

Tetranitro-*p*-azophenol (m. p. 261–262°, with dec.) was obtained by slowly adding dinitro-*p*-azophenol (1 g.) to fuming nitric acid (5 ml.), cooled in an ice-salt bath. After stirring for five minutes, the reaction mixture was poured on ice. The crude product (1 g.) was purified by crystallization from glacial acetic acid.

Anal. Calcd. for $C_{12}H_6O_{10}N_6$: C, 36.55; H, 1.52; N, 21.32. Found: C, 36.93; H, 1.73; N, 21.45.

Tetrabromoazophenol (m. p. 273–274°) was obtained in equal yield from both α - and β -azophenol. To a solution of the monohydrate of *p*-azophenol (2 g.) and sodium acetate (3 g.) in glacial acetic acid (130 ml.) was added a solution of bromine (3 g.) in glacial acetic acid (50 ml.). Mechanical stirring was employed during the period (twenty-five minutes) that bromine was added and for thirty minutes thereafter. A dark green precipitate (1.3 g.) was filtered off. After four crystallizations from glacial acetic acid, the tetrabromo derivative melted at 273–274°.

Anal. Calcd. for $C_{12}H_6O_2N_2Br_4$: C, 27.20; H, 1.14. Found: C, 27.04; H, 0.87.

The diacetate (m. p. 263–264°) was prepared in the usual way.

Anal. Calcd. for $C_{16}H_{10}O_4N_2Br_4$: C, 31.27; H, 1.63. Found: C, 31.32; H, 1.73.

The dibenzoate (m. p. 297–298°) was obtained by benzoylation in pyridine with benzoyl chloride.

Anal. Calcd. for $C_{26}H_{14}O_4N_2Br_4$: C, 42.28; H, 1.90. Found: C, 42.12; H, 2.37.

Summary

The recorded evidence for *cis-trans* isomerism in the case of *p*-azophenol has been reexamined and new findings have been introduced with the result that it may now be concluded that the so-called α - and β -forms of *p*-azophenol are not *cis-trans* isomers. The anhydrous *p*-azophenol does exist in two solid modifications, however.

MINNEAPOLIS, MINN.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Effect of Nuclear and Side Chain Substitution on the Oxonium Ion Catalyzed Iodination of Acetophenone Derivatives

BY LOIS ZUCKER¹ AND LOUIS P. HAMMETT

Nathan and Watson,^{2a} and Evans,^{2b} measured the rates of bromination of a number of acetophenone derivatives in acetic acid-water solutions containing hydrochloric acid, and found the effect on the rate of substitution of a methyl group for hydrogen in the side chain much greater than the effect of substitution in the ring. Since the reaction is subject to general acid catalysis,³ the specific bromination rate in a given medium is the sum of a series of specific catalytic bromination rates, one for each catalyst present, and the effect of a given substitution cannot be expected to be the same for different catalysts. This makes the observed rate in this medium an unnecessarily complicated function of the structure of the ketone,⁴ since undissociated acetic acid, hydrogen ion solvated with water (oxonium ion), and hydrogen ion solvated with acetic acid are possible catalysts. A more easily interpretable catalytic system is found in a not too concentrated aqueous solution of a strong monobasic acid, which can

contain only one effective catalyst, oxonium ion. Accordingly, we have measured the rates of iodination (equal to the rates of enolization) of some of these ketones, together with that of 2,4,6-trimethylacetophenone (not on the previous list), in 1.388 molar aqueous perchloric acid solution, using a colorimetric technique.

Experimental

Apparatus.—The iodinating solution was contained in a closed glass cell shown in Fig. 1, closure being made with a very well fitting ground glass joint, of which the colorimeter plunger forms the stopper. Error introduced by this closure, as far as optical alignment and effective depth of layer are concerned, was within the ordinary precision of matching, ± 0.17 mm. under the conditions of a kinetic run. A really well fitting glass joint is also necessary to retain iodine in an aqueous solution containing no iodide over a period of many hours. The double lines indicate brass, the single lines glass. The cell stood directly on a plane glass disk (removable for cleaning) which formed part of the bottom of a flattened cylindrical brass water jacket, of 80 cc. capacity with the cell mounted, which in turn was fastened to the colorimeter platform with a lock nut. Water was circulated from a large thermostat through insulated tubing and the likewise well insulated jacket at the rate of 5 cc. per sec. Temperature in the cell could be maintained at $25.00 \pm 0.01^\circ$, as checked by thermocouple, even when room temperature was as low as 17° .

