Aromatic Hydroxylation with an Iron(III)-Catechol-H_2O_2 System. Mechanistic Implication of the Role of Catechol

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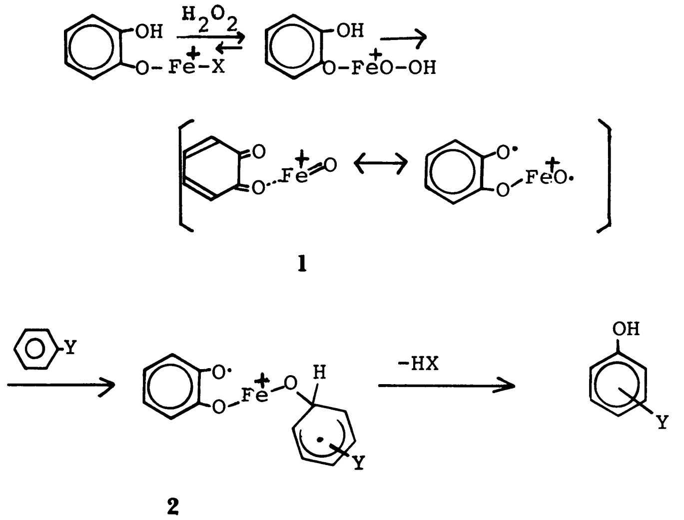
The role of catechol in benzene hydroxylation with Fe^{3+}/catechol/H_2O_2 system, the so-called Hamilton system, has been mechanistically investigated by using tiron as a substitute for pyrocatechol. The yield of phenol progresses linearly with reaction time. The phenol yield is dependent on the mole ratio of Fe^{3+} relative to tiron, and the ratio of more than unity is particularly important for the effective functioning of the catalyst system. The *o*-, *m*-, and *p*-product isomer distributions for a few aromatic hydrocarbons are nearly identical with those of the Fenton reaction. These and the separate experimental results are consistent with the mechanism involving the rate-limiting redox reaction between tiron and Fe^{3+} and then the follow-up radical chain sequence as in the Fenton reaction.

Since the first report of Udenfriend,[1)] an enormous number of model peroxidase systems such as the Udenfriend[2)] and Hamilton systems[3)] have received considerable attention thus far. However, the reaction mechanisms for the majority of those systems are the least understood and quite speculative. This paper describes the results of detailed reexamination of mechanistic aspects of the aromatic hydroxylation by the Hamilton system consisting of Fe^{3+}, a catechol, and H_2O_2. The hydroxylation of aromatic hydrocarbons by this system has been studied in details by Hamilton.[3)] The rate of the reaction was found to be first order in iron(III), H_2O_2, and catechol concentrations at a low concentration of catechol (2×10^{-4} M; 1 M=1 mol dm^{-3}). At higher concentrations of catechol, however, there was observed a decrease in rate, which may be due to the function of higher complexes of catechol with Fe^{3+} that is less reactive than the 1:1 complex. It has been postulated by Hamilton[4a)] and has hitherto been cited in the literature and books[4b)] that the reaction involves an *o*-quinone–iron oxide complex (**1**), which serves as an active oxidant to form a reactive intermediate **2**.



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Recently, Richter and Waddell[5)] have reported the evidence of a radical chain mechanism for the hydroxylation of a substrate, benzoic acid, with H_2O_2 in the presence of catalytic iron ion and 5-methyldihydrophenazine (H_2O_2/Fe^{3+}/MPH system) and have proposed the mechanism essentially resembling the classical Fenton reaction except that the new system requires the organic mediator (5-methyldihydrophenazine) to get the oxidized catalyst metal back to its original state. Thus, they classified this new system as the nonclassical Fenton system together with the Hamilton system. However, the mechanism for the Hamilton hydroxylation system is not yet perfectly understood, since no convincing evidence has been given; in particular, the functional roles of a catechol have not been exactly determined. In an attempt to find a mechanistic version of this reaction, we have replaced ordinarily used catechol by disodium catechol-3,5-disulfonate (tiron) which seems better suited for the mechanistic study of the Hamilton system with twofold reasons. (1) It is a bidentate ligand to form a deep blue Fe^{3+} complex, relatively far stable compared to the complex of catechol in a reaction pH range 2.0—3.5 and (2) it shows remarkable resistance to oxidative destruction during the reaction due to its bearing the aromatic ring highly substituted with two strongly electronegative sulfonato groups.

