COMMENTARY

Intermediates in the Reactions of Fenton Type Reagents

In a recent Account,[1] Sawyer, Sobkowiak, and Matsushita make the sweeping generalization that Fenton reagents (which they define broadly as combinations of lower valence Fe, Cu, Co, Mn, etc., with various attached ligands plus H_2O_2 or an alkyl hydroperoxide ROOH) "*do not produce* (a) free HO•, (b) free carbon radicals, (c) aryl adducts HO—Ar•" and they imply in the text that, with hydroperoxides, free alkoxy radicals RO• are not produced either.[2]
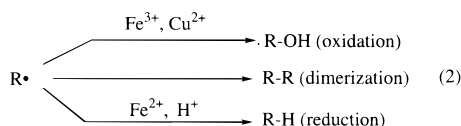
I believe that this generalization is quite unjustified and blithely overlooks a mass of experimental evidence that has accumulated over the past 50 years, evidence that is not only consistent with a, b, or c but is very difficult to explain convincingly by other means. I can only cite a few examples from hundreds available.

The carbon radical question is most easily disposed of. In 1962, Dixon and Norman[3] described a flow system for obtaining ESR spectra of intermediates in Fenton-type reactions, and in the next few years, many papers were published by Norman's group and others clearly showing carbon centered radicals derived from both aliphatic and aromatic substrates.[4] Further, several aromatic systems yielded the spectra of hydroxycyclohexadienyl radicals (HO—Ar•) identical with those reported in pulse radiolysis experiments in the absence of metal ions.[4]

One argument advanced by Sawyer et al. in their interpretation of Fenton-type systems is that, when hydroxyl radicals are generated in radiation chemistry and allowed to react with substrates, the products are chiefly dimers, while in Fenton-type systems, they are oxygenated products. This is only partially true and completely ignores the fact that, in Fenton systems, intermediate radicals, presumably produced by a sequence such as
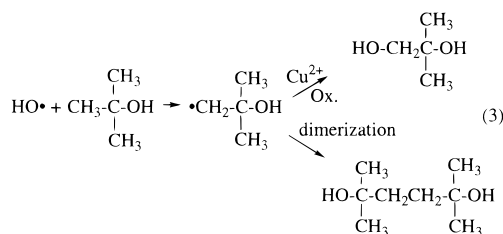
$$H_2O_2 + Fe^{2+} \longrightarrow FeOH^{2+} + HO• \xrightarrow{R-H} H_2O + R• \quad (1)$$

can be oxidized or reduced by the metal ions present to give a variety of nondimeric products.

$$R• \begin{cases} \xrightarrow{Fe^{3+}, Cu^{2+}} R\text{-OH (oxidation)} \\ \xrightarrow{} R\text{-R (dimerization)} \\ \xrightarrow{Fe^{2+}, H^+} R\text{-H (reduction)} \end{cases} \quad (2)$$

Further, product distributions can vary dramatically with small changes in reaction conditions. Such metal ion-radical reactions have been exhaustively studied,[5] and their mechanisms are well understood so that their effect in Fenton-type systems is quite predictable.
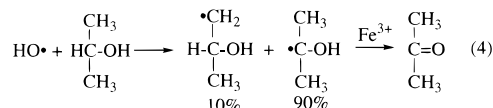
As examples, Fenton's reagent oxidation of *tert*-butyl alcohol gives dimer as essentially the sole product since primary radicals are not oxidized by Fe^{3+}. Addition of Cu^{2+}, which is a less discriminating oxidant, gives little dimer but, instead, 2-methyl-1,2-propanediol.[6] Again, in Fenton's re-

$$HO• + CH_3\text{-}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}\text{-OH} \rightarrow •CH_2\text{-}\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}\text{-OH} \xrightarrow[\text{dimerization}]{\overset{Cu^{2+}}{\text{Ox.}}} \begin{array}{c} \overset{\displaystyle CH_3}{|} \\ HO\text{-}CH_2\text{-}\underset{\underset{\displaystyle CH_3}{|}}{C}\text{-OH} \end{array}$$

$$\overset{\overset{\displaystyle CH_3}{|}\overset{\displaystyle CH_3}{|}}{HO\text{-}C\text{-}CH_2CH_2\text{-}C\text{-OH}}_{\underset{\displaystyle CH_3}{|}\underset{\displaystyle CH_3}{|}} \quad (3)$$

agent oxidation of acetonitrile,[7] the cyanomethyl radical produced is easily reduced by ferrous ion. If the latter is kept low by slow addition of ferrous ion to H_2O_2—acetonitrile, the reaction gives a substantial yield of succinonitrile from dimerization of the •CH_2CN radical. Addition of H_2O_2 to ferrous ion—acetonitrile gives only traces of any product whatsoever, since most of the cyanomethyl radicals are reduced back to starting material.[7]

