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CATALYTIC ACTIVITIES OF THE ANTITUMOUR COMPLEX BIS(ACETATO)BIS(IMIDAZOLE)COPPER(II) AND BIS(VALPROATO)BIS(IMIDAZOLE)COPPER(II) FOR THE OXIDATION OF ORGANIC SUBSTRATES

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Abstract—The catalytic activities of the antitumour complex bis(acetate)bis(imidazole) copper(II) (**1**) and bis(valproato)bis(imidazole)copper(II) (**2**) toward the aerobic oxidation of *N*,*N*,*N*′,*N*′-tetramethyl-*p*-phenylenediamine (TMPD) to $TMPD^+$ and 3,5-di-t-butylcatechol (DTBC) to 3,5-di-t-butyl-*o*-benzoquinone were determined. The rates were found to be first order with respect to both substrate and catalyst concentration. Complexes **1** and **2** were found to be effective catalysts for the oxidation cyclization of *o*-phenylenediamine (OPD) to 2,3-diaminophenazine, as well as oxidation of hydroquinone to 1,4-benzoquinone. The formation of a copper ion semiquinone species in solution, which may be the catalytic intermediate that reacts directly with oxygen, was demonstrated spectrophotometrically. The results suggested that the oxidation of OPD and DTBC takes place in two one-electron transfer steps. The copper(II) complex/OPD/PPh_3 catalyst system was found to catalyse the oxidation of triphenylphosphine (PPh_3) to $Ph_3P{=}O$ by molecular oxygen. The relevance of these copper(II) complexes to the biological functions of copper-containing proteins are discussed.

The catalytic oxidation of organic substrates involving oxygen complexes of copper(II) is of considerable interest due to the possible applications in a large variety of important synthetic, industrial and biological processes.[1,2] Efforts have been concentrated on developing model compounds for oxygen-binding or oxygen-activating copper proteins,[1,3-5] and many small molecular weight copper(II) complexes as models for oxidase enzymes have been synthesized.[3-7] Both mononuclear and binuclear complexes, in which the coordinated oxygen may be considered to exist primarily as a superoxo or peroxo moiety, have been found to mimic the behaviour of various metalloproteins in the oxidation of organic substrates by electron transfer (oxidase models) and oxygen insertion (oxygenase models).[1-8]

Complexes of copper(II) with carboxylate and imidazole ligands have been studied as models for copper proteins that contain both functionalities in the side chain.[9] In addition, some mononuclear copper(II) carboxylates with imidazoles have been found to have a variety of pharmacological effects, such as antitumour,[10,11] superoxide dismutase and catecholase activities.[12-14] For instance, the bis(acetato)bis(imidazole)copper(II) complex was recently found to have antitumour activity.[11] X-ray analysis demonstrated that this complex contains the $CuN_2O_2\cdots O_2$ chromophore.[15] The copper ion is essentially in a *trans*-square planar environment consisting of two imidazole nitrogen atoms and a carboxylate oxygen atom from each acetate ligand. The second oxygen atoms of the two carboxylate groups interact weakly with the copper ion, one above and one below the square plane, forming a distorted octahedral structure.

Recently, our spectroscopic studies on the copper(II) ternary complexes of the anticonvulsant drug valproate (2-propylpentanoate) with imidazoles demonstrated that the imidazole adduct exists as a bis-adduct which contains a $CuN_2O_2\cdots O_2$ chromophore,[13] and is similar to the

acetate analogue.[15] The catalytic activities of the antitumour complex, bis(acetato)bis(imidazole) copper(II) (**1**) had not previously been recognized. This article reports the catalytic activities of this complex and its copper(II) valproate-imidazole analogue (**2**) for the aerobic oxidation of *N,N,N′,N′*-tetramethyl-*p*-phenylenediamine (TMPD), 3,5-di-t-butylcatechol (DTBC), hydroquinone (HQ), *o*-phenylenediamine (OPD) (Scheme 1) and the oxygen insertion for the conversion of PPh_3 to $Ph_3P{=}O$ by the copper(II) complex/OPD/PPh_3 catalyst system. The importance of this reaction system lies in the ability to identify, spectroscopically, putative intermediate stages in the catalytic reaction processes and thereby to deduce possible mechanisms.

