1652 © 1989 The Chemical Society of Japan Bull. Chem. Soc. Jpn., 62, 1652—1657 (1989) [Vol. 62, No. 5

Oxidation of Methoxy- and/or Methyl-Substituted Benzenes and Naphthalenes to Quinones and Phenols by H_2O_2 in HCOOH

Hideo ORITA,* Masao SHIMIZU, Takashi HAYAKAWA, and Katsuomi TAKEHIRA
National Chemical Laboratory for Industry, Tsukuba, Ibaraki 305

(Received November 25, 1988)

The oxidation of a number of arenes (methoxybenzenes, methylbenzenes, and naphthalenes) to quinones and phenols by H_2O_2 in HCOOH has been examined. Methoxybenzenes were much more easily oxidized to *p*-benzoquinones than methylbenzenes (e.g., 1,3,5-trimethoxybenzene was oxidized to 2,6-dimethoxy-*p*-benzoquinone in a 75% yield and 1,2,4-trimethylbenzene to 2,3,5-trimethyl-*p*-benzoquinone in a 16% yield). Electron-withdrawing substituents, such as nitro, cyano, and chloro groups, lowered the conversion of reactants and changed the product selectivity from quinones to phenols. Methoxybenzonitriles were oxidized to corresponding phenols in a moderate yield (e.g., 2,6-dimethoxybenzonitrile to 3-hydroxy-2,6-dimethoxybenzonitrile in a 39% yield and a 64% selectivity).

Hydrogen peroxide is an economical and clean oxidant whose waste product is only water, and can oxidize a variety of organic substrates including arenes in the presence of catalysts. However, there are few applications to organic synthesis, excepting some examples such as the manufacturing of catechol and hydroquinone from phenol.

Some of quinones are naturally occurring materials with biological activities,[1] and are the key intermediates of medicines. For example, trimethyl-*p*-benzoquinone is key compound in synthesis of vitamin E, and 2,3-dimethoxy-5-methyl-*p*-benzoquinone is useful for production of coenzyme Q, and 2-methyl-1,4-naphthoquinone is the simplest synthesized vitamin K (vitamin K_3) and used for producing vitamin K_1.[2] On the other hand, there are few papers on the direct oxidation of arenes to quinones by H_2O_2.[3–5] Ito et al.[3] reported that $RuCl_3$ catalyzed the oxidation of trimethylphenol in acidic medium to trimethyl-*p*-benzoquinone in a high yield. In this case, the high cost of $RuCl_3$ requires its recovery for practical use, which is difficult in homogeneous system. Matsumoto et al.[4] showed that trimethoxybenzenes were oxidized to dimethoxy-*p*-benzoquinones by H_2O_2 in the presence of hexacyanoferrate(II or III) ion, which is harmful. A palladium catalyst supported on sulfonated polystyrene type resins was used for the oxidation of methylbenzenes and naphthalenes.[5] Naphthalenes were oxidized to naphthoquinones in fairly good yields, but methylbenzenes gave *p*-benzoquinones in poor yields of 3—8%.

In the present work, we have investigated the oxidation of arenes (methoxybenzenes, methylbenzenes, and naphthalenes) by H_2O_2 in HCOOH. The reaction rates and selectivity were very dependent on the substituents on aromatic ring. Electron-withdrawing substituents slowed down the reaction and changed the product selectivity from quinones to phenols.

Experimental

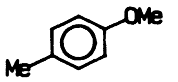
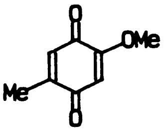
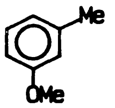
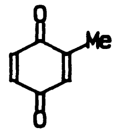
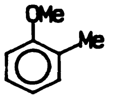
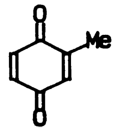
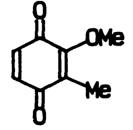
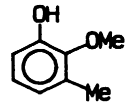
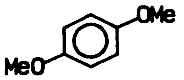
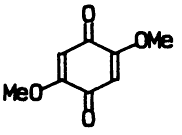
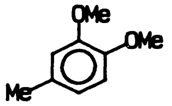
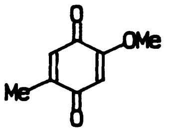
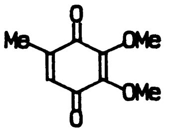
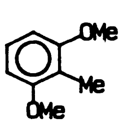
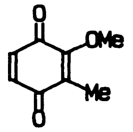
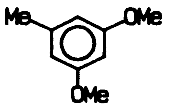
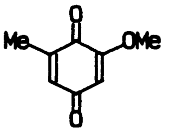
Reagents and Apparatus. 3,5-Dimethoxytoluene was prepared by the published procedure.[6] All other reagents were commercial products of the highest purity obtainable. Infrared (IR) spectra were measured by a JASCO FT/IR-7000 spectrometer. Mass spectra were recorded at 70 eV on a Shimadzu GCMS-QP 1000 mass spectrometer. A Hitachi R-40 (90 MHz) spectrometer was used to obtain ^1H nuclear magnetic resonance (NMR) spectra.

