Halogenation of Ketones

VII.* Base-Catalyzed Halogenation of Butanone-2. Evidence for two Different Reactions

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The halogenation of butanone-2 was studied. Two different base-catalyzed reactions were found. In one reaction, Hal B I, which was catalyzed by weak bases such as acetate and bicarbonate and operating at pH 5.5—7, the products were mostly 3-halogenated products. The other reaction, Hal B II, which was catalyzed by strong bases like hydroxides and operating at pH higher than 12, resulted exclusively in 1-halogenation. The three halogens chlorine, bromine, and iodine were studied.

In 1904 it was proposed by Lapworth that the rate determining step in the acid-catalyzed halogenation of ketones is the enolization of the ketone.[1] Later the same author proposed the same step as being rate determining in the base-catalyzed reaction.[2] In 1932 Watson and Yates proposed that the base-catalyzed halogenation of ketones involves both the enolate anion and the enol.[3] The currently accepted view is that the halogenation of ketones can proceed by either an acid- or a base-catalyzed reaction, in both cases the enolization or formation of the enolate anion being the rate determining step.[4–10]

From the acid-catalyzed halogenation mono-, di-, tri-, tetrahalo and even higher substituted ketones can be isolated, and general rules for the introduction of the halogen atoms have been found.[11–13] Up to very recently, no halogeno ketones seem to have been isolated from base-catalyzed reactions. It is considered that in the base-catalyzed halogenation of methyl ketones as in the haloform reaction it is the methyl group, which is exclusively halogenated.[4–10] Moreover, mono- and disubstituted ketones are considered to be halogenated faster than the unsubstituted ketone in the base-catalyzed halogenation. In the case of acetone, monochloro-, and 1,1-dichloroacetone, Bell and Lidwell have found that the ratio of halogenation is 1:400:3000.[14]

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Scheme 1

Scheme 2
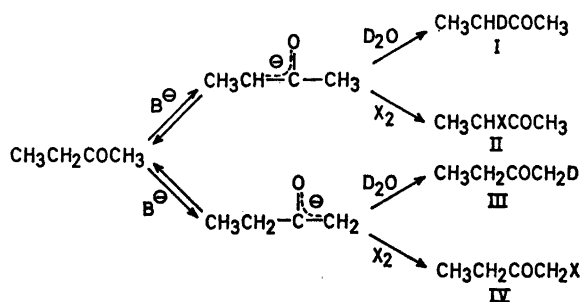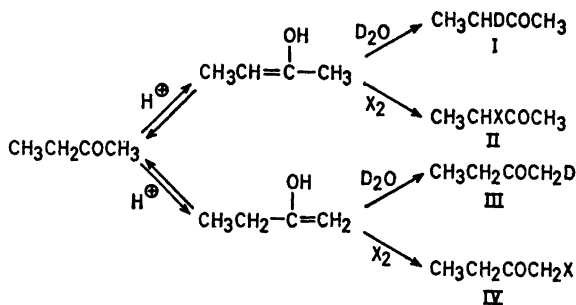
The deuteration of ketones is another reaction where enolization is considered to be the rate and product determining step of the reaction. Like halogenation, deuteration can be both acid- and base-catalyzed. Therefore the orientation of the halogenation and the deuteration should follow the same path. For the case of butanone-2 see Schemes 1 and 2.[5],[8],[10],[15],[16]

Recently the present author studied the deuteration of butanone-2 by means of NMR-spectroscopy.[17],[18] In the acid-catalyzed reaction 3-deuteration/1-deuteration = I/III = K_D was found to be about 2.5 (see Scheme 1). Contrary to what was reported by Warkentin and Tee for the base-catalyzed deuteration,[19] the same K_D-value (0.6—0.7) was found for reactions catalyzed by the strong base deuterioxide as by the weak base acetate.[17],[18]

In the present paper the halogenation of butanone-2 is studied. In the halogenation the three halogens chlorine, bromine, and iodine are used. Special attention is paid to the products formed at various pH's in the base-catalyzed reactions.

