Fenton's Reagent Revisited

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Received August 30, 1974

Just 80 years ago H. J. H. Fenton reported[1] that ferrous ion strongly promotes the oxidation of malic acid by hydrogen peroxide. Subsequent work has shown that the combination of H_2O_2 and a ferrous salt, "Fenton's reagent," is an effective oxidant of a wide variety of organic substrates.

Forty years later, Haber and Weiss[2] proposed that the hydroxyl radical is the actual oxidant in such systems. In the 1940's Merz and Waters, in a series of elegant papers,[3] showed how, using the Haber–Weiss scheme, stoichiometric relations could be employed to determine the relative susceptibilities of various substrates to hydroxyl radical attack and the fate of subsequent radical intermediates.

Since then the importance and ubiquity of hydroxyl radicals have become increasingly apparent. They are major products in the radiation chemistry of water, are technically important in many redox polymerizations, and have been suggested as intermediates in many other processes. Their gas-phase reactions are significant in the atmosphere and in the chemistry of smog. They are even found widely distributed in interstellar space.
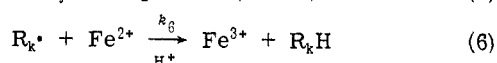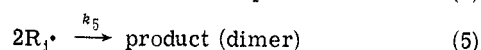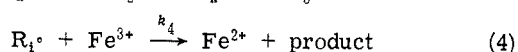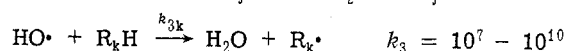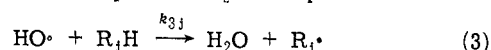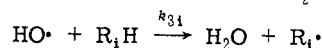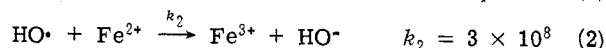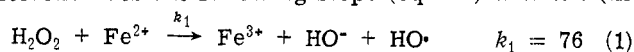
Consequently, hydroxyl radicals have been studied with increasing vigor, by means of ever-more-sophisticated techniques and apparatus. As examples, their production by flow systems in an ESR cavity, a technique originated by Dixon and Norman,[4] has been used to generate a variety of radicals and to study both their reactions and the details of their ESR spectra. The largest body of data has been supplied by radiation chemists, who, combining pulse radiolysis and competition techniques, have determined the absolute rates of hydroxyl radical reactions with several hundred substrates with varying degrees of precision.[5]

In the late 1950's and 1960's much of my research group's activities had been concerned with alkoxy radical chemistry. In 1969 I decided to include the hydroxyl radical in our studies, and took the rather anachronistic course of turning back to Fenton's reagent (which had received only sporadic attention in the meantime; in fact the actual participation of hydroxyl radicals in its action had even been thrown into question) and the simple stoichiometric analysis of Merz and Waters. This Account summarizes our

results and some of the extensions we have been able to make to other systems.[6]

The Stoichiometry of Fenton's Reagent; Radical Oxidation and Reduction

In our model (a slightly updated version of the Merz and Waters scheme[7]) a Fenton's reagent oxidation involves the following steps (eq 1–6) with k's (in

$$H_2O_2 + Fe^{2+} \xrightarrow{k_1} Fe^{3+} + HO^- + HO\cdot \qquad k_1 = 76 \quad (1)$$

$$HO\cdot + Fe^{2+} \xrightarrow{k_2} Fe^{3+} + HO^- \qquad k_2 = 3 \times 10^8 \quad (2)$$

$$HO\cdot + R_iH \xrightarrow{k_{3i}} H_2O + R_i\cdot$$

$$HO\cdot + R_jH \xrightarrow{k_{3j}} H_2O + R_j\cdot \qquad\qquad (3)$$

$$HO\cdot + R_kH \xrightarrow{k_{3k}} H_2O + R_k\cdot \qquad k_3 = 10^7 - 10^{10}$$

$$R_i\cdot + Fe^{3+} \xrightarrow{k_4} Fe^{2+} + product \qquad (4)$$

$$2R_j\cdot \xrightarrow{k_5} product\ (dimer) \qquad (5)$$

$$R_k\cdot + Fe^{2+} \xrightarrow[H^+]{k_6} Fe^{3+} + R_kH \qquad (6)$$

l./(mol sec)), where known, taken from the literature. Reactions 3 are written as hydrogen abstractions but, with unsaturated molecules, may be replaced by kinetically equivalent additions. They assume the possible formation of three types of radicals, $R_i\cdot$, $R_j\cdot$, and $R_k\cdot$, which respectively undergo oxidation (and thus regenerate Fe^{2+} to propagate a redox chain), dimerize, or are reduced. The resulting stoichiometry may be conveniently investigated by adding a small known amount of H_2O_2 slowly to a well-stirred solution containing excess Fe^{2+} and substrate[8] and determining the Fe^{2+} oxidized.

(1) H. J. H. Fenton, *J. Chem. Soc.*, **65**, 899 (1894).

(2) F. Haber and J. J. Weiss, *Proc. Roy. Soc. London, Ser. A*, **147**, 332 (1934).

(3) J. H. Merz and W. A. Waters, *Discuss. Faraday Soc.*, **2**, 179 (1947); *J. Chem. Soc.*, S15, 2427 (1949).

(4) W. T. Dixon and R. O. C. Norman, *Nature (London)*, **196**, 891 (1962). In such systems Ti^{3+}–H_2O_2 is generally used because of its faster reaction.

(5) L. M. Dorfman and G. E. Adams, National Bureau of Standards Report No. NSRDS-NBS-46, U.S. Government Printing Office, Washington, D.C., 1973.

(6) To me, an engaging feature of this project is that almost all experiments have been carried out with a buret, ordinary laboratory glassware, and a GLC analytical unit, aided by a digital integrator (although we have used a desk-top computer for data analysis and have carried out some titrations with a pH-stat). I hope our results give encouragement to investigators with limited facilities and equipment budgets.

(7) Merz and Waters clearly demonstrated the three reaction alternatives (eq 4–6), but they wrote (4) as its kinetic equivalent

$$R_i\cdot + H_2O_2 \rightarrow ROH + HO\cdot \qquad (4')$$
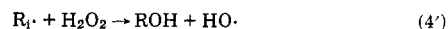
However, (4) is now well established, and should be much faster than (4') under our conditions.

