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A THEORETICAL APPROACH TO THE ASSESSMENT OF PROTONATION ON INHIBITION EFFICIENCY OF AN EXPIRED DRUG

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Abstract

*The quantum theoretical calculations were performed to elucidate the corrosion inhibition efficiency of an expired drug. For this purpose, molecular orbital analysis, which is used in the analysis of chemical interactions and gives detailed data about the electronic structure of molecules, was used to gain insight into the electronic properties of the selected drug molecule in neutral and aqueous form. The calculations were carried out at the (B3LYP) 6-311G**(d,p) basis set level utilizing density functional theory (DFT) to examine the relationship between the molecular structure and inhibition efficiency of the corresponding drug molecule. Various quantum chemical descriptors such as highest occupied molecular orbital energy (HOMO), lowest unoccupied molecular orbital energy (LUMO), energy gap (ΔE), dipole moment (μ), ionization potential (I), electron affinity (A), electronegativity (χ), hardness (η), softness (σ), back donation ($\Delta E_{back\text{-}donation}$) and fraction of electrons transferred (ΔN) were calculated and correlated to the inhibition efficiency. The most probable nucleophilic and electrophilic reactive sites of studied drug molecule were analyzed through computed Fukui indices. Overall, obtained theoretical data indicate that the quantum chemical parameters correlate well with the inhibition performance.*

Keywords: Density Functional Theory (DFT), Inhibition efficiency, Quantum chemical descriptors, Fukui function

SON KULLANMA TARİHİ GEÇMİŞ BİR İLACIN İNHİBİSYON ETKİNLİĞİ ÜZERİNE PROTONASYONUNUN DEĞERLENDİRİLMESİNE YÖNELİK TEORİK BİR YAKLAŞIM

Özet

*Son kullanma tarihi geçmiş bir ilacın korozyon önleme etkinliğini aydınlatmak için kuantum teorik hesaplamalar yapılmıştır. Bu amaçla, kimyasal etkileşimlerin analizinde kullanılan ve moleküllerin elektronik yapısı hakkında ayrıntılı veriler veren moleküler orbital analizi, seçilen ilaç molekülünün nötr ve sulu formdaki elektronik özellikleri hakkında fikir edinmek için kullanılmıştır. Hesaplamalar, ilgili ilaç molekülünün moleküler yapısı ve inhibisyon etkinliği arasındaki ilişkiyi incelemek için yoğunluk fonksiyonel teorisi (DFT) kullanılarak (B3LYP) 6-311G**(d,p) baz seti seviyesinde gerçekleştirilmiştir. En yüksek dolu moleküler orbital enerji (HOMO), en düşük boş moleküler orbital enerji (LUMO), enerji boşluğu (ΔE), dipol moment (μ), iyonlaşma potansiyeli (I) elektron afinitesi (A), elektronegatiflik (χ), sertlik (η), yumuşaklık (σ), geri bağış ($\Delta E_{back\text{-}donation}$) ve transfer edilen elektronların fraksiyonu (ΔN) gibi çeşitli kuantum kimyasal tanımlayıcılar hesaplanmış ve inhibisyon etkinliği ile ilişkilendirilmiştir. Çalışılan ilaç molekülünün en olası nükleofilik ve elektrofilik reaktif bölgeleri hesaplanan Fukui indeksleri aracılığıyla analiz edilmiştir. Genel olarak, elde edilen teorik veriler kuantum kimyasal parametrelerinin inhibisyon performansı ile iyi korelasyon gösterdiğini ortaya koymaktadır.*

Anahtar Kelimeler: Yoğunluk Fonksiyonel Teorisi (DFT), İnhibisyon etkinliği, Kuantum kimyasal tanımlayıcılar, Fukui fonksiyonu

Cite

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1. Introduction

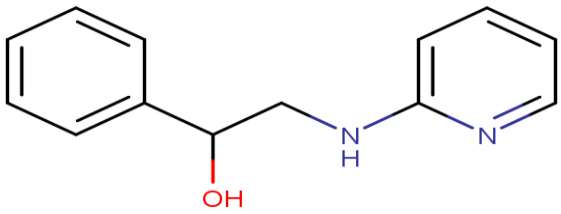
Corrosion is the process by which metals lose their metallic characteristics through chemical or electrochemical reactions with their environment. Corrosion directly or indirectly causes great economic and health problems worldwide. Therefore, the development of corrosion prevention techniques is of crucial importance in industrial and scientific areas [1].

