J. Org. Chem. 1987, 52, 697-699 697

Evidence for the Intermediacy of *o*-Quinones in Peroxide Cleavages of Catechols. The Fe(III)-Catalyzed Peroxide Ring Cleavage of 3,5-Di-*tert*-butylcatechol and 3,5-Di-*tert*-butyl-*o*-benzoquinone

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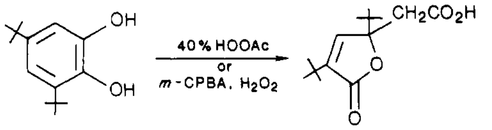
Received September 30, 1986

The oxidations of 3,5-di-*tert*-butylcatechol with dioxygen[1,2] and 3,5-di-*tert*-butyl-*o*-benzoquinone with hydrogen peroxide[1,3] have been reported to give products which appear to result from oxidative ring cleavage. These reactions are important not only from a general synthetic and mechanistic viewpoint but also because of their relationship to the action of the dioxygenase, pyrocatechase.[4]

We recently reported on the mechanism of the Fe(III)-catalyzed peracetic acid oxidation of catechol to *cis,cis*-muconic acid as a biomimetic reaction for pyrocatechase.[4] We now report our results on the oxidation of 3,5-di-*tert*-butylcatechol (1) and 3,5-di-*tert*-butyl-*o*-benzoquinone (2) employing peracetic acid (HOOAc), *m*-chloroperoxybenzoic acid (*m*-CPBA), and hydrogen peroxide as oxidants.

Results and Discussion



1 3

1 is oxidized to 2,4-di-*tert*-butyl-4-hydroxy-(*Z*)-2-hexenedioic acid lactone (3)[8] with peracetic acid. Trace quantities of Fe(III) increase the yield of lactone 3 as shown in Table I (compare runs 1 and 2). The lactone is not formed when 30% H_2O_2 is used as the oxidant. It most likely results from intradiol oxidative ring cleavage to give the dicarboxylic acid 4 followed by Markovnikov addition of the C-1 carboxyl group to the C-4 double bond to form the five-membered ring lactone 3. The driving force for the cyclization is the formation of the very stable γ-lactone with ring closure being enhanced by the *tert*-butyl groups. The lactone 3 was found to be stable to the reaction conditions. Markovnikov addition of the C-6 carboxyl group to the C-2 double bond would give the less stable δ-lactone. We have no evidence for δ-lactone formation in our reaction. The previously unreported methyl ester of lactone 3 was prepared and characterized.

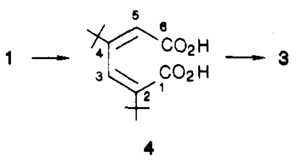


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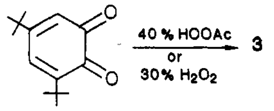
Table I. Peroxide Oxidations of 3,5-Di-*tert*-butylcatechol (1) and 3,5-Di-*tert*-butyl-*o*-benzoquinone (2)

run	substrate	oxidant[a]	Fe(III)	% yield of 3
1	1	HOOAc	yes	56
2	1	HOOAc	no	32
3	2	HOOAc	yes	59
4	2	HOOAc	no	58
5	2	H_2O_2	yes	33[b]
6	2	H_2O_2	no	33[b]

[a] HOOAc is an equilibrium mixture consisting of 41% HOOAc, 39% HOAc, 13% H_2O, and 5% H_2O_2. Hydrogen peroxide is a 30 wt % aqueous solution. [b] ±5%; see Experimental Section.

Lactone 3 was also obtained when 3,5-di-*tert*-butyl-*o*-benzoquinone (2) was oxidized with 40% peracetic acid or 30% hydrogen peroxide, although the peracetic acid oxidation was cleaner. The yields are shown in Table I (runs 3-6).