Such radical—metal ion reactions must also be taken into account in evaluating ESR spectra. In 1965, Shiga[8] reported that, in the oxidation of 2-propanol with iron—H_2O_2, spectra indicated the 2-hydroxy-1-propyl radical, while with Ti^{3+}, the 2-hydroxy-2-propyl radical was seen, and he suggested that two different oxidizing species were involved. We subsequently showed[6] that with iron about 90% of attack was on carbon-2 as expected, but that the 2-hydroxy-2-propyl radical was immediately oxidized to acetone by the ferric ion.

$$HO• + \overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{HC}}\text{-OH} \longrightarrow \underset{\underset{10\%}{}}{\overset{\overset{\displaystyle •CH_2}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{H\text{-}C}}\text{-OH}} + \underset{\underset{90\%}{}}{\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{•C}}\text{-OH}} \xrightarrow{Fe^{3+}} \overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}\text{=O} \quad (4)$$

Accordingly, in Shiga's experiment, only the 10% or so of 1-propyl radical remained to be seen. On the other hand, Ti^{4+} is not a strong oxidant and the major product appeared in the spectra.

Fenton-type oxidations of aromatics are particularly complicated but, I believe, are still consistent with a scheme involving initial formation of a hydroxycyclohexadienyl radical which may be oxidized to a phenol by Fe(III) or Cu(II) or undergo a reversible acid-catalyzed dehydration to a radical cation. This can be reduced back to starting material by Fe(II) or, with alkylaromatics, undergo side-chain fragmentation to give a benzylic radical which may dimerize or be oxidized further.[9]

(5)
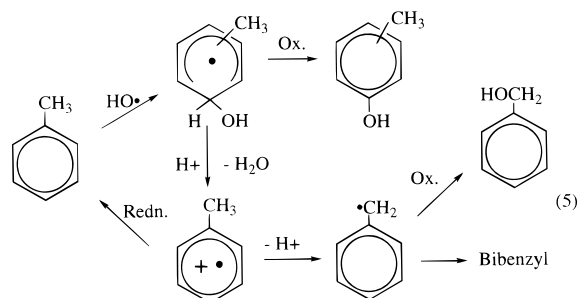
By adjusting conditions with toluene or phenylacetic acid, the major product may be shifted between a mixture of phenols, bibenzyl, benzyl alcohol, or nothing at all. Further, the isomer distribution among the phenols may vary appreciably with experimental conditions.[9] In short, arguing the nature of the oxidant in Fenton-type oxidations of aromatics on the basis of product distributions is a risky business unless the experimental conditions are exactly specified.

Proof that hydroxyl radicals are intermediates in Fenton systems involving H_2O_2 is complicated by the fact that an alternate interpretation involving an intermediate ferryl radical FeO^{2+} or $FeOH^{3+}$ rather than $HO^{\bullet}$ has long been available[10] and predicts identical kinetics and stoichiometry. A major argument for $HO^{\bullet}$ is that relative reactivities of a whole range of substrates (usually compared with the rate of reduction of the oxidant ($HO^{\bullet}$ or ferryl ion) by Fe^{2+}) are in substantial agreement with rates of reaction of $HO^{\bullet}$ measured by radiation chemists in metal-free systems.[9] Such coincidence for a ferryl intermediate seems unlikely, but more conclusive tests have been difficult to devise. One, originally used successfully by radiation chemists to distinguish between the reactions of hydrogen atoms and solvated electrons, is the Brønsted Bjerrum treatment of the effect of ionic strength: reactions between ions and neutral species will be unaffected by ionic strength, but those between ions of like charge will be accelerated. To my knowledge, this has only been applied to one system, the Fenton's reagent oxidation of methanol.[9,11] Here the relative rates of attack of the intermediate oxidant on methanol and ferrous ion were indistinguishable with and without addition of 0.5 M $NaClO_4$. Had the species been a charged ferryl ion, the rate of the latter should have been increased by a factor of about 10. This simple test could certainly be applied to other aqueous systems.

