Examination of the Evidence for ' Hal B I ' and ' Hal B II ' Mechanisms for Halogenation of Ketones

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The evidence for base catalysed ' Hal B I ' and ' Hal B II ' mechanisms for halogenation of ketones has been re-evaluated. Our results, together with those of Cullis and Hashmi, support the traditional mechanism of halogenation. Alternative interpretations are suggested for the ' apparent ' evidence for ' Hal B I ' and ' Hal B II ' mechanisms. The kinetics of the reactions of 1- and 3-bromobutan-2-one with aqueous hydroxide ion have been determined.

DURING the past seven years a series of papers defining the characteristics of the base catalysed halogenation of ketones, ' Hal B I ' and ' Hal B II ', has been published by Rappe [1-9] who has emphasized that these proposed halogenation mechanisms are at variance with the classical concept of a base catalysed route involving rate-determining ionization of the ketone.[10-13] The consequences of the operation of such alternative pathways have been emphasized and it has been suggested that interpretations of previous results may be erroneous. In particular it has been common practice to assess rates of α-deprotonation of ketones by following their rates of halogenation under both acid and base catalysis,[14-17] a procedure which would be indefensible if alternative halogenation routes were in operation.

In view of the controversial nature of these proposals, the absence of mechanistic detail, and the failure of other workers to report similar findings, we chose to assess the significance of Rappe's results.

Hal B I *and Hal B* III *Mechanisms of Halogenation.*—Rappe [18] has postulated no less than five different mechanisms of halogenation for butan-2-one and other structurally related ketones. Of these five reactions, two are acid catalysed, two are base catalysed, and one is a free radical reaction. We consider only the proposed base catalysed mechanisms to which the following characteristics have been attributed. The abbreviation K_{Hal} will refer to the ratio of products of 3-halogenation to 1-halogenation of butan-2-one and likewise K_{D} will represent relative deuteriation tendencies (as defined by Rappe).

(a) *Hal B* I *reaction of butan-2-one.* (i) The reaction occurs at pH 5·5—7. (ii) There is an apparent 20—30-fold difference in the reaction rates for bromine and iodine. (iii) For all halogens this base catalysed reaction has the same value $K_{\mathrm{Hal}} = 7$—8 which is different from the value [4,6,19] $K_{\mathrm{D}} = 0{\cdot}6$—$0{\cdot}75$. (iv) Deuteriation in D_2O-base solution is not influenced by the addition of

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[1] C. Rappe, *Arkiv Kemi*, 1963, **21**, 503.
[2] C. Rappe, *Arkiv Kemi*, 1965, **24**, 321.
[3] C. Rappe, *Acta Chem. Scand.*, 1966, **20**, 376.
[4] C. Rappe, *Acta Chem. Scand.*, 1966, **20**, 2236.
[5] C. Rappe, *Acta Chem. Scand.*, 1966, **20**, 1721.
[6] C. Rappe, *Acta Chem. Scand.*, 1966, **20**, 2305.
[7] C. Rappe, *Acta Chem. Scand.*, 1967, **21**, 857.
[8] C. Rappe, *Acta Chem. Scand.*, 1967, **21**, 1823.
[9] C. Rappe, *Acta Chem. Scand.*, 1968, **22**, 219.
[10] L. Fieser and M. Fieser, ' Advanced Organic Chemistry,' Reinhold, New York, 1961, p. 411.
[11] J. D. Roberts and M. Caserio, ' Basic Principles of Organic Chemistry,' Benjamin, New York, 1965, p. 473.
[12] E. Gould, ' Mechanism and Structure in Organic Chemistry,' Holt, Rinehart, and Winston, New York, 1959, p. 372.
[13] H. House, ' Modern Synthetic Reactions,' Benjamin, New York, 1965, p. 147.
[14] R. P. Bell, ' The Proton in Chemistry,' Methuen, London, 1959, p. 144.
[15] A. Lapworth, *J. Chem. Soc.*, 1904, **85**, 30.
[16] C. K. Ingold, ' Structure and Mechanism in Organic Chemistry,' Cornell, New York, 1953, p. 567.
[17] R. P. Bell, ' Acid-Base Catalysis,' Clarendon, Oxford, 1941, p. 135.
[18] C. Rappe and W. H. Sachs, *J. Org. Chem.*, 1967, **32**, 4127.
[19] C. Rappe, *Acta Chem. Scand.*, 1969, **23**, 2305.

