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A study on structural aspects of indoline-2, 3-dione-3-oxime: Experimental and theoretical approach

K. Laxmi

Department of Chemistry, Chaitanya Bharathi Institute of Technology(CBIT),Gandipet, Hyderabad -500 075

Email address:
katangurulaxmi@gmail.com

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Abstract: Indoline-2,3-dione-3-oxime(IDOX) was synthesized and characterized by IR, mass and ^{1}H-NMR. The HyperChem 7.5 software was used for quantum mechanical calculations. The geometry optimization was carried out using Ab Initio method. The theoretical spectral data and QSAR parameters were generated with semi empirical single point AM1 method. The HOMO and LUMO frontier orbital energies were also computed for the optimized keto and enol forms of IDOX molecule. The experimental and theoretical spectral data are nearly comparable. The pH- metry studies indicated presence of one dissociable proton in IDOX.

Keywords: IDOX, Hyperchem 7.5 Software, QSAR

1. Introduction

Isatins (2,3-indoline-dione) are an important group of heterocyclic compounds which are biologically active and of significant importance in medicinal chemistry[1]. A literature survey identified several isatin derivatives in the development phase as potential new drugs. Isatin derivatives that have been reported to show considerable pharmacological actions such as antimicrobial, anticancer, antiviral, anticonvulsant, antiinflammatory and analgesic[2]. Indoline-2,3-dione-3-oxime abbreviated as IDOX synthesized by the condensation of isatin with hydroxyl amine was found to have number of applications.

Epilepsy is a brain disorder that causes people to have recurrent seizure. A large number of populations of different age groups and sex are affected by this disease. The estimated number of people in 2011 with epilepsy would be 11.5 million in India. The number of new cases with epilepsy, each year would be close to half a million.

Therefore, studies have been carried out for designing of newer antiepileptic drugs with reduced neurotoxicity. Recently it has been found that isatin is a novel template for designing of new anticonvulsants[3-5].

Indoline-2,3-dione-3-oxime (Isatin -3-oxime)was found to have anticonvulsant activity[6]. Literature studies revealed that anticonvulsant screening of Indoline-2,3-dione-3-oxime (IDOX)was performed by Maximal Electroshock (MES) model at dosage of 30, 100 and 300 mgkg^{-1}. IDOX was found to be active in the MES test at a lower dose of 100mgkg^{-1} .This compound IDOX was also found to be more potent than standard drug sodium valproate.

In view of biological importance of Indoline-2,3-dione-3-oxime (IDOX) ,in the present paper we report the structural aspects of IDOX in detail, both experimentally and theoretically using hyperchem 7.5 software.

2. Experimental

IDOX was prepared by refluxing an ethanolic solution (50ml) of isatin (8.5 g,0.057M) and hydroxyl amine(4.0g,0.028m) for 45 min. The reaction mixture was cooled and left aside for 1 h. A yellow crystalline product was obtained. The product was filtered and recrystallised from ethanol. Yield 75%, m.p. 243°C.Molecular weight of the ligand from mass spectra was found to be 162.

3. Physical Measurements

IR spectrum of Indoline-2,3-dione-3-oxime (IDOX) was recorded in KBr phase on Perkin-Elmer Model no. 435. ^{1}H spectra of IDOX in $CDCl_3$ and DMsO-d_6 using tetra methyl silane (TMS) as standard was recorded on Bruker WH (270MHz) spectrometer. Mass spectra of IDOX was recorded on Micro Mass V.G70-70H spectrometer operating at 70ev using direct inlet system.

The proton-ligand dissociation constant of IDOX was determined potentiometrically using Irwing –Rossoti pH

titration technique. The pH measurements were made with a Digisun DI-707 digital pH meter, consisting of a combined glass electrode and calomel electrode.

The molecule IDOX was built by Hyperchem tools [7-12], then the geometry optimization was carried out by employing Ab Initio optimized semi empirical single point AM1 method.