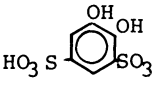
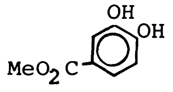
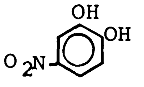
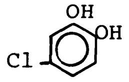
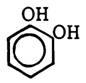
Experimental

Materials: Substituted catechols were commercially available as special grade and used without further purification.

Hydroxylation of Benzene: The hydroxylation were generally perfomed at ambident temperature in an aqueous solution of pH 3 adjusted with H_2SO_4 under nitrogen. A standard reaction was carried out in a two-phase system of H_2O (50 ml) and benzene (1 ml), containing $Fe_2(SO_4)_3$ (0.05 mmol) and tiron (0.1 mmol). Benzene was used in excess to minimize the further oxidation of product phenol. H_2O_2 (0.5 M, 2 ml, 1 mmol) was then added to the solution all at once. The mixing was performed with a mechanical shaker for 2.5 h. Analysis of products was done according to those described in the previous paper.[6)] In any case, phenol was obtained as the major product. No appreciable amount of by-products such as biphenyl, catechol, and quinone (if any, less than 1%) was detected. All the phenol yields were based on H_2O_2 added. Under the standard conditions the phenol yield was 38%.

Kinetics: The rate of decomposition of a Fe^{3+}-catechol complex in water was determined as follows: The equal volumes of the stock solutions of Fe^{3+} and a catechol (8×10^{-4} M each) was pipetted out and placed into a UV cell and the disappearance of the blue color due to the complex (λ_{max} shown in Table 1) was monitored with a Hitachi 220 spectrometer. The k_{obs} thus obtained was also listed in the third column of Table 1.

Table 1. Absorption Maximum and Redox Reaction Rate for Catecholate-Fe^{3+} Complexes (pH 3.0, 25 °C)

Catechol	λ_{max}/nm	k/min^{-1}
	660(ε=1780)	0.018
	660	0.075
	650	0.14
	720	9.1
	720	too fast

Conditions: [Fe^{3+}], 4×10^{-4} M; [catechol], 4×10^{-4} M.

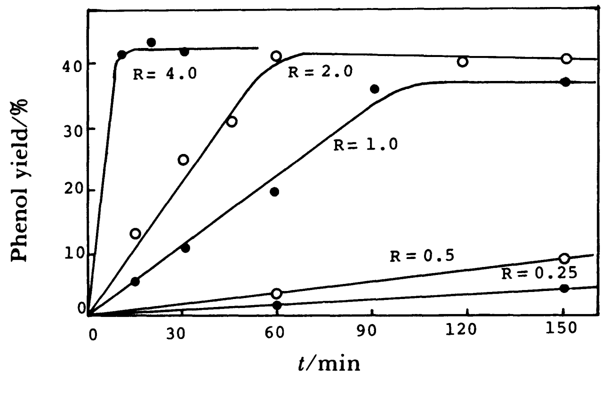


Fig. 1. Yield vs. time profile at varying [Fe^{3+}]/[tiron] ratio. R=[Fe^{3+}]/[tiron]. [Fe^{3+}]=2×10^{-3} M.

