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Fe(III)-Catalyzed Aromatic Hydroxylation with H_2O_2 in the Presence of a Variety of Electron-Transfer Agents

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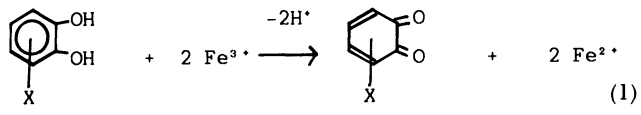
Electron-transfer agents such as *N,N,N',N'*-tetramethylphenylenediamine (TMPD), ferrocenes, and phenothiazines have been found to mediate the hydroxylation of benzene with H_2O_2 in the presence of Fe^{3+}. Of these, TMPD catalyst is the most effective to provide phenol in 80% or better yield based on added H_2O_2 under the optimized conditions. A general mechanism, involving the rate-determining reduction of Fe^{3+} to Fe^{2+} with such mediators, is suggested.

Since the initial report of Udenfriend,[1] many workers have studied the scope and mechanism of a number of non-enzymic hydroxylation systems, described by Udenfriend, Grinstead,[2] Hamilton,[3] and Ullich.[4] Richter and Waddell[5] studied the decomposition of H_2O_2 and hydroxylation of benzoic acid in the presence of catalytic Fe^{3+} and 5-methyldihydrophenazine (MPH) and have proposed that the oxidant inducing the aromatic hydroxylation is the hydroxyl radical produced in an iron-catalyzed one-electron reduction of H_2O_2. The rate was found to be expressed as $-d[H_2O_2]/dt=k[MPH]([Fe^{3+}]+\alpha)$. Recently, we have also shown that catechol-3,5-disulfonate, a substitute for catechol (CT), mediates electron transfer in the catalytic hydroxylation. Most of the phenomenon appears to be accounted for by the general features proposed by Richter and Waddell. The rate-determining step has been confirmed to be the redox reaction of Fe^{3+} with the catechol (Eq. 1), and the quinone or semiquinone thus formed is used to oxidize the 1-hydroxycyclohexadienyl radical intermediate (**8**) to phenol (Eq. 2). The catechol displays dual functions as a reductant toward Fe^{3+} and as an oxidant toward 1-hydroxycyclohexadienyl radical through shuttling between catechol and quinone.



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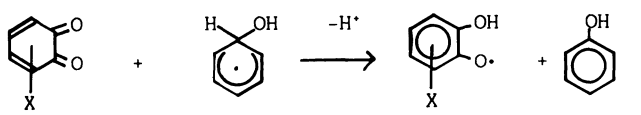


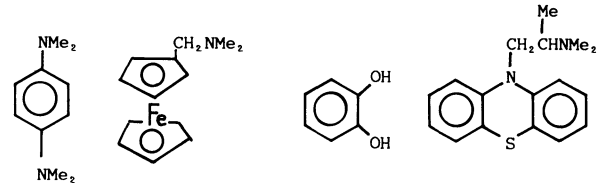
8 (2)

A set of these hydroxylating systems, referred to as a nonclassical Fenton reaction, have been suggested to commonly require catalytic electron-transfer agents (mediators) to return the oxidized Fe^{3+} to its reduced state.[5] However, only a limited number of mediators have been recognized so far; of these, the reduced 5-methylphenazinium cation has frequently been utilized in biological studies. The use of catechols has been reported by Hamilton[3] and by us.[6] We have recently reported 1,2-naphthoquinone-4-sulfonate to mediate the aromatic hydroxylation with H_2O_2 to produce phenols in 40% yields.[7]

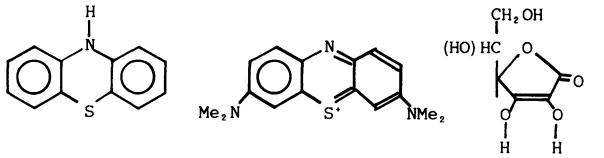
In order to fully understand these hydroxylations, we consider it of interest to extend our studies to other new mediators. In this paper we present the results of a thorough kinetic study of the mediator-dependent hydroxylations.

