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Research Article

Theoretical study of the effect of heteroatom on the electronic and molecular properties of isoindoline monomers

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Abstract: Theoretical calculations were carried out in the gas phase and in solution in order to study the influence of the heteroatom on the electronic and structural properties of some isoindoline derivatives and likewise to demonstrate the effect of the solvent on the tautomeric process encountered in this type of equilibrium. The most stable structures were analyzed and the possible equilibrium displacements were studied. Total energies results obtained with HF, MP2 and DFT methods showed, that the isoindoline forms are the most stable; and the replacement of the NH heteroatom by an oxygen heteroatom increases the stability of the compound. Calculations in solution indicated that heterocycle electronic properties were influenced by the used solvent. However, all tautomeric forms were more stable in DMSO than in THF. The predominance of the isoindoline form in the gas phase and in solution was confirmed as experimentally observed.

Keywords: *isoindoline, isoindole, heterocycle, heteroatom, solvent effect, MP2, DFT*

1. Introduction

In recent years, a growing interest has been devoted to *isoindolines* and their derivatives. They play an important role in organic synthesis and constitute the basic core of various biologically active heterocyclic compounds due to their diversified pharmacological profile [1]. Their anti-inflammatory [2], anticonvulsant [3], antiproliferative [4], antimicrobial [5] and anticancer [3,6-8] activities have been demonstrated by several experimental studies. *Isoindolines* and their *isoindoles* derivatives are heterocyclic compounds constituted of a benzene ring fused with an azoline ring for *isoindolines* or

with a pyrrole ring for *isoindoles*. They are widely used as synthetic intermediates, especially in the preparation of pharmaceutical active ingredients. In particular, *isoindoline-1,3-dione* has recently attracted considerable scientific interest because of its action against cancer and inflammatory diseases recently discovered. Its wide range of biological activities arise from its ability to moderate the action of cytokines in cancer and inflammatory diseases [1c,9].

We investigated in this work, the influence of the extracyclic heteroatoms X and Y (X, Y = O, NH) on the electronic and structural properties of some *isoindolines* derivatives. The transfer of the

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proton from the NH group to the substituent X or Y leading to a mixture of two (or three) forms called tautomers, these heterocyclic studied exhibit the phenomenon of prototropy, in which a hydrogen atom can bind either to the heteroatom X or Y (Fig. 1). Our interest then focused on the study of different tautomeric couples in solution, in order to demonstrate the effect of the solvent on tautomeric process encountered in this type of equilibrium. For this purpose, two solvents of different polarity were used, these solvents are the most used in synthesis [10] and are represented by their dielectric constants, namely DMSO (dimethylsulfoxide) of dielectric constant ($\epsilon=46.7$) and THF (tetrahydrofuran) of dielectric constant ($\epsilon=7.6$). The different equilibriums of studied tautomers are presented in Fig. 1.

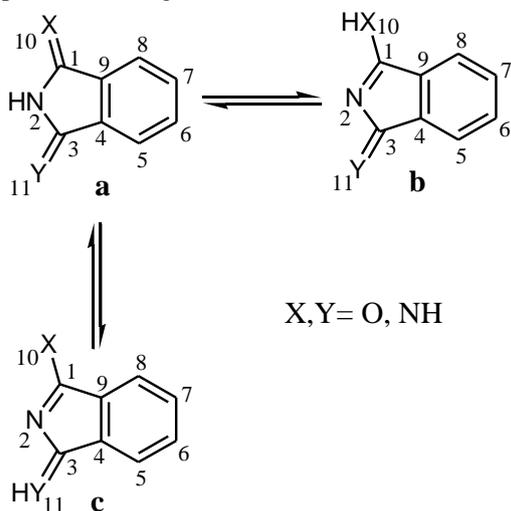


Fig. 1. Tautomers, *isoindoline* (a)-*isoindole* (b or c).

