Direct Conversion of Phenols to *o*-Quinones by Copper(I) Dioxygen. Questions Regarding the Monophenolase Activity of Tyrosinase Mimics

Lawrence M. Sayre* and Durgesh V. Nadkarni

Department of Chemistry
Case Western Reserve University
Cleveland, Ohio 44106

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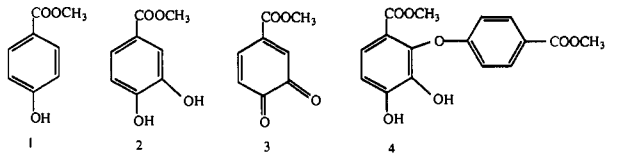
The conversion of phenols to *o*-quinones by the binuclear copper enzyme tyrosinase is usually considered to proceed via the intermediacy of catechols.[1,2] Evidence for independent monophenolase (phenol *o*-oxygenation) and catecholase (catechol dehydrogenation to *o*-quinones) activities rests primarily on the facts that (i) the enzyme can efficiently oxidize catechols to *o*-quinones and (ii) "priming" of the enzyme with a catechol or equivalent ancillary reductant (e.g., ascorbate) is required to avert the induction period otherwise observed when one starts with phenol. The resting state of the enzyme is Cu(II)–Cu(II), and two-electron reduction to Cu(I)–Cu(I) is required to permit binding and processing of dioxygen. Based on the historical presumption that the binuclear Cu(I) form of tyrosinase is a monophenolase, many efforts have been made to devise model binuclear Cu(I) systems with monooxygenase activity. The failure to observe such a reaction except in a particular family of reactions where the central peri aryl ring position of a *m*-xylyl-bridged, nitrogen-based, binucleating *ligand* is hydroxylated[3–8] makes any report of the conversion of *external* phenols to catechols unusually noteworthy. Evidence is provided in this communication that the actual initial products in such latter cases are actually *o*-quinones rather than catechols.[9] The recognition of copper mediation of *direct* oxygenation of phenols to *o*-quinones without the intermediacy of catechols brings into question the necessity of invoking a monophenolase activity for tyrosinase mimics.

Copper-promoted phenol oxygenation to produce selectively ortho- as opposed to para-quinones has been known for many years,[10,11] but the question of whether catechols were true intermediates in *o*-quinone formation was never resolved, principally because such catechols would be readily oxidized under the reaction conditions, especially in the case of di-*tert*-butyl substitution.[12,13] In this light, one's curiousity is aroused regarding two recent reports of the high-yield conversion of phenols to *catechols* by copper-based systems.[14,15] In both cases, the key factor is the initial coordination of the reactant conjugate base phenolates to Cu(I) prior to exposure to O_2. One system involved oxygenation of (phen)(Ph_3P)Cu(I)OAr generated *in situ* from

Chart 1



(phen)(Ph_3P)Cu(I)BH_4 and ArOH in THF.[14] The other system involved oxygenation of the complex formed from equimolar quantities of a tetra(benzimidazolylmethyl)-*m*-xylylenediamine-based binuclear Cu(I) complex and Na^+ArO^-,[15] the latter generated from ArOH and $NaBH_4$.[16] In both cases, solvated BH_3 is present as a byproduct, and the role of this as a potential reductant in these systems was not directly addressed. Since the BH_3 present might reduce *o*-quinones under the reaction conditions, one cannot unambiguously conclude whether the initial products of the copper-mediated oxygenation step are catechols or the corresponding *o*-quinones. Thus, we sought to reproduce both model systems as closely as possible but avoiding the generation of BH_3 (e.g., by using BF_4^- instead of BH_4^-).

