

borations. When the hydroboration was complete, the reaction flask was fitted with a short reflux condenser and several drops of 1 *N* NaOH solution was added. Then 2 drops of 30% H₂O₂ was added causing the reaction mixture to reflux. The pH of the mixture was maintained at *ca.* 9 by dropwise addition of 1 *N* NaOH as 3 ml of 30% H₂O₂ was added at a rate which maintained reflux. Stirring was continued for 15 min after all of the H₂O₂ had

been added. Sodium chloride (1 g) was added and the products were extracted with three 2-ml portions of ether. The ether solution was washed with saturated sodium chloride solution, dried (MgSO₄), and analyzed by glc (183 × 0.2 cm, 5% Carbowax 20M, 50 to 180°, *n*-nonane internal standard). The yields of the products, identified by comparison with authentic materials, are reported in Table III.

Fenton's Reagent. II. Reactions of Carbonyl Compounds and α,β -Unsaturated Acids¹

Cheves Walling*² and Gamil M. El-Taliawi

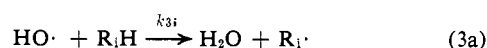
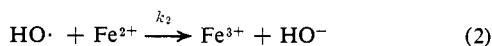
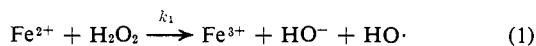
Contribution from the Departments of Chemistry, Columbia University, New York, New York 10027, and University of Utah, Salt Lake City, Utah 84112. Received August 7, 1972

Abstract: Carbonyl compounds such as acetone are readily attacked by hydroxyl radicals generated by the reaction of Fe²⁺ and H₂O₂, but the resulting carbonyl conjugated radicals are reduced to starting material by additional Fe²⁺. As hydroxyl radical traps, they thus retard the oxidation of methanol, and rate constants for hydroxyl radical reactions derived from the competitive inhibition are in good agreement with those from radiation chemistry. Hydroxyl radicals add readily to the double bonds of α,β -unsaturated acids, and the resulting radicals are also reduced with a net addition of water; *e.g.*, maleic acid is converted to malic acid. The acids inhibit alcohol oxidation by trapping both hydroxy and α -hydroxyalkyl radicals, the latter process providing an interesting possible synthesis of lactones.

In their investigation of Fenton's reagent (ferrous ion-hydrogen peroxide) reported in 1949,³ Merz and Waters noted that substrates such as acetone were not oxidized and had no effect on the stoichiometry of the Fe²⁺-H₂O₂ reaction but markedly retarded the oxidation of such other materials as methanol. They proposed that in these cases hydroxyl radical attack on the substrate indeed takes place, but that the resulting radicals are reduced back to starting material by ferrous ion.

This paper describes a reexamination of such systems, using the analysis which we have shown to be successful for interpreting the behavior of aliphatic alcohols⁴ and also a study of the related reaction of Fenton's reagent with α,β -unsaturated acids.

Kinetic Scheme. If H₂O₂ is added to an aqueous system containing an organic substrate and excess Fe²⁺ at pH 0-2, the hydroxyl radicals generated attack the substrate, and the subsequent course of the reaction and stoichiometry (moles of Fe²⁺ oxidized/mole of H₂O₂ added: $\Delta[\text{Fe}^{2+}]/\Delta[\text{H}_2\text{O}_2]$) depend upon the fate of the organic radicals so produced. For a system containing a variety of C-H bonds, the postulated reaction steps are the following.⁵



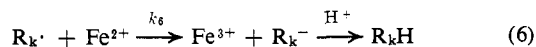
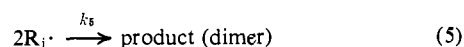
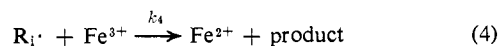
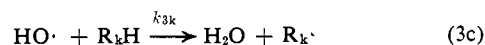
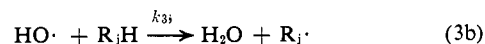
(1) Taken from the Ph.D. Thesis of G. El-Taliawi, Columbia University, 1972. Support of this work by a grant from the National Science Foundation is gratefully acknowledged.

