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Copper(II)-Mediated Autoxidation of *tert*-Butylresorcinols

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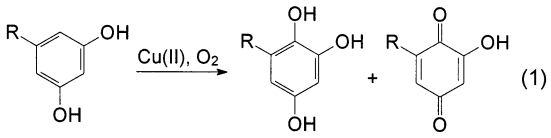
Although copper(II)-mediated oxidation of phenols results in oxidative coupling rather than in oxygenation, it was recently reported that naturally occurring 5-alkylresorcinols undergo oxygenation in the presence of copper(II). To explore the generality of this reaction, the copper(II)-mediated autoxidation of 4-*tert*-butylresorcinol and 4,6-di-*tert*-butylresorcinol was investigated and was found to result in direct oxygenation at open activated positions and, at the *tert*-butyl-substituted positions, in oxygenation with competing loss of (as isobutylene) and 1,2-rearrangement of the *tert*-butyl group. 5-*tert*-Butyl-2-hydroxy-1,4-benzoquinone is the major product from both starting materials, and the final product mixture reflects, in part, coupling of metastable initially formed electrophilic and nucleophilic side products. Mechanisms that are consistent with the observed products and control reactions are proposed. The key step appears to be equilibration of a copper(II)−resorcinolate with a charge-transfer radical form that reacts regioselectively with O_2 as prescribed by resonance.

Introduction

Copper-mediated *oxygenation* of phenols[1] is of interest both in terms of commercial production of benzenediols and quinones and in terms of understanding the mechanism of action of copper enzymes that carry out arene monooxygenation.[2] All such reactions that have been examined in detail require the use of Cu^{I}−ligand complexes for initial activation of O_2, and the most well understood examples involve a stoichiometric oxygenation by a binuclear μ-η^2:η^2-biscopper(II) peroxo core, leaving a copper(II)−O−copper(II) byproduct.[3] The latter species would have to be reduced back to copper(I) to make the process catalytic in copper. Although copper(II)-mediated *oxidation* (dehydrogenation) of hydroquinones and especially catechols to the corresponding *p*- and *o*-benzoquinones is well precedented,[4] there has been no definitive demonstration of a copper(II) (as opposed to copper(I)) mediated arene *oxygenation*. However, copper(II)-mediated oxygenations should be possible for molecules where coordination to Cu^{II} promotes the otherwise uncatalyzed *autoxidation* of the compound.

Copper(II)-mediated autoxidation of alkylphenols results in oxidative coupling rather than in oxygenation.[5] However, a recent study reported that Cu^{II} can catalyze autoxidative oxygenation of 5-alkylresorcinols to give 6-alkylbenzene-1,2,4-triols and 6-alkyl-2-hydroxy-1,3-benzoquinones (eq 1).[6] The different behavior may reflect



(1)

the more electron rich nature of resorcinols compared to phenols. The symmetry of 5-alkylresorcinols and the lack of substitution at the most activated C4-position (*ortho* to one OH and *para* to the other) result in a fairly clean reaction in this case. In considering the generality of such a reaction, it is unclear what the fate would be of 4-alkylresorcinols under such conditions, where one of the two most activated positions is substituted.

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(1) (a) Brackman, W.; Havinga, E. *Recueil* **1955**, *74*, 937−955. Tsuji, J.; Takayanagi, H. *Tetrahedron* **1978**, *34*, 641−644. (b) Demmin, T. R.; Swerdloff, M. D.; Rogic, M. M. *J. Am. Chem. Soc.* **1981**, *103*, 5795−5804. (c) Maumy, M.; Capdevielle, P. *J. Mol. Catal., A: Chem.* **1996**, *113*, 159−166. (d) Chioccara, F.; Chiodini, G.; Farina, F.; Orlandi, M.; Rindone, B.; Sebastiano, R. *J. Mol. Catal., A: Chem.* **1995**, *97*, 187−194.

(2) (a) Casella, L.; Monzani, E.; Gullotti, M.; Cavagnino, D.; Cerina, G.; Santagostini, L.; Ugo, R. *Inorg. Chem.* **1996**, *35*, 7516−7525. (b) Monzani, E.; Quinti, L.; Perotti, A.; Casella, L.; Gullotti, M.; Randaccio, L.; Geremia, S.; Nardin, G.; Faleschini, P.; Tabbi, G. *Inorg. Chem.* **1998**, *37*, 553−562. (c) Santagostini, L.; Gullotti, M.; Monzani, E.; Casella, L.; Dillinger, R.; Tuczek, F. *Chem.−Eur. J.* **2000**, *6*, 519−522. (d) Rodríguez-López, J. N.; Varón, R.; García-Cánovas, F. *Int. J. Biochem.* **1993**, 1175−1182. (d) Karlin, K. D.; Kaderli, S.; Zuberbühler, A. D. *Acc. Chem. Res.* **1997**, *30*, 139−147. (e) Sayre, L. M.; Nadkarni, D. V. *J. Am. Chem. Soc.* **1994**, *116*, 3157−3158.

(3) (a) Pidcock, E.; Obias, H. V.; Abe, M.; Liang, H.-C.; Karlin, K. D.; Solomon, E. I. *J. Am. Chem. Soc.* **1999**, *121*, 1299−1308. (b) Itoh, S.; Kumei, H.; Taki, M.; Nagatomo, S.; Kitagawa, T.; Fukuzumi, S. *J. Am. Chem. Soc.* **2001**, *123*, 6708−6709. (c) Holland, P. L.; Tolman, W. B. *Coord. Chem. Rev.* **1999**, *190*−*192*, 855−869.

(4) (a) Malachowski, M. R.; Tomlinson, L. J.; Davidson, M. G.; Hall, M. J. *J. Coord. Chem.* **1992**, *25*, 171−174. (b) Balla, J.; Kiss, T.; Jameson, R. F. *Inorg. Chem.* **1992**, *31*, 58−62. (c) Paraskevas, S. M.; Konstantinidis, D.; Vassilara, G. *Synthesis* **1988**, 897−899. (d) Speier, G. *J. Mol. Catal.* **1986**, *37*, 259−267. (e) Kamau, P.; Jordan, R. B. *Inorg. Chem.* **2002**, *41*, 3076−3083.

(5) (a) Kushioka, K. *J. Org. Chem.* **1984**, *49*, 4456−4459. (b) Tsuruya, S.; Kinumi, K.; Hagi, K.; Masai, M. *J. Mol. Catal.* **1983**, *22*, 47−60.

(6) (a) Singh, U. S.; Scannell, R. T.; An, H.; Carter, B. J.; Hecht, S. M. *J. Am. Chem. Soc.* **1995**, *117*, 12691−12699. (b) Starck, S. R.; Deng, J.-Z.; Hecht, S. M. *Biochemistry* **2000**, *39*, 2413−2419.

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As part of another study, we recently reported that 4-*tert*-butylresorcinol readily undergoes Cu^{II}-mediated autoxidation to give mainly 5-*tert*-butyl-2-hydroxy-1,4-benzoquinone, as well as a side product.[6] The details of this reaction are now disclosed along with additional studies identifying another side product of the reaction and efforts to clarify the mechanistic nature of the Cu^{II}-mediated oxygenations. Oxygenation of 4-*tert*-butylresorcinol occurs at both the unsubstituted 6-position and at the 4-position, in the latter case resulting in either loss or rearrangement of *tert*-butyl.