EXPERIMENTAL

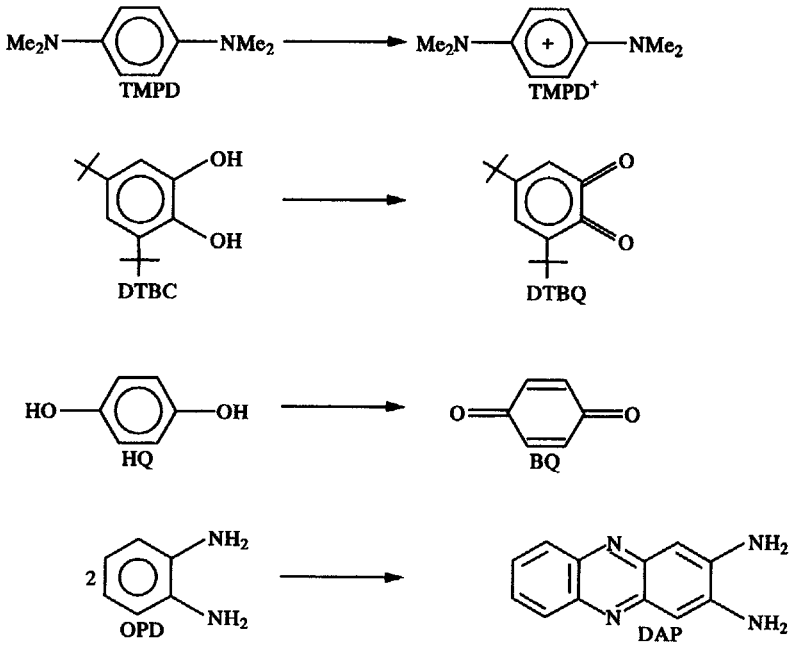
Materials

All chemicals were of high purity grade (Aldrich) and used without further purification. Bis (acetato)bis(imidazole)copper(II) $[Cu(OAc)_2(im)_2]$ (**1**). Found (Calc. for $C_{10}H_{14}N_4O_4Cu$): C, 37.8 (37.9); H, 4.4 (4.4); N, 17.6 (17.7)%. Bis(valproato)bis(imidazole)copper(II) $[Cu(valp)_2\ (im)_2]$ (**2**). Found (Calc. for $C_{22}H_{38}N_4O_4Cu$): C, 54.3 (54.1); H, 7.8 (7.8); N, 11.5 (11.7)%. Both complexes were prepared and characterized as described previously.[13,15]

The catalytic activities of these complexes in air were obtained spectrophotometrically with a Bausch and Lomb Spectronic 2000. Nujol mulls sealed between polyethylene sheets or CH_2Cl_2 solutions were used to obtain IR spectra in the 4000–200 cm^{-1} region with a Perkin–Elmer model 843 IR spectrophotometer. A Varian 360A-60 MHz spectrometer was used to obtain NMR spectra.

Catalytic and kinetic studies

The catalytic activities of complexes **1** and **2** for the air oxidations of TMPD, HQ, OPD and DTBC involved in this investigation to their respective products ($TMPD^+$, BQ, DAP, DTBQ) were followed spectrophotometrically in a 1 cm quartz cell at 298 K. Specific wavelengths characteristic of the product were chosen to follow the progress of the reaction ($TMPD^+$, 565 nm; BQ, 360 nm; DAP, 430 nm; DTBQ, 400 nm). In typical experiments the following reaction mixtures were obtained in methanol solutions: TMPD, 1.3 cm^3 copper(II) complex (1.25×10^{-5}–1.25×10^{-4} M) and 1.3 cm^3 TMPD (1.25×10^{-4}–1.25×10^{-3} M); HQ, 0.3–0.9 cm^3 copper(II) complex (1×10^{-3} M) and 1.5 cm^3 hydroquinone (0.1 M), keeping [HQ] constant by diluting with methanol when required; OPD, 1.3 cm^3 copper(II) complex (1.5×10^{-4} M) and 1.3 cm^3 OPD (1.0×10^{-2} M); DTBC, 0.1–1.0 cm^3 copper (II) complex (1×10^{-3} M) and 0.3–1.5 cm^3 DTBC (2×10^{-3} M), keeping [Cu^{II} complex] or [DTBC]



Scheme 1.

constant by diluting with methanol when required. The kinetics of oxidations were determined by the method of initial rates.

The oxygen insertion for the conversion of Ph_3P to Ph_3PO was obtained by adding a solution of complex **1** or **2** (0.1 g) in 10 cm^3 methanol to a solution containing Ph_3P (0.3 g) and OPD (0.2 g) in 30 cm^3 methanol. The wine-red solution formed was stirred at about 50°C for 5 h, while oxygen was slowly bubbled through the solution. Methanol was evaporated and the dark brown precipitate was extracted with anhydrous diethyl ether. The ether filtrate was evaporated and the yellowish-brown precipitate was identified as $Ph_3P{=}O$ as a major product with some DPA through comparisons of TLC, IR [$\nu(P{=}O) = 1190$ cm^{-1}] and UV–vis (methanol; strong band with hyperfine structure centred around 270 nm) spectra with authentic $Ph_3P{=}O$.

RESULTS AND DISCUSSION

Catalytic activity for the oxidation of TMPD

TMPD is a colourless compound, but its oxidized form, $TMPD^+$, is blue, showing strong absorption bands in alcohol in the visible spectra at 565 and 608 nm.[16] The catalytic oxidation of TMPD to $TMPD^+$ by copper(II) complexes can be easily followed spectrophotometrically. The change in absorbance at 565 nm versus time for the first 30 min of the reaction with complexes **1** and **2** was obtained. $TMPD^+$ was produced when complex **1** or **2** was mixed with TMPD under air oxygen, indicating that these mononuclear complexes have catalytic activity for the oxidation of TMPD.

