Aminoketone Enolisation: Influence of Increasing Chain Length on Intramolecular Catalysis

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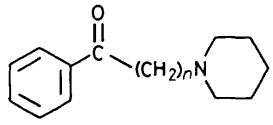
Kinetic results are reported on the rates of ionisation of piperidino- and morpholino-phenones of varying chain length [$PhCO(CH_2)_nNCH_2CH_2XCH_2CH_2$], X = CH_2 or O; n = 2—5] in buffer and dilute hydroxide solution, as measured by their rates of halogenation. For both series of aminoketones two important factors are responsible for a high reactivity relative to acetophenone: the positive charge on the protonated (and *N*-methylated) derivatives, which has a strong influence in the α- (n = 1) and β- (n = 2) position, and intramolecular general base catalysis by the neutral amino group, which has a maximum effect for the δ- (n = 4) derivative. Results for the more acidic protonated morpholinoketones are almost identical to those of corresponding piperidinoketones and show no evidence of intramolecular general acid catalysis. The reduced basicity of the morpholino group is reflected in lower rate constants for the intramolecular general base-catalysed reaction.

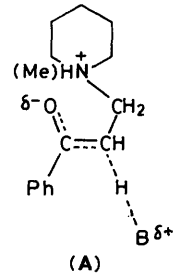
Several examples have been reported[1-9] in which an appropriately located amino group may greatly assist the ionisation of a CH bond adjacent to a carbonyl or other activating group. Rate accelerations may, in principle, arise from several factors, including intramolecular proton transfer involving N or NH^+, electrostatic stabilisation of the developing negative charge on the substrate by NH^+ (or NMe^+), electrostatic interactions with negatively charged catalysts, and inductive effects.

We have recently investigated enolisation reactions of the aminoketones [(1)—(3)] and their *N*-methylated derivatives [(1Me$^+$)—(3Me$^+$)].[5,8] For the β-piperidino derivative (2) in



(1) - (3) n = 1-3 respectively

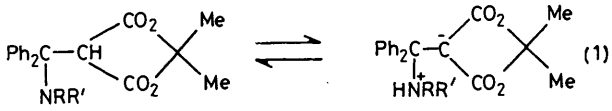
buffer solutions with pH less than pK_a(2H$^+$) (and even in dilute hydroxide solutions), the dominant reaction is that between the external base and the protonated substrate (2H$^+$), which is over 10^3 times more reactive than the neutral aminoketone. The reactivity of (2H$^+$) is slightly greater than that of (1H$^+$) and (1Me$^+$), despite a much larger inductive effect in the latter compounds, and closely similar to that of (2Me$^+$). All of these observations suggest that the effect arises mainly from intramolecular electrostatic stabilisation of the developing negative charge on the carbonyl oxygen, as in (A). No evidence



(A)

was observed for intramolecular base catalysis by the unprotonated amino group, or for intramolecular acid catalysis *via* proton transfer or H-bond formation involving NH^+; the NMe^+ derivative is in fact slightly more reactive than the NH^+ derivative.

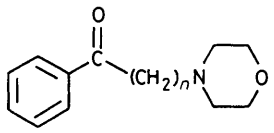
The absence of intramolecular base catalysis in (2) is not unexpected as direct proton transfer from C–H to N would require a highly strained four-membered ring (including the transferring proton). However, Bernasconi and co-workers[3,6,9] have presented evidence supporting intramolecular proton transfer from carbon to nitrogen in amino adducts of benzylidene Meldrum's acid and related systems [equation (1)].



(1)

This reaction also formally requires a similar four-membered ring but it was suggested that the proton-transfer step involves the intervention of one or more water molecules. Within the aminoketone series (1)—(3), evidence supporting intramolecular base-catalysed proton transfer was obtained only for (3). The effect, however, was not large and the intramolecular reaction of (3) could not be confidently separated from the kinetically equivalent reaction between (3H$^+$) and OH^-. Distinguishing between kinetically equivalent pathways involving intramolecular and external catalysts is, of course, central to the interpretation of results in studies of intramolecular catalysis.

In this paper we present an extension of our earlier work on aminoketones to investigate further two different aspects of the reactions. In the first place we report results for the δ- and ε-piperidinophenones [*i.e.* analogues of (1)—(3) with n = 4 [(4) and (4Me$^+$)] and n = 5 [(5) and (5Me$^+$)]. For these substrates electrostatic effects are expected to be considerably less important than for (1)—(3), whereas intramolecular base catalysis should be much more favourable on the basis of ring size. Secondly we report results for the related morpholino derivatives [(6)—(8) and (6Me$^+$)—(8Me$^+$)].

