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Theoretical Studies on *ortho*-Oxidation of Phenols with Dioxygen Mediated by Dicopper Complex: Hints for a Catalyst with the Phenolase Activity of Tyrosinase

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Dedicated to Professor M. Shibasaki on the occasion of his 60th birthday.

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Abstract: Theoretical studies on the chemo- and regioselective *ortho*-oxidation reaction of phenols mediated by a biomimetic (μ–η^2:η^2peroxo)dicopper(II) complex were performed using unrestricted hybrid density functional theory (UB3LYP) calculations, with the aim of providing a guide for the development of new bio-inspired catalysts with the phenolase activity of tyrosinase. Energetic, structural, and electronic analyses suggested the involvement of a side-on (μ–η^2:η^2)-Cu_2O_2 complex as an active intermediate, and a single electron transfer (SET)-induced electrophilic aromatic substitution mechanism is proposed for the rate-determining C–O bond forming process; this is consistent with experimental observations. Moreover, the inherent roles of, and requirement for, two copper ions in this reaction have been elucidated.

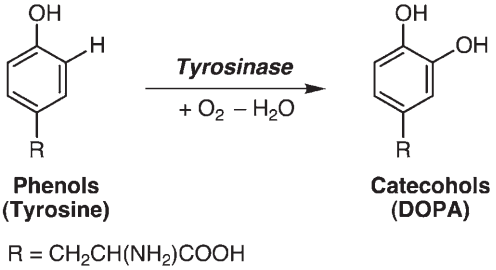
Keywords: copper; oxidation; peroxo complexes; phenols; theoretical calculations; tyrosinase

Introduction

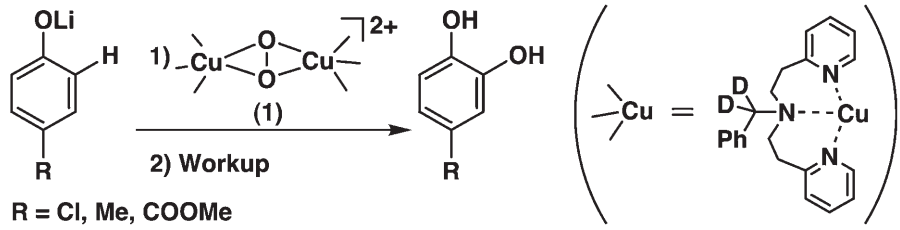
Regio- and chemoselective functionalization of aromatic compounds remains one of the most important targets in modern synthetic chemistry.[1] Although organic and organometallic synthetic chemists have made breakthroughs in methodologies for regio- and chemoselective functionalization,[2,3] *ortho*-oxidation of aromatic compounds to yield multi-functionalized phenols remains a challenge. In the course of our recent studies on the direct functionalizations of aromatic compounds using ate complexes (heterobimetal reagents),[4,5] we have become interested in the ability of tyrosinase, a dicopper-containing enzyme, to catalyze the *ortho*-oxidation of phenols (tyrosine) readily and smoothly to afford 1,2-diphenols (DOPA), using O_2 under mild conditions (Scheme 1).[6–8]

Extensive spectroscopic and synthetic modeling studies have been performed to elucidate the functional principles of this enzyme.[9–16] An excellent biomimetic system has been reported by Itoh et al., who used the designed (μ–η^2:η^2peroxo)dicopper(II) complex **1** to achieve an efficient *ortho*-oxidation reaction of the lithium salt of phenols to give 1,2-diphenols (Scheme 2).[17,18]

The complex **1** has extremely high reactivity (the reaction proceeds at −94 °C) and chemoselectivity (the corresponding *o*-quinones and coupled dimers are not



Scheme 1.



Scheme 2.

formed).[19] Therefore, this system has been regarded not only as a good model for enzymatic reactions, but also, from the viewpoint of synthetic chemistry, as a promising starting point for the development of new bio-inspired catalysts. However, details of the mechanism, e.g., the mechanism of entry of the oxygen atom into the aromatic ring and the roles of the two copper ions are still uncertain, though such information is important to provide a guide to the design of novel catalysts for regio- and chemoselective *ortho*-oxidation of aromatic compounds.

In the present computational/theoretical studies based on the unrestricted hybrid density functional theory (UB3LYP), we focused on the chemo- and regioselective *ortho*-oxidation reaction of phenols mediated by a biomimetic (μ–η^2:η^2peroxo)dicopper(II) complex **1**, with the aim of providing a detailed mechanistic insight into this dioxygen-mediated oxidation reaction. We highlighted the C–O bond forming step, as it is considered to be rate-determining, and therefore may be the key to the high chemoselectivity.[17] We also addressed the role of the two copper ions in the oxidation.

