The Iron(III)-Catalyzed Oxidation of Acetoin by Oxygen and Hydrogen Peroxide. A Model for Some Enzymic Redox Reactions[1]

Paul K. Adolf and Gordon A. Hamilton*[2]

Contribution from the Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802.
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Abstract: The kinetics, stoichiometries, and mechanisms of the following oxidations of acetoin (3-hydroxy-2-butanone) to biacetyl (2,3-butanedione) have been investigated: (1) the Fe(III)-catalyzed oxidation by O_2, (2) the Fe(III)-catalyzed oxidation by H_2O_2, and (3) oxidation by Fe(III) under anaerobic conditions. In addition, approximate rate constants for the acid-catalyzed enolizations of acetoin have been determined. At 25°, ionic strength *ca.* 0.2 *M*, and pH 1.5–2.3, the rate of O_2 uptake in reaction 1 follows the expression: rate = $(9.1 \times 10^{-7}$ $sec^{-1})$[Fe(III)][acetoin]/[H^+], and 2 mol of acetoin reacts with 1 mol of O_2 to give 2 mol of biacetyl. Under comparable conditions reaction 2 proceeds faster than reaction 1 and can occur by two different mechanisms, one (2a) which involves Fe(II) as an intermediate, and another (2b) in which Fe(II) is not an intermediate. In both cases 1 mol of acetoin reacts with 1 mol of H_2O_2 to give 1 mol of biacetyl. At 25°, ionic strength *ca.* 0.2 *M* and pH 1.6–2.1 the disappearance of H_2O_2 in reaction 2b follows the expression: rate = $(2.5 \times 10^{-3}$ M^{-1} $sec^{-1})$[Fe(III)]·[acetoin][H_2O_2]/[H^+]. Under similar conditions (pH 1.5–2.1) the disappearance of Fe(III) in reaction 3 follows the expression: rate = $(1.6 \pm 0.2 \times 10^{-6}$ $sec^{-1})$[Fe(III)][acetoin]/[H^+] and 1 mol of acetoin is oxidized by 2 mol of Fe(III) to 1 mol of biacetyl and 2 mol of Fe(II). The data indicate that free radicals derived from acetoin are not intermediates in any of reactions 1, 2b, or 3. Nonradical mechanisms consistent with the data are presented. The applicability of similar mechanisms to some metalloenzyme-catalyzed redox reactions and to reactions catalyzed by some metalloisomerases is considered.

It is now apparent that several metalloenzymes catalyze the oxidation or reduction of organic compounds by mechanisms which do not involve organic free radicals as intermediates.[3,4] However, the development of a more complete understanding of mechanisms for the enzymic reactions has been hampered by the fact that few related nonenzymic reactions have been characterized and studied thoroughly. Therefore, we have been investigating the mechanisms of a number of nonenzymic metal ion catalyzed oxidation–reduction reactions.[1,3–7] Our results on the Fe(III)-catalyzed oxidation of acetoin (3-hydroxy-2-butanone) to biacetyl (2,3-butanedione) by O_2 and H_2O_2 are reported here.

Several groups of workers have investigated the oxidation of acyloins by metal ions and metal ion complexes.[8–16] However, the metal ion catalyzed oxidation of acyloins by O_2, H_2O_2, or other oxidants has received little attention. In a general search for some metal ion catalyzed oxidations of organic compounds we observed that acetoin is readily oxidized by O_2 when Fe(III) is present at pH *ca.* 2. Since H_2O_2 is an expected product of the reaction, but could not be identified as such, we investigated the oxidation of acetoin by H_2O_2, and observed that Fe(III) is a catalyst for this reaction as well. Because preliminary experiments indicated that both these Fe(III)-catalyzed reactions can proceed by nonradical mechanisms, we have investigated the mechanisms of these reactions in detail. In addition, rate constants for the acid-catalyzed enolizations of acetoin and some characteristics of the Fe(III) reduction by acetoin in the absence of O_2 were determined. The results suggest that mechanisms proposed previously[3,4] for several metalloenzyme-catalyzed redox reactions, especially that for galactose oxidase, are reasonable. Furthermore, they indicate that metal ions are effective catalysts for enediol formation from α-hydroxy ketones; this step is presumably involved in enzymic isomerizations catalyzed by aldose–ketose isomerases which contain metal ions.

Experimental Section

Materials. Unless otherwise stated, all compounds were of the best reagent grade commercially available, and were used without further purification. Some of the salts used were: $Co(NO_3)_2 \cdot 6H_2O$, $[Co(NH_3)_5H_2O](NO_3)_3$, $Cr(NO_3)_3 \cdot 5H_2O$, CuCl, $Cu(NO_3)_2 \cdot 3H_2O$, $MgCl_2$, $MnSO_4 \cdot H_2O$, $Ni(NO_3)_2 \cdot 6H_2O$, $Ti(SO_4)_2 \cdot 9H_2O$, and $Zn(NO_3)_2 \cdot 6H_2O$. The method of Christensen[17] was used to prepare $Mn(C_2H_3O_2)_3 \cdot 2H_2O$. The preparation of $Fe(NO_3)_2$

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from $Fe(ClO_4)_2$ was effected by anion exchange on Dowex-I resin. Wet resin (50 ml) in the chloride form (capacity 1.3 mmol/ml) was purified and converted to the nitrate form by boiling successively with 50-ml volumes of 0.5 *M* NaOH, 0.5 *M* HNO_3, and 0.5 *M* $NaNO_3$, and rinsing twice with 50-ml volumes of distilled H_2O after each such treatment. The purified material was then packed into a column (18 mm × 18 cm) and eluted with 100 ml of 0.01 *M* HNO_3. Typically, 25-ml solutions of 0.15 *M* $Fe(ClO_4)_2$ were exchanged; the eluent was collected, thoroughly purged, and stored under a blanket of N_2 in the dark. The stock solutions of $Fe(NO_3)_2$ were kept at pH 2 (HNO_3) and were standardized regularly against $KMnO_4$, both with and without prereduction by the $SnCl_2$ method.[18] These titrations verified the absence of ferric ion. It was found that with proper deoxygenation less than 0.5% of a stock solution autooxidized per month. A stock solution of $Fe(NO_3)_3 \cdot 9H_2O$ (0.34, *M*, pH 1.2) was standardized in the same manner.[18]

All H_2O used in this research was doubly distilled, the second time on a Kontes WS-2 glass still following percolation through Barnsted organic and ion exchange columns. D_2O (99.8% D) was purchased from Diaprep, Inc., and $NaBD_4$ and $CDCl_3$ from Merck, Sharp and Dohme of Canada, Ltd. The 1 *N* DCl in D_2O solution was prepared using dry HCl gas and D_2O; therefore, it contained approximately 1% hydrogen. All solutions of H_2O_2 were prepared from Fisher Certified Reagent Grade 30% H_2O_2, and were standardized regularly against $KMnO_4$. Dilute H_2O_2 solutions (*ca.* 0.03 *M*) stored in dark bottles at pH 2 decomposed to the extent of about 5% per month.