Results and Discussion

Product Identification. A mixture of 4-*tert*-butylresorcinol (**1**) and 0.1 equiv of $Cu(ClO_4)_2 \cdot 6H_2O$ in air-equilibrated acetonitrile−water was found to generate 5-*tert*-butyl-2-hydroxy-1,4-benzoquinone (**2**) and a side product (**3**) in a 3:1 ratio,[7] along with another, nonisolable minor side product. Product **3** formed red crystals in the NMR tube (CD_3CN) and was isolated as such. The structure could not be assigned using NMR spectroscopy and mass spectral data, though it was clear that it contained the equivalents of two mol of **1** minus one *tert*-butyl group, suggesting the generation of 2-hydroxy-1,4-benzoquinone (**4**) from **1**. The same reaction run at a 10-fold dilution afforded much reduced levels of **3** relative to **2** (along with a substantial amount of unreacted **1**), implicating **3** as derived from bimolecular coupling of initial products. The identity of **3** as 3-(4-(1,1-dimethylethyl)-5-hydroxy-2-oxo-(5*H*)-furan-5-yl)-5-hydroxybenzofuran-2,6-dione was revealed by X-ray diffraction. Compound **3** incorporates the elements of a des-*tert*-butylquinone nucleus joined as a quinone methide to a muconic acid oxidative cleavage product apparently derived from **2**. Details of the structural determination are provided in the Supporting Information. Although **3** contains a chiral center, crystals of **3** are racemic and contain both enantiomeric forms. Hydrogen bonding in the molecule involves carbonyl oxygen O6 forming proximate contacts with both H7−O7 (O6−O7 = 2.762(2) Å) and H2−O2 (O6−O2 = 2.735(2) Å) in different molecules.

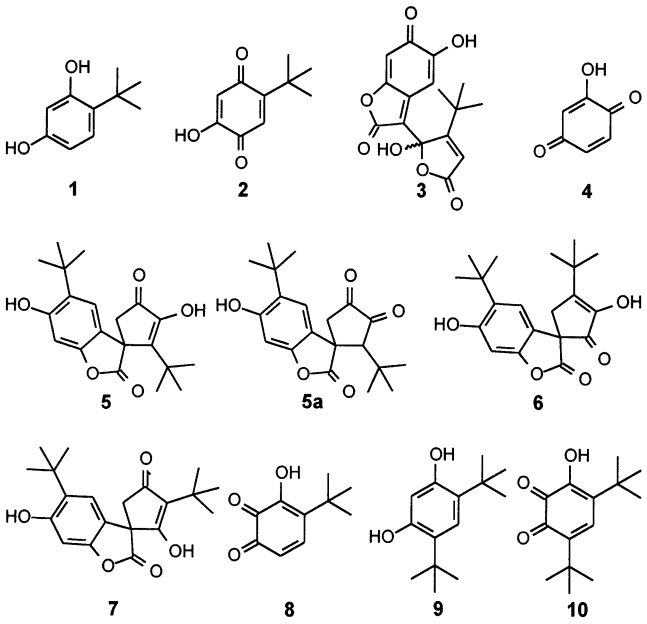


TABLE 1. HMQC and HMBC Data of Product 5 in DMSO-d_6 (ppm)[a]

HMQC	HMBC
–	9.99 ↔ 157.1, 132.5, 99.1
–	9.90 ↔ 199.5, 152.5, 147.2
7.01 ↔ 121.2	7.01 ↔ 157.1, 151.1, 51.3, 34.4
6.69 ↔ 99.1	6.69 ↔ 157.1, 151.1, 132.5, 119.3
2.77 ↔ 46.0	2.77 ↔ 199.5, 179.6, 152.5 (w), 147.2, 119.3 (w), 51.3
2.58 ↔ 46.0	2.58 ↔ 199.5, 179.6, 152.5 (w), 147.2, 119.3, 51.3
1.33 ↔ 29.5	1.33 ↔ 132.5, 34.4, 29.5
0.97 ↔ 27.4	0.97 ↔ 147.2, 34.6, 27.4

[a] The symbol ↔ denotes the C−H correlation, while "w" in parentheses means weak C−H correlation.

The unusual structure of **3** inspired a preliminary examination of its mode of formation. The reaction rate increased over the pH range 7−11, but the **2**:**3** product ratio was unchanged. Importantly, the starting resorcinol **1** was recovered from the reaction run in the presence of a metal chelator (diethylenetriaminepentaacetic acid) or in the strict absence of either Cu^{II} or O_2. The reaction outcome was also solvent dependent: the same reaction in pH 11 phosphate buffer in the absence of CH_3CN gave no **3** and instead **2** as the major product, along with an increased amount of the side product seen in the aqueous CH_3CN reaction. Although the reaction in buffer alone was more complex, and several polar neutral products were present that could not be identified, the side product could now be isolated and was shown by HRMS to derive from two molecules of resorcinol **1**, one molecule of O_2, loss of one H_2O, and a further dehydrogenation (or addition of $^3/_2O_2$ and loss of two waters).

The new dimer could not be crystallized, but its ^1H NMR spectrum exhibited two different *tert*-butyl groups (0.97 and 1.32 ppm), an isolated diastereotopic methylene (2.58 and 2.77 ppm, J = 18.7 Hz), and only two aryl singlets (6.69 and 7.01 ppm), suggesting the presence of only one of the original two aromatic rings, containing two *para* protons. The ^{13}C NMR spectrum displayed only two carbonyl groups, and two carbonyl absorptions are found in the IR spectrum at 1802 and 1706 cm^{-1}. The IR spectrum also showed a broad hydroxy band at 3404 cm^{-1}, but no absorption corresponding to a carboxyl group (∼2500 cm^{-1}). Considering the molecular formula and various mechanisms for oxygenative dimerization, several isomeric structures could be drawn that fit the above findings to varying degrees. HMQC and HMBC data in $CDCl_3$ permitted elimination of all structures except for three, **5**−**7**. Using the phenolic and enolic protons as structural probes, HMQC and HMBC experiments in DMSO-d_6 (Table 1) ruled out structure **7**. The key evidence was the observation of a three-bond correlation of the enol proton (9.90 ppm) with the carbonyl carbon (199.5 ppm) in the HMBC spectrum (see Figure 1 and the Supporting Information). If the structure were **7**, this correlation would have been with the quaternary carbon at 51.3 ppm. Finally, the structure was assigned as **5** rather than **6** on the basis of NOE difference experiments. Irradiation of the *tert*-butyl protons at 0.97 ppm resulted in strong enhancements of the aryl signal at δ 7.01 (0.32%) and the enolic OH signal at δ 9.90 (0.25%) and a

(7) Lee, Y.; Jeon, H.-B.; Huang, H.; Sayre, L. M. *J. Org. Chem.* **2001**, *66*, 1925−1937.

TABLE 2. Copper(II)-Mediated Oxidation of Resorcinols[a]

phenol (concn, mM)	copper(II) (concn, mM)	solvent (pH)	atmosphere	reaction time (h)	conversion (%)	products[b] (yield, %)
1 (10)	$Cu(ClO_4)_2$ (1)	$MeCN/H_2O$ (10)[c]	air	1.5	98	**2** (57), **3** (13), **5** (8)
1 (10)	$Cu(ClO_4)_2$ (10)	$MeCN/H_2O$ (10)[c]	air	0.5	100	**2** (53), **3** (12), **5** (7)
1 (10)	$Cu(ClO_4)_2$ (10)	$MeCN/H_2O$ (10)[c]	argon	3	47	**11** (62), **12** (19)
1 (10)	$CuSO_4$ (1)	buffer (11)[d]	air	1.5	38	**2** (27), **5** (17)
1 (10)	$Cu(ClO_4)_2$ (1)	buffer (11)[d]	air	1.5	39	**2** (30), **5** (13)
9 (10)	$Cu(ClO_4)_2$ (1)	$MeCN/H_2O$ (10)[c]	air	1.5	99	**2** (45), **10** (12)
9 (10)	$CuSO_4$ (1)	buffer (11)[d]	air	1.5	89	**2** (40), **10** (13)

[a] The conversion of substrates and the product distribution were determined by ^1H NMR using 1,4-dimethoxybenzene as an internal standard. [b] Based on consumed resorcinols. [c] The ratio for $MeCN/H_2O$ was 1:1 (v/v), and the pH was controlled by adding aqueous NaOH and monitored using a pH meter. [d] 0.1 M phosphate buffer.

