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Catecholase catalytic properties of copper (II) complexes prepared in-situ with heterocyclic ligands: Experimental and DFT study

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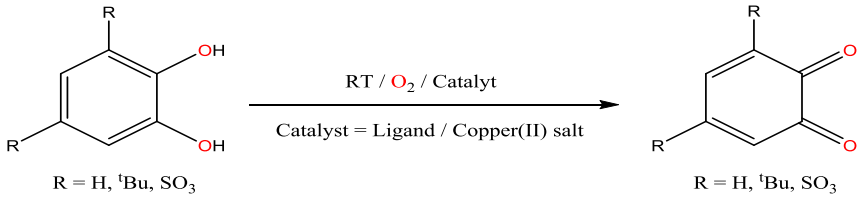
Abstract

The objective of our work is the preparation of the new catalysts for catecholase, whose principle is based on the catechol oxidation reaction which presents a major challenge in both biology and medicine. First, we synthesized nine pyrazole and triazole ligands, then we evaluated the catalytic properties of certain of those ligands in situ complexes to catalyze the oxidation reaction of catechol to o-quinone. The aim of this study is to find the right models to reproduce the catalytic activity of the enzyme (catecholase), so we used complexes formed in situ by pyrazole and triazole derivatives with copper (II) salts. The reason behind the interest of these complexes is their resemblance to biological systems, capability of activating the catalyst for many chemical reactions. Among these complexes, some of them showed good catalytic activity for this reaction. We have demonstrated that the nature of ligand, the concentration of ligand, the nature of the solvent and the nature of the copper (II) salt, influences the efficiency of the catecholase activity. Pyrocatechol is benzene-1,2-diol (nomenclature IUPAC), also known as catechol with formula $C_6H_6O_2$ crude used in many organic syntheses. Some catecholamines have important physiological functions. The Government of Canada has determined that catechol is "toxic" as defined by the Canadian Environmental Protection Act, 1999. So, to reduce the toxic effect of catechol we try to oxidize o-quinone which is less dangerous than catechol. The DFT study has big interest in many researches to know the reactivity of the ligands by calculating different quantum descriptors as: EHOMO, ELUMO, The gap energy, Ionisation potential, The electron affinity and The hardness..

Keywords: *Oxidation, Catechol, Pyrazole, Triazole, Quinone, DFT.*

1. Introduction

The compounds based on Pyrazole and triazole have occupied also an important place in modern chemistry due to their various applications in many fields such as pharmacology [1, 2], catalysis [3-7], electronics [8], complexation [9-11], inhibitor for corrosion [12], cytotoxic activities [13], Lithium cation transportation [14], Lithium and Cesium cations extraction [15, 16] antifungal and antibacterial activities [17, 18]. Copper is crucial to all organisms living in oxygen-rich environments. It is present in the active sites of many metalloenzymes and metalloproteins [19, 20] also it is involved in oxygen transport, oxygenation reactions, electron transfer, and nitrite reduction [21-24]. Moreover, several reports brought to attention that copper complexes have antibacterial, antiviral, anti-inflammatory activities [25] and antitumor agents [26]. Additional applications of copper complexes include catalytic chemical bond activation [27] supra-molecular assembly [28, 29], magnetic behavior [30, 31]. The copper complexes build from pyrazole have a remarkable biologic activity [32-35], and used for construction of various artificial helical structures [36] candidates for nanocarriers for drug delivery and imaging [37]. Notable progress has been made to mimic tyrosinase activity using multidentate heterocyclic amine copper complexes [38]. Several catechol derivatives were used in the literature as models for these kinds of studies [3, 39-41] (Scheme 1).



Scheme (1) : Oxidation of catechol derivatives to o-quinones.

New catalysts build from copper (II) complexes and N-donor chelating ligands such as Pyrazole and triazole have been used in situ as catalyst for oxidation of catechol to o-quinone under mild condition. The complexes based on the ligands (L_1-L_9) and copper (II), where used to study catecholase activities. The effect of counterion of copper (II) salts, Cu $(CH_3COO)_2$, $CuSO_4$ and $CuCl_2$, beside the concentration of ligand and the nature of solvents MeOH and will be investigated. Otherwise, we used DFT [42] method to investigate the theoretical properties of our prepared ligands with B3LYP basis 6-31G (d,p), which is very known to know the reactivity of the ligands by calculating many quantum descriptors like: Egap, E_{HOMO}, E_{LUMO} and Dipolar moment using GAUSSIAN09W [43].

