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Synthesis and Catecholase Activities of New Bipyrazolic Tripodal Compounds

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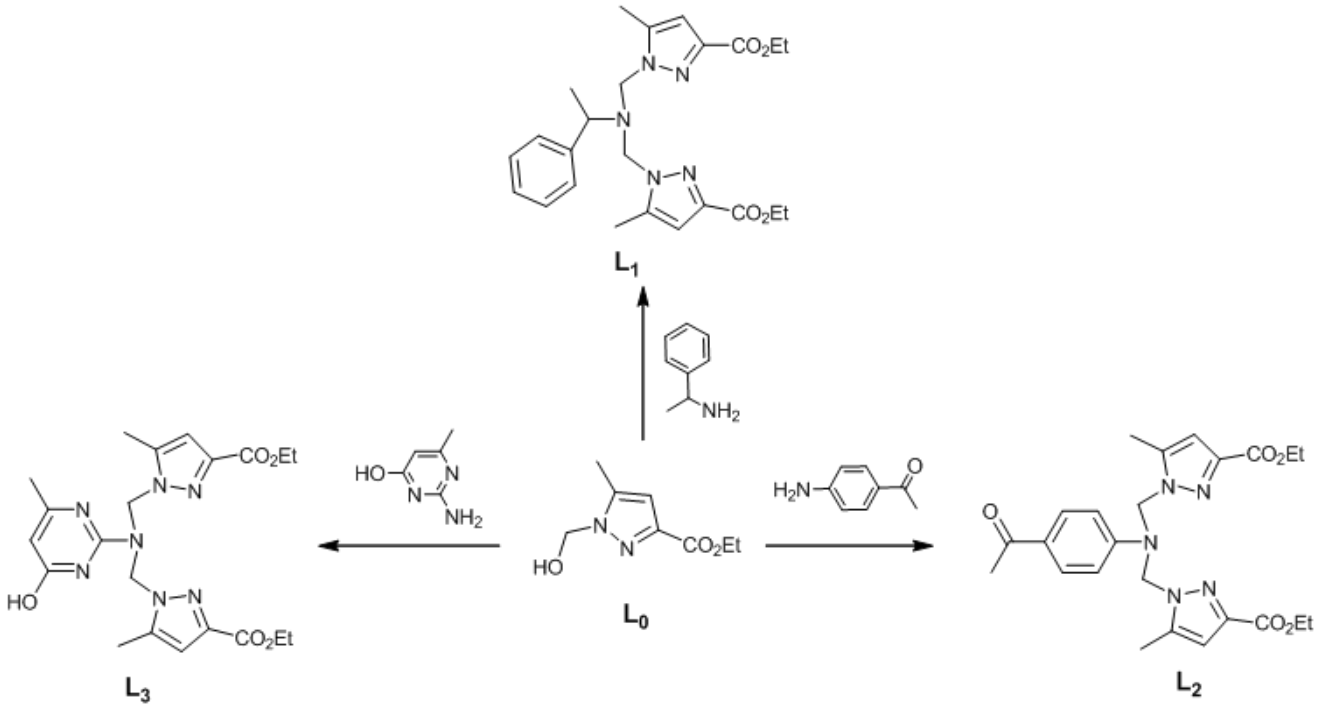
Abstract
A synthesis of functional N-donor tripodal pyrazolyl ligands: diethyl 1,1'-(1-phenylethylazanediyl) bis(methylene)bis(5-methyl-1H-pyrazole-3-carboxylate) L_1 ; diethyl 1,1'-(4-acetylphenylazanediyl) bis(methylene)bis(5-methyl-1H-pyrazole-3-carboxylate) L_2 and diethyl 1,1'-(4-hydroxy-6-methylpyrimidin-2-ylazanediyl)bis(methylene)bis(5-methyl-1H-pyrazole-3-carboxylate) L_3 is reported. The substituents effect of divers bulkiness and electron donor/acceptor power that have been introduced to these tridentate molecules is visualized by ^{1}H and ^{13}C NMR spectroscopy. Compounds L_1 and L_2 have been examined for their catalytic oxidative activities. The dioxygen complexes of copper (II) were generated *in-situ* by stirring copper salts and the tridentate pyrazole ligands. It has been found that these compounds are able to oxidize catechol substrate to the corresponding *o*-quinone with dioxygen at ambient condition. The best rate was given by the combination L_1+2$CuSO_4$. The ligand structure and the nature of the anion salts of copper (II) have a significant effect on the catalytic activity.

