

Synthesis, Spectroscopic Characterization, and Theoretical Investigation of a Cobalt (II)-Ciprofloxacin Complex: Binding Sites, Coordination Geometry, and Thermodynamic Stability

Mohanad A. Sultan¹ *, Salih M. Salih² , Nabaa B. Ali³ , Adiba A. Mahmmod⁴ , Ahmed Kandory⁵ , Ali E. Karim⁶  and Azza Al-metwali⁷ 

1,3,4Department of Chemical Engineering, College of Engineering, University of Diyala, Baquba, 32001, Iraq.

2 Department of Science, College of Basic Education, University of Diyala, Baquba, 32001, Iraq.

5 Department of Chemistry, College of Science, University of Diyala, Baquba, 32001, Iraq.

6 Department of Physiology and Biochemistry, College of Veterinary Medicine, University of Diyala, Baquba, 32001, Iraq.

7 Department of Chemistry, College of Pure Science, University of Diyala, Baquba, Iraq.

*Corresponding Author: Mohanad A. Sultan

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ABSTRACT: This study reports the synthesis, spectroscopic characterization, and theoretical investigation of a cobalt (II)-ciprofloxacin complex to find its actual binding sites, its geometry, and stability. The study highlights the interaction of cobalt ions with ciprofloxacin by applying several spectroscopic methods, such as FTIR and UV-Vis, and using semi-empirical computational approaches. The findings from FTIR analysis reveal that the carboxylate group and the oxygen atom of the ketone groups of ciprofloxacin bind with cobalt (II) ion, indicated by shifts in C=O stretching frequency and the appearance of new bands corresponding to M-O and COO-M vibrations. Additionally, UV-Vis spectroscopy showed d-d transitions and metal-to-ligand charge transfer (MLCT) bands consistent with an octahedral geometry. The results from computational modeling confirm strong cobalt-oxygen interactions, a high-spin octahedral arrangements, as well as favorable ligand field stabilization energy (LFSE) values. Theoretical parameters, including HOMO-LUMO energy gaps, hydration energy, and log p suggested low aqueous solubility and a hydrophobic nature. These combined methods give a detailed understanding of cobalt (II)-ciprofloxacin coordination chemistry, supporting its potential use in various medicinal and catalytic applications.

Keywords: Binding sites, Cobalt complex, Ciprofloxacin, Computational modeling, Molecular geometry, Spectroscopic analysis.



1. INTRODUCTION

The synthesis of Cobalt (II) ciprofloxacin coordination compounds has been a topic of interest in chemistry for several years. This compound combines ciprofloxacin, a commonly used antibiotic, with Cobalt (II) ions to create a complex molecule. The potential applications of this compound are numerous, ranging from its use as a drug delivery system to catalysis and other chemical reactions. The use of transition metals in complexes with ciprofloxacin can result in targeted therapies and new catalysts, making it essential to understand their binding reactions [1].

One of the key advantages of the Cobalt (II) ciprofloxacin coordination compound is its ability to selectively target specific types of cells or tissues. This is because the compound can be designed to bind specifically to particular proteins or enzymes found only in these cells. This makes it an ideal candidate for drug delivery systems, where drugs

can be directly targeted to the disease site without affecting healthy cells. In addition, the compound's unique properties make it useful in catalysis and other chemical reactions, where it can act as a catalyst or reactant to facilitate the formation of new compounds.

Numerous donor atoms in ciprofloxacin, which belongs to the fluoroquinolone family, coordinate with metal ions. Three oxygen atoms can bind to a metal ion in the ciprofloxacin structure. Two of these oxygen atoms are in the carboxylate substituent (when deprotonated), and one is in the ketone group adjacent to the carboxylate unit. The ketone and carboxylic acid groups in these positions are primarily responsible for the coordination of ciprofloxacin with a metal. They act as binding sites for metal ions, forming a coordination complex [2].

The nitrogen attached to the cyclopropyl group, which is opposite the ketone group, and the nitrogen that is part of the piperazine ring both have a lone pair of electrons. However, the alkyl substituent crowded both nitrogens, making the lone pair of electrons unavailable for binding.