Anhydrous diethyl ether (Mallinckrodt Analytical Reagent) used for extraction procedures was shaken over a small amount of $Fe_2SO_4 \cdot 7H_2O$ to decompose peroxides, and decanted before use. Benzoin, benzil, and lactic acid were supplied by Matheson Coleman and Bell and were used in preliminary experiments without further purification. Crude 2,3-butanedione (biacetyl, Aldrich Chemicals) was distilled through a vacuum jacketed Vigreux column. The fraction at 89–91° was collected and found to be pure by glpc and nmr.

3-Hydroxy-2-butanone. Crude acetoin (Aldrich, 85% aqueous solution) was distilled through a vacuum jacketed Vigreux column and three fractions at 89–91, 99.5–101, and 142.5–143.5° were collected. They contained biacetyl, 15% acetoin–H_2O azeotrope,[19] and acetoin respectively. The acetoin fraction was repeatedly distilled until pure by glpc and free of H_2O by nmr integration. Pure acetoin was then weighed and diluted with distilled H_2O and the pH adjusted with dilute HNO_3 to give 0.60 *M* acetoin, pH 2.2. The solution was stored in a dark bottle under a blanket of nitrogen because acetoin is slowly air oxidized.[20] So treated, less than 0.5% of the acetoin is oxidized to biacetyl over a period of 3 months.

3-Deuterio-3-hydroxy-2-butanone (Acetoin-*d*). To a stirred solution of biacetyl (15 g, 0.17 mol) in 50 ml of methanol in an ice-cooled flask was slowly added by dropping funnel a solution of 1 g of $NaBD_4$ (0.024 mol) dissolved in 20 ml of methanol and 5 drops of 2 *N* NaOH. After addition was complete, the mixture was allowed to warm up to room temperature, at which time 30 ml of H_2O was added, and the pH adjusted to *ca.* 4 with concentrated HNO_3. Aliquots (25 ml) of this mixture were chromatographed on a column (25 mm × 35 cm) of 28–200 mesh silica gel, using anhydrous diethyl ether as the eluent. After 75 ml (column volume) had passed through the column, 40 ml of a deep yellow band (biacetyl) was collected. The next 175-ml fraction contained the bulk of acetoin-*d* with a trace of methanol. A mixture of H_2O, 2,3-butanediol-d_2, borate salts, and methanol was obtained when the column was finally eluted with 100 ml of acetone. The combined acetoin-*d* fractions (700 ml) were stripped of solvent, and the remaining methanol and biacetyl removed by pumping at 1.0 mm. Water was added to the residue which contained acetoin-*d* plus high boiling organic contaminants, and acetoin-*d* was distilled as its aqueous azeotrope (bp 99.5–101°). The solution was found to be free of impurities by nmr; the spectrum showed only the expected proton resonances for 3-deuterio-3-hydroxy-2-butanone in water: singlet, δ 2.25 (3 H), singlet, 1.35 (3 H), and HOH at 5.0. To the limits of nmr detection, no acetoin-*h* characteristic resonances could be found. The concentration of acetoin-*d* in solution was determined by glpc using an internal standard and a solution of known concentration of acetoin-*h* for comparison of peak areas. The yield of acetoin-*d* was 10.4% (0.89 g, 10^{-2} mol). The same precautions against autoxidation were taken here as previously described.

Analytical and Kinetic Procedures. Proton nmr spectra were measured on a Varian A60-A spectrometer using $CDCl_3$ with tetramethylsilane (TMS) standard or D_2O with sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) standard. A Radiometer pH meter 4 was used for all pH measurements. Glpc analyses were performed on a Perkin-Elmer Model 800 gas chromatograph equipped with dual flame ionization detectors, two 11 ft × 1/8 in. copper columns packed with 20% Carbowax 20M on 80–100 mesh Gas Chrom Z, and Honeywell 1.0 mV strip chart recorder. With an N_2 carrier gas flow rate of 0.4 cc/sec and an isothermal column temperature of 95°, the retention times of biacetyl and toluene are 5 and 8 min, respectively. Thereafter, a programmed increase in the column temperature at a rate of 48°/min to 160° starting at 10 min results in acetoin and deuterated acetoin emerging at 15 min.

The procedure for all biacetyl analyses involved pipetting 2.0 ml of the aqueous reaction mixture into a vial containing 1.0 ml of 0.5 *M* Na_2HPO_4 to quench the reaction. To this mixture were added 0.5 g KNO_3 (to salt out the organic constituents) and 2.0 ml of anhydrous ether containing toluene (5×10^{-3} *M*) as an internal standard. After vigorous shaking 1–3 μl of the ether layer was injected into the gas chromatograph. For each set of biacetyl analyses the amount of biacetyl present in the starting material acetoin was determined, and the analytical method was checked using standard solutions containing a known amount of biacetyl added to a typical reaction mixture. Although only about 40% of the biacetyl is extracted into the ether layer under the above conditions, the use of the internal standard allowed the amounts of biacetyl to be determined to within ±10%.

Oxygen uptake in preliminary, stoichiometric, and kinetic experiments was measured by standard Warburg manometry[21] on a Gibson Model WB-3 apparatus, calibrated by the method of Lazarow. The accuracy of Warburg measurements is of the order of 5%. In most cases the reaction was initiated by adding a solution of the metal ion but no difference in reaction rates could be observed when initiated by the addition of an acetoin solution.

A modification of the method of Erlenmeyer, *et al.*,[22] was used for the H_2O_2 analyses. Aliquots (0.5 ml) of the reaction mixture were added to 2.5-ml portions of 5.0×10^{-3} *M* $Ti(SO_4)_2$ in 3.0 *N* H_2SO_4 and the absorbances of the resulting solutions were determined at 410 nm (ϵ 737) using a Zeiss PMQ II spectrophotometer. Control experiments indicated that none of the other components in the various reaction solutions interfered with this method. The initial velocities of the H_2O_2 reactions (acetoin always in excess) were calculated from measurements of the H_2O_2 concentrations made within the first 15% of the reaction. The reported rates were duplicated to better than ±5%.