2. Material and Methods

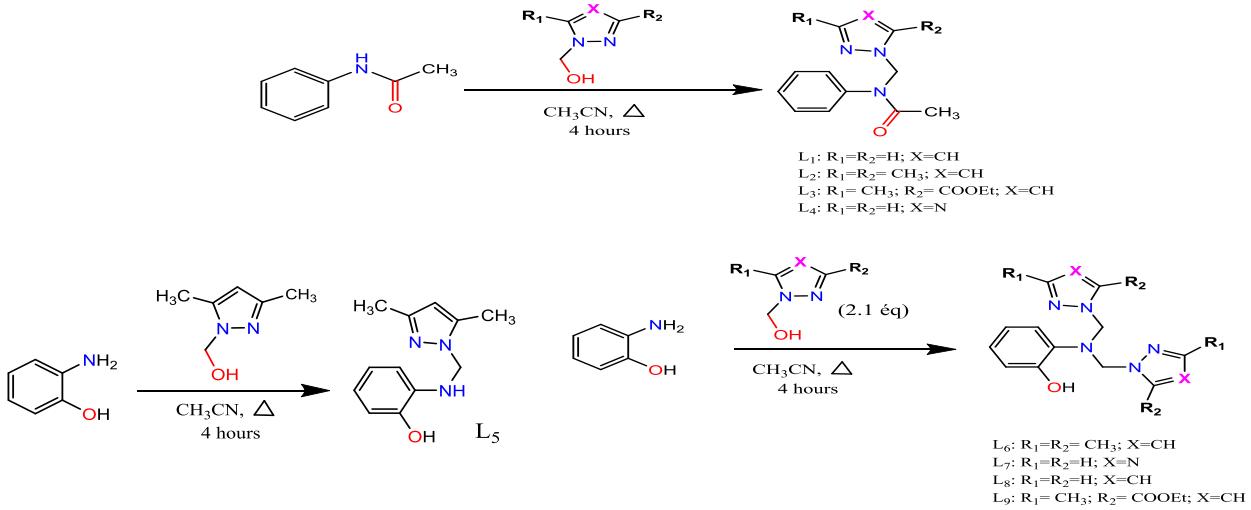
2.1. Synthesis of the ligands

The ligands L_1-L_9 were prepared according to the method described in the literature [44-46]. Catechol or 3,5-DTB-catechol, MeOH and THF were obtained from sigma -Aldrich. At a constant temperature of 60 °C, (1 eq) of N-phenyl acetamide was dissolved in the minimum amount of acetonitrile with (1 eq) of ((1H-pyrazol-1-yl) methanol to prepare L_1, (3,5-dimethyl-1H), pyrazol-1-yl) methanol for L_2, (1H-1,2,4-triazol-1-yl) methanol for L_4, and ethyl 1-(hydroxymethyl)-5-methyl-1H-pyrazol-3-carboxylate for L_3 in the minimum of acetonitrile heated to reflux and stirring for 4 hours. Elsewhere, the preparation of the other ligands is by the change of the amine to aminophenol. (1eq) of aminophenol was dissolved in the minimum of acetonitrile, heated to T = 60 °C and mixed with (2eq) of (3,5-dimethyl-1H-pyrazol-1-yl) methanol, (1H-1,2,4-triazol-1-yl) methanol, ((1H-pyrazol-1-yl) methanol, ethyl 1-(hydroxymethyl) -5-methyl-1H-pyrazol-3-carboxylate dissolved in the minimum of acetonitrile, to prepare L_6, L_7, L_8 and L_9 respectively. To prepare L_5 we used (1eq) of ((3,5 -dimethyl-1H-pyrazol-1-yl) methanol), the mixture is heated for 4 hours (Scheme 2).

L_1 was obtained white crystal. ^{1}H NMR (400 MHz, $CDCl_3$): δH = 2.13 (s, 3H, CH_3), 5.36 (s, 2H, CH_2), 6.52 (t, 1H, CH_{py}), 7.05-7.15 (m, 6H, Ar-H), 8,30-8,12 (d, 2H, Ar-H; ^{13}C NMR (100 MHz, $CDCl_3$): δC = 10.13 (CH_3), 70.22 (CH_2), 104.12 (CH_{py}), 106.06 (CH_{Ar}), 111.33 (CH_{Ar}), 111.9 (CH_{py}), 139.90 (CH_{py}), 158.09 (C_{Ar}), 162.5(C).

L_2 was obtained white crystal. ^{1}H NMR (400 MHz, $CDCl_3$): δH = 2.10 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 5.42 (s, 2H, CH_2), 5.83 (s, 1H, CH_{py}), 7.05-7.30 (t, 2H, Ar-H), 7.47-7.57 (d, 2H, Ar-H; ^{13}C NMR (100 MHz, $CDCl_3$): δC = 10.53 (CH_3), 13.03 (CH_3), 24.23 (CH_3), 69.96 (CH_2), 104.85 (CH_{py}), 106.06 (CH_{Ar}), 120.03 (CH_{Ar}), 124.3 (CH_{py}), 139.90 (CH_{py}), 148.74(C_{Ar}), 168.23(C).

L_3 was obtained white crystal. ^{1}H NMR (400 MHz, $CDCl_3$): δH = 1.39 (t, 3H, CH_3), 2.53 (s, 3H, CH_3), 2.57 (t, 3H, CH_3), 3.48 (q, 2H, CH_2), 6.55 (s, 2H, CH_2), 7.28 (s, 1H, CH_{py}), 7.20-7.45 (m, 6H, Ar-H), 8,28-8,40 (d, 2H, Ar-H; ^{13}C NMR (100 MHz, $CDCl_3$): δC = 11.36 (CH_3), 14.41 (CH_3), 24.36 (CH_3), 53.72 (CH_2), 60.99 (CH_2),108.27 (CH_{py}), 113.94 (CH_{Ar}), 135.69 (CH_{Ar}), 139.90 (C_{py}), 143.5(C_{py}), 150.09 (C_{Ar}), 162.3(C), 165.5(C).



