Mechanism of Oxygenation of 2,6-Di-*tert*-butylphenol Derivative

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The base-catalyzed oxygenation of phenol or naphthol derivatives has been of interest in both biological and synthetic system.[1-8] In general, when phenoxide anions **1** are exposed to triplet molecular oxygen, the corresponding epoxy alcohols **7** are formed in nearly quantitative yield. Possible reaction pathway for the oxidation process is proposed as shown in Scheme 1.[7,8] Reaction of the phenoxide anions **1** and molecular oxygen results in the peroxides **4**, which then undergo intramolecular conjugate addition to form the dioxetane enolate anions **5**. Finally, dioxetane ring opening by nucleophilic displacement yields the epoxy alcohols **6**. However, the reaction pathway of molecular oxygen and phenoxide anions **1** to form the peroxides **4** might be unfavorable because the singlet phenolate anions **1** cannot react in a single step with triplet molecular oxygen to yield the singlet products.[9]

To overcome the spin-forbidden rule, two possible mechanisms of base-catalyzed oxygenation of phenol derivatives have been proposed.[10] One is a charge transfer mechanism (pathway 1), where the phenolate anion **1** interacts with π-orbital of molecular oxygen to afford a triplet charge transfer complex **2**. The complex then experiences intersystem crossing *i.e.*, one of unpaired electrons undergoes the spin inversion from the triplet charge transfer complex to the singlet complex, giving a singlet oxygen. Alternative pathway is an electron transfer mechanism (pathway 2). The phenoxide anions **1** react with molecular oxygen to give the phenoxyl radicals **3** and superoxide by one-electron transfer. The phenoxyl radicals **3** then trap superoxide to yield the peroxy anions **4**. Here we report theoretical and experimental investigations of the possible intermediate involved in the base-catalyzed oxygenation of phenol derivative.

Previously, we synthesized the cyclopropyl derivative **8** of 2,6-di-*tert*-butylphenol to distinguish phenoxide anion **11** from the phenoxy radical **12** in the course of autoxidation[11]

because rearrangement of the cyclopropyl radical to homoallylcarbinyl radical was thought to be effective in the short-lived radical trap.[12] When a solution of potassium phenolate **9** in tetrahydrofuran was stirred under an atmosphere of oxygen at room temperature, the corresponding epoxy alcohol **10** was formed and no ring-opened product **14** was detected in the reaction mixtures. Therefore, we suggested a charge transfer mechanism describing the action of base-catalyzed oxygenation of phenols.

Although it has been suggested that α-cyclopropylbenzyl radicals undergo fairly rapid rearrangement,[12] little is known about the stabilities of cyclopropylcarbinyl radical **12** with the radical-stabilizing group and homoallylcarbinyl radical **13**. Interestingly, in this study, our semi-empirical calculation using AM1 indicated that the Gibbs free energies of radical **12** and radical **13** are −4266.39 kcal/mol and −4265.70 kcal/mol, respectively, showing that the free energy change of rearrangement is endothermic by 0.69 kcal/mol. This result suggests that ring-opening of **12** can not be only reversible but that equilibrium may favor the ring closed form, and the radical probe **8** might give an unclear guide to charge transfer mechanism in the previous work.[11] To examine whether singlet oxygen was really produced via energy transfer, we then carried out the oxygenation reaction of potassium phenolate **9** in the presence of 1,4-diazbicyclo[2.2.2]-octane(Dabco), which has been known to inhibit singlet oxygen reactions but has little effect on free radical reactions. However, addition of Dabco did not have any influence, indicating that singlet oxygen was not a primary oxidizing species in the base-catalyzed autoxidation.