(8) Our experiments have in general been done with perchlorate salts at pH <2 in the absence of O_2, which upsets the stoichiometry by reacting with the intermediate radicals. When $[Fe^{2+}]$ is to be minimized, inverse addition (addition of Fe^{2+} to excess H_2O_2 + substrate) can be employed and may lead to striking changes in product.

Cheves Walling is Distinguished Professor at the University of Utah. He received his A.B. from Harvard in 1937 and the Ph.D. from the University of Chicago in 1939. After 13 years in industry with Du Pont, the U.S. Rubber Company (now Uniroyal), and Lever Brothers Company, he was appointed Professor of Chemistry at Columbia, and moved to Utah in 1970. His research has concerned various aspects of physical organic chemistry, chiefly free-radical reactions.

This Account is based on his James Flack Norris Award address, given at the April 1971 meeting of the American Chemical Society in Los Angeles. Walling says, however, that many of the results described here were merely hopes at that time.
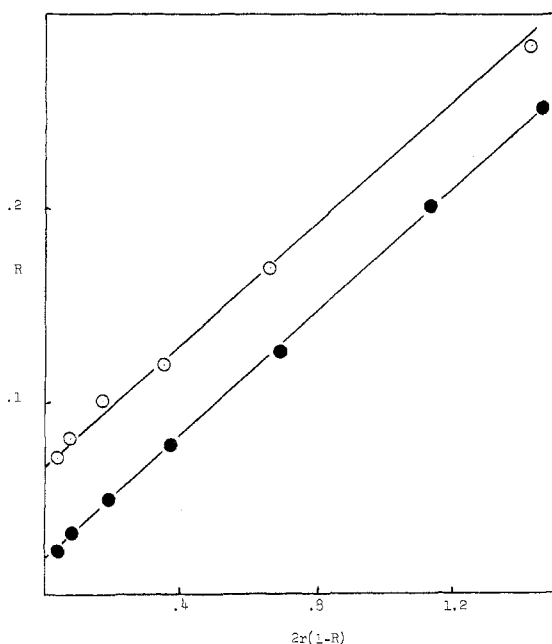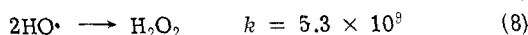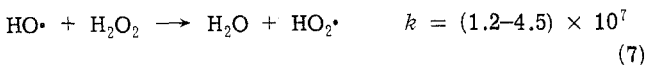
Figure 1. Plot of eq 9 for isopropyl alcohol, 0.02 M Fe^{2+}, pH 0.82. Solid circles, 0.04 M Cu^{2+} added.

These conditions are chosen to minimize the competing processes

$$HO\cdot + H_2O_2 \longrightarrow H_2O + HO_2\cdot \qquad k = (1.2{-}4.5) \times 10^7 \tag{7}$$

$$2HO\cdot \longrightarrow H_2O_2 \qquad k = 5.3 \times 10^9 \tag{8}$$

Equations 1–6 predict a stoichiometry

$$\frac{\Delta[Fe^{2+}]}{2\Delta[H_2O_2]} = $$

$$\frac{2k_2[Fe^{2+}] + k_{3j}[R_jH] + 2k_{3k}[R_kH]}{2k_2[Fe^{2+}] + 2k_{3i}[R_iH] + 2k_{3j}[R_jH] + 2k_{3k}[R_kH]} \tag{9}$$

When RH's represent different reactive sites on the same molecule, (9) may be put in the rectified form

$$R = 2ar(1 - R) + b \tag{10}$$

where $R = \Delta[Fe^{2+}]/2\Delta[H_2O_2]$, $r = [Fe^{2+}]/2[RH]$, $a = k_2/\Sigma k_3$, $b = (k_{3j} + 2k_{3k})/2\Sigma k_3$.

Application of (9) was first made by S. Kato[9] to isopropyl alcohol, which proved a fortunate choice. The resulting plots (Figure 1) were invariant with [H+], added [Fe3+], total concentrations of reagents, and rates of H_2O_2 addition, and showed that the alcohol was 6.65 times as reactive as Fe^{2+} but yielded two radicals in a ratio of 7.23:1 of which only the major one was capable of further oxidation by Fe^{3+}. The obvious interpretation, that the major point of attack is at C-2, but that some occurs as well on the methyl groups, has been confirmed by deuterium substitution, product analysis (Table I), and the effect of Cu^{2+} on both stoichiometry and products.[10] A similar analysis has been successful with other alcohols[9] and a variety of other substrates.[11,12] The

(9) C. Walling and S. Kato, *J. Am. Chem. Soc.*, **93**, 4275 (1971).
(10) Copper is a much less discriminating radical oxidant than iron, and in our scheme converts R_j·'s to R_i·'s via

$$Cu^{2+} + R\cdot \rightarrow product + Cu^+$$

$$Cu^+ + Fe^{3+} \rightarrow Cu^{2+} + Fe^{2+}$$
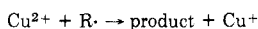
This effect of copper has thus been a critical tool in our analysis.

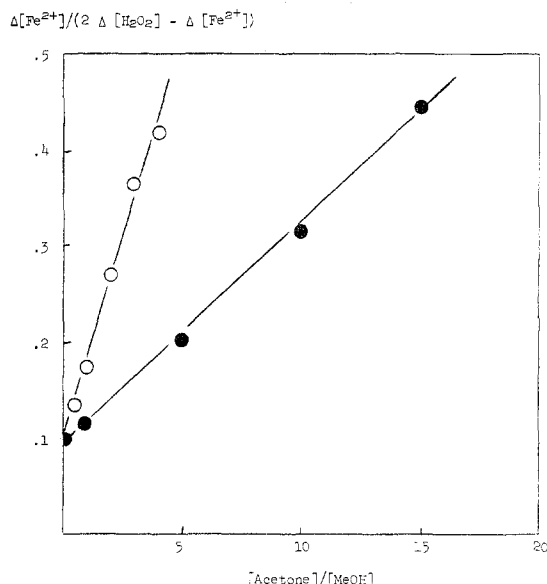**Figure 2.** Plot of eq 11 for the acetone–methanol system. Open circles, CH_3COCH_3; solid circles, CD_3COCD_3. Conditions: [H+] = 0.1 M; Fe^{2+}, 0.02 M; MeOH, 0.1 M.