The most important process in controlling corrosion of metals is the elimination, modification or slowing down of the interactions between the metal and the environment. Since many materials are made of metals, they suffer significantly from corrosion. Therefore, preventing corrosion of metals is very important from an economic, safety and resource preservation perspective. Several methods are used to minimize or completely prevent corrosion from a technical and economic point of view [2-4]. One of the most important methods is the determination and addition of the appropriate inhibitor to the metal environment. Corrosion inhibitors are substances added to the corrosion medium to reduce or prevent the corrosive effect. Organic compounds with a ring structure containing heteroatoms (as N, S, O and P) and conjugated bonds are known to have high inhibition activity. [5,6].

Many studies using organic inhibitors to prevent corrosion of metals are available in the literature [7-10]. Recent studies have focused on the use of non-toxic or less toxic inhibitors. In this context, drugs comprise one of the most important categories of environmentally friendly corrosion inhibitors because they are non-toxic, inexpensive and soluble in aqueous media. Although there are many existing studies in the literature in which various types of drugs have been used effectively as corrosion inhibitors [11-14], there are very few studies on the use of expired drugs for this purpose [15-18]. For this reason, our study was focused on the use of expired drugs containing in their composition active materials with inhibition efficiencies. This evaluation method for expired drugs can solve two major drawbacks: prevention of environmental pollution and reduction of the waste costs of such drugs [19].

In recent years, quantum chemical methods which are an important step in the verification of experimental methods have been the subject of many corrosion researches [20-24]. Calculated optimized structure, electronic properties and many other results give us an easy way to find accurate solutions with quantum chemical approach. Theoretical methods are mainly correlated with the quantum molecular parameters including highest occupied molecular orbital energy (E_{HOMO}), lowest unoccupied molecular orbital energy (E_{LUMO}), energy gap (ΔE), dipole moment (μ), ionization potential (I), electron affinity (A), electronegativity (χ), hardness (η), softness (σ), fraction of electrons transferred (ΔN) and Fukui indices. Several quantum parameters related to corrosion inhibitors are evaluated in the vacuum phase. Indeed, acidic inhibitors are widely employed in acidic solutions and can thus be protonated. The protonated form of the inhibitor molecule and the solvent effect must also be considered in the theoretical calculation on these type inhibitors.

The purpose of the present study is to examine theoretically the inhibition efficiency of an expired drug using DFT method that do not have an experimental study on their use as a corrosion inhibitor in the literature. Phenyramidol molecule selected for study, trade name Cabral, is a pharmaceutical drug. Phenyramidol is in a class of analgesic and muscle relaxant drugs and is used to relieve mild to moderate musculoskeletal pain, or the pain associated with muscle spasms which may be caused by sprains. The structure of studied drug molecule is shown in Figure 1.



phenyramidol

Figure 1. 2D molecular structure of drug molecule

2. Material and Method

In this study DFT (density functional theory) Becke's three parameter functional with the Lee, Yang, and Parr correlation functional (B3LYP) 6-311G**(d,p) basis set were applied in vacuum and aqueous solvent with Orca 5.0.4 [25,26]. Avogadro 1.2.0n software for the theoretical calculation of phenyramidol molecule as acidic media corrosion inhibitors were used [27]. HOMO and LUMO densities were obtained from IboView v20150427 [28]. Fukui indices and ESP (electrostatic surface potential) analysis also were calculated with Multiwfn 3.7 [29, 30]. VMD 1.9.4 software for the visualization of ESP [31]. Theoretical corrosion inhibitor descriptors like the Highest Occupied Molecular Orbital energy (E_{HOMO}), Lowest Unoccupied Molecular Orbital energy (E_{LUMO}), the energy gap (ΔE), ionization potential (I), electron affinity (A), electronegativity (χ), hardness (η), softness (σ) and the fraction of electrons transferred (ΔN) were calculated in a vacuum and aqueous phase [32, 33].

