with 4 drops of Jones reagent followed by the usual workup gave 4 mg of ciliarin as a gum which could not be crystallized because of the small amount but whose TLC behavior and IR, mass, and NMR spectra were identical with those of authentic material.

Conversion of Orizabin to Tagitinin C. A mixture of 15 mg of orizabin, 40 mg of anhydrous sodium acetate, and 1 mL of acetic anhydride was heated at 100 °C for 30 min, the reaction being monitored by TLC. Dilution with H_2O, extraction with $CHCl_3$, evaporation of the washed and dried extract, and purification of the residue by preparative TLC (Bz–EtOAc, 2:1) furnished 10 mg of tagitinin C, identical on TLC with authentic material. The IR, NMR, and mass spectra were superimposable.

Reaction of 4c with Lead Tetracetate. A solution of 40 mg of **4c** and 100 mg of $Pb(OAc)_4$ in 1.5 mL of glacial acetic acid was refluxed for 7 h, the reaction being monitored by TLC. After disappearance of the starting material the mixture was cooled, diluted with H_2O, and extracted thoroughly with $CHCl_3$. Evaporation of the washed and dried extract and preparative TLC (Bz–EtOAc, 8:1) gave two fractions. The less polar gummy material (8 mg) was a poorly defined mixture (NMR spectrum); the more polar fraction (15 mg), also noncrystalline, was **15**: IR 1775, 1730, 1705, 1605, 1200, 1130, 1030, 955, 100 cm^{-1}; NMR (270 MHz) δ 5.55 (H-2), 3.16 (m, H-4, $J_{4,5}$ = 7, 11 Hz, $J_{4,15}$ = 6.5 Hz), 2.45 (m) and 2.23 (m, H-5), 4.42 (br dd, H-6, $J_{5,6}$ = 10, 1 Hz, $J_{6,7}$ = 5 Hz), 3.05 (br d H-7, $J_{7,8}$ < 1 Hz), 4.93 (br dd, H-8), 2.66 (dd, $J_{8,9a}$ = 5 Hz, $J_{9a,9b}$ = 15 Hz) and 2.10 (dd, $J_{8,9b}$ = 1.5 Hz, H-9), 2.98 (m), 2.5 (m), 2.3 (m, H-13 and H-2″), 1.43 (H-14), 1.35 (d, H-15, $J_{6,5}$ = 1.0 Hz), 2.95 (m, H-2′), 1.14 (d) and 1.12 (d, J = 7 Hz, H-3′, H-4′).

Anal. Calcd for $C_{21}H_{26}O_8$: mol wt 406.1626. Found: mol wt (mass spectrum) 406.1607.

Other significant peaks in the high-resolution mass spectrum were at m/e (composition, relative intensity) 336 ($C_{17}H_{20}O_7$, 1.1), 318 ($C_{17}H_{18}O_6$, 4.2), 300 ($C_{17}H_{16}O_5$, 5.5), 264 ($C_{15}H_{20}O_4$, 2.6), 258 ($C_{15}H_{14}O_4$, 2.5), 125 ($C_7H_9O_2$, 100), 71 (C_4H_7O, 53.6).

Acknowledgment. We thank Mr. R. C. Das for some NMR spectra, Dr. Suryanarayanan for IR spectra, Dr. K. P. Madhusudanan for low-resolution mass spectra, and Dr. A. Romo de Vivar, Universidad Nacional Autonoma de Mexico, for a generous sample of orizabin.

Registry No. 4c, 69440-09-1; **5b**, 30412-87-4; **6b**, 34367-14-1; **6b** (C-1 epimer), 34367-14-1; **7**, 59979-56-5; **8a**, 75197-64-7; **8b**, 75197-65-8; **8c**, 75197-66-9; **9a**, 75197-67-0; **9b**, 75197-68-1; **10a**, 75197-69-2; **10b**, 75197-70-5; 11, 75197-71-6; **12**, 75197-72-7; **13**, 72301-73-6; **14** (isomer 1), 75197-73-8; 14 (isomer 2), 75247-16-4; **15**, 75197-74-9; propanoic acid, 2-methyl-2,3,3a,4,5,6,7,8,9,11a-decahydro-3-bromo-3-(bromomethyl)-6,10-dimethyl-8-hydroxy-2,7-dioxo-6,9-epoxycyclodeca[*b*]furan-4-yl ester, 75213-89-7.