Table I
Effect of Cu^{2+} on Products of Alcohol Oxidation

	% yield	
Alcohol and Products	Fe alone	Cu^{2+} added
Isopropyl alcohol		
CH_3COCH_3	93	84
$(CH_3CHOHCH_2)_2$	0.7	4.4
$CH_3CHOHCH_2OH$		11.2
tert-Butyl alcohol		
$((CH_3)_2COHCH_2)_2$	84.4	1.6
$(CH_3)_2COHCH_2OH$		86.2

behavior of *tert*-butyl alcohol is particularly striking since the 2-hydroxy-2-methyl-1-propyl radical is oxidized by Cu^{2+} but not Fe^{2+}; a small amount of Cu^{2+} completely changes the stoichiometry and products; cf. Table I.

When a substrate belongs to the R_kH class, yielding solely reducible radicals, its presence has no effect upon the stoichiometry of the Fe^{2+}–H_2O_2 reaction. However, as again shown by Merz and Waters, its reactivity can be determined by measuring its retarding effect on the chain oxidation of an R_iH type molecule such as methanol. Under these conditions, eq 9 can be put in the form

$$\frac{\Delta[Fe^{2+}]}{2\Delta[H_2O_2] - \Delta[Fe^{2+}]} = \frac{k_2[Fe^{2+}]}{k_{3i}[R_iH]} + \frac{k_{3k}[R_kH]}{k_3[R_iH]} \tag{11}$$

If [Fe2+] and [RiH] are held constant while the [RkH]/[RiH] ratio is varied, (11) yields a linear plot with slope k_{3k}/k_{3i}. The validity of (11) was first demonstrated in our group by El Taliawi[13] for the acetone–methanol system, (Figure 2) and yields an

(11) C. Walling and G. M. El Taliawi, *J. Am. Chem. Soc.*, **95**, 848 (1973).
(12) C. Walling, G. M. El Taliawi, and R. A. Johnson, *J. Am. Chem. Soc.*, **96**, 133 (1974).
(13) C. Walling and G. M. El Taliawi, *J. Am. Chem. Soc.*, **95**, 844 (1973).

Table II
Relative Reactivities (k_3/k_2) toward Hydroxyl Radicals[a]

| Substrate	k_3/k_2	Lit.[b]	k_α/k_2	k_β/k_2	k_γ/k_2
Alcohols					
Methyl	4.03	2.82 (1.6–3.6)	1.34		
Ethyl	7.00	6.01 (2.4–6.2)	3.66	0.23	
n-Propyl	11.3	9.0 (8.2–9.3)	3.36	1.34	(0.625)
Isopropyl	6.65	6.7 (5.9–7.3)	5.73	0.15	
Isobutyl	14.0	11	3.04	4.22	(0.625)
tert-Butyl	1.9	1.73 (1.4–2.1)		0.21	
Neopentyl	12.0		2.11		0.625
2,2-Trifluoroethyl	0.53		0.28		
2,2,2-Trichloroethyl	0.95		0.48		
Ethers					
Tetrahydrofuran	6.76	9.0	1.45	0.23	
Carbonyl compounds					
Acetone	0.322	0.22–0.4	0.054		
Acetic acid	0.089	0.26 (0.003–0.28)	0.030		
Dimethylformamide	6.0	4.0	0.97	~0.12	

[a] k_α/k_2 etc. are per C–H bond; values in parentheses assumed. [b] Calculated from "best values" of ref 5, assuming $k_2 = 3 \times 10^8$. In some cases ranges of reported values are also indicated.

acetone/methanol reactivity of 0.080. The assumption that hydroxyl radical attack yields the acetonyl radical (eq 12) rather than, e.g., involving addition

$$HO\cdot + CH_3COCH_3 \longrightarrow H_2O + \cdot CH_2COCH_3 \quad (12)$$
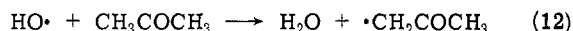
to the carbonyl group was shown by the large kinetic isotope effect with perdeuterioacetone ($k_H/k_D = 3.54$) and the isolation of small yields of dimer (2,5-hexanedione) in inverse addition experiments. Subsequently the same technique has been applied successfully to other systems and data treatment via eq 10 and 11 has been the mainstay of our stoichiometric investigations.

Accumulating data have clarified the classification of radicals in regard to their ease of oxidation and reduction. Radicals yielding relatively stable carbonium ions, e.g., those containing α-OH, α-OR, or amide N and *tert*-alkyl radicals are effectively quantitatively oxidized by Fe^{3+}. Allylic and benzylic radicals are marginal in that oxidation chain lengths depend on $[Fe^{3+}]$, so that the clean dichotomy between $R_i\cdot$ and $R_j\cdot$ is obscured, while primary and secondary alkyl radicals are inert. In contrast, Cu^{2+} effectively oxidizes all these species. Carbonyl conjugated radicals and similar species with relatively stable corresponding anions are inert to oxidation by either Cu^{2+} or Fe^{3+}, but are readily reduced by Fe^{2+} and thus belong to class $R_k\cdot$. Vinyl radicals, obtained by hydroxyl radical addition to acetylenes, are unique in that they are both oxidized by Cu^{2+} (but not Fe^{3+}) and reduced by Fe^{2+}.[11] Thus acetylene yields acetaldehyde in the absence of Cu^{2+} and hydroxyacetaldehyde in its presence (eq 13).

