Halogenation of Ketones

VIII.* Studies on the Mechanisms of the two Base-Catalyzed Halogenations of 2-Butanone. Indications of Non-Enolic Mechanisms

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The mechanisms of the two base-catalyzed halogenations of 2-butanone (Hal B I and Hal B II) have been studied. In both reactions brominations were found to be faster than iodinations. Halogenations in D_2O provided additional support for the hypothesis that halogenation of this ketone follows another mechanism than the base-catalyzed deuteration, in which reaction an enolization is involved. Non-enolic ketonic components are proposed in both halogenations.

According to the currently accepted mechanism, both base-catalyzed halogenation and deuteration of ketones proceed *via* the enolate anion (or enol). This means that the orientation and the reaction rate for the two reactions would be identical or nearly identical.[1-7]

Recently, the present author studied the orientation of the halogenation and deuteration of 2-butanone.[8,9] The ratio 3-substitution/1-substitution was called K_{Hal} and K_D, respectively, for the two types of reaction. The value for K_D was found to be 0.6—0.7 for all base-catalyzed reactions (pH 6—14).[8] Unexpectedly, it was found that in the halogenation two different reactions existed, one operating at pH 5.5—7 and the other at pH's over 12. The two reactions were called Hal B I and Hal B II, respectively. Moreover, it was also unexpected to find that the orientation of halogenation did not agree with the orientation of deuteration. The K_{Hal}-values for reaction Hal B I using the three halogens chlorine, bromine, and iodine was found to be 7.0—7.5, and for reaction Hal B II the value was found to be 0.[9]

From these disagreements it was concluded that contrary to the currently accepted opinion, neither of the two halogenations proceeds *via* the same mechanism as the deuteration, or at least the rate determining step is not identical in the two reactions. If the traditional enolate mechanism operates

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in both cases, it becomes difficult to explain how the same base could catalyze the formation of different anions in the two reactions.

In the present investigation the mechanisms of the two reactions Hal B I and Hal B II will be studied in two ways: by a cursory comparison of the reaction rates of bromination and iodination, and from halogenations using D_2O as solvent. In all experiments 2-butanone was used, and the discussion is valid only for 2-butanone and probably for structurally similar monoketones.

STUDIES OF THE RELATIVE RATES OF HALOGENATION

The generally accepted theory of the formation of enols or enolate anions as being the rate determining step in all base-catalyzed halogenations and deuterations of ketones is based mainly on kinetic investigations.[1-7] These investigations have been performed in different ways: a) comparison of the reaction rates for different halogens, b) comparison of the rates of racemization, deuteration and halogenation, c) examination of the complete kinetic expression.

The rate of base-catalyzed halogenations is reported to be of first-order with respect to base and ketone, and independent of the concentration and nature of halogen; see for instance Refs. 10—14. However, exceptions from this general behaviour are reported, but these exceptions are generally not discussed. It was observed by Bartlett that the hydroxide-catalyzed chlorination of acetone was several hundred times slower than the corresponding bromination and iodination.[15] On the other hand, Van Arendonk and Cupery have reported that in the haloform reaction of acetophenone, hypochlorite reacted much faster than hypobromite and hypoiodite.[16]

Hsü and Wilson have found that the rate of the acetate-catalyzed racemization and bromination of d-2-o-carboxybenzylindan-1-one are equal.[17] For optically active phenyl-sec-butyl ketone Hsü, Ingold and Wilson have found that the rate of deuterioxide-catalyzed racemization in a dioxane/D_2O solution is the same as the rate of the deuteration in the same solvent.[18] It seems that these two investigations are the only ones where the rate of racemization is compared with the rate of deuteration and halogenation for base-catalyzed reactions.

The complete kinetic expression has been carefully studied in the case of halogenation of acetone in acetate buffers, and it was found to be complicated. It contained six terms one of which was [HOAc] [OAc$^-$].[19,20] On this basis it was suggested by Swain that a concerted mechanism for the formation of the enol was of major importance in the base-catalyzed enolization and halogenation of ketones.[20] However, Bell and Jones have advanced some general arguments against this interpretation. These authors consider the direct formation of the enolate anion as the rate determining step in the base-catalyzed halogenation of ketones.[13] For a comprehensive discussion of this subject see Ref. 3.

