Oxidation Reactions of a Macrocyclic Dinuclear Copper(I) Dioxygen Complex and a Dinuclear Copper(II) Complex

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Recently a solution phase copper(I) dinuclear complex of the ligand 3,6,9,16,19,22-hexaazatricyclo-[22.2.1.1^{11,14}]-octacosa-1(26),2,9,11,13,15,22,24-octaene, $(FD)_2(DIEN)_2$ (**1**), and its dioxygen adduct were spectroscopically characterized. In this report, the use of the dinuclear complex in performing oxidation reactions with hydroquinones, phenols, catechols, ascorbic acid, and 3,4-dimethylaniline in a 3:1 mixture of methanol and acetonitrile is described. It has been determined that the copper(I) dioxygen complex of $(FD)_2(DIEN)_2$ (**3**) catalytically converts hydroquinones to the corresponding benzoquinones, ascorbic acid to dehydroascorbic acid, and phenols to their 1,4-benzoquinones and diphenoquinones, in the presence of excess dioxygen. Turnover numbers range between 5 and 20 h^{-1}. Under the same conditions 4-*tert*-butylcatechol (4-TBC) was transformed to the γ-lactone of the corresponding muconic acid ester, 3,5-di-*tert*-butylcatechol (3,5-DTBC) was oxidized to the corresponding 1,2-benzoquinone, and 3,4-dimethylaniline (3,4-DMA) was converted to 3,4-nitrosobenzene, all with turnover numbers of less than 1. These reactions were found to occur under stoichiometric conditions as well. Hydroquinones, phenols and ascorbic acid, but not catechols and 3,4-DMA, were also found to be oxidized, under stoichiometric conditions, by a dinuclear copper(II) complex **5**, prepared from the 2:1 stoichiometric reaction between $CuCl_2$ and **1** in methanol. The rates for the stoichiometric oxidations were determined to be 5 to 100 times greater for copper(I)–dioxygen oxidations than for corresponding copper(II) oxidations. On the basis of these observations, a catalytic scheme based on the copper(I) complex as the initial active species is proposed. The following steps are suggested: (i) formation of a dinuclear copper(I)–dioxygen adduct, (ii) oxidation of the substrate by the dioxygen adduct with simultaneous formation of a Cu(II) dinuclear complex, and (iii) oxidation of the substrate by the copper(II) complex to produce a copper(I) dinuclear complex and the oxidation product of the substrate.

Introduction

The enzyme tyrosinase is a copper-containing monooxygenase which functions as a creolase (performing ortho hydroxylation of phenols) and a catecholase (performing oxidation of catechols). Increasing interest in the understanding of the oxygen absorption and reaction characteristics of this enzyme led researchers to prepare low molecular weight copper(I) complexes,[1-18] several of which were shown to be spectroscopic analogs of the active site of tyrosinase.[2,7,19,20] A μ-peroxo center, which is electronically coupled,[21,22] is formed at the dinuclear copper sites on oxygenating the enzyme. The existence of related dinuclear copper(II) complexes, containing a bridging peroxo group, has been demonstrated.[1,6-9,11,12,15-17,23] Among others, one disadvantage of these model complexes is that they have been found to be stable for an extended period of time only at low temperatures (–60 to –80 °C). The work described in this paper has focused on the preparation and room temperature investigation of the oxidation properties of dinuclear copper(I) macrocyclic dioxygen complexes. Such systems have been chosen because of their inherent stability[24] and for the reason that the rigidity of the metal centers permits examination of the important role of metal–metal separation in accomodating a peroxo bridge in a manner similar to the dinuclear copper centers of tyrosinase. Generation of a dinuclear copper(I) macrocyclic complex, $[Cu_2(MX)_2(DIEN)_2^{2+}]$[25] (where MX represents a bridging *m*-xylyl moiety), has been previously reported and this complex was successfully used in hydroxylating an endogenous xylyl function. Attention is now turned to the search for model systems with oxidation properties which mimic the catecholase activity of tyrosinase.

A previous investigation[26] presented spectroscopic evidence for the generation of a relatively long-lived dinuclear copper(II) peroxo bridged intermediate **3**[27] on oxygenating a solution

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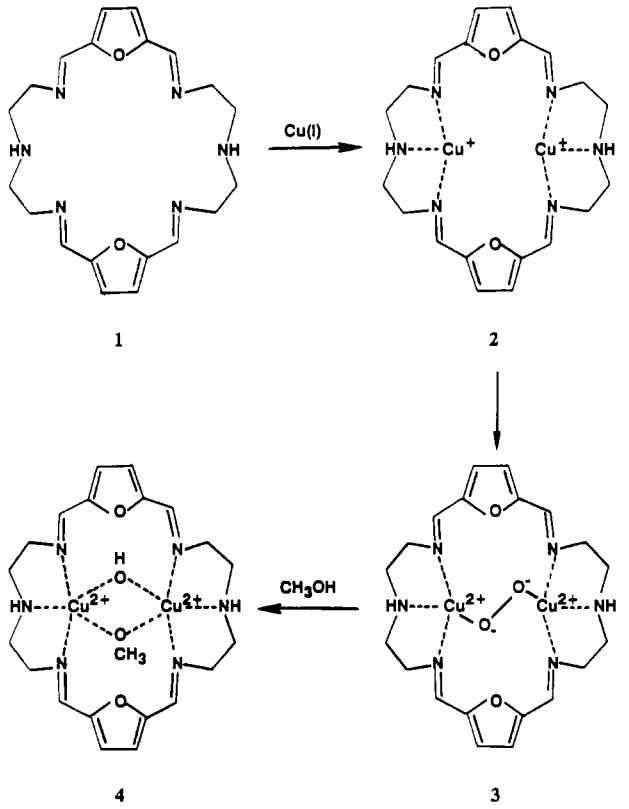
Scheme I



containing the Cu(I) complex, **2**, of $(FD)_2(DIEN)_2$ (**1**) at room temperature (Scheme I). The oxygenated dinuclear Cu(I) complex degrades to a dinuclear macrocyclic complex, **4**, with a half-life of about 1 h. A dinuclear copper(II) complex of $(FD)_2(DIEN)_2$ (**5**) was also prepared and was found to possess spectroscopic properties similar to the degradation product **4** in the solution phase. Although several such model systems with copper(I) dioxygen complexes have been prepared, relatively few studies[28-30] have reported their reactivities in relation to externally introduced substrates. This type of investigation is considered to be important since oxygen activation capabilities of model complexes are pertinent to biological studies and organic synthesis. Presented here are the studies of oxidation reactions of hydroquinones, phenols, ascorbic acid, catechols, and 3,4-dimethylaniline with oxygenated $[Cu_2(FD)_2(DIEN)_2^{2+}]$ (**3**) and a copper(II) complex of $(FD_2)(DIEN)_2$ (**5**), at room temperature. A brief preliminary report of these reactions has appeared in the literature.[31]

Experimental Section

Instrumentation. The products of oxidation reactions were characterized by standard techniques such as melting point determination, proton and carbon 13 nuclear magnetic resonance spectroscopy, and infrared spectroscopy. Melting points were determined on a Fisher-Johns melting point apparatus. ^1H and ^{13}C nuclear magnetic resonance spectra were recorded on a Varian XL 200 FT spectrometer. Chemical shifts are reported relative to tetramethylsilane as an internal standard. Infrared spectra were recorded on an IBM IR/44 Version 1.0 FT spectrophotometer with samples prepared as KBr pellets. Ultraviolet–visible spectral measurements were made on a Perkin-Elmer Model 553 fast-scan spectrophotometer. Oxygen absorption measurements were made as previously described.[32]

Materials. Reagent grade anhydrous methanol was obtained from Baker Chemicals and stored over a molecular sieve (Davison 4 A Grade 514). Reagent grade anhydrous acetonitrile was obtained from EM Chemicals and was also stored over a molecular sieve before use. Solid hydroquinones, phenols, and catechols were obtained from Aldrich Chemical Co. Tetra-*tert*-butylhydroquinone was recrystallized from a methanol/chloroform mixture and 2,6-di-*tert*-butylphenol was recrystallized from methanol. Ascorbic acid was obtained from Fisher Scientific and recrystallized from ethanol before use. All other reagents were obtained from Aldrich Chemical Co. and were used without further purification.

Preparations. 3,6,9,16,19,22-Hexaazatricyclo[22.2.1.$1^{11,14}$]octacosaneocta-1(26),2,9,11,13,15,22,24-ene, $(FD)_2(DIEN)_2$, was prepared as previously described.[26]

Stoichiometric Oxidation Reactions. (A) Reactions with $[Cu_2(FD)_2(DIEN)_2]^{2+}$ and Dioxygen. The reaction vessel was equipped with inlet and outlet adapters for argon and oxygen purging and evacuation and a manometer for maintaining the pressure of oxygen at 1 atm. The general procedure involved generating the peroxo-bridged complex **3** by dissolving approximately 0.11 mmol of **1** in 20 mL of degassed methanol and adding a stoichiometric amount of $Cu(CH_3CN)_4PF_6$ dissolved in 10 mL of degassed acetonitrile, followed by oxygenation of the reaction system at ~5 °C for 15 min. The excess oxygen was removed by evacuating the reaction system and purging with argon. The substrate was introduced in excess and the reaction was allowed to take place at room temperature until oxygen absorption ceased. The results of each reaction are summarized in Table I.

Oxidation of Hydroquinones. Hydroquinone (HQ). The substrate (18.7 mg) was added to a solution of the oxygenated form of **2** (prepared, according to the general procedure stated above, with 61.2 mg of **1** and 119 mg of $Cu(CH_3CN)_4PF_6$). When oxygen absorption ceased, the solvent was reduced to approximately 3 mL on a rotary evaporator and the remaining solution was chromatographed on silica gel (grade 62 special). The first component eluted from the column with *n*-hexane was identified as a mixture of HQ and benzoquinone. The amount of benzoquinone was calculated as 67% from the ^1H NMR spectrum of the mixture giving a yield of 1.54 mg (11%). ^1H NMR ($CDCl_3$) (benzoquinone): δ 5.30 (s). ^{13}C NMR ($CDCl_3$): δ 136.50 (C=C), 187.2 (C=O).