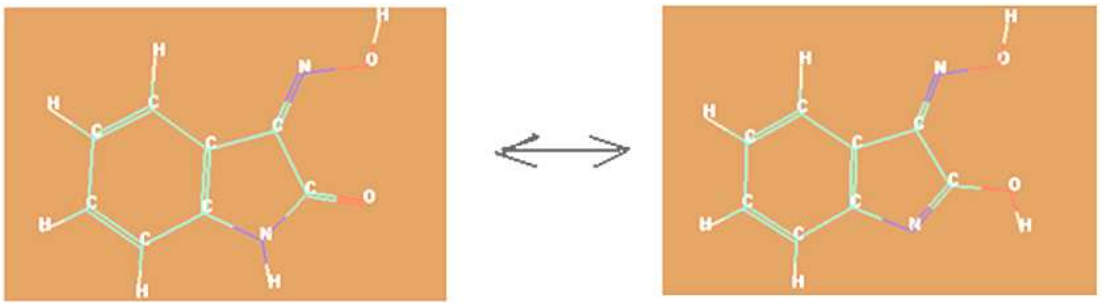
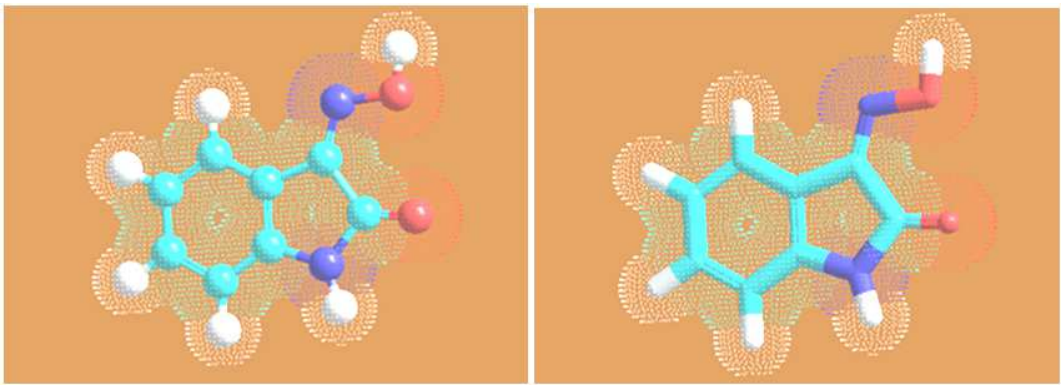


Fig. 1. *(a) keto form of IDOX (b) enol form of IDOX*

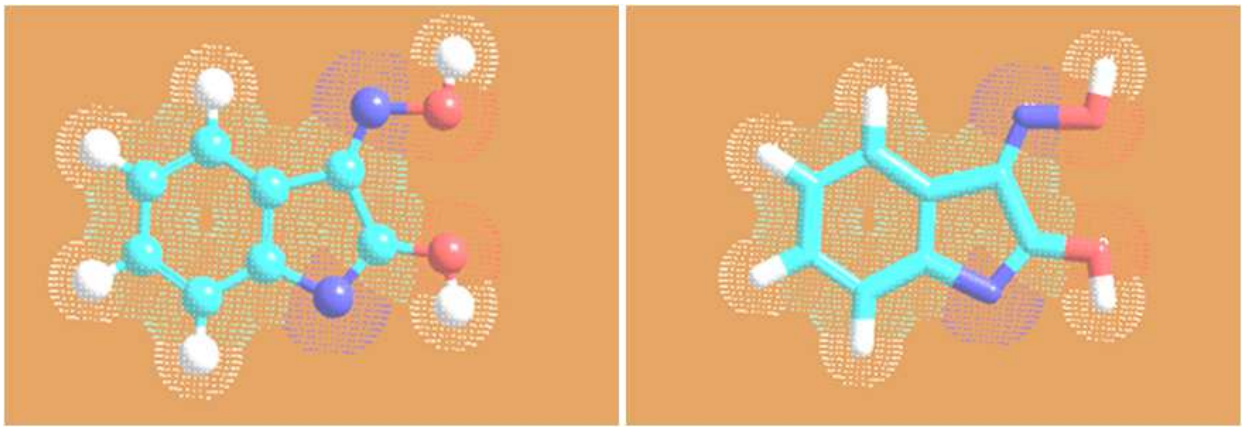


ball and cylinders tubes model

Fig.2. *Structure of keto form of Indoline-2,3-dione-3-oxime(IDOX)*

4. Results and Discussion

The HyperChem 7.5 software was used for quantum mechanical calculations to generate spectral data. After building molecule by Hyperchem tools, the geometry optimization was done using Ab Initio method(Figs.1 to 3). The spectral data is generated with single point AM1 method approximation, for both keto and enol forms of IHA. The calculations are sensitive to the values of input parameters such as molecular geometry, bond lengths and values of coulombic, resonance and overlap integrals.



ball and cylinders model tubes model

Fig.3. *Structure of enol form of Indoline-2,3-dione-3-oxime(IDOX)*

From Potentiometric titrations it has been observed that there is only one dissociable proton present in the ligand IDOX. This is attributable to dissociation of proton from the ligand in enol form. From the calculations the pKa value of IDOX was found to be 10.00 in 70%(v/v) DMF-water medium.

