

Rapid Autoxidation of Phenol Derivative under Atmospheric Pressure of Molecular Oxygen

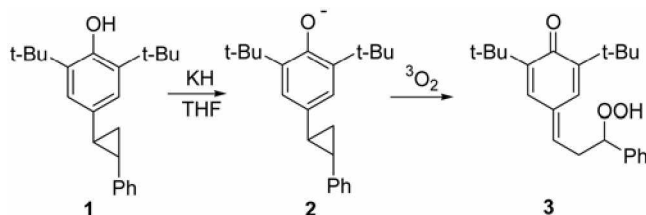
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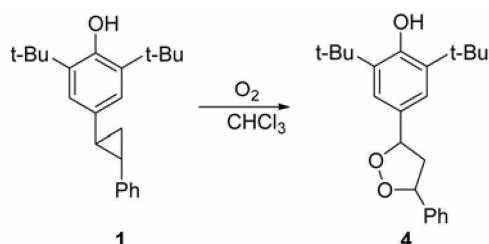
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The oxygenation of phenolic and naphtholic compounds has been investigated in great details, partly due to the attractive biological activity of this class of molecules.¹⁻³ It is generally believed that the oxygenation is occurred *via* the singlet oxygen generated by chemical means. It is well known that triplet oxygen does not react readily with most organic molecules because of the spin restriction. However, several reports pointed out the possibility of hydroperoxidation by the triplet oxygen.^{4,6,8} We have recently published results on the mechanism studies of base-catalyzed oxygenations of phenols and naphthole.⁹ In current project, we used 4-cyclopropyl substituted 2,6-di-*t*-butylphenol **1** as a new mechanistic probe to investigate the reaction of molecular oxygen and phenolate anion **2**. We suggested that the reaction of phenoxyl anion **2** with molecular oxygen to form the phenoxy radical and then to form superoxide by electron transfer could be a process happened in the biological system.⁹ As a consequence of this process, the corresponding hydroperoxide **3** was observed under atmospheric pressure of oxygen.



In the course of preparation of phenyl substituted cyclopropane derivative, we found that compound **1** even in the solid state slowly decomposed in air at room temperature. Compound **1** is a ground singlet, the autoxidation reaction of **1** with molecular oxygen was conveniently monitored by ¹H NMR using CDCl₃ as a solvent. The resonance peaks which were later assigned belonging to compound **4** immediately appeared. The peaks corresponding to the starting material

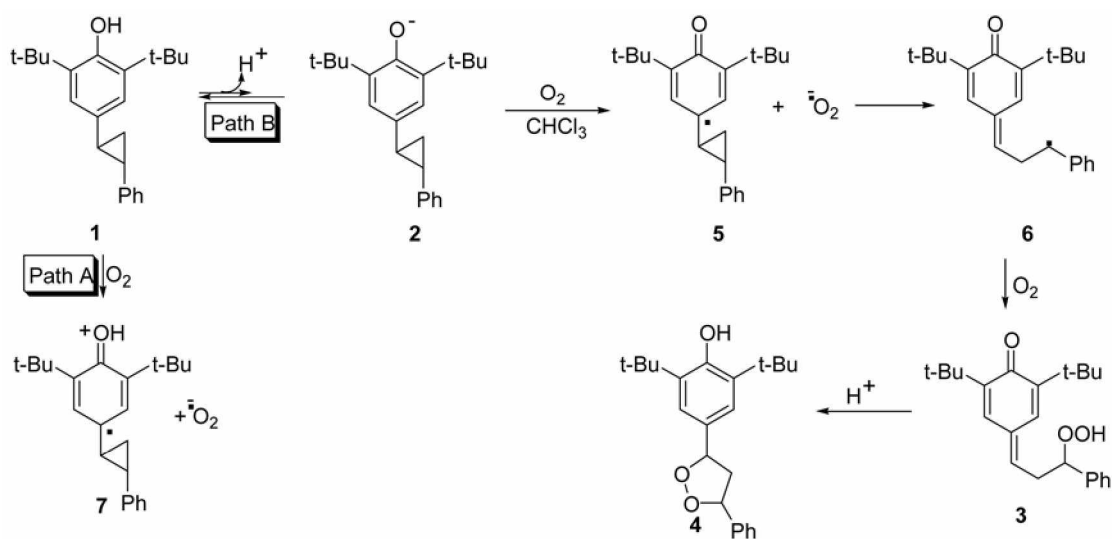


were completely disappeared within 30 min. The product **4** was purified by chromatography in 90% yield.¹⁰

