Halogenation of Ketones

IV. * The Deuteration of Butanone-2

CHRISTOFFER RAPPE

Institute of Chemistry, University of Uppsala, Uppsala, Sweden

The deuteration of butanone-2 has been studied. In the acid and base catalyzed reactions both α-carbons are deuterated. Extended Hückel calculations are in agreement with the deuterations.

In the generally accepted theories of acid and base catalyzed halogenations of ketones, the enolization of the ketone is the rate and product determining step of the reaction.[1-7] As a consequence of this, the enolization of ketones has mostly been studied by halogenation, preferably bromination, experiments.[1-4]

In view of recent results of the halogenation of ketones, this seems unsatisfactory. In acid media, it has been shown that bromoketones, especially polybromoketones, rearrange easily.[8,9] It was recently found by the present author that when a monohaloketone is halogenated, the second halogen atom attacks the halogenated α-carbon.[10] This observation is opposite to the previously accepted view.[5] However, in bromination experiments, it is mostly α,α'-dibromoketones that are isolated. This is due to secondary rearrangements.[8-10]

Recent work by the present author indicates that in base catalyzed brominations, the situation is more complex than expected. The products formed with the use of moderate bases, such as sodium acetate and bicarbonate, are different from those formed with the use of strong bases, e.g., carbonates and hydroxides.[11]

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 studies of the deuteration of ketones can also give valuable information about the enolization of ketones.[2,5,7]

Although several authors report having prepared α-deuterated ketones,[12,13] the question of the direction of deuteration has been only slightly investigated. House and Kramar have studied the direction of sodium carbonate catalyzed

---

* Part III. *Acta Chem. Scand.* **20** (1966) 376.

deuteration of 2-methyl-3-pentanone by means of mass spectrometry.[14] These authors found that the ratio of the exchange rate at position 4 to the exchange rate at position 2 is approximately 20 to 1.

House and Kramar have also studied the equilibrium of potassium enolates of certain unsymmetric ketones in 1,2-dimethoxyethane.[14] The enolates were prepared by reaction of the ketone with the strong base triphenylpotassium. In one series of experiments the equilibrium mixture was quenched by deuterio-acetic acid in deuterium oxide. The monodeuterated ketones were isolated, and the distribution of deuterium was studied by mass spectrometry. In the case of unbranched methyl ketones they found approximately equal amounts of the two different enolates. About the same distribution was obtained when the equilibrium mixture was quenched with acetic anhydride or methyl iodide.[14] It was surprising to find, that in other experiments where sodium or lithium salts were studied instead of potassium salts, the equilibria were shifted.[14]

Recently, the present author studied the direction of both acid and base catalyzed deuterations of ketones using NMR-techniques.[10,15] Although these investigations were only of a preliminary nature and no kinetic measurements were made, they showed that NMR is an excellent tool in such studies. As expected, in the acid catalyzed deuteration of butanone-2, the protons of the methylene group are removed faster than those of the methyl group.[10] In the base catalyzed deuteration, only haloketones were studied. Here it was found that protons are more readily removed from groups containing one or two
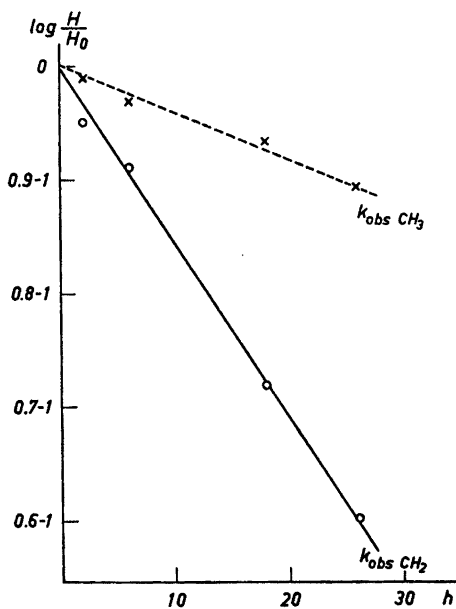

