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Computational Studies for Oxidation Reduction Reactions of Cinnoline - 4(1H)-One, in Aqueous Phase by Density Functional Theory

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Author's contribution

The only author NSB performed the whole research work. Author NSB wrote the first draft of the paper. Author NSB read and approved the final manuscript.

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ABSTRACT

The reduction and oxidation reactions of Cinnolin-4(1H)-one were studied in terms of reduction and oxidation potentials in aqueous phase. Geometry optimizations were performed at the 6-311++G (d, p) level by using the B3LYP functional theory. Cinnolin-4(1H)-one (I) has lower reduction potential (-0.184V) than that of of 2, 3-dihydrocinnolin-4(1H)-one (II) (-0.064 V). Oxidation potential of 2, 3-dihydrocinnolin-4(1H)-one (II), has greater negative value (-0.134V) than oxidation potential of 1, 2, 3, 4-tetrahydrocinnolin-4-ol (IV) (-0.091V). HOMO and LUMO energies are in increasing order: IV > II ≈ V > III > I and IV > II > V > I > III respectively, which is the same order as the strength of donating electrons in gas and aqueous phase. The values of μ, η, ω, and ΔN_{max} show, compound (III) is good electrophile comparison of the other compounds in gas and aqueous phase. Therefore compound (III); the greater is the tendency of the oxidized form to get reduced by accepting electrons.

Keywords: Cinnolin-4(3H)-one; density functional theory; chemical potential (μ); chemical hardness (η) and global electrophilicity (ω).

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1. INTRODUCTION

Heterocyclic rings [1-2], which were the reason for the activity of most of the drugs of natural origin leads to the discovery of the many synthetic drugs possessing the heterocyclic rings. Heterocyclic nitrogenous [3-4] compounds and their fused analogs represent an important class of heterocyclic compounds that exist in numerous natural products displaying a wide range of biological and pharmaceutical activities.

Cinnoline [5] is important skeletons that are found in natural products and pharmaceuticals and potential candidates for biologically important molecules. The development of their facile synthesis has been an important issue. The Cinnoline scaffold can be an attractive structural template in agriculture, biology, and medicine. In fact, over the past few years Cinnoline derivatives have been patented as agro chemical and pharmaceutical drugs [6]. They can also be used in organic nonlinear optics (NLO) materials by utilizing a polarized hetero aromatic π-system [7]. Crinoline ring is a versatile lead molecule [8] that has been investigated widely in medicinal chemistry due to its important pharmacological activities. The nucleus gives out different derivatives with different biological activities [9-15]. It has been reported to exhibit antimicrobial, anti-tubercular, anti-malarial, antihypertensive, anti-convulsant, neurological disorders, anti-depressant, anti-pyretic, analgesic, anxiolytic, antidiabetic, anesthetic, anti-thrombolytic, cardio tonic, anti-tumor, herbicidal, agrochemical insecticidal, inhibition of linolenic acid in wheat root etc.

Recently, theoretical investigation of redox potentials of compounds in aqueous solutions has been attracted attention. The electron transfer process constitutes the basic feature of chemical, biochemical and, especially, electrochemical reactions. Therefore, the ability to calculate redox potentials accurately using the theoretical methods would be advantageous in a number of different areas, particularly where the experimental measurements are difficult, due to the complex chemical equilibria and the reactions of the involved chemical species.