(1) Part of a thesis submitted by Lois Zucker in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science of Columbia University.

(2) (a) Nathan and Watson, *J. Chem. Soc.*, 217 (1933); (b) Evans, *ibid.*, 785 (1936); see also (c) Evans, Morgan and Watson, *ibid.*, 1167 (1935).

(3) Zucker and Hammett, *THIS JOURNAL*, **61**, 2785 (1939).

(4) Hammett, *Trans. Faraday Soc.*, **34**, 156 (1938).

The colorimeter was the Klett-Beaver model,⁵ with the above-described cell mounted on one side, and on the other side the standard two-cup, two-plunger system for maintaining a constant 5 cm. depth of absorbing layer, with variable contributions from the colorimetric standard and pure water. The fields were viewed through a dense

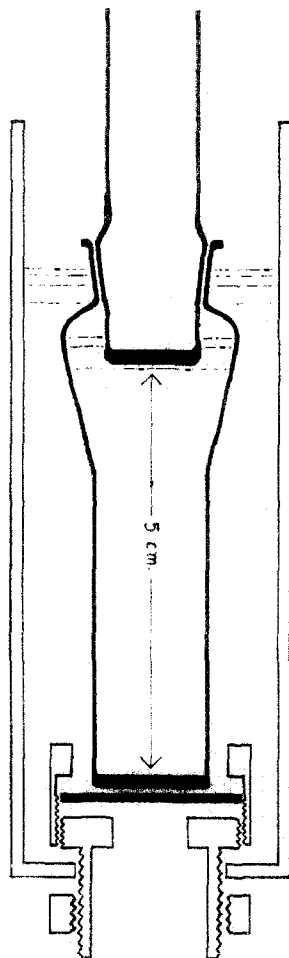


Fig. 1.

blue filter, Wratten L50; applied to the usual incandescent bulb it supplies a deep blue-violet light representing a fairly narrow spectral band. The filters were placed inside the prism housing immediately over the ends of the plungers.

Method.—The reaction products, derivatives of phenacyl iodide, are rather insoluble in any aqueous media. The maximum concentration of iodine which can disappear from solution before the appearance of insoluble phenacyl iodide is 17×10^{-5} molar, and some of the substitution products of phenacyl iodide are considerably less soluble. Iodine concentrations used in runs were accordingly of this order of magnitude, so that large relative changes in iodine concentration could be observed; the range of iodine concentrations covered was 30

to 0.5×10^{-5} . The more dilute of these solutions, although hardly distinguishable from water by general illumination, have reasonably strong color when viewed through the blue filter used, since the filter cuts out most of the light not appreciably absorbed by aqueous iodine solutions. Because of the great instability in an open cup of aqueous iodine solutions containing no iodide, we had to use an artificial colorimetric standard—a dilute (4 mg. per liter) solution of methyl orange in water. Although this solution differs markedly in color from iodine solutions in general illumination, when viewed by the light transmitted by the filter methyl orange and iodine solutions are in-

distinguishable by eye over the range of concentrations covered.

Beer's law was shown to apply to this system by determining the depth of layer of the standard methyl orange solution necessary to match the same 5-cm. layer of at least eight different iodine solutions covering the range of iodine concentrations used, and made up by adding an excess of sodium iodate or sodium nitrite to a known acidified solution of potassium iodide. Then

$$c_{I_2} = \frac{c_{MeO} \bar{k}_{MeO}}{h_{I_2} \bar{k}_{I_2}} \times h = mh$$

where c_{I_2} and c_{MeO} are the molar concentrations of iodine and methyl orange, \bar{k}_{I_2} and \bar{k}_{MeO} are the effective molecular extinction coefficients of iodine and methyl orange for the spectral region employed,⁶ h_{I_2} is the depth of layer of iodine solutions (close to 5 cm.), h the depth of layer of methyl orange solution necessary for match, and m is the slope of the linear plot of c_{I_2} against h .

