Comparative Study of the Catalytic Oxidation of Catechols by Copper(II) Complexes of Tripodal Ligands

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Copper(II) complexes of the ligands tris(2-pyridylmethyl)amine (tpyma), tris(2-pyridylethyl)amine (tpyea), tris(3,5-dimethylpyrazol-1-ylmethyl)amine (tpzma) and tris(3,5-dimethylpyrazol-1-ylethyl)-amine (tpzea) were prepared. The complexes, [Cu(ligand)Cl]Cl or [Cu(ligand)(H_2O)][BF_4]$_2$, were characterized by a combination of absorption and EPR spectroscopies and chemical analysis. The ability of the complexes to oxidize 3,5-di-*tert*-butylcatechol to 3,5-di-*tert*-butyl-*o*-benzoquinone has been studied and the results show that the rate of reaction is dependent on the nature of the heterocyclic donor, its basicity, steric considerations, the chelate ring size and the type of exogenous donor present. Large variations in the rate were observed with the most effective catalysts being those with pyridine donors which formed six-membered chelate rings; the complex [Cu(tpyea)(H_2O)][BF_4]$_2$ was the most active while [Cu(tpzea)(H_2O)][BF_4]$_2$ and [Cu(tpzea)Cl]Cl were inactive. Electrochemical data for the series of compounds show that there is a non-linear relationship between their ability to oxidize catechols and their reduction potentials. The most effective catalysts were those complexes which exhibited reduction potentials close to 0.00 V, while those that deviated from that potential by 200–300 mV in either direction were largely inactive. Within the range of complexes which were active, a steric match between the substrate and the complex also largely defined their reactivity. Comparisons to the biological system tyrosinase are drawn.

Tripodal ligands continue to find extensive use in the synthesis of metal complexes because of their ease of preparation, the wealth of spectroscopic and X-ray crystallographic data which has been generated for their metal complexes, and the predictable changes in the physical properties of the metal complexes as the ligand sets are varied. We are particularly interested in using nitrogen-containing tripodal ligands as models for the protein backbone of the enzyme tyrosinase. Spectroscopic and physical studies indicate that this metalloenzyme has two copper atoms at the active site, each bound to three nitrogens of histidine residues from the protein backbone.[1–4] Tyrosinase is a monooxygenase and, as is shown in Fig. 1, it is responsible for the air oxidation of phenol to catechol (benzene-1,2-diol) (cresolase activity) and the subsequent oxidation of catechol to *o*-benzoquinone (catecholase activity).

Models for biological systems can be designed to reproduce the structural, spectroscopic or reactivity properties of the protein of interest. In this study we are particularly interested in developing a better understanding of the parameters which lead to effective catalysis for synthetic copper(II) complexes. Synthetic model studies of the reactivity of copper(II) complexes towards catechols implicate the geometry around the copper ions as the most dominant feature in determining the catalytic activity of the complexes.[5] Non-planar mononuclear complexes and binuclear complexes with the two coppers separated by *ca.* 3–4 Å catalyse the oxidation process, while square-planar mononuclear complexes and dinuclear complexes with a large Cu–Cu distance (>5 Å) are generally unreactive towards catechol.[6–17] No correlation between the redox potential of the copper complexes and the rate of the oxidation has been uncovered; instead, the determining factor is thought to be a steric match between the substrate and the copper ion. Systematic studies which selectively change the structural and electronic features of copper complexes and assess the effect on their catalytic properties should help explain which features of tyrosinase are primarily responsible for its activity. In addition, studies of this type would allow for the rational design and synthesis of more efficient catalysts.

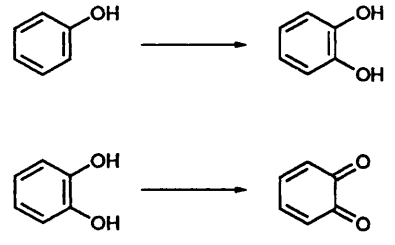


Fig. 1 Reactions catalysed by tyrosinase

There is a rich chemistry associated with the reactivity of copper complexes of tripodal ligands. Germane to this work are the reactivity studies on copper(I) complexes of quinoline and pyridine tripodal ligands which have been shown to form copper–oxygen complexes of varying stoichiometry depending on the nature of the ligand.[18,19] Kinetic and thermodynamic properties have been determined for the reactions between O_2 and the copper(I) tripodal complexes which show that ligand modifications dramatically effect the rate of formation and dissociation of the Cu–O_2 adducts.[20,21] Copper–oxygen adducts have been shown to be important intermediates in a number of protein active sites including tyrosinase,[22] haemocyanins,[23,24] amine oxidases,[25] phenylalanine hydroxylase[26] and dopamine B-hydroxylase.[27]

As part of our studies on the electron-transfer properties of copper(II) complexes, we have shown that the tripodal ligand tris(3,5-dimethylpyrazol-1-ylmethyl)amine (tpzma) forms copper(II) complexes which are capable of mediating electron transfer to both negative and positively charged

proteins.[28] Nafion-coated glassy carbon electrodes containing the copper(II) complex show electron transfer to cytochrome c or to tyrosinase, a result which is unobtainable with the untreated electrode. A second-order EC (electrochemical–chemical) catalytic reaction mechanism is operative at the reduction potential of the copper complex for both the reduction of cytochrome c and tyrosinase.