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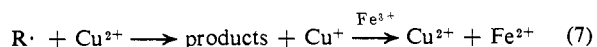
(3) J. H. Merz and W. A. Waters, *J. Chem. Soc.*, 515 (1949).

(4) C. Walling and S. Kato, *J. Amer. Chem. Soc.*, **93**, 4275 (1971).

(5) k_{31} , k_{3j} , and k_{3k} replace k_{31} , k_{32} , and k_{33} in our previous treatment.⁴



It is assumed the radicals produced in (3) behave as belonging to three distinct classes: those oxidized by Fe³⁺, R_i·; those which are inert and dimerize, R_j·; and those which undergo reduction by Fe²⁺, R_k·. As proposed by Merz and Waters and demonstrated further in our previous work, the α -hydroxy radicals from alcohols belong to the first group, and simple carbon radicals (such as those arising from hydroxyl radical attack on remote C-H bonds of alcohols) belong to the second. However, addition of cupric ion makes the latter oxidizable as well



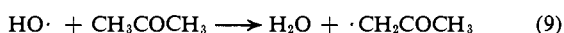
Thus the effect of added cupric ion on the Fenton's reagent system provides a useful tool for its analysis. If we assume with Merz and Waters that radicals from acetone and similar substrates belong to the third, reducible group, and consider a system containing methanol (R_iH) and acetone (R_kH), application of usual steady-state kinetics to eq 1-6 yields the stoichiometric equation

$$\frac{\Delta[\text{Fe}^{2+}]}{2\Delta[\text{H}_2\text{O}_2] - \Delta[\text{Fe}^{2+}]} = \frac{k_2[\text{Fe}^{2+}]}{k_{3i}[\text{R}_i\text{H}]} + \frac{k_{3k}[\text{R}_k\text{H}]}{k_{3i}[\text{R}_i\text{H}]} \quad (8)$$

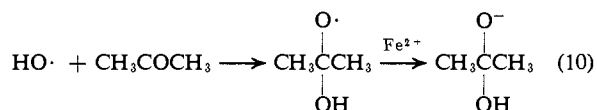
If ferrous ion consumption is measured in a series of

reactions in which the methanol/ Fe^{2+} ratio is held constant and the acetone varied, a plot of the left-hand side of (8) vs. the acetone/alcohol ratio should be linear with slope and intercept yielding k_{3k}/k_{3i} and k_2/k_{3i} , respectively. Equation 8 thus provides the basis of our analysis.

Acetone. A plot as just described for data from acetone-methanol systems is shown in Figure 1 and yields results in excellent agreement with predictions from the model on which our analysis is based. From the intercept, $k_{3i}/k_2 = 4.3$, the same value we reported previously⁵ for methanol systems alone. The slope yields $k_{3k}/k_{3i} = 0.081$ satisfactorily within the range of values of the ratio (0.066–0.197) calculated from the rate constants measured by the quite independent techniques of radiation chemistry and listed in the summary of Anbar and Neta.⁶ Further, comparison of the results obtained with acetone and perdeuterioacetone indicates a large kinetic isotope effect, $k_{3k}(\text{H})/k_{3k}(\text{D}) = 3.54$, showing that the reaction is the expected hydrogen abstraction (9) rather than some alternative



process such as the addition (10) proposed by Merz



and Waters.³

That the acetyl radical should be subject to relatively easy reduction is a plausible finding and, as shown below, reduction appears to be a general property of carbonyl-conjugated radicals. The acidity of acetone compared with hydrocarbons implies a large stabilization of the enolate anion, while both Russell⁷ and Benson⁸ conclude that the acetyl radical derives little stabilization from the adjacent carbonyl group. Finally, we find that added cupric ion has no effect on the acetone-methanol system, producing data identical with those in Figure 1. There is no evidence for oxidation of acetyl radicals by Cu^{2+} analogous to that observed with unsubstituted carbon radicals.⁹

Other Substrates. Product Studies. Investigation of several other carbonyl compounds yields similar results, and data are summarized in Table I. Both reactivities relative to methanol and absolute rate constants are listed, the latter calculated assuming $k_2 = 3.2 \times 10^6$. Comparison with radiation chemistry data, where available, shows good agreement as to relative reactivities, but somewhat higher absolute values, the same discrepancy noted in our alcohol studies.