Scheme 2 . Structure of ligands L_1-L_9 used in the oxidation of catechol

2.2. Catechol oxidation measurements

Kinetic measurements by a UV-Vis spectrometer, **UV-2510TS** (*Higher Institute of Nursing and Health Professions techniques* (ISPITS)- Oujda-Morocco). The metal complex (prepared in situ from copper salts and the ligand) [3, 47]. To determine the catecholase activities, the complexes formed in-situ by mixing successively 0.15 mL ($2x10^{-3}$mol/L) of a solution of the different copper salts $Cu(CH_3COO)_2$, $CuSO_4$ and $CuCl_2$ with 0.15 mL ($2x10^{-3}$mol/L) of ligand solution. The complexes formed in situ were treated with 2mL (10^{-1}mol/L) of catechol in different solvent MeOH and THF. The appearance of o-quinone over time at room temperature at 390 nm.

3. Results and discussion

3. 1. Catecholase studies

Catecholase activity for the ligands (L_1-L_9), was investigated with different ligand: metal ratio (1:1, 2:1 and 1:2), type of counterion Cu $(CH_3COO)_2$, $CuSO_4$ and $CuCl_2$ and the two solvents were MeOH and THF.

3.2. Catecholase studies of in situ complexes formation of ligands L_1-L_9 in methanol and THF solvents

In the oxidation of catechol to o-quinone, we used the complexes formed in situ by heterocyclic ligands and copper (II) salts by varying the ratio ligand/copper salt and changing the solvent to methanol then tetrahydrofuran in the

normal conditions. The table 1 and the figures 1-4 for example, shows the oxidation reaction rate of catechol to o-quinone with in-situ complex formed by all combinations used in this study. Figures 1-4 shows the absorption evolution of o-quinone in the presence of (L_6/$CuCl_2$ -1L/1M in MeOH), (L_6/Cu ($CH_3COO)_2$ -2L/1M in MeOH), (L_6/$CuCl_2$ -1L/2M in MeOH) and (L_9/Cu ($CH_3COO)_2$ -1L/1M in THF).

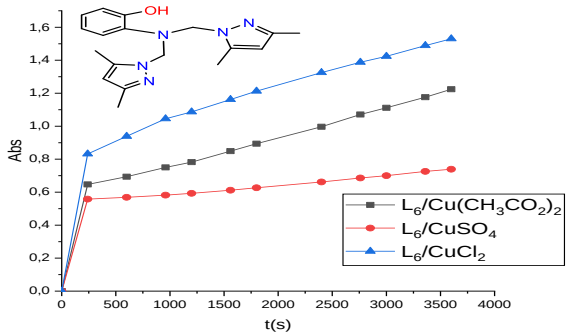


Figure 1. Absorbance evolution of o-quinone in presence of complexes formed by L_6 and different copper salts (1L/1M) in MeOH

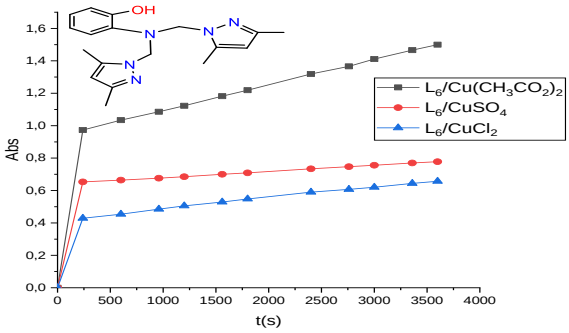


Figure 2. Absorbance evolution of o-quinone in presence of complexes formed by L6 and different copper salts (2L/1M) in MeOH

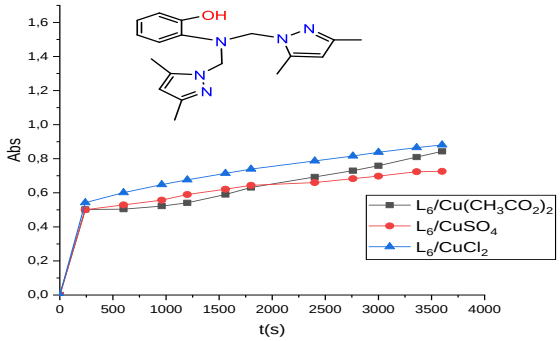


Figure 3. Absorbance evolution of o-quinone in presence of complexes formed by L6 and different copper salts (1L/2M) in MeOH

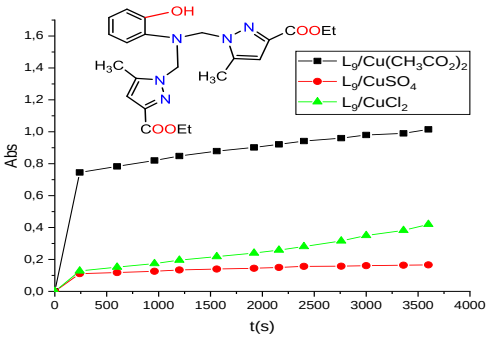


Figure 4. Absorbance evolution of o-quinone in presence of complexes formed by L9 and different copper salts (1L/1M) in THF

Table 1: Reaction rate V (µmol L^{-1} min^{-1}**)** of catechol oxidation in MeOH and THF with different ligand: metal ratio

