

The Kinetics of the Cupric Ion Oxidation of α -Hydroxyacetophenone¹

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The kinetics of the oxidation of α -hydroxyacetophenone by copper(II) in buffered aqueous pyridine have been studied spectrophotometrically. The reaction follows the rate law $v = k_1[\text{ketol}] + k_2[\text{ketol}][\text{Cu}^{+2}]$. The first term corresponds to the independently determined rate of enolization and the second term is the major one at Cu^{II} concentrations greater than 0.01 M. A kinetic isotope effect, $k_{\text{H}}/k_{\text{D}} = 7.4$, was observed, and the effect of substituents correlated with a ρ of 1.24. The rate-determining step for the second term appears to involve the removal of a proton from the copper(II) chelate of the ketol. These results make the previously obtained data for oxidations in aqueous solutions more intelligible.

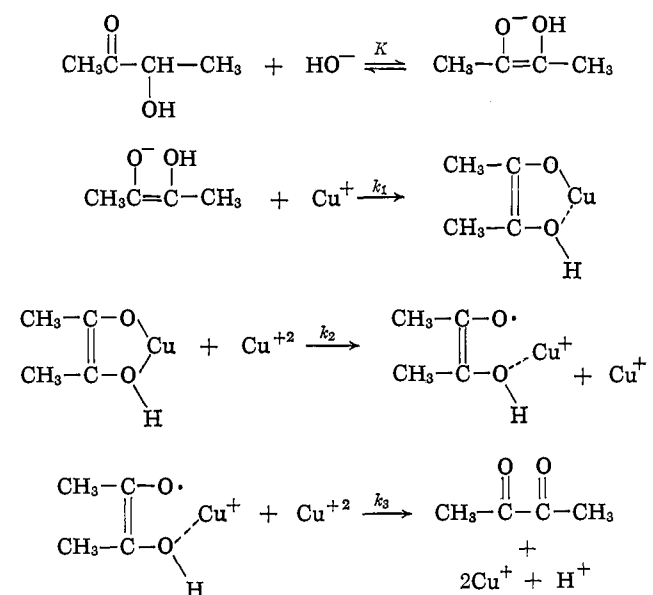
Although the oxidation of ketols by alkaline solutions of copper(II) has been known for many years,² the first kinetic study of the reaction was reported by Weissberger and his students in 1930.³ They found that the rate of oxidation of benzoin to benzil was first order with respect to the concentrations of benzoin and hydroxyl ion, but independent of the initial concentration of copper(II). Further, the rate of oxidation was equal to the rate of autoxidation or of racemization of benzoin under the same conditions. These data, coupled with the observation that the effect of substituents was the same for autoxidation as for oxidation with Fehling's solution, suggested that enolization was the rate-determining step.

Parrod,⁴ Singh,⁵ and their co-workers have investigated the kinetics of other α -hydroxycarbonyl compounds. Unfortunately, these workers used reducing sugars such as glucose and fructose as model compounds. Under the conditions used for the oxidation, these sugars undergo extensive epimerization. However, the rate of oxidation is still independent of the concentration of Cu^{II} and remains approximately first

order with respect to the concentrations of hydroxide ion and reductant.

The most recent work is that of Marshall and Waters.⁶ The oxidations of acetoin and benzoin using Benedict's solution were found to follow the rate law previously observed. The reaction has a short induction period, and this could be almost entirely eliminated by removal of dissolved oxygen before the reaction is initiated. Even in the absence of oxygen, the oxidation was found to exhibit a brief autocatalytic stage before becoming zero order with respect to cupric ion. The effect could be eliminated by the addition of copper powder or a portion of a partly reacted mixture to the reaction system.

These workers also reported that "oxidation occurs much less rapidly than does enolization." In order to account for these observations, they proposed the mechanism



Here, the rate-determining step was assumed to be that characterized by k_1 . The cuprous ion will be present in solution in constant concentration once the cuprous oxide begins to precipitate. Thus the rate of reaction will be independent of the concentration of cupric ion used.

In order to test this ingenious explanation, we have investigated the oxidation of a ketol, α -hydroxyaceto-

(6) B. A. Marshall and W. A. Waters, *J. Chem. Soc.*, 2392 (1960); 1579 (1961).

(1) This work was supported by a grant from the National Science Foundation.

