

Functional phenoxazinone synthase models

Kinetic studies on the copper-catalyzed oxygenation of 2-aminophenol

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Abstract

Several copper compounds (CuCl, CuCl₂, CuSO₄, Cu(NO₃)₂, Cu(OAc)₂, Cu(OCH₃)₂, and Cu(OCH₃)(Cl)) have been used as catalysts for the oxidation of 2-aminophenol with dioxygen at 60 °C in DMF to 2-aminophenoxazine-3-one; a comparison of their activities was made through kinetic measurements. Stronger coordinating donor *N*-ligands (bpy, phen) accelerate the reaction rate remarkably and the amount of ligand influences the molecularity of the CuCl-catalyzed reaction. The overall second order rate equation was found at CuCl to phen ratio of 1:0 ($k_2/60\text{ °C} = 11.3 \pm 0.5 \times 10^2 \text{ mol}^{-3} \text{ l}^3 \text{ s}^{-1}$), while the reaction is zero order with respect to 2-aminophenol concentration at a CuCl to phen ratio of 1:2 ($k_0/60\text{ °C} = 13.9 \pm 0.7 \times 10^{-2} \text{ mol}^{-3} \text{ l}^3 \text{ s}^{-1}$). The kinetics of the CuCl(phen)-catalyzed reaction measured at 60 °C resulted in a rate equation with first order dependence on copper, dioxygen and 2-aminophenol. The rate constant, activation enthalpy, and entropy at 333.16 K are as follows: $k_{\text{obs}} = 2.42 \pm 0.22 \text{ mol}^{-2} \text{ dm}^6 \text{ s}^{-1}$, $E_a = 25 \pm 1 \text{ kJ mol}^{-1}$, $\Delta H^\ddagger = 22 \pm 1 \text{ kJ mol}^{-1}$ and $\Delta S^\ddagger = -170 \pm 13 \text{ J mol}^{-1} \text{ K}^{-1}$. The catalytic systems investigated can be viewed as functional models of the enzyme phenoxazinone synthase.

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1. Introduction

The importance of copper in biology has been increasingly realized in recent years as a result of identification of copper-containing active sites in numerous oxidase, oxygenase, and other metalloenzymes. Detailed structures and the role of copper centers in these enzymes are not well defined at present and may differ from enzyme to enzyme [1–5]. Modeling studies on the activation of dioxygen and/or substrates of these enzymes may contribute to our understanding of the mechanistic feature of these processes [6–9].

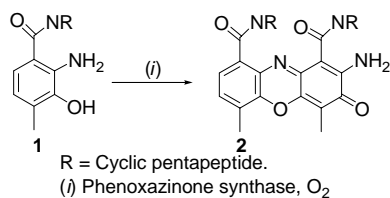
The naturally occurring antibiotic actinomycin D (2, AMD) inhibits DNA-directed RNA synthesis [10,11] and is used clinically to treat Wilm's tumor, gestational choriocarcinoma, mixed metastatic embryonal carcinoma of the testes, and other tumors [12–14]. Phenoxazinone synthase catalyzes the oxidative coupling of two molecules of a substituted 2-aminophenol (1) to the phenoxazinone chro-

mophore in the final step in the biosynthesis of actinomycin D (Scheme 1) [15]. The reaction represents a six-electron oxidative coupling and appears to take place stoichiometrically in a series of three two-electron oxidation steps. Cyclization occurs with the concomitant reduction of molecular oxygen to water. The enzyme phenoxazinone synthase, a type 2 copper-containing oxidase (subunit molecular mass 88 000, 3.7 Cu per subunit) [16] is naturally found in the bacterium *Streptomyces antibioticus* and has been cloned and over expressed in *S. lividans* [17].

Actinomycin biosynthesis has generated interest in the conversion of 2-aminophenol to 2-amino-3*H*-phenoxazine-3-one catalyzed by transition-metal complexes, with a view to the possible modeling of phenoxazinone synthase activity. Recently, the oxidative coupling reaction of 2-aminophenol to 2-aminophenoxazine-3-one with dioxygen in the presence of cobalt(II) salts [18], a cobalt(II) phthalocyanine derivative [19], and some cobaloxime(II) derivatives [20,21] has been reported in connection with the biosynthesis of actinomycins, but the selectivity of these reactions is not high. Stoichiometric oxidation of 2-aminophenol with K₃Fe(CN)₆ also affords 2-aminophenoxazine-3-one via

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Scheme 1.

o-benzoquinone imine as intermediate [22]. Catalytic oxidation of 2-aminophenol with the complex [Co(salen)] [H₂salen = *N,N'*-bis(salicylidene)ethane-1,2-diamine] as catalyst in methanol at room temperature also provides 2-aminophenoxazine-3-one in almost quantitative yield [23], although Benedini et al. [24] reported the formation of 2,2'-dihydroxyazobenzene in the above reaction under rather drastic conditions. Only a limited number of copper-containing systems (Cu, Cu₂O, CuO, CuCl, and CuCl₂) are known in the literature as catalysts for the oxidation of 2-aminophenol and the mechanism of this type of oxidative coupling reaction of various aminophenols is still obscured [25].