Along with their electron-transfer properties, we have also been probing the catalytic properties of copper(II) complexes.[6–8] The kinetic results for the oxidation of catechol to benzoquinone using the copper(II) complexes of the tripodal ligands tpzma and tris(3,5-dimethylpyrazol-1-ylethyl)amine (tpzea) have recently been reported.[8] The trigonal-bipyramidal tpzma complexes were found to act as efficient catalysts towards the oxidation of catechol, while the square-pyramidal complexes formed from tpzea did not catalyse this oxidation. Regardless of the various permutations present (monomeric or dimeric, the nature of the fifth ligand, or the counter ion), the copper(II) complexes of tpzma catalysed the oxidation of catechol and substituted catechols, while those of tpzea did not.

The lack of reactivity exhibited by the square-pyramidal tpzea complexes is striking since simple copper(II) salts such as $CuCl_2$ will catalyse the reaction. In order to determine whether the results obtained using the pyrazole-containing ligands are a general feature of the reactivity for trigonal-bipyramidal and square-pyramidal copper(II) complexes, the pyridine analogues of these two ligands, tris(2-pyridylmethyl)amine (tpyma) and tris(2-pyridylethyl)amine (tpyea) and a variety of their copper(II) complexes have been prepared. The reactivity of the complexes towards 3,5-di-*tert*-butylcatechol was studied using UV/VIS spectroscopy and the results compared to those previously found for the tpzma and tpzea complexes. In addition, electrochemical data were obtained in order to attempt to correlate the reduction potentials to the reactivity of the complexes.

Experimental

General.—All reagents and solvents were purchased from commercial sources and used as received unless noted otherwise. 1-(Hydroxymethyl)-3,5-dimethylpyrazole,[29] tris(3,5-dimethylpyrazol-1-ylethyl)amine (tpzea),[30] tris(3,5-dimethylpyrazol-1-ylmethyl)amine (tpzma),[8] and $[Cu(tpzea)(H_2O)][BF_4]_2$[30] were prepared by the literature methods. Melting points were obtained with the use of a Fisher-Johns apparatus and are uncorrected. The C, H and N elemental analyses were performed at Desert Analytical, Tucson, AZ. Metal contents were determined complexometrically by indirect titration with $Na_2(H_2edta)$ (H_4edta = ethylenediaminetetraacetic acid) and zinc acetate after destruction of the sample with concentrated nitric acid.[31]

Electronic spectroscopy was performed on a Uvikon 860 spectrophotometer using methanol as the solvent, while IR spectra were recorded on a Nicolet 5ZDX instrument. Proton NMR spectra were recorded on a Bruker WM 250 instrument using $CDCl_3$ as the solvent. All chemical shifts are reported in ppm relative to an internal standard of $SiMe_4$. X-Band EPR spectra were recorded on a Varian E-3 spectrophotometer at 77 K in methanol solution using diphenylpicrylhydrazyl (dpph) as the calibrating field marker. Kinetics were followed spectrophotometrically on a Uvikon 860 spectrophotometer by following the appearance of 3,5-di-*tert*-butyl-*o*-benzoquinone over time using the 390 nm peak. The metal complex (0.3 cm^3 of a 1×10^{-3} mol dm^{-3} methanol solution) and a 2.0 cm^3 solution (1×10^{-1} mol dm^{-3} methanol solution) of 3,5-di-*tert*-butylcatechol were added together in the spectrophotometric cell at 25 °C.

Electrochemistry was performed in an aqueous solution that was 0.1 mol dm^{-3} in Tris [tris(hydroxymethyl)methylamine] buffer. The concentration of metal complex was 1×10^{-3} mol dm^{-3}. All complexes undergo chemically reversible oxidation–reduction reactions at a glassy carbon electrode with an Ag–AgCl reference electrode and a platinum wire as the auxiliary electrode.

CAUTION: perchlorates may explode violently.

Syntheses of Ligands.—*Tris(2-pyridylmethyl)amine (tpyma).* To a solution of tris(2-pyridylmethyl)ammonium perchlorate[32] (6.0 g, 0.015 mol) in H_2O (200 cm^3) was added 5 mol dm^{-3} NaOH (40 cm^3). The solution was stirred at room temperature for 3 h and extracted with $CHCl_3$ (3 × 50 cm^3). The $CHCl_3$ solution was dried over Na_2SO_4, filtered, and evaporated to 10 cm^3. After cooling overnight to −20 °C, white crystals formed (2.66 g, 61%), m.p. 84–86 °C (lit.,[32] 84.5–86.5 °C); $\delta_H(CDCl_3)$ 4.05 (6 H, s, CH_2), 7.11–7.65 (9 H, m, py), 8.40–8.52 (3 H, d, py).

