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Mechanism of action of base-catalyzed oxygenation of phenol derivatives

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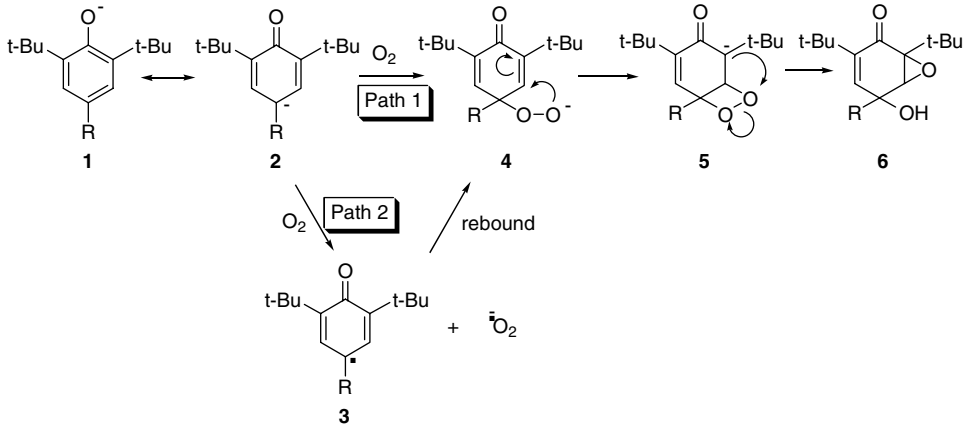
Abstract—Cyclopropyl derivative of 2,6-di-*tert*-butylphenol is synthesized as a probe to investigate the mechanism of base-catalyzed autooxidation of phenol derivatives. Our study indicates that one electron reduction of molecular oxygen from phenolate gives phenoxyl radical **3**, a key intermediate of autooxidation. The coupling of phenoxyl radical and superoxide radical gives peroxylate anion **4** and produces the final epoxy alcohol adduct **6**.

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 or naphthoxide anions are exposed to molecular oxygen, the corresponding epoxy alcohols are formed in nearly quantitative yield. Possible reaction pathway for the oxidation process is proposed as shown in path 1 (Scheme 1).[7,8] Molecular oxygen directly reacts with phenoxide anion **1**. The resulting peroxide **4** then undergoes intramolecular conjugate addition to form the dioxetane enolate anion **5**. Finally, dioxetane ring opening by nucleophilic displacement yields the epoxy-*p*-quinol **6**.

From the mechanism proposed in path 1 (Scheme 1), the reaction of molecular oxygen and phenolate anion **2** to form peroxide **4** has been considered as a key step.



Scheme 1.

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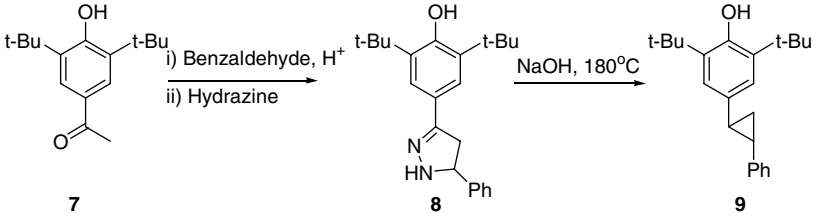
However, this reaction might be unfavorable because the spin-forbidden rule states that the singlet phenolate anion **2** will not react in a single step with triplet molecular oxygen to yield the singlet product **4**.[9] To address this mechanistic issue, we propose here an alternative pathway (Scheme 1, path 2). We suggest that the phenolate anion **2** reacts with molecular oxygen to give the phenoxy radical **3** and superoxide by electron transfer. The phenoxyl radical **3** then traps superoxide to yield the peroxylate anion **4**, which is converted to the epoxy alcohol adduct **6**.

