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Computational and electrochemical studies on the redox reaction of for quinoxalin-2(*H*)-one and its derivatives in aqueous solution

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ABSTRACT

The Quinoxalin-2(H)-one (QO) and its derivatives of 3-methylquinoxalin-2(1H)-one (MQO) and 3-aminoquinoxalin-2(1H)-one (AQO) electrode potentials were calculated in aqueous phase. For this purpose, the DFT/B3LYP method, with the 6-311G basis set was utilized. The calculated value of the redox potentials relative to SHE were 0.123 eV, 0.015 eV and -0.254 eV for QO, MQO and AQO respectively. The amino derivative is (-0.76 eV) negative reduction potential because of amino group is more electron donating group comparison of methyl group. Energies of the highest occupied molecular orbital (HOMO) and the energy of the lowest unoccupied molecular orbital (LUMO) of the studied compounds were calculated in gas phase and water. Both electron donor and electron acceptor substituents are effective in reducing the energy gap between HOMO and LUMO. In addition, chemical potential (μ), chemical hardness (η), global electrophilicity (ω) and dipole moments were calculated. From the results shows that, quinoxalin-2-one, the greater is the tendency of the oxidized form to get reduced by accepting electrons and the amino derivative of quinoxalin-2-one is, the greater is the tendency of the reduced form to get oxidized by donating electrons.

Keywords: Density functional theory, Redox potential, HOMO and LUMO, chemical potential (μ), chemical hardness (η) and global electrophilicity (ω).

INTRODUCTION

With the family of biologically active heterocyclic templates, the quinoxalin-2-one (quinoxalione) core has received much attention in recent years as on important pharmacophore in numerous biologically active compounds. Substituted quinoxalines are an important class of benzoheterocycles, which constitute the building blocks of wide range of pharmacologically active compounds having antibacterial [1,2] antifungal[3], anticancer[4], antitubercular [5], antileishmanial [6], antimalarial [7] and antidepressant activities [8].Also, some quinoxalin-2-ones and quinoxaline-2,3-diones have been reported to show antimicrobial [9], novel, potent antithrombotic [11], anti-pain and anti-inflammatory [12,13] activities.

In particular, quinoxalines were found as a core unit in a number of biologically active compounds. Quinoxaline including their fused ring derivatives display diverse pharmacological activities such as neuroprotective agents, antifungal, antibacterial, radio protective, anticonvulsant, antimalarial, anticancer, potent antithrombotic, analgesic, anti-inflammatory, antiglaucoma, antiparasite, antituberculosis, hypoglycemic, antiviral, anti-HIV, anthelmintic activities, antidepressant, NMDA receptor antagonist, and antimalarial activities [14–16].

The oxidation–reduction reactions are a well known type of electron transfer reactions, which play an important role in many area of chemistry [17].Accurate calculation of electrode potentials is advantageous specially where the experimental measurement is difficult due to complex chemical equilibrium [18]. Besides, for few cases, it is claimed that the experimental estimates are found to be associated with large uncertainty and the theoretical approaches may indeed be as reliable as experimental ones for determining redox properties of molecule [19]. It is also suggested that in some cases where there is a great discrepancy between theory and experiment, a reexamination of the experimental data may be warranted [20]. Therefore, it is essential to be able to predict the redox potentials.

Recently, Electrochemical methods are widely used for the study of electroactive compounds in pharmaceutical forms and physiological fluids due to their simple, rapid, and economical properties [21].Computational chemistry has evolved to the point that it is sometimes competitive to experiment to obtain precise values for certain molecular properties. Density functional theory (DFT) has played a predominant role in this evolution in the last decade [22].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 equilibrium and the reactions of the involved chemical species. Recently, *ab*intio methods have been employed for the calculation of redox potential of different species in aqueous solutions [23]. In this paper, the redox potential of Quinoxalin-2(H)-one(QO) was calculated with the employment of the density functional theory (DFT) at the B3LYP/6-311G level of theory. The Polarisable Continuum Model (PCM) [24] was used to calculated the free energy salvation of species involved in the reaction.