Experimental

Materials. TMPD (**1**), (dimethylaminomethyl)ferrocene (DAMF, **2**), catechol (CT, **3**), hydroquinone (HQ), promethazine (PMZ, **4**), phenothiazine (PTZ, **5**), Methylene Blue (MB, **6**), thianthrene, *N*-methylacridinium iodide and ascorbic acid (AsH_2, **7**) were all commercially available as special grade and used as received. 10-Methyl-9,10-dihydroacridine (MDA) and the reduced Methylene Blue were prepared by the reduction of *N*-methylacridinium iodide and Methylene Blue, respectively. Moreover, 1,3,10-trimethyl-1,5-dihydroisoalloxazine (TMDIA) were synthesized according to the method described in the literature.[8]



1 **2** **3** **4**



5 **6** **7**

Hydroxylation of Benzene. A standard hydroxylation procedure was effected as follows: Fe^{3+} (0.01 mmol, 0.2 mM; 1 M=1 mol dm^{-3}), an appropriate organic mediator (0.01 mmol, 0.2 mM), and benzene (1 ml) were added to 50 ml of H_2O adjusted with H_2SO_4 to pH 3. The air in the vessel was purged with nitrogen gas, and H_2O_2 (1 mmol, 2 mM) was

then added all at once. After mechanical shaking for 2.5 h, the solution was thoroughly extracted with ether and then the amount of phenol in the ether was determined with HPLC using anisole as an internal standard at 270 nm. The product yields are all based on an added amount of H_2O_2. When the yield was less than 5%, the reaction was examined again by increasing the amounts of Fe^{3+} and/or the mediator each ten-fold to obtain convenient rates. The results thus obtained are collected in Tables 1—5 along with Fig. 1.

Kinetics of the Reaction between Organic Mediator and Fe^{3+}. For the very fast redox reaction, the reaction rate was determined with a stopped flow apparatus with two mixing chambers (Union Giken Model RA 401) by monitoring the appearance of the absorption of the final products (radical cations), namely, at 610 nm for TMPD and at 615 nm for DAMF.[9] For PMZ having a relatively slow rate, a Hitachi 220 spectrophotometer equipped with temperature-controlled cell-holders was used to monitor the appearance of an increasing absorption at 513 nm. The initial concentrations of TMPD and DAMF were 5×10^{-5} and 1.25×10^{-4} M, respectively. The concentrations of Fe^{3+}(as $Fe_2(SO_4)_3$) were changed in the range 2.5—25×10^{-4} M, depending on mediators.

Isomer Distribution. The hydroxylation procedure was as usual except for employing methyl phenylacetate instead of benzene; conditions: TMPD, 0.01 mmol; Fe^{3+}, 0.01 mmol; H_2O_2, 1 mmol; methyl phenylacetate, 1 mmol in 50 ml of H_2O (pH 3) at 25 °C. The products were analyzed by using HPLC (Nihon Bunko Uniflow-221) with Packed Column SS-05 eluted with hexane/methyl acetate/methanol 9:1:1 at 290 nm. *o*-Methoxyphenol was an internal standard.

Results

It is clear from Table 1 that the optimum pH is about 3, just similar to that for the catechol-catalyzed hydroxylation reported previously by Hamilton.[3]

Table 2 shows that thianthrene, 10-methyl-9,10-dihydroacridine (MDA), ascorbic acid (AsH_2), and a pteridine are all ineffective even at a high level (2 mM) of catalyst concentrations. On the other hand, TMPD, DAMF, and CT work well even at a low level (0.2 mM) of these concentrations. The reaction solutions are

Table 1. . pH Effect on Phenol Yield (25 °C, 2.5 h, N_2)[a]

Mediator	pH	Yield/%
TMPD	1	9.7
	3	41.7(39.8)[b]
	5	2.3(1.9)[c]
DAMF	1	8.0
	3	38.8
	5	13.5

a) Conditions: mediator, 0.01 mmol; Fe^{3+}, 0.01 mmol; benzene, 1 ml; H_2O_2, 1 mmol; 50 ml H_2O. The solution was adjusted to a desired pH with H_2SO_4 or NaOH. b) 0.1 M acetate buffer, pH 3.19. c) 0.1 M acetate buffer, pH 5.0.

