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Short Communication

p-Quinoneimine as an intermediate in the oxidative coupling of 2-amino-5-methylphenol to 4a,7-dimethyldihydro-2-aminophenoxazinone catalyzed by a monomeric copper(II) complex

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ABSTRACT

Copper(II) complex of a tetradentate *N*-picolatedbisbenzimidazolyl ligand is synthesized and characterized. XRD study reveals that copper(II) is in a distorted square plane comprising of two imine nitrogen, one oxygen atom from nitrate and another from a water molecule. This complex carries out the oxidative coupling of aminomethylphenol to phenoxazinone through an intermediate p-quinoneimine. The reaction is pseudo first order with respect to the catalyst and is self-inhibiting with increasing substrate concentration. Anion like acetate is found to increase the rate of reaction by nine times. EPR monitoring indicates the formation of a Cu(I) species which is the likely cause of inhibition of the catalytic reaction.

1. Introduction

Copper and its metalloproteins are utilized in a variety of biological functions [1–3], including electron transfer, oxygen transport and substrate oxidation [4–11]. Phenoxazinone synthase is a copper(II) containing enzyme that catalyzes the oxidative coupling of two molecules of aminophenol to phenoxazinone chromophore [12]. The oxidative coupling reaction has been the center of various studies using transition metal ion complexes as catalyst [13–21].

Kinetics of the oxidation of 2-aminophenol to 2-aminophenoxazine-3-one shows a first order dependence on copper catalyst, dioxygen and substrate concentration using CuCl(Phen) catalyzed reaction [21], while another report shows saturation kinetics on the concentration of 2-aminophenol and dioxygen pressure [22]. First order rate of reaction at low concentration of 2-aminophenol and zero order at its higher concentration have also been reported [23]. A free radical pathway has been proposed for this coupling reaction [24–27], and a 2-aminophenoxyl radical has been found to be the key step in the activation process [28].

Earlier we have reported the oxidation of 2-aminophenol to phenoxazinone using iron(III) and a copper(II) complex [29,30]. In continuation of our earlier studies the present work reports, a copper(II) complex of a tetradentate bisbenzimidazolyl [L1] ligand, and the catalytic oxidation of 2-amino-5-methylphenol, to an intermediate species p-quinoneimine, and finally to 4a,7-dimethyldihydro-2-aminophenoxazinone (Scheme 1). To the best of our information this is the first report where a clear intermediate has been detected spectrophotometrically and its decay kinetics studied.

2. Experimental

Instrumentations and synthesis of ligand and its copper(II) complex are provided in supplementary content (S2–S3).

2.1. Kinetics of oxidation of 2-amino-5-methylphenol (OAMPH)

The copper(II) complex $[Cu(L_1)(H_2O)(NO_3)]\cdot NO_3$ was employed as a catalyst for the oxidation of 2-amino-5-methylphenol in a mixed methanol:acetonitrile solution, in the presence of molecular oxygen. The experiment was followed spectrophotometrically. The detailed procedure is as follows:

Molecular oxygen was passed for 10 min in a septum sealed 2 ml methanolic solution of the copper complex (2.15 mM). This was then transferred to 2 ml acetonitrile solution of 2-amino-5-methylphenol(14.33 mM). A 0.2 ml of this reaction mixture was diluted to 2 ml with acetonitrile and was placed in a 1 cm path length optical cell in a spectrophotometer. The final concentration of the copper complex is 0.098 mM and 0.65 mM for 2-amino-5-methylphenol. The ratio of copper(II) catalyst:2-amino-5-methylphenol is 1:6.6. Spectra

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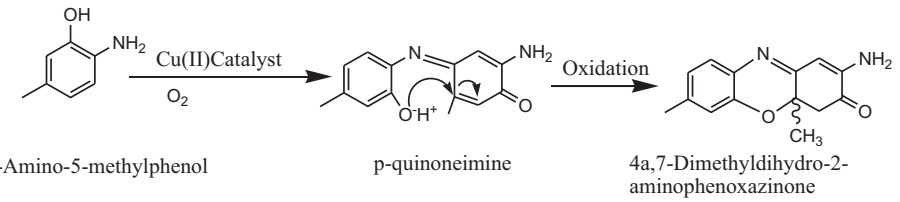