Tris(2-pyridylethyl)amine (tpyea). A solution of 2-vinylpyridine (25.0 cm^3, 0.238 mol) (purified by passage through an alumina column) and ammonium acetate (3.0 g, 0.039 mol) in MeOH–H_2O (2:1, 300 cm^3) was refluxed for 5 d. The solvent was evaporated, the residue dissolved in 20% NaOH (100 cm^3) and then extracted with CH_2Cl_2 (4 × 100 cm^3). The combined organic solvents were dried over Na_2SO_4, filtered and evaporated. The product was purified using flash chromatography on silica using MeOH as the eluent. A colourless oil (5.6 g, 43%) was obtained; $\delta_H(CDCl_3)$ 2.53 (6 H, t, CH_2), 3.02 (6 H, t, CH_2), 7.09–7.84 (9 H, m, py), 8.63–8.82 (3 H, d, py).

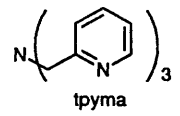
Syntheses of Metal Complexes.—$[Cu(tpyma)(H_2O)][BF_4]_2$ **1**. A solution of $Cu(BF_4)_2 \cdot 6H_2O$ (0.46 g, 1.3 mmol) in MeOH (25 cm^3) was filtered into a solution of tpyma (0.39 g, 1.3 mmol) in MeOH (10 cm^3). The solvent was reduced in volume to 5 cm^3 and diethyl ether was slowly added. Blue crystals (0.30 g, 43%) formed on standing at −20 °C (Found: C, 39.30; H, 4.05; Cu, 11.90; N, 10.40. $C_{18}H_{20}B_2CuF_8N_4O$ requires C, 39.65; H, 3.70; Cu, 11.65; N, 10.25%).

[Cu(tpyma)Cl]Cl **2**. A solution of $CuCl_2 \cdot 2H_2O$ (1.17 g, 6.88 mmol) in MeOH (50 cm^3) was filtered into a solution of tpyma (2.00 g, 6.88 mmol) in MeOH (25 cm^3). The solution was filtered and green-blue crystals (1.52 g, 52%) formed on standing at −20 °C (Found: C, 50.55; H, 4.70; Cu, 15.25; N, 12.95. $C_{18}H_{18}Cl_2CuN_4$ requires C, 50.90; H, 4.30; Cu, 14.95; N, 13.20%).

$[Cu(tpyea)(H_2O)][BF_4]_2$ **3**. A solution of $Cu(BF_4)_2 \cdot 6H_2O$ (2.08 g, 6.02 mmol) in MeOH (50 cm^3) was filtered into a solution of tpyea (2.00 g, 6.02 mmol) in MeOH (25 cm^3). Slow evaporation of the solvent in air led to the isolation of blue crystals (1.95 g, 55%) (Found: C, 43.20; H, 4.50; Cu, 10.85; N, 9.60. $C_{21}H_{26}B_2CuF_8N_4O$ requires C, 42.90; H, 4.45; Cu, 10.80; N, 9.55%).

[Cu(tpyea)Cl]Cl **4**. A solution of $CuCl_2 \cdot 2H_2O$ (1.03 g, 6.02 mmol) in MeOH (50 cm^3) was filtered into a solution of tpyea (2.00 g, 6.02 mmol) in MeOH (25 cm^3). Green crystals (2.05 g, 73%) formed on standing at −20 °C (Found: C, 54.35; H, 5.30; Cu, 13.70; N, 11.75. $C_{21}H_{24}Cl_2CuN_4$ requires C, 54.00; H, 5.20; Cu, 13.60; N, 12.00%).

$[Cu(tpzma)(H_2O)][BF_4]_2 \cdot H_2O$ **5**. A solution of $Cu(BF_4)_2 \cdot 6H_2O$ (2.04 g, 5.90 mmol) in MeOH (50 cm^3) was filtered into a solution of tpzma (2.00 g, 5.90 mmol) in MeOH (25 cm^3). On allowing the solution to stand overnight at −20 °C, blue crystals (1.67 g, 46%) were formed (Found: C, 35.55; H, 5.25; Cu, 10.40; N, 16.45. $C_{18}H_{31}B_2CuF_8N_7O_2$ requires C, 35.15; H, 5.10; Cu, 10.40; N, 15.95%).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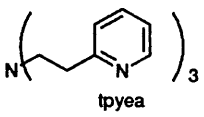
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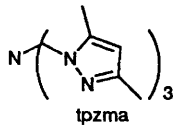
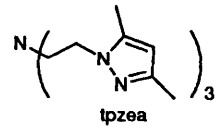

tpzma


tpzea

[Cu(tpzma)Cl]Cl **6**. A solution of $CuCl_2 \cdot 2H_2O$ (1.01 g, 5.90 mmol) in MeOH (50 cm^3) was filtered into a solution of tpzma (2.00 g, 5.90 mmol) in MeOH (25 cm^3). The solution was filtered, reduced in volume to 25 cm^3, and cooled to −20 °C from which small green crystals (1.71 g, 61%) formed (Found: C, 45.00; H, 6.00; Cu, 13.20; N, 20.55. $C_{18}H_{27}Cl_2CuN_7$ requires C, 45.45; H, 5.75; Cu, 13.35; N, 20.60%).