General Procedure for Oxidation of Arenes by H_2O_2. Aqueous hydrogen peroxide (31%, 2 ml, ca. 20 mmol) was added to a solution of an arene (4 mmol) in formic acid (10 ml). The reaction mixture was stirred for 1—24 h (usually 2 h) at a desired temperature (30—50 °C) under nitrogen atmosphere. The solution was poured into water and the products were extracted with CH_2Cl_2. The organic layer was washed with water, and dried with $MgSO_4$. Generally, the products were analyzed by gas chromatography using a Thermon 3000 column (10% on Celite 545, 1 m, thermal conductivity detector) and *o*-dichlorobenzene as an internal standard. Some quinones (e.g., 2,5- and 2,6-dimethoxy-*p*-benzoquinone) are not well soluble in either H_2O or CH_2Cl_2. In these cases, the extracted organic solution was evaporated and the residue was rinsed with methanol or hexane to separate crystals of a quinone. The organic solution was analyzed by gas chromatography to determine the conversion of a reactant. The identification of products was carried out by means of ^1H NMR and/or FT-IR after separation by column (Merck, silica gel 60) and/or thin-layer (Whatman, silica gel 150A, PLK5F) chromatography. The products were also identified by GC-MS.

Results and Discussion

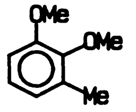
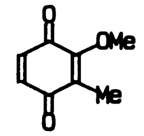
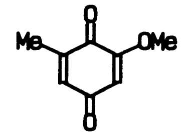
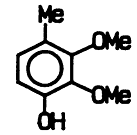
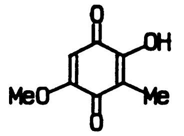
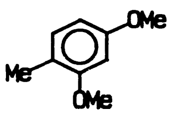
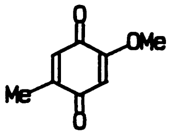
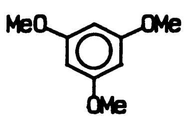
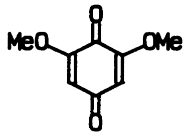
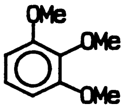
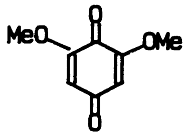
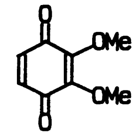
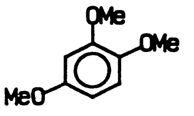
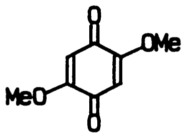
Oxidation of Methoxybenzenes. Various methoxybenzenes (methoxytoluenes, dimethoxybenzenes, dimethoxytoluenes, trimethoxybenzenes, and trimethoxytoluenes) were oxidized by H_2O_2 in HCOOH, and the results are tabulated in Table 1. Generally, *p*-benzoquinones were obtained as main products in relatively good yields, but some phenols were produced occasionally in small yields (Runs 3 and 8). When the para-position for methoxyl group is not substituted, a *p*-benzoquinone which has one less methoxyl group than the starting methoxybenzene is obtained as a main product. 3,4,5-Trimethoxyphenol was oxidized to 2,6-dimethoxy-*p*-benzoquinone under the same re-

Table 1. Oxidation of Methoxybenzenes by H_2O_2 in HCOOH

No.	Temp	Time	H_2O_2 aq.		Reactant	Conv.	Product	Yield	Sel.
	°C	h	wt%	ml		%		%	%
1	40	2	31	2		85		40	47
2	40	2	31	1		83		30	36
3	40	2	31	1		68		11	16
								6	9
								7	10
4	40	2	31	2		98		29	30
5	40	2	31	1		96		68	70
								3	3
6	40	2	31	2		100		12	12
7	40	2	31	2		100		65	65

action conditions (Run 16). Therefore, the oxidation yielding quinones probably proceeds through the corresponding phenols which are produced by the hydroxylation of benzene ring at the para-position for methoxyl group, as proposed previously.[4] If the para-position for methoxyl group is substituted (Runs 1 and 4), a corresponding *p*-benzoquinone without loss of methoxyl group is obtained. It is considered that these quinones are produced through the hydroxylation of benzene ring at the ortho-position for methoxyl group followed by the further oxidation of phenols. Under the present reaction conditions, 1,2,3-substituted benzenes gave a poor yield of quinones (Runs 6, 8, and 11). These poor yields of quinones can be explained as follows: two hydroxyl groups can be introduced very easily at the para-positions for the two methoxyl groups before the oxidation to a quinone occurs, because these positions are not crowded sterically, and the further oxidation of these hydroxylated compounds proceeds rapidly. In Run 8, 2-hydroxy-5-methoxy-3-

