# Copper(II)-Induced Oxidations of Aromatic Substrates: Catalytic Conversion of Catechols to *o*-Benzoquinones. Copper Phenoxides as Intermediates in the Oxidation of Phenol and a Single-Step Conversion of Phenol, Ammonia, and Oxygen into Muconic Acid Mononitrile

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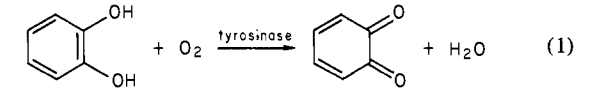
**Abstract:** Cupric chloride or bis(1-phenyl-1,3,5-hexanetrionato)dicopper(II) complex in the presence of triethylamine or copper(II) species produced by reaction of cuprous chloride with oxygen in an aprotic solvent in the absence of added base all catalyze conversion of 3,5-di-*tert*-butylcatechol and 4-*tert*-butylcatechol with oxygen to the corresponding 1,2-benzoquinones. It appears that the catalytic sequence involves (a) formation of the dicopper(II) catecholate intermediate, (b) electron transfer from the aromatic ring to two copper(II) centers in the intermediate providing *o*-benzoquinone and two copper(I) centers, (c) irreversible reaction of the generated copper(I) species with oxygen to give the active copper(II) reagent, and (d) reaction of this reagent with catechol leading to regeneration of the dicopper(II) catecholate intermediate and formation of the water byproduct. Under anaerobic conditions the extent of the electron transfer from the substrate is determined by the thermodynamic stabilities of the copper(II)/copper(I) pairs. Copper(II) species produced by oxidation of cuprous chloride in pyridine reacted with phenol to give a copper(II) reagent which converted both *o*-benzoquinones and catechols under anaerobic as well as under aerobic conditions to monophenyl esters of muconic acid; the same reaction with phenol itself occurred only in the presence of oxygen. It was concluded that the latter reaction involves copper phenoxides as intermediates and subsequently demonstrated that this was indeed the case by using bona fide copper phenoxides. Using anhydrous ammonia as a nonhydroxylic nucleophile instead of alcohol or phenol nucleophiles in the reaction with copper–oxygen species resulting from the oxidation of cuprous chloride in pyridine provided a new copper(II)/ammonia reagent. This "$CuO/NH_3$" reagent reacts with *o*-benzoquinones and catechols under anaerobic and aerobic conditions to give muconic acid mononitriles, and with *n*-heptaldehyde, benzaldehyde, and cinnamaldehyde it provides the corresponding nitriles. Conversion of phenol to muconic acid mononitriles required oxygen. A different copper reagent, obtained by the addition of anhydrous ammonia to pyridine cupric methoxy chloride in pyridine, converts 4-*tert*-butylcatechol, 3,5-di-*tert*-butyl-1,2-benzoquinone, and 3-methoxy-4-*tert*-butylcatechol into the corresponding substituted muconic acid imides. Possible mechanisms for these transformations were discussed, and the conclusions about the role of oxygen were presented.

Recently we reported on the copper(II)-induced cleavage of *o*-benzoquinones, catechols, and phenols to muconic acid monoalkyl esters.[1-6] Unlike the reaction of *o*-benzoquinones and catechols that could occur even under anaerobic conditions, the reaction with phenol could take place only in the presence of molecular oxygen.

In this paper we shall present results of our studies, first, of the catalytic oxidation of catechols to *o*-benzoquinones and, second, of the role of oxygen[7] in the overall transformation of phenol and copper phenoxides to muconic acid half esters, and third, we shall describe a novel single-step conversion of phenol and derivatives, with ammonia and oxygen, to muconic acid mononitriles.[5] We shall also discuss briefly possible mechanistic interpretations of the experimental results and the implication regarding the importance of the multicopper concept in mimicking the so-called copper type 3 centers in tyrosinases.

The efforts directed toward elucidation of the role of copper in transformation of catechols to *o*-benzoquinones[8] catalyzed by tyrosinase (eq 1) involve syntheses of model copper compounds



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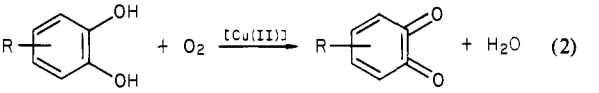

(2)

that would mimic both known spectroscopic characteristics[9] as well as the chemical behavior of the biological systems.[10] One particular aspect of these efforts is the elucidation of how the

(1) Rogić, M. M.; Demmin, T. R.; Hammond, W. B. *J. Am. Chem. Soc.* **1976**, *98*, 7441.

(2) Rogić, M. M.; Demmin, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 5472.

(3) Rogić, M. M.; Demmin, T. R. "Aspects of Mechanisms and Organometallic Chemistry"; Brewster, J. H., Ed.; Plenum Press: New York, 1978; p 141–168.

(4) Demmin, T. R.; Rogić, M. M. *J. Org. Chem.* **1980**, *45*, 1153.

(5) Demmin, T. R.; Rogić, M. M. *J. Org. Chem.* **1980**, *45*, 2737.

(6) Demmin, T. R.; Rogić, M. M. *J. Org. Chem.* **1980**, *45*, 4210.

(7) For the discussion of the kinetics of reduction of oxygen by copper(I) species see: Hopf, F. R.; Wolf, J. F.; Rogić, M. M., to be submitted for publication.

(8) For a general discussion, including a discussion of the "activation" of molecular oxygen, see: Hayaishi, O. "Molecular Mechanisms of Oxygen Activation"; Hayaishi, O., Ed.; Academic Press: New York, 1974, Chapter 1 and references therein. Schoot-Viterkamp, A. J. M.; Mason, H. S. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 993. Jolley, R. L.; Evans, L. H.; Makino, N.; Mason, H. S. *J. Biol. Chem.* **1974**, *249*, 335. Makino, N.; McMahill, P.; Mason, H. S.; Moss, T. H. *Ibid.* **1974**, *249*, 6062. Ochiai, E. I. "Bioinorganic Chemistry"; Allyn and Bacon: Boston, 1977; Chapter 9, pp 218–262; Chapter 10, pp 263–278.

(9) A common feature of multicopper enzymes is that they contain so-called type 3 copper centers which are strongly antiferromagnetically coupled. For some more recent efforts to mimic these characteristics, see: Fenton, D. E.; Lintvedt, R. L. *J. Am. Chem. Soc.* **1978**, *100*, 6367. Butcher, R. J.; Sinn, E. *Inorg. Chem.* **1976**, *15*, 1604. DeCourcy, J. S.; Waters, T. N. *J. Chem. Soc., Chem. Commun.* **1977**, 572. Moreland, J. A.; Doedens, R. J. *Inorg. Chem.* **1978**, *17*, 674. Grzybovski, J. J.; Merrell, P. H.; Urbach, F. L. *Ibid.* **1978**, *17*, 3078.

(10) Fenton, D. E.; Schroeder, R. R.; Lintvedt, R. L. *J. Am. Chem. Soc.* **1978**, *100*, 1931. Tsuruya, S.; Lintvedt, R. L. "Abstracts of Papers", 176th National Meeting of the American Chemical Society, Miami, Sept 1978; American Chemical Society: Washington, D.C., 1978. Brackman, W.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 937, 1021, 1070, 1100, 1107. Kinoshita, K. *Bull. Chem. Soc. Jpn.* **1959**, *32*, 777, 780, 783.

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biological systems overcome the low kinetic reactivity of molecular oxygen.[8]

In the following section we describe a simple chemical analogue of tyrosinase (eq 2) and elucidate the role of molecular oxygen in this transformation.

## Results and Discussion

**(1) Copper(II)-Catalyzed Oxidation of Catechols to *o*-Benzoquinones. Importance of the Relative Stabilities of the Copper(II) and Copper(I) Species in the Redox Process. (a) Reactions in the Absence of Oxygen.** Neither 3,5-di-*tert*-butylcatechol (DTBC) nor 4-*tert*-butylcatechol (TBC) reacts under anaerobic conditions with cupric chloride in the absence of base (Table I, experiments 1 and 2). While it was found that DTBC would react with cupric chloride in the presence of 1 molar equiv of triethylamine to give ca. 60% of 3,5-di-*tert*-butyl-1,2-benzoquinone (DTBQ), TBC under the same conditions gave only trace amounts of 4-*tert*-butyl-1,2-benzoquinone (TBQ, experiments 3 and 4). Attempted *anaerobic* oxidations of either DTBC or TBC *with an excess* of bis(1-phenyl-1,3,5-hexanetrionato)dicopper(II) complex[10] ($Cu_2(BAA)_2$) in the absence or presence of triethylamine gave barely detectable amounts of *o*-benzoquinone (experiments 5–7). When, however, the reaction of DTBC with $Cu_2(BAA)_2$ was carried out still under anaerobic conditions but in the presence of cupric chloride, a small quantity of DTBQ was produced (experiments 8 and 9). The same experiment in the presence of 1 molar equiv of triethylamine gave a 60% yield of DTBQ (experiment 10, compare with experiments 3 and 5).

**(b) In the Presence of Oxygen.** As recently reported,[10] $Cu_2(BAA)_2$ in the presence of 1 molar equiv of triethylamine efficiently catalyzed the reaction of DTBC with molecular oxygen and gave practically quantitative yield of DTBQ (experiment 11). Moreover, a similar reaction of DTBC with oxygen in the presence of a catalytic amount of cupric chloride and 1 molar equiv of triethylamine (experiment 13) also provided essentially quantitative yield of DTBQ. The reaction of TBC with oxygen in the presence of cupric chloride and 1 molar equiv of triethylamine in methylene chloride also gave almost a quantitative yield of TBQ (experiment 14). It is significant that the reaction with oxygen of both DTBC and TBC in the presence of cupric chloride but *in the absence of triethylamine* (experiments 13 and 15) occurred only after pronounced induction period.[11] While in these experiments the TBC was consumed, only a small amount of TBQ was detected, suggesting that other oxidation products were formed, presumably by further transformations of TBQ.

Even copper(II) species (eq 3), produced by the reaction of

$$4CuCl + O_2 \xrightarrow[CH_2Cl_2]{4py} [2CuCl_2 + (py)_2Cu\langle O_2 \rangle Cu(py)_2] \quad (3)$$

oxygen with a solution of cuprous chloride in methylene chloride containing 4 molar equiv of pyridine,[12] effectively catalyzed oxidations of both DTBC and TBC to the corresponding *o*-benzoquinones in quantitative yields (experiments 16 and 17).

**(c) Importance of the Relative Stabilities of the Copper(II) and Copper(I) Species in the Redox Processes.** In the previous work we showed that the anaerobic oxidation of catechols with active copper(II) reagents in pyridine was a reversible process.[2,3] The overall extent of the reversible electron transfer from catechol to copper(II) species and from copper(I) species to *o*-benzoquinones was shown to depend on the nature of both copper(II) and copper(I) species. It seems therefore reasonable that the higher yields

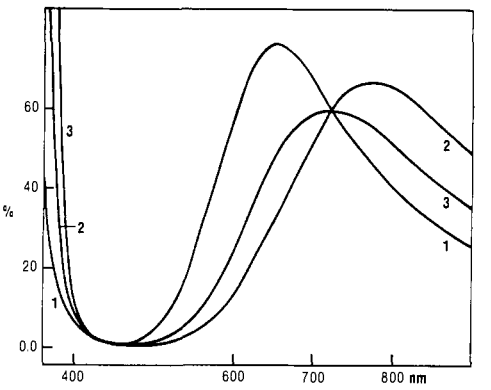



**Figure 1.** "Reaction" of cupric acetate ($8.92 \times 10^{-3}$ M) and cupric chloride ($4.71 \times 10^{-3}$ M) in pyridine: **1** = cupric acetate; **2** = cupric chloride; **3** = 1:2 (v/v) of **1** + **2**.