$$HO\cdot + HC\equiv CH \longrightarrow$$
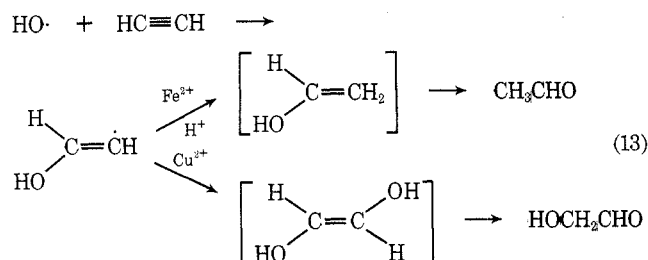
These reactivity patterns lead to some interesting consequences. Hydroxyl radicals add readily to maleic acid, giving a radical which is reduced to malic acid[13,14] (eq 14).
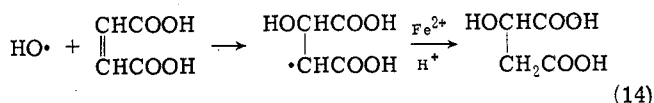
Thus maleic acid has no effect on the stoichiometry of the Fe^{2+}–H_2O_2 reaction and the reduction of H_2O_2 has in effect been "coupled" with the hydration of maleic acid. The reactivity of maleic acid can be determined by measurement of the inhibition of methanol oxidation, but only in the presence of relatively high concentrations of Fe^{3+}. Otherwise the hydroxymethyl radicals from the methanol add to the maleic acid to yield, eventually, paraconic acid. This sort of process suggests a general synthesis of γ-lactones, via a redox chain of which we have demonstrated a few examples.[13]
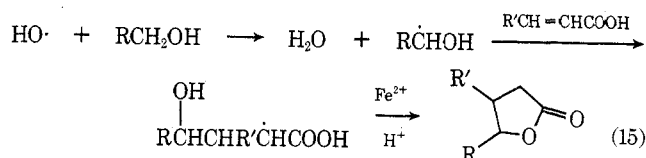
Structure–Reactivity Relations: the Reality of Hydroxyl Radicals

Our data yield not only overall reactivities relative to the $HO\cdot$–Fe^{2+} reaction, k_3/k_2 ($k_3 = k_{3i} + k_{3j} + k_{3k}$), but also (sometimes with reasonable assumptions such as that similarly situated methyl groups show similar reactivities) a dissection into relative rates of attack on different types of C–H bonds (Table II). Overall rates are chiefly of interest for comparison with those from radiation chemistry in order to validate our reaction scheme, and in general our data are in agreement with radiation results within the rather large uncertainty of the latter.[15]

(14) C. Nofre, Y. LeRouse, L. Goudot, and A. Cier, *Bull. Soc. Chim. Fr.*, 2451 (1964).

However, it should be pointed out that for many years an alternative interpretation of the $Fe^{2+}-H_2O_2$ has existed[16] which postulates the step

$$H_2O_2 + Fe^{2+} \longrightarrow H_2O + FeO^{2+} \qquad (16)$$
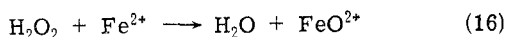
The resulting ferryl radical (FeO^{2+} or $FeOH^{3+}$) is kinetically equivalent to HO· in all of our reaction schemes, although one would have to assume that the selectivities of ferryl and hydroxyl were fortuitously almost identical. However, a comparison of the relative rates of hydroxyl (or ferryl) radical attack on Fe^{2+} and methanol at different perchlorate concentrations[12] has shown no dependence on ionic strength, indicating that the carrier must be an uncharged species. Again, ESR spectra of products formed in flow systems have also provided a basis for doubt that hydroxyl radicals are involved in the Fenton's reagent system. With *i*-PrOH-H_2O_2-Ti^{3+}, Shiga[17] reported observing the expected 2-hydroxy-2-propyl radical, but, with Fe^{2+}-EDTA in place of Ti^{3+}, the 2-hydroxy-1-propyl radical was found. We believe the difference lies in the relative ease of oxidation of the first radical by Fe(III). Both radicals are produced in each system (the first in much larger amounts), but, in the presence of Fe(III), only the second survives in sufficient quantity to be seen. Similar results with a number of other alcohols and ethers can be accounted for in the same way.[18]

If we accept the reality of hydroxyl radicals in our systems, Table II also gives a good picture of their selectivity. For C–H bonds both α and β to OH, the usual primary < secondary < tertiary order is observed, but it is also clear that reactivity is significantly enhanced by potentially electron-donating groups (α-OH, α-OR, and amide N) and decreased by electronegative substituents (cf. acetic acid, acetone, halo alcohols). In summary, HO· is only moderately selective (the full range in our data is a few hundred) with reactivity patterns dominated by polar effects, a plausible result for a series of strongly exothermic reactions of an electronegative radical.

Although not included in the table, both our results and those from radiation chemistry show that hydroxyl radical additions to double bonds are also very rapid (k's = 10^9–10^{10} or 3 to 30 × k_2). In the competition between addition and abstraction of allylic hydrogen HO· thus resembles Cl· rather than RO·.[19]

Mechanisms of Metal Ion–Radical Reactions

The pattern of metal ion oxidation and reduction of radicals disclosed by our work implies significant mechanistic conclusions. Oxidation by Fe^{3+} is selective, paralleling stabilities of the corresponding carbonium ions, and can be very fast (for ·CH_2OH we have estimated $k_4 > 4 \times 10^8$). In contrast, ligand exchange reactions of Fe^{3+} have rate constants <10^4. Both observations are thus consistent with an outer-sphere electron transfer to yield a carbonium ion type product.

$$R \cdot + Fe^{3+} \rightleftharpoons R^+ + Fe^{2+} \qquad (17)$$
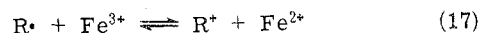
Primary and secondary alkyl radicals are not oxidized, perhaps because here equilibrium 17 is reversed. Evidence that this is actually the case is the observation that solvolysis of ethyl triflate in concentrated $Fe(ClO_4)_2$ solution initiates the polymerization of acrylonitrile and produces signficant oxidation to Fe^{3+} and butane formation.[9] Radical reductions by Fe^{2+} are also very fast[20] with an ease paralleling carbanion stability, so it is likely that these are outer-sphere electron transfer as well.

$$Fe^{2+} + R \cdot \rightleftharpoons Fe^{3+} + R^- \qquad (18)$$
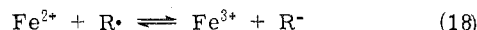
If (17) is reversed for primary and secondary radicals, Cu^{2+}, a weaker oxidizing agent, can hardly oxidize them by outer-sphere electron transfer. Rather, our data seem consistent with the mechanism proposed by Kochi involving an intermediate organocopper species which, in our systems, chiefly undergoes an internal displacement by ligand-bound water to give the hydroxylic products observed.[21]

$$\qquad (19)$$
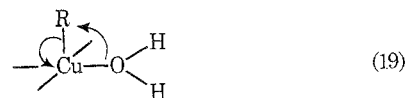
Oxidations by Cu^{2+} appear significantly slower than the fastest ones observed with Fe^{3+}, and ligand exchange at Cu^{2+} is rapid enough to permit this sort of path.

