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Polyphenol oxidase activities by cobalt (II) complex with Benzopyran Derivatives, Synthetic, Characterization, Kinetics Study and Molecular Modeling Studies

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Abstract

The Cobalt complex of 2-Amino-4-(2-chloro-5-nitrophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo- 4H-chromene-3-carbonitrile) (CNB) was synthesized. The organic ligand CNB was previously synthesized using an environment friendly method using microwave irradiation. The cobalt complex cobalt (II)-CNB was characterized by different tools such as IR, electronic spectroscopy, elemental analysis, Thermal analysis and mass spectroscopy. The mode of metal binding shows that the cobalt binds with the ligand through the nitrogen atoms of the amino and cyanide groups. The cobalt complex cobalt (II)-CNB has been used in the homogenous oxidation of polyphenol 1, 2, 3-trihydroxybenzene in presence of a green oxidant H_2O_2 as biomimetic metalloenzymes. Kinetic parameters were calculate k_{cat} $1.0971\times10^{-5}S^{-1}$, K_M1.412 $\times10^{-2}$ M, Vmax $7.68\times10^{-4}MS^{-1}$ and catalytic efficiency 7.769×10^{-7} .The oxidation reaction is inhibited by competitive inhibition by kojic acid with IC_{50} = 200 μM and molecular modeling studies geometrical optimization ,(HOMOs) ,(LUMOs and electrostatic potentials (ESP).

Key words; Benzopyran derivative; oxidation; trihydroxybenzene. biomimetic; metalloenzymes.

1. Introduction

Oxidation reactions are the most important reactions that are used to synthesize organic chemicals and pharmaceutical compounds on a large scale in industrial using heavy metals oxides resulting in environmental pollution[1].polyphenols oxidation is one of the important biological processes are widely distributed in in animals, micro-organisms and plants [2, 3] A lot of different oxidants, aqueous hydrogen peroxide has been one of the most common ‘‘green oxidants’’, of the advantages of safety in storage and being cheap, readily available, operation, environmentally benign and of highly effective oxygen content and with a water as a product out [4].Metal complex gained in recent great interest in medicinal chemistry and pharmaceutical chemistry diagnoses, in spite of the adoption of Medicinal Chemistry in the previous organic compounds and natural products [5, 6].Different catalysts, such as polyoxometallates and transition-metal complexes, have been used for H_2O_2- based oxidation of polyphenol [7] Cobalt complexes have been extensively used to catalyze oxygen activation in the oxidation of phenols [8,9] Many researchers are focused on producing systems which can mimic not only structural but also catalytic properties of metalloenzymes[10,11] Biomimetic studies of metalloenzymes can provide catalysts created in laboratories and these compounds use dioxygen in the initial oxidation.[12] Biomimetic studies helps to understand of mechanical reaction to identify active sites of metalloenzymes[13].The discovery of tyrosinase inhibitors one of the important things in the pharmaceutical industry and the cosmetic.[14] several compounds were used as inhibitors of medical products. tyrosinase inhibitors, such as arbutin have been ability to prevent excess production of melanin so tested in pharmaceuticals and cosmetics. [15,16] kojic acid [17,18,19] hydroquinone [20] azelaic acid [21]. Benzopyran compounds are involved in many drug activities [22, 23]. The pyran pharmacophore was an important core structure of many natural products showing, antitumor, antiallergic, antibiotic hypolipidemic immune modulating activates antibacterial [24]. Many benzopyran derivatives possess a high capacity in cardiac muscle and other

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smooth muscles relaxant activity on blood vessels [25, 26]. The use of organic solvents in the preparation of organic compound have a very significant dangerous on the environment but using microwave radiation to enhance organic reaction is much better and represents green chemistry and are inexpensive, not dangerous and enhances the rate of the reaction [27].

2. Experimental

2.1. Materials and Methods.

4-(2-chloro-5-nitrophenyl) were purchased from Aldrich Chemical Co. Dimedone were purchased from Across Organics Co. (Belgium) .and malononitrile, Kojic acid and cobalt chloride were obtained from Merck Co., Germany.