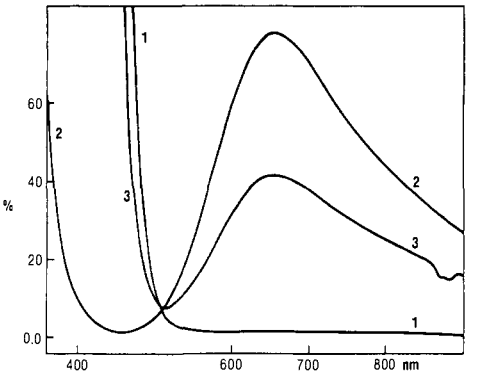



**Figure 2.** Reaction of cupric acetate ($8.92 \times 10^{-3}$ M) and cuprous chloride ($8.77 \times 10^{-3}$ M) in pyridine. **1** = cuprous chloride; **2** = cupric acetate; **3** = 1:1 (v/v) of **1** + **2**.

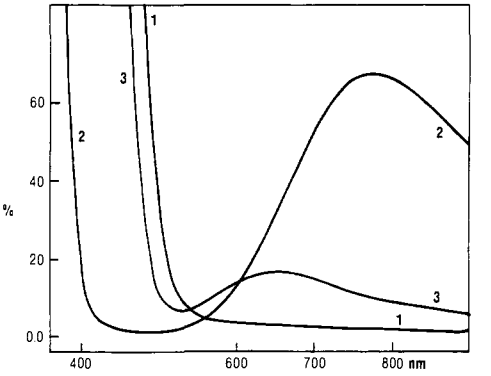
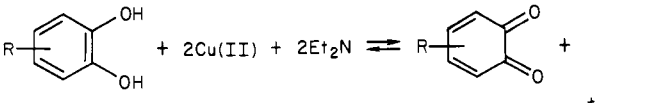



**Figure 3.** Reaction of cuprous acetate ($5.96 \times 10^{-3}$ M) and cupric chloride ($4.71 \times 10^{-3}$ M) in pyridine: **1** = cuprous acetate; **2** = cupric chloride; **3** = 1.5:1 (v/v) of **1** + **2**.

of *o*-benzoquinones in experiments 8–10 (equivalent to a more favorable equilibrium in eq 4) were similarly a direct consequence




(4)

of different thermodynamic stabilities of the $Cu_2(BAA)_2/Cu^I(HBAA)$ and $CuCl_2/CuCl$ pairs. It is well-known that the stabilities of copper(II) and copper(I) states are strongly solvent dependent.[13,14] Both bispyridine cupric chloride and cupric acetate react with copper metal in pyridine to give cuprous chloride[2] and

(11) Presumably, a free radical reaction of oxygen with the substrate, followed by the oxidation of the radical by cupric chloride, leads to the production of copper(I) species which then reacts with oxygen to generate the active copper(II)–oxygen species.[2,3]

(12) This reaction, just as the oxidation of cuprous chloride in pyridine mentioned earlier,[2,3] as well as those in eq 10 and 11, involves a normal $4Cu(I)/O_2$ stoichiometry. Presumably, thus generated copper(II) reagent, by analogy with the reagent resulting from the reaction of cuprous chloride with oxygen in pyridine alone[2,3] (eq 11), is a mixture of cupric chloride and copper(II)–oxygen species coordinated by pyridine ligands as indicated in eq 3 and 13.

(13) Nelson, I. V.; Larson, R. C.; Iwamoto, R. T. *J. Inorg. Nucl. Chem.* **1961**, *22*, 279.

(14) Drago, R. S.; Purcell, K. F. *Prog. Inorg. Chem.* **1964**, *6*, 280.

Table I. Oxidation of Catechols to *o*-Benzoquinones[a,b]

| no. | catechol[c] (mmol) | Cu(II)[c] (mmol) | base (mmol) | $O_2$, mmol | solvent/time | *o*-benzoquinone[c] (%) |
|---|---|---|---|---|---|---|
| 1 | 3,5-DTBC (10) | $CuCl_2$ (20) | | | $CH_2Cl_2$/24 h | 3,5-DTBQ (trace) |
| 2 | 4-TBC (10) | $CuCl_2$ (20) | | | py/24 h | 4-TBQ (trace) |
| 3 | 3,5-DTBC (10) | $CuCl_2$ (20) | $Et_3N$ (22) | | $CH_2Cl_2$/1 h–10 days[d] | 3,5-DTBQ (~60) |
| 4 | 4-TBC (10) | $CuCl_2$ (20) | $Et_3N$ (22) | | $CH_2Cl_2$/24 h | 4-TBQ (trace) |
| 5 | 3,5-DTBC (2.5) | $Cu_2(BAA)_2$ (3.2) | $Et_3N$ (3) | | $CH_2Cl_2$/18 h | 3,5-DTBQ (trace) |
| 6 | 3,5-DTBC (2.5) | $Cu_2(BAA)_2$ (3.2) | | | py/5 days | 3,5-DTBQ (trace) |
| 7 | 4-TBC (5.0) | $Cu_2(BAA)_2$ (5.0) | $Et_3N$ (5) | | py/3 days | 4-TBQ (trace) |
| 8 | 3,5-DTBC (2.5) | $Cu_2(BAA)_2$ (1.5) + $CuCl_2$ (2.5) | | | py/1–10 days[d] | 3,5-DTBQ (5–10) |
| 9 | 3,5-DTBC (10) | $Cu_2(BAA)_2$ (0.1) + $CuCl_2$ (20) | | | py/1 day | 3,5-DTBQ (5–10) |
| 10 | 3,5-DTBC (10) | $Cu_2(BAA)_2$ (0.1) + $CuCl_2$ (20) | $Et_3N$ (22) | | $CH_2Cl_2$/1 h–10 days[d] | 3,5-DTBQ (~60) |
| 11 | 3,5-DTBC (10) | $Cu_2(BAA)_2$ (0.1) | $Et_3N$ (22) | ~5 | $CH_2Cl_2$/10 h[e] | 3,5-DTBQ (>95) |
| 12 | 3,5-DTBC (10) | $CuCl_2$ (2) | $Et_3N$ (2) | ~5 | $CH_2Cl_2$/24 h | 3,5-DTBQ (>95) |
| 13 | 3,5-DTBC (10) | $CuCl_2$ (2) | | ~5 | py/24 h | 3,5-DTBQ (>95) |
| 14 | 4-TBC (10) | $CuCl_2$ (2) | $Et_3N$ (2) | ~5 | $CH_2Cl_2$/24 h | 4-TBQ (>95) |
| 15 | 4-TBC (10) | $CuCl_2$ (2) | | ~10 | py/48 h | 4-TBQ (trace)[f] |
| 16 | 4-TBC (10) | [$CuCl_2$ + CuO] (2)[g] | | ~5 | $CH_2Cl_2$/4 h | 4-TBQ (>95) |
| 17 | 3,5-DTBC (10) | [$CuCl_2$ + CuO] (2)[g] | | ~5 | $CH_2Cl_2$/4 h | 3,5-DTBQ (>95) |
| 18 | 3,5-DTBC (10) | Ⓟ-py·$CuCl_2$[h] (20) | | | $CH_2Cl_2$/4 h | 3,5-DTBQ (trace) |
| 19 | 3,5-DTBC (10) | Ⓟ-py·$CuCl_2$[h] (20) | | trace[i] | $CH_2Cl_2$/4 h | 3,5-DTBQ (trace) |
| 20 | 3,5-DTBC (10) | Ⓟ-py·$CuCl_2$[h] (20) | $Et_3N$ (22) | ~5 | $CH_2Cl_2$/2 h | 3,5-DTBQ (>95) |
| 21 | 4-TBC (10) | Ⓟ-py·$CuCl_2$[h] (20) | $Et_3N$ (22) | ~5 | $CH_2Cl_2$/2 h | 4-TBQ (>95) |
| 22 | 3,5-DTBC (10) | Ⓟ-py·$CuCl_2$[j] (2) | $Et_3N$ (22) | ~5 | $CH_2Cl_2$/4 h | 3,5-DTBQ (>95) |
| 23 | 4-TBC (10) | Ⓟ-py·$CuCl_2$[j] (2) | $Et_3N$ (22) | ~5 | $CH_2Cl_2$/4 h | 4-TBQ (>95) |
| 24 | 3,5-DTBC (10) | Ⓟ-py·[$CuCl_2$ + CuO][k] (10) | | | $CH_2Cl_2$/1 h | 3,5-DTBQ (~40) |
| 25 | 4-TBC (10) | Ⓟ-py·[$CuCl_2$ + CuO][k] (10) | | | $CH_2Cl_2$/1 h | 4-TBQ (~40) |
| 26 | 3,5-DTBC (10) | Ⓟ-py·[$CuCl_2$ + CuO][k] (2) | | ~5 | $CH_2Cl_2$/4 h | 3,5-DTBQ (>95) |
| 27 | 4-TBC (10) | Ⓟ-py·[$CuCl_2$ + CuO][k] (2) | | ~5 | $CH_2Cl_2$/4 h | 4-TBQ (>95) |
| 28 | 3,5-DTBC (10) | Ⓟ-py·[$CuCl_2$ + CuO][k,l] (2) | | ~5 | $CH_2Cl_2$/4 h | 3,5-DTBQ (>95) |

[a] All experiments carried out in a flask equipped with a mechanical stirrer and an inlet for maintaining the desired atmosphere. When oxygen was used, the amount that reacted was measured in a gas burette. All experiments at room temperature. [b] The analyses were carried out by NMR. [c] 3,5-DTBC = 3,5-di-*tert*-butylcatechol; 3,5-DTBQ = 3,5-di-*tert*-butyl-1,2-benzoquinone; 4-TBC = 4-*tert*-butylcatechol; 4-TBQ = 4-*tert*-butyl-1,2-benzoquinone; $Cu_2(BAA)_2$ = bis(1-phenyl-1,3,5-hexanetrionato)dicopper(II). [d] The yield did not change over a period of 1 h–10 days. [e] Reaction times were not optimized and they should not be taken to mean the actual reaction rate. [f] Most of 4-TBC was consumed in the reaction but only a small amount of 4-TBQ was detected, suggesting that other oxidation products were formed, presumably by further transformation of the *o*-benzoquinone. However, the nature of the products was not determined. [g] Cu(II) reagent resulting from the oxidation of cuprous chloride in methylene chloride containing 4 molar equiv of pyridine. For the nature of the reagent see ref 2 and 3. [h] Prepared by reaction of commercial poly(4-vinylpyridine) with cupric chloride; see Experimental Section. [i] Same experiment as in 18 except under oxygen. [j] Based on mole/equivalent of cupric chloride in a polymer complex; see Experimental Section. [k] Copper(II) polymer complex prepared by oxidation of Ⓟ-py·CuCl in methylene chloride; see Experimental Section. [l] Using copper(II) catalyst recovered from the experiment 26.