Several publications by Nishida, Kida and coworkers have discussed the importance of structural factors (planar vs non-planar; mononuclear vs dinuclear) in the catalytic activity of copper(II) complexes towards aerobic oxidation of TMPD.[16–19] They concluded that dinuclear copper (II) complexes have catalytic activity, while square planar mononuclear complexes are either poor catalysts or are inactive. The mechanism for this catalytic reaction predicted a second-order reaction with respect to TMPD and first-order with respect to dinuclear copper(II) complex. It is believed that two proximate metal atoms are needed for the formation of an intermediate complex formed by two molecules of TMPD, a dinuclear copper(II) complex and dioxygen.[16–19] The formation of this intermediate is necessary to transfer two electrons simultaneously from two molecules of TMPD to a dioxygen molecule, since a two-electron transfer process is more favoured for reduction of dioxygen than a one-electron transfer process from the thermodynamic point of view.[1] The catalytic activity of non-planar mononuclear copper(II) complex having distorted tetrahedral structure was attributed to the ease of the fifth coordination of tetrahedral complexes caused by the spatial distribution of the electron hole of the copper(II) ion.[16] Accordingly, the distorted tetrahedral copper(II) complexes can form a dioxygen adduct intermediate much easier than can square planar, square pyramidal or trigonal bipyramidal complexes. The catalytic reaction mechanism in distorted tetrahedral mononuclear copper(II) complexes predicted a second-order reaction with respect to both TMPD and copper(II) complex.[16,17]

In complexes **1** and **2** used as catalysts in this report, the geometry is a severely distorted octahedron that contains the *trans* $CuN_2O_2\cdots O_2$ chromophore.[13,15] The copper ion environment consists of two imidazole nitrogen atoms and a carboxylate oxygen atom from each acetato (complex **1**) or valproate (complex **2**) ligand. The second oxygen atoms are weakly coordinated as the fifth and the sixth donors. The weakly interacting oxygen atoms are likely to dissociate to provide sites on copper(II) for dioxygen bonding during the catalytic reaction. Dissociation of the weakly bonding donors would also facilitate any necessary ligand rearrangement induced by reaction of TMPD with the copper(II) complex. Kinetic studies of the air oxidation of TMPD catalysed by these complexes were carried out using the method of initial rates.[18,20] The initial reaction velocities $V_0 = -(d[TMPD]/dt)_{t=0}$ were determined from the change in absorbance at 565 nm versus time, as reported in the literature.[18,20] Plots of log (initial rate) versus log (reactant) are shown in Fig. 1. Slopes of these plots were used to determine the reaction order for each copper(II) complex and TMPD. For both complexes the rate law shows a first-order dependence on the catalyst and TMPD concentrations, and may be expressed as:

$$\text{rate} = k_{obs}\,[\text{complex}]\,[\text{TMPD}].$$

Averaged values for the observed rate constants, k_{obs}, for the two catalysts, **1** and **2**, were found to be 2.3×10^6 M^{-1} min^{-1} and 2.7×10^6 M^{-1} min^{-1}, respectively.

These results indicate that in the rate-determining step, one molecule of TMPD reacts with one molecule of mononuclear copper(II) complex and an electron-transfer from TMPD to copper(II) occurs. According to these results, the oxidation of TMPD by mononuclear copper(II) complexes and oxygen may proceed by the mechanism:

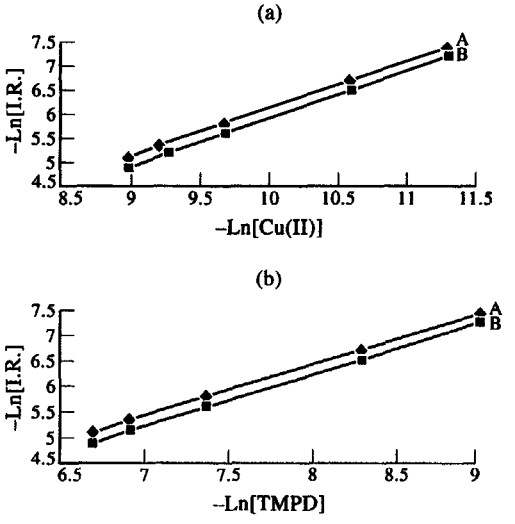


Fig. 1. (a) Plots of log initial rate (I.R.) vs log [copper(II) complexes], **1** (A) and **2** (B), at constant TMPD concentration (1.25×10^{-3} M). Slopes indicate reaction order for copper(II) complexes equal to 1.0. (b) Plots of log (I.R.) vs log [TMPD] at constant copper(II) complex concentration (1.25×10^{-4} M), **1** (A) and **2** (B). Slopes indicate that reaction order for TMPD equals 1.0.