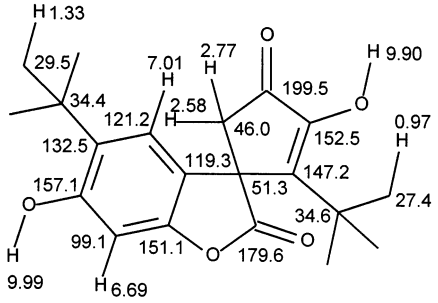


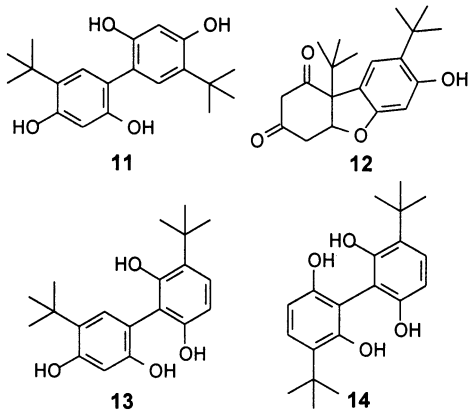
FIGURE 1. ^1H and ^{13}C chemical shifts of product **5**.

weak enhancement of the aryl signal at δ 6.99 (0.06%), but only very weak enhancement of the methylene signals at δ 2.58 and 2.77 (both 0.02%). The latter should be the most strongly enhanced if the structure is **6**.

The fact that the dimer exists in enol form **5** rather than its keto tautomer **5a** is consistent with reports on 1,2-cyclopentanedione derivatives, which were shown by NMR to exist in the enol form in most solvents.[8] With the identification of **5**, the product profile of the Cu^{II}-promoted autoxidations of **1** can be summarized as in Table 2. Although the perchlorate salt of Cu^{II} was used in most cases for convenience, the observed oxidation is not derived from ClO_4^-, as $CuSO_4$ gave the same results (compare entries 4 and 5 in Table 2).

The finding that Cu^{II}-mediated autoxidation of **1** resulted in partial loss of the 4-*tert*-butyl group *ortho*/*para* to the hydroxyls and in oxygenation apparently only at the other *ortho*/*para*-position (i.e., there was no evidence for oxygenation at C2 to give **8**) led us to investigate the same reaction with 4,6-di-*tert*-butylresorcinol (**9**). The question is whether **9** might be forced to react at least partly at C2 now that both activated *ortho*/*para*-positions are *tert*-butyl substituted. In fact, **9** was found to afford the suspected *o*-quinone **10** (minor) and the des-*tert*-butylquinone **2** (major) as the only isolable products, regardless of reaction solvent (Table 2). When the autoxidation of **9** was run in a closed air-equilibrated system with CCl_4 added as a second solvent phase, analysis of the CCl_4 layer by ^1H NMR in $CDCl_3$ revealed the presence of isobutylene, suggesting this was the major fate of the *tert*-butyl group.

Studies on Reaction Mechanism. Consumption of **1** was found to proceed to completion using 0.1 mol equiv of Cu^{II}, implicating a catalytic role of copper. However, autoxidation of **1** was found to occur more rapidly using a stoichiometric concentration of Cu^{II} (Table 2). Although no reaction of **1** was apparent in the absence of O_2 using 0.1 mol equiv of Cu^{II}, the use of stoichiometric Cu^{II} under argon did accomplish a slow conversion of **1** in pH 10 aqueous acetonitrile. The major products in this case were shown to be dimer **11** and the Pummerer's ketone **12** (Table 2), while the other two possible dimers (**13** and **14**) were not found. The finding that this latter reaction

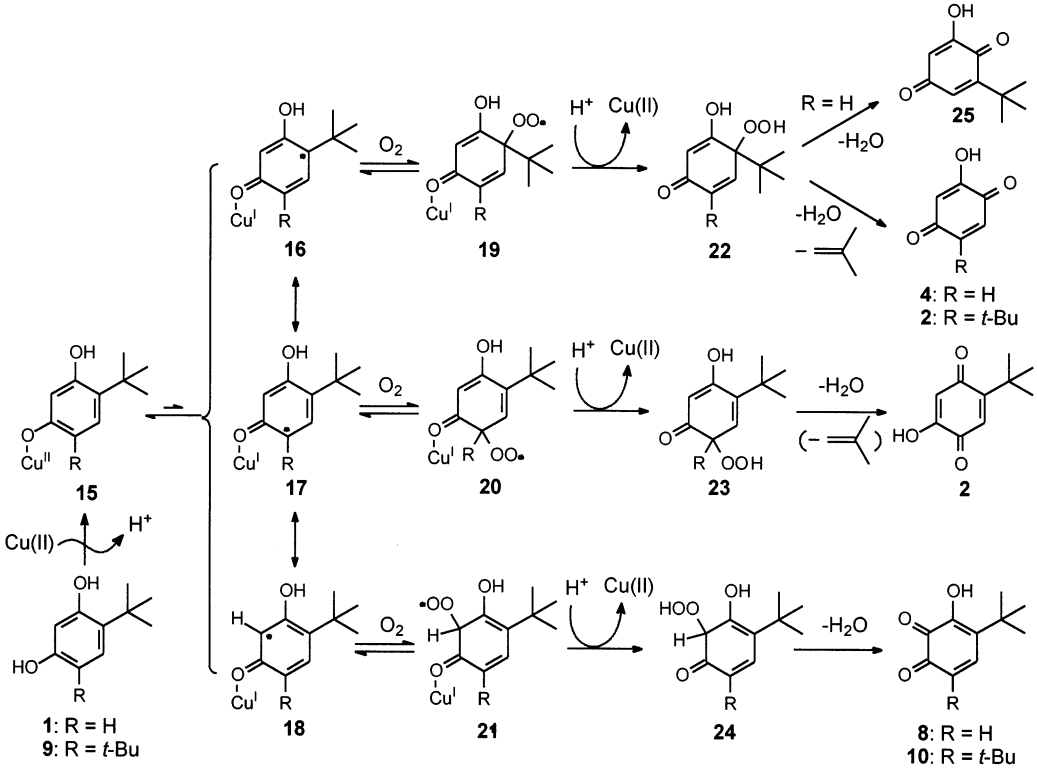


is so slow indicates that simple Cu^{II}-induced oxidation of the resorcinol or the coordinated resorcinolate to a radical that can either couple or react with O_2 is *not* a kinetically competent step in the normal Cu^{II}-catalyzed autoxidation pathway. This assertion and the observed advantage of higher pH suggest that the rate-limiting step of autoxidation is direct reaction of O_2 with a copper(II)−resorcinolate complex, which otherwise dimerizes only slowly on its own.