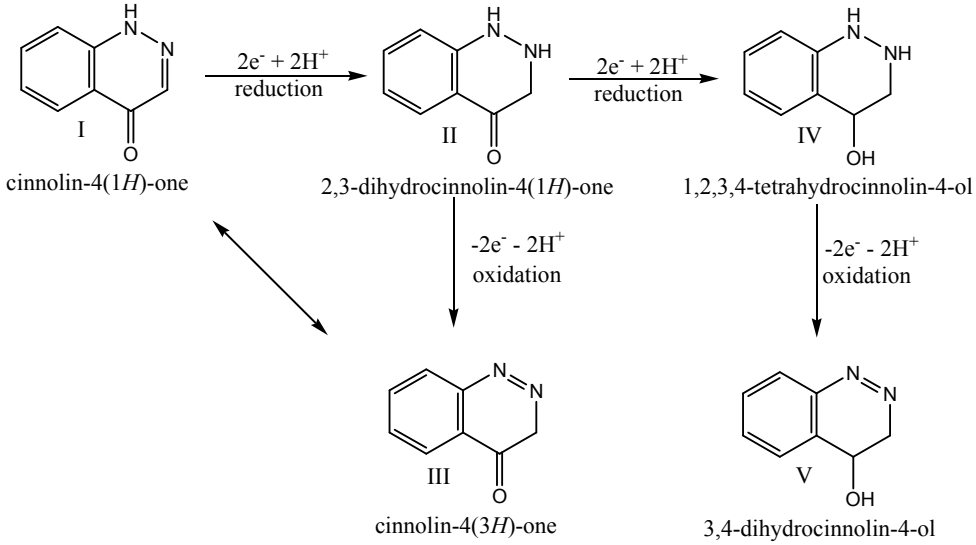
In the present work, we use high-level ab initio molecular orbital theory (DFT) to calculate the accurate values for the absolute redox potential of the Cinnolin-4(3H)-one reduction and oxidation reactions in aqueous phase.

2. COMPUTATIONAL DETAILS

All calculations were performed by using the Gaussian 09 software [16]. Geometry optimizations were performed at the 6-311++G (d, p) level by using the density functional theory (B3LYP) [17]. Frequency calculations were used to verify that the structure lies in a minimum of the potential energy surface. Salvation energies (G_{sol}) of the molecules in aqueous solution were computed with the polarizable continuum model (PCM) at the same level of theory. Specifically, a polarized continuum model (PCM) wherein the shape of the dielectric cavity is built up by putting a sphere around each heavy atom, was used. Hydrogen atoms are enclosed in the sphere of the atom to which they are bonded. Structures were always re optimized in solvent.

The reduction and oxidation reactions of Cinnolin-4(3H)-one are shown in scheme 1. Cinnolin-4(1H)-one (I) in acid solution is reducible in two, two electron steps. The product from the first two – electron reduction is 2,3-dihydrocinnolin-4(1H)-one (II). This compound is a derivative of phenylhydrazine and can thus be oxidized anodically in alkaline solution to an

azo compound (III), which then tautomerize to (I). The carbonyl group of (II) is activated by phenyl ring and in contrast to 2, 3-dihydrocinnolin-4(1H)-one (II) is further reduced to yield 1, 2, 3, 4-tetrahydrocinnolin-4-ol (IV). This compound further oxidized anodically in alkaline solution to yield 3, 4-dihydrocinnolin-4-ol (V).



Scheme 1. The reduction and oxidation reactions of Cinnolin-4(1H)-one

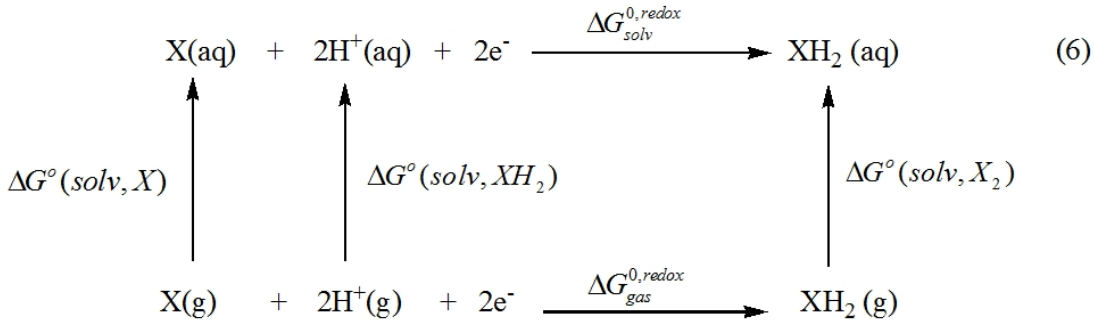
Reduction reactions		Oxidation reactions	
$I(ox) + 2H^+ + 2e^- \longrightarrow II\ (red)$	(1)	$II(red) \longrightarrow III(ox) + 2H^+ + 2e^-$	(3)
$II(ox) + 2H^+ + 2e^- \longrightarrow IV(red)$	(2)	$IV(red) \longrightarrow V(ox) + 2H^+ + 2e^-$	(4)