5. Spectral Studies

5.1. IR Spectral Data of IDOX

The experimental IR spectral data of the ligand IDOX is compared with the data generated for both keto and enol forms of IDOX by Ab Initio optimized semi empirical single point AM1 method(Figs.4,5).

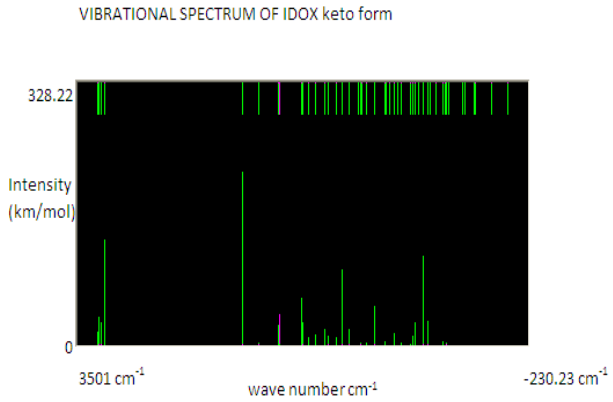


Fig.4. *IR spectrum of IDOX keto form*

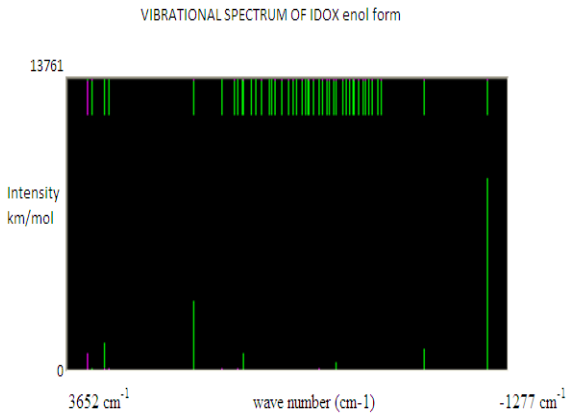


Fig.5. *IR spectrum of IDOX enol form*

In IR spectrum[13-17] of IDOX recorded experimentally the peaks appeared at 3180 cm^{-1} (υN-OH), 3050 cm^{-1} (υN-H), 2896 cm^{-1} (υC-H), 1713 cm^{-1} (υC=O). The IR spectral data obtained experimentally is in good agreement with the data generated by Ab Initio optimized semi empirical single point AM1 method(Table.1)

Table 1. *IR Spectral data of IDOX (Experimental)*/ keto & enol forms of IDOX*

	υN-OH	**υN-H**	**υC=O**	**υC-H**	**$\upsilon_{C=N}$**	**$\upsilon_{C=C}$**	**υ_{O-H}**	**υ_{N-H} bending**
IDOX*	3180 cm^{-1}	3050 cm^{-1}	1713 cm^{-1}	2896 cm^{-1}	1633 cm^{-1}	1823-1606 cm^{-1}	1408 cm^{-1}	1324 cm^{-1}
IDOX keto	3331 cm^{-1}	3274 cm^{-1}	1825 cm^{-1}	3305--2133 cm^{-1}	1647 cm^{-1}	1839-1647 cm^{-1}	1456 cm^{-1}	1304 cm^{-1}
IDOX enol	3428 cm^{-1}			3238--2238 cm^{-1}	1693,1686 cm^{-1}	1920-1786 cm^{-1}	1479 cm^{-1}	

The mass spectrum [13-17] of the title compound IDOX showed the molecular ion peak M^+ at m/z 162(100) which is also base peak. This mass of IDOX is in good agreement with mass determined by QSAR studies for keto and enol forms of IDOX ,which is recorded with single point approximation .

Mass spectral data of IDOX also indicates its composition is of $C_8H_6N_2O_2$ which is also in agreement with elemental analysis data.(Found : C= 59.62, H=3.72, N=17.39% while calcd C=59.25; H=3.70; N=17.28%)

5.2. ^{1}H NMR Spectral Data of IDOX

To establish the existence of keto-enol tautomerism in Indoline-2,3-dione-3-oxime(IDOX) both keto and enol forms of IHA were built by using Hyperchem.