(2) Tommer, *Ann. Chem. Pharm.*, **39**, 360 (1841); H. Fehling, *Ann.*, **72**, 106 (1849).

(3) A. Weissberger, W. Schwarze, and H. Mainz, *ibid.*, **481**, 68 (1930); A. Weissberger, A. Dörken, and W. Schwarze, *Ber.*, **B64**, 1200 (1931); A. Weissberger and T. H. James, *J. Am. Chem. Soc.*, **59**, 2040 (1937).

(4) J. Parrod, *Compt. rend.*, **212**, 610 (1941).

(5) M. P. Singh and S. Ghosh, *Proc. Natl. Acad. Sci. India*, **A23**, 15 (1954); M. P. Singh and S. Ghosh, *Z. physik. Chem. (Leipzig)*, **204**, 1 (1955); M. P. Singh, B. Krishna, and S. Ghosh, *ibid.*, **205**, 285, 294 (1956); M. P. Singh and S. Ghosh, *ibid.*, **207**, 187, 198 (1957); M. P. Singh, *ibid.*, **208**, 265, 273 (1958); M. P. Singh, B. Krishna, and S. Ghosh, *Proc. Natl. Acad. Sci. India*, **A28**, 21, 39 (1959); M. P. Singh, *Z. physik. Chem. (Leipzig)*, **216**, 13, 17 (1961).

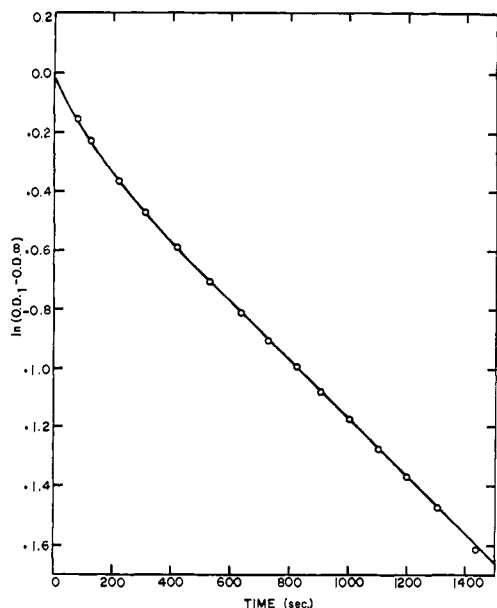


Figure 1. Typical first-order plot of oxidation of α -hydroxyacetophenone in unbuffered aqueous pyridine at 25°.

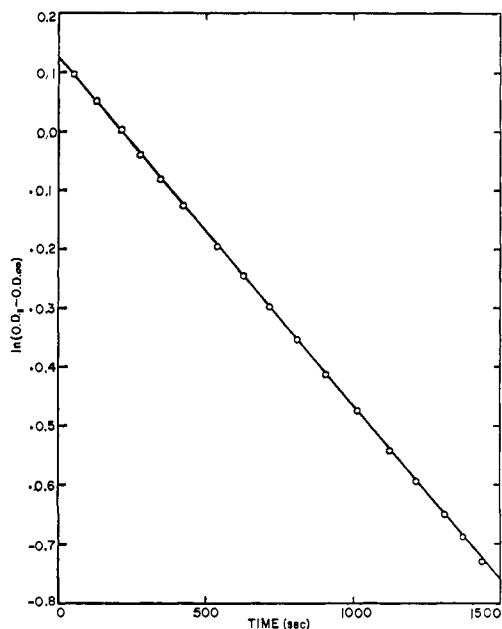
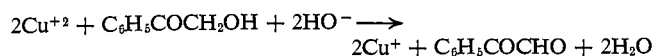


Figure 2. Typical first-order plot of oxidation of α -hydroxyacetophenone in buffered aqueous pyridine at 25°.

phenone, by copper(II) in aqueous pyridine solution. Under these conditions, cuprous ion remains in solution because of the good complexing ability of pyridine towards this ion. The oxidation leads to phenylglyoxal as the product which is only slowly oxidized to other products. Although the nature of the reaction medium is such that it is difficult to isolate the phenylglyoxal in good yield, the fact that the stoichiometry was found to involve two copper(II) for each ketol consumed makes it reasonably certain that the reaction may be adequately described by



The rate of the oxidation was followed spectrophotometrically (650–850 $m\mu$) under pseudo-first-order condi-