Density functional theory (DFT) is the most commonly performed method for understanding molecular characteristics and investigating inhibition performance to describe the behavior of atoms on molecules. [34, 35]. Koopman's theorem supplies an alternative approach for calculate the ionization energy and electron affinity of molecules. [36]. By this theorem, the negative values of the highest occupied and lowest unoccupied molecular orbital energies, respectively, refer to the ionization energy and electron affinity.

$$I = -E_{HOMO} \quad (1)$$

$$A = -E_{LUMO} \quad (2)$$

The HOMO and LUMO energies are related to the molecule's ability to donate and accept electrons, respectively. The energy difference between the HOMO and LUMO defined as energy gap (ΔE) and a small value of ΔE indicates relatively high chemical reactivity.

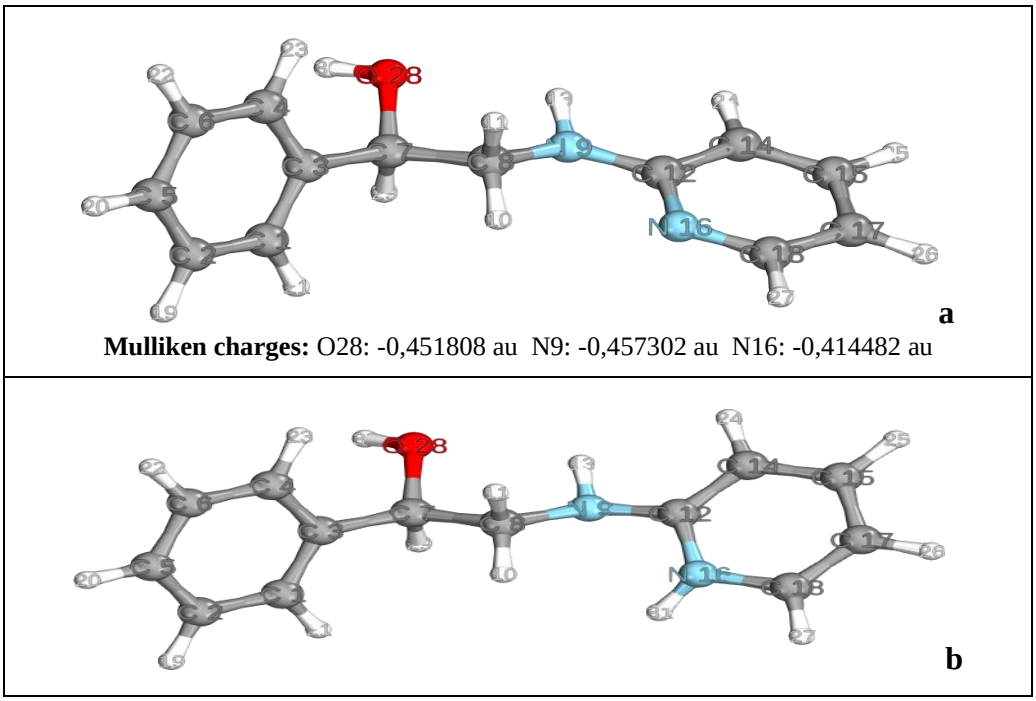
$$\Delta E = E_{LUMO} - E_{HOMO} \quad (3)$$

The electronegativity and the hardness relate to electron affinity (A) and ionization potential (I) and also the softness is defined as the inverse of the hardness.

$$\chi = \frac{I+A}{2} \quad (4)$$

$$\eta = \frac{I-A}{2} \quad (5)$$

$$\sigma = \frac{1}{\eta} \quad (6)$$



Mulliken charges: O28: -0,451808 au N9: -0,457302 au N16: -0,414482 au

Figure 2. Optimized structure of a) neutral form and b) protonated form of drug molecule

The fraction of electrons transferred (N) between the inhibitor molecule and metal surface are calculated by the below given equation;

$$\Delta N = \frac{\chi_{Fe} - \chi_{inh}}{2\,(\eta_{Fe} + \eta_{inh})} \quad (7)$$

χ_{Fe} and χ_{inh} express the absolute electronegativity of iron and the inhibitor, respectively. η_{Fe} and η_{inh} on the other hand, define the absolute hardness of iron and the inhibitor, respectively.

