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Halogenation of Ketones

IX.* Studies on the Halogenating Agent in the Base-Catalyzed Halogenations of Ketones. Reactions between Hypobromous Acid and 2-Butanone

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The halogenating agent in the two base-catalyzed reactions was studied. In reaction Hal B I, working at pH 5.5—7, where the unenolized ketone was found to react, it is proposed that the halogenating agent is formed in a reaction between hypohalous acids and halides. In reaction Hal B II, working at pH > 12, it is proposed that the unenolized ketone is attacked by hypohalite ions. In addition, two acid-catalyzed and one free-radical halogenation were found to exist. In one acid-catalyzed halogenation the mechanism is proposed to be a reaction between the unenolized ketone and hypohalous acidium ions, H_2XO^+.

I. INTRODUCTION

The present author has discussed the halogenation of 2-butanone in a series of papers.[1–4] It was found that in fact three different reactions existed, one acid-catalyzed and two base-catalyzed. Of the two base-catalyzed reactions, one, called Hal B I, was found to operate when the pH of the solvent was between 5.5 and 7. The other reaction, called Hal B II, operates at pH greater than 12.[3,4]

The most significant difference between the two reactions is in the orientation of the substitution. The orientation can be given as K_{Hal}-values, which are defined as the amount of 3-halogenation/amount of 1-halogenation. In the same way the orientation of the deuteration can be given as K_{D}-values (3-deuteration/1-deuteration).[5–8]

A comparison showed that the orientations of substitution in the two base-catalyzed halogenations (Hal B I; $K_{\text{Hal}} = 7-7.5$, Hal B II; $K_{\text{Hal}} = 0$) were different from the orientation of base-catalyzed deuteration, which was found to be the same at pH 5—14 ($K_{\text{D}} = 0.6-0.7$). This leads to the hypothesis that different mechanisms operate in the three reactions.[3]

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Halogenations performed in D_2O at pD 6.8 and 13 showed that the halogenations and the deuteration are not competitive reactions. At both pD the amount and orientation of deuteration is independent of added halogen. Therefore it can be assumed that the two halogenations are reactions with the unenolized ketone.[4] In this situation, a discussion of modifications of the accepted mechanism should be valuable, and special interest should be accorded to the halogenating component. Three different halogenating species have been discussed previously in connection with base-catalyzed halogenations of ketones: free halogens,[9-13] hypohalite ions as suggested by Bartlett and Vincent [14] and Hulett,[15] or hypohalous acids, which have been suggested by Cullis and Hashmi for the haloform reaction.[16-18]

A discussion of the reactions between the halogens and aqueous bases should be valuable at this stage. This is a very complex field, but some of the main reactions are reactions A—F, Scheme 1.

The hydrolysis of halogens, reaction A, are slow reactions, but there is a great difference in the behaviour of the halogens. In the case of chlorine, equilibrium is reached after some hours,[19] in the case of iodine, first after several months.[20] It may also be mentioned here that hypoiodous acid is very unstable.[21,22] In contrast, the alkaline hydrolysis of the halogens, reaction B, are fast reactions especially when strong bases are used.[22] It is clear that addition of halides has a negative catalytic effect on the hydrolysis of the corresponding halogen.[23,24]

$$\begin{array}{lll}
\text{A.} & X_2 + H_2O & \rightleftharpoons & HXO + H^+ + X^- \\
\text{B.} & X_2 + H_2O + B^- & \rightleftharpoons & HXO + HB + X^- \\
\text{C.} & HXO + OH^- & \rightleftharpoons & XO^- + H_2O \\
\text{D.} & 3\,HXO & \rightleftharpoons & HXO_3 + 2\,X^- + 2\,H^+ \\
\text{E.} & 5\,HXO & \rightleftharpoons & HXO_3 + 2\,X_2 + 2\,H_2O \\
\text{F.} & X_2 + X^- & \rightleftharpoons & X_3^-
\end{array}$$

Scheme 1

The equilibria in reaction C are determined by the acidity constants of the hypohalous acids. As the atomic weight of the halogens increases, the strength of the acids decreases: HClO $pK_a = 7.6$, HBrO $pK_a = 8.5$, HIO $pK_a = 9.7$.[25-27]

Again there is a difference between the halogens in the disproportionation of the hypohalous acids, reactions D and E. Hypochlorous acid is sparingly disproportionated, while hypobromous acid (hypobromite) is significantly disproportionated in carbonate solutions. For hypoiodous acid (hypoiodite), the formation of iodate is rapid in solutions of carbonates and hydroxides.[21,22,28-30]

Reaction F, the equilibrium between halogens, halide anions, and trihalide ions, is known to be immediately established when halogens and halides are brought together.