In this paper we are calculated the half-wave potential, $E_{1/2}$, the electron affinity of the reduced species in the gas phase (A), the ionization potential (I), the energy of the highest occupied molecular orbital (HOMO, the energy of the lowest unoccupied molecular orbital (LUMO) for Quinoxaline-2(H)-one (QO) and its derivates in the gas and in the aqueous phase.

COMPUTATIONAL DETAILS

The molecular structure, vibrational frequencies and energy of the optimized geometry of QO(ox.), QOH_2 (red.) and its derivatives MQO (0x.), $MQOH_2$ (red.) and AQO (ox.),$AQOH_2$ (red.) were computed employing the DFT method using Gaussian 09 [25] program package employing 6-311G basis set based on Becke's three parameters (local, non-local and Hartree-Fock) hybrid exchange functional with Lee-Yang- Parr correlation functional (B3LYP) [26].Frequency calculations were used to verify that the structure lies in a minimum of the potential energy surface. The oxidation reactions of Quinoxalin-2(H)-one and its derivatives are shown in scheme 1. To obtain the redox potential, it is necessary to calculate the standard free energy change (ΔG^0) for reaction (1).

$$QO(sol) + 2H^+(sol) + 2e^- \rightarrow QOH_2\ (sol) \quad (1)$$

ΔG^0 is related to the absolute redox potential through the following thermodynamic relation:

$$E^0 = -\Delta G^0/nF \quad (2)$$

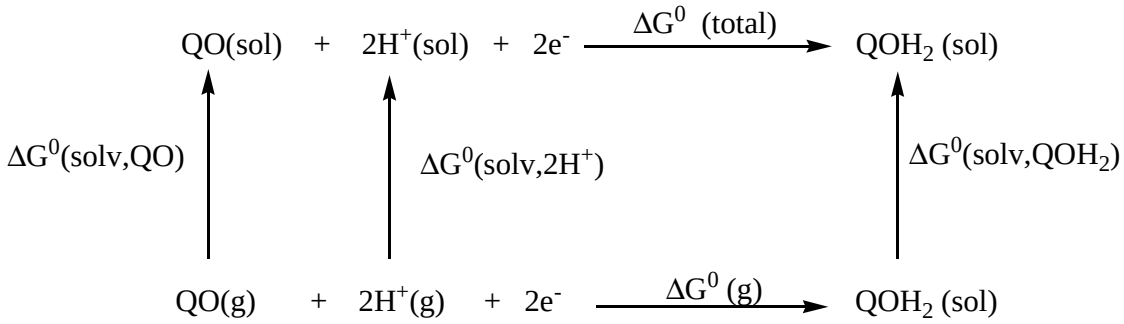
where *n* is the number of transferred electrons in the reaction which is equal to 2 for reaction (1) and *F* is the Faraday constant (96485 C mol^{-1}). The calculated value of redox potential (E^0) is thereby relative to the reduction potential of a reference electrode. Here we will use the normal hydrogen electrode (NHE):

$$H^+(aq) + e^- \longrightarrow \tfrac{1}{2} H_2(gas) \quad (3)$$

with an associated free energy change of - 4.44 eV.

