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Studies of Catecholase Activities of N-donor Bidentates Ligands derivated from Benzoxazole with Copper (II) Salts

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Abstract

Three functional, N-donorbidentates ligands, **L1**: 2-(pyridin-2-yl)benzoxazole **L2**: 2-(quinolin-2-yl)benzoxazole and **L3**: 2-(4-(trifluoromethyl)pyridin-2-yl)benzoxazole have been examined for their catalytic oxidative activities. The dioxygen complexes of Cu(II) were generated in situ by stirring copper salts and bidentates ligands derivated from benzoxazole. It has been found that these compounds are very efficient to give o-quinone. The nature of the ligands, the counter anion copper (II) salts and solvent have been investigated. These three parameters have an important effect on the oxidation reaction rate.

Keywords: Oxidation; Catechol; Bidentate; Copper (II); benzoxazole; Catalysis.

1.Introduction

Nitrogenous heterocyclic ligands based on pyrazoles, triazoles, pyridines and benzoxazoles have given rise to animmense interest in analytical chemistry,organometallic synthesis [1-4] and catalytic activity [5-11]. Aromatic compounds containing nitro groups are very important synthetic intermediates in the chemical academic research and drugs industry, and can be used in the production of plastics, dyes, explosive materials and many practical medicines [12-14]. Derivatedfrom benzoxazole are commonly used in natural products, pharmaceuticals, as well as inagrochemicals[15-20]. Aryl-benzoxazoles are important bi-aryl pharmacophores with a low toxicity, and some researchesshowed that they have a variety of biological activities, such as anti-HIV, anti-inflammatory, anti-microbial, antibiotic and anti-tumor properties [21,22].So, 2-(2-nitroaryl)benzoxazole can also become a kind of promising organic substance in the fields of pharmaceutical research and industry. Herein, we report our recent results in developing palladium-catalyzed chelation assisted ortho-nitration of 2-aryl-benzoxazole [14]. A comparative study by UV and emission spectroscopies was carried out and electro-luminescent properties of the related complexes on benzoxazole based compounds are reported [23]. The complexes of benzoxazole derivatives ligands were evaluated as catalysts in hydrogenation reactions of alkenes and alkynes under mild conditions as the hydrogenation of styrene to form ethyl benzene and two-step hydrogenation of phenyl-acetylene to ethyl-benzene via the styrene intermediate [5]. Notable progress has been made to minimize the tyrosinase activity using copper complex coordinated to multidentate heterocyclic amine ligands [24]. Several catechol derivatives were used in the literature as models for these kinds of studies [11, 25-27] (**Figure 1**).

Figure1: Oxidation of catechol derivatives to *o*-quinones

For this purpose, we report the catecholase activities of complexes prepared in situ with three functionals N-donor derivated from benzoxazole ligands **L1-L3** (**Figure 2**) with copper (II) salts namely $Cu(CH_3COO)_2$, $CuCl_2$ and $Cu(NO_3)_2$. The nature of the ligand, the counter anion and the solvent has been studied.

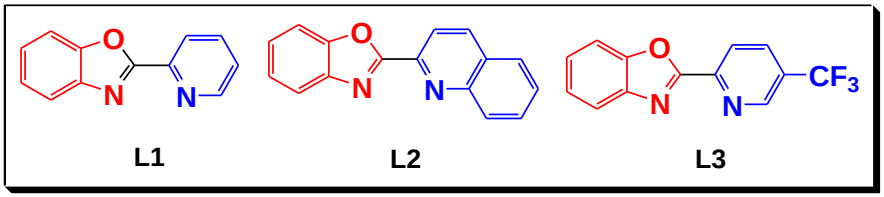

Figure2: Structures of the tested bidentates ligands

2. Experimental section

2.1. Synthesis of the ligands

We have reported the oxidation reaction of catechol and 3,5-di-tert-butyl catechol by complexes formed in situ between the bidentate ligands **L1-L3** and copper(II) salts, these ligands were obtained from the reaction of 1 mmol of 2-bromopyridine, 2-bromo(quinolin-2-yl) and 2-bromo-4-trifluoropyridine with 2 mmol of benzoxazole respectively

according to the method described elsewhere [28, 29]. These bidentate ligands **L1-L3** provide two hybridized nitrogen (sp^2), one is the heteroaryl bromide while the other is the benzoxazole, form the coordinate site capable of coordinating one copper atom [29] (**Figure 2**).