II. REACTION HAL B I

As mentioned above, it was recently suggested that this reaction, which takes place at pH 5.5—7, is a reaction with the unenolized ketone.[4]

Among the possible halogenating species, the free halogens seem to be excluded by the fact that a reaction between this species and the unenolized ketone is not a base-catalyzed reaction. It is known that in the absence of any catalyst, halogenation of ketones is very slow.[31] Other evidence for the base-catalyzed reaction is given in Table 1, where the halogenation rates have been determined by NMR-spectroscopy. In Ref. 4 are given a number of objections against kinetic investigations using the iodometric titration method. Besides, it may be mentioned that the disappearance of halogen is no measure of the rate of the formation of bromoketones. Therefore, a new kinetic method was needed. 2-Butanone was used in a large excess in the reactions, and as its concentration remains essentially constant, it can serve as an internal standard for the determination of the amount of 3-bromo-2-butanone. Samples were taken after 1 h and, after the excess of bromine was destroyed with sodium pyrosulphite, sodium acetate and sodium halides were added to achieve constant ionic strength within the series. From Table 1 it can be seen that sodium acetate has a positive catalytic effect on the reaction rate (expts. 1—3).

Table 1. Reaction rates of bromination experiments (250 ml of H_2O, 10 ml of 2-butanone and 4.0 g of bromine; 1 h at 25°C).

Expt. No.	Amount NaOAc g	Amount halide g	Amount bromoketone %
1	5	—	0.5
2	25	—	2
3	50	—	8
4	25	26 g of NaBr	0
5	25	14.5 g of NaCl	2

The question arises as to whether hypohalous acids or hypohalite ions are the halogenating agent. Information about this question can be obtained from a comparison between the pK_a of the hypohalous acids and the course of the halogenation at various pH-values. Reaction Hal B I takes place at pH 5.5—7 and as the pH of the solution increases to over 7, the amount of reaction Hal B I decreases. As the pK_a values are in the region 7.6—9.7 this behaviour is not in agreement with a reaction involving hypohalite ions.

More information about the mechanism of reaction Hal B I was obtained from experiments with added sodium bromide and sodium chloride, expts. 4 and 5, Table 1. Sodium bromide showed a pronounced negative catalytic effect, while sodium chloride had no visible effect.

The kinetics of the acetate-catalyzed halogenation of acetone has been carefully investigated in two papers.[32,33] Here the complete kinetic expression was given, but although this was very complex, the effect of halides on the halogenation rate of ketones was neither observed nor discussed.

The observed catalytic behaviour of sodium halides seems to exclude trihalic anions as the halogenating agent. Moreover, the behaviour is in accordance with that predicted above for the hydrolysis of halogens; see reaction A, Scheme 1. Therefore, it can indicate that somewhere in the reaction scheme the hydrolysis of halogens is involved. It would be of interest to study the reaction between hypohalous acids and ketones under various conditions.

The results of some reactions between hypobromous acid and 2-butanone are collected in Table 2. An aqueous solution of hypobromous acid is prepared by the action of mercuric oxide on bromine. In these experiments the same analytical method was used as in Table 1. In addition, the K_{Br}-values of the products were determined and the results are also given in Table 2.

Table 2. Reaction rates for reactions with hypobromous acid at 25°C (4.0 g of bromine in 100 ml of H_2O, HgO added, filtered; 10 ml 2-butanone added).

Expt. No.	Catalyst	Amount	Further addition	Time h	Amount bromoketone %	K_{Br}	Remarks
6	—	—	—	12	0	—	Not filtered
7	NaOAc	7.0 g	—	12	0	—	—»—
8	—	—	—	2	3.5	4.5	
9	NaOAc	7.0 g	2.0 g of HgO	12	0	—	
10	NaOH	1.0 g	—	0.1	fast reaction	0	
11	—	—	exposed to sunlight	1	20	15	
12	2 N HCl	5 ml	—	0.5	20	3.5	
13	NaOAc	7.0 g	—	1	4	7.0	
14	—»—	—»—	2.0 g of Br_2	—»—	7	7.0	[a]
15	—»—	—»—	7.0 g of NaBr	—»—	5.5	7.0	
16	—»—	—»—	3.9 g of NaCl	—»—	6	6.5	
17	—	—	7.0 g of NaBr	1/12	4	7.4	
18	—	—	3.9 g of NaCl	1	3.5	7.0	
19	—	—	2.0 g of Br_2	1	2.5	7.6	[a]

[a] half amount of HBrO.

