Intramolecular Catalysis in the Enolisation of β-Piperidinopropiophenone and its Methiodide Derivative

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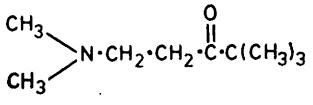
Measurements have been made on the rates of iodination of β-piperidinopropiophenone and its methiodide derivative, and on the rates of bromination of β-piperidinopropiophenone. The rates are independent of halogen concentration, except at low pH and high iodide concentrations when the iodination reactions are reversible, and represent the rate of ionisation or enolisation of the substrates. The reactions are base-catalysed and catalytic constants for a number of bases have been determined. The rates of ionisation of the protonated and *N*-methylated aminoketones are closely similar, and are up to 4 000 times larger than those of corresponding reactions of the neutral aminoketone and acetophenone. The close similarity between the reactivities of the protonated and *N*-methylated aminoketone suggests that the effect is due to an intramolecular electrostatic stabilisation of the negative charge developing on the carbonyl oxygen in the transition state. The results are discussed in relation to those of earlier studies on related systems.

FACILITATION of proton abstraction from a CH group adjacent to a carbonyl group by a suitable placed carboxylate or carboxylic acid group within the same molecule is well established.[1-5] Examples attributable both to direct abstraction of the proton by the carboxylate group and to interaction between the carboxylic acid and carbonyl groups have been reported. The same effects should also be observable for other acidic–basic groups such as dialkylamino, but detailed kinetic information on the behaviour of aminoketones is scarce.

In a study of the enolisation of a wide range of β-aminoketones (Mannich bases), Coward and Bruice [6] found in a number of cases pH–rate profiles which were consistent with intramolecular participation by the β-amino-group. In most cases the results could not be interpreted quantitatively because of the possibility of enolisation to either side of the carbonyl group, and because data for comparison with related systems involving intermolecular catalysis only were not available. The results for aminoketone (I), however, are of some

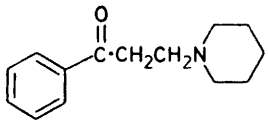


(I)

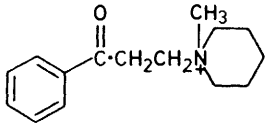
interest as intramolecular base catalysis by the amino-group is extremely unlikely, and they suggested the involvement of the $^{+}NH(CH_3)_2$ group, acting either as a general acid catalyst, or by electrostatic stabilisation of the negative charge developing upon the carbonyl oxygen in the transition state.

More recently Bell and Timimi have studied the iodination of 4-diethylaminobutan-2-one and 5-diethylaminopentan-2-one.[7] Both systems are complicated by the possibility of ionisation or enolisation of the methylene or methyl groups, but gave definite evidence for the participation of the amino-group. The kinetics were consistent either with an attack by OH^- on the protonated aminoketone, or with reaction of the neutral aminoketone. Indirect evidence favouring the latter mechanism was presented.

The present paper reports a study of the halogenation of β-piperidinopropiophenone (II) and its methiodide derivative (III) in the presence of several different buffers



(II)



(III)

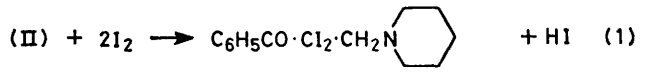
and dilute hydroxide solutions, covering a wide range of pH. In this reaction, the halogen (iodine or bromine) acts as a scavenger by reacting rapidly with the enol or enolate formed on proton transfer from the CH_2 group adjacent to the carbonyl group (see below). The results are compared with corresponding values for the halogenation of acetophenone.

EXPERIMENTAL AND RESULTS

Materials.—The hydrochloride of (II) was prepared according to Mannich and Lammering [8] and purified by recrystallisation from ethanol, m.p. 142—143 °C. Methiodide (III) was prepared by reaction of (II) with excess of CH_3I in anhydrous diethyl ether at room temperature [9] and purified by recrystallisation from ethanol–water (1 : 1 v/v) in the presence of a trace of HI, m.p. 153—155 °C (lit.,[9] 148—155 °C). Both were crystalline solids, stable if stored in a desiccator in the dark. Aqueous solutions of (II) were stable for several days, but solutions of (III) showed evidence of some decomposition after several hours. Acetophenone was purified by distillation under reduced pressure. The buffers used (see below) were prepared from commercial materials, purified by standard means where appropriate.