2.1 Theoretical Background

2.1.1 Redox potentials

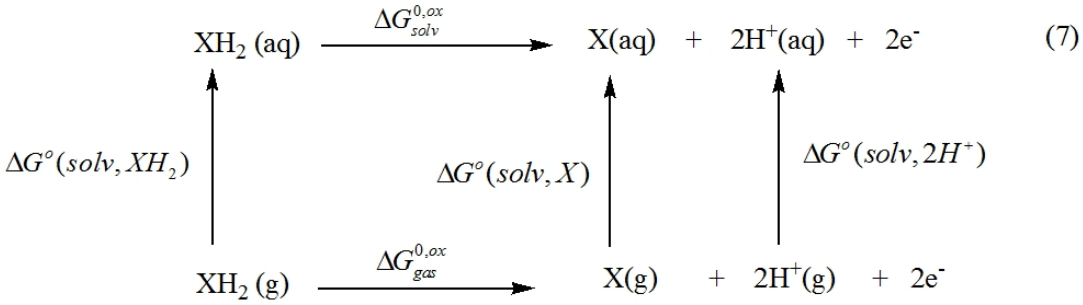
There are currently several protocols that exist for the theoretical prediction of the standard redox potentials in solution. One of the more popular methods uses the Born-Haber cycle shown in Schemes 2 and 3, where the standard Gibbs free energy of redox half reaction, $\Delta G_{solv}^{0,redox}$ consists of the free energy change in the gas phase and the solvation free energies of the oxidized and reduced species. These values are then used to calculate the overall reaction of the standard Gibbs free energy energy, $\Delta G_{solv}^{0,redox}$ /kcal·mol^{-1} (Eq. 5);

$$\Delta G_{solv}^{0,redox} = \Delta G_{g}^{0,redox} + \Delta G_{s}^{0}(\mathrm{Re}\,d) - \Delta G_{s}^{0}(Ox) \quad (5)$$



(6)

Scheme 2. Thermodynamic cycle for obtaining the a ΔG^0 (sol) of reduction reactions for (1) and (2)



(7)

Scheme 3. Thermodynamic cycle for obtaining the a ΔG^0 (sol) of oxidation reactions for (2) and (3)

ΔG^0_{solv} is the solvation Gibbs free energy, ΔG^0_{gas} is the Gibbs free energy in the gas phase and ΔG^0_{aq} is the Gibbs free energy in the aqueous phase. The gas phase free energies i.e. the standard Gibbs free energy of each molecule in the gas phase at its standard state is obtained by equation (8)[18]:

$$\Delta G^0_{gas} = E_{0K} + ZPE + (\Delta\Delta G_{0\rightarrow 298K}) \quad (8)$$

The Zero –point energy (ZPE) and the Gibbs free energy from 0 to 298.15 K $(\Delta\Delta G_{0\rightarrow 298K})$ are calculated from the vibrational frequencies calculated using quantum mechanics QM. The total energy of molecules at 0 K ($E_{0\,K}$) is calculated at the optimum geometry from QM [19]. The gas phase standard free energy to convert from its standard state of 1 atm gas phase/1M solution to with standard state of 1M gas/1M solution phase, it is necessary to add equation (9) to equation (8).

$$\Delta G^0_{gas}(1M) = \Delta G^0_{gas}(1\ atm) + RT\ ln\ (24.46) \quad (9)$$

The standard free energy of each species (XH_2, X and H^+) in solution, ΔG^0_{solv}, can be written as the subtraction of the standard free energy in water, $\Delta G^0_{aq,}$ and the gas phase standard free energy ΔG^0_g.