For the *acid-catalyzed* bromination of butanone-2, Cardwell and Kilner have determined the ratio II/IV = 3-bromination/1-bromination = K_{Br} as 2.7.[11] It has been found that bromoketones easily rearrange in acid media.[13],[20],[21] As chloroketones in general do not rearrange, it was desirable to make the same determination of the chlorination products, see expt. 1, Table 1. The value found here $K_{Cl} = 2.7$ is the same as the value given by Cardwell and Kilner.[11]

Table 1. Composition of the ketonic extracts from the halogenation experiments (0.125 mole halogen/mole ketone).

Expt. No.	Catalyst	pH	Equiv.base / Equiv.halogen	Halogen	Time	a %	b %	c %	d %	e %	f %	g %	a+d %	K_{Hal}
1	HCl	-	-	Cl$_2$	-	73	-	-	27	-	-	-	100	2.7
2	Buffer A	6.3— 5.4	-	"	4 h	88	-	-	12	-	-	-	100	7.3
3	"	6.3— 5.6	-	Br$_2$	"	73	4	-	3	2	3	15	76	6.8
4	Buffer B	7.1— 5.0	-	Cl$_2$	"	87	-	-	13	-	-	-	100	6.8
5	"	7.1— 6.1	-	Br$_2$	"	67	8	-	3	-	9	13	70	5.0
6	NaOAc	7.8— 5.0	2.5	"	"	74	6	-	6	3	5	6	80	4.8
7	"	7.8— 5.5	8.0	"	"	75	6	5	9	-	-	5	84	7.4
8	"	5.2— 4.8	"	"	"	60	6	17	12	3	-	3	72	3.8
9	NaHCO$_3$	8.1— 5.7	2.5	"	2 h	76	12	-	4	2	6	-	80	7.3
10	"	8.1— 8.0	8.0	"	0.5 h	47	3	-	28	2	-	18	75	1.6
11	"	8.1— 8.0	"	"	4.5 h	20	3	-	4	4	-	73	24	-
12	Na$_2$CO$_3$	10.9—10.7	10.0	"	1 min	25	7	-	12	8	-	48	37	1.6

a = 3-halo-, b = 3,3-dihalo-, c = 1,1,1,3-tetrahalo-, d = 1-halo-, e = 1,1-dihalo-, f = 1,1,1-trihalobutanone-2, g = haloforms.

Table 2. Composition of the acidic extracts from the halogenation experiments (0.5 mole halogen/mole ketone).

Expt. No.	Catalyst	pH	Halogen	Time	CH$_3$CH$_2$COOH %	CH$_3$CHXCOOH %	CH$_3$CX$_2$COOH %
13	Buffer A	6.3— 5.0	Br$_2$	4 h	-	97	3
14	NaHCO$_3$	8.1— 7.3	"	"	40	56	4
15	Na$_2$CO$_3$	10.9—10.0	"	2 h	75	25	-
16	Buffer C	12.3—11.8	Cl$_2$	"	100	-	-
17	"	12.3—10.8	Br$_2$	"	93	7	-
18	"	12.3—11.8	"	"	99	1	-
19	NaOH	13.2—13.0	"	5 min	100	-	-

As mentioned above, the products from the *base-catalyzed* halogenation have been only little studied. In a recent paper, the present author discussed the existence of *two* different mechanisms for the base-catalyzed halogenation of ketones.[22] In these experiments about 2.5 equiv. base/equiv. halogen were used.