All the above experiments were carried out by slow addition of H_2O_2 to systems approximately 0.02 M in ferrous ion. In order to demonstrate the actual existence of the radical intermediates, product studies

(6) M. Anbar and P. Neta, *Int. J. Appl. Radiat. Isotop.*, **18**, 493 (1967).

(7) G. A. Russell and J. Lokensgard, *J. Amer. Chem. Soc.*, **89**, 5059 (1967).

(8) R. K. Solly, D. M. Golden, and S. W. Benson, *Int. J. Chem. Kinet.*, **2**, 11 (1970).

(9) The lack of effect of Cu^{2+} is also evidence for no appreciable contribution of (10) to the reaction. Unless reduction was remarkably rapid, some β -scission of the intermediate radical would be anticipated yielding methyl radicals which would be oxidized by Cu^{2+} and thus perturb the stoichiometry (also no acetic acid is detected among the products of the acetone reaction).

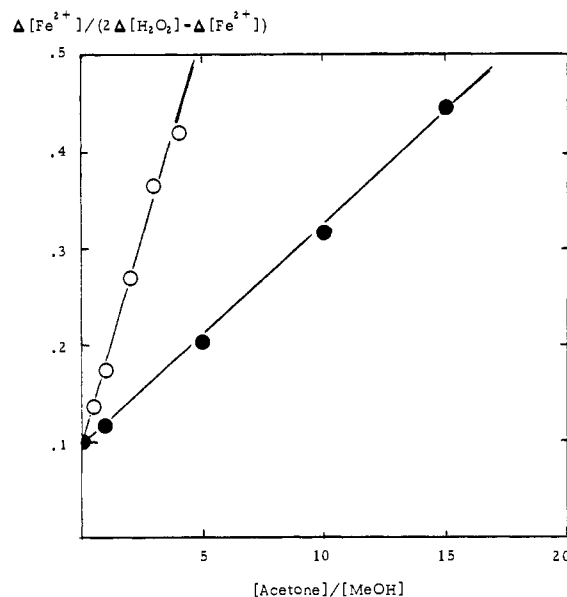


Figure 1. Plot of eq 8 for the acetone-methanol system: O, CH_3COCH_3 ; ●, CD_3COCD_3 . Conditions: $[\text{H}^+] = 0.1 \text{ M}$; $[\text{Fe}^{2+}]$, 0.02 M; $[\text{MeOH}]$, 0.1 M.

Table I. Reaction of Fenton's Reagent with Carbonyl Compound—Methanol Systems^a

Carbonyl compd	k_{3k}/k_{3i}	$10^{-7}k_{3k}$	Lit. ⁶
Acetone	0.080	11.1	4.3–7.7
Acetone- <i>d</i> ₆	0.026	3.6	
Acetic acid	0.022	3.0	1.4
Malonic acid	0.017	2.3	3.3–18 ^b
Succinic acid	0.097	13.3	

^a HClO_4 , 0.02 M; Fe^{2+} , 0.02 M; CH_3OH , 0.1 M; H_2O_2 , carbonyl compound variable; $T = 30^\circ$. ^b Malonate anion.

were carried out with acetone and acetonitrile as described, and also by inverse slow addition of ferrous ion to H_2O_2 -substrate solutions in order to maintain as low a ferrous ion concentration as possible. Results by glc analysis appear in Table II. They show sig-