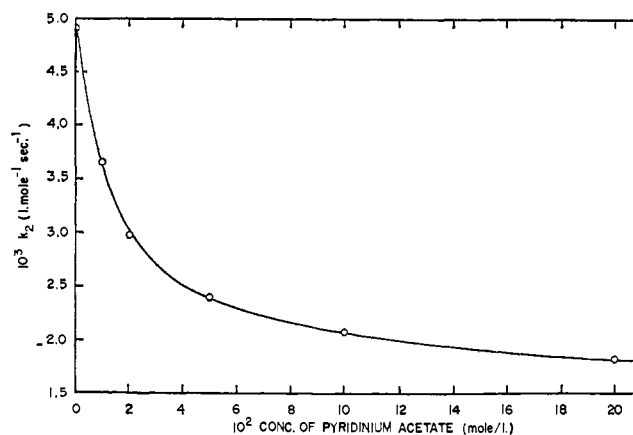


Figure 3. The effect of pyridinium acetate on the rate of oxidation of α -hydroxyacetophenone at 25°.

tions. The copper(II) solution was isolated from the reductant solution during the process of degassing using the cells described previously.⁷ The solutions were brought to the reaction temperature in the evacuated cell which was then inverted to mix the solutions. Unless otherwise stated the following data will refer to a 50 mole % pyridine–water mixture and a temperature of 25.0°.

The initial absorbance of the reaction mixture, obtained by extrapolation of the kinetic data, agreed with the absorbance of a solution identical with it in every way except that the ketol was not present. This indicates that there was no mixing of the solutions before initiation of the reaction. In most cases, the rate constants were determined in duplicate or quadruplicate runs. The average deviation between these runs varied from ± 0.5 to $\pm 3.4\%$; typical data are shown in Table I.

Table I. Reproducibility of the Rate of Oxidation of α -Hydroxyacetophenone by Copper(II) in 50 Mole % Pyridine–Water at 25.0°

Run no.	$k_1 \times 10^4, \text{sec.}^{-1} \text{ }^a$
134	2.26
135	2.22
136	2.22
137	2.23
283	2.27
294	2.26
295	2.21
286	2.34

^a $[\text{Cu}^{II}] = 0.014 \text{ M}$, $[\text{ketol}] = 0.70 \text{ M}$, $[\text{PyH}^+] = 0.020 \text{ M}$, $\mu = 0.25 \text{ M}$.

The oxidation of α -hydroxyacetophenone (0.20 M) by cupric acetate (0.014 M) exhibited an initial self-retardation (Figure 1), but became first order with respect to the concentration of copper after 50% reaction. This is expected since the stoichiometric relation indicates that acetic acid is formed in the reaction. Since the aqueous pyridine solution is essentially unbuffered, the basicity of the medium will decrease and this should result in a decrease in rate. The effect could be eliminated by the addition of pyridinium acetate (0.020 M) and the reaction gave a good, first-order kinetic plot (Figure 2). The effect of

(7) K. B. Wiberg and P. A. Lepse, *J. Am. Chem. Soc.*, **86**, 2612 (1964).

pyridinium acetate addition on the rate of reaction was determined over a range of concentrations giving the data shown in Figure 3. The linear portion of the kinetic curve decreased to 40% reaction when the pyridinium acetate concentration was raised to 0.20 M.

The rate law was determined by measuring the effect of varying the concentrations of the reactants on the rate constants. The effect of copper(II) concentration is summarized in Table II. Except at very low con-

Table II. Effect of Initial Copper(II) Concentration on the Rate of Oxidation of α -Hydroxyacetophenone^a

[Cu ^{II}]	$10^3 k_2$, l. mole ⁻¹ sec. ⁻¹
0.002	$(8.2 \pm 0.1 \times 10^{-6})^b$
0.007	2.80 ± 0.03
0.014	2.03 ± 0.01
0.024	1.77 ± 0.01
0.035	1.61 ± 0.01
0.050	1.53 ± 0.01
0.065	1.54 ± 0.01
0.080	1.59 ± 0.02
0.100	1.65 ± 0.01
0.125	1.75 ± 0.01
0.140	1.72 ± 0.01

^a Each rate constant is based on a duplicate determination. [ketol] = 0.70 M, [PyH⁺] = 0.20 M, μ = 0.50 M. ^b First-order rate constant (sec.⁻¹), i.e., the zero-order rate constant for the disappearance of copper(II) divided by the ketol concentration.

centrations, the reaction shows a first-order dependence on the concentration of oxidant. The effect of α -hydroxyacetophenone at a copper(II) concentration of 0.014 M is shown in Figure 4. Here, a good linear dependence is found indicating a first-order dependence on the concentration of ketol. It was not possible to determine the effect of hydroxyl ion concentration on the rate of reaction for even low concentrations resulted in precipitation of cupric hydroxide. This occurred even in the presence of the better complexing agent, bipyridyl.