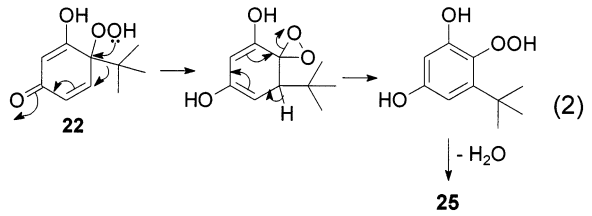
The finding that **2** was the major product arising from **9** shows that dealkylation at the most activated *ortho*/*para*-position is preferred over oxygenation at the less activated but unsubstituted *ortho*/*ortho*-position, at least in the case of *tert*-butyl. A unified depiction of the reaction pathways for **1** and **9** that rationalizes the observed product outcome is shown in Scheme 1. For the purposes of discussion, we have depicted the key copper(II)−resorcinolate **15** to be in unfavorable equilibrium with a charge-transfer complex that has three resonance forms, **16**−**18**. This analysis leads to oxygenation of the complex at three possible sites on the benzene ring to give peroxy radicals **19**−**21**, respectively, in analogy to what was proposed in the Cu^{II}-mediated oxygenation of 5-alkylresorcinols.[6] It should be noted that, for **1**, there are two possible starting copper(II)−resorcinolates, though the identical outcome shown in Scheme 1 arises if copper is coordinated alternatively to the 3-hydroxy group.

(8) Ponaras, A. A. *Tetrahedron Lett.* **1980**, *21*, 4803−4806 and references therein.

SCHEME 1



For resorcinol **1**, oxygenation at the site indicated by resonance structure **16** gives rise to the *ipso*-substituted hydroperoxide intermediate **22**, which is precedented in cobalt(II)-mediated autoxidation of 2,6-di-*tert*-butylphenol.[9] This intermediate can undergo a cyclic electronic reorganization to generate the des-*tert*-butylquinone **4** along with isobutylene and water.[10] In the case of **9**, resonance structures **16** and **17** (R = *tert*-butyl) are identical and lead to the major des-*tert*-butyl product **2** by the same mechanism. At the same time, we have shown that *ipso*-peroxy intermediates arising from copper-mediated oxygenation of *tert*-butylated phenols can rearrange to quinones with 1,2-migration of the *tert*-butyl group.[11] In the case of resorcinol **1**, **22** (R = H) should thus lead to quinone **25**, whereas the same rearrangement starting with resorcinol **9** would lead to a sterically unfavorable *o*-di-*tert*-butyl-substituted quinone, and was not observed. In addition to the mechanisms previously discussed,[11] rearrangement of **22** (R = H) to **25** could proceed via a dioxirane intermediate (eq 2). Further precedent for the simultaneous oxygenative loss and 1,2-rearrangement of the *tert*-butyl group is found in the previously studied base-catalyzed autoxidation of **9**, which was reported to give both **2** and 5,6-di-*tert*-butyl-2-hydroxy-2-cyclohexene-1,4-dione.[12]



(2)

For resorcinol **1**, oxygenation of resonance form **17** would lead to species **23** (R = H), which would simply dehydrate to give **2**. Oxygenation at the remaining site, indicated by resonance structure **18**, is evidently less favorable, since the predicted product **8** from **1** was not found. In the case of **9**, however, since the only other alternative requires expulsion of *tert*-butyl, the pathway through **24** can now compete, and *o*-quinone **10** is now seen as a minor product. It is interesting to note that dimers **13** and **14**, which represent oxidative coupling at the 2-position of one or both molecules of resorcinol, were not found in the stoichiometric Cu^{II}-mediated anaerobic coupling of **1**. This result and the apparent absence of **8** in the oxidation of **1** together suggest that the resonance form **18**, representing localization of unpaired electron density at C2 of the resorcinoxy radical, is a minor contributor to the resonance hybrid. Overall, although we depict the reactions in Scheme 1 in terms of a mononuclear Cu^{II}–resorcinolate species, we have no data that bear on the nature of the actual complex undergoing reaction with O_2, and binuclear or higher order complexes could well be involved, possibly linking both coordination sites in the reactant.

According to the oxygenation mechanism in Scheme 1, the new oxygen atom in the major product **2** during autoxidation of **1** and **9** derives from O_2. Although O_2 is absolutely required to get **2**, a theoretically possible alternate mechanism might involve O_2 only as the oxidant required to induce a copper-mediated addition

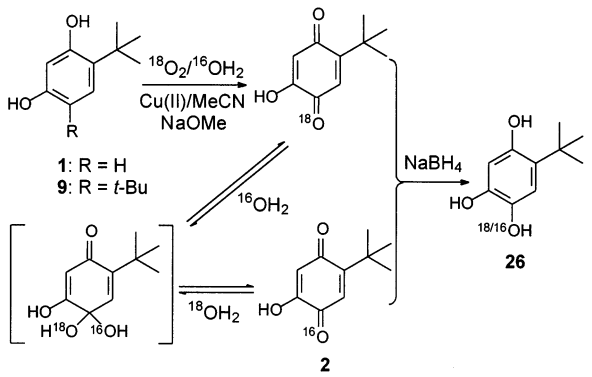
(9) Nishinaga, A.; Shimizu, T.; Toyoda, Y.; Matsuura, T. J.; Hirotsu, K. *J. Org. Chem.* **1982**, *47*, 2278−2285 and references therein.

(10) Loss of *tert*-butyl could also proceed by Criegee rearrangement of **22** to give a *tert*-butyl hemiketal that cyclodehydrates to quinone **4** and isobutylene, though simple dissociation to **4** and *tert*-butyl alcohol might also be expected.

(11) Mandal, S.; Macikenas, D.; Protasiewicz, J. D.; Sayre, L. M. *J. Org. Chem.* **2000**, *65*, 4804−4809.

(12) Musso, H.; Maassen, D. *Liebigs Ann. Chem.* **1965**, *689*, 93−108.

SCHEME 2

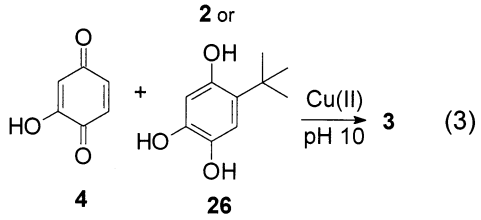


of H_2O to resorcinol, either by activation of the water (to a species with HO^+ or HO• character) or by activation of the resorcinol toward nucleophilic water addition. To distinguish whether the new oxygen in **2** derives from O_2 or from H_2O, an ^{18}O-labeling experiment was conducted. Thus, both **1** and **9** were allowed to undergo Cu^{II}-mediated autoxidation to **2** using $^{18}O_2$ in the presence of excess $^{16}OH_2$. The caveat of this experiment is that **2** is known to undergo carbonyl oxygen exchange in water at the position where the new oxygen is incorporated, especially at elevated pH levels.[13] Although this exchange can be suppressed by conducting the autoxidation in anhydrous media, the final product **2** in this case would be ^{18}O labeled regardless of mechanism, since any water becoming available (from reduction of O_2) would also be labeled. To minimize exchange, we had to find conditions that achieved a compromise in converting **1** and **9** to **2** in a reasonably short time, but at a modest basic pH.

The reaction conditions chosen involved conducting the autoxidation with $^{18}O_2$ in acetonitrile in the presence of 10 equiv of $^{16}OH_2$ (with respect to resorcinol) using anhydrous $Cu(CF_3SO_3)_2$ and NaOMe as base (aqueous NaOH was insufficiently miscible with CH_3CN). To ensure minimal carbonyl oxygen exchange in **2**, a short reaction time (10 min), a stoichiometric amount of $Cu(CF_3SO_3)_2$, and a minimum amount of NaOMe were used, and the major product **2** was characterized in its reduced form **26** by a reductive quench of the reaction ($NaBH_4$), at which point no further exchange would occur (Scheme 2). Higher pH (initially 11, dropping to 8) was needed for sufficient conversion of **1** to **2** than of **9** to **2** (initial pH 9, dropping to 7), so we expected in the former case a greater degree of exchange in **2** during the 10 min reaction time prior to reductive quenching. Our finding that the abundance of ^{18}O-labeled **26** was 28% for autoxidation of **1** and 75% for autoxidation of **9** (see the Experimental Section) is consistent with the oxygenation mechanism in Scheme 1. If the source of new oxygen were from water, the ^{18}O incorporation should have been no more than ~9% since, using 10 equiv of $^{16}OH_2$, the ^{18}O content of the water would have reached only 1 part in 11 by the end of the reaction.