In order to gain more insight into the mechanism of these reactions we initiated studies on copper-mediated oxygenation of 2-aminophenol. In this paper we present our results on the reaction of 2-aminophenol with molecular oxygen catalyzed by various copper compounds under ambient conditions together with kinetic and spectroscopic data on these reactions, and propose a plausible mechanism for this phenoxazinone synthase mimicking reaction.

2. Experimental

2.1. Materials and methods

2-Aminophenol (OAP), copper compounds, *N,N,N',N'*-tetramethylethylenediamine (tmeda), 2,2'-bipyridine (bpy), 3,3'-iminobis(*N,N*-dimethyl-propylamine) (idpa), and 1,10-phenanthroline (phen) were of highest purity grade from Aldrich. Cu(OCH₃)₂ and Cu(OCH₃)Cl were prepared by literature methods [26]. DMF was purchased from Aldrich and used as supplied. Gaseous dioxygen from Messergriesheim was 99.6% and passed through P₂O₅ and Blaugel in order to remove traces of water and other impurities. IR spectra were recorded in either Nujol mull or KBr pellets on a Specord IR-75 (Carl Zeiss) spectrometer. Electronic spectra were measured on a Shimadzu UV-160A spectrophotometer using quartz cells.

2.2. Synthesis of 2-aminophenoxazine-3-one (APX)

In a typical reaction 2-aminophenol (1.09 g, 10 mmol), CuCl (0.1 g, 1 mmol) in DMF were stirred at 60 °C under dioxygen for 10 h. Diethyl ether was layered then on the solution and left at –20 °C for 2 h to afford a red–brown

solid material, which was then filtered off and recrystallized from benzene to give 2-aminophenoxazine-3-one as red crystals (0.77 g, 73%), m.p. 250–252 °C. This could easily be identified as the same product obtained upon oxidation of 2-aminophenol by HgO [27].

2.3. Kinetic experiments

Kinetic measurements were carried out at constant partial pressure of dioxygen with vigorous stirring in a thermostated reaction vessel equipped with a syringe inlet for taking samples at regular time intervals. The samples taken were chilled, stored at ice temperature and then subjected to UV-Vis analysis. Dioxygen uptakes were also measured in a constant pressure gas-volumetric apparatus. The volume of absorbed dioxygen was read periodically using a gas burette. The solubility of dioxygen in DMF at 60 °C was taken as 6.25 × 10^{–3} M [28]. The validity of Dalton's law was assumed for the calculation of dioxygen concentration at different partial pressures [29].

3. Results and discussion

3.1. Copper-catalyzed oxygenation of 2-aminophenol

As a continuation of our studies on the oxidation of substituted phenols we have used the copper compounds CuCl, CuCl₂, CuSO₄, Cu(NO₃)₂, Cu(OAc)₂, Cu(OCH₃)₂, and Cu(OCH₃)Cl as catalysts, and *N,N,N',N'*-tetramethylethylenediamine, 2,2'-bipyridine, 3,3'-iminobis(*N,N*-dimethyl-propylamine), and 1,10-phenanthroline as ligands for the oxidation of 2-aminophenol with O₂ in DMF at 60 °C. A comparison of their activities was made through kinetic studies and determination of the yields of the reactions. The results of these experiments obtained by using different copper compounds and ligands are collected in Table 1.

Table 1
Copper-catalyzed oxygenations of 2-aminophenol in DMF solution^a

Experiment no.	Complex	Ligands	Conversions ^b	Yields ^c
1	CuCl	–	78	73
2	CuSO ₄	–	79	74
3	CuCl ₂	–	8	3
4	Cu(OCH ₃)Cl	–	73	65
5	Cu(NO ₃) ₂	–	91	84
6	Cu(OAc) ₂	–	82	72
7	Cu(OCH ₃) ₂	–	64	53
8	CuCl	tmeda	76	67
9	CuCl	idpa	47	35
10	CuCl	bpy	89	78
11	CuCl	phen	93	81

^a [OAP]₀ = 2.50 × 10^{–2} M, [Cu]₀ = 2.50 × 10^{–3} M, [L]₀ = 2.50 × 10^{–3} M, 40 cm³ DMF, 60 °C.