Results and Discussion

We first explored the structure of the model peroxodicopper complex **2**. Among several possible structures, an open singlet state of **2** was fully optimized as a stationary point (Figure 1).

The complex is best described as an antiferromagnetically coupled (μ–η^2:η^2)peroxodicopper(II) complex. The peroxodicopper forms a bent diamond Cu_2O_2 structure with reasonable values of O^1–O^2: 1.44 Å, Cu^1–Cu^2: 3.78 Å, Cu–O_{avg}: 2.06 Å, Cu–N_{avg}: 2.10 Å and Cu^1–O^1–O^2–Cu^2 dihedral: 157.7°. Mulliken atomic spins of +0.45 and −0.45 were computed on the Cu ions, showing antiferromagnetic coupling of the two coppers, with Cu_2(II, II) oxidation states. These structural and electronic properties are in good agreement with reported data on $Py2^R$ complexes and tyrosinase.[20] The corresponding spin silent state was also optimized as a stationary point (spin densities: Cu 0.00, Cu 0.00, a square-planar diamond structure with a dihedral angle of 174.2° for Cu^1–O^1–O^2–Cu^2) although this state was disfavored in energy by +7.1 kcal mol^{-1}.

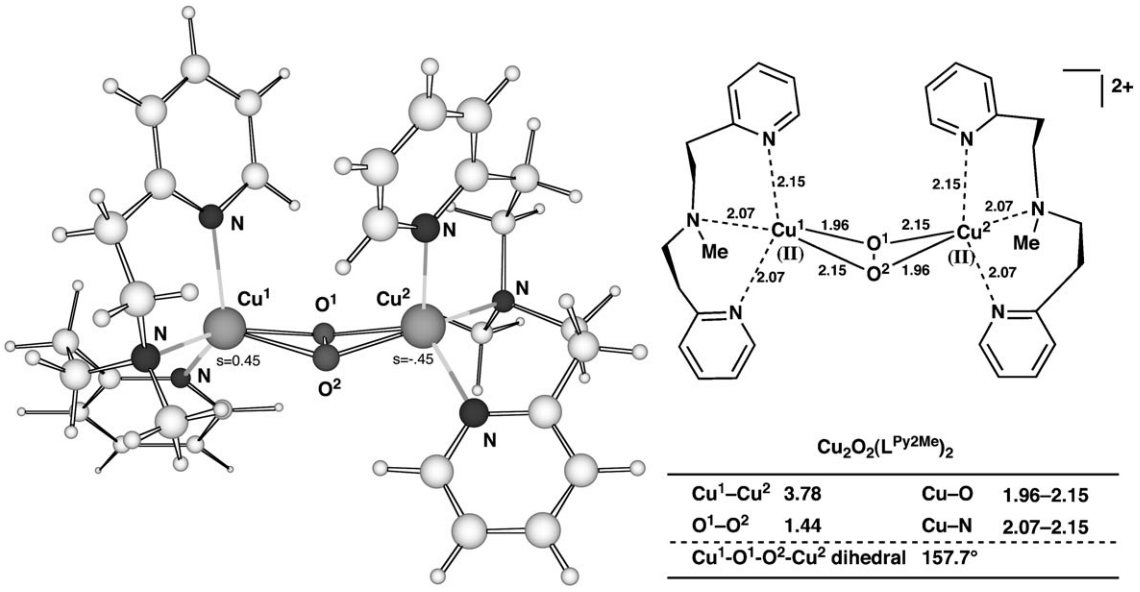
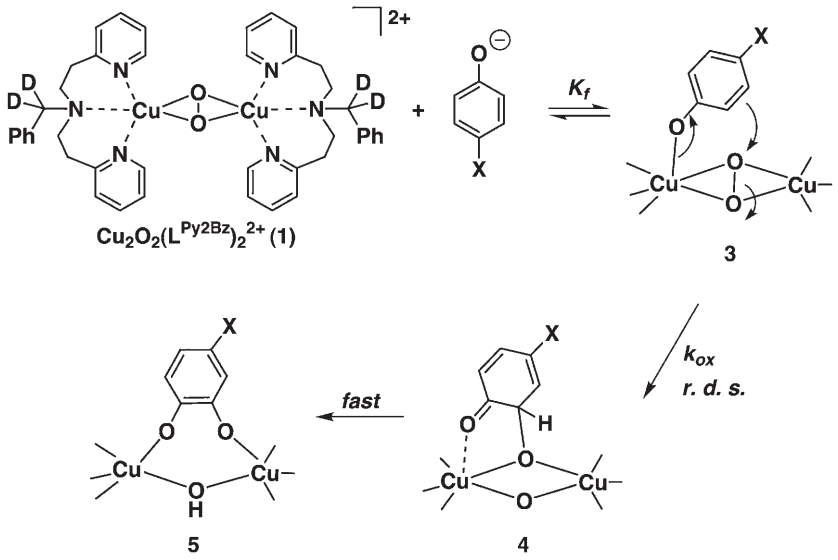
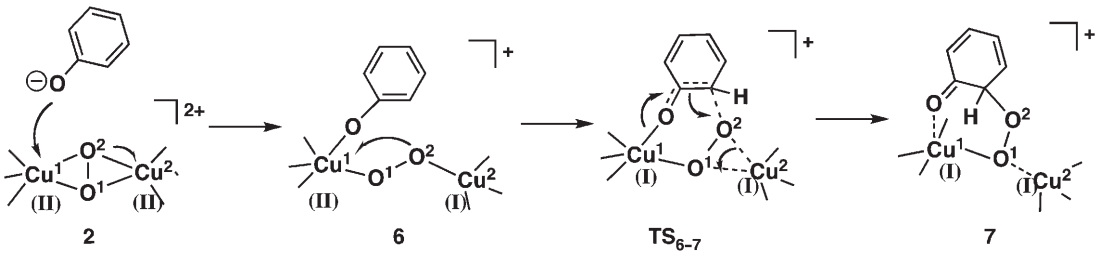