Table 2. Hydroxylation of Benzene with Fe^{3+}/Mediator/H_2O_2 Systems[a]

Run	Mediator/mmol		Fe^{3+}/mmol	Phenol yield/%[b]
1	None	—	0.1	1.9
2	TMPD	0.01	0.01	41.7
3	TMPD	0.01	0.001	12.0
4	DAMF	0.01	0.01	38.8
5	Ferrocene	0.01	0.01	40.9
6	CT	0.01	0.01	40.5
7	HQ	0.01	0.01	3.4
8	HQ	0.1	0.1	20.9
9	TMDIA	0.01	0.01	3.5
10	TMDIA	0.01	0.1	4.8
11	TMDIA	0.1	0.01	32.8
12	TMDIA	0.1	0.1	39.1
13	PMZ	0.01	0.01	1.8
14	PMZ	0.01	0.1	3.2
15	PMZ	0.1	0.01	1.5
16	PMZ	0.1	0.1	33.3
17	PTZ	0.01	0.01	5.3
18	PTZ	0.1	0.1	40.6
19	MB	0.01	0.01	3.2
20	MB	0.1	0.1	43.3
21	12N4S[d]	0.01	0.01	33.1[7]
22	Thianthrene	0.1	0.1	0.9
23	MDA	0.1	0.1	1.1
24	AsH_2	0.1	0.1	2.3
25	A18DS[e]	0.1	0.1	3.6[7]
26	Pteridine	0.1	0.1	6.0[c]
27	Cobaltcene	0.1	0.1	1.8

a) Unless otherwise noted, 2.5 h; 25 °C; benzene, 1 ml; H_2O_2, 1 mmol; 50 ml H_2O under N_2. b) The yield was based on H_2O_2 added. c) 2-Amino-4-hydroxy-6,7-dimethyl-5,6,7,8-tetrahydropteridine. d) 1,2-Naphthoquinone-4-sulfonate. e) Anthraquinone-1,8-disulfonate.

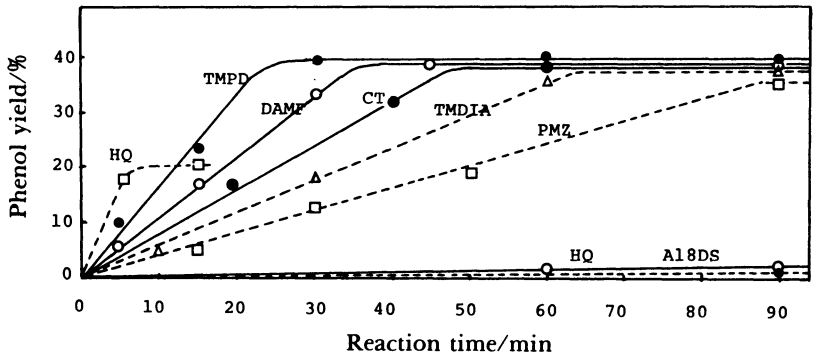


Fig. 1. Time course of hydroxylation with various mediators.
(——): Fe^{3+} 0.01 mmol; mediator 0.01 mmol. (---): Fe^{3+} 0.1 mmol; mediator 0.1 mmol. For reaction conditions, see text. Reaction conditions, see text.

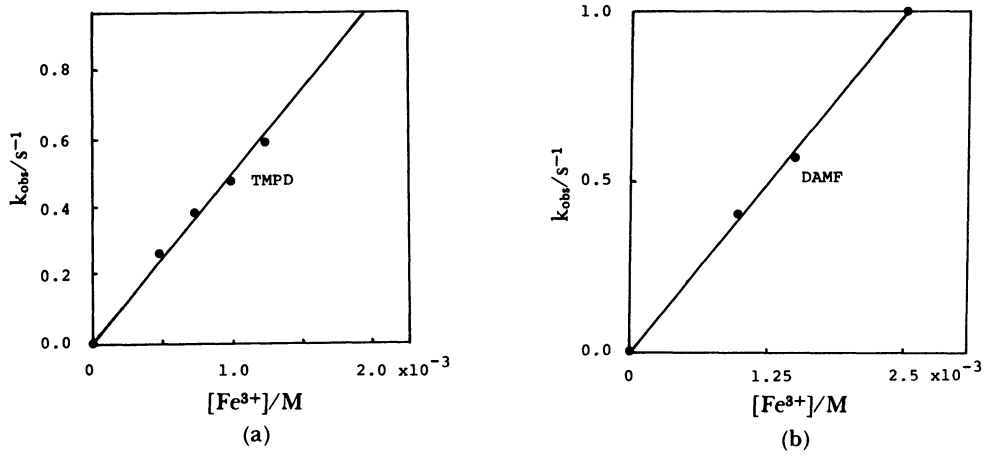


Fig. 2. Effect of concentration of Fe^{3+} on the redox rate. For reaction conditions, see text.