2.2. Catechol oxidation measurements

The kinetic measurements were made by spectrophotometry on a UV-Vis spectrophotometer (UV1650 PC Shimadzo,(in the COSTE - Oujda-Morocco), following the appearance of quinone over time at room temperature at 390 nm for o-quinone and 400 nm for tBu-o-quinoneversus time (390 or 400 nm absorbance maximum, ε = 1600 L mol^{-1} cm^{-1} in ethanol, ε = 1900 L mol^{-1} cm^{-1} in THF and 1900 L mol^{-1} cm^{-1} in CH_3CN). To determine the catecholase activities of the complexes formed in-situ by mixing successively 0.3 mL (2×10^{-3}mol/L) of solutions of different copper salts $Cu(CH_3COO)_2$, $CuCl_2$ and $Cu(NO_3)_2$ with 0.3 mL (2×10^{-3}mol/L) of ligand solution. The complexes formed in situ were treated with 2mL (10^{-1}mol/L) of catechol or tBu-catechol in ethanol (EtOH) orintetrahydrofuran (THF) or in acetonitrile (CH_3CN) under aerobic conditions.

3. Results and discussion

3. 1. Catecholase study

The progress of the catechol oxidation reaction is conveniently followed by monitoring the strong absorbance peak of o-quinone in the UV–Visible spectra. The complexes (prepared in situ from Cu salts and ligands) [11, 30] and catechol solution were placed together in the spectrophotometer cell at 30°C. The formation of *o*-quinone was monitored by the increase in absorbance at 390 nm or 400 nm as a function of time; in all cases, the catecholase activity was noted. **Figures 3–8** show the absorbance versus time for the first 60 min of the reaction for the Cu(II) complexes while the activities are given in **Tables 1-3**.

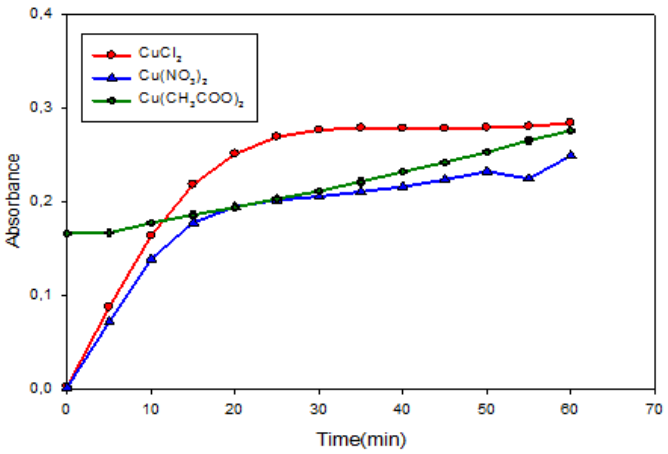

Figure 3: Absorbance evolution of o-quinone in presence of complexes formed by **L1**and different Cu salts in EtOH.

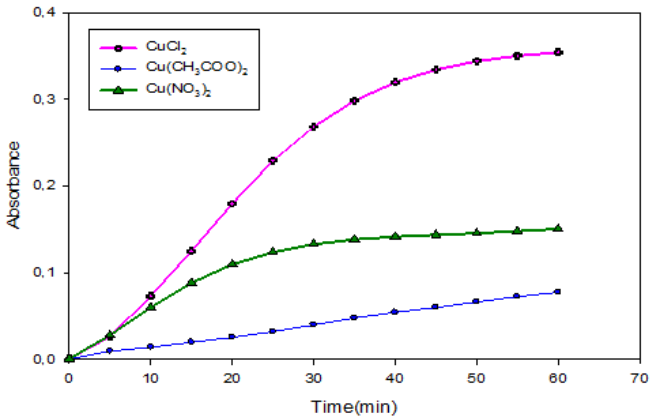

Figure 4: Absorbance evolution of o-quinone in presence of complexes formed by **L2** and different Cu salts in EtOH.