Hydroxyl Radical Reactions with Aromatics

Radiation chemistry results show that hydroxyl radicals add very rapidly to aromatics (k's = 10^9–10^{10}) and the resulting hydroxycyclohexadienyl radicals can be observed directly by uv or ESR spectroscopy.[5] Although for benzene products are clearly biphenyl and phenol (from dimerization followed by dehydration and from further oxidation of the initial addition products), recent work has shown that, with substituted benzenes, the overall reactions are much more complicated. Thus Norman[22] finds that ESR spectra are pH dependent and indicate both hydroxylation and side-chain cleavage, while Hamilton[23] has suggested that the initial reaction may be electron transfer to yield an aromatic radical cation rather than addition.

A study by R. A. Johnson[24] of product distributions for several aromatics under a variety of conditions confirms this complexity and appears consis-

(15) We have taken the rate of the HO·-Fe^{2+} reaction as 3 × 10^8, but published results vary from 2.6 × 10^8 to 5.0 × 10^8. Dorfman and Adam's review[5] shows many similar spreads, although they attempt to indicate best values.

(16) W. G. Bray and M. Gorin, *J. Am. Chem. Soc.*, 54, 2134 (1932); cf. A. E. Cahill and H. Taube, *ibid.*, 74, 2312 (1952).

(17) T. Shiga, *J. Phys. Chem.*, 69, 3805 (1965).

(18) ESR spectra respond to concentration, not significance: the species observed may range from the major transient species involved in a reaction to the most stable minor by-product.

(19) Alkoxy radicals, RO·, are seemingly unique in their preference for allylic H abstraction over double bond addition. Although only ad hoc explanations have been advanced for this property, it makes *tert*-butyl hypochlorite an efficient allylic halogenating agent; cf. C. Walling and W. Thaler, *J. Am. Chem. Soc.*, 83, 3877 (1961).

(20) A semiquantitative estimate based on a 2.3% yield of dimer in an inverse addition experiment with acetone indicatrs a $k \geq 10^{7}$.[13]

(21) J. F. Kochi in "Free Radicals," J. F. Kochi, Ed., Vol. 1, Wiley, New York, N.Y., 1973, Chapter 11.

(22) R. O. C. Norman and R. J. Pritchett, *J. Chem. Soc. B*, 926 (1967); C. R. E. Jefcoate and R. O. C. Norman, *ibid.*, B, 48 (1968).

(23) M. E. Snook and G. A. Hamilton, *J. Am. Chem. Soc.*, 96, 960 (1974).

(24) C. Walling and R. A. Johnson, *J. Am. Chem. Soc.*, 97, 363 (1975).

tent with the following scheme (illustrated for phenylacetic acid, a typical substrate).
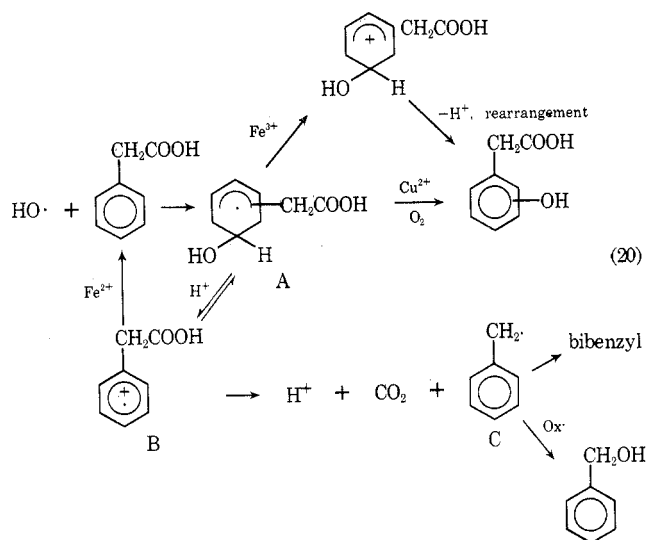

(20)

Table III shows typical data on which the scheme is based. We assume that hydroxyl radical attack is predominantly by addition, but that the initial mixture of hydroxycyclohexadienyl radicals (A) suffers a rapid, reversible, and acid-catalyzed collapse to radical cation B which undergoes competitive reduction back to starting material by Fe^{2+} and side-chain cleavage to benzyl radicals C. These, in turn dimerize to bibenzyl, or, in the presence of Cu^{2+} or Fe^{3+}, are oxidized to benzyl alcohol. At high oxidant levels A is largely trapped by oxidation to phenols, convincing evidence that it is the major initial product. Here a notable feature is that Cu^{2+} and O_2 yield much more meta isomer than does Fe^{3+}. We believe that Cu^{2+} and O_2 give the isomer distribution typical of A (i.e., somewhere between that determined by initial $HO\cdot$ attack and equilibration). On the other hand, Fe^{3+}, an electron-transfer oxidant, may be more selective, reacting chiefly with ortho–para isomers which yield more stable carbonium ions. Further, if the meta carbonium ion is produced, it offers the possibility of further rearrangement, e.g.

(21)
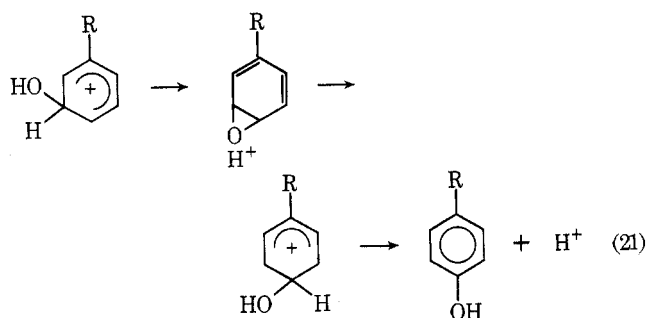
Whether such a protonated epoxide is a real intermediate in equilibrium with the epoxide is unknown, but it is pertinent that acid-catalyzed opening of such epoxides of alkylbenzenes give exclusively ortho- and para-substituted phenols.[25]

Table III shows that, under proper conditions, very

(25) Cf. D. M. Jerina, *Chem. Tech.*, 120 (1973).

