Inter- and Intra-molecular Catalysis in the Iodination of *o*-Hydroxyacetophenone

By **Ronald P. Bell,*** **Derek W. Earls,** and **Bakir A. Timimi,** University of Stirling, Stirling, Scotland

The kinetics of the iodination of *o*-hydroxyacetophenone have been investigated at 25° in aqueous buffer solutions prepared from 1,1,1,3,3,3-hexafluoro-2-methylpropan-2-ol or from boric acid. The kinetic order with respect to iodine is between zero and unity, and the rates of ionisation or enolisation of the ketone can be derived by extrapolating to infinite concentration of iodine. These rates increase with increasing concentration of the basic constituent of the buffer, but the rate of intramolecular ionisation or enolisation of *o*-hydroxyacetophenone can be obtained by extrapolating to zero buffer concentration. In interpreting these results kinetic measurements were also made on the cyclisation of ω-chloro- and ω-bromo-*o*-hydroxyacetophenone to give coumaran-3-one, the iodination of ω-chloro-*o*-hydroxyacetophenone and of coumaran-3-one, and the condensation of *p*-hydroxyacetophenone with 1-bromobutan-2-one. The p*K* values of *o*-hydroxyacetophenone and of 1,1,1,3,3,3-hexafluoro-2-methyl-2-propanol have also been measured.

The rates of intramolecular processes are compared with those of similar intermolecular reactions. The intramolecular cyclisation of the anion of ω-bromo-*o*-hydroxyacetophenone is much more efficient than the analogous intramolecular proton transfer in the anion of *o*-hydroxyacetophenone. Explanations are suggested for the fact that intramolecular reactions involving nucleophilic displacements are in general much more effective than those involving proton transfers.

THIS paper continues earlier investigations [1-3] of the abstraction of protons bound to carbon by suitably situated basic groups in the same molecule. Such a process is likely to occur in the anion of *o*-hydroxyacetophenone, where the strongly basic phenoxide group is well placed to remove a proton from the methyl group. This system resembles the previously investigated [2] anion of *o*-carboxyacetophenone but has the advantage that the undissociated molecule is not in equilibrium with appreciable amounts of a cyclic tautomer. As in the earlier investigations the rate of intramolecular ionisation (or enolisation) was deduced from the rate of reaction with iodine, which acts as a scavenger for the anion formed. The reaction is not quite of zero order with respect to halogen, and extrapolation of the rate to infinite concentration of halogen is necessary to obtain the velocity of the proton-transfer process. Self-buffered solutions giving convenient reaction velocities were found to be insufficiently resistant to changes of pH, and all measurements were therefore carried out with added buffer systems. Extrapolation to zero concentration of the added buffer gives the rate of the intramolecular process, and the variation of rate with buffer concentration gives information about catalysis by the basic component of the buffer, which is of interest for comparison with the intramolecular catalysis.

EXPERIMENTAL

o-Hydroxyacetophenone giving a single g.l.c. peak was obtained by partially freezing a commercial sample. A commercial sample of 1,1,1,3,3,3-hexafluoro-2-methylpropan-2-ol gave the correct ^{1}H n.m.r. spectrum, and was >98% pure by g.l.c. Other materials were of AnalaR grade.

The u.v. spectra of partly ionised *o*-hydroxyacetophenone solutions show four well-defined isosbestic points at 242, 262, 284, and 332 nm. At 278 and 353 nm the molar absorption coefficients (ε) of the undissociated compound are $4{\cdot}65 \times 10^3$ and $9{\cdot}30 \times 10^3$ mol^{-1} dm^2, respectively; the corresponding values for the anion are $8{\cdot}55 \times 10^3$ and $4{\cdot}79 \times 10^4$. (Each value represents the mean of four

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[1] R. P. Bell and M. A. D. Fluendy, *Trans. Faraday Soc.*, 1963, **59**, 1623.

[2] R. P. Bell, B. G. Cox, and J. B. Henshall, *J.C.S. Perkin II*, 1972, 1232.

[3] R. P. Bell and B. A. Timimi, *J.C.S. Perkin II*, 1973, 1518.

determinations.) In determining the p*K* of *o*-hydroxyacetophenone partially neutralised solutions were prepared, their pH values were measured (glass electrode), and the proportions of the acidic and basic forms were determined from the measured absorbance at 353 nm, by using the foregoing molar absorption coefficients. The mean of determinations at two concentrations at each of nine pH values between 8·74 and 9·47 was 10·27 ± 0·01 at 25 °C. The ionic strength varied between 0·11 and 0·14M, and the correction for activity coefficients was calculated from the Davies equation (1).

$$-\lg \gamma_{\pm} = [0{\cdot}5\, I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}})] - 0{\cdot}2\, I \qquad (1)$$

In another set of experiments the p*K* value was determined by combining the measured pH value with the stoicheiometric buffer ratio, corrected for hydrolysis. Five experiments at pH values between 9·14 and 9·88 gave a mean p*K* value of 10·21 ± 0·02 after application of activity coefficients as before. This is probably less reliable than the preceding result, which employed buffer ratios determined optically.