The effect of solvent composition on the rate of reaction was determined giving the data in Table III. The effect is quite small. In view of the lack of data

Table III. Effect of Pyridine Concentration on the Rate of Oxidation of α -Hydroxyacetophenone at 25.0°

Mole % C ₅ H ₅ N	$k_2 \times 10^3$, l. mole ⁻¹ sec. ⁻¹ ^a
5	8.39 ± 0.02
10	7.23 ± 0.00
20	4.73 ± 0.02
30	3.36 ± 0.00
40	2.77 ± 0.08
50	2.63 ± 0.02
60	3.00 ± 0.02
80	5.02 ± 0.02

^a Average of duplicate determinations; the error is the observed average deviation. [Cu^{II}] = 0.014 M, [ketol] = 0.20 M, [PyH⁺] = 0.020 M, μ = 0.062 M.

for analogous reactions in this solvent system, it is not possible to make any interpretations from these data. The effect of ionic strength on the rate of reaction was also determined giving the data in Table IV. Here again, the effect is quite small. The rate constant for the oxidation was determined at 15.0, 25.0, and 35.0°

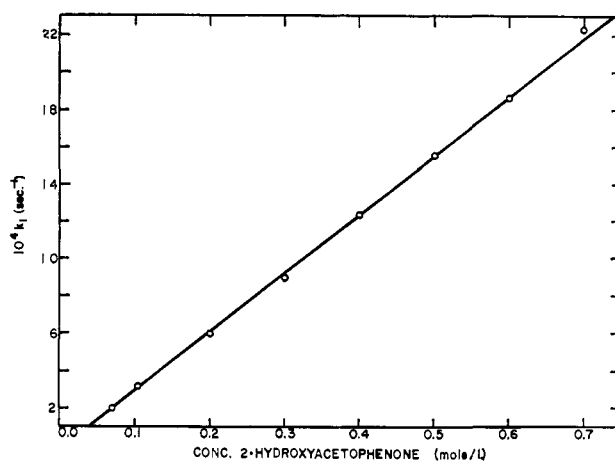


Figure 4. The effect of the concentration of α -hydroxyacetophenone on the rate of Cu(II) reduction.

($k = (0.95 \pm 0.02) \times 10^{-3}$; $(2.97 \pm 0.02) \times 10^3$, and $(8.69 \pm 0.15) \times 10^{-3}$ sec.⁻¹, respectively) giving the activation parameters $\Delta H^* = 18.9 \pm 0.4$ kcal./mole and $\Delta S^* = -6$ e.u.

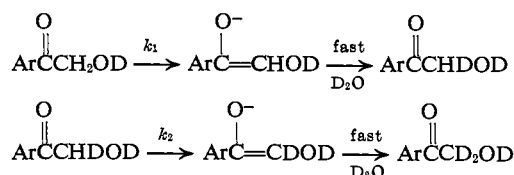
Table IV. Effect of Ionic Strength on the Rate of Oxidation of α -Hydroxyacetophenone in 50 Mole % Pyridine-Water

μ , M	$k_2 \times 10^3$, l. mole ⁻¹ sec. ⁻¹ ^a
0.062	2.97 ± 0.02
0.187	2.98 ± 0.02
0.250	2.97 ± 0.02
0.375	3.09 ± 0.03
0.500	3.16 ± 0.05
0.717	3.17 ± 0.01

^a Average of quadruplicate determinations except the last which was run in duplicate. The errors given are the observed average deviations. [Cu^{II}] = 0.014 M, [ketol] = 0.20 M, [PyH⁺] = 0.020 M.

The above data indicate that the rate law is $v = k[\text{Cu}^{\text{II}}][\text{ketol}]$ when the copper(II) concentration is greater than 0.01 M. A base is probably involved at some step in the reaction, but the order with respect to it cannot easily be defined since the solvent would be the base. At very low concentrations of copper(II) the rate law becomes $v = k[\text{ketol}]$ and is independent of the copper(II) concentration. The cuprous ion which is formed in the reaction has no effect on the rate even though it remains in solution.