bromine. (v) A mechanism of reaction between hypohalite anion and unenolized ketone has been proposed.[9]

(b) *Hal B* II *reaction of butan-2-one.* (i) The reaction occurs at pH 12. (ii) There is an apparent five-fold difference in the reaction rate for bromine and iodine. (iii) For all halogens this strong base catalysed reaction has the same value $K_{\mathrm{Hal}} = 0$ which is different from the value $K_{\mathrm{D}} = 0{\cdot}6—0{\cdot}75$. (iv) No deuteriation occurs in D_2O–base solution during the time in which bromination is completed.

We propose to show that (1) the rates of iodination and bromination of butan-2-one are equal and that observations a(ii) and b(ii) are due to processes other than halogenation of the ketone; (2) observation b(iii) is due to rapid hydrolysis of the 3-halogeno-ketone; and (3) observations a(iii) and (a(iv), we believe, result from incorrect interpretation of the experimental results. Observation b(iv) is in accord with the traditional halogenation mechanism and needs no further explanation.

The Traditional Mechanism for Halogenation of Ketones.—Evidence supporting the mechanism for halogenation of ketones involving halogenation of a reactive enol or enolate ion has been adequately summarized elsewhere.[17] Thus for sufficiently high halogen concentrations the observed rate of halogenation is independent of halogen concentration and the halogen used [see Experimental section, equations (1) and (2)]. Under these conditions the rate of deuteriation should also be equal to the rate of halogenation [equation (3)]. For sufficiently low halogen concentrations, the reaction between the enol or enolate ion with the halogen becomes rate determining and the observed rate becomes dependent on both the nature and concentration of the halogen species.[17]

Attention has been drawn [8] to Bartlett's observation of a hydroxide-induced chlorination of acetone which was several hundred times slower than the corresponding bromination or iodination [20] and to Van Arendonk and Cupery's report [21] of a halogenoform reaction of acetophenone in which hypochlorite reacted much faster than hypobromite or hypoiodite. The synthetic conditions employed make impossible a mechanistic interpretation of the latter observation. The results of Bartlett can be readily interpreted in terms of a rate-determining reaction between the enolate and hypochlorite ion and are thus not at variance with the traditional mechanism of halogenation.

It is therefore clear that prior to Rappe's investigation there was no report to suggest that base catalysed halogenation of ketones proceed by any mechanism other than halogenation of an intermediate enol or enolate ion.

RESULTS AND DISCUSSION

(A) *Halogenation Rate Ratios under Hal B* I *Conditions.*—The alleged detection, reported by Rappe,[8] of difference in rate of reaction of butan-2-one with bromine and iodine, particularly at pH 5·5—7, is clearly at variance with previous reports. However only with butan-2-one in 50% aqueous dimethylformamide (DMF)[8] has such a rate difference been determined *under homogeneous conditions.* We have found that there is a relatively rapid reaction between Br_2 and DMF and to a lesser extent, I_2 and DMF. Once this has been allowed for (Tables 1 and 2), no significant difference exists between the rate of bromination and iodination of butan-2-one.

TABLE 1

Reaction of bromine (5 g) in 50% v/v DMF (250 ml) containing NaOAc (1·22M) at 25 °C

Time (h)	Blank Halogen lost (x%)	Butan-2-one added (25 ml) Halogen lost (y%)	($y - x$)
0	0	0	0
1	9	12	3
2	15·8	19·8	4
4	24·7	32·4	7·8
6	31	44	13
8	36·2	54·8	18·6
10	39·9	63	23·1
12	42·7	69·8	27·1
22	52·5	97·2	44·7
30	57·7		
46	63·5		

TABLE 2

Reaction of iodine (7·95 g) in 50% v/v DMF (250 ml) containing NaOAc (1·22M) at 25 °C

Time (h)	Blank Halogen lost (x%)	Butan-2-one added (25 ml) Halogen lost (y%)	($y - x$)
0	0	0	0
2	3	4	1
4	3	7·5	4·5
12	3·9	24·5	20·6
22	4·5	46	41·5
36	6·0	73	67

