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ANTI-CORROSION CHARACTERISTICS OF AMPICILLIN AND FLUCLOXACILLIN DRUGS: A THEORETICAL STUDY

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ABSTRACT. To determine the inhibition efficiency of a corrosion inhibitor, multiple experimental measurements need to be carried out, which is a time-consuming and resource-intensive task. On the other hand, quantum chemical methods are useful research tools for corrosion scientists. In this study, the corrosion inhibition effects of ampicillin and flucloxacillin at the molecular level were evaluated considering some descriptors by density functional theory (DFT) at B3LYP/6-311++G(d,p) level.

1. INTRODUCTION

Most industrial sectors, including oil and gas, desalination, and chemical, are plagued by various corrosion issues causing huge economic loss. Much of this loss can be avoided by using some strategies to control corrosion, one of which is to use corrosion inhibitors. A corrosion inhibitor can be defined as a material that, when added at appropriate levels to a corrosive medium, dramatically reduces the corrosion rate [1].

The active ingredients of pharmaceuticals have been extensively investigated with respect to the presence of structures in their molecules that facilitate interactions with metals: aromatic rings, N, O or S atoms containing lone pair electrons, etc. [2-4]. In this context, Alfakeer et al. has recently reported the successful use of two expired drugs, viz.

Keywords. Corrosion, inhibition, density functional theory, ampicillin, flucloxacillin.

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ampicillin and flucloxacillin (Figure 1), as corrosion inhibitors of mild steel in aqueous sulfuric acid (1.0 M H_2SO_4) [5]. They carried out weight loss, electrochemical potentiodynamic polarization, and electrochemical impedance spectroscopy measurements to test the protective effect of those two inhibitors. Given that this work possesses a pronounced experimental dimension, it needs to be addressed more deeply through computational research.

Computational chemistry has become an important complement to experimental corrosion science. As computational methods continue to improve, their use in corrosion studies is likely to become even more widespread [6]. This paper throws light on the origin of the observed inhibition properties of the drugs mentioned above by using the density functional theory (DFT) method.

2. COMPUTATIONAL DETAILS

Two structures are subjected to geometry optimization using B3LYP/6-311++G(d,p) in Gaussian 09W, followed by frequency calculations to confirm that the optimized molecule represents geometry minima [7]. The re-optimization in water was achieved by the integral equation formalism version of the polarizable continuum model. Global reactivity descriptors were calculated by Eqs. 2.1–2.4 [8]:

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v}\left(\underset{r}{\rightarrow}\right) \approx -\frac{(IP+EA)}{2} = \frac{E_{\mathrm{LUMO}}+E_{\mathrm{HOMO}}}{2} = \chi \tag{2.1}$$

$$\eta = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v}\left(\underset{r}{\rightarrow}\right) = \left(\frac{\partial \mu}{\partial N}\right)x_{v}\left(\underset{r}{\rightarrow}\right) = \frac{E_{LUMO}-E_{HOMO}}{2} \tag{2.2}$$

$$S = (2\eta)^{-1} \tag{2.3}$$

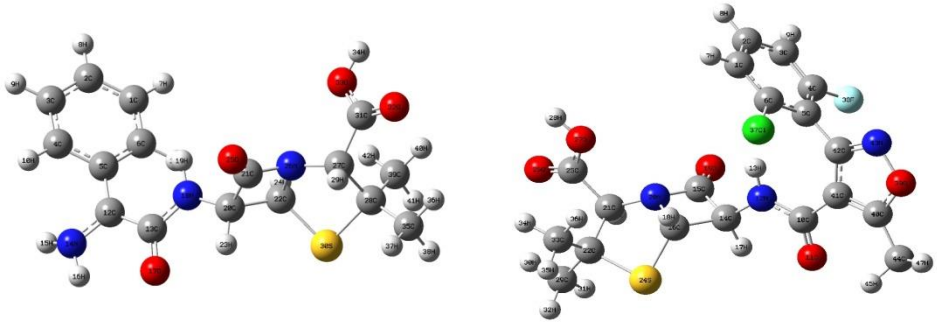
$$\omega = \frac{\mu^2}{2\eta} \tag{2.4}$$