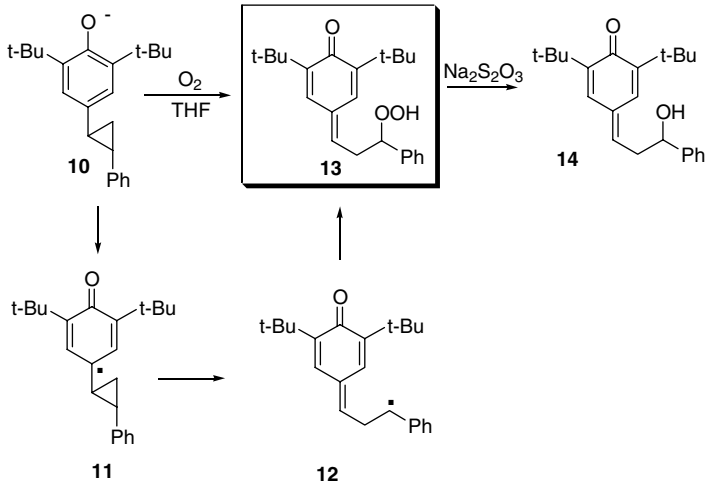
To prove our hypothesis, we have synthesized cyclopropyl derivative **9** of 2,6-di-*tert*-butylphenol as a probe. This molecule can be used to distinguish the phenolate anion **2** from the phenoxyl radical **3** because the ring-opening reaction of cyclopropylcarbinyl radical has a rate constant of $\sim 10^{11}\ s^{-1}$, which has been shown to be an effective trap for short-lived radicals.[10,11] As shown in Scheme 2, chalcone derivative obtained from aldol condensation of 3,5-di-*tert*-butyl-4-hydroxyacetophenone and benzaldehyde in the presence of H_2SO_4 was refluxed with hydrazine in ethanol to yield pyrazoline derivative **8**.[12] This compound was then reacted with sodium hydroxide without solvent and the mixture was heated at 180 °C for 30 min under a nitrogen atmosphere. The crude product was purified by column chromatography to give cyclopropane derivative **9**. We found compound **9** underwent slow oxygenation at room temperature, even in the solid state. All of the isolated intermediates were characterized by ^1H NMR analysis.

With a probe molecule **9** in hands, we next conducted the mechanistic study of the oxygenation of phenol derivative (Scheme 3). A THF solution of potassium phenoxide **10** generated from the reaction of potassium hydride and cyclopropanyl phenol **9**, was slowly treated with 2 equiv of molecular oxygen by a gas tight-syringe and the reaction mixture was stirred at room temperature for 30 min. After protonation with saturated ammonium chloride solution, the corresponding ring-opening product **13** was obtained as the only product. This was easily identified by ^1H NMR spectrum from the crude product and no other product was observed by a 500 MHz ^1H NMR analysis. Purification by the crude product by flash chromatography afforded the stable hydroperoxide **13** in 89% yield. Although authentic sample of **13** was not able to be prepared for identification, all spectral data of **13** are in good agreement with the expected product.[13] Moreover, reduction of the hydroperoxide **13** with sodium thiosulfate provided the hydroxyl compound **14**, which showed clearly the different spectral characteristics.

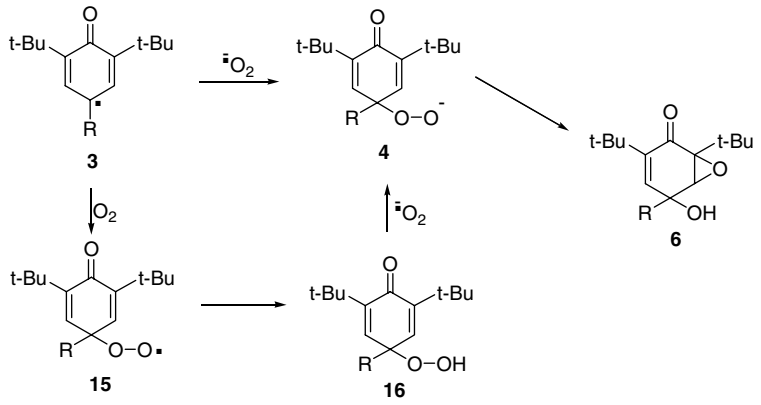
Throughout the mechanism study, we believe that electron transfer in the first step (Scheme 1, path 2) is reasonable because there is a reported example that reduction of molecular oxygen by the phenolate anion of a vitamin E model produced superoxide anion which has been



Scheme 2.