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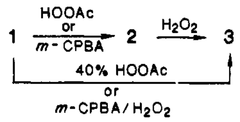
These results are consistent with our proposed mechanism for the oxidation of catechol to *cis,cis*-muconic acid,[4] and they further demonstrate the relationship between the chemical model and pyrocatechase. Catechol (1) is oxidized to lactone 3 with 40% peracetic acid, which is an equilibrium mixture containing peracetic acid, acetic acid, hydrogen peroxide, and water. This result is consistent with the idea that peroxy acid is required for the oxidation of catechol (1) to quinone 2 and that hydrogen peroxide is required for the oxidation of quinone 2 to lactone 3, which represents ring cleavage. We have actually isolated 2 in a reaction in which we oxidized 1 with *m*-chloroperoxybenzoic acid/hydrogen peroxide by quenching the reaction before completion. Thus, 2 is an intermediate in the oxidation of 1 to 3, and 2 is oxidized to 3 by 40% peracetic acid because of its H_2O_2 content. We have also oxidized 2 to 3 with H_2O_2 alone (*no* peroxy acid present), but the yields are low (ca. 33%) because of the inherently large amounts of water present in 30% H_2O_2.[5] We have further determined that quinone 2 is *not* oxidized to lactone 3 by *m*-chloroperoxybenzoic acid (a pure peroxy acid as opposed to 40% HOOAc which contains H_2O_2) but is oxidized to lactone 3 by the mixed oxidant H_2O_2/*m*-chloroperoxybenzoic acid. This result clearly indicates that *both* H_2O_2 and peroxy acid are required for the complete oxidation to occur.



The oxidation of the stable *o*-quinone 2 to lactone 3 gives strong evidence for the intermediacy of unstable *o*-benzoquinone in the oxidation of catechol to *cis,cis*-muconic acid by both peracetic acid and pyrocatechase. Presumably, 1 can be oxidized to lactone in the absence of Fe(III) because the quinone intermediate 2 is stable compared to *o*-benzoquinone, the proposed intermediate in the oxidation of catechol to *cis,cis*-muconic acid. This result strongly suggests that Fe(III) plays an important role in stabilizing *o*-benzoquinone[6] in the oxidation of catechol

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(1) Grinstead, R. R. *Biochemistry* **1964**, *3*, 1308-1314.

(2) Funabiki, T.; et al. *J. Chem. Soc., Chem. Commun.* **1979**, 754-755.

(3) Speier, G.; Tyeklar, Z. *J. Chem. Soc., Perkin Trans 2* **1981**, 1176-1179.

(4) Pandell, A. J. *J. Org. Chem.* **1983**, *48*, 3908-3912, and references cited therein.

(5) We have previously shown (ref 4) that water lowers the yield in Fe(III)-catalyzed peroxy acid oxidations of catechol.

(6) Crowley, P. J.; Haendler, H. M. *Inorg. Chem.* **1962**, *1*, 904-909.

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to *cis,cis*-muconic acid since little or no *cis,cis*-muconic acid is formed in the absence of Fe(III). Furthermore, the results described in this paper, taken together with those previously reported,[4] lend support to the idea that pyrocatechase oxidizes catechol via a peroxide (i.e., two-electron) rather than a free radical mechanism.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. NMR spectra were recorded on a Perkin-Elmer R12B and chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane: s = singlet, m = multiplet.

Materials. The peracetic acid was obtained from FMC Corp. as a 40 wt % solution in acetic acid solvent. The acetic acid was Matheson Scientific, reagent. The hydrogen peroxide was obtained from Spectrum Chemical as a 30 wt % solution in water. The ferric acetate (purified powder basic) was obtained from City Chemical Corp. The 3,5-di-*tert*-butylcatechol and 3,5-di-*tert*-butyl-*o*-benzoquinone were obtained from Aldrich Chemical Co. and used as received. Solvents used were reagent grade from Spectrum Chemical Co. Silica gel thin layer chromatography (TLC) plates containing F-254 indicator were obtained from Brinkman or Analabs. Silica gel, 28–200 mesh, for column chromatography and thionyl chloride, practical grade, were obtained from MCB.

