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Studies of some metal ions complexes and her antimicrobial activity by DFT and molecular Docking.

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In court discovering new drugs for the purpose of our work is to confirm the tridentate ligand complexations mechanism 2, 5-Diamino-1, 3, 4-tiadiazole [1] with Co (II), Ni (II) and Cu (II) using the DFT. The metal chelates have antimicrobial activity and for this we studied the molecular docking of these complex and penicillin binding proteins (PBPs) for the best complex of the enzyme with the metal complex to discover new drugs. Density functional theory (DFT) was used, using the B3LYP functional and the 6-31G (d) basis set. This level of calculation was used to find the complex structure and Fukui function values (NK), Local indices Nk and chemical reactivity parameters stemming from conceptual DFT and molecular docking using the UCSF Chimera software to predict the activity antimicrobial of these complexes and also the enzyme. For our work we confirmed the attack sites for the ligand 2, 5-Diamino-1, 3, 4-tiadiazole using conceptual DFT and for that training octahedral complex that we tune antimicrobial activity. It makes docking of these metallic complexes to study theirs antimicrobial activities with the Chimera software and found that the best complex is copper complex then this is the best inhibitor.

Keywords: Metal complexes, Conceptual DFT, Interaction, Molecular Docking.

INTRODUCTION

The increasing resistance of the microorganisms towards antibiotics has been led to serious health problems in the recent years. Most infection-causing bacteria are resistant to at least one of the antibiotics that are generally used to eradicate the infection. [2]This problem encourages the researchers to study the new agents which can effectively inhibit microbial growth.

Metallo-antibiotics can react with many bimolecular like DNA, RNA, necessary protein receptors and lipids, creating them very exclusive and significantly bioactive. [3-4]

The efficacies of many therapeutic agents are known to improve coordination; therefore the metal-based drug is seen as possible alternative for present drugs. [5] In this work is to confirm the mechanism of complexations of tridentate ligand 2, 5-diamino-1-3, 4-tiadiazole [1] with Co(II), Ni(II) and Cu(II) using DFT. The importance of these compounds, a part from their structural characteristics and various chemical, stems not only from their potential but also their proved application as bio-active molecules and a broad spectral range of activity [6]Density functional theory (DFT) [7] is one of the important tools of quantum chemistry to understand the popular chemical concepts like electro negativity and chemical potential [8]The electron density based local reactivity descriptors; local hardness $h(r)$ [9]local softness $s(r)$ and the Fukui function $f(r)$ [10]were proposed to explain the chemical selectivity or reactivity at a particular site of a chemical system. Recently [11] showed that these local descriptors of DFT are essentially important in searching the “similarity of reactivity” of a group of molecules or atoms that are similar (in their struc-

ture and by extension in their electron density distribution). Electron density *r*(*r*) is a property that contains all of the information about the molecular system and plays an important role in calculating almost all these chemical quantities. It has also been shown that local hardness *h*(*r*) is a reliable intermolecular reactivity descriptor [12] and the local softness *s*(*r*) and Fukui function *f* (*r*) are more reliable intramolecular site selectivity descriptors [13-20]

II. Basic concepts

The first derivative of the chemical potential *í* with respect to the external potential *ù* (r), or equivalently, as the first derivative of the electron density F (r) with respect to the number of electrons N

$$\mu = (\delta E / \delta N)\, v(r) = -\chi \quad (1)$$

The concept of hardness (*è*) has found its mathematical identification in DFT as the second derivative of the total energy with respect to the number of electrons, *N* [21, 22]

$$\eta = (\delta^2 E / \delta N^2)\, v(r) = (\delta \mu / \delta N)\, v(r) \quad (2)$$

Where the chemical potential *í*, is the first derivative of the total energy relative to the electron number. Derivatives are taken at constant external potential, *ù*(**r**). Softness is defined as the inverse of hardness

$$\sigma = 1/\eta \quad (3)$$

Ionization potential (I) is defined as the amount of energy required to remove an electron from a molecule [23]. It is related to the energy of the E_{HOMO} through the equation:

$$I = -E_{HOMO} \quad (4)$$

Electron affinity (A) is defined as the energy released when a proton is added to a system [23]. It is related to E_{LUMO} through the equation

$$A = -E_{LUMO} \quad (5)$$

Using a finite difference method working equations for the calculations of χ and η may be given as

$$\chi = (I+A)/2 \quad (6)$$

$$\eta = I - A \quad (7)$$

Where I is the ionization potential and A is the electron affinity. If ε_{HOMO} and ε_{LUMO} are the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), respectively. The equations (5) and (6) can rewrite using Koopman's theorem [24].