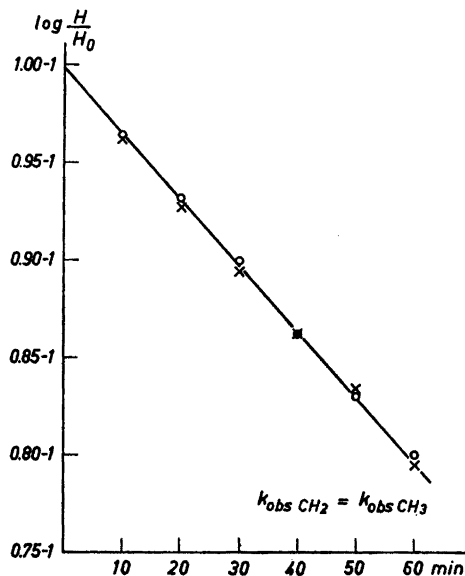*Fig. 1.* First-order plot of DCl-catalyzed deuteration of butanone-2.

Fig. 2. First-order plot of Na_2CO_3-catalyzed deuteration of butanone-2.
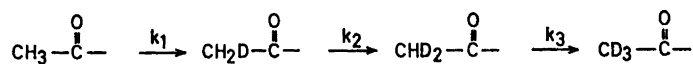
halogens than from those containing no halogen; [15] this is in agreement with accepted theories.[5],[6]

In the present investigation the direction of acid and base catalyzed enolization of butanone-2 will be studied by means of deuteration experiments. The deuterations will be followed by NMR.
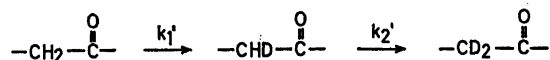
The deuteration of methyl and methylene groups of ketones are two series of consecutive first-order reactions, and they will give a rather complex kinetic situation.[16],[17] In order to clarify the problems concerning the observed speed of deuteration and the rate constants in different reactions, the kinetics of the system will be studied in greater detail.

KINETICS OF THE DEUTERATION

Making first-order plots of the data obtained in the deuteration experiments, two straight lines would be obtained, one for the methyl group with the observed k-value $k_{obs\,CH_3}$ and the other for the methylene group $k_{obs\,CH_2}$, see Figs. 1 and 2.

$$CH_3-\overset{O}{\overset{\|}{C}}- \xrightarrow{k_1} CH_2D-\overset{O}{\overset{\|}{C}}- \xrightarrow{k_2} CHD_2-\overset{O}{\overset{\|}{C}}- \xrightarrow{k_3} CD_3-\overset{O}{\overset{\|}{C}}-$$

Scheme 1

$$-CH_2-\overset{O}{\overset{\|}{C}}- \xrightarrow{k_1'} -CHD-\overset{O}{\overset{\|}{C}}- \xrightarrow{k_2'} -CD_2-\overset{O}{\overset{\|}{C}}-$$

Scheme 2

The stepwise deuteration of the methyl and methylene groups of a ketone is shown in Schemes 1 and 2. The sequence of reactions for the methyl group may be symbolized as

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C \xrightarrow{k_3} D$$
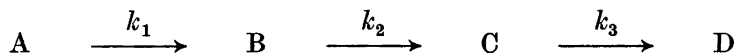
and for the methylene group,

$$E \xrightarrow{k_{1'}} F \xrightarrow{k_{2'}} G$$

If we neglect a presumably small secondary isotope effect, the rate of proton removal will depend upon the number of protons in the group. Thus:

$$k_1 = 3\ k_3$$
$$k_2 = 2\ k_3$$
$$k_{1'} = 2\ k_{2'}$$

As the kinetics of the reactions were studied by NMR, only the concentrations of proton-bearing groups (A, B, C, E, and F) are of interest. The concentrations of these groups as a function of time are given by

$$[A] = [A]_0 \exp(-k_1 t)$$

$$[B] = [A]_0 \frac{k_1}{k_2 - k_1} [\exp(-k_1 t) - \exp(-k_2 t)]$$

$$[C] = [A]_0 \frac{k_1 \cdot k_2}{k_3(k_2 - k_1)} [-\tfrac{1}{2} \exp(-k_1 t) + \exp(-k_2 t) - \tfrac{1}{2} \exp(-k_3 t)]$$

$$[E] = [E]_0 \exp(-k_{1'} t)$$

$$[F] = [E]_0 \frac{k_{1'}}{k_{2'} - k_{1'}} [\exp(-k_{1'} t) - \exp(-k_{2'} t)]$$