Scheme 1. Reaction for oxidation of 2-amino-5-methylphenol.

were recorded with time interval of five minute's in the range of 300–900 nm at room temperature for a period of 135 min and are depicted in Fig. 1. A band at 520 nm appears and is assigned to the formation of p-quinoneimine[(z)-2-amino-4-(2-hydroxy-4-methylphenylimino)-5-methylcyclohexa-2,5-dienone] (dark red solution) [18]. This band decays and could be observed clearly up to 100 min. Within 5–10 min of the initiation of the reaction another band starts to appear around 415 nm. The solution slowly turns yellow after 25–30 min. The presence of the band at a 415 nm confirms the formation of 4a,7-dimethyldihydro-2-aminophenoxazinone (APX) [18]. This band increases in intensity with time over a period of 135 min of serial scanning. An isobestic point is obtained at approximately 470 nm, between the decaying band at 520 nm and the generation of the new band at 415 nm. The concentration of the phenoxazinone formed was obtained from absorbance at time t and extinction coefficient (ε) [18]. The product of the reaction was isolated using preparative TLC. The yield of the product was found to be 57.5%. IR and ^{1}H NMR spectra confirm the formation of 4a,7-dimethyldihydro-2-aminophenoxazinone [detailed procedure in supplementary content (S13)]. This oxidation reaction is carried out in a mixed MeOH-MeCN solution, as it was found that in pure MeOH, the p-quinoneimine band(520 nm) decay was very quick, while its rate of decay was slower in mixed solvent system. It was found that the addition of external hydrogen peroxide to the above reaction caused a lowering in the rate of reaction suggesting that during the reaction there could be a buildup of hydrogen peroxide [details in S14]. Although the p-quinoneimine is spectrally stable all efforts to isolate it failed as it rapidly oxidized to the yellow dimethyldihydroaminophenoxazinone as has been reported earlier [18].

3. Result and discussion

3.1. Crystal structure description

The ORTEP diagram of the ligand bis(1-(pyridin-2-ylmethyl)-1,2-bis(2-benzimidazolyloxamethyl)benzene is shown in Fig. S3. While the complex $[Cu(C_{34}H_{28}N_6O_2)(H_2O)(NO_3)]\cdot NO_3\cdot 2H_2O\cdot CH_3OH$ is shown in Fig. 2. The complex crystallizes in a triclinic crystal system with P-1 space group. The Cu(II) atom is coordinated by two imine nitrogen of two benzimidazole moieties, one oxygen atom of one of the nitrate anion and one oxygen from the water molecule, affording a square planar coordination geometry. Table. S2 gives the selected bond lengths and bond angles. The ligand and its copper(II) complex were characterized by electronic spectroscopy, IR and EPR spectral technique (details are provided in supplementary content (S6,S7)).

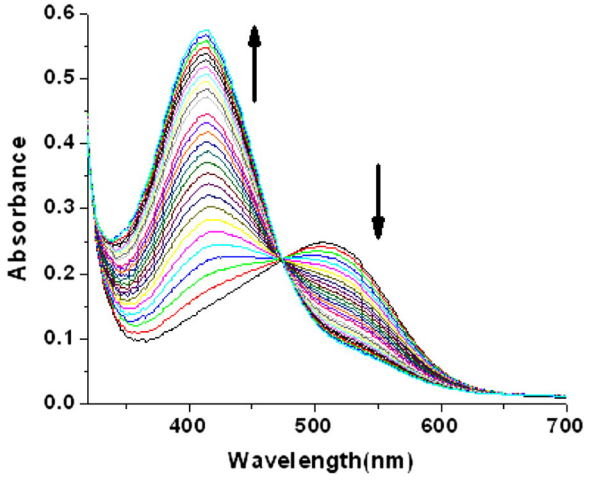

Fig. 1. Time dependant UV–visible spectral changes for the oxidation of 2-amino-5-methylphenol in 1:19 MeOH:MeCN solvent system catalyzed by the copper(II) complex in dioxygen at room temperature up to 135 min.

