Anomalous Rate of Bromination of a Ketone: First-order Dependence on Bromine Concentration

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Summary The rate of acid-catalysed bromination of 2,4,6-trimethylacetophenone in 50% aqueous acetic acid is first-order in bromine, in contrast with acetophenone and other reported ketones at comparable concentrations.

Reactions of halogens with a variety of ketones have been studied[1] under acidic and basic conditions; the rates of these reactions are independent of concentration and nature of halogen except, predictably, at very low halogen concentrations.[2,3] The rate-determining step is established[4] as the acid- or base-catalysed conversion of ketone into enol (or enolate) followed by a fast halogenation step,

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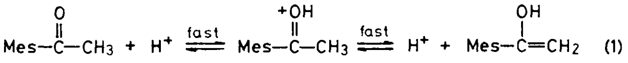
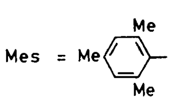
according to the original classical Lapworth[1] mechanism. We report for the first time the bromination of a ketone in which the rate is dependent on the concentration of bromine at relatively high concentrations.

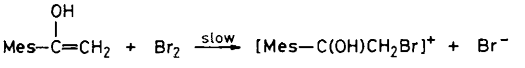
During previous studies[5] with hindered ketones, unexpectedly rapid reactions with bromine in CCl_4 were qualitatively noted and we have tried to determine the cause of this anomalous behaviour. 2,4,6-Trimethylacetophenone (**1**) was selected as a representative hindered ketone for the present study and the concentrations of bromine were followed spectrophotometrically. Surprisingly, the reactions were found to have a pseudo-first-order dependence (ketone in excess) on bromine concentration in several solvent systems, CCl_4, $MeCO_3H$, and $MeCO_2H$. An induction period (resulting from formation of catalytic hydrogen bromide) was eliminated by strong acids, hydrobromic and perchloric acid being the most effective. Under these conditions at constant ionic strength (sodium perchlorate) the overall reaction was second-order in bromine and ketone. In a representative case {[(**1**)] = 0·05 M, [HBr] = 0·1 M, [$NaClO_4$] = 0·4 M, 50% aq. $MeCO_2H$, 25 °C} for bromine concentrations of 1·17—10·0 × 10^3 M the observed k values were 1·8 × $10^3\ s^{-1}$. The effects of bromide (as added hydrogen and sodium bromide), chloride, acetate, and perchloric acid on the rate were studied, the pseudo-first-order dependence on bromine holding in all of these cases. The monobrominated ketone was isolated from a preparative-scale experiment and identified.[6] For comparison with the non-hindered analogue of (**1**), the bromination of acetophenone under the same conditions was investigated for [Br_2] = 1·49—3·80 × 10^3 M and was zero-order in bromine [k(ave.) = 1·23 × 10^7 mol $l^{-1}\ s^{-1}$], (**1**) showing a much faster rate of uptake of bromine than acetophenone.



$$\mathrm{Mes{-}\overset{O}{\overset{\|}{C}}{-}CH_3} + \mathrm{H^+} \xrightleftharpoons{\text{fast}} \mathrm{Mes{-}\overset{^+OH}{\overset{\|}{C}}{-}CH_3} \xrightleftharpoons{\text{fast}} \mathrm{H^+} + \mathrm{Mes{-}\overset{OH}{\overset{|}{C}}{=}CH_2} \qquad (1)$$

(1)



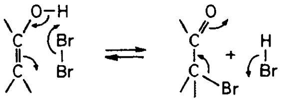


$$\mathrm{Mes{-}\overset{OH}{\overset{|}{C}}{=}CH_2} + \mathrm{Br_2} \xrightarrow{\text{slow}} \mathrm{[Mes{-}C(OH)CH_2Br]^+} + \mathrm{Br^-} \qquad (2)$$

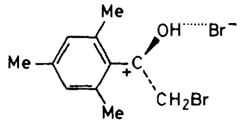
(2)

$$\mathrm{[Mes(COH)CH_2Br]^+} + \mathrm{Br^-} \longrightarrow \mathrm{HBr} + \mathrm{MesCOCH_2Br} \qquad (3)$$

(2)



(4)



(3)

The first step of the reaction is postulated to be a fast conversion of the keto into the enol form following the initial protonation of the carbonyl oxygen, equation (1). The rate-determining step, equation (2), may be reaction of molecular bromine with the enol to form an intermediate mono-brominated species (**2**). Subsequent nucleophilic attack of bromide ion on (**2**) to give the mono-brominated ketone and hydrogen bromide, equation (3), is then postulated to be a fast step. The nature of the mono-brominated intermediate and of the transition state leading to it are important.

Apparently, the first mechanism proposed for reaction of bromine with an enol is that of Newman,[7] equation (4), who studied the reverse reduction reaction of α-bromoketones with hydrogen bromide. Yates and Wright[3] suggested bromonium[8] and carbonium type intermediates in the reaction of bromine at low concentrations with ketones. In the present case models indicate that the formation of a bromonium ion would be sterically inhibited because of non-bonded interactions, whereas a carbonium ion-type intermediate (**3**) can adopt a relatively low-energy conformation with little non-bonded interaction. However, conclusive decision between the latter and Newman's cyclic mechanism[8] cannot be made at present. An interesting question is why the rate of enolization should be so rapid in the present case.

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‡ The brominating species was determined to be predominantly molecular bromine (*ca.* 99%) from the dissociation constants of the Br_3^-/Br_2, Br^- equilibrium.

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[6] C. O. Guss, *J. Am. Chem. Soc.*, 1953, **75**, 3177 and W. G. Dauben and J. B. Rogan, *ibid.*, 1956, **78**, 4135 prepared the α-brominated monoketone, m.p. 55—56 °C by reaction of bromine with (**1**) in acetic acid. The compound was previously prepared by W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, 1951, **21**, 455, by a Friedel–Crafts reaction of bromoacetyl chloride with mesitylene. Our n.m.r. and i.r. spectra confirm the structure and showed that this was the only product formed.

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