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

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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. 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. 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. Indoline-2,3-dione-3-oxime (Isatin -3-oxime)was found to have anticonvulsant activity. 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. 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 CDC$_3$ 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 VG70-70H 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](image)

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

![Fig. 2. Structure of keto form of Indoline-2,3-dione-3-oxime(IDOX)](image)

**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).

![Fig. 3. Structure of enol form of Indoline-2,3-dione-3-oxime(IDOX)](image)

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

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.

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](image)

![Fig.5. IR spectrum of IDOX enol form](image)

In IR spectrum 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).

| υN-OH | υN-H | υC=O | υC-H | υC=O bending |
|-------|-------|-------|-------|---------------|
| IDOX  | 3180 cm\(^{-1}\) | 3050 cm\(^{-1}\) | 1713 cm\(^{-1}\) | 1633 cm\(^{-1}\) |
| IDOX keto | 3331 cm\(^{-1}\) | 3274 cm\(^{-1}\) | 1825 cm\(^{-1}\) | 3305--2133 cm\(^{-1}\) |
| IDOX enol | 3428 cm\(^{-1}\) | 3238--2238 cm\(^{-1}\) | 1693,1686 cm\(^{-1}\) | 1920-1786 cm\(^{-1}\) |

The mass spectrum 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\(_8\)H\(_6\)N\(_2\)O\(_2\) 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](image)

| 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 | δ(CH)$_{formal}$ |
|----------|---------|-------|--------------|-----------------|
| IDOX*    | 10.59 ppm | 13.2 ppm | 7.30-8.47 ppm |                 |
| 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 of IDOX at 24 °C in CDCl$_3$ + 3 drops of DMSO-d6 shows peaks at δ 13.2 ppm (1H enolic –OH), δ 10.599 ppm (1H=–N-OH) and δ 7.30-8.47 (4H Ar-H).

**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 Å$^2$ | 233.75 Å$^2$ |
| Surface area (Grid)   | 323.64 Å$^2$    | 323.09 Å$^2$     |
| Volume           | 483.41 Å$^3$    | 487.02 Å$^3$     |
| Hydration energy  | -12.34 kcal/mol | -16.07 kcal/mol  |
| Log P            | 0.39            | 1.43             |
| Refractivity     | 46.19 Å$^3$     | 46.42 Å$^3$      |
| Polarisability   | 16.34 Å$^3$     | 16.47 Å$^3$      |
| Mass             | 162.15 amu      | 162.15 amu       |

**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/mol    | 3.78 kcal/mol     |
| Gradient X           | 0.00061 kcal/mol  | 0.0000 kcal/mol   |
| Gradient Y           | 10.27 kcal/mol    | 2.49713 kcal/mol  |
| Gradient Z           | 22.38 kcal/mol    | 2.83741 kcal/mol  |

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)

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. 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.

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 respectively.
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\textsuperscript{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 $E_{LUMO}$) 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=O 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.
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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