Values obtained previously for the p*K* of this compound are 10·06 at 20 °C in 0·10—0·15M-KCl,[4] and 10·82 at 25 °C in 3·0M-$NaClO_4$.[5]

1,1,1,3,3,3-Hexafluoro-2-methylpropan-2-ol (subsequently referred to as 'fluoro-alcohol') and its anion do not absorb at any convenient wavelength, and no p*K* values have been reported. Values were obtained by the method described in the last paragraph. The mean of determinations at two concentrations at each of 11 pH values between 8·74 and 9·74 was 9·80 ± 0·01.

The rate of iodination was determined by following the decrease of absorption by tri-iodide ion at 278 nm, since at the more usual wavelength of 353 nm there is strong absorption by the anion of *o*-hydroxyacetophenone. Measurements were made in 5 mm cells with a Gilford 2400 recording spectrophotometer, the cell compartment of which was controlled at 25 ± 0·05 °C. It was not found possible to prepare self-buffered solutions of *o*-hydroxyacetophenone which were sufficiently resistant to pH changes and at the same time gave convenient rates of iodination, and some difficulty was experienced in finding suitable buffer systems: thus buffers prepared from *p*-chlorophenol, *m*- and *p*-hydroxyacetophenone, and 4-chloro-2,6-dimethylphenol all reacted too rapidly with iodine, presumably by nuclear halogenation. No such difficulty was experienced with buffer solutions prepared from borate or fluoro-alcohol, which were used in all kinetic measurements. Reaction mixtures were prepared by mixing buffer solutions and solutions of *o*-hydroxyacetophenone, brought to the same pH: each solution contained potassium iodide (0·1 mol dm^{-3}). The concentrations of the acidic and basic forms of *o*-hydroxyacetophenone in the mixed solution were determined from absorbance measurements at 353 nm, and the reaction was then initiated by adding tri-iodide solution from a micro-syringe. The initial stoicheiometric concentration of iodine in the reaction mixture was in the range 5×10^{-5} to 10^{-4}M. Because of slight reversible hydrolysis of iodine its apparent molar absorption coefficient varied slightly with pH in the range investigated, being $3{\cdot}05 \times 10^{5}$ at pH 9·5 and $3{\cdot}17 \times 10^{5}$ $mol^{-1}\ dm^{2}$ at pH 8·7; this was taken into account in calculating the rate of iodination.

The apparent order with respect to iodine was throughout between zero and unity: hence the plots of absorbance against time were not strictly linear, though their average slope over a limited concentration range could be measured accurately. This behaviour arises because neither the ionisation (or enolisation) step nor the halogenation step is fully rate-determining. For our present purpose the rate of the former is required, which in principle requires an extrapolation of the observed rate v to infinite concentration of halogen. It will be shown in the following section that the correct method of extrapolation is to plot v^{-1} against $[I_3^-]^{-1}$, which should give a straight line with an intercept v_∞^{-1}, where v_∞ is the required rate of ionisation [*cf.* equation (4)]. Typical plots of this kind are shown in Figure 1, where the values of v are taken partly from sections of a given kinetic experiment, and partly from separate experiments with different initial concentrations of iodine. An equivalent and sometimes more convenient method of extrapolation is to plot v against $v/[I_3^-]$ [equation (5)], giving a straight line with intercept v_∞, and examples of this type of plot are given in Figure 2. Identical values of v_∞ were obtained by both methods of extrapolation, one or both of which were used in obtaining all the values of v_∞ discussed subsequently.

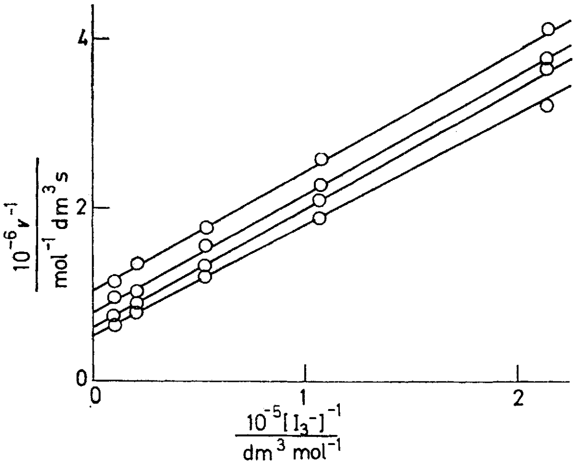

FIGURE 1 Extrapolation plots according to equation (4); [HSH] = $1{\cdot}02 \times 10^{-3}$ mol dm^{-3}, $[SH^-]$ = $1{\cdot}56 \times 10^{-4}$ mol dm^{-3}, pH = 9·34, $[B^-]$ = 0·012, 0·018, 0·024, and 0·030 mol dm^{-3}