3.2. Kinetic studies

The oxidation reaction between 2-amino-5-methylphenol (AMPH) and dioxygen in the presence of catalytic amount of $[Cu(L1)(H_2O)(NO_3)]\cdot NO_3$ was performed at room temperature under the following conditions:

3.2.1. Catalyst variation

(i)The amount of copper(II) catalyst (0.032, 0.065, 0.081, 0.098, 0.114, 0.130 mM) was varied while keeping the amount of 2-amino-5-methylphenol (substrate) fixed at 0.65 mM. A plot of concentration of aminophenoxazinone formed ($\lambda = 415$ nm) against time, was obtained. Experimental data points were best fit using linear fit software available in origin 8. This is shown in Fig. S5 (a). The average rate of the formation of aminophenoxazinone was calculated from the slope of the above best fit plot and the rates are given in Table 1. Average rate of reaction versus concentration of catalyst is shown in Fig. 3; this depicts a linear increase in the rate of reaction, up to an optimum ratio of substrate:complex (6.6:1). The logarithm of average rate of reaction was plotted against the ln[catalyst] while keeping the concentration of substrate constant. This plot is shown in Fig. S5(b) from where the slope is found to be 0.75 suggesting a pseudo first order dependence of the catalytic reaction in a limited range.

(ii) Fig. 1 also depicts the decay of the 520 nm band attributed to p-quinoneimine [18]. The decay reaction was also studied under similar conditions as reported above.

Plot of decay of concentration of p-quinoneimine versus time is shown in Fig. S5(c) and the rate of decomposition is tabulated in Table S3. The plot of rate of decay of p-quinoneimine versus catalyst concentration is shown in Fig. 3(inset). The behavior of decay of p-quinoneimine is parallel to the formation of dimethyldihydroaminophenoxazinone, as is apparent from a comparison in Fig. 3, confirming that p-quinoneimine is the key intermediate in the conversion of 2-amino-5-methylphenol to dimethyldihydroaminophenoxazinone.

3.2.2. Substrate variation

(i) The amount of substrate (0.65, 0.86, 0.97, 1.3, 1.9 mM) was varied while keeping the amount of catalyst fixed at 0.098 mM. The plot of concentration of dimethyldihydroaminophenoxazinone formed against time is shown in Fig. S6(a) and the rates are given in Table 2. The rate of oxidation reaction with varying substrate concentration is given in Fig. 4. This shows that the rate of formation reaction decreases as the concentration of the substrate increases at a fixed catalyst concentration. An inverse saturation behavior is observed and may be considered as a case of self-inhibition.