[Cu(tpzea)Cl]Cl **8**. To a solution of $CuCl_2 \cdot 2H_2O$ (1.13 g, 6.60 mmol) in MeOH (50 cm^3) was added tpzea (2.53 g, 6.60 mmol) in MeOH (25 cm^3). After filtration, the green solution was slowly treated with diethyl ether. It was cooled to −20 °C from yielding green crystals (1.23 g, 36%) (Found: C, 48.20; H, 6.30; Cu, 12.30; N, 18.75. $C_{21}H_{33}Cl_2CuN_7$ requires C, 48.70; H, 6.45; Cu, 12.25; N, 18.90%).

Results

Synthesis.—Pyrazole- and pyridine-containing ligands have found extensive use in a variety of multidentate ligands complexed to metal ions which serve as models for metalloproteins.[33] The donor ligands in this study were chosen because of their demonstrated similarity to the biological donor imidazole.[34] Tripodal compounds are attractive candidates for ligands because of the variety and predictability of geometries which are possible for their subsequent metal complexes.

Tris(2-pyridylmethyl)amine (tpyma) was synthesized using a modification of the method of Anderegg and Wenk[32] *via* the condensation of 2-(chloromethyl)pyridine and 2-(aminomethyl)-pyridine through the isolation of the intermediate perchlorate salt of the amine. Tris(3,5-dimethylpyrazol-1-ylmethyl)amine (tpzma) was synthesized from ammonium chloride and 1-(hydroxymethyl)-3,5-dimethylpyrazole using the method of Driessen[29] for the pyrazolylmethylation of amines, while tris(2-pyridylethyl)amine (tpyea) was prepared from ammonium acetate and 2-vinylpyridine using an adaptation of Reich and Levine[35] for the pyridylethylation of amines. Tris(3,5-dimethyl-pyrazol-1-ylethyl)amine (tpzea) was prepared from tris(2-chloroethyl)amine and the 3,5-dimethylpyrazolate anion as described by Sorrell and Jameson.[30]

A variety of copper(II) complexes formed from these ligands were isolated in crystalline form. A methanolic solution of the ligand was added to either $Cu(BF_4)_2 \cdot 6H_2O$ or $CuCl_2 \cdot 2H_2O$ in methanol from which the complexes were isolated directly.

Spectroscopy.—Elemental analyses, EPR spectroscopy and electronic spectroscopy show the complexes to exist as five-co-ordinate species of the form $[Cu(ligand)(H_2O)][BF_4]_2$ or [Cu(ligand)Cl]Cl. In the case of tpzma with $Cu(BF_4)_2 \cdot 6H_2O$ two different complexes can be isolated, a blue form and a green one. The blue compound has been identified as a dimer of formula $[Cu_2(tpzma)_2F(H_2O)_2][BF_4]_3$ in the solid state.[36] Evidence for its formulation as a dimer came from elemental analysis, solid-state EPR spectroscopy and the crystal structure of the analogous cobalt complex. However, it was shown by conductivity studies that even in nitromethane, the dimer breaks down to monomeric cations. In our work, we have isolated the green complex and studied its solution properties by EPR spectroscopy and electrochemistry (see later); neither technique shows evidence of a dimer in solution and the elemental analysis is consistent with the formulation $[Cu(tpzma)(H_2O)][BF_4]_2 \cdot H_2O$.

Copper(II) complexes formed from tripodal ligands typically exist as five-co-ordinate species of either trigonal-bipyramidal or square-pyramidal geometry, depending on the length of the arms connecting the donor atoms. It has previously been shown using a combination of X-ray crystallography, electronic spectroscopy and EPR spectroscopy that numerous copper(II) complexes formed from tpzea and tpyea (which have three atoms separating the donor atoms) exist both in solution and in the solid state as five-co-ordinate mononuclear species with square-pyramidal geometry.[30,37] In comparison, complexes of tpzma and tpyma (which have two atoms separating the donors) generally form copper(II) complexes with trigonal-bipyramidal geometry.[36,38] Chemical and spectroscopic analyses of the copper(II) complexes prepared here are in accord with those assignments.

Electronic and EPR spectroscopic data for the complexes are given in Table 1. The EPR spectra for complexes of tpyea and tpzea display $g_{\|} > g_{\perp} > 2.00$ and $A_{\|} = (120–150) \times 10^{-4}$ cm^{-1}, typical of a square-pyramidal geometry.[39] An illustration of this is the frozen solution spectrum of $[Cu(tpzea)(H_2O)][BF_4]_2$ **7** which has $g_{\|} = 2.23$, $g_{\perp} = 2.09$ and $A_{\|} = 156 \times 10^{-4}$ cm^{-1}. This is in contrast to complexes formed from tpyma and tpzma which give EPR spectra consistent with a trigonal-bipyramidal geometry ($g_{\perp} > g_{\|} > 2.00$, $A_{\|} = (60–100) \times 10^{-4}$ cm^{-1}). For example, for [Cu(tpyma)Cl]Cl **2** $g_{\|} = 1.98$, $g_{\perp} = 2.26$ and $A_{\|} = 80 \times 10^{-4}$ cm^{-1}.