In one experiment (expt. 6), where hypobromous acid was prepared *in situ* (mercuric oxide present) no reaction could be observed, and the addition of acetate did not bring about any change (expt. 7). It was also observed that an aqueous solution of hypobromous acid from which the mercuric salts were filtered off and which was kept in the dark, reacted rather slowly with 2-butanone (expt. 8). The reaction studied could be accelerated by various catalysts: mineral acids, weak bases, sodium bromide, sodium chloride, free bromine and direct sunlight. It was also of interest to note that addition of mercuric oxide to the aqueous solution of hypobromous acid, acetate, and 2-butanone completely stopped the reaction (expt. 9).

The K_{Br}-values of the products indicate that different reactions take place when different catalysts are used. The reaction catalyzed by strong bases has $K_{Br} = 0$ (expt. 10), and this reaction will be discussed in section III. Another reaction is catalyzed by light, $K_{Br} = 15$ (expt. 11), and this reaction will be treated in section IV. The autocatalyzed reaction gave products with almost the same K_{Br}-value as those from the reaction with mineral acids as catalysts, indicating that the same mechanism operates in the two cases (expts. 8 and 12). This reaction will be discussed below in this section.

Of special interest was the observation that the acetate-catalyzed reaction with hypobromous acid gave products with the same K_{Br}-values as those from the acetate-catalyzed bromination of 2-butanone using free bromine; *cf.* Ref. 3 and expt. 13. This observation and the hypothesis above that free halogens are not the halogenating agent in reaction Hal B I make it plausible that these two acetate-catalyzed reactions follow the same mechanism, reaction Hal B I.

As mentioned above, the halogenations in D_2O indicate that reaction Hal B I is a reaction with the unenolized ketone. The failure of hypobromous acid to react with 2-butanone in the presence of mercuric oxide (expt. 9) provides another indication of this hypothesis. It would otherwise be difficult to explain why this agent completely inhibits the enolization. In addition, two other valuable conclusions may be drawn from this experiment:

a) The reaction cannot be a concerted mechanism involving hypohalous acid and acetate in the attack on the ketone.

b) Hypohalous acids alone cannot react with the ketone.

In the light of these conclusions it seems plausible to assume that the ketone is attacked by a halogenating agent formed in a base-catalyzed reaction of hypohalous acids. The same halogenating agent is also formed in a secondary reaction to the base-catalyzed hydrolysis of halogens.

Other reactions, where hypohalous acids are used as halogenating agents (additions to olefins, halogenations of phenols and aromatic amines) are found to be electrophilic reactions, where halogen containing cations are considered to be the halogenating agent. These ions were found to be more powerful reagents than the halogens themselves. The nature of the electrophile has been much discussed; for a recent review of this field, see Ref. 24. It can be either the positive halogenonium ion (X^+) or the strongly acidic hypohalous acidium ion (H_2XO^+). From kinetic measurements in aqueous solutions it is not possible to distinguish between these two species. At the present state the question of the exact nature of the "positive halogenating agent" is still open.[24]

Bell and Yates have recently studied the reaction between aqueous hypochlorous acid and acetone.[34] They found this reaction to be faster than the enolization, and from preliminary kinetic experiments they suggested that the mechanism involves an attack by the hypochlorous acidium ion, H_2ClO^+, on acetone, without the preliminary formation of the enol. This suggested mechanism is in keeping with the observation in the present paper that mineral acids catalyze the reaction. As pointed out above, the same mechanism seems to be valid in the autocatalyzed reaction as in reactions catalyzed by mineral acids. The small difference in K_{Br}-values (expts. 8 and 12, Table 2) is possibly because that in the autocatalyzed reaction, part of the products is formed from reaction Hal B I.

The products from reaction Hal B I were different from those obtained from the acid-catalyzed reaction with hypobromous acid (Table 2). This seems to rule out a reaction with the electrophilic hypohalous acidium ion for reaction Hal B I. This agent can also be ruled out by the moderate pH of the solution (*cf.* Ref. 24) and by the observed catalytic effect by acetate on the reaction rate.