	$Cu(CH_3COO)_2$				$CuSO_4$				$CuCl_2$			
L/M	1L/1M MeOH	2L/1M MeOH	1L/2M MeOH	1L/1M THF	1L/1M MeOH	2L/1M MeOH	1L/2M MeOH	1L/1M THF	1L/1M MeOH	2L/1M MeOH	1L/2M MeOH	1L/1M THF
L_1	0.85	13.17	3.44	3.81	0.70	3.82	4.27	0.60	0.13	2.89	2.27	2.00
L_2	9.44	0.10	4.75	7.68	2.16	1.79	4.37	0.57	1.08	1.77	0.76	2.03
L_3	8.02	4.97	1.41	6.24	1.42	1.39	3.35	0.88	0.68	1.12	1.38	1.03
L_4	6.10	4.65	1.03	8.42	1.71	2.50	2.04	1.28	0.95	0.03	1.36	2.21
L_5	12.90	8.05	7.29	5.86	4.65	4.78	1.44	1.35	3.25	1.30	0.08	2.78
L_6	12.75	15.62	8.78	6.54	7.69	8.10	7.56	0.92	15.93	6.84	9.17	1.94
L_7	4.61	14.64	5.82	4.91	4.25	3.68	3.53	2.63	5.94	3.97	3.42	2.70
L_8	7.38	9.75	1.47	5.11	2.39	8.08	9.58	0.84	1.89	1.46	0.05	2.90
L_9	8.27	5.97	7.87	8.90	5.13	4.01	3.26	1.45	3.56	4.56	1.62	3.68

3.2.1. The effect of counterion and ligand

From the Figures and the table sitting before, we note that the catalytic activities depend strongly on both the form of the ligand and the type of inorganic anion. Its noted that the rate of oxidation of catechol to o-quinone for the nine ligands is very high in the case of using the ($L_6/CuCl_2$) in MeOH and low in the case ($L_1/CuCl_2$) complex in MeOH. The nature of the ligand particularly the electronic effect of substituent group could have an effect on the coordination. Figures 2-5 shows the absorption evolution of o-quinone in the presence of $L_6/CuCl_2$, $L_6/Cu\ (CH_3COO)_2$, $L_6/CuCl_2$ and $L_9/Cu\ (CH_3COO)_2$ and the table 1 shows the kinetic data of the different combinations ligand and copper (II) salt.

3.2.2. The effect of (ligand: metal) ratio

In the case of (1L/2M) ratio, table 1 show all of the complexes catalyze the oxidation reaction of catechol to o-quinone with the rate varying from a high of 9.17 µmol L^{-1} min^{-1} when ($L_6/CuCl_2$) complex used to a low value of 0.05 µmol L^{-1} min^{-1} when ($L_8/CuCl_2$) complex is used. In the case of (2L/1M) ratio the high catalytic activity reaches 15.62 µmol L^{-1} min^{-1} when ($L_6/Cu\ (CH_3COO)_2$) ratio is used while the low activity 0.03 µmol L^{-1} min^{-1} when ($2L_4/1CuCl_2$) is used (table 1). Also, increasing the concentration of the salt has a negative effect on the oxidation of catechol to o-quinone.

3.2.4. Effect of solvent

Table 1 shows that the highest rate of reaction is 15.93µmol L^{-1} min^{-1} when $L_1/(CuCl_2)$ and MeOH is used while the lowest rate is 0.13µmol L^{-1} $min^{-}1$ when $L_1/CuCl_2$ is used in the same solvent. In general, with all ligand (L_1-L_9) and different combinations ligand and salt of copper (II), the catalytic activity is enhanced when MeOH as polar protic solvent is used relative to polar non protic solvent THF. These results clearly indicate that the smooth conversion of catechol to o-quinone, catalyzed by combinations formed in-situ by ligands L_1-L_9 with different copper salts, and it was important when the solvent is MeOH.

3.2.5. Kinetic study

The kinetics of the oxidation of catechol was determined by the method of initial rates by monitoring the increasing in the characteristic quinone absorption band at 390 nm under air as a function of time for the best catalyst ($L_{5:}$ Cu $(CH_3COO)_2$: MeOH ; $L_{6:}$ $CuCl_2$: MeOH) for the catechol oxidation. The ligands and salt copper (II) concentration were ($2x10^{-3}$ $mol.L^{-1}$) and the catechol concentration was varied in the range $6x10^{-1}mol.L^{-1}$ to $2.5x10^{-2}$ $mol.L^{-1}$. The evolution of absorbance of o-quinone at 390 nm was monitored for the first 5 minutes of the reaction time, and linear relationship for the initial rates and the substrate concentration was obtained. The conversion of catechol to *o*-quinone was monitored with time at a wavelength of 390 nm. The rate versus concentration of substrate data were analyzed on the basis of Michaelis–Menten approach of enzymatic kinetics to get the Lineweaver–Burk (double reciprocal) plot as well as the values of the various kinetic parameters. Figures 6-9 show the Michaelis-Menten and Lineweaver–Burk model for the four best catalyst. In the table 2, the value K_m and maximal rate V_{max} for the two catalysts are presented and the best one is $L_6/Cu\ Cl_2$ in MeOH for the catechol oxidation reaction. From figures 6-9 the kinetic study for L_5 and L_6 ligands shows that there is a linear relationship for initial velocities and substrate concentration, so the Michaelis-Menten model is applied to obtain kinetic parameters of the best catalyst. The V_{max} speeds of the $L_5/Cu\ (CH_3COO)_2$ combinations are 57 $\mu mol.L^{-1}.min^{-1}$ and for $L_6/CuCl_2$ is 59 $\mu mol.L^{-1}.min^{-1}$ (Table 2). with a low value of K_m (0.02 $mol.L^{-1}$) for combination $L_6/CuCl_2$ with respect to the K_m (0.14 $mol.L^{-1}$) of $L_5/Cu(CH_3COO)_2$ combination, which explains why the affinity is strong in MeOH, so in our case the combination $L_6/CuCl_2$ gives a better result for oxidation catechol. Graphical representation of rates (V) as a function of substrate concentration increases, which means that the reaction rate increases rapidly.