^b Conversions were calculated from O₂-uptake.

^c Isolated yield.

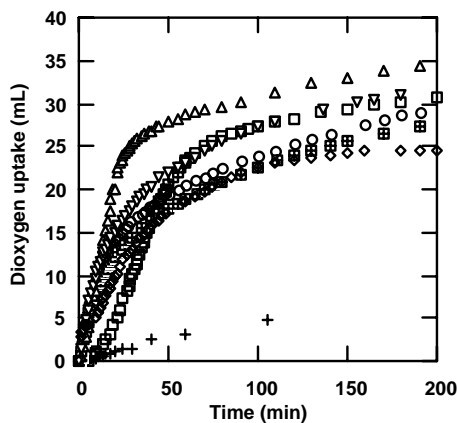


Fig. 1. Dioxigen uptakes as a function of time for the copper salt-catalyzed oxidation of 2-aminophenol in DMF (○ CuCl; □ CuSO₄; + CuCl₂; ■ Cu(OCH₃)Cl; △ Cu(NO₃)₂; ▽ Cu(OAc)₂; ◇ Cu(OCH₃)₂; experiments 1–7, Table 1).

The course of the reactions can be seen in Fig. 1, in which the dioxigen uptake is plotted as a function of time for the oxidation of 2-aminophenol by dioxigen in DMF catalyzed by various copper salts and complexes. The dioxigen uptakes ended rather abruptly, the highest reaction rate of dioxigen uptake was observed with Cu(NO₃)₂, but high activities were also found by the use of Cu(OAc)₂, CuSO₄, and CuCl, whereas the activity of CuCl₂ was rather poor. By extending the scope of our research, we have explored also how the addition of *N*-containing ligands influence the activity and selectivity of the CuCl-catalyzed reaction (Fig. 2). It can be seen that in the presence of 2,2′-bipyridine or 1,10-phenanthroline 2-aminophenol is converted to 2-aminophenoxazine-3-one in rather good yields (Table 1). In every case, free 2-aminophenoxazine-3-one was identified as the sole reaction product in yields up to 80%. This could easily be identified by comparison with the main product obtained upon the oxidation of 2-aminophenol by

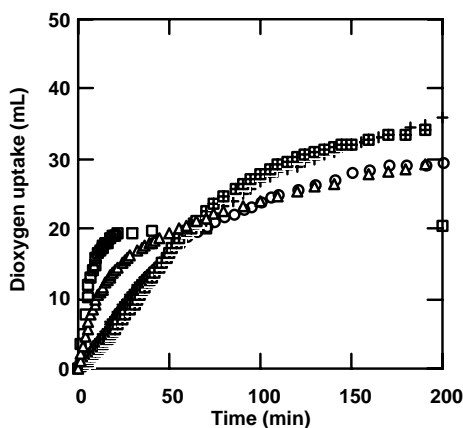
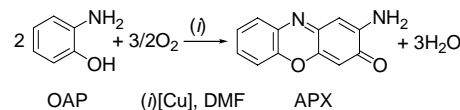


Fig. 2. Dioxigen uptakes as a function of time for the CuCl-catalyzed oxidation of 2-aminophenol in the presence of *N*-ligands in DMF (○ tmeda; + phen; ■ bpy; △ no added ligand; experiments 1, 8–10, Table 1).



Scheme 2.

HgO [26]. Efforts to characterize copper complexes formed during the reaction failed and no other organic products except APX was detected. It could also be established that at the end of the run the number of moles of O₂ used for each mole of 2-aminophenoxazine-3-one produced is 1.5 indicating the validity of the overall stoichiometry of the reaction as given in Scheme 2.

3.2. Kinetic measurements

The reactions between 2-aminophenol and dioxigen in the presence of catalytic amounts of CuCl(phen) were performed in DMF solution and examined in the temperature range from 333.16 to 363.16 K with a ratio between initial concentrations of CuCl(phen) to 2-aminophenol in the range 1:3–20. Experiments were also carried out at different dioxigen concentrations. The experimental conditions and kinetic data obtained are summarized in Table 2.