The thiocyanate method described by Woods and Mellon[23] was used for determining Fe(III) concentrations in the experiments involving acetoin oxidation by Fe(III) under anaerobic conditions. Pseudo-first-order rate constants for the disappearance of Fe(III) were calculated from the slopes of the usual log plots of the original data and were reproducible to better than ±15%.

Kinetic and stoichiometric experiments involving the reduction of H_2O_2 or Fe(III) by acetoin were carried out at 25 ± 0.1° in flasks sealed with rubber septums. Aliquots of the reaction mixtures were withdrawn by syringe and analyzed by the above methods. For those reactions run under anaerobic conditions, O_2 was removed by purging the reactants (contained in vials capped with rubber septums) with a stream of moist N_2 for 30 min. Syringes were used for all transfers required to initiate the reactions.

For all kinetic experiments, except those specified otherwise, and the acid-catalyzed enolization experiments described below, HNO_3 or $NaHCO_3$ was used to bring the pH to the desired value, Fe(III) and Fe(II) were added as their nitrate salts, and the ionic strength was kept approximately constant at 0.2 by adding KNO_3. Actually all reaction solutions were prepared so that their calculated ionic strength is 0.25 assuming that the Fe(III) is present in its triply charged form. However, the data of Bray and Hershey[24]

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Table I. Some Kinetic Data for the Fe(III)-Catalyzed Oxidation of Acetoin by O_2[a]

Acetoin, M	[Fe(III)], $M \times 10^2$	$[H^+]$, $M \times 10^3$	[Fe(II)], $M \times 10^3$	$-d[O_2]$[b]$/dt$ M sec$^{-1} \times 10^7$	k_{O_2},[c] sec$^{-1} \times 10^7$
0.200	0	6.0	0	0	0
0.200	1.05	6.1	0	3.1_2	9.1
0.200	2.10	6.7	0	5.5_8	8.9
0.200	4.20	7.7	0	10.0_0	9.2
0.100	2.10	6.6	0	2.8_5	9.0
0.300	2.10	6.8	0	8.7_2	9.4
0.200	2.10	9.7	0	3.8_8	9.0
0.200	2.10	12.5	0	3.0_5	9.1
0.200	2.10	18.2	0	2.0_7	9.0
0.100	3.15	23.7	0	1.27[d]	9.5
0.200	4.20	8.3	0	9.49[d]	9.4
0.200	2.10	7.1	0	6.82[e]	11.5
0.200	3.95	13.0	0	3.02[f]	5.0
0.200	3.95	8.6	0	4.26[f]	4.6
0.332[g]	4.20	12.3	0	2.3_4	2.1
0.274[g]	4.20	9.0	0	1.9_0	1.5
0.274[g]	3.95	19.0	0	1.4_4	2.5
0.100	0	7.2	15.3	0	0
0.100	3.15	8.8	5.1	3.8_4	10.5
0.100	3.15	7.8	10.2	4.1_8	10.4
0.100	3.15	7.9	15.3	4.2_2	10.5
0.100	4.20	9.2	5.1	4.5_7	10.0
0.100	2.10	9.5	5.1	3.1_4	14.2
0.100	1.05	9.1	5.1	1.7_1	14.8
0.200	2.10	9.3	5.1	6.2_4	13.9
0.300	2.10	9.7	5.1	8.8_3	13.6
0.200	1.05	8.7	5.1	3.9_7	16.5
0.100	3.15	12.5	10.2	3.2_1	12.8
0.100	3.15	14.4	10.2	3.0_3	13.8
9.100	3.15	18.1	10.2	2.6_7	15.3
0.100	3.15	12.8	10.2	3.80[d]	15.4
0.200	3.95	11.6	5.1	4.50[f]	6.6
0.200	3.95	26.9	5.1	2.40[f]	8.1
0.274[g]	3.95	17.7	5.1	1.8_3	3.0

[a] Ionic strength *ca.* 0.2, temperature 25.0 ± 0.1°, and P_{O_2} = 0.2 atm (air) unless otherwise noted. [b] Each value is the average of two or more determinations; in each case the reactions were followed for at least 1 hr. [c] See text for definition. [d] P_{O_2} = 1.0 atm. [e] Ionic strength *ca.* 0.1. [f] Ionic strength *ca.* 1.2. [g] 3-Deuterio-3-hydroxy-2-butanone used instead of acetoin.

and Sykes[25] on the stability constants for such species as $FeOH^{2+}$ and $FeNO_3^{2+}$ indicate the above assumption to be invalid. Since the Fe(III) may also form acetoin complexes whose stability and ionization constants are not known, it is not possible to calculate the true ionic strength. Therefore, it may vary somewhat, depending on the acidity of the solution and the Fe(III) concentration, but such variation would be small enough to affect the observed rate constant only slightly (see Results for the effect of ionic strength on the rate constants).

The rate constants for the enolizations of acetoin were estimated by studying the loss of the carbon-bound hydrogens in 1 N DCl in D_2O solutions (plus a few drops of 70% $HClO_4$ where necessary to lower the pH) at 25 ± 0.1° using integrated nmr intensities with DSS as an internal standard. The second-order rate constants (k_e) for enolization were calculated from the absolute values for the initial (less than 20% reaction) rates of loss of hydrogen, *i.e.*,

$$k_e = \frac{-d[H]/dt}{[\text{acetoin}][D^+]}$$

For enolization to give 2-butene-2,3-diol k_{e_1} was calculated from the initial rate of disappearance of the peak at δ = 4.42 ppm, and for enolization to give 1-butene-2,3-diol, k_{e_2} was calculated from the initial rate of disappearance of the peak at δ = 2.25 ppm (in this case $-d[H]/dt$ equals 3 times the rate of disappearance of the peak). The concentration of D^+ ions was determined by titration. The rate constants for enolization determined in this way using 0.96–1.25 M D^+ are accurate to only ±30%.

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Results

In a preliminary search for a system amenable for study various aqueous reaction mixtures containing a variety of metal ions and activated secondary alcohols were surveyed for O_2 uptake. Lactic acid proved to be largely unreactive. The low solubility of benzoin limited its use. With acetoin as substrate it was found that Cu(I), Cu(II), Co(II), Co(III), Cr(III), Mn(II), Mn(III), Mg(II), Ni(II), and Fe(II) do not catalyze any appreciable O_2 uptake in the pH range 2–10. In some cases this may be due to precipitation of the metal hydroxides.