Two possible mechanisms are proposed for the autoxidation reaction. One is a charge transfer mechanism, where the electron-rich phenol or phenoxyl anion interacts with π -orbital of molecular oxygen to afford a triplet charge transfer complex, and then the complex undergoes intersystem crossing.⁴ It has been previously reported that reaction of 1,1,2,2-tetraanisylcyclopropane with both thermally and photochemically generated singlet oxygen afforded the corresponding 1,2-dioxolane by $[\pi^2+\pi^2+\sigma^2]$ -cycloaddition.¹¹ The self-sensitized autoxidation in the presence of light and molecular oxygen, but without requirement for a photosensitizer was also reported.¹² Therefore, we conducted the oxygenation reaction of compound **1** with singlet oxygen. Thus, when **1** was photooxygenated with tetraphenylporphine (TPP) as a singlet oxygen sensitizer in CHCl₃, compound **4** was obtained quantitatively. To examine whether singlet oxygen was really produced *via* energy transfer, we then carried out the control oxygenation reactions. However, when the reaction was carried out under atmospheric pressure of triplet oxygen in the absence of light, the oxygenation was not inhibited and the reaction rate was not changed. Addition of excess 1,4-diazabicyclo[2,2,2]octane (DABCO), a known singlet oxygen quencher, to the reaction mixture also did not have any influence. These experiments suggested that singlet oxygen was not an oxidizing agent.

Electron transfer mechanism is an alternative pathway for autoxidation. The organic compounds react with molecular oxygen to give the organic radical and the superoxide by one-electron transfer.¹³ The radical then traps oxygen to yield the oxygenated products. Scheme 1 shows the possible pathway for the formation of 1,2-dioxolane from compound **1** by electron transfer. For the electron transfer from phenols to molecular oxygen, the relative one-electron reduction potential of phenols and molecular oxygen controls the equilibrium. Since the redox potential for molecular oxygen to superoxide ion is -0.5 V vs NHE¹⁴ in aprotic solvent and the reduction potential of *t*-butyl substituted phenol is 1.1-1.5 V,¹⁵ which suggests that the direct electron transfer of phenols to oxygen (Path A) is an unfavorable reaction by the overall potential by 1.6-2.0 V.

To overcome the thermochemical weakness, we believe that the reduction of molecular oxygen by the equilibrated anion of the model **1** might produce superoxide anion and



Scheme 1

phenoxy radical **5** as shown in the previous studies.⁸ Fast ring-opening of cyclopropylcarbonyl radical **5** followed by addition of molecular oxygen to the radical intermediate **6** yields a peroxy radical which abstracts a hydrogen to form hydroperoxide **3** and then converts to the product **4** via the 1,6-addition. The *cis*-configuration between two aromatic moieties was unambiguously determined by 2D-ROESY NMR analysis (Data not shown). Phenol and 2,6-di-*t*-butyl 4-methylphenol shows no reactivity under the atmospheric pressure of triplet oxygen. At the B3LYP/6-31+G(d) level, the calculated gas-phase protonation energies for phenoxyl anion and anion **2** are 351.0 kcal/mol and 340.8 kcal/mole, respectively.¹⁶ Interestingly, compound **2** appears to be more acidic than phenol owing to the phenylcyclopropyl group. These experimental observation and theoretical consideration seem to suggest that our mechanistic pathway is indeed operative.

For the consideration of the electron transfer from phenoxyl anions to oxygen, one-electron reduction potential of phenoxy radical is about -0.29 V vs SCE in CH_3CN ,¹⁵ and the overall potential for electron transfer of phenoxide anion to oxygen is about 0.2 V. This potential is not as high as that for electron transfer of phenols to oxygen, but still implies the unfavorable reaction with the free-energy change of about 3 kcal/mol. However, *ab initio* calculation indicated that the Gibbs free energy change of rearrangement from radical **5** to radical **6** is exothermic by -2.98 kcal/mol, indicating that the ring-opening of cyclopropyl radical is favorable. Moreover, our model undergoes a partial combustion with molecular oxygen in the course of oxygenation and more than ample energy is available to overcome their electro-potential weakness for the phenoxyl radical and superoxide formation.

In summary, the autoxidation of organic electron-rich phenols proceed at high oxygen pressures and elevated temperatures to yield the corresponding hydroperoxide at slow rates. The origin of this chemistry appears to involve an unfavorable electron transfer from the substrates to oxygen.

In the case of cyclophenyl derivative **1**, the acidity of **1** and preferable ring opening of cyclopropyl radical to homoallylcarbonyl radical initiates the rapid autoxidation at mild conditions.

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- The structure of phenolic dioxolane was determined by ^1H NMR (800 MHz, CDCl_3 , 25 °C) analysis which has peaks at δ 1.41 (s, 18H), 2.78 (ddd, 1H, $J = 12.5, 7.7, 6.7$ Hz), 3.45 (br dt, 1H, $J = 12.5, 7.4$ Hz), 5.27 (s, 1H), 5.36 (br t, 1H, $J = 7.6$ Hz), 5.52 (br t, 1H, $J = 7.1$ Hz), 7.17 (s, 1H), 7.34 (t, 1H, $J = 7.2$ Hz), 7.41 (t, 2H, $J = 7.2$ Hz), and 7.50 (d, 2H, $J = 7.2$ Hz). The ^{13}C NMR (150 MHz, CDCl_3 , 25 °C) spectrum showed signals at δ 33.4, 34.6, 51.4, 83.3, 84.4, 124.6, 126.4, 127.7, 128.1, 128.9, 136.3, 140.5, 154.4.
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