2. 2.1. Synthesis of 2-Amino-4-(2-chloro-5-nitrophenyl)-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo- 4H-chromene-3-carbonitrile) (CNB) - under microwave irradiation.

2.2.2. Synthesis of arylidenemalononitrile under microwave irradiation

In the present work, firstly, this method has been examined in Knoevenagel condensation for the preparation of different arylidene derivatives. An equal molar quantity of the aromatic aldehyde 1 and malono-nitrile 2 were mixed together in water in a tightly closed tube and subjected to microwave irradiation from 0.5 to 2 minutes, pure products were

Scheme 1: Synthesis of arylidenemalononitrile

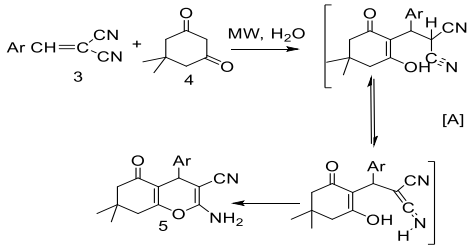
obtained in excellent yields and proven to be arylidene 3 by melting point, mixed melting point and comparative IR and ^{1}HNMR (Scheme 1). The results are shown in Table (1)

Table(1).Knoevenagel condensation between aldehydes and malononitrile in water using microwave irradiation under pressure.

Entry	Ar	Reaction time(min)	Isolated yield (%)	MP. (˚C)
CNB	2-Cl-5-NO_2-C_6H_3	1	95	118-119

2.2.3. Synthesis of Tetrahydrobenzopyran-4-methoxyphenyl under microwave irradiation.

Then, these simple reaction conditions have been applied in synthesis of benzopyran-5-one derivatives. When a mixture of arylidene **3** and dimedone **4** in water was subjected to microwave irradiation for a suitable time (2-5 min) in a tightly closed tube, the corresponding chromene derivatives **5** were produced efficiently without any catalyst in excellent yield *via* cyclization of inter-mediate (Scheme 2). The results are shown in (Table 2).



Scheme 2: Synthesis of Tetrahydrobenzopyran-4-methoxyphenyl under microwave irradiation.

Table (2). Michael addition reaction of 3 to 4 in water,using microwave irradiation under pressure.

Entry	Ar	Reaction time(min)	Isolated yield (%)
CNB	2-Cl-5-$NO_2C_6H_3$	3	95

2.3. Synthesis of cobalt (II)-CNB complex.

Cobalt (II) chloride (0.1 mole) dissolved in ~ 40 ml absolute ethanol was added to 0.1 mole of the ligand CNB dissolved in ~ 40 ml absolute ethanol. The mixture was heated under reflux for ~ 2 h. The bluish precipitate was formed, filtered off and finally washed by hot ethanol several times and dried in an open air.

2.4. Physical methods.

Carbon, hydrogen and nitrogen contents were determined at the Micro analytical Unit, Cairo University, Egypt. IR spectra of the ligand and its solid complexes were measured in KBr on a Mattson 5000 FTIR spectrometer. The electronic spectra and kinetic measurements were performed using Varian Cary 4 Bio UV/VIS spectrophotometer.

^{1}H- NMR spectrum of the ligand was recorded on Joel-90Q Fourier Transform (200 MHz) spectrometers in [D_6] DMSO. The mass spectra of the ligand and its metal complex was recorded on a Shimadzu GC-S-QP 1000 EX spectrometer using a direct inlet system. Thermal analysis measurements (TGA) were recorded on a Shimadzu thermo-gravimetric analyzer model TGA-50 H, using 20 mg samples. The flow rate of nitrogen gas and heating rate were 20 cm^3 min^{-1} and 10°C min^{-1} respectively. The magnetic susceptibility measurement for the cobalt (II) complex was determined by the Gouy balance using Hg [Co $(NCS)_4$] as a calibrate at room temperature.