Unlike the results from the solid-state analysis of $[Cu_2(tpzma)_2F(H_2O)_2][BF_4]_3$,[36] in the frozen solution EPR spectrum of the green complex formed from tpzma and $Cu(BF_4)_2 \cdot 6H_2O$ a half-field signal is not observed. Along with the electrochemical results described below, we believe that the complex exists as $[Cu(tpzma)(H_2O)][BF_4]_2$ in the solid state and in solution.

The electronic absorption spectra of five-co-ordinate copper(II) complexes also fall into two general categories.[40] Square-pyramidal complexes typically show a high-energy absorption band in the visible region with a low-energy shoulder. In contrast, trigonal-bipyramidal complexes have a low-energy absorption band with a high-energy shoulder in the visible region. As shown in Table 1, the results for complexes **1**–**8** are consistent with these criteria. For example, the electronic spectrum of [Cu(tpyea)Cl]Cl **4** shows a visible absorption band maximum at 660 nm (ε 185 dm^3 mol^{-1} cm^{-1}) with a low-energy shoulder at 950 nm (ε 54 dm^3 mol^{-1} cm^{-1}). In contrast, the electronic spectrum of [Cu(tpzma)Cl]Cl **6** shows a maximum at 855 nm (ε 225 dm^3 mol^{-1} cm^{-1}) with a high-energy shoulder at 708 nm (ε 77 dm^3 mol^{-1} cm^{-1}).

Electrochemistry.—The cyclic voltammetric data for complexes **1**–**8** are shown in Table 2, and cyclic voltammograms of the representative complexes $[Cu(tpyea)(H_2O)][BF_4]_2$ **3** and [Cu(tpyma)Cl]Cl **2** are shown in Fig. 2. In all cases, a one-electron reduction is observed. This is of particular

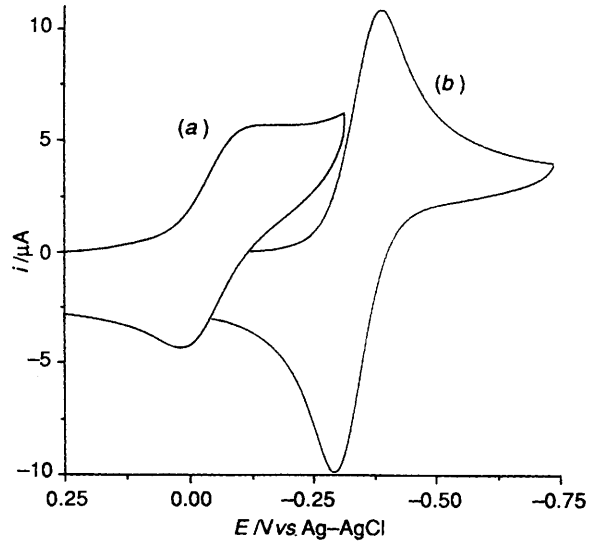


Fig. 2 Cyclic voltammograms for: (*a*) $[Cu(tpyea)(H_2O)][BF_4]_2$ **3** (0.5 mmol dm^{-3} solution, $E_{\frac{1}{2}} = -0.032$ V, $\Delta E_p = 0.15$ V) and (*b*) [Cu(tpyma)Cl]Cl **2** (1.0 mmol dm^{-3} aqueous solution, $E_{\frac{1}{2}} = -0.32$ V, $\Delta E_p = 0.073$ V). Both scans recorded in 0.1 mol dm^{-3} Tris buffer (pH 7.0) at a scan rate of 0.050 V s^{-1} against a Ag–AgCl reference electrode

Table 1 UV/VIS absorption data and EPR spectral data for copper complexes **1–8**

	UV/VIS	EPR		
Complex	λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1})	$g_{\|}$	$g_{\perp}$	$10^4 A_{\|}$/cm^{-1}
1 [Cu(tpyma)(H_2O)][BF_4]$_2$	930 (205), 640 (85)	1.99	2.22	90
2 [Cu(tpyma)Cl]Cl	855 (225), 708 (77)	1.98	2.26	80
3 [Cu(tpyea)(H_2O)][BF_4]$_2$	890 (70), 680 (240)	2.27	2.01	160
4 [Cu(tpyea)Cl]Cl	950 (54), 660 (185)	2.21	2.02	154
5 [Cu(tpzma)(H_2O)][BF_4]$_2$	847 (210)	2.03	2.26	85
6 [Cu(tpzma)Cl]Cl	708 (77), 855 (225)	1.98	2.26	80
7 [Cu(tpzea)(H_2O)][BF_4]$_2$	800 (63), 660 (61)	2.23	2.09	156
8 [Cu(tpzea)Cl]Cl	760 (70), 630 (60)	2.19	2.06	150

Table 2 Catalytic activities and cyclic electrochemical* data for copper complexes **1–8**

Complex	Activity (μmol substrate per mg catalyst per min)	$E_{\frac{1}{2}}$/V
1 [Cu(tpyma)(H_2O)][BF_4]$_2$	0.000 471	−0.31
2 [Cu(tpyma)Cl]Cl	0.001 34	−0.32
3 [Cu(tpyea)(H_2O)][BF_4]$_2$	84.9	−0.03
4 [Cu(tpyea)Cl]Cl	63.2	−0.04
5 [Cu(tpzma)(H_2O)][BF_4]$_2$	0.523	+0.06
6 [Cu(tpzma)Cl]Cl	0.238	−0.01
7 [Cu(tpzea)(H_2O)][BF_4]$_2$	No reaction	+0.21
8 [Cu(tpzea)Cl]Cl	No reaction	+0.32