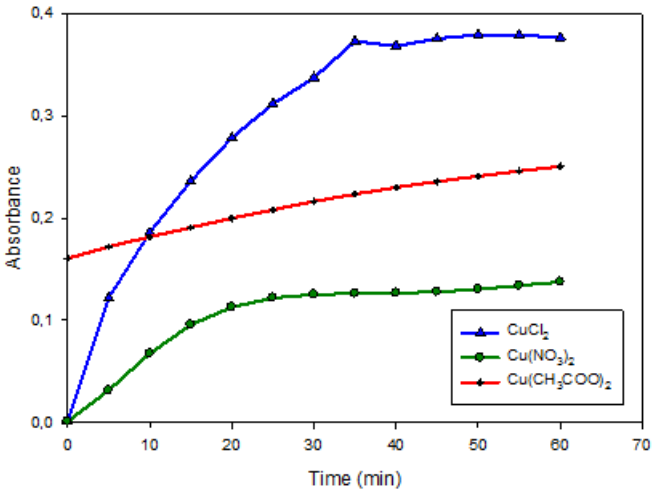

Figure 5: Absorbance evolution of *o*-quinone in presence of complexes formed by **L3** and different Cu salts in EtOH.

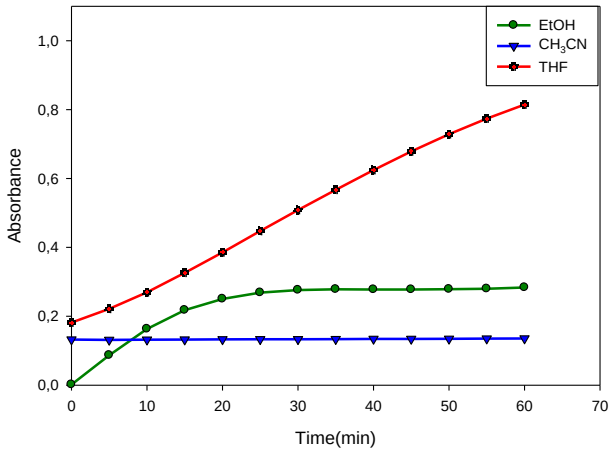

Figure 6: Absorbance evolution of *o*-quinone in presence of complexes formed with **L1** and **$CuCl_2$** in EtOH, CH_3CN and THF.

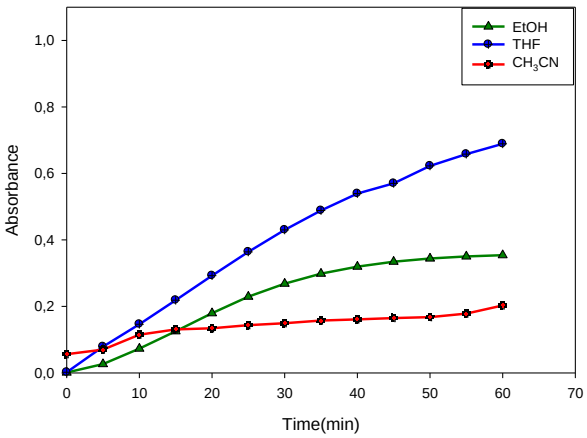

Figure 7: Absorbance evolution of *o*-quinone in presence of complexes formed with **L2** and **$CuCl_2$** in EtOH, CH_3CN and THF.

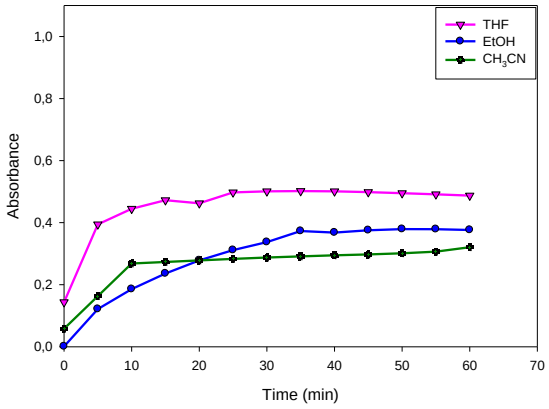

Figure 8: Absorbance evolution of *o*-quinone in presence of complexes formed with **L3** and **$CuCl_2$** in EtOH, CH_3CN and THF.