2. Methods of calculation

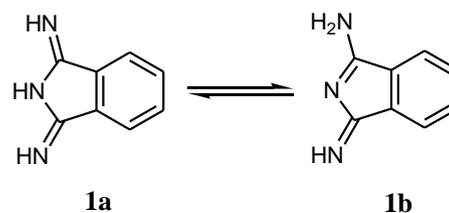
Ab initio [11] calculations of Hartree-Fock type [12] with 6-311++G (d,p) basis set, which requires relatively short computation time, were first performed to rapidly get qualitative results. In order to obtain more accurate results, calculations were carried out with the same 6-311++G (d,p) basis set, using two other methods, the post-Hartree-Fock one at the MP2 level and the density functional theory (DFT) one [13,14] using the functional of Becke [15] for the exchange and the functional of Lee-Yang-Parr [16] for the correlation (B3LYP functional). Calculations were realized first in the gas phase and then in the presence of THF and DMSO solvents, using the PCM model (Polarizable Continuum Model) [17]. Calculations were carried

out with Gaussian03 program [18] and compound structures were drawn using ChemDraw program [19].

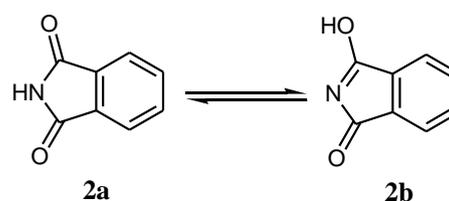
3. Results and Discussion

Detailed plot of different studied tautomeric couples are shown in Fig. 2.

1. Case of $X=Y=NH$



2. Case of $X=Y=O$



3. Case of $X=NH$ and $Y=O$

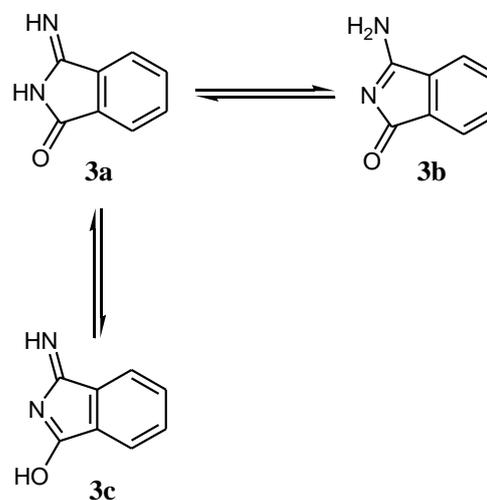


Fig. 2. Tautomeric equilibriums.

3.1. Stability

Complete optimization of molecular geometries of *isoindole-isoindoline* compounds was carried out using three methods of calculation, Hartree-Fock method, Post Hartree-Fock method and Density Functional Theory method.

Total energies results of different tautomers computed in the gaseous state and in the presence of THF (underlined values) and DMSO (values in parenthesis) solvents are given in Table 1. Results showed that *isoindoline* forms **1a**, **2a** and **3a** have the lowest total energies and are therefore more stable than *isoindole* forms, i.e., the migration of hydrogen from the imine function to X and Y substituents is difficult.

In presence of solvent, the order of stability remains the same as in gaseous state, i.e., *isoindolines* are always more stable compared to

isoindoles. Moreover, the stabilities of the tautomers studied in solution increase with the solvent polarity, thus the tautomers are more stable in DMSO solvent than in THF. For example, the gas phase study showed that the form **2a** is thermodynamically the most stable; the presence of solvent, which clearly affects the stability of studied compounds, gives this tautomeric form an energy gain in DFT method, of 11.3 Kcal/mol and 13.8 Kcal/mol in THF and DMSO, respectively.

Table 1. Energies (in a.u.) of studied tautomers in the gas phase and in the presence of THF (underlined values) and DMSO (values in brackets) solvents calculated with HF/6-311++G(d,p), MP2/6-311++G(d,p) and DFT(B3LYP)/6-311++G(d,p) methods

