[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Enolization as Directed by Acid and Basic Catalysts. II. Enolic Mechanism of the Haloform Reaction

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Studies of the halogenation of ketones in the presence of strong bases are always complicated by the presence of salts of hypohalogen acids, in equilibrium with the base and the free halogen. These hypohalites are strong halogenating agents on their own account. They exert a vigorous direct halogenating action on many compounds which are not capable of forming enols or other unsaturated intermediates. For example, the active hydrogen atoms of ammonia, amines, alcohols, and monosubstituted acetylenes are all directly replaced by bromine when these compounds are treated with sodium hypobromite.

It is well known that acid catalysts, on the one hand, and basic catalysts, on the other, cause the halogenation of ketones to take very different courses. This may be ascribed to different modes of enolization induced by the two types of catalysts. But before making this interpretation, it is necessary to show that halogenation of a ketone proceeds through the enol even in the presence of hypohalites, and that these salts exert no direct action upon the active hydrogen of the ketone.

The simplest case of the haloform reaction—the reaction of acetone with sodium hypohalite—is a very rapid process. Nevertheless, by working with sufficiently dilute solutions, kinetic measurements can be made which show the nature of the reaction. This reaction is usually formulated in successive steps

$$CH_3COCH_3 \longrightarrow CH_3COCH_2X \longrightarrow CH_3COCHX_2 \longrightarrow CH_3COCX_3$$

$$CH_3COCX_3 \xrightarrow{H_2O + NaOH} CH_3COONa + HCX_3$$

In the cases of hypobromite and hypoiodite the kinetic study shows that the first step is so much the slowest that it controls the rate entirely, and that the rate of this first step is the rate of enolization of acetone and is independent of the halogen concentration, just as in the much studied halogenation of ketones in acid media.[1] Figure 1 shows graphically the results obtained in the reaction between acetone and sodium hypobromite and hypoiodite. The reaction was followed from the beginning until over 90% of the halogen had disappeared. The rate of the reaction is proportional to the concentration of free alkali which catalyzes the enolization. The rate is the same for hypobromite as for hypoiodite.

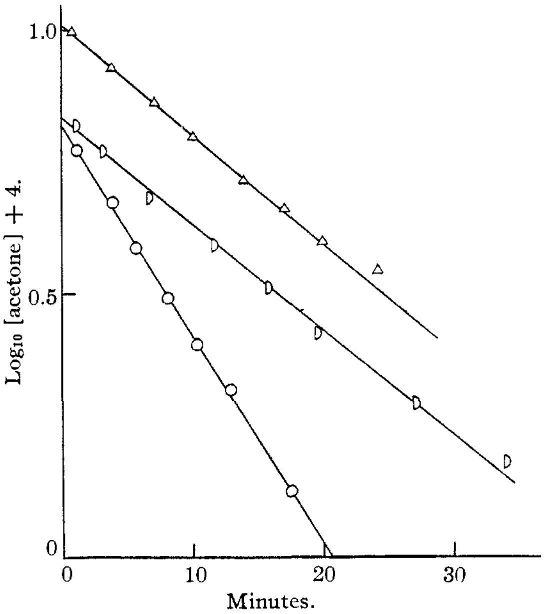

Fig. 1.—△, NaOI + acetone, [OH⁻] = 0.0322 – 0.0343; D, NaOBr + acetone, [OH⁻] = 0.0337 – 0.0355; O, NaOBr + acetone, [OH⁻] = 0.0710 – 0.0728.

The reaction of acetone with sodium hypochlorite is several hundred times slower, and is bimolecular. This reaction is slow enough so that the enol is present at substantially its equilibrium concentration at all times

$$CH_3COCH_3 \xrightleftharpoons{\text{relatively rapid}} CH_3C(OH){=}CH_2$$

$$CH_3C(OH){=}CH_2 + OCl^- \xrightarrow{\text{slow}} CH_3COCH_2Cl + OH^-$$

The evidence for this formulation is as follows.

The active chlorinating agent must be one of the three: free chlorine, hypochlorous acid, or hypochlorite ion. If free chlorine is the active agent, the rate of the reaction should be greatly increased by the addition of chloride ion, which shifts the equilibrium

$$Cl_2 + H_2O \rightleftharpoons H^+ + Cl^- + HOCl$$

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[1] Lapworth, *J. Chem. Soc.*, **85**, 30 (1904); Dawson and co-workers, *ibid.*, **99**, 1740 (1911); further references in Watson, *Chem. Rev.*, **7**, 173–201 (1930).