To calculate $\Delta G^{0,}$ it is necessary to use the following (scheme 2) thermodynamic cycle (Born-Haber) which is used for transferring all of the species involved in the reaction (1) from the gas to solution phase. Based on the scheme 2, thermodynamic cycles, ΔG^0(total) can be written as

$$\Delta G^0(total) = \Delta G^0(g) + \Delta G^0(solv, QOH2) - \Delta G^0(solv, QO) - 2\Delta G^0(solv, H^+) \quad (4)$$



Scheme 2 . Thermodynamic cycle for obtaining the a ΔG^0 (sol) of reaction in solution from the ΔG^0 a(g) of reaction in gas phase for Quinoxalin-2(1H)- one.

whereΔG^0 (g) is the change of the standard free energy of reaction (1) in the gas phase, ΔG^0 (solv, QOH_2), ΔG^0 (solv, QO) and ΔG^0 (solv, H^+) are the standard free energy solvation of QOH_2, QO and H^+ respectively. The standard Gibbs free energyof each state in the gas phase is obtained by using Equation (5):

$$\Delta G^0_{gas} = E_{0K} + ZPE + \Delta\Delta G_{0 \rightarrow 298} \quad (5)$$

The energy at 0 K (E_0) is calculated by using DFT at the optimum geometry. Zero-point energies (ZPEs; unscaled) and thermal contributions ($\Delta\Delta G_{0 \rightarrow 298}$) together with entropies have been used to convert internal energies to Gibbs free energies at 298.15 K [38]. In Equation (5), an extra term should be introduced to convert the ΔG^0_{gas} state from 1 atm to 1M:

$$\Delta G^0_{gas}(1M) = \Delta G^0_{gas}(1\ atm) + RT\ ln(24.46) = \Delta G^{0 \rightarrow *} \quad (6)$$

The connection between the gas and aqueous phases is made through the calculation of the salvation Gibbs free energy of the specific species. In this study, we used a polarized continuum approach (PCM) to describe the solvent and the interactions with the solute. The ΔG^0_{solv} values were computed from Equation (7):

$$\Delta G^0_{solv} = \Delta G^0_{aq} - \Delta G^0_{gas} \quad (7)$$

in which ΔG^0_{aq} is the total Gibbs free energy of the system in solution and ΔG^0_{gas} is the equivalent quantity in a vacuum. To take into account small changes in geometry when going from gas to solvent, we reoptimised the geometry of the molecule in PCM.

In order to calculate ΔG^0 (g),the standard free energy of QO and QOH_2were calculated in the gas phase at the DFT-B3LYP level of theory using 6-311 basis set. To do this, the molecular structure of QO and QOH_2 were optimized at B3LYP/6- 311G level of theory, separately and then, the vibrational frequencies calculation, at the same level of theory and basis set, were performed on the optimized structures to confirm that they are at the global minima and obtain the standard free energy of QO and QOH_2 in gas phase. 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 (3.720 kJ.mol^{-1}) and entropy (0.022734 kJ mol^{-1} k^{-1}) at 298 K [27]. The Gibbs free energy of H^+ (g) has been reported to be -26.3 kJ.mol^{-1} [28].

In order to calculate the solvation energy for QO and QOH_2, the Polarized Continuum Model (PCM) which defines the cavity as the union of a series of inter locking atomic sphere [29], was used for ab initio calculations. Similar to gas phase calculations, the molecular structure of QO, and QOH_2 were re-optimized in aqueous phase using PCM model at the same level of theory and basis set. Then, the vibrational frequency calculations were performed to obtain the Gibbs free energy of QO and QOH_2 in solution. ΔG^0 (solv,QOH2) and (solv,QO) are is obtained from the subtraction the standard Gibbs free energy of each compound in solution from the corresponding value in gas phase. We have used the literature value of -1104.6 kJ.mol^{-1} for ΔG^0 (solv,H^+) [30]. 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 reaction (4) in solution, we need to add $\Delta n\Delta G^{0\rightarrow *}$ toΔG^{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}). $\Delta G^{0\rightarrow *}$ value calculated from equation (6). 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}.

RESULTS AND DISCUSSION

The geometrical optimization was the most significant step for the calculation of the formal electrode potential, on the grounds that the molecular parameters were controlled by the molecular geometry. The molecules of QO assumed as C1 point group of symmetry and the optimized geometrical parameters and vibranational frequencies of the title compound were calculated by DFT (B3LYP) levels with the 6-311G basis set. The labeling of atoms in QO and QOH_2 are given in Figure 1.