3. Result and Discussion

The optimized molecular structures with atomic numeration of phenyramidol molecule for neutral and protonated forms are shown in Figure 2. The quantum chemical studies about protonated N-heterocyclic compound in the acid solution indicate that the proton affinity is clearly favored toward the hetero N atom of the heterocyclic ring [37]. It is known that the inhibitor molecule can form coordination bonds between the unshared electron pairs of the O, N or S atom and the vacant d-orbitals of the metal atom [38]. The larger negative charge of the atom, the better is the action as an electronic donor. By comparison of Mulliken charges on the atoms of the drug molecule obtained from the optimized structure, the higher negative atoms are found in N16 atom and this atom acts as acceptor for H atom.

The HOMO and LUMO densities of neutral form of drug molecule in vacuum and aqueous phase are given in Figure 3. The red color on the HOMO density surface indicates that the possible sites of where the inhibitor molecule loses electrons. The HOMO density for neutral form of drug molecule in vacuum phase are observed on the pyridine ring and N9 atom. On the other hand, the LUMO density in the red region for a molecule indicate the negative charge. The LUMO density for neutral form of the drug molecule in vacuum phase are observed on the benzene ring and O atom, and also partially on the N atoms. The HOMO density for neutral form of drug molecule in aqueous phase is same as vacuum phase. Differently, the LUMO density for neutral form of molecule in aqueous phase are observed on the benzene ring.

Since corrosion generally happens in the aqueous phase, it is necessary to take into account the solvent effect in the theoretical approaches. The HOMO and LUMO densities of

protonated form of the drug molecule in aqueous phase are given in Figure 4. The HOMO intensity for the protonated form of the drug molecule is observed to be similar to the neutral form but more intense on the pyridine ring and the N9 atom. The LUMO density for protonated form of drug molecule are observed on the pyridine ring, and also partially on the N atoms. In protonated form, clear intensity is observed on N atoms in both the HOMO and LUMO energy densities. This can be explained by the back-donation of the protonated molecule in the aqueous phase from the vacant d orbital of the metal.