Table 1: Reaction rate V (µmol L^{-1} min^{-1}**)** and turnover number T (min^{-1}) of catechol oxidation in EtOH solvent.

Salts / Ligands		**L1**	**L2**	**L3**
$CuCl_2$	V	2.95	3.69	3.92
	T	11310	14145	15026
$Cu(NO_3)_2$	V	2.59	1.56	1.43
	T	9930	5980	5480
$Cu(CH_3COO)_2$	V	0.27	0.80	2.60
	T	11000	3085	9965

Table 2: Reaction rate V (µmol L^{-1} min^{-1}**)** and turnover number T (min^{-1}) of catechol oxidation by the complexes formed with **$CuCl_2$.**

Solvents / Ligands		**L1**	**L2**	**L3**
THF	V	7.14	6.04	4.27
	T	27418	23194	16397
EtOH	V	2.95	3.69	3.92
	T	11310	14145	15026
CH_3CN	V	1.41	4.75	0.60
	T	5415	18240	2304

Table 3: Kinetic parameter of the oxidation of catechol using ligands **L1-L3** with **$CuCl_2$** in **THF**.

	Turnover (min^{-1})	Km (mol l^{-1})	V_{max}(mol l^{-1} min^{-1})
L1	27370	0.013	7.14
L2	23153	0.014	6.04
L3	16368	0.016	4.27

3.2. Catecholase study in ethanol solvent

As can be seen from **Table 1**, all complexes catalyze the oxidation reaction of catechol to o-quinoneand the rate varies from a high value (3.92 µmol L^{-1} min^{-1}) for the (L3)[$CuCl_2$)] complex to a low value (0.27 µmol L^{-1} min^{-1}) for (L1)[$Cu(CH_3COO)_2$] complex. The catalytic activity depends strongly on both the form of the ligand and the type of inorganic anion. It is noted that the oxidation rate of catechol to o-quinone for the three ligands is very important with Cu (II) chloride. The nature of the ligand and particularly the electronic effect of the substituent group could modify the coordination. The presence of quinoline in the ligand **L2** and CF_3 group substituent in ligand **L3** rich in electrons, explain that the complexes with these ligands have the highest catalytic activity. **Figures 3–5** show the evolution of the absorption over time for the three anions Cl^-, NO_3^- and CH_3COO^-.

3.3. Solvent effect

In this part, we have realized the oxidation reaction catalyzed by the best combination between the three ligands **L1-L3** and **$CuCl_2$** in different solvents: ethanol (EtOH), tetrahydrofuran (THF) and acetonitrile (ACN) after monitoring the evolution of the absorbance product of the reaction, we found that the nature of the solvent has a huge effect on the catechol oxidation (**Figures 6-8**). So, we can conclude that THF is the best solvent for this reaction in three combinations with **L1-L3** and **$CuCl_2$**, followed by ethanol and then by acetonitrile. This result can be due to both the polarity of the solvent and the nature of the ligand. The determination of catechol oxidation rate in the presence of Cu complexes with three ligands **L1–L3** in ethanol, acetonitrile and THF, led to results gathered in **Table 2**. From results obtained by UV-Vis spectrophotometryand reaction rates, we observed that the nature of the solvent has an important effect on the catalytic activity of the studied complexes. The protic and polar THF appears better than ethanol and acetonitrile which are aprotic and polar.