2.5. Kinetic Measurements of polyphenol oxidase activities.

The catalytic activity of the cobalt (II)-CNB complex toward the homogenous oxidation of trihydroxy benzene (THB) in ethanol solution at 25 °C was determined by measuring the initial rate of THB oxidation. The increase of the absorption at 420 nm (ε = 4.583 $M^{-1}cm^{-1}$) due to the oxidation product with time was obtained on a Varian Cary 3E spectrophotometer [28]. A plot of the formation of the product with respect to time gives the initial rate. To study the effect of the catalyst concentration on the rate of the reaction, various amounts of the cobalt(II)

complex (10 - 300 µM) have been used with 100 µM H_2O_2 for oxidation of 1.0 mM THB at 25°C. At the same time, 40 µ M of the catalyst has been used in the oxidation of different concentrations of the substrate (5 –120 µM) in presence of 100 µM H_2O_2 to study the effect of THB concentration on the reaction. The rate laws were determined and rate constants obtained. The auto-oxidation rate of THB was determined under the same conditions in the absence of cobalt (II)-CNB. Study the effect of inhibitors on the oxidation process of catalytic and kinetic measurements using 200 µM of Kogic acid as inhibitors. Various kinetic parameters were evaluated applying Michaelis–Menten model.

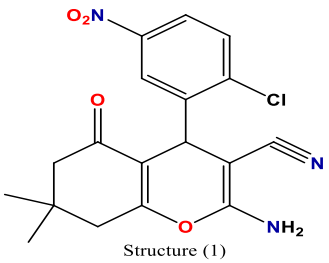
2.6. Computational study:

The target compounds were built using and minimized their energy with PM3 through MOPAC then DFT using B3LYP/6-311G. All the Quantum chemical computations were performed, using the PM3 semi-empirical Hamiltonian molecular orbital calculation MOPAC16 package, then employing density function theory in Gaussian 09 W program package with the Becke3-Lee-Yang-parr (B3LYP) level using 6-311G* basis as implemented in MOE 2015 package (MOE). The optimization Geometry for molecular structures were carried out, for improve knowledge of chemical structures. Our compounds were introduced into the binding sites according to the published crystal structures.

3. Results and Discussion

3.1. Characterization of 4-(2-chloro-5-nitrophenyl) (CNB).

The infrared spectrum in (figure1) of the 2-chloro-5-nitrophenyl benzo pyran CNB shows weak bands at 3000 and 2839 cm^{-1}. These bands are assigned to the aromatic and aliphatic C-H stretches respectively. A strong band observed at 2186 cm^{-1} is likely to be due to νC≡N [29] Vibration absorption bands which appeared at 3447 cm^{-1} with one at 3332 $cm^{-1}$are assigned to νNH_2. The ligand also shows band at 1664cm^{-1} assigned to νC=O[30] .The ^{1}H-NMR spectra reveal peaks attributed δ = 1.03 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 2.23 (d, 1H, J_{AB} = 16 Hz, H-8a), 2.31 (d, 1H, J_{AB} = 16 Hz, H-8b), 2.45 (s, 2H, C^6-H), 3.79 (s, 3H, OCH_3), 4.02 (s, 1H, C_4-H), 4.95(s, 2H, NH_2, D_2O exchangeable), 7.11-7.29 (m, 4H, Ar-H).the molecular weight from the mass spectroscopy (m/s = 324.3) and elemental analysis determined suggest the structure of the ligand as shown in the structure(1).



Structure (1)

Table (3) Elemental analysis of (CNB).

Calcd:	C	57.84%	H	4.31%	N	11.24%
Found:	C	57.96%	H	4.40%	N	11.03%

3.2. Characterization of cobalt (II)-CNB.

In the FT-IR spectrum in figure (1) of the ligand a sharp band appeared at 2200 cm^{-1} which is attributed to the νC≡N vibrations. In the FT-IR spectra of the Co (II) complex this band was disappeared. With each other, the NH_2 bands were shifted from 3370 and 3275 cm^{-1} in the ligand to 3440 and 3325 cm^{-1} in the complex spectrum. The band corresponding to νC=O appears at the same position in the ligand and complex spectra, indicating to not participation in the coordination.