Where μ is the electronic chemical potential, η is chemical hardness, ω is the electrophilicity index, E is the total energy, and v is the external potential. IP and EA refer to $-E_{\mathrm{HOMO}}$ (the energy of the highest occupied molecular orbital) and $-E_{\mathrm{LUMO}}$ (the energy of the lowest unoccupied

molecular orbital), respectively. The fraction of electrons transferred (ΔN) was also estimated by Eq. 2.5.

$$\Delta N = \frac{\chi_{Fe}-\chi_{inh}}{2(\eta_{Fe}+\eta_{inh})} = \frac{\Phi-\chi_{inh}}{2\eta_{inh}} \quad (2.5)$$

Here, Φ is the work function that corresponds to the iron's theoretical electronegativity value (Φ = χ_{Fe} = 4.82 eV), and the global hardness accounts for the iron heft (η_{Fe} = 0 eV) [9].



a **b**

Figure 1. Optimized structures at the B3LYP/6-311++g(d,p) level for (a) ampicillin and (b) flucloxacillin in aqueous phase.

3. RESULTS AND DISCUSSION

Ampicillin, belonging to the penicillin group of beta-lactam antibiotics, differs from penicillin only by the presence of an amino group. On the other hand, flucloxacillin, as a member of the isoxazolyl series of semisynthetic penicillins, has an isoxazolyl group on the side chain of the penicillin nucleus, which is responsible for its ß-lactamase resistance. As reported by Alfakeer et al. [5], higher inhibition efficiency (IE) values found for ampicillin compared to those of flucloxacillin could be explained in terms of the steric impacts and the extent of the electronic density of donor atoms involved in the molecules. The properties of these compounds in their neutral forms can be analyzed even more thoroughly. Molecular orbital analysis, widely used in chemical interaction analysis, gives helpful hints on their electronic structure.

The essence of HOMO-LUMO interaction has been understood in connection with the alteration of molecular geometry along the reaction coordinate. Although, in an actual sense, this can never be a simple concept, E_{HOMO} is an unwavering measure of the propensity for the electron donation of a molecule. Higher values of E_{HOMO} are thus considered indicators of better electron donation. This gives rise to enhanced adsorption of the inhibitor on mild steel and elevated inhibition efficiency. However, the opposite is true for the E_{LUMO}. Since this parameter manifests the electron acceptance tendency, its lower values are deemed compatible for the best efficiency. The difference between the E_{LUMO} and E_{HOMO} is the energy gap of the molecule (i.e., $\Delta E_{L-H} = E_{LUMO} - E_{HOMO}$), and this, in fact, makes possible the dexterous use of the softness or hardness of a molecule. Soft molecules are more reactive than hard molecules. It would then be useful to compare the electronic properties in light of these explanations. Some quantum chemical parameters associated with these molecular electronic structures were correlated with the corresponding percent experimental inhibitory efficacy in Table 1.

TABLE 1. The molecular electronic parameters of two drugs calculated at theB3LYP/6-311++G(d,p)level of theory.

Parameters	Phase [b]	Ampicillin	Flucloxacillin
IE (%)[a]		91.02	88.99
E_{HOMO} (eV)	G	-4.831	-6.887
	A	-4.783	-6.841
E_{LUMO} (eV)	G	-1.002	-1.618
	A	-1.052	-1.494
ΔE (eV)	G	3.829	5.269
	A	3.731	5.347
ω	G	2.222	3.433
	A	2.282	3.249
X	G	2.917	4.253
	A	2.918	4.168
η	G	1.915	2.635
	A	1.866	2.674

