






## Deciphering the effect of amine *versus* imine ligands of copper(II) complexes in 2-aminophenol oxidation

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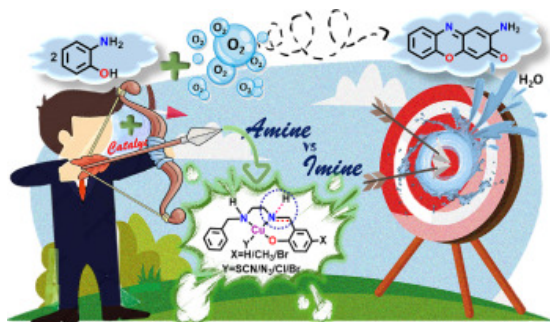
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### Abstract

A series of amine (**1–6**) and imine (**5',6'**) based copper(II) complexes with tridentate (NNO) ligand donors were synthesized and characterized using modern analytical techniques. All the complexes were subjected to 2-aminophenol (OAP) oxidation to form 2-aminophenoxazin-3-one, as a functional analogue of an enzyme, phenoxazinone synthase. In addition, a critical comparison of the reactivity using the amine-based complexes with their respective imine counterparts was achieved in both experimental as well as theoretical studies. For instance, the kinetic measurement revealed that the imine-based copper(II) complexes ( $k_{\text{cat}}$ ,  $2.4 \times 10^5$ – $6.2 \times 10^6 \text{ h}^{-1}$ ) are better than amine-based ( $k_{\text{cat}}$ ,  $6.3 \times 10^4$ – $3.9 \times 10^5 \text{ h}^{-1}$ ) complexes. The complex-substrate adducts [Cu(L3)(OAP)] (**7**) and [Cu(L3')(OAP)] (**7'**) were characterized for both systems by mass spectrometry. Further, the DFT study was performed with amine- (**3**) and imine- (**3'**) based copper(II) complexes, to compare their efficacy in the oxidation of OAP. The mechanistic investigations reveal that the key elementary step to determine the reactivity of **3** and **3'** is the proton-coupled electron transfer (PCET) step occurring from the intermediates **7/7'**. Further, the computed HOMO-LUMO energy gap of **7'** was smaller than **7** by 0.8 eV, which indicates the facile PCET compared to that of **7**. Moreover, the coupling of the OAP moiety using imine-complexes ( $\Delta G_{\text{R,E}} = -5.8 \text{ kcal/mol}$ ) was found to be thermodynamically more favorable than amine complexes ( $\Delta G_{\text{R,E}} = +3.3 \text{ kcal/mol}$ ). Overall, the theoretical findings are in good agreement with the experimental results.

### Graphical abstract

The role of electronic and auxiliary ligands in copper(II) complexes were studied for PHS mimicking activity.



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## Introduction

Over the past few years, the biomimetic catalytic systems utilising metal complexes exhibited diverse applications that are similar to the active sites of metalloproteins [1], [2], [3], [4], [5], [6], [7], [8]. Among the several metal complexes, the copper complexes are of ceaseless importance as they catalyze broad array of bioprocesses using the enzymes such as tyrosinase [9], catechol oxidase [10], quercetin-2,3-dioxygenase [11], phenoxazinone synthase [12], particulate methane monooxygenase [13], galactose and glyoxal oxidases [14], superoxide dismutase [15], *etc.*

Among the aforementioned enzymes, phenoxazinone synthase (PHS) is a prominent multi-copper oxidase enzyme that catalyzes the oxidative condensation of two molecules of 3-hydroxy-4-methylanthranilic acid pentapeptide lactone to give phenoxazinone chromophore by means of a six-electron oxidation process [12]. This particular reaction is involved in the final step of the biosynthesis of the antineoplastic drug, actinomycin-D. Initially, the enzyme PHS was isolated by Katz and Weissbach in the year 1962 [16], then it took more than 45 years to solve the structure by Allen and Francisco [10(c)]. Successively, several studies showed up to understand the function, inherent mechanism, and also to upgrade the catalytic performances for large-scale applications.