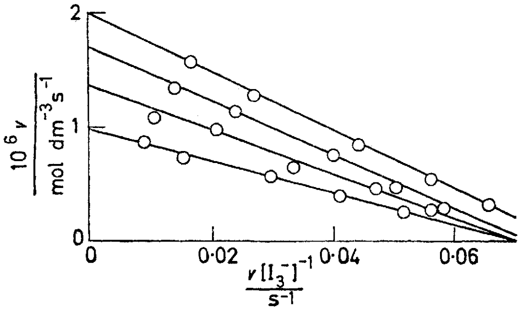

FIGURE 2 Extrapolation plots according to equation (5); same solutions as for Figure 1

RESULTS AND DISCUSSION

The abbreviations which will be used for the various forms of *o*-hydroxyacetophenone are shown in Scheme 1.

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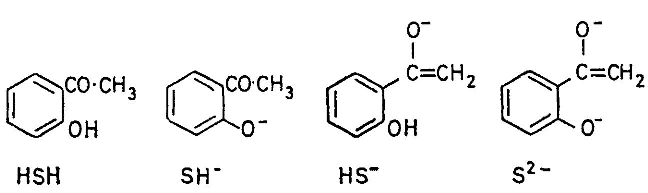
[4] A. Agren, *Acta Chem. Scand.*, 1955, **9**, 49.

[5] D. D. Perrin, *Nature*, 1958, **182**, 741.



SCHEME 1

The kinetic scheme for reaction with tri-iodide in a buffer solution BH + B⁻ is then:

$$HSH \rightleftharpoons SH^- + H^+ \quad \text{equilibrium constant } K_s$$
$$BH \rightleftharpoons B^- + H^+ \quad \text{equilibrium constant } K_{BH}$$
$$SH^- \overset{k_1}{\rightleftharpoons} HS^- \quad \text{intramolecular}$$
$$\left.\begin{array}{l} HSH + B^- \overset{k_2}{\rightleftharpoons} HS^- + BH \\ SH^- + B^- \overset{k_3}{\rightleftharpoons} S^{2-} + BH \end{array}\right\} \text{intermolecular}$$
$$HS^- + I_3^- \overset{k_4}{\rightleftharpoons} \text{products}$$
$$S^{2-} + I_3^- \overset{k_5}{\rightleftharpoons} \text{products}$$

We shall assume that the equilibrium $HS^- \rightleftharpoons S^{2-} + H^+$ is established instantaneously, before halogenation takes place, so that we have always $[HS^-]/[S^{2-}] = [HS^-]_e/[S^{2-}]_e = \alpha/(1 - \alpha)$, where α depends upon the pH. If v is the rate of decrease of $[I_3^-]$, a steady state treatment of the above scheme together with the principle of detailed balancing yields equation (2), in which v_∞ and K_e^* are as defined by equation (3).

$$v^{-1} = v_\infty^{-1} + \{[I_3^-]K_e^*[SH^-][\alpha k_4 + (1 - \alpha)k_5]\}^{-1} \quad (2)$$

$$v_\infty = k_1[SH^-] + (k_2[HSH] + k_3[SH^-])[B^-]$$
$$K_e^* = ([HS^-]_e + [S^{2-}]_e)/[SH^-]_e = [HS^-]_e/\alpha[SH^-]_e \quad (3)$$

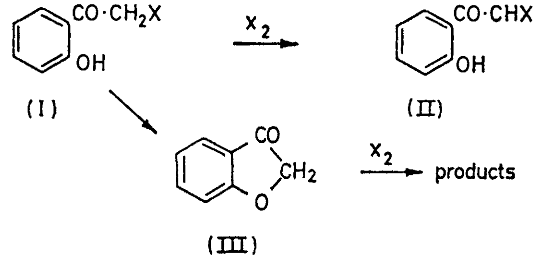
Although the pK for the dissociation $HS^- \rightleftharpoons S^{2-} + H^+$ is not known, it is certainly greater than 11, so that under our experimental conditions of pH between 8·7 and 9·5 we can write $\alpha \doteq 1$: further, since k_5 is unlikely to be considerably greater than k_4 (because of the greater electrostatic repulsion involved) we have also $\alpha k_4 + (1 - \alpha)k_5 \simeq k_4$. Equation (2) now becomes equation (4), where v_∞ is still given by (3), and $K_e = [HS^-]_e/[SH^-]_e$. An alternative form of (4) is equation (5), and

