

IMPACT OF THIOCYANATE ON THE CATECHOLASE ACTIVITY OF Cu(II) AND Fe(III) COMPLEXES OF 2-((4-(2-HYDROXY-4- METHYLBENZYL)PIPERAZIN-1-YL)METHYL)- 5-METHYLPHENOL (A MANNICH BASE)

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Abstract: Four metal complexes viz Cu(II) and Fe(III) with or without thiocyanate have been synthesized from a Mannich base prepared by a simple synthetic route. These complexes were characterized by elemental and spectroscopic techniques. Bonding modes of the thiocyanate group with the metal complexes as studied by infrared spectroscopy revealed the presence of bridging N- and S- bonding modes. Detailed kinetic studies of these complexes were carried in the evaluation of their catecholase activity. The Fe(III) complex demonstrated the highest catalytic activity using 3,5-di-tert-butyl catechol (3,5-DTBC) as substrate with a turnover rate (k_{cat}) of 112.32 h^{-1} .

Keywords: Mannich, thiocyanate, biomimetic, catecholase activity, turnover rates

Introduction

Mannich reaction involving phenols and acetophenones with secondary amines can yield a wide variety of polydentate ligands capable of various biological and industrial applications upon coordination to metal

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complexes.¹⁻³ One of such applications, is the biomimetic studies of metal complexes on catechol.⁴

The enzyme *catecholase oxidase*, also referred to as *o*-diphenol oxidase catalyzes exclusively the oxidation of catechols (i.e., *o*-diphenols) to the corresponding *o*-quinones in a process called catecholase activity. The formed quinones rapidly autopolymerize to form brown polyphenolic catechol melanins, this process is important in the protection of damaged plant tissues against insects and pathogens.^{5,6} Therefore, studies on model compounds capable of mimicking *catecholase oxidase* are very useful and offer promising alternatives for the development of newly efficient and bioinspired catalysts for *in vitro* oxidation reactions. Metal complexes [Cu(II), Ni(II) and Fe(III)] of Mannich bases often with a range of endogenous and exogenous bridging moieties (including acetato, hydroxido and phenoxido), have thrived in this regard.⁷⁻⁹ Few reports to the best of our knowledge are available on the impact of thiocyanates on catalytic processes of this nature.

The Mannich base that served as the ligand in this work has been prepared previously by Anbu and Kandaswamy,¹⁰ but a less cumbersome synthetic route is presented herein. In addition, we report the synthesis, characterization and detailed kinetic studies of the catecholase activity of Cu(II) and Fe(III) complexes of a Mannich base with those bearing thiocyanate.

Results and Discussion

The metal complexes are air stable and soluble in DMF and DMSO. The synthesized compounds were characterized by various physico-chemical techniques, such as ¹H and ¹³C NMR, IR, UV-Vis spectroscopy and elemental analysis. The elemental analysis and some physical data for the complexes are listed in Table 1. Elemental analysis supports (1:1) metal to ligand ratio (mononuclear) for all the metal complexes except **2**, (which is dinuclear) (in 2:1 ratio) and deprotonated ligand is only encountered in complexes **3** and **4**. The thiocyanate complexes have molar conductivity values between 55 and 90 Ω¹.cm².mol⁻¹ and so are 1:1 electrolytes while **1** and **2** are non-electrolytes.¹¹

Table 1. Physical and analytical data for 2-((4-(2-hydroxy-4-methylbenzyl)piperazin-1-yl)methyl)-5-methylphenol (H₂L) and its metal complexes.