General Procedure for Peracetic Acid Oxidations of 3,5-Di-*tert*-butyl-*o*-benzoquinone. With the exceptions of varying the ratio of oxidant to starting material and/or deleting the metal catalyst, the same procedure was followed. The following procedure, without Fe(III) catalysis, is typical. Glacial acetic acid (5 mL) and peracetic acid (15 mL) were placed in a 250-mL Erlenmeyer flask and stirred magnetically with a Teflon-coated stirring bar while a solution of 3,5-di-*tert*-butyl-*o*-benzoquinone (1.017 g, 0.00462 mol) dissolved in glacial acetic acid (10 mL) was added dropwise from an addition funnel over a period of 30 min. A color change from red to light yellow was observed as the reaction proceeds. After being stirred at 25 °C for 20 hr, the reaction mixture was transferred to a 250-mL, round-bottomed flask and the solvents were removed on a rotoevaporator. The resulting, thick, yellow liquid was dissolved in 50 mL of ether and extracted (3 × 20 ml) with aqueous sodium bicarbonate. The combined aqueous layers were acidified and extracted with ether. The ether layer was dried ($MgSO_4$), filtered, and evaporated on a rotoevaporator. Obtained was 0.68 g of a white solid, mp 133–134 °C. (Similar results were obtained by triturating the thick, yellow liquid with hexane.) An NMR spectrum ($CDCl_3$) showed the following absorptions: δ 0.98 (s, *tert*-butyl), 1.23 (s, *tert*-butyl), 2.85 (m, CH_2), 6.93 (s, C=CH), 8.68 (s, CO_2H). Addition of D_2O removed the singlet at 8.68 ppm. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.1; H, 8.66; M_r, 254. Found: C, 66.20; H, 8.65; M_r (by osmomitry) 249. This compound is identical with 2,4-di-*tert*-butyl-4-hydroxy-(*Z*)-2-hexenedioic acid lactone (3) which has been previously reported.[2] The purified yield was 58%. Similar yields are obtained when trace quantities of Fe(III) are added (1 mg) and when the quantity of peracetic acid is reduced to 1.5 mL.

General Procedure for the Peracetic Acid Oxidation of 3,5-Di-*tert*-butylcatechol. The following Fe(III)-catalyzed oxidation illustrates the general procedure. To a magnetically stirred solution of glacial acetic acid (5 mL), 40% HOOAc (2.2 mL), and ferric acetate (0.0033 g, 0.0000168 mol) in a 250-mL Erlenmeyer flask, was added, dropwise, over 1 h from a micrometer addition funnel, a solution of 3,5-di-*tert*-butylcatechol (1.05 g, 0.0047 mol) dissolved in glacial acetic acid (10 mL). The exothermicity of the reaction necessitates the use of an ice/water bath during this addition. The reaction was allowed to spontaneously warm to room temperature. A color change from red to light yellow was observed over 3 h. After being stirred for 20 h at 25 °C, the reaction was stripped of solvents on the rotoevaporator and purified by extraction with aqueous sodium bicarbonate as described above. Obtained was 0.67 g (56%) of the lactone 3, mp 130–132 °C. NMR absorptions were identical with those reported above. Consistently lower yields (30–44%) were obtained when Fe(III) was not present.

General Procedure for the Hydrogen Peroxide Oxidation of 3,5-Di-*tert*-butyl-*o*-benzoquinone. The following Fe(III)-catalyzed oxidation illustrates the general procedure for H_2O_2 oxidations. To a magnetically stirred solution of 5 mL of HOAc, 3.0 mL of 30% H_2O_2 (1.00 g, 0.0295 mol), and 0.0043 g (0.0000218 mol) of ferric acetate in a 250-mL Erlenmeyer flask was added, dropwise over 30 min, from an additional funnel, a solution of 0.723 (0.0033 mol) of 3,5-di-*tert*-butyl-*o*-benzoquinone in 5 mL of acetic acid. A color change from red to amber occurred slowly over 48 h. KI starch test paper indicated the presence of peroxides. TLC of the reaction solution indicated four major and two minor components. One of the major components had an R_f identical with that of lactone 3. The reaction was diluted with ether and extracted three times with equal volumes of water. The ether was dried with $MgSO_4$ containing activated carbon to remove any remaining peroxides. This solution was filtered, stripped of ether, and extracted with aqueous $NaHCO_3$ to give a wet, yellow solid. TLC indicated this solid contained the lactone and two other compounds.

A slurry packed silica gel (50 g) column using gradient elution from 10% $CHCl_3$/hexane to 50% $CHCl_3$/hexane was employed for additional separation. Cuts of 50 mL each were taken and followed by TLC. The pure lactone was obtained in the middle range of cuts (18–29). The mp was 132–134 °C, and the NMR spectrum was identical with that reported above for lactone 3. All other column cuts contained mixtures of all three compounds and were not pursued. Thus, the yield of this reaction could not be determined accurately but was estimated to be 33 ± 5%.