Redox potentials

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 [31]. The calculation of the Gibbs free energy is summarized in Equation (4) which show the thermodynamic cycles for the redox potential of quinoxalin-2-one. The redox potentials of quinoxalin-2-one and its methyl and amine derivatives are tabulated in Table 1. From the results quinoxalin-2-one is high reduction potential (0.123 eV) comparison of its derivates. The methyl derivate is (0.015 eV) and the amino derivative is (-0.76 eV) are less than quinoxalin-2-one because of methyl group and the amino group are electron donating groups. The amino derivative is (-0.254 eV) negative reduction potential because of amino group is more electron donating group comparison of methyl group. Therefore quinoxalin-2-one, the greater is the tendency of the oxidized form to get reduced by accepting electrons and the amino derivative of quinoxalin-2-one is, the greater is the tendency of the reduced form to get oxidized by donating electrons.

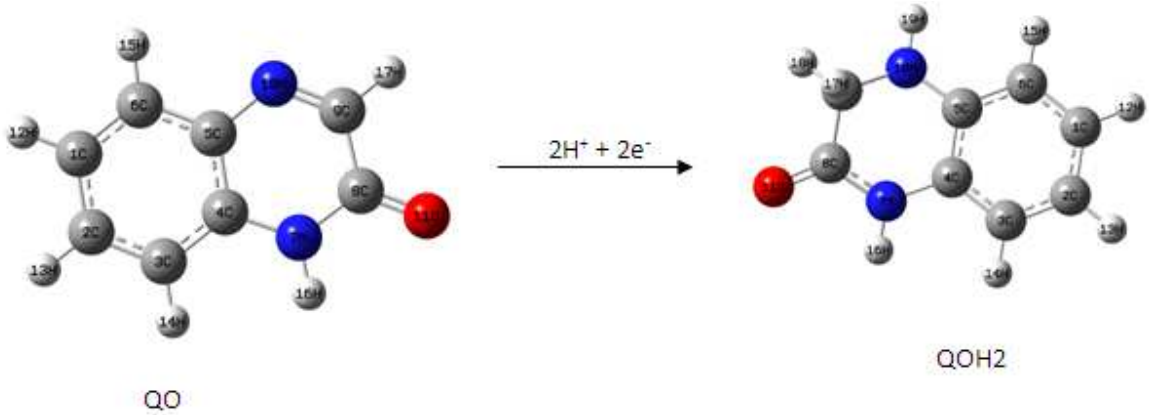


Figure (1) Optimized structures of QO (oxidized form) and QOH_2 (reduced form) in gas phase.

HOMO-LUMO energies

The energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the title compound and its derivatives in the ground state are calculated by using B3LYP method with 6-311G basis set. The HOMO and LUMO are the main orbital that take part in chemical stability. The HOMO represents the ability to donate an electron, LUMO as an electron acceptor represent the ability to obtain an electron. The energy of the HOMO is directly related to the ionization potential and the energy of the LUMO is directly related to the electron affinity. High value of HOMO energy is likely to indicate a tendency of the molecule to donate electrons to appropriate acceptor molecule of low empty molecular orbital energy. The lower values of LUMO energy show more probability to accept electrons. So, the gap energy (Eg), i.e. the difference in energy between the HOMO and LUMO, is an important stability index. 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. The calculated HOMO level, LUMO level, and Eg are summarized in Table 2 and the HOMO and LUMO diagrams in ground state are represented by Fig (2).