Keywords: Pyrazole, Oxidation reaction, Catecholase activity

1. Introduction
Catechol oxidase is an enzyme containing the type-3 active site that catalyzes the oxidation of phenols such as catechols to the o-quinones coupled with the reduction of oxygen to water [1,2]; this process is known as a catecholase activity. The enzyme found in a wide range of soil bacteria [3,4] and plants tissues[5,6],contains a binuclear copper center which represents the active site of this metaloprotein; wherein each copper ion is coordinated by three histidine nitrogen atoms.
To mimic the function of catecholase [7–13], various works have been reported to the copper complexes of pyrazole based ligands. This aptitude is mainly owed to the presence of sp^2 hybrid nitrogen donors [14-15]. Many factors affecting the catalytic activity of the complexes have been highlighted, such as the geometry of the complex [16], the steric and electronic features of the ligands [17] and the nature of the exogenous bridging ligand [18-21].
In connection with a several research aimed to mimic the environment of the metal active site of the enzyme catécholase, we report here the synthesis of a series of new ligands based on pyrazolic moieties (Scheme 1) and the test of their *in-situ* generated complexes. Furthermore, complexes of the transition metal on the dioxygen affinities and biomimetic catalytic oxidation performance were investigated.

2. Experimental
2.1. Apparatus
Melting points are uncorrected and were determined by Kofeler melting point apparatus. IR (cm^{-1}) spectra were recorded (KBr disk) on a Shimadzu FT-IR-8400S spectrophotometer. The ^{1}H NMR (DMSO-d_6 ; 300 MHz) spectra and ^{13}C NMR (DMSO ; 75 MHz) were recorded on a Bruker NMR spectrometer, the chemical shift is

expressed in δ value (ppm) using TMS as an internal reference. Mass spectra were performed on Micromass API 3200 LC/MS/MS spectrometer using direct inlet.



Scheme 1: Synthesis of tridentates pyrazolyl ligands L_1, L_2 and L_3

2.2. General method for synthesis of ligands L_1-L_3

A mixture of ethyl 1-(hydroxymethyl)-5-methyl-1H-pyrazole-3-carboxylate L_0 (10 mmol) and arylamines (5 mmol) in acetonitrile (25 ml) was stirred and refluxed for 4 h. The acetonitrile layer was dried from the water formed by treatment with anhydrous MgSO4. After filtration, the solvent was removed under vacuum, and the crude products were washed with ether, and putted in vacuum desiccators (Scheme 1), we take Pz for pyrazole, Py for pyrimidine, Ph for phenyl, Ar for aromatic and Al for aliphatic.

2.3. Characteristic data of new compounds L_1-L_3

Diethyl 1,1'- (1-phenylethylazanediyl) bis (methylene) bis (5 -methyl-1H-pyrazole-3-carboxylate) L_1 **:**
White powder; Yield = 69%; Mp = 63-65 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm : 7.34 – 7.27 (m, 3H, *m,p*-C_6H_5); 7.20 (d, 2H, *o*-C_6H_5, *J* = 7.9 Hz); 6.50 (s, 2H, H_{Pz}); 5.18 and 5.07 (2d, 4H, N-C$\underline{H}_2$-N, $^2J_{HH}$ = 13,5 Hz); 4.24 (q, 4H, O-C$\underline{H}_2$-CH_3, *J* = 7.0 Hz); 4.09 (q, 1H, N-C$\underline{H}$-CH_3, *J* = 6.9 Hz); 1.91 (s, 6H, -CH_3 pz); 1.32 (d, 3H, N-CH-C$\underline{H}_3$, *J* = 6.9 Hz); 1.28 (t, 6H, O-CH_2-C$\underline{H}_3$, *J* = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm : 162.26 (C=O), 142.04 (Cpz=N), 141.87 ($\underline{C}_{ph}$-C*), 141.06 (Cpz-N), 128.67 (*m*-C_{Ph}), 128.09 (*o*-C_{Ph}), 127.70 (*p*-C_{Ph}), 108.75 (Cpz-H), 63.87 (N-$\underline{C}H_2$-N), 60.47 (O-$\underline{C}H_2$-CH_3), 56.56 (C*H), 15.84 (-CH-$\underline{C}H_3$), 14.67 (O-CH_2-$\underline{C}H_3$), 10.41 (-CH_3 pz). FTIR (KBr, υ cm^{-1}): 3024 ($\nu_{C–H\ Aromatic}$); 2985 ($\nu_{C-H\ Aliphatic}$); 1732; 1716 ($\nu_{C=O}$); 1699; 1653; 1541; 1456; 1220 (ν_{C-O}); 1138; 1039; 1024; 783; 740; 704 . MS (ESI) m/z (%): Calcd for $[M]^+$ $C_{24}H_{31}N_5O_4$: (m/z) = 453,24. Found for $[M+H]^+$ (m/z) = 454,1 (7%) ; $[M+Na]^+$ (m/z) = 475,9 (100%).
Diethyl 1,1'-(4-acetylphenylazanediyl) bis (methylene) bis (5-methyl-1H-pyrazole-3-carboxylate) L_2 :
White powder; Yield = 76%; Mp = 97-99 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm : 7.87 (d, 2H, *m*-C_6H_5, *J* = 8.9 Hz); 7.13 (d, 2H, *o*-C_6H_5, *J* = 8.9 Hz); 6.49 (s, 2H, H_{Pz}); 5.79 (s, 4H, N-C$\underline{H}_2$-N); 4.35 (q, 4H, O-C$\underline{H}_2$-CH_3, *J* = 7.1 Hz); 2.52 (s, 3H, -CO-C$\underline{H}_3$); 2.24 (s, 6H, -CH_{3Pz}); 1.36 (t, 6H, O-CH_2-C$\underline{H}_3$, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm : 196.80 (C=O), 162.44 (O-C=O), 149.49 (Cph-N), 143.46 (Cpz=N), 140.36 (Cpz-N), 131.15 (*p*-C_{Ph}), 130.40 (*m*-C_{Ph}), 117.22 (*o*-C_{Ph}), 109.19 (Cpz-H), 64.56 (N-$\underline{C}H_2$-N), 61.03 (O-$\underline{C}H_2$-CH_3), 26.46 (-CO-$\underline{C}H_3$), 14.49 (O-CH_2-$\underline{C}H_3$), 11.45 (-CH_3 pz). FTIR (KBr, υ cm^{-1}): 3012 ($\nu_{C–H,}$ aromatic); 2982 ($\nu_{C-H,}$ aliphatic); 2908; 1716($\nu_{C=O\ ester}$); 1680 ($\nu_{C=O}$); 1600 ; 1541 ; 1518; 1357; 1273 ; 1209 (ν_{C-O}); 1149; 1033 ; 827;