Table 2: Kinetic data for the oxidation of catechol by two combinations ligand/salt copper (II) **in MeOH**

Combination (L/M)	$L_5/Cu\ (CH_3COO)_2$	$L_6/CuCl_2$
V_{max} (µmol.L^{-1}.min^{-1})	57	59
K_m (mol.L^{-1})	0.14	0.02

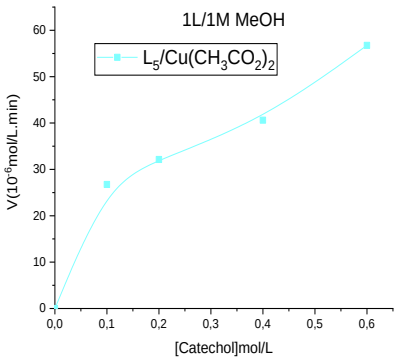


Figure 5. Graphical representations of Vi as a function of substrate concentration for $L_5/Cu\ (CH3COO)_2$ in MeOH

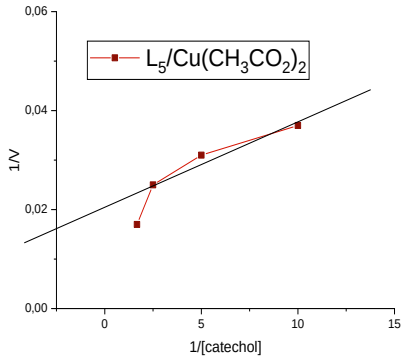


Figure 6. Reaction dependence on the concentration of catechol using $L_5/Cu\ (CH3COO)_2$ in MeOH

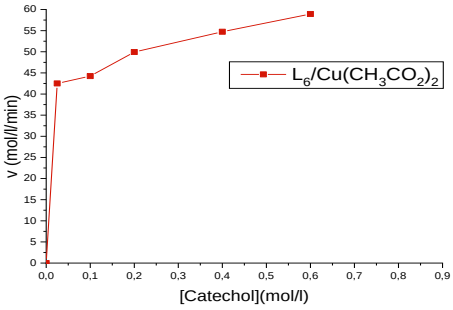


Figure 7. Graphical representations of Vi as a function of substrate concentration for $L_6/CuCl_2$ in MeOH

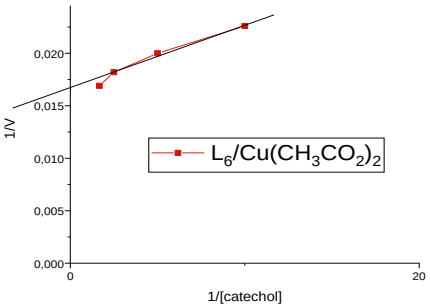


Figure 8. Reaction dependence on the concentration of catechol using $L_6/CuCl_2$ in MeOH

3.5. UV-Vis spectrophotometric study

To confirm the important catalytic activity of the L_6/ $CuCl_2$ and $L_9/Cu(CH_3CO_2)_2$ combinations (the best catalysts of our complexes), the o-quinone formation kinetics was determined by mixing 0.15 mL of ligand (2.10^{-3} mol.L^{-1}), and 0.15 ml of copper (II) salt (2.10^{-3} mol.L^{-1}) followed by the addition of 2 ml of catechol (10^{-1} mol.L-1) , and the evolution of the absorbance of o-quinone was recorded in every 5 min. The kinetic experiments were performed at room temperature. The catecholase activity for catechol by the complexes $L_6/CuCl_2$ and $L_9/Cu\ (CH_3COO)_2$ was studied in MeOH and THF respectively, shows the change of spectral behavior immediately after the addition of a solution of complex to the catechol solution the bands appear and increase. The results are shown in figures 10 and 11. Clearly show that band centered at around 390 nm is observed when reaction is realized in MeOH and THF respectively, which explain that combination arising from all ligand and copper salt catalyzes the oxidation of catechol to o-quinone. In the two solvent, the absorbance of o-quinone increases with time, confirming that the oxidation reaction of catechol to o-quinone was feasible.

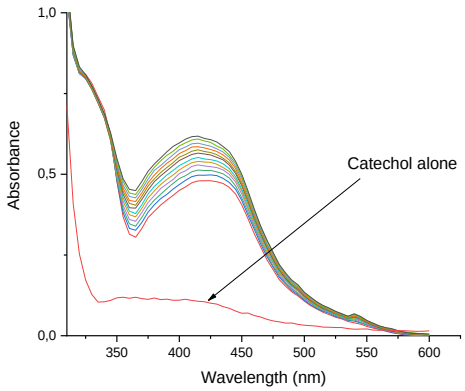


Figure 9. Increase of o-quinone band at 390 nm after addition of the catechol solution to a solution containing $L_6/CuCl_2$ in MeOH. The spectra were recorded after every 5 min