The experimental ^{1}H-NMR spectral data of the ligand IDOX is compared with the data generated by Ab Initio optimized semi empirical single point AM1 method.

^{1}H-NMR Spectral data of keto and enol forms of IDOX were recorded with single point approximation. The results are shown in figs 6,7 and Tables.2,3 as follows

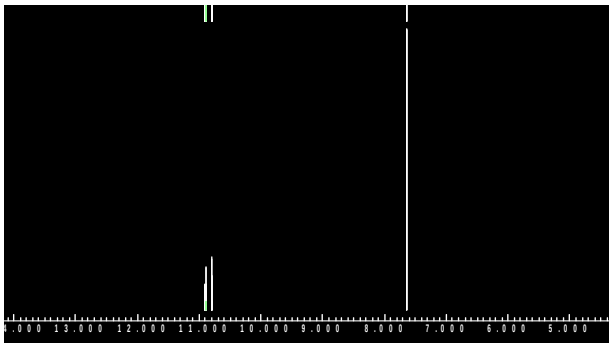


Fig. 6. *^{1}H-NMR spectrum of IDOX keto form*

Table.2. *^{1}H-NMR spectral data of IDOX keto form*

Index	**1-13(H)**	**1-14(H)**	**1-15(H)**	**1-16(H)**	**1-17(H)**	**1-18(H)**
Shielding	16.305	16.305	16.305	16.305	13.054	13.154
Shift	7.646	7.646	7.646	7.646	10.897	10.797
Tau	2.354	2.354	2.354	2.354	-0.897	-0.797

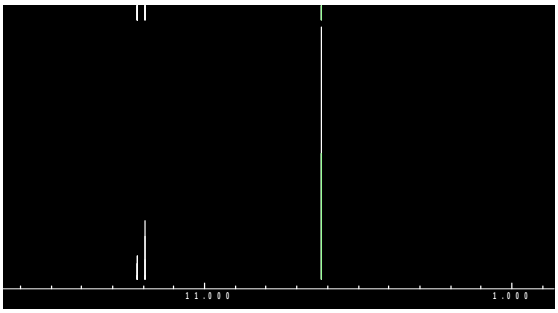


Fig. 7. *^{1}H-NMR spectrum of IDOX enol form*

Table.3. *^{1}H-NMR spectral data of IDOX enol form*

Index	1-13(H)	1-14(H)	1-15(H)	1-16(H)	1-17(H)	1-18(H)
Shielding	16.748	16.748	16.748	16.748	11.02	10.77
Shift	7.203	7.203	7.203	7.203	12.931	13.181
Tau	2.797	2.797	2.797	2.797	-2.931	-3.181

Table.4. *^{1}H NMR Spectral data of IDOX (Experimental)*/ keto & enol forms of IDOX*

Compound	δ ,=N-OH	δ -NH	δ enolic –OH	$\delta(CH)_{aromatic}$
IDOX*	10.59 ppm		13.2 ppm enolic –OH	7.30-8.47ppm
IDOX keto	10.797 ppm	10.897 ppm		7.644 ppm
IDOX enol	13.181 ppm		12.93 ppm	7.203 ppm

^{1}H NMR spectrum[13-17] of IDOX at 24 °C in $CDCl_3$ + 3drops of DMSO-d6 shows peaks at δ 13.2 ppm (1H ,enolic –OH), δ 10.59ppm (1H,=N-OH) and δ 7.30-8.47 (4H,Ar-H).

^{1}H-NMR spectral data obtained experimentally is in good agreement with the data generated by Ab Initio optimized semi empirical single point AM1 method (Table.4).

The above spectral data recorded for both keto and enol forms of IDOX,is in good agreement with the experimental spectral data . This strongly confirms the existence of keto-enol tautomerism in IDOX.

5.3. Quantitative structure activity relationship studies (QSAR studies)

QSAR Properties allows calculation and estimation of a variety of molecular descriptors commonly used in Quantitative structure activity relationship (QSAR)studies[18,19]. Most of the methods were developed for and are primarily applicable to organic molecules. This analysis represents an attempt to relate structural descriptors of compounds with their physicochemical properties and biological activities.