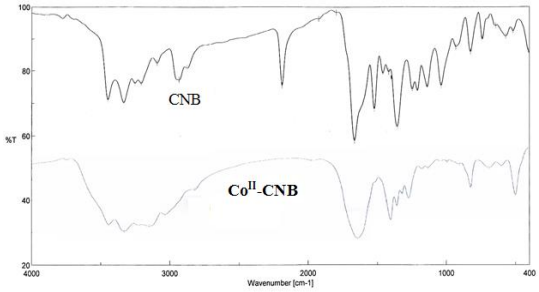


Figure 1. FTIR spectra of the CNB and cobalt(II)-CNB complex**.**

The coordination of the nitrogen atoms to the metal is also consistent with the presence of a new band at 584 cm^{-1} due to νCo–N. This shift could be attributed to a weakening of the νCo–N bonds this can be explained by the donation of electrons from the nitrogen atom to the empty d-orbitals of the metal atom [31]. The proposed structure is also supported by the presence of a new band at 520 cm^{-1} attributed to νM–O [32].

3.2.1. Electronic spectral data of cobalt (II)-CNB complex

The electronic spectra of the complex figure (2), exhibit absorption in the region (250 nm and 400 nm) the bands assigned to the transitions:

$^4T_{1g}$ *(F)* → $^4T_{2g}$ *(F)* — (*v*1), $^4T_{1g}$ → $^4T_{2g}$—(*v*2), $^4T_{1g}$ *(F)* → $^4T_{2g}$ *(P)*—(*v*3), Characteristic for an octahedral geometry [33]. Cobalt (II) complex show magnetic moment in the range 4.3 BM in good agreement with that expected for a magnetically isolated Co^{2+} in distorted octahedral arrangement [34]

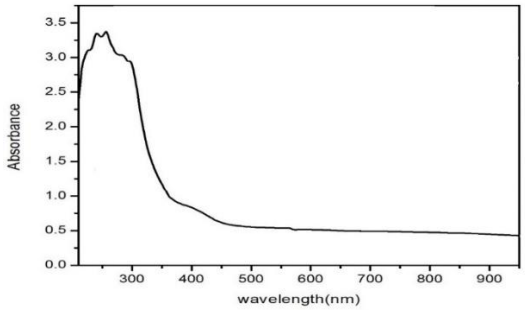


Figure 2. Electronic spectra of cobalt(II)-CNB complex.

3.2.2. Mass spectroscopy of cobalt (II)-CNB complex.

The mass spectrum of cobalt complex cobalt (II)-CNB figure (3), shows a molecular ion peak at m/z =538 corresponding to the cobalt complex moiety ($C_{18}H_{20}Cl_3CoN_3O_6$). The base peak was found in the spectrum at m/z = 157(100%).

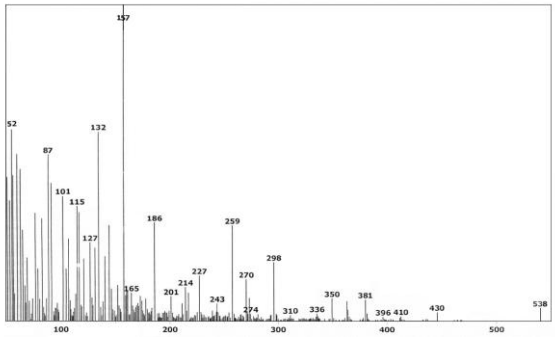


Figure 3. Mass spectrum of cobalt (II)-CNB complex.

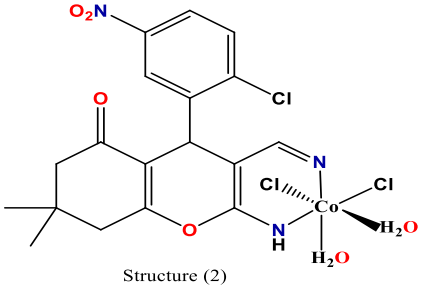
3.2.3. Thermal analysis of cobalt (II) -CNB complex.