It is possible that the rate observed at low copper(II) concentrations corresponds to enolization of the ketol. The rate of enolization was determined in the reaction solvent by following the rate of hydrogen-deuterium exchange using the disappearance of the τ 5.12 methylene band in the n.m.r. as the analytical tool. The reaction involves two hydrogens and is an example of consecutive, first-order reactions which may be sym-



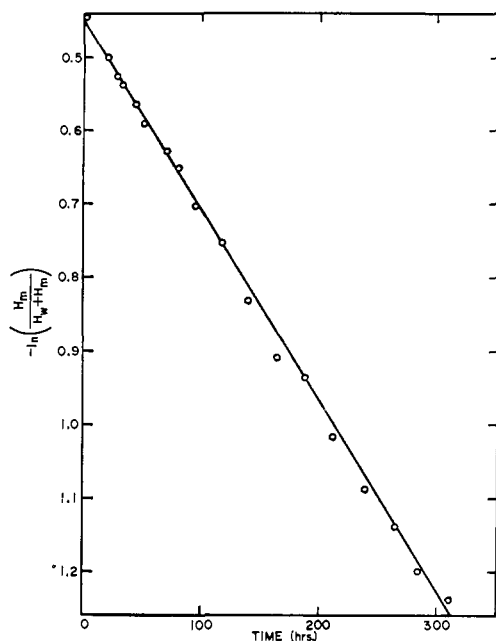
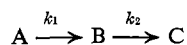


Figure 5. First-order plot of deuteration of α -hydroxyacetophenone at 25°.

bolized as



The concentrations of A and B as a function of time are given by

$$[A] = [A]_0 e^{-k_1 t}$$

$$[B] = \frac{[A]_0 k_1}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t})$$

Since A contains two enolizable hydrogens whereas B contains only one, the rate of proton removal from A will be twice that from B (neglecting a presumably small secondary isotope effect).

$$k_1 = 2k_2$$

Similarly, A will contribute twice as much to the τ 5.12 signal as B. The relationship between the concentrations of A and B and the observed peak area, D, will be

$$2[A] + [B] = \alpha D$$

where α is a proportionality constant.

A combination of the previous equations gives

$$\alpha D = [A]_0 \left[2e^{-k_1 t} + \frac{k_1}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t}) \right]$$

or

$$\alpha D = 2[A]_0 e^{-k_2 t}$$

Taking logarithms, we obtain

$$\ln D = -k_2 t + c$$

A typical plot for the data obtained is shown in Figure 5. The values of $k_1(2k_2)$ which were obtained are summarized in Table V. The value of the Hammett reaction constant, ρ , based on the three compounds studied, was +1.6.

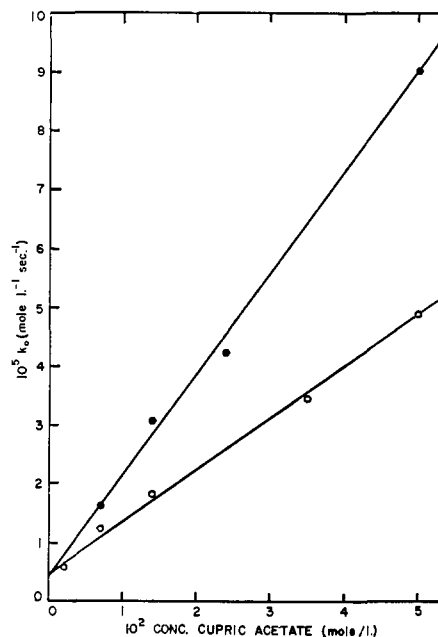


Figure 6. The effect of the concentration of cupric acetate on the initial rate of Cu(II) reduction at 25°.