$$v^{-1} = v_\infty^{-1} + (K_e k_4[SH^-][I_3^-])^{-1} \quad (4)$$

$$v = v_\infty - (v/[I_3^-])v_\infty(K_e k_4[SH^-])^{-1} \quad (5)$$

equations (4) and (5) together justify the extrapolation methods described in the last section for obtaining v_∞. Moreover, the dependence of the slopes of these extrapolation plots upon experimental conditions accords with these equations. Thus the slopes of the plots of v^{-1} against $[I_3^-]^{-1}$ are independent of $[B^-]$ (see Figure 1). They are also independent of pH, but inversely proportional to $[SH^-]$, as shown by the plot in Figure 3, which includes measurements at nine different pH values between 8·7 and 9·5.

The foregoing analysis assumes that only one molecule of iodine reacts with each molecule of *o*-hydroxyacetophenone, which may be incorrect. In the analogous reaction of *o*-carboxyacetophenone [2] the assumption is justified because there is good evidence [6] that the monoiodo-derivative cyclises very rapidly to give a lactone, which offers no possibility of intramolecular catalysis in its further halogenation. In the present instance the probable sequence of reactions is as shown in Scheme 2, where X is Cl, Br, or I. [Although the reactions of (I) probably take place through its anion, it is written in the acidic form since its pK is unknown.] Under basic conditions the rate of halogenation (ionisation) of (I) is likely to be about 10^3 times greater than that of *o*-hydroxyacetophenone, both for intermolecular and intramolecular catalysis,† and since in our experiments the ratio $[HSH] : [I_3^-]$ was initially between 10 and 200, in the absence of the cyclisation reaction (I) ⟶ (III) the consumption of close to two moles of iodine per mole of HSH is to be anticipated. The substance (I; X = I) does not appear to have been isolated, but the analogues with X = Br or Cl and also (III) (coumaran-3-one) were prepared by published methods.[8,9]



SCHEME 2

A fairly extensive kinetic study of these three compounds was carried out, but since the results are of limited relevance in the present context only a summary will be given here. The cyclisation of (I; X = Cl or Br) was followed by the change in absorbance at 335 nm. The pH range was 5·8—8·0 [phosphate or tris(hydroxyethyl)aminomethane buffers] for X = Cl, and 4·6—6·6 (acetate or phosphate buffers) for X = Br. The reactions followed a first-order course and the first-order rate constants were independent of buffer concentration and proportional to $[OH^-]$; $k = 7{\cdot}5 \times 10^3\ [OH^-]\ s^{-1}$ and $7{\cdot}5 \times 10^4\ [OH^-]\ s^{-1}$ for X = Cl and X = Br, respectively.

The form of this rate law indicates a first-order elimination reaction of the anion, and if it is assumed that (I) has pK *ca.* 10·0 (by analogy with *o*-hydroxyacetophenone), this corresponds to first-order rate constants of about 0·7 and 7 s^{-1} for X = Cl and X = Br, respectively.

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† This estimate is based on a comparison of the rates of base-catalysed halogenation of $CH_3CO{\cdot}CH_3$ and $CH_3CO{\cdot}CH_2X$.[7]

[6] E. T. Harper and M. L. Bender, *J. Amer. Chem. Soc.*, 1965, **87**, 5625.

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

[8] R. L. Shriner and M. Witte, *J. Amer. Chem. Soc.*, 1939, **61**, 2328.

[9] K. Fries and W. Pfaffendorf, *Ber.*, 1910, **43**, 214.

These intramolecular processes are themselves of interest, and a comparison was made with the rate of the analogous intermolecular reaction:

$$p\text{-MeCO}\cdot\text{C}_6\text{H}_4\cdot\text{O}^- + \text{CH}_2\text{Br}\cdot\text{COEt} \longrightarrow p\text{-MeCO}\cdot\text{C}_6\text{H}_4\cdot\text{O}\cdot\text{CH}_2\cdot\text{COEt}$$

1-Bromobutan-2-one was prepared by the method of Catch *et al.*[10] ^{1}H N.m.r. analysis showed that it contained about 4% of 3-bromobutan-2-one, the presence of which was allowed for in the kinetic measurements by assuming it to react four times as fast as the 1-bromo-compound, this being the ratio of the rates at which the two substances react with hydroxide ion.[11] The reaction was followed at 25 °C by observing the decrease in absorbance of the p-hydroxyacetophenone anion at 335 nm. Measurements were made at pH 6·30 (2,6-lutidine buffer) and 7·00 and 8·00 (phosphate buffers). The concentration of bromo-ketone was in the range 2×10^{-3} to 5×10^{-2}M, and was between 10 and 400 times the total initial concentration of p-hydroxyacetophenone. Under these conditions it is easy to show that the reaction should follow a first-order course with a velocity constant given by equation (6), where k_2 is the desired second-order velocity constant and K the acid dissociation constant of p-hydroxyacetophenone.