Stoicheiometry.—Both ketones were titrated with iodine (in the absence of added iodide, to avoid problems of reversibility) in tris buffers at pH 8. The titrations were monitored amperometrically using a modification [10] of the dead-stop method. At this pH, two distinct reactions were observed, a relatively fast reaction which consumed 2

mol of iodine per 1 mol of ketone, and a second much slower reaction (more than 20-fold slower) which ultimately consumed a further 2 mol of iodine. All kinetic work refers to the first of these reactions, assumed to be a normal enolisation reaction as in equation (1). This has been con-



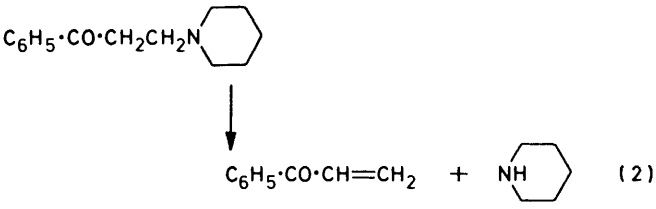
(II) + $2I_2$ → $C_6H_5CO\cdot CI_2\cdot CH_2N$ + HI (1)

firmed by n.m.r. studies of the reaction in tris buffers, which shows the loss of two protons, and a strong downfield shift of the methylene β-protons of (II) centred at δ *ca.* 3.5 to lower field, δ 6.32, as expected. The subsequent slower reaction presumably involves iodination of the remaining methylene group leading to the tetraiodo-derivative.

The hydrogen atoms involved will be relatively acidic and it is also possible that there is some intramolecular assistance by the nitrogen, resulting in formation of an aziridinium iodide as an intermediate in the reaction.

Spectrophotometric studies of the reaction of the aminoketone (II) with excess of OBr^- at high pH (>12) also showed a relatively fast consumption of 2 mol of OBr^-, followed by a much slower additional consumption of OBr^-.

It was important to test for the possible involvement of a deamination reaction (2) as this could, in principle, show



$C_6H_5\cdot CO\cdot CH_2CH_2N$ → $C_6H_5\cdot CO\cdot CH{=}CH_2$ + NH (2)

similar kinetic behaviour to the enolisation reaction if the vinyl ketone reacts rapidly with I_2–I^- under the experimental conditions employed. Coward and Bruice [6] have examined the reactions for the products of a retrograde Mannich reaction, under similar experimental conditions to those used here and found no positive evidence, and neither the overall stoicheiometry nor the n.m.r. studies are consistent with any significant participation of the deamination reaction (2). In addition, separate studies on phenyl vinyl ketone showed that it reacts only slowly with I_2–I^- in the aqueous buffers used in the kinetic studies of the iodination of the aminoketones (II) and (III).

pK_a *Determinations.*—The pK_a of the aminoketone was determined at 25 °C by means of standard pH titrations monitored with a Radiometer pH meter. The result obtained was pK_a 9.20 (±0.05) at zero ionic strength. This compares quite favourably with an earlier value of pK_a 9.3 (temperature and ionic strength not given).[11]

Kinetic Measurements.—All reactions were followed spectrophotometrically using either a Gilford 2400S, Unicam SP700, or Beckman DU instrument. The rate of disappearance of iodine was followed by the decrease in absorbance due to tri-iodide at 353 nm. In all reactions, iodide concentrations were in the range $0.002 \leqslant [I^-] \leqslant 0.01$M, normally 0.01M, and the initial iodine concentration was in the range $1—7 \times 10^{-5}$M. Under these conditions ($[I^-]$ 0.01M), the effective molar absorbance of iodine is 2.30×10^4 l mol^{-1} cm^{-1}. In each series of reactions the ionic strength was made up to a constant value by the addition of $NaClO_4$ or KCl. Bromination rates were measured for aminoketone (II) in dilute hydroxide solution (0.015—0.01M) using excess of bromine. In such solutions bromine is entirely in the form of OBr^-, and its rate of disappearance was followed by the decrease in absorbance at 330 nm. The cell compartments of the spectrophotometers were controlled at 25 (±0.1) °C.

Iodination of Acetophenone.—For the purposes of comparison with the aminoketones, rates of iodination of acetophenone were measured in dilute HCl, acetate buffers, and pyridine buffers. Acetophenone concentrations were in the range $2.2 \times 10^{-2} \leqslant$ [acetophenone] $\geqslant 4.8 \times 10^{-2}$M and the ionic strength was maintained at 0.3 by the addition of KCl, The reactions were strictly zero-order with respect to iodine, demonstrating that the rate of ionisation (or enolisation) of the acetyl group is being measured, with the observed rate law being given by equation (3), in which $[I_2^*]$ refers the

$$-d[I_2^*]/dt = k_e\,[\text{acetophenone}] \qquad (3)$$

total concentration of iodine ($[I_2] + [I_3^-]$). The following results were obtained.