to the left. An amount of potassium chloride was added which would increase the chlorine concentration 160-fold, but there was a change only of about 22% in the rate of reaction (Fig. 2). If hypochlorous acid is the chlorinating agent, the rate of reaction should be diminished by the addition of free alkali; however, doubling the amount of sodium hydroxide present *increased* the reaction rate about 50%, ruling out this second possibility. There remains only the negative hypochlorite ion to which the reactivity may be ascribed.[2]

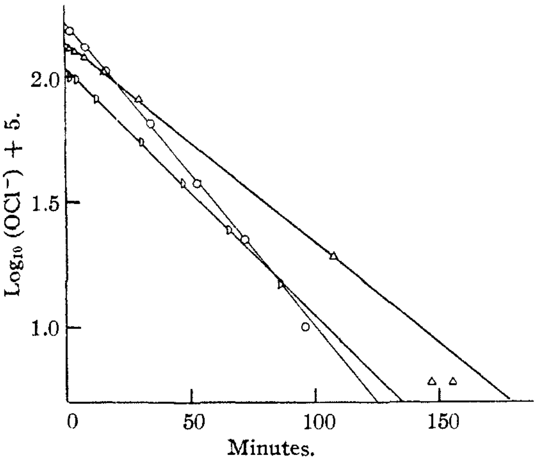

Fig. 2.—Reaction of NaOCl with acetone: △ $[OH^-] = 0.0336 - 0.0350$, no salt added; D $[OH^-] = 0.0344 - 0.0354$, KCl added; ○ $[OH^-] = 0.0700 - 0.0715$, no salt added.

That the enol is involved in this slow bimolecular reaction is indicated by the effect of alkali in accelerating the reaction. Changing activities of hydrogen and hydroxyl ions alter the equilibrium concentrations of the enol, and this might produce the kind of accelerating effect of alkali which has been observed. The use of this effect to measure the acid strengths of enols which are present in vanishingly small quantities is now being investigated.

Experimental

All rate determinations were made at 0°. A typical run with sodium hypobromite was carried out as follows.

One hundred cc. of a standard sodium hydroxide solution of 0.0821 *N*, 100 cc. of distilled water, and 10 cc. of a 0.0155 *M* solution of acetone were placed in a 250-cc. glass-stoppered flask, and cooled to exactly 0°. Some 0.0398 *M* bromine water was separately cooled, and 10 cc. of this pipetted into the other solution to start the reaction. Times were taken with a decimal stop watch. Twenty-five cc. portions of the reacting solution were added at various times to 5 cc. of 0.3 *M* acetic acid solution containing an excess of solid sodium iodide, added just before the sample. The liberated iodine was titrated with thiosulfate. The end-points were sharp and did not drift, indicating that there was no detectable quantity of halogenated ketone present in the solution at any time.

The hypochlorite reactions were carried out in a similar manner, but the reaction in this case was so much slower that a larger concentration of acetone was used. Instead of 10 cc. of 0.0155 *M* solution, 3.97 g. of pure acetone was added from a pipet. The constants determined from these runs showed a tendency to be higher at the end than at the beginning of the run. This is probably because the large excess of acetone allows a slight accumulation of chlorinated acetones in the course of the reaction.

Calculation of Results

In the hypobromite and hypoiodite runs, the acetone concentration was determined by the relation

$$[\text{acetone}] = 1/3[OX^-] + C$$

where C is a constant determined from the initial concentrations of reactants. This relation follows from the fact that the second and third introductions of halogen into the acetone molecule follow so closely upon the first that actually three halogen molecules disappear for every molecule of acetone consumed. The velocity constants were determined graphically by plotting the logarithm of the acetone concentration against time. The straight lines obtained are shown in Fig. 1.

In the hypochlorite runs, because of the great excess of acetone, its concentration was considered constant, and here the logarithm of the hypochlorite concentration was plotted against time. The apparent first order reaction here is actually a second order reaction, in which one of the reactants (acetone) is present in great excess. The rate constants tabulated below for this reaction are true bimolecular constants in which the acetone concentration has been taken into account.

Discussion of Results

The information obtained may be summarized as follows.

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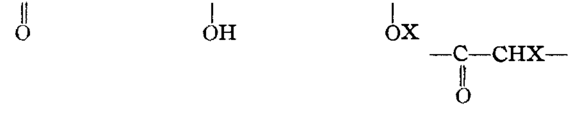
(2) Straus and Kühnel [*Ber.*, **66**, 1834 (1933)] have very recently come to the same conclusion. On the basis of their study of the reaction between hypohalites and tertiary alcohols of the allyl type, they propose the following quite likely course for the halogenation of ketones by hypohalites



$$-\underset{\underset{\displaystyle O}{\|}}{C}-CH_2- \longrightarrow -\underset{\underset{\displaystyle OH}{|}}{C}=CH- \longrightarrow -\underset{\underset{\displaystyle OX}{|}}{C}=CH- \longrightarrow -\underset{\underset{\displaystyle O}{\|}}{C}-CHX-$$

Evidence recently presented by Howk and McElvain [THIS JOURNAL, **54**, 282 (1932), and **55**, 3372 (1933)] would indicate that in the cases of certain β-keto esters the last reaction of this series is a reversible one.

