

## SYNTHESIS AND CATECHOLASE ACTIVITY OF Cu(II) AND Fe(III) COMPLEXES OF 4-METHYL-2- ((PIPERIDIN-1-YL)METHYL)PHENOL

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**Abstract:** This study is aimed at evaluating the impact of *N*- and *S*- bonding modes of thiocyanate substituent on catecholase activity as its presence in the coordination sphere of the metal complex can either reduce catecholase activity or otherwise. 4-Methyl-2-((piperidin-1-yl)methyl) phenol - the Mannich base and its synthesized metal complexes were characterized by various spectroscopic techniques including NMR, IR, and UV-Vis spectroscopy. Turnover rates obtained from the Cu(II) and Fe(III) complexes ranged between 6.02 - 22.72 h<sup>-1</sup> with the thiocyanate mode in the Fe(III) complex leading to increased catecholase activity.

**Keywords:** aminomethylation, monobase, oxidation, piperidine, quinone

## INTRODUCTION

Mannich bases and their metal complexes have been extensively studied due to their medicinal properties. Also, biomimetic studies of the metal complexes with regards to various enzymes including catecholase oxidase, phenoxazinone synthase, and ascorbic acid oxidase that involve the catalytic oxidation of oxygen are given great attention [1 – 3]. Some of our previous work [4, 5] has been directed towards the design of novel Mannich bases and synthesizing their Cu(II) and Fe(III) complexes especially as candidates to mimic *catecholase oxidase* with type-3 copper centers that catalyze exclusively the oxidation of *o*-diphenols to the corresponding *o*-quinones. The highly reactive quinones auto-polymerizes to brown polyphenolic catechol melanins, a process that is essential in the protection of damaged plants from pathogens or insects [6, 7]. Even though the oxidation process requires two Cu(II) centers in close proximity, some mononuclear metal complexes have yielded enviable results [8, 9], thus necessitating further investigation into an array of newly synthesized metal complexes.

Detailed spectroscopic studies of bioactive Mn(II) and Cu(II) complexes of similar Mannich bases obtained from catechol is also reported in addition to the ability of Zn(II) complexes of a Mannich base 2-((diethylamino)methyl)-4-methyl phenol to hydrolyze  $\beta$ -lactam antibiotics and toxic organophosphotriesters [10, 11]. To the best of our knowledge, neither the synthesis nor the applicability of this Mannich base and its metal complexes has been reported in the literature.

In this paper, the synthesis and characterization of Mannich base [4-methyl-2-((piperidin-1-yl)methyl)phenol] and its Cu(II) and Fe(III) complexes with or without thiocyanate is reported while also pointing out some of their different spectroscopic properties in the metal complexes. Also, the impact of thiocyanate within the coordination sphere of the metal ion on catecholase activity was further evaluated kinetically. All the synthesized compounds were obtained in very good quantity, the ligand was isolated purely by using purification techniques and was structurally characterized with the help of  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectroscopy amongst other spectroscopic techniques.

## MATERIALS AND METHODS

All reagents as purchased from Sigma Aldrich were of analytical grade and used as received without further purification. C, H, and N analyses were obtained on an Elementar Analysensysteme VarioMICRO V1.62 GmbH analysis System.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  on a Bruker AMX 300 MHz spectrometer with tetramethylsilane (TMS) as an internal standard for  $^1\text{H}$ . Infrared spectra ( $4000 - 650 \text{ cm}^{-1}$ ) were measured with a PerkinElmer Spectrum 400 spectrophotometer at room temperature using the ATR technique. Electronic spectra (250 – 900 nm) were recorded for the solutions of the synthesized compounds in DMF on a Perkin Elmer UV-Vis spectrophotometer model Lambda 25. The melting points were determined on a Gallenham melting point apparatus by using open capillary tubes. The molar conductance ( $10^{-3} \text{ M}$  solution in DMSO) of complexes was measured at  $20 \pm 1 \text{ }^\circ\text{C}$  using 86555 AZ Multiparameter Benchtop pH/ ORP/ Conductivity/ TDS/ Salinity meter (cell constant  $K = 0.9477$ ).