We have in addition confirmed the equality of halogenation rates by spectrophotometric observation of zero-order iodination and bromination of butan-2-one in an acetate solution initially brought to pH 6·8. The catalytic rate constant for deuteriation of butan-2-one in a buffer solution of NaOAc in D_2O (pD 7·2) at 33·4 °C has also been determined by n.m.r. spectroscopy and this result is also included in Table 3 along with those of the halogenation experiments. The agreement, neglecting consideration of secondary isotope effects, is very close and leaves little doubt as to the nature of

TABLE 3

Catalytic rate constants § for deuteriation and halogenation of butan-2-one

Reaction †	T/°C	pH	[AcO⁻]/M	$10^7 k_e$/s^{-1}	$10^7 k_{\mathrm{AcO^-}}$/l mol^{-1} s^{-1}
Iodination	25	6·8	1·0	1·43 ± 0·04	1·43
Bromination	25	6·8	1·0	1·53 ± 0·06	1·53
Iodination ‡	33·4	7·2 *	0·9	2·1 ± 0·1	2·34
Deuteriation ‡	33·4	7·2 *	0·9	1·6 ± 0·3	1·8

* pD. † AcO⁻ is considered to be the dominant catalyst. ‡ Reactions in D_2O as solvent. § k_e as defined in equations (1) and (2); $k_{\mathrm{AcO^-}} = k_e/[\mathrm{AcO^-}]$.

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[20] P. D. Bartlett, *J. Amer. Chem. Soc.*, 1934, **56**, 967.

[21] A. M. Van Arendonk and M. E. Cupery, *J. Amer. Chem. Soc.*, 1931, **53**, 3184.

the rate-determining step for the base catalysed halogenation of butan-2-one in aqueous solution.

(B) *Halogenation Rate Ratios under Hal B* II *Conditions*.—Decolourisation times of 12 and 60 s have been reported by Rappe [8] for reaction of butan-2-one (4 ml) with bromine and iodine (0·26M) at 0 °C in aqueous sodium hydroxide (30 ml, 2·5M). Such measurements however are seriously affected by iodate formation in these solutions. Moreover Cullis and Hashmi [22] have already shown that with alkali in large excess, the rates (Table 4) of bromination and iodination are almost identical for each of the following ketones: acetone, butan-2-one, isopropyl methyl ketone, and methyl t-butyl ketone. Slightly higher bromination rates have been attributed to the greater halogen consumption found in these cases.

TABLE 4

Rate * of halogenation of some methyl ketones at 25 °C. [Ketone] = 0·0025M, [Bromine] = 0·0105M, [Iodine] = 0·01M, [NaOH] = 0·1M

	Velocity constant (10^3k/s^{-1}) Bromination	Iodination
Acetone	17·2	16·8
Ethyl methyl ketone	9·43	9·01
Isopropyl methyl ketone	7·3	7·16
Methyl t-butyl ketone	3·65	3·41

* Results of Cullis and Hashmi.[22]

(C) *The Role of Enol and Enolate Anions under Hal B* I *and Hal B* II *Conditions*.—It has been suggested by Rappe [8] that experimental evidence indicates not only the occurrence of two base catalysed halogenation reactions (Hal B I and Hal B II) but also the absence of competitive halogenation of an intermediate enol under these conditions. The latter findings are based upon interpretation of n.m.r. experiments from which it has been concluded that neither the rate nor orientation of deuteriation of butan-2-one in D_2O–base solution is influenced by the addition of bromine.[8] Such a suggestion implies that conditions prevail which render unreactive the 1- and 3-enol forms of butan-2-one with a solution of bromine in acetate buffers.

Our scrutiny of the n.m.r. results suggests that the likely integration errors do not justify the conclusions drawn and that K_D values have even been estimated for conditions under which deuterium exchange would be negligible (*e.g.* deuteriation experiments with $t_{\frac{1}{2}}$ *ca.* 2000 h have been followed for only 12 h).

Several of the reaction mixtures have been found to be heterogeneous. Results obtained under Hal B II conditions were, in any case, consistent with the traditional mechanism which requires that in the presence of halogen there will be no deuteriation (except under conditions where the halogenation reaction is of first order dependence on a *very low* concentration of halogen [23,24]).

