BULLETIN
OF THE
KOREAN CHEMICAL SOCIETY

VOLUME 17, NUMBER 7
JULY 20, 1996

BKCS 17(7) 573-666
ISSN 0253-2964

Communications

Mechanistic Investigation of Base-Catalyzed Oxygenation of Phenol Derivatives

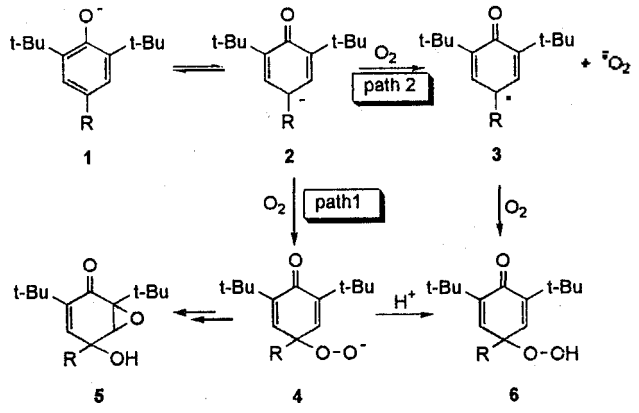
Seung Wook Ham*, Kyo Chul Lee, Keum-Joo Lee, and Doo-Hyeon Lim

Department of Chemistry, Chung-Ang University, Seoul 156-760, Korea

Received December 27, 1996

Over the past two decades base-catalyzed oxygenation of phenol derivatives, or organic compounds has increasingly been of interest in both biological and synthetic systems.[1~7] In the case of the oxygenation of phenolate, the autooxidation pathway and the oxidizability of phenolate depending on the nature of the substituents on the aromatic ring were reported.[1~2] However, the particularly important step that we should reconsider is the combination between molecular oxygen and the phenolate anion.[1]

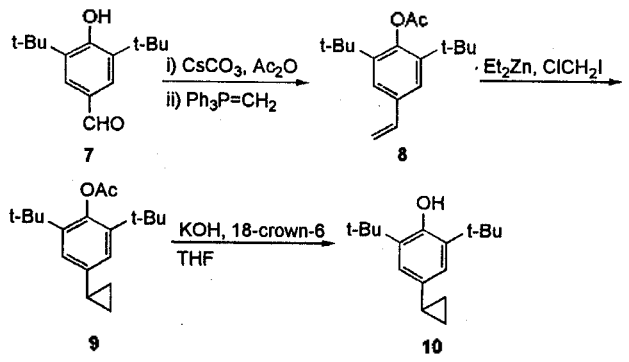
As shown in Scheme 1, there are two possible pathways for the formation of the products, the epoxy-*p*-quinol **5** and the hydroperoxide **6** by the oxygenation of phenolate. One of the possible pathways proposed is that the phenolate anion **2** reacts directly with molecular oxygen (path 1).[1~4] The resulting peroxide **4** also undergoes intramolecular addition to the unsaturated carbonyl system of **4** yielding the dioxetane enolate anion. Finally, dioxetane ring opening by nucleophilic displacement yields the epoxy-*p*-quinol **5**. However, it might be unfavorable because the spin-forbidden rule implies that the singlet phenolate anion **2** cannot react in a single step with a triplet molecular oxygen to yield the singlet product **4**. To overcome the spin-forbidden rule, Russell's explanation of base-catalyzed oxygenation[8] is that the phenolate anion **2** reacts with molecular oxygen to give the phenoxy radical **3** and superoxide. The phenoxy radical **3** then traps molecular oxygen to yield the peroxy radical, which is converted to the hydroperoxy adduct **6** by hydrogen abstraction (path 2). However, since mechanistic detail for establishing the sequence of steps has not been validated, the mechanism of the addition of molecular oxygen to phenolate is still unclear at present.



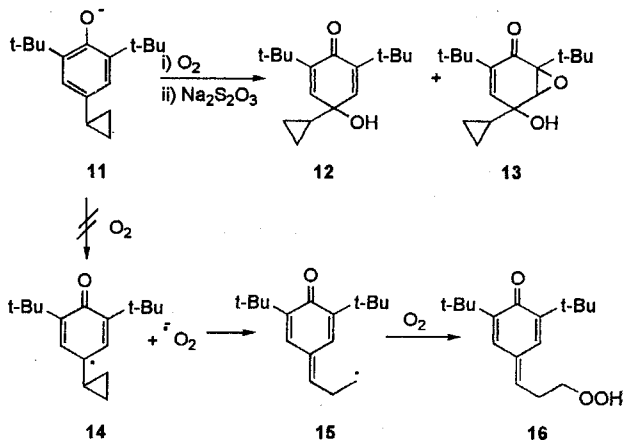
Scheme 1.

In this study, our approach to this kind problem was to devise a chemical model that could serve to directly elucidate the chemical principles involved. We have chosen the cyclopropyl derivative **10** of 2,6-di-*tert*-butylphenol as a mechanistic probe. This material could distinguish the phenolate anion **2** from the phenoxy radical **3** because the cyclopropyl- to homoallylcarbinyl radical rearrangement has been shown to be effective in the short-lived radical trap.[9~11]

In considering the preparation of cyclopropanyl phenol **10**,



Scheme 2.