### Synthesis of 4-methyl-2-((piperidin-1-yl)methyl)phenol (HL)

Following the literature procedure with some modifications, a mixture of piperidine (1.448 g, 17.0 mmol), paraformaldehyde (0.510 g, 17.0 mmol), and *p*-cresol (1.784 mL, 17.0 mmol) was refluxed in 5 mL of isopropanol for 4 hrs. After the reaction, the mixture was poured into water and refrigerated overnight. White solid precipitates obtained were collected and recrystallized from water: ethanol mixture to give a white crystalline solid (1.850 g, yield = 53 %).

### Synthesis of the metal complexes

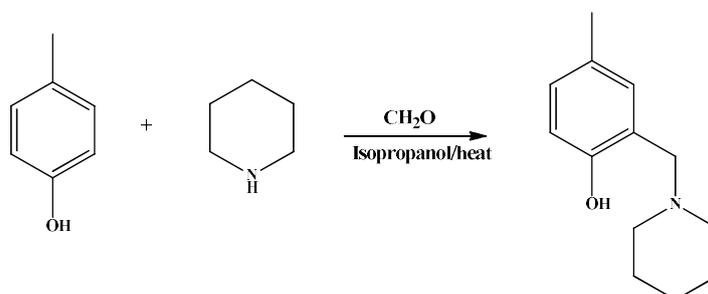
Metal complex **I** was prepared by a solution of CuCl<sub>2</sub>·2H<sub>2</sub>O (0.852 g, 5.00 mmol) in 5 mL methanol added gradually to a solution of the ligand (1.026 g, 5.00 mmol) in 5 mL chloroform. The reaction mixture was stirred at room temperature for 6 h. The desired product was obtained as precipitate after allowing the reaction mixture to stand for a few minutes after completion. This was collected, washed with the methanol-chloroform mixture, and dried in a desiccator. Similar techniques were used for the preparation of the other metal complexes. Metal complex **II** was prepared by adding an equimolar quantity of potassium thiocyanate in methanol to a similar solution used to prepare complex **I**. While FeCl<sub>3</sub>·6H<sub>2</sub>O was used to prepare complex **III** with an equimolar quantity of potassium thiocyanate in methanol added to a similar solution of complex **III** to obtain complex **IV**.

### Catecholase activity

Kinetic experiments were performed for complexes **I** - **IV** on the substrate 3,5-di-*tert*-butylcatechol (3,5-DTBC) in DMF, a constant concentration of  $1 \times 10^{-4}$  M of the metal complex was added to varying concentration of 3,5-DTBC ( $1 \times 10^{-3}$  M -  $1 \times 10^{-2}$  M). The conversion of 3,5-DTBC to the oxidation product 3,5-di-*tert*-butylquinone (3,5-DTBQ) was monitored with time at a wavelength of 400 nm. The rate for each concentration of the substrate was determined by the method of initial rate from a plot of  $\log[A_{\infty}/(A_{\infty}-A_t)]$  vs time.

## RESULTS AND DISCUSSION

The synthesis of the ligand is depicted in Scheme 1.



*Scheme 1. Synthesis of the Mannich base (HL)*

The analytical and physical data of the synthesized compounds are reported in Table 1 and Table 2. All the compounds except the ligand have high melting points and are highly soluble in DMF and DMSO. The metal complexes conformed to a 1:1 metal to ligand ratio as confirmed from elemental analysis. Molar conductivities of the metal complexes in DMSO ranged from 4.38 – 33.74  $\Omega^{-1}\cdot\text{cm}^2\cdot\text{mol}^{-1}$  thus indicating that the metal complexes are non-electrolytic in solution [12].