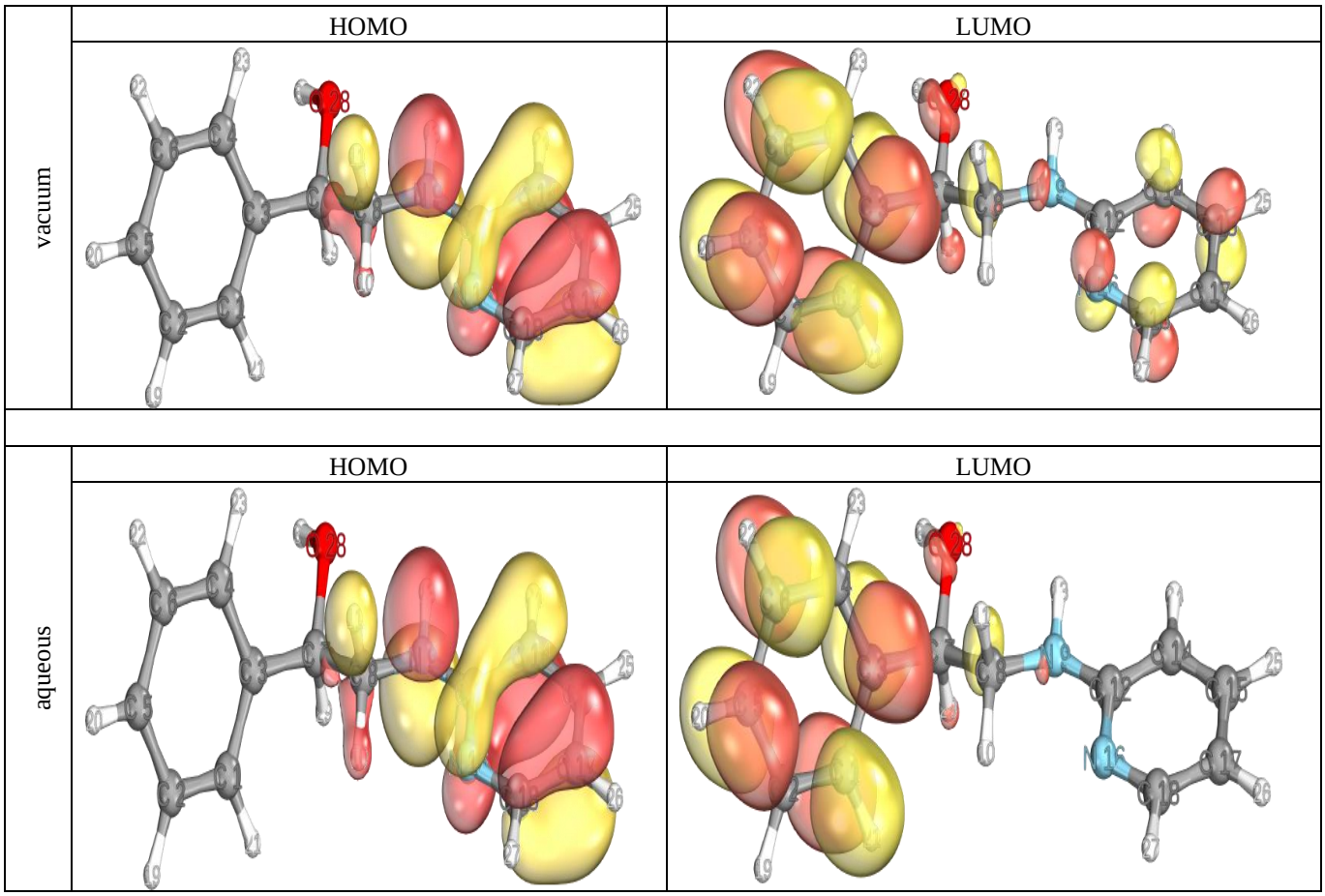


Figure 3. The HOMO and LUMO densities of neutral form drug molecules in vacuum and aqueous phase

The charge distribution variation on neutral and protonated form of drug molecule is shown in Figure 5 as electrostatic surface potentials (ESP). Red and blue colorings on the ESP map correspond to the repulsion and attraction regions on the molecule, respectively. Examining the ESP map of the neutral form, it was observed that both the aqueous and vacuum phases were similar. The electrostatic potential surface of the protonated form shows that the electron density is mostly localized on the 9N atom. It is thought that electrons are given to the vacant d orbital of the metal from this region. The blue colored region on the ESP map is observed to be positively charged and electrons to be acceptor.

The calculated quantum chemical parameters for neutral and protonated forms of drug molecule in aqueous phase are given in Tables 1. The energy of HOMO and LUMO are related to the electron donating and accepting abilities of the molecules, respectively. The high value of HOMO energy indicates that the molecule tends to donate electrons to suitable acceptor molecules with low energy and vacant molecular orbitals. In spite of this, the lower value of LUMO energy indicates the molecule to accept electrons. This means bonding interaction between the inhibitor molecule and the metal surface [39]. On the contrary, lower values of the energy gap (ΔE) will provide good inhibition efficiency. In the direction of this information analyzing the data in Table 1, it is observed that the protonated form of the drug molecule has a greater inhibition efficiency compared to the neutral form.