Table III
Fenton's Reagent Oxidations of Phenylacetic Acid[a]

| [Fe³⁺] | [Cu²⁺] | % Yield | | | Phenol isomers, % | | |
		BzOH	(Bz)₂	Phenols	o	m	p
		12	54	1			
b		2	3	7	66	34	0
0.16		60	6	7	91	6	3
	0.08	27	0	47	60	29	11
	0.08ᶜ	4	0	69	45	31	24
	0.16	17	0	50	58	31	11
	0.16ᵈ	58	0	15	77	21	2

[a] 0.05 M $HClO_4$, 0.02 M Fe^{2+}, 0.06 M substrate under N_2 unless indicated. Yields based on H_2O_2 added; Bz = benzyl. [b] O_2 saturated. [c] 0.25 M $HClO_4$. [d] 0.02 M NaOAc added.

high selectivities to specific products can be obtained: 81% to bibenzyl with no added oxidant; 82% to benzyl alcohol at high [Fe^{3+}], 94% to phenols at low [H^+] and high [Cu^{2+}]. Toluene behaves quite similarly, and even benzyl and α- and β-phenylethyl alcohols, which Hamilton reports to give solely cleavage products, yield 21–40% phenols in the presence of Cu^{2+}. With benzene, where there is no possibility of cleavage, total product yields are pH dependent since in strong acid most of the hydroxycyclohexadienyl radicals collapse to radical cations and are reduced back to starting material.[26]

Recently we have extended our studies to the $S_2O_8^{2-}$–Fe^{2+} system.[27] Here side-chain cleavage reactions are well known, but we find that benzene, toluene, and even β-phenylethyl alcohol in the presence of Cu^{2+} give yields of phenols comparable to those obtained with H_2O_2. Aryl sulfates are not intermediates (since they are stable under these conditions but not detected), so our results support the reversibility of the A $\rightleftarrows$ B equilibrium in (20), and we propose the sequence

$$S_2O_8^{2-} + Fe^{2+} \longrightarrow SO_4\cdot^- + SO_4^{2-} + Fe^{3+} \quad (22)$$

(23)
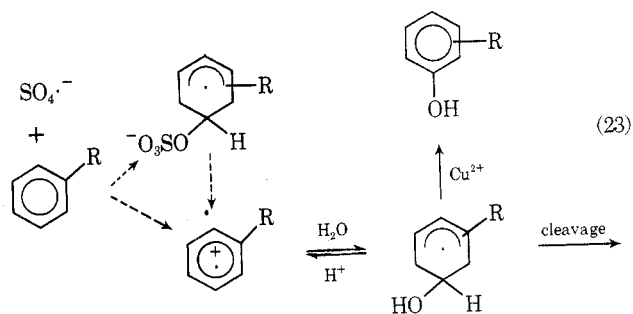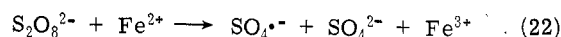
(26) On the basis of ESR spectra A. L. Buley, R. O. C. Norman, and R. J. Prichett, *J. Chem. Soc. B*, 849 (1966), have proposed an analog to this behavior of hydroxycyclohexadienyl radicals in aliphatic systems
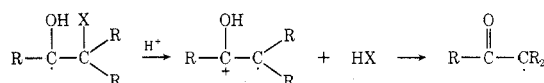
where X is OH or another suitable leaving group. We have confirmed this interesting process by both stoichiometric and product studies. Thus Fenton's reagent isomerizes 2,3-dihydroxybutane to 2-butanone (R. A. Johnson, unpublished work).
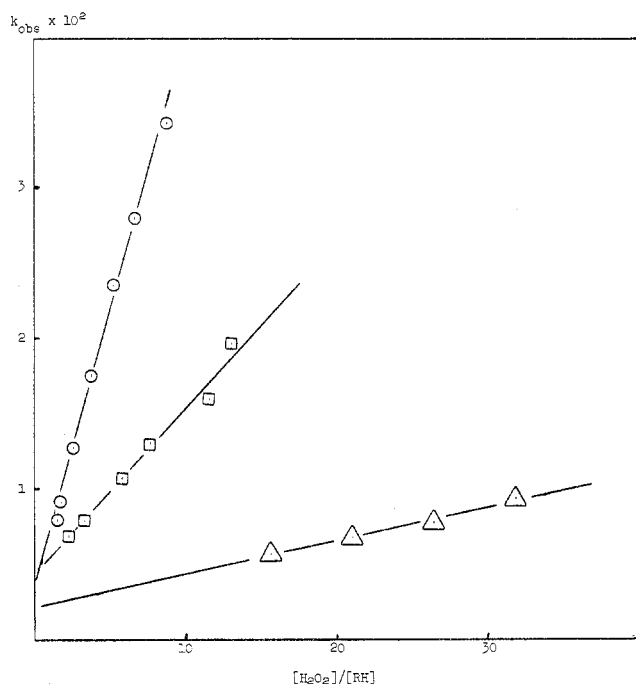
(27) D. Camaioni, unpublished work.

Figure 3. Effect of substrates on Fe^{3+}-catalyzed decomposition of H_2O_2 at $30°$, $[H^+]$, $1.92 \times 10^{-2}\ M$; $[Fe^{3+}]$, $3.92 \times 10^{-3}\ M$; $[H_2O_2]$, $0.392\ M$. Circles, acetic acid; squares, acetone; triangles, *tert*-butyl alcohol.

Whether the $SO_4\cdot^-$ radical adds to the aromatic and is then lost as SO_4^{2-} or oxidizes the aromatic directly by electron transfer is still obscure.
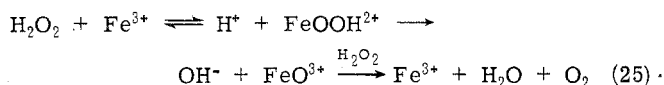
While most of the steps in our reaction scheme are not new, our data draw them into a more coherent whole and show how aromatic hydroxylation can be made to yield a variety of products in a predictable manner and in encouraging high yield. In fact, the extreme sensitivity of product distributions to conditions suggests that many previous conclusions (based on such distributions) about the intermediacy or nonintermediacy of hydroxyl radicals in metal ion induced oxidations or aromatics need reexamination.

