[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Mechanism of the Acetophenone–Iodine–Pyridine Reaction

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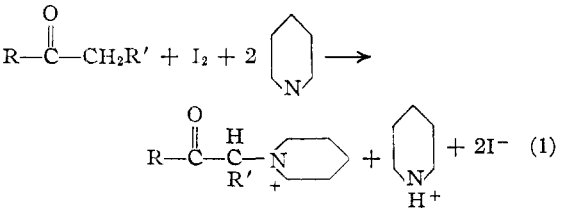
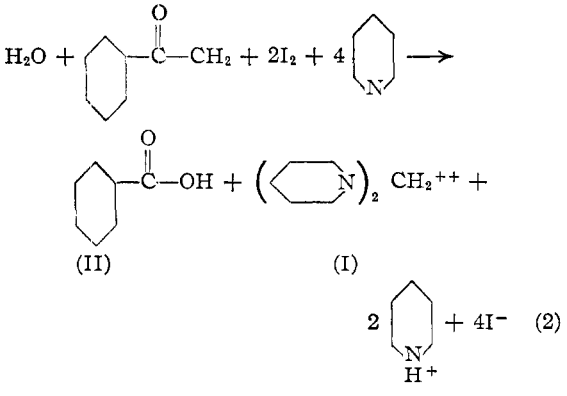
Recently it has been shown by King that ketones react with iodine in the presence of excess pyridine to give high yields of β-ketoalkyl pyridinium iodides.[1] The reaction is formulated as

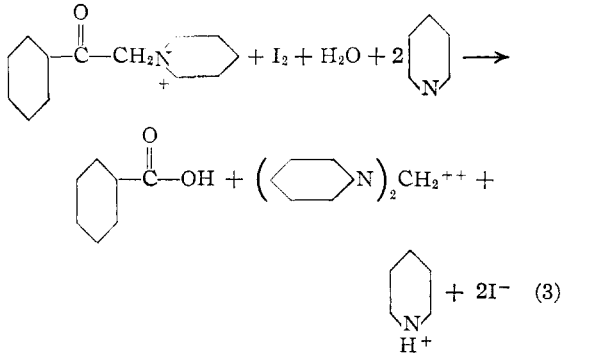


The reaction has been extended to include a variety of ketones and heterocyclic amines.[2] Inasmuch as the usual phenomenon in the base catalyzed halogenation of ketones is polyhalogenation, *e. g.*, the iodoform reaction of methyl ketones, it was thought worth while to study the mechanism of reaction (1) for a single representative ketone using kinetic methods.

It was found that the kinetics are influenced by small quantities of water and, because of the difficulty of maintaining pyridine absolutely anhydrous, a solvent consisting of 20% pyridine and 80% water by volume was used.[3] It was found that the reaction of acetophenone and iodine in this solvent, if the concentrations used were small enough to maintain homogeneity at all time, gave as the main products N,N′-dipyridiniummethylene diiodide (I), benzoic acid (II) and pyridine hydroiodide according to equation (2).



Only a trace of phenacylpyridinium iodide (III), the product expected according to (1), was formed. Inasmuch as it is known that the reaction of (III) with iodine in the presence of pyridine and water gives rise to (I) and (II) it seems reasonable to assume that the expected product (III) is formed first and then reacts with excess iodine to give the observed products as in (3).[4]



Accordingly, two sets of kinetic measurements were made, one on the rate of reaction of acetophenone with iodine and the other on the rate of the phenacylpyridinium iodide–iodine reaction, the pyridine–water solvent being used for both. The extent of reaction was determined by the large change in electrical conductance of the solutions as the reaction proceeds.

Experimental

Preparation of Materials.—Eastman Kodak Co. white label acetophenone was fractionated through a helix-packed column rated at ten theoretical plates and a small constant boiling middle fraction was used (f. p. 17.50–17.60°). Medicinal grade pyridine was used without further treatment. Resublimed iodine of analytical grade was used. Phenacylpyridinium iodide (m. p. 218–219°) and perchlorate (m. p. 189–190°) were recrystallized from water.[5] Solutions were made up by weighing the solute in a 100-ml. glass-stoppered volumetric flask, adding 20 ml. of pyridine and diluting with water to the mark. Acetophenone solutions were about 0.3 molar, iodine solutions about 0.005 molar containing small amounts of sulfuric acid, and the phenacylpyridinium salts about 0.01 molar. Blank runs indicated a slow irreversible reaction between iodine and pyridine, hence these solutions were prepared fresh for each run.[6]

General Procedure.—Selected volumes of the solutions of the two reactants were mixed together at the reaction temperature and a stop watch started concurrently. A sample was drawn into a stoppered conductance cell and readings of the resistance made with a Jones bridge at intervals of several minutes. The cell was thermostated and temperature controlled to ±0.02°. The acetophenone–iodine reaction was measured at 20 to 25° and the more rapid reaction of iodine and the phenacylpyridinium salts at 0°. The time of measurement ran from twenty minutes to several hours and covered up to 90% of the reaction. A final reading of the equilibrium resistance was made after a day or two.