Proposed Pathways to Products 5 and 3. Although quinones **4** and **25**, postulated to be generated from **1**, are not observed as isolated products of the reaction, they are the key species proposed to result in products **3** and **5**, respectively. In the case of **25** (6-*tert*-butyl-2-hydroxy-1,4-benzoquinone), the C5-position is electrophilic and could couple to the activated C6-position of starting resorcinol **1** by a Friedel−Crafts-like aromatic substitution (Michael addition of **1** to **25**)[14] to give **27** (Scheme 3). This same reaction with **1** might be considered for major product **2**, except that the electrophilic position in **2** is *tert*-butyl substituted. Intermediate **27** would be subject to oxidation and intramolecular cyclization, leading to a benzilic ester-like rearrangement[15] to the enol tautomer of observed product **5** (Scheme 3).

The potential for **4** to be the precursor of the des-*tert*-butyl portion of **3** was shown by the finding that the reaction of independently prepared **4** with **2**, to some extent, or especially triol **26** in the presence of a catalytic amount of Cu^{II} at pH 10 afforded **3** in a higher yield (comparable to that of recovered **2**) than was obtained from **1** under the same conditions (eq 3). The formation of **3** was strictly Cu^{II} dependent; in the absence of Cu^{II}, **4** was decomposed to unidentified products and only **2** could be isolated.



On the basis of the above findings, Scheme 4 outlines proposed mechanisms for generation of **3** from **2** and **4**. Any mechanism must provide for the oxygenative cleavage of **2** to provide the *tert*-butylmuconic acid portion of **3**. We propose Baeyer−Villiger formation of muconic anhydride **28** initiated by addition of one of the peroxide intermediates generated in the oxygenation of **1** to the electrophilic carbonyl of **2**. Enol **28** could then undergo conjugate addition to the electrophilic C5-position of **4** to give **29** (Scheme 4, path A). Nucleophilic carbon addition to **4** has been observed previously.[16] Intramolecular lactonization of **29** followed by two-electron oxidation of the vinylogous hydroquinone **31** in equilibrium with **30** would generate the ring-opened tautomer **32** of observed product **3**. Alternatively, since **4** is also well-known to undergo conjugate addition of *heteroatom* nucleophiles,[17] anhydride **28** could first hydrolyze (Scheme 4, path B), followed by conjugate addition of the more nucleophilic carboxylate of **33** to the C5-position of **4** to give benzenetriol ester **34**. Oxidation of the **34** would generate ester intermediate **35** that would be expected to cyclocondense to give **32**. Since either pathway requires a two-electron autoxidation expected to generate H_2O_2, the key oxygenative cleavage of **2** would likely be effected mainly by H_2O_2 rather than by ROOH after a short period

(13) Mandal, S.; Lee, Y.; Purdy, M. M.; Sayre, L. M. *J. Am. Chem. Soc.* **2000**, *122*, 3574−3584.

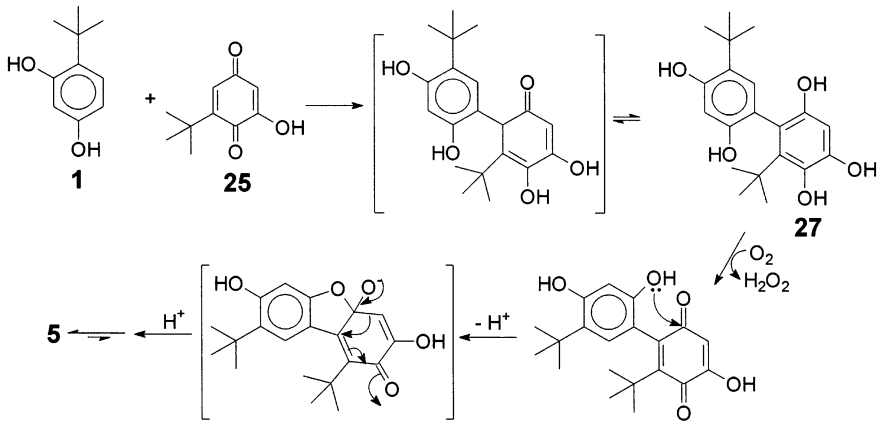
(14) Musso, H.; Gizycki, U. v.; Zahorszky U. I.; Bormann, D. *Liebigs Ann. Chem.* **1964**, *676*, 10−20.

(15) Cuntze, U.; Maassen, D.; Musso, H. *Chem. Ber.* **1969**, *102*, 2851−2861.

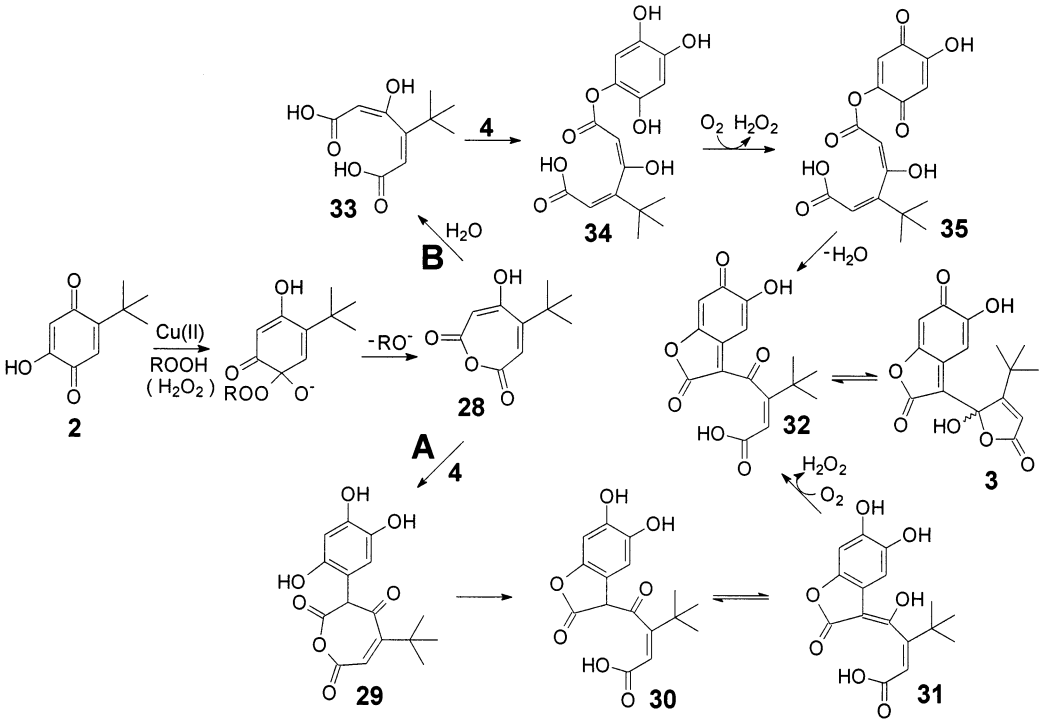
(16) Butsugan, Y.; Muto, Masao, M.; Kawai, M.; Araki, S.; Murase, Y.; Saito, K. *J. Org. Chem.* **1989**, *54*, 4215−4217. Cheng, A. C.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1982**, *47*, 5258−5262.