In contrast, some studies present a coordination pattern between fluoroquinolone and metal ions established through a coupling process. In this process, the metals are attached to the nitrogen atoms of ciprofloxacin. Levofloxacin coordinates with zinc(II), forming biomolecules with unusual coordination through nitrogen atoms situated in the piperazine ring [3]. Another example of this type of coordination- using nitrogen donor atoms from the piperazine ring is found in the complex formed by platinum and ciprofloxacin [4].

The third example of an unexpected metal-ciprofloxacin complex formed through the same nitrogen atom was provided by S. Ouattara et al.'s research group. The structure was formed using ciprofloxacin and copper (II) in 1 M HCl to employ the ligand as a potential inhibitor of copper. The experimental study confirmed product formation by the weight loss technique, and the theoretical calculation, Density Functional Theory, demonstrated that an adsorption process existed in which nitrogen was connected to copper [5].

The stability of the ciprofloxacin-metal complex is affected by the choice of metal. Various metal-ciprofloxacin compounds have different stability constants, which reflect the degree of connection between the ciprofloxacin ligand and the metal cation. To determine the stability constants for iron (III), aluminum (III), and magnesium (II) with ciprofloxacin complexes, capillary zone electrophoresis tests were performed at pH 3.25 for both iron (III) and aluminum (III) complexes and at pH 8.02 for the magnesium (II) complexes. Each experiment was conducted at 298 K, and the separation potential was recorded at 30 kV. This study discovered that the coordinated compounds had similar stability constants for Al (III) and Fe (III), 14.184 and 14.117, respectively. In contrast, the stability constant of the Mg (II) compound was much smaller and was below a fourth of that of the Al (III) and Fe (III) complexes. The study stated that the stability of these complexes was driven by the oxidation state and particular metal ion [6].

A study on how temperature affects stability constants revealed changes in enthalpy during the reaction of ciprofloxacin with Ca(II) and Mg(II). The parameter ΔH_1 represents the enthalpy change involved when a single ciprofloxacin ligand coordinates with the metal ion, while ΔH_2 corresponds to the enthalpy during the coordination of a second ciprofloxacin ligand. Both values are negative, suggesting the formation of bonds between the metal ions and the ciprofloxacin ligand. Interestingly, the enthalpy change for ΔH_1 resembles that of an O-bound ligand compared to other typical bond enthalpies. Both of these metal (II) complexes have considerably smaller ΔH_2 values. These data selectively specify that the second ciprofloxacin molecule is bound to the metal (II) ion approximately five orders of magnitude less tightly than the first one. This pattern can be attributed to the fact that a weaker electrostatic attraction is produced after incorporating the second ciprofloxacin molecule into the already synthesized [metal(II)(ciprofloxacin)] complex through the oxygen donor atom on the carboxylate in the ligand [7].

Nevertheless, early research on metal-ciprofloxacin transformation stated that the configuration of the metal complex was coordinately saturated with carboxylate and keto groups.

Zhengde Tan et al. reported the synthesis and antibacterial activities of Cu (II), Mn (II), and Zr (II)-ciprofloxacin complexes. Firstly, the authors made the phases by mixing an appropriate amount of M(II) and ciprofloxacin at different PH levels. The researchers then performed IR, DSC, and UV techniques for structural determination. This study observed that M(II)-ciprofloxacin phases had a 1:1 stoichiometry ratio, in which C=O carbonyl groups were engaged in coordination with M(II) [8].

The coordination fashion of OH and ketone groups was reported for some transition metals, and infrared and UV-visible techniques mostly confirmed the ciprofloxacin complexes. A clear example is the formation of Cobalt (II), nickel (II), zinc (II), and copper (II) complexes by Chohan, Z. H et al. These complexes were made in an acidic medium (0.1 M HCl) in an aqueous metal (II) chloride solution and the ligand. The geometric shapes of the complexes were suggested as octahedral and square-planar geometries. These systems were found to have a stoichiometric ratio of 1:2 for the metal and ligand [9].