Table 5. *QSAR properties of Indoline-2,3-dione-3-oxime(IDOX)*

QSAR properties	keto form of IDOX	enol form of IDOX
Net charge	0.00	0.00
Surface area (approx)	246.73 °A^2	233.75 °A^2
Surface area (Grid)	323.64 °A^2	323.09 °A^2
Volume	483.41 °A^3	487.02 °A^3
Hydration energy	-12.34 kcal/mol	-16.07 kcal/mol
Log P	0.39	1.43
Refractivity	46.19°A^3	46.42 °A^3
Polarisability	16.34°A^3	16.47 °A^3
Mass	162.15 amu	162.15 amu

QSAR method included data collection , molecular descriptor selection correlation model development, and finally model evaluation. QSAR studies have predictive ability and simultaneously provide deeper insight.The main success of the QSAR method is the possibility to estimate the characteristics of new chemical compounds.

QSAR properties like surface area, volume, hydration energy, log P, refractivity, polarisability, mass, total energy etc. of keto and enol forms of IDOX were determined by single point AM1 method. (Table 5)

Table 6. *Molecular properties of Indoline-2,3-dione-3-oxime(IDOX)*

Molecular properties	keto form of IDOX	enol form of IDOX
Total energy	-49784.78 kcal/mol	-49777.968 kcal/mol
Binding energy	-2004.237 kcal/mol	-1997.422 kcal/mol
Heat of formation	20.61 kcal/mol	27.43 kcal/mol
Electronic energy	-232715.51 kcal/mol	-231853.1875 kcal/mol
Nuclear energy	182930.73 kcal/mol	182075.2188 kcal/mol
MP2 energy	-421.3955078 kcal/mol	-419.8165283 kcal/mol
Dipole moment	3.16 D	1.2984 D
Dipole X	-3.095 D	0.19053D
Dipole Y	0.5055D	-1.28433 D
Dipole Z	- 0.0002D	0.00000 D
RMS gradient	24.63 kcal/°A mol	3.78 kcal/°A mol
Gradient X	0.00061 kcal/°A mol	0.0000 kcal/°A mol
Gradient Y	10.27 kcal/°A mol	2.49713 kcal/°A mol
Gradient Z	22.38 kcal/°A mol	2.83741 kcal/°A mol

According to the AM1 calculation binding energy of keto and enol forms IDOX is about -2004.237 kcal/mol and-1997.422 kcal/mol respectively.The heat of formation of keto and enol forms IDOX is about 20.61 kcal/mol and

27.43 kcal/mol kcal/mol respectively and it is endothermic. Dipole moment of keto and enol forms IDOX is 3.16 D and 1.2984 D. respectively. The trends of the molecular properties(Table.6) obtained by calculations are in good agreement with the experimental results[7-12].

This analysis represents an attempt to relate structural descriptors of compounds with their physicochemical properties and biological activities.

6. Quantum Chemical Studies

Quantum chemical calculations have been widely used to study reaction mechanisms. Figs 8-11 shows the values of some quantum chemical parameters, namely the energy of the highest occupied molecular orbital (E_{HOMO}), energy of the lowest unoccupied molecular orbital (E_{LUMO}), the energy gap ($E_{LUMO-HOMO}$). These values of E_{HOMO}, E_{LUMO}& $E_{LUMO-HOMO}$ for keto form of Indoline-2,3-dione-3-oxime(IDOX) were found to be -9.1405 eV, -0.7536139 eV & 8.3868 eV respectively. (Figs 8,9)

While the values of E_{HOMO}, E_{LUMO}& $E_{LUMO-HOMO}$ for enol form of Indoline-2,3-dione-3-oxime(IDOX) were found to be -8.979 eV, -0.983402 eV & 7.9955 eV respectively. (Figs 10,11)

The frontier molecular orbital energies (*i.e.*, E_{HOMO} and E_{LUMO})[20,21] are significant parameters for the prediction of the reactivity of a chemical species. The E_{HOMO} is often associated with the electron donating ability of a molecule. The E_{LUMO} indicates the ability of the molecule to accept electrons.

Therefore higher value of E_{HOMO} indicates higher tendency for the donation of electron(s) to the appropriate acceptor molecule with low energy and empty molecular orbital. The highest occupied molecular orbitals are localized on the carbon atoms having double bond and on the C=N bonds in the central part of the molecule. In Fig.8,10 the electron density occupying the molecular orbitals appears around CO, NH and C=N groups. These molecular orbitals represent the highest occupied molecular orbitals.