3.4. Kinetic study

To better understand the influence of the solvent on the oxidation rates of catechol, we carried the following study. Thekinetic study determined by the initial rate method was performed with the best catalysts **L1 / $CuCl_2$**, **L2 / $CuCl_2$**

and **L3 / $CuCl_2$** in THF solvent (**Figure 9**). The oxidation kinetics of catechol were determined by the initial rates by monitoring the absorbance of the band at 390 nm of o-quinone in THF, the ligands **L1-L3** (0.15mL, 2×10^{-3} mol.L^{-1}) and **$CuCl_2$**(0.15mL, 2×10^{-3} mol.L^{-1}), which give the best catalyst for the catechol oxidation, and the of catechol concentration range (10^{-1} – 1mol.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 versus the substrate concentration was obtained. The michaelis-Menten model, developed for enzyme kinetics, is applied to obtain the kinetic parameters of the best catalyst. **Figure 9** represents the dependence of initial rate on the concentration of catechol for complex arising from **L1-L3** and **$CuCl_2$**. A first order dependence was observed at low concentrations of the substrate. However, the complexes formed from **L1-L3** and **$CuCl_2$** showed saturation kinetic at higher concentrations of catechol. **Figure 9** shows the Michaelis-Menten model for the best catalyst; the experimental kinetic parameters are presented in **Table 3**. The K_m value (0.013 mol.L^{-1}) and the initial rate V_{max}(7.14µmol L^{-1} min^{-1}) (**Table 3**) for the combination **L1/$CuCl_2$** in THF and the kinetic parameters such as Turnover number (T =27370 min^{-1}) show that the complex formed is a good catalyst for the catechol oxidation reaction.

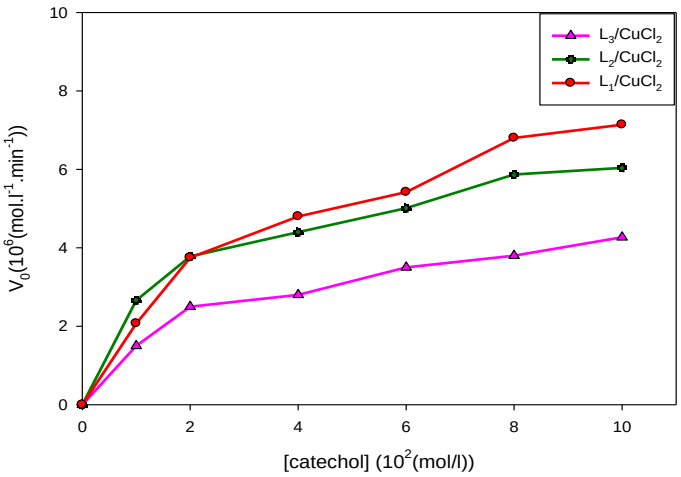

Figure 9: The dependence of the reaction rates on the catechol concentration for the oxidation reaction catalyzed by complexes arising from three ligands **L1-L3** and **$CuCl_2$** in **THF** solvent.

3.5. Oxidation of 3.5-di-tert-butylcatechol with complexes formed by L1-L3 with $CuCl_2$ in THF.

To study the substrate effect on the catalytic activity of our combinations [**L1-L3/$CuCl_2$**], the kinetics of the oxidation reaction of different substrates (3,5-DTB-Catechol) were studied by observing the evolution of the absorbance versus time at 400 nm for the oxidation products of 3,5-DTB-Catechol substrate in THF.

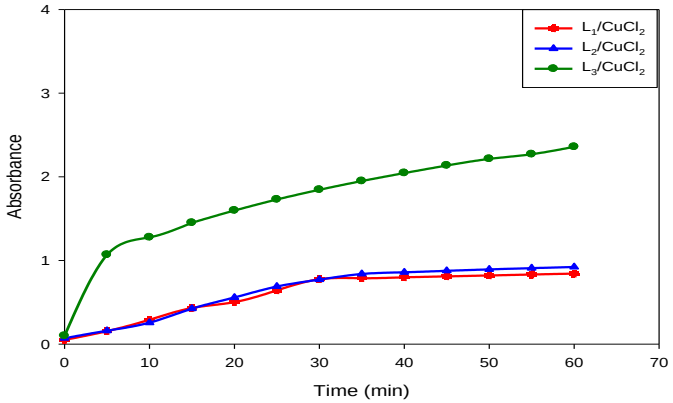

Figure 10: Oxidation of 3,5-DTB-Catechol by complexes formed in situ by **L1-L3** with **$CuCl_2$** in **THF.**

According to **Figure 10** and **Table 4**, a difference of the absorbance value for each substrate which shows that the substrate influence for the catecholase activity of the studied systems and 3,5-DTB-catechol can be easily oxidized to the corresponding quinine. So, it remains the best substrate for reproducing the catalytic activity of the enzymatic catecholase, because of its low potential for the couple quinone / catechol, leading to easy oxidation to quinone and because of its bulky substituent which limits the degradation of the substrate, this was confirmed recently by Ronan et al. [31].