Further support for the structure of the metal-ciprofloxacin complex and information indicating the coordination nature of the structural units came from both studies conducted by Kowalczyk et al. Kowalczyk and Nagaraj et al. They discussed the spectroscopic characterization of ciprofloxacin-biguanide bismuth complex formation, emphasizing that the formation of the complex was observed, especially when dealing with the ciprofloxacin ligand. The metal ion is covalently bonded to ciprofloxacin through a hydroxide anion of the carboxylic moiety and a ketone group [10] [11].

Although there is numerous information on metal-ciprofloxacin complexes, specific research about cobalt (II) ions' coordination with ciprofloxacin is still lacking. Currently, the areas where cobalt and ciprofloxacin interact are not fully

understood, particularly when using both experimental tools and computer models. This lack of understanding limits how cobalt-based complexes can be used for targeted drug delivery and catalysis, stressing the need for better studies.

A complete synthesis of the cobalt (II)-ciprofloxacin complex is presented, followed by examining it by FTIR, UV-Vis spectroscopy, and semi-empirical computations. The study provides clarity on the chemical ratios, the ways the compounds bind, and the arrangement of atoms within the complex.

The purpose of this study is to address the limited understanding of Co(II) coordination chemistry by conducting both lab experiments and theoretical analyses. Such combination offers valuable knowledge for improving cobalt compounds for both medical and catalytic uses and lays down the foundation for future work in transition metal complexation.

2. METHODOLOGY

2.1 MATERIALS

Pure ciprofloxacin, (analytical grade, melting point 225 °C), was sourced from the Kendy Pharmaceutical company, Iraq and used without further purification. Cobalt chloride hexahydrate ($\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, ≥ 98 purity) was purchased from Sigma-Aldrich, USA. Methanol (HPLC grade) and potassium bromide (KBr, spectroscopic grade) were supplied by Merck, Germany. All reagents were of analytical grade and used as received. Distilled water was prepared in the laboratory and used for all aqueous solutions.

All measures for spectroscopic analysis were mixed with KBr (1:100 ratio). The pellets included two compositions: one with KBr and ciprofloxacin, and another had KBr together with the cobalt-ciprofloxacin complex. FTIR spectroscopy was used to examine the pellets and discover which chemical groups and bonds are involved. The spectra generated were then analyzed and explained in the Results and Discussion sections. FTIR spectra were recorded using a Shimadzu IRTreacer-100 DTGS detector spectrometer in the range 4000-400 cm^{-1} , 4 cm^{-1} resolution.

Moreover, the UV-Vis absorption spectra were obtained using a Jasco V-730, deuterium & tungsten-halogen lamps UV-Visible Spectrophotometer between 200 and 800 nm, 1 nm resolution using methanol as the solvent. The melting points were measured with a Stuart SMP10 digital melting point apparatus. Computational studies, including molecular geometry calculations, were carried out using HyperChem Professional 8.0 software.

2.2 SYNTHESIS OF THE CIPROFLOXACIN-COBALT COMPLEX

The cobalt-ciprofloxacin complex was made by mixing 10 millimoles of cobalt chloride solution with 0.02 grams of ciprofloxacin dissolved in about 10 millilitres of methanol. The samples were dissolved and mixed at room temperature. The mixture was then placed on a hot plate set to 60 °C and stirred inside a closed container for two hours to help complex formation. The container was drawn out from the heat source and it was not touched for three days so the complex could form. At this stage, yellow precipitate appeared and was filtered using a Buchner funnel before being dried according to suitable conditions. Under the right conditions, the solvent used in alcoholic hydrolysis is removed by drying [12].

3. RESULTS AND DISCUSSION

The synthesized complex was stable and demonstrated non-hygroscopic properties, with a higher melting point than the free ligand. The melting point of the complex was observed to be above 300 °C, while the melting point of the free ligand was recorded as 225 °C. This indicated that the complex is more thermally stable than the free ciprofloxacin ligand. However, thermal gravimetric (TGA) or differential scanning calorimetry (DSC) analyses were not carried out in this study. Such measurements should be performed in the future work to obtain crucial assessments of thermal decomposition behavior.

The complex exhibited a yellowish color. Infrared spectroscopy was performed with UV-visible light analysis to confirm its chemical structure. The structure of the complex was determined by comparing the spectrum of the free ligand with that of the metal complex, supported by theoretical investigations.