In the presence of Fe(III), however, O_2 uptake occurs readily at room temperature and pH *ca.* 2 when acetoin is the substrate (benzoin reacts similarly). With acetoin in excess (*ca.* 0.1 M) the O_2 uptake is linear with time over several hours reaction time; there is no discernible induction period. The presence of added Fe(II) or H_2O_2 does not affect the linearity of the O_2 uptake. In the absence of acetoin, solutions containing biacetyl and high concentrations of Fe(III) and/or Fe(II) show no appreciable O_2 uptake at pH *ca.* 2.

Kinetics of the Fe(III)-Catalyzed O_2 Reaction with Acetoin. Table I summarizes some kinetic results. In other experiments not listed in Table I it was found that the rate of O_2 uptake is inhibited by the presence of SO_4^{2-}, Cl^-, phosphate, and acetate, presumably because they complex with Fe(III). Therefore, these ions were not used in the detailed kinetic study. Neither a

Table II. Some Kinetic Data for the Fe(III)-Catalyzed Oxidation of Acetoin by H_2O_2[a]

[Acetoin], M	[Fe(III)], $M \times 10^2$	$[H_2O_2]_i$, $M \times 10^3$	$[H^+]$, $M \times 10^3$	$-d[H_2O_2]_i/dt$,[b] M sec$^{-1} \times 10^6$	$k_{H_2O_2}$, M^{-1} sec$^{-1} \times 10^3$
0.20	1.05	1.65	7.85	1.09	2.5
0.20	1.05	3.30	8.50	1.77	2.2
0.10	1.05	1.65	7.35	0.59	2.5
0.10	1.05	3.30	7.20	1.16	2.4
0.10	0.53	3.30	7.85	0.52	2.4
0.10	2.10	3.30	7.20	2.08	2.2
0.05	2.10	6.10	7.15	2.67[e]	3.0
0.10	1.05	9.90	8.50	2.88	2.4
0.10	2.10	3.60	25.00	0.84[e]	2.8
0.10	2.10	3.10	9.15	1.69[e]	2.4
0.21[d]	4.20	3.00	7.35	4.42[e]	1.2

[a] Ionic strength *ca.* 0.2; aerobic conditions; temperature 25.0 ± 0.1°. [b] Each value is the average of two or more determinations. [c] 2,2'-Bipyridine at a concentration equal to 2% of [Fe(III)] also present in the reaction mixture. [d] 3-Deuterio-3-hydroxy-2-butanone used instead of acetoin.

large excess of biacetyl nor H_2O_2 in amounts that would be produced by the O_2 reduction has any noticeable effect on the rate of the O_2 reaction.

As indicated in Table I, no O_2 reacts in the absence of Fe(III) even if Fe(II) is present. In the absence of Fe(II), and at relatively constant ionic strength, the results indicate that the O_2 uptake follows the rate expression

$$\frac{-d[O_2]}{dt} = k_{O_2}\frac{[Fe(III)][acetoin]}{[H^+]}$$

As shown by the last column of Table I, the k_{O_2}, calculated from this expression, remains constant when the concentrations of each of acetoin, Fe(III), H^+, and O_2 are varied severalfold; a particularly notable result is that the rate is zero order in the concentration of O_2. Since an increase in the ionic strength causes a decrease in k_{O_2} (compare experiments marked with footnotes *e* and *f* with the others), the ionic strength was kept constant for most of the kinetic experiments. There is a marked kinetic deuterium isotope effect (k_H/k_D *ca.* 5) when 3-deuterio-3-hydroxy-2-butanone is substituted for acetoin (experiments marked with footnote *g*).

When Fe(II) is also present in the complete reaction solution, it can be seen that the rate is increased slightly, and k_{O_2} does not remain as constant when the concentrations of the various species are varied. However, one point which is clear is that the rate of the O_2 uptake does not depend directly on the concentration of Fe(II); a threefold increase in the Fe(II) concentration causes no increase in the rate under otherwise comparable conditions. No simple kinetic equation could be derived which would lead to the calculation of a rate constant that remains constant when the concentrations of the various reactants are varied. In all probability the small effect of Fe(II) is due to the trapping of O_2 by some secondary radical process, most probably resulting from the reaction of Fe(II) with H_2O_2 (see next section). The kinetic deuterium isotope effect and the effect of ionic strength are essentially the same in the presence of Fe(II) as in its absence.

Kinetics of the Fe(III)-Catalyzed Oxidation of Acetoin by H_2O_2. An expected product of the O_2 reaction with acetoin is H_2O_2, but it could not be detected in typical reaction solutions. The reason is because Fe(III) catalyzes a further oxidation of acetoin by H_2O_2. In the absence of Fe(III), H_2O_2 does not react appreciably with acetoin or biacetyl at pH 2. As shown by the results illustrated in Figure 1, the time course of the Fe(III)-catalyzed H_2O_2 reaction is complex. Initially there is a relatively slow disappearance of H_2O_2 which is followed by an autocatalytic phase. The

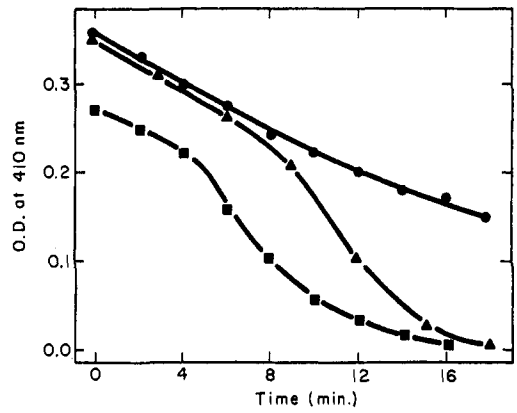


Figure 1. Typical plots of disappearance of H_2O_2 *vs.* time under the following reaction conditions: 25°; (O_2) = 0.2 atm; ionic strength *ca.* 0.2; pH = 2.1; [acetoin] = 0.1 *M*; [Fe(III)] = 2.1 × 10^{-2}*M*; ●, $[H_2O_2)_i$ = 3.3 × 10^{-3} *M* and [2,2'-bipyridine] = 2.5 × 10^{-4} *M*; ▲, $[H_2O_2]_i$ = 3.3 × 10^{-3} *M*; ■, $[H_2O_2)_i$ = 2.6 × 10^{-3} *M* and [Fe(II)] = 5.9 × 10^{-7} *M*.

autocatalytic part begins earlier in the reaction if small amounts of Fe(II) are added, and it can be eliminated altogether by the presence of small amounts (2% of the Fe(III) concentration) of 2,2'-bipyridine (bipyridine complexes Fe(II) strongly). The onset of the autocatalytic phase is accompanied by a color change of the solution from yellow to amber. It seems most likely that the autocatalytic part is due to a free radical reaction initiated by Fe(II) and probably involving the hydroxyl radical. However, the kinetic details of this reaction were not studied further. Since the initial part of the Fe(III)-catalyzed reaction clearly does not involve Fe(II) as an intermediate, it probably does not proceed by a free radical mechanism and thus the characteristics of this reaction were studied in more detail.