$$\Delta G^0_{solv} = \Delta G^0_{aq} - \Delta G^0_{gas} \quad (10)$$

To calculate ΔG^0(g), we need to know the standard free energy of free electron and H^+(g). To obtain the standard free energy of electron, we used its energy (3.720kJ.mol^{-1}) and entropy (0.022734 J.mol^{-1}K^{-1}) at 298 K [20]. The Gibbs free energy of H^+ (g) has been reported to be -26.3 kJ.mol^{-1} [21]. We have used the literature value of -1104.6 kJ.mol^{-1} for ΔG^0 (solv,H^+) [22]. It should be mentioned that this value is the change in the standard Gibbs free energy of reaction (1) in solution in the standard state of gas phase (1 atm). To obtain the change in the standard free energy of reactions (1, 2, 3 and 4) in solution, we need to add $\Delta n \Delta G^{0\rightarrow *}$ to ΔG^0 (total) where $\Delta G^{0\rightarrow *}$ is the correction for changing the standard state from gas phase (1atm) to solution (1 mol.L^{-1}). $\Delta G^{0\rightarrow *}$ values calculated from equation (8). Δn is the change of moles in reaction (1) which is equal to 2. The value of $\Delta G^{0\rightarrow *}$ is equal to 7.9 KJ.mol^{-1}. $\Delta G^{0,redox}_{solv}$ is related to the absolute redox potential through the following thermodynamic relation: [Eq. (11)]:

$$\Delta G^{0,redox}_{solv} = -nFE^o_{cal} \quad (11)$$

where *n* is the number of transferred electrons in the reaction and *F* is the Faraday constant (96.485KJ.mol^{-1}V^{-1}). Reduction and oxidation potentials are usually reported relative to the normal hydrogen electrode (NHE) potential is 4.44 eV [23].

2.1.2 Global and local reactivity descriptors

Based on density functional theory several global chemical reactivity descriptors of molecules such as hardness (η), chemical potential (μ), softness (S), and electron negativity (χ) have been defined as [24-28].

$$\eta = \frac{1}{2}\left(\frac{\partial^2 E}{\partial N^2}\right)_{V(\bar{r})} = \frac{1}{2}\left(\frac{\partial \mu}{\partial N}\right)_{V(\bar{r})} \quad (12)$$

$$\mu = \left[\frac{\partial E}{\partial N}\right]_{V(\bar{r})} \quad (13)$$

$$\chi = -\mu = -\left[\frac{\partial E}{\partial N}\right]_{V(\bar{r})} \quad (14)$$

where E and $V(\bar{r})$ are electronic energy and external potential of an N-electron system, respectively. Softness is a property of molecules that measures the extent of chemical reactivity. It is the reciprocal of hardness,

$$S = \frac{1}{\eta} \quad (15)$$

We focus on the HOMO and LUMO energies in order to determine if correlations with interesting molecular/atomic properties and chemical quantities exist. In simple molecular orbital theory approaches, the HOMO energy (ε_{HOMO}) is related to IP by Koopmanns' theorem [29] and the LUMO energy (ε_{LUMO}) has been used to estimate the electron affinity (EA).Using Koopmans' theorem for closed-shell molecules, η, μ and χ can be redefined as:

$$\eta \approx \frac{1}{2}\left(I - A\right) \approx \frac{1}{2}\left(\varepsilon_{LUMO} - \varepsilon_{HOMO}\right) \tag{16}$$

$$\mu \approx -\frac{1}{2}\left(I + A\right) \approx \frac{1}{2}\left(\varepsilon_{HOMO} + \varepsilon_{LUMO}\right) \tag{17}$$

$$\chi = \frac{I + A}{2} \tag{18}$$

$$I \approx -\varepsilon_{HOMO} \quad \text{and} \quad A \approx -\varepsilon_{LUMO} \tag{19}$$

where I and A are the ionization potential and electron affinity of the molecules, respectively. Electron affinity refers to the capability of a ligand to accept precisely one electron from a donor. However in many kinds of bonding viz. covalent, dative or hydrogen bonding, partial charge transfer takes place.