$$k_{\text{obs}} = k_2[\text{bromo-ketone}]K(K + [\text{H}^+])^{-1} \quad (6)$$

In fact the reaction rate fell off more rapidly than it should for a first-order reaction, and this was traced to consumption of hydroxide ion by reaction with bromo-ketone and consequent increase of [H$^+$]: this could be anticipated from the results of Cox and Knipe,[11] and was verified by pH measurements during the reaction. The value of k_2 was therefore obtained by applying equation (6) to the observed initial rates, and the mean of eight experiments gave $10^2\ k_2 = 1\cdot8 \pm 0\cdot2$ dm^3 mol^{-1} s^{-1}, independent of phosphate concentration over the range 2×10^{-3} to 5×10^{-2}M.

The iodination of (I; X = Cl) and of (III) was followed by the usual method. These reactions are approximately of zero order with respect to iodine, and of first order with respect to substrate. For compound (I) the rate in phosphate and in tris(hydroxyethyl)-aminomethane buffers is independent of buffer concentration but proportional to [OH$^-$]: it can therefore be attributed to intramolecular catalysis in the anion of (I). It is easily shown that the observed first-order constant is the sum of those relating to iodination (ionisation) and cyclisation, k' and k'', respectively. Comparison with the results in the preceding paragraph gave $k'' = 7\cdot5 \times 10^3$ [OH$^-$] s^{-1}, $k' = 2\cdot9 \times 10^4$ [OH$^-$] s^{-1}, so that in this case cyclisation is only about one third as fast as the introduction of a second halogen atom. However, when X = Br instead of Cl, k'' becomes $7\cdot5 \times 10^4$ [OH$^-$] s^{-1}, while k' is likely to be little affected,[7] so that when X = Br or I cyclisation probably predominates over the introduction of a second iodine atom into o-hydroxyacetophenone, at least in the early stages of the reaction.

There is a further complication, in that in the presence of bases coumaran-3-one (III) itself reacts fairly rapidly with iodine, presumably because the enol and its anion constitute aromatic systems derived from benzofuran. The iodination reaction was studied in buffer solutions of pH 9·2—9·3, and the observed first-order velocity constants were 2·7 [B$^-$] s^{-1} and $4\cdot6 \times 10^{-2}$ [B$^-$] s^{-1} in buffers prepared from the fluoro-alcohol and borate, respectively. Calculation then shows that the contribution of this reaction to the iodine consumption in the main kinetic experiments will rarely exceed 10%: moreover, it will not contribute significantly to the extrapolated velocity constants at zero buffer concentration, since there is no possibility of intramolecular catalysis in the halogenation of coumaran-3-one.

We shall therefore assume in the following that the rate of iodination of o-hydroxyacetophenone can be equated to the rate of ionisation or enolisation of the methyl group. In the fluoro-alcohol buffers 72 solutions were investigated, with nine pH values between 8·74 and 9·47. The stoicheiometric concentration of o-hydroxyacetophenone was between 8×10^{-4} and 3×10^{-3}M, and the concentration of its anion, [SH$^-$], was determined directly from the measured absorbance at 353 nm. The total buffer concentration varied between 2×10^{-3} and 3×10^{-2}M, and for each solution v_∞ (the rate at infinite iodine concentration) was obtained by the extrapolation procedure previously described [equations (4) and (5)]. In principle these results should yield values of the three velocity constants k_1, k_2, and k_3 in equation (3), but in practice it was not found possible to obtain a value for k_3: this is essentially because the last two constants probably have similar values, and the ratio [HSH]/[SH$^-$] is between 5 and 30 in the solutions investigated. We have therefore made the simplifying assumption $k_3 = k_2$, when equation (3) can be conveniently written as equation (7).

$$v_\infty/[\text{SH}^-] = k_1 + k_2[\text{B}^-](1 + [\text{HSH}]/[\text{SH}^-]) \quad (7)$$

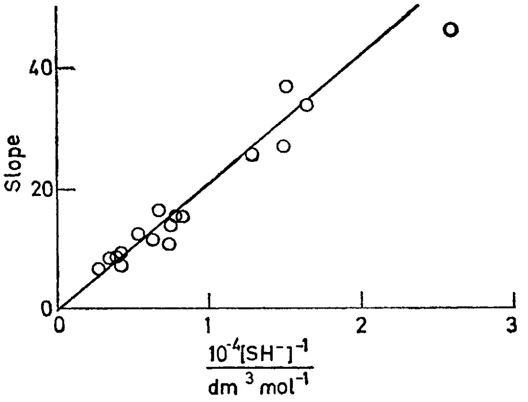

FIGURE 3 Slopes of extrapolation plots [equation (4)] plotted against [SH$^-$]$^{-1}$

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[10] J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 1948, 272.