HCl *catalysis.* $1 \times 10^{-3} \leqslant [HCl] \leqslant 3 \times 10^{-2}$M. $k_e/s^{-1} = 1.04 + 10^{-8} + 1.00 \times 10^{-5}[HCl]$.

Acetate catalysis. $0.02 \leqslant [OAc^-] \leqslant 0.3$M and at several buffer ratios, r, where $r = [OAc^-]/[HOAc]$. $r = 0.5$; $k_e/s^{-1} = 0.25 \times 10^{-8} + 9.01 \times 10^{-7}[OAc^-]$. $r = 1.0$; $k_e/s^{-1} = 1.21 \times 10^{-8} + 7.82 \times 10^{-7}[OAc^-]$. $r = 2.0$; $k_e/s^{-1} = 1.06 \times 10^{-8} + 8.42 \times 10^{-7}[OAc^-]$. $r = 3.0$; $k_e/s^{-1} = 2.26 \times 10^{-8} + 8.25 \times 10^{-7}$ $[OAc^-]$. The results show no evidence for catalysis by HOAc and give an average value of k_{OAc} of 8.4 (±0.3) $\times 10^{-7}$ l mol^{-1} s^{-1}.

Pyridine catalysis. $0.012 \leqslant [Py] \leqslant 0.9$M. $r = [Py]/[PyH^+] = 3.0$. $k_e/s^{-1} = 1.0 \times 10^{-7} + 1.43 \times 10^{-5}[Py]$.

The intercepts in all cases are subject to large uncertainties. From the results, however, we estimate a value for the spontaneous rate of k_0 *ca.* 1.0×10^{-8} s^{-1}. Detailed studies of the halogenation of acetophenone in sodium hydroxide solutions by Jones [12] gave a value for catalyses by OH^- of k_{OH} 0.26 mol^{-1} dm^3 s^{-1}.

Halogenation of β-*Piperidinopropiophenone* (II).—The rates of iodination of aminoketone (II) were studied in a number of buffer systems, and in dilute $HClO_4$ solutions. Aminoketone concentrations were varied over a wide range, $10^{-3} \leqslant$ [aminoketone] $\leqslant 10^{-1}$M, but kinetic measurements were normally carried out with [aminoketone] *ca.* $1—3 \times 10^{-3}$M. At iodide concentrations of *ca.* 0.1M or larger, particularly at lower pH, the iodination reactions showed marked deviations from linearity in absorbance–time plots, with a steady decrease in the rate of iodine consumption until finally an equilibrium position was obtained. For iodide concentrations ⩽ 0.01M in the presence of buffers with pH ⩾ *ca.* 3, there was no evidence of reversibility, and a zero-order loss of iodine was observed (over at least 90% of reaction). The results again suggest that the rate of ionisation (or enolisation) of the aminoketone is being measured.

Under basic conditions, the monoiodo-derivative would be expected to be iodinated at least 100 times more rapidly than the parent aminoketone,[3] and, as initial iodine concentrations were 0.1—4% of the substrate concentrations, significant acceleration of iodine uptake might be expected (particularly at lower substrate concentrations). No such acceleration was observed, and this is probably attributable to the reversibility of the second iodination step under the kinetic conditions employed. By contrast, the analytical work was carried out at relatively high pH and in the

absence of added iodide. It is therefore assumed in calculating the rate constants for the zero-order rates of iodination that only 1 mol of iodine is consumed for each 1 mol of aminoketone that reacts. There is some doubt about the validity of this assumption for the kinetic work in the pipes and tris buffers used to determine the rate of reaction between OH^- and the protonated aminoketone-(IIH^+), as the rates were too fast to see the initial portion of the reaction, and hence to check whether any acceleration occurred. The maximum effect, if 2 mol were consumed with a single rate-determining step, would be a factor of two.

The observed rate law has the form shown in equation (4), in which $(IIH^+)_T$ refers to the stoicheiometric con-

$$-d[I_2^*]/dt = k_e[IIH^+)_T \quad (4)$$

centration of the aminoketone hydrochloride added to the reaction mixture. Rates were measured initially in dilute solutions of $HClO_4$. Values of k_e were independent of $[HClO_4]$ up to *ca.* 0.01M. Beyond this concentration, curvature due to reversibility was so severe that even at low (<0.01M) $[I^-]$, it was not possible to obtain reliable values. The average value of k_e obtained at the lower concentrations of $HClO_4$ was $0.9(\pm 0.1) \times 10^{-6}$ s^{-1}.