2.1.3 Electrophilicity index

Parr et al. [24] have proposed electrophilicity index as a measure of energy lowering due to maximal electron flow between donor and acceptor. They defined electrophilicity index (ω) as follows:

$$\omega = \frac{\mu^2}{2\eta} \tag{20}$$

The electrophilicity is a descriptor of reactivity that allows a quantitative classification of the global electrophilic nature of a molecule within a relative scale. The usefulness of this new reactivity quantity has been recently demonstrated in understanding the toxicity of various pollutants in terms of their reactivity and site selectivity [30, 31].

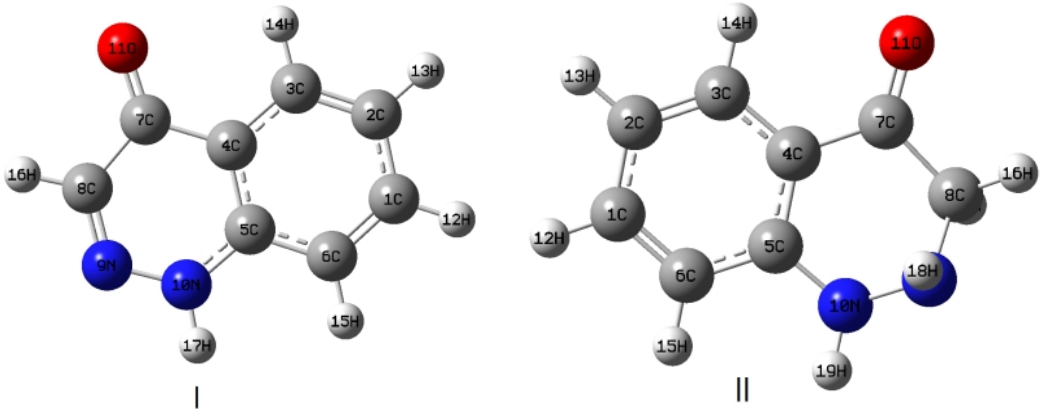
On the other hand, the maximum amount of electronic charge that an electrophile system may accept is given by [32]:

$$\Delta N_{max} = -\frac{\mu}{\eta} \tag{21}$$

The maximum charge transfer ΔN_{max} towards the electrophile was evaluated using Eq. (21).Thus, while the quantity defined by Eq. (20) describes the propensity of the system to acquire additional electronic charge from the environment; the quantity defined in Eq. (21) describes the charge capacity of the molecule.

3. RESULTS AND DISCUSSION

The geometrical structures of studied molecules were optimized using hybrid DFT method, viz. B3LYP, with 6-311++G (d, p) basis set. During complete geometry optimization, the molecules are assumed as C1 point group symmetry. The molecular structures of I, II, III, IV and V, and of their atoms numbering are depicted in Fig. 1. The calculation of the redox potential is highly sensitive to perturbations in the Gibbs free energy. As 1 kcalmol^{-1} corresponds to a redox potential change of 0.043 V, an error of 0.13 V corresponds to 3.0 kcal /mol. The source of this error should be found in the incompleteness of the description of the solvent and Improvements in salvation models will therefore result in more accurate calculations of redox potential. The most appropriate way of calculating the redox potential is by using a thermodynamic cycle linking the process in the gas phase with that in solvent [33]. The calculation of the Gibbs free energy is summarized in equations (5) and (6) which show the thermodynamic cycles for the redox and oxidation potential of Cinnoline -4(1H)-one. The redox and oxidation potentials of Cinnoline -4(1H)-one and its products are tabulated in Table 1. From the results it was seen that the reaction (1) has a lower reduction potential (-0.184V) than reaction (2) (-0.064 V). Thus reaction (2) is a more favorable reaction compared to of reaction (1), as higher the reduction potential value; the greater is the tendency of the oxidized form to get reduced by accepting electrons. In the case of oxidation reactions, the reaction (3) has a higher negative value (-0.134V) than reaction (4) (-0.091V). Thus reaction (3) is a more favorable reaction compared to reaction (4). Because of the higher the negative value, greater is the tendency of the reduced form to get oxidized by donating electrons.