***tert*-Butylhydroquinone (TBHQ).** The hydroquinone (28.2 mg) was reacted with **3**, which was prepared with 61.7 mg of **1** and 120 mg of $Cu(CH_3CN)_4PF_6$. When the reaction terminated, the solvent was reduced to approximately 3 mL on a rotary evaporator and chromatographed on silica gel. Elution with *n*-hexane produced an initial fraction which ^1H NMR showed to be an impurity and a second fraction which was identified as *tert*-butylbenzoquinone (29.1 mg, 33%). ^1H NMR ($CDCl_3$): δ 1.29 (s, 9H) 6.68 (d, 1H) 6.60 (t, 2H). ^{13}C NMR ($CDCl_3$): δ 29.05 (CH_3), 35.25 ($C(CH_3)_3$), 131.48 ($CCC(CH_3)_3$), 134.88 (CCO), 138.63 (CCCO), 156.02 ($CCC(CH_3)_3$), 187.50 (CO), 188.30 (CO). Mp: 58–60 °C; lit. 56–57 °C.

Oxidations of Phenols. 2,6-Di-*tert*-butylphenol (2,6-DTBP). The substituted phenol (68.1 mg) was allowed to react with **3** (prepared from 42.1 mg of **1** and 82.1 mg of $Cu(CH_3CN)_4PF_6$) according to the general procedure. During the reaction a precipitate formed. The solid product was filtered, dried, and identified as 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (12.8 mg, 57%). ^1H NMR ($CDCl_3$): δ 1.37 (s, 36H), 7.71 (s, 4H), ^{13}C NMR ($CDCl_3$): δ 29.58 (CH_3), 36.02 ($C(CH_3)_3$), 126.00 ($CCC(CH_3)_3$), 136.12 ($CCC(CH_3)_3$), 150.43 (CC), 186.46 (CO). Mp: 245 °C; lit. 243 °C.

2,6-Dimethoxyphenol (2,6-DMP). For the oxidation of this phenol, the complex **3** was prepared from 65.0 mg of **1** and 127 mg of $Cu(CH_3CN)_4PF_6$, and 51.8 mg of the phenol was added to the reaction solution. During the course of the reaction a red-brown precipitate formed. The solid product was filtered, dried, and identified as 3,3′,5,5′-tetramethoxydiphenoquinone (16.0 mg, 62%). ^1H NMR ($CDCl_3$): δ 3.83 (s, 12H) δ 7.35 (s, 4H). Mp: 287 dec; lit. 290 dec. An attempt was made at obtaining a ^{13}C NMR spectrum; however, only very weak signals were obtained.

Oxidation of Ascorbic Acid. The reaction solution was prepared with 57.4 mg of **1**, 112 mg of $Cu(CH_3CN)_4PF_6$, and 52.8 mg of ascorbic acid. During the reaction a brown precipitate formed. The solid was filtered, dried, and identified as dehydroascorbic acid (7.83 mg, 30%) according

(27) In this paper the dinuclear copper(I) dioxygen complex **3** may also be described as the peroxo bridged dinuclear Cu(II) complex. The dioxygen complex is in an intermediate state between Cu(I) and Cu(II) and coordinated dioxygen and μ-peroxo. It should be distinguished from the Cu(II) complexes **4** and **5**.

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Table I. Oxidation Reactions with the Dioxygen Adduct of $[Cu_2(FD)_2(DIEN)_2]^{2+}$

reacn	mmol of complex 3	mmol of substrate	mmol of $(C_2H_5)_3N$ base	Ar	O_2	time, min	product (yield)
1	0.13	hydroquinone (0.17)		×		60	benzoquinone (11%)
2	0.16	*t*-butylhydroquinone (0.17)		×		60	*t*-butylbenzoquinone (33%)
3	0.17	2,6-dimethoxyphenol (0.33)		×		60	3,3′,5,5′-tetramethoxydiphenoquinone (62%)
4	0.11	2,6-di-*t*-butylphenol (0.33)		×		60	3,3′,5,5′-tetra-*t*-butyldiphenoquinone (57%)
5	0.15	ascorbic acid (0.30)		×		60	dehydroascorbic acid (30%)
6	0.11	4-*t*-butylcatechol (0.20)	0.40	×		60	γ-lactone[a] (~1%)
7	0.15	3,5-di-*t*-butylcatechol (0.25)	0.50	×		60	3,5-di-*t*-butyl-1,2-benzoquinone (~2%)
8	0.13	3,4-dimethylaniline (0.13)		×		60	3,4-dimethylnitrosobenzene (~1%)
9	0.10	hydroquinone (1.0)			×	60	benzoquinone (11%)
10	0.11	*t*-butylhydroquinone (1.2)			×	40	*t*-butylbenzoquinone (35%)
11	0.10	2,6-dimethoxyphenol (1.0)			×	5	3,3′,5,5′-tetramethoxydiphenoquinone (77%)
					×		2,6-dimethoxy-1,4-benzoquinone (<1%)
12	0.13	2,6-di-*t*-butylphenol (1.4)			×	10	3,3′,5,5′-tetra-*t*-butyldiphenoquinone (64%)
							2,6-di-*t*-butyl-1,4-benzoquinone (<1%)
13	0.14	ascorbic acid (1.6)			×	45	dehydroascorbic acid (13%)
14	0.12	4-*t*-butylcatechol (1.3)	2.6		×	60	γ-lactone[a] (6%)
15	0.19	3,5-di-*t*-butylcatechol (1.8)	3.6		×	60	3,5-di-*t*-butyl-1,2-benzoquinone (3%)
16	0.12	3,4-dimethylaniline (1.3)			×	20	3,4-dimethylnitrosobenzene (2%)

[a] Of 3-hydroxy-4-*t*-butylmuconic acid.

to a procedure developed by Roe *et al.*[33] The precipitate (2.14 mg) was dissolved in 10 mL of 2,4-dinitrophenylhydrazine–thiourea reagent (prepared by dissolving 2 g of 2,4-dinitrophenylhydrazine in 100 mL of 18 M sulfuric acid and adding 4 g of reagent grade thiourea with vigorous stirring) and placed in a water bath at 36 °C for 4 h. The red brown 2,4-dinitrophenylhydrazone derivative which formed was slowly dissolved in 85% sulfuric acid and made up to the mark in a 50-mL volumetric flask. The absorbance of this solution was measured at 540 nm. The amount of dehydroascorbic formed was determined with a calibration curve which was prepared in the following manner. A solution of ascorbic acid (51.68 mg in 50 mL of 10% acetic acid) was oxidized with bromine according to the method of Roe *et al.*[33] The oxidized solution (5 mL) was pipetted into a 250 mL volumetric flask containing 10 mL of the 2,4-dinitrophenylhydrazine–thiourea reagent. The solution was made up to the mark with 85% sulfuric acid while cooling. This stock solution was used to prepare solutions of various concentrations of the 2,4-dinitrophenylhydrazone derivative for which absorbances were measured to obtain the calibration curve.

Oxidation of Catechols. 4-*tert*-Butylcatechol (4-TBC). The substrate 4-TBC was oxidized in a reaction with a solution of **3** which was prepared with 44.7 mg of **1** and 87.1 g of $Cu(CH_3CN)_4PF_6$. To this solution was added 19.7 mg of 4-TBC (0.119 mmol) followed by 0.06 mL (0.2 mmol) of triethylamine, and the reaction mixture was stirred until oxygen absorption had ceased. The resulting solution was reduced to approximately 3 mL on a rotary evaporator and then chromatographed on silica gel. The first fraction was eluted from the column with 1:1 *n*-hexane/dichloromethane and identified by ^{1}H NMR spectroscopy as unreacted 4-TBC. The second fraction was eluted with 1% methanol in dichloromethane and identified as the γ-lactone of 3-hydroxy-4-*tert*-butylmuconic acid ester (approximately 0.1 mg, <1%). ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 9H), 3.90 (s, 3H), 5.79 (s, 1H), 6.30 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 29.58 (CH_3C), 36.30 ($C(CH_3)_3$), 56.27 (OCH_3), 103.33 (*C*HCOO), 125.77 (*C*HCOOCH$_3$), 158.88 (*C*C(CH$_3$)$_3$), 170.59 (CO), 178.68 (COO), 181.49 (*C*OOCH$_3$).

3,5-Di-*tert*-butylcatechol (3,5-DTBC). The substrate 3,5-DTBC (158 mg) was reacted with **3** (71.1 mg of **1** and 139 mg of $Cu(CH_3CN)_4PF_6$) according to the procedure stated above for 4-TBC. The resulting solution was chromatographed on silica gel. Elution with 2% dichloromethane in *n*-hexane gave 3,5-di-*tert*-butyl-1,2-benzoquinone (approximately 0.2 mg, <1%). ^{1}H NMR ($CDCl_3$): δ 1.21 (s, 9H), 1.26 (s, 9H), 6.20 (d, 1H), 6.92 (d, 1H). ^{13}C NMR: δ 27.87 (CH_3), 29.20 (CH_3), 35.47 ($C(CH_3)_3$), 36.02 ($C(CH_3)_3$), 122.08 (CH), 133.46 (CH), 149.93 (*C*C(CH$_3$)$_3$), 163.32 (*C*C(CH$_3$)$_3$), 180.03 (CO), 181.12 (CO).