Table 4: Kinetic parameters of the oxidation of catechol and 3,5-DTBC using ligands **L1-L3** with **$CuCl_2$** in **THF**.

Ligands/substrates	Catechol		3,5-DTB-Catechol	
	V(mol l^{-1} min^{-1})	T (min^{-1})	V(mol l^{-1} min^{-1})	T (min^{-1})
L1	2.95	11310	7.39	28328
L2	3.69	14145	8.08	30973
L3	3.92	15026	20.06	78583

3.3. Pproposed Reaction Pathway.

The mechanism of the enzymatic reaction is based mainly on the spectroscopy and theoretical studies [32] andrecent series of crystal structures of the various intermediates of catechol oxidase [33]. The **derivatives of catechol**molecules are oxidized per cycle and O_2 is reduced to hydrogen peroxide [34]. To give an explanation of the oxidation reaction of catechol derivatives, we try to present an oxidation mechanism of 3,5-DTB-catechol, according to **Figure 11**, the mechanism of catecholase activity (outer circle) starts from the complex 3,5-DTB-catechol binds to the complex (for example), followed by the oxidation of the substrate to the first 3,5-DTB-quinone and the reduced of copper.

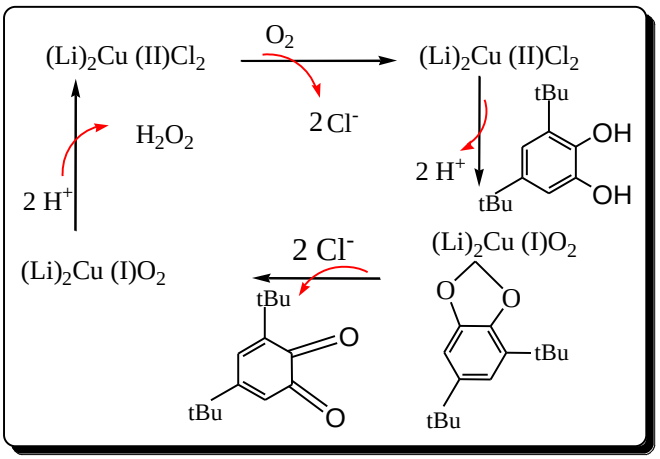

Figure 11: Proposed mechanistic pathway of the catalytic oxidation of 3,5-DTB-Catechol using complexes formed by ligands **L1-L3** and **$CuCl_2$**.

3.4. UV-Vis spectrophotometric study:

The catecholase activity for catechol and *3,5-DTB*-catechol by complex **L3-$CuCl_2$** was studied in EtOH and THF respectively, shows the change of spectral behavior immediately after addition of the complex solution to the catechol and 3,5-DTB-catechol solution, and the bands appear and increase. The results are given in **Figures 12** and **13**.