IR spectrum of ciprofloxacin shows that 3528 cm^{-1} is attributed to vibration absorption of the OH of carboxylic acid on the benzene ring, while 1269 cm^{-1} is assigned to the C-F wagging bond. In addition, the low intensity at a frequency of 1507 cm^{-1} is believed to be C=C— bending of the alkene. The carbonyl stretch C=O of carboxylic acid is reported to have a wave number of 1725 cm^{-1} . It is also observed that the absorption band at approximately 2921 cm^{-1} is linked to C-H aliphatic stretching vibrations. A peak of 1628 cm^{-1} indicates C=O stretching for a ketone group, as shown in Figure 1.

A broad absorption band at 3466 cm^{-1} in the complex IR spectrum was attributed to the M-OH group. This band showed lower intensity compared to the free ligand spectrum, confirming that the O-H group is one of the coordination sites in ciprofloxacin. This suggests that the functional group on the ciprofloxacin molecule binds to the metal ion without losing its hydrogen atom. Similarly, the C=O band in ciprofloxacin, typically observed in the spectrum, was also present in the complex spectrum but showed a shift in intensity to 1600 cm^{-1} . This shift indicates that the C=O group serves as another coordination site for the metal ion. The position of this band aligns with the theoretical

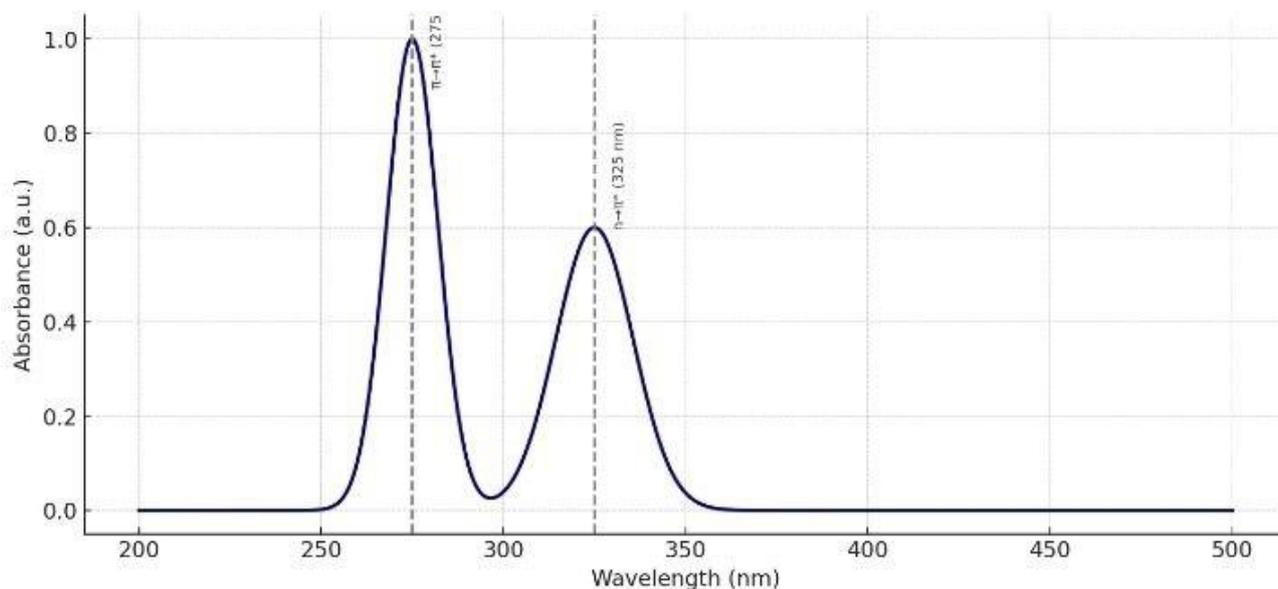


FIGURE 3. - UV.Vis Spectrum of Ciprofloxacin.