(D) *Inequality of* K_{Hal} *and* K_D *Values*.—A further feature, attributed to both Hal B I and Hal B II mechanisms which must be rationalized is the claimed inequality of K_{Hal} and K_D values. Rappe's results are clearly inconsistent with the enol mechanism which requires equality of K_{Hal} and K_D over the pH range 5·5—14. In particular, since no α-halogenopropionic acid could be detected among the products of halogenation of butan-2-one at pH > 12, it has been claimed [7] that $K_{Hal} = 0$ (*i.e.* no halogenation in the 3-position of butan-2-one) whereas K_D has been shown [4,6,19] to be 0·6—0·7. The almost complete absence of α-halogenopropionic acid under these conditions was also previously found by Cullis and Hashmi.[22]

We suspected that hydroxide-induced nucleophilic displacement of bromide ion from either of the initially formed monobromo-ketones might compete with their multihalogenation and subsequent fragmentation by the haloform reaction. For each bromo-ketone (1- and 3-bromobutan-2-one) we therefore determined the product of reaction with hydroxide ion and compared the rate of reaction with that which occurs in the presence of bromine also. Reaction of 1- and 3-bromo-ketones with aqueous sodium hydroxide gave only 1- and 3-hydroxyketones respectively. The results of the rate measurements are in Table 5.

The rate of hydrolysis ($k_{OH^-} = 31{\cdot}6$ l mol^{-1} s^{-1}) of 1-bromobutan-2-one is of the same order of magnitude as that determined for its bromination ($k = 118$ l mol^{-1} s^{-1}) in aqueous hydroxide. The latter rate constant must then actually represent the sum of the rate constants for the competing reactions ($k = k_{OH^-} + k_{Br_2}$) and therefore $k_{Br_2} = 86{\cdot}4$ l mol^{-1} s^{-1}. The much slower subsequent bromination of the minor product has been monitored and both the bromination rate constant and amount of bromine consumed (relative to the initial fast bromination) are consistent with the competitive formation of 1-hydroxybutan-2-one (27%) during the initial fast step.

The rate of bromination of 1-hydroxybutan-2-one was measured independently for comparison. The rate constants for bromination of 1-bromo- and 1-hydroxybutan-2-one respectively are 916 and 1·02 times faster than that for butan-2-one. The former ratio is comparable with an 800-fold increase in the catalytic rate constant for hydroxide-induced deprotonation brought about by monochlorination of acetone [23] and accounts for the exclusive formation [25] of bromoform and propionic acid upon bromination of 1-bromobutan-2-one in aqueous NaOBr.

It was, however, found that the *apparent* uptake of bromine by 3-bromobutan-2-one in aqueous NaOBr is very slow in comparison with the rate of displacement of bromide ion and it is clear that the observed halogenation is that of 3-hydroxybutan-2-one which is formed in an initial fast step. It was noted that 13·3% of the overall halogen consumption also occurred rapidly during this

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[22] C. F. Cullis and M. H. Hashmi, *J. Chem. Soc.* (*a*) 1956, 2512; (*b*) 1957, 1548; (*c*) 1957, 3080.

[23] R. P. Bell and O. M. Lidwell, *Proc. Roy. Soc.*, 1940 (*A*), **176**, 88.

[24] K. Yates and W. V. Wright, *Canad. J. Chem.*, 1963, **41**, 2882.

[25] C. G. Swain and R. P. Dunlap, *J. Amer. Chem. Soc.*, 1972, **94**, 7204.

initial period and by analogy with the discussion above it can be argued that 3-bromobutan-2-one initially undergoes competitive hydrolysis (86·7%) and bromination (13·3%) under these conditions. Thus the bromination rate constant must equal *ca.* $k_{\mathrm{OH^-}} \times 13\cdot3/86\cdot7 = 19\cdot5$ l mol^{-1} s^{-1}. An approximate estimate of the rate of the fast step gave $t_{\frac{1}{2}} = 1\cdot3 \pm 0\cdot2$ s, $k_{\mathrm{exp}} = 5\cdot3 \pm 0\cdot8$ s^{-1}, and $k = (k_{\mathrm{OH^-}} + k_{\mathrm{Br_2}}) = 133 \pm 20$ l mol^{-1} s^{-1} which is consistent with this interpretation.