$$\text{TMPD} + \text{Cu}^{\text{II}}\text{ complex} \rightleftharpoons [\text{TMPD} \cdot \text{Cu}^{\text{II}}]\ \text{(fast)}$$

$$[\text{TMPD} \cdot \text{Cu}^{\text{II}}] \xrightarrow{\text{electron transfer}} \text{TMPD}^{+} + \text{Cu}^{\text{I}}\text{ complex (slow)}$$

$$\text{Cu}^{\text{I}}\text{ complex} \xrightarrow{\text{oxidation}} \text{Cu}^{\text{II}}\text{ complex (fast).}$$

Oxidation of HQ

Both complexes, **1** and **2**, were found to catalyse the air oxidation of HQ in methanol as judged by the disappearance of the 686 nm band [*d–d* transitions of copper(II) complexes] due to reduction of copper(II) to copper(I) and by the growth of an absorption band at 360 nm attributed to BQ.[21] Confirmation of the oxidation product was achieved by isolation of BQ in about 80% yield from the reaction of copper(II) complex (1×10^{-3} mol) with HQ (0.1 mol) in methanol. Evaporation of methanol from this reaction and chloroform extraction gave a product whose IR [ν(CO) = 1660 cm^{-1}] and NMR (6.7 ppm) spectra were compared with an authentic sample of BQ.

Kinetic data for the oxidation process performed under excess HQ concentration over catalyst concentration revealed that the reaction rate has first-order dependence upon the concentration of catalyst **1** or **2**. These results, along with the previous ones,[21,22b] suggested that deprotonation of one hydroxyl group in HQ accomplished by carboxylate group of copper(II) complex makes the anion ($R—OHC_6H_4O^-$) available for binding to the metal centre. The rate-determining step in these oxidation reactions was suggested previously[22] to be an internal electron transfer from the coordinated anion to copper(II) to give a copper(I)–semiquinone species that releases the semiquinone radical ($R—OHC_6H_4O^{\cdot}$). This radical then disproportionates into HQ (a substrate) and BQ (the final product):

$$\text{Cu}^{\text{II}}\text{ complex} + R—OHC_6H_4OH \longrightarrow [\text{Cu}^{\text{II}}(R—OHC_6H_4O^-)]\ \text{complex}$$

$$[\text{Cu}^{\text{II}}(R—OHC_6H_4O^-)] \xrightarrow{\text{electron transfer}} [\text{Cu}^{\text{I}}(R—OHC_6H_4O^{\cdot})]\ \text{complex}$$

$$[\text{Cu}^{\text{I}}(R—OHC_6H_4O^{\cdot})] \longrightarrow \text{Cu}^{\text{I}}\text{ complex} + R—OHC_6H_4O^{\cdot}(SQ)$$

$$2\,SQ \longrightarrow HQ + BQ$$

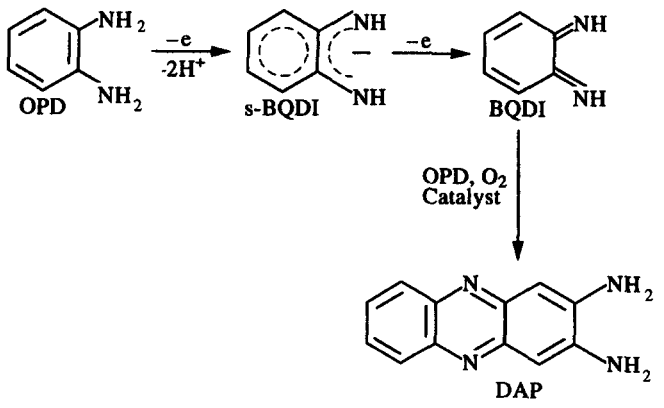
$$\text{Cu}^{\text{I}}\text{ complex} \xrightarrow{\text{oxidation}} \text{Cu}^{\text{II}}\text{ complex.}$$

The behaviour of copper(II) complexes used in this study mimics the activity of the copper-containing enzyme laccase.[1,2] This enzyme has a broad specificity for substrates acting on *p*- and *o*-diphenols, monophenols and some phenylenediamines such as TMPD.[18,22a] Spectroscopic studies indicated that copper(II) in the oxidized enzyme is reduced by the substrate (e.g. TMPD or HQ) and the primary oxidation product derived from the substrate is a free radical, such as $TMPD^+$ (from TMPD) or semiquinone (from HQ). The semiquinone then disproportionates into HQ (a substrate) and the corresponding quinone (the final product).[22b] Copper(I) is then reoxidized to copper(II) by O_2.

Catalytic oxidation of OPD

The dehydrogenation then dimerization coupling reactions of OPD catalysed by transition metal ions have been reported to produce DAP[23–27] (Scheme 2).

DAP shows a strong absorption band in water at 415–445 nm, in the pH range 12–4, respectively, and at 430 nm in diethyl ether or methanol.[23] The catalytic oxidation of OPD to DAP by complex **1** or **2** in methanol was followed spectrophotometrically. The change in absorbance at 430 nm versus time for the first 33 min of the reaction with complex **2** is shown in Fig. 2, as a representation of the catalytic reaction.