One of the principal problems in the design of phenol monooxygenation experiments is the ease of oxidation of the putative catechol under the reaction conditions. Electron-withdrawing groups have been relied on to avert such subsequent oxidation,[15,17] and much of the work described below utilizes the 4-carbomethoxy substituent. Stirring (phen)(Ph_3P)Cu(I)BH_4[18] with an excess of methyl 4-hydroxybenzoate (**1**, Chart 1) in THF under Ar, as described,[14] followed by exposure to O_2, gave as the only product 4-carbomethoxycatechol (**2**) in 40% yield, based on Cu(I) complex. In contrast, when (phen)(Ph_3P)Cu(I)BF_4, prepared *in situ* in THF, was reacted under Ar with 1 equiv of the tetra-*n*-butylammonium 4-carbomethoxyphenolate and 1 equiv of the free phenol **1**, we observed 15% conversion of **1** to the catechol **4**,[19] representing Michael addition of **1** to 4-carbomethoxy-1,2-benzoquinone (**3**).

A much better yield of **4** was obtained using the binuclear Cu(I) complex of *N,N,N',N'*-tetra-(2-(*N*-methylbenzimidazol-2-yl)ethyl)-*m*-xylylenediamine (**5**).[15] Thus, whereas exposure to O_2 of the complex formed from **5**–Cu(I)$_2$ and sodium 4-carbomethoxyphenolate in CH_3CN gave a 40–50% yield of catechol **2**, as reported,[15] when the sodium phenolate was generated *in situ* from **1** and $NaBH_4$,[16] 40–50% conversion of **1** to **4** was observed instead using the *authentic* sodium phenolate (from **1** and NaOH). In the latter case, no evidence for the presence of any other product, namely the catechol **2** or *o*-quinone **3**, could be obtained, even with quenching of the reaction at very short reaction times. Although the Michael adduct **4** derived from *o*-quinone **3** might conceivably arise from oxidation of initially formed catechol **2**, we determined that **2** (either as its monosodium salt or as its disodium salt) is inert to oxidation under reaction conditions where **5**–Cu(I)$_2$ undergoes complete O_2-dependent oxidation to the blue Cu(II) state. In finding that the *p*-carbomethoxy substituent retards catechol → *o*-quinone oxidation under these reactions conditions, our result demonstrates that *o*-quinone **3** (precursor to Michael adduct **4**) *must arise directly from phenol 1 without the formal intermediacy of catechol 2.*

In the absence of direct observation of *o*-quinone **3**, we sought to verify that isolated Michael adduct **4** would indeed arise when

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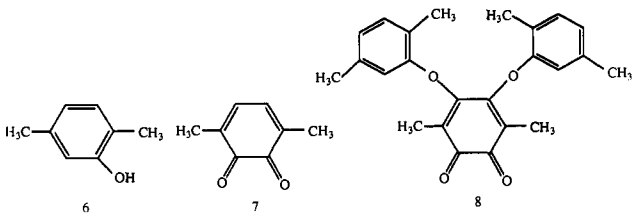
Chart 2



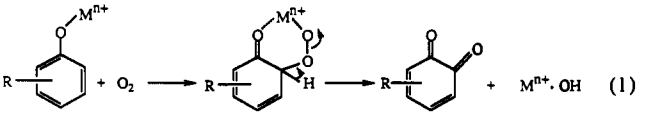
6 7 8

3 is generated in the presence of the phenolate reactant. The *o*-quinone 3 is unknown, and we have so far been unable to isolate it from oxidation of catechol 2 (such *o*-quinones are notoriously unstable with respect to self-Diels–Alder condensation).[20] Nonetheless, we could identify adduct 4 (diethyl ester) as the only product in low yield (10%) when 2 (ethyl ester) was oxidized[21] by $NaIO_3$ in ethanol–water at 25 °C followed rapidly by addition of sodium 4-carbethoxyphenolate. Furthermore, our contention that 4 arises from Michael addition to an initially-formed 3 in copper-mediated oxygenation of 1 requires that 4 incorporate exactly one oxygen atom from O_2. Carrying out the reaction of 5-Cu(I)$_2$ with Na^+–1^- in CH_3CN under Ar followed by exposure to $[^{18}O]O_2$ gave 4, which exhibited a parent peak in the mass spectrum at the expected M + 2 value.[22]

An alternate strategy for achieving phenolate–copper coordination which avoids a prior phenol deprotonation is the Cu(0) corrosion method.[17] We found that a 60% yield of 4 could be obtained most simply by stirring an equimolar mixture of 1 and *N,N'*-bis(2-(2-pyridyl)ethyl)benzylamine as ligand with 1.5 equiv of copper powder in CH_3CN under O_2 for 6 h at 60 °C.

