Research Article

Investigation of the Stability of Indole and Analogue Rings Using Quantum Mechanics Computation

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ABSTRACT

*This study aimed at investigating factors affecting the stability as well as structural properties of different indole isomers based on Density Functional Theory (DFT) calculations at B3LYP/6-311+G** theoretical level. Important thermochemical parameters (enthalpy, entropy and free energy of Gibbs) were employed to determine the stability on this isomer series. Qualitative relationships between relative stabilities for indole, isoindole and indolizine were obtained. In addition, the length of bond's average was used as parameter to corroborate thermochemical data. Finally, HOMO-LUMO gaps (ΔE), electro-negativity (μ), hardness (η), softness (ζ), electrophilicity (ω) and structural parameters were also calculated in the same theoretical level. The results show that indolizine is the most stable than isoindole and indole systems, respectively.*

Keywords: Indole, Isoindole, Indolizine, DFT, stability

INTRODUCTION

The indole ring can be found in a large number of compounds with biological and industrial importance [1,2]. The indole structure is present in many organic compounds such as in the amino-acid tryptophan, and in a large variety of alkaloids, including drugs or drug candidates with interesting and promising therapeutic use, for central nervous system disorders, respiratory disorders, obesity, osteoporosis, neurodegenerative disorders and cerebellar disorders, acute and chronic pain, osteoarthritis, rheumatoid arthritis, cancer, asthma, bronchitis, Pick's disease and glaucoma, heart diseases, obesity or antithrombotic with potential for the treatment and prevention of thrombus-embolic diseases [1]. In industry, they are widely used especially as dyes, perfume fixatives and have potential as corrosion inhibitors [1,2].

Isoindole compounds that are able to undergo intra-molecular hydrogen bonding are significant contributors in diverse applications for example, high-energy radiation detectors, ultra-violet photostabilizers, fluorescent probes and laser dyes [3]. Substituted isoindoles, specially N-substituted ones, can be used as organic light-emitting diodes (OLEDs), because they are more stable than the non-substituted ones [3,4]. Additionally, this compounds have prominent effects on molecular structures and properties in terms of lipophilicity, membrane permeability, water solubility and rationales for drug design [3].

Indolizines are important chemical compounds having an important place both in organic synthesis and in biochemistry as they represent promising molecules with potential applications in the fields of pharmaceuticals, total synthesis, organic materials as novel fluorescent sensors and as key intermediates in organic synthesis [5]. In

addition, indolizine showed potent anti-mitotic and anti-proliferative activity, and that this compound can serve as important tool for the development of anticancer therapeutics [5,6].

Theoretical methods based on quantum chemistry are useful for predicting important properties that, in general, confirm the experimental data [7]. The thermochemical parameters, especially the enthalpies of formation, have great importance, because they are needed, for example, to calculate the amount of energy involved in chemical processes, to calculate other thermodynamic functions and to evaluate and interpret the stability of the molecules [1].

In the present work, computational techniques, based on B3LYP/6-311+G** theoretical level, were employed to obtain additional thermochemical knowledge about indole, isoindole e indolizine systems and their structural stability. Furthermore, the properties of structural geometry, frontier orbitals (HOMO and LUMO), energy gap, electronegativity, electrophilicity, hardness, softness for all compound were determined using B3LYP/6-311+G** level of theory [8].

EXPERIMENTAL SECTION

In this study, all calculations were performed using the SPARTAN version 14 program [8]. Starting geometries of compound were taken from ARGUSLAB program [9]. The molecular structure of the compound in the ground state was optimized using 6-311+G level** of theory [10,11].

In Density Functional Theory (DFT) calculations, hybrids functional were used, the Becke's three gradient - corrected exchanges terms. For the compounds, vibration frequencies were calculated using DFT/B3LYP with 6-311+G level** basis set [10,11]. The DFT method was chosen for this study because it is faster, less computationally intensive, takes electron correlation into account and has a precise accuracy in reproducing experimental data [12]. In addition, highest occupied molecular orbital (HOMO), lowest unoccupied molecular orbital (LUMO), energy gap ($\Delta E = E_{HOMO} - E_{LUMO}$), electronegativity ($\mu$), hardness ($\eta$), softness ($\zeta$), and electrophilicity (ω) of the compounds were calculated using 6-311+G level** of theory [8]. The Equations are shown below:

$$\mu \sim -x = -\frac{I+A}{2} \ (Electronegativity)$$

$$\eta \sim \frac{I-A}{2} \ (Chemical\ hardness)$$

$$\zeta = \frac{I}{2\eta} \ (Chemical\ Softness)$$

$$\psi = \frac{\mu^2}{2\eta} \ (Electrophilicity\ index)$$

where *I* and *A* is ionization potential and electron affinity, $I = -E_{HOMO}$ and $A = E_{LUMO}$, respectively [8,13]. Molecules which have a large HOMO-LUMO energy gap are called "hard" and which have a small HOMO-LUMO energy gap are called "soft" [8].