In addition to the objections given above against the kinetic investigations, it can be noted that in all the kinetic investigations concerning methyl

ketones it was assumed that the halogenations resulted in the trihalo ketones. In view of the results in Ref. 9 this seems to be an oversimplification.

Moreover, the kinetic determinations are very often performed with iodometric titrations.[10-26] However, it was found by Bańkowska that both chloroacetone and bromoacetone react with potassium iodide giving free iodine; bromoacetone about five times faster than chloroacetone.[27] A test by the present author on a polybromoketone (1,1,3,3-tetrabromo-2-butanone) gave an immediate strong colour of iodine. It can be expected that in acid media iodoketones also give free iodine. In view of these observations it is easily understood that kinetic investigations carried out with iodometric titrations are of limited importance. It seems to be necessary to carry out a kinetic investigation of the halogenation of ketones, using a more direct method for the determination of the components. One possible method would be the "isotope dilution technique."

Both halogenation and deuteration of ketones are considered to be general acid- and base-catalyzed reactions.[28] Bell and Lidwell have studied the catalytic constants for the iodination of acetone and some halogenated acetones.[21] As bases, they used hydroxides and salts of carboxylic acids (e.g. acetate, trimethylacetate, chloroacetate, and glycolate). In a Brønsted plot they found the catalytic constants for the weak bases to give a straight line, while the constants for hydroxides were three to four powers of ten too small. In spite of this, the base-catalyzed halogenation of ketones is considered to be a general base-catalyzed reaction.[21,28] However, the behaviour is in better accordance with two different base-catalyzed halogenations, which is now suggested.[9]

As comparison it can be noted that in the base-catalyzed deuteration of ketones, which has recently been studied by the present author, a Brønsted plot including the bases acetate, bicarbonate, carbonate, and deuterioxide, gives a straight line.[8] In this investigations [8] it was found that for deuteration the difference in the catalytic rate constants between acetate and hydroxide was 10^4, while Bell and Lidwell [21] found the difference for the same catalysts in the iodination of acetone to be 10^6.

In the present paper a preliminary, brief investigation of the halogenation rates was performed. First it may be noted, that eventual disappearance of the halogen colour does not indicate complete consumption of halogenating agent. In many cases the reaction mixture after acidifying became strongly coloured by free halogen. Thus the time of decolorization is no accurate measure of the halogenation rate.

The halogenation rates of 2-butanone for the two halogens bromine and iodine have been roughly determined and compared. Sodium acetate and sodium hydroxide have been used as bases. The experimental conditions are given in Table 1. Samples were taken and, in the absence of any better method, iodometrically titrated.

The comparison of the reaction rates for the two halogens shows that the brominations were faster than the iodinations. The greatest difference (a factor of 30) was found in aqueous solutions of the acetate-catalyzed halogenations, reaction Hal B I. Here 15 % of the bromine had reacted after 1 h, while an equivalent amount of iodine had reacted after 30 h (expts. 1 and 2, Table 1). Since these two experiments were performed in two-phase systems, it was

Table 1. Comparison of reaction rates of bromine and iodine.

Expt. No.	Solvent	Amount ml	Base	Amount g	2-Butanone ml	Halogen	Amount g	Temp. °C	Time	Halogen reacted %
1	H_2O	100	NaOAc	15.0	10	Br_2	4.0	25	1 h	15
2	»	»	»	»	»	I_2	6.3	»	30 h	»
3	H_2O/DMF 1:1	»	»	»	»	Br_2	4.0	»	1 h	20
4	»	»	»	»	»	I_2	6.3	»	22 h	»
5	H_2O	30	NaOH	3.0	4.0	Br_2	1.25	0	12 sec	90
6	»	»	»	»	»	I_2	2.0	»	60 sec	»

desirable to study the behaviour in a one-phase system. A mixture of water and DMF (1/1) was chosen, and in this solvent the ratio of the reaction rates was 22, see expts. 3 and 4, Table 1.

In the hydroxide catalyzed reactions (Hal B II) it was found that about 90 % of the halogens had reacted when the colour disappeared. Therefore, the time of decolorization is an acceptable measure of the reaction rate. It was found that bromine reacted 5 times as fast as iodine, see expts. 5 and 6, Table 1.

HALOGENATION IN DEUTERIUM OXIDE

Halogenations performed in deuterium oxide provided a possibility for a direct comparison between the rate of halogenation and the rate of deutera- tion. Various catalysts were used. The resuits of these experiments are given in Table 2. The values given in this table are peak areas and equivalents of protons exchanged.

