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Synthesis, characterization and catecholase activity of copper (II) complexes with bispyrazole tri-podal Ligands

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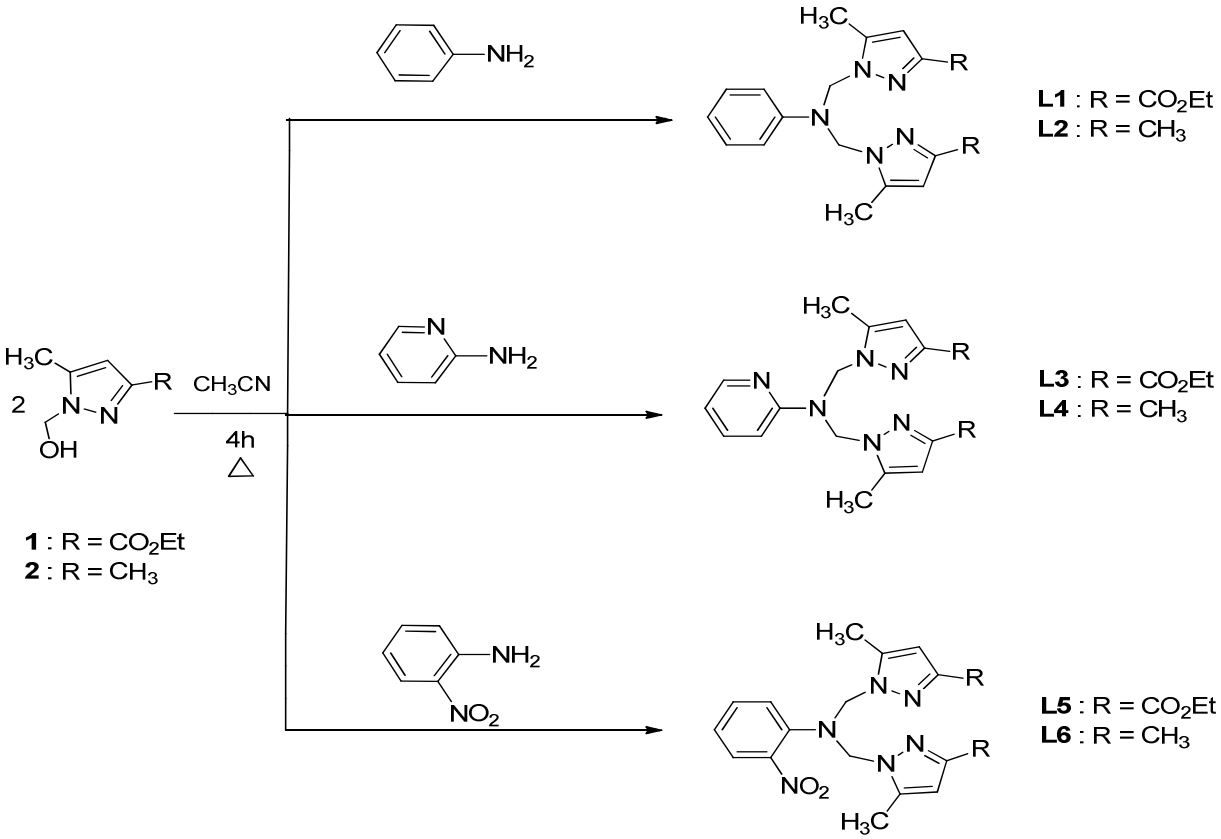
Abstract
The synthesis of series of tripodal ligands: N,N-bis((3-carboxyethyl-5-dimethyl-1H-pyrazol-1-yl)methyl)phenylamine **L1**, N,N-bis((3,5-dimethyl-1H-pyrazol-1-yl)methyl)phenylamine **L2**, N,N-bis((3-carboxyethyl-5-dimethyl-1H-pyrazol-1-yl)methyl)pyridin-2-ylamine **L3**, N,N-bis((3,5-dimethyl-1H-pyrazol-1-yl)methyl)pyridin-2-amine **L4**, N,N-bis((3-carboxyethyl-5-dimethyl-1H-pyrazol-1-yl)methyl)-2-nitrophenylamine **L5**, N,N-bis((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-2-nitrophenylamine **L6** were reported. Copper (II) complexes of these compounds prepared *in-situ* were examined for their catalytic oxidative activities. The effect of the nature of the ligand and the copper salts on the catecholase activities will be also investigated. Mechanistic studies were also discussed.

Keywords: Nitrogen ligands, oxidation catalysis, catecholase, copper (II) complexes; catechol and kinetics.

1. Introduction
Since, the middle of the last century a variety of powerful techniques have become available for investigating the chemistry of metals within biological systems. As a result an increasingly detailed understanding of the roles of metals in living organisms is now emerging. In a medicinal context one particular example is provided by work on the mechanism of action of the anticancer drug cisplatin [1]. Meanwhile, Nature has evolved quite a few metalloenzymes that catalyse the controlled and selective oxidation of organic compounds via molecular oxygen activation. Catechol dioxygenases are mononuclear non-heme metallo-proteins found in a diverse range of soil bacteria [2-10]. On the one hand, nitrogenous systems have attracted more attention in these last years due to their interesting properties in coordination chemistry [11-12]. This aptitude is mainly owed to the presence of sp^2 hybrid nitrogen donors [13-14], with the involvement in some cases, of other sites donors as oxygen and sulphur atoms [15-16]. Moreover, polydentate pyrazolic receptors are well known for their ability to complexes with transition metal ions [17-18]. And on the other hand, binuclear copper (II) complexes have attracted immense attention with the onset of the studies of metalloproteins [11, 18a]. Proteins and enzymes have binuclear metallocites in which the metals are essential for the biological activity [19-20]. The enzymes like hemocyanin [21], tyrosinase [22], have binuclear copper centers in their active sites. Though these proteins have binuclear copper centers, the functions of the centers vary. For example hemocyanin acts as oxygen carriers, tyrosinase acts as phenolic oxidases. Therefore the properties of the binuclear centers are defined by the geometry, the coordination sites, the bridging ligands between the centers, etc. With the aim of understanding the properties of the metallo-proteins, many

binucleating ligands and their copper (II) complexes have been synthesized and studied [23-24]. In this paper, we report the synthesis of series on new ligands based on pyrazolic moieties (**Scheme 1**) and the ability of the *in-situ* generated copper (II) complexes to oxidize catechol to o-quinone for miming catecholase enzymatic studies.



Scheme 1: Structure of prepared compounds

2. Experimental

NMR spectra (^{1}H, ^{13}C) were recorded on a BRUKER 300 (operating at 300,13MHz for ^{1}H and 75,47MHz for ^{13}C) spectrometer. Chemical shifts are listed in ppm and were reported relative to tetramethylsilane (^{1}H, ^{13}C). Residual solvent peaks being used as internal standard. The mass spectra have been obtained on a Micromass LCT spectrometer, **L2** is known compound and have spectral data in according to the literature data [25].

*2.1. General experimental procedures for preparing ligands **L1-L6** :*

The products were prepared by the addition of aniline, pyridin-2-amine and 2-nitrobenzenamine to ethyl 1-(hydroxymethyl)-5-methyl-1H-pyrazole-3-carboxylate **1** or (3,5-dimethyl-1H-pyrazol-1-yl)methanol **2**. The compounds were easily prepared from the condensation of two equivalents **of 1 or 2** with one equivalent of the desired amine under mild conditions with anhydrous acetonitrile as solvent and the mixture was continued at room temperature for 4–5 days. The formed compound was precipitated by addition of cold water to acetonitrile solution, washed with hexane and dried under vacuum (**Scheme 1**), we take pz for pyrazole, py for pyridine and nb for nitrobenzene.

*2.2. N,N-bis((3-carboxyethyl-5-dimethyl-1H-pyrazol-1-yl)methyl)phenylamine (**L1**):*

White powder; Yield = 88%; Mp = 142-144 °C; ^{1}H NMR (300MHz, $CDCl_3$) δ ppm: 1,45(t, 6H, -$OCH_2C\underline{H_3}$, J = 6,9 Hz); 2,30(s, 6H, CH_3pz); 4,48(q, 4H, -$OC\underline{H_2}CH_3$, J = 3,45 Hz); 5,50(s, 4H, NCH_2N); 5,68(s, 2H, CHpz); 6,60-7,20(m, 5H, C_6H_5). ^{13}C NMR (75MHz, $CDCl_3$) δ ppm: 11,50(CH_3pz); 14(-$OCH_2\underline{C}H_3$); 59,50(NCH_2N); 61($O\underline{C}H_2CH_3$); 109(CHpz); 114; 120; 129(CH_2 and C_6H_5); 140($\underline{C}$=C); 143(C=N); 145(C=N); 162.5(C=O). IR (KBr, □cm^{-1}): 3360(=C-H, Ar); 3144(C-H, CH_3); 2987(CH); 1703(C=O); 1602(C=N); 1506

and 1487 (C=C); 1286(C=N); 1244 and 1209(C-O); 1116; 1028; 750; 692. Calcd for $[M]^+$ $C_{22}H_{27}N_5O_4$: (m/z) = 425,21. Found for $[M+Na]^+$ (m/z) = 448,34 (45%).