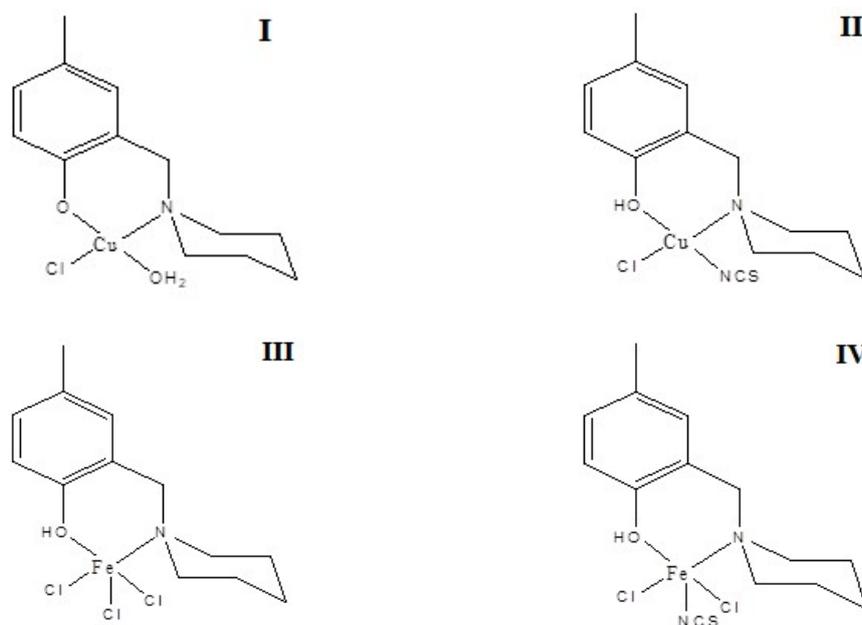
**Table 1.** Analytical data for 4-methyl-2-((piperidin-1-yl)methyl)phenol (HL) and its metal complexes

Compound	Molecular formula	% Found (Calculated)			$\Lambda_M$ [ $\Omega^{-1}\cdot\text{cm}^2\cdot\text{mol}^{-1}$ ]
		C	H	N	
<b>HL</b>	$\text{C}_{13}\text{H}_{19}\text{NO}$	75.64 (76.05)	9.44 (9.32)	6.80 (6.82)	---
<b>I</b>	$[\text{Cu}(\text{L})\text{ClH}_2\text{O}]$	48.58 (48.58)	6.96 (6.59)	4.00 (4.35)	4.38
<b>II</b>	$[\text{Cu}(\text{HL})(\text{NCS})\text{Cl}]$	46.44 (46.41)	5.65 (5.88)	7.26 (7.73)	33.74
<b>III</b>	$[\text{Fe}(\text{HL})\text{Cl}_3]\cdot\text{CHCl}_3$	25.17 (25.23)	5.30 (5.65)	2.60 (2.45)	5.33
<b>IV</b>	$[\text{Fe}(\text{HL})(\text{NCS})\text{Cl}_2]\cdot 4\text{H}_2\text{O}$	30.53 (36.37)	5.58 (5.88)	5.83 (6.05)	27.96

**Table 2.** Physical data for 4-methyl-2-((piperidin-1-yl)methyl)phenol (HL) and its metal complexes

Compounds	M.P [°C]	Molar mass	Colour
<b>HL</b>	47 - 48	205.29	White
<b>I</b>	136 - 138	321.35	Green
<b>II</b>	182 - 184	362.29	Dark green
<b>III</b>	161 - 163	571.20	Brown
<b>IV</b>	220 - 222	462.28	Light brown

The proposed structures for the metal complexes are given in Figure 1.



**Figure 1.** Proposed structures of metal complexes

The NMR data of the ligand with the characteristic peaks are reported in Table 3. The most important peak discussed herein is that of the aminomethylated group with the proton signals appearing upfield at 3.62 ppm while the carbon atom signal appears at 62.27 ppm. The integration supports the formation of a Mannich monobase as previously noted in the literature [13].