The orientation of the halogenation of butanone-2 was studied in a series of experiments, where various bases were used in large excess, usually 8—10 equiv. base/equiv. halogen. The following bases were used: an acetåte buffer with pH = 6.3 (buffer A), sodium acetate, a phosphate buffer with pH = 7.1 (buffer B), sodium bicarbonate, sodium carbonate, a phosphate buffer with pH = 12.2 (buffer C) and sodium hydroxide. The pH of the reaction mixture was studied during and after the reaction. The products were analyzed by NMR as in Ref. 22 and the values are given in Table 1. In the experiments with buffers B and C and bicarbonate the reactions were run in two-phase systems, and in the other experiments in one-phase systems.

The orientation of the halogenation is given by the K_{Hal}-values, 3-halogenation/1-halogenation (II/IV, see Schemes 1 and 2). As the amount of halogen used is difficult to calculate in the case of chlorine, bromine was preferably used.

As has been pointed out before it is difficult to estimate whether haloforms and 1,3-substituted polyhalo ketones are formed from a primary 1- or 3-halogenation.[22] Therefore it was found favourable to interrupt the syntheses before the bromine colour disappeared, in which case the amount of these compounds was small. If they were present, the same approximation was made here as before: two-thirds of these compounds are formed from a primary 3-halogenation, one-third from a primary 1-halogenation.[22]

In the carbonate- and hydroxide-catalyzed reactions the amount of bromoform was high even when the syntheses were interrupted after one minute (expt. 12). Therefore the direction of substitution could not be determined by analyzing the ketonic extracts. Acidic extracts were collected and analyzed by NMR. In Table 2 these results are given together with the corresponding values from the acetate- and bicarbonate-catalyzed reactions.

The results in Tables 1 and 2, especially those where the reactions were performed in the buffers, where the pH was rather constant, shows that the orientation of the substitution (K_{Hal}) is dependent of the pH of the reaction mixture. It was found to be independent of the halogen (chlorine and bromine) and base used. Moreover, the results were about the same in one- and in two-phase systems.

At least two different mechanisms are operating in the base-catalyzed halogenation of butanone-2. One mechanism, here and subsequently called Hal B I, operates at pH 5.5—7, giving mainly substitution in the methylene group, 3-halogenation ($K_{Hal} = 7—7.5$). The other mechanism, called Hal B II, operates in more alkaline solutions, pH over 12. Here the tendency for halogenation of the methyl group (1-halogenation) is great, *i.e.* the haloform reaction ($K_{Hal} = 0$). The results from reactions in solutions with pH's 7—12 can be best interpreted if both reactions, Hal B I and Hal B II, are taking place. They are competitive reactions.

In addition to the K_{Hal}-values, *i.e.* the orientation of substitution, the two reactions Hal B I and Hal B II behave differently with respect to polyhalogenation. Reaction Hal B I yielded measurable amounts of monosubstituted products, especially with small amounts of halogen, while reaction Hal B II yielded almost exclusively 1,1,1-trisubstituted ketones (and subsequent carbon-carbon fission) even when only very little halogen was consumed.

In this connection it can be of interest to discuss the behaviour of other ketones with regard to pH and acid-/base-catalyzed reactions. Hsü and Wilson, who studied the racemization of 2-*o*-carboxybenzylindan-1-one, reported that in a buffer of 2 % of sodium acetate in 16.0 N acetic acid the racemization is mainly a base-catalyzed reaction.[23] α-Haloketones are known to undergo base-catalyzed reactions in even more acidic solutions. Watson and Yates have reported that the bromination of 1,1,3-tribromoacetone is a base-catalyzed reaction in 2 N hydrochloric acid.[3]

Iodine is considered to behave like the other halogens, bromine and chlorine, in the base-catalyzed halogenation of ketones, giving a haloform reaction. The iodoform test of methyl ketones and methyl carbinols has been carefully investigated.[24-26]