		E _T (a.u.)		
		HF	MP2	DFT
Tautomer 1 X=Y=NH	<i>1a</i>	-470.488	-470.482	-473.449
		<u>-470.512</u>	<u>-470.505</u>	<u>-473.471</u>
	(-470.518)	(-470.511)	(-473.477)	
	<i>1b</i>	-470.480	-470.474	-473.443
<u>-470.507</u>		<u>-470.500</u>	<u>-473.468</u>	
	(-470.514)	(-470.507)	(-473.474)	
Tautomer 2 X=Y=O	<i>2a</i>	-510.206	-510.200	-513.237
		<u>-510.226</u>	<u>-510.219</u>	<u>-513.255</u>
	(-510.230)	(-510.223)	(-513.259)	
	<i>2b</i>	-510.160	-510.153	-513.193
<u>-510.187</u>		<u>-510.179</u>	<u>-513.218</u>	
	(-510.194)	(-510.186)	(-513.224)	
Tautomer 3 X=O Y=NH	<i>3a</i>	-490.349	-490.343	-493.346
		<u>-490.370</u>	<u>-490.363</u>	<u>-493.365</u>
		(-490.375)	(-490.368)	(-493.370)
	<i>3b</i>	-490.338	-490.332	-493.335
		<u>-490.365</u>	<u>-490.358</u>	<u>-493.360</u>
		(-490.371)	(-490.365)	(-493.366)
<i>3c</i>	-490.304	-490.297	-493.303	
	<u>-490.333</u>	<u>-490.324</u>	<u>-493.329</u>	
	(-490.340)	(-490.332)	(-493.336)	

3.2. Orbital analysis

It seemed justified to take only the DFT method results which give energies of the frontier molecular orbital (FMO) close to those of HF and MP2 methods and with the same order of magnitude. The FMOs energies as well as the HOMO-LUMO gaps obtained after complete

optimization in the gas phase and in solution, showed that the solvent does not influence the HOMO-LUMO gaps, where very similar results are obtained with a maximum deviation of 0.09 eV in both phases and in both solvents for all used compounds and methods. By confirming the results of the total energies, *isoindoline* compounds **1a**, **2a**

and **3a** possess the highest HOMO-LUMO gaps values, hence the highest stability of these compounds. While tautomers **1b**, **2b** and **3b** have sufficiently low energy gaps for electrons to have a non-negligible probability of crossing them by simple thermal excitation when the temperature increases, it is found that the complex **3a** has the

largest HOMO-LUMO gap (5.0 eV). Moreover compound **2b** has a high electron affinity of 2.8 eV in the gas phase and in solution, which reveals an important electro-acceptor character. While compound **1b** with ionization energy of 6.2 eV is ionized more easily and thus reflects a considerable electro-donor character.

Table 2. Frontier orbital energies (E, eV) and HOMO-LUMO gaps ($\Delta E_{HOMO-LUMO}$, eV) of studied tautomers given by the DFT method in the gas phase and in presence of THF (underlined values) and DMSO (values in parenthesis) solvents.

	<i>1a</i>	<i>1b</i>	<i>2a</i>	<i>2b</i>	<i>3a</i>	<i>3b</i>	<i>3c</i>
E_{HOMO} (eV)	-6.39 <u>-6.39</u> (-6.40)	-6.17 <u>-6.23</u> (-6.26)	-7.44 <u>-7.45</u> (-7.41)	-7.18 <u>-7.15</u> (-7.12)	-7.14 <u>-7.09</u> (-7.07)	-6.65 <u>-6.70</u> (-6.72)	-6.93 <u>-6.85</u> (-6.84)
E_{LUMO} (eV)	-1.79 <u>1.69</u> (-1.68)	-1.81 <u>-1.83</u> (-1.85)	-2.56 <u>-2.52</u> (-2.52)	-2.80 <u>-2.78</u> (-2.78)	-2.14 <u>-2.07</u> (-2.06)	-2.22 <u>-2.29</u> (-2.31)	-2.32 <u>-2.25</u> (-2.25)
$\Delta E_{HOMO-LUMO}$ (eV)	4.60 <u>4.70</u> (4.72)	4.36 <u>4.40</u> (4.41)	4.88 <u>4.93</u> (4.89)	4.38 <u>4.37</u> (4.34)	5.00 <u>5.02</u> (5.01)	4.43 <u>4.41</u> (4.41)	4.61 <u>4.60</u> (4.59)

3.3. Atomic charge analysis

The study of electronic properties of *isoindoline-isoindole* tautomers allowed determining some of their electronic parameters. In order to facilitate comparison between different tautomers, DFT method values were taken into consideration. Only the most representative values of atomic charges are compiled in Table 3. Numbering of studied compounds is shown in Fig. 1.