Base-Catalyzed Oxygenation of *tert*-Butylated Phenols. 4.[1] Mechanism of Base-Catalyzed Ortho Regioselective Dioxygen Incorporation into 4-Aryl-2,6-di-*tert*-butylphenols

Akira Nishinaga,* Tadashi Shimizu, Tomoyuki Fujii, and Teruo Matsuura

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto, Japan

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Base-catalyzed dioxygen incorporation into 4-alkyl-2,6-di-*tert*-butylphenols has been suggested to involve equilibria among the phenolate (i) and peroxy anions (iii and iv) including a π-complex intermediate (ii, Scheme I).[1] The equilibrium is influenced by the solvent and the substituent R. When the anionic species are not associated with the countercation of bases (in EtOH, DMF), the equilibrium is extremely shifted to iii, accomplishing para regioselectivity.[1,2] By contrast, the oxygenation of 2,4,6-tri-*tert*-butylphenol in a *t*-BuOK/*t*-BuOH system, where the anionic species are associated with the potassium cation, leads to the formation of products resulting exclusively from dioxygen incorporation into the ortho position.[2,3] The ortho regioselective dioxygen incorporation with 2,4,6-tri-*tert*-butylphenol has been shown, however, to involve two distinct steps, formation of iii (R = *t*-Bu) in the first step followed by the exclusive migration of the peroxy group to the ortho position,[1] indicating that the initial attack by O_2 in oxygenation of i takes place always on the para position. The subsequent efficient migration of the peroxy group to the ortho position has been concluded to result from stabilization of iv by chelation (v) of the associated form of peroxy anion.[1]

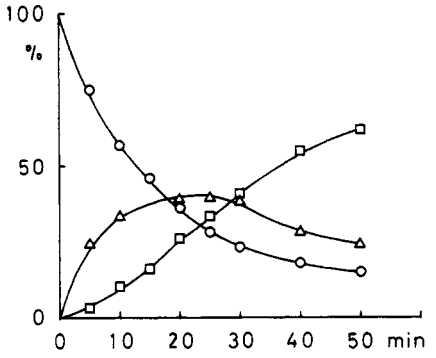
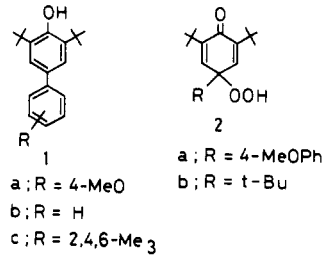


Figure 1. Time course of oxygenation of **1a** in *t*-BuOH–hexane containing *t*-BuOK at −16 °C: [**1a**], 50 mM; ○, **1a**; △, **2a**; □, **3a**.

On the other hand, base-catalyzed oxygenation of 4-aryl-2,6-di-*tert*-butylphenols (**1**) in a *t*-BuOK/*t*-BuOH system where dioxygen is incorporated only into the ortho position, giving rise to the products **3**–**5**, has been postulated to involve direct attack by O_2 on the ortho position.[1,4]

We now find that at −16 °C the oxygenation of 2,6-di-*tert*-butyl-4-(4-methoxyphenyl)phenol (**1a**) also affords the peroxy-*p*-quinolate intermediate of type iii in Scheme I. Such an intermediate has never been detected at higher temperature or after a long time reaction even at low temperature.[4] Careful examination of the base-catalyzed reaction of the peroxy-*p*-quinol (**2a**) independently synthesized gave a clue to the present findings.



Results and Discussion

Base-Catalyzed Reaction of Peroxy-*p*-quinol 2a. The base-catalyzed reaction of **2a**[5] under nitrogen gave the

(1) Part 3: A. Nishinaga, T. Shimizu, and T. Matsuura, *J. Org. Chem.*, **44**, 2983 (1979).

(2) A. Nishinaga, T. Itahara, T. Shimizu, and T. Matsuura, *J. Am. Chem. Soc.*, **100**, 1820 (1978).

(3) A. Nishinaga, T. Shimizu, and T. Matsuura, *Tetrahedron Lett.*, 3748 (1978).

(4) A. Nishinaga, T. Itahara, T. Matsuura, A. Rieker, D. Koch, K. Albert, and P. B. Hitchcock, *J. Am. Chem. Soc.*, **100**, 1826 (1978).

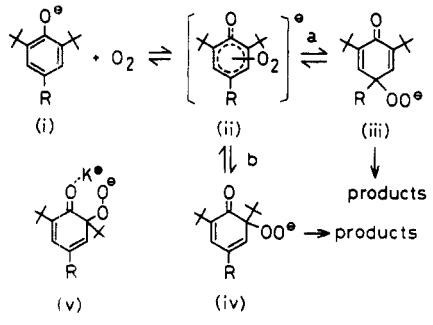
0022-3263/80/1945-4997$01.00/0

Table I. Base-Catalyzed Reaction of 2a[a]

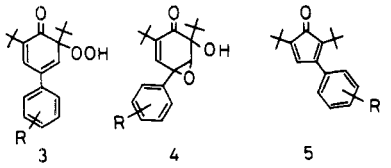
solvent	base	reaction temp, °C	% conversion	product, % yield[b] 1a	3a	4a	5a	other
DMF	*t*-BuOK	25	100	99		trace		
DMF	*t*-BuOK	−16[c]	100	99		trace		
THF	*t*-BuOK	25	100	80		12		8[e]
THF	*t*-BuOK	−16[c]	100	74		12		8[e]
t-BuOH	*t*-BuOK	25	100	33	trace	47	14	
t-BuOH[d]	*t*-BuOK	−16[c]	56	30	70			
90% EtOH	KOH	25	100	82	7	4		
90% EtOH	KOH	−16[c]	17	35	65			

[a] Molar ratio of base/2a, 5. Reaction at 25 °C was complete within a few minutes. [b] Determined by ^{1}H NMR and TLC. [c] Reaction time, 15 min. [d] An equal volume of petroleum ether was added to avoid freezing. [e] A reduction product, the corresponding *p*-quinol.