Expts. 7—11 are reactions with sodium acetate as catalyst, where D_2O is present in a large excess compared with halogen. The pD was found to be 6.8 during the reactions. At this pD, halogenation Hal B I dominates,[9] and this reaction gives mainly 3-halo-2-butanones, which could be detected by NMR. In this way it was found that 50—60 % of the bromine had reacted after 4 h, when the colour had just disappeared. Due to the much slower rate of iodination, the iodine colour still persisted after 12 h, when only small amounts of iodoketones (the 3-iodo isomer) were found.

In expts. 7, 8, and 10 the products were distilled and the fraction of 2- butanone was analyzed by NMR. This compound was found to be deuterated both in the methyl and in the methylene group, see Table 2. In blank tests (expts. 9 and 11), where no halogen was added, 2-butanone was deuterated to the same extent during the same time using the same amount of catalyst.

In expts. 12—18, where the stronger bases sodium carbonate and sodium deuterioxide were used, the pD was higher, about 10 (sodium carbonate) or about 13 (sodium deuterioxide). At these higher pD's reaction Hal B II is favoured and at pD 12 this halogenation is operating alone.[9] Samples 12, 14, and 16 were taken just after disappearance of the bromine colour, the other samples after longer times. The NMR-analyses could be performed without distilling the products, and the values are given in Table 2.

DISCUSSION

The halogenations in the present investigation gave further indications for the proposed hypothesis that both halogenation and deuterations of 2-butanone do not proceed *via* the same enolate anion (or enol) mechanism. Especially the halogenations in D_2O gave valuable information about the ketonic component in the two halogenation reactions.

Before discussing these two mechanisms it will be useful to discuss the mechanism of the base-catalyzed deuteration of ketones.

Table 2. Peak areas and equiv. of protons exchanged of 2-butanone from reactions in D_2O.

Expt. No.	Catalyst	Halogen	pD	Temp. °C	Time	CH_3 (triplet)	CH_3 (singlet)	CH_2 (quartet)	Methyl-D (mequiv.)	Methylene-D (mequiv.)	$K_D{}^a$
7	NaOAc	Br_2	6.8	20	4 h	208	200	134	115	66	0.58
8	"	I_2	"	"	"	218	209	140	124	73	0.59
9	"	—	"	"	"	215	206	138	131	74	0.56
10	"	I_2	"	"	12 h	206	189	125	247	180	0.73
11	"	—	"	"	"	207	189	125	260	188	0.72
12	Na_2CO_3	Br_2	10.2	"	3 min	213	212	142	14	—	—
13	"	"	"	"	12 min	230	222	149	105	56	0.53
14	Na_2CO_3+ NaOD	"	11.1	0	2 min	193	195	128	—	—	—
15	NaOD	"	13.1	"	5 min	177	173	115	68	51	0.75
16	"	"	"	"	6 min	212	200	134	170	103	0.61
17	"	"	"	"	10 min	204	186	125	265	162	0.61
18	"	"	"	"	21 min	226	186	125	532	340	0.64

^{a} Calculated from the ratio methylene-D/methyl-D.

Base-catalyzed deuteration of ketones. As mentioned above, the mechanism of the enolization of ketones has been much discussed. However, in these papers the discussion was based only upon halogenation experiments. During the last decade several works have been published, where the mechanism of the enolization is discussed from measurements of isotope effects or from deuteration experiments.[29-34] In all these papers it is generally accepted that an enolization of the ketone is involved in the deuteration reaction, and it seems difficult to find any plausible alternative mechanisms. The detailed view of the enolization mechanism is discussed.

From a determination of the isotope effect in the enolization, Swain and co-workers propose a concerted mechanism for the enolization, especially when acetate buffers were used.[29,30] Although no termolecular term seems to have been reported, the nature of the termolecular transition state has been discussed. On the basis of primary and secondary isotope effects, Emmons and Hawthorne[31] suggest that this approximates an enolate anion, while Shechter et al.[32] propose that the transition state approximates the starting ketone.