Results of the Mulliken atomic charges [20] indicated that the intracyclic heteroatoms of all studied compounds have a significant negative charge due to their high electronegativity and their participation in the aromaticity of the cycle. All obtained values showed that there is an alternation of positive and negative charges throughout each molecule. The N₂, X₁₀ and Y₁₁ atoms carrying the highest negative charges in all *isoindoline* and *isoindole* compounds; might indicate the high potential reactivity of these intracyclic and extracyclic heteroatoms. C₁ and C₃ atoms are positively charged and present a nucleophilic attack sites. It should also be noted that for *isoindolines* (form **a**), the highest negative charge is carried by the intracyclic nitrogen atom (N₂), indicating that

this center constitutes a favorable site for protonation. The positive charge in *isoindolines* is carried by C₁ and C₃ atoms which have the same values in the case of tautomers **1** and **2**, while C₃ atom is the most negatively charged in the case of tautomers **3**. For *isoindoles* (form **b**), the most negatively charged atom is that of number 10 (O₁₀ or N₁₀). The most positively charged atoms are C₁ (for **1** and **2** tautomeric couple) and C₃ (for **3** tautomeric couple).

The study in solution showed that the atomic charges were clearly influenced by DMSO and THF solvents in different ways. THF solvent increases significantly the positive charge of atoms while DMSO decreases it slightly. On the other hand, THF solvent decreases the negative charge of atoms which become more negatively charged while DMSO solvent increases it slightly. For example, the charge of C₁ atom of compound **1a** changes from 0.382 in gas phase to 0.643 in THF and to 0.357 in DMSO, while the charge of N₂ atom of the same compound passes from -0.759 in gas phase to -1.004 and -0.727 in THF and DMSO, respectively. This can certainly be explained by the polarity of the used solvent.

Table 3. Distributions of Mulliken atomic charges in the gas phase and in solvent, computed with the DFT method.

		Solvents		
		Gas phase	THF ($\epsilon=7.6$)	DMSO ($\epsilon=46.7$)
<i>1a/1b</i>	C ₁	0.357/0.409	0.643/0.361	0.382/0.404
	N ₂	-0.727/-0.515	-1.004/-0.441	-0.759/-0.438
	C ₃	0.357/0.198	0.643/0.399	0.382/0.214
	N ₁₀	-0.567/-0.764	-0.697/-0.431	-0.483/-0.754
	N ₁₁	-0.566/-0.560	-0.696/-0.570	-0.482/-0.494
<i>2a/2b</i>	C ₁	0.510/0.363	0.508/0.408	0.492/0.374
	N ₂	-0.709/-0.463	-0.708/-0.493	-0.705/-0.357
	C ₃	0.510/0.407	0.507/0.197	0.492/0.350
	O ₁₀	-0.461/-0.449	-0.449/-0.762	-0.389/-0.534
	O ₁₁	-0.460/-0.579	-0.448/-0.537	-0.388/-0.356
<i>3a/3b/3c</i>	C ₁	0.504/0.396/0.363	0.503/0.392/0.365	0.341/0.200/0.387
	N ₂	-0.712/-0.455/-0.514	-0.709/-0.430/-0.497	-0.700/-0.402/-0.425
	C ₃	0.352/0.181/0.406	0.350/0.176/0.402	0.495/0.370/0.364
	N ₁₀	-0.541/-0.527/-0.492	-0.527/-0.504/-0.471	-0.463/-0.475/-0.740
	O ₁₁	-0.494/-0.560/-0.741	-0.479/-0.589/-0.472	-0.406/-0.567/-0.385

3.4. Dipole moment

Dipole moments obtained in gas and solution phases by HF, MP2 and DFT methods increase from *isoindoline* form (**a**) to *isoindole* form (**b**). This change in dipole moment is mainly due to the modification of the electronic distribution, resulting in a strong polarity of *isoindoline* forms. Furthermore, the dipole moments increase with increasing electronegativity of the heteroatom. Note that the component μ_z of the dipole moment is practically zero, indicating that all the molecules are plane.