Reactions were also carried out in a variety of buffers. The observed rate constant, k_e [equation (4)], was of the form shown in equation (5), in which B represents the basic component of the buffer. Table 1 lists values of k_0 and k_B

$$k_e = k_0 + k_B[B] \quad (5)$$

obtained in the different buffer solutions. In each case, k_e values were measured at five or more different concentrations of B. Unless otherwise stated, values of k_e calculated from equation (5), using k_0 and k_B values from Table 1 agreed within 5% with experimental values. Figures 1 and 2 show typical plots of k_e *versus* [B]. Individual rate constants obtained in the various buffer systems are available upon request.

Values of k_0 determined in buffers with pH < *ca.* 7 are subject to large uncertainties, as small changes in the slopes of k_B *versus* [B] plots lead to large variations in k_0 (*e.g.* Figure 1). Values determined in tris buffers are more reliable as k_0 makes a much larger contribution to observed k_e values (Figure 2). At the higher pH values (tris buffers, *r* 1.70 and 9.8) the rates were approaching the limit of the

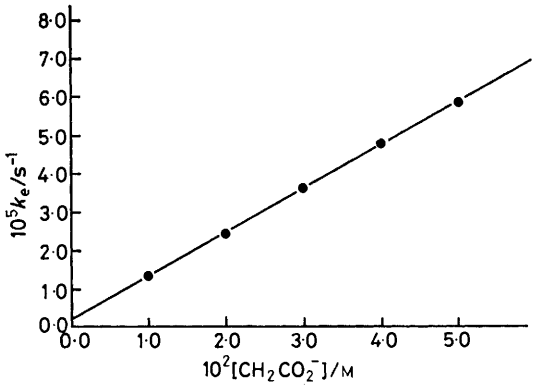


FIGURE 1 Iodination of (IIH^+) in acetate buffers at 25 °C. $[CH_3CO_2^-] = 4\,[CH_3CO_2H]$

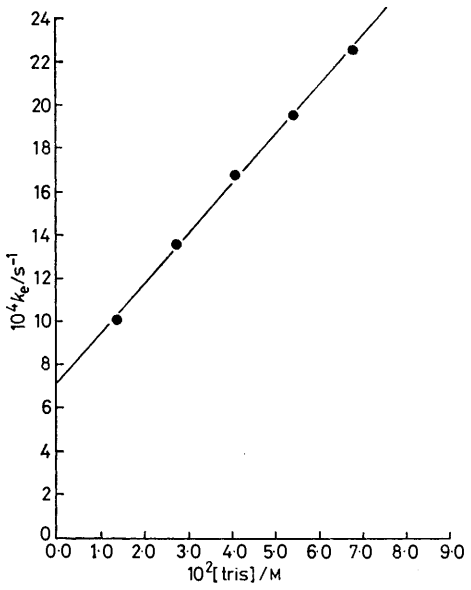


FIGURE 2 Iodination of (IIH^+) in tris buffers at 25 °C. [tris] = 1.7[trisH$^+$]

TABLE 1

Rates of iodination [a] of (IIH^+) in buffers at 25 °C

Base (B)	*r* [b]	[B]/M	Ionic strength [c]	$10^5k_0/s^{-1}$	$10^4k_B/mol^{-1}$ dm^3 s^{-1}
				0.09	
Chloroacetate	0.5	0.01—0.09	0.10	0.10	0.560
Chloroacetate	1.0	0.01—0.09	0.10	0.10	0.553
Chloroacetate	2.0	0.01—0.09	0.10	0.11	0.524
Mandelate [d]	1.0	0.01—0.09	0.10	0.13	1.88
β-Chloropropionate	2.2	0.01—0.06	0.07	0.10	4.83
Acetate	0.33	0.01—0.06	0.07	0.10	11.5
Acetate	1.0	0.01—0.06	0.07	0.12	11.6
Acetate	2.0	0.01—0.06	0.07	0.24	10.7
Acetate	4.0	0.01—0.06	0.07	0.22	11.4
Acetate	20.0	0.01—0.06	0.07	0.76	11.1
Pyridine	3.0	0.03—0.15	0.06	1.5 (±1)	46.0
Pipes [e]	1.71	0.004—0.025	0.10	4.0 (±1)	360
Tris [f]	0.33	0.005—0.025	0.09	15.0 (±2)	289
Tris [f]	0.79	0.01—0.05	0.07	33.0 (±2)	284
Tris [f]	1.70	0.015—0.07	0.05	71.0 (±5)	231
Tris [f]	9.8	0.02—0.10	0.05 [g]	250 (±20)	160

