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The Oxidation of 2,6-Di-*tert*-butyl-4-methylphenol Using Hydrogen Peroxide-Heteropolyacid System

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Synopsis. The oxidation of 2,6-di-*tert*-butyl-4-methylphenol (**1**) with hydrogen peroxide in the presence of heteropolyacids was carried out in acetic acid to give 2,6-di-*tert*-butyl-4-hydroperoxy-4-methyl-2,5-cyclohexadien-1-one (**2**), 2,6-di-*tert*-butyl-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one (**3**), and 2,6-di-*tert*-butyl-*p*-benzoquinone (**4**). Conversion of **2** into **4** under acidic conditions suggests that **2** could be a precursor of **4**. The oxidation mechanism of phenols was discussed based on isolated intermediates.

In recent years, much attention has been paid to the hydrogen peroxide-heteropolyacid system which can selectively oxidize olefins[1,2] and alcohols.[1] On the other hand, only a few papers and patents were reported on the oxidation of phenols using the hydrogen peroxide-heteropolyacid system[3] to give *p*-benzoquinones or mixture of hydroquinones and catechols. In the preceding paper,[4] we reported the synthesis of *p*-benzoquinones from phenols using hydrogen peroxide-heteropolyacid, but the mechanism of the aromatic ring oxidation remained obscure.

It has been frequently suggested that an intermediate in the oxidation of phenols to *p*-benzoquinones with hydrogen peroxide is a hydroquinone species as proposed in the oxidation of alkyl-substituted phenols catalyzed by ruthenium chloride, which works as a Lewis acid catalyst.[5] However, the hydroquinone intermediate was not detected in this system because the hydroquinone can be oxidized more rapidly to the *p*-benzoquinone than the phenol.[5] Therefore, we have attempted to clarify the oxidation mechanism of phenols to *p*-benzoquinones by using *p*-substituted phenols as the substrate to prevent tautomerization of a 4-hydroxy-2,5-cyclohexadien-1-one derivative to the corresponding hydroquinone. It has already been reported that hydroperoxides were formed in the oxidation of *p*-alkyl substituted phenols with hydrogen peroxide in the presence of transition metal ions.[6]

The present paper deals with the oxidation of 2,6-di-*tert*-butyl-4-methylphenol with hydrogen peroxide-heteropolyacid system to give the hydroperoxide, which converts into the *p*-benzoquinone under acidic conditions.

Results and Discussion

When 2,6-di-*tert*-butyl-4-methylphenol (**1**) was treated with 60% hydrogen peroxide in the presence of 12-molybdophosphoric acid as a catalyst at 30 °C for 5 h, 2,6-di-*tert*-butyl-4-hydroperoxy-4-methyl-2,5-cyclohexadien-1-one (**2**) was obtained as a major product along with 2,6-di-*tert*-butyl-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one (**3**) and 2,6-di-*tert*-butyl-*p*-benzoquinone (**4**). Structures of these compounds were determined by ^{1}H NMR and IR spectra. Representative results of the oxidation with several heteropolyacids are listed in Table 1. When sodium molybdate instead of heteropolyacids was examined, a very small amount of **2** was obtained. Thus, heteropolyacids seem to play a crucial role in the oxidation. A time course of the oxidation is shown in Fig 1. It took ca. 7 h to give the maximum yield of **2**. However, the yield of **4** was gradually increased with time showing no maximum value. These results suggest that **2** could be an intermediate in the oxidation of phenols to benzoquinones.