Oxidation of 3,4-Dimethylaniline (3,4-DMA). The complex **3** was generated (45.6 mg $(FD)_2(DIEN)_2$ and 158 mg $Cu(CH_3CN)_4PF_6$) and reacted with 3,4-DMA (157.8 mg) according to the procedure described for the oxidation of 4-TBC. The final solution was evaporated to approximately 3 mL and chromatographed on silica gel. Unreacted 3,4-DMA was eluted with 1:1 *n*-hexane/dichloromethane, and the oxidation product was eluted with 1% methanol in dichloromethane and identified as 3,4-dimethylnitrosobenzene (approximately 0.2 mg, <1%). ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H), 2.30 (s, 3H), 7.00–7.20 (multiplets), ^{13}C NMR ($CDCl_3$): δ 19.40 (CH_3), 19.89 (CH_3), 115.89 (CH), 118.29 (CH), 122.54 (*C*CH$_3$), 130.38 (CH), 135.53 (*C*CH$_3$), 146.72 (CN); IR 1490 cm^{-1} (N=O).

(B) Oxidations with the $Cu^{II}_2(FD)_2(DIEN)_2$ Complex. Generation of the Copper(II) Complex and General Procedure. In a typical reaction the green copper(II) complex, **5**, was prepared by dissolving approximately 0.05 mmol of $(FD)_2(DIEN)_2$ in 20 mL of degassed methanol followed by the addition of 2 equiv of $CuCl_2$ in 10 mL of degassed methanol. The solution was stirred for 1 h in order to ensure the formation of the copper(II) complex. The substrate was introduced into the solution of the copper(II) complex in 10 mL of degassed methanol, and the reaction mixture was stirred with a magnetic stir bar, under argon. The end of the reaction was denoted by the termination of oxygen uptake. The products were separated and identified as stated in section A. The results of the oxidation reactions with **5** are summarized in Table II.

Oxidation of Hydroquinones. Hydroquinone. The reaction solution consisted of the active species **5** (generated with 61.2 mg of **1** and 43.0 mg of $CuCl_2$) and 57.2 mg of HQ. The oxidation product was identified as benzoquinone (<2%).

***tert*-Butylhydroquinone.** The reaction solution was prepared with 42.1 mg of **1**, 29.6 mg of $CuCl_2$, and 101 mg of TBHQ. The oxidation product was identified as *tert*-butyl-1,4-benzoquinone (<2%).

Oxidation of Phenols. 2,6-Di-*tert*-butylphenol. This phenol was oxidized in a reaction system consisting of 57.4 mg of **1**, 40.4 mg of $CuCl_2$ and 51.6 mg of the phenol. The product obtained was identified as 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (approximately 4%).

2,6-Dimethoxyphenol. This phenol was oxidized in a reaction system containing 61.2 mg of **1**, 43.0 mg of $CuCl_2$, and 32.3 mg of the phenol. The oxidation product was identified as 3,3′,5,5′-tetramethoxydiphenoquinone (approximately 4%).

Oxidation of Ascorbic Acid. A reaction solution was prepared with 49.7 mg of **1**, 34.9 mg of $CuCl_2$, and 96.9 mg of ascorbic. The product obtained was identified as dehydroascorbic acid (approximately 2%).

Oxidation of Catechols. 4-*tert*-Butylcatechol. The oxidation of 4-TBC was attempted in a system consisting of 45.9 mg of **1**, 32.3 mg of $CuCl_2$, 249 mg of the catechol, and 0.50 mL of triethylamine. Only a trace amount of oxidation product (the γ-lactone of 3-hydroxy-4-*tert*-butylmuconic acid methyl ester, identified by ^{1}H NMR) was obtained after 48 h.

3,5-Di-*tert*-butylcatechol. The oxidation of this catechol was attempted in a reaction system comprising of 61.2 mg of **1**, 43.1 mg of $CuCl_2$, 333 mg of the catechol, and 0.60 mL of triethylamine. Only a trace amount of the corresponding quinone (identified by ^{1}H NMR) was obtained after 48 h.

Oxidation of 3,4-Dimethylaniline. The oxidation of 3,4-DMA was attempted in a reaction system with 45.9 mg of **1**, 32.3 mg of $CuCl_2$ and 157 mg of 3,4-DMA. No product was obtained after 48 h.

The experiments described above were repeated, for hydroquinones, phenols, and ascorbic acid, in the presence of triethylamine and it was found that the yields were increased. The results of such experiments are summarized in Table II (experiments 25–29).

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Table II. Oxidation Reactions with the $[Cu^{II}_2(FD)_2(DIEN)_2]^{4+}$ Complex

rescn	mmol of complex **5**	mmol of substrate	mmol of $(C_2H_5)_3N$ base	Ar	O_2	time	product (yield)
17	0.14	hydroquinone (0.52)		×		8 hr	benzoquinone (~2%)
18	0.11	*t*-butylhydroquinone (0.61)		×		8 hr	*t*-butylbenzoquinone (~4%)
19	0.16	2,6-dimethoxyphenol (0.21)		×		8 hr	3,3′,5,5′-tetramethoxydiphenoquinone (~5%)
20	0.15	2,6-di-*t*-butylphenol (0.25)		×		8 hr	3,3′,5,5′-tetra-*t*-butyldiphenoquinone (~3%)
21	0.13	ascorbic acid (0.55)		×		8 hr	dehydroascrobic acid (~2%)
22	0.12	4-*t*-butylcatechol (1.5)	3.0	×		48 hr	γ-lactone[a] (~1%)
23	0.16	3,5-di-*t*-butylcatechol (1.5)	3.0	×		48 hr	3,5-di-*t*-butyl-1,2-benzoquinone (<1%)
24	0.12	3,4-dimethylaniline (1.3)		×		48 hr	3,4-dimethylnitrosobenzene (<1%)
25	0.23	hydroquinone (0.25)	0.25	×		4 hr	benzoquinone (20%)
26	0.22	*t*-butylhydroquinone (0.23)	0.20	×		4 hr	*t*-butylbenzoquinone (25%)
27	0.25	2,6-dimethoxyphenol (0.27)	0.30	×		6 hr	3,3′,5,5′-tetramethoxydiphenoquinone (31%)
28	0.27	2,6-di-*t*-butylphenol (0.34)	0.31	×		6 hr	3,3′,5,5′-tetra-*t*-butyldiphenoquinone (28%)
29	0.27	ascorbic acid (0.29)	0.58	×		8 hr	dehydroascorbic acid (30%)
30	0.17	hydroquinone (2.2)			×	90 min	benzoquinone (34%)
31	0.16	*t*-butylhydroquinone (1.3)			×	45 min	*t*-butylbenzoquinone (28%)
32	0.17	2,6-dimethoxyphenol (2.0)			×	1 hr	3,3′,5,5′-tetramethoxydiphenoquinone (45%)
33	0.15	2,6-di-*t*-butylphenol (1.8)			×	72 min	3,3′,5,5′-tetra-*t*-butylphenoquinone (40%)
34	0.11	ascorbic acid (1.1)			×	1 hr	dehydroascorbic acid (49%)
35	0.13	4-*t*-butylcatechol (1.3)	2.6		×	48 hr	γ-lactone[a] (<1%)
36	0.16	3,5-di-*t*-butylcatechol (2.0)	4.0		×	48 hr	3,5-di-*t*-butyl-1,2-benzoquinone (<1%)
37	0.12	3,4-dimethylaniline (1.3)			×	48 hr	3,4-dimethylnitrosobenzene (<1%)

[a] Of 3-hydroxy-4-*t*-butylmuconic acid.

Catalytic Oxidation Reactions. (A) Reactions with $[Cu_2(FD)_2(DIEN)_2]^{2+}$ and Dioxygen. General Procedure. Experiments on the catalytic oxidation of organic substrates were performed at 25.0 ● 0.1 °C and 1 atm of oxygen. The reactants were prepared in deoxygenated solvent which was previously degassed by purging with argon for a minimum period of 30 min. In a typical reaction, the copper(I) complex $[Cu_2(FD)_2(DIEN)_2]^{2+}$ (**2**) was generated in situ and under argon by dissolving approximately 0.10 mmol of the ligand in 20 cm^3 of anhydrous methanol then adding 2 equiv of copper(I) as $Cu(CH_3CN)_4PF_6$ dissolved in acetonitrile. A 10-fold excess of substrate was dissolved in 10 cm^3 of anhydrous methanol and added to the reaction flask under argon. The solution was stirred for 10 min in order to allow complete formation of the dinuclear complex, **2**. The system was then oxygenated by removing the argon atmosphere by means of a vacuum pump prior to introducing oxygen. An atmosphere of oxygen was maintained over the solution for the entire duration of the reaction. The reaction solution was stirred and oxygen absorption was continually monitored by observing changes in the mercury level in the gas burette. The mercury level in the burette was constantly aligned with that in the reservoir in order to maintain atmospheric pressure of oxygen over the reaction mixture. The reaction was deemed to have terminated when oxygen absorption was no longer observed. The products were separated and identified as stated in section A of the stoichiometric reactions. The results of each reaction are summarized in Table I.

Hydroquinone. The dinuclear complex $[Cu_2(FD)_2(DIEN)_2]^{2+}$ (38.2 mg of **1** and 74.4 mg of $Cu(CH_3CN)_4PF_6$) and the reaction solution containing the substrate (110 mg) were prepared by the standard procedure described above. When the system was exposed to oxygen the solution acquired a red brown color. At the end of the reaction the product was separated and identified, as before, as benzoquinone (11.6 mg, 11%).

***tert*-Butylhydroquinone.** The deep orange color of the copper(I) dinuclear complex changed to red brown on oxygenating the reaction solution containing $[Cu_2(FD)_2(DIEN)_2]^{2+}$ (42.1 mg **1** and 82.1 mg of $Cu(CH_3CN)_4PF_6$) and TBHQ (119 mg). The product obtained was *tert*-butylbenzoquinone (66.9 mg, 35%).