[11] B. G. Cox and A. C. Knipe, *J.C.S. Perkin II*, 1973, 1391.

Figure 4 shows a plot of $v_\infty/[SH^-]$ against $[B^-](1 + [HSH]/[SH^-])$. The random scatter is largely due to errors in the extrapolation procedure used to obtain v_∞. Other variable factors may arise from the neglect of intermolecular rates proportional to $[HSH][SH^-]$ and the possibility of some iodination in the aromatic nucleus, though the latter cannot make a considerable contribution since it would not conform to the observed dependence of rate upon iodine concentration [equations (4) and (5); Figures 1—3]. The slope and intercept of the plot in Figure 4 give the values $10^3\,k_1 = 2{\cdot}6 \pm 0{\cdot}2\ s^{-1}$, $10^2\,k_2 = 4{\cdot}5 \pm 0{\cdot}5\ dm^3\ mol^{-1}\ s^{-1}$.

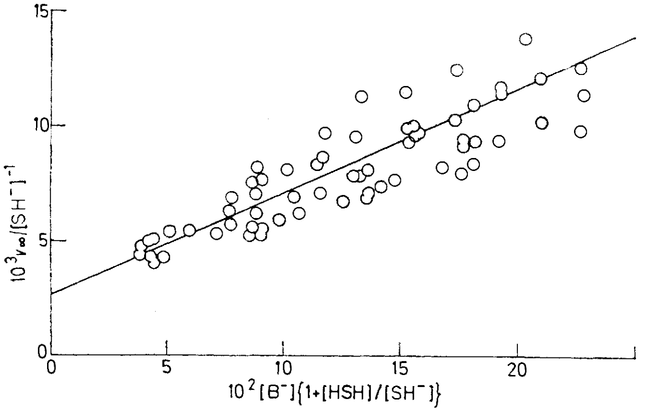


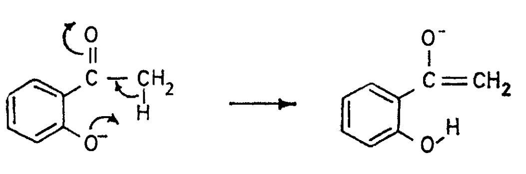
FIGURE 4 Plots of $v_\infty\ [SH^-]^{-1}$ against $[B^-]\ (1 + [HSH]/[SH^-])$

Similar but less extensive measurements were made in borate buffers, 19 solutions of pH 8·91 or 9·09 being investigated. The stoicheiometric concentration of *o*-hydroxyacetophenone was between 6×10^{-4} and 6×10^{-3}M, and that of borate ion between 0·01 and 0·06M. The values of v_∞ were treated as described in the preceding paragraph, giving $10^3\ k_1 = 2{\cdot}3 \pm 0{\cdot}1\ s^{-1}$ (indistinguishable from the value obtained in fluoro-alcohol buffers), $10^3\ k_2 = 1{\cdot}1 \pm 0{\cdot}1\ dm^3\ mol^{-1}\ s^{-1}$.

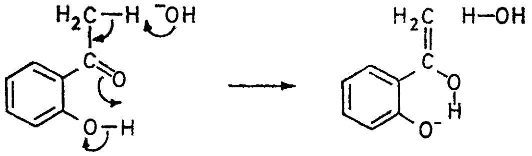
The relevant results for comparing the rates of intra- and inter-molecular processes are thus as given in the Table.

Reaction	Velocity constant
Intramolecular proton transfer in anion of *o*-hydroxyacetophenone	$2{\cdot}4 \times 10^{-3}\ s^{-1}$
o-Hydroxyacetophenone + anion of fluoro-alcohol	$4{\cdot}5 \times 10^{-2}\ dm^3\ mol^{-1}\ s^{-1}$
o-Hydroxyacetophenone + borate	$1{\cdot}1 \times 10^{-3}\ dm^3\ mol^{-1}\ s^{-1}$
Intramolecular cyclisation of anion of *o*-hydroxy-ω-bromoacetophenone	$7\ s^{-1}$
Anion of *o*-hydroxyacetophenone + 1-bromobutan-2-one	$1{\cdot}8 \times 10^{-2}\ dm^3\ mol^{-1}\ s^{-1}$