The iodination of butanone-2 in an acetate buffer has recently been studied by Schellenberger and Hübner.[27] These authors used radioactive iodine for the halogenation, and in this reaction they considered that only monosubstituted iodoketones were formed, but they did not isolate any products from this reaction. Thereafter they treated the reaction mixture with excess iodine in strong alkaline solution and the radioactivity of the components formed in the haloform fission was determined. From this determination a K_I-value of 0.37 can be calculated. However, the authors considered both iodinations to be base-catalyzed reactions, but the interesting fact that the two reactions gave different products was not discussed in the paper: it seems to have been overlooked. In view of the results of the deuteration and bromination in acetate buffers obtained in this paper and in Refs. 17, 18, and 22, it was of interest to reexamine the iodination of butanone-2. Moreover, the method according to which Schellenberger *et al.* obtained their K_I-values seems a little questionable. According to the same method they found the K_I-value for the acid-catalyzed iodination to be 450,[27] the corresponding chlorination (expt. 1, Table 1) and bromination gave $K_{Hal} = 2.7$.[11]

A series of base-catalyzed iodinations was performed using the same experimental conditions as for the halogenations above. The K_I-values were determined in the same way, and the results are given in Tables 3 and 4.

In this NMR-determination it was found that the direction of iodination in an experiment where the pH of the solution was changed from 6.3 to 5.7 (buffer A, expt. 20) gave a K_I-value of 7.2. This is the same as the value from the brominations and chlorinations in experiments with the same pH and quite different from the value given by Schellenberger and Hübner.[27] This indicates that reaction Hal B I operates at pH 5.5—7 in the iodination too. In reactions performed in solutions with pH 12, reaction Hal B II operates (the haloform reaction).

The results from one of the bicarbonate-catalyzed iodinations (expt. 22) gave greater amounts of 1-substitution (lower K_I-values) than from the

Table 3. Composition of the ketonic extracts from the iodination experiments (0.125 mole halogen/mole ketone).

Expt. No.	Catalyst	pH	Equiv.base / Equiv.halogen	Time	a %	b %	c %	d %	e %	f %	g %	a+d %	K_I
20	Buffer A	6.3 – 5.7	–	70 h	87	–	–	7	–	5	–	94	7.2
21	Buffer B	7.1 – 6.4	–	17 h	86	–	–	14	–	–	–	100	6.1
22	NaHCO$_3$	8.1 – 7.8	2.5	24 h	55	–	–	45	–	–	–	100	1.2
23	NaHCO$_3$	8.1 – 8.0	8.0	*	43	–	–	40	–	–	17	83	1.2
24	Na$_2$CO$_3$	10.9 –10.0	10.0	15 min	20	–	–	–	–	–	80	20	–

a = 3-iodo-, b = 3,3-diiodo-, c = 1,1,1,3-tetraiodo-, d = 1-iodo-, e = 1,1-diiodo-, f = 1,1,1-triiodobutanone-2, g = iodoform.

Table 4. Composition of the acidic extracts from the halogenation experiments (0.5 mole halogen/mole ketone).

Expt. No.	Catalyst	pH	Time	CH$_3$CH$_2$COOH	CH$_3$CHICOOH	CH$_2$Cl$_2$COOH
25	NaHCO$_3$	8.1 – 7.5	48 h	35	60	5
26	Na$_2$CO$_3$	10.9 –10.0	5 h	80	20	–
27	Buffer C	12.3 –11.8	4 h	97	3	–
28	NaOH	13.2 –13.1	15 min	100	–	–

bromination experiment using the same amount of base (expt. 9). This is due to two reasons.

Above, it was proposed that in the pH interval 7—12 the two reactions Hal B I and Hal B II are competitive reactions. Due to the slower hydrolysis of iodine as compared with the other two halogens, the iodination with bicarbonate was performed at higher pH than the bromination, where the lower pH value was reached rather soon. This difference in the pH favours reaction Hal B II (1-halogenation) over reaction Hal B I (3-halogenation), cf. also expt. 10 ($K_{Br} = 1.6$, pH = 8).