Physical and chemical change of the complexes occurs when exposed to heat energy. Cobalt complex showed three stages of decomposition Co (II) complex starts to decompose at 36°C and this step continues up to133°C. The second step starts after 133°C and was completed at 276°C. The final solid product of thermal decomposition is cobalt oxide. The first weight loss stage in complexes corresponds to the elimination of crystalline water molecules as shown. The thermal decomposition is finally yielding the corresponding metal oxides, carbides, metallic residue or mixtures.

Table (4) Elemental analysis of the complex

Complex M.Wt.	% C		% H		% N		%Co		MP
	Cal.	Found	Cal.	Found	Calc.	Found	Cal.	Found	
538	40.06	39.87	3.27	3.71	7.78	7.13	10.74	10.03	285

The electronic spectral data, mass spectroscopy, elemental analysis in table 4, together with the IR, thermal analysis and magnetic moment suggest that the structure of the cobalt complex is shown in the structure (2).



Structure (2)

3.3. Kinetic and Catalytic activity study of polyphenol.

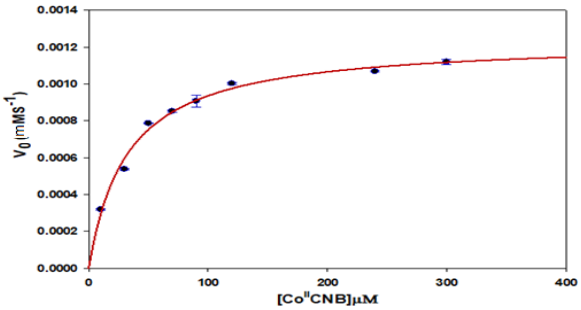
3.3.1. Study effect of concentration of catalyst Co^{II}-CNB.

In directive to explore influence of concentration of cobalt complex catalyst (cobalt (II)-CNB) on oxidation of 1,2,3-tryhydroxybenzene (THB) using different concentrations of cobalt complex. Measuring the velocity by determining the rate of product formation the shape is hyperbolic the initial rate Vi= 1.238×10^{-3} from shape get convenient concentration of catalyst is 70 µM (cobalt (II)-CNB to oxidation substrate as in biomimetic metalloenzymes figure (4).

Figure(4) Plot of initial rate versus different concentration of Co^{II}-CNB in ethanol at temperature 25°C.

3.3.2. Catalytic oxidation of polyphenol.

Spectrophotometric method was used to study the



oxidation of 1,2,3-tryhydroxybenzene (THB) by

Figure (4) Plot of initial rate versus different concentration of Co^{II}-CNB in ethanol at temperature 25°C.

molecular dioxygen in presence of catalytic at temperature 25°C. The initial rate is measured by following the increasing of the absorbance at 420 nm with the time the concentration of oxidized product increase with time even hyperbolic [28]. The oxidation rates of THB by 70 µM cobalt (II)-CNB at different concentrations of THB (Figure 5) have been determined in the presence of 100 µM H_2O_2. The rate of THB oxidation is found to be nonlinear, reaching saturation at high THB concentrations which here is model compound or mimetic enzyme kinetics. This kinetics can be described as the binding of THB with the catalyst cobalt (II)-CNB to form an intermediate THB- cobalt (II)-CNB complex, followed by the conversion of the bound substrate (THB) into products. In absence of the catalysts a blank test was execution under the same empirical condition, there no considerable growth of spectral band is observed, supporting the role of catalysts in such reaction. The kinetics is expressed quantitatively in the Michaelis-Menten kinetics equation as enzyme catalysis values of the kinetic parameters V_0, V_{max}, K_M,k_{cat}(kinetic efficiency) and(catalytic efficiency) k_{cat}/K_M table (5) were obtained from the corresponding plot of V_0 versus [S] (different concentration of polyphenol) The turnover numbers (TON) of the catalysts after that studied by by dividing the value of Vmax by the concentration of catalyst used and the value has been $1.0971\times10^{-5}S^{-1}$ then the catalysts catalytic efficiency were calculated and value are found to be7.769×10^{-7},

small value of K_M indicate that good binding between catalyst and substrate.