very clean and the formation of neither appreciable amount of by-products such as biphenyl and hydroquinone (<1%) nor dark deposit was observed. These mediators are at least an order of magnitude more active than TMDIA, PMZ, and PTZ. Figure 1 illustrates the profiles of the time courses of the reactions. Thus, the mediator dependency of the hydroxylation rate is obvious. The rate follows the order: TMPD>DAMF>CT>HQ>TMDIA>PMZ=PTZ. The phenol yields are found to increase linearly with reaction time and reach a limiting value irrespective of changing mediators. This linearity indicates that H_2O_2 is not involved in the rate-determining step of the reaction.

The highest reactivity of TMPD seems to be due to the fast redox reaction between Fe^{3+} and TMPD giving rise to Fe^{2+} and the TMPD radical cation. In order to ascertain this speculation, the kinetic experiments on the reaction of Fe^{3+} with TMPD and some other mediators was done under pseudo-first-order conditions in the presence of a 10-fold excess of Fe^{3+} in unbuffered aqueous solution of pH 2.5 at 25 °C by means of a stopped flow apparatus. In every case examined, the reaction is first-order with respect to each reactant and obeys strictly bimolecular kinetics; only representative data are shown in Fig. 2 and the second-order rate constants are given in Table 3. The rate is obviously mediator-dependent and follows the order: TMPD>DAMF>CT>HQ>PMZ. With regard to these effective mediators, this dependency clearly parallels the rate order for the hydroxylation, unambiguously indicating that the reduction of Fe^{3+} to Fe^{2+} takes place in the rate-determining step in these

Table 3. Second-Order Rate Constants for Oxidation of Some Mediators with Fe^{3+} (pH 2.5, 25 °C))

Mediator	$k_2/M^{-1}\,s^{-1}$
TMPD	492
DAMF	392
CT	60
HQ	27
PMZ	0.11

Table 4. Effect of Chelating Agents on Phenol Yield in the Hydroxylation with TMPD/H_2O_2 System (pH 3, 25 °C)[a] without Added Fe^{3+}[b]

Additive/mmol		Phenol yield/%
None	—	7.4
2,2′-Bipyridine	0.05	0.0
1,10-Phenanthroline	0.05	0.0
EDTA	0.05	0.0
Pyridine	0.05	5.8
Quinoline	0.05	3.2
8-Quinolinol	0.05	4.9

a) TMPD, 0.1 mmol; H_2O_2, 1 mmol; 50 ml H_2O. b) The reagents employed contain adventitious iron ions as trace contaminants.

Table 5. *o*-, *m*-, and *p*-Isomeric Distributions in Phenolic Products from Methyl Phenylacetate

Mediator	Total phenol yield/%	*o*	*m*	*p*
		Yield/mol%		
TMPD[a]	27.9	46	32	22
DAMF[a]	35.3	46	30	24
CT[a]	9.4	47	30	23
Fenton[b]	4.9	53	28	19
CT[c]	24.6	49	28	24
Fenton[c]	4.5	47	30	23

Unless otherwise noted, the reaction conditions were the same as the standard reaction. H_2O_2, 1 mmol; H_2O, 50 ml. a) Mediator, 0.01 mmol; Fe^{3+}, 0.01 mmol. b) Fe^{2+}, Cu^{2+}, 1 mmol each. c) Phenylacetic acid as the substrate.

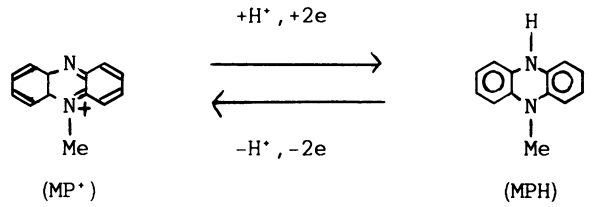
hydroxylation reactions.

Meanwhile, addition of 1,10-phenanthroline, 2,2′-bipyridine, and EDTA, typical metal-chelating agents, in an excess over Fe^{3+} completely inhibited the progress of both the redox and the hydroxylation reactions, but pyridine and quinoline only slightly did it (Table 4). The implication is that the strong complexation of Fe^{3+} with, for example, EDTA leads to substantial lowering of the reduction potential of ferric ion from +0.7 to +0.17 (pH 4),[10] so that the redox reaction in question might not occur. Actually, in the presence of EDTA, no consumption of H_2O_2 was observed. The details will be discussed later.