[a] $[I^-]$ 0.01M. [b] *r* [base]/[acid]. [c] $NaClO_4$ or KCl. [d] $C_6H_5CH(OH)CO_2^-$. [e] 1,4-Bis-(2-sulphonatoethyl)tetrahydropyrazine. [f] $H_2N{\cdot}C(CH_2OH)_3$. [g] $[I^-]$ 0.04M.

apparatus, and individual k_e values were reproducible only to ±10%.

Ionisation rates in dilute hydroxide solution were too rapid to measure using zero-order iodination conditions as described above. The rates were measured under pseudo-first-order conditions as rates of bromination, in solutions containing a slight excess of bromine.[10] Under these conditions, the aminoketone hydrochloride was converted quantitatively into the free aminoketone, and the observed rate law is shown in equation (6). In dilute hydroxide solutions Br_2 exists as OBr^-, and the rates were measured

$$-d[OBr^-]/dt = k_e[II] \quad (6)$$

by following the decrease in absorbance due to OBr^- at 330 nm. Values of k_e obtained (I 0.1) are shown in Figure 3,

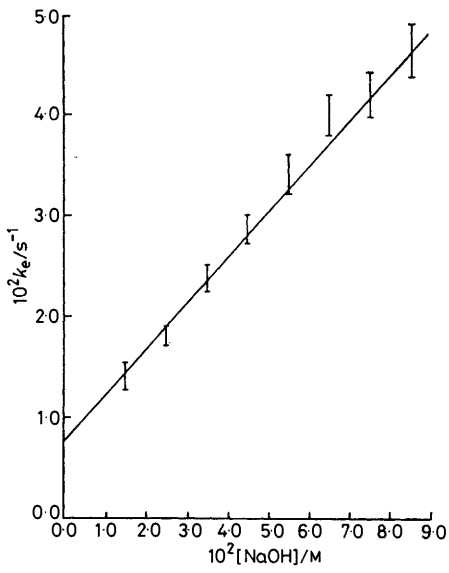


FIGURE 3 Bromination of (II) in hydroxide solutions at 25 °C

the solid line drawn corresponding to equation (7). The observed rate constants here do not depend upon the

$$k_e/s^{-1} = 7.5(\pm 2) \times 10^{-3} + 0.46[OH^-] \quad (7)$$

number of moles of bromine consumed, provided that the first step is rate determining, as the reactions are followed under first-order rather than zero-order conditions.

Iodination of β-Piperidinopropiophenone Methiodide (III). —The rates of iodination of the *N*-methylated aminoketone (III) were measured under conditions similar to those used for (II). Reactions in $HClO_4$ showed a significant amount of reversibility, but from initial slopes, a value of $k_e = 2.3 \times 10^{-6}$ s^{-1} was estimated. Rates were also measured in β-chloropropionate, acetate, and pipes buffers with the following results: (i) β-chloropropionate (r 2.2, ionic strength 0.07, [B] 0.01—0.06M), $k_e = (1.0) \times 10^{-6} + 1.50 \times 10^{-3}$[β-chloropropionate]; (ii) acetate (r 20, ionic strength 0.07M, [B] 0.01—0.06M), $k_e = 8 \times 10^{-6} + 2.47 \times 10^{-3}$[acetate]; (iii) pipes ($r$ 1.71, ionic strength 0.10M, [B] 0.004—0.025M), $k_e = 9.0(\pm 2) \times 10^{-5} + 5.13 \times 10^{-2}$[pipes]. As in the case of aminoketone (II), intercepts (k_0 values) in β-chloropropionate and acetate buffers are approximate only. The corresponding value in pipes buffer is also subject to a significant error, but may be used to estimate a value for reaction of (III) with OH^- (see below).

DISCUSSION

It is convenient for the purposes of the discussion to compare first the behaviour of the aminoketone (II) with its *N*-methylated derivative (III), and secondly the results for the two aminoketones with those for acetophenone.