Under ordinary conditions only one atom of iodine from each iodine molecule is introduced into the ketone, the other being liberated as iodide ion. Because the resultant gradual increase in concentration of the intensely yellow polyiodide ions would cause a change in the color value and intensity of the solution, and because iodide ion undergoes oxidation by dissolved oxygen which is relatively rapid in acid solution, and finally to avoid reversal of the reaction, most of the runs were made in the presence of an oxidizing agent, either sodium nitrite or sodium iodate, which converts iodide to iodine as fast as it is formed. This device is due to Bartlett,⁷ who used nitric acid as the oxidizing agent in glacial acetic acid. Then

$$\Delta c_{KH} = f \Delta c_{I_2} = mf \Delta h \quad (1)$$

where Δc_{KH} is the change in concentration of the ketone as a result of the iodination, Δc_{I_2} and Δh are the corresponding changes in iodine concentration and in colorimeter setting. The factor f has the value 2.5 if the oxidizing agent is iodate, 2 if it is nitrite. Some runs were made with each ketone with nitrite, some with iodate—agreement of the rates is evidence that neither oxidizing agent is interfering with the rate measurement. Good agreement was found for all the ketones except 2,4,6-trimethylacetophenone and isobutyrophenone; in the latter case both oxidizing agents obviously were causing some other reaction, accom-

(6) Kortüm, *Z. angew. Chem.*, **50**, 193 (1937); Müller, *Ind. Eng. Chem., Anal. Ed.*, **31**, 1 (1939).

(7) Bartlett and Vincent, *This Journal*, **55**, 4992 (1933).

(5) Beaver, *J. Opt. Soc. Am.*, **18**, 41 (1929).

panied by the production of a brown color in the case of the iodate, and a precipitate in the case of the nitrite. Runs were made with both these ketones without any oxidizing agent, small portions of the reacting solution being read in the colorimeter at suitable time intervals, immediately after the addition of a slight excess of nitrite. The reverse reaction between iodide ion and phenacyl iodide derivative cannot be neglected if iodide is allowed to accumulate, so that the apparent rate does fall off; nevertheless the initial part of the reaction is not affected appreciably. Isobutyrophenone could be studied only by this method. The rate of iodination of 2,4,6-trimethylacetophenone in the absence of an oxidizing agent was found to be in excellent agreement with the rate in the presence of nitrite; it was therefore concluded that the discrepancy between runs with nitrite and with iodate is in this case due solely to some side reaction with the iodate.

The usual procedure was to weigh a suitable quantity (about 9 cc.) of a solution containing known concentrations of ketone and perchloric acid into the reaction cell, which was equipped with a spare stopper, and bring to temperature in the large thermostat while water was circulated through the water jacket on the colorimeter. About 0.2 cc. of a known aqueous potassium iodide solution was added from a weight pipet, the solution mixed, and left in the thermostat ten minutes longer. The reaction was started by the addition of a small crystal of solid oxidizing agent, the cell was transferred to the colorimeter, and readings were taken. The total time of mixing and transfer from one thermostat to the other was not more than twenty seconds. Time was measured from the instant of addition of oxidizing agent to the nearest one-tenth minute with a stop watch calibrated against an electric clock. This procedure allows a very satisfactory approximation to instantaneous mixing since the ketone concentration, upon which alone the rate depends, is at its correct initial value even before mixing.

For the runs without oxidizing agent each point on the time curve had to be determined on a separate portion of the reacting solution. In the case of 2,4,6-trimethylacetophenone it was most convenient to make up the solution in the colorimeter cell by the rapid addition from a weighing bottle of about 9 cc. of a solution of the ketone in perchloric acid, already at temperature, to about 0.1 cc. (known weight) of an aqueous solution containing potassium iodide and not quite an equivalent of sodium iodate, in the colorimeter cell also at temperature. After a suitable time interval a drop of an aqueous sodium nitrite solution was added, amounting to a slight excess over the concentration necessary to take care of the probable iodide concentration in the reacting solution. Readings were completed within five minutes of this addition.

