers, with values ranging between 4.51 and 10.21 D. The Zap conformer emerges as the most polar, with values of 10.21 D and 8.64 D for C_1 and C_2, respectively. DMSO, being a polar aprotic solvent, enhances polarity. The decreasing order of dipole moments for the conformers in DMSO remains consistent across both compounds. This order is as follows:

Zap > Zsp > Esp> Eap >

Table 1. *Dipole moments.*

Conformers	μ_{gaz} (D)	μ_{DMSO} (D)
C1_Esp	6,39	8,33
C1_Eap	3,21	4,56
C1_Zsp	6,91	8,68
C1_Zap	6,43	10,21
C2_Esp	5,33	7,09
C2_Eap	3,40	4,51
C2_Zsp	6,04	7,72
C2_Zap	4,51	8,64

3.2. Stability

The relative stability of the conformers was determined from the Gibbs free energy calculated from the following equation:

$$G(298K) = E_e + G_{corr} \quad (1)$$

Ee represents, the total electronic energy of the molecule, and

Gcorr denotes the thermal correction to Gibbs free energy of the molecule.

The conformer with lowest Gibbs free energy is consid-

ered the most stable.

The results are presented in Table 2.

Negative values of the Gibbs free energy indicate that the conformers are formed *via* a spontaneous reaction. The Esp conformer exhibits the lowest Gibbs free energy value for both compounds in both environments, thus indicating its superior stability among the four conformers. The relative stability of the other conformers is determined from the energy difference (ΔG) between the most stable conformer and the others. A smaller ΔG, signifies greater stability. The results are shown in Figure 3.

In the gas phase, for both compounds (C_1 and C_2), Esp is the most stable conformer, followed by Eap, Zsp, and finally Zap. Hence, the conformers of C_1 and C_2 share the same stability order:

Esp > Eap > Zsp > Zap.

In DMSO, the order of stability mirrors that of the gas phase but with reduced energy differences. This indicates a notable stabilization of the conformers in this solvent. Mesey and colleagues suggest that a relative energy difference of 10 Kcal/mol is a reasonable threshold for predicting the existence of stable species [26, 27]. In the case of the benzymidazole-hydrazide-hydrazones conformers under study, the largest energy difference is 10 Kcal/mol. Hence, we can argue that all eight conformers studied can exist both in the gas phase and in DMSO.

Furthermore, literature reviews have established that in benzymidazoles-hydrazides-hydrazones, the Z configuration is less stable than the E configuration due to steric hindrance [28, 29]. Consequently, our results align perfectly with the literature.

Table 2. *Gibbs free energy.*

Compounds	G_{gaz} (ua)	ΔG_{gaz} (Kcal/mol)	G_{DMSO} (ua)	ΔG_{DMSO} (Kcal/mol)
C1-Esp	-1619,9077	0,00	-1619,9277	0,00
C1-Eap	-1619,9031	2,89	-1619,9235	2,64
C1-Zsp	-1619,9017	3,77	-1619,9188	5,58
C1-Zap	-1619,8925	9,54	-1619,9162	7,22
C2-Esp	-1719,1486	0,00	-1719,1681	0,00
C2-Eap	-1719,1450	2,23	-1719,1655	1,65
C2-Zsp	-1719,1419	4,21	-1719,1600	5,06
C2-Zap	-1719,1327	10,00	-1719,1567	7,12