Figs.9,11 shows unoccupied molecular orbital regions that can accept electrons. E_{LUMO} as an electron acceptor represents the ability to obtain an electron. In keto form of IDOX the lowest unoccupied molecular orbitals are present mainly on the C=O and C=N bonds, while in enol forms of IDOX these orbitals are present on the C=N bonds. But however LUMO's are delocalized through the acceptors and pi bridges. Therefore, from the lower value of E_{LUMO} of keto and enol forms of IDOX it is more apparent that the molecule would accept electrons.

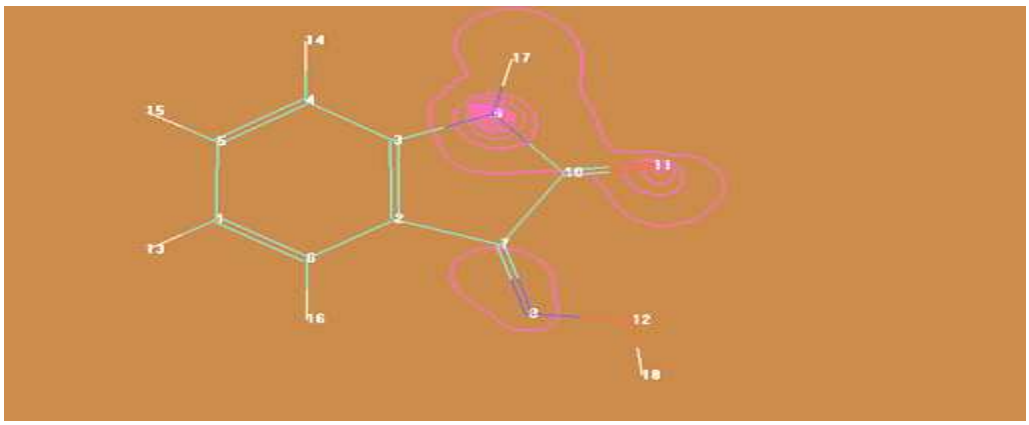


Fig 8. *Highest occupied molecular orbital (HOMO) of keto form of Indoline-2,3-dione-3-oxime(IDOX) E= -9.1405 eV*

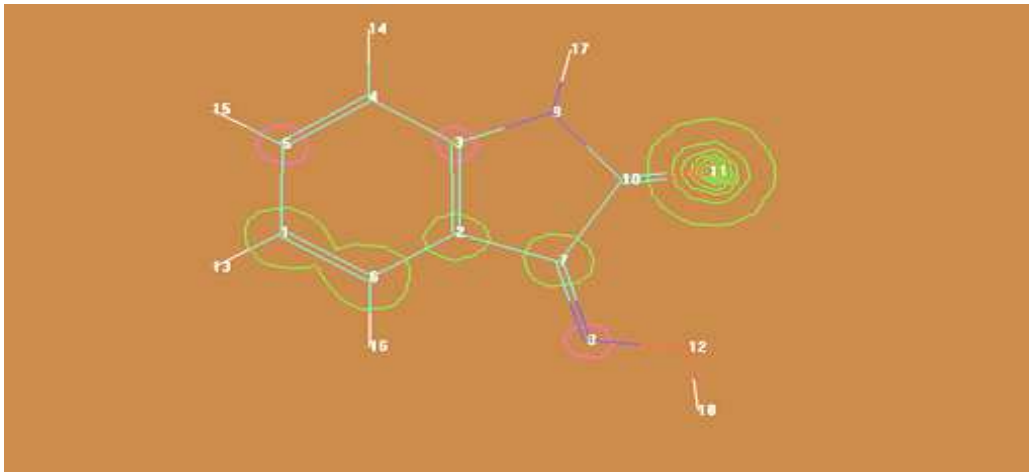


Fig 9. *Lowest unoccupied molecular orbital (LUMO) of keto formof Indoline-2,3-dione-3-oxime(IDOX) E= -0.7536139 eV*