Compound	M.P (°C)	Molar mass	Molecular formula	Colour	% Found (calculated)				Λ_M ($\Omega^{-1} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$)
					C	H	N	S	
H ₂ L	210 - 212	326.42	C ₂₀ H ₂₆ N ₂ O ₂	White	73.55(73.59)	8.44(8.03)	8.70(8.58)	---	3.83
1	135 - 136	514.96	[Cu(H ₂ L)Cl ₂].3H ₂ O	Dark green	46.93(46.64)	6.25(6.26)	5.71(5.44)	---	39.20
2	180 - 181	776.96	[Cu ₂ (H ₂ L)(NCS) ₃ Cl].3H ₂ O.½X	Brown	35.65(35.90)	3.17(3.40)	9.32(9.10)	12.39 (12.38)	88.80
3	230 - 232	433.77	[FeLCl].H ₂ O	Ash	54.92(55.37)	7.85(7.04)	6.40(6.45)	---	48.90
4	150 - 152	528.41	[FeL(NCS)].5H ₂ O	Dark brown	47.47(47.73)	6.75(6.49)	7.66(7.95)	5.71 (6.06)	57.71

X = chloroform

Characterization of ligand by NMR Spectroscopy

The NMR data of the ligand were recorded in CDCl_3 . Conclusion is made for substitution at both ends of piperazine judging from the data obtained from ^1H and ^{13}C NMR spectroscopy. This observation is also supported by results from the elemental analysis. The most important peaks to show a successful aminomethylation leading to a symmetrical ligand are the signals for the aminomethylated group (at 3.69 and 61.19 ppm) for the protons and carbon signals respectively.¹² In addition, the piperazine unit of the ligand showed a single signal at 2.90 and 52.31 ppm for the hydrogen and carbon signals respectively. The data presented here are comparable to those previously reported.¹⁰

Infrared Spectral Studies

The infrared data for 2-((4-(2-hydroxy-5-methylbenzyl)piperazin-1-yl)methyl)-4-methylphenol (H_2L) with its copper(II) and iron(III) complexes are reported in Table 2. Very strong intramolecular bonding in the metal complexes are expected because of the ligand's ability to form a six membered ring through hydrogen bonding and this is indicated by the νOH value of 3023 cm^{-1} .¹³ This value shifts to higher frequency in the range $3362 - 3387\text{ cm}^{-1}$ with the intensity increased; this is indicative of the hydroxyl groups of the phenol participating in the complexation and/or the presence of water molecule. The $\nu\text{C-O}$ of the ligand observed at 1242 cm^{-1} shifts by $19 - 36\text{ cm}^{-1}$ to lower frequencies in **1** and **2** while and upward shift to higher wavenumbers was observed in **3** and **4**. This suggests the involvement of hydroxyl group of the ligand in complexation with subsequently the loss of the H-bonding in the copper(II) complexes (**1** and **2**) and deprotonation in the iron complexes (**3** and **4**) to leading to a direct phenolate bond.¹⁴

Table 2. Mid-infrared data for 2-((4-(2-hydroxy-5-methylbenzyl)piperazin-1-yl)methyl)-4-methylphenol (H₂L) and its metal complexes (cm⁻¹).

Compounds	νOH	νCN	$\nu\text{C-O}$	νCNC	νCS
H ₂ L	3023	---	1242	1150	---
1	3363	---	1206	1128	---
2	3387	2173w, 2086sp	1223	1132	758
3	3365	---	1258	1206	---
4	3362	2025br	1256	1207	739

sp = split, br = broad, w = weak

The stretching mode of νCNC is observed at a single frequency and showed a very interesting pattern. A single frequency is assigned to this ring vibration at 1150 cm⁻¹ in the ligand and downward shift ~ 18 – 22 cm⁻¹ are observed in **1** and **2** and upward shift ~ 56 – 57 cm⁻¹ are observed in **3** and **4** with the intensities remain unchanged. This is indicative of the involvement of the N-atoms of the Mannich base in the complexation in all cases with the direction of the shifts dictated by the boat-chair conformations of piperazine.^{15,16}

In thiocyanate containing complexes **2** and **4**, the stretching vibration νCN is observed at 2086 cm⁻¹ (strong, split) in the copper complex and 2025 cm⁻¹ (broad) in the iron complex leads to the conclusion that S-bonding takes place in the copper(II) complexes and N-bonding in the iron(III) complexes as supported by the infrared data obtained. The assertion is supported by the observation of the νCS at 758 cm⁻¹ and 739 cm⁻¹ for the copper and iron complexes respectively.^{17,18}