(17) Alt, C.; Eyer, P. *Chem. Res. Toxicol.* **1998**, *11*, 1223−1233. Manthey, M. K.; Pyne, S. G.; Truscott, R. J. W. *Aust. J. Chem.* **1989**, *42*, 365−373.

SCHEME 3



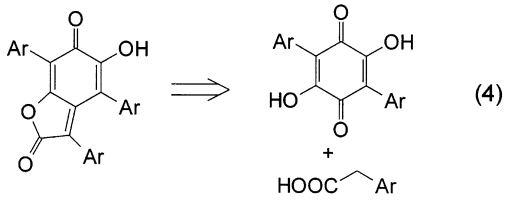
SCHEME 4



of reaction.[18] Also, if the initial peroxide adding to **2** were **22** (R = H), the byproduct would be 5-*tert*-butyl-1,2,4-benzenetriol (**26**), which would be oxidized to **2** as part of Scheme 1, generating H_2O_2 from O_2.

The proposed routes for generation of **3** and **5** *in the same reaction* bring up the question of potential competing reactions. In both cases, the initial bimolecular coupling involves a nucleophile−electrophile combination, **28** with **4** in the case of **3** and **1** with **25** in the case of **5**. The alternate pairing of the two possible nucleophiles and two possible electrophiles would lead to two additional products that were not observed, though there were several minor unidentified products generated in the reaction. It is possible that the reaction outcome is controlled by the fact that **28** is expected to be the more reactive nucleophile and **4** is the more reactive electrophile, so that these two species react preferentially with each other.

The structure of **3** shares its benzofuran-2,6-dione core with that of a family of structurally characterized red pigments called xylerythrins from the fungus *Peniophora sanguinea*.[19] The latter represent formally the lactone form of quinone methide Perkin-like condensation products of 3,6-diaryl-2,5-dihydroxy-1,4-benzoquinones with arylacetic acids (eq 4), which have been synthesized by

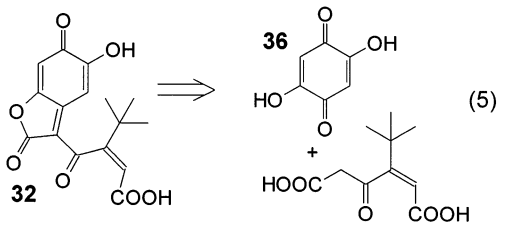


(4)

such a route.[20] We thus considered that **3** might arise alternatively from such a condensation. If so, the ret-

(18) The requirement for peroxide-induced cleavage of **2** (Scheme 4) explains why **3** was obtained in much higher yield from reaction of **4** with triol **26** as opposed to **2**: autoxidation of triol **26** would give both the required **2** and H_2O_2.

rosynthetic analysis shown in eq 4 would suggest condensation of the des-*tert*-butyl precursor 2,5-dihydroxy-1,4-benzoquinone (**36**) with a ring-opened β-keto acid derived from oxidative cleavage of **2** (eq 5). However,



(5)

reaction of independently generated **36** with either **2** or its reduced triol form **26** in the presence of air and Cu^{II} did not afford any **3**, giving instead **2** as the only organic extractable material (no significant reaction occurred in the absence of Cu^{II}). Thus, even if **36** were formed in the Cu^{II}-mediated oxidation of **1**, it evidently would not lead to **3** under the reaction conditions. As far as why **36** did not serve as a precursor to **3**, it should be noted that the xylerythrin syntheses are conducted under acidic conditions, and under the basic conditions used here, **36** likely becomes an inactive electrophile relative to competing base decomposition processes.

In conclusion, facile Cu^{II}-mediated oxygenation of **1** has been shown to afford **2** as the main product, reflecting oxygenation at the unsubstituted position *ortho*/*para* to the two resorcinol hydroxyls. In addition, on the basis of the isolation of two side products (**3** and **5**), oxygenation also evidently occurs at the *ortho*/*para*-position bearing the *tert*-butyl group. This can result in either loss of *tert*-butyl, leading to quinone **4** that serves as a precursor to **3**, or a 1,2-shift of the *tert*-butyl group to give the quinone **25**, proposed as the precursor to **5**. Although oxygenation at the *ortho*/*ortho*-position (C2) of **1** is not observed, C2 oxygenation does compete as a minor pathway in the reaction of **9**, where both *ortho*/*para*-positions (identical) are *tert*-butyl substituted. The observed facile Cu^{II}-mediated oxygenation of 4-alkylresorcinols parallels the reaction seen for 5-alkylresorcinols, and is notable in that Cu^{II}-mediated autoxidation of simple phenols results only in oxidative coupling, whereas phenol oxygenation requires the involvement of Cu^{I-}ligand catalysis. The difference is probably due to greater ease of one-electron oxidation of resorcinols compared to phenols, permitting Cu^{II} to activate the resorcinol, through charge-transfer coordination, toward reaction with O_2. The resorcinol oxygenations appear worthy of additional investigation.

Experimental Section

General Information. 5-*tert*-Butyl-2-hydroxy-1,4-benzoquinone (**2**) was prepared according to our previous work.[21] 2-Hydroxy-1,4-benzoquinone[22] (**4**) was prepared freshly before use by stirring 1,2,4-benzenetriol (2.5 mmol) with 2 equiv of 50% Ag_2CO_3 on Celite in 200 mL of refluxing toluene for 10 min, cooling, filtering, concentrating until a solid appeared, and then collecting the yellow solid which crystallized. 4,6-Di-*tert*-butylresorcinol (**9**) was prepared by mixing resorcinol and 2 equiv of *tert*-butyl alcohol in phosphoric acid.[23] All other reagents and solvents were obtained from commercial sources and used as received unless otherwise noted. Reactions in aqueous solution were carried out using Millipore purified water. All reactions were carried out at room temperature (25 °C) with magnetic stirring unless otherwise noted, and all evaporations were carried out at reduced pressure with a rotary evaporator. The ^{1}H NMR spectra were obtained at 200 or 300 MHz (^{13}C NMR at 50 or 75 MHz), with chemical shifts being referenced to the TMS or solvent peak(s), expressed on the δ scale. Attached proton test (APT) designations for ^{13}C NMR spectra are given in parentheses. Two-dimensional HMQC and HMBC spectra were recorded using a 600 MHz spectrometer. High-resolution mass spectroscopy (HRMS) was done in either electron impact (EI) mode (24 eV) or fast atom bombardment (FAB) mode (glycerol matrix). Thin-layer and preparative-layer chromatographies were run on silica gel 60 plates with a 254 nm indicator.

Copper(II)-Catalyzed Oxidation of 4-*tert*-Butylresorcinol (1) in Aqueous Acetonitrile. A mixture of **1** (166 mg, 1 mmol) and $Cu(ClO_4)_2 \cdot 6H_2O$ (37 mg, 0.1 mmol) in 100 mL of acetonitrile−water (1:1) was adjusted to pH 10.0 by adding 4 N NaOH. The solution was stirred vigorously in an open 250 mL Erlenmeyer flask at 25 °C with monitoring of the pH. As the reaction progressed, the pH dropped and was readjusted to pH 10 by addition of 4 N NaOH. After 1.5 h of stirring, the reaction mixture was acidified with HCl to pH 3.0, concentrated to remove the CH_3CN, and extracted with EtOAc (50 mL). The organic layer was dried (Na_2SO_4) and evaporated, and the residue was dissolved in CD_3CN. The ^{1}H NMR spectrum showed a mixture of **2** and **3** in a ratio of 3:1. Red crystals that formed in the NMR tube after 2 days at room temperature were filtered and washed with CH_3CN to give pure 3-(4-(1,1-dimethylethyl)-5-hydroxy-2-oxo-(5*H*)-furan-5-yl)-5-hydroxybenzofuran-2,6-dione (**3**; 27 mg, 9%): ^{1}H NMR (DMSO-d_6) δ 1.13 (s, 9H), 6.27 (s, 1H), 6.32 (s, 1H), 6.88 (s, 1H), 8.69 (br s, 1H, OH); ^{13}C NMR (APT, DMSO-d_6) δ 29.4 (−), 33.8 (+), 100.1 (−), 104.5 (+), 104.6 (−), 118.4 (−), 121.4 (+), 144.8 (+), 153.7 (+), 158.8 (+), 164.4 (+), 169.3 (+), 174.8 (+), 181.6 (+); FAB HRMS exhibited the M + 1 ion for the reduced form of **3**,[24] *m*/*z* calcd for $C_{16}H_{17}O_7$ 321.0974 found 321.0987.