If we now consider the CH_3-peak, the observed NMR peak-area of this group, H_{CH_3}, will be

$$\alpha H_{CH_3} = 3[A] + 2[B] + [C]$$

where α is a proportionality constant. Using the values of the concentrations as a function of time given above, we obtain:

$$\alpha H_{CH_3} = 3[A]_0 \exp(-k_3 t)$$

or

$$\ln H_{CH_3} = -k_3 t + c$$

Thus: $k_{obs\ CH_3} = -k_3$

$$k_1 = -3k_{obs\ CH_3}$$

Taking the CH_2-group we obtain

$$\alpha H_{CH_2} = 2[E] + [F]$$
$$\alpha H_{CH_2} = 2[E]_0 \exp(-k_{2'} t)$$

or

$$\ln H_{CH_2} = -k_{2'} t + c$$

Thus: $k_{obs\ CH_2} = -k_{2'}$

$$k_{1'} = -2k_{obs\ CH_2}$$

RESULTS OF THE DEUTERATIONS

Our primary interest was to study the direction of the enolization, see Schemes 3 and 4. Therefore we calculated

$$K_D = \frac{k_{1'}}{k_1} = \frac{2k_{obs\ CH_2}}{3k_{obs\ CH_3}} = \frac{k_{c\ CH_2}}{k_{c\ CH_3}}$$

The results from the different experiments using various catalysts are given in Table 1.

It seems reasonable to assume that only two mechanisms operate in the deuteration of ketones, one in acid catalyzed and the other in base catalyzed reactions. From our results given in Table 1 it can be seen that for the acid catalyzed reaction the ratio of 3-/1-deuteration, $K_D = k_{1'}/k_1$ was about 2.5, and for base catalyzed reactions 0.6—0.7. The observation that in base cata-

Table 1. Results of the deuteration experiments.

Expt. No.	Catalyst	$k_{obs\ CH_2}$ sec⁻¹	k_c CH₂ l·mole⁻¹sec⁻¹	$k_{obs\ CH_3}$ sec⁻¹	k_c CH₃ l·mole⁻¹sec⁻¹	K_D	pK_a
1	DCl	2.5×10^{-6}	5.0×10^{-5}	6.6×10^{-7}	2.0×10^{-5}	2.54	—
2	—»—	4.9×10^{-6}	4.8×10^{-5}	1.3×10^{-6}	2.0×10^{-5}	2.48	—
3	—»—	9.3×10^{-6}	4.6×10^{-5}	2.5×10^{-6}	2.0×10^{-5}	2.50	—
4	DOAc	2.0×10^{-7}	3.4×10^{-6}	5.5×10^{-8}	1.4×10^{-8}	2.40	—
5	D₂O	2.1×10^{-8}	8.6×10^{-10}	8.9×10^{-9}	5.4×10^{-10}	1.60	—
6	NaOAc/DOAc	2.5×10^{-7}	—	9.8×10^{-8}	—	1.70	—
7	—»—	2.7×10^{-7}	—	1.4×10^{-7}	—	1.28	—
8	—»—	4.3×10^{-7}	—	3.7×10^{-7}	—	0.77	—
9	NaOAc	6.1×10^{-7}	2.4×10^{-6}	5.8×10^{-7}	3.6×10^{-6}	0.70	4.76
10	NaHCO₃	2.1×10^{-6}	8.2×10^{-6}	2.2×10^{-6}	1.3×10^{-5}	0.62	6.33
11	—»—	1.1×10^{-6}	8.8×10^{-6}	1.1×10^{-6}	1.3×10^{-5}	0.67	6.33
12	—»—	6.2×10^{-7}	1.0×10^{-5}	5.9×10^{-6}	1.4×10^{-5}	0.70	6.33
13	Na₂CO₃	1.2×10^{-4}	4.8×10^{-4}	1.2×10^{-4}	7.2×10^{-4}	0.65	10.37
14	Li₂CO₃	1.1×10^{-4}	4.4×10^{-4}	1.1×10^{-4}	6.6×10^{-4}	0.67	10.37
15	NaOD	7.2×10^{-4}	2.8×10^{-2}	7.2×10^{-4}	4.5×10^{-2}	0.67	16.22