The Electronic Spectra

Electronic spectral data are summarized in Table 3. Bands observed include d-d transitions at 751 and 831 nm for complex **1** in DMF and DMSO respectively. These are attributed to the single transitions each expected in an octahedral environment corresponding to ${}^2\text{E}_g \rightarrow {}^2\text{T}_{2g}$, the

proposed geometry is in line with the molecular formulae.¹⁹ Also charge transfer (metal to ligand) bands are observed at 426 and 417 nm in DMF and DMSO respectively for complex **1**. The spectra of complex **2** are quite similar to that complex **1** though the elemental analysis suggests a dinuclear complex and the transitions occur at higher energies. The values of the d-d transitions are typical of those of binuclear Cu(II) complexes in distorted square pyramidal geometry. Other transitions in **2** at about 407 nm in both solvents are assigned to ligand to metal charge transfer bands typical of thiocyanates.²⁰

Table 3. UV/Visible data for H₂L and its metal complexes (nm).

Compounds	Solvent	Observed transitions			
		$\pi - \pi^*$	$n - \pi^*$	CT	d-d
H₂L	DMF	285	290	---	---
	DMSO	276	292	---	---
1	DMF	285	---	426	751
	DMSO	272	297	417	831
2	DMF	284	323	407	591
	DMSO	271	299	408	692
3	DMF	289	---	363	---
	DMSO	278	297	364	---
4	DMF	293	321	363	---
	DMSO	269	298	345	---

The expected d-d transitions in the Fe(III) complexes appear hidden under the phenolate ($\pi 1$) \rightarrow Fe(III)($d\pi$)charge-transfer band (345 – 365 nm) and so meaningful conclusions could not be arrived at. Similar observation has been made by Ray et al., based on UV spectra of Fe(III) complex of 2,6-Bis(N-phenyl-carbamoyl)pyridine in MeCN, DMF, and DMSO solution.²¹

The proposed structures for metal complexes 1 – 4 are given in Figure 1 below.

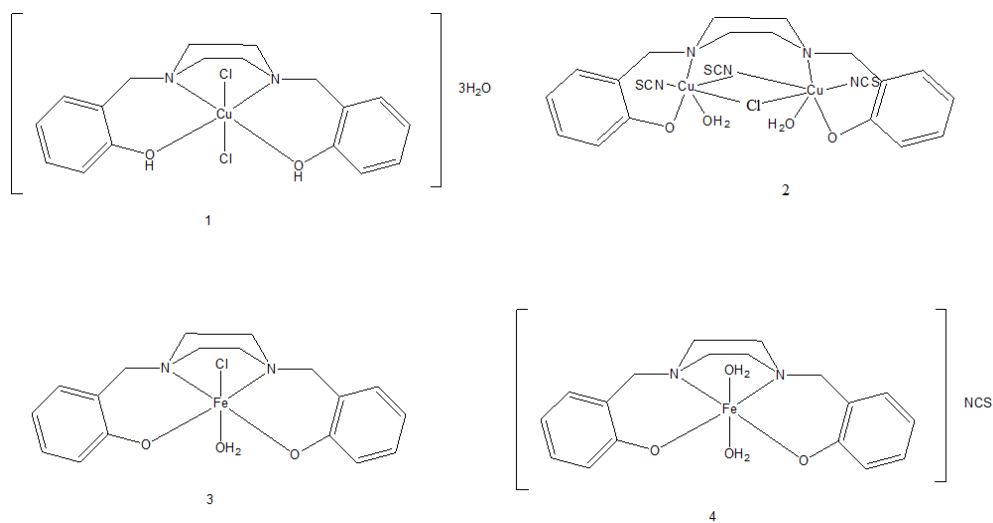


Figure 1. Proposed structures for metal complexes 1 – 4.

Catecholase Activity

The catecholase activities of complexes 1 - 4 were evaluated in a reaction with 3,5-di-tert-butylcatechol (DTBC) at 25 °C. The absorption around 400 nm which is characteristic of the formed quinone, 3,5-di-tert-butyl-*o*-benzoquinone (DTBQ) that has low redox potential and makes it easy to oxidize while its bulky tert-butyl substituents prevent further over-oxidation reactions such as ring-opening was measured as a function of time.^{8,22} The experiments were run in duplicates using DMF solutions saturated with dioxygen. The spectra for complex 4 is are presented in Figure 2 as a representative for this group.