Figure 1. Fully optimized structure of the model peroxodicopper complex $Cu_2O_2(L^{Py2\,Me})_2^{2+}$ **2** at the B3LYP/631 A level of theory. Distances and angles are shown in Å and degrees, respectively. Spins larger than 0.05 are marked.



Scheme 3.



Scheme 4.

As the present theoretical method appeared to be reliable enough for our purpose, we next investigated the reaction pathway of phenoxide with **2**. An electrophilic aromatic substitution reaction is a plausible mechanism based on experimental kinetic studies, and the following reaction pathway has been proposed by Itoh et al. (Scheme 3).[17,21]

Thus, we initially tried to obtain the proposed transition state structure of the *ortho*-oxidation reaction of phenoxide (**3** to **4** in Scheme 3). However, no such TS could be found, probably because it involves a disfavored hexacoordinated copper center. No other structure with reasonable energy could be identified. Instead, an alternative process has been obtained with a reasonable energy barrier (Scheme 4, Figure 2).

The phenoxide anion coordinates very smoothly without energy barrier to one (the left) Cu^1 of **2**, involving deformation of the side-on oxygen binding of **2**, and reduction of the other (right), less anionic copper ion Cu^2(II) to Cu^2(I) by peroxide to yield the (μ–η^1:η^1)-Cu_2(I, II) peroxide **6**, in which the two coppers are coordinated by oxygen in an end-on manner. The formal oxidation states of the coppers were confirmed by the spin changes (Figure 1 and Figure 2b) and NPA charge changes (Figure 3, **2**–**6**).

The experimentally observed tendency that the use of a ligand with 4 donors in place of the present 3 donors is likely to give an end-on Cu_2O_2(μ–η^1:η^1) complex rather than a side-on (μ–η^2:η^2) Cu_2O_2 complex supports the credibility of the complex **6** as an active intermediate candidate over **3**.[20]

The following oxidation process is characterized as single electron transfer (SET)-induced aromatic electrophilic substitution reaction. The reaction from **6** to **7** proceeds with an activation barrier of 15.7 kcal mol^{-1}. The aromatic *ortho*-carbon attacks the peroxide orthogonally to the aromatic plane (O^2–C^{Ar2}–C^{Ar5} angle: 103.5°), forming the C–O bond (O^2–C^{Ar2} bond length: **6** 3.07 Å, $\mathbf{TS_{6-7}}$ 1.89 Å, **7** 1.42 Å), while the phenoxide is dissociating from Cu^1 (O^{Ar}–Cu^1 distance: **6** 1.95 Å, $\mathbf{TS_{6-7}}$ 1.99 Å, **7** 2.20 Å) to form the *ortho*-oxidized σ-complex **7**. Notably, Cu^2 migrates from O^2 to O^1 as the reaction proceeds. Intermediate **6** undergoes another electron transfer from O_2 to Cu^1(II) [confirmed by spin changes and charge changes (Figure 3, $\mathbf{6\text{-}TS_{6-7}\text{-}7}$)], forming cationically activated peroxide and anionically activated phenoxide. This