(1) King, THIS JOURNAL, **66**, 894 (1944).

(2) King, *ibid.*, **66**, 1612 (1944); King and McWhirter, *ibid.*, **68**, 717 (1946).

(3) All reactants are sufficiently soluble in this medium at the concentrations used.

(4) King, forthcoming publication.

(5) Kindly supplied by Dr. L. C. King.

(6) A period of standing of even half an hour changed the concentration of iodine by an appreciable amount.

Calculations and Results.—Neglecting the change of equivalent conductance with ionic strength, the reciprocal of the resistance was assumed to be proportional to the ionic concentration and hence to the extent of reaction. The constant of proportionality was found from the value of the equilibrium resistance since the reactions go to completion. In addition, the effect of any initial conductance on the resistance has to be considered. In general if a is the initial concentration of the limiting reactant, x is the amount reacted, R_0, R and R_e are the resistances at time = 0, time = t, and time = ∞, then

$$a = \left(\frac{1}{R_0} - \frac{1}{R_e}\right)z$$
$$x = \left(\frac{1}{R_0} - \frac{1}{R}\right)z \qquad (4)$$

where z is a proportionality constant. It follows that

$$\frac{x}{a} = \frac{R_e(R_0 - R)}{R(R_0 - R_e)} \text{ and } \frac{a}{a - x} = \frac{(R_0 - R_e)R}{R_0(R - R_e)} \qquad (5)$$

In the reaction of acetophenone with iodine, the ketone and the pyridine were present in sufficiently large excess so that their concentrations remained essentially constant. It was found that a plot of $1/R$ against time gave a straight line until the reaction was about 75% complete. This is shown, for example, in Fig. 1.[7] This linearity of t with x means a constant value of the slope dx/dt which is consistent with a rate determining step involving the concentrations of the ketone and the pyridine and independent of the iodine concentration. This is what would be expected for the base catalyzed halogenation of a ketone.[8] Changing the concentration of the acetophenone gave changes in slope which showed that the reaction was essentially first order with respect to the ketone. Extrapolation of the straight line portions of the curves to the equilibrium resistance gave the hypothetical times necessary to complete the reactions if the rate remained constant throughout. These, together with the initial concentrations of iodine, enable a calculation of the pseudo zero order rate constant k_0. It is more convenient to correct these for the molarity of the ketone and calculate the pseudo first order constant, k_1. For example, if 0.00318 mole per liter of iodine reacted to completion in 27.6 minutes at constant rate then $k_0 = dx/dt$ is (1/2) (0.00318) (1/27.6) moles/liter-minute. The factor 1/2 appears because of the disappearance of two molecules of iodine after the successful completion of the rate determining step. Finally the pseudo first order constant is obtained by dividing k_0 by the concentration of the acetophenone,

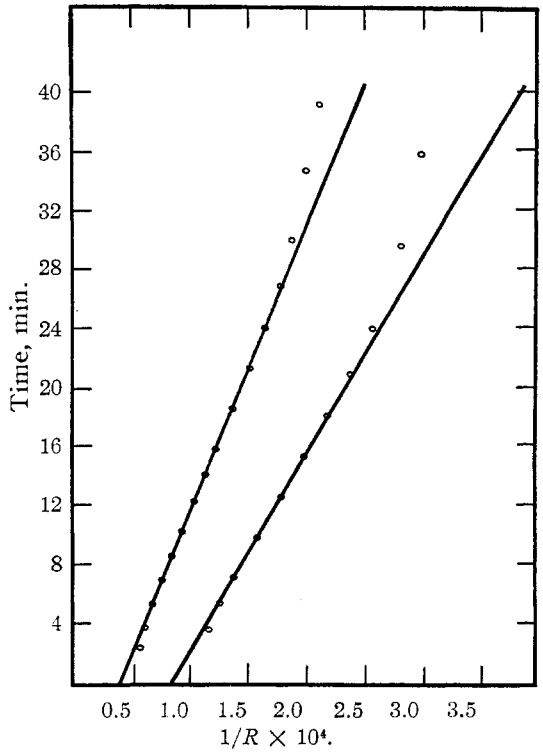


Fig. 1.—Lower curve, 0.086 M acetophenone + 0.00248 M iodine; upper curve, 0.053 M acetophenone + 0.00184 M iodine.