Molecules with larger electrophilicity index, means electron acceptor, and molecules with smaller electrophilicity index, means electron donor [10].

RESULTS AND DISCUSSION

The relation between stability of three isomers indole's analogues (Figure 1) is investigated employing different parameters such as length of bonds, energy of Gibbs, hardness, softness electronegativity and electrophilicity. In addition, a comparison between data and results from quantum mechanics calculation was performed to explain the stability of the indole's analogues and their relation with aromaticity.
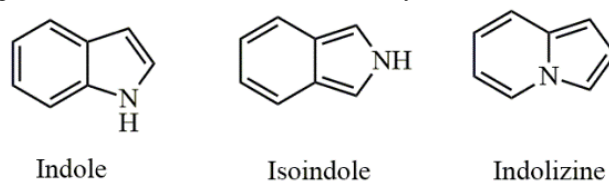

Indole   Isoindole   Indolizine

Figure 1. Different Indole analogues

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An alternative, total energy, is the heat of a hypothetical reaction that creates a molecule from a collection of separated nucleus and electrons [14]. Like the heat of formation, total energy cannot be measured directly, and is used solely to provide a standard method for expressing and comparing energies [14]. Total energies are always negative numbers and, in comparison with the energies of chemical bonds, are very large. It is used to calculate the thermochemistry of a balanced chemical reaction (reactant 1 + reactant 2 + . . . → product 1 + product 2 + . . .):

$$\Delta E_{(reaction)} = E_{product\ 1} + E_{product\ 2} + ... - E_{reactant\ 1} - E_{reactant\ 2} - ...$$

A negative ΔE indicates an exothermic (thermodynamically favorable) reaction, while a positive ΔE an endothermic (thermodynamically unfavorable) reaction [10,14].

Gibbs energies determination, in order to take proper account of the role of entropy was calculated starting from the equilibrium constant (K_{eq}), which according to the Boltzmann equation, is related to the Gibbs energy (ΔG), as below [14]:

$$K_{eq} = exp(- \Delta G/RT)$$

Here R is the gas constant and T is the temperature (in Kelvin). ΔG has two components, the enthalpy of reaction (ΔH) and the entropy of reaction (ΔS) [10,14]. These are defined as follows:

$$\Delta G = \Delta H - T\Delta S$$

where, ΔH and ΔS parameters are determined by the equations:

$$\Delta H \approx \Delta E = E_{product\ 1} + E_{product\ 2} + ... - E_{reactant\ 1} - E_{reactant\ 2} - ...$$

$$\Delta S = S_{product\ 1} + S_{product\ 2} + ... - S_{reactant\ 1} - S_{reactant\ 2} - ...$$

In general terms, free Gibbs energy is related with stability of a molecule, if this energy value is small, then that molecule has a good stability [1,10,11]. Among these isomers, it is founded that the most stable is indolizine system, which has the smallest amount of free Gibbs energy, followed by isoindole and indole (Table 1).

Table 1. Calculated ΔG values for indole's analogues by DFT-B3LYP/6-311+G**

Compound	ΔH (kJ mol-1)	ΔS (kJ mol-1)	*ΔG (kJ mol-1)
Indole	8.485	43.329	-12753.083
Isoindole	8.790	43.978	-13096.66
Indolizine	11.292	57.931	-17252.343

*: values calculated by the equation $\Delta G = \Delta H - T\Delta S$, where T= 298.15 kelvin.

In general, all the optimized geometries for the compounds kept good planarity. This result is a great indication for the validity of the computational method [11]. Among several methods to explain the stability of molecules, the length of bonds appears as one of the most effective parameters that can be used to justify this property [10].

For this type of study, the length of bond's average parameter was measured and specified for each compound and the results are shown in Figure 2. The similarity of the derivatives to the parent molecule explains the similarity in bond lengths in all molecules [11].
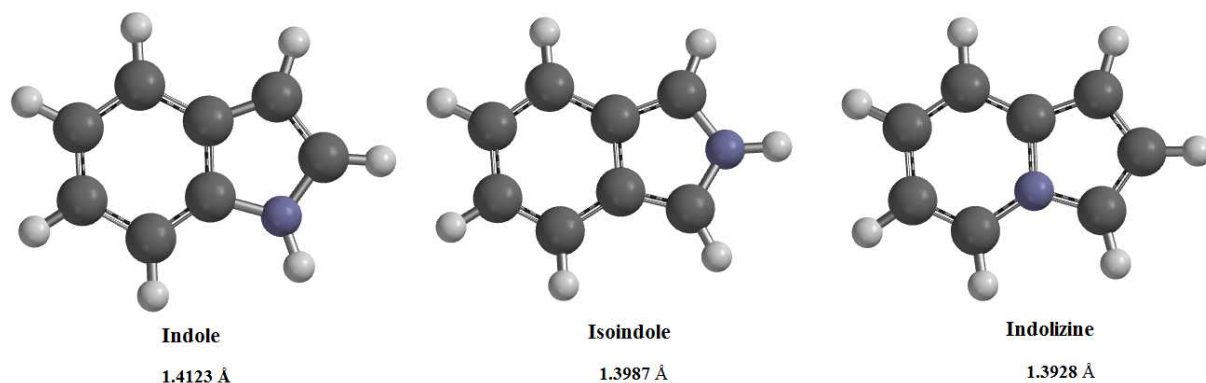