Ferric Ion Catalyzed Decompositions of Hydrogen Peroxide

The long-known catalysis of hydrogen peroxide decomposition by Fe^{3+} in dilute acid solution

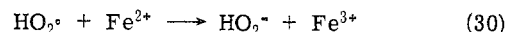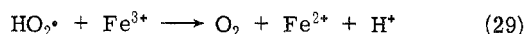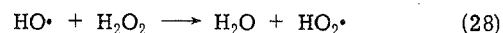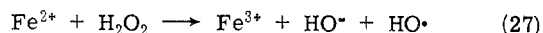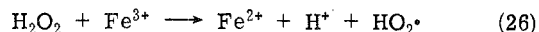$$2H_2O_2 \xrightarrow{Fe^{3+}} 2H_2O + O_2 \qquad (24)$$
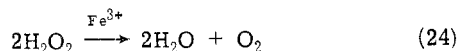
is an important process in which the role of hydroxyl radicals has been in dispute. Kremer and Stein[28] have proposed a nonradical, nonchain sequence (eq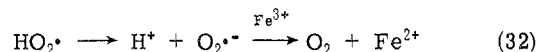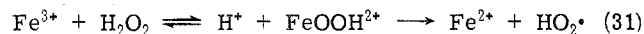 25) which has been attractive to biochemists as a possible model for their systems. The older, redox chain formulation was originally proposed by Haber and Weiss and was put in its most recent form by Barb, Baxendale, George, and Hargrave.[29] The postulated steps are

$$H_2O_2 + Fe^{3+} \rightleftharpoons H^+ + FeOOH^{2+} \longrightarrow$$

$$OH^- + FeO^{3+} \xrightarrow{H_2O_2} Fe^{3+} + H_2O + O_2 \quad (25)\cdot$$

$$H_2O_2 + Fe^{3+} \longrightarrow Fe^{2+} + H^+ + HO_2\cdot \qquad (26)$$

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + HO^- + HO\cdot \qquad (27)$$

$$HO\cdot + H_2O_2 \longrightarrow H_2O + HO_2\cdot \qquad (28)$$

$$HO_2\cdot + Fe^{3+} \longrightarrow O_2 + Fe^{2+} + H^+ \qquad (29)$$

$$HO_2\cdot + Fe^{2+} \longrightarrow HO_2^- + Fe^{3+} \qquad (30)$$

with both (26) and (29) being complex and pH dependent, presumably because of prior equilibria

$$Fe^{3+} + H_2O_2 \rightleftharpoons H^+ + FeOOH^{2+} \longrightarrow Fe^{2+} + HO_2\cdot \quad (31)$$

$$HO_2\cdot \longrightarrow H^+ + O_2\cdot^- \xrightarrow{Fe^{3+}} O_2 + Fe^{2+} \quad (32)$$

so that the termination step (eq 30) is effectively the reverse of the second part of (31). Both schemes predict rates proportional to $[H_2O_2][Fe^{3+}]/[H^+]$ at high $[H_2O_2]/[Fe^{3+}]$ ratios (as observed) and deviations at lower ratios which have been in some dispute.

Various organic substrates were known to retard the decomposition, and it occurred to us that, if the Barb and Baxendale scheme were correct, retardation could be because the substrates were acting as hydroxyl radical traps and introducing a new termination sequence

$$HO\cdot + RH \longrightarrow H_2O + R\cdot \qquad (33)$$

$$R\cdot + O_2 \longrightarrow RO_2\cdot \xrightarrow{Fe^{2+}} RO_2^- + Fe^{3+} \qquad (34)$$
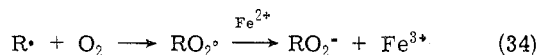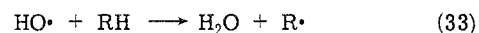
Replacement of (30) by (33–34) and solving the kinetic equations with the usual steady-state assumption yield

$$\frac{-d[H_2O_2]}{dt} = 2k_{24}[H_2O_2][Fe^{3+}](1 + (k_{26}[H_2O_2]/k_{31}[RH])) \qquad (35)$$

$$\frac{d[O_2]}{dt} = k_{24}[H_2O_2][Fe^{3+}](k_{26}[H_2O_2]/k_{31}[RH]) \qquad (36)$$

From (35–36) retarded reactions should again be first order in $[Fe^{3+}]$ and $[H_2O_2]$ but with k_{obsd} linear in $[H_2O_2]/[RH]$ and extrapolating to $2k_{24}$ for H_2O_2 disappearance and zero (with half as large a slope) for O_2 evolution. A. Goosen[30] has shown that such behavior is actually obeyed, first with acetone (Figure 3) and then with acetic acid and *tert*-butyl alcohol. Gratifyingly, all systems yielded similar k_{24}'s as required and slopes satisfactorily close to those predicted from values of k_{26} and k_{31} taken from radiation results or our own measurements with Fenton's reagent. Further analysis showed that kinetic chains in the unretarded reaction were approximately 30 (a more plausible value than Barb's much larger earlier estimate) and gave a value of k_{27} in good agreement with radiation results. Since these results would be very hard to account for in a "complex" scheme such as (25), the redox chain mechanism seems firmly established.[31]

However, it should be noted that some substrates give more complex results. Methanol retards the decomposition and yields plots similar to Figure 3, but

(28) M. L. Kremer and G. Stein, *Trans. Faraday Soc.*, **55**, 595 (1959); M. L. Kremer, *ibid.*, **58**, 702 (1962); **59**, 2535 (1963).

(29) W. G. Barb, J. H. Baxendale, P. George, and K. R. Hargrave, *Trans. Faraday Soc.*, **47**, 591 (1951).

(30) C. Walling and A. Goosen, *J. Am. Chem. Soc.*, **95**, 2987 (1973).