* Electrochemistry was performed in a solution that was 0.1 mol dm^{-3} in Tris buffer. The concentration of metal complex was 1×10^{-3} mol dm^{-3}. All complexes undergo chemically reversible oxidation–reduction reactions at a glassy carbon electrode with an Ag–AgCl reference electrode and a platinum wire as the auxiliary electrode.

importance in the case of [Cu(tpzma)(H_2O)][BF_4]$_2$ **5** since the blue form was formulated as a dimer in the solid state.[36] The electrochemical data, along with the EPR results previously described, establish that the complex exists as a monomer in solution. The reduced forms of complexes **1–8** all display reasonable chemical stability on the time-scale of the cyclic voltammetry experiment; ratios of reverse to forward currents (i_a/i_c) range between 0.72 and 1.00 at a scan rate of 0.050 V s^{-1}.

The electrochemical data show that the reduction potentials of the bound copper(II) species depend more on the nature of the resulting chelate ring than on the fifth donor or counter ion. In general, the $E_{\frac{1}{2}}$ values for the complexes which form six-membered chelate rings (tpzea and tpyea) are more positive than the corresponding complexes which form five-membered rings (tpzma and tpyma). These values are in accord with what is expected as the size of the chelate ring is changed.[37] Significant (and predictable) electronic differences can be built into metal complexes by changing the length of the tripodal arms connecting the donor atoms.

When the fifth donor is changed from chloride to H_2O, and the counter ion from Cl to BF_4, the reduction potentials of complexes formed with the same tetradentate ligand change very little. It can also be gleaned from the $E_{\frac{1}{2}}$ values that pyrazole-containing complexes have more positive reduction potentials than the corresponding pyridine complexes. This is illustrated by comparing complex **7** ($E_{\frac{1}{2}}$ = 0.21 V) with **3** ($E_{\frac{1}{2}}$ = −0.03 V). These results suggest that the pyrazole-containing ligands are weaker ligands than the pyridine ones and that the co-ordination environment of the complexes is softer for the pyrazole complexes.[41] Similar results have been found for other pyrazole and pyridine systems.[42] Consequently, differences in the chelate ring size and the nature of the heterocyclic donor largely determine the electrochemical properties of the complexes.

Reactivity with 3,5-*Di*-tert-*butylcatechol*.—The reactivity of the copper(II) complexes **1–8** towards 3,5-di-*tert*-butylcatechol under catalytic conditions (0.3 cm^3 of a 1.0×10^{-3} mol dm^{-3} methanol solution of catalyst and 2.0 cm^3 of a 0.1 mol dm^{-3} methanolic solution of 3,5-di-*tert*-butylcatechol) in the presence of atmospheric O_2 was studied using electronic spectroscopy by following the appearance of the absorption maximum of the quinone at 390 nm over time. The results of the oxidations are presented in Table 2 and it is clear that there are profound differences in the ability of the complexes to catalyse the oxidation reaction.

Discussion

The two-electron oxidation of substituted *o*-catechols to quinones was investigated because this is one of the reactions that the copper-containing enzyme tyrosinase catalyses. There are a number of factors which need to be considered in explaining the differences in the catalytic properties of complexes **1–8**. These include (*a*) the electrochemical properties of the complexes, (*b*) the geometry imposed by the ligands on the metal ion, (*c*) the nature of any exogenous donors, (*d*) the basicity of the donor atoms and (*e*) the steric features of the ligands. Of these factors, (*b*), (*c*), (*d*) and (*e*) are inherent features of the molecules while factor (*a*) is a secondary effect derived from those. All of these factors will be considered sequentially.

Electrochemical Considerations.—Upon oxidizing catechol, both tyrosinase and the synthetic copper(II) complexes studied here are reduced to Cu^{I}. Therefore, electrochemistry was used to establish whether there is a correlation between the redox potential and catalytic capabilities of the copper complexes and to assess the ease of reduction of the complexes. A comparison of the $E_{\frac{1}{2}}$ values for the eight complexes studied with the observed catalytic properties yields a number of interesting results. First, the four complexes with appreciable activity in the oxidation of 3,5-di-*tert*-butylcatechol (**3–6**) have reduction potentials intermediate between the most positive and negative potentials in the group. Thus, complexes exhibiting reduction potentials close to 0.00 V demonstrate activity, while those that deviate from that potential by 200–300 mV in either direction lead to significant or complete loss of activity. Complexes **7** and **8** have the most positive reduction potentials and, as a result, are catalytically inactive since the pyrazole donors stabilize the Cu^{I} site at the expense of the Cu^{II} form; at the other extreme, complexes **1** and **2** have the most negative potentials and are difficult to reduce from the Cu^{II} state.