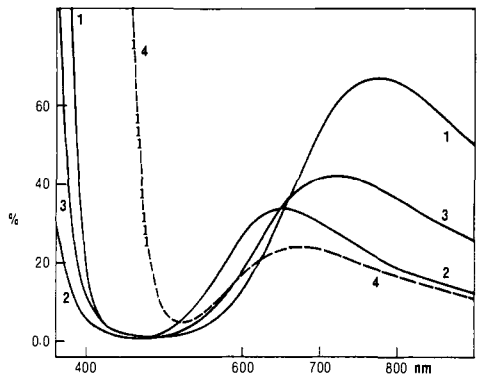
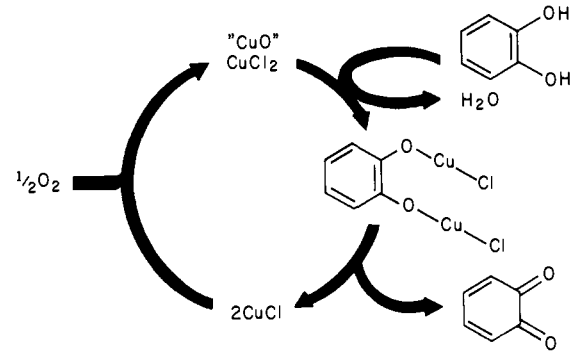



**Figure 4.** Reaction of cupric chloride ($4.71 \times 10^{-3}$ M) and cupric acetate ($3.88 \times 10^{-3}$ M) with an excess of copper(0) in pyridine: **1** = cupric chloride; **2** = cupric acetate; **3** = 1:1.21 (v/v) of **1** + **2**; **4** = same as **3** but after being stirred with copper(0) under nitrogen for 4 days.

cuprous acetate smoothly.[15] The disproportionation between cupric chloride and cupric acetate in pyridine to give cupric chloroacetate apparently does not take place (Figure 1). There is also no reaction between cupric chloride and cupric methoxide in pyridine, but in methanol the reaction between bispyridine cupric chloride and cupric methoxide gave pyridine cupric methoxy chloride.[16] We have now determined that cuprous chloride in

**Scheme I**




pyridine does not react with cupric acetate (eq 5; Figure 2), while cuprous acetate and cupric chloride do react to give cuprous chloride and presumably cupric chloroacetate which immediately disproportionates to thermodynamically stable mixture of cupric chloride and cupric acetate (equations 6, 6a, and 7; Figures 3 and 4).

$$Cu(OAc)_2 + CuCl \xrightarrow[py]{} CuClOAc + CuOAc \quad (5)$$

$$CuCl_2 + CuOAc \xrightarrow[py]{} [CuClOAc] + CuCl \quad (6)$$

$$[2CuClOAc] \xrightarrow[py]{} CuCl_2 + Cu(OAc)_2 \quad (6a)$$

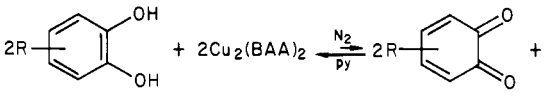
$$CuCl_2 + Cu(OAc)_2 + Cu(0) \xrightarrow[py]{} Cu(OAc)_2 + 2CuCl \quad (7)$$

In an attempt to obtain some information about relative stability of the copper(I) species that may be produced from the $Cu_2$-

(15) Ogura, T.; Fernando, Q. *Inorg. Chem.* **1973**, *12*, 2611. Kirchner, S. J.; Schubert, S. A.; Mounts, R. D.; Fernando, Q. *Inorg. Chim. Acta* **1978**, *27*, L80.

(16) Finkbeiner, H.; Hay, A. S.; Blanchard, H. S.; Endres, G. F. *J. Org. Chem.* **1966**, *31*, 549.

$(BAA)_2$ complex,[17] we stirred the complex with an excess of copper metal in pyridine under nitrogen over an extended period of time. After 48 h essentially all of the Cu(0) was recovered unchanged, and we had to conclude that the expected $Cu_2^I(BAA)$ product could not have any significant stability in pyridine.[18] Therefore, the increased yield of DTBQ in the reaction of DTBC with $Cu_2(BAA)_2$ in the presence of cupric chloride (experiments 8 and 9) clearly reflects greater thermodynamic stability of the $Cu_2(BAA)_2$/CuCl pair relative to $CuCl_2/Cu^I(HBAA)$ pair. Presumably, the copper(I) species resulting from the electron transfer from catechol to the $Cu_2(BAA)_2$ reagent (eq 8) undergoes an efficient ligand exchange with cupric chloride present to give thermodynamically more stable $Cu_2(BAA)_2$/CuCl pair (eq 9), thus assuring the observed conversion of catechol to *o*-benzoquinone. In the presence of oxygen the conversion of catechols



$$4Cu^I(HBAA) \quad (8)$$

$$4Cu^I(HBAA) + 2CuCl_2 \underset{py}{\overset{N_2}{\rightleftharpoons}} 4CuCl + Cu_2(BAA)_2 + 2H_2BAA \quad (9)$$

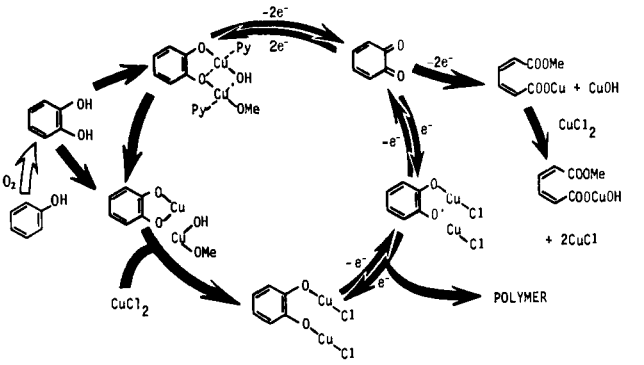
to *o*-benzoquinones becomes quantitative (experiments 11–14 and 16–17) because copper(I) species are continuously reoxidized (eq 10 and 11).

$$4Cu^I(HBAA) + O_2 \xrightarrow[py]{} 2Cu_2(BAA)_2 + 2H_2O \quad (10)$$

$$4CuCl + O_2 \xrightarrow[py]{} [2(py)_2CuCl_2 + (py)_nCu(O_2)Cu(py)_n] \quad (11)$$

**(d) The Active Species and Schematic Representation of the Catalytic Cycle.** The most plausible explanation of the experimental results is that the electron transfer from catechol to the copper(II) reagent begins only after catechol and copper(II) reagent form some copper(II) catecholate intermediate. Under anaerobic conditions this intermediate could be formed either by the reaction of copper(II) centers with the catecholate anion generated with an external base (experiments 3 and 10) or by the replacement of a neutral ligand (weaker "acid") from a copper(II) complex by a stronger acid, catechol itself (e.g., replacement of $H_2BAA$ from $Cu_2(BAA)_2$ or replacement of methanol from cupric methoxide[2]). Alternatively, the required copper(II) catecholate intermediate can be formed by a direct reaction of catechol with the resulting basic copper(II)–oxygen species (experiments 16 and 17) produced by the reaction of copper(I) species with oxygen[12] (eq 3 and 11).

Scheme II




It is of interest to recall that in order that the electron transfer from the organic ligand to the copper(II) centers in the monocopper(II) catecholates could begin to take place, the monocopper(II) catecholates first had to be converted into a dicopper(II) catecholate intermediate.[2,3] In their study of the kinetics of the reaction of DTBC with oxygen catalyzed by the $Cu_2(BAA)_2$ complex, Lintvedt and Tsuruya demonstrated[10] that the overall reaction was first order in the substrate and second order in Cu(II), thus in fact confirming that the active reaction intermediate involved in the rate-determining step was indeed such a dicopper(II) catecholate complex.

While precise details of the overall mechanism of the copper(II)-catalyzed transformations remain to be determined, Scheme I emphasizes the main features of the catalytic process: (i) formation of dicopper(II) catecholate intermediate; (ii) electron transfer from the aromatic ring to two copper(II) centers in the intermediate providing *o*-benzoquinone and two copper(I) centers; (iii) irreversible reaction of the generated copper(I) species with oxygen to give copper(II)–oxygen "reagent", and (iv) reaction of this "reagent" with catechol leading to regeneration of the dicopper(II) catecholate intermediate and formation of water as the byproduct. As the oxidation progresses, the water accumulates and begins to compete with catechol for the copper–oxygen species, probably leading to inert cupric oxide and ultimately to the interruption of the catalytic cycle.

Very efficient catalysts for this transformation can also be prepared in an "insoluble" form, by complexing copper species on a suitable polymer, as described in the next section.

**(e) Use of Copper(II) Reagent Supported on Polymer.** Addition of commercial poly(4-vinylpyridine) to a solution of cupric chloride in methanol led to the removal of the Cu(II) from the solution. The resulting copper(II) polymer complex, Ⓟ-py·$CuCl_2$, was insoluble in methylene chloride, and it was ineffective as a reagent for the oxidation of catechols under anaerobic as well as under aerobic conditions (Table I, experiments 18 and 19). However, the addition of 1 molar equiv of triethylamine to the suspension of the copper(II)–polymer complex in methylene chloride, followed by addition of catechols, led to the formation of *o*-benzoquinones (experiments 20 and 21). The same reaction can also be carried out by using a catalytic amount of the Ⓟ-py·$CuCl_2$ complex in the presence of oxygen (experiments 22 and 23).

When the same polymer was added to a solution of cuprous chloride in acetonitrile, a quantitative removal of the copper(I) from the solution was achieved[19] (eq 12). The resulting yellow

$$Ⓟ\text{-py} + CuCl \xrightarrow[CH_3CN]{N_2} Ⓟ\text{-py·CuCl}\downarrow \quad (12)$$

copper(I)–polymer complex is insoluble in methylene chloride; on exposure to oxygen with stirring the oxidation of copper(I)—to copper(II)—takes place. After an amount of oxygen required to convert copper(I) to copper(II) was consumed, the oxygen uptake ceased[12] (eq 13). The brown-green polymer complex is insoluble in methylene chloride, and it can be recovered by a simple fil-

(17) There is no indication that $Cu^I(HBBA)$ species were observed previously.[10]

(18) Similarly, reactions of other strongly chelated copper(II) complexes, copper(II) acetylacetonate and copper(II) catecholates,[2] with copper metal in pyridine also do not take place. It is instructive, however, that copper(I) species such as cuprous acetate and cuprous *tert*-butoxide undergo very rapid disproportionation in acetylacetone solvent to give the $Cu(acac)_2$ and copper metal.

$$2CuOAc \xrightarrow[CH_3COCH_2COCH_3]{\text{room temp}} Cu(acac)_2 + Cu(0) + 2CH_3COOH$$

$$2CuO\text{-}t\text{-}Bu \xrightarrow[CH_3COCH_2COCH_3]{\text{room temp}} Cu(acac)_2 + Cu(0) + 2\text{-}t\text{-}BuOH$$

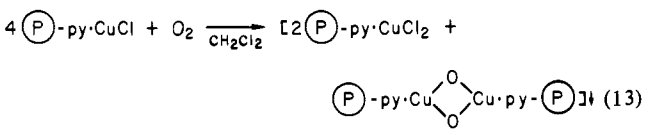
Under the same conditions cuprous chloride appears inert. Presumably, a ligand exchange of cuprous acetate or cuprous *tert*-butoxide with acetylacetone provides the corresponding copper(I) acetylacetonate and acetic acid or *tert*-butyl alcohol. The copper(I) acetylacetonate then undergoes the disproportionation to give the $Cu(acac)_2$ and Cu(0).

$$CuX + CH_3COCH{=}C(CH_3)OH \underset{CH_3COCH_2COCH_3}{\rightleftharpoons} CuOC(CH_3){=}CHCOCH_3 + HX$$

$$2CuOC(CH_3){=}CHCOCH_3 \xrightarrow[CH_3COCH_2COCH_3]{} Cu(acac)_2 + Cu(0)$$

The analogous reaction with cuprous chloride does not take place. In this case the initial formation of copper(I) acetylacetonate would also involve formation of hydrochloric acid, a process which is not thermodynamically favored.

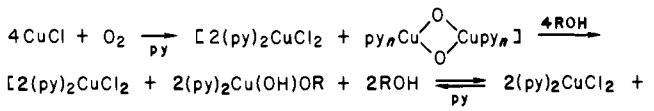
(19) Interestingly, in pyridine this complex is not formed nearly as efficiently as in acetonitrile.