A simple rate law for the catalytic reaction between 2-aminophenol and dioxigen catalyzed by CuCl(phen) is given in Eq. (1).

$$\frac{-d2[\text{OAP}]}{dt} = \frac{d[\text{APX}]}{dt} = k_1 [\text{OAP}]^m [\text{CuCl(phen)}]^n [\text{O}_2]^q \quad (1)$$

In order to determine the rate dependence on the various reactants, oxygenation runs were performed at different substrate (Table 2; experiments 1–6), catalyst concentrations (Table 2; experiments 7–11), and at different dioxigen pressures (Table 2; experiments 2, 10–14). Assuming a constant concentration of the catalyst during each reaction, as well as a constant dioxigen pressure for the experiments the pseudo-first-order rate law (Eq. (2)) is obtained where $k' = k_1 [\text{CuCl(phen)}]^n [\text{O}_2]^q$.

$$\frac{-d2[\text{OAP}]}{dt} = k' [\text{OAP}]^m \quad (2)$$

The time course of the reaction was determined by measurement of the dioxigen uptakes. Plots of log[OAP] versus time were linear in experiments 1–14, indicating that the reaction is first order with respect to substrate concentration. Columns k' and R in Table 2 report slopes and the correlation coefficients obtained by the least-squares method for these linear regressions. A typical first-order plot is shown in Fig. 3 (Table 2; experiment 2).

The reaction was also simultaneously monitored by UV-Vis spectroscopy, measuring the absorbance of the reaction mixture at 433 nm ($\log \epsilon$ 3.743) [λ_{max} of a typical band of 2-aminophenoxazine-3-one] (Fig. 4).

Table 2
Kinetic data for the CuCl(phen)-catalyzed oxidation of 2-aminophenol in DMF solution

Experiment no.	Temperature (°C)	10^3 [O ₂] (mol l ⁻¹)	10^3 [Cu] ^a (mol l ⁻¹)	10^2 [OAP] ^a (mol l ⁻¹)	10^5 k' (s ⁻¹)	R^b (%)	k (mol ⁻² l ² s ⁻¹)	10^6 v_0 (mol l ⁻¹ s ⁻¹)
1	60	6.25	2.50	1.26	2.30	99.00	1.47 ± 0.04	1.56
2	60	6.25	2.50	2.50	5.19	99.72	3.32 ± 0.02	1.55
3	60	6.25	2.50	3.12	7.71	99.62	4.93 ± 0.04	1.83
4	60	6.25	2.50	3.75	7.13	99.85	4.56 ± 0.03	2.56
5	60	6.25	2.50	4.38	5.94	99.59	3.80 ± 0.03	2.91
6	60	6.25	2.50	5.00	2.77	99.17	1.77 ± 0.02	2.97
7	60	6.25	2.54	3.75	5.27	99.63	3.32 ± 0.03	
8	60	6.25	5.08	3.75	7.62	99.69	2.40 ± 0.02	
9	60	6.25	7.83	3.75	9.74	99.78	1.99 ± 0.02	
10	60	6.25	9.95	3.75	10.64	99.96	1.71 ± 0.01	
11	60	6.25	12.68	3.75	16.57	99.97	2.09 ± 0.01	
12	60	1.30	2.50	3.75	1.02	99.94	3.14 ± 0.02	
13	60	3.57	2.50	3.75	2.74	99.95	3.07 ± 0.02	
14	60	4.40	2.50	3.75	4.10	99.47	3.73 ± 0.03 2.42 ± 0.22 ^c	
15	70	6.56	2.50	3.75	7.20	99.91	4.43 ± 0.02	
16	80	6.83	2.50	3.75	9.66	99.81	5.49 ± 0.03	
17	90	7.48	2.50	3.75	13.05	99.95	6.98 ± 0.04	

^a In 40 cm³ DMF.

^b Correlation coefficients of least-squares regressions.

^c Mean value of the kinetic constant k and its standard deviation $\sigma(k_1)$ were calculated as $k_1 = (\sum_i w_i k_i / \sum_i w_i)$ and $\sigma(k) = (\sum_i w_i (k_i - k)^2 / (n - 1) \sum_i w_i)^{1/2}$, where $w_i = 1/\sigma_i^2$.