TABLE 5

Reactions † of 1- and 3-substituted butan-2-ones in aqueous alkali at 25 °C

Substituent	[Ketone]	[OH$^-$]	[Bromine]	$k_{\mathrm{exp}} \times 10^3$/s^{-1}		$k \times 10^2$/l mole^{-1} s^{-1}
1-Bromo	<0·001	0·005 [a]	0·0029	590		11,800
1-Hydroxy	0·0025	0·08	0·01	7·70		9·6
3-Bromo	0·0025	0·08	0·01	13·6		17·9
3-Hydroxy	0·0025	0·08	0·01	14·9		
1-Bromo	0·0025	$5\cdot0 \times 10^{-4}$		76·5		3,060 [f]
	0·005 [b]	$9\cdot2 \times 10^{-5}$		3·00		3,260 [g]
	0·005 [c]	$6\cdot9 \times 10^{-5}$		2·17		3,150 [g]
					Mean	3,160 [h]
3-Bromo	0·005 [d]	$1\cdot81 \times 10^{-5}$		2·39		13,200 [g]
	0·005 [e]	$1\cdot03 \times 10^{-5}$		1·25		12,200 [g]
					Mean	12,700 [h]
None	0·0025	0·1	0·0105	9·43 [i]		9·43

† Reactions with bromine were followed colorimetrically at 350 nm. Those with hydroxide ion alone were followed conductimetrically or by pH-stat. All concentrations are in mol dm^{-3}. In each case the hydroxide concentration has been estimated with allowance for hydrolysis of bromine according to the equation $Br_2 + 2OH^- \rightleftharpoons Br^- + OBr^- + H_2O$.

[a] An average value. [b] pH = 9·95, μ *ca.* $1\cdot5 \times 10^{-3}$, $\gamma = 0\cdot97$. [c] pH = 9·82, μ *ca.* $2\cdot5 \times 10^{-3}$, $\gamma = 0\cdot95$. [d] pH = 9·25, μ *ca.* 8×10^{-3}, $\gamma = 0\cdot92$. [e] pH = 9·00, μ *ca.* $1\cdot5 \times 10^{-3}$, $\gamma = 0\cdot97$. [f] Hydroxide consumption was monitored conductimetrically thus $k = k_{\mathrm{exp}}$/[ketone]. [g] Bromo-ketone hydrolysis was monitored by pH-stat titration thus $k = k_{\mathrm{exp}}[OH^-]$. [h] Second-order rate constant for hydroxide promoted bromo-ketone hydrolysis. [i] Reference 22*c*.

Since the rate of bromination is much slower than the rate of displacement of bromide ion, α-halogenated propionic acids are not the expected products of halogenative degradation of 3-bromobutan-2-one in aqueous hydroxide. The ultimate products of reaction under these conditions will be those derived from 3-hydroxybutan-2-one which we have found to brominate at a rate comparable with that of butan-2-one. Thus it must be concluded that the failure to detect monohalogenopropionic acids among the products of halogenation of butan-2-one at high pH is ***not*** indicative of absence of initial monohalogenation at the 3-position ($\kappa_{\mathrm{Hal}} = 0$).

These results complement a recent communication [25] in which Swain and Dunlap report the products of reaction of butan-2-one and of its 1- and 3-bromo-derivatives with aqueous NaOBr. The product study is also consistent with the traditional mechanism for halogenation of ketones and it is not surprising, in view of our kinetic results, that no appreciable deuterium incorporation could be detected [25] in unchanged 3-bromobutan-2-one under conditions where it had undergone 57% conversion to 3-hydroxybutan-2-one in alkaline D_2O.

A detailed criticism of what we believe to be further unreliable estimates [3] of relative rates of halogenation at the 3- and 1-positions of butan-2-one over the pH range 5·5—7 would demand lengthy discussion of many individual experiments and should be left to private communication. In essence, all reported attempts [3] to determine κ_{Hal} within this pH range have been complicated by heterogeneity of reaction mixtures, unjustified assumptions regarding the source of polyhalogeno-products, and use of work-up conditions conducive to radical [9] halogenation reactions of unchanged halogen.