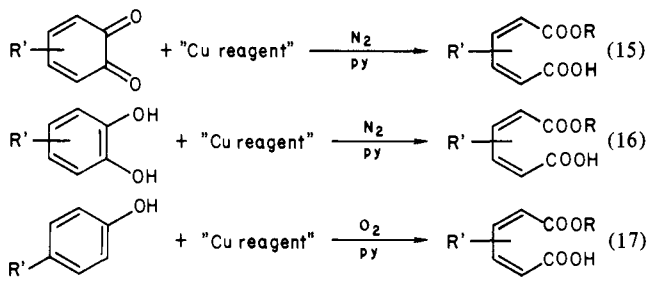
(13)

tration. Otherwise, addition of catechols to the suspended copper(II)–polymer complex in methylene chloride under nitrogen led to the generation of *o*-benzoquinones (experiments 24 and 25). When the reaction with catechols was carried out in the presence of oxygen, a quantitative yield of the corresponding *o*-benzoquinones was realized (experiments 26 and 27). The products were isolated by a simple filtration of the insoluble copper(II)–polymer complex and evaporation of the solvent. The recovered Ⓟ-py; $Cu^{II}$ complex can be used again as a catalyst (experiment 28).

**(2) Oxidation of Phenol to Muconic Acid Derivatives. (a) Active Copper(II) Reagent Derived from Phenol.** Scheme II summarizes the overall transformations of catechols and *o*-benzoquinones to muconic acid monoesters with the copper(II) reagents (prepared by the addition of a "nucleophile", ROH, to the products of oxidation of cuprous chloride in pyridine (eq 14 and 15, R = Me, Et, *n*-Pr, etc.)), that was discussed previously.[2,3] Black arrows



(14)



(15)

(16)

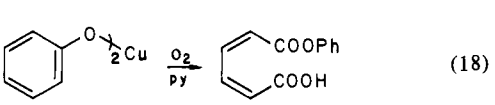
(17)

in the scheme indicate individual reaction steps which do not require the presence of molecular oxygen (see eq 15 and 16). Unlike these reactions, the conversion of phenol to the muconic acid ester (eq 17, presumably through the intermediacy of catechol and *o*-benzoquinone) occurs only in the presence of oxygen, and for emphasis this particular reaction step(s) in Scheme II is represented by a "white" arrow.

We have now established that copper(II) reagents based on phenols rather than alcohols (eq 14, R = Ph) convert these substrates to the corresponding monophenyl esters. Thus, addition of required amount of phenol to the degassed solution containing the products of oxidation of cuprous chloride in pyridine (eq 14, R = Ph), followed by addition of *o*-benzoquinone (eq 15, R = Ph, R′ = *t*-Bu), catechol (eq 16, R = Ph, R′ = H, 4-*tert*-Bu, 3,5-*t*-$Bu_2$), or phenols (eq 17, R = Ph, R′ = H, *t*-Bu), gave the corresponding monophenyl esters of muconic acid in good yields.

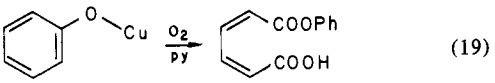
The present experiments suggest that the addition of phenol instead of methanol to the products of oxidation of cuprous chloride (eq 14) produces a mixture of bispyridine cupric chloride and cupric phenoxyhydroxide or cupric phenoxide and water (eq 14, R = Ph). Copper(II) reagent containing cupric phenoxyhydroxide (eq 14, R = Ph) produced by transformations presented in eq 15–17 is chemically analogous to the corresponding copper(II) reagent containing cupric methoxy hydroxide[2,3] (eq 14, R = Me). Moreover, it also follows that a bona fide cupric phenoxide or cupric hydroxy phenoxide should also react with oxygen and provide monophenyl ester of muconic acid.

**(b) Reactions of Copper(II) and Copper(I) Phenoxides with Oxygen.** Reaction of cupric phenoxide with oxygen in pyridine at room temperature proceeds rapidly and after typical workup gives the monophenyl ester of muconic acid in ca. 60% yield (eq 18). When the reaction was repeated at 0 °C, a short induction



(18)

period was detected.[20] The reaction of cuprous phenoxide with oxygen in pyridine at room temperature also gave the monophenyl ester of muconic acid (eq 19). This oxidation proceeded sig-



(19)

nificantly faster than the one with cupric phenoxide, and unlike in the latter reaction there was no evidence of any induction period even at −20 °C.

The induction period in the reaction of cupric phenoxide was eliminated by addition of catalytic amount of either cuprous chloride or hydrogen peroxide.

The fact that the yields of monophenyl muconic acid ester in the reactions of copper(II) and copper(I) phenoxides with oxygen were practically identical with the yields of monophenyl muconate produced in reactions of catechol or phenol itself with the corresponding "Cu reagent" (eq 16 and 17, R = Ph, R′ = H) suggests strongly (a) that the reaction with phenol (eq 17, R = Ph, R′ = H) involves copper phenoxides as intermediates and (b) that both copper(II) and copper(I) phenoxides undergo the overall transformation through a common intermediate. It appears reasonable that such common intermediate might be either dicopper(II) phenoxy peroxide or the corresponding bis(μ-oxo)copper(III) phenoxide[7,20,21] which could be formed by either a two- or four-electron reduction of molecular oxygen by two copper(I) phenoxides. In the following section we briefly discuss possible reaction pathways that may lead to such an intermediate and how its further transformations could provide the observed reaction products.

**(c) Possible Mechanism for the Reaction of Copper Phenoxides with Oxygen.** The "induction period" in the reaction of copper(II) phenoxide with oxygen[22] suggests an initial attack of triplet oxygen on the phenoxide anion. The oxidation of the resulting free radical by cupric phenoxide would provide copper(I) phenoxide that then can enter a spin-allowed reaction with oxygen just as any other reactive copper(I) species.[7] We have shown that, contrary to the literature reports,[23,24] the reaction of cuprous chloride with oxygen in pyridine is third order in cuprous chloride and first order in oxygen.[7] Thus far we were unsuccessful in measuring the kinetics of the reaction of cuprous phenoxide with oxygen, and hence we cannot say much about the mechanism of this reaction. Nevertheless, unlike in the reaction of cuprous chloride with oxygen in which the reduction of oxygen to thermodynamically stable reduced species required 4 equiv of copper(I), in the reaction with cuprous phenoxide, the oxygen does not have to react with 4 equiv

(20) For the involvement of copper(III) species in oxidation catalyzed by galactose oxidase see: Dirkacz, G. R.; Libby, D.; Hamilton, G. A. *J. Am. Chem. Soc.* **1976**, *98*, 626.

(21) For the description and properties of a dimeric copper(III) hydroxide intermediate see: Gray, E. T., Jr.; Taylor, R. W.; Margerum, D. W. *Inorg. Chem.* **1977**, *16*, 3047. This dimer is a strong oxidizing agent with $E^{\circ} = 0.82$ V (vs. NHE) in 1 M NaOH. These authors suggested that their hydroxide-bridged copper(II) dimer appears to be an effective oxidation catalyst because of its ability to give up two electrons to form the Cu(III) dimer. Measurements of reaction entropies of a copper(III, II) peptide redox couple indicated the absence of axial solvent coordination in copper(III) peptide complex in accord with a square-planar coordination for the $d^8$ electronic configuration. In anhydrous media the reduction potential of the copper(III) complex was significantly reduced, suggesting that in biological systems in hydrophobic protein environment the copper(III) state might be much more easily accessible than has been realized: Youngblood, M. P.; Margerum, D. W. *Inorg. Chem.* **1980**, *19*, 3068.

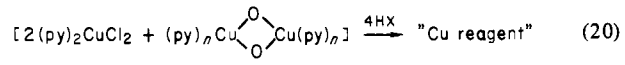
(22) Unlike the induction period in reaction of catechols with oxygen in the presence of cupric chloride[11] (Table I, experiments 13 and 15), the induction period in this reaction was very short and even at 0 °C was only 10–20 s.

(23) Coudurier, G.; Praliend, H.; Mathieu, H. V. *Spectrochim. Acta, Part A* **1974**, *30A*, 1399.

(24) Tsuchida, E.; Kaneko, M.; Nishide, H. *Makromol. Chem.* **1972**, *151*, 221.

of copper(I) phenoxide to gain third and fourth electrons in order to provide thermodynamically stable reduced oxygen species.[25] Further stabilization of the partially reduced oxygen species after the initial two-electron reduction by two copper(I) phenoxides can be achieved unimolecularly by an intramolecular transfer of the required two electrons from the ortho position of the phenoxy group to the electrophilic oxygen attached to the same copper center. Scheme III illustrates these possible transformations that could provide either a dicopper(II) catecholate as an intermediate or the corresponding *o*-benzoquinone and two copper(I) centers. Reaction of *o*-benzoquinone with cupric phenoxy hydroxide will give copper(I) salt of muconic acid half ester and another copper(I) species.[2,3] The propagation of the reaction would then be assured by reaction of oxygen with copper(I) phenoxide. It appears reasonable that the direct conversion of phenol into muconic acid half esters[2,3] must also involve in situ generation of copper(I) phenoxide which then undergoes the same reaction with oxygen as a bona fide cuprous phenoxide.

**(3) Reactions of *o*-Benzoquinones, Catechols, and Phenols with Other Copper(II) Reagents. (a) Formation of Muconic Acid Mononitriles.** From the preceding section and earlier[2,3] discussions, it appears that the active component of the copper(II) reagent, effecting the carbon-carbon bond cleavage of *o*-benzoquinones and catechols, is generated by the reaction of copper(II)–oxygen species with a nucleophile ROH that could be an alcohol or even phenol itself (eq 14, R = Me, Ph). It is of interest that the copper(II) reagent, generated with water as a nucleophile (eq 20, HX = $H_2O$), reacted with 4-*tert*-butylcatechol under nitrogen to give a lactone of 3-hydroxy-4-*tert*-butylmuconic acid (eq 21).



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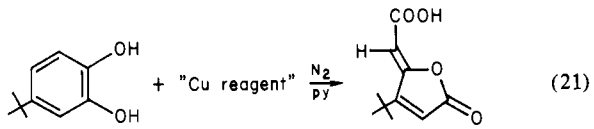
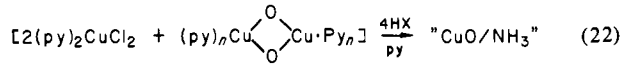


(21)

Using anhydrous ammonia as a *nonhydroxylic* nucleophile HX in eq 22 produced a new copper(II) reagent abbreviated as



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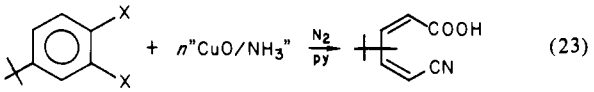

(23)

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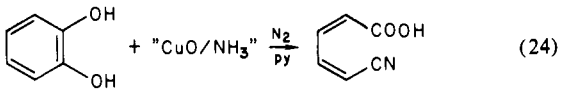
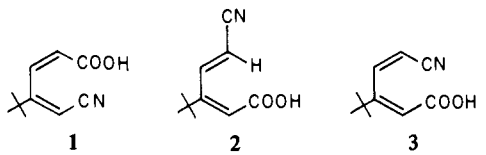


(24)

4

"$CuO/NH_3$", which was capable of converting *o*-benzoquinones (eq 23, X = O, *n* = 0.5), and catechols (eq 23, X = OH, *n* = 1, and eq 24) as well as phenols (eq 25) to the corresponding muconic acid nitriles in a single step.

Thus, the reactions with 4-*tert*-butyl-1,2-benzoquinone and 4-*tert*-butylcatechol under nitrogen (eq 23), followed by a typical workup, afforded the same mixture of isomeric muconic acid mononitriles **1**, **2**, and **3**, in ratios of 5:4:1 in approximately 60–70% yield.