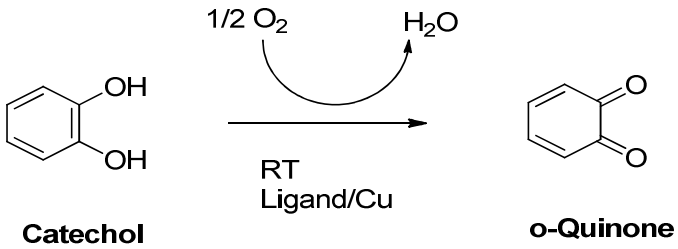
*2.3. N,N-bis((3-carboxyethyl-5-dimethyl-1H-pyrazol-1-yl)methyl)pyridin-2-ylamine (**L3**):*
White powder; Yield = 73%; Mp = 128-133°C; ^{1}H NMR (300MHz, $CDCl_3$) δ ppm: 1,35(t, 6H, $OCH_2C\underline{H}_3$, J = 7,05 Hz); 2,50(s, 6H, CH_3pz); 4,35(q, 4H, -$OC\underline{H}_2CH_3$, J = 7,05Hz); 5,70-5,75(d, 4H, NCH_2N); 6,45(s, 2H, CHpz); 6,55-8,10(m, 4H, CHpy). ^{13}C NMR (75MHz, $CDCl_3$) δ ppm: 11(CH_3pz); 15($OCH_2\underline{C}H_3$); 55(NCH_2N); 61($O\underline{C}H_2CH_3$); 108(CHpz); 109(CHpy); 115(CHpy); 138(C=Cpy); 141($\underline{C}$=Cpz); 143(C=Npz); 147(C=Npy); 156(C-Npy), 163(C=O). IR (KBr, □ cm^{-1}): 3321(=C-H, Ar); 3136(C-H, CH_3); 2987(CH); 1703(C=O); 1606(C=N); 1525/1487(C=C); 1433; 1390; 1298(C-N); 1244; 1213(C-O); 1147; 1109; 1028; 1004. Calcd for $[M]^+$ $C_{21}H_{26}N_6O_4$: (m/z) = 426,2; Found for $[M+Na]^+$ (m/z) = 449,10 (51%).

*2.4. N,N-bis((3,5-dimethyl-1H-pyrazol-1-yl)methyl)pyridin-2-amine (**L4**):*
White powder; Yield = 75%; Mp = 104-107°C; ^{1}H NMR (300MHz, $CDCl_3$) δ ppm: 2,2(2s, 6H, CH_3pz); 2,35(2s, 6H, CH_3pz); 5,50(2s, 4H, NCH_2N); 5,80(s, 2H, CHpz); 6,75-8,15(m, 4H, CHpy).^{13}C NMR (75MHz, $CDCl_3$) δ ppm: 11,50(CH_3pz); 14(CH_3pz); 57(NCH_2N); 107(CHpz); 115(CHpy); 117,50(CHpy); 127(CHpy); 133(CHpy); 137($\underline{C}$=Cpz); 139(C=Npy), 144(C=Npz); 148(C-Npy). IR (KBr, □ cm^{-1}): 3294(=C-H, Ar); 3153(C-H, CH_3); 2982; 2945; 2852(CH); 1652(C=N); 1554; 1533(C=C); 1487; 1458; 1421(C-N); 2359; 1307; 1288; 1070. Calcd for $[M]^+$ $C_{17}H_{22}N_6$: (m/z) = 310,19; Found for $[M+Na]^+$ (m/z) = 333,18 (13.04%).

*2.5. N,N-bis((3-carboxyethyl-5-dimethyl-1H-pyrazol-1-yl)methyl)-2-nitrophenylamine (**L5**):*
Yellow powder; Yield = 84%; Mp = 124-125°C; ^{1}H NMR (300MHz, $CDCl_3$) δ ppm: 1,40(t, 6H, $OCH_2C\underline{H}_3$, J = 6Hz); 2,40(s, 6H, CH_3pz); 4,35(q, 4H, $OC\underline{H}_2CH_3$, J = 7,05Hz); 5,7(s, 4H, NCH_2N); 6,60(s, 2H, CHpz); 6,80-8,70(m, 4H, CHnb). ^{13}C NMR (75MHz, $CDCl_3$) δ ppm: 11(CH_3pz); 14($OCH_2\underline{C}H_3$); 58(NCH_2N); 61($O\underline{C}H_2CH_3$); 110(CHpz); 112(CHnb); 115(CHnb); 118(CHnb); 127(C-NO_2); 137(C=Cnb); 140(C=Cpz); 143(C-Nnb); 148(C=Npz); 162(C=O). IR (KBr, □ cm^{-1}): 3377(=C-H, Ar); 2982(C-H, CH_3); 2893(CH); 1705(C=O); 1616(C=N); 1573; 1556(C=C); 1510; 1338(NO_2); 1473; 1444; 1427; 1390(C-N); 1236; 1213(C-O); 1166; 1031; 1003. Calcd for $[M]^+$ $C_{22}H_{26}N_6O_6$: (m/z) = 470,48; Found for $[M+Na]^+$ (m/z) = 493,76 (39.13%).

*2.6. N,N-bis((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-2-nitrophenylamine (**L6**):*
Yellow powder; Yield = 75%; Mp = 116-118°C; ^{1}H NMR (300MHz, $CDCl_3$) δ ppm: 1,30(s, 6H, CH_3pz); 4,30(s, 4H, NCH_2N); 5,50(s, 2H, CHpz); 6,40-6,80(m, 4H, CHnb). ^{13}C NMR (75MHz, $CDCl_3$) δ ppm: 11(CH_3pz); 14(CH_3pz); 61(NCH_2N); 109(CHpz); 116(CHnb); 118(CHnb); 124(CHnb); 126($C=C_2$); 141(C=Cnb); 142(C-Npz), 143(C=Cpz); 162(CNO_2). IR (KBr, □ cm^{-1}): 3389(C-H, Ar); 2976; 2918; 2864(CH); 1653; 1620(C=N); 1573; 1552(C=C); 1506; 1330(NO_2); 1419; 1369; 1330(C-N); 1274; 1232; 1170. Calcd for $[M]^+$ $C_{18}H_{22}N_6O_2$: (m/z) = 354,41; Found for $[M+Na]^+$ (m/z) = 377,4 (100%).

2.7. Catecholase studies:
The progress of the catechol oxidation reaction is conveniently followed monitoring the strong absorbance peak of quinone in the UV/Vis spectrophotometer (**Scheme 2**). Kinetic measurements were made spectrophotometrically on UV–Vis spectrophotometer following the appearance of o-quinone over time at 25°C (390 nm absorbance maximum, ε =1600M^{-1} cm^{-1} in methanol). The metal complex (prepared in situ [26]: 0,3mL of a 10^{-3}M methanol solution) and a solution (2mL of a 10^{-1}M methanol solution) of catechol were mixed in the spectrophotometric cell.



Scheme 2: Reaction model for our studies

3. Result and discussion

3.1. Chemistry

New functional tridentate ligands **L1- L6** were synthesized respectively by condensation of two equivalents of 3,5-dimethyl-1H-pyrazol-1-yl)methanol derivatives **1-2** with one equivalent of aniline, pyridin-2-amine and 2-nitroaniline, **L2** is already known [25] (**Scheme 1**). All reactions were stired at refluxed acetonitrile for four hours. All new compounds were isolated with good yield (73-96%) and characterized by IR, ^{1}H-NMR and ^{13}C-NMR and mass spectrometry. The influence of different **R** groups is visible on the chemical shift in ^{1}H-NMR of hydrogen atoms of principal groups such as N-C$\underline{H_2}$-N and CHpz (**Table 1**).

Table 1: Comparative study between tripodal ligands

Compound	Yield %	^{1}H RMN δ (N-CH_2-N) ppm	^{13}C RMN δ (N-CH_2-N) ppm	^{1}H RMN δ (CHpz) ppm	^{13}C RMN δ (CHpz) ppm
L1	88 (65)[25d]	5,50	59,50	5, 68	109
L2	96	5,35	58	5,50	106
L3	73	5,70 and 5,75	55	6,45	108
L4	75	5,50	57	5.80	107
L5	84	5,7	58	6,60	110
L6	75	4,30	61	5,50	109

In the proton NMR spectra pyrazolic protons (CHpz) appears as signals between 5,50 and 6,45 ppm. In the case of ligands **L1** and **L6**, the influence of R group is visible on the chemical shift in the proton NMR of the hydrogen atoms of methylene brides between the atom central nitrogen and the pyrazolic rings 5,50 and 4,30 ppm respectively.