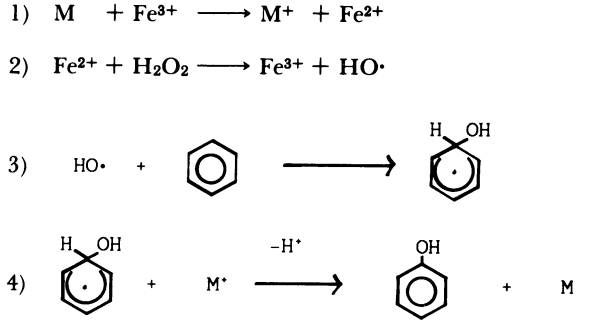
In order to further elucidate reaction mechanisms whether OH radicals are formed, an examination of isomer distributions in the product phenols was carried out. In Table 5 are compared the *o*-, *m*-, and *p*-isomer distibutions for the present hydroxylating systems with that for the Fenton system. Methyl phenylacetate was the substrate. These *o*-, *m*-, and *p*-distributions are roughly the same for all mediators although far from a statistically random distribution of 2:2:1, supporting the occurrence of the hydroxyl radical as the reactive oxidant.

Discussion

The kinetic and yield data available could be accounted for by the essential steps 1)—4), as illustrated in Scheme 1, which combine to form a catalytic cycle; 1) the rate-determining reaction between Fe^{3+} and a reduced mediator giving Fe^{2+} and the corresponding oxidized mediator. 2) The production of an OH radical by the reaction of H_2O_2 with Fe^{2+}, followed by the subsequent phenol-forming steps 3) and 4) which include the 1-hydroxycyclohexadienyl radical as the key intermediate. Since TMPD and DAMF have no labile proton, Scheme 1, unlike the reaction mechanism proposed by Richter and Waddell, involves no protonation and deprotonation events accompanying the redox reaction; for example,



Scheme 1.



(M denotes an organic mediator in the reduced state.)

As can be seen from Table 2, MDA and AsH_2 are catalytically inactive. The two-electron redox potentials of MDA^{2+}/MDA (0 V) and dAs/AsH_2 (+0.17 V at pH 4; +0.06 V at pH 7)[10,11] are negative enough to reduce Fe^{3+}; nevertheless, those potentials seem to be too low to oxidize the 1-hydroxycyclohexadienyl radical to phenol. As for MDA, therefore, the one-electron oxidation by MDA^{2+} of the 1-hydroxylcyclohexadienyl redical (step 4) seems to be endothermic. The same argument can be given for catalytically inactive anthraquinonesulfonates[7] bearing a relatively low potential ($E°<-0.1$ V).[10,12] However, there is another explanation for the inactivity of ascorbic acid; dehydroascorbic acid (dAs) exists in hydrated form as the 2,3-bis-(gem-diol) in aqueous solution, which has no ability to oxidize the 1-hydroxycyclohexadienyl radical.

PMZ has a rather low activity, because it has a higher one electron-oxidation potential ($E°$=+0.86 V at pH 7)[13] than Fe^{3+}/Fe^{2+} couple ($E°$=+0.771 V; +0.74 at pH 3); hence, the reaction between Fe^{3+} and PMZ (step 1) is slightly endothermic. The lack of catalytic activity of thianthrene is due probably to the same reason.

Meanwhile, an organic mediator which possesses a redox potential somewhere between the $E°$ values of the Fe^{3+}/Fe^{2+} and 1-hydroxycyclohexadienyl radical/phenol couples, particularly, in the favorable range of about +0.2 and about +0.6 V, is quite effective. TMPD (+0.27 V), DAMF (+0.44 V), CT(+0.55 V), and HQ (+0.46 V)[13] meet well this requirement. These reactions follow the same mechanistic pattern. In addition, the oxidation potential of the 1-hydroxycyclohexadienyl radical is roughly estimated to lie somewhere between +0.1 and −0.1 V. Electrochemical potentials of various redox pairs are summarized in Fig. 3.