lyzed reactions both α-groups are deuterated is in agreement with the general rule for unbranched methyl ketones given by House and Kramar.[14] In addition the base catalyzed deuterations showed that the primary enolate anion, I, is a little more stabilized than the secondary anion, II; see Scheme 3.
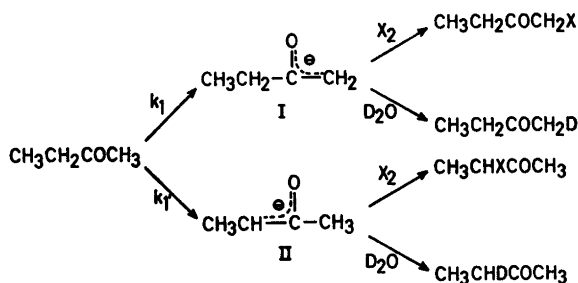
Scheme 3

No significant differences for the K_D-values could be observed, when either weaker bases such as sodium acetate and sodium bicarbonate were used, or when stronger bases such as sodium carbonate and sodium deuterioxide were used. It can be noted here that lithium carbonate gave the same K_D-value as the sodium salts (expt. 14), which is in contrast to the observation of House and Kramar. In experiments where they used very strong bases, these authors observed that the equilibria for sodium and lithium enolates were shifted.[14] Furthermore, both sodium carbonate and lithium carbonate had the same k_c-values; see Table 1. In the case of acid catalyzed reactions, deute-

$$CH_3CH_2COCH_3 \xrightarrow{k_1} \overset{OH}{\underset{III}{CH_3CH_2-C=CH_2}} \begin{cases} \xrightarrow{X_2} CH_3CH_2COCH_2X \\ \xrightarrow{D_2O} CH_3CH_2COCH_2D \end{cases}$$

$$CH_3CH_2COCH_3 \xrightarrow{k_1'} \underset{IV}{CH_3CH=C-CH_3 \atop OH} \begin{cases} \xrightarrow{X_2} CH_3CHXCOCH_3 \\ \xrightarrow{D_2O} CH_3CHDCOCH_3 \end{cases}$$

Scheme 4

rioacetic acid gave the same K_D-value as deuterium chloride. Here the secondary enol, IV, was favoured over the primary enol, III; see Scheme 4.

From Table 1 it can be seen that strong acids and bases gave faster deuteration than weak reagents. For two catalysts, deuterium chloride (expts. 1, 2, and 3) and sodium bicarbonate (expts. 10, 11, and 12) a series of deuterations were performed using various amounts of the catalyst. The catalytic constants obtained within these two series ($k_{c\ CH_3}$ and $k_{c\ CH_2}$) are about the same. This is in agreement with the general behaviour of acid and base catalyzed reactions.

In Fig. 3 a Brønsted plot of the catalytic constants of various bases used in these experiments are given. The straight line obtained here is further evidence for the base catalyzed reaction. It can be pointed out here that Bell and Lidwell, who studied the catalytic constants of various bases for the halogenation of acetone and chloroacetones, found the catalytic constants for sodium hydroxide to be $1000-10\ 000$ times too low.[18] In spite of this they considered the halogenation to be a general base catalyzed reaction.

Various mixtures of acetic acid and sodium acetate were studied in expts. 6, 7, and 8. Here the K_D-values were between 1.7 and 0.80. An increasing amount of sodium acetate gave a smaller K_D-value. This can indicate that in acetate buffers both acid and base catalyzed deuterations occur, an increasing amount of base being found to give an increasing amount of base catalyzed reaction.

Fig. 3. Brønsted-plot of the base catalyzed deuteration of butanone-2.