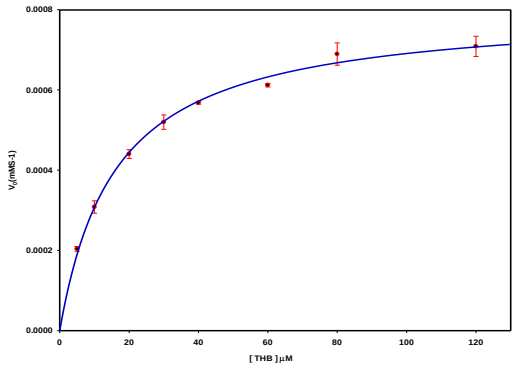


Figure (5) Oxidation of different concentration of THB by using 70 µM cobalt (II)-CNB and 100 µM of H_2O_2 at 25°C.

Table (5): Kinetic parameters of oxidation of polyphenol by cobalt (II) CNB catalyst.

Substrate	Catalyst	Vmax (MS^{-1})	KM (M)	kcat (S^{-1})
THB	cobalt (II)-CNB	7.68×10^{-4}	1.412×10^{-2}	1.0971×10^{-5}

3.3 .3. Inhibition of trihdyroxybenzene oxidation by kojic acid:

Kojic acid is a compound used in the process of competitive inhibition reversible inhibitors of polyphenol oxidation by oxidases [35]. It has been used to inhibit the cobalt (II)-CNB complex toward oxidation of trihydroxybenzene. figure (6) shows that the Kojic acid significantly inhibits the oxidation of THB with IC50 ~ 200 µM in competitive inhibition raises K_m only and no change in the V_{max} value.

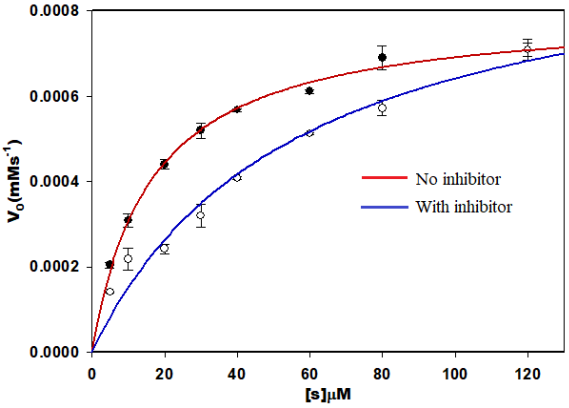


Figure 6 : Inhibition of THB oxidation using 70 µM cobalt (II)-CNB with different concentrations of kojic acid and 100 µM H_2O_2 at 25°C.

4. Molecular modeling studies.

The electronic structural parameters were performed to understanding interaction mode of complex with zeolite, and rationalize the experimental data based on computed molecular characters. All the quantum chemical calculations were performed using DFT/B_3LYP at 6-311G basis set level. From the calculated energy and geometrical optimization for the ligand [36, 37] and its Cu-BOA (figure 7), exhibited the following common features:

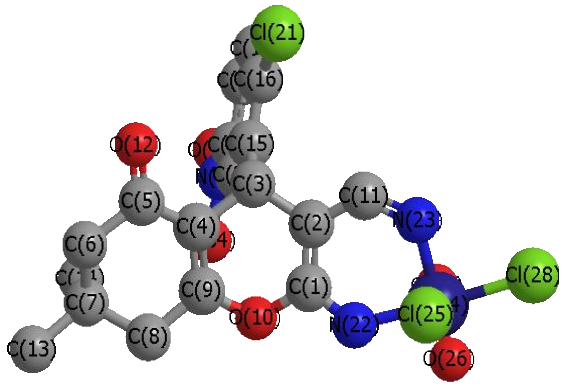


Figure 7: optimization geometry of cobalt (II)-CNB.

The metal complex (cobalt (II)-CNB)) was stabilized by arranged of Benzoxzole moiety in plane with metal core (figure 7). The bond lengths of all the active groups taking part in coordination are changed compared already exist in the ligand due to complexation [37].