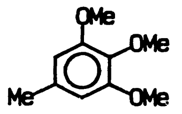
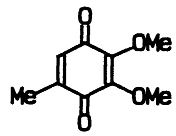
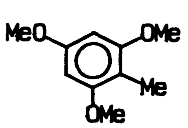
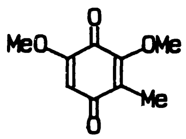
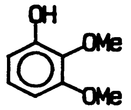
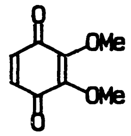
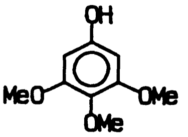
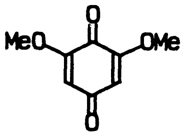
Table 1. (Continued)

No.	Temp	Time	H_2O_2 aq.		Reactant	Conv.	Product	Yield	Sel.
	°C	h	wt%	ml		%		%	%
8	40	2	31	1		63		4	6
								9	14
								5	8
								27	42
9	40	2	31	1		93		72	77
10	40	2	31	2		100		75	75
11	30	2	31	1		83		10	12
								6	7
12	40	2	31	2		100		45	45

methyl-*p*-benzoquinone was obtained in a moderate yield, which is considered to form through the oxidation of 2,3-dihydroxy-5,6-dimethoxytoluene as the intermediate. On the other hand, 1,2,4-, 1,3,4-, or 1,3,5-substituted benzenes gave a good yield of corresponding *p*-benzoquinones (Runs 5, 7, 9, 10, and 12). In these cases, it is considered that only one hydroxyl group can be introduced into benzene ring, because the para-positions for methoxyl groups are crowded, and that the oxidation yielding quinones proceeds smoothly. When the reaction was carried out in methanol or acetonitrile, no quinone was obtained. The oxidation of 3,4,5-trimethoxytoluene in acetic acid gave only a 4% yield of 2,3-dimethoxy-5-methyl-*p*-benzoquinone at a 40% conversion (cf. Run 13). The active species of this reaction system is not clear at the present stage, but the most probable candidate is performic acid which is produced in situ from the reaction with H_2O_2.

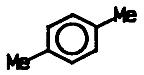
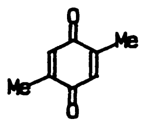
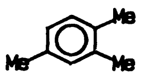
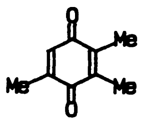
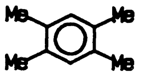
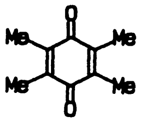
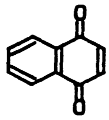
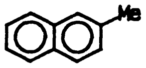
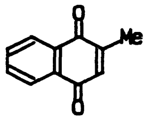
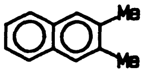
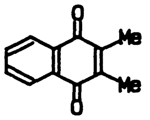
Oxidation of Methylbenzenes and Naphthalenes. Oxidation of methylbenzenes and naphthalenes by H_2O_2 in HCOOH was also examined, and the results are shown in Table 2. Methylbenzenes were oxidized to

Table 1. (Continued)

No.	Temp	Time	H_2O_2 aq.		Reactant	Conv.	Product	Yield	Sel.
	°C	h	wt%	ml		%		%	%
13	30	1	31	1		97		48	49
14	40	2	31	1		97		46	47
15	40	1	31	1		80		27	34
16	40	1	31	1		—a)		61	—a)

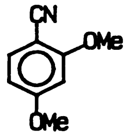
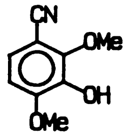
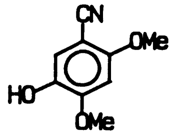
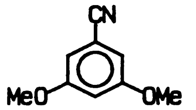
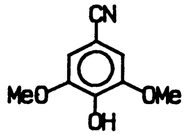
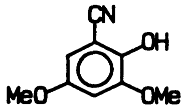
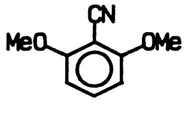
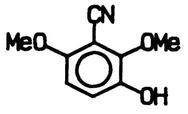
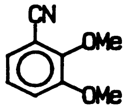
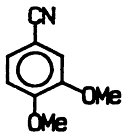
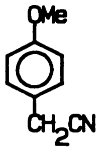
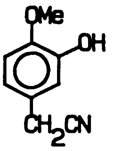
Reactant 4 mmol, HCOOH 10 ml. a) Not measured.