3.2. Catecholase studies

The progress of the catechol oxidation reaction is conveniently followed monitoring the strong absorbance peak of quinone in the UV/Vis spectrophotometer.

The metal complex and a solution of catechol were added together in the spectrophotometric cell at 25°C. Formation of *o*-quinone was monitored by the increase in absorbance at 390 nm as a function of time (**Scheme 2**) [27-31].

In all cases, catecholase activity was noted. **Figures 1-10** show the absorbance versus time spectrum for the first 60 min of the reaction for the copper (II) complex while the oxidation rates are shown in Table 2.

As it can be seen from **Table 2**, all complexes catalyze the oxidation reaction of catechol to quinone with the rate varying from a high of 15.00 μmol L^{-1} min^{-1} for the **L2[Cu(CH_3CO_2)$_2$]** complex to a weaker rate of 1,12 μmol L^{-1} min^{-1} for **L1[Cu(CH_3CO_2)$_2$]** ; **L2[Cu(NO_3)$_2$]** and **L3[Cu(NO_3)$_2$]** complex.

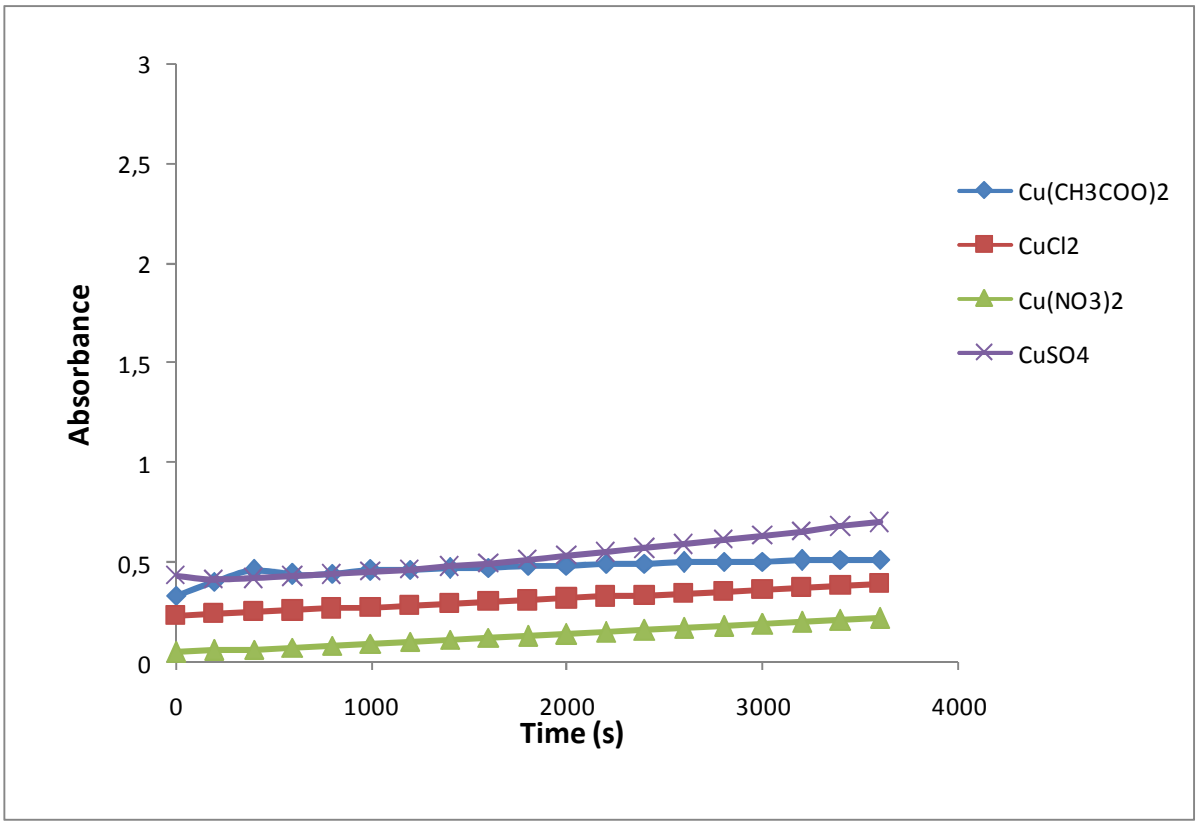


Figure 1: Oxidation of catechol by complexes of ligand **L1**

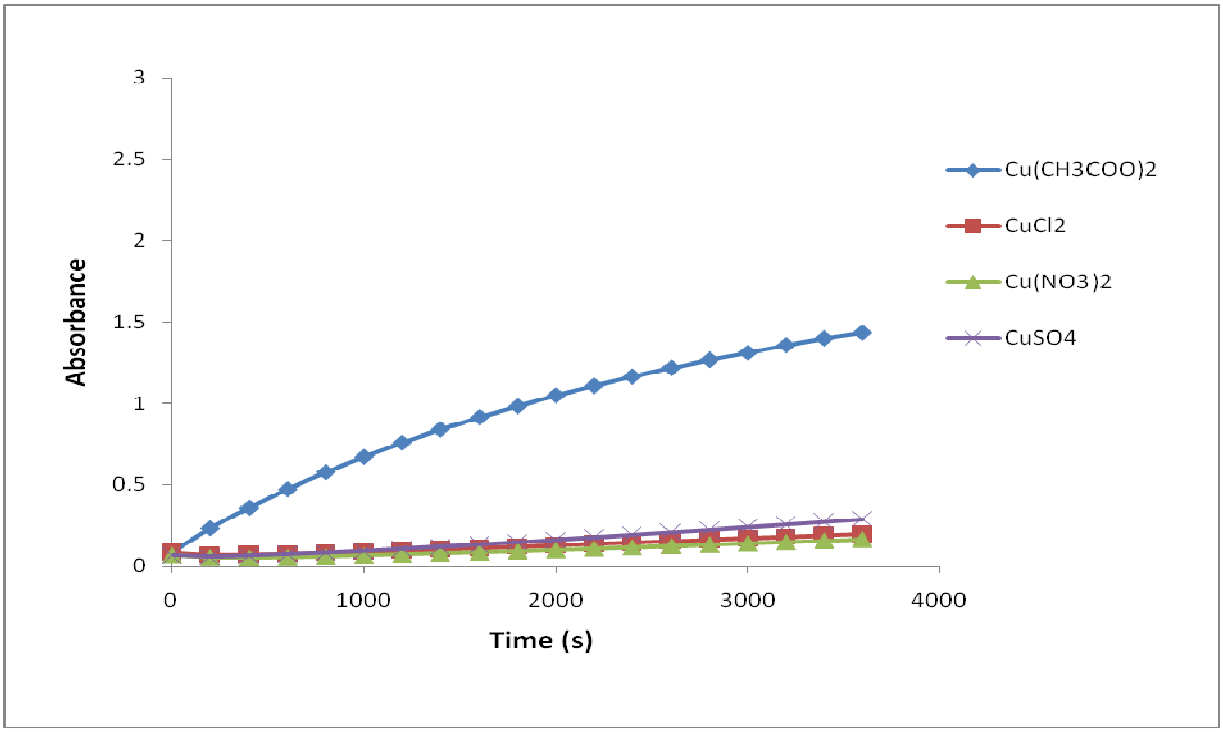


Figure 2: Oxidation of catechol by complexes of ligand L**2**

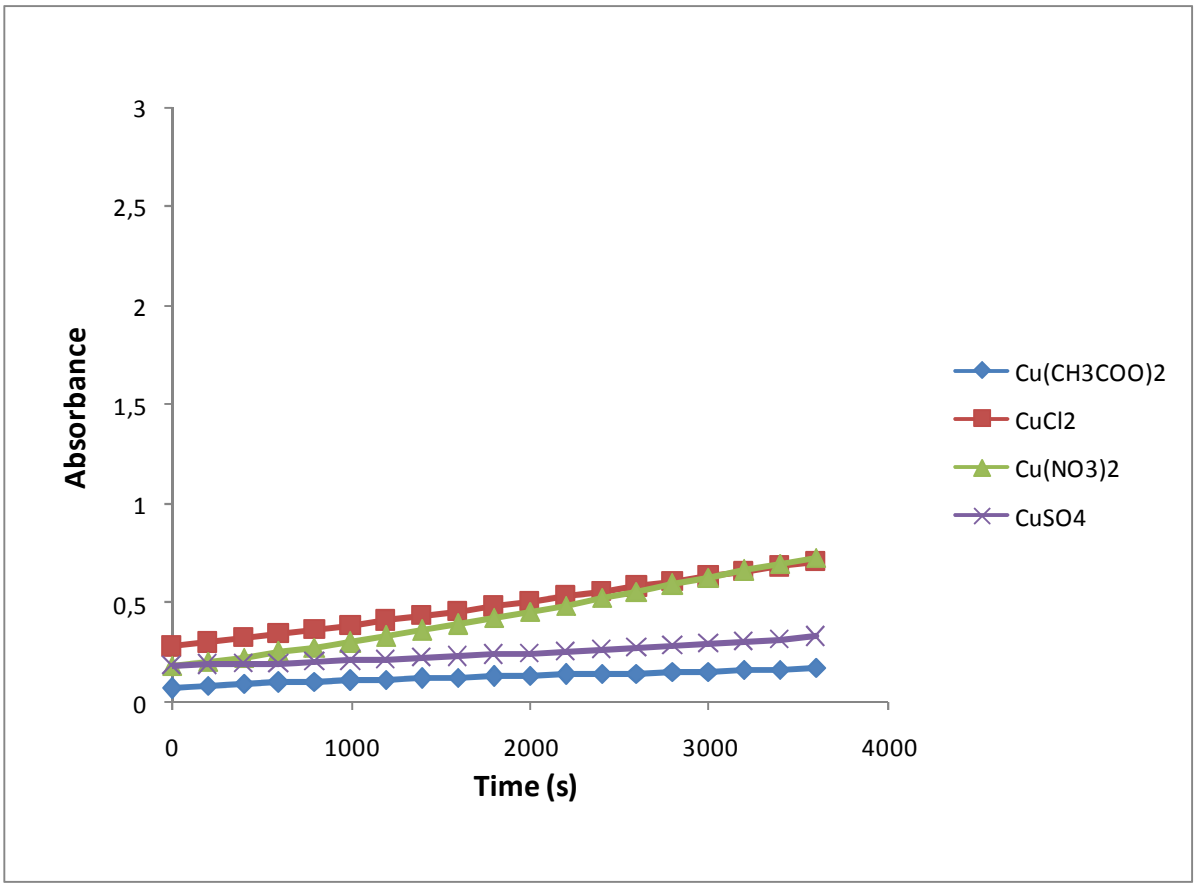


Figure 3: Oxidation of catechol by complexes of ligand **L3**

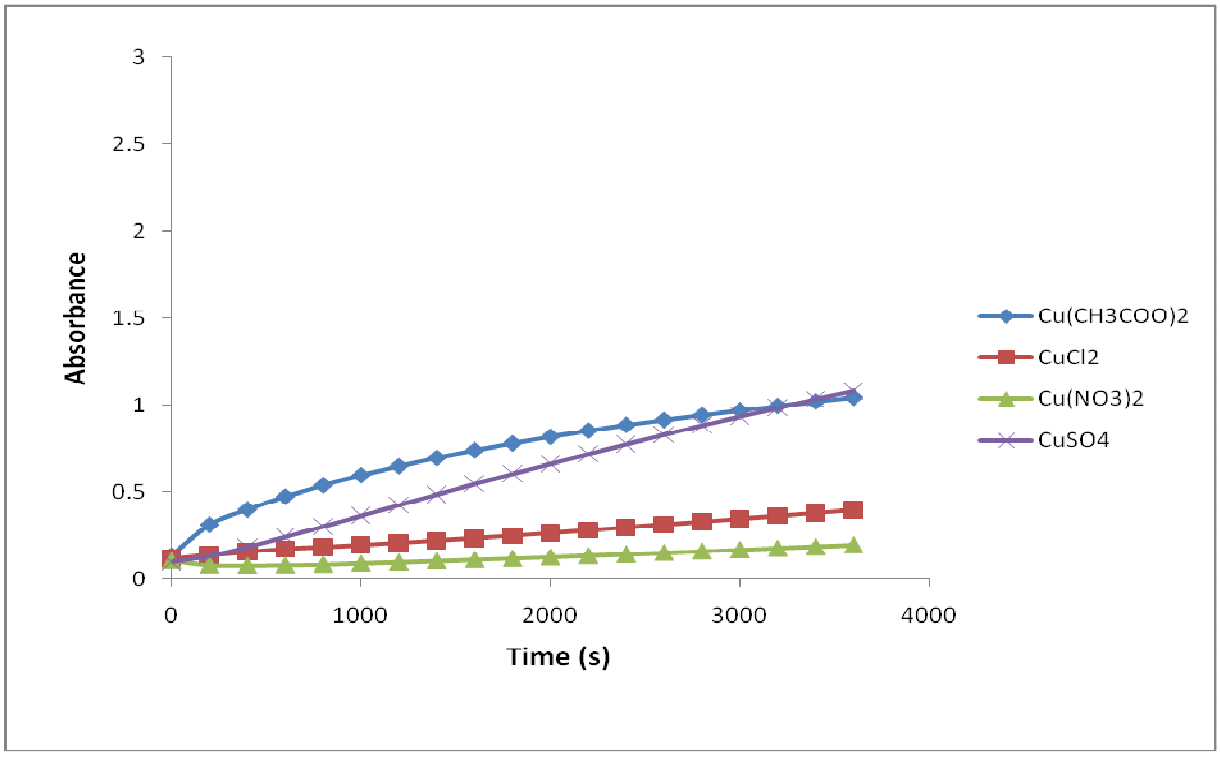


Figure 4: Oxidation of catechol by complexes of ligand **L4**

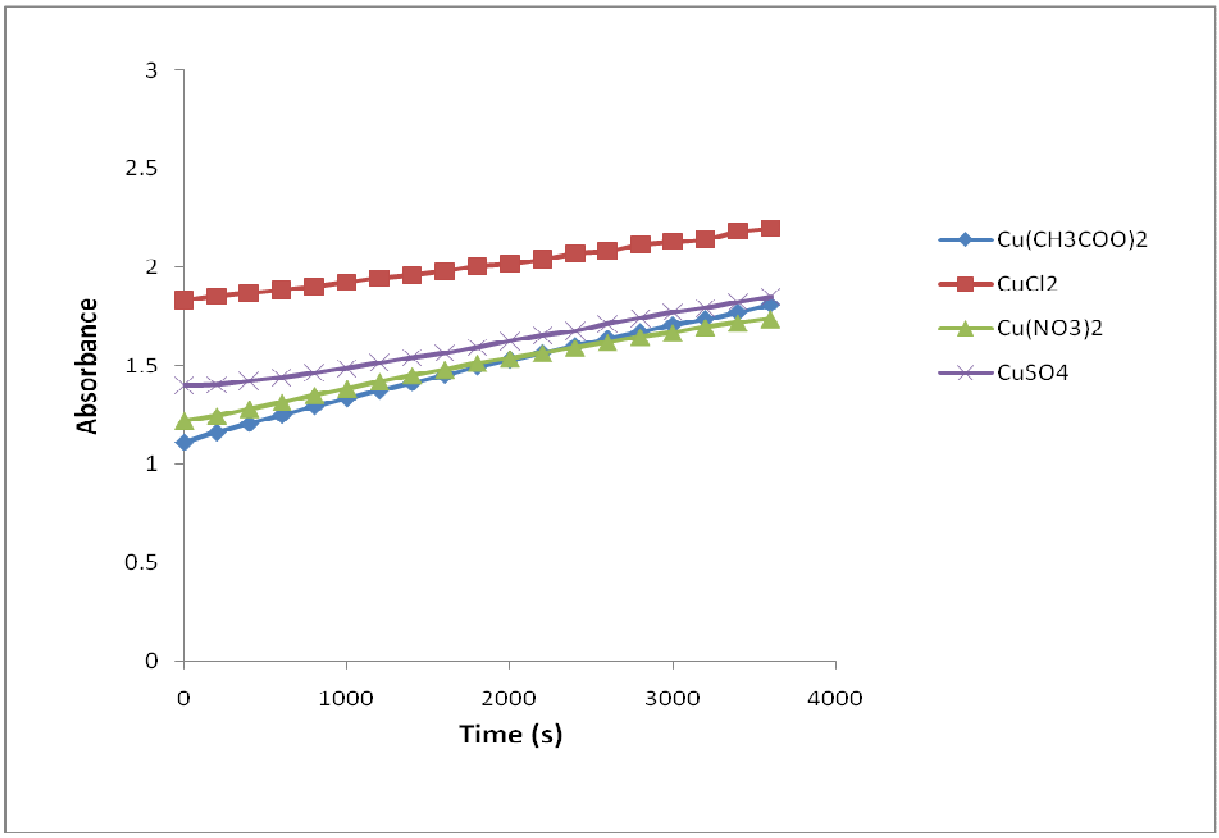


Figure 5: Oxidation of catechol by complexes of ligand **L5**