In interpreting the spectrum of the complex, we can identify the geometry of the synthesized compound. The electronic absorption spectrum shows that the Co(II) complex exhibited low-energy absorption at 26316 (25000) cm^{-1} and a high-energy band at 32764(26316) cm^{-1} . The lower energy absorption was attributed to $4T1g(F) \rightarrow 4T2g(F)$, and the higher energy band accounted for $4T1g(F) \rightarrow 4T1g(P)$ electron transition [13]. Figure 4 represents the U.V. Vis. Spectrum of the cobalt(II)-ciprofloxacin complex. Furthermore, the high-energy band was assigned to metal-to-ligand transfer.

Similarly, the results from the theoretical electronic spectrum, empirical, show that the complex has two band absorptions: one with a lower energy equal to 8797 cm^{-1} , and the second with a higher energy, equal to 10266 cm^{-1} . After calculating ligand Field Stabilization Energy to determine which electron spins are possible, the obtained results increase stability, as will be discussed later, and favors high spin configuration.

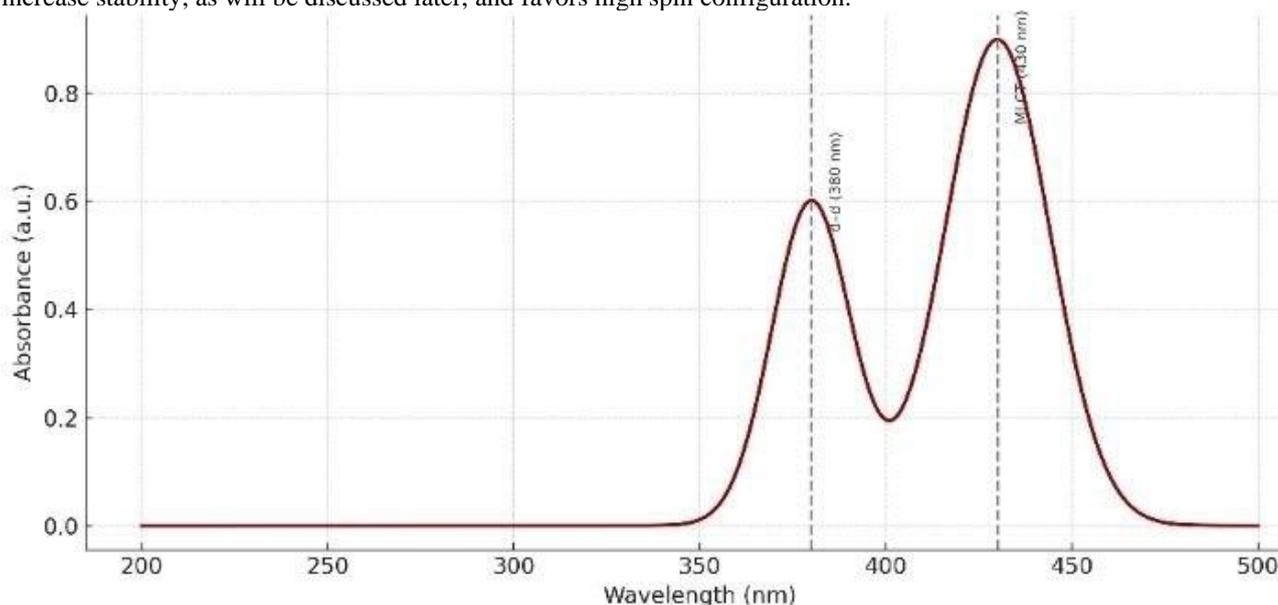


FIGURE 4. - UV.Vis Spectrum of Co(II)-Ciprofloxacin.

3.1 THEORETICAL STUDY OF THE LIGAND AND THE COMPLEX

The theoretical investigation, HyperChem programming 8.0, initially concerned the reactivity of the ligand, determining electron electrostatic potential, and the total charge density of the molecules, both of which describe the interaction energy of the molecular system and binding sites on the ligand [14]. Electrostatic potential and total charge density were calculated and plotted as 3D contours to show the active site structure on the ligand. It can be seen from Figure 5 that electrostatic potential and charge density are located on some fringes of the molecule, in which reactive groups with high electron density are found, serving as a manifestation of the chelate effect in the ligand.