$$\chi = (\varepsilon_{LUMO} - \varepsilon_{HOMO}) \quad (8)$$

$$\eta = \varepsilon_{LUMO} - \varepsilon_{HOMO} \quad (9)$$

The Fukui function measures how sensitive a system's chemical potential is to an external perturbation at a particular point. Actually, great attention is paid to the computation of FF values as indicators of reactivity, which may avoid the precise study of the energy hypersurface. For a molecular or atomic system, the above derivatives are discontinuous and difficult to evaluate. Hence, different operational definitions of FF are still being developed [25-26] and applied [27-28].

The most common definitions used are those proposed by Yang and Parr [29]

$$f^{+}_{K} = q_{N+1} - q_N \quad \text{governing nucleophilic attack,} \quad (10)$$

$$f^{-}_{K} = q_N - q_{N-1} \quad \text{governing electrophilic attack,} \quad (11)$$

Where q_N, q_{N+1} and q_{N-1} are the electronic population of the atom k in neutral, anionic and cationic systems. According to Domingo et al. [30, 31], the global nucleophilicity index, N, is defined by the following formula

$$N = \varepsilon_{HOMO(Nu)} - \varepsilon_{HOMO(TCE)} \quad \text{in eV units} \qquad (12)$$

Where εHOMO $_{(Nu)}$ is associated to the HOMO energy within the Kohn–Sham scheme [32, 33] and εHOMO $_{(TCE)}$ corresponds to the HOMO energy of the tetracyanoethylene (TCE) taken as reference. Satisfactory linear correlation has been found between experimental ionization potentials and calculated nucleophilicities for a large series of molecules. The local nucleophilicity index $N_{k.}$

The global nucleophilicity index (N) can be expressed as the sum of local nucleophilicities condensed to all atoms of the molecule:

$$N = \Sigma N_k \qquad (13)$$

From the above definition of the global nucleophilicity, it is possible to define the local nucleophilicity condensed to an atom k through the nucleophilic Fukui function, f^-k [34]

$$N_k = N f^-_k \qquad (14)$$

DFT provided a quantitative measure for a qualitative concept that was so successfully used in a description of Lewis acids and bases [35]. Parr and Pearson also derived simple expressions for the amount of charge transfer ΔN and energy change ΔE which accompany the formation of A: B complex from acid A and base B. These expressions are

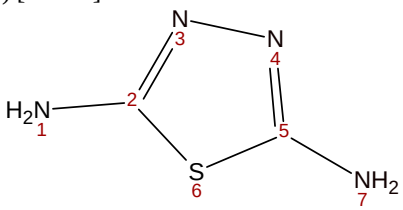
$$\Delta E = -(\chi_A - \chi_B)^2 / 4(\eta_A + \eta_B) \qquad (15)$$

$$\Delta N = (\chi_A - \chi_B) / 2(\eta_A + \eta_B) \qquad (16)$$

RESULTS AND DISCUSSION

III.1.1. Part one: Geometry optimization

The equilibrium geometry optimization for our legend (figure 1) has been achieved by energy minimization, using DFT at the B3LYP level, employing the basis set 6-31G (d). The electronic populations as well as the Fukui indices and local nucleophilicities are computed using different populations' analysis MPA (Mullikan population analysis) and NPA (natural population analysis) [36- 39]



2,5-Diamino-1,3,4-thiadiazole

Figure 01: 2, 5-Diamino-1, 3, 4-thiadiazole

Table01: The Fukui function values f^- and f^+, locals nucleophilicity indexes NK of the sites N1, N3, N4, N7, and S6