Other attempts to compare the redox properties of copper(II) complexes with catalytic activity have failed to show a direct correlation.[5] While our data do suggest an interdependency between the catalytic properties of the complexes and their redox potentials, it is clear that electronic effects do not totally control the reactivity and that other factors are also at work in the catalytic cycle. This is best illustrated by examining the reactivity of complexes **4** (63.2 μmol substrate per mg catalyst

per min) and **6** (0.238 μmol substrate per mg catalyst per min) which have virtually identical reduction potentials but enormously different rates of reaction. There are other examples of copper(II) complexes which have essentially identical reduction potentials but drastically different catalytic properties.[11] The origin of these differences in reactivity will be discussed below. Regardless of these other factors though, one can assume that a balance between ease of reduction (more positive reduction potential) and subsequent reoxidation (more negative reduction potential) by molecular oxygen must be maintained for efficient catalysis to occur; this would imply that a window of $E_{\frac{1}{2}}$ values exists wherein effective catalysis can take place. If the reduction potential is too negative, reduction to Cu^{I} would be unattainable; on the other hand, if the reduction potential is too positive, the catalytic cycle would be short-circuited because once reduced to Cu^{I}, the complexes would be unable to be easily reoxidized to Cu^{II} by O_2. Within a certain range of $E_{\frac{1}{2}}$ values catalysis is possible, while outside that range the drop off in rate is quite significant.

It should be noted that the enzyme tyrosinase isolated from mushroom (*Agaricus bisporus*) has a reported value for E_o of 0.36 V *vs.* the standard calomel reference;[43] this value lies at the positive end of the series of our complexes. It is obvious however, that the enzyme has been able to balance successfully the requirements of the different oxidation states of the metal in performing its catalytic tasks.

Geometrical Effects.—The geometry of the pyrazole-containing complexes was probed in our earlier work.[8] The data for complexes **1**–**8** show that first, and most importantly, the square-pyramidal complexes $[Cu(tpzea)(H_2O)][BF_4]_2$ **7** and [Cu(tpzea)Cl]Cl **8** are unique in their inability to catalyse the oxidation of 3,5-di-*tert*-butylcatechol. As shown in Table 2, the square-pyramidal complexes $[Cu(tpyea)(H_2O)][BF_4]_2$ **3** and [Cu(tpyea)Cl]Cl **4** do catalyse the oxidation reaction. Our original premise that a geometrical effect may be responsible for the lack of reactivity of the square-pyramidal tpzea complexes is clearly inoperative since complexes of tpyea catalyse the reaction, as do the trigonal-bipyramidal tpzma and tpyma complexes. Therefore, in considering five-co-ordinate copper(II) complexes, either square-pyramidal or trigonal-bipyramidal complexes are capable of serving as catalysts for oxidation reactions so other factors must be responsible for the differences in rate.

Exogenous Donors.—We have previously shown that changing the nature of the fifth donor atom, the counter ion, or any bridging group bound to the copper ions has an effect on the rate of catalysis.[6,7] In addition, it has been shown that electron transfer from catechol to Cu^{II} can begin only after catechol and the Cu^{II} species form a Cu^{II} catecholate intermediate;[44] this situation would require a vacant co-ordination site on the metal so that complexation of the catechol can occur. The results for the complexes described here affirm that the reaction is dependent on either the rate of dissociation of the fifth donor, or the differences in the dissociation constants for the loss of the fifth donor. This is evident when one compares the reactivity of the systems having the same tetradentate ligand but different fifth donors, such as $[Cu(tpyma)(H_2O)][BF_4]_2$ **1** and [Cu(tpyma)Cl]Cl **2**. In these cases, the activities are 4.71×10^{-4} and 1.34×10^{-3} μmol substrate per mg of catalyst per min respectively. However, when comparing different ligand sets with identical fifth donors, no trend which would correlate the nature of the fifth donor with the reactivity of the complex is apparent. The differences in rate as a result of changes in the fifth donor are relatively minor compared to other effects described below. Since the catalysis is performed in methanol, the relatively small differences may be a result of the formation of $[Cu(ligand)(CH_3OH)]^{2+}$ *via* a solvolysis reaction which occurs after dissociation of the fifth donor.

Basicity.—The fourth consideration in assessing the reactivity of these complexes is the basicity of the donor atoms. Pyrazole has a pK_b value of 11.5 while pyridine has $pK_b = 8.7$.[45] Since the biological donor imidazole has a pK_b value of 7.0, this suggests that if basicity alone is considered, pyridine is a better mimic for imidazole. Analogous to results found for the tpyma ligand and its quinoline ($pK_b = 9.1$) derivatives,[19] replacing pyridine by pyrazole should result in a more stable Cu^{I} for the pyrazole complexes because of its higher pK_b. This feature will affect the reduction potentials of the complexes by shifting the pyrazole $E_{\frac{1}{2}}$ values to more positive values compared to their pyridine counterparts. In contrasting complexes **1** with **5** or **2** with **6**, it can be seen that this is the case. The data are consistent with the premise that the basicity of the donor atoms is one of the primary factors in modulating the resultant electrochemical properties of the complexes.