Scheme 2.

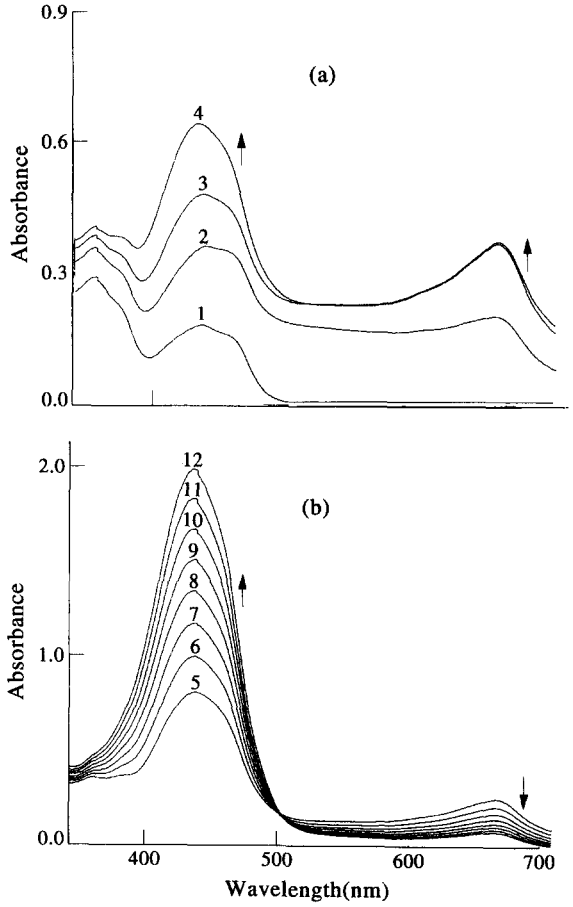


Fig. 2. (a) Spectral changes observed in the reaction of 1.3 cm^3 (1×10^{-2} M) OPD and 1.3 cm^3 (1.5×10^{-4} M) of complex **2** in methanol: (1) before addition of **2** to a solution of OPD stored in methanol for 72 h; (2) immediately after mixing; (3) 4 min and (4) 8 min after addition. (b) Spectral changes observed for the above reaction after 12 min (5), and with a cycle time = 3 min.

The aerobic catalytic oxidation dimerization of OPD to DAP by transition metal compounds was suggested to proceed via intermediate stages through complex formation between metal ion, OPD and oxygen,[23,26] to produce anionic radical *o*-benzosemiquinonediimine (s-BQDI) then benzequinonediimine (BQDI). The very unstable compound BQDI is then transformed to DAP via a complex route.[23] BQDI has never been prepared in the free state and s-BQDI is too reactive to be isolated. However, both can be stabilized under certain conditions by coordination to transition metal ions.[28,29] The formation of the reactive compound BQDI was demonstrated spectrophotometrically in the dehydrogenation reaction of OPD with choranil and in the oxidation reaction with PbO_2 in several organic solvents.[23,30] BQDI has a characteristic band at about 352 nm in methanol. Evidence for the formation of intermediates BQDI and s-BQDI during the oxidation dimerization of OPD to DPA in the absence and in the presence of complexes **1** and **2** was obtained by observing the spectroscopic course of the reaction system in methanol. If OPD is left to stand in methanol for 72 h prior to the addition of the copper(II) complex, the pale yellow solution obtained exhibits weak absorption bands at about 352 and 430 nm characteristic of BQDI and DAP, respectively [Fig. 2, spectrum a(1)]. Addition of complex **1** or **2** to this pale yellow solution leads to the formation of dark purple solution. The spectral changes observed in the system as a function of time are shown in Fig. 2. For the first 10 min three absorption bands appear with time at 656, 430 and 352 nm (Fig. 2a). The intense band at 656 nm lies in the wavelength range characteristic of metal–semibenzoquinonediiminate complexes,[27,28] including that reported for the copper complex.[29] The bands at 430 and 352 nm are for DPA and BQDI, respectively. After it is formed (approximately 10 min after the addition of copper complex to OPD solution), the copper–semi-

benzoquinonediiminate complex reacts with oxygen to form a copper (s-BQDI)–O_2 species. The formation of this intermediate was proposed previously as the rate-determining step in the oxidation process, which decays with production of free radical, then undergoes further fast reactions to the final oxidation product.[24] This was demonstrated by the spectral changes with time (Fig. 2b). The absorption band at 656 nm decreases while the band at 430 nm, due to the formation of DPA, increases more rapidly with an isosbestic point at about 490 nm. The final spectrum of the system contains a band at 430 nm characteristic of DPA and the 686 nm band of the copper(II) complex.

The formation of the proposed copper ion–semiquinone intermediate which reacts directly with oxygen was used to catalyse the oxygenation of Ph_3P to $Ph_3P{=}O$ in the following section. In addition, the formation of an analogue intermediate was also demonstrated in the catecholase mimicking activity of complexes **1** and **2** for the oxidation of DTBC to DTBQ (see below).