Results and Discussion

Time Course of Hydroxylation: First, the time courses for the hydroxylation were determined at varying mole ratios of Fe^{3+} to tiron, keeping the Fe^{3+} concentration fixed. Figure 1 shows the results. The yield of phenol increases linearly with time, indicating zero-order dependence of the rate on H_2O_2 concentration. Thus, H_2O_2 is not involved in the rate-limiting step.

Furthermore, a comparison of the rates at different mole ratios of Fe^{3+}/tiron, keeping the concentration of the Fe^{3+} constant, shows that the reaction at the ratio of 0.5 runs slower than that at 2.0, in spite of formation of a two-fold amount of the complex in the former; namely, the rate is independent of the quantities of the complex formed in solution, clearly demonstrating that, as opposed to the suggestion of Hamilton,[3] the Fe^{3+}-catechol complex itself can not be an active catalyst.

Effect of Fe^{3+}/Tiron Ratio on Phenol Yield. The effect of altering ratios of Fe^{3+}/tiron on the phenol yield was examined. The results are illustrated in Fig. 2. A plot of the phenol yield versus the mole ratio produces the characteristic sigmoidal profile; the phenol yield is quite low (<10%) in the ratio range below unity. This is not a result of formation of a lot of by-products but a result of no reaction, since the consumption of H_2O_2 was not observed.

The phenol yield begins to steeply rise as the ratio being close to unity, and then finally approaches a limiting value 40% when a slight excess of Fe^{3+} relative to tiron is added, suggesting that free Fe^{3+} is required for the activation of the catalyst system. As mentioned in the introductory section, tiron binds with Fe^{3+} to form only a 1:1 stable complex with an equilibrium constant $K \fallingdotseq 10^4$ M^{-1} rather than highly coordinated Fe^{3+} complexes even at a large excess of tiron over

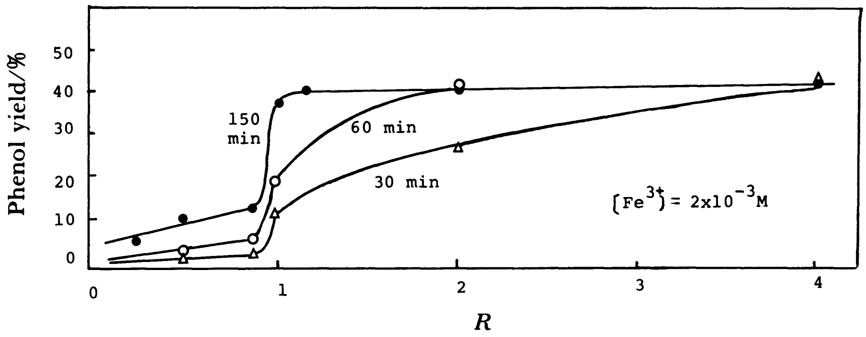


Fig. 2. Plots of phenol yield vs. [Fe^{3+}]/[tiron]. Reaction time: 30 (△); 60 (○); 150 min (●).

Fe^{3+} concentrations. Therefore, addition of an slight excess (less than 1.5 fold) of tiron brings about the complete lack of free Fe^{3+} in solution and would thus remarkably depress the phenol yield.

Kinetics of Tiron Oxidation with Fe^{3+}: In order to confirm further the above conclusion, the oxidation of tiron with iron(III) was kinetically examined at an Fe^{3+}/tiron mole ratio (R) of 1:1 by monitoring the disappearance of the absorption band of the tiron–Fe^{3+} complexes, holding the tiron concentration constant. The rate constants thus obtained are plotted as a function of R. Figure 3 shows those results. The rate is dependent on the ratio in the same characteristic fashion as observed in the benzene hydroxylation. That is, the reaction is extremely slow in the ratio range less than unity, while very fast in the range larger than unity. In the latter range, in particular, the rate increases linearly with increasing Fe^{3+} concentrations, explicitly demonstrating that an excess of Fe^{3+} over tiron is essential for the tiron oxidation as well as for the hydroxylation, and hence these two reactions commonly involve the oxidation of tiron by uncomplexed Fe^{3+} leading to a semiquinone and then to a quinone.