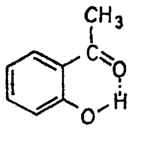
It is first necessary to establish that the constant $k_1 = 2{\cdot}4 \times 10^{-3}\ s^{-1}$ does correspond to intramolecular proton transfer in the anion of *o*-hydroxyacetophenone. It is certainly much too high to be attributed to proton abstraction by a water molecule, since this process has a rate constant of *ca.* $10^{-10}\ s^{-1}$ for simple aliphatic ketones, and reaches only *ca.* $10^{-6}\ s^{-1}$ even for a highly activated ketone such as $(CH_2Cl)_2CO$.[12] The most obvious mechanism therefore involves intramolecular proton transfer as in reaction (i). There is a second possible interpretation, since in virtue of the equilibrium $SH^- + H_2O \rightleftharpoons HSH + OH^-$ the rate term $k_1[SH^-]$ could equally well be written as $k_{OH}[HSH][OH^-]$, where $k_{OH} = k_1K_s/K_w = 13\ dm^3\ mol^{-1}\ s^{-1}$. This is considerably greater than would be expected for proton abstraction from HSH by hydroxide ion, since this process has $k_{OH} = 0{\cdot}24\ dm^3\ mol^{-1}\ s^{-1}$ for acetophenone, with similar values for a number of ring-substituted acetophenones.[13] However, for *o*-hydroxyacetophenone there is the additional possibility of forming the enol of SH^- (which would also react rapidly with halogens) by the internally assisted mechanism (ii), where the timing of the two proton transfers remains an open question. It is difficult to estimate how much acceleration could be caused by this type of intramolecular assistance. A comparison of the acetate-catalysed iodination of 2-oxobicyclo[2.2.2]octan-1-carboxylic acid and methyl ester[14] suggested a rate enhancement of about 20-fold due to this cause, but the interpretation is not free from ambiguity, and the reaction is not a close analogue of the present one. Moreover, when the same problem is considered for the iodination of aliphatic keto-acids,[1] *o*-carboxyacetophenone,[2] and amino-ketones[3] the values obtained for k_{OH} are too high to be explained by mechanisms analogous to (ii), while for the last class of substance additional reasons were found for preferring (i) to (ii). We shall therefore interpret our present results in terms of reaction (i).



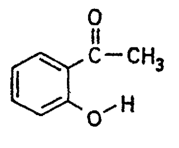
(i)



(ii)



(A)



(B)

The quantitative interpretation of the proton-transfer reactions is complicated by the different conformations possible for the acetyl group. Undissociated *o*-hydroxyacetophenone is likely to exist predominantly in the hydrogen-bonded form (A). This view is supported by

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[12] From values collected by R. P. Bell, G. R. Hillier, J. W. Mansfield, and D. G. Street, *J. Chem. Soc.* (*B*), 1967, 827.

[13] J. R. Jones, R. E. Marks, and S. C. Subba Rao, *Trans. Faraday Soc.*, 1967, **63**, 111, 993.

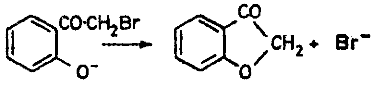
[14] R. P. Bell and M. I. Page, *J.C.S. Perkin II*, 1973, 1681.

the observation[15] that the acid-catalysed iodination of *o*-hydroxyacetophenone is undetectable, in contrast with the behaviour of the *para*-isomer. The measured p*K* of the *ortho*-compound (10·27) therefore refers essentially to (A), whereas the postulated intramolecular reaction (i) demands a conformation such as (B), in which the phenolic and methyl groups are close together. For the purposes of this reaction, therefore, the basic strength of the phenoxide group is best measured by the p*K* of conformation (B), rather than by that of (A). Although p*K*(B) cannot be measured, it will certainly be less than 10·3, since (in the absence of hydrogen bonding) the acetyl group should act as an acid-strengthening group. In fact *m*- and *p*-hydroxyacetophenone have p*K* 9·2 and 8·05, respectively,[14] and since the effect of the acetyl group will be largely mesomeric, we shall take 8·05 as the appropriate p*K* value for the intramolecular process.