The rate of disappearance of copper(II) is twice the rate of ketol consumption, and thus the rate of oxidation must be divided by two to give the rate of disappearance of the ketol. In Figure 6 are shown the

Table V. Rates of Enolization of α -Hydroxyacetophenones in 50 Mole % Pyridine-Deuterium Oxide at 25°

Compd.	Concn., M	$k_1 \times 10^7$, sec. ⁻¹ ^a
<i>p</i> -CH ₃ OC ₆ H ₄ COCH ₂ OH	0.700	3.4 ± 0.1
C ₆ H ₅ COCH ₂ OH	0.700	14.8 ± 0.1
<i>m</i> -BrC ₆ H ₄ COCH ₂ OH	0.400	56.0 ± 0.2

^a The error is the average deviation of duplicate determinations. Each solution contained 0.020 M pyridinium acetate.

initial rates of oxidation of α -hydroxyacetophenone using different copper(II) concentrations. The intercept using either 0.020 or 0.20 M pyridinium ion was $(0.4 \pm 0.1) \times 10^{-5}$ mole l.⁻¹ sec.⁻¹. In terms of disappearance of ketol, the rate constant is 2×10^{-6} mole l.⁻¹ sec.⁻¹. In Table VI it is shown that the re-

Table VI. Kinetic Hydrogen Isotope Effects in the Oxidation of α -Hydroxyacetophenone by Copper(II)

[C ₆ H ₅ - COCH ₂ OH]	Solvent	$10^3 k_2$, l. mole ⁻¹ sec. ⁻¹ ^a
0.200	H ₂ O	2.97 ± 0.02
0.200	D ₂ O	2.44 ± 0.06
0.700	H ₂ O	3.19 ± 0.01
0.700	D ₂ O	2.96 ± 0.02
0.700 ^b	H ₂ O	0.434 ± 0.004
0.700 ^b	D ₂ O	0.375 ± 0.010

^a Each solution contained 0.014 M cupric acetate and 0.020 M pyridinium acetate, $\mu = 0.25$ M. ^b The ketol contained deuterium in the methylene position.

placement of water by deuterium oxide causes a reduction in rate of oxidation by a factor of 1.2. In

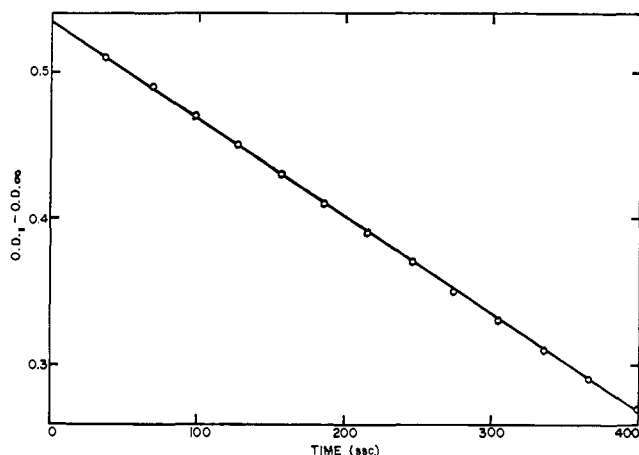


Figure 9. Typical zero-order plot of oxidation of α -methoxyacetophenone in buffered aqueous pyridine at 35°.

rate is observed. As additional bipyridine is added, the formation of a ketol-copper(II) chelate becomes less favorable and the rate of oxidation decreases. When enough bipyridine is added to effectively compete for all six coordination sites about copper(II), the rate of oxidation of ketol approaches the value corresponding to the rate of enolization.

In order to gain a better understanding of the ketol oxidation, the reaction of α -methoxyacetophenone with copper(II) was studied. The data are presented in Table VII. At low concentrations of copper(II)

Table VII. Rate of Oxidation of α -Methoxyacetophenone by Cu(II) in 50 Mole % Pyridine-Water

[Cu ^{II}]	[Ether]	[PyH ⁺]	μ , M	Temp., °C.	$10^6 k_1$, sec. ⁻¹
0.0020 ^a	0.700	0.020	0.03	25.0	0.99 ± 0.01
0.0065	1.000	0.200	0.50	35.0	8.22 ± 0.03
0.0140	0.200	0.200	0.50	35.0	14.0 ± 0.1
0.0140	0.700	0.020	0.25	25.0	3.27 ± 0.07
0.0140	0.700	0.020	0.25	35.0	8.97 ± 0.05
0.0140	0.700	0.200	0.50	25.0	4.51 ± 0.08
0.0140	1.000	0.200	0.50	35.0	10.2 ± 0.1
0.0350	1.000	0.200	0.50	35.0	12.8 ± 0.1
0.0650	1.000	0.200	0.50	35.0	18.5 ± 2.1

^a Deuterium oxide was used in the solvent in this case.