This procedure applied to isobutyrophenone would have made the reaction cell unavailable for other measure-

ments for weeks; therefore the initial solution was made up in 130-cc. quantities in bottles of about 140-cc. capacity with very well ground glass stoppers, and at suitable intervals a portion of the solution was poured into the dry cell for reading. Experiments showed that with smooth pouring the first portion run into the cell is of the same iodine concentration as that in the bottle before pouring; however, with each opening of the bottle to pour out a portion, the iodine concentration of the solution in the bottle decreases slightly and this effect is the more pronounced the larger is the ratio of gas volume to liquid volume in the bottle. (The vapor pressure of iodine at 25° is 0.311 mm.⁸; these solutions have approximately one-fourth of the saturation concentration.) Only two portions could be taken from each bottle.

Materials.—Aqueous acid iodine solutions prepared from weighed portions of potassium iodide with an excess of either sodium iodate or sodium nitrite, formed the primary colorimetric standards. The sample of potassium iodide used throughout was of c. p. grade. It was dried at 105° and kept in a desiccator. At various times solutions prepared from the standard sample of potassium iodide were compared with solutions nominally of the same iodine concentration prepared from two other samples of potassium iodide of different origins and a sample of sodium iodide, and found to have the same color intensity within the error of the determination. Sodium iodate and sodium nitrite were of c. p. grade. Iodine solutions made up from the same iodide solution with iodate and with nitrite had the proper concentration ratio of 6 to 5.

Methyl orange was of the ordinary commercial grade for indicator use. The sample used appeared not entirely homogeneous with respect to depth of color of various particles. The secondary colorimetric standard was a stock solution of 100 mg. of methyl orange in 1 liter of aqueous solution, from which the working standard was prepared at frequent intervals by a 1 to 25 dilution. The stock solution retained the same iodine equivalence for over a year.

Perchloric acid solutions were made up from 60% reagent grade, ACS specification, and standardized against 0.1 normal sodium hydroxide, the primary standard being Bureau of Standards potassium acid phthalate.

Acetophenone,^{9a,b} *p*-methylacetophenone,^{9c} 2,4,6-trimethylacetophenone and *p*-bromoacetophenone^{9c} previously had been purified carefully. The first three were purified further by fractionating three times *in vacuo*; the *p*-bromoacetophenone was recrystallized once from ethanol-water solution. Propiophenone and *n*-butyrophenone obtained from the Eastman Kodak Company, and isobutyrophenone, made by Friedel-Crafts synthesis from benzene and isobutyryl chloride (Eastman), were recrystallized several times each from purified petroleum ether in an acetone-dry-ice bath, separation between crystals and liquid being effected by an Emig immersion filter. They were then each fractionated three times *in vacuo*. The purified samples all distilled within a temperature range of 0.2°.

(8) "International Critical Tables," Vol. III, p. 201.

(9) (a) Morgan and Lammert, *THIS JOURNAL*, **46**, 881 (1924); (b) Flexser, Hammett and Dingwall, *ibid.*, **57**, 2103 (1935); (c) Flexser and Hammett, *ibid.*, **60**, 885 (1938).

Ketone	$^{\circ}\text{C.}^{\text{B. p.}}$	Mm.	F. p., $^{\circ}\text{C.}$	$n_{\text{D}}^{25.5^{\circ}}$
Acetophenone	67	5	19.6-19.65	1.53142
Propiophenone	85	7	18.4-18.5	1.52436
<i>n</i> -Butyrophenone	75	4 ^{1/2}	12.65-12.7	1.51741
Isobutyrophenone	97	10	-1.35 to -1.3	1.51480
<i>p</i> -Methylacetophenone	72	4		1.53161
<i>p</i> -Bromoacetophenone			52.2-52.5	
2,4,6-Trimethylacetophenone	105	9		1.51444

Rate Calculations.—The reaction is first order in ketone and independent of iodine concentration, following the equation

$$-dc_{\text{KH}}/dt = kc_{\text{KH}} = k(c_{\text{KH}}^0 - \Delta c_{\text{KH}})$$

where c_{KH}^0 is the initial concentration of ketone. Substitution of equation (1) converts this to

$$-mf \frac{dh}{dt} = mfk \left(\frac{c_{\text{KH}}^0}{mf} - \Delta h \right)$$

whose integrated form is

$$\log \left(\frac{c_{\text{KH}}^0}{mf} - \Delta h \right) = -\frac{k}{2.303}t + \log \frac{c_{\text{KH}}^0}{mf} \quad (2)$$