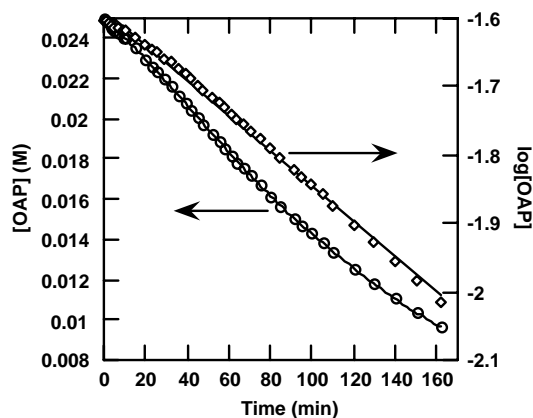


Fig. 3. Time course (gas-volumetry) and log[OAP] plot for the CuCl(phen)-catalyzed oxidation of 2-aminophenol in DMF (experiment 2, Table 2).

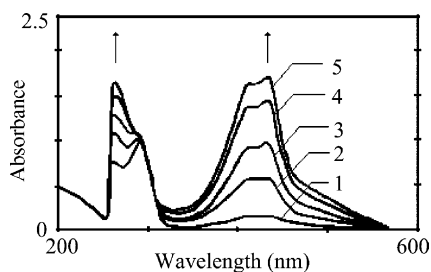


Fig. 4. Time course (UV-Vis) for the CuCl(phen)-catalyzed oxidation of 2-aminophenol in DMF (experiment 2, Table 2).

From variations of the reaction rates, plots of initial $-d[\text{OAP}]/dt$ (v_0) versus initial OAP concentrations ($[\text{OAP}]_0$) (Fig. 5) were also linear ($R = 98.46$), reinforcing that the reaction is indeed first order with respect to 2-aminophenol concentration (Table 2; experiments 1–6). This means that $m = 1$ in Eq. (1).

Kinetic measurements of the reaction rate with respect to catalyst concentration ($[\text{CuCl}(\text{phen})]$) (Table 2; experiments 7–11) indicate a first order dependence. Plots of k' versus $[\text{CuCl}(\text{phen})]_0$ for the above five experiments gave a straight line with a correlation coefficient of 97.44% (Fig. 6).

Experiments carried out at different dioxygen concentrations (calculated from literature data assuming the validity

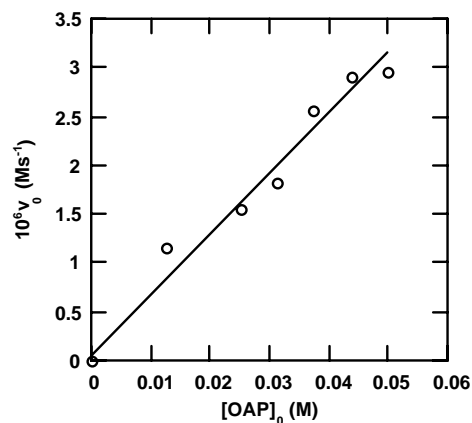


Fig. 5. Plot of reaction rate vs. the initial 2-aminophenol concentrations for the CuCl(phen)-catalyzed oxidation of 2-aminophenol in DMF (experiments 1–6, Table 2).

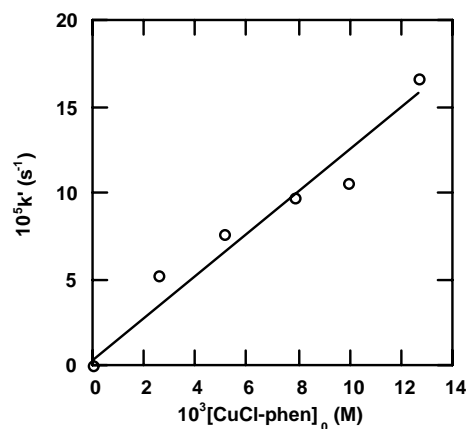


Fig. 6. Plot of reaction rate constant (k') vs. the initial catalyst concentration for the CuCl(phen)-catalyzed oxidation of 2-aminophenol in DMF (experiments 7–11, Table 2).

of Dalton's law, the dissolved concentration of O_2 being $6.25 \times 10^{-3} \text{ mol dm}^{-3}$ at 60°C and $760 \text{ mmHg } O_2$ pressure) show that the reaction is first order with respect to dioxygen concentration (Table 2; experiments 2, 12–14). Plotting k' against $[O_2]$ for the above four experiments resulted in a straight line with a correlation coefficient of 99.40% (Fig. 7). According to the kinetic data obtained, the oxygenation of 2-aminophenol with the catalyst CuCl(phen) obeys an overall third-order rate equation with $m = n = q = 1$ in Eq. (1), from which a mean value of the kinetic constant k_1 of $2.42 \pm 0.22 \text{ mol}^{-2} \text{ l}^2 \text{ s}^{-1}$ at 333.16 K was obtained (Table 2).