Table 2. Oxidation of Methylbenzenes and Naphthalenes to Quinone by H_2O_2 in HCOOH

No.	Temp	Time	H_2O_2 aq.		Reactant	Conv.	Product	Yield	Sel.
	°C	h	wt%	ml		%		%	%
1	50	6	60	2		96		19	20
2	50	4	60	1		100		16	16
3	50	5	31	2		96		19	20
4a)	40	4.5	31	2		43		12	28
5a)	40	4	31	2		86		22	26
6a)	40	2	31	2		92		52	57

Reactant 4 mmol, HCOOH 10 ml. a) HCOOH 10 ml+AcOH 10 ml.

Table 3. Oxidation of Methoxybenzonitriles to Phenols by H_2O_2 in HCOOH

No.	Temp	Time	H_2O_2 aq.		Reactant	Conv.	Product	Yield	Sel.
	°C	h	wt%	ml		%		%	%
1	40	4	31	2		59		10	17
								18	31
2	40	2	31	1		35		4	11
								10	29
3	40	2	31	2		61		39	64
4	40	2	31	2		0	—		
5	40	24	31	2		0	—		
6	40	4	31	2		17		7	41

Reactant 4 mmol, HCOOH 10 ml.

corresponding quinones, but the yields were rather poor, and higher temperature and concentration of H_2O_2 were required. Many unidentified by-products which probably formed through the oxidation of methyl groups were observed with GC-MS. The yield of quinones was not dependent on the number of methyl groups in benzenes, but increased with the number of methyl groups in naphthalenes (the solubility of naphthalenes in HCOOH is small, and so the mixed solvent of formic and acetic acid was used).

Oxidation of Benzenes Substituted with Electron-Withdrawing Groups. The effect of electron-withdrawing groups such as cyano, nitro, and chloro groups on the reaction was investigated, and Table 3 lists the results of oxidation of methoxybenzonitriles. In these cases, phenols were obtained as main products, but quinones were not. When one cyano group is introduced into benzene ring, the conversion of reactants decreased up to about 60% (e.g., compare Runs 5, 9, and 12 in Table 1 with Run 1 in Table 3). Some dimethoxybenzonitriles did not give phenols in a yield more than 1% and the conversion of benzonitriles was negligible (Runs 4 and 5). The hydroxyl group is introduced only at the positions where resonance effect of both two methoxyl groups is working (i.e., the ortho- and ortho-, or para- and ortho-position for either methoxyl group). Therefore, it is considered that cyano group reduces the reactivity of methoxybenzenes by decreasing electron density of benzene ring (one cyano group effectively cancels the reactivity enhancement originated from resonance effect of one methoxyl group), and it inhibits the further oxidation of phenols to quinones.

Nitro group also retarded the oxidation greatly and only a trace of phenols was obtained. In the case for chloro group, which is a weak electron-withdrawing substituent and shows ortho–para-orientation in electrophilic aromatic substitutions, chloroanisoles were oxidized to phenols. For example, *m*-chloroanisole was oxidized to three isomers of phenols in a 19% yield at a 35% conversion (hydroxyl group is introduced at two ortho- and one para-positions for methoxyl group at approximate ratio of 1 : 1 : 1). Accordingly, the electron-withdrawing substituents decrease the reactivity of benzene ring with H_2O_2 in HCOOH and inhibits the further oxidation of phenols to quinones.

References

1) H. Otsuka, T. Komiya, S. Fujioka, M. Goto, Y. Hiramatsu, and H. Fujimura, *Yakugaku Zasshi*, **101**, 1108 (1981).

2) S. Yamada, T. Takeshita, and J. Tanaka, *Yuki Gosei Kagaku Kyokai Shi*, **40**, 268 (1982).

3) S. Ito, K. Aihara, and M. Matsumoto, *Tetrahedron Lett.*, **24**, 5249 (1983).

4) M. Matsumoto, H. Kobayashi, and Y. Hotta, *J. Org. Chem.*, **50**, 1766 (1985).

5) S. Yamaguchi, M. Inoue, and S. Enomoto, *Bull. Chem. Soc. Jpn.*, **59**, 2881 (1986).

6) R. N. Mirrington and G. I. Feutrill, *Org. Synth.*, **53**, 90 (1973).