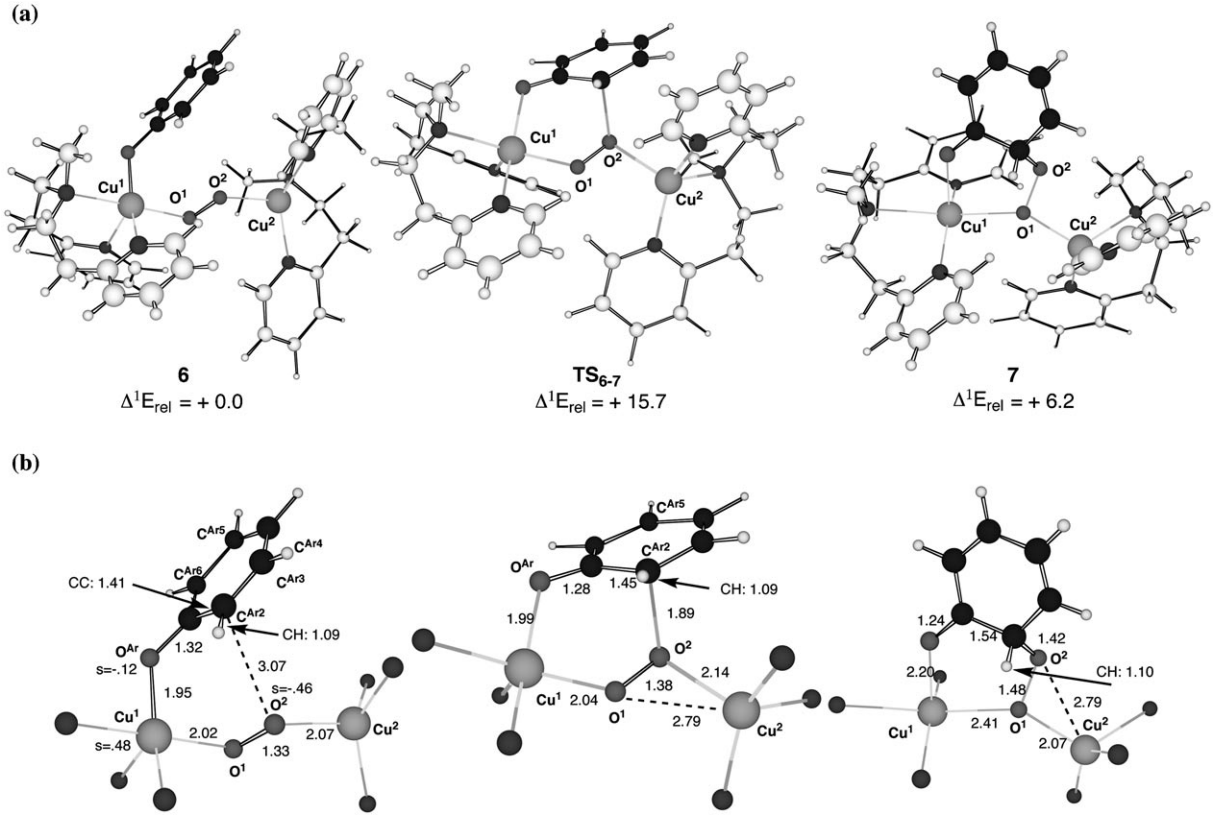


Figure 2. (a) Structures of the stationary points along the C–O bond formation process at the B3LYP/631A level of theory and **(b)** expanded view of those structures omitting ligand C, H atoms. Distances and angles are shown in Å and degrees, respectively. Spins larger than 0.05 are marked.