**Table 3.** NMR data of the Mannich base (HL):  $\delta$  (ppm)

<sup>1</sup> H-NMR (300 MHz, CDCl <sub>3</sub> )	1.49 – 1.66 (m, 6H, (CH <sub>2</sub> ) <sub>3</sub> ), 2.24 (s, 3H, CH <sub>3</sub> -Ar), 2.50 (t, 4H, (CH <sub>2</sub> ) <sub>2</sub> N), 3.62 (s, 2H, Ar-CH <sub>2</sub> ), 6.71 – 6.97 (m, 3H, Aromatic)
<sup>13</sup> C-NMR (75 MHz, CDCl <sub>3</sub> )	20.57, 24.28, 25.98, 54.02, 62.27, 115.9, 121.5, 128.0, 129.0, 129.1, 155.7

The infrared data of the ligand with its metal complexes (Table 4) supports the formation of these metal complexes.

**Table 4.** Mid-infrared data for 4-methyl-2-((piperidin-1-yl)methyl)phenol (HL) and its metal complexes (cm<sup>-1</sup>)

Compounds	vOH	vCN	vC-O	vCNC	vCS
<b>HL</b>	3014	---	1252	1115	---
<b>I</b>	3398	---	1260	1136	---
<b>II</b>	---	2076s, sh	1256	1135	783
<b>III</b>	3272	---	1266	1154	---
<b>IV</b>	3349	2042s, br	1258	1153	824

sh = sharp, s = strong, br = broad

The Cu(II) ion in **I** is bonded to the deprotonated form of the ligand. The vOH of the ligand is centered at 3014 cm<sup>-1</sup> a moderate-intense, broad band, a feature in support of strong intramolecular hydrogen bonding but shifts upward to 3298 – 3372 cm<sup>-1</sup> in the metal complexes. The band is not observed in the thiocyanate copper(II) complex **II** of the ligand indicating deprotonation of the hydroxyl group of the ligand before complexation and the absence of coordinated water molecules. In the Fe(III) complexes, the broad nature of the absorption band of the hydroxyl group vOH may be indicative of the presence of coordinated water molecules [14, 15].

The stretching mode of vCNC showed a positive shift ~ 20 – 40 cm<sup>-1</sup> in the metal complexes compared to the free ligand with the intensities also reduced. This is indicative of the involvement of the N-atom of the Mannich base in complexation [16].

The stretching vibration vCN in the thiocyanato complexes is observed at 2076 cm<sup>-1</sup> (strong, sharp) in the copper complex and 2049 cm<sup>-1</sup> (broad) in the iron complex. In both metal complexes, N-bonding can be inferred because of the nature of the vCN absorption band. The assertion is supported by the observation of the vCS in the range of 783 cm<sup>-1</sup> and 824 cm<sup>-1</sup> for the copper and iron complexes respectively [17, 18].

UV/Visible spectra data of the ligand and its metal complexes are reported in Table 5. The transitions around 285 nm were assigned to  $\pi \rightarrow \pi^*$  transition within the aromatic ring and the band shifted complexation. Complex I showed only one transition in DMF at 692 nm and may reflect a distorted square planar. In DMSO, the (phenolato-Cu) charge transfer band is observed at 454 nm in addition to a d-d transition at 733 nm leading to the conclusion on an octahedral geometry by the metal ion in DMSO.

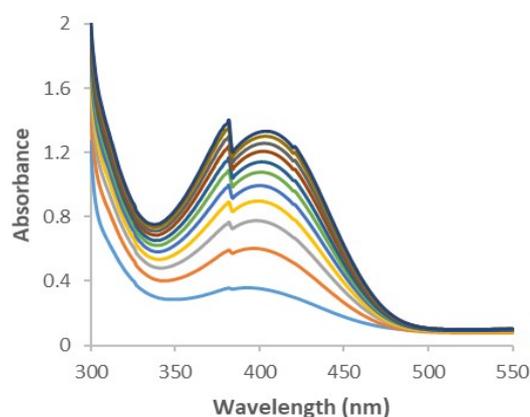
**Table 5.** UV/Visible data for HL and its metal complexes (nm)