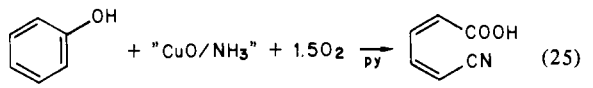



1 2 3

Reaction with the catechol produced previously unknown cis,cis isomer of muconic acid mononitrile **4** in about 50% yield (eq 24).

These products were formed in virtually the same yields when the corresponding reactions were carried out in the presence of oxygen. From the amounts of oxygen consumed it appears that oxygen was used to reoxidize copper(I) species produced in the reaction of substrates with the copper(II) reagent.

In the absence of oxygen phenol does not react with the "$CuO/NH_3$" reagent and was isolated from the reaction mixture unchanged. However, in the presence of oxygen, just as in the case of oxidations to muconic acid monoalkyl esters,[2,3] phenol does react and gave the *cis,cis*-muconic acid mononitrile **4** in 60–70% yield (eq 25). This particular transformation, compared with



(25)

4

the corresponding reaction with catechol (eq 24), that gives the same product, was significantly slower. At room temperature and under atmospheric pressure of oxygen the complete oxygen uptake required about 16 h.

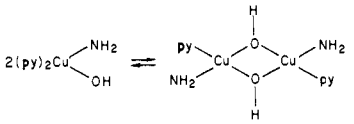
The nature of the "$CuO/NH_3$" reagent is not yet fully understood.[26] The solid reagent can be isolated from pyridine by filtration at 0 °C, stored in a refrigerator protected from moisture, and used again without appreciable loss of activity. The reagent analyzes for $Cu_2Cl_2ON_4H_{12}$. The solid appears totally insoluble in pyridine that contain an excess of ammonia. When the solid was suspended in pyridine that did not contain ammonia, it appeared that ammonia was given off. The pyridine became slightly colored (black-green color), indicating that small amounts of copper(II) was now in solution. Addition of 4-*tert*-butylcatechol under nitrogen to this suspension, followed by the usual workup, afforded the same mixture of isomeric muconic acid nitriles **1**, **2**, and **3**, in approximately 50% yield. This demonstrates that the isolated solid reagent can be used to produce the same reactive copper(II) species that are present in the reagent generated in situ.[27]

A reactive "$CuO/NH_3$" reagent can also be generated by oxidizing copper(I) chloride in ammonium hydroxide solution. Moreover, the conversion of phenol and catechol to the acid nitrile **4** was also possible in this aqueous solvent system. This suggests that the nature of the solvent used in this reaction[28] may not be critical, provided that the solvent is capable of effective solvaton of both copper(II) and copper(I) species.[13,14]

**(b) Possible Mechanism for the Muconic Acid Nitrile Formation.** At this time it is not known how "$CuO/NH_3$" reagent introduces the nitrogen into the substrate to give the muconic acid nitrile. It appears that the muconic acid nitrile is not formed by the dehydration of the corresponding amide, since the treatment of an amide with the "$CuO/NH_3$" reagent under comparable re-

(25) In other words, unlike $4Cu(I)/O_2$ stoichiometry in reduction of oxygen by cuprous chloride or cuprous acetate, a $2Cu(I)/O_2$ stoichiometry is sufficient for the complete reduction of oxygen by cuprous phenoxide.

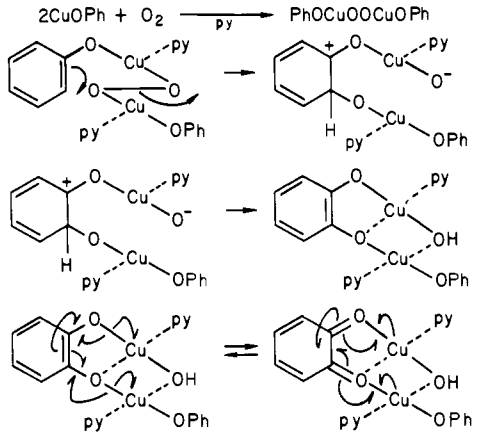
(26) Formally, "$CuO/NH_3$" reagent is a mixture consisting of either bispyridine cupric chloride or cupric chloride complexed with ammonia, or both, and the product(s) of the reaction of monomeric, dimeric, or oligomeric cupric oxide with ammonia. By analogy with the active component of the reagent(s) used in converting the same substrates to muconic acid monoalkyl esters[2,3] (eq 14), the active component of this reagent may be viewed as a dimeric copper(II) amide hydroxide present in equilibrium with the corresponding monomeric and oligomeric species complexed with pyridine or ammonia.




(27) It should be noted that the "$CuO/NH_3$" reagent refers to a mixture of several copper species[26] resulting from the reaction whose stoichiometry is indicated in eq 22, assuming a minimum ratio of $Cu/NH_3$ of 2. The "stoichiometries" in eq 23–26 indicate amounts of the "$CuO/NH_3$" reagent that would be required for the appropriate oxidations; however, in the actual experiments an excess of the reagent was used (see Experimental Section).

(28) Other solvents, including *N,N*-dimethylformamide and *N*-methylpyrrolidone, have also been successfully used in the reaction.

Scheme III

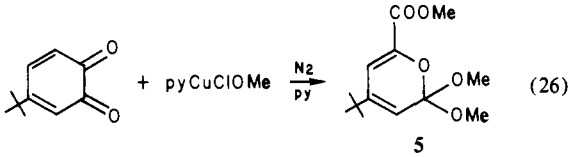



action conditions did not produce any of the expected nitrile. While aromatic *o*-diamines react with certain copper(II) reagents in the presence of oxygen to give muconic acid dinitriles,[29] an attempted reaction of *o*-aminophenol with the "$CuO/NH_3$" reagent did not produce any muconic acid mononitrile.

It is of interest, however, that *n*-heptaldehyde, benzaldehyde, and cinnamaldehyde all reacted with the "$CuO/NH_3$" reagent under nitrogen and gave the corresponding nitriles in good yields. While this may suggest that muconic acid mononitrile was produced from the muconic acid monoaldehyde, it is difficult to envision how *o*-benzoquinone could give muconic acid half aldehyde, a product which is at the same oxidation level as the *o*-benzoquinone itself.

Consequently, it is very likely that the mechanism of the cleavage of carbon–carbon bond may be similar to the proposed mechanism for the cleavage of *o*-benzoquinone to monoalkyl ester of muconic acid.[2,3] An initial interaction of *o*-benzoquinone with the copper(II) center of "$CuO/NH_3$" reagent, followed by transformations summarized in Scheme IV, could provide a pathway for the oxidative two-electron carbon–carbon bond cleavage directly to copper(I) salt of the muconic acid mononitrile and another copper(I) species.

**(c) Copper Reagent Prepared by Reaction of Pyridine Cupric Methoxy Chloride with Ammonia in Pyridine.** Previously we have shown[6] that pyridine cupric methoxy chloride in pyridine under anaerobic and anhydrous condition reacted with 4-*tert*-butylcatechol and 4-*tert*-butyl-1,2-benzoquinone to give 2,2-dimethoxy-6-(carbomethoxy)-4-*tert*-butyloxacyclohexa-3,5-diene (**5**) in reasonable yields (eq 26).

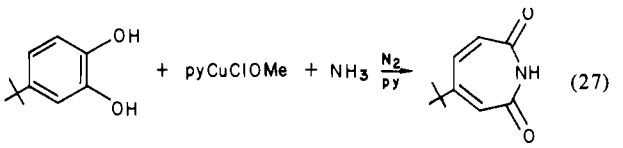



(26)

**5**

We have now established that this reagent shows still another different redox behavior with the same substrates under anhydrous and anaerobic conditions in the presence of anhydrous ammonia. Addition of anhydrous ammonia to a pyridine solution of pyridine cupric methoxy chloride under nitrogen, followed by addition of 4-*tert*-butylcatechol, gave approximately 50% of 4-*tert*-butylmuconic acid imide (**6**) (eq 27). 3,5-Di-*tert*-butyl-1,2-benzoquinone and 3-methoxy-4-*tert*-butylcatechol gave the corresponding substituted 4-*tert*-butylmuconic acid imides in similar yields.

**(4) Implications Regarding So-Called Type 3 Copper-Containing Enzymes.** It is intriguing that even such a simple copper(II) system, formed by the reaction of oxygen with cuprous chloride in aprotic solvents like pyridine or even methylene chloride (eq 3 and 11), can act as an efficient catalyst for the conversion of




(27)

**6**

catechols to *o*-benzoquinones. Moreover, even cupric chloride catalyzed efficiently the same reaction in the presence of bases such as triethylamine. We have discussed elsewhere both the spectroscopic and chemical properties of the active component of the copper(II) reagent resulting from the reduction of oxygen by cuprous chloride.[2] Here we emphasize the fact that the copper(II) centers of this component are, just as the copper(II) centers of more elaborate enzyme molecules and certain chemical models,[9] strongly antiferromagnetically coupled and ESR inactive.

The premise that an efficient electron-transfer process in oxidation of catechols to *o*-benzoquinones requires *a special reagent* in which the metal center must be held together in a highly organized environment[9] is, at least in the present cases, too restrictive. Evidently, *two copper(II) centers in the dicopper(II) catecholate intermediate* generated in situ *are held together effectively enough by the substrate itself* to ensure a rapid, albeit reversible,[2,3] electron transfer *without the need for an auxilliary constraining environment.* Under anaerobic conditions the extent of the electron transfer to the metal centers is determined by the thermodynamic stabilities of the copper(II)/copper(I) pair(s) (eq 8 and 9). If the generated copper(I) species are thermodynamically unstable, only a small amount of *o*-benzoquinone would be present at the equilibrium. In the presence of oxygen, however, the electrons from the generated copper(I) species are transferred to $O_2$ (eq 10 and 11) which acts as the ultimate electron acceptor. This assures that the initial equilibrium between catechol and *o*-benzoquinone (eq 8 and 9) will be displaced in favor of the latter until catechol is completely converted into *o*-benzoquinone. Since the final transfer of electrons to molecular oxygen occurs from the copper(I) species (eq 10 and 11) rather than from the organic substrate, a special mechanism for activation of molecular oxygen is not required. Clearly, it is attractive to hypothesize that certain biological transformations like those catalyzed by tyrosinases, lacases, and other enzymes[8-10] containing the type 3 copper centers may also proceed by basically similar mechanisms. Accordingly, the role of oxygen in these transformations may also be to act as a thermodynamic driving force by reoxidizing generated copper(I) species back to the active copper(II)–oxygen species.

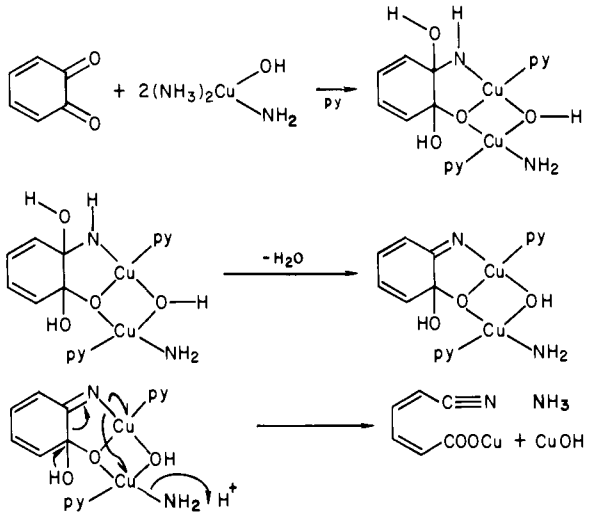
## Conclusions

The overall transformations of phenol either to monoalkyl esters of muconic acid or to muconic acid mononitrile involve sequential oxidations of phenol to catechol, of catechol to *o*-benzoquinone, and of *o*-benzoquinone to the muconic acid derivatives. The first step in this sequence occurs only in the presence of oxygen, and the subsequent steps are effected by respective copper(II) reagents even in the absence of oxygen. In principle, the overall conversion of phenol to muconic acid derivatives in the presence of oxygen should be catalytic in copper. While there is some indication that this may indeed be so, at this time it is not yet known how to do this experimentally. It is certain, however, that the second step, oxidation of catechols to *o*-benzoquinones, can indeed be carried out efficiently in the presence of catalytic amounts of certain copper(II) species. In this case, the oxygen simply drives the reaction toward its thermodynamic conclusion. Earlier studies of the stoichiometric reaction demonstrated a multicomponent nature of the copper(II) reagent and elucidated the role of individual components in the reaction sequence. The active component of the copper(II) reagent could be generated not only by reaction with alcohols as nucleophiles but also with phenols as well as by reaction with nonhydroxylic nucleophiles such as ammonia.