Hydrogen Peroxide Oxidation of 3,5-Di-*tert*-butylcatechol. The procedure described for the H_2O_2 oxidation of the benzoquinone was used. Several runs were attempted. Each gave a complex mixture of several compounds. This result is consistent with the observation of Vesely and Scmerling who report that the oxidation of catechol with H_2O_2 leads to complex reaction mixtures.[7] Several attempts were made to determine if the lactone 3 was present in the reaction mixtures.

The product of one reaction was applied to a preparatory (500 μm) TLC plate. After development (20:78:2 THF/EtOAc/H_2O), each band was removed, extracted, and analyzed by NMR and TLC. Each band contained three–five compounds and none had an R_f equal to that of lactone 3 by TLC. No band had an NMR spectrum consistent with that of lactone 3. Extensive silica gel column chromatography was attempted. The $CHCl_3$/hexane gradient elution system was tried as was 4:96 THF/hexane and 4:16:80 THF/EtOAc/hexane. In every case each cut contained three or more compounds and none of these compounds had the same R_f as lactone 3.

Stability of the Lactone. A known amount of pure lactone 3 was mixed with the experimental amounts of Fe(III), HOAc, and H_2O_2. The solution was stirred for 12 days at room temperature and followed by TLC. The amount of lactone 3 did not change and no other new spots were detected. About 90% of lactone 3 was recovered unchanged.

Fe(III)-Catalyzed *m*-Chloroperoxybenzoic Acid/H_2O_2 Oxidation of 3,5-Di-*tert*-butylcatechol: Formation of 3,5-Di-*tert*-butyl-*o*-benzoquinone. A solution of 1.02 g (0.00459 mol) of 3,5-di-*tert*-butylcatechol dissolved in 7 mL of glacial acetic acid was added dropwise from a buret period of 1 h to a magnetically stirred solution of 0.0032 g (0.0000168 mol) of ferric acetate, 0.965 g (0.00558 mol) of *m*-chloroperoxybenzoic acid, 1 mL of 30% H_2O_2 (0.0098 mol), and 5 mL of glacial acetic acid. The reaction was quenched after 2 h by adding 10 mL of water. The solvents were removed by rotary evaporation, leaving a thick liquid which was dissolved in 50 mL of ether and extracted (3 × 50 mL) with saturated, aqueous $NaHCO_3$. The ether layer was dried ($MgSO_4$) and filtered, and the solvent was removed by rotary evaporation, leaving a thick green liquid which was subjected to preparative TLC to give a 35% yield of 3,5-di-*tert*-butyl-*o*-benzoquinone (mp, R_f, and vis–UV were identical with those of a known sample).

Preparation of the Methyl Ester of Lactone 3: 2,4-Di-*tert*-butyl-4-hydroxy-(*Z*)-2-hexenedioic Acid, Lactone, Methyl Ester (5). Lactone 3 (0.745 g, 0.0029 mol) and thionyl

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(7) Vesely, J. A.; Schmerling, L. *J. Org. Chem.* **1970**, *35*, 4029.

(8) The lactone can also be named as a derivative of furan: 2,4-di-*tert*-butyl-2,5-dihydro-5-oxo-2-furanacetic acid.

chloride (5 mL) were refluxed for 1 h in a 50-mL, round-bottomed flask. After removal of the thionyl chloride on a rotoevaporator, absolute methanol (25 mL) was added, and the resulting mixture was allowed to stand overnight. The methanol was removed on a rotoevaporator, and the resulting yellow solid was recrystallized from hexane to give 0.53 g (67%) of light yellow crystals, mp 68–70 °C. The proton NMR spectrum of this compound was consistent with that expected for the methyl ester.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Communications

Oxygen-17 and Carbon-13 Identification of the Dimethyldioxirane Intermediate Arising in the Reaction of Potassium Caroate with Acetone

Summary: Starting with ^{17}O-labeled or 2-^{13}C-labeled acetone, ^{17}O and ^{13}C NMR evidence could be gathered which supports the dioxirane structure for the peroxide intermediate isolated from reaction solutions containing potassium caroate and acetone.