The results for (III) are consistent with a simple rate-determining reaction between the substrate and the added base [equations (8)]. As the rate-determining step involves a reaction between a cation and an anion, the reaction will be subject to a significant salt effect. The measured catalytic constants, k_B, have been corrected to zero ionic strength, using activity coefficients calculated from the Davies equation (9),[13] in which I is the ionic strength, and A the Debye–Hückel parameter.

$$\log\gamma \pm = -AZ^2I^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) + AZ^2I^{\frac{1}{2}}/3 \quad (9)$$

The results are summarised in Table 2. The value of k_{OH} quoted in Table 2 was obtained from the intercept

TABLE 2

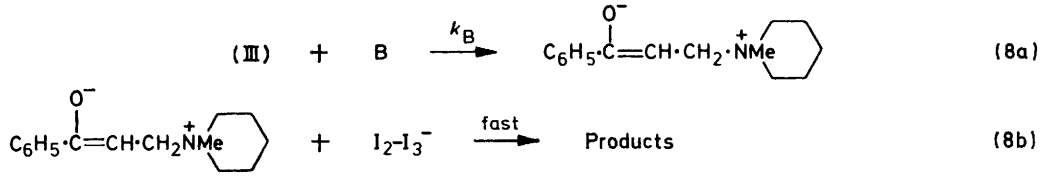
Catalytic constants for the base-catalysed iodination of (III) at 25 °C

Base	k_B [a]/mol^{-1} dm^3 s^{-1}
β-Chloropropionate	2.31×10^{-3}
Acetate	3.80×10^{-3}
Pipes	1.43×10^{-1}
OH^-	$1.15 (\pm 0.25) \times 10^3$

[a] Catalytic constants corrected to $I = 0$, k_B ±5% except where otherwise stated.

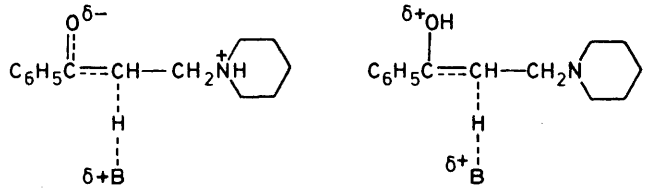
($k_0 = k_{OH}[OH^-]$) of the results in pipes buffer, using pK_a (pipes) = 6.72 at 25 °C (ionic strength 0.1M).[14]

The results for (II) are more difficult to interpret unambiguously, as a reaction between (IIH^+) and the basic component of the buffer, B, is kinetically indistinguishable from that between (II) and BH^+. Transition states



for the two mechanisms (ignoring for the moment possible intramolecular catalysis) can be written as (A) and (B) respectively, by analogy with the accepted mechanisms for acid- and base-catalysed enolisation reactions,[15] *i.e.* the transition states differ only in the position of the most acidic proton. However, it is noticeable that under comparable conditions the protonated aminoketone (II)

and the *N*-methylated aminoketone (III) react at very similar rates. Thus, as (III) is unable to form a transition state analogous to (B), but may form a transition state which formally differs from (4) only in the replacement of NH^+ by NMe^+, we assume for the remainder of the discussion that the protonated aminoketone reacts *via* transition state (A), *i.e.* by a rate-determining reaction between (IIH^+) and base B.



(A) (B)

In order to refer catalytic constants to the protonated aminoketone, observed values (Table 1) obtained from equation (4) must be corrected for dissociation *via* equation (10), in which $(IIH^+)_T$ again refers to the

$$(IIH^+) = \frac{[H^+]}{K_a + [H^+]} (IIH^+)_T \qquad (10)$$

stoicheiometric concentration of aminoketone hydrochloride added. In all buffers except tris (pK_a 8.07),[14] corrections are negligible. Values of k_B for tris, obtained by the application of equation (10) to the results in Table 1 were (for the various buffers in order of increasing buffer ratio): 10^2k_B 2.95, 3.01, 2.76, and 2.70 mol^{-1} dm^3 s^{-1}, *i.e.* k_B $2.8(\pm0.2) \times 10^{-2}$ mol^{-1} dm^3 s^{-1}. Similarly, a value for k_{OH} may be obtained from the intercepts in the pipes and tris buffers. The results obtained in the pipes and various tris buffers were respectively: $10^{-2}k_{OH}$ $5.1(\pm1.2)$, $3.91(\pm0.4)$, $3.68(\pm0.2)$, $4.20(\pm0.3)$, and $3.72(\pm0.4)$ mol^{-1} dm^3 s^{-1}, at an average ionic strength of 0.07M, *i.e.* k_{OH} $4.0(\pm0.5) \times 10^2$ mol^{-1} dm^3 s^{-1}. Correction to infinite dilution gives a value of k_{OH} of $6.2(\pm0.6) \times 10^2$ mol^{-1} dm^3 s^{-1}. The values show a considerable amount of scatter, largely because of uncertainties in intercepts of catalytic plots as discussed above, and in the case of pipes buffers, possibly because of a large (and uncertain) correction for activity coefficient (arising from the double negative charge on pipes) used in calculating the hydroxide ion concentration. The combined catalytic constants, corrected where appropriate to infinite dilution, are reported in Table 3. Comparing results in Tables 2 and 3, it may be seen that on average, the *N*-methylated aminoketone is approximately twice as reactive as the protonated aminoketone.