(31) An original objection to the Barb et al. scheme, the behavior of the Fe^{3+}–H_2O_2 system at high $[Fe^{3+}]/[H_2O_2]$ ratios, has also been removed by showing that data are actually consistent with behavior predicted by numerical integration of the complete differential equations (C. Walling and T. Weil, *Int. J. Chem. Kinetics*, **6**, 507 (1974)).

the slopes indicate that it is a much less effective retarder than would be calculated from its reactivity toward hydroxyl radicals. Presumably here some of the resulting hydroxymethyl radicals are reoxidized by Fe^{3+} rather than reacting with O_2 and thus propagate the redox chain.

A number of complexed ferric ions also catalyze the decomposition of H_2O_2, and we are applying our techniques to the study of these systems. Fe(III)-EDTA forms an intensely purple complex with H_2O_2 at pH 8 and above.

$$[Fe \cdot EDTA \cdot OH]^{2-} + H_2O_2 \rightleftharpoons$$
$$[Fe \cdot EDTA \cdot O_2]^{3-} + H_2O + H^+ \quad (37)$$
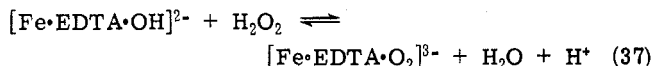
The complex has not been isolated, but some time ago[32] we showed that, in the pH region where the complex is formed, Fe(III)-EDTA is a catalyst both for the decomposition of H_2O_2 and the oxidation of organic substrates (including bound and free EDTA). Kinetics were complex, and the reaction was retarded by both excess EDTA and other substrates. We have recently reexamined this system,[33] and, with acetone and *tert*-butyl alcohol, obtain plots similar to Figure 3 with similar intercepts for the two substrates and slopes inversely proportional to their reactivities toward HO·. However, total retardations are small and actual slopes indicate lower reactivities for the substrates than would be calculated. A plausible explanation of this finding lies in the very high reactivity of EDTA ($k = 2.76 \times 10^9$)[34] and presumably its complexes toward hydroxyl radicals. Our structure–reactivity studies indicate the chief point of attack should be the ethylene bridge, to yield a very easily oxidized radical, i.e.

$$(38)$$
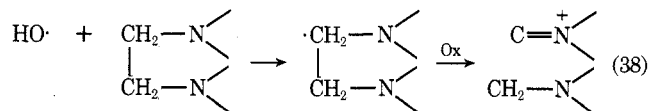
so that (38) as well as (28) could at least partially propagate the chain as in the case of methanol. Attack on an Fe(III)-EDTA complex would give a product containing its own oxidant, so that the two steps of (38) might be almost concerted. Finally, the high rate of the HO· + Fe(III)-EDTA reaction makes it likely that some fraction of the process is actually a cage reaction between freshly generated HO· and Fe(III)-EDTA pairs. These considerations predict very complex overall kinetics, but assuming that chain propagation is via both (28) and (38) gives calculated slopes in substantial agreement with experiment.

Some other ferric complexes give similar results. The nitrilotriacetic acid (NTA) complex is a catalyst for H_2O_2 decomposition above pH 5 (although no spectroscopically demonstrable H_2O_2 complex is observed), and again *tert*-butyl alcohol and acetone strongly retard the decomposition, with *tert*-butyl

alcohol being considerably more effective. Similarly, at pH 9, acetone retards the decomposition of H_2O_2 by hemin. At this point our results suggest that hydroxyl radical chains may provide quite a general path for transition metal catalyzed decompositions of H_2O_2, and I propose that strong retardation of any such decomposition by organic substrates which are good HO· traps (particularly when the effect of several substrates parallel their expected reactivities and extrapolate to the same completely retarded rate) provides *prima facia* evidence for such a path.

Extensions

The systems which we have examined to date are part of a much larger whole of great technical and biochemical interest: the entire set of processes in which O_2, H_2O_2, and peroxides oxidize organic substrates under the mediation of transition metal ions and complexes. A primary question is: in which of these are simple oxygen radicals (HO·, RO·, HO_2·, etc.) the reactive transients, and in which are metal oxygen complexes (e.g., the ferryl ion, FeO^{2+}) involved?[2] Although it has been popular to invoke some example of the latter group, suitably tailored to fit the data, to explain a variety of phenomena,[35] this seems to me an unnecessary hypothesis if simple oxygen radicals adequately account for the results, and in several systems we have now shown this to be the case.

As the properties of the oxygen radicals become better characterized, this approach can be extended. As possible examples, Dearden, Jefcoate, and Lindsay-Smith[36] have described the hydroxylation of toluene and anisole induced by the autoxidation of various complexes of Fe(II), Ti(III), Cu(I), and Sn(II), but discounted a hydroxyl radical mechanism because of the variability of the isomer distributions observed. However, as we and others have shown, wide variability is now plainly possible for the hydroxyl radical reaction.

Finally, and much more speculatively, biochemists have been reluctant to consider hydroxyl radicals as intermediates in enzymic hydroxylations because of their high and indiscriminate reactivity.[37] However, since their fastest reactions are diffusion controlled, it is conceivable that a system might generate a hydroxyl radical in juxtaposition to an absorbed substrate, and then immediately convert the resulting radical to stable product by oxidation by a suitably positioned metal ion (possibly just oxidized in the HO·-forming process).

(32) C. Walling, M. Kurz, and H. T. Schugar, *Inorg. Chem.*, **9**, 931 (1970).

(33) C. Walling, R. Partch, and T. Weil, *Proc. Natl. Acad. Sci. U.S.A.*, in press.

(34) S. N. Bhattacharnya and K. P. Kundu, *Int. J. Radiat. Phys. Chem.*, **4**, 31 (1972).

(35) The formulation of "complexes" to explain reactions and kinetic data is a great temptation but, particularly when they cannot be independently demonstrated, has little more intellectual justification than invoking malignant spirits. However, since suitable complexes can fit almost any data, the temptation is real, and I have done it myself.

(36) M. B. Dearden, C. R. E. Jefcoate, and J. R. Lindsay Smith, *Adv. Chem. Ser.*, No. 77, 260 (1968).

(37) Since such formulations imply a high hydroxyl radical flux in one's liver, their reluctance has been understandable.