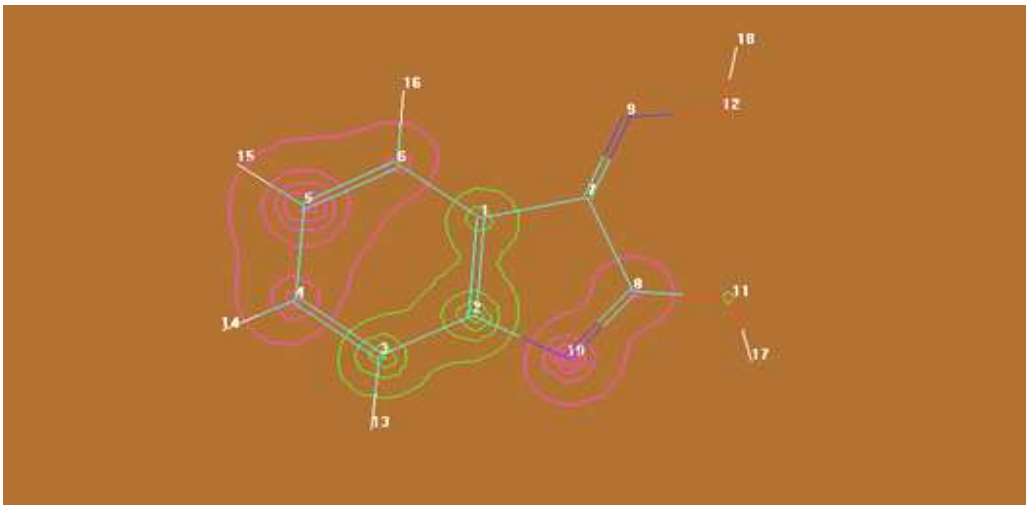


Fig 10. *Highest occupied molecular orbital (HOMO) of enol form of Indoline-2,3-dione-3-oxime(IDOX). E= -8.979 eV*

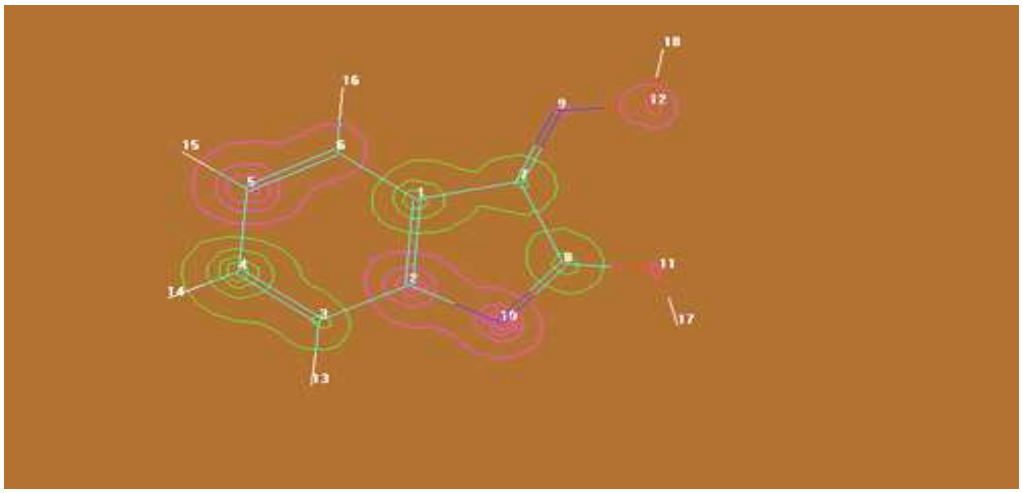


Fig 11. *Lowest unoccupied molecular orbital (LUMO) of enol formof Indoline-2,3-dione-3-oxime(IDOX) E= -0.983402 eV*

The frontier molecular orbital energy gap namely $E_{\text{LUMO-HOMO}}$ gap (Eg) was calculated and it reveals that the energy gap reflects the chemical activity of the molecule. $E_{\text{LUMO-HOMO}}$ gap (Eg) energy separation was used as an index of kinetic stability. $E_{\text{LUMO-HOMO}}$ gap (Eg)of keto and enol forms of IDOX molecule is about 8.3868 eV and 7.9955 eV respectively. Greater the $E_{\text{LUMO-HOMO}}$ gap (Eg) smaller is delocalization of electrons.[7-12]

7. Conclusions

The theoretical and experimental methods of study on the Indoline-2,3-dione-3-oxime (IDOX) compound is informative in understanding various physicochemical aspects of compounds. The HOMO and LUMO frontier orbital energies computed for the optimized molecules of keto and enol forms of IDOX indicated that the above compounds possess potential electron donor atoms. The computed IR ,[1] H NMR data spectral data and QSAR parameters generated with semi empirical single point AM1 method for the above compound are nearly in good agreement with experimental data

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