In Table 1 are listed the λ_{max} values of the complexes due to the catecholate-to-Fe(III) charge-transfer band along with the rate constants for disappearance of their absorption bands (650—720 nm depending on catechols) at a 1:1 Fe^{3+}/catechol ratio.[7] The substitution of electron-donating groups on the catechol ring resulted in a red shift of the CT band and acceleration of the rate, as would be generally expected for oxidation reactions, while the electron-withdrawing ones decelerated the rates. Of these catechols studied here, tiron was the most stable with regard to its oxidation reaction.

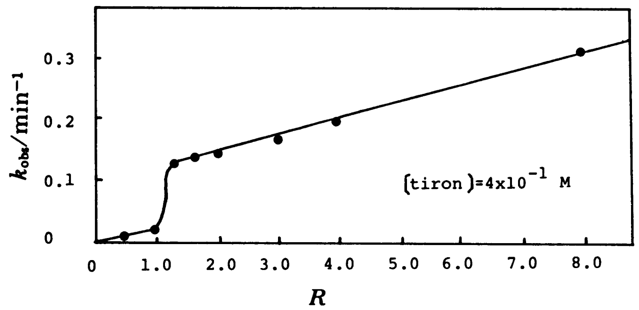


Fig. 3. Plot of the rate of the complex decomposition vs. [Fe^{3+}]/[tiron]. Varying concentrations of Fe^{3+} (0—3.2×10^{-3} M) in unbuffered solution (pH 3) changed the reaction pH from 3.0 to 2.6. In a separate experiment, however, such a pH change had no significant effect on the rate. Therefore, the solution was not buffered here. Rate/min^{-1} (pH): 0.14 (3.05); 0.151 (3.00); 0.148 (2.91); 0.150 (2.75); 0.145 (2.5); 0.104 (1.9); 0.060 (1.7).

Table 2. Effect of the Common Salt on the Redox Rate. Decomposition of the Tiron–Fe^{3+} Complex in the Presence of the Foreign Fe^{2+} Ion (25 °C)

Fe^{2+}/M	k_{obs}/min^{-1}
0	0.165
0.5	0.10
1.0	0.056
2.0	0.018
4.0	0.005

[tiron], 4×10^{-4} M; [Fe^{3+}], 16×10^{-4} M.

Table 2 provides further evidence for the mechanism of tiron oxidation, i.e., the preequilibrium formation of the semiquinone, followed by the rate-determining semiquinone oxidation. According to this mechanism, an increase of Fe^{2+} in the reaction solution would move the equilibrium to the left, which should be attributable to the common ion effect of Fe^{2+} ion on the catechol–semiquinone preequilibrium. In fact, addition of foreign Fe^{2+} ion to the reaction system resulted in marked rate drop.

Baxendale et al.[8] undertook the kinetic study of the reaction between Fe^{3+} and catechol in detail and observed the deviation (Eq. 1) from the second-order kinetics attributable to the reverse reaction of Fe^{2+} with an intermediate. A mechanism (Scheme 1) involving a preequilibrium formation of the semiquinone intermediate was proposed there.

Scheme 1.

$$Fe^{3+} + H_2Q \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Fe^{2+} + HQ + H^+$$

$$Fe^{3+} + HQ \xrightarrow{k_3} Fe^{2+} + Q + H^+$$

$$-d[H_2Q]/dt = k_1k_3[Fe^{3+}]^2[H_2Q]/(k_2[Fe^{2+}] + k_1[Fe^{3+}]) \tag{1}$$

***o*-, *m*-, and *p*-Products Distribution.** In order to understand the nature of hydroxylating species, the *o*-, *m*-, and *p*-isomer distributions in phenols derived from a few aromatics were examined under various conditions. The results are summarized in Table 3. The hydroxylating species generated from the present system reacts with phenylacetic acid and anisole to afford *o*-, *m*-, and *p*-hydroxyphenylacetic acids and anisoles with isomeric distributions of 49:29:22% and 82:8:10%, respectively.