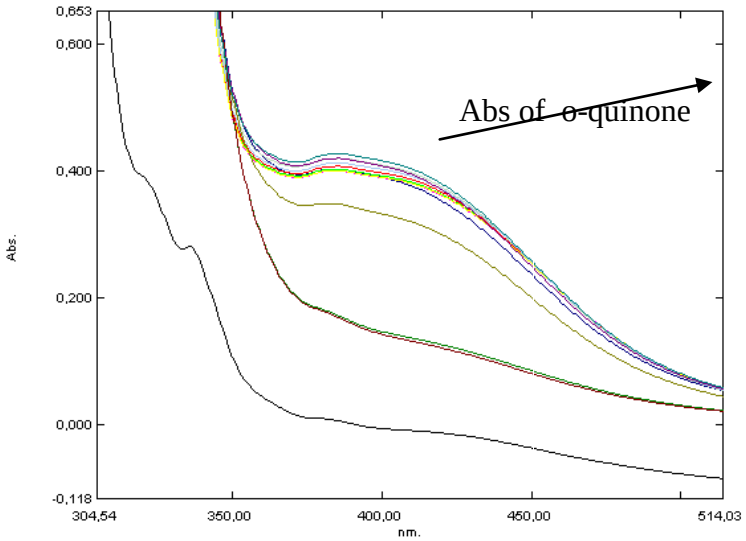

Figure 12: Increase of o-quinone band at 390 nm after addition of the catechol solution (2mL, 10^{-1}mol.L^{-1}) to a solution containing one equivalent of ligand **L3** (0.15mL, $2x10^{-3}$ mol.L^{-1}) and one equivalent of **$CuCl_2$** (0.15mL, $2x10^{-3}$ mol.L^{-1}) in EtOH. The spectra were recorded after every 10 min

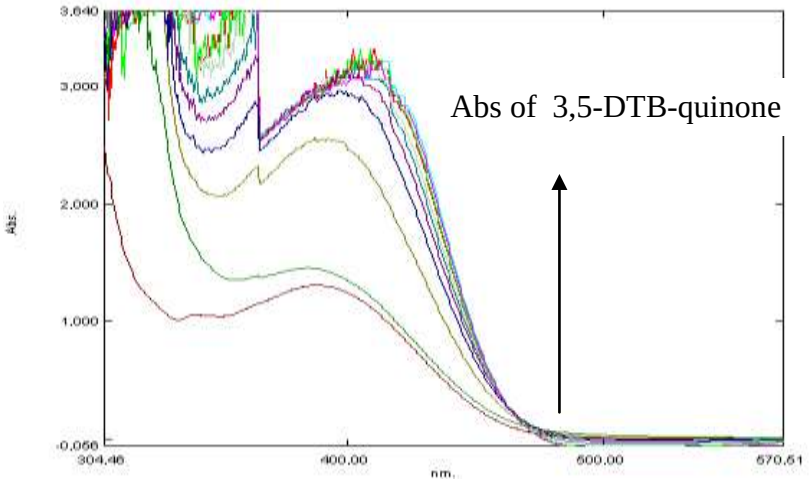

Figure 13 : Increase of 3,5-DTB-quinone band at 400 nm after addition of the 3,5-DTB catechol solution (2ml, 10^{-1} mol.L^{-1}) to a solution containing one equivalent of ligand **L3** (0.15mL, $2x10^{-3}$ mol.L^{-1}) and one equivalent of **$CuCl_2$**(0.15mL, $2x10^{-3}$ mol.L^{-1}) in THF. The spectra were recorded after every 10 min

To confirm that EtOH and THF were activated, the oxidation of catechol and 3,5-DTB-catechol, the oxidation of derivative of catecholwere carried out by monitoring the increase of the intensity of derivative of quinine bands at 390 and 400 nm with time (Figures 12- 13) after mixing 0.15 mL of L3, 0.15 mL of $CuCl_2$ and 2 mL of derivative of catechol. The derivative of quinone absorbance was recorded at regular time intervals of 10 min and the oxidation reaction was carried out in EtOH and THF at room temperature under the oxygen.

Figures 12-13 clearly show that the bands centered at 390 and 400 nm are observed when the reaction is realized in **EtOH**and THF respectively, which explain that the combination arising from ligand L3 and $CuCl_2$ catalyzes smoothly the oxidation of catechol to *o*-quinone. In different solvents, the absorbance of *o*-quinone and ***3,5-DTB*–quinine** increases with time, thus confirming that the oxidation of catecholto derivative of quinine is feasible.

4. Conclusion

In this paper, complexes arising from three ligands derived from benzoxazole **L1-L3** and Cu salts with different anions, are reported and studied for their catecholase activity. The complexes of Cu (II) were generated in situ. The study of various Cu (II) salts showed that the catalytic activity is mainly controlled by the nature of the anion. The results of this work indicated that the catalytic activity of these complexes is influenced by many factors namely the nature of ligand, counter anion, and solvent.

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