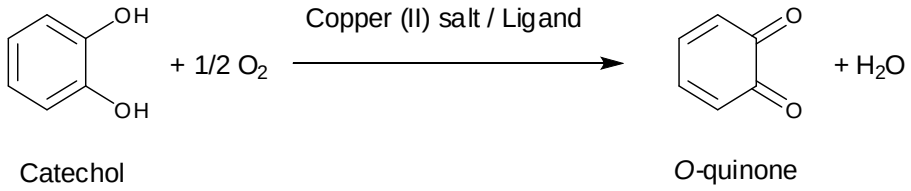
775 . MS (ESI) m/z (%): Calcd for $[M]^+$ $C_{24}H_{29}N_5O_5$: (m/z) = 467,22. Found for $[M+H]^+$ (m/z) = 468,0 (11%) ; $[M+Na]^+$ (m/z) = 490,0 (100%).

Diethyl 1,1'-(4-hydroxy-6-methylpyrimidin-2-ylazanediyl) bis (methylene) bis (5-methyl-1H-pyrazole-3-carboxylate) L_3 :

White powder; Yield = 73%; Mp = 226-228 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm : 10.78 (s, 1H, O*H*); 7.57 (s, 1H, H_{Py}); 6.47 (s, 2H, H_{Pz}); 5.53 (s, 4H, N-CH_2-N); 4.22 (q, 4H, O-C$\underline{H}_2$-CH_3, *J* = 7.1 Hz); 2.48 (s, 6H, -CH_3 pz); 2.03 (s, 3H, -CH_3 py); 1.24 (t, 6H, O-CH_2-C$\underline{H}_3$, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm : 165.66 (C_{Py}-OH), 164.51 ($\underline{C}_{Py}$-CH_3), 162.98(Cpy-N),162,21 (O-C=O),142.70 (Cpz=N), 141,45 (Cpz-N), 107,94 (C-H_{Pz}), 102.50 (Cpy-H), 60,50(N-CH_2-N), 54,07 (O-$\underline{C}H_2$-CH_3), 24,24 (-CH_{3Py}), 14,67 (O-CH_2-$\underline{C}H_3$),11,09 (-CH_{3Pz}). FTIR (KBr, υ cm^{-1}): 3236 (ν_{O-H}); 3082 ($\nu_{C-H\ aromatic}$); 2982 ($\nu_{C-H\ aliphatic}$); 1716 ($\nu_{C=O}$); 1662; 1645; 1637; 1606; 1541 ;1533; 1448; 1431; 1388; 1300; 1246; 1217 (ν_{C-O}); 1028; 817; 781.

2.4. Catecholase activity measurements.

Kinetic measurements were made spectrophotometrically on UV–Vis spectrophotometer, following the appearance of *o*-quinone at ambient condition. The metal complex were prepared *in-situ* [28,29], by mixing successively 0.15 ml of a solution (2.10^{-3} mol/l) of copper salt CuX_2, nH_2O (with X = Cl^-, Br^-, NO_3^-, SO_4^{2-}) with 0.15 ml of ligand solution (2.10^{-3}mol/l), then 2 ml of catechol solution with concentration 10^{-1} mol/l were added in the spectrophotometric cell. The evolution of product absorbance was followed by the increase in absorbance at 390 nm (maximum absorbance), in methanol (99.99%) as a function of time.