Regarding electron transfer from the phenoxide anion to molecular oxygen (pathway 2), it has been proposed that superoxide ion does not couple with 2,6-di-*tert*-butylphenoxy radicals but reduces radicals to give the corresponding phenoxide anions, and mechanism involving for the base-
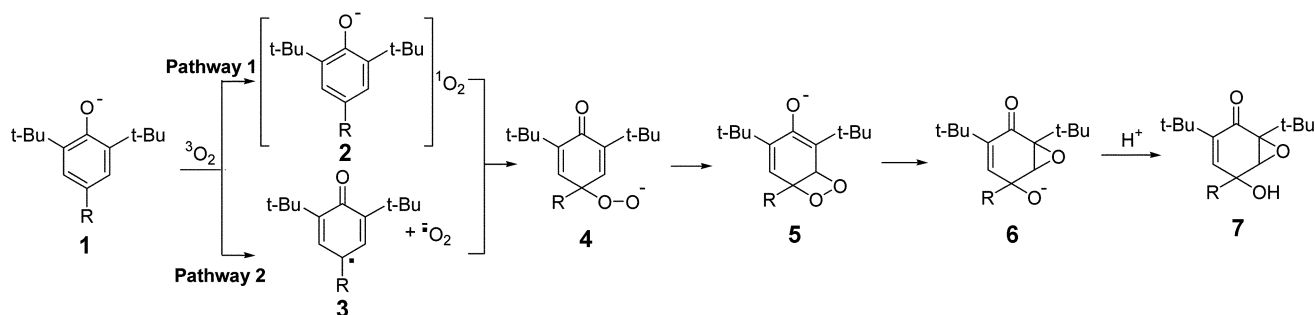
Scheme 1
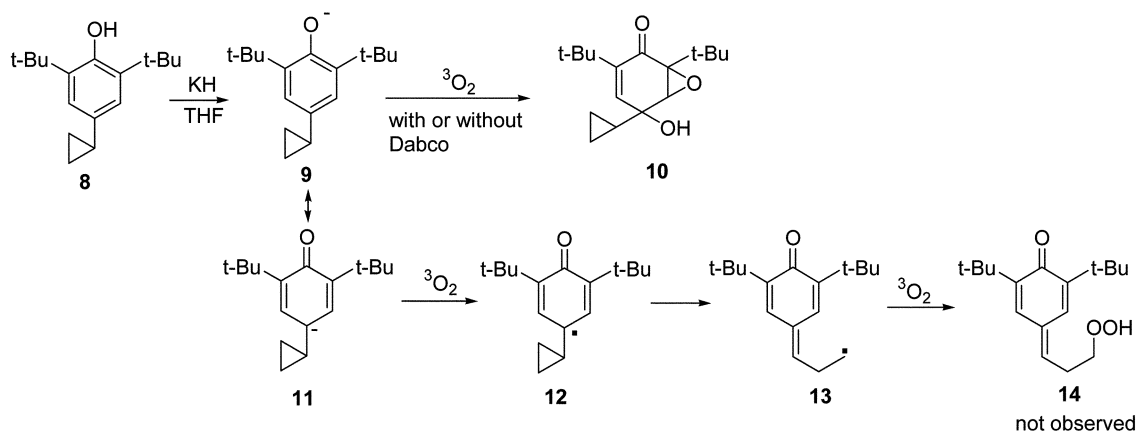
Scheme 2

catalyzed oxygenation of 2,6-di-*tert*-butylphenols is an ionic process.[13] Therefore, the second control experiment was carried out by treating the phenoxide anion **9** with $^{18}O_2$. After $^{18}O_2$ [96% enriched in 18-oxygen (ICON), 100 mL] was delivered to a solution of **9** from a sealed tube, the mass spectrum reveals that two atoms of ^{18}O have been incorporated into the hydroxyl group and epoxide of the product **10**. However, when the ^{18}O label was employed with excess KO_2 in presence of 18-crown-6, the peak at *m/z* 278 in the mass spectrum of product is 21% as intense as the peak at *m/z* 282. If superoxide can not couple with phenoxyl radical **12**, the molecular ion of the product will consist of only ion cluster at *m/z* 282 corresponding to incorporation of two atoms of ^{18}O from $^{18}O_2$. Although the fractional amount of unlabeled product was produced because of the KO_2 solubility or the fast rebound reaction with newly synthesized superoxide-18, the decrease of ^{18}O in the epoxy alcohol **10** from the labeling experiment indicates the possibility of superoxide coupling, and this is most reasonably ascribed to the phenoxy radical mechanism (pathway 2).

The relative one-electron reduction potential of phenoxide anion controls the position of the equilibrium. The equilibrium constant is approximately $10^{\Delta E/0.06}$, where $\Delta E = E(O_2/superoxide) - E(phenoxy\ radical/phenoxide\ anion)$ and the potentials are in volts. Reduction potential of oxygen is -0.82 V

$$Ph{-}O^- + O_2 \rightleftharpoons Ph{-}O^\bullet + O_2^{\bullet-}$$

vs SCE in CH_3CN[14] and one-electron reduction potential of phenoxy radical is about -0.29 V *vs* SCE in CH_3CN.[15] Therefore, the overall potential for electron transfer of phenoxide anion to oxygen is about -0.5 V implying an unfavorable reaction with the free-energy change of about 11 kcal/ mol. Moreover, oxygenation transformed the weak phenolic base of $pK_a = 9$ to strong alkoxide base of $pK_a = 20$, and energy of approximately 15 kcal/mol is required to elevate the base strength in the reaction leading to the tertiary alkoxide. Therefore, it seems to be neither thermodynamically nor kinetically favorable in the course of oxygenation. However, thermochemical analysis in the similar oxygenation reaction reveals that heat of reaction of -60 kcal/mol was derived for oxygenation of the naphthoxide to the corre-

sponding epoxy alkoxide.[16] 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 superoxide formation as well as thermodynamic disadvantage for enhancement of the base strength.

Judging from the results on the theoretical investigations and control experiments, the mechanism for base-catalyzed oxygenation of phenol derivatives involves one electron reduction of molecular oxygen from phenoxides to give phenoxy radicals. This is the key intermediates for autoxidation and coupling of phenoxy radicals and superoxide radical anion to give peroxy anions and then lead the final epoxy alcohol adducts. Studies are underway to provide firmer evidences for the reaction mechanism.

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