In Table II are summarized some kinetic results on the initial rate of disappearance of H_2O_2. These rates are not affected by the presence or absence of O_2 nor, as shown in the table, by the presence of small

Table III. Stoichiometries of the Various Acetoin Oxidations

Reaction conditions[a]						Amounts reacted or produced[b] (μmole/3 ml of reaction solution)			
[Acetoin], M	[Fe(III)], $M \times 10^2$	[Fe(II)], $M \times 10^3$	pH	Vapor phase	Reaction duration, min	Fe(III) reduced	H_2O_2 reacted	O_2 reacted	Biacetyl formed
0.100	5.0	0	2.5	Air	180			14.5	26
0.100	5.0	0	2.3	Air	180			13.0	24
0.100	5.0	2.5	2.3	Air	180			14.6	22
0.100	5.0	25	2.3	Air	180			13.2	15
0.100	2.1	0	2.2	N_2	10		24.8[c]		26
0.100	2.1	0.05	2.2	N_2	10		24.8[c]		25
0.100	4.2[d]	0	2.1	N_2	36		24.8[c]		24
0.100	5.0	0	2.5	Air	180		9.3[c]	14.0	37
0.100	5.0	0	2.4	Air	30		9.3[c]	2.6	15
0.100	5.0	0	2.4	Air	30		18.6[c]	2.6	24
0.200	2.1	0	2.1	N_2	310	30			15
0.200	4.2	0	1.7	N_2	330	43			22

[a] Temperature, 25.0 ± 0.1°; ionic strength *ca.* 0.2. [b] Each number is the average of two or more determinations. [c] Amount added to the reaction solution at time zero. [d] Reaction solution also contains 5×10^{-4} M bipyridine.

amounts of bipyridine. As indicated by the constancy of $K_{H_2O_2}$ (last column of Table II), the initial rate of disappearance of H_2O_2 is well described by the rate expression

$$\frac{-d[H_2O_2]_i}{dt} = \frac{k_{H_2O_2}[Fe(III)][acetoin][H_2O_2]}{[H^+]}$$

The last experiments listed in the table indicate that the kinetic deuterium isotope effect (k_H/k_D) is approximately 2 when 3-deuterio-3-hydroxy-2-butanone is substituted for acetoin.

Kinetics of Fe(III) Reduction by Acetoin under Anaerobic Conditions. In the absence of O_2 acetoin will reduce Fe(III) to Fe(II). Since it seemed probable that this reaction is related to the Fe(III)-catalyzed oxidation of acetoin by O_2, a few characteristics of the Fe(III) reduction reaction under similar conditions were investigated. Good kinetics could only be obtained from pH 1.5 to 2.1; at higher pH's complications arose probably due to polymerization of the Fe(III) during the rather long times required for the reactions. From pH 1.5 to 2.1, the rate of disappearance of Fe(III) follows the rate expression

$$\frac{-d[Fe(III)]}{dt} = k_{Fe(III)}\frac{[Fe(III)][acetoin]}{[H^+]}$$

At 25° and ionic strength *ca.* 0.2, $k_{Fe(III)} = 1.6 \pm 0.2 \times 10^{-6}$ sec^{-1}. When 3-deuterio-3-hydroxy-2-butanone is substituted for acetoin the rate is decreased *ca.* sevenfold.

Stoichiometries of the Various Acetoin Oxidations. In Table III are summarized some results showing the amount of biacetyl formed and the amount of oxidant consumed in the various oxidations. For the Fe(III) catalyzed O_2 reaction, when Fe(II) is not present, it can be seen that 2 mol of biacetyl are formed for each mole of O_2 consumed. When Fe(II) is added in relatively large amounts the stoichiometry changes and approaches 1 mol of biacetyl formed per mole of O_2 consumed. For the Fe(III)-catalyzed H_2O_2 oxidation the stoichiometry is 1 mol of biacetyl formed per mole of H_2O_2 consumed irrespective of mechanism. The amount of biacetyl formed in the Fe(III)-catalyzed reactions is additive if both O_2 and H_2O_2 are acting as oxidants concurrently. As expected, in the oxidation of acetoin by Fe(III), 1 mol of biacetyl is formed for every 2 mol of Fe(III) reduced.

The D^+-Catalyzed Enolizations of Acetoin. The second-order rate constant (k_{e1}) for the D^+-catalyzed enolization of acetoin at 25° to give 2-butene-2,3-diol was found to be 1.1×10^{-6} M^{-1} sec^{-1}. The second-order rate constant (k_{e2}) for the related reaction to give 1-butene-2,3-diol was found to be 5.7×10^{-6} M^{-1} sec^{-1}. These rate constants are in fair agreement with data recently reported by Lubach and Drenth.[15,26]

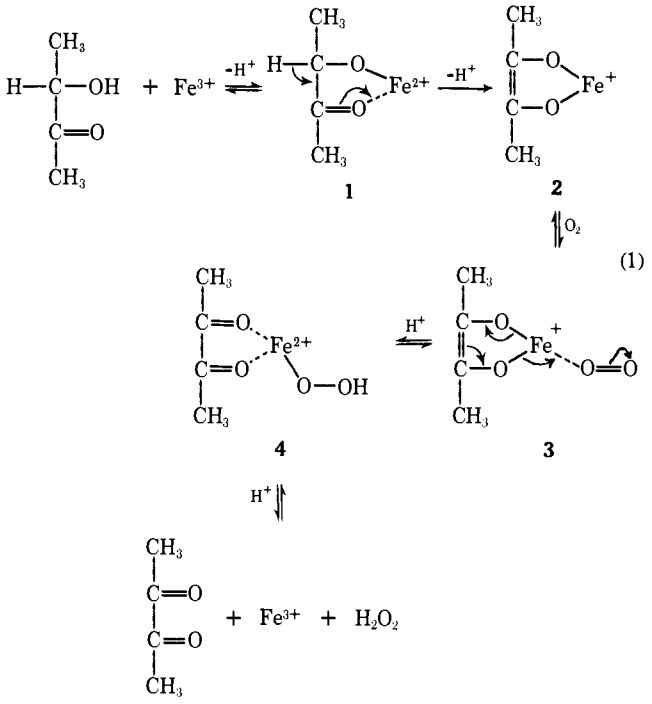
Discussion

Mechanism of the O_2 Reaction. No direct evidence could be obtained for H_2O_2 being an intermediate in the Fe(III)-catalyzed oxidation of acetoin by O_2. However, all the results are consistent with this hypothesis. The observation that H_2O_2 reacts rapidly under the reaction conditions makes it a reasonable intermediate. Also, indirect evidence for its presence is the observation that, if large amounts of Fe(II) are present, only approximately 1 mol of biacetyl is formed per mole of O_2 reacted (Table III). This result indicates that Fe(II) is trapping some intermediate, presumably H_2O_2; Fe(II) is known to be rapidly oxidized by H_2O_2.[27] In the following discussion it will be assumed that H_2O_2 is an intermediate in the O_2 reaction.