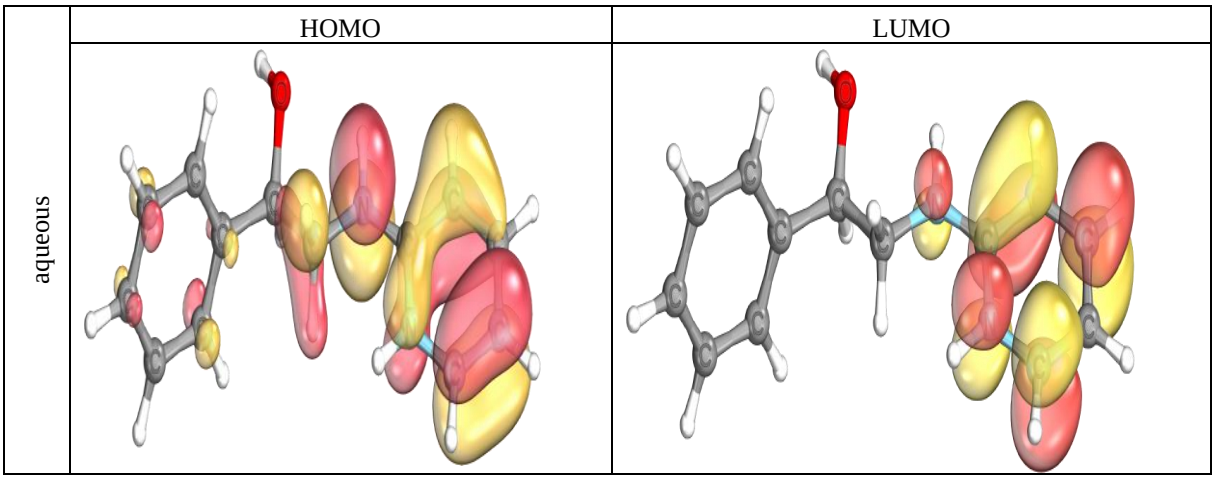


Figure 4. The HOMO and LUMO densities of protonated form drug molecules in aqueous phase