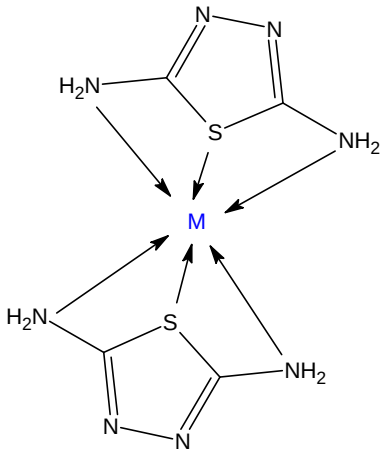
	neutre	cation	anion	f^+	f^-	W^+	NK
N1	-0,9576	-0,22012	-0,47656	-0,48104	0,73748	-0,01579495	2,76436848
N3	-0,31658	-0,01407	-0,1802	-0,13638	0,30251	-0,00447804	1,13392785
N4	0,33962	0,21067	0,17968	0,15994	-0,12895	0,00525163	-0,48335591
N7	-0,95654	-0,21993	-0,48775	-0,46879	0,73661	-0,01539272	2,76110738
S6	-0,32139	-0,01388	-0,18196	-0,13943	0,30751	-0,00457818	1,15266984

Table02: The HOMO and LUMO energies, HOMO-LUMO gaps, Potential, Hardness, Electrophily and Nucleophily

Legend	HOMO	LUMO	GAP	POTENTIAL	HARDNESS	ELECTROPHILY	NUCLEOPHILY
Energies (KJ/mol)	-0.21104	-0.00587	-0.20517	-0.108455	0.20517	0.0328501	3.7483979

Analysis of the local nucleophilicity indices and Fukui function values NK given in Table 01 show that the N1, N7 and S6 sulfur atom are characterized by the highest values, local nucleophilicity of indices and values of the function Fukui and other data also show that N1, N7 and S6 atoms are the attacks centers.

The HOMO energy, -0.21104 a.u, of the reference system (TCE) has been calculated at the same computational level.



The structure of complex(M=Co(II), Ni(II), Cu(II))

Figure 02: The structure of complex (M=Co(II), Ni(II), Cu(II))

III.1.2. Coordination 4 and 6 around the central atom

Previous work reported that the interaction between our ligand in the figure 01 and metals ions, being an important branch of analytical chemistry and they presented contributes to a deeper understanding of the coordination modes of sulfur and Nitrogen of the amines groups to transitions metal ions. [40]

As a result, the atoms N1, N7 and S6 are the most reactive centers, which have the greatest ability to bind to the metal surface.

Ligands bind copper ions, and nickel Cobalt through mode polydentate coordination with N1, N7 and S6. Only coordination 6 around the central atom has been considered. The central atom Cu (II), Co (II) and Ni (II) coordinated with four nitrogen atoms N per square plane (coplanar) and the apical position (axial) in two sulfur molecules (Fig 2.) also for Nickel and Cobalt.

The 2, 5-diamino-1, 3, 4-thiadiazole coordinate with nitrogen of the amines and sulfur atom forming three binding chelating sites. So the proposed structure is octahedral [41]

III.2. Part two: Molecular Docking

For this part was used for Chimera software studying the Inhibit the enzyme (PDB ID: 3HUM) was obtained from protein data bank. 3D with the three complexes (copper, nickel and cobalt) were built using EMO (Energy of Molecule) program, and docked into the active site of the enzyme after energy minimized.

The studies of the metal complexes and ligand gave the antimicrobial activity of the compounds. Generally, the metal complexes and ligand show antimicrobial effect against the tested organism species [1]

Table03: The energies of the docking of our complexes and the enzyme

Complexes	Copper complex	Nickel complex	Cobalt complex
Energies(KJ/mol)	**-7.4**	-6.8	-6.0

From Table 03 we see that the energy of the copper complex of complexation with the enzyme is the lowest so you could say that the copper complex is the best inhibitor.

Figure 03: The complex of copper and 3HUM enzyme

We notice in Figure 03 that the complex binds copper in the active site and reacts as an inhibitor to change the enzymatic reaction rate of Penicillin binding proteins that catalyze the final step of murein biosynthesis.