Since Fe(II) is not oxidized by O_2 under the reaction conditions, a mechanism for the first stage of the O_2 reaction, involving reduction of Fe(III) to Fe(II) by acetoin followed by reoxidation of Fe(II) by O_2, is untenable. In fact any free radical mechanism for the reaction is unlikely because such mechanisms would also most certainly involve Fe(II) as an intermediate which is then reoxidized by O_2. The small effects (Table I) of added Fe(II) on the kinetics do not indicate that Fe(II) participates directly in the O_2 reaction; rather, the effects are probably due to subsequent radical reactions of Fe(II) and H_2O_2.

A mechanism for the first stage of the Fe(III)-catalyzed O_2 reaction, which is consistent with all the results reported here, is shown in eq 1 (although not illustrated, the Fe(III) will have other charged or uncharged ligands associated also). It is suggested that

(26) J. W. Marsman, J. Lubach, and W. Drenth, *Recl. Trav. Chim. Pays-Bas*, **88**, 193 (1969).
(27) J. H. Baxendale, M. G. Evans, and G. S. Park, *Trans. Faraday Soc.*, **42**, 155 (1946).



(1)

acetoin and Fe(III) are in equilibrium with a complex such as **1** which in the rate-determining step loses a proton and is converted to the enediol complex, **2**. That this step is rate determining is consistent with the kinetic deuterium isotope effect and the observed rate law; the inverse first power dependence on the hydrogen ion concentration indicates that the transition state has one less positive charge than the reactants. Since the state of the Fe(III) in the reaction solution is not known with certainty (see Experimental Section), one cannot be more specific concerning the transition state, for example, whether the conversion of **1** to **2** is subject to base catalysis or not. In subsequent fast reactions it is suggested that O_2 complexes with **2** to give **3**[28] which by protonation and electron reorganization as shown gives **4**. This is expected to be in rapid equilibrium with biacetyl and free H_2O_2.

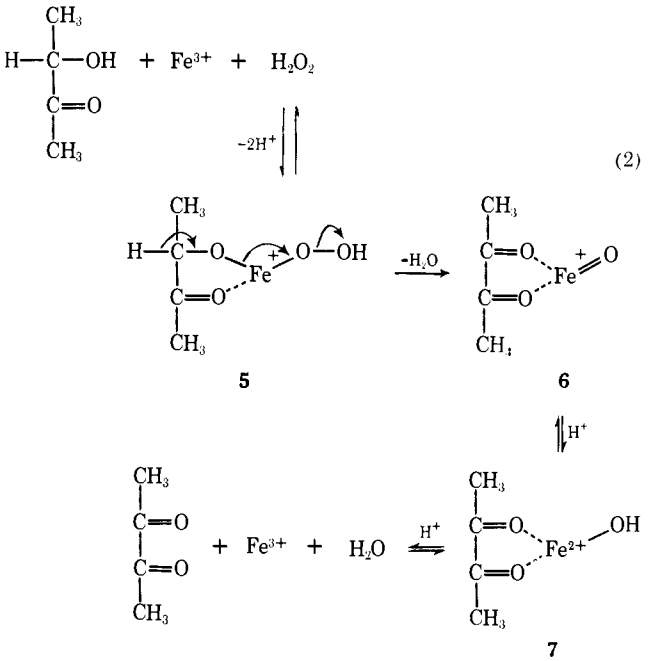
If, as suggested, the rate-determining step is an Fe(III)-catalyzed enolization of acetoin, the O_2 reaction must occur more rapidly than the acid-catalyzed enolization. From the observed second-order rate constant ($1.1 \times 10^{-6}\ M^{-1}\ sec^{-1}$) for the D^+-catalyzed enolization of acetoin to give 2-butene-2,3-diol, one can estimate[29] that the rate constant for the H^+-catalyzed reaction should be approximately $5 \times 10^{-7}\ M^{-1}\ sec^{-1}$. Therefore, at pH 2 and 0.1 *M* acetoin the rate of the H^+-catalyzed enolization is approximately $5 \times 10^{-10}\ M\ sec^{-1}$. One can calculate from the data in Table I that at pH 2, 0.1 *M* acetoin, and $10^{-2}\ M$ Fe(III) the rate of the O_2 reaction is approximately $10^{-7}\ M\ sec^{-1}$. Since this is over two orders of magnitude faster, it is reasonable that the rate-determining step in the O_2 reaction is an Fe(III)-catalyzed enolization.

(28) Although O_2 readily binds to transition metal ions, the structure of most such complexes is not known.[3] The structure illustrated in **3** is a formalism; it is not meant to imply the exact nature of the O_2 complex. The important point is that when the orbitals on O_2 overlap with those on a metal ion, which is complexed to a reduced ligand, protonation and electron shifts, such as in the conversion of **3** to **4**, should occur very readily.

(29) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., p 250.