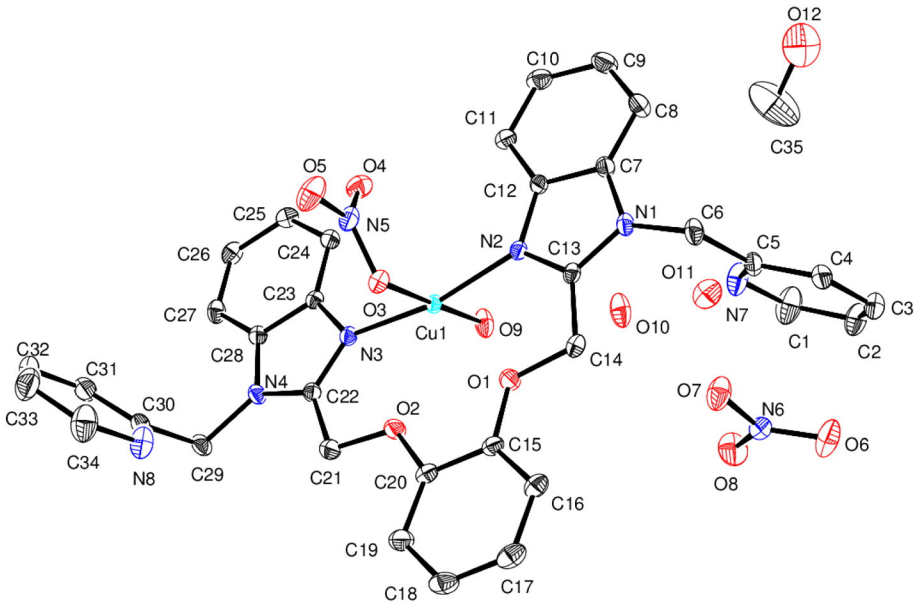

Fig 2. ORTEP diagram of the copper(II) complex drawn in 30% thermal probability ellipsoids showing atomic numbering scheme. Hydrogen atoms have been omitted for clarity.

(ii) Fig. S6(b) shows the concentration versus time plot for the decay of p-quinoneimine at 520 nm and the average decay rate is given in Table. S4. The decomposition of p-quinoneimine with substrate variation follows the same pattern as for the formation of dimethyldihydroaminophenoxazinone [Fig. 4(inset)].

The scope of the reaction has been tested on two more substrate's e.g. o-phenylenediamine and 2-amino-4-tertbutylphenol. (Detailed procedure and rate of formation of product are given in SI).

3.3. Effect of the presence of anions

An experiment was carried out to check the effect of anions like acetate 2 M (10 μl, 5 μl), oxalate 0.02 M(10 μl), and phosphate 0.02 M(10 μl). The procedure adopted was similar to that reported under experimental section the anions were added as sodium salts. For this experiment the ratio of 2-amino-5-methylphenol and the catalyst $[Cu(L)NO_3 \cdot H_2O] \cdot NO_3$ was kept at 10:1. Different anions (10 μl) were added to the catalyst; 0.2 ml of this reaction mixture was diluted with acetonitrile to make a 2 ml solution (MeOH:MeCN, 1:19 solvent system) and was studied spectrophotometrically.

The spectra show that there is in general a blue shift in the 415 nm and 520 nm bands upon the addition of PO_4^{3-}, $C_2O_4^{2-}$and OAc^- anions. While PO_4^{3-} and $C_2O_4^{2-}$anions tend to retard the reaction, the rate of reaction is found to be nine times higher when the reaction is carried out in the presence of acetate anion; with marked spectral changes (details are provided in supplementary content (S15)). This suggests that deprotonation may be an important step in the catalytic cycle. To confirm this, the rates of oxidation reaction were compared in pure MeOH and MeOD medium. It is found that the rate of MeOH/rateMeOD is 3:1. Implying that a KIE is operative (Figs. S11 and S12), thus confirming the above details.

To understand the effect of solvent and added acetate anion on the blue shift of the product band, the oxidation reaction was carried out in 1:19 MeOH:MeCN medium as reported in the experimental section and the product band is found at λ_{max} 415 nm shown in Fig. 1. While when the oxidation reaction was carried out in pure methanolic medium in the absence of acetate anion it was found that the product band blue shifts to λ_{max} 400 nm shown in Fig. S11. The solvent dependence is understood in terms of H-bonding of hydroxylic solvents causing blue shifts and vice versa [31,32]. When the oxidation reaction is carried out in the presence of acetate anion in 1:19 MeOH:MeCN solvent medium the product band blue shifts back at λ_{max} 400 nm as shown in Fig. S10. This suggests that the addition of acetate anion, to a mainly non-hydroxylic solvent system restores H-bonding of the product causing blue shift. The acetate anion facilitates deprotonation and rate enhancement and also restores H-bonding of the formed product.

Table. 1
Rate of oxidation of 2-amino-5-methylphenol with varying catalyst concentration.