On the contrary, other authors discuss a stepwise bimolecular mechanism.[33,34] Hine et al.[34] have studied the deuteration exchange of isobutyraldehyde-2-*d* in aqueous buffers of tertiary amines and oxygen bases. In these buffers large deviations from the Brønsted catalysis equation were observed, especially for 2- and 6-methylsubstituted pyridines. These deviations were explained on the basis of steric hindrance in the formation of the enolate anions.[34]

Recently the present author found satisfactory agreement between the results from an extended Hückel calculation of the two anions derived from 2-butanone and the observed orientation of the base-catalyzed deuteration. The agreement between the calculation and the observed orientation of substitution in reactions Hal B I and Hal B II is not so good.[8]

Reaction Hal B I. First, it can be noted that the brominations according to reaction Hal B I is 20—30 times faster than the corresponding iodinations, which is in disagreement with the traditional enolate anion (or enol) mechanism.

However, the most instructive information about the mechanism of this reaction was obtained from the halogenations in D_2O using sodium acetate as catalyst; expts. 7—11, Table 2.

In Ref. 8 it was found that the catalytic constants of acetate are larger than those of acetic acid. Thus we can neglect the enolizing effect of the acid formed in the halogenation. The only enolizing species is, therefore, acetate, which is present in the same quantities in all experiments. Since part of the acetate is consumed in the halogenation of the ketone and in the hydrolysis of the halogen, we can predict a slightly decreased amount of enolization in these experiments (expts. 7, 8, and 10). If we assume that both halogenation and deuteration take part *via* the enolate, (the observed difference in the orientation of these two reactions could be explained by assuming that the deuterating and the halogenating agents differ in the efficiency in capturing the enol) the orientation and the amount of substitution should follow two rules.

1. The sum of deuterated and halogenated ketones in the experiments where the amount of deuterated ketones is small, would be slightly smaller than the amount of deuterated ketones in the experiments without any halogen added.

2. Since 3-halogenated ketones are the main products in the halogenation, 1-deuteration would be favoured, resulting in lower K_D-values in these experiments.

The observed behaviour is quite different. The sum of halogenated and deuterated ketones is larger than the amounts of deuterated ketones in the experiments where no catalyst was consumed during the reaction. Moreover, the amount and orientation of deuteration is independent of added halogen. Therefore it can be adduced that the halogenation according to reaction Hal B I is a reaction with the *unenolized ketone*.

Reaction Hal B II. In aqueous hydroxides the difference in rate between bromine and iodine was a factor of 5. Although this value is lower than that for Hal B I, it remains in conflict with a traditional enolate mechanism.

The general features for halogenation in D_2O, assuming both halogenation and deuteration to proceed *via* enolates, which are discussed above for reaction Hal B I, are also valid for reaction Hal B II. However, in this case 1-halogenation is strongly favoured, which would result in higher K_D-values.

Due to the higher catalytic constants of the stronger bases, it is not possible to compare the rate of deuteration in experiments without and with added halogen. However, the observed behaviour differs in three ways from the predicted one:

1. In expts. 12 and 14, where the samples were taken just when the bromine colour had disappeared, no deuteration of the ketone could be detected.

2. The rate of deuteration is independent if halogenation is going on. The samples with sodium deuterioxide are taken during the halogenation (expt. 16), and after all halogen was consumed (expts. 17 and 18). The values of deuteration in these samples gave good first-order plots.

Table 3. Composition of the halogenations in D_2O (0.36 g 2-butanone in 5 ml D_2O).

Expt. No.	Catalyst	Amount g	Halogen	Amount g	Time
7	NaOAc	0.50	Br_2	0.20	4 h
8	»	»	I_2	0.32	»
9	»	»	—	—	»
10	»	»	I_2	0.32	12 h
11	»	»	—	—	»
12	Na_2CO_3	0.60	Br_2	0.20	3 min
13	»	»	»	»	12 min
14	Na_2CO_3 + NaOD	0.50 + 0.125	»	»	2 min
15	»	»	»	»	5 min
16	NaOD	0.20	»	»	6 min
17	»	»	»	»	10 min
18	»	»	»	»	21 min

3. The orientation of deuteration is independent of added halogen.

From this it follows that deuteration and Hal B II are not competitive reactions, which the traditional enolate mechanism predicts. The results can indicate that Hal B II is a reaction with the *unenolized ketone*.