2,6-Di-*tert*-butylphenol. When the reaction solution which was prepared according to the standard procedure was oxygenated (49.7 mg of **1**, 96.9 mg of $Cu(CH_3CN)_4PF_6$ and 289 mg of 2,6-DTBP), the system acquired a dark red color and a red-brown precipitate formed. The precipitate was identified as 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone. The filtrate was concentrated to approximately 3 mL on a rotary evaporator and chromatographed on a silica gel column. The first fraction was eluted from the column with 1% methanol in dichloromethane and identified as 2,6-di-*tert*-butyl-1,4-benzoquinone. ^1H NMR ($CDCl_3$): δ 1.28 (s, 18H), 6.51 (s, 2H). Only a trace (<0.1 mg) amount of this product was obtained. The second product from the column was identified as 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (183 mg, 64%).

2,6-Dimethoxyphenol. The oxygenated reaction solution, which was prepared by the standard procedure (38.2 mg of **1**, 74.5 mg of $Cu(CH_3CN)_4PF_6$ and 154 mg of 2,6-DMP) was dark red in color. A red-purple precipitate which formed during the course of the reaction and after separation was identified as 3,3′,5,5′-tetramethoxydiphenoquinone (108 mg, 77%). The filtrate was concentrated to approximately 3 mL on a rotary evaporator and chromatographed on silica gel. Eluting with 1% methanol in dichloromethane gave a trace (<0.1 mg) amount of the 2,6-dimethoxybenzoquinone. ^1H NMR: δ 5.87 (s, 6H), 9.88 (s, 2H).

Ascorbic Acid. The reaction solution was prepared according to the standard procedure (53.5 mg of **1**, 104 mg of $Cu(CH_3CN)_4PF_6$, and 282 mg of ascorbic acid). When the orange solution of the copper(I) dinuclear complex, **2**, in the presence of ascorbic acid, was exposed to oxygen, the color changed to brown-orange and a precipitate formed. The product was identified as dehydroascorbic acid (37.8 mg, 13%).

Attempted Catalytic Oxidation of 4-*tert*-Butylcatechol, 3,5-Di-*tert*-butylcatechol and 3,4-Dimethylaniline. Attempts were made at catalytically oxidizing 4-TBC, 3,5-DTBC, and 3,4-DMA with **2**, which was generated with 0.10 mmol of $(FD)_2(DIEN)_2$ and 0.20 mmol of $Cu(CH_3CN)_4PF_6$ along with a 10-fold excess of substrate. The reactions involving catechols were performed in the presence of 2 equiv of triethylamine. The procedure for reaction solution preparation and product separation and identification was the same as that described for the catalytic oxidation of phenols and hydroquinones. The results presented in Table I show that the amount of product obtained in each case was less than one turnover.

(B) Oxidations with the $Cu^{II}_2(FD)_2(DIEN)_2$ Complex. The copper(II) complex of $(FD)_2(DIEN)_2$ (**1**) was prepared according to the procedure described for the stoichiometric oxidations with copper(II) by dissolving approximately 0.10 mmol of the ligand, **1**, in 30 cm^3 of methanol and adding a methanolic solution containing 2 equiv of $CuCl_2$. The substrate was introduced (in approximately 10-fold excess), into the stirred solution of **5**, in 10 mL of methanol and the reaction was allowed to occur until oxygen absorption ceased. The final solution was treated by the same procedure for product separation and identification as that described for the corresponding catalytic oxidations with copper(I). The quantities of **5** and substrate employed and the results of the experiments performed are summarized in Table II.

Hydroquinones. Hydroquinone was oxidized to benzoquinone (34%) and TBHQ was oxidized to *tert*-butylbenzoquinone (28%).

Phenols. 2,6-Dimethoxyphenol was oxidized to 3,3′,5,5′-tetra-methoxydiphenoquinone (45%) and 2,6-di-*tert*-butylphenol was oxidized to 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (40%).

Ascorbic Acid. The substrate ascorbic acid was oxidized to dehydroascorbic acid (49%).

Catechols and 3,4-Dimethylaniline. The substrates 4-TBC, 3,5-DTBC, and 3,4-DMA were obtained in trace amounts after a reaction time of 48 h.

Kinetic Studies. The reactions between $[Cu_2(FD)_2(DIEN)_2O_2]^{2+}$ (**3**) and phenols, hydroquinones, and ascorbic acid involved in this investigation were studied in a 100-mL water-jacketed reaction vessel containing an inlet and outlet for gases and fitted with a septum for introducing liquids by syringe. The vessel was thermostated at 25.0 °C and connected to a quartz flow cell of 1.0-cm path length. The flow cell was placed in the cell holder compartment of the ultraviolet–visible spectrophotometer, and the reaction solution was circulated through the flow cell by means

Table III. Activity of $[Cu_2(FD)_2(DIEN)_2]$ + Dioxygen

substrate	turnover/h^{-1}	time of reacn, min
hydroquinone	7	60
t-butylhydroquinone	5	42
2,6-di-*t*-butylphenol	25	5
2,6-dimethoxyphenol	30	10
ascorbic acid	6	45

of a peristaltic pump. In a typical experiment the reaction flask was first purged with argon, and 49.9 mg (0.131 mmol) of $(FD)_2(DIEN)_2$ was dissolved in 20 mL of degassed methanol. To this solution was added 2 equiv of $Cu(CH_3CN)_4PF_6$ (in 10 mL of degassed anhydrous acetonitrile) which is required for the formation of **2**. The peroxo complex $[Cu(FD)_2(DIEN)_2O_2]^{2+}$ (**3**) was generated by exposing the system to oxygen for 5 min. This time period was predetermined by observing the formation of **3** through the time dependence of the spectral changes on oxygenating a 3:1 methanol/acetonitrile solution of **2**. The oxygen atmosphere was removed by purging the system with argon for 10 min. The substrate was introduced in 10 mL of methanol, and the spectral changes of the solution were monitored over the wavelength range 800–300 nm. In the study of the formation rates of products specific wavelengths characteristic of the product were chosen to follow the progress of the reaction (3,3′,5,5′-tetra-*tert*-butyldiphenoquinone, 422 nm; 3,3′,5,5′-tetramethoxydiphenoquinone, 428 nm; dehydroascorbic acid, 425 nm; benzoquinone, 360 nm; *tert*-butyl-1,4-benzoquinone, 370 nm).

The same procedure was employed to follow the time dependence of the formation of 3,3′,5,5′-tetramethoxydiphenoquinone under stoichiometric conditions in the presence of **2** and dioxygen at various concentrations of **2** and 2,6-DMP.

The procedure described above was also used to study the formation of 3,3′,5,5′-tetramethoxydiphenoquinone under catalytic conditions in the presence of **5**.

Results

Tables I and II summarize the results of the reactions of **3** and **5** with the listed substrates under various conditions. The quantities of reactants and the yield of product are given for each reaction. Catalytic reactions are those which were performed under conditions of excess oxygen and substrate. All reactions performed under argon are stoichiometric in nature with catalyst as the limiting reagent. The products were identified by ^1H and ^{13}C NMR spectroscopy except in experiments for the oxidation of ascorbic acid in which case the oxidation product was identified by the method of Roe *et al.*[33]

Reactions in the Presence of Excess Dioxygen and Substrate. (A) Reactions with $[Cu_2(FD)_2(DIEN)_2]^{2+}$. Oxidation of Hydroquinones. When HQ and TBHQ were oxidized aerobically in the absence of **2**, only a trace amount of the *p*-benzoquinone products were obtained and very little oxygen uptake was recorded. Repetitive spectral scans of **2** in the presence of substrate showed no changes from that of **2** alone over a period of 30 min. In a solution containing **2** and substrate but no oxygen, a reaction was not observed within a time period of 30 min. When reactions were conducted in the presence of **2**, excess oxygen, and substrate, the solution changed color from orange to red brown and an oxidation product was extracted from the reaction mixture (experiments 9 and 10, Table I). The reaction of HQ in the presence of **2** and excess oxygen resulted in the production of benzoquinone, and a substantial amount of unreacted HQ was recovered (33% of the product material). The copper dioxygen complex, **3**, performed the catalytic oxidation of TBHQ producing the corresponding 1,4-benzoquinone as the oxidation product. The turnover number for each substrate is presented in Table III.

Oxidation of Phenols. Neither 2,6-DTBP nor 2,6-DMP was aerobically oxidized to an appreciable extent within 3 h in the absence of **2**. No spectral changes were observed over a 30-min period when a solution of the substrate was added to a solution of **2**. However, when a solution containing substrate and catalyst at 25.0 °C was oxygenated, its color changed from orange to red brown and eventually to brown orange in the case of 2,6-di-*tert*-butylphenol and from orange to red brown to purple brown when 2,6-dimethoxyphenol was the substrate (experiments 11 and 12, Table I). In each instance a precipitate was produced. The oxidation products for 2,6-di-*tert*-butylphenol were determined as 2,6-di-*tert*-butylbenzoquinone and 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone whereas the oxidation products of 2,6-dimethoxyphenol were 3,3′,5,5′-tetramethoxydiphenoquinone and a trace amount of 2,6-dimethoxybenzoquinone. The turnover numbers of Table III show that the reactions are catalytic in **3**.

Oxidation of Ascorbic Acid. A 5 mM solution of ascorbic acid in methanol was slowly oxidized (in 4–5 h) aerobically in the absence of **2**. A solution containing **2** and ascorbic acid, in the absence of oxygen, showed no spectral changes over the case of a solution of **2** alone within the wavelength range 800–350 nm. However, in the presence of oxygen a color change from orange to brown orange was observed and a precipitate of dehydroascorbic acid formed (experiment 13, Table I). The product was detected by forming the red-brown 2,4-dinitrophenylhydrazone of dehydroascorbic acid in 85% sulfuric acid and recording its absorption spectrum in the region 800–220 nm (λ_{max} = 494, 325 nm). Table III shows that ascorbic acid is catalytically converted to dehydroascorbic acid in the presence of **2** and dioxygen.