S	G	0.261	0.189
	A	0.268	0.187
ΔN	G	0.497	0.108
	A	0.510	0.122

[a]Ref. [5]. [b]G, gas phase (ε = 1.0); A, aqueous phase (ε = 78.5)

The frontier molecular orbital pictures of both molecules are shown in Figure 2. As can be seen, the HOMO orbitals for ampicillin are enriched near benzene rings, whereas LUMO orbitals are mainly dominated by orbitals originating from the 2-amino-2-phenylacetamido group, i.e., penam ring. The HOMO orbitals of flucloxacillin are distributed on ß-lactam moiety fused with thiazolidine ring, while the LUMO orbitals have significant orbital density on the 6ß-[3-(2-chloro-6-fluorophenyl)-5-methyl-1,2-oxazole-4-carboxamido] side chain.

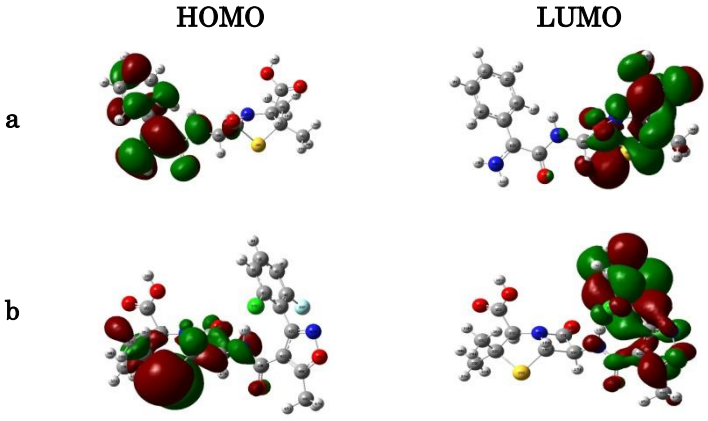


Figure 2. Plots of the HOMO and LUMO orbital distribution for (a) ampicillin and (b) flucloxacillin.

From the resulting data shown in Table 1, it is evident that the HOMO energies of ampicillin are higher, and the LUMO energies of ampicillin are lower than those of flucloxacillin in both phases. Accordingly, the energy gap values of ampicillin are smaller than those of flucloxacillin. Consequently, the electron transfer from HOMO to LUMO in ampicillin is relatively easier than that in flucloxacillin. A more reactive nucleophile

is recognized by a low value of ω, while conversely, a good electrophile is one characterized by a high value of ω. In this regard, ampicillin behaves as a nucleophile in both phases. A hard molecule has a large energy disparity, and a soft molecule has a small one. Soft molecules are more reactive than hard ones because they can easily offer electrons to an acceptor. As is seen, the values of η for ampicillin are lower than those of flucloxacillin, whereas S values are found to be higher in both phases.
In general, the fraction of transferred electrons is also the largest for ampicillin. ΔN values showed that the inhibition efficiency resulting from electron donation is in accordance with Lukovits's study [10, 11]. If $\Delta N <$ 3.6, the inhibition efficiency increases by increasing the electron-donating ability to the metal surface. Therefore, the inhibitive effectiveness order is ampicillin > flucloxacillin. As a result, a satisfactory agreement has been found between the calculated and experimental data.

4. CONCLUSION

DFT calculations correlated the electronic structure parameters of both drugs with the corrosion inhibition. The reliability of the B3LYP/6-31++G(d,p) method employed here is confirmed by a perfect correlation between the theoretical and experimental data. On account of the predominance of dipole interactions by water in aqueous phase calculations, the structures of the compounds in the gas phase are found to have proportionately less pronounced effects on the observed inhibition efficiency. The calculations reveal that ampicillin, with the more favorable parameter values, exhibits better inhibition performance than flucloxacillin, which is in agreement with the electrochemical measurements.

Author Contribution Statement Gökhan Gece—Planning, execution, analysis, calculation, interpretation, writing, editing. Semra Bilgiç—Planning, interpretation, review.

Declaration of Competing Interests The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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