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Iron-Catalyzed Oxidative Decarboxylation of Benzoylformic Acid[1]

Sir:

To identify the chemical roles of iron in biological oxidations and, as well, to develop selective iron oxidants for organic synthesis, we have initiated a mechanistic study of the chemistry of nonporphyrin oxidase enzyme models.[2,3] We herein report a mechanistic characterization of the significant catalysis by soluble iron salts in the oxidative decarboxylation of benzoylformic acid (**1**) to benzoic acid (**2**). This process

$$\underset{\mathbf{1}}{\mathrm{PhC(=O)C(=O)OH}} + \mathrm{H_2O_2} \xrightarrow{Fe^{2+}} \underset{\mathbf{2}}{\mathrm{PhCO_2H}} + \mathrm{CO_2} + \mathrm{H_2O}$$

mimics, and may thus provide a partial model for, the conversion of α-ketoglutaric acid (αKG) into succinic acid by that class of αKG-dependent mixed-function oxidase enzymes. To the extent that iron in acidic solutions of hydrogen peroxide can produce a manifold of reactive intermediates,[4] our results may have bearing on the role of iron in other Fenton reagent based oxidative processes, such as the Ruff degradation and related decarboxylations.[5]

In aqueous solutions of hydrogen peroxide at pH (H_0) between -1 and $+2$, **1** undergoes relatively slow decarboxylation to form **2** in essentially quantitative yields.[6,7] The addition of catalytic amounts of ferrous salts (perchlorate, sulfate) to these reaction mixtures causes a dramatic pH-dependent rate enhancement, without reducing the yield of **2.** As listed in Table I, at pH 2.0 ($HClO_4$) the concentration corrected[8] ratio of catalyzed to uncatalyzed reaction rates is 5.6×10^4!

We have previously noted the effects of pH on the kinetics of conversion of **1** into **2** in the absence of iron salts.[6] Hydronium ion and water (spontaneous) catalyzed addition of peroxide to the α-ketocarbonyl of **1** is largely rate limiting in acidic media. The apparent *base*-promoted conversion of **1** into **2** over the pH range -1–2 in the presence of added iron salts (see Table I, k_{cat} increases with increasing pH) clearly demands a new path to product.[9] Likely catalytic roles for iron under our reaction conditions may be to (A) produce hydroxyl radicals, which are responsible for conversion of **1** into **2,** (B) chelate both **1** and an equivalent of hydrogen peroxide to promote decarboxylation through subsequent interactions of these ligands, and (C) undergo oxidation to form a highly oxidized and very reactive iron species prior to the decarboxylation. We conclude that the prior oxidation process is most consistent with the following data.

A radical mechanism propagated by ·OH may be excluded based on experiments in which added EDTA[10] diminishes the rate enhancement induced by iron,[11] since iron–EDTA complexes in aqueous hydrogen peroxide are a recognized source of hydroxyl radicals.[4] Thus, as the EDTA concentration increases from 0 to 4.8×10^{-4} M (at which point the molar ratio of EDTA to iron is unity), k_{obsd} smoothly decreases from 2.8×10^{-2} s^{-1} to 1.5×10^{-3} s^{-1}, the value of k_{obsd} in the absence of added iron (see Table II), and remains invariant with increased concentrations of EDTA. A reasonable interpretation of these data involves simple preferential chelation and sequestering of iron by EDTA, rather than **1.**[12,13] Indeed, the catalytic effect of iron can also be completely deleted by adding fluoride ion which can coordinate and sequester the iron from **1.**[13] Similarly, high concentrations (0.5 M) of phosphate and various carboxylate salts also suppress the rate enhancement due to iron.[13,14]

To differentiate between mechanisms B and C, we have examined (see Table II) the effect of several other metal ions on the kinetics of the oxidative decarboxylation of **1.** Quite likely, many metals would be effective as Lewis acids (for example Al^{3+} or Zn^{2+}), whereas only selected ions could be oxidized to produce metal oxidants that are more reactive than hydrogen peroxide. Iron clearly stands out as a uniquely effective catalyst. Of the other metals studied, only copper and ruthenium exhibit any significant rate enhancement. Most ions have no kinetic effect, and several of the metals (for example, Zn^{2+} and Ag^+) *retard* the conversion of **1** into **2,** most likely through coordinative stabilization of the α-dicarbonyl functionality.[15] Ferric and ferrous salts appear as equally effective catalysts. A critical issue here is identification of the rate-limiting step in the overall conversion of **1** into **2.**[16] One possibility is that interaction of the metal ion with **1** and hydrogen peroxide is slow. This would result from either slow metal ion oxidation or slow ligand substitution. Alternatively, the de-