Catalytic oxidation of Ph_3P

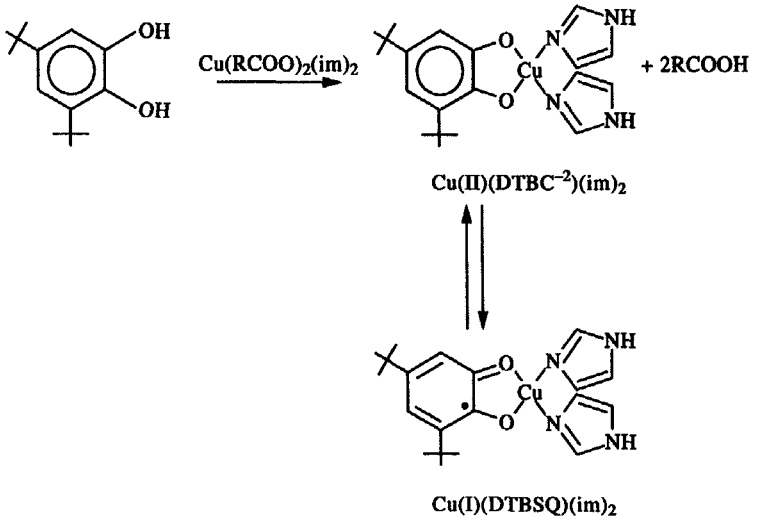
Addition of copper(II) complex (**1** or **2**) to a methanolic solution containing OPD and Ph_3P led to a wine-red coloration. The UV–vis spectrum of this solution showed an intense band at about 500 nm. This band decays slowly with time. A similar band was obtained previously[27b] during the catalytic oxidation of Ph_3P added in excess over a cobalt(II) and OPD mixture. The catalytic system was proposed to contain a Co–OPD–Ph_3P–peroxo species which catalyses the oxidation of Ph_3P to Ph_3PO. A Co^{III}–s-BQDI–Ph_3P species was isolated and characterized from the catalytic system at the end of the Ph_3P oxidation stage.[28] In this study, the Cu^{2+}/OPD/Ph_3P/O_2 catalytic system leads to the oxidation of Ph_3P to Ph_3PO (oxygen insertion). When a blank reaction without OPD was performed, no Ph_3PO could be isolated. The formation of Ph_3PO was identified by comparing its TLC, IR and UV–vis spectra with authentic Ph_3PO. A strong, sharp band at 1190 cm^{-1} characteristic of $\nu(P{=}O)$ was observed and a strong band with hyperfine structure centred around 270 nm was also observed in methanol in the UV–vis spectrum, which is characteristic of Ph_3PO.

Catalytic activity for the oxidation of DTBC

Since DTBQ shows a characteristic absorption band at 400 nm (ε = 1900 $dm^3\,mol^{-1}\,cm^{-1}$ in methanol),[31] the catalytic oxidation of DTBC to the corresponding quinone (DTBQ) by copper(II) complexes can be easily followed spectrophotometrically. The change in absorbance at 400 nm versus time for the first 30 min of the reaction with complexes **1** and **2** was obtained. Both complexes show catecholase-like catalytic activity towards aerobic oxidation of DTBC to DTBQ. The calculated turnovers (moles of DTBQ produced per mole of catalyst per hour) were found to be 19 and 22 for complexes **1** and **2**, respectively.

Small molecular weight dinuclear and mononuclear copper(II) complexes have been studied as models for copper oxidase enzymes, such as the copper-containing protein tyrosinase.[1,2,8,13,14,21,32,33] In tyrosinase and in synthetic copper(II) dinuclear models, it is believed that two proximate metal atoms are needed to bond to the two hydroxyl atoms of catechols in the oxidation to *o*-quinones.[1,32] In non-planar mononuclear copper(II) models, it has been proposed that the two copper(II) atoms must be located at a distance of less than 5 Å apart for bonding to the hydroxyl groups of catechols, a mode which would facilitate electron transfer to dioxygen.[1,32] In addition, Thompson and Calabrese[34] isolated and characterized a series of mononuclear copper(II)–3,5-di-t-butyl-*o*-semiquinone complexes from reaction of the corresponding catechol or benzoquinone with dinuclear and mononuclear copper(II) or copper(I) complexes, respectively. It was concluded that the single-step two-electron oxidation of catechol by copper(II) complexes is not observed and *o*-benzoquinone was obtained only after exposure of copper(II)–*o*-semiquinone to dioxygen or by the addition of small molecules such as pyridine. Their studies indicated that the formation of mononuclear copper(II)–*o*-semiquinone complexes as an intermediate should be considered in catecholase-mimetic activity of copper(II) complexes. For the complexes used in this study, the geometry is distorted octahedral that contains the *trans*-$CuN_2O_2\cdots O_2$ chromophore,[13,15] and the dissociation of the acetate or valproate groups is very likely to provide sites on the copper(II) plane for catechol bonding. Optimal electron transfer rates would require equatorial coordination to copper(II) in order to maximize overlap between the catechol donor and the half-empty $d_{x^2-y^2}$ copper(II) orbital, and to form a copper–3,5-di-t-*o*-semiquinone-imidazole adduct, Cu^{I}(DTBSQ) $(im)_2$, as an intermediate during the oxidation process (Scheme 3), similar to Thompson and Calabrese's copper(II)–3,5-di-t-butyl-*o*-semiquinone diimine complexes.[34a]