TABLE 3

Catalytic constants for the base-catalysed iodination of (IIH^+) at 25 °C

Base	k_B [a]/mol^{-1} dm^3 s^{-1}
Chloroacetate	8.4×10^{-5}
Mandelate	2.89×10^{-4}
β-Chloropropionate	7.43×10^{-4}
Acetate	1.73×10^{-3}
Pyridine	4.60×10^{-3}
Pipes	9.7×10^{-2}
Tris	$2.8 (\pm0.2) \times 10^{-2}$
OH^-	$6.2 (\pm0.6) \times 10^2$

[a] Catalytic constants corrected to $I = 0$, k_B values ±5% unless otherwise stated.

In the buffers considered so far, there was no evidence for reaction between B and the unprotonated aminoketone. However, in dilute hydroxide solutions [Figure 3 and equation (7)] the rates of reaction between (II) and OH^- could be measured. As the pH is increased, it can be shown that, in the absence of reaction between OH^- and the unprotonated aminoketone, the observed rate constant k_e [equation (4) or equivalent for bromination] should reach a maximum value, given by equation (11), where k_{OH} is the rate constant for reaction between

$$k_e(\text{max}) = k_{OH}K_W/K_a \qquad (11)$$

protonated aminoketone (II) and OH^-, and K_a is the acidity constant for the protonated aminoketone. Qualitatively, this arises from the fact that at pH values substantially above the pK_a (*ca.* 2 units or more) the increase in rate resulting from increasing $[OH^-]$ is exactly counterbalanced by the decrease in rate resulting from the decrease in (IIH^+). Substitution of measured values into equation (11) gives $k_e(\text{max.}) = 9.8(\pm1) \times 10^{-3}$ s^{-1}. This compares reasonably with the intercept [Figure 3, equation (8)] of $7.5(\pm2) \times 10^{-3}$ s^{-1}. The slightly higher value predicted by substitution of experimental values into (11), if real, suggests a small contribution from the second iodination step to the results in tris and pipes buffers, as discussed above. From the variation in rate with $[OH^-]$ shown in Figure 3, a value of k_{OH} of 0.46 mol^{-1} dm^3 s^{-1} may be obtained for the reaction of unprotonated ketone with OH^-. This is quite similar to the corresponding value (k_{OH} 0.26 mol^{-1} dm^3 s^{-1}) for the ionisation of acetophenone.[12]

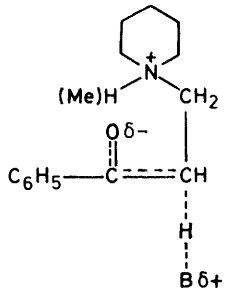
Where comparison is possible, it is clear that the *N*-methylated and protonated aminoketones are considerably more reactive than acetophenone and the neutral aminoketone (Table 4). The effects are large, rate accelerations of >4 000-fold being observed in some cases, and would seem to be much too large to be attributable to a simple inductive effect of the positive charge. Thus the most likely origin of the higher reactivities is electrostatic stabilisation of the negative change developing upon the carbonyl oxygen in the transition state as in (C). In the case of the protonated aminoketone-(IIH^+), the proton is of course potentially able to interact more directly with the carbonyl group *via* hydrogen-

TABLE 4

Comparison of catalytic constants for the iodination of acetophenone and the aminoketones (II) and (III) at 25 °C

	k_B/mol^{-1} dm^3 s^{-1}			
Base (B)	(III)	(IIH^+)	Acetophenone	(II)
Acetate	3.8×10^{-3}	1.7×10^{-3}	8.4×10^{-7}	
Pyridine		4.6×10^{-3}	1.4×10^{-5}	
Hydroxide	1 150	620	0.26	0.46

bond formation in a mechanism involving general acid catalysis. Because of the low acidity of the protonated nitrogen a strong specific interaction would not be expected, and in fact the *N*-methylated ketone is slightly more reactive. Thus it is likely that simple electrostatic stabilisation accounts for the high reactivities of both substrates. The higher reactivity of the *N*-methylated ketone is perhaps surprising as inductive and steric



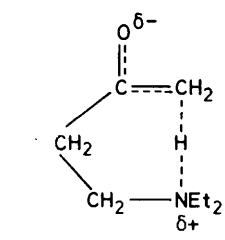
(C)

factors might be expected to favour protonated (II) over (III). A higher degree of solvation of the positive charge on the protonated amide could account for its lower reactivity, but in view of the small magnitude of the effect any interpretation must be speculative.