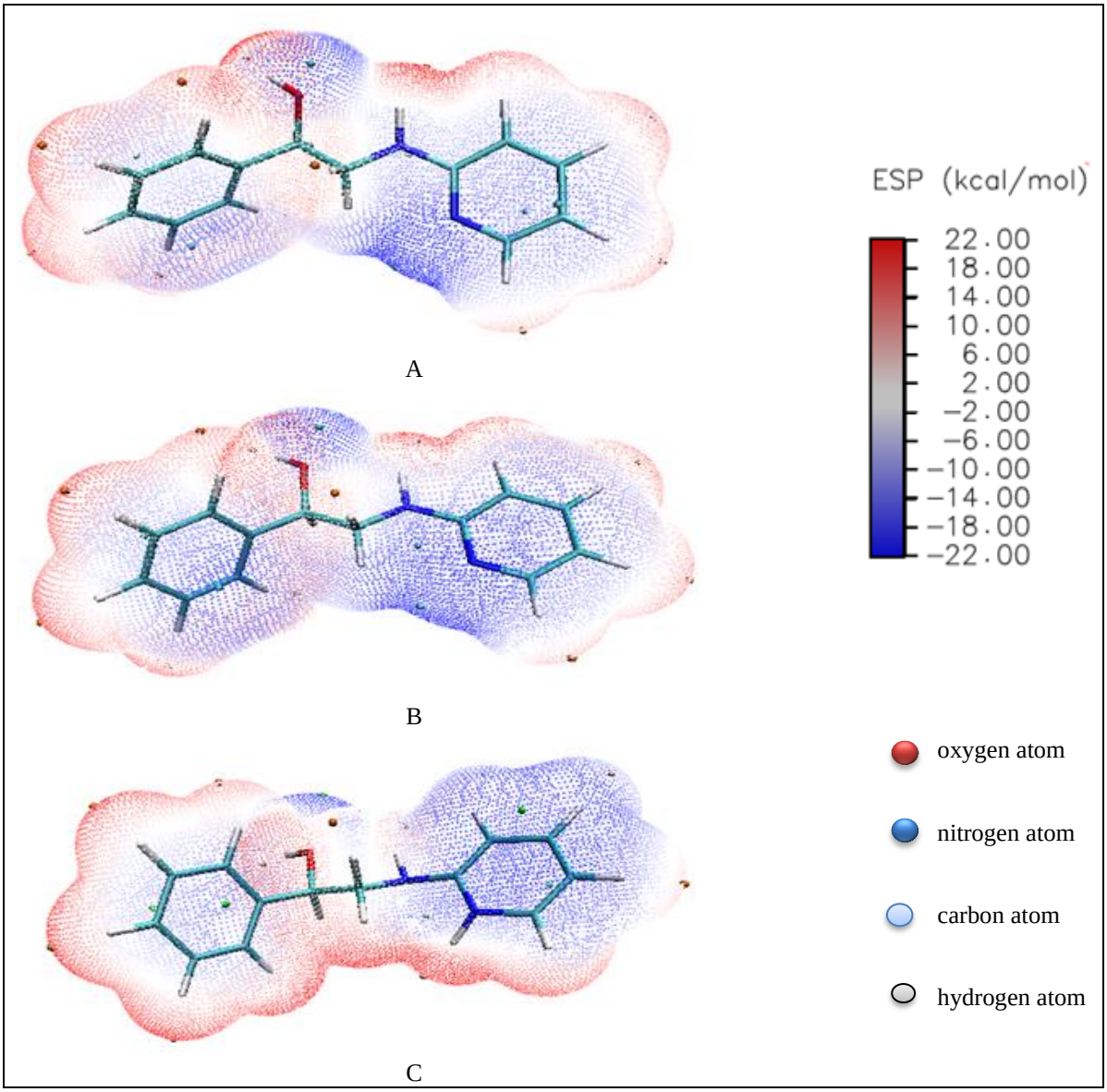


Figure 5. The electrostatic surface potential (ESP) for a) neutral form in vacuum phase b) neutral form in aqueous phase c) protonated form in aqueous phase of drug molecule

The most widely used parameter to describe polarity is the dipole moment of a molecule. Protonated form of the drug molecule has higher value of dipole moment than neutral form as seen in Table 1, which means the inhibition efficiency enhances on protonated form through electrostatic force.

Electronegativity, another important parameter in the estimation of the inhibition efficiency of molecules, expresses the power of chemical structures to attract electrons. A higher electronegativity value refers to stronger attraction of the molecule resulting in higher inhibition efficiencies. Comparing the calculated electronegativity values in Table 1, it can be observed that the protonated form of the drug molecule has a higher value than the neutral form and is a better corrosion inhibitor.

Chemical hardness is a parameter related to the resistance of an atom to charge transfer. Chemical softness is the inverse of chemical hardness and indicates the reactivity of inhibitor molecules. The protonated form of the drug, which is a softer molecule with a low ΔE value, is a good corrosion inhibitor because it can easily donate electrons to metal [40-42].

Table 1. Calculated quantum chemical parameters for neutral and protonated forms of drug molecule in aqueous phase

	E_{HOMO}	E_{LUMO}	ΔE	I	A	χ	η	σ	μ	ΔE_{bd}	ΔN
neutral	-5.681	-0.582	5.099	5.681	0.582	3.131	2.550	0.392	3.005	-0.637	4.932
protonated	-6.722	-1.862	4.861	6.722	1.862	4.292	2.430	0.411	9.990	-0.608	3.291

$\Delta E_{back\text{-}donation}$ is defined as the transfer of electrons from the metal's surface to the inhibitor molecule. $\Delta E_{back\text{-}donation}$ is calculated on the equation below:

$$\Delta E_{back-donation} = -\frac{\eta}{4} \quad (8)$$

when $\Delta E_{back\text{-}donation}$ <0 or η>0, back-donation from the inhibitor molecule to metal is energetically favoured. Higher the value of $\Delta E_{back\text{-}donation}$, the higher the inhibition efficiency. In this content, protonated from of drug molecule has a higher backdonation value.

The fraction of electrons transferred (ΔN) indicates that inhibition ability resulting from electron donation. This parameter refers the transfer of electrons from molecule to metal if ΔN > 0, and from metal to molecule if ΔN < 0 [43]. The obtained positive values of ΔN from Table 1 shows the electrons are transfer from drug molecule to metal.