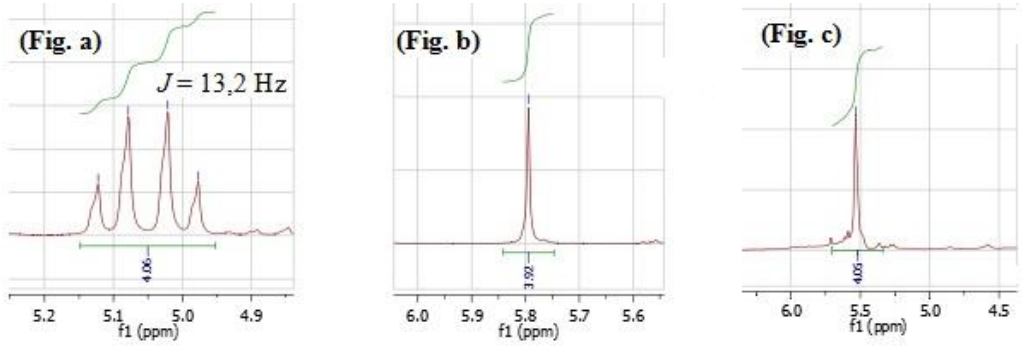
Scheme 2: Catechol oxidation reaction by *in-situ* copper (II) complexes at ambient condition

3. Results and discussion

3.1. Chemistry

New functional tridentate ligands L_1- L_3 as outlined in Scheme 1 were prepared respectively by condensation of two equivalents of ethyl 1-(hydroxymethyl)-5-methyl-1H-pyrazole-3-carboxylate **L_0** with one equivalent of 1-phenylethanamine, 1-(4-aminophenyl)ethanone and 2-amino-6-methylpyrimidin-4-ol in anhydrous solvent of acetonitrile. All reactions were carried out at reflux under stirring for 4 hours. The compounds were isolated with good yield and characterized by IR, ^{1}H-NMR and ^{13}C-NMR and mass spectrometry.

The proton NMR spectra of the pyrazolic ligands revealed signals at 4.16–5.79 ppm corresponding to the hydrogen atoms (N-CH_2-N) of methylene bridges between the nitrogen atom and the pyrazolic rings. This variation of the proton's shift of the methylene groups (4.16–5.79 ppm) could be correlated with the variation of the electronic characteristics of the substituent on amines and pyrazolic moieties, which is in agreement with the reported literature [22-24]. The compound L_1 shows two inequivalent signals of methylene groups (N-CH_2-N) as a consequence of the chiral carbon center; the environment of the two protons has a significant effect on chemical shift. The two geminal protons of methylene groups are diastereotopic and anisochrones in the chiral ligand L_1, (Fig. a) and their signals appear as two doublets of an AB system with similar coupling constant of 13,2 Hz, this result is in agreement with the literature [22,24]. In the ligand L_2 and L_3, the N-CH_2-N groups are observed as a singlet at 5.79 ppm for L_2 (Fig. b) and 5.53 ppm for L_3 (Fig. c).



3.2. Catecholase studies.

The kinetic studies of the oxidation reaction of catechol with O_2 catalyzed by the complexes of copper formed with ligands L_1-L_2 were carried out by monitoring the increase of the concentration of *o*-quinone in the UV/Vis spectrophotometer. The metal complex prepared in situ from copper salt and the ligand [25] and a solution of catechol were added together in the spectrophotometric cell at 25 °C. The UV–Vis spectra were recorded by monitoring the strong absorbance peak of *o*-quinone at the characteristic band at 390 nm as a function of time in methanol.

The results show that the catalytic activity depending on the complex, the obtained results are summarized below (figures 1–7), and the kinetic data were calculated and collected in Tables 1-3.
As can be seen from Tables 1-3, catecholase activity was proved. The calculated reaction rates indicate that the catalytic activity varies from a high of 3.83 µmol l^{-1} min^{-1} for the L_1 + $2CuSO_4$ complex to a weaker rate of 0,03 µmol l^{-1} min^{-1} for $2L_2$ + $CuBr_2$ complex. Changes observed in the UV-Vis spectra can be explained by differences in the type of inorganic anion and the nature of ligands. The non solubility of product L_3 in methanol prevented the study of its properties in the catalyses of the oxidation reaction of catechol.

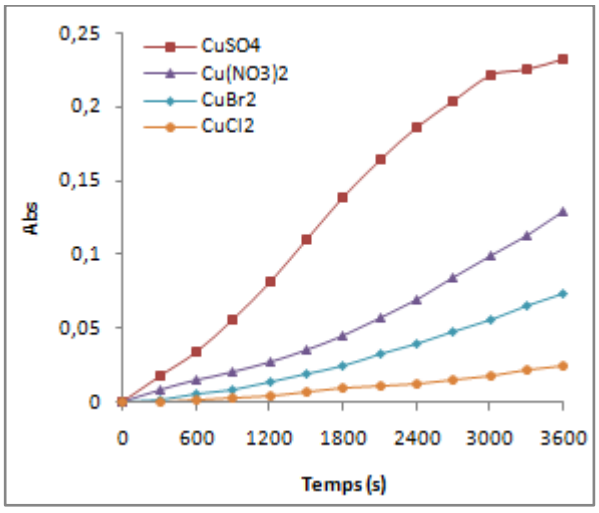


Fig. 1: Oxidation of catechol by complexes of ligand L_1 (1eq of L_1 for 1 eq of Cu(II) salt).