EXPERIMENTAL

The NMR-spectra were recorded on a Varian model A-60 spectrometer. The pD-determinations were made on a Vibret laboratory pH meter using the equation [35]

$$pD = pH \text{ meter reading} + 0.4$$

Halogenation in D_2O. The composition of the different runs are given in Table 3. With the exception of expts. 12 and 13, the runs were carried out in one-phase systems. Samples were withdrawn and extracted with 0.3 ml of carbon tetrachloride. In those experiments where the halogen colour still persisted, sodium bisulfite was added to destroy halogen. The organic phase was analyzed by NMR. Integrals were recorded until a predominant trace was apparent, thus averaging to zero temporary instabilities within the instrument.

REFERENCES

1. Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, Cornell, New York 1953, p. 567.
2. Bell, R. P. *Acid-Base Catalysis*, Clarendon Press, Oxford 1941, p. 135.
3. Bell, R. P. *The Proton in Chemistry*, Methuen, London 1959, p. 144.
4. Gould, E. *Mechanism and Structure in Organic Chemistry*, Holt, Rinehart and Winston, New York 1959, p. 372.
5. Sykes, P. *A Guidebook to Mechanism in Organic Chemistry*, Longmans, London 1965, p. 226.
6. Hine, J. *Physical Organic Chemistry*, McGraw, New York 1962, p. 233.
7. House, H. O. *Modern Synthetic Reactions*, Benjamin, New York 1965, p. 147.
8. Rappe, C. *Acta Chem. Scand.* **20** (1966) 2236.
9. Rappe, C. *Acta Chem. Scand.* **21** (1967) 857.
10. Lapworth, A. *J. Chem. Soc.* **85** (1904) 30.
11. Dawson, H. M. and Key, A. *J. Chem. Soc.* **1928** 2154.
12. Bell, R. P. and Longuet-Higgins, H. C. *J. Chem. Soc.* **1946** 636.
13. Bell, R. P. and Jones, P. *J. Chem. Soc.* **1953** 88.
14. Bell, R. P. and Yates, K. *J. Chem. Soc.* **1962** 1927.
15. Bartlett, P. D. *J. Am. Chem. Soc.* **56** (1934) 967.
16. VanArendonk, A. M. and Cupery, M. E. *J. Am. Chem. Soc.* **53** (1931) 3184.
17. Hsü, S. K. and Wilson, C. L. *J. Chem. Soc.* **1936** 623.
18. Hsü, S. K., Ingold, C. K. and Wilson, C. L. *J. Chem. Soc.* **1938** 78.
19. Dawson, H. M. and Spivey, E. *J. Chem. Soc.* **1930** 2180.
20. Swain, C. G. *J. Am. Chem. Soc.* **72** (1950) 4578.
21. Bell, R. P. and Lidwell, O. M. *Proc. Roy. Soc. (London)* [A] **176** (1940) 88.
22. Cullis, C. F. and Hashmi, M. H. *J. Chem. Soc.* **1956** 2512.
23. Cullis, C. F. and Hashmi, M. H. *J. Chem. Soc.* **1957** 1548.
24. Cullis, C. F. and Hashmi, M. H. *J. Chem. Soc.* **1957** 3080.
25. Fischer, A., Packer, J. and Vaughan, J. *J. Chem. Soc.* **1963** 226.
26. Hulett, J. R. *J. Chem. Soc.* **1965** 430.
27. Bańkowska, Z. *Bull. Acad. Polon. Sci., Sér. Sci. Chim. Géol. Geograph.* **7** (1959) 473.
28. Stewart, R. *The Investigation of Organic Reactions*, Prentice-Hall, Englewood Cliffs 1966, p. 101.

29. Swain, C. G., Stivers, E. C., Reuwer, J. F., Jr. and Schaad, L. J. *J. Am. Chem. Soc.*
    80 (1958) 5885.
30. Swain, C. G., Di Milo, A. J. and Cordner, J. P. *J. Am. Chem. Soc.* **80** (1958) 5983.
31. Emmons, W. D. and Hawthorne, M. F. *J. Am. Chem. Soc.* **78** (1956) 5593.
32. Shechter, H., Collis, M. J., Dessy, R., Okuzumi, Y. and Chen, A. *J. Am. Chem. Soc.*
    84 (1962) 2905.
33. House, H. O. and Kramar, V. *J. Org. Chem.* **28** (1963) 3362.
34. Hine, J., Houston, J. G., Jensen, J. H. and Mulders, J. *J. Am. Chem. Soc.* **87** (1965)
    5050.
35. Glasoe, P. K. and Long, F. A. *J. Phys. Chem.* **64** (1960) 188.