Table I. Kinetics for Oxidative Decarboxylation of Benzoylformic Acid[a]

pH (H_0)[b]	$10^3 k_0$, M^{-1} s^{-1} [c,e] no iron	k_{cat}, M^{-2} s^{-1} [d,e] iron added	rel rate, enhancement[f] due to iron
−1.0	13	0	0
0.0	7.5	10	1.3×10^3
1.0	4.8	41	8.5×10^3
2.0	2.7	150	5.6×10^4

[a] Reactions were followed spectrophotometrically at 350 nm, at 25 °C. The initial concentration of **1** was 4.8×10^{-3} M. At each pH listed the experimentally determined rate law followed $k_{obsd} = k_0[H_2O_2] + k_{cat}[H_2O_2][Fe]$ over the given concentration ranges.[c,d] [b] Degassed aqueous $HClO_4$–$NaClO_4$ solutions at 1.0 M ionic strength; see ref 7. [c] Second-order rate constants determined from pseudo-first-order reactions by varying H_2O_2 concentrations between 0.2 and 1.0 M. [d] Third-order rate constants determined at 0.48 M H_2O_2 and catalytic concentrations of $Fe(ClO_4)_2$ of $<5 \times 10^{-4}$ M. [e] Error limits ±10%. [f] Enhancement factor defined by $(k_{cat}/k_0) \times 1$ M; see ref 8.

Table II. Kinetics of Metal Ion Catalyzed Oxidative Decarboxylation of Benzoylformic Acid[a]

metal ion added[b]	$10^3 k_{obsd}$, s^{-1} [c]	metal ion added[b]	$10^3 k_{obsd}$, s^{-1} [c]	metal ion added[b]	$10^3 k_{obsd}$, s^{-1} [c]
none	1.6	Co^{2+}	1.4	Cd^{2+}	1.5
Na^+	1.5	Ni^{2+}	1.6	In^{3+}	1.8
Mg^{2+}	1.2	Cu^{2+}	4.8	Os^{4+}	1.6
Al^{3+}	1.5	Zn^{2+}	0.9	Ir^{3+}	0.9
V^{3+}	1.5	Mo^{6+}	1.9	Pt^{2+}	1.5
Cr^{3+}	1.5	Ru^{3+}	7.6	Au^{3+}	1.0
Mn^{2+}	1.6	Rh^{3+}	1.6	Hg^{2+}	0.7
Fe^{2+}	28.0	Ag^+	0.7	Tl^{1+}	1.3

[a] Temperature 32 °C, pH 2.0, $[H_2O_2] = 0.48$ M, other reaction conditions as described in Table I. [b] Metal ion concentration is 4.8×10^{-4} M. [c] Error limits ±10%.

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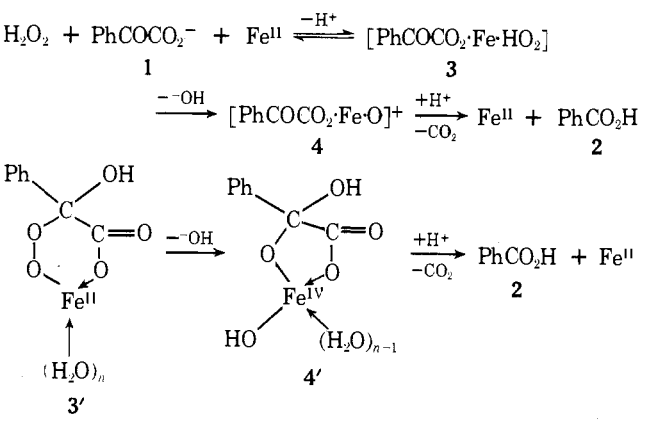
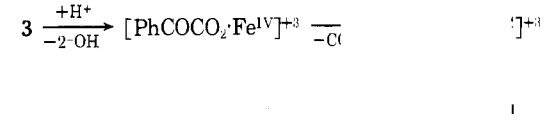
Scheme I



Scheme II



carboxylation of **1** may be rate limiting. That the slow step involves formation of a reactive iron oxidant (mechanism C) is supported by the following observations:[17] (1) iron catalyzes the decarboxylation of other α-keto acids and exhibits a value for k_{cat} that is insensitive to the structure of the α-keto acid and (2) the rate for iron-catalyzed loss of hydrogen peroxide (through either disproportionation or decarboxylation) is independent of the presence or absence of the α-keto acid.