Moreover, in unpublished results it was found that the iodination rate in reaction Hal B I was 20—30 times slower than the bromination rate, while the difference for the two halogens in reaction Hal B II was only 4—5 times. Therefore, at constant pH the amount of iodination according to reaction Hal B II is more favoured than the iodination according to reaction Hal B I compared with the corresponding bromination.

The composition of the acidic extracts are given in Tables 2 and 4. From these tables it is evident that the haloform reaction is preferably performed in media where the pH is higher than 12 throughout the whole reaction, in this case the amount of α-halogenated acids is very low. The main acidic component in reactions performed at pH 5—7 was monohalo propionic acid. As the pH of the solvent increases, the amount of unhalogenated propionic acid increases.

Cullis and Hashmi studied the acidic components from hydroxide-catalyzed haloform reactions. They used chromatographic methods, and they also found small amounts of monohalogenated acids.[24-26]

As said before, in both the acid- and base-catalyzed halogenation and deuteration of ketones, the rate and product determining step in the two reactions is considered to be the enolization. This means that the two reactions should give the same orientation in the substitution; K_D (3-deuteration/1-deuteration) = K_{Hal} (3-halogenation/1-halogenation); see Schemes 1 and 2.

As has been pointed out above, we have two different base-catalyzed halogenations working at different pH. In the case of butanone-2 the K_{Hal}-values for these two reactions are 7.0—7.5 for reaction Hal B I working at pH 5.5—7 and $K_{Hal} = 0$ for reaction Hal B II working at pH higher than 12. The base-catalyzed deuteration of butanone-2 gave a value $K_D = 0.6—0.7$, which value is independent of pH, the base used, and the concentration of the base.[17,18] In neither of the two halogenations does the orientation of substitution follow the same path as the deuteration.

This comparison of the orientation of substitution of the two reactions indicate that the base-catalyzed halogenation and deuteration of ketones cannot follow the same mechanism. Both kinds of base-catalyzed halogenations of ketones can be assumed to partly or completely follow another mechanism than the deuteration. In this situation an investigation has been started to find modifications of the accepted mechanism or other possible mechanisms for the reaction.

Table 5. Composition of the halogenation experiments where the ketonic extracts were analyzed.

Expt. No.	Butanone-2 ml	H$_2$O ml	Catalyst	Amount	Halogen	Amount g
1	200	—	HCl	250 ml	Cl$_2$	—
2	9.2	—	Buffer A	350 ml	»	—
3	»	—	»	175 ml	Br$_2$	2.0
4	»	—	Buffer B	150 ml	Cl$_2$	—
5	»	—	»	»	Br$_2$	2.0
6	18.5	70	NaOAc	7.5 g	»	4.0
7	»	350	»	24 g	»	»
8	»	»	»	»*	»	»
9	»	70	NaHCO$_3$	7.5 g	»	»
10	»	350	»	24 g	»	»
11	»	»	»	»	»	»
12	»	»	Na$_2$CO$_3$	27 g	»	»
20	9.2	—	Buffer A	175 ml	I$_2$	3.2
21	»	—	Buffer B	150 ml	»	»
22	18.5	70	NaHCO$_3$	7.5 g	»	6.3
23	»	350	»	24 g	»	»
24	»	»	Na$_2$CO$_3$	27 g	»	»

* 5 ml HOAc added.

Table 6. Composition of the halogenation experiments where the acidic extracts were analyzed (4.6 ml of butanone-2).

Expt. No.	H$_2$O ml	Catalyst	Amount	Halogen	Amount g
13	—	Buffer A	350 ml	Br$_2$	4.0
14	350	NaHCO$_3$	24 g	»	»
15	»	Na$_2$CO$_3$	27 g	»	»
16	—	Buffer C	200 ml	Cl$_2$	—
17	—	»	»	Br$_2$	4.0
18	—	»	»	»	1.0
19	100	NaOH	15 g	»	4.0
25	350	NaHCO$_3$	24 g	I$_2$	6.3
26	»	Na$_2$CO$_3$	27 g	»	»
27	—	Buffer C	200 ml	»	1.6
28	100	NaOH	15 g	»	6.3

EXPERIMENTAL

The NMR-spectra were recorded on a Varian model A-60 spectrometer. The pH-determinations were made on a Vibret laboratory pH meter.