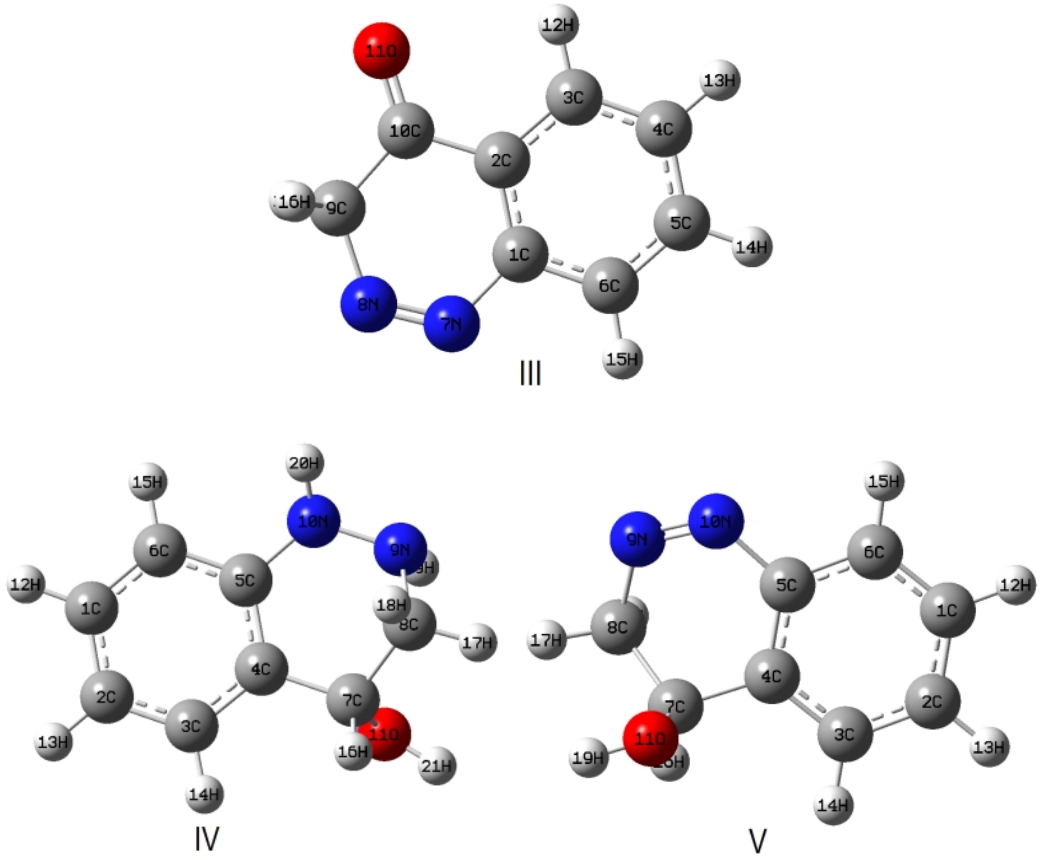


Fig. 1. Optimized structures for cinnolin-4(3H)-one(I); 2,3-dihydrocinnolin-4(1H)-one(II); cinnolin-4 (3H)-one(III); 1,2,3,4-tetrahydrocinnolin-4-ol(IV); 3,4-dihydrocinnolin-4-ol(V)

Table 1. The Energy, enthalpy and Gibbs free energy of the studied molecules for both in the gas phase and the aqueous phase, along with the change of the Gibbs free energy ΔG^0(gas),Gibbs free energy of solvation(ΔG^0_{solv}) and potentials (E^0) of the reactions (1,2,3 and 4)