Meanwhile, use of the modified Fenton reagent,[9] consisting of H_2O_2 and a stoichiometric amount of Fe^{2+} in the presence of Cu^{2+}, afforded 47:30:23 and 87:3:10%, respectively. The Fenton reagent has been established to produce hydroxyl radicals as the reactive hydroxylating species.[9] Therefore, a close parallelism between tiron and Fenton's systems in the patterns of isomeric distributions strongly supports that OH radicals are reactive species common to these two hydroxylations.

Mechanism. The kinetic and yield data presently available are accounted for by the following reaction sequence in which elemental steps 1—5 combine to form an overall catalytic cycle. (Scheme 2)

The similarity in shape of the curvatures obtained on the hydroxylation (Fig. 2) and the redox reaction (Fig. 3) clearly indicates that both reactions take place through the same sequence up to the rate-determining step of the reaction. As Fig. 3 shows, the pseudo-first-order rate constant, k_{obs}, increases linearly with increasing [Fe^{3+}] in the range of the [Fe^{3+}]/[tiron] ratio>1, supporting that there is the reversible breakdown of the Fe^{3+}-tiron complex, yielding one semiquinone radical and one Fe^{2+} (1b), then followed by rate-determining attack of a second Fe^{3+} on the semiquinone radical, giving an *o*-quinone and Fe^{2+} (1c). The reversibility of step 1b is substantiated further by the observation of the common ion effect of foreign Fe^{2+} ions on the rate of the step 1b. The step 1c must be more rapid than the disproportionation of the semiquinone radical to the corresponding quinone and catechol (5), because the breakdown of the complex needs a second Fe^{3+}.

Table 3. Isomer Distributions in Phenolic Products from Phenylacetic Acid and Anisole

Catechol	Total yield %	*o*	*m* /%	*p*
Anisole				
(a) Tiron	9.4	82	8	10
(b) Catechol	18.4	67	3	30
(c) 4-Nitrocatechol	6.0	88	2	10
(d) Fenton	5.0	87	3	10
Phenylacetic acid				
(a) Tiron	44.6	49	29	22
(b) Catechol	24.6	49	29	24
(d) Fenton	4.5	47	30	23

Conditions: (a) Fe^{3+}(0.1 mmol)/tiron(0.1 mmol)/H_2O_2 (1.0 mmol)/phenylacetic acid(1.0 mmol)/50 ml H_2O (pH 3). (b,c) Fe^{3+}(0.1 mmol)/catechol(0.1 mmol)/H_2O_2 (1.0 mmol)/phenylacetic acid(1.0 mmol)/50 ml H_2O. (d) Fe^{2+}(1.0 mmol)/H_2O_2(1.0 mmol)/Cu^{2+}(1.0 mmol).