Oxidation of Catechols. The reactions between **3** and catechols did not proceed in the absence of base and under conditions of excess oxygen. However, when a 2:1 mole ratio of triethylamine to catechol was added to the reaction solution, 3,5-di-*tert*-butyl-1,2-benzoquinone was obtained as the oxidation product of 3,5-DTBC and the γ-lactone of 3-hydroxy-4-*tert*-butylmuconic acid ester resulted from the oxidation of 4-TBC (experiments 14 and 15, Table I). Under conditions of excess substrate and dioxygen the catechols were not found to be catalytically converted to their respective oxidation products. Addition of substrate to a solution of **2** did not result in a color change until triethylamine was added. The observed color change in each case was from orange to red. The catechols were not catalytically transformed to their oxidation products since the conversion amounted to less than one turnover (Table I).

Oxidation of 3,4-Dimethylaniline. When a solution of 0.110 mmol of **2** in 40 mL of a 3:1 methanol/acetonitrile mixture in the presence of a 10-fold excess of 3,4-DMA was oxygenated, the color of the solution changed from orange to brown and, after oxygen absorption ceased, 3,4-dimethylnitrosobenzene was obtained as the oxidation product (experiment 16, Table I). The reaction was not catalytic in the presence of **2** and excess oxygen and 3,4-DMA (Table I).

(B) Reactions with the $Cu_2^{II}(FD)_2(DIEN)_2$ Complex. Oxidation of Hydroquinones. Hydroquinone and TBHQ were oxidized by **5** in the presence of excess oxygen and substrate producing the corresponding 1,4-benzoquinone as the oxidation product. Addition of the substrate to a solution of **5** resulted in the slow discharge of the green color of the copper(II) complex and the appearance of the red-brown color of the resulting copper(I) complex (experiments 30 and 31, Table II). The visible absorption spectrum of this solution did not display bands within the wavelength range 800–400 nm, which indicates the presence of only a copper(I) species. The solution finally reverted to a green color, with the absorption spectrum of this solution showing an absorption maximum within the range 690–700 nm. No substrate was found in the product solution at the end of the reaction.

Oxidation of Phenols. Both 2,6-DTBP and 2,6-DMP were oxidized by **5** in the presence of excess oxygen and substrate giving the corresponding diphenoquinone as the only oxidation product (experiments 32 and 33, Table II). On addition of the substrate to the solution of **5**, the visible absorption spectrum recorded showed a disappearance of the band maximum in the range 690–700 nm which is characteristic of the copper(II) complex **5**. The resulting absorption spectrum, which showed no features in the visible region, suggests that a copper(I) complex is formed. At the end of the reaction the solution reverts to a green color, displaying a spectrum which is consistent with the presence of a copper(II) complex. When 1.0 mmol of 2,6-DTBP

Table IV. Initial Rates in the Cu(I)–Dioxygen and Cu(II) Oxidations of Substrates

substrate	product	initial, pseudo-first-order rate, M s^{-1}	
		Cu(I) + O_2	Cu(II)
hydroquinone	benzoquinone	1.1×10^{-4}	2.2×10^{-5}
t-butylhydroquinone	*t*-butylbenzoquinone	1.2×10^{-4}	1.6×10^{-5}
2,6-di-*t*-butylphenol	3,3′,5,5′-tetra-*tert*-butyldiphenoquinone	2.4×10^{-4}	5.8×10^{-5}
2,6-dimethoxyphenol	3,3′,5,5′-dimethoxydiphenoquinone	7.4×10^{-3}	5.6×10^{-5}
3,5-di-*t*-butylcatechol	3,5-di-*tert*-butyl-1,2-benzoquinone	1.4×10^{-8}	~0
3,4-dimethylaniline	3,4-dimethylnitrosobenzene	6.5×10^{-5}	~0
ascorbic acid	dehydroascorbic acid	5.9×10^{-4}	1.9×10^{-5}
4-*t*-butylcatechol	γ-lactone of muconic acid methyl ester	1.05×10^{-8}	~0

was added to a methanolic solution of 0.1 mmol of **5**, the green color of the copper(II) complex persisted for approximately 1 h before the red-brown color of the corresponding copper(I) complex began to develop. When similar quantities of 2,6-DMP and **5** were employed in the reaction, the time period for the color change was 3 min. The slower reaction time encountered with 2,6-DTBP may be partly understood in terms of the hindered nature of the substrate.

Oxidation of Ascorbic Acid. Dehydroascorbic acid was the product obtained when ascorbic acid was oxidized by **5** in the presence of excess oxygen (experiment 34, Table II). The color change of a solution of **5** on addition of ascorbic acid was from green to brown-orange and, as was the case for phenols and hydroquinones, the solution eventually acquired a green color and showed spectral properties similar to those of **5** within the wavelength range 800–400 nm.

Oxidation of Catechols and 3,4-Dimethylaniline. Reactions with **5** also required triethylamine before oxidation products were detected. These reactions were extremely slow and trace amounts of products were detected only after the reaction was continued for 48 h (experiments 35–37, Table II).

Reactions in an Atmosphere of Argon. (A) Reactions with the Dioxygen Complex of $[Cu_2(FD)_2(DIEN)_2]^{2+}$. Oxidation of Hydroquinones. The oxidation products of HQ and TBHQ were the corresponding 1,4-benzoquinones when **3** was allowed to react with the substrates in an atmosphere of argon (experiments 1 and 2, Table I). Addition of the substrate to a solution of **3** resulted in a darkening of the initial red brown of the solution which arose from reaction with the copper(I) dioxygen complex. The features of the electronic absorption spectrum of the reaction solution suggest that a copper(II) species was formed at the end of the reaction.

Oxidation of Phenols. When 2,6-DTBP and 2,6-DMP were each reacted with **3** in an atmosphere of argon color changes were from red brown to brown orange and red brown to purple brown respectively. The respective oxidation products were 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone and 3,3′,5,5′-tetramethoxydiphenoquinone (experiments 3 and 4, Table I). The electronic spectral features of the solution at the end of the reaction indicated the presence of copper(II).

Oxidation of Ascorbic Acid. A color change from red brown to brown orange was observed when ascorbic acid was added to a solution of **3** under argon. The oxidation product was identified as dehydro-ascorbic acid (experiment 5, Table I).

Oxidation of Catechols. The reaction between **3** and each of 4-TBC and 3,5-DTBC, under argon, did not proceed to an appreciable extent within 24 h in the absence of base. When triethylamine was part of the reaction mixture a small amount of oxidation products was obtained. The substrate 4-TBC produced the γ-lactone of 3-hydroxy-4-*tert*-butylmuconic acid whereas 3,5-DTBC produced 3,5-di-*tert*-butyl-1,2-benzoquinone (experiments 6 and 7, Table I).

Oxidation of 3,4-Dimethylaniline. Addition of 3,4-DMA to a solution of **3** under argon produced a color change from red brown to orange brown. The oxidation product was identified as 3,4-dimethylnitrosobenzene (experiment 8, Table I).

(B) Reactions with the Cu^{II}_2 $(FD)_2(DIEN)_2$ Complex. Oxidation of Hydroquinones. Hydroquinone and TBHQ were oxidized with **5** under argon but only minor amounts of oxidation products were obtained (experiments 17 and 18, Table II). The solution underwent a color change from green to dark red brown when the substrate was added to the reaction solution. The yield of products was improved when the reaction was performed in the presence of triethylamine (experiments 25 and 26 Table II). The respective products obtained in each case were benzoquinone and *tert*-butylbenzoquinone. The electronic spectral features of the final solution under argon indicated the presence of a copper(I) complex, and on prolonged exposure of this solution to oxygen there was a reversion to the original green color.

Oxidation of Phenols. Both 2,6-DTBP and 2,6-DMP were oxidized by **5** in an atmosphere of argon. The oxidation products were determined to be the respective diphenoquinones (experiments 19 and 20, Table II). The color changes encountered here were from green to dark brown orange for 2,6-DTBP and from green to purple brown for 2,6-DMP. In a manner similar to the oxidation of hydroquinones, the yields of these reactions were improved on the addition of triethylamine (experiments 27 and 28, Table II) and the spectral features of the final solution indicated the presence of copper(I). On prolonged exposure to oxygen this solution acquired a green color, and its spectral features indicated the presence of a copper(II) complex.

Oxidation of Ascorbic Acid. Dehydroascorbic acid was the oxidation product of the reaction between **5** and ascorbic acid under argon (experiment 21, Table II). The solution underwent a color change from green to brown orange when substrate was added to the reaction solution. The yield was improved by adding triethylamine to the reaction mixture (experiment 29, Table II). Exposure of the final solution to oxygen resulted in the solution acquiring a green color. The electronic absorption of this solution indicated the presence of a copper(II) complex.

Oxidation of Catechols and 3,4-Dimethylaniline. The reaction between **5** and 4-TBC, 3,5-DTBC, and 3,4-DMA produced only trace amounts of oxidation products (experiments 22, 23 and 24, Table II). In the case of 3,4-DMA, the introduction of triethylamine did not improve the yield of the oxidation product.