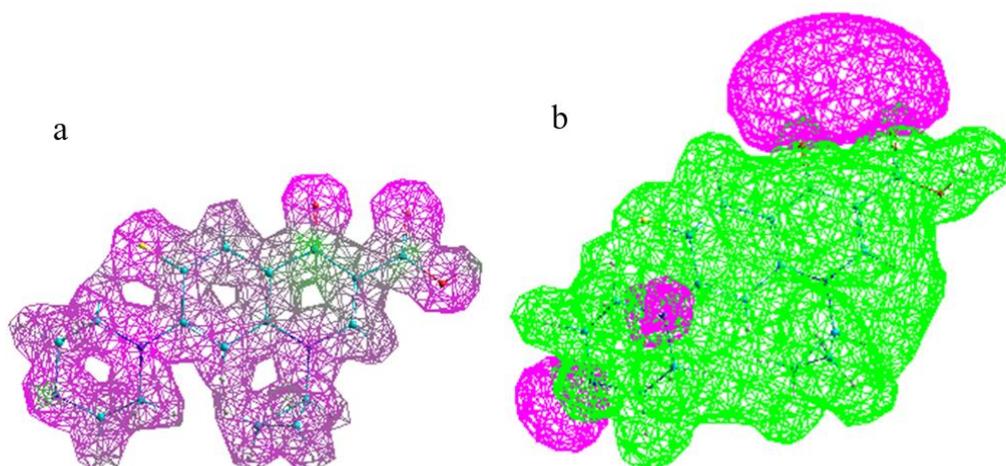


FIGURE 5. - (a) electrostatic potential; (b) the charge density of the ligand

Moreover, theoretical investigation of the metal complex using HyperChem programming is rolled out in an apparent bid to measure the heat of formation, binding energy, and total energy [15]. Furthermore, HyperChem programming is used to investigate the metal complex, so that the heat of formation, binding energy and total energy for the synthesized complex can be understood. Deeper insights can be reached by analyzing both the HOMO and LUMO of the molecular orbitals for the compound to learn more about the electronic transitions and the nucleophilic and electrophilic attraction. These findings from these studies help explain how different molecules are linked and the chemical configuration they adopt.

The energy levels of the molecular orbital order HOMO and LUMO in Table 1 show the possible electronic interaction between the ligand and the metal.

Table 1. - Theoretical Data of the Co (II)-Ciprofloxacin Complex

Parameter	Value
HOMO (Co–CO)	-0.527
LUMO (Co–CO)	-0.121
ΔE (LUMO–HOMO) (Co–CO)	0.406
Hardness (Co–CO) (eV)	0.203
Softness (Co–CO) (eV)	4.926
Polarizability (Co–CO) (\AA^3)	63.92
Refractivity (Co–CO) (\AA^3)	177.27
Electronic Energy (Co–CO) (Kcal/mol)	-109114.78
Dipole Moment (Debye)	1.4
Binding Energy (Kcal/mol)	125981.7873
Heat of Formation (KJ/mol)	-119854.66
RMS Gradient (Kcal/mol. \AA)	0.07173
Nuclear Energy (Co–CO) (KJ/mol)	9577.31
HOMO (Co–OH)	-0.973
LUMO (Co–OH)	-0.562
ΔE (LUMO–HOMO) (Co–OH)	0.411
Hardness (Co–OH) (eV)	0.205
Softness (Co–OH) (eV)	4.878
Polarizability (Co–OH) (\AA^3)	32.88
Refractivity (Co–OH) (\AA^3)	90.12
Electronic Energy (Co–OH) (Kcal/mol)	2039417.78
Nuclear Energy (Co–OH) (KJ/mol)	55605606.54

These measurements indicate the Lewis base and Lewis acid attraction between cobalt and C=O and OH groups. It is also noticeable from Table 1 that the energy gaps of such interactions are of negative values, meaning favorable coordination between cobalt and the O atoms of both the ketone hydroxide groups. The energy levels of the molecular orbital order HOMO and LUMO are represented in Figure 6.