It appears that copper(I) phenoxide is the active reaction intermediate involved in the oxidation of phenol. Most plausible mechanistic interpretation of the experimental results involves

(29) Kajimoto, T.; Takahashi, H.; Tsuji, J. *J. Org. Chem.* **1976**, *41*, 1389.

Scheme IV



either a two- or a four-electron reduction of a single molecule of oxygen by two copper(I) phenoxides to give an intermediate which could be represented either as a dicopper(II) phenoxy peroxide or as a corresponding bis($\mu$-oxo)copper(III) complex. Intramolecular transfer of the required electrons from the ortho position of the phenoxy group to the electrophilic oxygen attached to the same copper center provides a dicopper(II) catecholate intermediate which then undergoes further reaction to give *o*-benzoquinone and two copper(I) species. Transformation of *o*-benzoquinone to muconic acid derivatives proceeds by already discussed chemistry, providing copper(I) species such as cuprous hydroxide or cuprous muconate. The efficiency by which phenol is being converted into muconic acid products depends on the competition between propagation and termination steps in the overall reaction cycle. Clearly, the propagation would be assured by exclusive reduction of oxygen by cuprous phenoxide. On the other hand, if oxygen is also being reduced by other copper(I) species such as those just mentioned (including cuprous chloride), the resulting copper(II) species will become "inactive" as far as phenol is concerned, and the new reaction cycle would have to be initiated again, for example, by a reaction of triplet oxygen with phenoxide anion. It seems, therefore, that a successful development of a copper-catalyzed conversion of phenol and oxygen into muconic acid derivatives (monoalkyl esters or mononitriles) would depend on successful solution of these problems.

Conversion of *o*-benzoquinones by "$CuO/NH_3$" reagent to muconic acid mononitriles probably occurs by the mechanism similar to the one for formation of muconic acid monoalkyl esters. The active component of the "$CuO/NH_3$" reagent can be represented as a dimeric copper(II) amide hydroxide present in equilibrium with the corresponding monomeric and/or oligomeric species complexed with pyridine and/or ammonia.

The fact that copper(II)–oxygen species produced by reduction of oxygen with cuprous chloride in aprotic solvents such as pyridine or methylene chloride was efficient as the catalyst for oxidation of catechols to *o*-benzoquinones clearly demonstrates that rapid electron transfer from the substrate to the copper catalyst, albeit reversible, can take place even in the absence of auxilliary ligand systems that otherwise would assure antiferromagnetic coupling between two copper(II) centers. Consequently, it is attractive to hypothesize that those biological transformations catalyzed by tyrosinase, lacase, and other enzymes that contain so-called type 3 copper centers may also operate by basically similar mechanism, utilizing molecular oxygen as a thermodynamic driving force to reoxidize copper(I) species produced in the forward reaction back to the active copper(II)–oxygen species.

## Experimental Section

The reported melting points are uncorrected. GLC analyses were generally carried out on a Hewlett-Packard 5700A instrument by using 3- or 6-ft of either 10% SE-30 or 10% Carbowax 20M columns packed on Chromosorb W. $^1H$ NMR spectra were recorded on either a Varian A-60 or Varian T60-A 60-MHz or HA 100-MHz instrument, while $^{13}C$ NMR spectra were measured on a Varian CFT-20 instrument using tetramethylsilane as an internal standard. EPR spectra were taken on a Varian E-12 EPR spectrometer. Routine chemical ionization mass spectra were obtained on a Finnigan 3100D mass spectrometer, while high-resolution mass spectra were obtained on an AEI M.S. 902 instrument.

Catechol, 4-*tert*-butylcatechol, 3,5-di-*tert*-butylcatechol, and phenol were commercial products which were purified by crystallization and stored under dry and inert atmosphere. Pyridine, methylene chloride, and other solvents were freshly distilled before use, and other solvents were purified similarly. Cuprous chloride was a commercial product which was prereduced by sulfurous acid according to the standard literature procedure.[30] Cupric chloride was an anhydrous commercial product. Bis(1-phenyl-1,3,5-hexanetrionato)dicopper(II) complex ($Cu_2(BAA)_2$) was prepared by the method of Fenton and Lintvedt.[9,10] Cupric phenoxide and cuprous phenoxide were prepared by reaction of phenol with cupric methoxide and cuprous *tert*-butoxide in pyridine and stored under dry and inert atmosphere.

The typical reaction vessel used was a three-neck 250- or 500-mL flask equipped with a mechanical stirrer, an addition funnel, and an inlet attached either to a nitrogen bubbler or to an oxygen buret.

**Cupric Chloride Oxidations of 3,5-Di-*tert*-butylcatechol and 4-*tert*-Butylcatechol to *o*-Benzoquinones. (a) In Methylene Chloride. Under an Inert Atmosphere.** A typical reaction flask was charged with 100 mL of freeze-thawed methylene chloride and 2.69 g (20 mmol) of cupric chloride under a helium atmosphere. To the resulting suspension was added triethylamine (2.23 g, 22.0 mmol) causing some of the cupric chloride to dissolve. An additional funnel was charged with a solution of 3,5-di-*tert*-butylcatechol (2.22 g, 10 mmol) or 4-*tert*-butylcatechol (1.66 g, 10 mmol) in 30 mL of methylene chloride and added over 30 min with stirring at room temperature. After quenching by addition of 50 mL of 3 N hydrochloric acid, the reaction mixture was worked up by the usual procedure. Methylene chloride solution was dried over sodium sulfate and evaporated in vacuo. The resulting products were analyzed by TLC and NMR, and the results are summarized in Table I. The same procedure was used in the experiments without triethylamine.

**(b) In Pyridine.** When the reactions were carried out in pyridine, the addition of cupric chloride led to precipitation of blue bispyridine cupric chloride. Addition of catechols, however, caused the reaction to occur. After complete reaction the pyridine was evaporated in vacuo at room temperature, and the resulting reaction products were analyzed as before. The results are summarized in Table I.

**Oxidations of Catechols with the $Cu_2(BAA)_2$ Reagent under an Inert Atmosphere. (a) In the Absence of Cupric Chloride.** The attempted oxidations in both methylene chloride and in pyridine, in the absence or in the presence of triethylamine, provided only trace amounts of *o*-benzoquinones (Table I).

**(b) In the Presence of Cupric Chloride.** When the oxidations of 3,5-di-*tert*-butylcatechol were carried out in the presence of cupric chloride, but in the absence of triethylamine, about 5–10% of 3,5-di-*tert*-butyl-1,2-benzoquinone was obtained. In the presence of triethylamine, however, the yield of the *o*-benzoquinone was increased to about 60% (Table I).

**$Cu_2(BAA)_2$-Catalyzed Oxidation of 3,5-Di-*tert*-butylcatechol.** Oxidation of 3,5-di-*tert*-butylcatechol (2.22 g, 10 mmol), in methylene chloride catalyzed by $Cu_2(BAA)_2$ (0.053 g, 0.1 mmol), in the presence of a slight molar excess of triethylamine (2.2 g, 22 mmol), consumed 5 mmol of oxygen and after usual workup gave a 95% yield of the 3,5-di-*tert*-butyl-1,2-benzoquinone (Table I).

**Cupric Chloride Catalyzed Oxidation of Catechols. (a) In Methylene Chloride.** A solution of 3,5-di-*tert*-butylcatechol (2.22 g, 10 mmol) or 4-*tert*-butylcatechol (1.66 g, 10 mmol), in methylene chloride (100 mL), containing cupric chloride (0.27 g, 2 mmol), and 2 mmol of triethylamine (0.2 g) was exposed to oxygen with stirring. After 1 molar equiv of oxygen was taken up, the reaction mixture was worked up to give essentially quantitative yields of the corresponding *o*-benzoquinone (Table I).

**(b) In Pyridine.** While an analogous experiment in pyridine in the absence of triethylamine gave the 3,5-di-*tert*-butyl-1,2-benzoquinone quantitatively, the same experiment with 4-*tert*-butylcatechol consumed an excess of oxygen but it did not afford the *o*-benzoquinone.

**Oxidation of Catechols Catalyzed by the Copper Reagent Prepared by Reaction of Cuprous Chloride with Oxygen.** A solution of cuprous chloride (0.198 g, 2.00 mmol) and pyridine (0.633 g, 8.00 mmol) in 150 mL of methylene chloride was exposed to oxygen. After the oxygen uptake ceased, to the resulting light green solution of the copper reagent

(30) Keller, R. N.; Wycoff, H. D. *Inorg. Synth.* **1946**, *2*, 1.

was added a solution of either 4-*tert*-butylcatechol or 3,5-di-*tert*-butylcatechol (10 mmol) in 30 mL of methylene chloride under oxygen. After 1 molar equiv of oxygen was consumed, the reaction ceased and it was worked up as usual. In both cases essentially quantitative yields of *o*-benzoquinones were obtained (Table I).

**Oxidation of Catechols Catalyzed by Cupric Chloride Supported on Poly(4-vinylpyridine). (a) Preparation of the Reagent.** To a suspension of a commercial poly(4-vinylpyridine) (4.2 g, 40 mmol), in 100 mL of methanol was added cupric chloride (1.34 g, 10 mmol). After the solution was stirred for 30 min, the solid was filtered and washed with methanol. Practically all of the cupric chloride was retained by the polymer. The powdery solid was dried under nitrogen and then stored under dry and inert atmosphere.

**(b) The Oxidation Procedure.** To a suspension of 1.11 g of cupric chloride–polymer complex (2.00 mmol of copper(II) equivalent) in 150 mL of methylene chloride was added 1 molar equiv of triethylamine (0.202 g, 2.00 mmol), followed by the addition of 10 mmol of catechol. The suspension was flushed with oxygen and the mechanical stirrer started. When the oxygen uptake ceased, the resulting *o*-benzoquinone was isolated in a highly pure state by removing the catalyst by filtrations and evaporating the solvent (Table I).

**Oxidation of Catechols by Copper Reagent Prepared from Cuprous Chloride and Supported on Poly(4-vinylpyridine). (a) Preparation of the Reagent.** To a solution of cuprous chloride (4.94 g, 50 mmol) in 250 mL of acetonitrile was slowly added poly(4-vinylpyridine) (8.4 g, 80 mmol) with vigorous stirring under nitrogen. After the solution was stirred for 30 min, the suspended solid was filtered and washed with the same solvent. Evaporation of the acetonitrile filtrate did not leave any copper material, indicating that the all cuprous chloride was bound to the polymer. The yellowish powdery material was dried and then stored under dry and inert atmosphere.