Kinetic Measurements on Stoichiometric Reactions. A kinetic study on stoichiometric reactions of **3** and **5** with substrates was undertaken in order to establish whether the steps involving copper(I) and copper(II) species may be distinguished in the catalytic cycle. Initial rates were recorded in order to avoid the complication introduced by oxidation by copper(II) which may be produced from the degradation of **3** and also from the oxidation of substrate. The reactions with **3** were carried out under conditions of a 20-fold excess of substrate in order to simulate pseudo-first-order conditions and obtain initial rates which were convenient to measure. Under these conditions the rate contribution from the degradation of **3** to **5** is expected to be negligible. The initial rates obtained for hydroquinones, phenols and ascorbic acid in this study are shown in Table IV. The results show that, in each case, the initial rate is significantly higher for copper(I) reactions. Figure 1 shows the time course of the reactions of **3** and **5** with both 2,6-DMP and 2,6-DTBP in which a notable feature is the slower rate of oxidation of 2,6-DTBP over that for 2,6-DMP for reactions of both **3** and **5**. The slow initial rate of formation of the oxidation product, 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone noted implies that there may be a brief induction period. The

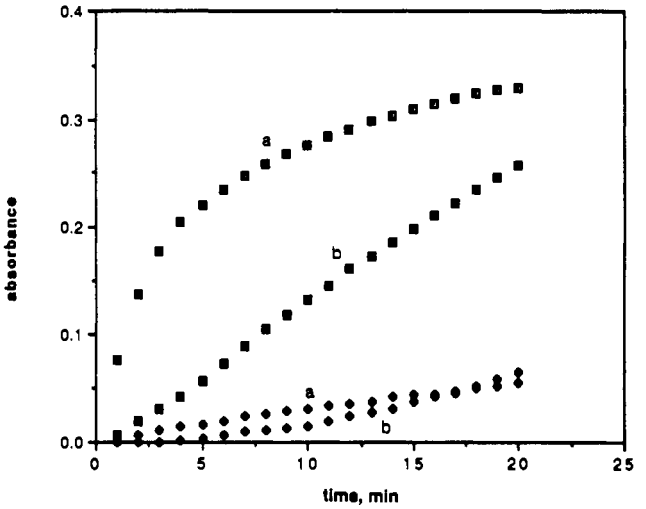

Figure 1. Time course for the formation of 3,3′,5,5′-tetramethoxydiphenoquinone (a) and 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (b) with **3** (upper curves) and **5** (lower curves).

fact that this delay in appearance of product is not observed for the other substrates in this study (which are unhindered) suggests that the induction period is associated with substrate binding. When the course of the reaction of **5** with 2,6-di-*tert*-butylphenol is followed spectrophotometrically, the green color and spectral characteristics of the copper(II) dinuclear complex disappear on addition of the substrate and the solution acquires a deep orange color. Moreover, the appearance of the characteristic peak of the oxidation product at 422 nm is observed subsequent to the initial color change, and the solution ultimately becomes brown orange in color. These observations are consistent with a sequence of events where substrate binding occurs prior to oxidation. A similar sequence of changes is observed for the reaction between **5** and 2,6-DTBP, hydroquinones, and ascorbic acid. In these cases the color changes were less visually obvious. Therefore the reaction was followed using the spectral properties of the reaction system.

The plots of the time course for the reactions of **3** and **5** each with HQ, TBHQ and ascorbic acid display essentially the same features as those shown in Figure 1, in which the initial rate with **3** is substantially greater than that with **5**, except that no induction period was observed in these cases.

The rates of formation of 3,3′,5,5′-tetramethoxydiphenoquinone were studied in the presence of **3** and in an inert atmosphere. The initial rates of formation of the diphenoquinone, as determined from the maximum slopes of the absorbance versus time plots, were plotted as a function of [**2**] (Figure 2). A similar plot was made for the rate of formation of the diphenoquinone as a function of [DMP] (Table V). The rates were found to be first order with respect to both [**2**] and [DMP].

The time dependence of the formation of the diphenoquinone in the presence of **5**, 2,6-DMP and excess dioxygen is shown in Figure 3. An initial slow rate followed by a more rapid rate after approximately 50 min is evident. This binodal nature of the plot suggests that there are two mechanisms of oxidation in operation. The initial slope ought to correspond to oxidation by **5** alone since this is the initial active oxidant in solution. The composition of the reaction solution is calculated as 72% copper(II) complex and 28% copper(I) complex after 30 min. After 50 min the quantity of copper(I) is sufficient for its contribution to the second mechanism of oxidation to be evident.

Discussion

It has been previously shown that exposing a solution of **2** to dioxygen results in the formation of a μ-peroxo intermediate, **3**. The species was inferred from the electronic absorption spectrum which displays bands at 504 and 360 nm which are characteristic

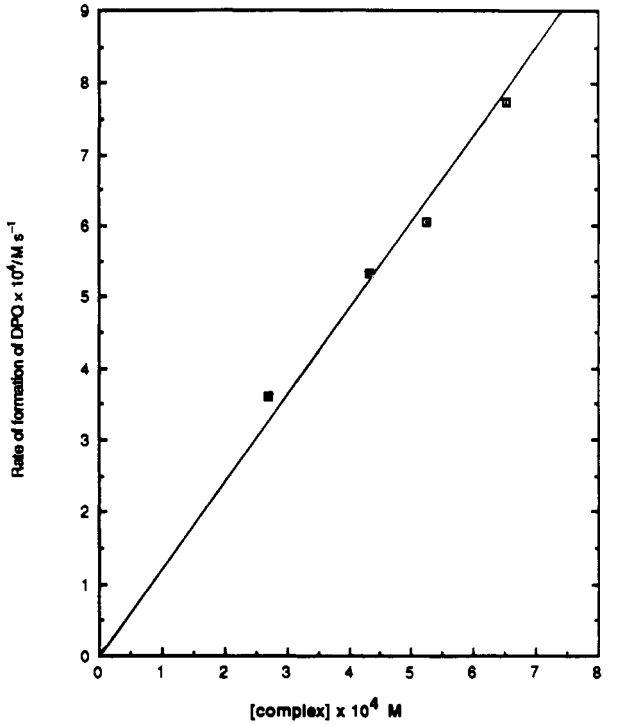

Figure 2. Dependence of the rate of formation of 3,3′,5,5′-tetramethoxydiphenoquinone on the concentration of **3**.

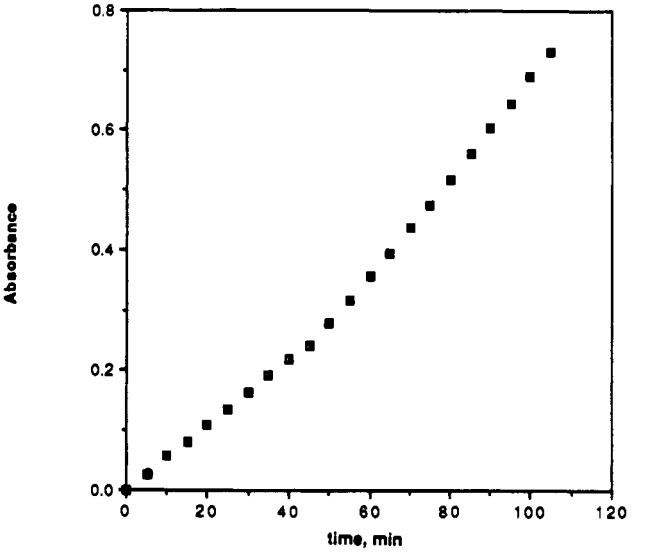

Figure 3. Time dependence of the catalytic formation of 3,3′,5,5′-tetramethoxydiphenoquinone in the presence of **5** (3.05×10^{-4} M) and excess dioxygen (P_{O_2} = 1 atm). The characteristic absorption band of the diphenoquinone was followed at 428 nm.

Table V. Dependence on Initial Rate of Formation of DPQ on Concentration of 2,6-DMP

[2,6-DMP]/M	initial rate/M s^{-1}	[2,6-DMP]/M	initial rate/M s^{-1}
5.10×10^{-3}	7.2×10^{-4}	1.02×10^{-2}	1.2×10^{-3}
8.39×10^{-3}	9.5×10^{-4}	1.19×10^{-2}	1.3×10^{-2}

of O_2–Cu transitions of a dinuclear copper(II)–peroxo unit.[34] The peroxo-bridged species is thermally unstable and decomposes to a μ-hydroxo–μ-methoxo dibridged dinuclear complex with a half-life of 2 h at 5 °C (Scheme I). It has since been observed that the μ-peroxo intermediate has a half-life of approximately 1 h at 25 °C. The intention at the onset of this project was to make use of this intermediate in performing oxidations on specific organic substrates since it was noted that the species encountered

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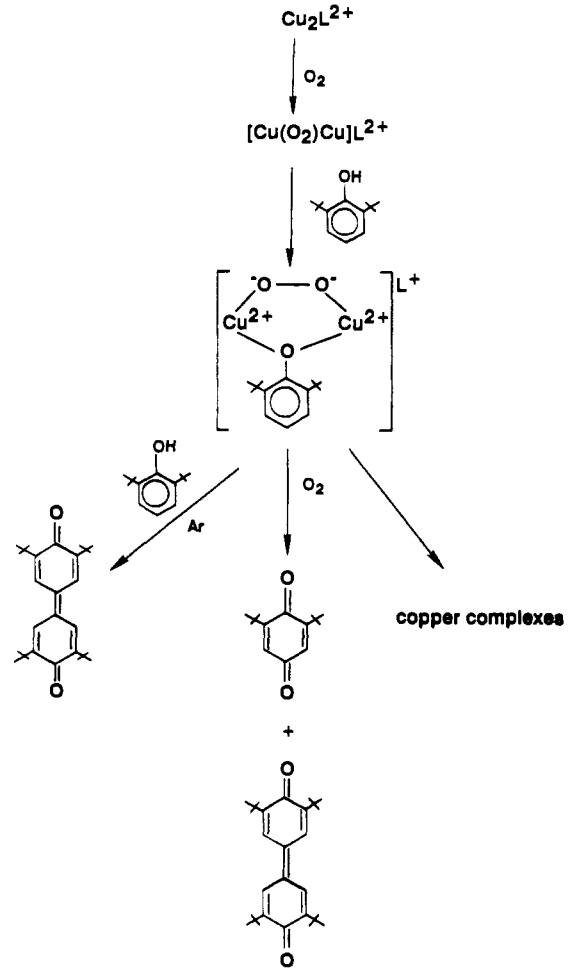
in this study possesses the qualities necessary for catalytic oxidation by copper(I). The electronic absorption spectrum implys that there is coplanarity in the Cu–O_2–Cu entity of **3** and that there are no other Cu–Cu bridges.[35] The requirements of molecular flexibility and coordination unsaturation which influence catalytic activity[36] seem to be satisfied in this case, enabling the simultaneous accommodation of dioxygen and substrates. At the time of writing isolation of the μ-peroxo intermediate has not been accomplished; however, the structure of the dinuclear copper(I) dioxygen complex, **3**, may be inferred from the X-ray crystal structure of the copper(II) degradation product **4**. X-ray crystal analysis on this compound[31] shows that copper is four-coordinated to two nitrogen atoms on each diethylenetriamine moiety and two oxygen atoms each from the hydroxy and methoxy bridges. It is reasonable to assume that, with the removal of the steric strain imposed by the methoxy and hydroxy bridges, each copper ion will be bonded to three nitrogen atoms of the diethylenetriamine unit in **2**. The result is that copper is more disposed to accepting substrates since the bridging units are removed and coordination unsaturation is maintained since each copper center is now only three-coordinated.