If only a small fraction of the total ketone present reacts

$$\frac{c_{\text{KH}}^0}{mf} \gg \Delta h, \text{ and } -h = \frac{kc_{\text{KH}}^0}{mf}t - h^0 \quad (3)$$

Since in all runs the change in iodine concentration during the run was limited to $\Delta c_{\text{I}_2} = m\Delta h$

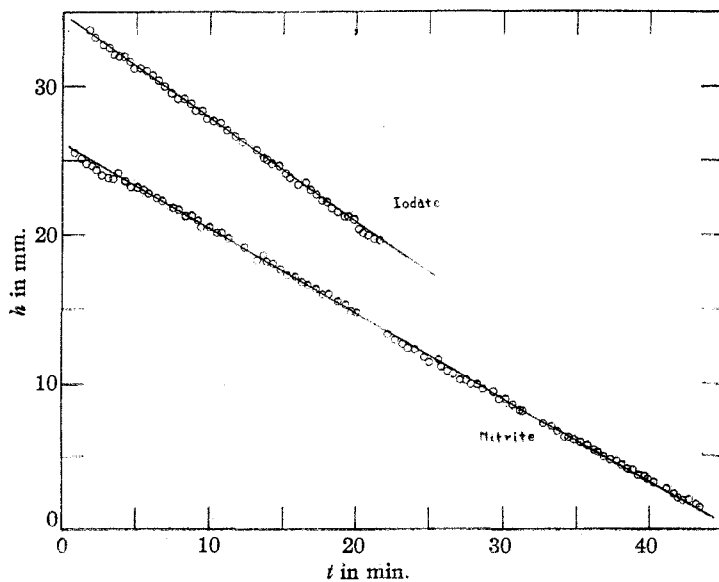


Fig. 2.

$\leq 17 \times 10^{-6}$, equation (3) could be applied to most of these ketones in spite of their small solubility. Equation (2) had to be used only for the most insoluble ketones, *p*-bromoacetophenone,

isobutyrophenone, and 2,4,6-trimethylacetophenone.

In all cases k was calculated from the slope of the line fitted by eye to the appropriate graphical plot of the data. The ketone concentration used in equation (3) was actually the average concentration for the run, which in no case differed from the initial concentration by more than 2%. The value of h^0 necessary for the application of equation (2) could be obtained either by extrapolation of a plot of h against t , or from the known initial iodide concentration of the solution by the application of the formulas

$$h^0 = \frac{c_{\text{I}_2}^0}{m} = \frac{c_{\text{I}^-}^0}{m(1-1/f)}$$

for solutions made up with excess oxidizing agent, and

$$h^0 = \frac{c_{\text{I}_2}^0}{m} = \frac{1}{2m}(c_{\text{I}^-}^0 - c_{\text{NaIO}_3}^0)$$

for solutions made up with iodide in excess over iodate, the oxidation being completed later with nitrite. Agreement of h^0 determined in these two ways shows the absence of any appreciable concentration of the enols of these ketones.

Precision.—The error in k calculated by the method outlined using equation (3) depends on the error in m (0.5%), in c_{KH}^0 (0.1%) and in the slope of the line fitted to the plotted points by eye. The important factors in the error in slope are the number of points (from 80 to 100 for most of these experiments) and the average deviation of the points from the best line, measured along the h -axis relative to the total length of the h -axis (Δh_{max}). The error in measurement of time can be neglected by comparison with the error in h . To estimate the error for one experiment (the longer run shown in Fig. 2), we have combined the standard deviation of the slope of the line¹⁰ calculated by the least squares technique (0.25%) with a reasonable estimate of the average deviation of the slope of a line fitted by eye from that of the least squares line (0.75%), the resultant figure being 0.8%. The error in the slope for other experiments, for which a least

squares line has not been calculated, was obtained from the 0.8% figure in the following way. The

(10) Wright and Hayford, "The Adjustment of Observations," D. Van Nostrand Company, New York, N. Y., 1906, p. 132.

average deviation in h , based on a large series of readings, is 0.17 mm. for h in the range 45–5 mm. The average deviation put on a comparable basis for a series of experiments is $0.17/\Delta h_{\max}$. The error in the slope certainly increases with an increase in this figure; we have assumed that the error in the slope is inversely proportional to Δh_{\max} , so that the estimated precision of the slope for the shorter run in Fig. 2 is 1.3%. Including the effect of the 0.5% error in m , the precision measures for all the runs using equation (3) range from 1 to 1.4%.