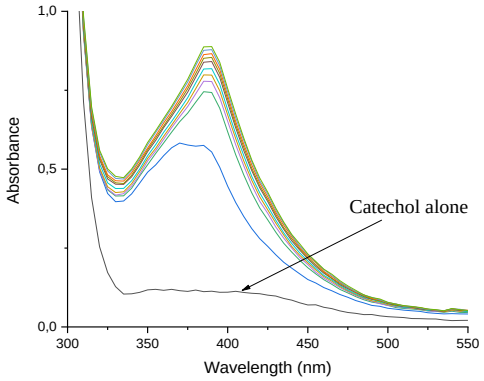


Figure 1. Increase of o-quinone band at 390 nm after addition of the catechol solution to a solution containing $L_9/Cu\ (CH_3CO_2)_2$ in THF. The spectra were recorded after every 5 min

3.6. Proposed mechanism for the oxidation of catechol

From the data provided by the kinetic study, we proposed a mechanism for the catechol oxidation reaction figure 11. The catechol molecules are oxidized by one cycle, and the oxygen is reduced to hydrogen peroxide. We try to present a catechol oxidation mechanism, as shown in figure 11, the mechanism of catecholase activity starts from the complex. The catechol binds to the complex (for example), followed by the oxidation of the substrate to the first o-quinone and the reduction of copper [4,5].

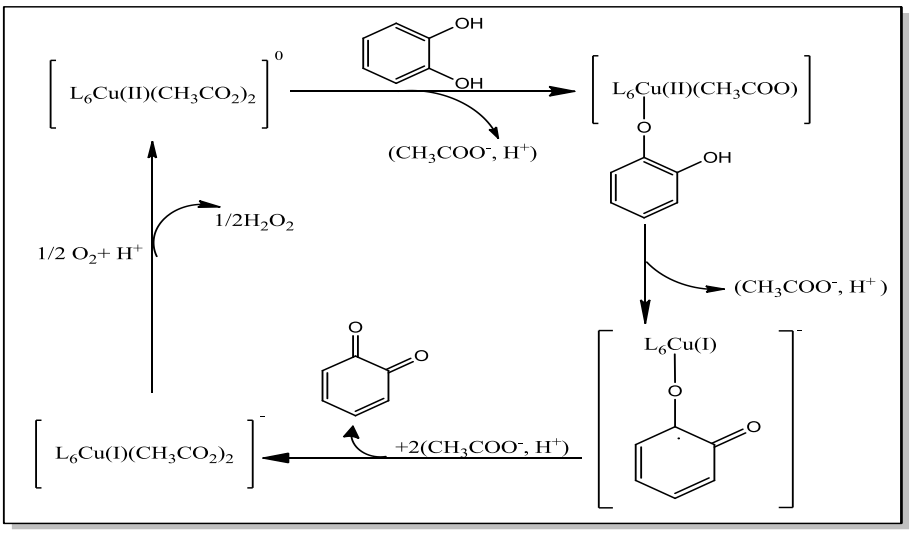


Figure 2. Proposed mechanism for the oxidation of catechol

4. DFT Study

The DFT study was executed on Dell OptiPlex 790 MT – Core i5-2400 @ 3,10 Ghz with 4 Gb RAM and windows 7 operating system. Using the GAUSSIAN 09W program suite [43], it calculate first the full geometry optimizations of all the studied ligands using DFT method with B3LYP exchange correlation [48–51] in combination with 6-31G (d, p) orbital basis sets for all atoms, and no symmetry constrains were applied.