Table 1. Oxidation of **1** Using H_2O_2-Heteropolyacid[a)]

Catalyst	Conv./%	Yield/%		
		2	**3**	**4**
$H_3PMo_{12}O_{40}\cdot nH_2O$	79.7	34.1	1.7	4.1
$H_3PW_{12}O_{40}\cdot nH_2O$	62.5	33.6	2.7	trace
$H_3SiMo_{12}O_{40}\cdot nH_2O$	81.3	44.7	1.4	6.8
$H_3SiW_{12}O_{40}\cdot nH_2O$	72.3	38.2	2.1	3.6
$Na_3PMo_{12}O_{40}\cdot nH_2O$	59.9	31.2	3.1	4.2
$Na_3PW_{12}O_{40}\cdot nH_2O$	33.7	14.7	4.1	trace
$Na_2MoO_4\cdot 2H_2O$	18.5	2.0	7.2	trace
none	15.9	11.8	trace	—

a) Reaction conditions: **1**, 2 mmol; H_2O_2 aq (60%), 2 ml; catalyst, 100 mg; AcOH, 10 ml; 30 °C, 5 h.

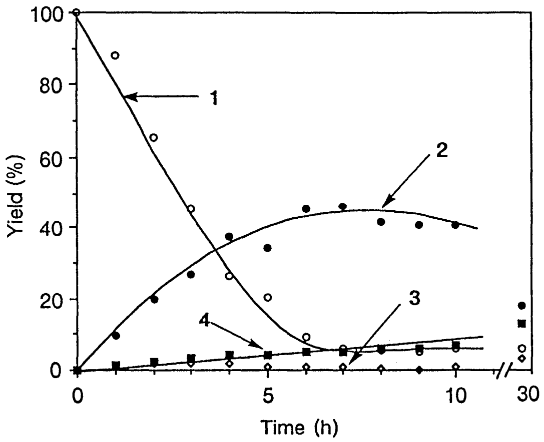
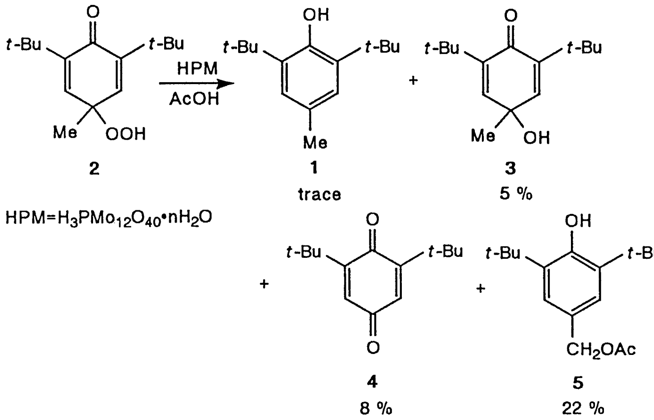


Fig. 1. Oxidation of **1** with H_2O_2 in the presence of $H_3PMo_{12}O_{40}\cdot nH_2O$.

The reactions of the intermediate compounds as substrates were carried out in the presence of or absence of hydrogen peroxide under the conditions in the experimental section (Eqs. 1—5). The treatment of **2** with 12-molybdophosphoric acid in acetic acid afforded **1**, **3**, **4**, and 4-acetoxymethyl-2,6-di-*tert*-butylphenol (**5**) (Eq. 1). It was thus confirmed that **4** was produced from **2**. The alcohol (**3**) also afforded **4** but did not produce **2** when **3** was treated with hydrogen peroxide in the presence of 12-molybdophos-



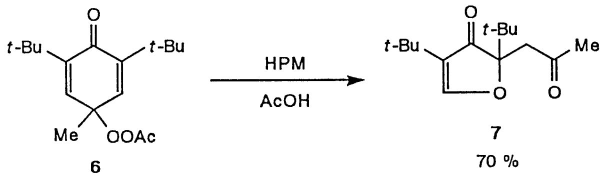
Eq. 1

$$\mathbf{3} \xrightarrow[\text{AcOH}]{\text{H}_2\text{O}_2/\text{HPM}} \mathbf{4}\ (44\ \%) \qquad \text{Eq. 2}$$

$$\mathbf{3} \xrightarrow[\text{AcOH}]{\text{HPM}} \mathbf{5}\ (85\ \%) \qquad \text{Eq. 3}$$