The main characteristics of the proposed mechanism for the transhydrogenation from acetoin to O_2 are: (1) both hydrogens are transferred as protons, and (2) the reduced metal ion or organic free radicals are not intermediates. As has been discussed in detail recently,[3,4] such mechanisms appear frequently in metal ion catalyzed organic and biological redox reactions. In the mechanism of eq 1 the metal ion performs several functions: (i) it catalyzes the conversion of acetoin to the enediol (**1** to **2**), (ii) by complexing with both the oxidant and reductant it provides a mechanism (orbital overlap) for transferring electrons from the reductant to the oxidant (**3** to **4**) without the necessity for free radical intermediates, and (iii) it allows the O_2 to react by an ionic mechanism. Oxygen in its ground state is a triplet molecule, and because of the spin conservation rule, it cannot react directly with a singlet organic molecule to give H_2O_2 and a singlet oxidized organic molecule. However, when O_2 is complexed to a transition metal ion (such as in **3**), which itself has unpaired electrons, it can react to give a peroxide directly (such as **4**) by an ionic mechanism, if **4** has the same number of unpaired electrons as **3**.[3,4]

Mechanism of the H_2O_2 Reaction. It is clear from the results reported here that the Fe(II)-catalyzed oxidation of acetoin by H_2O_2 can proceed by two mechanisms, (a) one in which Fe(II) is an intermediate, and (b) one in which Fe(II) is not an intermediate. Reaction a very probably is related to the Fenton reaction[30] which is free radical in nature, and it will not be considered further here. The fact that Fe(II) is not an intermediate in reaction b strongly indicates that it does not proceed by a free radical mechanism. Also, the observed kinetics of this reaction are not readily rationalized in terms of a free radical mechanism. A mechanism for (b) consistent with all the results is shown in eq 2.



(2)

Since reaction b proceeds more rapidly than the Fe(III)-catalyzed O_2 reaction, and also is dependent on the first power of the H_2O_2 concentration, a different

(30) J. R. L. Smith and R. O. C. Norman, *J. Chem. Soc.*, 2898 (1963).

rate-determining step from that of the O_2 reaction must be involved. It is suggested that Fe(III), acetoin, and H_2O_2 are in equilibrium with a complex such as **5**, and the rate-determining step is the elimination of a molecule of H_2O from **5** to give **6**. Such a rate-determining step would be consistent with the kinetic deuterium isotope effect and the observed rate law. Again the inverse dependence on the first power of the hydrogen ion concentration indicates that the transition state has one less positive charge than the reactants. Therefore, depending on the state of Fe(III) in the reaction solution the conversion of **5** to **6** might be subject to acid or base catalysis. The subsequent protonation of **6** to give **7** and decomposition of **7** to biacetyl and H_2O would be expected to occur rapidly.

Thus, as in the Fe(III)-catalyzed O_2 reaction, the transhydrogenation shown in eq 2 also proceeds by proton transfers exclusively. As before, free radicals are not required as intermediates because the metal ion complexes with both the oxidant and reductant and transfers electrons from one to the other in the redox step, the conversion of **5** to **6**. The mechanisms of eq 1 and 2 are related. Presumably the faster reaction of eq 2 occurs in the H_2O_2 reaction because H_2O_2 can form more stable complexes (*i.e.*, **5**) with Fe(III)–acetoin compounds than O_2 can. In the O_2 reaction, the slower enolization must occur first, but the subsequent oxidation of **2** to **4** would be expected to occur rapidly because it does not require the breaking of a carbon–hydrogen bond.

A mechanism similar to that of eq 2 has been suggested in the formation of the oxidizing agent in a system involving Fe(III), H_2O_2, and catechol.[6] Also, related mechanisms are probably involved in Cu(II)-catalyzed oxidations of hydrazine, hydroxylamine, and H_2O_2 by H_2O_2[31] as well as in the disproportionation of H_2O_2 catalyzed by Fe(III) complexes.[32] These have been considered in detail elsewhere.[3,4]

Mechanism of the Oxidation by Fe(III). The oxidation of acetoin by Fe(III) at pH *ca.* 2 under anaerobic conditions follows the same rate law as the Fe(III)-catalyzed oxidation by O_2, and the observed rate constant $k_{Fe(III)}$ is almost two times that (k_{O_2}) for the O_2 reaction. Furthermore, the reactions show similar large kinetic deuterium isotope effects. These results suggest that the two reactions have closely related mechanisms. Specifically, it appears that the rate-determining step for the Fe(III) reduction reaction is the same as that for the O_2 reaction (step **1** to **2**, eq 1). A factor of 2 difference in rate would be expected if the subsequent reaction of Fe(III) with **2** to give biacetyl and 2 mol of Fe(II) occurs rapidly. Since this is just an electron transfer reaction, it should occur readily. When both Fe(III) and O_2 are present (as in the Fe(III)-catalyzed O_2 reaction) there should be a competition between Fe(III) and O_2 for **2**. Apparently the reaction with O_2 under such conditions occurs more rapidly.

Thomas and coworkers[12] investigated the oxidation of acetoin by Fe(III) at pH's around zero, and observed the same rate law obtained in the present research. However, the rate constant which they obtained under their conditions is over one order of magnitude greater (after allowing for the temperature difference) than that obtained in the present research at pH's around 2. Actually there is no contradiction in these two sets of experimental results. It is probable that Thomas and his coworkers were measuring the reduction of Fe(III) by 2-butene-2,3-diol, the enediol of acetoin. They observed at high Fe(III) concentrations, or pH's much greater than zero, that their rate law is no longer obeyed and poor kinetics are obtained. One can calculate from the rate constant for the acid-catalyzed enolization reported here that these deviations from good kinetics occur when the rate of the Fe(III) reduction reaction starts becoming comparable to the rate of the acid-catalyzed enolization to give 2-butene-2,3-diol. Under conditions where they obtained good kinetics, the rate of the acid-catalyzed enolization is always much greater than the rate of the Fe(III) reduction reaction they were measuring.

The mechanism of the reduction of Fe(III) by 2-butene-2,3-diol at low pH is not clear. However, it is tempting to speculate that the rate-determining step is the formation of **2**. As suggested before, **2** would be expected to react rapidly with Fe(III) to give biacetyl and 2Fe(II). Such a mechanism would be consistent with the rate law observed by Thomas, *et al.*[12]

Related Enzymic Reactions. A large number of biological redox reactions, catalyzed by metalloenzymes, apparently proceed without free radicals being intermediates. Recently[3,4] one of the present authors has suggested that in most such reactions, the hydrogens are transferred as protons, and the metal ion functions to transfer electrons from the reductant to the oxidant within a complex that contains all three species. The importance of the present work is that it illustrates clearly that such reactions can occur in nonenzymic systems. Therefore, related mechanisms for the enzymic reactions appear more plausible.

One particular enzymic redox reaction which bears a close resemblance to the nonenzymic systems studied here is the reaction catalyzed by galactose oxidase.[33,34] In this reaction the alcohol at position 6 of galactose is oxidized to an aldehyde and O_2 is reduced to H_2O_2. Each molecule of enzyme contains 1 atom of Cu(II) which apparently does not change valence during the reaction.[35] It has been suggested[3,4] that the enzymic transhydrogenation occurs by proton and electron transfers within a complex of the alcohol, enzyme–Cu(II), and O_2 in a manner very similar to that suggested in the conversion of **5** to **6**. The difference is that O_2 is the complexed oxidant and a complexed peroxide is the initial product. Although such a ternary complex is not the reactive species in the model O_2 reaction studied here, it is reasonable that the enzyme could increase the binding affinity for O_2 so that such a complex could react as in the model H_2O_2 reaction. Therefore, the studies of the model acetoin oxidations make the suggested mechanism for the galactose oxidase reaction more likely.