With this latter methodology, 2,5-dimethylphenol (6, Chart 2) underwent 90% conversion under even milder conditions (25 °C, 3 h) to a single product identified as *o*-quinone 8 by NMR and mass spectrometry. The latter must arise from 3,6-dimethyl-1,2-benzoquinone (7) formed as initial product via two consecutive Michael addition/oxidation sequences. The distinction between 8 and the other possible symmetrical isomer, 2,5-bis(aryloxy)-3,6-dimethyl-1,4-benzoquinone was made on the basis of our ability to isolate an *o*-phenylenediamine cyclocondensate.[23] In contrast to 1, the absence of electron-withdrawing substituent in 6 means that the catechol derived from 6 would be rapidly oxidized to *o*-quinone 7, thereby preventing a determination of whether the catechol or 7 is the initial oxygenation product in this case. Nonetheless, unlike 1, where the presence of the 4-substituent precludes para functionalization, 6 can in theory be oxygenated at either ortho or para positions with equal steric facility. The formation of 8 thus demonstrates the complete ortho selectivity of the copper-mediated oxygenation step, as has been observed in related systems.[11,12,14,17] It is of interest to note that 8 is the only product formed from 6, in contrast to the substantial amounts of cleavage products (muconic acid derivatives) found in previously studied copper-mediated oxygenations of 2,4-di-*tert*-butylphenol.[11]

The direct generation of *o*-quinone reported here requires a reassessment of the mechanism of copper-mediated oxygenation, at least in the case of 1. The monooxygenation mechanism traditionally depicted to represent the alleged phenolase activity of tyrosinase[2] cannot be in force here, because the experiments carried out independently on catechol 2 reveal that 2 *would be the isolated product were it the initial product.* There is ample precedent for a different type of redox-active, metal-mediated oxygenation involving the postulated generation of 6-peroxy-2,4-cyclohexadienone metal salts, which undergo subsequent 1,2-elimination to give *o*-quinones (eq 1).[24] A 6-peroxy-Co(III)



(1)

species has been isolated in one case where 2,4,6-tri-*tert*-butyl substitution blocks the elimination pathway.[25] Since incorporation of dioxygen into the organic reactant occurs prior to O–O cleavage, such overall transformation corresponds to a four-electron reduction of O_2, distinct from the mechanisms depicted for true monooxygenases such as cytochrome P-450 and dopamine β-monooxygenase. In this regard, the O_2 incorporation of eq 1 is analogous to that proposed for the non-heme iron catechol 1,2-*dioxygenases*,[26,27] though the fate of the intermediate metal peroxide differs in this case (ring expansion) on account of the C-6 substituent being OH rather than H.[28]

Additional studies will be required to elucidate mechanistic details for the ortho-selective, copper-mediated phenolate oxygenation described here. We do know that there is a strict requirement for Cu(I) (no conversion of reactant occurs once all the copper is transformed to the Cu(II) state) and that electron-donating substituents stimulate reaction, but whether the mechanism involves binuclear or mononuclear involvement of copper at the oxygenation transition state is yet to be clarified. Also, the reaction is *not* merely a copper-mediated phenolate autoxidation, because this involves preferential para oxygenation.[29] In regard to the enzymologic implications of our results, it should be appreciated that there is no direct evidence (of which we are aware) for the intermediacy of catechols in the processing of phenols to *o*-quinones by tyrosinase.[30] It may thus be worth considering a reevaluation of the traditional monophenolase/catecholase description of the enzyme reaction pathway, at least in regard to the design of relevant biomimetic systems.[32]

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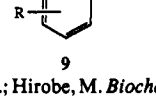
Supplementary Material Available: Experimental details for the O_2-dependent conversions of 1 to 4, 1 to 2, and 6 to 8 described in the text (3 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.



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