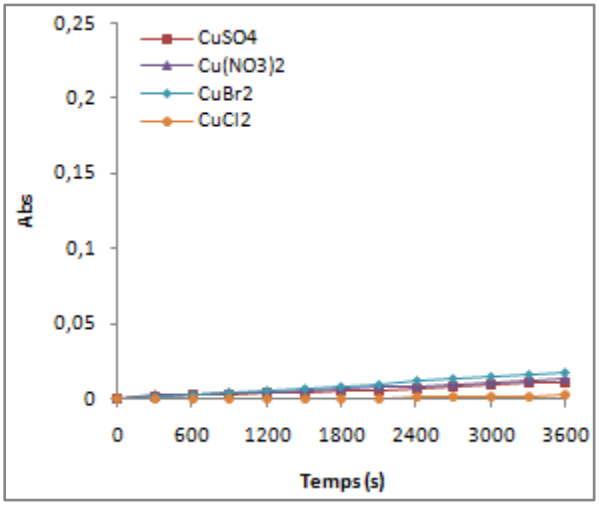


Fig. 2: Oxidation of catechol by complexes of ligand L_2 (1eq of L_2 for 1 eq of Cu(II) salt).

The results shown in Table 1 show that the oxidation rate of catechol using complex with ligand L_1 is greater than the oxidation rate of catechol by complex with ligand L_2 for the same counter anion. The highest rate activity was given by L_1+ $CuSO_4$ which take 2,66 µmol. l^{-1}.min^{-1}.
the lower reactivity of complexes with ligand L_2, is probably due to the conjugation of ketonic carbonyl group with the nitrogen of amine through aromatic ring by withdrawing mesomeric effect. The electronegative oxygen of ketone withdraws electrons by delocalization of π electrons and reduces the electron density on rest of the molecular entity, particularly on sp^3 hybrid nitrogen donor's sites of amine. This effect presented by this

molecule returns the complexes less stable and less efficient in the oxidation reaction of catechol. In other hand, the effect of the nature of the counter anion on the catalytic activity has been observed, this allowed us to note that the nature of the counter anion influences well the catalytic activity.

Table 1: Kinetic data for oxidation of catechol in methanol by ligands copper (II) complexes (1eq of ligand for 1 eq of Cu (II) salt).

Ligands	Copper(II) salts	R^2	V (μmol. $L^{-1}.min^{-1}$)	b (μmol. $L^{-1}.min^{-1}$)
L1	$CuSO_4$	0,98	2,66	20,41
	$Cu(NO_3)_2$	0,97	1,31	10,06
	$CuBr_2$	1,00	0,30	2,30
	$CuCl_2$	0,98	0,26	2,01
L2	$CuSO_4$	0,99	0,12	0,88
	$Cu(NO_3)_2$	0,99	0,11	0,86
	$CuBr_2$	1,00	0,08	0,58
	$CuCl_2$	0,97	0,04	0,29

R^2: Correlation coefficient

V: Rate of catalytic reaction (μmol. $l^{-1}.min^{-1}$)

b: Concentration of catalytic activity (μmol. $l^{-1}.min^{-1}$)

The spectrum of absorbance evolution of reaction product obtained by the spectrometer UV-Vis was registered according to time every 20 min, for the high catalyst of our complexes as shown in Fig. 3.

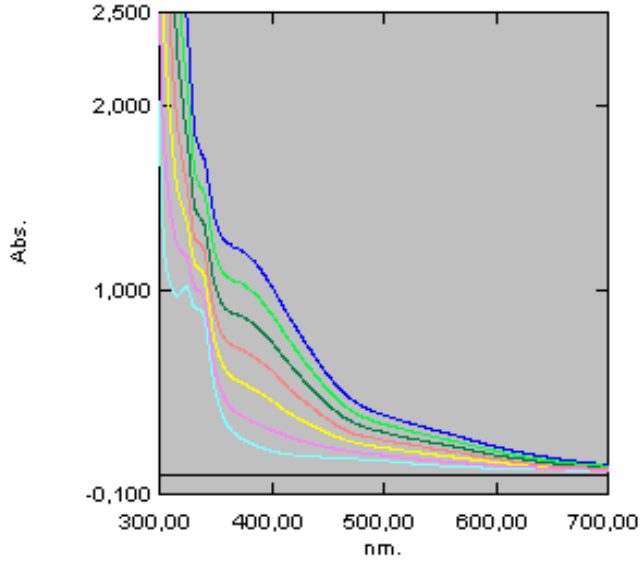


Fig. 3: The absorbance evolution of the *o*-quinone at 390 nm for the combination (L_1 + $2CuSO_4$).

As can be seen in Fig.3, the stronger rate of the catecholase reaction of the complex formed from the one equivalent of ligand L_1 with two equivalents of copper (II) sulfate shows the importance increase in absorbance at 390 nm as a function of time.