As shown in Table 2, the HOMO energy level of QO and its derivatives decreases in the order: (AQO > MQO > QO), which is the same order as the acceptor strength. The calculated band gap Eg of the studied model compounds increases in the following order AQO > MQO > QO. The much lower Eg of MQO and AQO compared to that of QO indicates a significant effect of intra molecular charge transfer. However, the Eg values of MQO are smaller than that of AQO. In MQO the lowering of the LUMO level by the presence of the acceptor moiety is more than compensated by the lowering of the HOMO level. A likely origin of this effect is that the backbone nitrogen atom localizes electrons and breaks the symmetry of the structures with consequent widening of the band gap of the two model compounds [32]. The HOMO value of AQO and MQO are high value comparison of QO, because of the substituents are an electron donor groups. However, both electron donor and electron acceptor substituents are effective in reducing the energy gap between HOMO and LUMO.

Correlation with molecular orbital theory

The most widely used theory by chemists is the molecular orbital (MO) theory. It is important that chemical hardness (η) and electronic chemical potential (μ) be put into a MO framework. This can readily be done within the limitations of Koopmans' theorem, the orbital energies of the frontier orbital's are given by

$- E_{HOMO} = I,$ $- E_{LUMO} = A.$

The global electrophilicity power has been recently defined by Parr et al.[33]by:

$$\omega = \frac{\mu^2}{2\eta} \quad (8)$$

which measures the stabilization in energy when the system acquires an additional electronic charge ΔN from the environment. In Eq. (1) μ and η are the electronic chemical potential and the chemical hardness of the ground state (GS) of atoms and molecules, respectively. These descriptors have been defined within the context of the density functional theory of Parr, Pearson and Yang [34, 35].While the electronic chemical potential μ describes the charge transfer pattern of the system in its ground state geometry, the chemical hardness η describes the resistance to the change. A very simple operational formula for μ, in terms of the one electron energies of HOMO and LUMO, ε_H and ε_L, is given by [36]:

$$\mu \approx (\varepsilon_H + \varepsilon_L)/2 \quad (9)$$

It is also possible to give a quantitative representation to the chemical hardness (η) concept introduced by Pearson as[35]:

$$\eta \approx \varepsilon_L - \varepsilon_H \quad (10)$$

Note that the electrophilicity index given in Eq. (8) encompasses both, the propensity of the electrophile to acquire an additional electronic charge driven by μ^2, and the resistance of the system to exchange electronic charge with the environment described by η, simultaneously. A high value of μ and a low value of η therefore characterize a good electrophile. On the other hand, the maximum amount of electronic charge that the electrophile system may accept is given by[33]:

$$\Delta N_{max} = - \frac{\mu}{\eta} \quad (11)$$

The maximum charge transfer ΔN_{max} towards the electrophile was evaluated using Eq. (11).Thus, while the quantity defined by Eq. (8) describes the propensity of the system to acquire additional electronic charge from the environment; the quantity defined in Eq. (11) describes the charge capacity of the molecule. Table .4, including the μ, η, ω, and ΔN_{max}. From the table 4, the NH_2 substituted Quinoxalin-2(H)-one is good electrophile comparison of the CH_3 substituted Quinoxalin-2(H)-one and Quinoxalin-2(H)-one in gas and aqueous phase. Therefore quinoxalin-2-one, the greater is the tendency of the oxidized form to get reduced by accepting electrons and the amino derivative of quinoxalin-2-one is, the greater is the tendency of the reduced form to get oxidized by donating electrons.

The electrophilicity of the QO may be drastically changed by suitable substitution. In Table 4 we summarize the enhanced electrophilicity pattern induced by substituent effect for compounds QO, MQO and AQO. The NH_2

substituted Quinoxalin-2(H)-one (AQO) has high value ω, comparison of the CH_3 substituted Quinoxalin-2(H)-one and Quinoxalin-2(H)-one in gas and aqueous phase because of NH_2 is strong electron donor group. AQO is a strong electrophile with an electrophilicity power 8.0939 eV. MQO and AQO are with electrophilicity values comprised within the 7.0566 and 6.3993 eV respectively. This classification is also consistent with the electronegativity pattern described by the negative of the electronic chemical potential. For instance, the AQO is characterized by the highest values in electronic chemical potential, thereby indicating that this compounds will more likely behave as electron donor species (i.e. as nucleophiles), on the other hand display the lowest value in electronic chemical potential for MQO and QO, thereby suggesting that they will in general act as electron acceptors. The maximum charge that each species may accept from the environment measured by ΔN_{max} almost parallel the variations in electrophilicity. This is also suggested that quinoxalin-2-one, the greater is the tendency of the oxidized form to get reduced by accepting electrons and the amino derivative of quinoxalin-2-one is, the greater is the tendency of the reduced form to get oxidized by donating electrons.