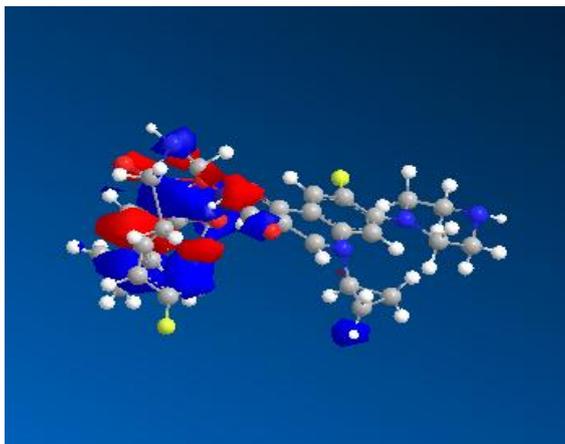


FIGURE 6. - Frontier orbitals LUMO and HOMO, blue is the positive value and red is the negative value)

Moreover, structural optimization was done to find the possible cobalt-carboxylate anion coordination featured in previous research papers. According to the theoretical findings, the band gap energy level of 2.001 is too large to maintain such coordination. Needless to say, the carboxylic functional group has a weak nucleophilic character, and nucleophilic attack from this group is improbable to produce a Co—O=C bond [16].

Figure 7 depicts that Co-ciprofloxacin coordination exhibits a distorted octahedral geometry. The axial connections are formed by two O atoms of different ketone groups (Co-O=C = 1.89348 Å), (Co-O=C = 1.89352 Å). The equatorial sites are occupied by two oxygen atoms from hydroxide moieties, with bond lengths of 1.88645 Å and 1.88694 Å. Another M-O bonds is 1.88979 Å in length. The shorter Co-O bond is found to be 1.88659 Å,

suggesting stronger bonding, which support the material's thermal stability above 300 °C [17]. This could explain why the material decomposes at temperatures higher than 300 °C instead of melting.

Computational studies were included to offer new details on coordination geometry and bond lengths and describe HO-Co-O=C, HO-Co-OH, and C=O-Co-O=C bond angles. However, the values of bond angles of H-O-Co-O=C are different. The HO-Co-O=C bond angle from one arrangement is found to be 94.1453 Å, while the second HO-Co-O=C bond angle from the other ligand fragment is projected to be 94.6612 Å. However, the HO-Co-OH bond angle is relatively more significant than the CO-Co-OC bond because the former bond has an angle of 178.892 Å, and the latter bond angle equals 95.3226 Å. Such a difference is influenced by the single and double nature of the carbonyl and the hydroxide group, where the delocalization of the C=O double bond of the ketone group could occur. This delocalization plays a significant role in the stabilization of the cobalt-ketone group. The Co-O=C and HO-Co-OH bond angles are very different in their angle values, only off by four degrees. The bond angle of HO-M-OH is 91.3353 Å. Interestingly, these bond angles are much more similar to those reported for the uncommon μ_2 -OH bridges in Cu dimers.

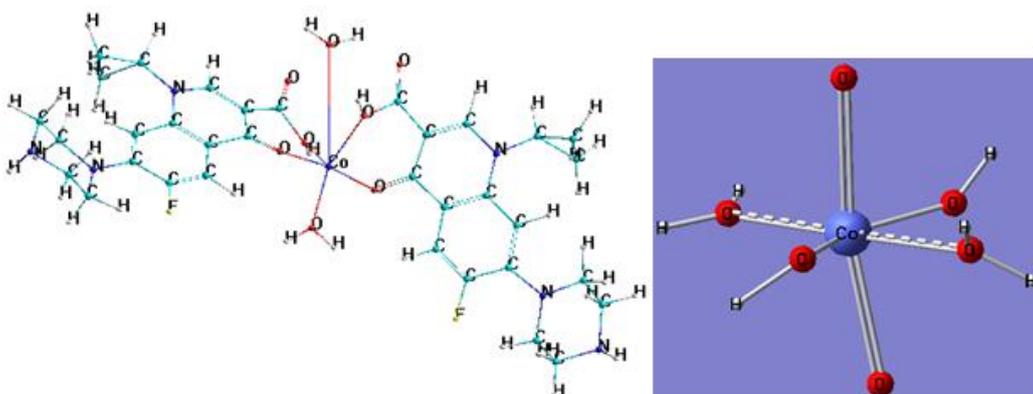


FIGURE 7. - Depicts the complex b- View of the coordination sphere of the center metal showing an octahedral geometry