3.3. Study of the concentration effect of the ligand and the copper (II) salts on the kinetics of the catechol in o-quinone oxidation.

This study aims to correlate the concentration modifications with the catecholase activity in order to determine the effect of copper (II) salts concentration on the catecholase activity of resultant complexes.

Firstly, copper (II) salt concentration changed to be two equivalents for one equivalent of ligand. The evolution of product absorbance versus time is collected in Fig.4-5.

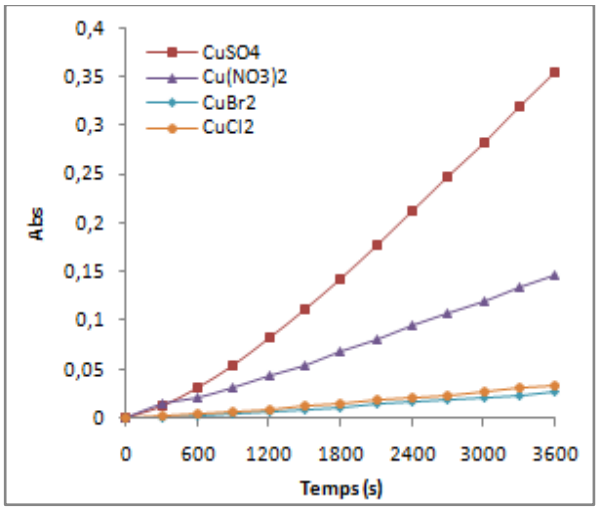


Fig. 4. Oxidation of catechol by complexes of ligand $\mathbf{L_1}$ (1eq of $\mathbf{L_1}$ for 2 eq of Cu(II) salt).

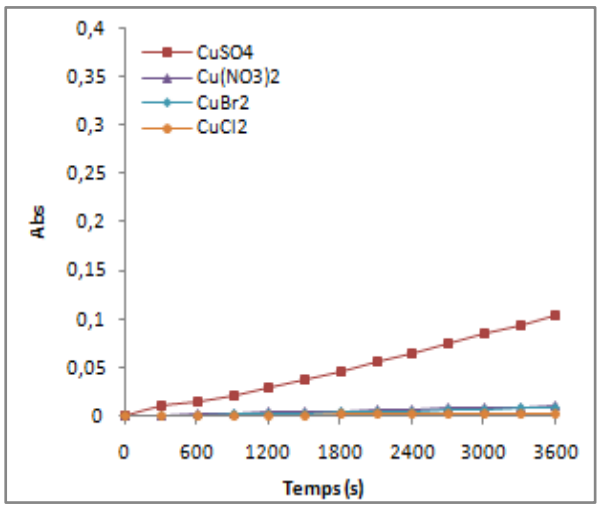


Fig. 5. Oxidation of catechol by complexes of ligand $\mathbf{L_2}$ (1eq of $\mathbf{L_2}$ for 2 eq of Cu(II) salt).

Table 2. Kinetic data for oxidation of catechol in methanol by ligands copper (II) complexes (1eq of ligand for 2 eq of Cu (II) salt).

Ligands	Copper(II) salts	R^2	V (μmol. L^{-1}.min^{-1})	b (μmol. L^{-1} .min^{-1})
L1	$CuSO_4$	0,99	3,83	29,33
	$Cu(NO_3)_2$	1,00	1,54	11,79
	$CuBr_2$	0,97	0,79	6,04
	$CuCl_2$	1,00	0,38	2,88
L2	$CuSO_4$	0,99	1,09	8,34
	$Cu(NO_3)_2$	0,99	0,13	1,00
	$CuBr_2$	1,00	0,19	1,44
	$CuCl_2$	0,92	0,04	0,29

The results shown in table 2 display that the oxidation rate of catechol increases with the increasing concentration of copper (II) salts for the two ligands. Therefore, increasing the concentration of the metal salt increases the probability of the complex formation, which causes the increase in the probability of contact between the complex and the substrate. Accordingly, the rate of formation of the product also increases; so, the catalytic reaction is faster when the concentration of metal salt is greater. Therefore, the order of the catalytic activity changes from one to another complex.

Secondly, ligand concentration changed to be two equivalents for one equivalent of copper (II) salt. The evolution of product absorbance versus time is shown in Fig.6-7.

As observed in table 3, in case of the complexes with ligand L_1, the obtained results show that the ligand concentration has an observable effect on the rate of catechol oxidation (expect with $CuSO_4$ where a precipitate

of copper complexes is formed, no useful solution spectra could be obtained). In the case of the complexes with ligand L_2, the reactivity of all complexes is not significantly changed. The catecholase activity was strongly influenced by the nature of ligand. This is not surprising if the high mesomeric effect properties of carbonyl groups towards nitrogen sites are taken into account.