$(1/2)(0.00318)(1/27.6)(1/0.1375) = 4.2 \times 10^{-4}$/min. Table I gives the results obtained.

TABLE I

KINETICS OF ACETOPHENONE, PYRIDINE AND IODINE AT 25°

Acetophenone, molar	Iodine, molar	Time for completion, min.	k_1 (min.$^{-1}$)
0.1375	0.00318	27.6	4.2×10^{-4}
.092	.00347	41.4	4.6×10^{-4}
.086	.00248	31.6	4.6×10^{-4}
.053	.00184	34.0	5.0×10^{-4}
.086	.00312	72.4	2.5×10^{-4} (20°)

For the reaction of phenacylpyridinium iodide (or perchlorate) with iodine it was found that a plot of $R/(R - R_e)$ was linear with the time regardless of the ratio of iodine to salt, providing the salt was in excess[9] (see Fig. 2). Furthermore, the slope of the line depended upon the initial concentration of iodine only and not upon the quaternary salt concentration. This indicates second order kinetics with respect to the iodine or some substance proportional to the amount of iodine present. The nature of this substance is indicated by the effect of acid (sulfuric acid or pyridine hydroiodide) upon the rate. As Table II brings out, acid depresses the rate constant by a considerable factor. Furthermore the extra-

(7) Reversible reaction of the iodine with the solvent (hydrolysis, etc.) gives an initial conductance which does not fall off linearly with the extent of the reaction. Hence, sulfuric acid (or in some cases pyridine hydroiodide) 0.001 to 0.002 molar was added to reduce this undesirable effect.

(8) See, for example, Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, chapt. IV and VIII.

(9) Studies were not made with iodine in excess because the reaction of the excess iodine with pyridine complicates the relating of resistance to extent of reaction.

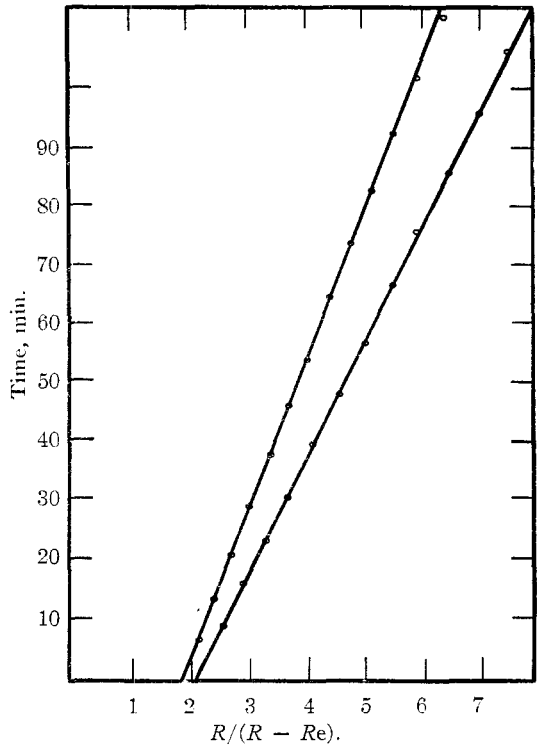


Fig. 2.—Lower curve, 0.00325 *M* phenacylpyridinium perchlorate and iodine; upper curve, 0.00391 *M* phenacylpyridinium iodide + 0.00260 *M* iodine.

polated values of R_0 show that the conductance of the solutions immediately after mixing corresponds to a considerable instantaneous gain in number of ions. Both phenacylpyridinium iodide and perchlorate were used to show that the reaction is characteristic of the cation only. From (5) and the usual kinetic expression the second order rate constant k' can be found

$$t + \frac{1}{ak'} = \left(\frac{a}{a - x}\right)\frac{1}{ak'} = \frac{1}{ak'}\frac{(R_0 - R_e)R}{R_0(R - R_e)} \quad (6)$$

so that the slope of the time *versus* $R/(R - R_e)$ plot divided by the intercept gives ak'.