The other electrophilic agent, the halogenonium ion (X^+) is ruled out by the observed positive catalysis of the corresponding halide ion. The halogenating rate in reactions with this agent is considered to be inversely proportional to the halide ion concentration.[24]

All the experimental data given previously [1-4] and in this paper for reaction Hal B I is in harmony with a reaction mechanism where the unenolized ketone is attacked by a halogenating agent, which is a product from hypohalous acid and another halogenated component, formed in a base-catalyzed reaction of hypohalous acid.

The formation of this halogenating agent is accelerated by halogens and halides (expts. 13—19) and completely inhibited by mercuric oxide (expt. 9). This latter agent is known to react with halogens and halides with the formation of insoluble mercuric halides. Concerning the rate difference between expts. 13 and 14, it may be noted that part of the catalyzing acetate was consumed in the hydrolysis of bromine; therefore the catalytic effect of bromine is still greater.

As mentioned above, the reaction between ketone and hypohalous acid in the absence of any catalyst is slow. However, it was observed that sodium bromide and chloride (still in the absence of acetate or any other base) strongly catalyzed the reaction (expts. 17 and 18, Table 2). This reaction was in fact faster than the reaction between ketone, hypobromous acid, and bromine (no acetate, expt. 19). Of special interest was the observation that the products from this reaction had a different K_{Br}-value than the products from the acid- and autocatalyzed reactions (expts. 8 and 12), *but the same* K_{Br}*-value as the products from reaction Hal B I.* Since no base was used, the halogenating agent in this sodium bromide-catalyzed reaction seems to be *a product from hypobromous acid and sodium bromide only,* see Scheme 2. This is another indication for the hypothesis that it is the unenolized ketone which reacts. Otherwise it is difficult to understand how sodium bromide can so markedly accelerate the enolization rate.

1. $X_2 + H_2O + B^- \rightleftharpoons HXO + HB + X^-$
2. $HXO + X^- \longrightarrow$ Halogenating agent
3. Unenolized ketone + Halogenating agent $\longrightarrow$ Haloketone

Scheme 2

Table 3. Amount of bromoketones (%) in expts. 13—19 at various times.

Time	Expt. No.						
	13	14	15	16	17	18	19
2.5 min	—	—	—	—	2	—	—
5 min	0	0	2.5	0.5	4	0	0
10 min	0.5	1	3.5	1	4	0.5	0.5
1 h	4	7	5.5	6	4	3.5	2.5
2 h	12	—	9	10	4	7	—

Additional support for the proposed mechanism can be obtained by following the formation of bromoketones in expts. 13—19, Table 3. The reactions were followed to 2 h and samples were taken at intervals and analyzed in the usual way.

The reaction between ketone, hypobromous acid, and sodium bromide (expt. 17) is very fast in the beginning, indicating that these three components take part in the reaction. (The corresponding reaction with ketone, hypobromous acid, and bromine, expt. 19, is much slower in the beginning). The reaction in expt. 17 stopped, however, after a few minutes, probably because of consumption of hypobromous acid (reaction A, Scheme 1, reverse).

In the experiment with hypobromous acid and sodium acetate, expt. 13, the figures of Table 3, indicate a series of consecutive reactions. After a slow introduction period, the reaction rate increased after about 1 h. The first step may be the formation of bromide ions due to the rather slow disproportionation of hypobromous acid (reaction D, Scheme 1).

In the experiment where sodium chloride was used instead of sodium bromide, and where the halide added does not influence equilibrium A, Scheme 1, the behaviour is different, see expt. 18, Table 3.

The isotopic exchange between hypohalous acids (hypohalites) and halide ions has been studied, and a fast reaction was found for chlorine, bromine, and idoine.[35-38] However, the kinetic expression was found to be different for chlorine and bromine, indicating different activated complexes in the two cases.[35-36] More experimental work is needed to ensure if these activated complexes take part in the halogenation of ketones, reaction Hal B I.