The frontier molecular orbitals (highest occupied molecular orbital, HOMO and lowest unoccupied molecular orbital, LUMO) are the most important orbitals in a molecule. These orbitals determine the way for the molecule interacts with other species. The FMOs gap of a molecule are important parameters for examination of reactivity and stability. The molecule with higher E_{HOMO} value is a prefect awarding electron. The lower E_{HOMO} value, referred to a soft power for giving electron. (HOMOs) and (LUMOs) of the studied systems in the S_0 states have been shown in (Figure 8), which suggests the delocalization and localization of molecular orbitals. The ***HOMO*** is localized over phenyl ring metal core for (cobalt (II)-CNB), while ***LUMO*** condensed over complex phenyl of pyrane ring (Figure 8). The HOMO→LUMO electron transition suggested, the electron flow from Metal ring to pyrane ring. The negative energy gap is indicated the enhancement of stability and intramolecular charge transfer take place for studied complex [38].

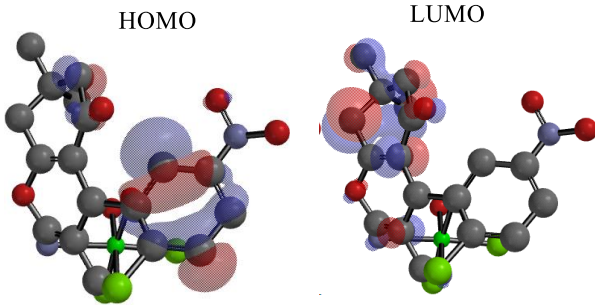


Figure 8: (HOMOs) and (LUMOs) cobalt (II)-CNB).

The total dipole moment is reflecting the ability interaction of the molecules with the surrounding environment, the (cobalt (II)-CNB) has shown dipole moment value, which increasing ability of interaction with the surrounding environments. Therefore, complex molecule is a suitable structure for several applications such as interaction enzyme [37].

The electrostatic potentials (ESP) mapped of (cobalt (II)-CNB) preformed, to examine the similarity in electronic and conformational properties. The pink colors indicate negative ESP regions and blue colors indicate positive ESP regions. ESP of complex indicated that increasing positive charge regions located on the center of coordinating metal (Figure.9). The electron density is localized in metal ring due to electron attractor power which caused from large bond order of Cu-core, so, the complex showed lower value for hardness and high values for softness and electrophilic capacity.

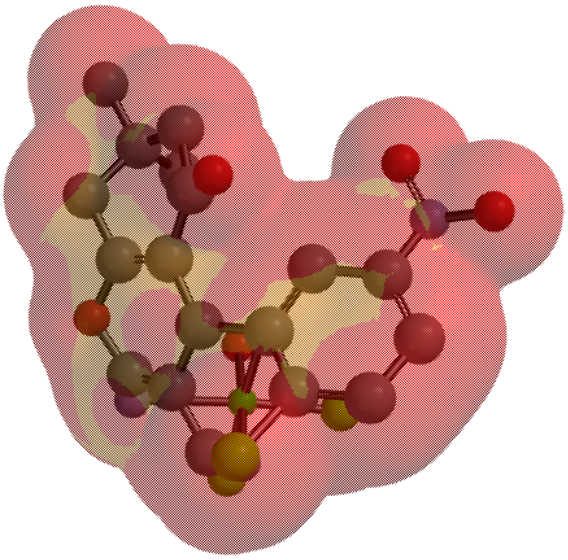


Figure 9: ESP of complex cobalt (II)-CNB.

5. Conclusion

The well-known 4-(2-Chloro-5-Nitrophenyl) Benzopyran have been used in the synthesis of cobalt (II) complex (cobalt (II)-CNB). This complex was fully characterized by different tools. The geometry around the cobalt ion is found to be octahedral geometry. Complex has been used as a catalyst in the oxidation of polyphenol 1,2,3- trihydroxybenzene in presence of H_2O_2 as a green oxidant. The cobalt complex affords a significant catalytic activity toward the oxidation of THB compared to the un-catalyzed reaction and kinetic parameters were calculate for reaction. The oxidation reaction herein is inhibited by kojic acid as competitive inhibition molecular modeling for electronic structural parameters were performed calculated energy and geometrical optimization.

6. References

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