To examine the case for alkoxy radicals in Fenton-type reactions involving hydroperoxides, there are two diagnostic reactions of alkoxy radicals which have often been used for their identification: β-scission and intramolecular hydrogen abstraction. There are innumerable examples of the first in Fenton-type reactions, one of the earliest being the Fenton's reagent oxidation of 1-hydroxycyclohexyl hydroperoxide to yield a C_{12} dibasic acid, $HOOC(CH_2)_{10}COOH$[12] (eq 6a).
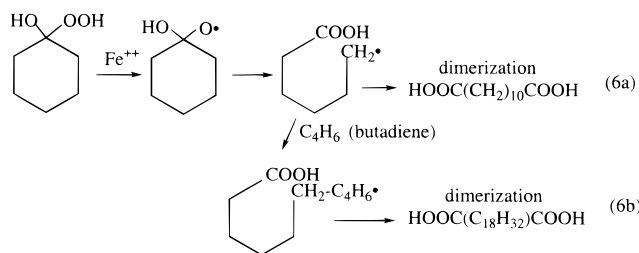
A recent interesting example is *o*-methylcumene hydroperoxide which rapidly undergoes both reactions to yield *o*-methylacetophenone plus a methyl radical and the *o*-(2-hydroxy-2-propyl)benzyl radical in a known ratio and thus provides a particularly convincing test for alkoxy radical production in Fenton-type systems.[13]
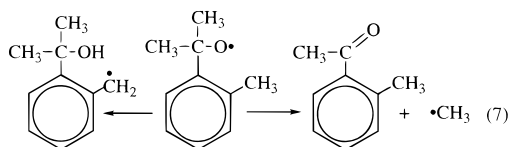
Even if these diagnostic tests indicate alkoxy radicals, the argument can be made that some "complexed species" just happens to behave like the free alkoxy radical. As examples accumulate, particularly when the data on competing rates are quantitative, this position becomes increasingly untenable.

Finally, there are a very large set of Fenton-type reactions in which the products are inexplicable except as the result of addition of an oxygen or carbon radical to another molecule in the system. The initiation of free radical polymerization by Fenton-type reagents has been known for over 50 years, and the efficiency of the initiation process was convincingly demonstrated by Baxendale, Evans, and Park in 1946.[14] Since then, such polymerizations have been studied exhaustively and millions of tons of synthetic rubber and other polymers manufactured using such initiator systems.

In 1951, Kharasch showed that under suitable conditions lower molecular weight products can also be obtained, e.g. from butadiene dimers $ROC_4H_6C_4H_6OR$ (R = H or *tert*-butyl) using ferrous ion and H_2O_2 or *tert*-butyl hydroperoxide, respectively.[15] With 1-hydroxycyclohexyl hydroperoxide−butadiene, the alkoxy radical undergoes ring opening before addition to give a C_{20} dibasic acid in yields of up to 75%[16] (eq 6b). Since then there have been dozens, if not hundreds, of examples of such trapping with results entirely consistent with observations when the intermediate oxygen and carbon radicals are generated by other means.

If I regard Sawyer et al.'s position as contrary to a mass of experimental data, I should state my own view. I certainly agree that H_2O_2 and ROOH are strong nucleophiles and Fenton-type reactions must start with some sort of association or complex formation between the peroxide and a metal ion. The question is what happens next, and when a substrate is attacked, what is the intermediate or actual oxidant? I think that there are at least three possibilities for which good experimental evidence exists in suitable cases.

(1) The complex itself is the oxidant with presumably no change in the valence of the metal. With higher valence metals which are not easily further oxidized, e.g. Mo(VI), V(V), and Ti(IV), there are several examples. The complexes are two-electron oxidants with many of the properties of peracids, notably the ability to epoxidize olefins. The "oxirane" process by which propylene oxide is manufactured from propylene and *tert*-butyl hydroperoxide is an example, as are Sharpless' stereospecific epoxidations using Ti(IV) coordinated with chiral ligands. I know of no evidence for radical intermediates in this group, and Ingold has shown conclusively that radicals are not intermediates in one Ti(IV) system.[17]

(2) The complex undergoes an internal two-electron oxidation to give a higher valence metal which then acts as the intermediate oxidant (in principle, this intermediate oxidant's subsequent attack on substrate could be either a one- or two-electron oxidation). The "ferryl" species mentioned earlier would be such a case. The most convincing examples are in enzymatic reactions involving iron porphyrins or (μ-oxo) diiron complexes in which the intermediate oxidants appear to be formally an Fe(V) species. Because of the biological interest in these reactions, there have been many efforts to devise simpler model systems which follow similar reaction paths using metal porphyrins or other metal chelates. As to their success, see below.

(3) The complex undergoes a net internal one-electron oxidation−reduction to give a higher valence metal and a free

oxygen radical, HO• or RO•, which then serves as the intermediate oxidant. Because of the enormous amount of data of the sort I have cited, I think this is the path of Fenton-type reactions which has been most frequently observed, which is the best understood, and, happily, one with highly predictable consequences (although they may be complex and very sensitive to reaction conditions). Accordingly, with new systems, I have long argued, this path needs to be rigorously excluded before introducing a mythology of complex-based intermediate oxidants with properties based solely on the experimental results which they were invented to explain.