The activation parameters for the catalytic oxidation reaction were determined from the temperature dependence of the kinetic constant k_1 . The Arrhenius plot of $\log k_1$ versus $1/T$ (Fig. 8) by using the k_1 values at 333.16 , 343.16 , 353.16 , and 363.16 K (Table 2; experiments 2, 15–17) was linear with a correlation coefficient of 99.77%. From the slope and the ordinate intercept of this line the parameters $E_a = 25 \pm 1 \text{ kJ mol}^{-1}$, $\Delta H^\ddagger = 22 \pm 1 \text{ kJ mol}^{-1}$ and $\Delta S^\ddagger = -170 \pm 13 \text{ J mol}^{-1} \text{ K}^{-1}$ were calculated.

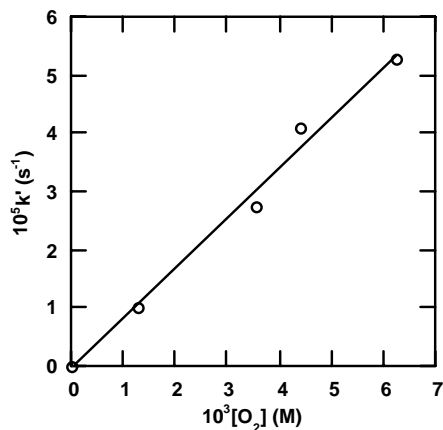


Fig. 7. Plot of reaction rate constant (k') vs. the O_2 concentration for the CuCl(phen)-catalyzed oxidation of 2-aminophenol in DMF (experiments 2, 12–14, Table 2).

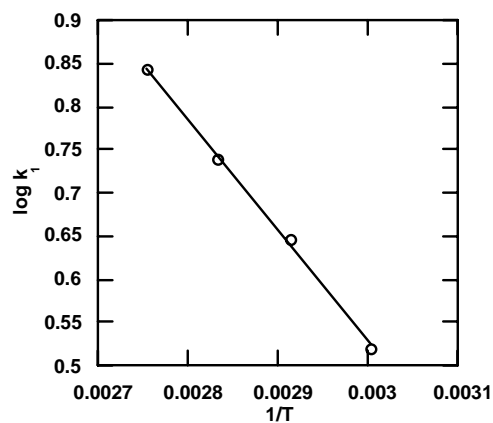


Fig. 8. Arrhenius plot for the CuCl(phen)-catalyzed oxidation of 2-aminophenol in DMF (experiments 2, 15–17, Table 2).

The influence of the amount of ligand phen on the CuCl-catalyzed oxidation was also studied with CuCl:phen ratios of 1:0–5. The time courses of the reactions can be seen in Fig. 9, which shows that the ligand has a marked effect on the reaction rate and also on reaction mechanism: an excess of 1,10-phenanthroline decreases the reaction rate and the overall reaction order too (Fig. 10). In the case of CuCl:phen = 1:0 the reaction is second order ($k_2 = 11.30 \pm 0.50 \times 10^2 \text{ mol}^{-3} \text{ l}^3 \text{ s}^{-1}$) while in the case of CuCl:phen = 1:2 the reaction is zero order ($k_0 = 13.90 \pm 0.70 \times 10^{-2} \text{ mol}^{-1} \text{ l s}^{-1}$) with respect to 2-aminophenol concentration.

It can be seen that the ratio of CuCl to phen influences the partial reaction order with respect to OAP. Since the substrate is also a good ligand, by missing the ligand phen more OAP is coordinated to the copper ion. This also has some effect on the overall reaction rates as well as on the rate constants as compiled in Table 3.

There are significant differences on the yields of the copper salt-catalyzed reactions of OAP. CuCl_2 is the less efficient (3%) while $\text{Cu}(\text{NO}_3)_2$ gave the best results (84%). It is also striking that the CuCl-catalyzed reaction results in 73% yield compared to that of the CuCl_2 -catalyzed one.

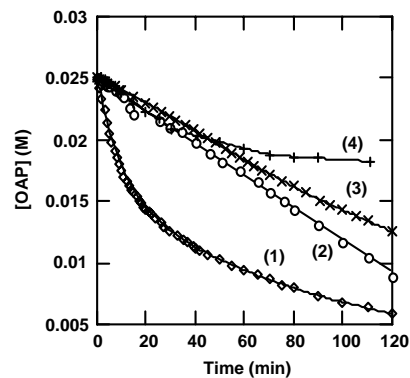


Fig. 9. Time courses for the $\text{CuCl}(\text{phen})_n$ -catalyzed ($n = 0, 1, 2, 5$) oxidation of 2-aminophenol in DMF (CuCl:phen = 1:0 (1); 1:2 (2); 1:1 (3); 1:5 (4)) (experiments 2 in Table 2 and 1–3 in Table 3).