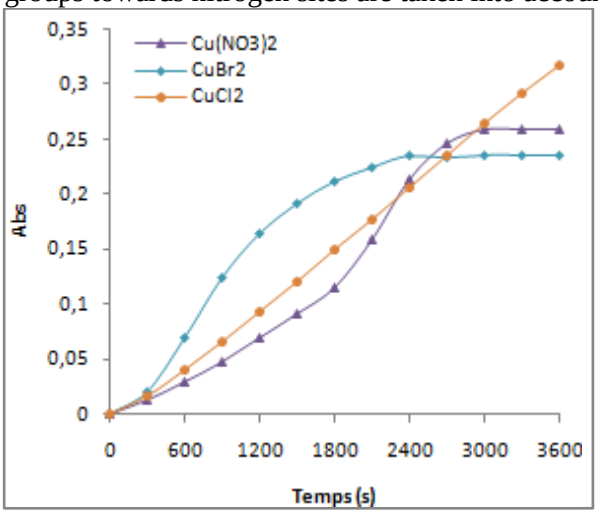


Fig. 6. Oxidation of catechol by complexes of ligand $\mathbf{L_1}$ (2 eq of $\mathbf{L_1}$ for 1 eq of Cu(II) salt).

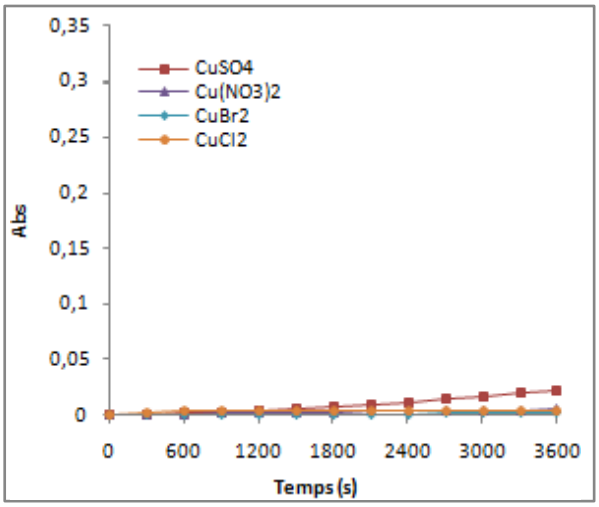


Fig. 7: Oxidation of catechol by complexes of ligand L_2 (2 eq of L_2 for 1 eq of Cu(II) salt).

Table 3. Kinetic data for oxidation of catechol in methanol by ligands copper (II) complexes (2 eq of ligand for 1 eq of Cu(II) salt).

Ligands	Copper(II) salts	R^2	V (μmol. $L^{-1}.min^{-1}$)	b (μmol. $L^{-1}.min^{-1}$)
L1	$CuSO_4$	-	-	-
	$Cu(NO_3)_2$	0,96	3,19	24,44
	$CuBr_2$	0,82	2,51	19,26
	$CuCl_2$	1,00	3,41	26,16
L2	$CuSO_4$	0,97	0,23	1,73
	$Cu(NO_3)_2$	0,99	0,05	0,40
	$CuBr_2$	0,98	0,03	0,20
	$CuCl_2$	0,39	0,04	0,29

However, the comparison of our new results with the previous work in this field [21, 24] showed that these rates are in the order of values reported for the similar tripodal ligand. We can conclude that the oxidation rate depends strongly on the nature of organic ligand and the character of the anions of metallic salt, which affects the potential of the copper complex .These factors can contribute to the explanation of the mechanism in the catalytic cycle of oxidation of catechol in *o*-quinone.

3.4. Kinetic study.

The kinetics of the catechol oxidation was determined by the initial rates method by monitoring the increase of the product *o*-quinone in a UV–Vis spectrophotometer, the reactions were accompanied at 390 nm in methanol ($\varepsilon = 1600$ l.mol^{-1}.cm^{-1}) under aerobic condition at ambient temperature.

Initially, a series of catechol substrate solution having different concentrations (10^{-2} to 2×10^{-1} mol/l) were prepared from a substrate concentrated stock solution by using methanol as solvent, the concentration of catalyst

was fixed in 10^{-3} mol/l. Then, 0,3 ml of complex solution was poured in a 1cm quartz cell and 2 ml of such substrate solution of catechol was added, and the absorbencies were measured. The data were treated by the initial rate method, and a treatment based on Michaelis-Menten model was used (Figs. 8–9). The results are given in table 4.