Solution study showed that the solvent increases the dipole moment values of tautomeric couples. These dipole moments are sensitive to solvents polarity. They are higher in a polar solvent (DMSO)

than in a less polar solvent (THF). *Isoindoline 1a* is the less polar with all methods and in all phases, indicating that it has good electron distribution. On the other hand, *isoindole 2b* is the most polar, which leads to a clear dissymmetry in the atomic charges distribution. It should also be noted that the dipole moment of all compounds according to all methods increases when passing from "a" form to "b" or "c" forms. This variation is mainly due to the distribution of charge, resulting in a high polarity of the bonds C---X and C---Y, especially in the case of the most electronegative heteroatom. Very close dipole moments were observed for "b" and "c" forms which have the largest dipole moments values.

Table 4. Dipole moments (in Debye) of studied tautomers in the gas phase and in presence of THF (underlined values) and DMSO (values in brackets) solvents.

		Methods		
		HF	MP2	DFT
Tautomer 1	<i>1a/1b</i>	0.88/6.39	0.77/6.77	1.02/5.96
X=Y=NH		<u>1.28/8.92</u>	<u>1.18/9.26</u>	<u>1.60/8.48</u>
		(1.43)/(9.57)	(1.43)/(9.86)	(1.80)/(9.14)
Tautomer 2	<i>2a/2b</i>	3.39/7.86	3.66/8.23	3.11/7.38
X=Y=O		<u>4.17/10.75</u>	<u>4.47/10.88</u>	<u>3.88/10.34</u>
		(4.30)/(11.52)	(4.61)/(11.52)	(4.02)/(11.16)

Table 4 continue.

	HF	MP2	DFT
Tautomer 3	4.55/7.40/7.50	4.79/7.76/7.87	4.18/7.05/6.98
X=O	<u>3a/3b/3c</u> <u>5.80/10.52/9.96</u>	<u>6.04/10.48/10.42</u>	<u>5.48/12.24/9.47</u>
Y=NH	(6.09)/(11.34)/(10.60)	(6.33)/(11.13)/(11.04)	(5.80)/(11.11)/(10.13)

3.5. Equilibrium constants and molar fractions

Obtained thermodynamic quantities were calculated at T=298.15 K and under 1 atm pressure. Equilibrium constants results were calculated as a

difference between the standard free enthalpies $\Delta G_{a,b/c}^{\circ}$ of the two forms *a* and *b* (or *a* and *c*).

Table 5. Equilibrium constants of studied tautomers in the gas phase and in presence of THF (underlined values) and DMSO (values in brackets) solvents.

	$K_{1a/1b}$	$K_{2a/2b}$	$K_{3a/3b}$	$K_{3a/3c}$
HF	2.24 10 ⁻⁴	1.13 10 ⁻²¹	3.90 10 ⁻⁵	1.31 10 ⁻¹⁶
	<u>8.70 10⁻³</u>	<u>1.72 10⁻¹⁸</u>	<u>3.42 10⁻³</u>	<u>1.95 10⁻¹⁵</u>
	(1.67 10 ⁻²)	(3.36 10 ⁻¹⁷)	(1.75 10 ⁻²)	(6.89 10 ⁻¹⁵)
MP2	1.29 10 ⁻⁴	3.38 10 ⁻²²	1.52 10 ⁻⁵	6.37 10 ⁻¹⁷
	<u>5.83 10⁻³</u>	<u>1.73 10⁻¹⁹</u>	<u>2.89 10⁻³</u>	<u>1.55 10⁻¹⁶</u>
	(1.59 10 ⁻²)	(2.02 10 ⁻¹⁸)	(1.24 10 ⁻²)	(4.55 10 ⁻¹⁶)
DFT	1.99 10 ⁻³	1.43 10 ⁻²⁰	4.80 10 ⁻⁵	1.91 10 ⁻¹⁵
	<u>2.28 10⁻²</u>	<u>8.61 10⁻¹⁸</u>	<u>2.49 10⁻³</u>	<u>1.47 10⁻¹⁴</u>
	(3.15 10 ⁻²)	(1.44 10 ⁻¹⁶)	(1.03 10 ⁻²)	(5.05 10 ⁻¹⁴)