(0.0065 and 0.0020 M), the data gave good, zero-order plots up to 50% reaction or better (Figure 9). As the initial concentration of copper(II) was raised to about 0.065 M, the data would fit a first-order plot about equally well. The first-order rate constants in Table VII were obtained by dividing the zero-order rate constants by the concentration of the ether.

A plot of k_1 against copper(II) concentration for entries 2, 7, 8, and 9 in Table VII gave the constants shown in the expression $\nu = 7.2 \times 10^{-6} + (1.8 \times 10^{-4})[\text{Cu}^{+2}]$. Since these correspond to 1.0 M ether, the second constant may be compared with the corresponding value for the oxidation of the ketol at 35°, 8.7×10^{-8} l. mole⁻¹ sec.⁻¹. Thus, methyl substitution reduced the rate of oxidation by a factor of 50. The rate of disappearance of the ether at 25° and 0.002 M copper(II) agrees with the rate of enolization measured *via* deuterium uptake. The former is 0.5×10^{-6} sec.⁻¹ (one-half the rate of disappearance of copper(II))

and the latter is 1.2×10^{-6} sec.⁻¹. A dependence of the first-order rate constants on the concentration of ether may also be noted from the third and seventh entries in Table VII. However, this may be a solvent effect resulting from the high concentration of ether used in the latter experiment.

We may now ask what relationship exists between the above data and those for aqueous solution. First, in aqueous solution using citrate or tartrate as the complexing agent, it is unlikely that a ketol could effectively compete for two of the coordination sites about copper(II). The above results suggest that the reaction should simply involve rate-determining enolization and should give the observed, zero-order dependence on copper(II). A re-examination of the data of Marshall and Waters⁶ leads us to the conclusion that considering the experimental errors in determining hydroxyl ion concentrations in strongly basic solutions in dioxane-water mixtures, especially at a high ionic strength, the rates of oxidation and enolization observed by them are the same within experimental error.

In one study, we have found that copper(I) is very easily oxidized by air to copper(II). Only by thoroughly degassing our reaction solutions before mixing them could we obtain good, first-order plots without initial curvature. From this we conclude that the initial curvature observed by Marshall and Waters was probably due to the presence of a small amount of residual oxygen. It appears to us that there is no experimental support for the mechanism which they proposed.

Experimental

Reagents. Pyridine (Fisher reagent grade) was heated to reflux over barium oxide for 2 days and then fractionally distilled through a 2.5×122 cm. Heli-Pak column. The pyridine-water solutions were made up by weight. Pyridinium acetate was prepared by mixing equimolecular amounts of purified pyridine and acetic acid (distilled from chromic acid under vacuum).

Sodium perchlorate monohydrate (G. F. Smith, reagent grade) was dried at 120°. Cupric acetate (Fisher, reagent grade), cupric perchlorate (G. F. Smith, reagent grade), deuterium oxide (99.7%), and bipyridine (Eastman White Label) were used as obtained.

The 2-methoxyacetophenone (Aldrich) was purified by preparative v.p.c. using an Aerograph Autoprep A-700, and a Dow 710 silicone column. Phenylglyoxal was prepared from acetophenone and selenium dioxide.¹¹ It was converted to the hydrate with water and recrystallized five times from water. Distillation under reduced pressure gave the free aldehyde.

α -Hydroxyacetophenones. Approximately 2 moles of diazomethane was generated in 3 l. of ether, from N-methyl-N-nitrosourea and 40% potassium hydroxide solution.¹² The ether solution was dried over potassium hydroxide pellets for 2 hr. To the cold solution was slowly added 0.27 mole of the acid chloride

(11) H. A. Riley and A. R. Gray, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 519.