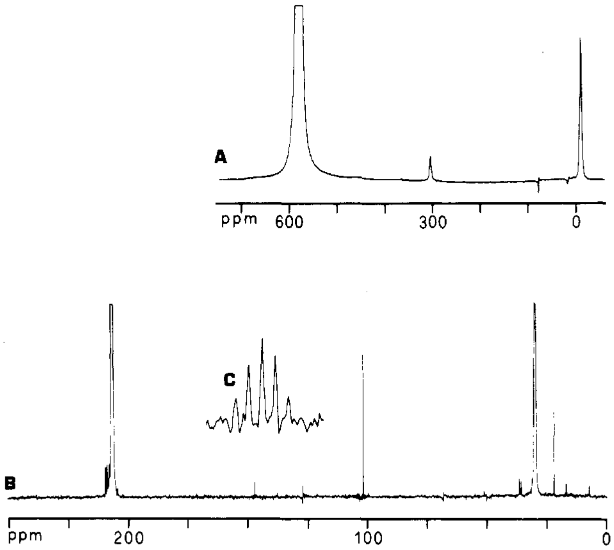

Figure 1. (A) ^{17}O NMR spectrum of ca. 0.06 M dimethyldioxirane (1; ^{17}O labeled) in acetone, at 4 °C (27.12 MHz, recorded over ca. 16 h, 570 000 scans, no sensitivity enhancement applied to FID before FT); (B) ^{1}H decoupled ^{13}C NMR spectrum of endocyclic carbon-labeled (ca. 5% ^{13}C) 0.06 M dimethyldioxirane in acetone, at 4 °C (50.03 MHz, 4040 scans, digital resolution 0.39 Hz/point, 0.16-s sensitivity enhancement); (C) insert (50-Hz sweep width, 5103-Hz sweep offset, 37 380 scans) shows the ^{1}H-coupled spectrum portion relative to the ^{13}C resonance at 102 ppm.

Sir: During the last decade we have collected kinetic, ^{18}O-labeling, and stereochemical data that stringently suggest dioxiranes—i.e., the smallest ring peroxide species containing carbon—are generated in the reaction of potassium peroxymonosulfate (caroate) with ketones.[1-3] Recently, the case for the existence of dioxiranes in the condensed phase was completed by Murray and Jeyaraman by showing that a number of low-molecular-weight dialkyldioxiranes can actually be isolated from buffered (pH 7, $NaHCO_3$) aqueous solutions containing caroate and the parent ketone.[4] Indeed, in the elegant procedure devised by these authors, room temperature distillation in a flow of inert gas allows one to remove from the reaction solution some of the dioxirane intermediate that builds up in a stationary concentration during the early stages of the reaction between the inorganic peroxide and the ketone (e.g., Scheme I).[4] Along with observations concerning reactivity, the spectroscopic evidence presented is convincing for the dioxirane structure.[4] Dimethyldioxirane solutions are observed to yield acetone diperoxide **3**,[4] and this even in the absence of Lewis acid catalysts (although much more slowly). Also in view of the debated dioxirane **1**–carbonyl oxide **2** dichotomy,[3,4,6-9] we have sought ^{17}O NMR confirmation of the structure of the peroxide intermediate generated as in Scheme I.

The difficulties routinely encountered in the detection of ^{17}O NMR resonances of peroxide oxygens in natural abundance are well understood.[10-13] In particular, as we

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(1) Edwards, J. O.; Pater, R. H.; Curci, R.; DiFuria, F. *Photochem. Photobiol.* **1979**, *30*, 63–70 and references therein.

(2) (a) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem.* **1980**, *45*, 4758–4760. (b) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem.* **1982**, *47*, 2670–2673. (c) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155–156.

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(4) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847–2853. (b) Murray, R. W.; Jeyaraman, R.; Mohan, L. *Tetrahedron Lett.* **1986**, *27*, 2335–2336; *J. Am. Chem. Soc.* **1986**, *108*, 2470–2472.

(5) The procedure and apparatus described by Murray and Jeyaraman (ref 4a) were used with only minor modifications: alternative to the addition of solid caroate, we found it also suitable to add a cold satured aqueous solution of $KHSO_5$ (containing ca. 10^{-3} M $EDTANa_2$, to cut down uncatalyzed peroxide decomposition) to the reaction flask containing water, acetone, and $NaHCO_3$ (or $KHCO_3$); argon instead of helium was used to remove dimethyldioxirane (and acetone) from the reaction solution, and a three-way distillation receiver was connected to a dry ice/$CHCl_3$-cooled condenser to allow collection of fractions.

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