Construction of Persistent Phenoxyl Radical with Intramolecular Hydrogen Bonding

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The oxidation of phenols has attracted much attention of chemists because of its involvement in biologically important processes.[1] One of its particularly interesting points lies in a formation of persistent phenoxyl radical such as tyrosine phenoxyl radical (tyrosyl radical) which is elucidated to play significant roles in a variety of biological systems involving proteins and enzymes.[2−9] Recent extensive research with X-ray crystallography, high-frequency EPR, and ENDOR spectroscopy provided some structural information about local protein environments surrounding the tyrosyl radical.[10a−f] The intriguing results imply that hydrogen bonding between phenol hydrogen and a properly oriented basic group such as histidine residue regulates the redox behavior of the tyrosine/tyrosyl radical (Scheme 1).[11a−h]

Development of proper model compounds may be helpful to precisely understand such regulation in the biological processes. However, there have been no precedent model compounds to show clearly the effect of hydrogen bonding on the redox behavior of phenols, though some models other than phenols do define the proton-coupled electron transfer.[12] The generation of phenoxyl radicals by oxidation of phenols commonly accompanies O−H bond dissociation, leading to an irreversible process as exemplified by the oxidation of phenol assisted with intermolecular phenol−hydrogen-coupled bases.[13]

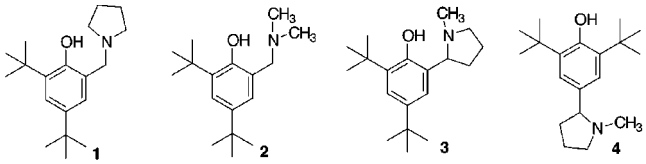
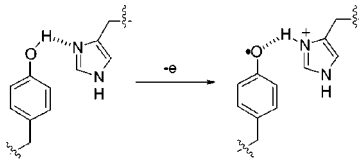


Figure 1. Phenol derivatives **1**−**4** having the α-alkylamino group at the *ortho* or *para* position.

Scheme 1. Postulated Proton-Coupled Electron Transfer To Form Hydrogen-Bonded Tyrosyl Radical with Histidine Residue



On the other hand, a recently reported B3LYP calculation suggests an involvement of a coupled spontaneous proton transfer in the oxidation of a phenol−imidazole hydrogen-bonded complex.[14] We present herein the first model compound that allows the reversible electron transfer between phenol and phenoxyl radical with an assistance of hydrogen bonding.

Our strategy to design the model compound was based on the following assumption. That is, in a biological system, (a) phenol moiety may be present in a sterically shielded field to avoid undesired side reactions such as phenolic coupling[15,16] and (b) phenol hydrogen may be associated with some basic functionality such as the imidazolyl group. Thus, we planned to synthesize sterically hindered 2,4,6-trisubstituted phenols having two *tert*-butyl groups at the 2 and 4 positions[17] and an α-alkylamino group at the 6 (*ortho*) position which was aimed for associating phenolic hydrogen intramolecularly. The reasons why the α-alkylamino group was selected as a basic functionality are as follows. First, the group at the *ortho* position could efficiently associate with phenolic hydrogen to form a six-membered intermediate. Second, the intervention of the alkyl group between aromatic ring and amino group would prevent a conjugation of the amino group with the aromatic ring, which might largely change the electronic character of phenols. On the basis of these consideration, the phenols **1**−**4** were synthesized (Figure 1).

Cyclic voltammograms (CV's) of phenols **1**−**3** in acetonitrile are shown in Figure 2a−c. Among them, phenol **3** showed a reversible redox couple on CV (Figure 2c), while phenols **1** and **2** did have partially reversible CV's (Figure 2a,b) and *para*-derivative **4** exhibited an irreversible CV (Figure 2S).

Controlled potential electrolysis of a solution of **3** in 20 mM acetonitrile or dichloromethane with a divided cell at the anodic peak potential of **3** afforded a blue species $\mathbf{3}^{\bullet+}$ that was persistent enough for spectroscopic characterization even at room temperature, though it gradually decayed over 30 min to give a yellow solution. The oxidized species was EPR active, though its hfc was not observed under a variety of conditions (Figure 3).[18] The oxidized species also exhibited typical UV−visible absorption

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(17) It is well-known that sterically hindered phenolate ions afford persistent phenoxyl radicals by one-electron oxidation; see ref 16.

(18) All EPR measurements of **3** gave a similar spectrum to that in Figure S4: 0.1 to 1.0 mM in frozen CH_3CN, C_6H_6, or CH_2Cl_2.

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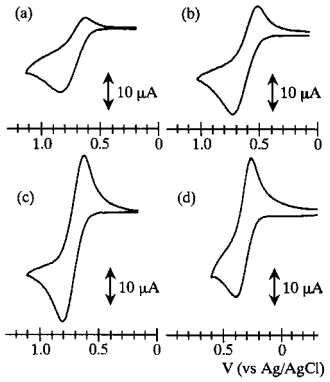


Figure 2. Cyclic voltammograms of **1** ((a) 5.0 mM), **2** ((b) 4.2 mM), **3** ((c) 5.9 mM), and **5** ((d) 20mM) in CH_3CN solution containing Et_4NBF_4 (0.1 M): Pt disk electrode (ϕ = 1.6 mm); scan rate 0.1 V/s; Ag/AgCl reference electrode.