ΔG is the change in the Gibbs free energy

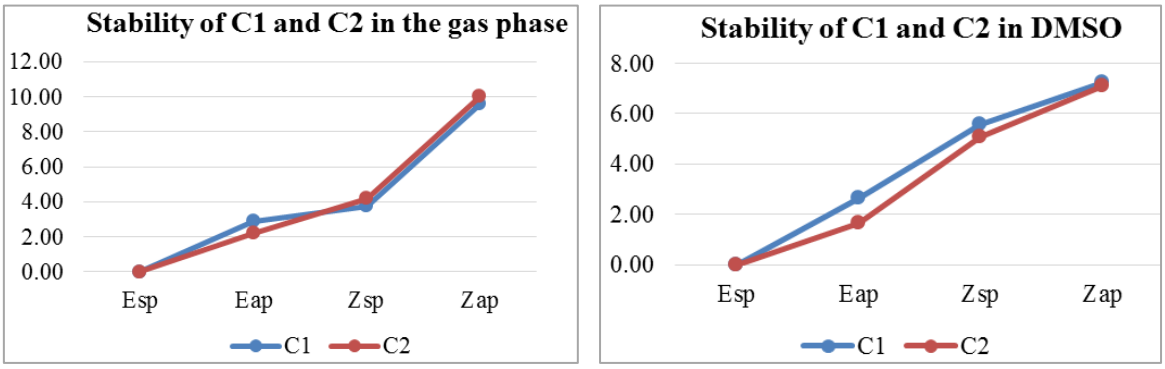


Figure 3. *Relative stability of conformers.*

3.3. Frontier Molecular Orbitals

The energy gap of a molecule is calculated by the frontier molecular orbitals, known as the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), play a crucial role in chemical reactions. A higher

HOMO energy corresponds to a more reactive molecule in reactions with electrophiles, while a lower LUMO energy is essential for molecular reactions with nucleophiles [30]. According to softness-hardness rule, a large HOMO-LUMO energy gap corresponds to hard molecules, while a small HOMO-LUMO energy gap is associated with soft molecules [31, 32].

The energy gap of a molecule is calculated by:

$$\Delta E = E_{LUMO} - E_{HOMO} \quad (2)$$

Calculated values of HOMO and LUMO energy (E) and their energy gap (ΔE) are presented in Table 3. The results indicate that in the gas phase, the Esp conformer has the lowest energy gap for both compounds with 4,02 eV for C_1 and 4,00 eV for C_2. These values suggest that the Esp conformer is the most reactive among the four conformers. Following it is the Zsp conformer, with an energy gap of 4,07 eV for C_1 and 4,05 eV for C_2. The third most reactive conformer corresponds to the Zap conformer, with anenergy gap of 4,31 eV for C_1 and 4,45 eV for C_2. The fourth more reactive conformer is Eap conformer, with an energy gap of 4,63 eV for C_1 and 4,60 eV for C_2. The reactivity decreases in the order: Esp > Zsp > Zap > Eap.

Thus, the most reactive conformer are Synperiplanars forms.

In the aqueous phase, the Esp conformer remains the most reactive. Comparing these findings with those of the gas phase, it is observed that the Eap conformer is more reactive than Zsp and Zap. In this phase, the order of decreasing reactivity is as follows: Esp > Eap > Zsp > Zap.

Table 3. *Molecular orbital energies and energy gap.*

Compounds	Gas Phase			DMSO Solution		
	E_{HOMO} (au)	E_{LUMO} (au)	ΔE (eV)	E_{HOMO} (au)	E_{LUMO} (au)	ΔE (eV)
C1-Esp	-0,21376	-0,06610	4,02	-0,22598	-0,05937	4,53
C1-Eap	-0,22666	-0,05640	4,63	-0,22931	-0,05919	4,63
C1-Zsp	-0,21314	-0,06355	4,07	-0,22604	-0,05555	4,64
C1-Zap	-0,21863	-0,06028	4,31	-0,22667	-0,05574	4,65
C2-Esp	-0,21469	-0,06759	4,00	-0,22613	-0,05866	4,56
C2-Eap	-0,22677	-0,05780	4,60	-0,22785	-0,05857	4,60
C2-Zsp	-0,21414	-0,06511	4,05	-0,22612	-0,05517	4,65
C2-Zap	-0,22194	-0,05835	4,45	-0,22684	-0,05521	4,67

3.4. Absorption Properties

To determine the nature and energy of singlet-singlet electronic transitions, predictions of the first 6 excited states are performed within the TD-DFT formalism. Throughout the discussion, we consider the lowest absorption energies and the absorption energies with the greatest oscillator strength value. The calculated absorption energy, corresponding wavelength, oscillator strength, and orbital coefficients are summarized in Table 4. The results indicate that for all conformers, the lowest energy transition occurs due to the excitation of electrons from HOMO to LUMO (H→L), except for Eap, which corresponds to the transition H-2→L.