Indole	Isoindole	Indolizine
1.4123 Å	1.3987 Å	1.3928 Å

Figure 2. Measured average amounts (in Å) for length of bonds for indole's analogues

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In according with Karimi et al. [10], smaller length of bonds mean that the molecule has a better stability. In sense, it was observed that the indolizine system is the most stable compound in this study, because has the least amount of length bonds, which is 1.3928 Ångström (Å). Therefore, this result corroborates with the free energy of Gibbs values, suggesting a good stability for this compound.

Based on the measured average amounts (in *Å*) for length of bonds, the stability follows this order:

Indolizine > Isoindole > Indole

The hardness is related with the stability of a molecule, for example, if a molecule is very "hard", so that is very stable [10]. It measures the resistance of a compound to changes in the electron density distribution or to electron charge transfer [11].

Considering the results in Table 2 the highest negative values of hardness, 2.15 electronvolt (eV), belong to isoindole and indolizine. And the least negative hardness value belongs to indole, with the amount of -1.31 eV. The calculated results for molecule's hardness can justify the good stability for the indolizine compound.

Table 2. Values for electronegativity (μ), electrophilicity (ω), hardness (η), softness (ζ) calculated in electron volt (eV)

Parameters	Indole	Isoindole	Indolizine
EHOMO	-2.75	-5.2	-5.34
ELUMO	-0.13	-0.9	-1.04
μ	-1.44	-3.05	-3.19
ω	-0.791	-2.16	-2.366
η	-1.31	-2.15	-2.15
ζ	1.049	1.209	1.241

The electronic chemical potential is defined as the negative of electronegativity of a molecule [11]. The smaller the electronic chemical potential value (μ), the more stable is the compound. Table 2 lists the calculated electronic chemical potential values for the three studied compounds. It is clear that since indolizine has the lowest μ value (-3.19 eV), it is expected to be the most stable while isoindole (-3.05 eV) and indole (-1.44 eV) systems.

The electrophilicity parameter (ω) is calculated using the electronic chemical potential or electronegativity (μ) and the chemical hardness (η) [11]. In a chemical process, it measures the capacity of a species to accept electrons and therefore measures the stabilization in energy after a system accepts additional electronic charges [11]. Among these compounds, the indolizine has the lowest ω value (-2.66 eV), suggesting that indolizine is a strongest electrophile. The electrophilic order can be considered as:

Indolizine > Isoindole > Indole

The most important orbitals in a molecule are the frontier molecular orbitals, called HOMO and LUMO [8,15–17]. HOMO implies that the outermost orbital filled by electrons, and behaves as an electron donor while LUMO can be thought as the first empty innermost orbital unfilled by electron and behaves as an electron acceptor [8,12,13]. The energy of the HOMO is directly related to the ionization potential and represents the ability of electron giving. But, LUMO energy is directly related to the electron affinity and represents the ability of electron accepting.

Quantum chemical calculations, in particular, molecular orbital calculations by density functional calculations, may be called on to furnish data to parameterize empirical energy functions for use in molecular mechanics and/or molecular dynamics calculations. Most important are data relating to torsional motions [14]. The function chosen to represent the energy of rotation about a single bond needs to reflect the inherent periodicity, it must repeat itself in 360°. In this step was selected a truncated Fourier series of calculations, as below:

$$E^{torsion}(\omega) = k^{torsion1}(1 - \cos(\omega - \omega^{eq})) + k^{torsion2}(1 - \cos2(\omega - \omega^{eq})) + k^{torsion3}(1 - \cos3(\omega - \omega^{eq})) + \ldots k^{torsionN}(1 - \cos N(\omega - \omega^{eq}))$$

where, ω^{eq} is the ideal dihedral angle and $k^{torsion1}$, $k^{torsion2}$, $k^{torsion3}$... and $k^{torsionN}$ are energetic parameters for each bond [14].