The Fukui functions are one of the local reactivity descriptors based on electron density and allow the estimation of the most nucleophilic and electrophilic regions on a molecule. The Fukui functions on a k atom are defined for nucleophilic (f_k^+) and electrophilic (f_k^-) attack as shown below:

$$f_k^+ = q_k\,[N] - q_k\,[N+1] \quad (9)$$

$$f_k^- = q_k\,[N-1] - q_k\,[N] \quad (10)$$

where $q_k\,[N+1]$, $q_k\,[N]$, and $q_k\,[N-1]$ define the charges at atom k on the anion, neutral, and cation species, respectively [44]. The values of Fukui indices for drug molecule are given in Table 2. The high f_k^+ and f_k^- mean values indicate that the atom has a high capacity to accept and give electrons, respectively.

Table 2. The calculated Fukui indices for neutral and protonated form in aqueous phase of drug molecule

Neutral			Protonated		
Atom	f_k^+	f_k^-	Atom	f_k^+	f_k^-
1C	0,001486	0,005316	1C	0,002505	0,029588
2C	0,001537	0,004041	2C	0,002333	0,029159
3C	0,000191	0,000224	3C	-0,000060	0,038287
4C	0,000994	0,006968	4C	0,002592	0,039423
5C	0,002254	0,006845	5C	0,003108	0,058273
6C	0,001639	0,004715	6C	0,002298	0,026934
7C	0,005791	0,010565	7C	0,008089	0,014711
8C	0,014792	0,031260	8C	0,021129	0,030510
9N	0,051341	0,163694	9N	0,085351	0,095051
12C	0,065935	0,054419	12C	0,086057	0,022975
14C	0,115124	0,096766	14C	0,078854	0,061753
15C	0,146867	0,045136	15C	0,128509	0,035322
16N	0,122269	0,074367	16N	0,094472	0,039058
17C	0,056076	0,111664	17C	0,050943	0,064789
18C	0,130315	0,075459	18C	0,107446	0,060474
28O	0,007854	0,010643	28O	0,009042	0,018266

Since the corrosion process is carried out in an acidic media, it is known that the inhibitor molecule is protonated from the most electrophilic region. Therefore, the examination of the protonated form of the selected drug molecule in the theoretical investigation is thought to give more accurate results. The Fukui indices of the neutral form, the values of f_k^- indicate that the 9N atom, can bond electrons to hydrogen atoms. In protonated form, the most reactive nucleophilic attack site is 16N atom, which can accept electrons from surface of the metal. The values of f_k^- on the 9N atom can give electrons to surface of the metal to form a coordinate bond.

4. Conclusions

In the present theoretical approach, quantum chemical parameters commonly accepted in corrosion studies have been calculated using the DFT methods at B3LYP level combined with four basis sets to clarify the inhibition performance of a selected drug molecule against corrosion of mild carbon steel. Regarding the theoretical method we can say that the DFT method is very useful in determining the design of inhibitor molecules without the need for experimental studies.

The other main conclusions are as follows:

- Theoretical studies for corrosion inhibitor indicate that the heteroatoms as N and O in the drug molecule can offer ideal sites for protection on the metal surface.

- Protonated form of phenyramidol molecule has a higher HOMO energy, a lower LUMO energy, and a lower energy gap value indicating a good corrosion inhibitor.

- Quantum chemical descriptors such as electronegativity (χ), global hardness (η), global softness (σ) and transferred electron rate (ΔN) are well exhibited for corrosion inhibitor behavior. The descriptor results indicate that the corrosion the inhibition efficiency to be due to the presence of heteroatoms and p electrons on the benzene ring which results in adherence to the metal surface through electrostatic interactions with the metal and/or charge transfer to the vacant d-orbital of the metal, resulting in bond formation with the metal.

- The calculation of Fukui indices gives an acceptable reactive system for the corrosion inhibition efficiency of the drug molecule under investigation.

- This theoretical study is shown that this class of organic molecules (phenyramidol derivatives) can be effective corrosion inhibitors.

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