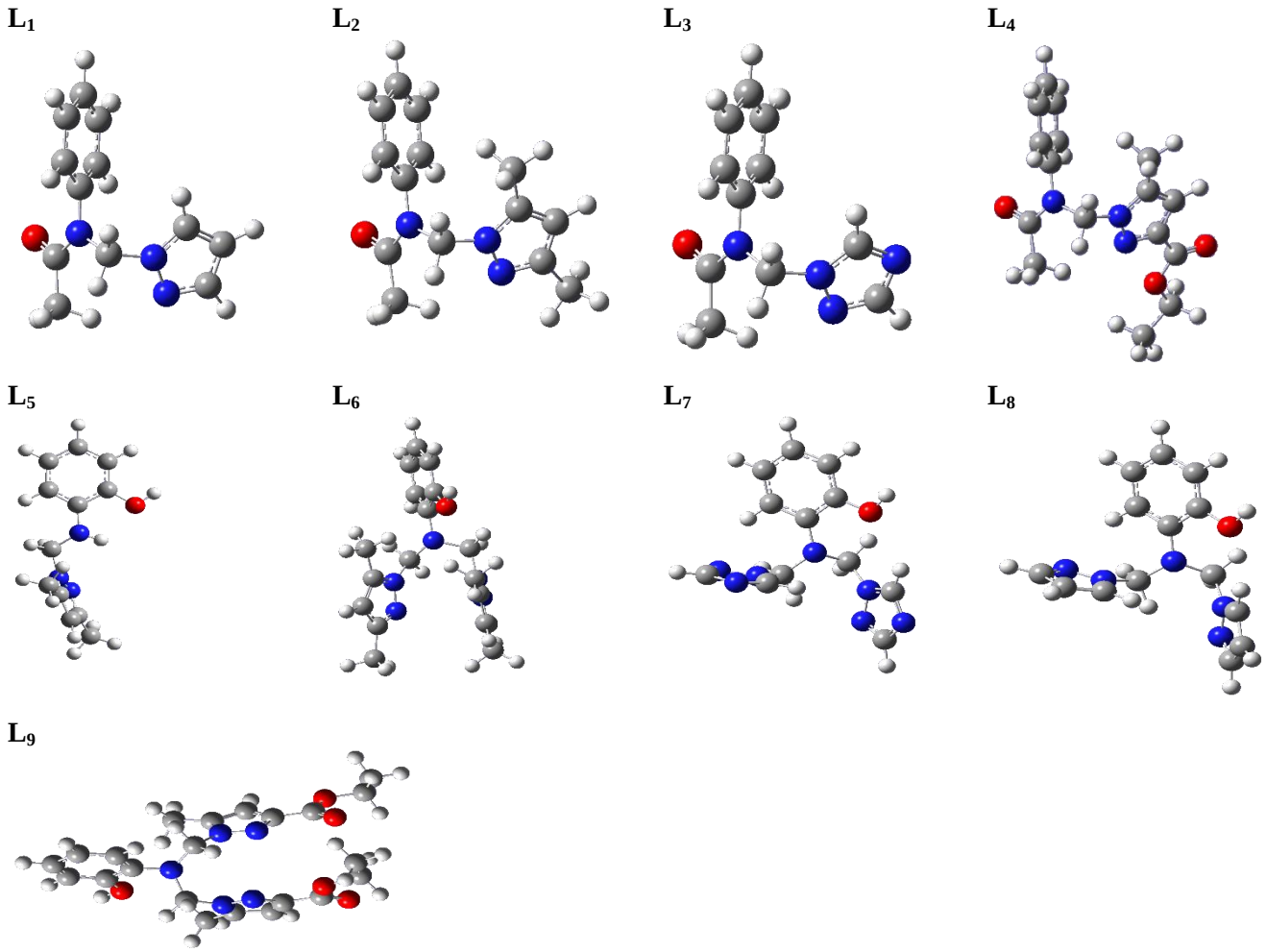


Figure 12. Geometrical Optimized structures of the ligands L_1-L_9

For the quantum descriptors, we found in the results after the calculation is done only E_{HOMO}, E_{LUMO} and we calculated using the following equations:

$$\Delta E_{gap} = |E_{HOMO} - E_{LUMO}| \qquad (1)$$

By Koopmans theory [51], we have:

$$I = -E_{HOMO} \qquad (2)\ ; \qquad A = -E_{LUMO} \qquad (3) \qquad \text{and} \qquad \eta = \frac{I - A}{2} \qquad (4)$$

From the data in table 3, we retrieve the following information: HOMO or the highest occupied molecular orbital (in energy) is the easiest orbital to give electron which L5 the electron donor due to the presence of the dimethyl substituents on the pyrazole ring and the free NH and OH on the aromatic ring, otherwise the LUMO or the lowest unoccupied molecular orbital (in energy) is the easiest orbital to accept electron, for our study it's the case of L_4 due the presence of the Triazole ring which is known as an attractor of the electrons. The gap energy is another important quantum descriptor [52] which represents the gap between HOMO and LUMO orbitals (in energy) so the necessary energy to do the first excitation of the ligand, so L_5 is the most reactive ligand between all of the studied ligands.

The ionization potential (I): L_5 has the lowest value of ionization potential so it has the highest reactivity of atoms and molecules.

The electron affinity (A): This parameter refers the capability of the molecule to accept precisely one electron from a donor, which is the case for L4 with the highest value of electron affinity. The hardness (**η**) reflects the ability of the ligand to resist faces to electron number change. The lowest value of it is assigned with the ability to give or accept

electron which is the case of L_5. For the Frontier molecular orbitals of the ligands, we used the same descry bed parameters for the DFT study, and it's very important to have an idea about the different sites in the ligand, and from the figure 13, we conclude that L_5 is the most reactive ligand and its differenced from other ligands by their large coverage of the molecular orbitals on all the sites either for HOMO or LUMO.