It can be shown that the error due to Δh in the ordinate, $\log(c_{\text{KH}}^0/mf - \Delta h)$, used in plotting equation (2), relative to the maximum value of that ordinate is

$$\frac{\epsilon_{\Delta h}}{\Delta h_{\max} + \frac{\Delta h_{\max}}{c_{\text{KH}}^0/mf} (1/2 \Delta h_{\max} - \Delta h)}$$

where ϵ represents error in the sense of average deviation. This is not a general equation, but is a valid approximation for all our experiments, since $\Delta h_{\max}/(c_{\text{KH}}^0/fm)$ (fraction of ketone reacting during the run) was maximally $1/4$. This average deviation of points from the line increases with extent of reaction, but even in the most extreme case differs from $\epsilon_{\Delta h}/\Delta h_{\max}$ by $\approx 13\%$. The average deviation is still approximately inversely proportional to Δh_{\max} . The situation is illustrated in Fig. 3, which shows plots according to equation (2) of one run with *p*-bromoacetophenone, with $\Delta h_{\max} = 15$, $\Delta h_{\max}/(c_{\text{KH}}^0/fm) = 0.1$, and one run with 2,4,6-trimethylacetophenone, with $\Delta h_{\max} = 5.4$, $\Delta h_{\max}/(c_{\text{KH}}^0/fm) = 0.25$. Precision measures have been calculated for these two ketones in the same way as before, and are 1.5 and 3.6%, respectively. The isobutyrophenone experiments are characterized by considerably greater experimental error, besides having a Δh_{\max} of only 6; the assigned precision measure in this case is 6%.

Results

The results are presented in Table I. The iodination of acetophenone is accurately first

order in acetophenone with a 7-fold variation in initial concentration, and zero order in iodine,

Ketone	No. of expts.	Av. k (min. ⁻¹)
Acetophenone	4	0.001104
Propiophenone	3	.000513
<i>n</i> -Butyrophenone	2	.000418
Isobutyrophenone	3	.0000224
<i>p</i> -Methylacetophenone	2	.001305
<i>p</i> -Bromoacetophenone	2	.000850
2,4,6-Trimethylacetophenone	3	.001625

with a 3-fold variation in initial concentration, and an 11-fold variation in iodine concentration during the course of a single run, in all a 22-fold variation in iodine concentration. We did not investigate the dependence of the rate on the concentrations of the reactants for any of the other ketones so fully. Aside from acetophenone, *n*-butyrophenone was the only ketone whose rate was shown to be first order in ketone concentra-

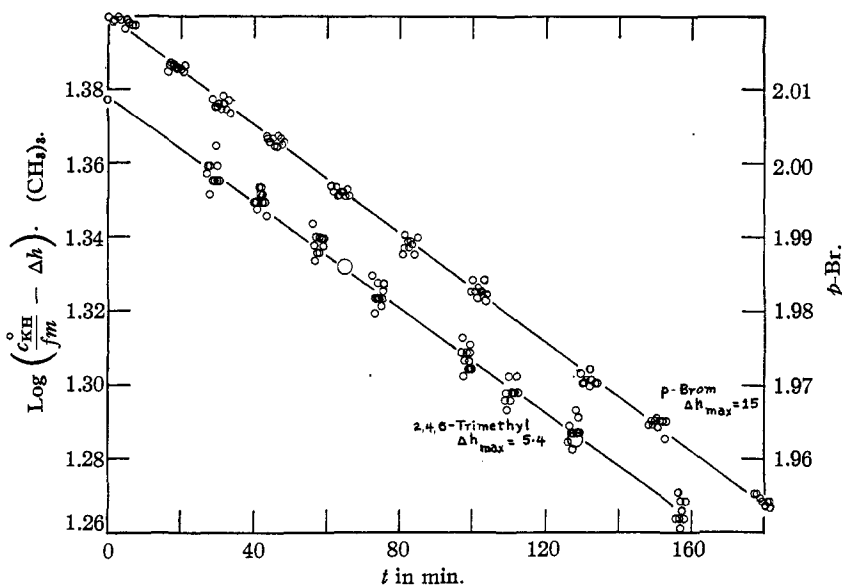


Fig. 3.—o, with oxidizing agent; O, without oxidizing agent.