The deuteration in deuterium oxide without any added catalyst is very slow; the reaction was followed for several months at 30°C. However, the K_D-value was estimated to be 1.6 indicating that both acid and base catalyzed reactions contribute to the deuteration, and a calculation showed that if only the acid and the base catalyzed reactions contribute, the acid catalyzed deuteration predominates in this medium. However, it is possible that here and perhaps also in acetate buffers another mechanism operates alone or together with the other two mechanisms. The situation in buffer solutions and in pure D_2O will be studied further.

This seems to be the first direct determination of the kinetic acidity of a ketone. The values given in several text-books refer to halogenation experiments made by Bell and Lidwell.[18] However, the value for acetone given by these authors is in agreement with the value for butanone-2 found in the present investigation.

Here it is of interest to note that the proton transfer from ketones to water is considered to involve only the enolate anions; see Refs. 19 and 20. Contrary to this, Dubois and Barbier who studied the bromination of acetone in the absence of any catalyst, regarded this reaction as an acid catalyzed reaction.[21] As pointed out above, both kinds of reaction seem to contribute.

As mentioned above, experimental evidence for two different mechanisms for the base catalyzed bromination of butanone-2 was recently observed.[11] In neutral solutions the halogenation of the methylene group was favoured ($K_{Br} = 5$).[11] With stronger bases, halogenation of the methyl group was found to be highly favoured, $K_{Br} = 0$ (haloform reaction).[1-6,22]

In the generally accepted theory for the base catalyzed halogenation of ketones, the rate and product determining step of the reaction is the base catalyzed formation of the enolate anion. This reaction is followed by a rapid halogenation of the enolate anion.[1-7] The same mechanism is considered to be valid for the base catalyzed deuteration of ketones.[2,5,7,23,24]

A paper containing a thorough comparison between the deuteration and the halogenation of ketones is under preparation.[25] At this point it can be stated that in the case of acid catalyzed reactions the agreement is good. *For base catalyzed reactions the deuteration experiments in Table 1 and the bromination experiments in Ref. 11 are not in agreement with this theory. We have two different halogenation reactions, and in neither of these does the substitution follow the same path as the deuteration.*

A study of the deuteration of other ketones than butanone-2 is in progress. In this investigation the direction of the deuteration and the kinetic acidity of the ketones will be studied by the use of the same NMR-technique as described above. This technique is more simple than the mass spectrometry method used by House and Kramar.[14] It can be used in those cases where it is easy to distinguish between the two α-groups by NMR. Preliminary results on 2-methyl-3-pentanone are in agreement with the results obtained by House and Kramar.[14]

EXTENDED HÜCKEL CALCULATION

In connection with these studies on the base catalyzed reactions of buta-none-2, extended Hückel calculations on the two enolate ions, I and II (see Scheme 3), which are intermediates in these reactions are of interest. The calculations were performed according to Hoffmann and with the parameters used by him.[26] The oxygen parameters were taken from Pritchard and Skinner.[27] The energy of anion I was calculated to be -560.641 eV, the value of anion II was -560.633 eV. This means that anion I was energetically favoured, but only by 0.2 kcal/mole. Deuteration experiments showed that enolate I was thermodynamically favoured by a factor of 1.5.

In the acid catalyzed reactions of butanone-2, the enols III and IV are intermediates (see Scheme 4), and here the experiments showed that enol IV was favoured by a factor of 2.5. As comparison, a calculation was done on these two enols. The energy levels are -563.699 eV for enol IV and -563.638 eV for enol III; enol IV is favoured by about 1.4 kcal/mole. In both cases the deuteration experiments and the Hückel calculations are in agreement.

EXPERIMENTAL

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

Deuterations. The composition of the different runs are given in Table 2. The reactions were performed in NMR-tubes kept at 30°C.

Table 2. Composition of the deuteration experiments with 0.1 ml of butanone-2.