Table 1. The Gibbs free energy of the studied molecules for both reduced (red.) and oxidized (ox.) forms in the gas phase and the aqueous phase, along with the change of the Gibbs free energy ΔG^0(gas) , Gibbs free energy of reaction (1), ΔG^0(total) , and electrode potentials (E^0).

	QO(ox)	QOH_2(red)	MQO(ox)	$MQOH_2$(red)	AQO(ox)	$AQOH_2$(red)
$^*G^0$(Gas)	-493.080427	-494.273322	-532.378688	-533.563333	-548.441777	-549.606706
$^*G^0$(aq)	-493.093981	-494.287134	-532.391564	-533.576816	-548.496086	-549.660560
$^a\Delta G^0_{(0x)solv}$	-35.586023		-33.805934		-142.58826	
$^a\Delta G^0_{(Red)sol}$		-36.263402		-35.399613		-141.39523
$^a\Delta G^0$(gas)	-3073.229231		-3051.568862		-2999.804512	
$^a\Delta G^0$(total)	-880.506601		-859.762543		-807.594532	
E^0(eV)	0.123		0.015		-0.254	

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

Table 2. The HOMO and LUMO energies and the energy gap between HOMO and LUMO (Eg), 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.

	QO(ox)	QOH_2(red)	MQO(ox)	$MQOH_2$(red)	AQO(ox)	$AQOH_2$(red)
HOMO(g)	-6.67958	-5.53698	-6.55387	-5.48691	-5.95902	-5.59602
LUMO(aq)	-4.31736	-4.92173	-4.42049	-4.89724	-4.32552	-4.95873
HOMO(g)	-6.66326	-5.53616	-6.58135	-5.51684	-6.03984	-5.65154
LUMO(aq)	-4.27137	-4.81587	-4.3824	-4.79982	-4.29369	-4.92145
Eg (g)	-2.36222	-0.61525	-2.13337	-0.58967	-1.6335	-0.63729
Eg (aq)	-2.39188	-0.72029	-2.19895	-0.71702	-1.74616	-0.73008
I(g)	6.67958	5.53698	6.55387	5.48691	5.95902	5.59602
I(aq)	6.66326	5.53616	6.58135	5.51684	6.03984	5.65154
A(g)	4.31736	4.92173	4.42049	4.89724	4.32552	4.95873
A(aq)	4.27137	4.81587	4.3824	4.79982	4.29369	4.92145
μ(g)	4.5761	3.2093	3.6818	3.1387	1.4497	2.5572
μ(aq)	6.224	4.1136	5.1495	4.1437	2.0553	3.3107

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
QO	-5.4984	-5.4903	2.3622	2.3459	6.3993	6.4247	2.3277	2.3404
MQO	-5.4871	-5.5009	2.1333	2.1608	7.0566	7.0018	2.5721	2.5458
AQO	-5.1422	-5.1826	1.6335	1.7143	8.0939	7.8340	3.1480	3.0232