**(b) The Oxidation Procedure.** A suspension of 1.04 g of cuprous chloride–polymer complex (2.00 mmol of copper(I) equivalent) in 150 mL of methylene chloride was stirred under oxygen until the oxygen uptake ceased (0.5 mmol). The resulting pale green solid could be filtered, washed with methylene chloride, and stored under dry atmosphere prior to use, or it could be used directly without the isolation. A solution of catechol (10 mmol) in methylene chloride was added to the suspension of the reagent and the oxygen uptake followed until the reaction ceased. The resulting *o*-benzoquinone was isolated by filtration of the insoluble catalyst and evaporation of the solvent. The yields were essentially quantitative (Table I), and the isolated catalyst could be reused without significant loss in efficiency.

**Reaction of Cupric Acetate with Copper Metal in Pyridine.** A solution of cupric acetate (0.35 g, 2 mmol) in pyridine (25 mL) was stirred with an excess of copper metal (a thin metal strip) under nitrogen. The original blue color of the pyridine solution gradually turned yellow at which time the maximum at 655 nm of cupric acetate completely disappeared.

**Attempted Reaction between Cupric Acetate and Cuprous Chloride in Pyridine.** A pyridine solution containing equimolar amounts of cupric acetate and cuprous chloride under nitrogen was monitored at the spectrophotometer for the changes in the cupric acetate spectrum. No apparent reaction was observed over 24 h (Figure 2).

**Reaction of Cupric Chloride with Cuprous Acetate in Pyridine.** To a solution of bispyridine cupric chloride in pyridine ($4.71 \times 10^{-3}$ M) was added an excess of cuprous acetate in pyridine ($5.96 \times 10^{-3}$ M) under nitrogen. The reaction was followed spectrophotometrically by observing the disappearance of the cupric chloride absorption at 765 nm and appearance of the cupric acetate peak at 655 nm (Figure 3).

**A Competing Reaction of Cupric Chloride and Cupric Acetate with Copper Metal in Pyridine.** A reaction mixture containing equimolar amounts of cupric chloride, cupric acetate, and copper metal in pyridine was stirred under nitrogen, and the reaction progress was monitored spectrophotometrically. After complete reaction only cupric chloride was reduced to cuprous chloride, the cupric acetate remaining unchanged (Figure 4).

**Attempted Reactions of $Cu_2(BAA)_2$ and $Cu(acac)_2$ with Copper Metal in Pyridine.** A mixture of the $Cu_2(BAA)_2$ complex and an excess of the copper metal in pyridine under nitrogen was stirred for 48 h. There was no apparent reaction. Similarly, there was no reaction between $Cu(acac)_2$ complex and an excess of copper metal in pyridine under nitrogen.

**Disproportionation Reactions of Cuprous Acetate and Cuprous *tert*-Butoxide in Acetylacetone.** Addition of cuprous acetate to an excess of acetylacetone under nitrogen gave a yellow solution which gradually turned dark with formation of a copper mirror. Visible spectrum of the solution was identical with the spectrum of the authentic $Cu(acac)_2$. Cuprous *tert*-butoxide behaved similarly, providing also $Cu(acac)_2$ and a copper mirror. Under identical conditions, there was no apparent reaction with cuprous chloride.

**Copper(II) Reagent Derived from Phenol.** A solution of cuprous chloride (3.96 g, 40 mmol) in pyridine (50 mL) was exposed to oxygen with stirring. After complete reaction (10.0 mmol of $O_2$), the solution was freeze–pump–thaw degassed and then a solution of phenol (3.76 g, 40 mmol) in 10 mL of pyridine was added under nitrogen. The resulting dark brown-green solution was then used as a Cu(II)–PhOH "reagent" for the reaction described below (see also eq 14–17).

**Reaction of 4-*tert*-Butyl-1,2-benzoquinone with the Cu(II)–PhOH "Reagent" in the Absence of Oxygen.** Addition of 4-*tert*-butyl-1,2-benzoquinone (1.64 g, 10.0 mmol) in 10 mL of pyridine, with stirring, to the above Cu(II)–PhOH "reagent" [20 mmol of Cu(II) equivalent] under nitrogen, followed by a typical workup procedure afforded a mixture of isomeric phenyl esters of 4-*tert*-butylmuconic acids in approximately 55% yield. The esters were not isolated, but they were characterized by NMR analysis and mass spectrometry.

**Reaction of Catechol with the Cu(II)–PhOH "Reagent" in the Absence of Oxygen.** A similar reaction of catechol (1.1 g, 10.0 mmol) with the Cu(II)–PhOH "reagent" afforded the phenyl ester of muconic acid in ca. 65% yield.

**Reaction of 4-*tert*-Butylcatechol with the Cu(II)–PhOH "Reagent" in the Absence of Oxygen.** The reaction with 4-*tert*-butylcatechol provided the mixture of the same isomeric esters as in the experiment above in about the same yield.

**Reaction of Catechol with the Cu(II)–PhOH "Reagent" in the Presence of Oxygen.** When the above reaction with catechol was carried out in the presence of oxygen, approximately 10 mmol of oxygen was taken up. A typical workup provided about 63% yield of the phenyl muconic acid ester.

**Reaction of Phenol with the Cu(II)–PhOH "Reagent".** When to the above prepared Cu(II)–PhOH "reagent" (60 mmol of Cu(II) equivalent) phenol was added (0.94 g, 10 mmol) under oxygen, a slower oxygen uptake ensued. After 18 h approximately 15 mmol of oxygen was consumed. Typical workup provided 70% of the phenyl muconic acid ester.

Similarly, a solution of cuprous chloride (1.0 g, 10 mmol) and phenol (0.466 g, 4.95 mmol) in 300 mL of pyridine was exposed to oxygen. After 7.5 h 6.7 mmol of oxygen was taken up. The reaction mixture was left overnight under oxygen (total oxygen uptake 7.00 mmol), evaporated to dryness, and then hydrolyzed as usual. The NMR and GLC analyses indicated that besides small amount of unreacted phenol, the *trans,cis*-muconic acid monophenyl ester was formed in 76% yield and accompanied by about 10% of 4-phenoxymuconic acid monophenyl ester.

***trans,cis*-Muconic acid monophenyl ester**: $^1$H NMR ($CDCl_3$) $\delta$ 11.3 (COOH), 8.6 (d of d, $J_{2,3}$ = 16 Hz, $J_{3,4}$ = 12 Hz, C*H*=CHCOOPh), 7.25 (m, OPh, 5 H), 6.82 (t, $J_{3,4} \simeq J_{4,5} \simeq$ 12 Hz, C*H*CH=CHCOOPh), 6.32 (d, $J_{2,3}$ = 16 Hz, CHCOOPh), 6.1 (d, $J_{4,5} \simeq$ 12 Hz, C*H*COOH); $^{13}$C NMR ($CDCl_3$) $\delta$ 170.5 (s, $CO_2H$), 164.35 (s, $CO_2Ph$), 150.59 (s, $CO_2C(CH)_5$), 142.35 (d, *C*H=CHCO$_2$H), 139.8 (d, *C*HCHCO$_2$Ph), 129.39 (d, 2 *m*-CH's in Ph), 128.99 (d, *p*-CH in Ph), 125.96 (d, *C*HCO$_2$H), 124.49 (d, *C*HCO$_2$Ph), 121.47 (d, 2 *o*-C's in Ph); CI mass spectrum (methane) MH$^+$ at *m/e* 219.

**4-Phenoxymuconic acid monophenyl ester**: CI mass spectrum (methane) MH$^+$ at *m/e* 311, 217 (MH$^+$ – PhOH), 123 (MH$^+$ – 2PhOH, 95 (PhOH$_2^+$); $^{13}$C NMR ($CDCl_3$) $\delta$ 171.16 (s, $CO_2H$), 165.33 (s, $CO_2Ph$), 164.46 (s, *C*CHCO$_2$H), 153.24 (s, (CH)$_5$*C*OC), 150.71 (s, (CH)$_5$*C*OCO), 135.74 (d, *C*HCHCO$_2$Ph), 130.36 (d, 2 *m*-CH's in $CO_2Ph$), 129.47 (d, 2 *m*-CH's in OPh), 126.17 (d, *p*-CH in $CO_2Ph$), 125.96 (d, *p*-CH in OPh), 125.30 (d, *C*HCO$_2$Ph), 121.50 (d, 2 *o*-CH's in $CO_2Ph$), 121.23 (d, 2 *o*-CH's in OPh), 102.10 (d, *C*HCO$_2$H).

**Preparation of Cupric Phenoxide.** To a suspension of cupric methoxide (6.25 g, 50 mmol) in 100 mL of pyridine was added a solution of phenol (9.4 g, 100 mmol) in the same solvent under nitrogen. A dark brown solution was stirred for 30 min and then the solvent was removed in vacuo in the absence of oxygen. The resulting brown solid was ESR inactive and its elemental analysis indicated py$Cu(OPh)_2$ formula, suggesting that in the solid state pyridine cupric phenoxide complex exists as a dimer. On the other hand, in a pyridine solution the ESR spectrum was consistent with the monomeric, pyridine-coordinated cupric phenoxide.

Alternatively, a simple mixing of solid cupric methoxide and phenol in a mortar in a drybox under nitrogen, followed by pumping to remove methanol, provides pyridine-free cupric phenoxide.

**Preparation of Cuprous Phenoxide.** With use of a similar procedure as above cuprous *tert*-butoxide (6.97 g, 50 mmol) and phenol (4.7 g, 50 mmol) were mixed in 100 mL of pyridine under nitrogen. There was an immediate reaction and the solution was stirred for about 30 min, and then the solvent and the liberated *tert*-butyl alcohol were removed in vacuo, making certain that during the entire operation air was carefully excluded. The resulting yellow-brown solid, very sensitive to oxygen and moisture, upon hydrolysis with dilute hydrochloric acid gave phenol quantitatively.

**Reaction of Cupric Phenoxide with Oxygen.** A solution of cupric

phenoxide (0.5 g, 2 mmol) in 25 mL of pyridine was exposed to oxygen with stirring at room temperature. The oxygen uptake occurred at a rapid rate, and when it significantly slowed down (more than 4 mmol of $O_2$ was taken up in about 30 min), the reaction mixture was worked up in the usual way to give a mixture of isomeric monophenyl esters of muconic acid in about 60% yield. The reaction was repeated at 0 °C, and it was observed that the oxygen uptake began only after some initial delay. This "induction period" was completely eliminated by addition of either a trace amount of cuprous chloride or a catalytic amount of hydrogen peroxide. The reaction products were not affected by this change in the experimental procedure.

**Reaction of Cuprous Phenoxide with Oxygen.** A solution of cuprous phenoxide (0.32 g, 2 mmol) in 25 mL of pyridine was exposed to oxygen at room temperature with stirring. A rapid and instantaneous oxygen uptake ensued; after 30 min about 2.5 mmol of oxygen reacted and the similar workup as above gave essentially the same yield of the isomeric monophenyl esters of muconic acid as in the experiment with cupric phenoxide. The same experiment at −20 °C showed no evidence for any "induction period".

**Reactions of Catechol with the Copper(II) Reagent Prepared from 1,4-Butanediol and Ethylene Glycol.** A standard procedure for the oxidation of cuprous chloride (3.46 g, 40 mmol) in pyridine (50 mL), followed by the addition of the corresponding diols (40 mmol), was used to generate the copper(II)/diol reagents. Addition of catechol (1.1 g, 10 mmol) to the just prepared reagents under atmosphere of oxygen followed by the usual workup provided the corresponding esters, which were identified by NMR and mass spectroscopy, but were not isolated in a pure state and were not completely characterized.