The formation of the copper ion–DTBSQ complex intermediate during the oxidation process was demonstrated in this study by following the spectral



Scheme 3.

changes of two reaction mixtures: a reaction between the copper(I) complex with DTBQ and a reaction between the copper(II) complex and DTBC as described below. Copper(II) complex (**1** or **2**) in methanol was reduced to copper(I) by the stoichiometric amount of HQ under nitrogen. DTBQ was then added to the solution and its UV–vis spectrum was recorded. Two absorption bands appeared with time: one very broad band with moderate intensity centred at about 770 nm and a sharp, intense band at 385 nm. The [Cu(diamine)(DTBSQ)]ClO_4 complexes reported by Thompson and Calabrese[34a] gave rise to similar spectra (broad maxima between 825 and 770 nm with moderate intensity and a sharp, intense band in the 380–395 nm region). These features are also similar to $[Cu(DTBC)(DTBSQ)]^-$ prepared electrochemically, $DTBSQ^-$ and $Zn(DTBSQ)_2$.[35a,36] These are ligand $DTBSQ^-$ bands and differ significantly from those of copper(II)–catecholate complexes, which have no intense absorption bands in these regions.[36,37a,38] The spectral results of these reactions demonstrated that reduced copper ion is an electron donor for reaction with quinone, yielding the copper(II)–semiquinone complex. Similar electron transfer, but from metallic copper to *o*-benzoquinones, occurred from reactions of the metal with a wide variety of substituted benzoquinones in the presence of an additional ligand (L) to form [Cu^I–semiquinone–L_2] complexes.[39] The geometry of these complexes is tetrahedral and they show EPR spectra indicating that the unpaired electron is localized on the semiquinone radical.[39]

The formation of copper ion–DTBSQ species during the oxidation process was demonstrated in this study by following the UV–vis spectral changes of the actual catalytic reaction mixture. When 0.02 mmol of complex **1** or **2** and 0.44 mmol DTBC were mixed in 20 cm^3 degassed methanol under nitrogen, three absorption bands appeared with time (Fig. 3), 770 and 385 nm bands characteristic of DTBSQ and a less intense band at 570 nm. This band may arise from a catecholato to copper(II) charge transfer transition by analogy to assignments made for other monomeric copper(II)–catecholato complexes.[37] When this solution was exposed to aerial oxygen, the bands at 770 and 570 nm decayed and the band at 385 nm shifted to *ca* 400 nm. The final spectrum contains two bands in the visible region, the 686 nm band characteristic of *d–d* transitions of the copper(II) complexes **1** or **2**, and the

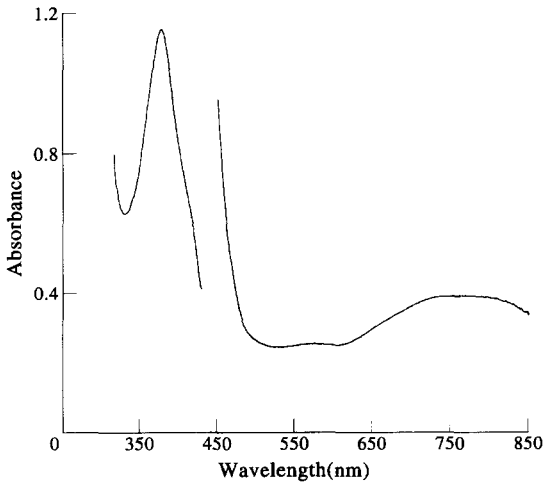


Fig. 3. Electronic spectrum of the reaction mixture between complex **2** (0.02 mmol) and DTBC (0.44 mmol) in 20 cm^3 methanol under nitrogen. The intense band at 385 nm is 10 times dilution of the mixture.

400 nm band characteristic of DTBQ.[31] Methanol was evaporated from the reaction mixture, the precipitate was extracted with anhydrous diethyl ether and filtered (complexes **1** and **2** do not dissolve in ether). Evaporation of the ether filtrate gave DTBQ, whose IR [CH_2Cl_2; ν(CO) = 1665 cm^{-1}], UV–vis (400 nm) and ^1H NMR [$CDCl_3$: δ 1.26 (1H), 6.20 (1H), 6.98 (18H)] spectra were compared with those of authentic DTBQ.