Steric Considerations.—There are a number of studies[19,30,41,46] on complexes of tripodal ligands which have considered the impact of changing the steric features of the ligands on the stability of the oxidized and reduced forms of the Cu^{I}–Cu^{II} couple; two are pertinent to the work described here. Sorrell and Jameson[30] have shown that as the steric bulk on a series of pyrazole ligands (one of which was tpzea) is increased, the Cu^{I} form is stabilized resulting in more positive reduction potentials for the sterically hindered complexes. Karlin and co-workers[19] reported similar effects when pyridine donors are replaced by the bulkier quinoline, suggesting that the change to non-polar quinolyl substituents leads to increased hydrophobicity which stabilizes the lower charged species (Cu^{I} over Cu^{II}).

Karlin *et al.*[21] have also generated oxygen complexes from their tripodal species where the differences in the relative stabilities of the oxygen complexes are attributed to steric factors. When exposed to the atmosphere at −80 °C, the copper(I) complex $[Cu(tpyma)(MeCN)]^{+}$ was shown to react *via* the initial reversible formation of the 1:1 $Cu:O_2$ complex $[Cu(tpyma)(O_2)]^{+}$ which reacts reversibly with the starting Cu^{I} species to form the 2:1 complex $[\{Cu(tpyma)\}_2(O_2)]^{2+}$.[21] In contrast, the complex with three quinoline donors is much bulkier than the pyridine-containing complex and as a result is unreactive towards O_2. A similar result was found as the size of the alkyl substituents was increased on the pyrazole arms of tpzea.[30] It is possible that similar copper–oxygen species exist during the reaction of the tripodal-containing complexes with 3,5-di-*tert*-butylcatechol prepared here; however, we have not probed the detailed mechanism of the reactions.

Differences in the steric features of the ligands can be manifested in a variety of ways. These include differences in the hydrophobicity of the complexes, accessibility of the substrate to the metal ion due to the steric bulk of the ligand, and the extent of the steric match between the substrate and the complex. If any of these steric considerations are important, the reactivity properties of the copper(II) complexes should be affected. An examination of Table 2 shows that the pyridine-containing complexes $[Cu(tpyea)(H_2O)][BF_4]_2$ **3** and [Cu(tpyea)Cl]Cl **4** are significantly more reactive than the corresponding pyrazole complexes $[Cu(tpzma)(H_2O)][BF_4]_2$ **5** and [Cu(tpzma)Cl]Cl **6**, even though their redox potentials are very similar. Activity values for the oxidation of 3,5-di-*tert*-butylcatechol by mononuclear copper(II) complexes typically fall in the range $(0.5–1) \times 10^{-3}$ μmol substrate per mg of catalyst per min.[6–8] However, complexes formed from the pyridine-containing tpyea have significantly higher rates of reaction, and indeed are the most active catalysts that we have studied.

There are other examples of enhanced reactivity for pyridine over pyrazole containing copper complexes. The most striking example is the hydroxylation of aromatic moieties by N_6 pyridine complexes while the analogous N_6 pyrazole systems do not activate O_2 for this reaction.[42,47,48] It has been hypothesized that the geometry needs to be optimized for

correct orientation of the bound peroxo group and the arene ring in order for hydroxylation to occur.[47] A more optimal steric match between complexes **3** and **4** and catechol or O_2 compared to that found for complexes **5** and **6** may be partly responsible for the differences in their reactivity towards catechols.

However, if steric factors were exclusively responsible for controlling the rates of reaction, then the pyrazole-based complexes should have slower rates than the corresponding pyridine-based complexes. As shown in Table 2, this is not always the case. Although complexes **3** and **4** are appreciably more reactive than **7** and **8**, the pyrazole-containing **5** and **6** are actually more reactive (by 10^2–10^3 times) than are **1** and **2**. It seems, then, that both the electrochemical properties of the molecules and their steric features determine whether or not the complexes will be active catalysts.

Conclusion

A series of square-pyramidal and trigonal-bipyramidal copper(II) complexes formed from tetradentate pyridine- and pyrazole-containing ligands have been prepared in an attempt to uncover the predominant features which define their catalytic action. In contrast to earlier work on pyrazole-containing ligands, the results for the pyridine complexes show that trigonal-bipyramidal and square-pyramidal copper(II) complexes can act as catalysts for the oxidation of catechols.

It is clear that substantial differences in catalytic ability can be built into copper(II) complexes by the judicious choice of ligand sets. The rate of catalysis for copper(II) complexes is linked to both the redox potentials and the steric match between the substrate and the complex. Substantial retardation of reactivity is evident if either steric or electronic factors are not optimal. Having a reduction potential in the appropriate range is of crucial importance in defining catalytic activity, however, this is a necessary but not sufficient requirement for truly effective catalysis. Although the electronic features determine whether catalysis will proceed, the steric match between the substrate and the catalyst is also of crucial importance. In complexes with identical reduction potentials, the pyridine-containing systems have substantially higher rates of reaction than do their pyrazole counterparts. This result suggests that a more optimal steric match exists between the pyridine complexes and catechol or O_2 than exists for the pyrazole systems. Efforts towards preparing copper(II) complexes with pyridine donors which have reduction potentials of intermediate values are being undertaken to determine whether these complexes can serve as more efficient catalysts.

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