Expt. No.	Solvent	Catalyst
1	0.5 ml of D_2O	1.85 mg of DCl
2	—»—	3.7 mg of DCl
3	—»—	7.4 mg of DCl
4	0.5 ml of solution B [a]	—
5	0.5 ml of D_2O	—
6	0.5 ml of solution B [a]	5.12 mg of NaOAc
7	—»—	20.5 mg of NaOAc
8	—»—	82 mg of NaOAc
9	0.5 ml of D_2O	20.5 mg of NaOAc
10	—»—	21.0 mg of $NaHCO_3$
11	—»—	10.5 mg of $NaHCO_3$ + 7.25 mg of NaCl
12	—»—	5.25 mg of $NaHCO_3$ + 11.0 mg of NaCl
13	—»—	13.3 mg of Na_2CO_3
14	—»—	9.25 mg of Li_2CO_3
15	—»—	2.1 mg of NaOD

[a] Solution B: 25 ml of deuterium oxide added to 50 ml of acetic anhydride.[15]

Added in proof: Shortly after this paper was delivered to the Editor for publication, a short communication by J. Warkentin and O.S. Tee was published (*Chem. Commun.* **1966** 190). These authors have also studied the relative rates in 1- and 3-position for the base catalyzed deuterium exchange in butanone-2, using the following bases: sodium deuteri-oxide, sodium *p*-nitrophenoxide and sodium acetate. The catalytic constants for the weaker bases were calculated by means of an "extrapolation technique". Contrary to the result in this paper they report *different K_D-values for the stronger and weaker bases* (NaOD; $K_D = 0.7$, NaOAc; $K_D = 1.4$). This contradictory paper will be discussed in a separate paper (*Acta Chem. Scand.* **20** (1966) 2305.

REFERENCES

1. Lapworth, A. *J. Chem. Soc.* **85** (1904) 30.
2. Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, Cornell, New York 1953, p. 567.
3. Bell, R. P. *Acid-Base Catalysis*, Clarendon Press, Oxford 1941, p. 135.
4. Bell, R. P. *The Proton in Chemistry*, Methuen, London 1959, p. 144.
5. Gould, E. *Mechanism and Structure in Organic Chemistry*, Holt, Rinehart and Winston, New York 1959, p. 372.
6. Sykes, P. *A Guidebook to Mechanism in Organic Chemistry*, Longmans, London 1965, p. 226.
7. Hine, J. *Physical Organic Chemistry*, McGraw, New York 1962, p. 233.
8. Rappe, C. *Arkiv Kemi* **23** (1964) 81.
9. Rappe, C. *Arkiv Kemi* **24** (1965) 73.
10. Rappe, C. *Arkiv Kemi* **24** (1965) 321.
11. Rappe, C. *Acta Chem. Scand.* **20** (1966) 376.
12. Dahn, H., Donzel, A., Merbach, A. and Gold, H. *Helv. Chim. Acta* **46** (1963) 994.
13. Bauder, A., Tank, F. and Günthard, H. H. *Helv. Chim. Acta* **46** (1963) 1453.
14. House, H. and Kramar, V. *J. Org. Chem.* **28** (1963) 3362.
15. Rappe, C. *Acta Chem. Scand.* **19** (1965) 276.
16. Frost, A. A. and Pearson, R. G. *Kinetics and Mechanism*, Wiley, New York 1961, p. 177.
17. Wiberg, K. and Nigh, W. *J. Am. Chem. Soc.* **87** (1965) 3849.
18. Bell, R. P. and Lidwell, O. M. *Proc. Roy. Soc.* [A] **176** (1940) 88.
19. Pearson, R. G. and Dillon, R. L. *J. Am. Chem. Soc.* **75** (1953) 2439.
20. Cram, D. J. *Fundamentals of Carbanion Chemistry*, Academic, New York 1965, p. 9.
21. Dubois, J.-E. and Barbier, G. *Bull. Soc. Chim. France* **1965** 682.
22. Hashmi, M. H. *Pakistan J. Sci.* **10** (1958) 159.
23. Cram, D. J., Rickborn, B., Kingsbury, C. A. and Haberfield, P. *J. Am. Chem. Soc.* **83** (1961) 3678.
24. Ref. 20, p. 93.
25. Rappe, C. *To be published.*
26. Hoffmann, R. *J. Chem. Phys.* **39** (1963) 1397.
27. Pritchard, H. O. and Skinner, H. A. *Chem. Rev.* **55** (1955) 745.