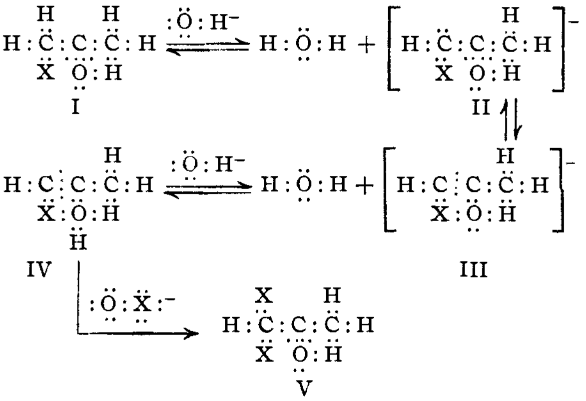
REACTION OF ACETONE WITH HYPOHALITES IN AQUEOUS SOLUTION AT 0°

Halogen used	$[X^-]$	$[OH^-]$	Molecular species determining rate of reaction	Velocity const. (concn. in moles/liter; time in minutes)
I_2	0.011	0.0322–0.0343	Acetone alone	0.0486
Br_2	.0018	.0337– .0355	Acetone alone	.0455
Br_2	.0018	.0710– .0728	Acetone alone	.0892
Cl_2	.0014	.0336– .0350	Acetone (enol) + OCl^-	.0613 (bimol.)
Cl_2	.223	.0344– .0354	Acetone (enol) + OCl^-	.0747 (bimol.)
Cl_2	.0015	.0700– .0715	Acetone (enol) + OCl^-	.0921 (bimol.)

These data show that, in the case of acetone at least, any direct action of alkali hypohalites upon the keto form is of negligible speed compared with the rate of enolization of the ketone. At the same time a probability is established, although it is not proved, that the successive substitutions after the first in the haloform reaction also involve enolization of the halogenated ketones.

In the light of these results, together with those of Hughes, Watson and Yates,[3] and Watson and Yates,[4] and the considerations outlined in Part I of this series,[5] the unsymmetrical halogenation of acetone can be described electronically as follows.[6]

The basic enolization catalyst functions by removing a proton directly from the monohalogenated ketone I. Of the five available protons, it has a strong preference for the two which are made unusually ionizable by the proximity of the strongly electron-attracting halogen atom X. When one of these protons is removed, the direction of enolization is determined, for the intermediate II can shift only into the enol ion III, and not into its isomer with the double bond on the other side of the carbonyl group. Accordingly, the reaction of the resulting enol IV with the halogenating agent—whatever its mechanism—leads to the unsymmetrical di-halogen acetone, V. In the last step of enolization, the lability of the hydrogen on the already substituted carbon atom is intensified by the presence of *two* halogen atoms. Only this proton is removed by the basic catalyst, yielding an enol which is halogenated to the readily hydrolyzed unsymmetrical tri-halogen ketone.



The fact that symmetrical bromination products of acetone can be prepared by the use of an acid catalyst is accounted for by the different mechanism of acid catalysis[3,4] in which the ketone is attacked at the carbonyl group, and the electron-affinity of the substituent tends to *prevent* the formation of a double bond on the carbon to which it is attached.

Finally, the present results make it more probable that the position principally taken by halogen when a ketone is treated with hypohalite salts really indicates the direction of enolization when catalyzed by the hydroxyl ion.

Summary

1. The reaction of acetone with strongly alkaline solutions of hypobromite and hypoiodite involves enolization of the acetone as a rate-controlling step.

2. The reaction of acetone with a strongly alkaline solution of hypochlorite is several hundred times slower than the rate of enolization at the concentrations employed. The rate of this reaction is controlled by a second order reaction between the enol and the hypochlorite ion.

3. An interpretation of the unsymmetrical halogenation of acetone is given, in terms of the electronic theory.

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[3] Hughes, Watson and Yates, *J. Chem. Soc.*, 3318 (1931).

[4] Watson and Yates, *ibid.*, 1207 (1932).

[5] THIS JOURNAL, **55**, 4992 (1933).

[6] In the *acid* mechanism for enolization (Part I of this series, *loc. cit.*) electronic formulas are necessary because they show the relation between the establishment of a double bond in a particular location and the electron affinities of the groups present. The *basic* mechanism now under discussion can be represented adequately without electronic formulations; these are included for the sake of consistency with the complementary material already published.