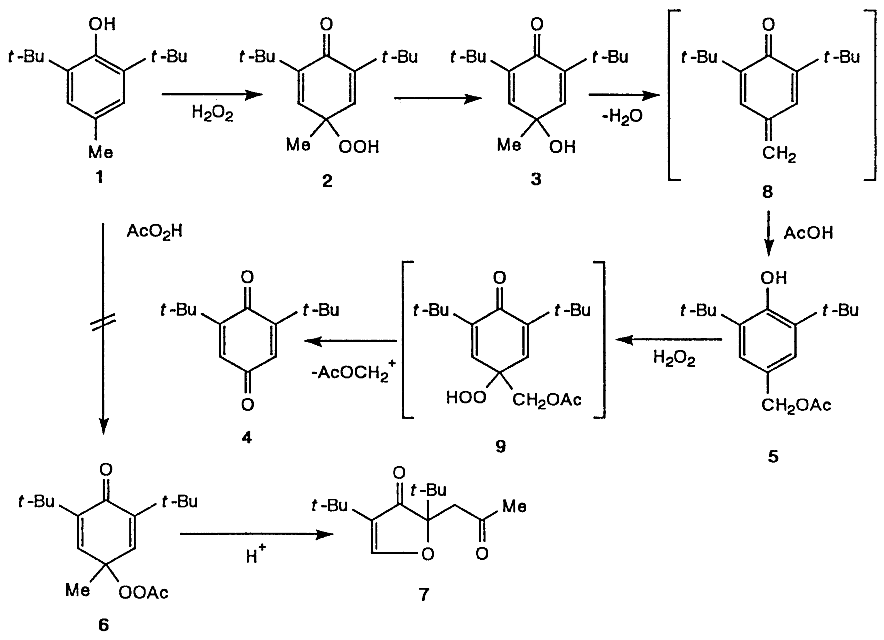
$$\mathbf{5} \xrightarrow[\text{AcOH}]{\text{H}_2\text{O}_2/\text{HPM}} \mathbf{4}\ (58\ \%) \qquad \text{Eq. 4}$$

$$\mathbf{5} \xrightarrow[\text{AcOH}]{\text{HPM}} \text{no reaction} \qquad \text{Eq. 5}$$



Eq. 6

phoric acid in acetic acid (Eq. 2). In the absence of hydrogen peroxide, **3** did not give **4** but produced **5** in 85% yield (Eq. 3). The reaction of **5** with hydrogen peroxide in the presence of 12-molybdophosphoric acid was found to give **4** in 58% yield (Eq. 4). **5** was stable to 12-molybdophosphoric acid in acetic acid



Scheme 1.

(Eq. 5). These results suggest that **5** easily converts into **4** in the presence of hydrogen peroxide. Therefore, in the reaction conditions where an excess amount of hydrogen peroxide existed, **5** would not be obtained.

Since the reaction of **1** and hydrogen peroxide was carried out in acetic acid with strong acid, i.e., heteropolyacid, peracetic acid would be formed under the reaction conditions and could react with phenols to give peroxy esters. Therefore, 4-acetylperoxy-2,6-di-*tert*-butyl-4-methyl-2,5-cyclohexadien-1-one (**6**) was synthesized by the acetylation of **2** and was treated with 12-molybdophosphoric acid in acetic acid to afford 2,4-di-*tert*-butyl-2-(2-oxopropyl)-3(2*H*)-furanone (**7**) as the sole product in 70% yield (Eq. 6), consistent with the results by Nishinaga et al.[7] This observation indicates that peracetic acid has no importance in the oxidation because **7** was not observed in the oxidation of **1**.

From these results, the mechanism of the phenol oxidation is proposed as shown in Scheme 1. The phenol (**1**) reacts with hydrogen peroxide to yield **2**. The alcohol (**3**) can form via O–O bond cleavage of **2** followed by protonation. The dehydration of **3** could produce 2,6-di-*tert*-butyl-4-methylene-2,5-cyclohexadien-1-one (**8**), which then converted to **5** by the addition of acetic acid in the presence of a strong acid.[8] Furthermore, hydrogen peroxide reacts with **5** to form **4** via a hydroperoxide (**9**).