The obtained results in gas phase and in presence of the two solvents indicated that equilibrium constants values were less than 1 for all studied tautomeric equilibria. This result as well as that of molar fractions (Table 6) confirms the results of total energies showing that *isoindoline* forms (*a*) are predominant. Indeed, we find results

experimentally known especially for *isoindoline-isoindole* equilibrium, in the case of *1a/1b* tautomeric couple which exists mainly in *isoindoline-1,3-diimine* form (*1a*) [21,22]. In a similar study performed for *2a/2b* tautomeric couple, the same result was observed experimentally by Singh and all for phthalimide or

Table 6. Molar fractions of studied tautomers in the gas phase and in the presence of THF (underlined values) and DMSO (values in brackets) solvents.

	[1a]/[1b]	[2a]/[2b]	[3a]/[3b]	[3a]/[3c]
HF	1.00/0.00	1.00/0.00	1.00/0.00	1.00/0.00
	<u>0.99/0.01</u>	<u>1.00/0.00</u>	<u>1.00/0.00</u>	<u>1.00/0.00</u>
	(0.98/0.02)	(1.00/0.00)	(0.98/0.02)	(1.00/0.00)
MP2	1.00/0.00	1.00/0.00	1.00/0.00	1.00/0.00
	<u>0.99/0.01</u>	<u>1.00/0.00</u>	<u>1.00/0.00</u>	<u>1.00/0.00</u>
	(0.98/0.02)	(1.00/0.00)	(0.99/0.01)	(1.00/0.00)
DFT	1.00/0.00	1.00/0.00	1.00/0.00	1.00/0.00
	<u>0.98/0.02</u>	<u>1.00/0.00</u>	<u>1.00/0.00</u>	<u>1.00/0.00</u>
	(0.97/0.03)	(1.00/0.00)	(0.99/0.01)	(1.00/0.00)

The comparison between values of equilibrium constants in solution and in gas phases, showed that the solvent influences the equilibrium displacements of *isoindoline* towards *isoindole*. Equilibrium constants increased when passing

from gaseous to liquid state in the presence of THF and DMSO solvents; DMSO values were the largest. The stability order of the tautomeric equilibrium is generally respected when the equilibrium constant is calculated in HF, MP2 and

DFT. The equilibrium constants for tautomeric couples *2a/2b* and *3a/3c* are very low in comparison with *1a/1b* and *3a/3c* couples and this for all states and used methods.

4. Conclusion

In this theoretical contribution, the structure and reactivity of heterocyclic compounds of *isoindoline-isoindole* type have been studied and discussed. This work presents an attempt to demonstrate the role of the extracyclic heteroatom X and Y (= NH, O) on the structural and electronic properties of the different tautomers using three different methods: HF, MP2 and DFT. Calculations were carried out in the gas phase and in solution with the presence of two solvents of different polarity (THF and DMSO). This study permitted the determination and the comparison of the relative stability of different conformations in solution and in gas phases as well as the study of possible equilibrium displacements. The results of total energies and HOMO-LUMO gaps showed, that *isoindoline* forms (*1a*, *2a* and *3a*) were the most stable which is in agreement with available experimental results. Mulliken atomic charges indicated that N₂ atom (for *isoindolines*) and O₁₀ or N₁₀ atoms (for *isoindoles*) were the favorable sites for protonation and electrophilic attack, whereas C₁ and C₃ atoms are the sites of nucleophilic attack. Values of dipole moment obtained by the three methods were increased from *isoindoline* (*a*) to *isoindole* (*b*). This change in dipole moment was mainly due to the modification of the electronic distribution, resulting in a strong polarity of *isoindoline* forms. The use of HF and MP2 methods with more extensive basis sets such as 6-311++G(d,p), which also introduces polarization functions, leads to results comparable to those of DFT method. The HF method gives reliable results and can be used in chemical reactivity because of its important advantages especially in terms of speed of calculation. However, the use of the density functional theory method (DFT) is more accurate and provides to good results despite that it is more cpu demanding.

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