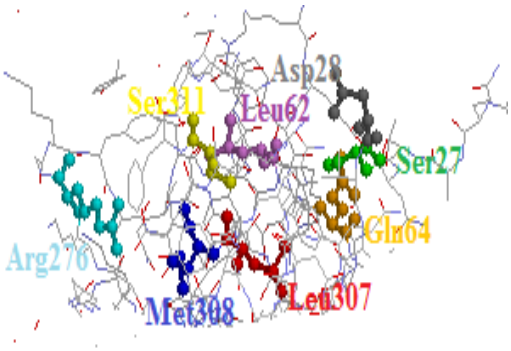


Figure 3: Residues of the active site

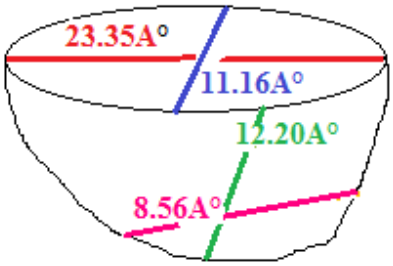
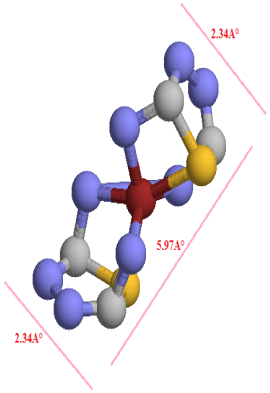
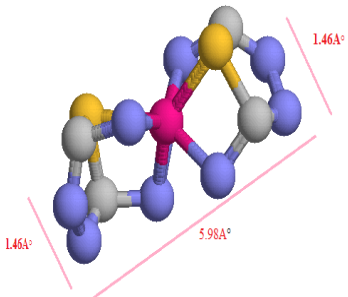


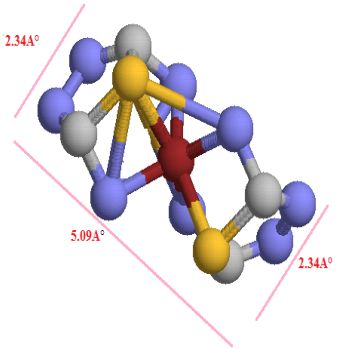
Figure 4: enzymatic cavity



Copper complex



Cobalt comlex



Nickel complex

Note that we can discuss complementarity in increasing or decreasing the interval size of the active site pocket, in our case with a geometry of 12.20 Å depths, opening 23.35 Å 11.16 Å, this pocket is narrowed up to a width of 8.56 Å

Table04: the distances between the amino-acids of the active site and our inhibitors of the same cavity

	Copper complex	Nickel complex	Cobalt complex
LEU307	2.826 Å	3.107 Å	3.775 Å
SER27	1.936 Å	3.054 Å	3.284 Å
MET308	2.686 Å	2.797 Å	3.078 Å
SER311	3.457 Å	3.257 Å	3.458 Å
LEU62	2.319 Å	3.274 Å	3.201 Å
GLN64	3.309 Å	3.527 Å	3.118 Å
ARG 276	2.178 Å	3.787 Å	3.921 Å
ASP28	3.292 Å	3.821 Å	3.971 Å

The measured distances of the complexes of copper vary between 1.936 Å and 3.457 Å.

The interactions between 2.5 Å and 3.1 Å are considered high and those between 3.1 Å and 3.55 Å are assumed averages. Interactions greater than 3.55 Å are weak or absent [42].We see the copper complex is the best because it allows to better present the key-lock rule and this according to their interactions with the different amino acids of the active site.

CONCLUSION

For our work we confirmed the attack sites for the legend 2, 5-Diamino-1, 3, 4-tiadiazole using conceptual DFT and for that training octahedral complex that we tune antimicrobial activity.

Quantum mechanical calculations used for calculated the Fukui functions values, f¯k, locals nucleophilicity indexes Nk, HOMO and LUMO energies, HOMO-LUMO gaps and other reactivity descriptors for found the governing nucleophilic attack, governing electrophilic attack and governing radical attack. In our study the local indices nucleophilicity Nk of our legend were discussed in a simple but precise manner. The distribution of the electron density shows that the compounds studied had many active centers in nucleophilicity. The areas containing the Sulfur and Nitrogen of the Amine atoms have more opportunity to form bonds with the metal ions surface, by donating electrons to the metal. However, sites N1, N7 and S6 are most favorable for electrophilic attack.

It makes docking of these metallic complexes to study theirs antimicrobial activities with the Chimera software and found that the best complex is copper complex then this is the best inhibitor to modify the enzymatic reaction rate which catalyses the final step of murein biosynthesis.

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