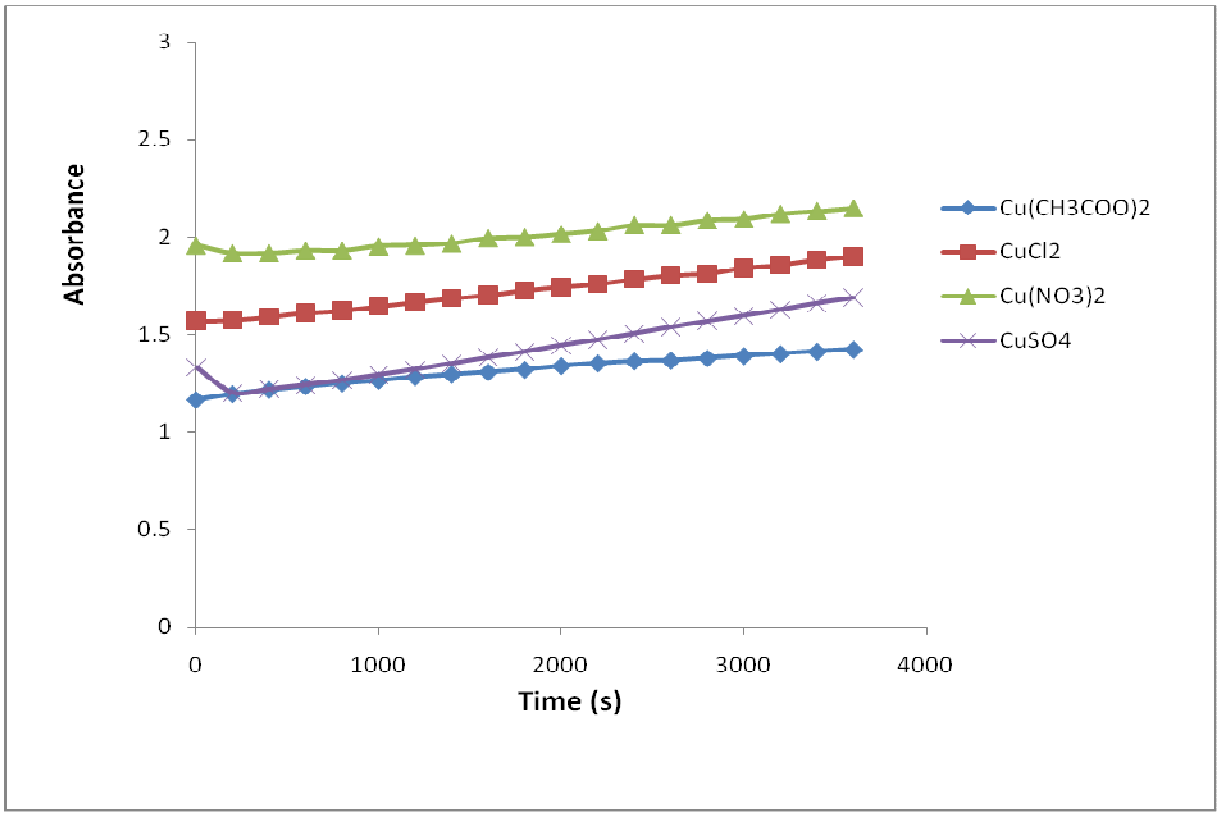


Figure 6: Oxidation of catechol by complexes of ligand **L6**

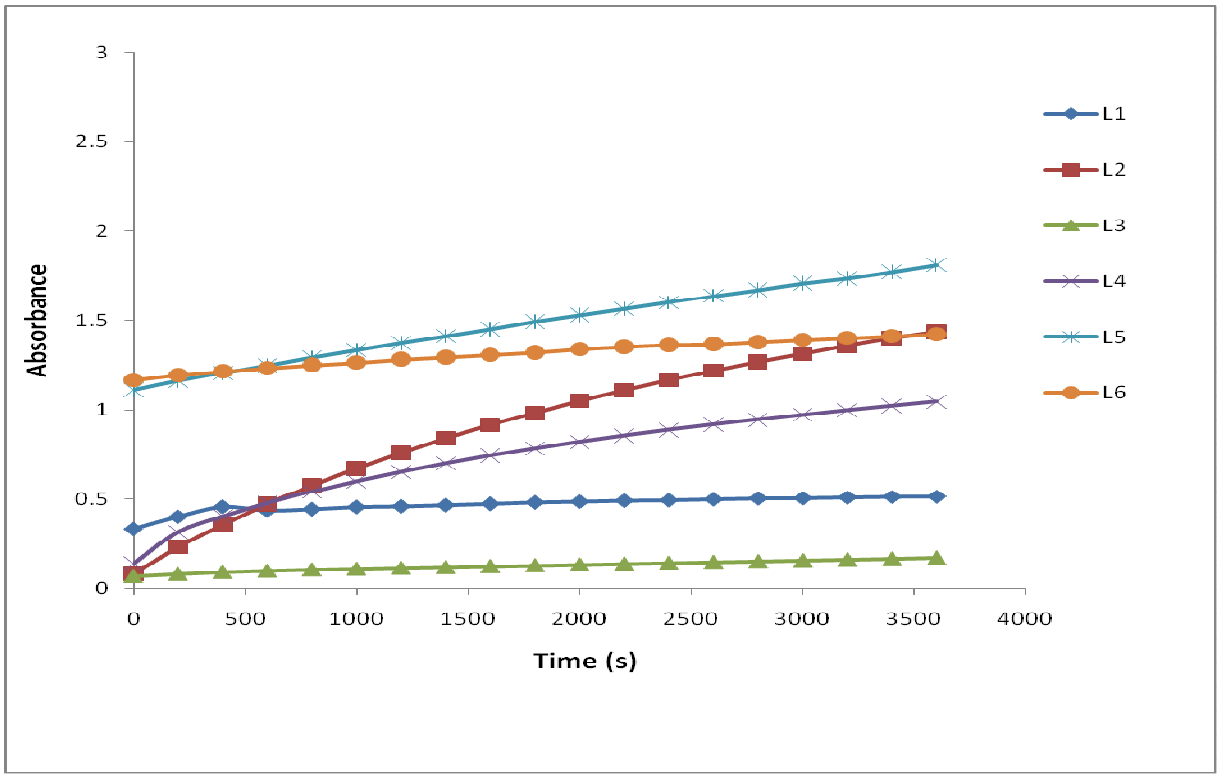


Figure 7: Oxidation of the catechol in presence of **$Cu(CH_3COO)_2$**

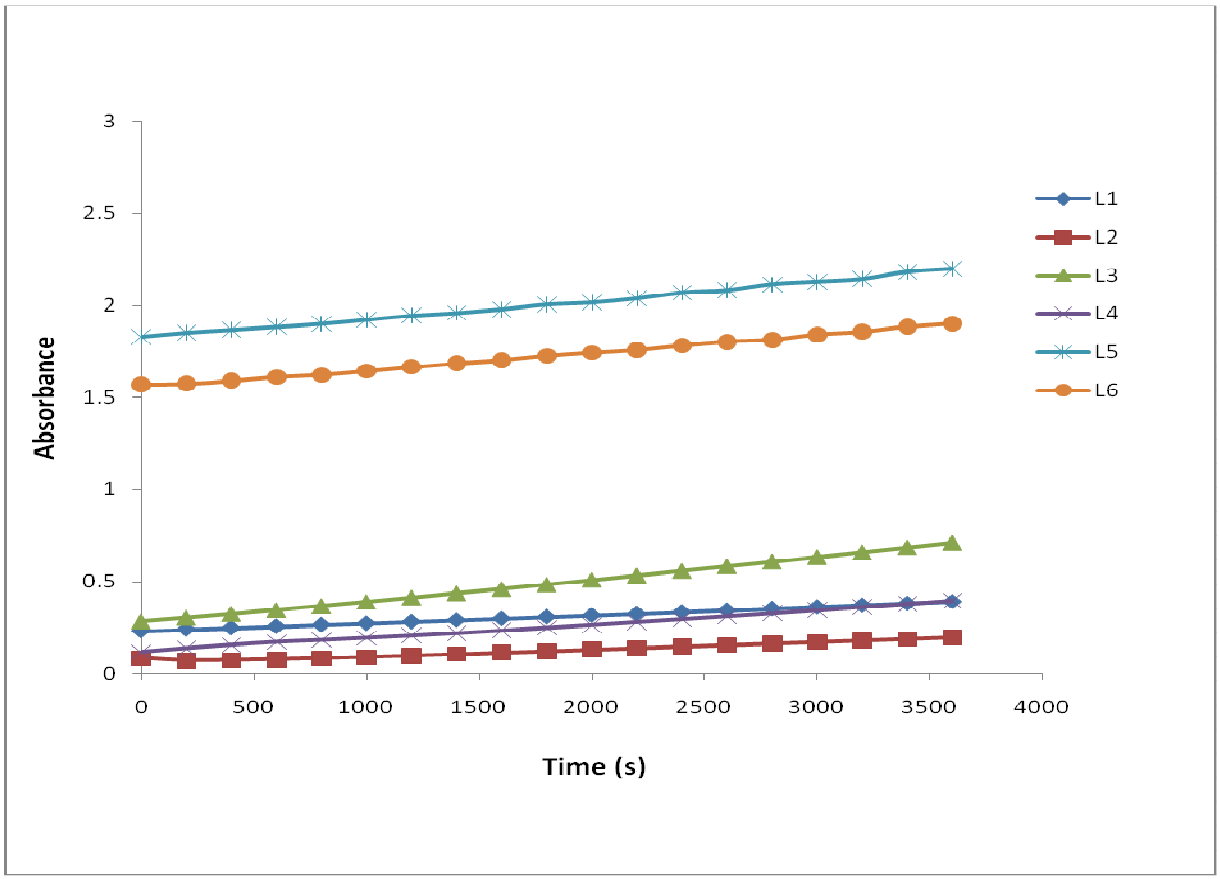


Figure 8: Oxidation of the catechol in presence of **$CuCl_2$**

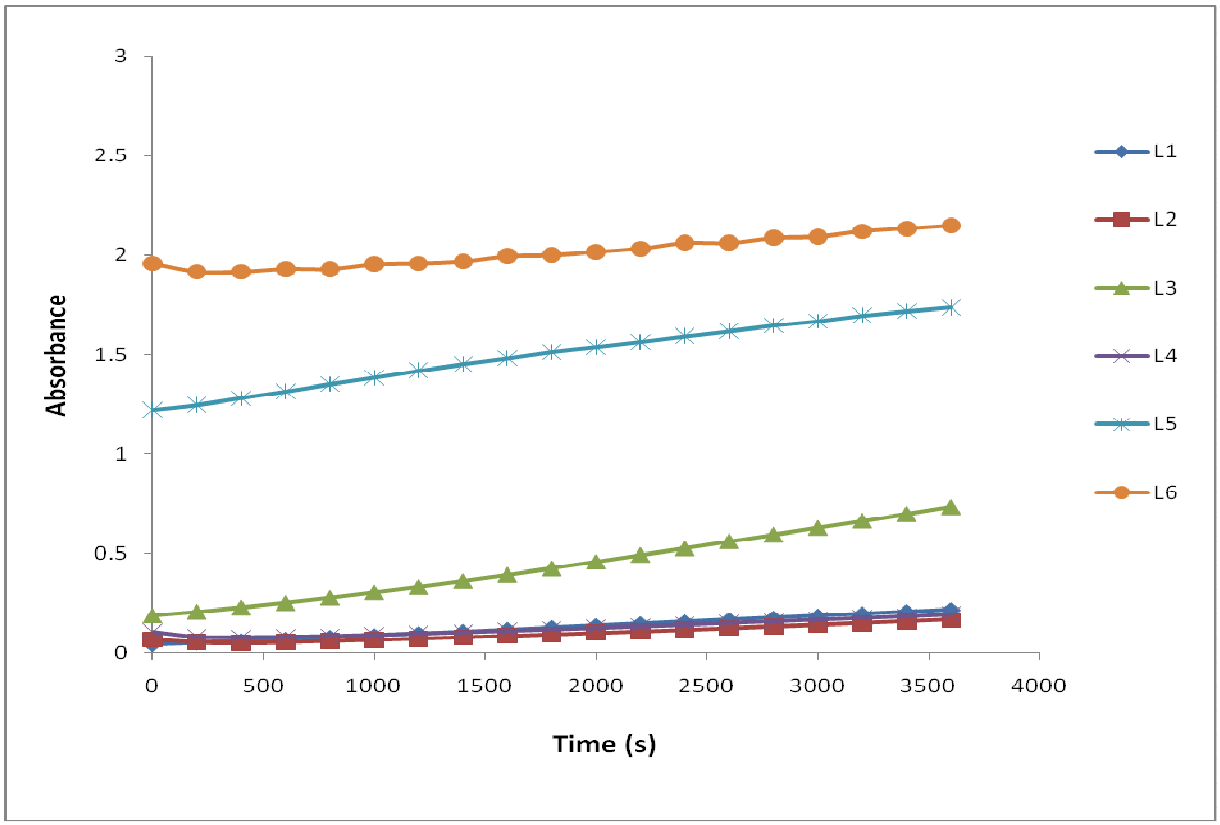


Figure 9: Oxidation of the catechol in presence of **$Cu(NO_3)_2$**

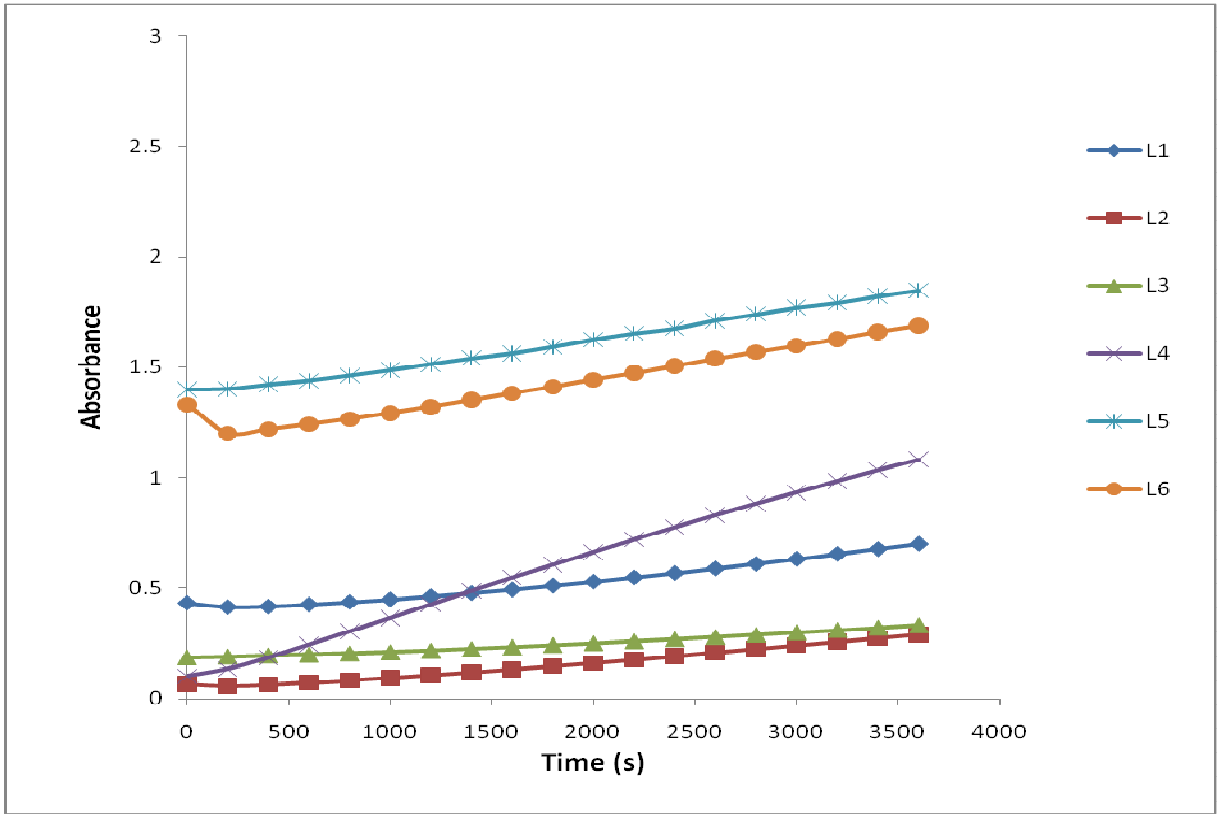


Figure 10: Oxidation of the catechol in presence of **$CuSO_4$**

The catalytic activities depend strongly on both of the aromatic moieties and the type of inorganic anion. All complexes with ligands having a methyl group in their pyrazolic moiety have an oxidation reaction rate more important than the others with methylic ester fonction, except in cases when the aromatic group is 2-nitrobenzene or aniline. The order of activity in cases of $Cu(CH_3CO_2)_2$ is (**L2 > L4 ≥ L5 > L6>L1**).

Table 2: Kinetic data for the oxidation of catechol by ligands copper (II) complexes [rates (µmol L−1 min−1)].

Ligand/salt	$Cu(CH_3COO)_2$	$CuCl_2$	$Cu(NO_3)_2$	$CuSO_4$
L1	1,12	1,50	1,87	3,00
L2	15,00	1,50	1,12	2,62
L3	1,12	3,75	7,50	1,50
L4	7,50	3,00	1,12	11,20
L5	7,50	3,75	3,75	3,75
L6	2,62	3,37	2,62	3,75

As it can be seen from **table 2**, we could consider that the nature of **R** groups have a large effect on the reaction rate. Two cases will be distinguished.