Table II. Coupling Products from Acetone and Acetonitrile

Substrate	% yield ^a	
	Normal	Inverse addn
Acetone	Trace	2.3
Acetonitrile	5	25

^a Of 2,5-hexadione and succinonitrile, respectively, based on H_2O_2 added. No other products were detected.

nificant coupling under the latter conditions and also demonstrate how proper understanding of the Fenton's reagent system permits control of its synthetic utility. From the data we can also calculate approximate values for k_6 . Ferrous ion was added at the rate of 0.00077 mol $\text{l}^{-1} \text{ min}^{-1}$, and the average H_2O_2 concentration was 0.01 M. Taking $k_1 = 76.5$ at 30° ,¹⁰ and recognizing that 2 mol of ferrous ion is oxidized per H_2O_2 consumed, the average concentration of ferrous ion was approximately $5 \times 10^{-4} \text{ M}$. If we assume $k_5 = 10^9$ for the dimerization of acetyl radicals (a typical value for

(10) T. J. Hardwick, *Can. J. Chem.*, **35**, 428 (1957).

$$\Delta[\text{Fe}^{2+}]/2\Delta[\text{H}_2\text{O}_2] - \Delta[\text{Fe}^{2+}]$$

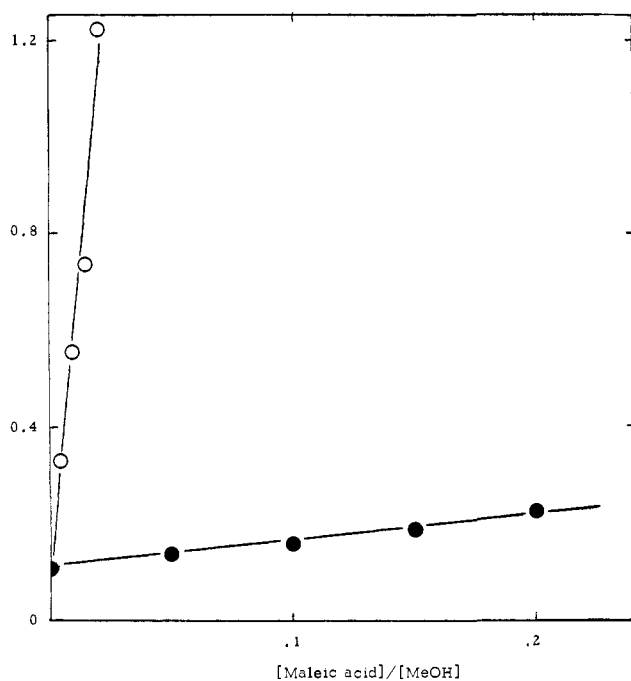
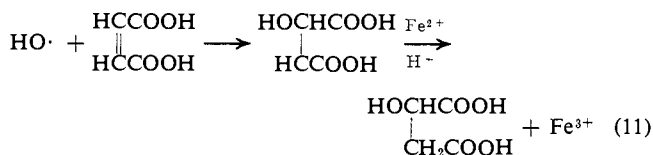


Figure 2. Plot of eq 8 for maleic acid-methanol: ●, 0.2 M Fe^{3+} added. Conditions: $[\text{H}^+]$, 0.1 M; $[\text{Fe}^{2+}]$, 0.02 M; $[\text{MeOH}]$, 0.1 M.

simple radicals in solution), we can calculate $k_6 \cong 1 \times 10^7$. A similar calculation for the normal reaction of acetonitrile ($\text{Fe}^{2+} = 0.02 \text{ M}$) gives $k_6 = 1.2 \times 10^6$.