Early research investigations have demonstrated that a multi-copper environment was required for improved PHS activity [17]. One year after the isolation of PHS, a *tetra*-nuclear copper complex was studied for PHS activity using *o*-aminophenol (OAP) as substrate [17(a)]. Similar studies using *tetra*-nuclear center were performed in the later studies as well [17(b-d)]. Eventually, binuclear systems that are similar to the type 3 copper core, were also proved as potential PHS-mimicking systems [18]. After a while, studies using metal complexes other than copper like Mn [19], Fe [20], and Co [21] and also heterobimetallic complexes were reported [22]. It is an emphasizing fact that although nature has created a multi-copper active site, the mononuclear metal complexes also proved as better catalysts for the conversion of *o*-aminophenol to phenoxazinone chromophore. In this context, some studies were done using different mononuclear copper complexes [23]. Notably, mononuclear copper complexes with ligands having (N,N), (N,O), (N,S) donor moieties where the ligands can bind to the metal with varied strengths that may stimulate the attack of substrates by opening the donor site to different extent that subsequently affects the catalytic rate [17], [18], [19], [20]. Although there are a few reports of PHS mimicking activity using Schiff base (imine) copper complexes [24], similar studies with the corresponding reduced Schiff base (amine) complexes are rare [25]. One such example has been recently reported that highlights the catalytic study using Schiff base and its reduced Schiff base copper complex with pseudohalide groups with a modest  $k_{cat}$  value of  $1.34 \times 10^2 \text{ h}^{-1}$  [25]. A very recent study from our group discussed the PHS activity using Schiff base ligated copper(II) complexes with remarkable  $k_{cat}$  values in the range of  $2.4 \times 10^5 \text{ h}^{-1}$ –  $6.2 \times 10^6 \text{ h}^{-1}$  [26].

Despite the reality that a variety of coordination compounds were tested as OAP oxidation catalysts, the studies were typically restricted to measuring the yield of products and the study of rate vs substrate concentration dependence, which tends to show a consistent pattern. Studies on other dependencies, particularly the one that focuses on how the substituents on the catalyst affect the reaction order are relatively rare. Moreover, the

challenges regarding the structure–function correlation, the underlying process of dioxygen reduction, and the factors regulating the PHS activity require further investigation. By bringing all the previous findings and challenges into the foreground, we hereby report the synthesis, characterization, and PHS mimicking studies of a series of amine and their corresponding imine copper(II) complexes with (NNO) donor moieties (Scheme 1).

Our primary objective is to examine (i) the effect of O<sub>2</sub> in the reaction. (ii) Also, to find out how the electronic variation in the ligand moieties affects the catalytic rate, for example, the electronic characteristics have been rationalized by modulating the ligand moiety by introducing groups with negative inductive (Br) as well as positive inductive (CH<sub>3</sub>) effect, (iii) Further, the extensive comparison on the reactivity and mechanism of the present amine complexes with their imine counterparts have been made, in light of density functional theory (DFT) calculations along with the experimental support, and finally, (iv) understanding the effect of auxiliary ligands in oxidation catalysis, that is by exchanging the pseudohalide (-SCN<sup>-</sup>) moiety of **3** with other ligands such as -N<sub>3</sub><sup>-</sup> (**4**), -Cl<sup>-</sup> (**5**), and -Br<sup>-</sup> (**6**) ions.

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## Section snippets

### Materials and reagents

Analytical reagent grade *N*-benzylethylenediamine and 5-bromosalicylaldehyde were purchased from Sigma Aldrich. Sodium borohydride and copper(II) perchlorate were purchased from alfa aesar. 5-methylsalicylaldehyde and *o*-aminophenol were purchased from TCI. Cupric chloride, methanol and dimethylformamide were purchased from Qualigens. Salicylaldehyde, potassium thiocyanate and diethyl ether were purchased from fisher scientific. Cupric bromide, triethylamine and sodium azide were purchased from...

### Synthesis and characterization of ligands and copper(II) complexes

The tridentate (NNO) ligands (**L1**(H)–**L3**(H) and **L3'**(H)) were synthesized by refluxing *N*-benzylethylenediamine with corresponding salicylaldehyde derivatives, and a good yield (67–87%) of oily ligands were obtained. The ligands were characterized using <sup>1</sup>HNMR, <sup>13</sup>CNMR, and IR spectroscopies. For example, the broad singlet peak of amine hydrogen in the range of 4.5 ppm and the singlet resonance from the benzylic protons around 3.7 ppm together confirms the formation of amine ligands. The copper(II)...

### Conclusion

The current study discloses the synthesis and characterization of a series of amine and imine based copper(II) complexes using tridentate NNO donor ligands. Interestingly, all the complexes exhibited remarkable reactivity in oxidising *o*-aminophenol as similar to the phenoxazinone synthase enzyme as functional models. Considerably, the reactivity of these complexes relies on the nature of the substituents over the ligand moieties as well as the incorporation of distinct auxiliary ligands on the...

### CRedit authorship contribution statement

**Thasnim P. Mohammed:** Data curation, Formal analysis, Investigation, Resources, Software, Writing – original draft, Writing – review & editing. **Akhila George:** Data curation, Formal analysis, Writing – review & editing. **Madhuri Priya Sivaramakrishnan:** Data curation, Formal analysis, Writing – review & editing. **Prabha Vadivelu:** Data curation, Formal analysis, Writing – review & editing. **Sridhar Balasubramanian:** Data curation, Formal analysis, Writing – review & editing. **Muniyandi Sankaralingam:**...

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper....

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