For quantitative analysis of the percent conversion of **1** and the yield of products, the same reaction was repeated, and the final EtOAc extract was concentrated to 10 mL. A 5 mL aliquot (corresponding to 0.5 mmol of starting **1**) was utilized for the ^{1}H NMR spectral determination ($CDCl_3$), with 138 mg (1 mmol) of 1,4-dimethoxybenzene being added as an internal standard (Table 2).

The same reaction described above occurred over the pH range 7.0−11.0, giving the same ratio of products (**2**:**3** in a ratio of 3:1), except that the reaction was slower at lower pH. The addition of 1 equiv of 2,2′-bipyridine (based on copper) to the reaction did not alter the results. However, Cu^{II} was found to be essential for this reaction, because a separate reaction performed without Cu^{II} for 1.5 h at pH 10 resulted in recovery of starting **1**.

Copper(II)-Catalyzed Oxidation of 1 in Phosphate Buffer. To a well-stirred 0.1 M pH 11 sodium phosphate buffer solution (500 mL) were added a clear solution of **1** (830 mg, 5 mmol) in 2 mL of methanol and then 500 μL (0.5 mmol) of 1 M aqueous $CuSO_4$. The mixture was stirred vigorously in air for 1.5 h, acidified with concentrated HCl to pH 2, and then

(19) Abrahamsson, S.; Innes, M. *Acta Crystallogr.* **1966**, *21*, 948−956. Gripenberg, J.; Hiltunen, L.; Pakkanen, T.; Pakkanen, T. *Acta Chem. Scand., B* **1980**, *34*, 575−578.

(20) Pattenden, G.; Pegg, Neil A.; Kenyon, R. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2363−2372.

(21) Lee, Y.; Sayre, L. M. *J. Am. Chem. Soc.* **1995**, *117*, 3096, 11823−11828.

(22) Musso, H.; Döpp, D.; Kuhls, J. *Chem. Ber.* **1965**, *98*, 3937−3951.

(23) Halfpenny, P. J.; Johnson, P. J.; Robinson, M. J. T.; Ward, M. G. *Tetrahedron* **1976**, *32*, 1873−1879.

(24) It is not uncommon for *tert*-butyl-containing quinones or quinone-like substances to undergo reduction in the mass spectrometer; see ref 11.

extracted with EtOAc (3 × 50 mL). The combined organic layer was dried (Na_2SO_4), evaporated to a small volume, and diluted to 50 mL with EtOAc. A 5 mL aliquot of the latter solution (corresponding to 0.5 mmol of starting **1**) was utilized for the ^{1}H NMR spectral determination ($CDCl_3$) of the percent conversion of **1** and the yield of products, with 138 mg (1 mmol) of 1,4-dimethoxybenzene being added as an internal standard (Table 2). The remainder of the EtOAc solution (45 mL) was evaporated and separated by silica gel column chromatography using hexanes and EtOAc as eluents to give **5**, **1,** and **2**. Data for compound **5**: white amorphous solid; IR (KBr) ν_{max}/cm^{-1} 3404 (br, OH), 1802 (s, C=O), 1706 (s, C=O); ^{1}H NMR (DMSO-d_6) δ 0.97 (s, 9H), 1.33 (s, 9H), 2.58 (d, 1H, J = 18.7 Hz), 2.77 (d, 1H, J = 18.7 Hz), 6.69 (s, 1H), 7.01 (s, 1H), 9.90 (s, 1H, OH), 9.99 (s, 1H, OH); ^{13}C NMR (APT, DMSO-d_6) δ 27.4 (−), 29.5 (−), 34.4 (+), 34.6 (+), 46.0 (+), 51.3 (+), 99.1 (−), 119.3 (+), 121.2 (−), 132.5 (+), 147.2 (+), 151.1 (+), 152.5 (+), 157.1 (+), 179.6 (+), 199.5 (+); HRMS (EI) *m*/*z* calcd for $C_{20}H_{24}O_5$ 344.1624, found 344.1630 (rel intens 52).

Essentially the same results were obtained using $Cu(ClO_4)_2$·$6H_2O$ instead of $CuSO_4$ as catalyst (Table 2).

Anaerobic Oxidation of 1 by Copper(II) in Aqueous Acetonitrile. A solution of **1** (332 mg, 2 mmol) and $Cu(ClO_4)_2$·$6H_2O$ (740 mg, 2 mmol) in 200 mL of acetonitrile−water (1:1, v/v) was placed in a three-necked round-bottom flask with an electromagnetic stirrer, fitted with a dropping funnel containing 0.1 M aqueous NaOH and a pH electrode with a septum seal. The middle neck contained a septum with inlet and outlet needles. The solution was first bubbled with argon for 30 min under continuous stirring, and then aqueous NaOH was slowly introduced from the dropping funnel until the pH reached 10. The mixture immediately turned to yellow-brown, and the pH was maintained at 10 throughout the reaction course by adding NaOH. After 3 h, the mixture was acidified with 1 M aqueous HCl to pH 2 and then evaporated under reduced pressure to remove the acetonitrile. The aqueous solution was extracted with EtOAc (3 × 20 mL), and the organic layer was dried (Na_2SO_4) and concentrated to 50 mL. A 5 mL aliquot was removed for NMR spectral analysis. The remainder of the solution was evaporated and separated by silica gel column chromatography with hexanes and EtOAc as eluent to afford **1**, **11,** and **12**. Data for dimer **11**: white amorphous solid; ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 18H), 5.25 (br, 2H, OH), 5.75 (br, 2H, OH), 6.36 (s, 2H), 7.08 (s, 2H); ^{13}C NMR (APT, $CDCl_3$) δ 29.9 (−), 34.2 (+), 104.6 (−), 115.0 (+), 129.8 (−), 130.0 (+), 151.7 (+), 155.3 (+); HRMS (FAB) *m*/*z* calcd for $C_{20}H_{26}O_4$ (M^+) 330.1831, found 330.1826 (rel intens 93). Data for Pummerer's ketone **12**: white amorphous solid; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H), 1.36 (s, 9H), 2.75 (dd, 1H, J = 4.0, 15.5 Hz), 2.92 (dd, 1H, J = 6.2, 15.5 Hz), 3.18 (d, 1H, J = 19.5 Hz), 3.33 (d, 1H, J = 19.5 Hz), 5.24 (dd, 1H, J = 4.0, 6.2 Hz), 5.32 (br, 1H, OH), 6.36 (s, 1H), 7.21 (s, 1H); ^{13}C NMR (APT, $CDCl_3$) δ 26.0 (−), 29.9 (−), 34.4 (+), 37.3 (+), 46.9 (+), 55.7 (+), 67.7 (+), 81.8 (−), 98.9 (−), 117.1 (+), 125.0 (−), 129.6 (+), 156.4 (+), 158.3 (+), 202.5 (+), 203.1 (+); HRMS (FAB) *m*/*z* calcd for $C_{20}H_{26}O_4$ (M^+) 330.1831, found 330.1825 (rel intens 15).