(12) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

with continuous stirring. The solution was allowed to stand at room temperature for 1 hr. The ether and excess diazomethane were removed by evaporation on a steam bath. To the resultant red oil was added 2 l. of 0.5 *N* sulfuric acid and the mixture was heated on a steam bath for 2 hr. After cooling, the acid solution was extracted with several portions of ether. The ether solution was dried over sodium sulfate and evaporated to give the crude ketol. The ketols were purified by sublimation, recrystallization from *n*-hexane (five times), and resublimation. In this way were prepared α -hydroxyacetophenone-C¹⁴, m.p. 85.5–86.5°; *p*-methoxy- α -hydroxyacetophenone, m.p. 105.0–105.5° (49%) (*Anal.* Calcd. for C₉H₁₀O₃: C, 65.1; H, 6.1. Found: C, 65.0; H, 5.8); *p*-methyl- α -hydroxyacetophenone, m.p. 93.0–93.5° (44%) (*Anal.* Calcd. for C₉H₁₀O₂: C, 72.0; H, 6.7. Found: C, 72.3; H, 6.6); *p*-bromo- α -hydroxyacetophenone, m.p. 134–135° (39%) (*Anal.* Calcd. for C₈H₇BrO₂: C, 44.7; H, 3.3; Br, 37.2. Found: C, 44.8; H, 3.2; Br, 37.0); and *m*-bromo- α -hydroxyacetophenone, m.p. 101–102° (20%) (*Anal.* Calcd. for C₈H₇BrO₂: C, 44.7; H, 3.3; Br, 37.2. Found: C, 44.7; H, 3.1; Br, 37.1).

α -Hydroxyacetophenone- α,α -d₂. α -Hydroxyacetophenone (50 g., 0.37 mole) was heated to reflux with 99.7% deuterium oxide (200 ml.) containing deuterio-sulfuric acid (2.0 g., 0.02 mole) for 16 hr. with rapid stirring. Upon cooling, the ketol crystallized from solution. The air-dried solid was equilibrated with another equal portion of deuterium oxide–deuterio-sulfuric acid for 18 hr. The ketol was filtered, dried over phosphorus pentoxide under vacuum, recrystal-

lized from *n*-heptane, and sublimed twice at 85° (0.1 mm.). Before use, the ketol was recrystallized five times from *n*-heptane and resublimed, m.p. 86.0 and 86.5°.

Kinetic Method. The solution of copper(II) in pyridine–water was placed in one arm of a U-tube attached at its center to a spectrometer cell, and the solution of the ketol in pyridine–water was placed in the other arm. The solutions were degassed under a good vacuum by successive freezing and melting. The solutions were thermostated at the reaction temperature, and then mixed by inverting the tube. The absorbance of the solution was determined as a function of time at a wave length in the range 650–850 m μ . From two to eight runs were made for each set of experimental conditions and the average values are reported.

Rate of Enolization. Acetic acid-*d* was prepared by heating an equimolar mixture of freshly distilled acetic anhydride and deuterium oxide. It was distilled through a Vigreux column at atmospheric pressure, b.p. 115.5–116°. To a weighed amount of this acid was added an equimolar amount of pyridine. The preparation of the buffer was completed by the addition of 50 mole % pyridine–deuterium oxide.

An aliquot of a freshly prepared solution of the enolizable compound in the deuterated solvent was placed in an n.m.r. sample tube, degassed by the freeze-melt process, and sealed under vacuum. The n.m.r. spectrum was taken periodically to determine the rate at which the methylene peak disappeared. The samples were kept in a 25° thermostat between measurements and at 25 \pm 2° while in the n.m.r. spectrometer.

Kinetic Demonstration of a Tetrahedral Intermediate in the Hydrolysis of Diethyl Acetylmalonate and Diethyl Acetylmalonate¹

Gustav E. Lienhard and William P. Jencks

Contribution No. 375 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02154. Received April 26, 1965

The rates of hydrolysis of diethyl acetylmalonate and diethyl acetylmalonate to acetic acid and diethyl malonate or diethyl ethylmalonate, respectively, have been measured at pH values between 0 and 14. The pH-rate profile of each shows two regions in which the rate of hydrolysis is independent of pH and two regions in which it is proportional to the concentration of hydroxide ion. This dependence on pH has been interpreted in terms of a change from rate-determining cleavage of the carbon-carbon bond in a hydrated ketone intermediate at low pH to rate-determining formation of the intermediate at

higher pH values. This interpretation is supported by the observations that the reaction is catalyzed by carboxylic acid buffers at pH 5 (slow hydration), whereas it shows no such catalysis at pH 3 (slow carbon-carbon bond cleavage), and that the catalytic constants for the buffers decrease with increasing buffer concentration at pH values in the range 4.25–4.98, which is caused by the (uncatalyzed) cleavage step becoming partially rate determining at high buffer concentrations.

Introduction

Kinetic studies on the reaction of a number of nucleophilic reagents with carbonyl groups have provided evidence for the initial formation of an adduct between the carbonyl group and the nucleophile (a

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