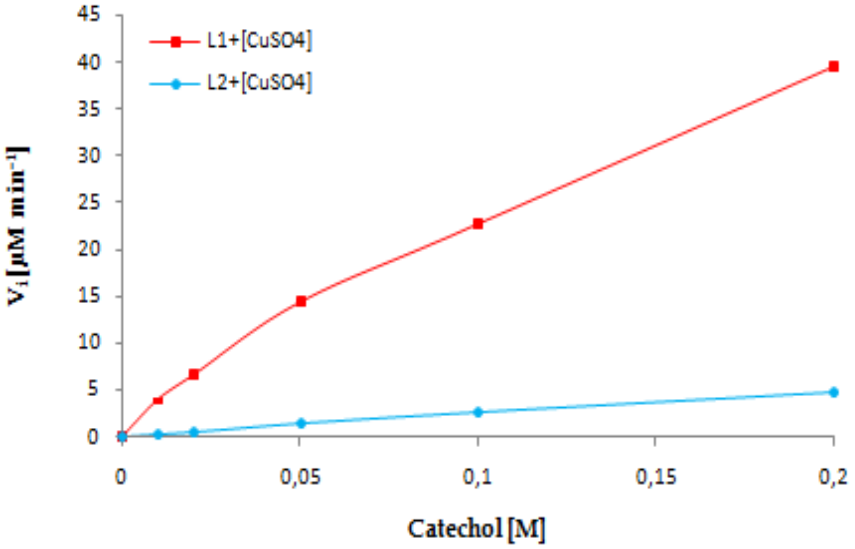


Fig. 8. Dependence of the initial rate on the catechol concentration for the oxidation promoted by complex $L_1 + CuSO_4$ and $L_2 + CuSO_4$.

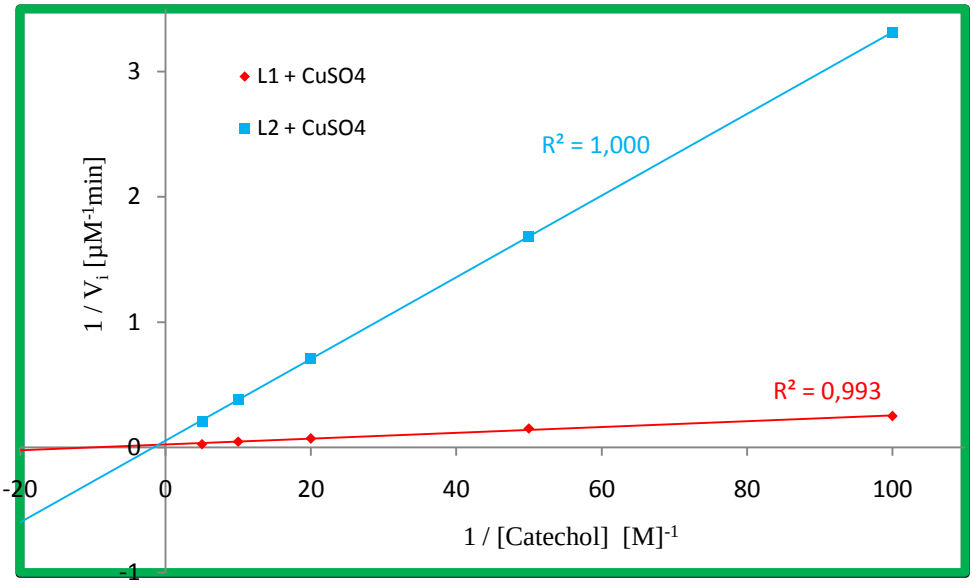


Fig. 9. The Lineweaver-Burk plot for the oxidation of catechol with dioxygen catalyzed by complex $L_1 + CuSO_4$ and $L_2 + CuSO_4$.

The reactions followed a Michaelis-Menten type kinetics and the Lineweaver-Burk plot can be seen in Fig. 9.
The kinetic parameters tabulated on table 4 demonstrate the V_{max} values as $47{,}50 .10^{-6}$ $mol.l^{-1}.min^{-1}$ for $L_1 + CuSO_4$ and $18{,}92.10^{-6}$ $mol.l^{-1}.min^{-1}$ for $L_2 + CuSO_4$ in MeOH.
The values proved that the ability of the complex $L_1 + CuSO_4$ to form an adduct with the substrate and converted them to product and released, is greater than the ability of the complex $L_2 + CuSO_4$.
The difference in the catalytic efficiency of these complexes can be explained from the electronic features of the R-substituent on the ligand which confirms the previous results.

Table 4. Parameters values of complexes L_1 + $CuSO_4$ and L_2 + $CuSO_4$ catalyzed reactions with catechol as substrate.

Complex	K_M [M]	V_{max} [µM. min^{-1}]
L_1 + $CuSO_4$	0,11	47,50
L_2+ $CuSO_4$	0,6	18,92

K_M is the Michaelis-Menten constant [M]
V_{max} is the maximum velocity of catalyst (µM. min^{-1})

Conclusion

The synthesis of new functional tripodal ligands was reported and the catechol oxidase as model system the aerobic oxidation of catechol to the corresponding *O*-quinone, employing the copper complexes of two pyrazolyl ligands was investigated. The kinetic measurements revealed that the catalytic oxidation of catechol catalyzed with copper complexes of ligand L_1 are greater than those observed with ligand L_2. We believe that the electronic effect of an electro-donating or electro-accepting group represents only one way to modify the coordination properties of the nitrogen donor sites. The study of various copper (II) salts shows that the catalytic activities are controlled by the nature of anion too.

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