Scheme 3.

the protection of hydroxy group was important, because phenol derivatives are air sensitive. Phenol derivatives were stable enough to allow purification as long as the hydoxy group was protected with an electron withdrawing group, and it was essential to retain the electron withdrawing group until the final step synthesis. Otherwise, the preparation of cyclopropanyl phenol **10** from the aldehyde[12] **7** proved to be straightforward (Scheme 2). The ^{1}H NMR (250 MHz, $CDCl_3$) spectrum showed peaks at δ 0.60-0.63 (m, 2H), 0.84-0.88 (m, 3H), 1.42 (s, 18H), 5.00 (s, ex, 1H), 6.90 (s, 2H). The IR spectrum (neat) showed bands at 3637 (s), 2957 (vs), 1438 (s). The mass spectrum showed peaks at m/e (rel. intensity): 246 (M^+, 39), 231 (100), 189 (77).

Attention was next focused upon oxygenation of cyclopropanyl phenolate **11**. A solution of potassium phenolate **11** in tetrahydrofuran, from reaction of the phenol **10** and 1 equivalent of KH, was stirred under an atmosphere of oxygen at room temperature for 2 hr in the presence of 18-crown-6. After protonation with saturated ammonium chloride solution followed by treatment with aqueous sodium thiosulfate, two major products **12, 13** were detected by the GC trace. Purification of the mixture by chromatography provided the alcohol **12** in 34% yield. The ^{1}H NMR (250 MHz, $CDCl_3$) spectrum showed peaks at δ 0.35-0.47 (m, 5H), 1.42 (s, 18H), 2.16 (s, ex, 1H), 6.44 (s, 2H). The IR spectrum (neat) showed bands at 3475 (br s), 2958 (vs), 1644 (s). The mass m/e (rel. intensity) showed peaks at m/e (rel. intensity): 262 (M^+, 3), 191 (100). Further elution with the same mixed solvent yielded the epoxy alcohol **13** in 35% yield. The ^{1}H NMR (250 MHz, $CDCl_3$) spectrum showed peaks at δ 0.43-0.84 (m, 5H), 0.97 (s, 9H), 1.21 (s, 9H), 2.31 (s, ex, 1H), 3.50 (s, 1H), 6.76 (s, 1H). The IR spectrum (neat) showed bands at 3484 (br s), 2962 (vs), 1677 (s) cm^{-1}. The mass spectrum showed peaks at m/e (rel. intensity): 278 (M^+, 1), 263 (10), 237 (95), 181 (100). By contrast, when oxygen was excluded from the reaction, the starting 4-cyclopropyl-2,6-di-tert-butylphenol (**10**) was recovered.

This observation, in conjunction with the control experiment, leads to the conclusion that the alcohol **12** and epoxy alcohol **13** were derived from the direct combination of the phenolate **11** and molecular oxygen as shown in Scheme 1. Alternatively, if one electron reduction of molecular oxygen from the phenolate gave cyclopropylcarbinyl radical and superoxide, the cyclopropylcarbinyl radical **14** then might undergo rapid rearrangement to the corresponding homoallylcarbinyl radical **15**[13] (Scheme 3). Finally, reaction of the allylcarbinyl radical **15** with oxygen followed by hydrogen abstraction would yield the hydrogen peroxide **16**. However, since the ring opening products other than **12, 13** were not found in the reaction mixtures, the radical pathway was not plausible.

However, as far as concerning the spin-forbidden rule, it might be hypothesized that the formation of peroxy anion occurred through the direct combination of phenolate and singlet oxygen. Thus, the phenolate anion interacts with the π-orbital of molecular oxygen to afford a triplet charge transfer complex, and then the complex undergoes intersystem crossing, *i.e.*, one of the two unpaired electrons undergoes spin inversion, giving a singlet oxygen,[14] which is finally converted in the reaction product. Detailed studies of this pathway are currently underway.

Acknowledgment. The research described here was generously supported by the Korea Science and Engineering Foundation (941-0300-039-2).

References

1. Nishinaga, A.; Itahara, T.; Shimizu, T.; Matsuura, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 1820.
2. Nishinaga, A.; Shimizu, T.; Toyoda, Y.; Matsuura, T. J. *J. Org. Chem.* **1982**, *47*, 2278.
3. Ham, S. W.; Dowd, P. *J. Am. Chem. Soc.* **1990**, *112*, 1660.
4. Dowd, P.; Hershiline, R.; Ham, S. W.; Naganathan, S. *Science* **1995**, *269*, 1684.
5. Frimer, A. A.; Strul, G.; Gottlied, H. E. *J. Org. Chem.* **1995**, *60*, 4521.
6. Chen, M. J.; Linehan, J. C.; Rathke, J. W. *J. Org. Chem.* **1990**, *55*, 3233.
7. Frimer, A. A.; In *The Chemistry of Enones*; Patai, S. Rapport, Z., Eds.; Wiley-Interscience: New York, 1989; pp 781-921.
8. Russell, G. A.; Janzen, E. G.; Bemis, A. G.; Geels, E. J.; Moye, A. J.; Mak, S.; Strom, E. T. *Adv. Chem. Ser.* **1965**, *51*, 112.
9. Newcomb, M.; Glenn, A. G. *J. Am. Chem. Soc.* **1989**, *111*, 275.
10. Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7024.
11. Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.
12. Cohen, L. *J. Org. Chem.* **1957**, *22*, 1333.
13. Little is known about this kinetics of cyclopropylcarbinyl radicals with radical-stablizing group. However, it has been reported that α-cyclopropylbenzyl radicals undergo fairly rapid and irreversible ring-opening: Masnovi, J.; Samsel, E. G.; Bullock, R. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1044.
14. Matsumoto, S.; Matsuo, M. *J. Org. Chem.* **1986**, *51*, 1435.