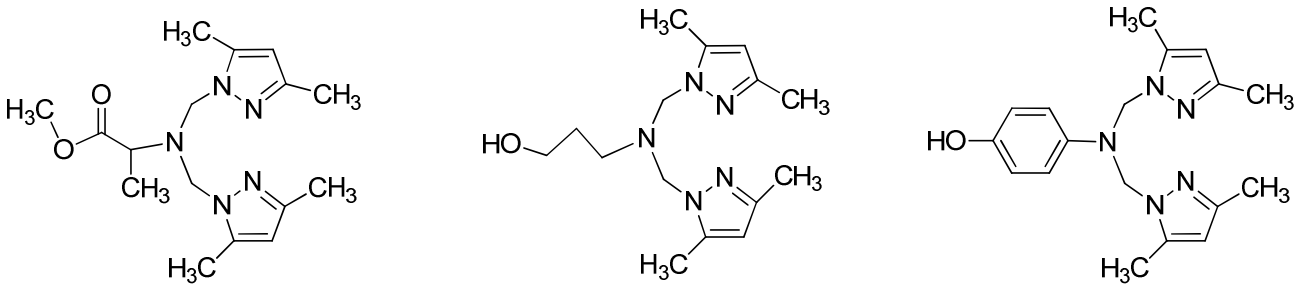
- *Case where* ***R*** *=* CH_3 *:*
The order of reactivity when we used NO_3^- anion is **L2 ≤ L4** < **L6**. The copper complex of ligand **L2** and **L4** were observed to be very weak in the oxidation of catechol. When we use the other anion $CH_3CO_2^-$; Cl^- and SO_4^{2-} the rate of the reactivity increase completely **L2**[$Cu(CH_3CO_2)_2$] =15,00 µmol L^{-1} min^{-1}; for **L4**[$CuSO_4$] = 11,20 µmol L^{-1} min^{-1} and for **L6**[$Cu(NO_3)_2$]= 2,62 µmol L^{-1} min^{-1}.

- *Case where R =* CO_2Et *:*
When we used NO_3^- anion, the complexes of **L3** and **L5** with a function in the aromatic group give an oxidation reaction rate higher than the complex with the ligand having a side aromatic containing any function (**L1** < **L5** < **L3**). When we use the other anions SO_4^{2-}; Cl^- and $CH_3CO_2^-$, there is a reversal reactivity orders between **L1[**$CuSO_4$] and **L3[**$CuSO_4$] in the two last other anion they are similar for **L1** [$Cu(CH_3CO_2)_2$] = 1,12 µmol L^{-1} min^{-1}; **L1**[$CuCl_2$] =1,50 µmol L^{-1} min^{-1}.

Table 3: Kinetic data for the oxidation of catechol by ligands copper (II) complexes [rates (µmol L^{-1} min^{-1})].

Ligand/salt	$Cu(CH_3COO)_2$	$CuCl_2$	$Cu(NO_3)_2$	$CuSO_4$
L7	11,82	1,35	1,87	-
L8	14,44	1,80	2,77	28,99
L9	0,11	0,13	0,10	-

However comparing our new results with what we have got concerning our previous work in this area (**Scheme 3**) and their catecholase activity summarized in **Table 3**.
We can conclude that our system **L2**[$Cu(CH_3CO_2)_2$] gives a better catalytic activity than **L7**, **L8** and **L9** with the same anion or with the others.



L7 **L8** **L9**

Scheme 3: Structures of our previous work in this area **L7** [27]; **L8** [31] and **L9** [30]

2.3. Mechanistic studies of the oxidation reaction

To understand the mechanism occurred in this catalytic reaction we have performed other analysis, which are summarized in the **Figures 11-13**; we have preformed three reactions the first one we used ligand **L2** alone with the cathecol substrate in the same rate of the catalytic reaction for 60 minutes we got catalytic activity rate equal to 0,0015 (µmol L^{-1} min^{-1}), then we add to the vial the $Cu(CH_3CO_2)_2$ we observe an increase in the reaction activity equal to 22,50(µmol L^{-1} min^{-1}) (**Figure 11**). The second operation we mixed the $Cu(CH_3CO_2)_2$ with the catechol substrate for 60 minutes we got a reaction rate equal to 7,50(µmol L^{-1} min^{-1}), then we add the ligand **L2** to the reaction mixture we observe an increase of the catalytic activity about 11,25(µmol L^{-1} min^{-1}) (**Figure 12**) in the last reaction we mixed the ligand **L2** and the $Cu(CH_3CO_2)_2$ under stirring for four hours then we added the catechol substrate we got an activity equal to 18,75(µmol L^{-1} min^{-1}) (**Figure 13**). From all this studies we can propose a mechanism of this reaction (**Scheme 4**).

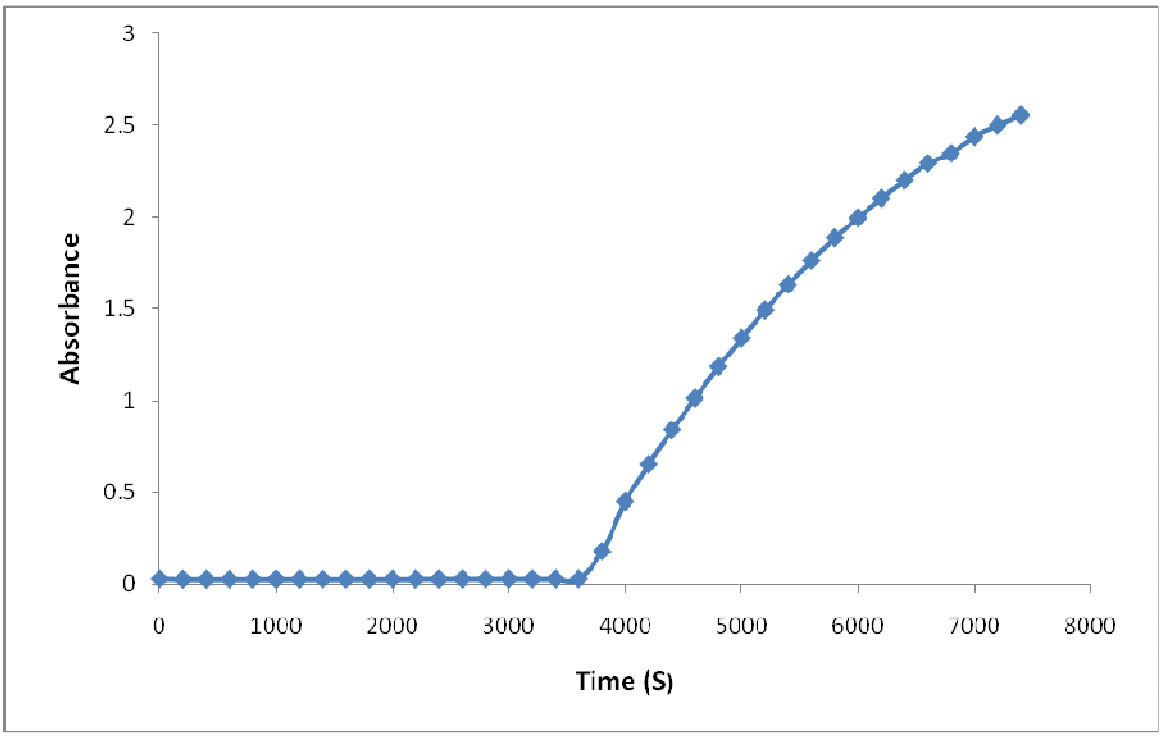


Figure 11: From 0 to 60 minutes we have mixed just ligand **L2** and the cathecol, after 60 minutes we have added to the reaction mixture the copper salt $Cu(CH_3CO_2)_2$