Compounds	Solvent	Observed transitions			
		$\pi-\pi^*$	$n-\pi^*$	CT	d-d
<b>HL</b>	DMF	285	---	---	---
	DMSO	289	---	---	---
<b>I</b>	DMF	288	---	---	692
	DMSO	270	313	454	733
<b>II</b>	DMF	288	---	434	722
	DMSO	265	290	345	457
<b>III</b>	DMF	292	---	369	513
	DMSO	287	---	370	---
<b>IV</b>	DMF	---	290	413	---
	DMSO	262	291	350	456

In complex **II** across the two solvents, two transitions assigned to CT and d-d transitions are observed. Thiocyanate complexes are well noted for their charge transfer transitions and that is observed at 434 and 345 nm in DMF and DMSO respectively [19]. The wavelengths at which the transitions occur in solution lead to the suggestion that the complex is square planar in shape. The d-d transitions are assigned to  ${}^2B_{1g} \rightarrow {}^2E_g$  observed for Cu(II) complexes of Mannich bases. Madhu *et al.* [20] have previously reported values in the range of 463 – 515 nm corresponding to the  ${}^6A_{1g} \rightarrow {}^4T_{1g}$  transition consistent with octahedral Fe(III) complexes [21, 22]. Furthermore, a strong band at 310 nm in complexes corresponds to charge-transfer transition.

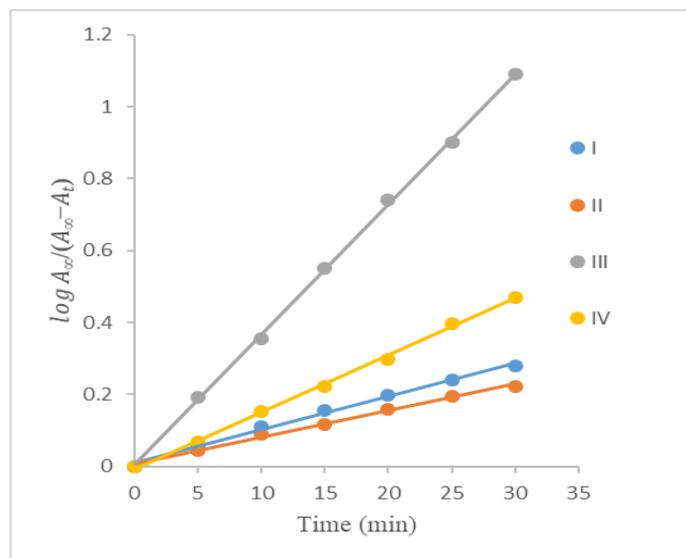
### Results of catecholase activity

The choice of 3,5-DTBC as a substrate is due to its two bulky *tert*-butyl substituents on the ring and low quinone-catechol reduction potential [23]. It was easily oxidized to the corresponding *o*-quinone, 3,5-DTBQ, which is highly stable and showed maximum absorption at 400 nm in DMF. The solution of the complexes was treated with 100 equivalents of 3,5-DTBC under aerobic conditions. After the addition of 3,5-DTBC, the time-dependent spectral scan showed a very smooth increase of the quinone band at 400 nm, which indicated the formation of 3,5-DTBQ as depicted in Figure 2.