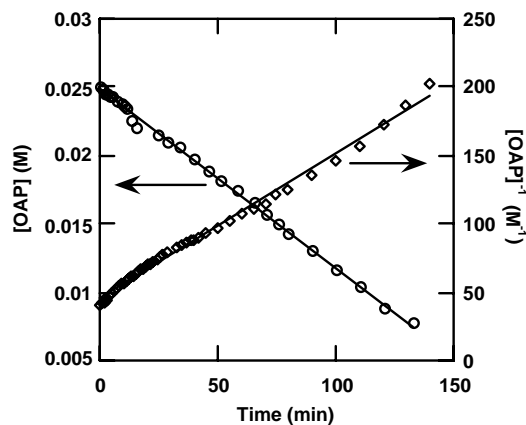


Fig. 10. Dependence of the reaction rate order on the CuCl to phen ratio in the $\text{CuCl}(\text{phen})_n$ -catalyzed ($n = 0, 2$) oxidation of 2-aminophenol in DMF (CuCl:phen = 1:0 (\diamond), [OAP] vs. time; 1:2 (\circ), $1/[\text{OAP}]$ vs. time) (experiments 2, Table 2).

The explanation of these differences (all the salts included) may come from the results of Zaki et al. [30] who studied the kinetics of the Co(III)-, Mn(III)-, and Cu(II)-oxalate complexes for the oxidation of OAP, *o*-phenylenediamine (OPDA), and *p*-phenylenediamine (PPDA). They found that the oxidation of OPDA and PPDA may follow a stepwise inner-sphere mechanism. An outer-sphere mechanism was assumed for the oxidation of OAP with the metal oxalate complexes. At the first reactions the reaction rates show a slight inverse dependence on the oxalate ion, $[\text{C}_2\text{O}_4^{2-}]$ appears in the denominator. At the oxidation of OAP the reaction rates were independent on the oxalate concentration. These tris(oxalato)metal complexes are considered to be kinetically inert and so inner-sphere of them are rather improbable. However, they undergo racemization, oxygen exchange, and aquation under ambient conditions. This is consistent with discussions of coordination sphere modifications, e.g. release of oxalate. In accordance with that we believe that the differences on the yields in the copper salt-catalyzed oxidation of OAP may be explained with this type of argumentation. Probably, the differences in the inner-sphere stability of the various copper salts makes alteration of the coordination around the copper(II) ion more or less difficult. In the case of CuCl_2 it seems to be reasonable to assume that the dissociation of the tightly bound

chloride is very difficult which renders it less active, while NO_3^- may dissociate more easily. So the necessary vacant coordination sites on copper may be reached by different easiness. That can explain the differences in the reaction rates as well.

The other factor which may be responsible for the differences in the yields is that in the case of Cu(II) salts there are at least two species which can oxidize OAP. These are the CuX_2 species and the $\text{Cu}(\text{O}_2)\text{X}$ type species which are formed after the reduction of CuX_2 to the Cu(I) state by the substrate and then due to the presence of O_2 $\text{Cu}(\text{O}_2)\text{X}$ or CuX_2 may be formed. The formation of $\text{Cu}(\text{O}_2)\text{X}$ can also be rate-determining as found in many cases in copper catalyzed oxidation/oxygenation reactions [31] or may have a different oxidation power as CuX_2 . Both factors may alter the overall oxidation rates of OAP.

Based on kinetic data on the copper-catalyzed oxidation of 2-aminophenol to 2-aminophenoxazine-3-one the following probable mechanisms as shown in Scheme 3 can be proposed. In the first case (a) we believe that CuCl (without any ligand) forms $\text{CuCl}(\text{OAP})_2$ in the presence of a large excess of 2-aminophenol in a pre-equilibrium process, which reacts then with dioxygen in a slow rate-determining step (k_2) to the superoxocopper(II) complex $\text{Cu}^{\text{II}}(\text{OAP})_2(\text{O}_2)\text{Cl}$. In the second case (b), where the CuCl to phen ratio is 1:1, there are two pre-equilibria namely the formation of $\text{CuCl}(\text{phen})$ and $\text{CuCl}(\text{phen})(\text{OAP})$ complexes. We believe that the latter one reacts with dioxygen in a rate-determining step (k_1). In the third case (c), it is reasonable to assume that CuCl forms a $\text{Cu}^{\text{I}}\text{Cl}(\text{phen})_2$ complex in the presence of 1,10-phenanthroline, which then reacts with dioxygen to form $\text{Cu}^{\text{II}}\text{Cl}(\text{phen})_2(\text{O}_2)$ (k_0) in a rate-determining step.