The absorption intensity is directly related to the dimensionless oscillator strength, and the dominant absorption bands are the transitions with the highest oscillator strength value [33]. For conformer Esp, the dominant absorption corresponds to the H-3→L transition. For Eap, it is associated with the H→L transition. For Zsp, it is related to the H-5→L transition. For Zap, it is associated with the H-4→L transition for C_1 and the H-3→L transition for C_2.

In C_1 conformers, the dominant absorption of Eap exhibits a red shift of about 1 nm compared to the dominant absorption of Esp, and Zap exhibits a red shift of about 2 nm compared to the dominant absorption of Zsp. In C_2 conformers, Eap has the same spectral features as Zap, and Esp has the same spectral features as Zsp. The dominant absorptions of C_2 conformers exhibit a red shift compared to the dominant absorptions of C_1 conformers, except for the conformer Zap. Thus, the substitution of a hydrogen atom of C_1 with one fluorine atom influences the spectrum by decreasing the absorption energy.

It is also worth noting that the absorption energy corresponding to the H→L transition leads to an order of reactivity identical to that of the energy gap in the gas phase. This

confirms the clear stability of the conformer Esp.

Table 4. *Absorption energy, wavelength and oscillator strengths in gas phase.*

Conformers	Orbital transitions	Absorption Energy (eV)	Wavelength (nm)	Oscillator Strenght
C1-E_SP	H→L (0.705)	3.60	345	0.0002
	H-3→L (0.696)	4.43	280	0.8193
C1-E_AP	H-2→L (0.478)	4.21	295	0.0479
	H→L (0.443)	4.42	281	0.5746
C1-Z_SP	H→L (0.703)	3.67	338	0.0002
	H-5→L (0.625)	4.53	273	0.4779
C1-Z_AP	H→L (0.684)	3.87	320	0.0027
	H-4→L (0.652)	4.51	275	0.3229
C2-E_SP	H→L (0.705)	3.58	346	0.0002
	H-3→L (0.696)	4.39	282	0.8145
C2-E_AP	H-2→L (0.453)	4.20	295	0.0608
	H→L (0.523)	4.39	282	0.6417
C2-Z_SP	H→L (0.703)	3.65	340	0.0002
	H-5→L (0.484)	4.51	275	0.2785
C2-Z_AP	H→L (0.676)	4.01	309	0.0047
	H-3→L (0.576)	4.51	275	0.3357

4. Conclusion

This work involved the investigation of some physico-chemical properties of two benzymidaz-ole-hydrazide-hydrazone compounds using the DFT and TD-DFT methods associated with the 6-31G(d,p) basis set.

The dipole moment values show that all the conformers exhibit polarity, with an increase in polarity in DMSO. However, halogenation reduces the polarity of benzimidaz-oles-hydrazides-hydrazones. The Zap conformer is the most polar for both compounds.

Regarding the stability of the conformers, the findings show that all the conformers can exist both in the gas phase as well as DMSO solution. The Esp conformer emerges as the most stable for both compounds in both phases.

The energy gap suggests that conformer Esp is the most reactive conformer for the two compounds. This outcome is corroborated by TD-DFT calculations. Furthermore, TD-DFT results reveal that substituting a hydrogen atom of C_1 with a fluorine atom effects the spectrum by decreasing the absorption energy.

Abbreviations

CPCM	Conductor-Like Colarizable Continuum Model
DNA	Deoxyribonucleic Acid
HOMO	Highest Occupied Molecular Orbital
IUPAC	International Union of Pure and Applied Chemistry
LUMO	Lowest Unoccupied Molecular Orbital

Author Contributions

Amon Benjamine Assoma: Conceptualization, Writing – original draft

Affou éLucie Bede: Validation

Patrick-Armand Achi: Resources

Siomenan Coulibali: Supervision

Conflicts of Interest

The authors declare no conflicts of interest.

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