To determine a favorably geometric arrangement, ligand Field Stabilization Energy (LFSE) measurements were performed to achieve the proper thermodynamic preferences. The resulting LFSE energies between the octahedral geometry and the tetrahedral geometry have a distinct difference. In an octahedral shape such as that in $[\text{Co}(\text{cip})_2(\text{OH}_2)_2]$ complex, LFSE has the value $-0.6 \Delta_o$ and Δ_o has the value 10265.7 cm^{-1} , so that the LFSE is -6159 cm^{-1} , or -17.6 Kcal/mole . For Cobalt in tetrahedral structure- $[\text{Co}(\text{cip})_2]$, the LFSE is $-0.36 \Delta_t$, Δ_t is 4645.1 cm^{-1} , so the LFSE is -1672.2 , or -4.8 Kcal/mole . These values show that the cobalt-coordinating environment in the octahedral case is thermodynamically favored. In this energy conservation mode, octahedral is dominant through the formation rather than the sequence of an event for octahedral to tetrahedral transformation in the coordination sphere of Cobalt, a situation in which LFSE indicates cobalt ion has to pay the price of $17.6 - 4.8 = 12.8 \text{ Kcal/mole}$ in LFSE in going from octahedral to tetrahedral. The energy of the cobalt ion in the octahedral is lowered by 75 %. The preferred structure specificity can also be rationalized regarding ligand type because weak-field ligands give a high-spin octahedral instead. Given these observations, this difference in ligand Field Stabilization Energy change favors octahedral over tetrahedral, given that geometry with more excellent stabilization is preferred. Thus, the suggestion involving octahedral over tetrahedral geometry was proposed, indicating that high spin rather than low spin is actually in operation.

The theoretical study also demonstrated quantitative structure-activity relationships (QSAR). One of the molecular properties with particular chemical activities is the surface area, which is considered a significant parameter when it comes to the molecule's biological and industrial applications [18]. The surface area (grid) of the compound was found to be $977.22 \text{ m}^2/\text{g}$. curiously; the synthesized material could possess porous sites to accommodate guest molecules.

Another molecular parameter related to chemical activities is the hydration energy. The hydration energy, the amount of energy absorbed as the substance is data dissolved in water, is regarded as a fundamental parameter for the hydrophilic property of the compound. The designated compound has a hydration energy of 29.16 kcal/mol . The lower the hydration energy, the better the substance dissolves in water. Consequently, the computational measurement for the

Log P parameter is calculated, in general, because of its value describing the hydrophilic and hydrophobic nature. A substance's biochemical interaction and bioactivity are caused by both hydrophilicity and hydrophobicity. A hydrophilic compound has a negative value of Log P, whereas a positive Log P means hydrophobicity. From the theoretical data, the optimized material has a value of -4.27 , indicating the complex's hydrophobic behaviour. The findings agree with the experimental one, which shows poor solubility of the Co(II) -ciprofloxacin complex, as it has only been found to be soluble in diluted acidic conditions. Although no experimental biological or reactivity tests were done, the small HOMO-LUMO gap ($< 0.45 \text{ eV}$) suggests high polarizability and potential chemical-biological reactivity. Narrow gaps are often associated with low energy required for electronic excitation and electron transfer processes [19].

4. CONCLUSION

This study allowed for the preparation and characterization of Co(II) -ciprofloxacin, giving vital information about its structure and the interaction of metal and ligand. FTIR spectra confirmed that cobalt coordinates primarily through the ketone and hydroxyl oxygen atoms, while UV-Vis analysis showed transitions of high-spin octahedral complexes. Theoretical modeling supported these observations, revealing strong cobalt-oxygen bonding, short Co-O distances, and thermodynamic preferences for octahedral geometry. The calculated HOMO-LUMO energy gaps, hydration energy, and log p values indicated that the low solubility in water, consistent with experimental observations. The integration of spectroscopic and computational provides valuable insight into the coordination chemistry of Co(II) -ciprofloxacin complexes, paving the way for their potential application in targeted drug delivery and catalysis.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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