Parameter	I	II	III	IV	V
E(gas)	-493.304233	-494.498910	-493.267456	-495.699509	-494.469329
H(gas)	-493.167651	-492.338392	-493.132587	-495.515200	-494.310531
E(aq)	-493.318098	-494.511102	-493.279057	-495.711156	-494.483637
H(aq)	-493.181376	-494.350608	-493.144160	-495.52837	-494.367546
*G^0(gas)	-493.209126	-494.380989	-493.176134	-495.558771	-494.353544
*G^0(aq)	-493.222643	-494.393237	-493.187227	-495.570418	-494.367546
[a]ΔG^0_{solv}	-35.4888531	-32.1570964	-29.1246465	-30.57917229	-36.762219
Potentials (E^0) in Volts		Reaction 1	Reaction 2	Reaction 3	Reaction 4
		-0.184	-0.064	-0.134	-0.091

**these energies are in atomic units, Hartree (1 Hartree = 2625.49975 kJ mol^{-1})*

[a] these energies are in kJ mol^{-1}

3.1 Molecular Orbital Calculations

Table 2 summarizes the highest occupied molecular (HOMO), the lowest unoccupied molecular orbital (LUMO) and HOMO and LUMO energy gaps for studied molecules calculated at DFT level in the 6-311++G(d,p) basis set. The eigenvalues of LUMO and HOMO and their energy gap reflect the chemical activity of the molecule. The HOMO and LUMO energy diagrams in ground state are represented by Fig. 2. The HOMO represents the ability to donate an electron, while LUMO as an electron acceptor represent the ability to obtain an electron. The smaller the LUMO and HOMO energy gaps, the easier it is for the HOMO electrons to be excited; the higher the HOMO energies, the easier it is for HOMO to donate electrons; the lower the LUMO energies , the easier it is for LUMO to accept electrons.

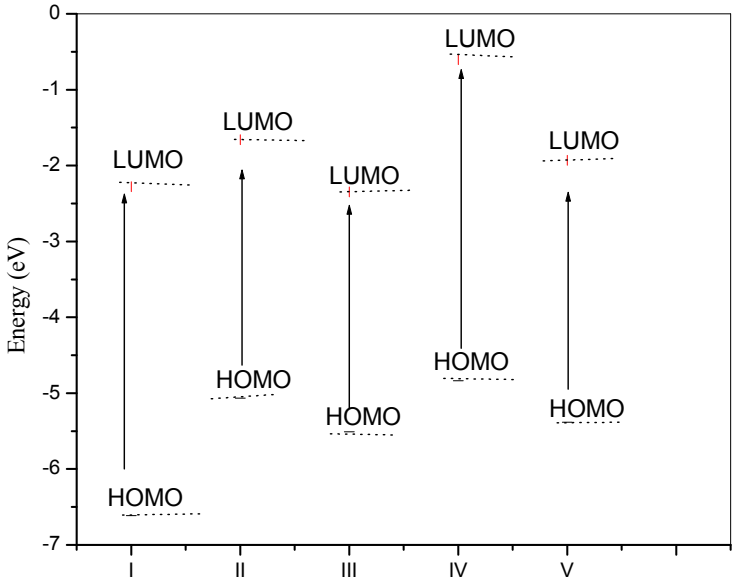


Fig. 2. Molecular orbitals calculated with DFT

From the resulting data shown in Table 2, the energies of LUMO of I has lower than those of II and the energy gap of I is smaller than that of II. Hence, transfer of electrons from HOMO to the LUMO in I is easier than in II. Based on energies of HOMO and LUMO and the energy gaps of I in both gas and water phases the energy of HOMO of II increases. Furthermore the energy gap of HOMO and LUMO of I in water is lower than that in the gas phase. Hence, it may be concluded that the activity of I in water is higher than in the gas phase. Donor-acceptor properties of these molecules, (IV) has higher HOMO and LUMO energies, therefore donation of electrons is easier for (IV). The molecule (IV) has higher HOMO value comparison of (II), consistent with the more difficult oxidation of (II). The order of HOMO and LUMO energies in increasing order: IV > II ≈ V > III > I and IV > II > V > I > III respectively, which is the same order as the strength of donating electrons in both phase.