The active species for the oxidation by copper(II) was prepared by reacting stoichiometric quantities of ligand $(FD)_2(DIEN)_2$ with $CuCl_2$ in methanol. The spectroscopic properties of the resulting species were found to be similar to those of the degradation product of the irreversible oxidation of **2** within the wavelength region 800–350 nm, the most salient feature being a broad absorption with a maximum in the region 640–650 nm. Since the absorption spectra of **4** and the synthetic copper(II) complex **5** are almost identical, then a reasonable conclusion is that complexes **4** and **5** are structurally similar in solution. The synthetic dinuclear copper(II) complex was prepared in anhydrous methanol; hence, it is likely to contain one or two methoxy bridges and possibly no hydroxo bridge. In fact, an OH absorption was not observed in the infrared spectrum of the isolated solid resulting from solvent evaporation. In contrast, the complex **4** was determined as having one methoxo and one hydroxo bridge.[31]

The degradation complex, **4**, was also found to be capable of oxidizing most of the substrates under investigation in this study. Moreover, the products obtained and the reactivity features parallel those of the synthetic dinuclear copper(II) complex, **5**. A previous investigation[26] has shown that oxygen absorption in an oxygenated system of **2** occurs to the extent described by the O_2:**2** ratio of 0.7, and the coordinated dioxygen is considered to ultimately undergo a four-electron reduction to water. The stoichiometry of this reaction has not been elucidated completely, therefore, in view of the structural similarities between **4** and **5** in solution (they have very similar absorption spectra), it was considered more convenient to prepare the copper(II) complex **5** directly from $(FD)_2(DIEN)_2$ and $CuCl_2$.

Reactions in an Inert Atmosphere: Oxidations with the Dioxygen Complex of $[Cu_2(FD)_2(DIEN)_2]^{2+}$ and the $Cu_2^{II}(FD)_2DIEN)_2$ Complex. In order to distinguish between copper(I)–dioxygen and copper(II) oxidations, reactions between listed substrates and **3** and **5** were performed under stoichiometric conditions. Since the reactions between complex and substrate were found to be first order in complex and substrate, a large excess of substrate was employed in order to simulate pseudo-first-order conditions. Initial rates were considered in order to avoid the complication of having to account for significant oxidation by copper(II) when reactions were performed with the copper(I)–dioxygen complex. Copper(II) reactions were performed under argon; therefore, the copper(I) which forms as a consequence of oxidation does not have the opportunity to further oxidize substrate since copper(I) is stable with respect to conversion to copper(II) and is inactive as an oxidant in the absence of dioxygen. The initial first order rates of Table IV show that the copper(I)–dioxygen dinuclear complex is a more rapid oxidant, by 5–100 times, than the copper(II) complex. One notable feature is that for the substrates 3,5-DTBC, 4-TBC, and 3,4-DMA the initial rates were immeasurably slow. The possible reason for such small yields will be discussed below.

Scheme II



Stoichiometric Oxidations of Phenols and Hydroquinones. The reaction of **3** with phenols and hydroquinones was found to proceed under conditions of excess oxygen with stoichiometric proportions of reactants and under argon. A reaction sequence for product formation is suggested in Scheme II. The sequence involves adding substrate to a solution of the copper(I) dinuclear complex **2**. The time dependent electronic absorption spectrum of the system did not show any initial changes when substrate was added to a solution of **2** under argon. The implication is that there is no binding of substrate at this point in the reaction. A plausible explanation is that deprotonation of the phenol to produce a phenolate anion is necessary before there is complexation with copper(I). Further support is provided by the observation that, for the substituted catechols, no spectral changes relating to substrate binding were observed before the addition of triethylamine. The conclusion made from this observation is that triethylamine accomplishes the deprotonation of catechols, making them available for binding to the metal center. When the reaction system is oxygenated, the peroxo intermediate **3** is formed, and this process allows the phenol to be deprotonated, forming a phenoxide anion which is now capable of coordinating to the copper centers as shown in Scheme II. The removal of protons by the copper(II)–peroxo complex **3** is considered to be a likely process since such complexes have a highly charged metal center. Once deprotonated, the phenol is expected to bind with the two copper centers. There is no evidence for the nature of the bonding between the phenol and the dinuclear copper(II) peroxo complex. However, Kitajima[29] has proposed that the phenols actually form bridges between the

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(36) Karlin, K. D.; Gultneh, Y. *Prog. Inorg. Chem.* **1985**, *35*, 219.

two copper centers. Although this is an interesting concept, it should be acknowledged that the phenolate groups do not necessarily have to be bridging. The dibridged arrangement is not considered in this instance for steric reasons. A more likely configuration is a molecular arrangement having each of the two substrate moieties singly coordinated to a metal center. The construction of CPK molecular models has demonstrated that such an arrangement is possible.

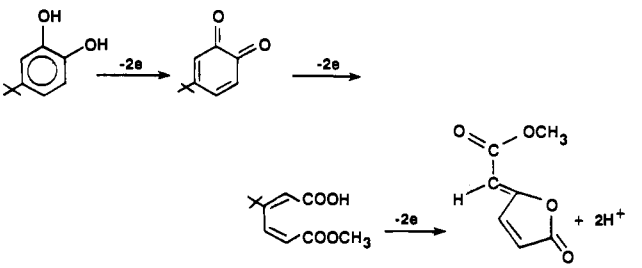
Scheme II shows that only the oxidatively coupled diphenoquinone is obtained when the reaction occurs under argon whereas both the coupled product and the 1,4-benzoquinone are produced in the presence of oxygen. The results are similar to those of Kitajima[29] where it was shown, by labeling studies, that the added oxygen in the product quinone originated in the oxygen atmosphere and not in the peroxo bridge. Since only the coupled diphenoquinone is obtained in the argon atmosphere, then it is reasonable to assume that the mechanism in operation is similar to that proposed by Kitajima in which a precursor to electron transfer, containing the copper complex and two substrate units, is formed. Karlin[37] has demonstrated that there is displacement of peroxide from copper(II) peroxo-bridged complexes, and this finding has been used by Kitajima[29] to propose the formation of two bridged phenols between the copper centers. Each phenol is capable of a one-electron transfer which results in the reduction of the copper(II) and the production of two phenolate radicals in close proximity. The diphenoquinone is subsequently formed through the coupling of two phenolate radicals.[38]

Oxidation reactions with **5** gave the same products as those for the corresponding oxidations with **3** except that no 1,4-benzoquinone was detected when phenols were oxidized under argon. In general, reactions of **5** with hydroquinones and phenols proceeded slowly and resulted in low yields when performed under argon and in the absence of base. The yields and rates were improved once triethylamine was added to the reaction mixture. On the basis of these observations, it was concluded that the complex **5** is not as effective as **3** in oxidizing the substrates under consideration.

Stoichiometric Oxidation of Ascorbic Acid and Catechols. The reported investigations have shown that ascorbic acid undergoes oxidation by **3** and **5** to dehydroascorbic acid both under stoichiometric conditions under argon and in the presence of excess oxygen. It was observed that for oxidations with **2** and dioxygen there was no spectroscopic evidence of substrate coordination to the complex before the generation of the bridged peroxo intermediate, **3**. Therefore, the argument of substrate deprotonation by **3** is plausible in this case.

In the absence of base, catecholes were not converted to their oxidation products in the presence of **3**. Therefore, it was concluded that the peroxo complex does not deprotonate catechols. An additional requirement in the case of catechols must be the presence of triethylamine, which is responsible for deprotonating these substrates and the formation of copper–catecholate complexes. Since there is only one molecule of substrate providing two electrons for the reduction of the two copper centers, it is reasonable to expect that the requirements for "steric match" as proposed by Oishi *et al.*[39] for electron transfer between ascorbic acid and dinuclear copper catalysts may influence the outcome of the reaction process. The importance of steric match has been extended to the oxidation of catechols where it has been determined that the efficiency of the catalyst is enhanced when the Cu–Cu distance is within the range 3–5 Å. With the aid of CPK models and the program Alchemy, a distance range of 4.0–5.5 Å was estimated for the Cu–Cu separation in **2**. Since a peroxo bridge ought to confer constraint on the Cu–Cu separation, the internuclear distance for the copper centers is estimated as less than 5.5 Å for **3**, presenting a borderline situation for the "steric match" condition. Although crystallographic data have not been obtained for **5**, the similarity in the absorption spectra of complexes **4** and **5** leads to the expectation that the two complexes are structurally similar in solution. A parallel may be drawn between the solid phase structures of **4** and **5** from which it may be assumed that the Cu–Cu distance in **5** is in the vicinity of 2.96 Å. The complex **3** was determined as the more efficient oxidant for catechols and the more efficient catalyst for ascorbic acid, implying that the steric condition may be better satisfied by the peroxo complex, **3**.