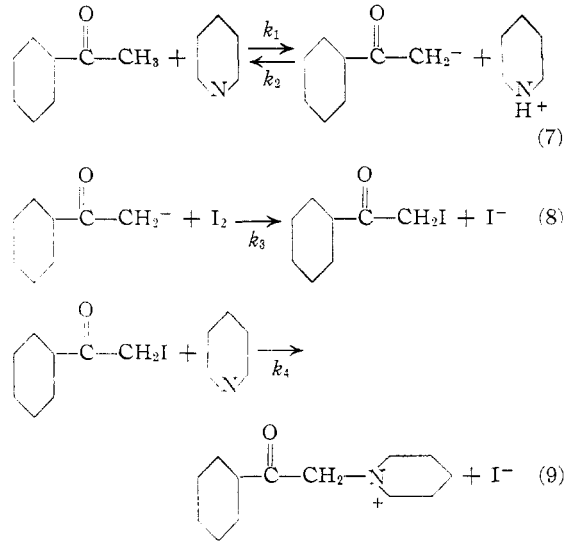
TABLE II

KINETICS OF PHENACYLPYRIDINIUM ION AND IODINE AT 0°

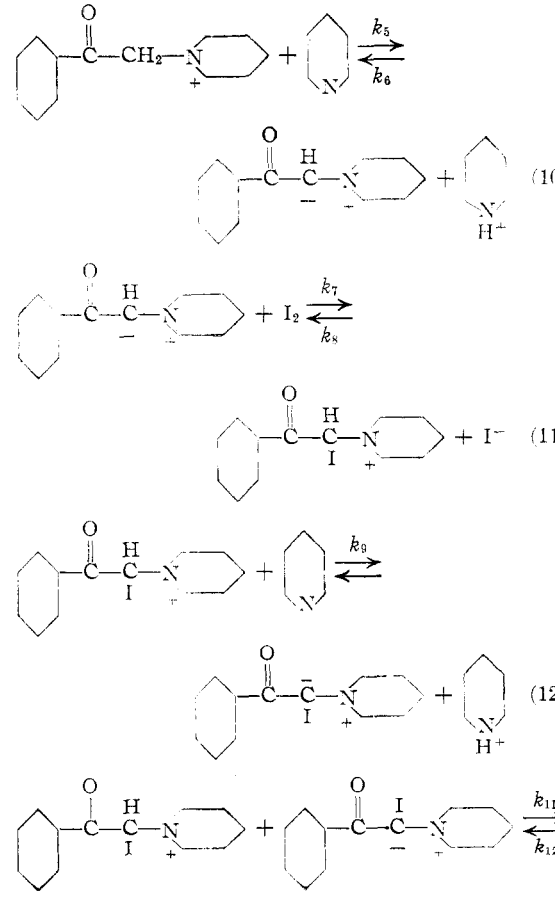
The units of k' are moles/liter and minutes.

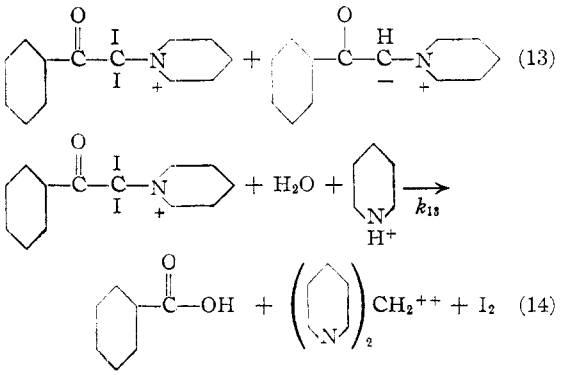
Phenacylpyridinium ion, molar	Iodine, molar	Added acid	k'
0.00300	0.00300	0	8.30
.00328 (as perchlorate)	.00328	0	8.00
.00500	.00331	0	8.10
.00300	.00250	0.0010	6.90
.00333	.00333	0.0043	4.30

Mechanism and Discussion.—In agreement with the experimental facts, the following mechanism is proposed for the formation of phenacylpyridinium iodide in the acetophenone–iodine reaction.



Of these, reaction (7) is the slowest and k_1 is rate determining. Then k_4 must be large and $k_3 \gg k_2$. The product of (9) then reacts rapidly with excess iodine according to (3) to give the observed products. The path of (3) under the condition of equivalent or excess phenacylpyridinium iodide appears to be the following





(13)

(14)

Here (10), (11) and (12) are postulated as equilibria and the rate controlling step is (13) the formation of the diiodo quaternary salt. The method whereby (14) occurs is subject to discussion. It is merely indicated here as being a rapid process. In the presence of excess iodine (13) would be replaced by a direct reaction (presumably more rapid) of iodine with the conjugate base of the iodo quaternary salt as formed in (12).