My concern here is solely with refuting Sawyer's sweeping generalization that path 3 does not exist for Fenton-type systems, and I have not considered the experimental data on the precise systems which he has examined. However, I must note that ,while type 1 or type 2 mechanisms have recently been proposed for a number of quite similar systems,[18] further experiments have shown quite convincingly that many actually follow type 3 paths with hydroxyl or alkoxyl radicals as the intermediate oxidants.[13,19]

Cheves Walling

Box 537
Jaffrey, New Hampshire 03452

References

(1) Sawyer, D. T.; Sobkowiak, A.; Matsushita, T. *Acc. Chem Res.* **1996**, *29*, 409.
(2) For clarity I shall refer to Fenton's original system of Fe^{2+} and H_2O_2 in acid solution as Fenton's reagent, and other metal ion−peroxide combinations as Fenton-type systems. Ideally the latter term should be restricted to combinations involving the same sort of intermediate oxidants as Fenton's reagent itself.
(3) Dixon, W. T.; Norman, R. O. C. *Nature (London)* **1962**, *196*, 891.
(4) Norman, R. O. C. *Adv. Phys. Org. Chem.* **1967**, *5*, 53.
(5) Sheldon, R. A.; Kochi, J. K. *Metal Catalysed Oxidations of Organic Compounds*; Academic Press: New York, 1981.
(6) Walling, C.; Kato, S. *J. Am. Chem. Soc.* **1971**, *93*, 4275.
(7) Walling, C.; El Taliawi, G. M. *J. Am. Chem. Soc.* **1973**, *95,* 844.
(8) Shiga, T. *J. Phys. Chem.* **1965**, *69*, 3805.
(9) Walling, C. *Acc. Chem Res.* **1975**, *8*, 125.
(10) Bray, W. G.; Gorin, M *J. Am. Chem. Soc.* **1932**, *54,* 2134.
(11) Walling, C.; El Taliawi, G. M.; Johnson, R. A. *J. Am. Chem. Soc.* **1974**, *96* 133. Unfortunately, this result was not adequately emphasized and has been generally overlooked.
(12) Hawkins, E. G. E. *J. Chem. Soc.* **1955,** 3463.
(13) MacFaul, P. A.; Arends, I. W. C.; Ingold, K, U.; Wayner, D. D. M. *J Chem. Soc., Perkin Trans. 2* **1997**, 135.
(14) Baxendale, J. H.; Evans, M. G.; Park, G. S. *Trans. Faraday Soc.* **1946**, *42*, 155.
(15) Kharasch, M. S.; Arimoto, F. S.; Nudenberg, W. *J. Org. Chem.* **1951**, *16*, 1556.
(16) Kharasch, M. S.; Nudenberg, W. *J. Org. Chem.* **1954**, *19*, 1921.
(17) Oldroyd, R. D.; Thomas, J. M.; Maschmeyer, T.; MacFaul, P. A.; Snelgrove, D. W.; Ingold, K. U.; Wayner, D. D. M. *Angew Chem., Int. Ed. Engl.* **1996**, *35*, 2787.
(18) Cf., e.g.: Barton, D. H. R.; Dollar, D. *Acc. Chem Res.* **1992**, *25*, 504. Leising, R. A.; Kim, J.; Perez, M. A.; Que, L., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 9524. Kojima, T.; Leising, R. A.; Yan, S.; Que, L., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 11328. Kim, J.; Harrison, R. G.; Kim, C.; Que, L. *J. Am. Chem. Soc.* **1996**, *118*, 8, 4373. Ellis, P. E., Jr.; Lyons, J. E. *Coord. Chem. Rev.* **1990**, *105*, 181.
(19) Cf., e.g.: Arends, I. W. C. E.; Ingold, K. U.; Wayner, D. D. M. *J. Am. Chem. Soc.* **1995**, *117*, 4710. MacFaul, P. A.; Ingold, K. U.; Wayner, D. D. M. *J. Am. Chem. Soc.*, submitted. Newcomb, M.; Simakov, P. A.; Park, S. U. *Tetrahedron Lett.* **1996**, *37*, 819. Snelgrove, D. W.; MacFaul, P. A.; Ingold, K. U.; Wayner, D. D. M. *Tetrahedron Lett.* **1996**, *37*, 823. Minisci, F.; Fontana, F.; Aranco, S. Recupero, F.; Zhao, L. *SYNLETT* **1996**, 119. Perkins, M. J. *Chem. Soc. Rev.* **1996**, 229. Grinstaff, M. W.; Hill, M. G.; Labinger, J. A.; Gray, H. B. *Science* **1994**, *264*, 1311. Moore, K. T.; Horvath, I. T.; Therien, M. J. *J. Am. Chem. Soc.* **1997**, *119*, 1791.