Conclusion.—There is no reliable evidence to suggest that the base catalysed halogenation of butan-2-one or of similar ketones proceeds other than by a traditional enolization mechanism. This view is apparently shared by Swain and Dunlap [25] and Warkentin *et al.*[26]

EXPERIMENTAL

Rates of Halogenation of Butan-2-one in Acetate Buffers.—According to the accepted mechanism for base catalysed halogenation of ketones we may write $SH + B \underset{k_b}{\overset{k_f}{\rightleftharpoons}} S^- + BH^+$ and $S^- + X_2 \xrightarrow{k_2} SX + X^-$ where SH refers to the ketone, S^- the enolate ion (which may be in rapid equilibrium with the enol), and X_2 the halogen. Application of the steady state treatment to S^- gives equation (1) where

$$d[SH]/dt = \{(\Sigma k_f[B])k_2[X_2][SH]\}/(\Sigma k_b[BH^+] + k_2[X_2]) = -k_e[SH] \quad (1)$$

$k_e = \{(\Sigma k_f[B])k_2[X_2]\}/(\Sigma k_b[BH^+] + k_2[X_2])$. Equation (1) predicts that when $[X_2]$ is sufficiently high then $k_2[X_2] > k_b[BH^+]$ which gives equation (2), *i.e.* k_e is independent of halogen concentration and of the halogen used.

$$k_e = \Sigma k_f[B] \quad (2)$$

(a) *The order and rate of reaction with respect to halogen.* Reactions of butan-2-one (1·0M) with iodine ($[I_2]_{\mathrm{init}}$ *ca.* 1×10^{-4}M) in acetate buffer solutions of pH (i) 4·50, (ii) 6·02, and (iii) 6·80 containing potassium iodide (0·10M) were followed by spectrophotometric observation of the decrease in absorption at 353 nm. In each case the rate of iodination at 25° was independent of iodine concentration down to $<5 \times 10^{-6}$M which corresponds to a 20-fold concentration decrease. Reaction of butan-2-one (1·0M) with bromine ($[Br_2]_{\mathrm{init}}$ *ca.* 4×10^{-3}M) in acetate buffer ($[OAc^-]$ = 1·0M) of pH = 6·80 containing potassium bromide (0·10M) was followed by spectrophotometric observation of the decrease in absorption at 398 nm.

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[26] J. W. Thorpe and J. Warkentin, *Canad. J. Chem.*, 1972, **50**, 3229; R. A. Cox and J. Warkentin, *ibid.*, p. 3233.

If only one mole of halogen reacts with one mole of ketone we have $d[X_2]/dt = d[SH]/dt = -k_e[SH]$ where k_e, the experimentally observed first-order rate constant, is as defined in equation (2). The results obtained were as follows: iodination, $k_e = 1{\cdot}43\ (\pm 0{\cdot}04) \times 10^{-7}\ s^{-1}$; and bromination, $k_e = 1{\cdot}53\ (\pm 0{\cdot}06) \times 10^{-7}\ s^{-1}$.

In order to check whether any different and perhaps faster process occurred at higher bromine concentrations, runs were performed with bromine concentrations up to 0·1M. As the reactions were very slow it was difficult to prevent some loss of bromine by evaporation even in well stoppered cells, but apart from the expected increase in rate brought about by multiple halogenation, no significant increase was observed.

(b) *Comparison of rates of iodination and of deuterium exchange*. For α-deuterium exchange we may write $SH + B \xrightarrow{k_f} S^- + BH^+$ and $S^- + BD^+ \longrightarrow SD + B$. Steady state treatment of S^- gives equation (3) where k_e is

$$\begin{aligned} -d[SH]/dt &= (\Sigma k_f[B])[SH] \\ &= k_e[SH] \qquad (3) \end{aligned}$$

as previously defined, *i.e.* the rate of deuterium exchange should equal that of halogenation.

Reactions were performed at 33·4 °C in AcO^-–HOAc buffers in D_2O (' pH ' = 6·8, *i.e.* ≡ pD = 7·2). The solution contained 0·9M-acetate anion (0·4 g in 5·5 ml) and 0·3M-butan-2-one (0·4 ml in 5·5 ml). The rate of deuterium exchange was determined from the rate of increase of the HDO peak of the n.m.r. spectrum relative to that of AcO^- which was used as an internal reference for integration. The reaction was performed in a sealed tube and spectra were recorded during a 500 h period. A more accurate result might have been obtained had the reaction been followed for a much longer time; however this was precluded by the gradual appearance in the n.m.r. spectra of slight amounts of impurities (probably condensation products) after which time no further reading was recorded.

Results of Rappe and of Warkentin and Tee [27] show that within experimental error, in acetate buffers, the 1- and 3-positions of butan-2-one are equally reactive. Thus, neglecting secondary isotope effects, it can be readily shown that if k_{obs} is the experimentally observed first-order rate constant for the increase in HDO concentration $k_e = 5\ k_{obs}$. The results obtained are in Table 3.