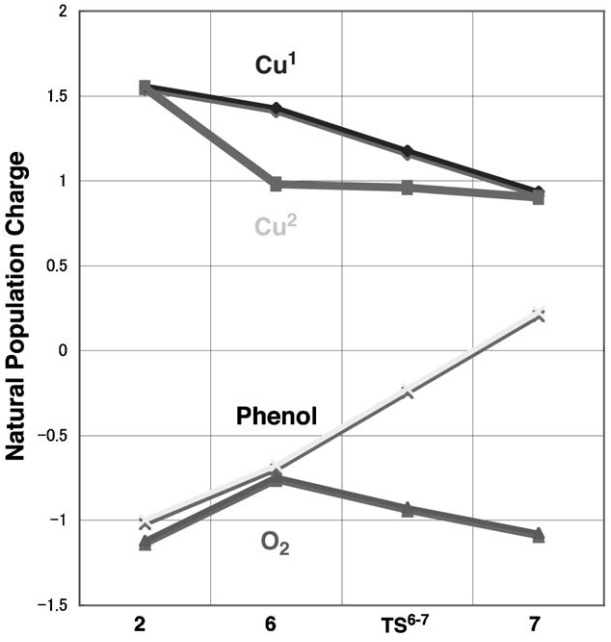


Figure 3. Natural population analysis (NPA) of Cu^1, Cu^2, O_2 and phenoxide along the reaction course. Charges of ligands on Cu are summed to the coordinated Cu atoms.

SET allows facile aromatic electrophilic substitution reaction of phenoxide to activated peroxide, introducing an oxygen atom into the aromatic ring. Because the transition state is already spin silent, the rate-determining step is not electron transfer, but electrophilic aromatic substitution, at least in this C–O bond formation process.

Some characteristic features of the roles of the two copper ions in this unique *ortho*-oxidation reaction can be drawn from the present computational/theoretical studies on the sequence of the electron transfer and chemical bond formation processes. Concerning electron transfer, both Cu ions are in the formal oxidation state of Cu(II). Initial coordination of phenoxide reduces Cu^1(II) to Cu^1(I), and during C–O bond formation the left Cu^2(II) is reduced to Cu^2(I). As for chemical bond formation, Cu^1 anchors both the nucleophile (PhO^-) and the electrophile (peroxide), and Cu^2 plays a role as a Lewis acid for the high mobility electrophile (hopping from Cu^2 to Cu^1), enhancing the electrophilicity of peroxide and promoting the reaction. It is noteworthy that electron transfer and C–O bond formation are strongly coupled in the reaction. This is consistent with the characteristic multifunctionality of the Cu ion, which has (1) moderate Lewis acidity, (2) optimal redox potential and (3)

high coordinative mobility toward O_2. It is also interesting that the two virtually symmetrical Cu ions play asymmetric roles in a cooperative way to achieve high reactivity, which would be difficult to achieve with a single Cu ion.

Conclusions

In summary, the present studies have addressed the inherent roles of the two coppers in *ortho* oxidation of phenoxide mediated by (μ–η^2:η^2peroxo)dicopper(II) species, a synthetic model for tyrosinase. A clear picture of the reaction profile, including unforeseen intermediates, transition state structure, and an unexpected SET-induced electrophilic aromatic substitution mechanism, has been obtained. The mechanistic results are consistent with experimental observations of both the current model complex $Cu_2O_2(L^{Py2Bn})_2^{2+}$ and the phenolase activity of tyrosinase.[22] Therefore, our theoretically derived conclusions may also be essentially applicable to the enzymatic system as well. Further exploration of related hetero-bimetallic systems is under way in our laboratory.

Experimental Section

Computational Details

All calculations were carried out with a Gaussian 03 (G03) program package[23] using the hybrid density functional method based on Becke's three-parameter exchange function and the Lee–Yang–Parr non-local correlation functional (B3LYP).[24] We used a basis set denoted as 631A, which consists of Ahlrichs' all-electron SVP basis set[25] for copper atoms and 6–31G(d)[26] for the other atoms. Geometry optimization and vibrational analysis were performed at the same level. The method and the basis sets used here have been demonstrated to give reliable results for the structures and reactivities of Cu-containing complexes.[27]

On the basis of the experimental findings, C–O bond formation between aromatic substrate and peroxide was investigated at each reaction step. We employed $Cu_2O_2(L^{Py2Me})_2^{2+}$ (**2**) as a chemical model for $Cu_2O_2(L^{Py2Bz})_2^{2+}$ (**1**), replacing two α,α-deuteriobenzyl side chains with methyl groups. The reaction coordinates of **2** with phenoxide anion were investigated. Although the current model requires as many as 90 atoms, including two copper ions, for **2** and phenoxide, it seemed to be the minimum realistic model. In our preliminary studies using models without bridging methylene linkers, undesired dissociation of the nitrogen ligand often occurred during geometry optimization. Modification of N–R or O–R to N–H or O–H has to be avoided because it is known that these simplifications result in false consideration of hydrogen bonding, which would not be present in a realistic model.[28] All stationary points were optimized without any symmetry assumptions and characterized by normal coordinate analysis at the same level of theory (the number of imaginary frequencies, NIMAGs, was 0 for minima and 1 for transition states, TSs).

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