Based on the observed metal ion specificity for rate enhancement, we favor mechanisms such as those shown in Schemes I and II[16] in which iron participates in the actual electron-transfer process (mechanism C).[18] Further support for this conclusion comes from the observation that iron also exhibits strong catalysis in the presence of peroxyacetic acid and *tert*-butyl hydroperoxide. If mechanism B were operative, internal delivery of a peroxo group chelated to iron would likely be possible only with the "double ended" oxidant, HOOH. If one of the hydrogens were replaced by an acyl or *tert*-butyl group, nucleophilic attack on **1** by a peroxide molecule coordinated to iron through a hydroxyl group would be blocked. All three peroxide derivatives are, however, capable of oxidizing iron to form a common reactive metal species, such as **4′**, that can convert **1** into **2**, as shown in the schemes. Moreover, highly oxidized iron species have been previously suggested as oxidants in other reactions.[20] Although both of these mechanisms are speculative in detail, each incorporates the formation of an iron(IV) species consistent with our observations. A major difference in these pathways lies in the presence (Scheme I) or absence (Scheme II) of an oxygen, perhaps derived from the peroxide, that is associated with the iron in the actual decarboxylation step. Additional studies to characterize this catalytic process more fully are in progress.

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References and Notes

(1) This work was presented in part at the 175th National Meeting of the American Chemical Society, Anaheim, Calif., March 1978.
(2) In contrast to the widespread use of iron as a redox element in biological systems, there are relatively few applications of iron-promoted oxidations in organic synthesis.[3]
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(4) For a review, see C. Walling, *Acc. Chem. Res.*, **8**, 125 (1975), and references therein.
(5) For an overview, see "Organic Peroxides", D. Swern, Ed., Wiley-Interscience, New York, 1971. We thank a referee for stressing this ramification of our investigation.
(6) B. Siegel and J. Lanphear, *J. Org. Chem.*, **44**, 942 (1979).
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(8) To compare first-, second-, and third-order rate processes, the higher order rate constants have been normalized to 1 M standard states.
(9) (a) C. A. Bunton, *Peroxide React. Mech., Pap. Conf., 1960*, 16 (1962); (b) G. A. Hamilton, *Prog. Bioorg. Chem.*, **1**, 83 (1971).
(10) EDTA is ethylenediaminetetraacetic acid.
(11) We have observed that the rate of hydrogen peroxide disproportionation by iron is increased in the presence of EDTA over the pH range 0–4.
(12) Although EDTA could act as a radical trap[4] to retard the decarboxylation of **1**, such a mechanism seems unlikely in view of the similar rate dimunition induced by fluoride, phosphate, and several carboxylate salts (see text).
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(17) B. Siegel and J. Lanphear, unpublished results.
(18) Since many of the metal ions studied (for example manganese and tin) are able to generate ·OH through the decomposition of hydrogen peroxide, the unique catalytic ability of iron provides further evidence against a hydroxyl radical path.[4,19]
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Carboxylic and Phosphate Esters of α-Fluoro Alcohols[1]

Sir:

Fluorine substituted substrate analogues have played an increasingly important role in the elucidation and rational perturbation of biological processes.[2,3] The exceptional utility of fluorine stems from its high electronegativity and small size, its Van der Waals radius (~1.35 Å) not greatly exceeding that of hydrogen (~1.10 Å).[4] This dimensional parity is particularly important in biological situations, where binding of substrates to sterically defined macromolecular sites is a prerequisite to fruitful interaction, although the unique electronic properties of fluorine also make it a standard tool in the study of chemical transformations. Owing to the absence of methods for their preparation, however, the rich potential of carboxylic and phosphate esters of α-fluoro alcohols as chemical and biochemical probes has never been exploited.[5] Although a few carboxylic esters of perfluorinated, and consequently atypical, alcohols have been reported,[6] to our knowledge no phosphorus ester of an α-fluoro alcohol has ever been prepared.

The most common synthesis of esters, the reaction of alcohols with esterifying reagents, is not viable with α-difluoro alcohols owing to their inherent instability. Thus, trifluoromethanol, the only simple α-fluoro alcohol which has been isolated, undergoes exothermic loss of HF at temperatures above −20 °C.[7,8] Furthermore, although α-fluorinated ethers

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