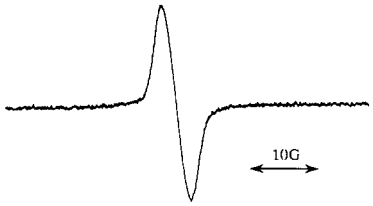


Figure 3. EPR spectrum of phenoxyl radical $\mathbf{3}^{\bullet+}$ generated by electrochemical oxidation of **3** in CH_2Cl_2 at room temperature; g = 2.0046, frequency = 9.238 GHz, field center = 332.00 mT, power = 1.0 mW, amplitude = 5.0 × 100.

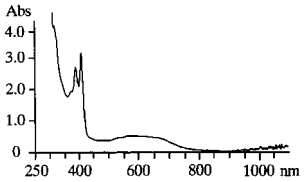


Figure 4. UV visible spectrum of phenoxyl radical $\mathbf{3}^{\bullet+}$ ganerated by electrochemical oxidation of **3** in CH_3CN.

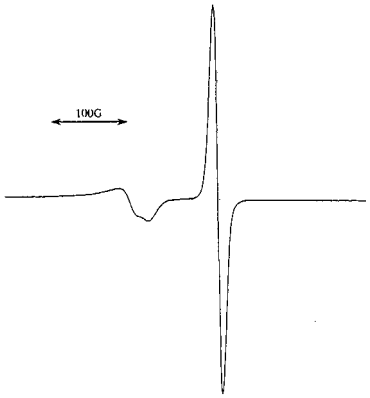


Figure 5. EPR spectrum of phenoxyl radical $\mathbf{3}^{\bullet+}$ oxidized by $Cu(ClO_4)_2$ (0.8 mM) of **3** (1.0 mM) in frozen CH_3CN: g = 2.0048, frequency = 9.248 GHz, field center = 300.00 mT, modulation = 100 kHz, power = 1.12 mW, amplitude = 1.25 × 10.

characteristic of phenoxyl radicals at around 600 nm (broad) and at 386 and 404 nm (strong bands) (Figure 4).[16] A similar spectrum was observed in a one-electron oxidation of **3** with Cu(II) (Figure S3). The species generated by Cu(II) oxidation seems to be an interesting example such as the Cu(I)-coordinated phenoxyl radical, which presented a strong EPR signal (Figure 5).

As noted in the introductory part, the oxidation of 2,4,6-tri-*tert*-butylphenol exhibits an irreversible CV since the process accompanies O−H bond dissociation.[19] In contrast with this fact,

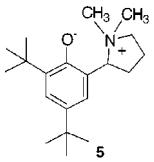
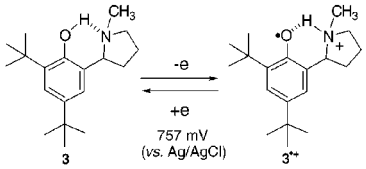


Figure 6. Zwitterionic phenolate **5**.

Scheme 2. Proposed Redox Process of **3**/$\mathbf{3}^{\bullet+}$ through Minimum Proton Migration



we observed a reversible CV for compound **3**. Thus, the processes from **3** to $\mathbf{3}^{\bullet+}$ and from $\mathbf{3}^{\bullet+}$ to **3** are considered to occur with an outer sphere electron transfer (Scheme 2).[20]

The redox potentials of **1** (Ep_a = 847 mV, Ep_c = 674 mV) and **2** (Ep_a = 816 mV, Ep_c = 691 mV) were similar to that of **3** (Ep_a = 826 mV, Ep_c = 687 mV). This observation suggests that the redox process of **1** and **2** is initiated by electron transfer from phenols associated with intramolecular hydrogen bonding in a similar way to that of **3**. On the other hand, the reversibility was reduced in order of **3** > **2** > **1**,[21] referring to the persistency of phenoxyl radical cations which may depend on the extent of hydrogen bonding.[22] The spin distribution of phenoxyl radical changed by hydrogen bonding[14] may be responsible for the persistency of phenoxyl radical cations.

The reversible redox potential of **3** ($E_{1/2}$ = 757 mV) was more positive than that of 2,4,6-tri-*tert*-butylphenolate ion ($E_{1/2}$ = −186 mV) and more negative than that of 2,4,6-tri-*tert*-butylphenol (E_p = 1487 mV).[19] The large potential shift observed in the CV of **3** is presumably due to an intramolecular hydrogen bonding and an electrostatic effect of a proton. To estimate the effect of the hydrogen bonding on the potential shift, we prepared a zwitterion **5** (Figure 6), which exhibited a reversible redox couple of **5**/$\mathbf{5}^{\bullet+}$ at $E_{1/2}$ = 333 mV on CV (Figure 2d). The observed potential difference (424 mV) between **3**/$\mathbf{3}^{\bullet+}$ and **5**/$\mathbf{5}^{\bullet+}$ may be responsible for an intramolecular hydrogen bonding.

In conclusion, we characterized phenoxyl radical cation $\mathbf{3}^{\bullet+}$ as a proper model for hydrogen-bonded phenoxyl radicals in biological systems. In this model, an intramolecular proton migration occurs at its redox process with the minimum nuclear motion requirement. This result suggests that some basic functional group located near the tyrosine residue in an active site of enzyme may control the redox potential of the tyrosyl radical with hydrogen bonding.[23] Further study on phenols having a variety of basic functionality and an effort for full characterization of $3^{\bullet+}$ are currently under investigation.

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Supporting Information Available: Full experimental data for compounds **1**−**5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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