Both 4-TBC and 3,5-DTBC were oxidized by **2** and dioxygen; however, only the latter gave the corresponding 1,2-benzoquinone product. When 4-TBC was used in reactions with **3**, the only oxidation product obtained was the γ-lactone which is derived from the muconic acid ester (the second oxidation product) according to the following sequence.



Although neither the 1,2-quinone nor the muconic acid ester has been detected, their existence is implied by the formation of the γ-lactone, and in the overall process six electrons are transferred. Since a simultaneous four-electron transfer to produce the muconic acid ester is highly improbable, then the reaction must occur through the intermediate quinone which results from a two-electron transfer. The fact that no quinone has been detected leads to the suggestion that the substrate release from the complex after the initial transfer of two electrons is a slow process. Therefore, the quinone remains bonded to the copper complex prior to the subsequent electron transfer process.

Catalytic Oxidations. Table IV shows that whereas significant rate constants were not obtained for 3,5-DTBC, 4-TBC, and 3,4-DMA in copper(II) oxidations, those substrates were oxidized by the copper(I)–dioxygen complex **3**. This observation is consistent with the fact that only those substrates which show significant rates with copper(II) are catalytically oxidized in the presence of excess dioxygen in cases where copper(I) is the active starting entity. The data obtained suggest that copper(II) oxidation is an important part of the cycle for the catalytic oxidation beginning with copper(I). The copper(I) produced from the copper(II) oxidation of substrates is capable of forming the dioxygen complex, **3**, in the presence of oxygen; consequently, the cycle is perpetuated. When oxidation does not occur with copper(II), the reaction is not catalytic in nature. On the basis of the results obtained, a likely catalytic cycle is proposed, in Scheme III, for the oxidation of phenols, hydroquinones, and ascorbic acid by **2** in an excess of dioxygen. The illustration is given for the oxidation of 2,6-DTBP as the example. The steps involve (i) oxygenation of the dinuclear copper(I) complex to produce a μ-peroxo species, (ii) formation of the substrate-bound precursor and the oxidation of two phenol units producing phenoxy radicals which dimerize to give the diphenoquinone and copper(II), and (iii) the oxidation of two phenol units by copper(II) to give once more the diphenoquinone. In step (iii) copper(I) is produced, and in the presence of dioxygen, the μ-peroxo complex is formed; therefore, the cycle is repeated. As the reaction progresses the water produced in step (ii) is expected to compete with the substrate and reacts with the macrocyclic complex resulting in gradual termination of the catalytic cycle. Substrates to which the proposed mechanism in Scheme III are applied are presented in

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Scheme III

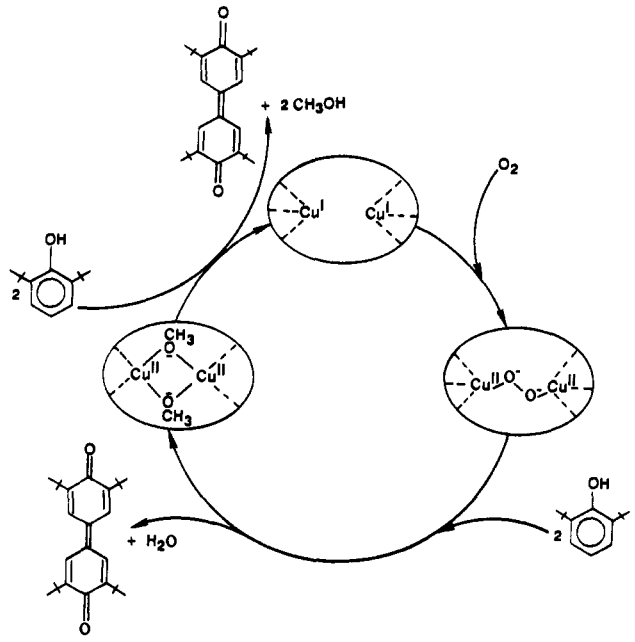

Table III. It is noted that catalytic activity is obtained only for those systems which show significant oxidation rates for both copper(I) and copper(II) macrocyclic complexes, hence the proposed involvement of both copper(I) and copper(II) in the catalytic process.

The catalytic oxidation of substrates by copper(II) was investigated in order to establish its importance in the cycle. In this regard the initial rates for the stoichiometric reaction between each substrate and **3** and **5** in turn were determined in an atmosphere of argon. The significantly higher rates recorded for reactions with **3** indicate that the oxidations with a peroxo species and oxidation with a copper(II) species are separate steps in the catalytic cycle. When the formation of 3,3′,5,5′-tetramethoxydiphenoquinone was followed as a function of time, in the presence of **5**, a two-phase reaction was observed (Figure 3). This implies that there are two mechanisms in operation. The data presented in Table II show that the oxidation reactions with copper(II) are expedited in the presence of the base triethylamine. The oxidative coupling of substrates with copper(II) has been demonstrated to be more facile in the presence of base.[40,41] A methoxo or hydroxo bridge may act as a base; however, in this case, the slow kinetics of the first reaction is interpreted as a consequence of **5** having poorer qualities as an oxidant than the peroxo complex **3**. The solution species **5** is considered to be a di-μ-methoxo complex which may function in a similar manner to a μ-hydroxo complex. The first slope of Figure 3 is thought to correspond to the slower oxidation of 2,6-DMP by the μ-methoxo complex, a reaction which is limited by the deprotonation of the substrate. The composition of the reaction solution is calculated as 28% dinuclear copper(I) dioxygen complex and 72% copper(II) dinuclear complex after 30 min. In the presence of excess dioxygen, when the dinuclear copper(I) complex is formed subsequent to copper(II) oxidation, it is proposed that the μ-peroxo complex is then formed, resulting in an increase in the catalytic rate since the reaction will now be proceeding as described in Scheme III. The second slope of Figure 3 therefore corresponds to the catalytic rate for the process described in Scheme III.

The oxidation of 4-TBC to the γ-lactone was not observed to be catalytic in the presence of **3**. This oxidation would be an essential step in the catalysis, in view of the role of copper(II) proposed in Scheme III. The substrate 3,5-DTBC behaved in a different manner in the presence of **3**. It was oxidized to 3,5-di-*tert*-butyl-1,2-benzoquinone by **3** under conditions of an argon atmosphere and an oxygen atmosphere. Catalytic activity was not recorded for this oxidation, and no corresponding γ-lactone was detected. The lack of catalytic activity may be attributed to the formation of copper(II)–catechol complexes which are inactive for reasons that will be discussed presently. Copper(II) oxidation of 3,5-DTBC resulted in only a trace amount of the corresponding 1,2-benzoquinone. As in the case of 4-TBC this observation may account for the lack in catalytic activity towards 3,5-DTBC.

The catechols under examination were not catalytically converted to oxidation products in the presence of **2** and dioxygen. An extensive line broadening ($1/T_2 = 62.8\ s^{-1}$) has been observed in the ^1H NMR spectrum of the second component to be eluted off the silica gel column during the separation of products in the oxidation of 3,5-DTBC. The observed line broadening has led to the conclusion that the species under examination here contains the catechol coordinated to a paramagnetic copper(II) center. This product is thought to be either a dinuclear or mononuclear copper(II) complex containing the catechol as part of its ligand system. Oxidation of 4-TBC and 3,5-DTBC with **5** produced only a trace amount of the γ-lactone and the *o*-benzoquinone respectively, the reason being the possible formation of substrate–copper(II) complexes which are reasonably stable and inhibit further product formation.

Ascorbic acid is oxidized catalytically by **3** and **5** giving dehydroascorbic acid as the sole oxidation product in each case. Observed paramagnetism in the ^1H NMR spectrum of one component of the product of copper(II) oxidation products suggests that a metal–substrate compound may be responsible for the termination of the catalytic cycle. Adding ascorbic acid to a solution of **5** shows that a copper(I) complex is produced initially, and should the system be exposed to excess dioxygen, the initial copper(II) complex is regenerated. This behavior is in direct contrast to that for catechols in which case the reaction system does not regenerate the original copper(II) complex.

Summary and Conclusion

The μ-peroxo intermediate, **3**, is relatively unique as a model for the active site of tyrosinase in that it has a reasonably long lifetime at room temperature when in the solution phase. This quality makes the species particularly useful for rapid room temperature oxidation reactions. Reactivity studies have demonstrated that the oxidation of HQ, TBHQ, 2,6-DTBP, 2,6-DMP, and ascorbic acid are catalyzed by **3** in the presence of dioxygen and that 4-TBC is also oxidized by **3** with C–C bond cleavage to give a γ-lactone. The substrates 3,5-DTBC and 3,4-DMA have also been oxidized by **3**. Catalytic activity was obtained with substrates which show activity for both macrocyclic complexes **3** and **5**. Therefore it was proposed that catalysis involves the participation of both copper(I) and copper(II) complexes. Spectroscopic investigations have demonstrated that the substrate binding process seems to be an important prerequisite for electron transfer. The lack of catalytic transformations for catechols and 3,4-DMA seems to be related to the formation of metal–substrate complexes which inhibit further oxidation reactions.

The fact that the peroxo intermediate **3**, produced by oxygenation of **2**, is capable of oxidizing phenolic type substrates demonstrates that the macrocyclic system may assist in understanding the catecholase activity of tyrosinase monooxygenase. The importance of the oxidizing ability of both the Cu(I) dioxygen (copper(II)–peroxo) and the copper(II) states in the macrocyclic system studies here may point to a parallel level of importance of such oxidation states in the catalytic capability of the active site of tyrosinase. In addition, the reactivity of **3** as described in this paper contributes to knowledge of structure–function relationships as they affect the μ-peroxo models for tyrosinase.

Acknowledgment. This research was supported by the Office of Naval Research.

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