(31) (a) H. Sigel, C. Flierl, and R. Griesser, *J. Amer. Chem. Soc.*, **91**, 1061 (1969); (b) H. Erlenmeyer, C. Flierl, and H. Sigel, *ibid.*, **91**, 1065 (1969); (c) R. Griesser, B. Prijs, and H. Sigel, *ibid.*, **91**, 7758 (1969); (d) J. Schubert, V. S. Sharma, E. R. White, and L. S. Bergelson, *ibid.*, 90, 4476 (1968).

(32) (a) J. H. Wang, *ibid.*, 77, 4715 (1955); (b) J. H. Wang, *Accounts Chem. Res.*, **3**, 90 (1970).

(33) D. Amaral, L. Bernstein, D. Morse, and B. L. Horecker, *J. Biol. Chem.*, **238**, 2281 (1963).

(34) G. Avigad, D. Amaral, C. Asenio, and B. L. Horcker, *ibid.*, **237**, 2736 (1952).

(35) W. E. Blumberg, B. L. Horecker, F. Kelly-Falcoz, and J. Peisach, *Biochim. Biophys. Acta*, **96**, 336 (1965).

The results reported here may be relevant to the mechanisms of some nonredox enzymic reactions as well. Several isomerases which catalyze aldose–ketose isomerizations are metalloenzymes[36] and the function of the metal ion may be to catalyze the formation of an enediol from the α-hydroxy aldehyde or ketone. The present work indicates that Fe(III) catalyzes such a reaction even at low pH. Using the observed rate laws one can estimate that at neutral pH the Fe(III)-catalyzed enediolization would be many orders of magnitude greater than the acid-catalyzed reaction. Therefore, perhaps one of the main functions of the enzyme is to keep the metal ion in solution at higher pH's. Of course, other metal ions, or a different ionized or complexed form of Fe(III), might not be as effective catalysts as Fe(III) at pH 2. However, the results with the model system indicate that catalysis of enediolization by metal ions can occur, and thus this is a reasonable step to suggest for the enzymic reactions.

(36) I. A. Rose in "Comprehensive Biochemistry," Vol. 17, M. Florkin and E. H. Stotz, Ed., Elsevier, Amsterdam, The Netherlands, 1969, p 107.

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Thermal and Photodecarboxylation of 2-, 3-, and 4-Pyridylacetic Acid[1]

F. R. Stermitz* and W. H. Huang

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521. *Received August 31, 1970*

Abstract: The 2-, 3-, and 4-pyridylacetic acids photodecarboxylate in water with high quantum efficiency. The photodecarboxylation quantum yield is a maximum at the isoelectric point and the zwitterion form is probably the ground state species absorbing 2537-Å (quartz filter) light and leading to decarboxylation. The quantum yield for photodecarboxylation of 3-pyridylacetic acid decreases with decreasing solvent polarity under 2537-Å irradiation (quartz filter), but increases with decreasing solvent polarity with a Pyrex filter. In the latter case, the nonionized ground state of the pyridylacetic acid is believed to be the absorbing species, which then leads to a zwitterion excited state before decarboxylation. Resonance stabilization of the intermediate formed from the excited state decomposition is suggested to be of little or no importance in determining the efficiency of the reaction. The 2- and 4-pyridylacetic acids decarboxylate thermally in high yield at 90°, while the 3-derivative is stable at that temperature. A maximum rate is observed at the isoelectric point and again the zwitterion form appears to be the reactive molecule. In the thermal process resonance stabilization of the intermediate formed in the decomposition is of prime importance in determining reactivity.

The liquid phase photodecarboxylations of a few, structurally quite diverse aryl-substituted acetic acids have been studied recently. Fischer[2] and later Melchior,[3] during investigations of tryptophan photodecomposition, showed that 3-indoleacetic acid aerobically photolyzed to 3-methylindole and indole, along with side chain oxidation products. Margerum observed[4] that 2-, 3-, and 4-nitrophenylacetate ions photodecarboxylated giving the same products in air or under nitrogen: 2- and 3-nitrotoluene from the 2- and 3-nitrophenylacetates and 4,4′-dinitrobibenzyl from the 4-nitrophenylacetate. Phenylacetate was found to photodecarboxylate only very slowly. On the other hand, Crosby[5] found that the aerobic photolysis of the 2-, 3-, and 4-chlorophenylacetates gave benzyl alcohol and benzaldehyde as the major products. Crosby also studied[6] aerobic and anaerobic photolyses of 1-naphthylacetate, finding in the former case 1-methylnaphthalene, 1-naphthalenemethanol, 1-naphthaldehyde, and 1-naphthoic acid and in the latter case only 1-methylnaphthalene. It was proposed that the 1-methylnaphthalene was the first product formed under both conditions. At the same time, Watkins showed[7] similar results in the aerobic case starting from 1-naphthylacetic acid rather than the acetate salt. Wang[8] found a quantitative photodecarboxylation of thymine-1-acetic acid to yield 1-methylthymine, while the corresponding uracil underwent both decarboxylation and 5,6-hydration. If these pyrimidines can be considered analogs of arylacetic acids, they fall into the same class of reactions. In summary, a pattern emerges of photodecarboxylation to yield a primary product where the carboxyl group has been replaced by hydrogen. The only exception to this was the coupled product (4,4′-dinitrobibenzyl) observed[4] from 4-nitrophenylacetate decomposition.

(1) Photochemistry of N-Heterocycles. VII. Previous paper: F. R. Stermitz, C. C. Wei, and C. M. O'Donnell, *J. Amer. Chem. Soc.*, **92**, 2745 (1970). This work was supported in part by Grant No. GM-15425 from the National Institute of General Medical Sciences, U. S. Public Health Service.

(2) A. Fischer, *Planta*, 43, 288 (1954).

(3) G. H. Melchior, *ibid.*, **50**, 262 (1957).

(4) J. D. Margerum, *J. Amer. Chem. Soc.*, 87, 3772 (1965); J. D. Margerum and R. G. Brault, *ibid.*, **88**, 4733 (1966); J. D. Margerum and C. T. Petrusis, *ibid.*, **91**, 2467 (1969).

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