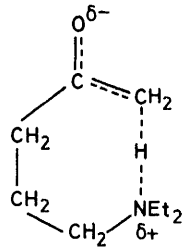
The results in Table 4 indicate that the charge on the attacking base has a noticeable effect, but does not alter the general picture. Thus a comparison of the results for the protonated aminoketone (II) and acetophenone shows that the rate ratios are 2 000 : 1 and 2 400 : 1 for OAc^- and OH^- respectively, and 330 : 1 for pyridine, *i.e.* the effect is *ca.* 7 times lower for pyridine. The reactivities of acetophenone and the neutral aminoketone are similar, indicating no special involvement of the free amino-group in the reaction.

The catalytic constants for reaction of the carboxylate ions (chloroacetate, mandelate, β-chloropropionate, and acetate) with protonated (II) show a regular increase with base strength (Table 3) They show quite a good Brønsted correlation,[15] with β 0.64.

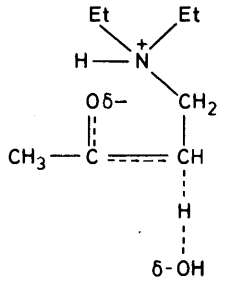
Finally, it is of interest to compare the present results with those obtained in earlier studies on aminoketones.[6,7] The results are in qualitative accord with those of Coward and Bruice [6] and suggest that the effects observed by them are best interpreted in terms of transition states analogous to (C). For the ionisation of 4-diethylaminobutan-2-one and 5-diethylaminopentan-2-one, Bell and Timimi considered two kinetically indistinguishable reactions: (i) the spontaneous reaction of the neutral aminoketones, corresponding to transition states (D) and (E), and (ii) the reaction between OH^- and the protonated aminoketone [(F) and (G)]. Species (F) and (G) are clearly analogous to (C), although there is the additional possibility of attack by OH^- on the CH_3 group rather than the CH_2 group as shown. It is not possible to draw a transition state analogous to (D) and (E) for the aminoketone (II) (except by invoking a ring of only four members, including the proton transferring from the α-methylene group). Bell and Timimi favoured (D) and (E), corresponding to intramolecular general base catalysis by the NEt_2 group. However, in light of the present results, we suggest that the results are better interpreted in terms of intramolecular assistance to



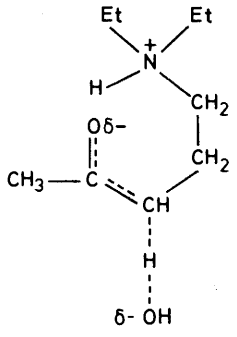
(D)



(E)



(F)



(G)

attack by external hydroxide as depicted in (F) and (G). Thus the rate constant for OH^- attack on the protonated 4-diethylaminobutan-2-one, calculated on the basis of this mechanism is k_{OH} 250 mol^{-1} dm^3 s^{-1}. This compares favourably with the value (620 mol^{-1} dm^3 s^{-1}) obtained here for protonated aminoketone(IIH^+). The two would be expected to react at similar rates as the lengths of the alkyl side chains are equal. The corresponding value for 5-diethylaminopentan-2-one is k_{OH} 76 mol^{-1} dm^3 s^{-1}, presumably reflecting the lower probability of the $\overset{+}{N}HEt_2$ group being near the carbonyl oxygen in this case because of the longer alkyl chain separating them. Similarly the rate constants for reaction of tris with the protonated aminobutanone and pentanone are k_{tris} 1.33 × 10^{-2} mol^{-1} dm^3 s^{-1} and 2.6 × 10^{-3} mol^{-1} dm^3 s^{-1}, respectively, which compare very favourably with the value for (II) of k_{tris} 2.8 × 10^{-2} mol^{-1} dm^3 s^{-1}. The close agreement between the results strongly suggest that both for the aminoketones studied by Bell and Timimi and those in the present study, the high reactivity towards ionisation is due to electrostatic stabilisation of the developing negative charge on the carbonyl oxygen.

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