Scheme 3.



Scheme 4.

directly detected by a low-temperature EPR measurement.[14] In the second step (Scheme 1, path 2), the reaction between radical **3** and superoxide is also plausible since it has been reported that peroxide anion was obtained from the reaction of thianthrene cation radical and superoxide ion.[15] However, one may also argue another product, peroxylate radical **15**, from the addition of oxygen to phenoxyl radical **3**, forming the corresponding hydroperoxide **16** by abstraction of hydrogen in an environment (Scheme 4). If the resulting superoxide anion can serve a base, compound **16** will rearrange to epoxy alcohol **6**. Although the pK_a for HO_2, conjugate acid of superoxide, in water is 4.88,[16] which implies that superoxide is a weak base, a number of weakly acidic organic compounds are deprotonated efficiently in the presence of superoxide ion.[17] However, when reaction of 4-acetyl-2,6-di-*tert*-butyl-6-hydroperoxy-2,4-cyclohexadione[18] with potassium superoxide was carried out in THF, no epoxy alcohol was detected and the starting material was recovered. Moreover, the base-catalyzed oxidation of 4-alkyl-2,6-di-*tert*-butylphenol with molecular oxygen in protic solvents (methanol, ethanol, or 2-propanol) gave rise to the *para*-hydroperoxide **16** in nearly quantitative yield, while oxygenation of phenolate in aprotic solvents such as DMF, DMSO, HMPT containing *t*-BuOK yielded the corresponding epoxy hydroxyl adduct **6**.[18] These results clearly indicated the presence of peroxide anion intermediate **4**.

Previously, it has been proposed that superoxide ion does not couple with 2,6-di-*tert*-butylphenoxy radicals but reduces radicals to give the corresponding phenolates, and mechanism involving for the base-catalyzed oxygenation of 2,6-di-*tert*-butylphenols is an ionic process.[19] Another mechanism proposed based on the consideration of spin forbidden rule was that the peroxylate anion occurred through the direct combination of phenolate and singlet oxygen produced by charge transfer and intersystem crossing.[14] However, our evidence presented here provides the novel mechanism for base-catalyzed oxygenation of phenol derivatives, involving one electron reduction of molecular oxygen from phenolate to give phenoxyl radical. This is the key intermediate for autooxidation and coupling of phenoxy radical and superoxide radical anion to give peroxylate anion and then lead the final epoxy alcohol adduct.

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13. Compound **13** showed IR absorption bands (neat, ν_{OH} 3200–3500 cm^{-1}; ν_{CO} 1654 cm^{-1}), ^1H NMR spectrum (300 MHz, $CDCl_3$) showed the peaks at δ 1.221 (s, 9H), 1.224 (s, 9H), 2.16–2.29 (m, 2H), 3.46 (dd, 2H, $J = 7$, 4.1 Hz), 4.98 (br t, 1H, $J = 7$ Hz), 6.08 (d, 1H, $J = 3$ Hz), 6.29 (d, 1H, $J = 3$ Hz), and 7.34–7.38 (m, 5H), and ^{13}C NMR spectrum (75 MHz, $CDCl_3$) showed the peaks at δ 29.383 (q, $J = 127$ Hz), 29.388 (q, $J = 128$ Hz), 35.15 (s), 35.56 (s), 38.65 (t, $J = 125$ Hz), 72.97 (d, $J = 162$ Hz), 125.91 (d, $J = 161$ Hz), 128.45 (d, $J = 163$ Hz), 139.17 (s), 143.50 (d, $J = 160$ Hz), 151.87 (s), 153.39 (s), 186.20 (s). The EI mass spectrum showed peaks at m/z (rel. intensity) 354 (M^+, 10), 336 (15), 308 (41), 248 (80), 233 (100). Exact mass calculated for $C_{23}H_{30}O_3$: 354.2195, found: 354.2196.
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