III. REACTION HAL B II

This reaction, which takes place at pH $>$ 12, yields exclusively 1-halogenation,[1-3] while deuterations at the same pH (pD) yield both 1- and 3-deuteration.[5,6,8] As mentioned above, it was recently suggested that this reaction is a reaction with the unenolized ketone.[4]

The strongly alkaline solutions used in this reaction seem to exclude both hypohalous acids and free halogens as the halogenating species; the halogenating agent is thus hypohalite ions. Other evidence for this hypothesis was found in two experiments where the ketone was added to the aqueous solution of sodium hypochlorite and sodium hypobromite (reverse addition). Analyses of the acidic extracts in these experiments gave the same composition as in experiments with normal addition (halogen was added to the alkaline aqueous solution of the ketone). Another possibility for the halogenating agent is that halate ion (XO_3^-) take part in the reaction, but this possibility is excluded by Morgan *et al.*,[39] who found that the yield of iodoform decreased the longer the hypoiodite was kept before addition to the ketone. This behavior was explained by the rapid disproportionation of hypoiodite as compared with the other hypohalites; reactions D and E, Scheme 1.

Additional support for the hypothesis of an attack by hypohalite ions on the unenolized ketone can be obtained from Table 4. Here the influence of various amounts of sodium hydroxide on the time of decolorization is given. It has previously [4] been found that the time of decolorization is a good measure of the reaction rate in the strong base-catalyzed halogenations. Normal and reverse additions did not give the same time, partly due to heat evolution in the hydrolysis of bromine. However, the reaction rate was the same in experiments with reverse addition with 0.8 and 1.6 g of sodium hydroxide, expts. 22, 23; the run rate is independent of additional base.

Table 4. Time for decolorizing 1.2 g of bromine in 25 ml H_2O + 4 ml 2-butanone at 5°C.

Expt. No.	Amount NaOH g	Addition	Time sec
20	0.8	Normal	10
21	1.6	»	5
22	0.8	Reverse	13
23	1.6	»	12

Reutov recently discussed the nature of the haloform reaction in connection with the rate of the reaction.[40] As it is a very fast reaction, he considered that it cannot be a reaction with two uncharged components. He proposed a reaction with an attack of an anion on an uncharged component, the mesomeric enolate anion and free halogen molecules. In the mechanism proposed in the present paper the kind of the two components is the same, but it is an attack by the negative hypohalite anion on the uncharged unenolized ketone. In this connection it may be said that a reaction with two negative components (hypohalite anions and the mesomeric enolate anion) seems less plausible.

IV. FREE-RADICAL REACTIONS

It was recently found by Rappe and Kumar that certain bromoketones could be prepared in good yields by a free-radical reaction.[41] The ketones were treated with N-bromosuccinimide in boiling carbon tetrachloride under irradiation by visible light. The selectivity of the free-radical halogenation followed the general rule: tertiary > secondary > primary. When 2-butanone was treated in this way, pure 3-bromo-2-butanone was obtained in a 53 % yield. An NMR-analysis of the crude product in this synthesis gave a K_{Br}-value of about 40, the main by-product being 3,3-dibromo-2-butanone.[41]

The reaction between hypobromous acid and 2-butanone could also be catalyzed by light. This reaction gave almost pure 3-bromo-2-butanone ($K_{Br} = 15$), but the purity was not so high as in the bromination using N-bromosuccinimide. This is probably because part of the reaction proceeds *via* the heterolytic autocatalyzed reaction ($K_{Br} = 4.5$). The main by-product in the light-catalyzed reaction of hypobromous acid was 3,3-dibromo-2-butanone. The pronounced tendency for 3-halogenation and the experimental conditions indicate that the light-catalyzed reaction of hypobromous acid and 2-butanone is a free-radical reaction.

V. CONCLUSIONS

First it must be pointed out that the conclusions reached in this paper and in Refs. 1—4 are valid only for 2-butanone and probably for other structurally similar monoketones, but not for all kinds of ketones.

Harper and Bender found a strong intramolecular catalysis by carboxylate anions in the iodination of *o*-acylbenzoic acids.[42] This is in harmony with the traditional enolate mechanism, and not with the mechanism proposed for reaction Hal B I. It has also been found that intramolecular catalysis is of major importance in the weak base-catalyzed racemization of *d*-2-*o*-carboxybenzylindan-1-one.[43] Like the ketones studied by Harper and Bender [42] this is an *ortho*-ketosubstituted benzoic acid with the enolizable C-atom in δ-position to the carboxylic group. Previously it was found that for this ketone the acetate-catalyzed rate of racemization was equal to the rate of halogenation,[44] in fact it seems that this is the only ketone where such an identity is reported. Thus it can be concluded that the halogenation of this ketone is intramolecularily catalyzed too, and this often discussed ketone [9,11,13] represents a class of ketones, where the halogenation proceeds *via* the enolate mechanism.