Copper(II)-Catalyzed Oxidation of 9. A mixture of 0.1 M pH 11 sodium phosphate buffer solution (500 mL), **9** (dihydrate, 1.29 g, 5 mmol, first dissolved in a small volume of methanol), and 500 μL (0.5 mmol) of 1 M aqueous $CuSO_4$ was stirred vigorously in air for 1.5 h, titrated with 0.1 M aqueous HCl to pH 2, and then extracted with EtOAc (3 × 50 mL). The combined organic layer was dried (Na_2SO_4), evaporated to a small volume, and diluted to 50 mL with EtOAc. A small aliquot was applied for ^{1}H NMR spectral determination as shown above, while the remainder of the solution was separated by column chromatography on silica gel using hexanes and EtOAc as eluents to afford **2** and **10**. Data for compound **10**: red oil; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.37 (s, 9H), 6.50 (s, 1H), 7.20 (s, exchangeable by D_2O, 1H, OH); ^{13}C NMR (APT, $CDCl_3$) δ 29.6 (−), 30.3 (−), 35.5 (+), 36.2 (+), 125.1 (−), 129.2 (+), 148.9 (+), 162.4 (+), 184.5 (+), 189.3 (+); HRMS (EI) *m*/*z* calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1419 (rel intens 60).

Essentially the same result was obtained when the above reaction was carried out in 1:1 acetonitrile−water with pH 10 (Table 2). No reaction occurred in the presence of diethylenetriaminepentaacetic acid.

Copper(II)-Catalyzed Oxidation of 1 and 9 in Acetonitrile Using $^{18}O_2$. To a 50 mL round-bottomed two-necked flask fitted with a vacuum line and a septum was injected 20 mL of a CH_3CN solution of either **1** or **9** (10 mM) containing 100 mM $^{16}OH_2$. The solution was deaerated by three freeze−pump−thaw cycles under argon, with $^{18}O_2$ (95% ^{18}O mixed 4:1 with N_2, 1 atm, Icon Services, Summit, NJ) being admitted in the fourth cycle. Argon was further admitted to maintain a slightly positive pressure. After vigorous stirring for 5 min, 0.5 mL of a degassed solution of $Cu(CF_3SO_3)_2$ (400 mM) in CH_3CN was injected through the septum, and the reaction was initiated by injecting a degassed methanolic solution of 2 M NaOMe (0.30 mL for **1** or 0.25 mL for **9**). The reaction mixture was vigorously stirred for 10 min before quenching by injection of a degassed aqueous solution of NaH_2PO_4 (40 mM, 20 mL) followed immediately by addition of $NaBH_4$ in small portions over 1 min with vigorous stirring until the red color of the quinone faded. The mixture was then adjusted to pH 2 with 0.1 N aqueous HCl, diluted with 50 mL of water, and then extracted with CH_2Cl_2 (50 mL). The combined organic layer was dried (Na_2SO_4) and evaporated. TLC analysis showed that triol **26** was the major product in both cases. The crude product mixtures were then subjected to mass spectral analysis. HRMS (FAB) *m*/*z* (rel intens) calcd for $C_{10}H_{14}{}^{16}O_3$ and $C_{10}H_{14}{}^{18}O^{16}O_2$ (M^+), 182.0943 and 184.0986, found 182.0931 (100) and 184.0980 (39) for reaction of **1** and 182.0930 (34) and 184.0982 (100) for reaction of **9**. The mass peak representing $C_{10}H_{14}{}^{18}O^{16}O_2$ was distinct from the expected M + 2 satellite of $C_{10}H_{14}{}^{16}O_3$ so that no correction was needed. A control experiment using air instead of $^{18}O_2$ confirmed the absence of $C_{10}H_{14}{}^{18}O^{16}O_2$ by HRMS in both cases.

Copper(II)-Catalyzed Reaction of Hydroxyquinone 2 or Triol 26 with 4 in Aqueous Acetonitrile. A mixture of either **2** (36.0 mg, 0.20 mmol) or **26** (36.4 mg, 0.20 mmol) with **4** (25.2 mg, 0.20 mmol) and $Cu(ClO_4)_2$·$6H_2O$ (7.5 mg, 0.02 mmol) in 10 mL of acetonitrile−water (1:1) was adjusted to pH 10.0 with 4 N NaOH and was maintained at pH 10 with stirring for 30 min before quenching with dilute HCl to pH 3.0. The solution was extracted with EtOAc (15 mL). The organic layer was dried (Na_2SO_4) and concentrated to give a crude product mixture. ^{1}H NMR spectral analysis revealed **2** and **3** in a ratio of 1:1 as the only identified products. Starting with **26**, the yield of the mixture of **2** and **3** was 66%, on the basis of integration of the eight *tert*-butyl signals observed in the crude ^{1}H NMR spectrum (estimated from peak heights; none of the unidentified products were present to an extent of >10%). Starting with **2**, the yield was 3-fold lower, and when either reaction was conducted under identical conditions but the starting concentrations were reduced by 13-fold, the yield of the 1:1 mixture of **2** and **3** was reduced in each case more than 2-fold, and the unidentified side products became much more numerous. The same reaction as described above in the absence of Cu^{II} gave **2** as the major product by far, only a trace of **3**, and several unidentified products.

Copper(II)-Catalyzed Reaction of Hydroxyquinone 2 or Triol 26 with 2,5-Dihydroxy-1,4-benzoquinone (36) in Aqueous Acetonitrile. An equimolar mixture of either **2** or **26** with **36** in acetonitrile−water (1:1) at a final concentration of either 1.5 or 20 mM, in the absence or presence of 0.1 equiv of $Cu(ClO_4)_2$·$6H_2O$, was adjusted to and maintained at pH 10.0 by addition of 4 N NaOH. After 30 min, the reaction was directly extracted (20 mM reaction) with EtOAc or first concentrated and then extracted (1.5 mM reaction), and the organic layer was dried (Na_2SO_4) and concentrated to give a crude product mixture. ^{1}H NMR spectral analysis revealed **2**

(or, in the case starting with **26**, a little **26**) as the major and only identifiable product.

X-ray Crystallography. Single crystals of **3** were grown from CD_3CN. Data were collected on a Siemens P4 diffractometer (Mo Kα radiation, $\lambda = 0.71073$ Å). A red block-shaped crystal having approximate dimensions $0.40 \times 0.24 \times 0.14$ mm^3 was glued to the end of a glass fiber. The crystal was judged to be acceptable on the basis of ω scans and rotation photography. A random search located reflections to generate a reduced primitive cell. Cell lengths were confirmed by axial photographs. Additional reflections with higher 2θ values were appended to the reflection array and yielded the refined cell constants reported in the Supporting Information. Data were corrected for absorption (empirical ψ scans). Direct methods (Siemens SHELXTL PLUS, version 5.0) revealed all nonhydrogen atoms. Hydrogen atoms were located from a Fourier map and their positional parameters refined, while thermal parameters were restricted to isotropic thermal parameters 1.2 times those of associated carbon or oxygen. All nonhydrogen atoms were refined anisotropically. The bond lengths and angles in the molecule are within established norms,[25] and selected values are listed in the Supporting Information.

Acknowledgment. We are grateful to the National Institutes of Health for support of this work through Grant GM 48812.

Supporting Information Available: ORTEP diagram and crystallographic data for **3**, ^1H and ^{13}C NMR spectra for compounds **3**, **5**, and **10**−**12**, and HMBC and HMQC spectra for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020582Y

(25) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1−S17.