**Reaction of 4-*tert*-Butylcatechol with the Copper(II) Reagent Prepared in the Presence of Water.** A standard procedure for the oxidation of cuprous chloride (3.96 g, 40 mmol) in pyridine (50 mL) followed by the addition of water (0.52 g, 50 mmol) provided the copper(II)/water reagent. To a degassed reagent was added a solution of 4-*tert*-butylcatechol (1.66 g, 10 mmol) in 10 mL of pyridine under nitrogen. After being stirred at room temperature for 30 min, the reaction mixture was worked up as usual to give approximately 35% yield of the lactone of 3-hydroxy-4-*tert*-butylmuconic acid: $^1$H NMR ($CDCl_3$) $\delta$ 9.9 (s, 1 H), 6.12 (s, 1 H), 5.7 (s, 1 H), 1.35 (s, 9 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 167.65 (s, $CO_2H$), 166.38 (s, COO) 163.99 (s, CO), 154.15 (s, C-*t*-Bu), 117.53 (d, $CHCO_2H$), 101.86 ($CHCOO$), 32.40 (s, $CMe_3$), 29.06 ($CH_3C$); CI mass spectrum (methane) $MH^+$ at *m/e* 197.

**Preparation of the "CuO/$NH_3$" Reagent.** A reaction mixture resulting from the oxidation of cuprous chloride (5.93 g, 60 mmol) in pyridine (60 mL) was flushed with nitrogen, degassed, and cooled to 0 °C. The gas inlet was connected to an ammonia cylinder, and an excess of ammonia was introduced with stirring. During this time a dark green precipitate separated out. Filtration under nitrogen provided a dark green solid and almost colorless pyridine mother liquor which did not contain any copper salts. After being washed with ether and drying at 0 °C in vacuo, the solid can be stored in a refrigerator under a dry inert atmosphere. Thus prepared, "CuO/$NH_3$" reagent was amorphous according to X-ray diffractometry. IR (KBr): 3330, 3210, 3160, 1610, 1610, 1230, 735 cm$^{-1}$.

Anal. ($Cu_2Cl_2ON_4H_{12}$): Cu, Cl, N, H.

The reaction with *o*-benzoquinones, catechols, or phenol can be carried out with the reagent prepared in situ or with the isolated solid as described later.

**Reaction of Catechol with the "CuO/$NH_3$" Reagent.** To the "CuO/$NH_3$" reagent prepared as above was added a solution of catechol (1.1 g, 10 mmol) in 20 mL of pyridine dropwise at 0 °C with stirring under nitrogen. After 30 min the volatiles were evaporated and dark residue was hydrolyzed at 0 °C with dilute hydrochloric acid in chloroform under nitrogen. After the usual sodium bicarbonate/acid workup, drying and evaporation of chloroform solution afforded previously unknown *cis,cis*-muconic acid mononitrile **4** (mp 136–138 °C) in about 50% yield: IR (Nujol) 3350–2230 ($CO_2H$), 2215 (CN), 1775 ($CO_2H$), 1675 (shoulder), 1621, 1564, 1452, 1347, 1305, 1262, 1198, 921, 840, 782, 693, and 667 cm$^{-1}$; UV $\lambda_{max}$ ($CH_3CN$) 259 nm ($\epsilon$ 15 900), 290 nm (sh), (MeOH) 257, ($\epsilon$ 16 000); $^1$H NMR ($(CD_3)_2CO$) $\delta$ 9.85 (b s, $CO_2H$, 1 H), 8.13 (t of d, $J$ = 11 and <1 Hz, $CHCCO_2^-$, 1 H), 7.00 (t of d, $J$ = 11 and <1 Hz, $CHCO_2^-$, 1 H), 6.12 (d of t, $J$ = 11 and <1 Hz, CHCN, 1 H), 5.78 (d of t, $J$ = 11 and <1 Hz, $CHCO_2$, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 169.81 ($CO_2H$), 149.97 ($C{=}CCO_2$), 139.11 ($CHCHCN$), 124.83 ($CHCO_2^-$), 115.09 (CN), 105.47 ($CHCN$); CI mass spectrum (ammonia) $MH^+$ at *m/e* 124.

Anal. ($C_6H_5NO_2$): C, H, N.

When the addition of catechol was carried out in the presence of oxygen, approximately 10 mmol of oxygen was consumed. The same workup provided muconic acid nitrile in approximately the same yield.

**Reaction of 4-*tert*-Butylcatechol with the "CuO/$NH_3$" Reagent.** When 4-*tert*-butylcatechol (1.66 g, 10 mmol) in 20 mL of pyridine was used in place of the catechol, the identical workup provided an oily mixture of isomeric muconic acid mononitriles **1**, **2**, and **3** in ratios 5:4:1 in approximately 60–70% yield. CI mass spectrum of the mixture using a Carbowax 20 M column (methane) gave the *m/e* 180 ($MH^+$) for each of the three isomers. A 100-MHz $^1$H NMR spectrum ($CDCl_3$) showed three AMX patterns which were assigned as follows: *cis,cis*-1-carboxy-3-*tert*-butyl-4-cyano-1,3-butadiene (**1**), $\delta$ 6.82 (d of d, $J_{1,2}$ = 12 Hz, $J_{2,4}$ = 1.5 Hz, $H_2$), 6.23 (d, $J_{1,2}$ = 12 Hz, $H_1$), 5.41 (d, $J_{2,4}$ = 1.5 Hz, $H_4$), 1.22 (s, *t*-Bu); *cis,trans*-1-carboxy-2-*tert*-butyl-4-cyano-1,3-butadiene (**2**), $\delta$ 7.41 (d of d, $J_{3,4}$ = 16 Hz, $J_{1,3}$ = 1.5 Hz, $H_3$), 5.52 (d, $J_{3,4}$ = 16 Hz, $H_4$), 5.96 (d, $J_{1,3}$ = 1.5 Hz, $H_1$), 1.22 (s, *t*-Bu); *cis,cis*-1-carboxy-2-*tert*-butyl-4-cyano-1,3-butadiene (**3**), $\delta$ 7.15 (d of d, $J_{3,4}$ = 12 Hz; $J_{1,3}$ = 1.5 Hz, $H_3$), 5.63 (d, $J_{3,4}$ = 12 Hz, $H_4$); 6.03 (d, $J_{1,3}$ = 1.5 Hz, $H_1$). The carboxyl group protons appeared as a singlet at $\delta$ 10.22. A crystallization of the mixture from methylene chloride/hexane (1:1) afforded the major isomer **1**: mp 124–126 °C; IR (Nujol) 2000–3100 (b), 2220, 1700, 1690 (sh), 1640, 1610, 1256, 1220, 930, 830 cm$^{-1}$; UV ($CHCl_3$) $\delta_{max}$ 210 ($\epsilon$ 9343); 60-MHz $^1$H NMR ($CDCl_3$) $\delta$ 11.6 (s, $CO_2H$), 6.68 (d of d, $J_{1,2}$ = 12 Hz, $J_{2,4}$ = 1.5 Hz, $H_2$), 6.12 (d, $J_{1,2}$ = 12 Hz, $H_1$), 5.27 (d, $J_{2,4}$ = 1.5 Hz, $H_4$), 1.17 (s, *t*-Bu); $^{13}$C NMR ($CDCl_3$), $\delta$ 169.37 ($CO_2H$), 169.06 ($CC(CH_3)_3$), 141.66 ($CH{=}CCO_2H$), 124.62 ($CHCO_2H$), 116.8 (CN), 95.0 ($CHCN$), 37.8 ($CC(CH_3)_3$), 28.63 ($C(CH_3)_3$).

Anal. ($C_{10}H_{13}O_2N$): C, H, N.

**Reaction of Pyridine Cupric Methoxy Chloride/Ammonia with 4-*tert*-Butylcatechol.** Anhydrous ammonia was bubbled at moderate rate into a solution of pyridine cupric methoxy chloride (8.4 g, 40 mmol) in 80 mL of pyridine at 0 °C for 20 min. To the resulting green solution 4-*tert*-butylcatechol (0.83 g, 5 mmol) in 5 mL of pyridine was added over a period of 15 min. After being stirred at room temperature for 40 min, the reaction mixture was evaporated at 25 °C. The remaining solid was hydrolyzed with dilute hydrochloric acid in the presence of methylene chloride. After washing with sodium bicarbonate, drying, and evaporation of the solvent, there was obtained 0.39 g (~48%) of 4-*tert*-butylmuconic acid imide (**6**): mp 150–151.5 °C (ether); CI mass spectrum (methane/ammonia) $MH^+$ at *m/e* 180; 100-MHz $^1$H NMR ($CDCl_3$), $\delta$ 9.77 (b s, NH), 6.90 (d of d, $J_{2,3}$ = 13.2 Hz, $J_{3,5}$ = 1.3 Hz, $H_3$), 6.53 (d, $J_{2,3}$ = 13.2 Hz, $H_2$), 6.52 (d, $J_{3,5}$ = 1.3 Hz, $H_5$), 1.27 (s, *t*-Bu); $^{13}$C NMR ($CDCl_3$) $\delta$ 164.98, 164.06 ($CONHCO$), 155.98 (*t*-Bu$C{=}$), 135.57 (*t*-Bu$CC$), 130.53 (*t*-Bu$CCC{=}O$), 126.39 ($HC{=}CC{=}O$), 37.49 ($C(CH_3)_3$), 28.24 ($CH_3$); IR (Nujol) 3195, 1660, 1678, 1615, 1390, 1370, 1249, 870 cm$^{-1}$.

Anal. ($C_{10}H_{13}NO_2$): C, H, N.

Acidification of the sodium bicarbonate extract, followed by extraction etc., afforded approximately 50% of a 1:1 mixture of 4-*tert*-butylmuconic acid monomethyl ester (two isomers).[2,3]

**2,4-Di-*tert*-butylmuconic Acid Imide.** Similar reaction with 3,5-di-*tert*-butyl-1,2-benzoquinone (4.40 g, 20 mmol) and pyridine cupric methoxychloride (12.54 g, 60 mmol) in 500 mL of pyridine containing an excess of anhydrous ammonia provided about 4.6 g of crude product which, according to NMR analysis, was predominantly the expected imide. Sublimation of a small sample afforded 2,4-di-*tert*-butylmuconic acid imide: mp 143–146 °C; CI mass spectrum (methane) showed $MH^+$ at *m/e* 326; NMR ($CDCl_3$) $\delta$ 9.5 (b s, NH), 6.82 (d, $J \approx 1.5$ Hz), 6.35 (d, $J \approx 1.5$ Hz), 1.27, 1.19 (*t*-Bu's).

**2-Methoxy-4-*tert*-butylmuconic Acid Imide.** The reaction of pyridine cupric methoxy chloride (5.29 g, 25.3 mmol) with 2-methoxy-4-*tert*-butylcatechol (1.02 g, 5.2 mmol) under similar conditions gave about 0.8 g of oily material which according to TLC analysis was predominantly the expected 2-methoxy-4-*tert*-butylmuconic acid imide: mp 132–140 °C; CI mass spectrum, $MH^+$ at *m/e* 210; NMR ($CDCl_3$) $\delta$ 9.2 (b s, NH), 6.36 (s), 6.18 (s), 3.83 (s, $OCH_3$), 1.23 (*t*-Bu).

**Cinnamic Acid Nitrile from Cinnamaldehyde.** To a suspension of 3.48 g (20.4 mmol) of "CuO/$NH_3$" reagent prepared as before in 200 mL of pyridine under anhydrous ammonia atmosphere was added a solution of cinnamaldehyde in pyridine (0.64 g, 4.84 mmol in 5 mL). The reaction mixture was stirred at room temperature overnight under nitrogen. After the solvent was removed in vacuo, the residue was extracted with ether and the ether solution dried and evaporated to give a crude product which was, according to GLC, a 9:1 mixture of cinnamic acid nitrile and the aldehyde.

Under similar conditions *n*-heptaldehyde and benzaldehyde gave the corresponding nitriles in good yields.

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