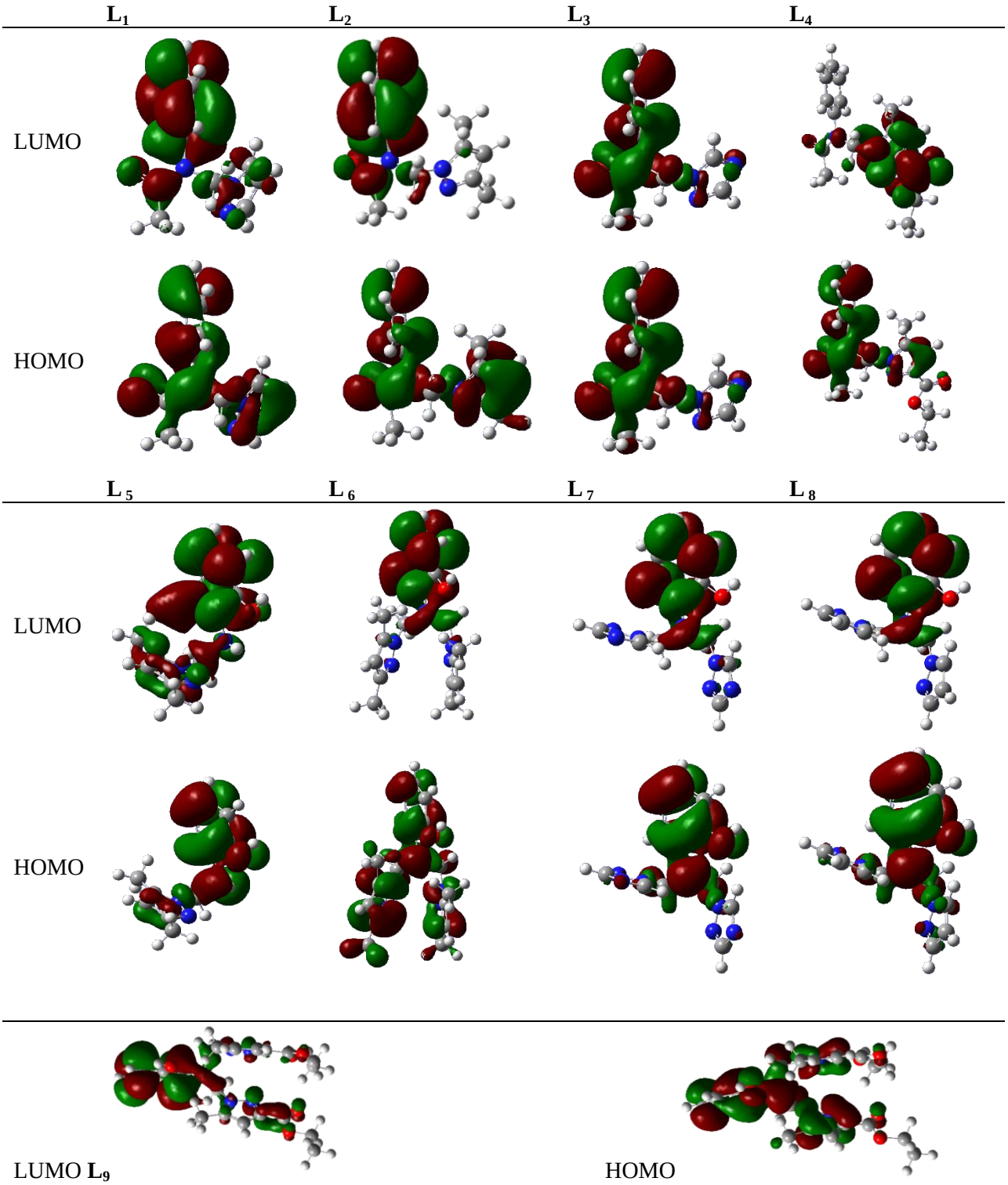


Figure 13. Frontier molecular orbitals of L_1-L_9

Table 3. The quantum descriptors values founded and calculated for the ligands L_1-L_9

	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE_{gap} (eV)	I (eV)	A (eV)	η (eV)
L_1	-6,37998484	-0,35674145	6,02324339	6,379984844	0,356741454	3,011621695
L_2	-6,30052755	-0,29170620	6,008821348	6,300527556	0,291706208	3,004410674
L_3	-6,61373077	-0,48817251	6,125558254	6,61373077	0,488172516	3,062779127
L_4	-6,53699462	-0,86967634	5,667318278	6,536994622	0,869676344	2,833659139
L_5	-5,25316077	0,109661942	5,362822712	5,25316077	-0,10966194	2,681411356
L_6	-5,72174107	-0,33497233	5,386768744	5,721741078	0,334972334	2,693384372
L_7	-5,98514743	-0,32953005	5,655617376	5,98514743	0,329530054	2,827808688
L_8	-5,62350792	-0,02476237	5,59874555	5,623507924	0,024762374	2,799372775
L_9	-6,15358599	-0,60817479	5,545411206	6,153585996	0,60817479	2,772705603

5. Conclusion

In this work, we studied the catalytic activity of pyrazole-based ligands and triazole with different copper salts (II), we found that all combinations can catalyze the oxidation reaction of catechol in o-quinone in ambient conditions, using atmospheric oxygen as oxidant (catecholase activity) but with different velocities. Our study indicates that the ligand nature really affects the catalytic efficiency of corresponding combinations, and the nature of the solvent plays an important role on the catalytic activity of the complexes prepared in situ. On the other hand, the combinations, in which the ligand is associated with the salt copper (II) $Cu(CH_3CO_2)_2$, is observed to be more effective for catalyzing the oxidation of catechol in the presence of molecular oxygen, which explains why the Anion counter nature also has an effect on catecholase activity. Our study also shows that the catalytic activity of different combinations studied is influenced by the ligand concentration, and the proportions (1eq/1eq) of (Ligand/Metal: 1/1) have been found to act as an excellent catalyst for oxidation of catechol to o-quinone. The best catalyst formed by the ligand L_6 and the salt $CuCl_2$ has been found to have catecholase activity, that is, to catalyze the oxidation of catechol to o-quinone.

From the theoretical investigations about our ligands using DFT method, we retrieve that L_5 is the electron donor with the highest value of E_{HOMO} due to the presence of the dimethyl substituents on the pyrazole ring and the free NH and OH on the aromatic ring, also the lowest value of the gap energy so it's very reactive.

L_5 has the lowest value of ionization potential so it has the highest reactivity of atoms and molecules, and the lowest value of the hardness which reflects the ability of the ligand to resist faces to electron number change. The lowest value of it is assigned with the ability to give or accept electron which is the case of L_5.

Finally the frontier molecular orbitals representation shows for us the large coverage of the molecular orbitals on all the sites either for HOMO or LUMO.

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