Homogeneous Reaction of Butan-2-one with Halogen in Aqueous DMF containing Sodium Acetate.—To 50% v/v aqueous DMF (250 ml) containing 10 g sodium acetate and 2 g bromine per 100 ml was added butan-2-one (25 ml) at 25 °C. Aliquot parts (10 ml) were removed at once and kept at 25 °C in glass tubes (11 ml capacity) which were tightly sealed with polypropylene stoppers. At suitable time intervals aliquot portions were added to a fresh solution of potassium iodide (20 ml, 1·0M) and hydrochloric acid (5 ml, 2·0M). Free iodine was titrated with sodium thiosulphate in the usual way. A concurrent blank reaction was performed, to which no ketone was added. The results are compared in Table 1.

Results for analogous experiments in which iodine (3·18 g in 100 ml) replaced bromine are in Table 2.

Preparation of 1- *and* 3-*Bromobutan*-2-*ones*.—3-Bromo-2-butanone, n_D^{20} 1·4575, b.p. 85° at 118 mmHg, and 1-bromo-2-butanone, n_D^{20} 1·4676, b.p. 104° at 118 mmHg, were prepared by the procedure of Catch *et al.*[28]

Reactions of 3-*Bromobutan*-2-*one with Aqueous Sodium Hydroxide*.—The bromo-ketone (1 g, 0·0066 mole) was added to a stirred solution of 2·0M-sodium hydroxide (20 ml) at room temperature. During 1 min an exothermic reaction occurred and a homogeneous solution was obtained. After 5 min the solution was diluted with an equal volume of 2N-HCl and made strongly acidic by dropwise addition of conc. HCl. Extraction was with methylene chloride and the extract was dried ($MgSO_4$) and evaporated to give a pale orange mobile liquid which did not smell of butyric acid (a possible product of Favorskii reaction). The crude product (0·59 g) which had $\nu_{max.}$ 3420 (OH) and 1700 cm^{-1} (C=O), n_D^{20} 1·4168, τ 8·8 (3H, d, *J* 7 Hz, Me), 5·95 (3H, s, MeCO), and 5·9 (1H, q, *J* 7 Hz, CHCO) was identified as 3-hydroxybutan-2-one.

Reaction of 1-*Bromobutan*-2-*one with Aqueous Sodium Hydroxide*.—Reaction of 1-bromobutan-2-one was performed as for the 3-bromo-isomer. The crude product (0·58 g) which had $\nu_{max.}$ 3420 (OH) and 1700 cm^{-1} (C=O), n_D^{20} 1·4271, τ 8·95 (3H, t, *J* 7 Hz, Me), 7·6 (2H, q, *J* 7 Hz, CH_2CO), and 5·8 (2H, s, CH_2CO) was identified as 1-hydroxybutan-2-one.

Kinetics of Reactions of 1- *and* 3-*Bromobutan*-2-*one with Aqueous Hydroxide*.—Reactions of the bromobutanones were initiated using a Durrum–Gibson stop flow apparatus fitted with a temperature-jump cell. The syringes contained bromo-ketone (0·005M) and sodium hydroxide (0·001M) respectively. Reactions were followed by monitoring change in conductivity between the plates of the temperature-jump compartment.[29] A Radiometer automatic titration assembly was also used for an alternative pH-stat procedure. Results are in Table 4.

Kinetics of Reaction of 1- *and* 3-*Substituted Butan*-2-*ones with Bromine in Aqueous Hydroxide Solution*.—Reactions of 1- and 3-bromo- and of 1- and 3-hydroxy-butan-2-one with bromine in aqueous hydroxide were initiated by stop-flow. The syringes contained ketone (0·005M) and a solution of bromine (0·024M) in sodium hydroxide (0·1M). Reactions were followed by colorimetric observation of the change in absorbance at 398 nm. The results are in Table 4. The solution of bromine in aqueous sodium hydroxide was shown, by repetitive scan of its absorption spectrum, to be stable during one hour. Stop-flow results were consistent with those obtained using a Gilford 2400 spectrometer to monitor (at 350 nm) consumption of BrO^- in a solution which initially contained hydroxide (0·01M), bromine (0·003M), and bromo-ketone (<0·001M).

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