Scheme I



phenol **1a** and the migration products **3a**, **4a**, and **5a** (Table I). It has been known that **4** is obtained only from



a; R = 4 MeO b; R = H c; R = 2,4,6-Me$_3$

3 and that **5** results from base-catalyzed decomposition of **4**.[4] The results summarized in Table I show that the peroxy anion of **2a** in the free state (in DMF) is quite unstable even at −16 °C and liberates O_2 instantaneously whereas in the associated form with K^+ (in THF, *t*-BuOH) and in the solvated form (in EtOH) migration of the peroxy group competes with the deoxygenation. At −16 °C in alcoholic solvents, the peroxy anion is somewhat stabilized and migration of the peroxy group predominates.

The base-catalyzed reaction of **2** follows first-order kinetics with respect to **2**,[3] and rate constants in a *t*-BuOK/*t*-BuOH system at 0 °C have been determined in the present work as follows: for the deoxygenation of **2a** and **2b**, 3×10^{-3} and 1.5×10^{-5} s^{-1}, respectively, and for the migration of the peroxy group in **2a** and **2b**, 7×10^{-3} and 4×10^{-5} s^{-1}, respectively. As seen from these results, the peroxy anion of **2a** is quite unstable compared to that of **2b**. This is the reason why peroxy-*p*-quinols **2** (R = substituted phenyl) have never been found so far in the base-catalyzed oxygenation of **1** (R = substituted phenyl).[4] The instability of **2a** in basic media is probably due to acceleration of sp^2 hybridization at the C-4 carbon of the dienone ring in **2a** by a conjugation effect of the aromatic substituent leading to the π-complex intermediate of type ii in Scheme I.

The lower reactivity of **2a** at −16 °C in alcoholic solvents (Table I) prompted us to investigate the kinetics of the oxygenation of **1a** at −16 °C. It is now found that the ortho regioselective oxygenation of **1a** at −16 °C also involves attack by O_2 on the para postion in the first step followed by the efficient migration of the resulting peroxy group to the ortho position (Figure 1). Similar results were obtained with **1b**, indicating that dioxygen attack on the para position is kinetically preferable also in cases with 4-aryl-2,6-di-*tert*-butylphenols.

On the other hand, in the oxygenation of **1c**, no peroxy-*p*-quinol **2** (R = mesityl) was detected at all even at −16 °C, but only peroxy-*o*-quinol **3c** was obtained. This is probably due to the fact that oxygen incorporation into the para position is sterically hindered by the mesityl group. It is therefore not necessary to conclude limitedly that the dioxygen incorporation takes place always at the para position. There may also be a possibility that the oxygenation takes place directly along path b in Scheme I.

In conclusion, it may be noted that in base-catalyzed oxygenation of 4-aryl-2,6-di-*tert*-butylphenols dioxygen incorporation is principally preferable on the 4-position, but the reaction path depends on the reaction temperature and bulkiness of the aromatic substituent. At high temperature or with a bulky aromatic group, O_2 may be incorporated into the ortho position via the π-complex intermediate (path b), supporting Scheme I as a general sequence as proposed previously.[1]

Experimental Section

Base-Catalyzed Reaction of Peroxy-*p*-quinol 2a. To a solution of base (2.5 mmol) in an appropriate solvent (10 mL) was added **2a** (0.5 mmol) under nitrogen bubbling. The resulting solution was allowed to stand at a given temperature under nitrogen. The mixture was acidified with a large excess of ice-cooled aqueous NH_4Cl solution and extracted with ether. The extract was dried (Na_2SO_4) and evaporated. The products **1a**, **3a**, **4a**, and **5a** in the resulting residue were identified by comparison with authentic samples[4] (^{1}H NMR and TLC). Yields of the products were determined from the ^{1}H NMR spectrum of the resulting mixture (Table I).

Kinetics of Base-Catalyzed Oxygenation of 1a. Oxygen was bubbled through a solution of **1a** (2.5 mmol) in a mixture (50 mL) of *tert*-butyl alcohol and hexane (1:1) containing *t*-BuOK (12.5 mmol) at −16 °C. Aliquots (5 mL) were taken out at the intervals shown in Figure 1, acidified with ice-cooled aqueous NH_4Cl solution, and extracted with ether. The extract was dried (Na_2SO_4) and evaporated. The resulting residue was shown to be a mixture of **1a**,[4] **2a**,[5] and **3a**[4] (^{1}H NMR and TLC), whose amounts were determined by ^{1}H NMR spectroscopy. The results are given in Figure 1.

Registry No. 1a, 6257-22-3; **2a**, 69892-33-7; **3a**, 60647-21-4; **4a**, 58282-04-5; **5a**, 58282-06-7; 2,6-di-*tert*-butyl-4-(4-methoxyphenyl)-*p*-quinol, 41252-35-1.

(5) A. Nishinaga, K. Nakamura, T. Matsuura, A. Rieker, D. Koch, and R. Griesshammer, *Tetrahedron*, **35**, 2493 (1979).