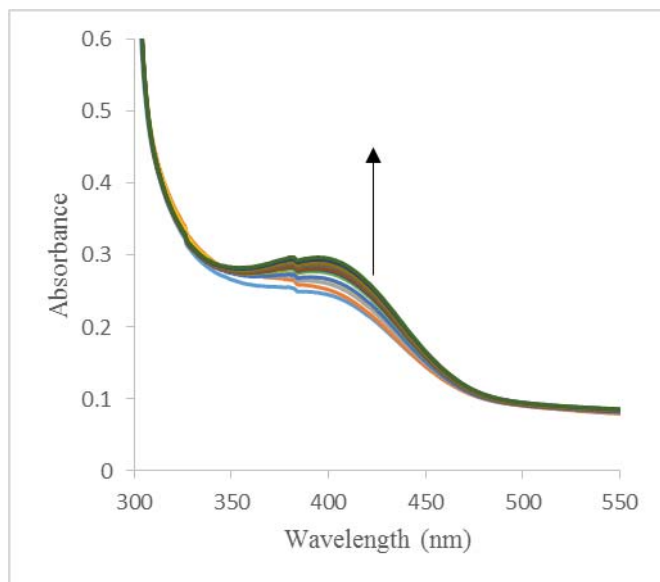


Figure 2. Increase in absorbance around 400 nm, after addition of 100 equivalents of 3,5-DTBC to a 10^{-4} M DMF solution of 4. The spectra were recorded every 5 min [inserted arrow shows the increasing absorbance].

The kinetic parameters were determined for 10^{-4} M solutions of the complex and 10^{-2} – 10^{-3} M solutions of the substrate by the method of initial rates. Determination of the rate constant for a particular complex/substrate mixture was from the $\log[A_{\infty}/(A_{\infty}-A_t)]$ vs time plot as shown in Figure 3.

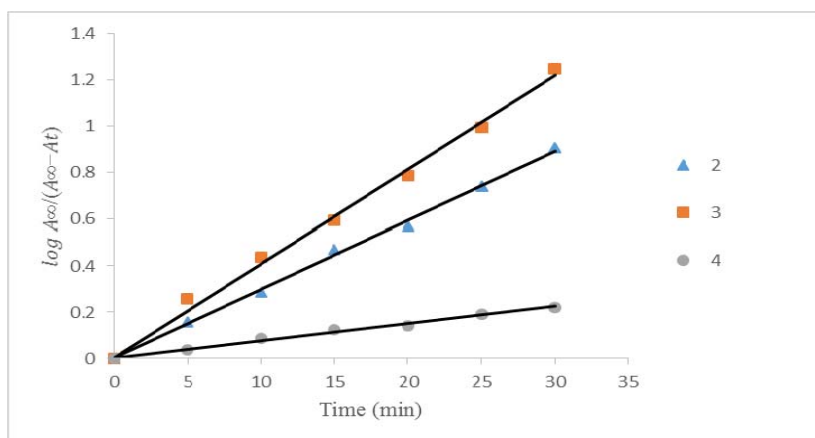


Figure 3. A plot of the difference in absorbance vs. time to evaluate the initial rate of the catalytic oxidation of 3,5-DTBC by 2 - 4 in DMF.

Michaelis–Menten kinetics was applied to analyse the data obtained, and the Michaelis–Menten constant (K_M) and maximum initial rate (V_{max}) were determined by linearization using Lineweaver–Burk plots (Figure 4). The turnover number (k_{cat}) values were calculated by dividing the V_{max} values by the concentration of the corresponding complex (Table 1). Values of the turnover rates [$5.80 - 112.32 \text{ h}^{-1}$] are comparable to those previously reported in the literature.²³⁻²⁵ The catecholase activity follows the order $3 > 2 > 4$ while complex 1 is catalytically inactive.