A comparison of the values of μ, η, ω, and ΔN_{max}, (Table 3) shows that the compound (III) is a stronger electrophile than the other compounds in both gas and aqueous phases. Therefore compound (III); the greater is the tendency of the oxidized form to get reduced by

accepting electrons. The maximum charge that each species may accept from the environment measured by ΔN_{max} almost parallel and the variations in electrophilicity. This also suggests that in the case of compound (III), the greater is the tendency of the oxidized form to get reduced by accepting electrons.

Table 2. The HOMO and LUMO energies and the energy gap between HOMO and LUMO (E), ionization potential (I), electron affinity (A) in eV units and dipole moment (μ) in debye units in the gas phase and the aqueous phase of studied molecules

	I	II	III	IV	V
HOMO(g)	-6.5953	-5.1025	-5.3628	-4.6998	-5.1287
LUMO(g)	-2.1998	-1.5648	-2.3471	-0.5686	-1.7736
HOMO(aq)	-6.6136	-5.0643	-5.5088	-4.8362	-5.3810
LUMO(aq)	-2.2779	-1.6607	-2.3467	-0.6026	-1.9306
E(g)	-4.3955	-3.5377	-3.0157	-4.1312	-3.3551
E(aq)	-4.3357	-3.4036	-3.1621	-4.2336	-3.4504
I(g)	6.5953	5.1025	5.3628	4.6998	5.1287
I(aq)	6.6136	5.0643	5.5088	4.8362	5.3810
A(g)	2.1998	1.5648	2.3471	0.5686	1.7736
A(aq)	2.2779	1.6607	2.3467	0.6026	1.9306
μ(g)	5.3168	3.8204	3.0427	2.0620	5.6753
μ(aq)	7.8265	5.4043	4.0943	2.8991	3.8953

Table 3. Global electrophilicity (ω), chemical potential (μ), chemical hardness (η) and the maximum charge transfer (ΔN_{max}) values for Quinoxalin-2(H)-one (QO) and its derivatives of 3-methylquinoxalin-2(1H)-one (MQO) and 3-aminoquinoxalin-2(1H)-one (AQO). All values are in eV

Molecule	μ		η		ω		ΔN_{max}	
	Gas	Water	Gas	Water	Gas	Water	Gas	Water
I	-4.3975	-4.4457	4.3955	4.3557	2.1998	2.2688	1.0000	1.0206
II	-3.3336	-3.3625	3.5377	3.4036	1.5706	1.6609	0.9423	0.9879
III	-3.8549	-3.9277	3.0157	3.1621	2.4638	2.4393	1.2782	1.2421
IV	-2.6342	-2.7194	4.1312	4.2336	0.8398	0.8733	0.6376	0.6423
V	-3.4511	-3.6558	3.3551	3.4504	1.7749	1.9367	1.0286	1.0595

4. CONCLUSION

The reduction and oxidation potentials were calculated according to the reduction and oxidation reactions of Cinnolin-4(3H)-one as shown in Scheme 1 in aqueous phase. The results show that the reaction (1) has lower reduction potential (-0.184V) than reaction (2) (-0.064 V). In case of oxidation reactions, the reaction (3) has higher negative value of oxidation potential (-0.134V) than reaction (4) (-0.091V). The order of HOMO and LUMO energies are increasing order: IV > II ≈ V > III > I and IV > II > V > I > III respectively, which is the same order as that of the strength of donating electrons in both phases. The values of μ, η, ω, and ΔN_{max} show, that compound (III) is a strong electrophile compared to the other compounds in gas and aqueous phases. Therefore in the case of compound (III); the greater is the tendency of the oxidized form to get reduced by accepting electrons.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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