Buffer A was prepared from 25.0 g of sodium acetate, 0.5 ml of acetic acid and 350 ml of water.

Buffer B was prepared from 36.0 g of disodium phosphate and 2.0 g of monosodium phosphate in 150 ml of water.

Buffer C was prepared from 38.0 g of trisodium phosphate, 2.0 g of disodium phosphate and 200 ml of water.

Halogenations. The composition of the different runs are given in Tables 5 and 6. The reactions were performed at room temperature. In the experiments with buffers B and C and bicarbonate the reactions were run in two-phase systems, in the other experiments in one-phase systems. The mixtures were thoroughly stirred, carbon tetrachloride was added and the heavier organic layer separated, the solvent was evaporated and the residues were analyzed by NMR. The acidic extracts were prepared by extracting the reaction mixtures with carbon tetrachloride, acidifying and re-extracting with ether, the ether was evaporated and the residues were analyzed by NMR.

REFERENCES

1. Lapworth, A. *J. Chem. Soc.* **85** (1904) 30.
2. Lapworth, A. *Mem. Proc. Manchester Lit. Phil. Soc.* **64** (1920) 13.
3. Watson, H. B. and Yates, E. D. *J. Chem. Soc.* **1932** 1207.
4. Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, Cornell, New York 1953, p. 567.
5. Bell, R. P. *Acid-Base Catalysis*, Clarendon Press, Oxford 1941, p. 135.
6. Bell, R. P. *The Proton in Chemistry*, Methuen, London 1959, p. 144.
7. Gould, E. *Mechanism and Structure in Organic Chemistry*, Holt, Rinehart and Winston, New York 1959, p. 372.
8. Sykes, P. *A Guidebook to Mechanism in Organic Chemistry*, Longmans, London 1965, p. 226.
9. Hine, J. *Physical Organic Chemistry*, McGraw, New York 1962, p. 233.
10. House, H. O. *Modern Synthetic Reactions*, Benjamin, New York 1965, p. 147.
11. Cardwell, H. M. E. and Kilner, A. E. H. *J. Chem. Soc.* **1951** 2430.
12. Rappe, C. *Arkiv Kemi* **21** (1963) 503.
13. Rappe, C. *Arkiv Kemi* **24** (1965) 321.
14. Bell, R. P. and Lidwell, O. M. *Proc. Roy. Soc.* [A] **176** (1940) 88.
15. Cram, D. J. *Fundamentals of Carbanion Chemistry*, Academic, New York 1965, p. 93.
16. House, H. O. and Kramar, V. *J. Org. Chem.* **28** (1963) 3362.
17. Rappe, C. *Acta Chem. Scand.* **20** (1966) 2236.
18. Rappe, C. *Acta Chem. Scand.* **20** (1966) 2305.
19. Warkentin, J. and Tee, O. S. *J. Am. Chem. Soc.* **88** (1966) 5540.
20. Rappe, C. *Arkiv Kemi* **23** (1964) 81.
21. Rappe, C. *Arkiv Kemi* **24** (1965) 73.
22. Rappe, C. *Acta Chem. Scand.* **20** (1966) 376.
23. Hsü, S. K. and Wilson, C. L. *J. Chem. Soc.* **1936** 623.
24. Cullis, C. F. and Hashmi, M. H. *J. Chem. Soc.* **1956** 2512.
25. Cullis, C. F. and Hashmi, M. H. *J. Chem. Soc.* **1957** 1548.
26. Cullis, C. F. and Hashmi, M. H. *J. Chem. Soc.* **1957** 3080.
27. Schellenberger, A. and Hübner, G. *Chem. Ber.* **98** (1965) 1938.