Our conclusions about the easy reduction of carbonyl conjugated radicals rationalize several results on esr spectra of radicals produced in metal ion- H_2O_2 -substrate flow systems. With either Fe^{2+} -EDTA or Ti^{3+} , cyclohexanone gives a signal corresponding to β - or γ -hydrogen abstraction with no evidence for the α -radical.¹¹ Similarly, with Ti^{3+} and diethyl ketone, spectra indicate only β -hydrogen attack.¹² Since our data show that acetone is only slightly less reactive towards hydroxyl radicals than are the methyl groups of isopropyl alcohol, considerable α -hydrogen abstraction should have occurred in both of these systems. However, the Fe^{2+} -EDTA complex and Ti^{3+} are both stronger reducing agents than is the ferrous ion. We conclude that α -attack occurs but is followed by rapid reduction. Accordingly only those radicals resulting from hydroxyl radical attack at other points in the molecules survive in sufficient concentration for detection.

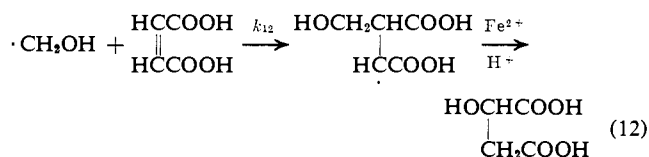
Maleic Acid. Since hydroxyl radicals are known to add to double bonds, our results with carbonyl compounds suggested that α,β -unsaturated acids such as maleic acid should react with Fenton's reagent to add



(11) T. Shiga, A. Boukhors, and P. Douzou, *J. Phys. Chem.*, **71**, 4264 (1967).

(12) R. O. C. Norman and B. C. Gilbert, *Advan. Phys. Org. Chem.*, **5**, 53 (1967).

the elements of water. The result is interesting in that the overall stoichiometry of the Fe^{2+} - H_2O_2 reaction is unchanged by the maleic acid, but the redox process is "coupled" with hydration in a manner similar to the coupling of reactions in biochemical systems. Experiments verified the predicted stoichiometry, reactions developed the characteristic lemon-yellow color of the malic acid-ferrous ion complex, and malic acid could be isolated from reaction mixtures as its dimethyl ester.¹³ As expected, maleic acid strongly inhibits the oxidation of methanol, but while a plot of the data using eq 8 is linear, Figure 2, the slope indicates an implausibly large value of $k_{3k} = 5.1 \times 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$. Since α -hydroxyalkyl radicals add readily to carbonyl conjugated double bonds,¹⁴ it occurred to us that maleic acid might also be acting as a trap for hydroxymethyl radicals, and thus interrupting the methanol oxidation at an additional point. If so, addition of ferric ion by increasing the rate of reaction 4 might eliminate (12) as a termina-



tion step. Experimentally, ferric ion sharply reduces the slope of plots of eq 8, which reach a constant value at $\text{Fe}^{3+} \geq 0.2 \text{ M}$, Figure 2. Under these conditions we calculate $k_{3k} = 7.1 \times 10^8$, a more reasonable value. As confirmation of the scheme, we have isolated paraconic acid (the lactone of the addition product) from our reaction mixtures as its methyl ester.

Experiments at intermediate ferric ion concentrations permit the determination of the relative reactivities of maleic acid and ferric ion toward the hydroxymethyl radical, k_{12}/k_4 . Combining (12) with (1-6) leads to the stoichiometric equation ($R_i\text{H}$ and $R_k\text{H}$ are methanol and maleic acid, respectively)

$$\frac{2\Delta[\text{H}_2\text{O}_2]}{2\Delta[\text{H}_2\text{O}_2] - \Delta[\text{Fe}^{2+}]} = \left(\frac{k_2[\text{Fe}^{2+}]}{k_{3i}[\text{R}_i\text{H}]} + \frac{k_{3k}[\text{R}_k\text{H}]}{k_{3i}[\text{R}_i\text{H}]} + 1 \right) \left(1 + \frac{k_{12}[\text{R}_k\text{H}]}{k_4[\text{Fe}^{3+}]} \right) \quad (13)$$

A plot of the left-hand side of (13) vs. $1/[\text{Fe}^{3+}]$ (holding other quantities constant) should be linear with predictable intercept, and from the slope k_{12}/k_4 can be calculated since the other quantities are known. The data show this behavior and yield $k_{12}/k_4 = 0.27$.