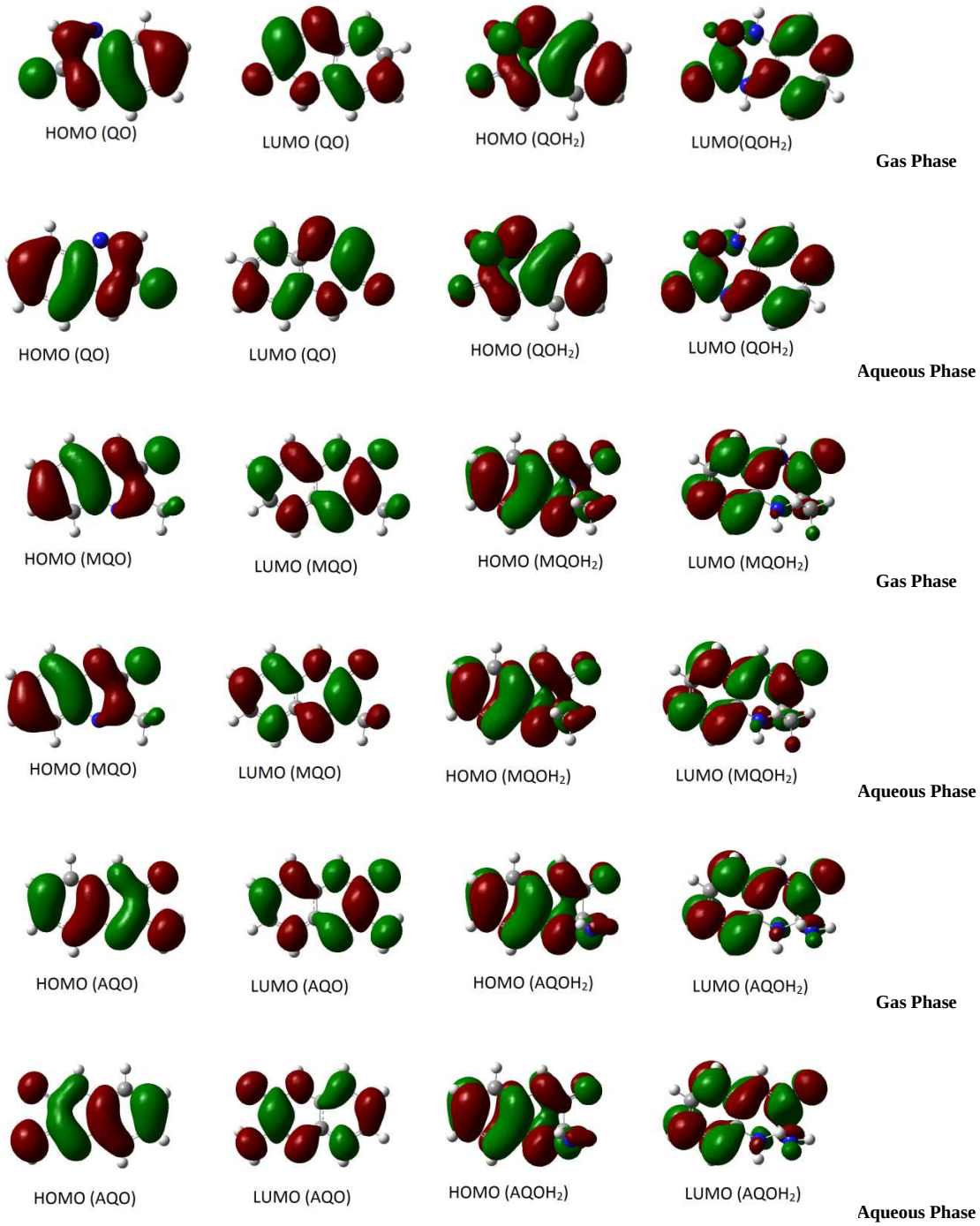
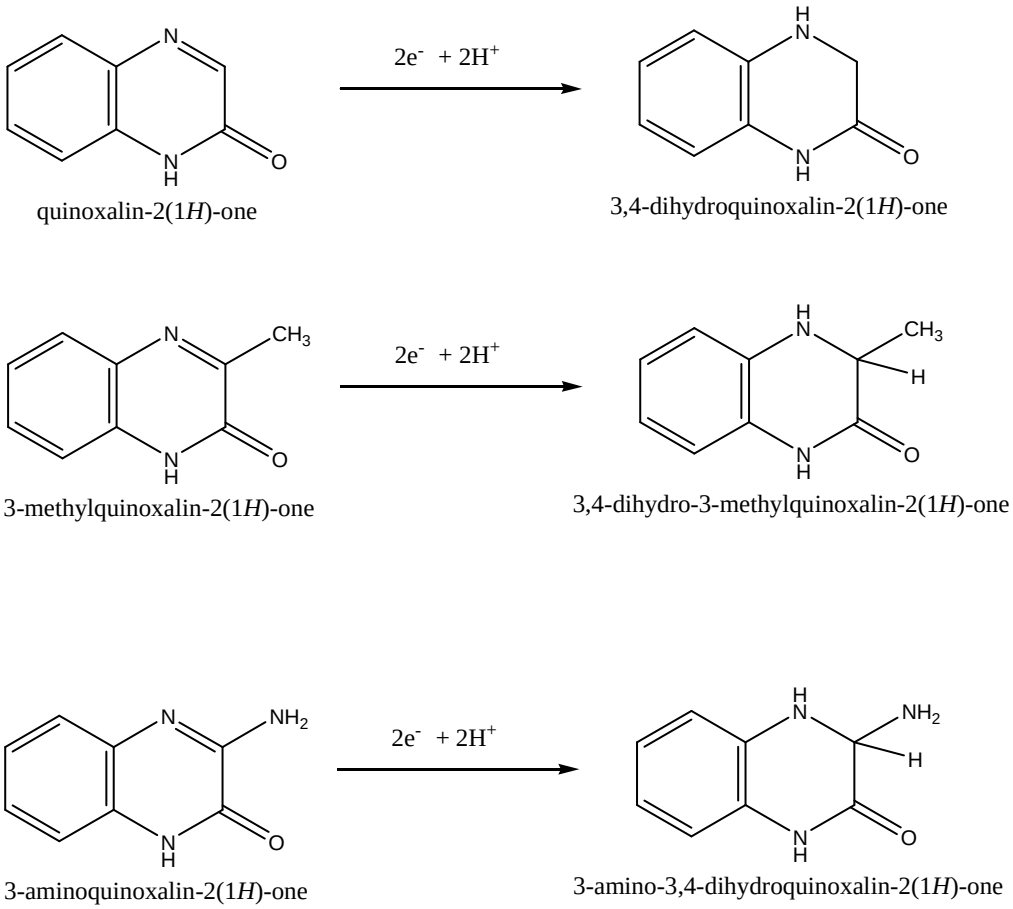


Fig (2) The HOMO and LUMO diagrams of studied molecules at B3LYP/6.311G basis set.



Scheame.1

CONCLUSION

The electrode potentials Quinoxalin-2(H)-one (QO) and its derivatives of 3-methylquinoxalin-2(1H)-one (MQO) and 3-aminoquinoxalin-2(1H)-one (AQO) were calculated in water. Results shows that quinoxalin-2-one, has greater tendency of the oxidized form to get reduced by accepting electrons and the amino derivative of quinoxalin-2-one has greater tendency of the reduced form to get oxidized by donating electrons. Both electron donor and electron acceptor substituents are effective in reducing the energy gap between HOMO and LUMO. The NH_2 substituted Quinoxalin-2(H)-one (AQO) has high value ω, comparison of the CH_3 substituted Quinoxalin-2(H)-one and Quinoxalin-2(H)-one in gas and aqueous phase because of NH_2 is strong electron donor group. Therefore quinoxalin-2-one, the greater is the tendency of the oxidized form to get reduced by accepting electrons and the amino derivative of quinoxalin-2-one is, the greater is the tendency of the reduced form to get oxidized by donating electrons.

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