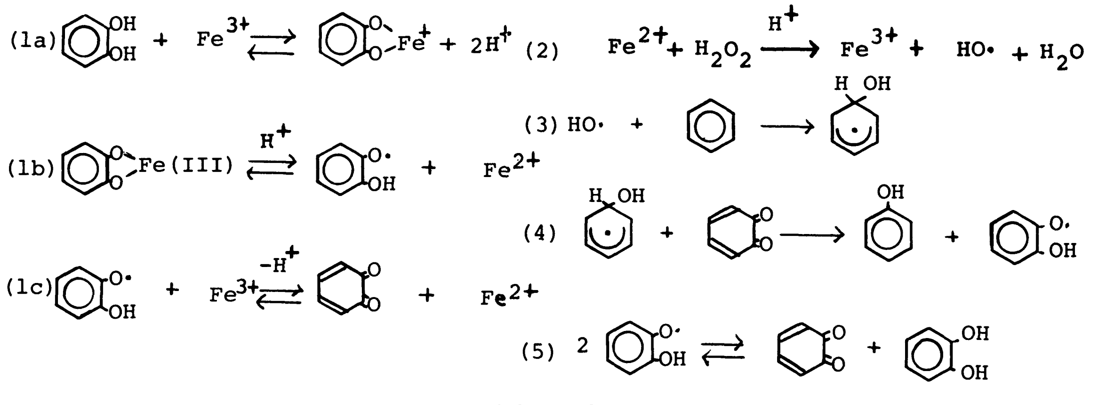
Fe^{2+} so formed triggers the Fenton reaction to yield an OH radical, immediately followed by steps 3 and 4, in which the OH radical attacks an aromatic ring giving rise to 1-hydroxycyclohexadienyl radical at a rate of almost diffusion control (10^{10} M^{-1} s^{-1}) and then the hexadienyl thus formed is oxidized by a quinone to phenol. The finding that quinones are good oxidants for such carbon radicals was reported by Steenken and Raghavan;[10] they estimated the rates of electron transfer between 1-methoxy-2-, 3-, and 4-hydroxycyclohexadienyl radical and *p*-benzoquinone to be 1.2×10^9, $<8\times10^5$, 4.4×10^9 M^{-1} s^{-1}, respectively. Thus, quinones are reduced back to the semiquinones or further to hydroquinones before the cyclohexadienyl radicals bimolecularly collapse to biphenyl, a coupling product. Actually, in sharp contrast to the original Fenton system, the present system gave no appreciable amount of biphenyl to be detected by HPLC analysis. The lifetime of an intermediate carbocation thus produced is $<1\times10^{-6}$ s[10] and hence phenol may be formed synchronously with the reduction of *p*-benzoquinone.

Meanwhile, the data of Table 4 shows that the isomer distribution is not appreciably affected by the presence

Table 4. Effect of Oxygen on the Phenol Yield and Isomer Distribution (pH 3, 2.5 h)

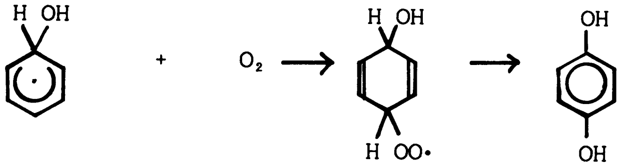
Conditions under	Benzene[a] Yield/%	Methyl phenylacetate[b] Total yield/%	*o*	*m* yield/%	*p*
N_2	36.2	36.2	46	29	25
Air	34.7	34.0	50	26	24
O_2	11.9	11.1	49	27	24

a) Tiron, 0.1 mmol; Fe^{3+}, 0.1 mmol; H_2O_2, 1.0 mmol; benzene, 2 ml; H_2O, 50 ml. b) Conditions were the same as a), except the substrate (1 mmol of methyl phenylacetate).



Scheme 2.

or absence of air. Under such a relatively low oxygen pressure the hexadienyl radical is more quickly oxidized to phenol than trapped by molecular oxygen. On the contrary, replacing air for the atmospheric pressure of oxygen considerably depressed the phenol yield more than 20%. This yield depression indicates the occurring of a concomitant irreversible trapping by molecular oxygen of the hexadienyl radical giving an intermediate 4-hydroxy-2,3-cyclohexadienylperoxyl radical, which would terminate the radical chain cycle; formation of such an intermediate in metal-catalyzed aromatic hydroxylation under an oxygen atmosphere was reported elsewhere.[11]



Thus, the overall mechanistic picture for the tiron system and related systems are basically similar to that for the MPH/Fe^{3+}/H_2O_2 system reported by Richter and Waddell. A catechol displays dual functions as a reductant toward Fe^{3+} and as an oxidant toward a 1-hydroxycyclohexadienyl radical through shuttling between catechol and quinone.

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