The kinetic data and other conclusions from this group of ketones[9–13,44] is therefore of minor importance in the discussion of the mechanisms of the base-catalyzed halogenations of ordinary monoketones, where the possibility of intramolecular catalysis does not exist.

Other ketones where the halogenation mechanism is still unclear, but where the traditional enolization mechanism seem probable are for both those having a high enol content, and for haloketones. Thus it has been reported that at pH = 0 the halogenation of 1,1,3-tribromoacetone is a base-catalyzed reaction.[45]

For 2-butanone and other structurally similar monoketones the discussion and consideration above lead to *five* different reactions for the halogenation of ketones. Of these five reactions, two are acid-catalyzed, two are base-catalyzed and one is a free-radical reaction.

The common acid-catalyzed reaction is a halogenation of the enol, which is formed in an acid-catalyzed enolization. In the case of 2-butanone this reaction has a K_{Hal}-value of 2.7.[3]

The other acid-catalyzed halogenation is a reaction where hypohalous acids are used. The mechanism for this reaction is considered to be a reaction between hypohalous acidium ion (H_2XO^+) and the unenolized ketone.[34] In this reaction 2-butanone has a K_{Hal}-value of 3.5.

Two different base-catalyzed halogenations exist, referred to as Hal B I and Hal B II in this paper. In reaction Hal B I, which operates at pH 5.5—7, both halogens and hypohalous acids can be used as the bulk agent. The reaction has a pronounced tendency for 3-halogenation ($K_{\text{Hal}} = 7-8$). It seems to be a reaction between the unenolized ketone and a halogenating agent formed in a reaction between hypohalous acids and halides, see Scheme 2. The experimental data, which have lead to this hypothesis are:

1. The observation of two different base-catalyzed halogenations.
2. The weak base-catalyzed reaction has the same K_{Hal}-value for all halogens which is different from the K_{D}-value.
3. A 20—30 fold difference in the reaction rate for bromine and iodine.
4. The reaction was performed at pH 5.5—7.
5. The deuteration in a D_2O/base solution is not influenced by the addition of bromine.
6. A positive catalytic effect by sodium acetate on reactions using free halogens.
7. Negative catalysis by sodium bromide, positive by sodium chloride on reactions using free halogens.
8. Slow reaction of the ketone with hypohalous acid only.
9. The reaction between hypobromous acid and ketone was catalyzed by sodium acetate.
10. In the absence of any basic catalyst, a fast initial reaction between ketone, hypobromous acid, and sodium bromide.
11. The same K_{Br}-values in the reaction under 9 and 10 as in the acetate-catalyzed halogenations using free halogens.
12. The acetate-catalyzed reaction between ketone and hypobromous acid was completely inhibited by mercuric oxide.
13. In the reaction under 9, indications were observed for a series of consecutive reactions.

In the other base-catalyzed halogenation, reaction Hal B II, which operates at pH > 12, the tendency for 1-halogenation is great in the case of 2-butanone ($K_{\text{Hal}} = 0$). A mechanism between hypohalite anion and the unenolized ketone is proposed. The experimental data, which indicate this mechanism are:

1. The observation of two different base-catalyzed halogenations.
2. The strong base-catalyzed reactions have K_{Hal}-values different from the K_{D}-values.
3. A 5-fold difference in the reaction rate for bromine and iodine.
4. The reaction was performed at pH > 12.
5. No deuteration in a D_2O/base solution occurs during the time under which the bromination is completed.
6. The same products were obtained with normal and reverse addition.
7. The run rate for reverse additions is independent of additional base.

The free-radical halogenations of ketones can be performed by N-bromosuccinimide, other N-haloimides, or a light-catalyzed reaction between ketone and hypohalous acids. In the case of 2-butanone the free-radical bromination gave almost exclusive 3-substitution, $K_{Br} = 15-40$.

EXPERIMENTAL

The NMR-spectra were recorded on a Varian model A-60 spectrometer.

Halogenations. The composition of the different runs are given in Tables 1, 2, and 4. The mixtures were thoroughly stirred, the excess of halogen was destroyed by addition of sodium pyrosulphite, and sodium acetate and halides were added in order to achieve constant ionic strength within the series. Carbon tetrachloride (1.0 ml Table 1, 0.3 ml Table 2) was added and the mixture stirred for 1 min and the heavier organic layer separated and analyzed by NMR. The acidic extracts were prepared by extracting the reaction mixtures with carbon tetrachloride, acidifying and re-extracting with ether; removing the ether, and analyzing the residue by NMR.

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