tion. The dependence of rate on iodine concentration was shown to be zero order for propiophenone, *p*-methylacetophenone, and *p*-bromoacetophenone. The acid catalyzed iodination of the reaction product, substituted phenacyl iodide, is so slow by comparison with that of the original ketone that it does not take place to any appreciable extent under the experimental conditions. This is so even for 2,4,6-trimethylacetophenone, where the ratio product/reactant reached a maximum value of $1/4$.

Rough experiments showed the rates of iodination of these ketones in 0.01 molar perchloric acid to be negligible by comparison with the rates in 1.388 molar perchloric acid, proving the absence of any effective water catalysis. These rates cannot be expected to be identical with those calculated from the specific catalytic constants for the oxonium ion catalyzed reaction in dilute aqueous solution, because of salt effect, but the salt effect should be small, and consequently of approximately equal effect on all the rates. Actually for acetophenone the ratio of the rates in 1.388 molar and 0.210 molar perchloric acid solutions is only 7% greater than the ratio of the molar concentrations of perchloric acid in the two solutions.

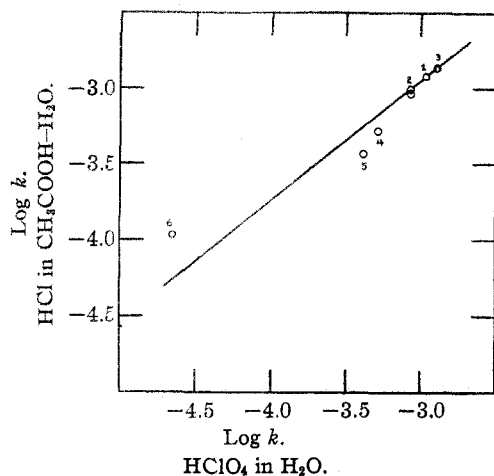


Fig. 4.—1, Acetophenone; 2, *p*-bromoacetophenone; 3, *p*-methylacetophenone; 4, propiophenone; 5, *n*-butyrophenone; 6, isobutyrophenone.

Discussion

Our results are in agreement with the conclusion of the Cardiff workers² as to the large effect of substitution on the alpha carbon on the rate of enolization. There is a quantitative difference in the results, whether due to the polycatalytic composition of the acetic acid medium, or to some other

medium effect of unknown nature; these differences are presented in the form of a plot of the logarithms of the rates in one medium against those in the other (Fig. 4). If there were no medium effect, the points would all lie on a straight line of unit slope. Medium effects for substitutions not too close to the seat of the reaction usually cause the points to form a straight line of arbitrary slope, with points representing compounds differing by an alpha substitution showing no simple relation to each other.⁴

Previous work on the effect of ortho methyl substitution on the reactions of phenyl ketones¹¹ shows strong suppression of only those typical ketone reactions which involve addition at the carbon of the carbonyl group. The most probable enolization mechanism involves addition of a proton to the carbonyl oxygen and removal of a proton from the alpha carbon¹²; if the above generalization is correct no steric hindrance of enolization is to be expected with ortho methyl substitution. And in fact ortho methyl substitution increases the rate of enolization, just as *p*-methyl substitution does.

Summary

The rates of iodination of the ketones acetophenone, *p*-bromoacetophenone, *p*-methylacetophenone, 2,4,6-trimethylacetophenone, propiophenone, *n*-butyrophenone and isobutyrophenone in 1.388 molar aqueous perchloric acid, and of acetophenone in 0.210 molar aqueous perchloric acid, have been measured by a colorimetric method. The rates are compared with those reported for some of the same ketones in 75% acetic acid-water solution 0.5 molar to hydrochloric acid. No steric hindrance was found in the iodination of 2,4,6-trimethylacetophenone.

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- (11) Kohler and Baltzy, *THIS JOURNAL*, **54**, 4015 (1932).
 (12) Pedersen, *J. Phys. Chem.*, **38**, 581 (1934).