The effect of metal-chelating agents is quite interesting. The hydroxylations were inhibited by the addition of EDTA and 1,10-phenanthroline (Table 4) and no consumption of H_2O_2 was observed in both cases. However, the mechanistic features of the inhibition appear to be different with each chelating agent, because the redox potentials of iron-EDTA and iron-phenanthroline differ much: Since a redox potential of the iron-EDTA complex is far low compared to that of the standard Fe^{3+}/Fe^{2+} couple, the complexation with EDTA stabilizes the Fe(III) rather than Fe(II) state and thus would stop the progress of the Fe(II) formation (step 1). On the contrary, 1,10-phenanthroline complex (+1.03 V) stabilizes the Fe(II) rather than Fe(III) state to inhibit the generation of the OH radical (step 2). The hydroxylation in the presence of metal-chelating agents has been investigated by many workers.[14] Their roles have received much attention, but has not yet been fully understood and further studies will be needed.

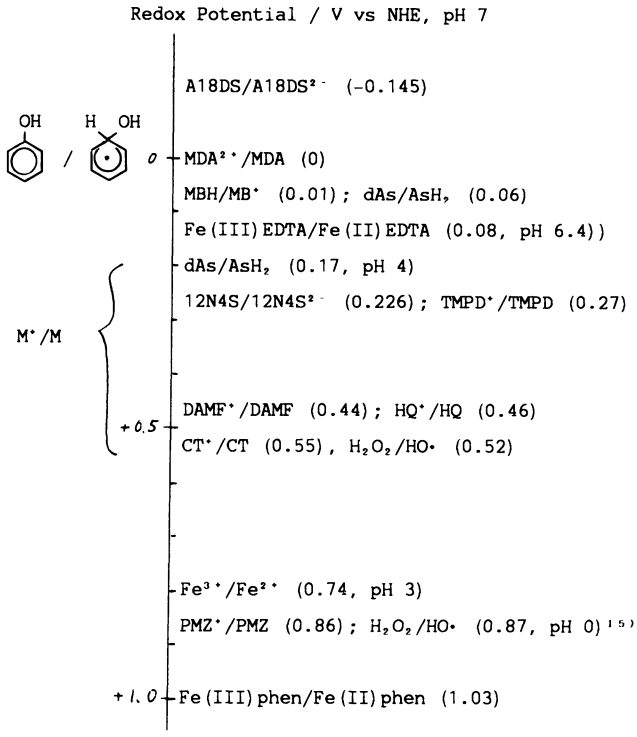


Fig. 3. Redox potentials (Volt vs. NHE, pH 7).

Table 6. Effect of Amounts of Benzene and H_2O_2 on Phenol Yield with $Fe^{3+}/TMPD/H_2O_2$

Benzene/ml	H_2O_2/mmol	Phenol yield/%
1	1	41.7
5	1	49.7
10	1	50.4
20	1	48.8
5	0.5	64.4
5	0.25	70.6
5	0.125	80.9

Reaction conditions: TMPD, 0.01 mmol; Fe^{3+}, 0.01 mmol; pH 3, 25 °C.

$$\underset{E°(V)\ 1.03}{\text{Fe(II)phen}} + H_2O_2 \xrightarrow{H^+,\ -H_2O} \underset{0.87}{\text{Fe(III)phen}} + HO·$$

Finally, it is worth mentioning that, under the standard conditions, as Fig. 1 shows, the phenol production reaches about 40% regardless of used mediators. Although we can not offer a conclusive explanation for this observation, it should be noted, however, that the final phenol yield is substantially dependent on the initial concentration of added H_2O_2. Actually, as inspection of the data of Table 6 reveals, the TMPD-catalyzed reaction affords phenol in more than 80% yields, when, in order to maximize the conversion of H_2O_2 to phenol by minimizing further oxidation of product phenol and side reactions of H_2O_2, a five-fold excess of benzene and an eight-fold decreased amount of H_2O_2 were employed. Obviously, the presence of too much H_2O_2 is the major cause to decrease the phenol yield. Perhaps, a reaction shown below effectively competes with Reaction 3. It is well-known that the hydroperoxy radical will not participate in the hydroxylation of aromatic hydrocarbons.

$$H_2O_2 + HO· \longrightarrow HOO· + H_2O$$

Use of less Fe^{3+} improves the yield but only slightly. To our knowledge, more than 80% yield is the highest yet attained in the hydroxylations of unactivated aromatic hydrocarbons by hydroxyl radicals.

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