Other α,β -Unsaturated Acids. Fumaric and acrylic acids give results similar to maleic acid, but crotonic acid provides a more complicated case, since here hydroxyl radicals may attack the methyl group as well as add to the double bond. Experiments on crotonic acid alone were analyzed by plotting R vs. $2r(1 - R)$ in the stoichiometric equation

$$R = 2ar(1 - R) + b \quad (14)$$

where $r = [\text{Fe}^{2+}]/2[\text{RH}]$, $R = \Delta[\text{Fe}^{2+}]/2\Delta[\text{H}_2\text{O}_2]$, $a =$

(13) Malic acid has previously been reported as one of a complex mixture of products resulting from the reaction of Fe^{2+} -EDTA with H_2O_2 and maleic acid at higher pH: C. Nofre, Y. LeRouse, L. Goudot, and A. Cier, *Bull. Soc. Chim. Fr.*, 2451 (1964). The authors suggest a reaction scheme similar to (11).

(14) (a) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, Chapter 6; (b) C. Walling and E. S. Huyser, *Org. React.*, **13**, 136 (1963).

$k_2/(k_{3i} + k_{3j} + k_{3k})$, and $b = (k_{3i} + 2k_{3k})/2(k_{3i} + k_{3j} + k_{3k})$, as we have done previously to distinguish the point of hydroxyl radical attack on alcohols.⁴ Results appear in Figure 3. Interestingly cupric ion has no effect on the stoichiometry, suggesting that the allylic radical produced by attack on the methyl group is readily oxidized by Fe^{3+} ion and that addition is to the β carbon (yielding a nonoxidizable radical) as expected. On this basis we assume that, in analyzing the data of Figure 3, $k_{3j} = 0$, k_{3i} represents attack on methyl, and k_{3k} addition.

Rate constants for all α,β -unsaturated acids studied are summarized in Table III. In most radical additions,

Table III. Reactions of Hydroxyl and Hydroxymethyl Radicals with α,β -Unsaturated Acids

Acid	k_{3k}/k_{3i}	$k_{3k} \times 10^{-8}$ ^a	k_{12}/k_4
Maleic	0.515	7.1	0.27
Fumaric	1.24	17.1	0.59
Acrylic	1.58	21.5	0.081
Crotonic	2.96	37	<i>b</i>

^a Calculated assuming $k_{3i}/k_2 = 4.30^4$ and $k_2 = 3.2 \times 10^8$.

^b Not determined. k_{3i} for attack on allylic H is 1.3×10^9 .

e.g., copolymerization, fumaric acid is more reactive than maleic acid, and all the disubstituted acids are less reactive than acrylic acid, the usual explanations being steric inhibition of resonance and steric hindrance to addition, respectively.¹⁵ The fumaric-maleic relation is obeyed in Table III, but hydroxyl radical additions are in the order crotonic > acrylic > fumaric, that expected for a nucleophilic radical little subject to steric hindrance, presumably because of its small size. Toward the hydroxymethyl radical, which behaves as an electron-donating species,¹⁴ the electron-accepting ability of the second carboxyl group apparently outweighs the steric hindrance it introduces.

Our observation of reaction 12 suggests that the action of Fenton's reagent on mixtures of alcohols and α,β -unsaturated acids might provide a general synthesis of γ -lactones, analogous to the usual radical addition of alcohols, but with fewer complications due to telomer formation.¹⁴ Products of reaction of methanol and ethanol with acrylic acid were investigated, but the corresponding lactones were detected in only small amounts, 1.1 and 0.2%, respectively. Similar experiments were then carried out in the presence of 0.1 M fluoride ion which complexes Fe^{3+} and reduces its oxidation potential in the hope that this would favor reaction 12 by reducing the rate of (4). Under these conditions, lactone yields rose significantly to 16 and 11%, respectively. We have not attempted to optimize the reaction conditions further, but the results are encouraging. In fact, the whole question of the effect of changing ligands on the ease of radical oxidation and reduction by metal ions is an intriguing one and well

(15) C. Walling, ref 14a, Chapter 4.