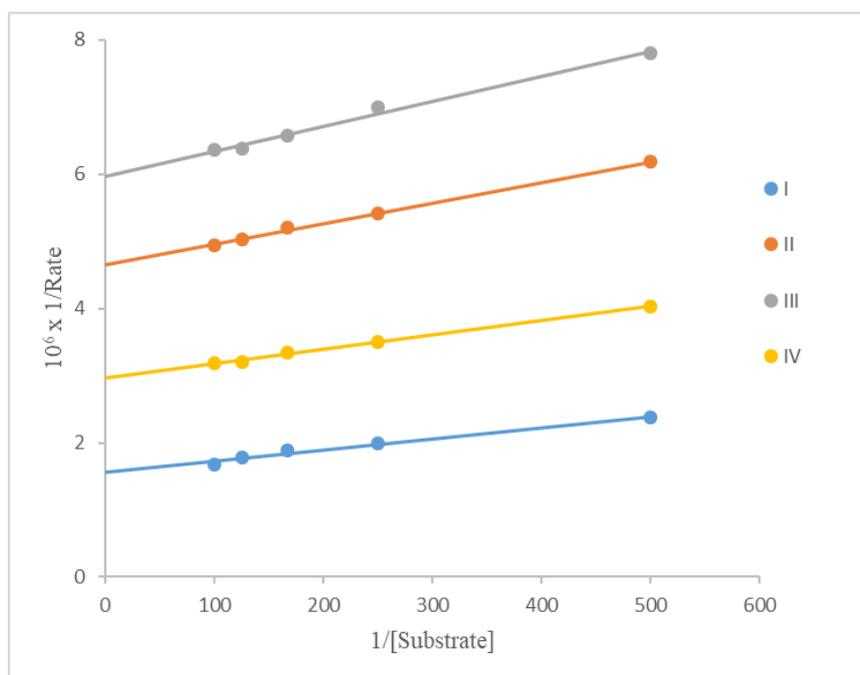
**Figure 2.** Changes observed in the absorption profile of a mixture of complex **II** (conc.  $1 \times 10^{-4} M$ ) with 100-fold 3,5-DTBC conducted at 5 mins interval for 1 hr

The plot of  $\log(A_{\infty}/A_{\infty}-A_t)$  versus time for catecholase activity of complexes **I** – **IV** is shown in Figure 3.