In addition to electronic spectra, IR spectra were used to provide information about the nature, i.e. catecholate or semiquinonate, of dioxolene ligands.[40] A very important feature of metal–catecholate complexes was the appearance of a rather intense IR band at about 1480 cm^{-1}. This band was also observed for free catechols and gained intensity upon coordination to a metal ion. It corresponds to a ring stretching mode.[40] Transition metal–semiquinone complexes usually have IR bands attributable to the C=O stretching modes in the range of about 1420–1460 cm^{-1}. IR spectra of complex **1** or **2** with DTBC in CH_2Cl_2 were obtained by mixing a stoichiometric amount of the complex with DTBC in CH_2Cl_2 under nitrogen. An IR band characteristic of the catecholate ligand was observed at about 1480 cm^{-1}, and several bands were observed at about 1470, 1460 and 1445 cm^{-1} characteristic of copper–DTBSQ species. These spectral observations are comparable with those reported previously, in which the DTBQ ligand present in both semiquinone and catecholate forms in transition metal complexes.[40] These IR results, along with the above electronic spectral results, indicate that both copper ion–catecholate and copper ion–semiquinone species are present in solution mixtures of copper(II) complexes and DTBC.

Kinetic data for the catalytic oxidation of DTBC revealed that the reaction rate has first-order dependence on the initial copper complex (**1** or **2**) and DTBC concentration, and may be expressed as:

$$\text{rate} = k_{obs}\,[\text{complex}]\,[\text{DTBC}].$$

Averaged values for the observed rate constants, k_{obs}, for the two catalysts, **1** and **2**, were found to be 5.6×10^5 M^{-1} min^{-1} and 6.5×10^5 M^{-1} min^{-1}, respectively. Collectively, the results obtained here and previously[34,35,41b] suggest that the oxidation of DTBC with these mononuclear copper(II) complexes proceeds by the mechanism:

$$\text{Step 1}: \mathrm{Cu(RCO_2)_2(im)_2} + \text{DTBC} \longrightarrow [\mathrm{Cu^{II}(DTBC^{2-})\,(im)_2}] + 2\text{RCOOH} \quad \textbf{(I)}$$

$$\text{Step 2}: \mathbf{I} \overset{\text{Internal electron transfer}}{\rightleftharpoons} [\mathrm{Cu^{I}(DTBSQ)(im)_2}] \quad \textbf{(II)}$$

$$\text{Step 3}: \mathbf{II} \xrightarrow{\text{oxidation}} \mathrm{Cu(RCO_2)_2(im)_2} + \text{DTBQ} + \mathrm{H_2O}.$$

In Step 1, two carboxylate groups are used to dehydrogenate the two hydroxyl groups of catechol, and complex **I** is formed (band at 570 nm and IR at 1480 cm^{-1}). In Step 2, an internal one-electron transfer from the coordinated catecholato dianion ($DTBC^{2-}$) to copper(II) gives the intermediate **II** (bands at 770 and 385 nm and IR at about 1470, 1460 and 1445 cm^{-1}), which is in equilibrium with **I**. In Step 3, air oxygen is used to oxidize copper(I) and DTBSQ to produce the copper(II) complex and DTBQ.

The internal electron transfer and the generation of the copper(I)–semiquinone which is in equilibrium with the copper(II)–catecholate (Step 2) have recently been demonstrated by Dooley and coworkers.[41b] Anaerobic substrate reduction of amine oxidase [a copper-containing enzyme which has imidazole ligands in its first coordination shell of copper(II) and 6-hydroxydopaquinone as another co-factor[41]] generates a copper(I)–semiquinone species which is in equilibrium with copper(II)-reduced quinone species. The copper(I)–semiquinone species was proposed to be the catalytic intermediate that reacts directly with oxygen and similar to the one suggested in this study. In addition, the internal electron transfer reactions between two isoelectronic couples, i.e. copper(II)–catecholate/copper(I)–semiquinonate and copper(II)–semiquinonate/copper(I)–quinone, were recently proposed in the reactivity properties of copper–dioxolene adducts.[42] The equilibrium between iron(II)–DTBSQ and iron(III)–catecholato have recently been demonstrated in the catalytic oxygenation of DTBC by $FeCl_3$ in a tetrahydrofuran–pyridine solvent system.[43] The formation of the iron(II)–DTBSQ species, which is the catalytic intermediate that reacts with oxygen, has been characterized by ESR ($g = 2.01$) and electronic spectroscopy (broad maximum centred about 760 nm).

CONCLUSIONS

Mononuclear copper(II) carboxylates with imidazole are effective catalysts for oxidation of the one-electron reducing agent TMPD. Simultaneous two-electron transfer from two molecules of TMPD to a dioxygen molecule through a dinuclear copper complex, as proposed previously,[16–19] is not necessary in the oxidation reaction. Finally, since the complex bis(acetato)bis(imidazole)copper(II) (**1**) was recently found to have antitumour activity and the copper(II) complex analogue of the anticonvulsant

drug valproate (**2**) has comparable catalytic activities to those of **1**, it would seem worthwhile to evaluate the antitumour activity of complex **2**.

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