In defense of the mechanism outlined in (7) to (9) it is possible to compare the experimental value of k_1 at 25° with independent determinations of the rate of enolization of acetophenone. Bell[10] has sufficient data to evaluate the rate constant for the enolization of acetophenone in water solution using a base with the same strength as pyr dine as a catalyst. The value of k_1 thus calculated for the same mole fraction of pyridine as in the solution used in this work is 2×10^{-4} min.$^{-1}$ at 25° which compares favorably with the values shown in Table I, considering that Bell used anions of weak acids as bases. The value of the activation energy of (5) calculated from the data at 20 and 25° is 20.9 kcal. which is a reasonable value for the base catalyzed enolization of a ketone.[11] Because of the non-appearance of iodoform in the presence of water it is necessary that step (7) occurs more rapidly than di- and tri-halogenation, both of which are more rapid than monohalogenation.[8] In pyridine solution alone where (9) might be somewhat slower, polyhalogenation may occur, but there is evidence to show that if no water is present to cause the iodoform cleavage, the polyhalogenated ketones will also give phenacylpyridinium iodide.[4,12]

An analysis of reactions (10) to (13) gives the following kinetic expressions if it is assumed that reactions (10) and (11) occur instantaneously: Let $[QI^+]$ = concentration of monoiodo quaternary salt; $[QI^{\pm}]$ = concentration of the conjugate base of QI^+; $[BH^+]$ = concentration of pyridinium ion (total acid); then

$$[QI^+] + [QI^{\pm}] = (a - x) \quad (15)$$

$$[QI^+] = \frac{k_{10}}{k_9}[QI^{\pm}][BH^+] \quad (16)$$

$$\frac{(a - x)}{1 + \frac{k_{10}}{k_9}[BH^+]} = [QI^{\pm}] \quad (17)$$

$$\frac{dx}{dt} = k_{11}[QI^+][QI^{\pm}] = \frac{k_{11}\frac{k_{10}}{k_9}[BH^+]}{[1 + \frac{k_{10}}{k_9}[BH^+]]^2}(a - x)^2 \quad (18)$$

or

$$dx/dt = k'(a - x)^2 \quad (19)$$

If the relatively small increase in $[BH^+]$ as the reaction proceeds[13] does not change the value of k' too much, then (19) gives the correct second order kinetics and if k_{10}/k_9 is large then it also gives the observed dependence of the measured slope upon added acid. The accuracy of the data does not permit a determination of k_{10}/k_9, but it can be seen that the value of k' upon the addition of an equivalent amount of acid will approach one-half of the value of k' in the absence of acid if k_{10}/k_9 is large. The instantaneous complete monoiodination of the quaternary salt shown in (10) and (11) explains the high value of the initial conductance as calculated from R_0. The rapidity of (10) depends upon the greatly increased acid strength of the quaternary cation, compared to acetophenone, due to the positive charge.[14] Equations (11) and (13) are written as equilibria to explain the nonformation of iodo or diiodo quaternary salts when β-ketoalkylpyridinium salts are treated with iodine under a variety of conditions in the absence of water.[4] That is, reaction (13) is driven to completion only by the occurrence of (14) or a similar cleavage process. Reaction (11) is readily reversed when any attempt is made to isolate the iodinated salt. That these positively charged halogenated compounds should be active halogenating agents is to be expected.

Summary

1. The rate constants for the reaction of iodine with acetophenone and pyridine in aqueous solution at 20 and 25° and of the phenacylpyridinium cation with iodine and pyridine in aqueous solution at 0° have been measured.

2. The reaction rate of the ketone with pyridine and iodine is independent of the halogen concentration and depends upon the usual base catalyzed enolization of the ketone.

3. The reaction of iodine with phenacylpyridinium cation appears to occur through a rapid monohalogenation followed by a slow, rate determining dihalogenation and a rapid cleavage to N,N′-methylenedipyridinium diiodide and benzoic acid.

4. Polyhalogenation of the quaternary salt is a reversible process in the absence of water.

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(10) Bell, *Trans. Faraday Soc.*, **39**, 253 (1943).

(11) Smith, *J. Chem. Soc.*, 1744 (1934).

(12) Krohnke, *Ber.*, **66**, 604 (1933); **69**, 921 (1936).

(13) The increase in $[BH^+]$ is due to the replacement of the acid QI^+ with the stronger benzoic acid. Both will be considerably ionized in the solvent used, the latter more than the former.

(14) Phenacylpyridinium cation is an acid with K_a about 10^{-11} in water solution. Work on the acid ionization constants of this and related substances is going on in this Laboratory.