The formed energy gap between HOMO and LUMO indicates the molecular chemical stability [8,14,15]. The energy gap between HOMO and LUMO is a critical parameter to determine molecular electrical transport properties [8].

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The gaps of energy of the one electron excitation from HOMO to LUMO for indole, isoindole and indolizine were calculated about -2.62, -4.3 ad -4.3 eV, respectively. This large HOMO-LUMO gap is an indication of good stability and a high chemical hardness for isoindole and indolizine systems. For all systems, 3D-plots of HOMO and LUMO were shown in Figure 3.
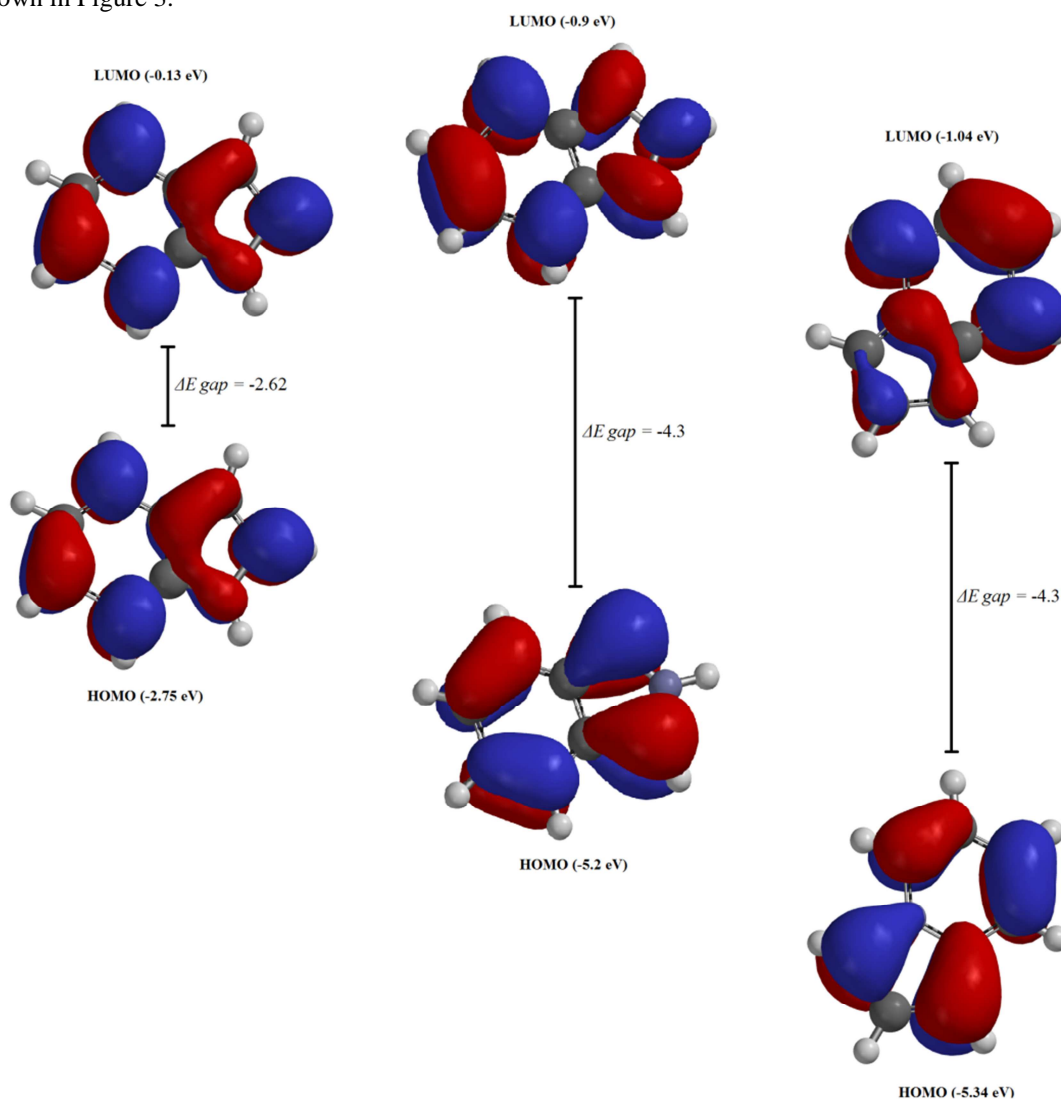

Figure 3. *ΔE$_{HOMO - LUMO}$* **gaps for indole, isoindole and indolizine systems**

CONCLUSİON

In indole's analogues, the indolizine is the most stable system. This can be justified by the calculation of energy (*ΔG, ΔH* and *ΔS*), average of length of bonds, as well as hardness/softness (*η* and *ζ*), electronic potentials (*μ* and *ω*) and HOMO-LUMO energies gap (*ΔE*).

Acknowledgements

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