In the preceding paper,[4] we tentatively considered hydroquinones as the intermediates in the oxidation of phenols to *p*-benzoquinones with hydrogen peroxide in the presence of heteropolyacid as suggested in previous work.[5] The results obtained in this work suggest that *p*-unsubstituted phenols are also able to be oxidized to the *p*-benzoquinones with hydrogen peroxide by way of hydroperoxide intermediates, where the hydroperoxides would be unstable due to rapid aromatization of the 2,5-cyclohexadien-1-one ring.

Experimental

Melting points were determined on a Yanagimoto micromelting apparatus. Gas chromatograph analyses were performed on a Shimadzu GC-7A gas chromatograph using a Thermon 3000 column. Liquid chromatograph analyses were performed on a Shimadzu LC-3A liquid chromatograph using an Inertsil ODS column with acetonitrile-water mixture (75 : 25) as solvent.

General Procedure for the Oxidation of a Substrate Using H_2O_2–Heteropolyacid. Aqueous hydrogen peroxide[9] (60%, 2 ml, ca. 44 mmol) was added dropwise to a solution of a substrate (2 mmol) and a catalyst (100 mg) in acetic acid (10 ml). The reaction mixture was stirred for 5 h at 30 °C under nitrogen atmosphere. Water was added to the solution and products were extracted with dichloromethane three times. The organic layer was washed with water and dried over anhydrous magnesium sulfate. Yields of the products were determined by an internal standard technique using the LC method for **2** and **3** and the GC method for **4** and **5**.

General Procedure for the Reaction of a Substrate with Heteropolyacid. The reaction was carried out as described above in the absence of aqueous hydrogen peroxide. The yield of **7** was determined by isolation.

Products. 2,6-Di-*tert*-butyl-4-hydroperoxy-4-methyl-2,5-cyclohexadien-1-one (**2**) was isolated from the reaction mixture. The crude product was chromatographed on silica gel using dichloromethane as eluent. The product was recrystallized from hexane; mp 113—115 °C (lit,[8] 115 °C).

2,6-Di-*tert*-butyl-4-hydroxy-4-methyl-2,5-cyclohexadien-1-one (**3**) was prepared according to the reported method, mp 106—108 °C (lit,[8] 112—113 °C).

4-Acetoxymethyl-2,6-di-*tert*-butylphenol (**5**) was prepared as follows: to the solution of 2,6-di-*tert*-butyl-4-hydroxymethylphenol (5 mmol) and triethylamine (5 mmol) in benzene (50 ml), acetyl chloride (5.5 mmol) was added. The solution was stirred for 4 h at room temperature. Water was added to the reaction mixture, and the product was extracted with dichloromethane three times. The organic layer was washed with water and dried over anhydrous magnesium sulfate. After the evaporation of the solvent, the crude product was chromatographed on silica gel using dichloromethane as eluent. The product was recrystallized from hexane; mp 100—102 °C (lit[8] mp 105—106 °C).

4-Acetylperoxy-2,6-di-*tert*-butyl-4-methyl-2,5-cyclohexadien-1-one (**6**) was prepared by the acetylation of **2** in the same manner as the preparation of **5**. The crude product was chromatographed on silica gel using benzene as eluent.

2,4-Di-*tert*-butyl-2-(2-oxopropyl)-3(2*H*)-furanone (**7**) was isolated from the reaction mixture. The crude product was chromatographed on silica gel using dichloromethane-acetone-methanol mixture (100 : 5 : 1) as eluent. The product was recrystallized from hexane; mp 66 °C (lit,[7] mp 68—70 °C).

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9) Aqueous 60% hydrogen peroxide was kindly supplied by Tokai Electro-Chemical Co., Ltd.