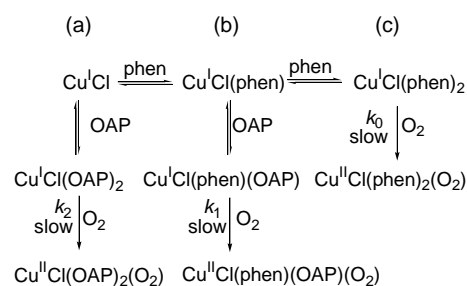
The fast consecutive reaction steps followed the formation of the copper(II) superoxide complexes are summarized in Eqs. (3)–(7) which describe first the formation of the key intermediate *o*-benzoquinone monoimine (BQMI). Its further conversion into the product APX can be rationalized by the reactions described in [16]. We think that the superoxocopper(II) derivatives, which are formed in the rate-determining steps, react with 2-aminophenol. This is followed then by an intra (a), (b) or intermolecular H-atom transfer (c) resulting in the 2-aminophenoxy radical (OAP^\bullet) in Eq. (3). After the fast disproportionation (Eq. (4)) the $\text{Cu}^{\text{II}}(\text{OH})$ complex formed reacts with OAP^\bullet resulting in BQMI and water. The

Table 3
The reaction rates and rate constants for the copper-catalyzed oxidation of 2-aminophenol by the use of CuClL_n (L = phen; $n = 0, 1, 2$) as catalysts

n	L	Reaction rate (M s^{-1})	k^a	m^b
0	phen	11.00×10^{-6}	$(11.30 \pm 0.50) \times 10^2 \text{ M}^{-3} \text{ s}^{-1}$	2
1	phen	1.30×10^{-6}	$3.32 \pm 0.02 \text{ M}^{-2} \text{ s}^{-1}$	1
2	phen	2.20×10^{-6}	$(13.90 \pm 0.70) \times 10^{-2} \text{ M}^{-1} \text{ s}^{-1}$	0

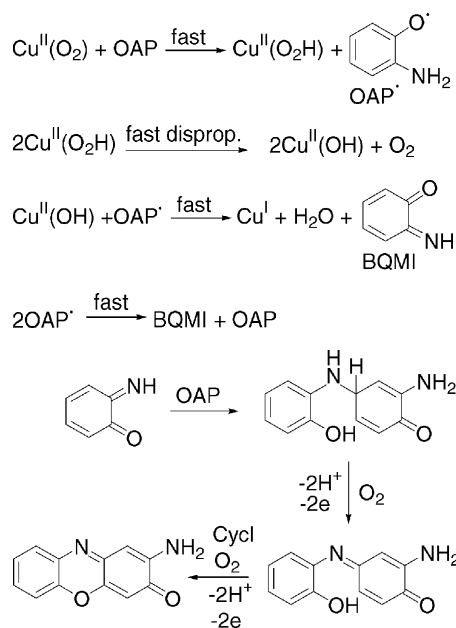
^a $[\text{OAP}]_0 = 2.50 \times 10^{-2} \text{ M}$, $[\text{Cu}]_0 = 2.50 \times 10^{-3} \text{ M}$, $[\text{O}_2] = 6.25 \times 10^{-3} \text{ M}$, 40 cm^3 DMF, 60°C .

^b Reaction order with respect to OAP.



Scheme 3.

disproportionation of OAP• (Eq. (6)) serves also BQMI. The overall reaction (Eq. (7)) requires several oxidative dehydrogenation steps involving OAP, O₂, and BQMI as reactants on the way to APX.



As a conclusion it can be said that the present work provides further support to the key role of the redox-active copper ion in these reactions, which may be regarded as functional models for phenoxazinone synthase. We think that the copper(I) ions in these model systems activate dioxygen to form peroxidic species, which then react with the substrate by abstracting a H-atom forming the reactive 2-aminophenoxy radical and *o*-benzoquinone monoimine, which is the key intermediate of the oxidative coupling reaction. H-atom abstraction from 2-aminophenol or *o*-phenylenediamine by TEMPO has also been observed leading to the same type of radicals [32,33]. Further work is in progress on other copper-containing functional phenoxazinone synthase models.

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