S. No.	Concentration(mM) (substrate:catalyst)	Ratio (substrate:catalyst)	Rate of reaction 10^{-5} (mM min^{-1})
1.	0.65:0.032	6.6: 0.32	9.4
2.	0.65:0.065	6.6: 0.66	14.1
3.	0.65:0.082	6.6:0.83	18.3
4.	0.65:0.098	6.6:1.0	21.48
5.	0.65:0.114	6.6:1.16	16.25
6.	0.65:0.130	6.6:1.30	14.09

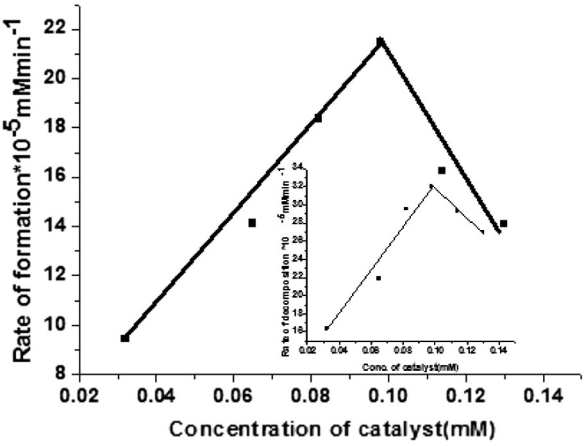

Fig. 3. Plot of rate of formation reaction for the oxidation of 2-amino-5-methylphenol vs. the concentration of catalyst at fixed substrate concentration. Inset: Rate of decomposition reaction for the intermediate p-quinoneimine (λ = 520 nm).

Table. 2
Rate of oxidation of 2-amino-5-methylphenol with varying concentration of substrate.

S. No.	Concentration(mM) (catalyst:substrate)	Catalyst: substrate	Rate of reaction 10^{-5} (mM min^{-1})
1.	0.098:0.65	1:6.6	21.4
2.	0.098:0.86	1:8.7	17.5
3.	0.098:0.97	1:9.8	13.7
4.	0.098:1.3	1:13.2	12.5
5.	0.098:1.9	1:19.3	12.0

3.4. EPR monitoring of the oxidation reaction with varying substrate concentration

An EPR titration experiment was carried out by taking a fixed amount of catalyst 0.0028 mmol and varying the amount of substrate and keeping the volume of solution same in all cases (5 ml). It was found that a mixture of the copper(II) catalyst plus four fold excess of 2-amino-5-methylphenol results in an EPR spectrum where the fourth g_{II} hyperfine line becomes part of the g line while g_{II} and A_{II} values change to 2.21 and 181 G in comparison to 2.37 and 161.6 G found for the parent copper (II) catalyst in the absence of substrate [Fig. S13]. The g_{II}/A_{II} ratio is an index of distortion of the square plane, for a tetragonal copper (II) complex. In the present case this changes to 122 from 146.5, indicating that the catalyst changes to a relatively more planar copper(II) species, during the interaction with the substrate. It is interesting to note that upon further increase in substrate concentration to six fold, eight fold there is a minor change in the g_{II} and A_{II} values for the intermediate copper(II) species. However the relative intensity of the overall spectrum drops. The g peak intensity drops by three times as the substrate concentration changes from four fold to eight fold relative to copper(II) complex [Fig. S13]. During the reaction there is no precipitation of a Cu(II) species, ruling out the possibility of a formation of less soluble Cu(II) species during reaction. The drop in overall intensity of the g peak is not due to the formation of strongly antiferromagnetically coupled polynuclear Cu(II) species, since such a species would still give a d–d band in the visible spectrum [27,33,34]. In contrast it is found that the d–d band of the present catalyst nearly vanishes upon the addition of a substrate (Fig. S14). This suggests that the active copper(II) complex, changes its redox state to copper(I), thereby diminishing the g signal intensity. It is apparent from Fig. S13 that the larger the concentration of substrate the greater the formation of copper(I) species, or loss of copper(II) species. It is also likely that the fraction of copper(I) species converting back to copper(II) may be low, causing lowered availability of the active copper(II)species for the catalytic reaction and thus resulting in the diminishing of the rate of reaction, with increasing substrate concentration. To confirm that Cu(I) is the catalytically inactive species an experiment where in Cu(II) catalyst was initially reduced by adding an excess of quinol was done (Fig. S15). This reduced Cu(I) species is then utilized for the oxidation of 2-amino-5-methylphenol. The experimental figure and the rate of reaction are given in SI. It is clearly seen that there is hardly any formation of dimethyldihydro-2-aminophenoxazinone [Fig. S15 (a)]. This clearly suggests that our catalyst in +1 oxidation state at best is only weakly capable of carrying out the oxidation of 2-amino-5-methylphenol.