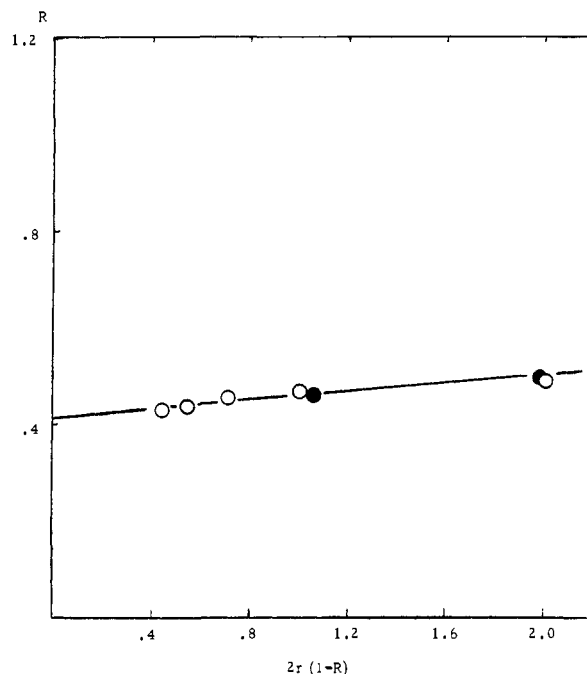


Figure 3. Plot of eq 14 for crotonic acid. Conditions: $[\text{H}^+]$, 0.1 M; $[\text{Fe}^{2+}]$, 0.02 M; ●, 0.04 M Cu^{2+} .

adapted to study by our techniques. Preliminary results show that fluoride ion significantly reduces the chain length of methanol oxidation, presumably by reducing the rate of hydroxymethyl radical oxidation to the point where radical coupling becomes important and thus blurring the distinction between "oxidizable" and "nonoxidizable" radicals.

Experimental Section

Materials. Stock solutions of reagents were prepared from analytical grade perchlorate salts, perchloric acid, and 30% H_2O_2 distilled under reduced pressure. Organic reagents were commercial materials, purified if necessary.

Competitive Kinetics. Reactions were carried out by adding H_2O_2 dropwise to Fe^{2+} -substrate solutions as described previously,⁴ and unreacted Fe^{2+} was determined by dichromate titration of aliquots. In general, experiments were carried out in 0.1 M acid and 0.02 M Fe^{2+} , and the amount of H_2O_2 was chosen to oxidize 5–10% of the Fe^{2+} present. Ratios of rate constants cited are all from least-squares fits to linear plots such as those shown.

Product Analyses. Yields of acetone and acetonitrile coupling products were determined by glc analysis after deionization of solutions with strong cation- and anion-exchange resins. Malic acid was identified as its dimethyl ester by adjusting a reaction mixture from 0.05 M maleic acid, 0.02 M $\text{Fe}(\text{ClO}_4)_3$, and 0.02 M H_2O_2 to pH 9, removing precipitated salts, reacidifying, evaporating, and extracting the residue with methanol. The methanol was evaporated and the residue taken up in ether and treated with CH_2N_2 . The ester was separated and identified by glc, yield 19%. Similar treatment of a maleic acid-methanol reaction mixture yielded methyl paraconate, separated by preparative glc and identified by ir and nmr spectra. Other lactones were identified by flame ionization glc of reaction mixtures using internal standards to determine yields. From ethanol-acrylic acid reactions, in addition to γ -valerolactone traces of δ -valerolactone were detected, presumably from the addition of β -hydroxyethyl radicals also formed in the reaction to acrylic acid.