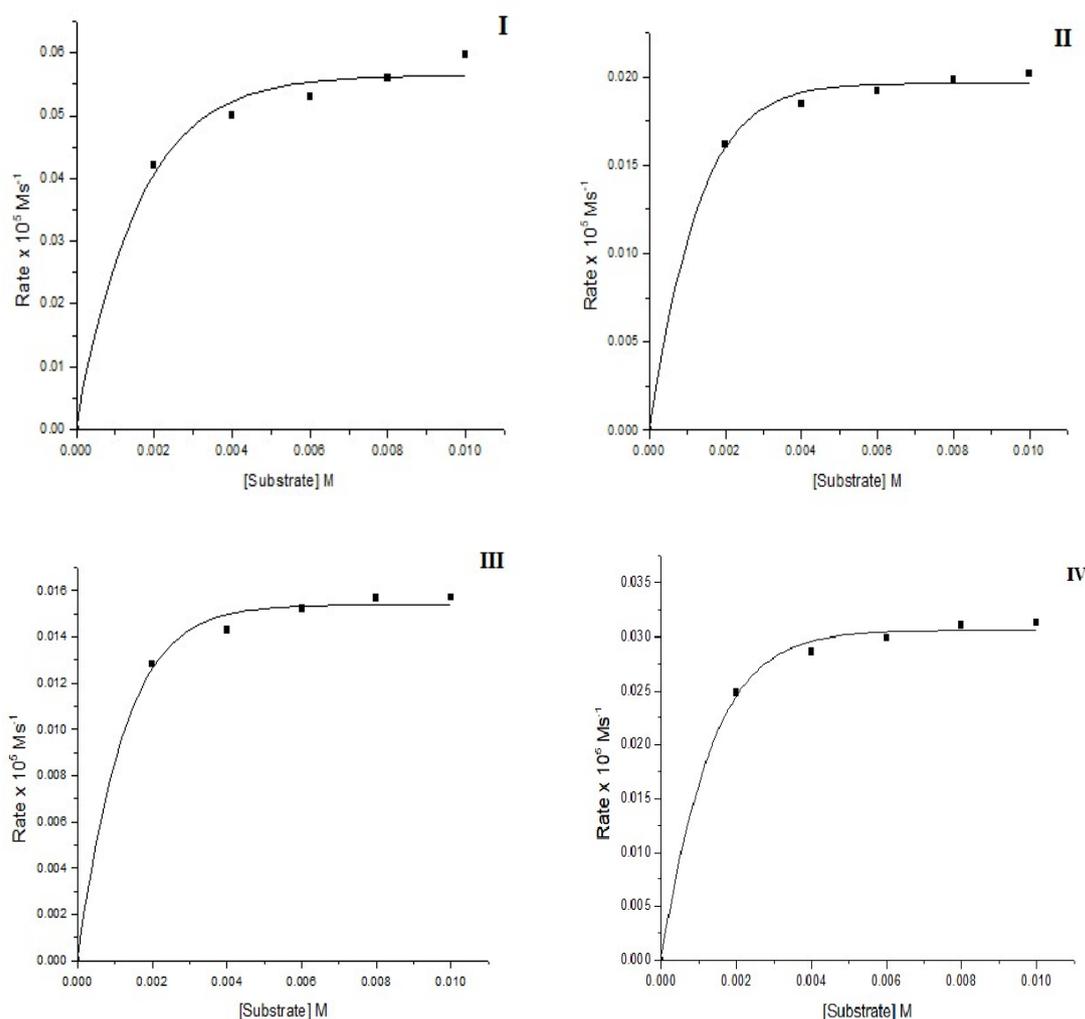


**Figure 3.** Catecholase activity of copper (II) and iron (III) complexes

The rate versus concentration of substrate data were analysed with Michaelis–Menten equation to get the Lineweaver–Burk (double reciprocal) plot as well as the various kinetic parameters  $V_{\max}$ ,  $K_M$  and  $k_{\text{cat}}$ . The Lineweaver–Burk plot is given in Figure 4 while the observed rate vs. [substrate] plot in DMF solution is depicted in Figure 5.



**Figure 4.** Lineweaver–Burk plots for complex **I** – **IV** in DMF medium for the oxidation of 3,5-DTBC



**Figure 5.** Dependence of the rate of reaction on substrate concentration for complexes **I** - **IV** (100 mM) at 25 °C in DMF for the oxidation of 3,5-DTBC

The kinetic parameters of the metal complexes are listed in Table 6. All the metal complexes demonstrated catecholase activity.

**Table 6.** Kinetic parameters for the oxidation of the model substrate 3,5-DTBC

Complex	$K_M$ [M]	$V_{max}$ [ $M \cdot s^{-1}$ ]	$k_{cat}$ [ $h^{-1}$ ]
<b>I</b>	$(1.04 \pm 0.06) \times 10^{-3}$	$(6.31 \pm 0.33) \times 10^{-7}$	$22.72 \pm 1.01$
<b>II</b>	$(6.32 \pm 0.41) \times 10^{-4}$	$(2.06 \pm 0.04) \times 10^{-7}$	$7.42 \pm 0.50$
<b>III</b>	$(6.22 \pm 0.41) \times 10^{-4}$	$(1.67 \pm 0.09) \times 10^{-7}$	$6.02 \pm 0.41$
<b>IV</b>	$(7.08 \pm 0.43) \times 10^{-4}$	$(3.33 \pm 0.17) \times 10^{-7}$	$12.00 \pm 0.78$

Turnover rates ranging from 6.02 to 22.72  $h^{-1}$  are found to be comparable to those reported by Reim *et al.* [24] and Neves *et al.* [25] but are significantly lower than those reported by Yang *et al.* [26] and Wang *et al.* [27]. The comparative order of catecholase activity is in the order **I** > **IV** > **II** > **III**. Summarily, the nature of the bonding of the thiocyanate or isothiocyanate appears to disfavor or favor the biomimetic abilities of the metal complexes involved. The negative impact of thiocyanate on catecholase activity

or similar biomimetic studies has previously been highlighted in the literature [28, 29]. We also propose that the highest catecholase activity demonstrated by **I** may be attributed to the deprotonated nature of the ligand which may enhance a stronger Cu-O bond.

## CONCLUSIONS

Four metal complexes which are potential catalysts for the oxidation of catechol to quinone by measuring the rate of aerial oxidation of 3,5-DTBC to 3,5-DTBQ in their presence have been synthesized and characterized as well as the Mannich base-ligand on which they are based. The presence of thiocyanate or isothiocyanate within the coordination sphere has been shown to either reduce or increase the efficiency depending on the ease of oxidation of the metal complex as well as the availability of the coordination site for the substrate.

## ACKNOWLEDGMENTS

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