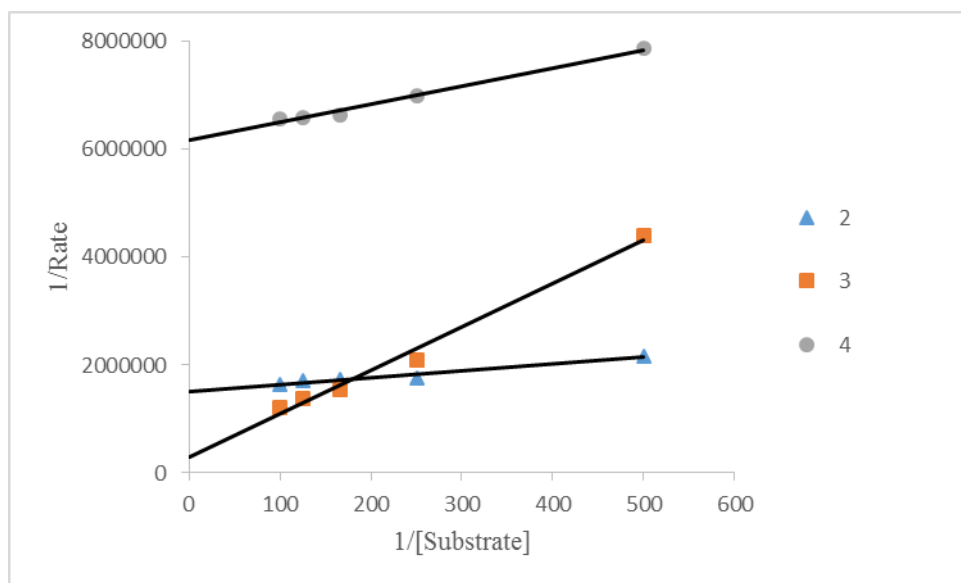


Figure 4. Lineweaver–Burk plots for complexes 2 – 4.

A similar metal complex to 1 [CuL] a four-coordinate specie alongside others prepared by Amby and Kandaswamy and only the initial rate with 100 fold 3,5-DTBC measured demonstrated low activity of $2.6 \times 10^{-7} \text{ Ms}^{-1}$. But a similar 6-coordinate specie studied in the work is catalytically inactive. The lack of reactivity may be as a result of the uneasy formation of the metal-substrate adduct for the 6-coordinate metal complex owing to the lack of leaving groups that can be easily removed.²⁶ Also the

presence of thiocyanate in the iron(III) complexes appear to impact catecholase activity negatively as previously reported in similar catalytic processes owing to its stronger binding abilities than chlorides for example thus not making readily available a coordination site for an incoming substrate.^{27,28}

The presence of hydrogen peroxide was detected through iodimetric titration thus indicating that the oxidative process passes through the formation of semiquinolate species with the isolation and identification of 3,5-DTBC were carried out through ¹H NMR spectroscopy.

Table 4. Kinetics parameters for the oxidation of 3, 5-DTBC catalyzed by metal complexes of H₂L.

Complex	K _M (M)	V _{max} (Ms ⁻¹)	k _{cat} (h ⁻¹)
1	I	I	I
2	(8.40 ± 0.33) x 10 ⁻⁴	(6.67 ± 0.37) x 10 ⁻⁷	24.01 ± 0.91
3	(2.51 ± 0.15) x 10 ⁻²	(3.12 ± 0.20) x 10 ⁻⁶	112.32 ± 3.72
4	(5.40 ± 0.31) x 10 ⁻⁴	(1.61 ± 0.09) x 10 ⁻⁷	5.80 ± 0.41