4. Conclusion

We have synthesized a new copper(II) complex with a tetradentate *N*-picolyl-bisbenzimidazolyl ligand. The copper(II) ion forms a square planar complex and is capable of oxidizing 2-amino-5-methylphenol to 4a,7-dimethyldihydro-2-aminophenoxazinone. This reaction is monitored spectrophotometrically and a clear p-quinoneimine intermediate is also observed, that decays to form phenoxazinone. The rate of decomposition reaction of p-quinoneimine is much faster than the rate of formation of phenoxazinone. The effect of the presence of externally added anions shows that in the presence of acetate anion the rate of reaction is nine times higher, while phosphate and oxalate anion tend to inhibit the rate of reaction. The reaction also forms a Cu(I) species, as found from EPR studies. This is not reoxidized reversibly back to copper(II) and causes the inhibition of the catalytic reaction.

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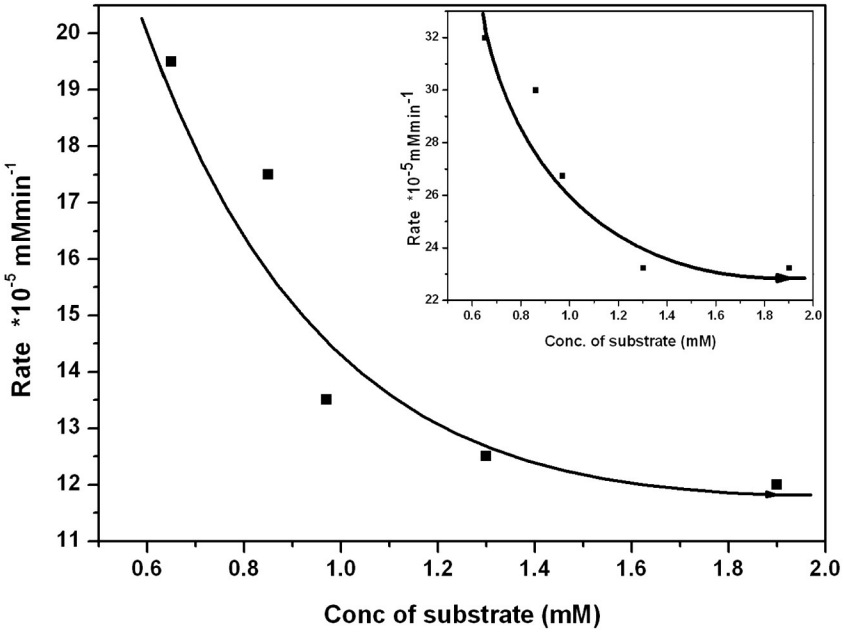

Fig. 4. Plot of rate of formation reaction for the oxidation of 2-amino-5-methylphenol vs. the concentration of substrate, at fixed catalyst concentration. Inset: Rate of decomposition reaction, for the intermediate p-quinoneimine ($\lambda = 520$ nm).

Supporting material

CCDC 940405 and 940406 contain the supporting crystallographic data for the paper this paper. These data can be obtained free of charge from the Cambridge crystallographic data center via www.ccdc.cam.ac.uk/data_request.cif. ^{1}H NMR, ^{13}C NMR of ligand and product, X-ray crystallographic tables are given in supporting information.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2014.06.001. These data include MOL files and InChiKeys of the most important compounds described in this article.

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