We therefore wish to compare the intramolecular rate with intermolecular catalysis by a hypothetical base having p*K* 8·05. The observed rate for the anion of the fluoro-alcohol (p*K* 9·80) refers to a base which is 56 times stronger, and this rate should therefore be divided by a factor $(1/56)^{0\cdot80}$, where 0·80 is a typical value for the Brönsted exponent in reactions of this kind. This gives $k_2^* = 4\cdot5 \times 10^{-2} \times (1/56)^{0\cdot80} = 1\cdot8 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}, and hence for the ' effective concentration ' in the intramolecular process, $c_i = k_1/k_2^* = 2\cdot4/1\cdot8 = 1\cdot3$ mol dm^{-3}. However, this value is probably too low, since the value of k_2 employed in calculating it refers to the molecule HSH rather than to the ion SH$^-$. Not only is there a difference in charge, but the enolisation of HSH [conformation (A)] may be internally assisted by the type of process shown in reaction (ii): hence the observed value of k_2 may be too high for direct comparison with the intramolecular process, and the resulting value of c_i too low. An alternative though less direct comparison makes use of measured rates of ionisation of acetone and acetophenone. The rate constants for acetone + acetate ion[16] or hydroxide ion[17] are respectively $2\cdot4 \times 10^{-7}$ and 0·15 dm^3 mol^{-1} s^{-1}, while that for acetophenone + hydroxide ion[13] is 0·24 dm^3 mol^{-1} s^{-1} being little affected by ring substituents), whence it (may be estimated that acetophenone + acetate ion has $k \simeq 4 \times 10^{-7}$ dm^3 mol^{-1} s^{-1}. For abstraction of a proton from acetophenone by the anion of an acid with p*K* 8·05 this leads to $k = 4 \times 10^{-7} \times (1\cdot8 \times 10^{-5}/9 \times 10^{-9})^{0\cdot8} = 1\cdot7 \times 10^{-4}$ dm^3 mol^{-1} s^{-1}, and if acetophenone is regarded as an adequate model for SH$^-$, the effective concentration for intramolecular proton transfer in the latter becomes $c_i = 2\cdot4 \times 10^{-3}/1\cdot7 \times 10^{-4} = 14$ mol dm^{-3}, which is probably to be preferred to the previous value of 1·3M and suggests that the reaction between HSH and $(CF_3)_2CH{\cdot}O^-$ is accelerated about ten-fold by intramolecular assistance. The two values bracket c_i = 5 mol dm^{-3} reported previously for intramolecular proton transfer in the anion of *o*-carboxyacetophenone.

If the value of k_2 for borate ion is used to assess the effective concentration for the intramolecular process, values of c_i about eight times as great as the above are obtained. However, this is not a satisfactory procedure, since there is good evidence[18] that in aqueous solution boric acid and the borate ion have the structures $B(OH)_3$ and $B(OH)_4^-$, respectively: hence the borate ion cannot act as a simple proton acceptor and cannot be compared with the phenoxide group. The chief value of the measurements in borate buffers is therefore to confirm the value of the intramolecular rate constant k_1.

A more direct comparison is possible between intra- and inter-molecular processes for the two reactions (iii)

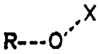


(iii)

$$p\text{-MeCO}{\cdot}C_6H_4{\cdot}O^- + CH_2Br{\cdot}COEt \rightarrow p\text{-MeCO}{\cdot}C_6H_4{\cdot}O{\cdot}CH_2COEt + Br^- \quad \text{(iv)}$$

and (iv), which were found to have velocity constants of 7 s^{-1} and $1\cdot8 \times 10^{-2}$ dm^3 mol^{-1} s^{-1}. For these systems there is no ambiguity of mechanism and there are no complications due to hydrogen bonding, so that the effective concentration for reaction (iii) is given by $c_i = 7/(1\cdot8 \times 10^{-2}) \simeq 400$ mol dm^{-3}, which is much greater than the values just estimated for the closely analogous proton-transfer reaction (7). This is consistent with the general experience that intramolecular processes are relatively much more efficient for nucleophilic displacements than for acid–base reactions, though it is not often possible to compare reactions as similar as (i) and (iii). A possible explanation of this difference is given in the next paragraph.

It has been shown by Page and Jencks[19] that values of c_i as high as 10^8 mol dm^{-3} can be accounted for by the loss of rotational and translational entropy which accompanies the formation of the transition state in the intermolecular reaction, but which is absent in a corresponding intramolecular process. In nucleophilic attack by (for example) a reagent RO$^-$ upon a centre X the valency requirements of the oxygen atom will lead to a bent transition state such as (C), in which vibrations



(C)

R---H---X

(D)

involving a change of the angle ROX will have relatively high frequencies, and rotation around the bonds R–O and O–X will be hindered. On the other hand, in a

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[15] A. Schellenberg, G. Oehme, and G. Hübner, *Chem. Ber.*, 1965, **98**, 3578.

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

[17] J. R. Jones, *Trans. Faraday Soc.*, 1965, **61**, 95; 1969, **65**, 2138.

[18] For references and details, see R. P. Bell, J. O. Edwards, and R. B. Jones in ' The Chemistry of Boron and its Compounds,' ed. E. L. Muetterties, Wiley, New York, 1966, pp. 209—221.

[19] M. I. Page and W. P. Jencks, *Proc. Nat. Acad. Sci., U.S.A.*, 1971, **68**, 1678.

proton-transfer reaction the most stable transition state will be linear, as in (D), with a low bending frequency and effectively free rotation about the bonds R–H and H–X. The entropy loss on forming the transition state will therefore, other things being equal, be lower than for the nucleophilic reaction, and the difference between inter- and intra-molecular reactions smaller, as observed.

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