I = inactive

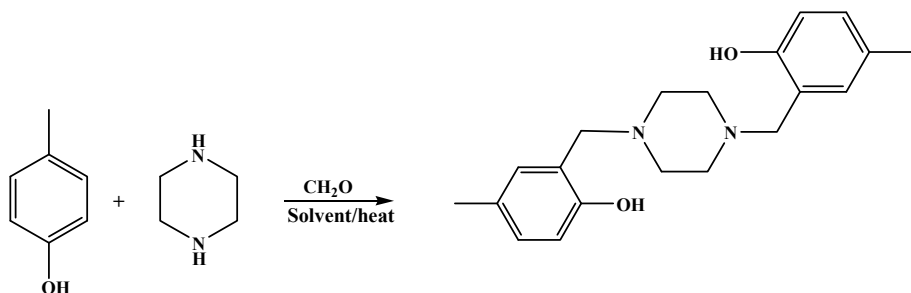
Experimental

Piperazine, *p*-cresol, formaldehyde solution, potassium thiocyanate, triethylamine and 3,5-di-tert-butylcatechol (3,5 DTBC) were purchased from Sigma Aldrich and used as such. Methanol, ethanol and chloroform were purchased from Sigma Aldrich. The metal salts were in the hydrated form, i.e. CuCl₂·2H₂O (copper chloride dehydrate) and FeCl₃·6H₂O (iron chloride hexahydrate). Elemental analysis (C, H, N) were carried out using Elementar Analysensysteme VarioMICRO V1.62 GmbH analysis System. NMR spectra (¹H and ¹³C NMR) were recorded in CDCl₃ using Bruker

AMX 300 MHz spectrometer with tetramethylsilane (TMS) as an internal standard for ^1H . Attenuated total reflection Fourier transform infrared (ATR-FTIR) spectra for all the samples were recorded on a PerkinElmer Spectrum400 spectrophotometer in the range 4000 to 650 cm^{-1} . Electronic spectra were recorded for the solutions of the synthesized compounds in DMF and DMSO on a Perkin Elmer UV-Vis spectrophotometer model Lambda 25. Molar conductivities were measured in DMSO using a 10^{-3} M solution on AZ 86555 conductivity meter. The melting points were determined on a Gallenhamp melting point apparatus and are uncorrected.

Synthesis of the Ligand

A mixture of piperazine (5 mmol, 0.4309 g) with 5 mL of formaldehyde solution (37%) was stirred in 20 mL of ethanol for 30 minutes and *p*-cresol (10 mmol, 1.0815 g) was then added and refluxed. The progress of the reaction was monitored by TLC. After 6 hours a solid product separated out and this was filtered hot from the reaction mixture and washed with hot ethanol. Recrystallization was carried out in chloroform: ethanol mixture to give a white precipitate. Yield (70 %). The formation of the ligand is depicted in Scheme 1 below.



Scheme 1: Synthesis of the ligand H₂L.

^1H NMR (300 MHz, CDCl_3): 2.28 ($\text{CH}_3\text{-Ar}$, s, 6H), 2.90 ($(\text{CH}_2)_2\text{N}$, s, 8H), 3.69 ($\text{Ar-CH}_2\text{N}$, s, 4H), 6.61 (Ar-H , d, 2H), 6.65 (Ar-H , s, 2H), 6.86 (Ar-H , d, 2H), 3.50 (Ar-OH , s, 2H).

^{13}C NMR (75 MHz, CDCl_3): 20.35 ($\text{CH}_3\text{-Ar}$), 52.31 ($(\text{CH}_2)_2\text{N}$), 61.19 ($\text{Ar-CH}_2\text{N}$), 115.8, 120.45, 128.36, 129.23, 129.29, 155.06 - aromatic carbons.

Synthesis of metal complexes

Preparation of the four metal complexes (**1** - **4**) was carried out by a general procedure. To a solution of the ligand (5 mmol) in 5 mL of warm chloroform was added an equimolar methanolic solution of the metal salt. The resulting mixture was stirred at room temperature for 6 h leading to the formation of a precipitate which was filtered off and washed twice with a 1:1 methanol: chloroform mixture. The synthesis of the thiocyanate metal complexes involved the addition of an equal mole of potassium thiocyanate dissolved in methanol while few drops of triethylamine was added during the preparation of the Fe(III) complexes.

Conclusions

We have synthesized and characterized four metal complexes that can act as potential catalysts for the oxidation of catechols to quinones thus mimicking the catecholase activity of *catecholase oxidase* and measured their catecholase activity by monitoring the rate of aerial oxidation of 3,5-DTBC to 3,5-DTBQ. The iron(III) complexes are more active than copper(II) mono or binuclear one. The presence of thiocyanate moiety drastically drops down the complex activity

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