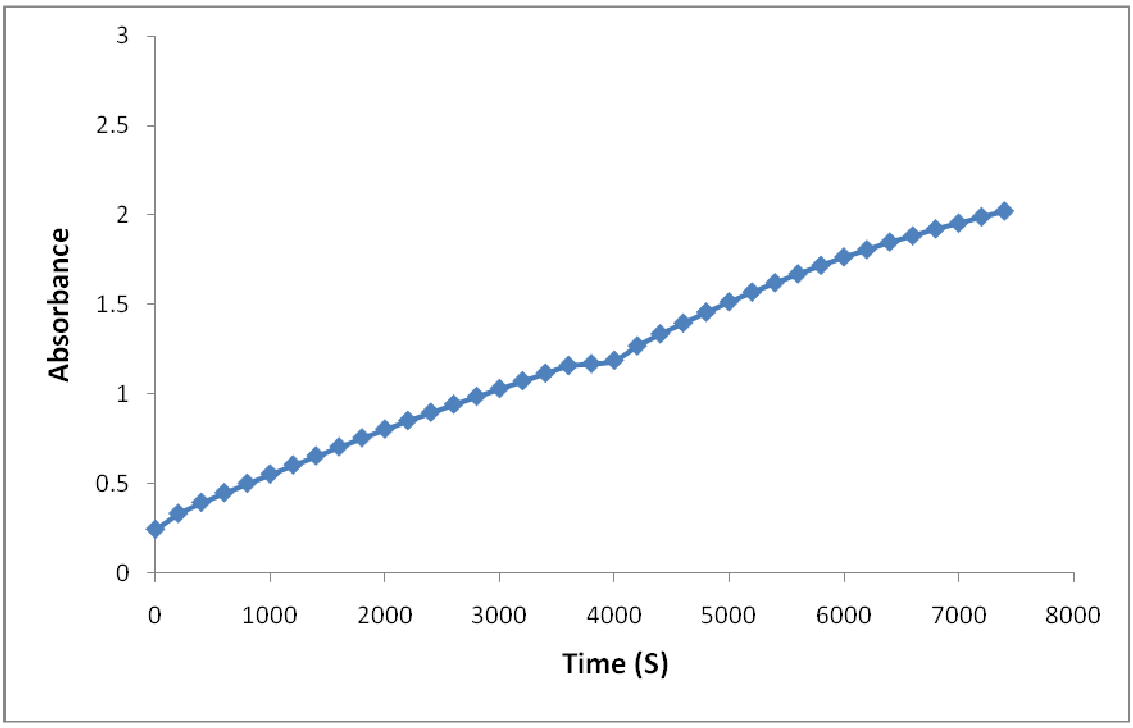


Figure 12: From 0 to 60 minutes we have mixed just the copper salt $Cu(CH_3CO_2)_2$ and the cathecol, after 60 minutes we have added to the reaction mixture the ligand **L2**

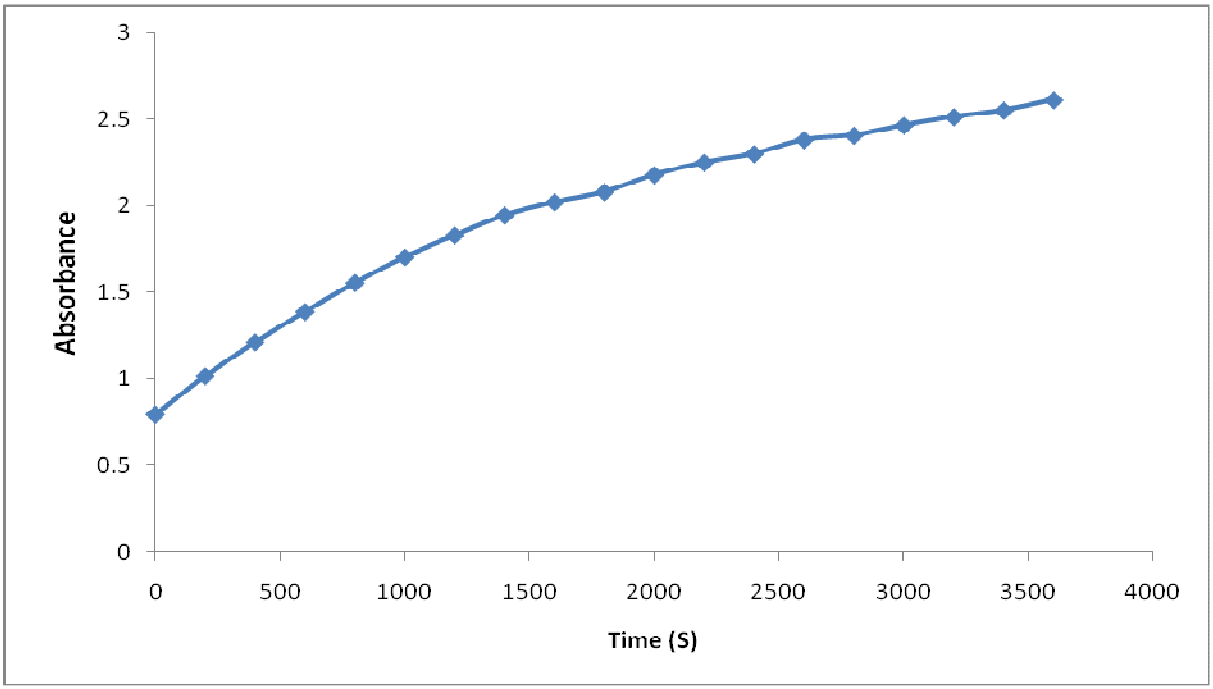
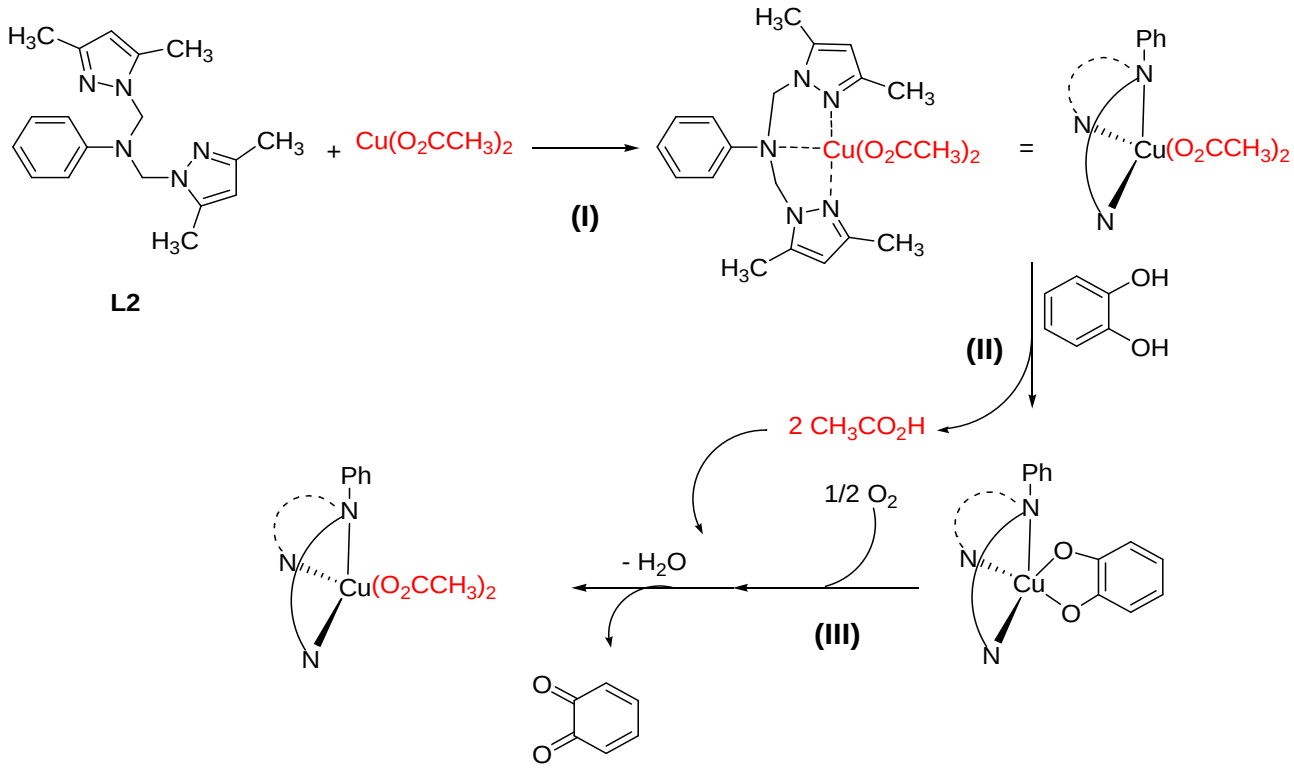


Figure 13: Oxidation of the catechol in presence of complex which was prepared alone by stirring the ligand **L2** and the copper salt $Cu(CH_3CO_2)_2$ for 4 hours

This hypothesis is supported by the dependence of the reaction rate on both substrate and complexes, without the formation of the coordination between the ligand and the metal no reaction is occurred, it started by the coordination of the tridendate ligand with the copper salts **(I) [**31-35] then followed by the insertion of the catechol to the complex **(II) [**36-37] after the insertion of oxygen the release of the *o*-quinone (**III-IV**).



Scheme 4: Proposed mechanism for the catechol oxidation using **L2**[$Cu(CH_3CO_2)_2$] system

Conclusion

We have described the synthesis of new functional tripodale ligands. The oxidation reaction of catechol is very efficient to give *o*-quinone by *in-situ* generated copper (II) complexes of six compounds. We have demonstrated that the nature of aromatic side chain has a large effect on the oxidation reaction rate.

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