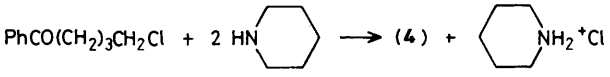


(6)–(8) n = 2–4 respectively

The morpholino derivatives are some 3 orders of magnitude more acidic than the corresponding piperidino derivatives. Their kinetic behaviour is, therefore, of interest in relation to the question of whether the NH^+ group can assist the reaction by general acid catalysis as well as by electrostatic stabilisation. Similarly they should be much less effective as base catalysts than the piperidinophenones. As in earlier studies[1,2,5,8] the rates of proton transfer were derived from rates of halogenation (iodination or bromination), as the halogen acts as a scavenger by reacting rapidly with the enolate species formed.

Experimental and Results

Materials.—*δ-Piperidinovalerophenone* (**4**). The free base[10] was prepared from the corresponding chloro derivative by refluxing with piperidine in the absence of solvent for 7 h:



The resulting product had b.p. 146 °C (2 mmHg), m.p. 25—27 °C. The chloroderivative [b.p. 110—112 °C (2 mmHg), m.p. 48—50 °C (lit.,[11] 48—49 °C)] was prepared according to Bordwell and Bramer[12] from bromobenzene (0.1 mol), Mg (0.1 mol) in anhydrous diethyl ether (100 ml) and then commercial δ-chlorovaleronitrile ($N{\equiv}C[CH_2]_4Cl$, 0.09 mol) in anhydrous diethyl ether (100 ml).

(**4H**$^+$) *and* (**4Me**$^+$). The hydrochloride of (**4**) was prepared by reaction of (**4**) with hydrogen chloride in anhydrous diethyl ether, and recrystallised from anhydrous ethanol (m.p. 170—173 °C). (**4Me**$^+$**I**$^-$) was prepared from (**4**) and MeI (10-fold excess). After filtering and washing with diethyl ether the product had m.p. 144—147 °C. The elemental analyses of (**4H**$^+$**Cl**$^-$) and (**4Me**$^+$**I**$^-$) were both satisfactory.

ε-Piperidinohexanophenone (**5**) was prepared from the corresponding chloro derivative and piperidine using the procedure described for (**4**). The chloro derivative was again prepared according to Bordwell and Bramer[12] from bromobenzene, Mg, and commercial ε-chlorohexanenitrile. ε-Chlorohexanophenone: b.p. 119—120 °C (2 mmHg); ε-piperidinohexanophenone: b.p. 137—138 °C (1 mmHg).

(**5H**$^+$) *and* (**5Me**$^+$). The hydrochloride (**5H**$^+$**Cl**$^-$) and methodide (**5Me**$^+$**I**$^-$) of (**5**) were prepared by an identical procedure to that described for the corresponding δ-derivatives. (**5H**$^+$**Cl**): m.p. 148—151 °C [recrystallised from light petroleum–CH_2Cl_2 (1:1 v/v)]; (**5Me**$^+$**I**$^-$): m.p. 150—157 °C. Both samples gave satisfactory CHN analyses.

β-Morpholinopropiophenone (**6**). The hydrochloride of (**6**) was prepared by the Mannich reaction and purified as previously described[5] (m.p. 180 °C; lit.,[13] 179—180 °C).

(**6Me**$^+$). This compound was prepared from (**6**) and MeI (6 mol excess). The solid was recrystallised from acetone: m.p. 144—145 °C, satisfactory CHN analysis.

γ-Morpholinobutyrophenone (**7**), *δ-morpholinovalerophenone* (**8**), (**7H**$^+$**Cl**$^-$), (**7Me**$^+$**I**$^-$), (**8H**$^+$**Cl**$^-$), *and* (**8Me**$^+$**I**$^-$). The compounds were prepared and purified in an identical manner to the corresponding piperidino derivatives, using morpholine in place of piperidine: (**7H**$^+$), m.p. 182—183 °C; (**7Me**$^+$), m.p. 201—207 °C; (**8H**$^+$), m.p. 143—146 °C; (**8Me**$^+$), m.p. 145—151 °C.

pK_a *Determination.*—The pK_a of the γ- and δ-morpholino derivatives were determined at 25 °C by means of standard pH titrations monitored with a Radiometer pH meter. The results obtained corrected to zero ionic strength (I = 0) were as follows: pK_a(**7H**$^+$) 7.26 (± 0.04); pK_a(**8H**$^+$) 7.50 (± 0.07). The pK_a of the β-morpholino derivative (**7H**$^+$) has been reported previously (pK_a 6.6).[14] The δ- and ε-piperidinophenones in the free base forms were not sufficiently soluble to enable reliable determination of their pK_a values by simple titration techniques.

Kinetic Measurements.—All reactions were followed spectrophotometrically using a Gilford 2400S, a UVIDEC 510, or a Durrum–Gibson stopped-flow apparatus. 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 $0.001 \leqslant [I^-] \leqslant 0.01$M, normally 0.01M, and the initial iodine concentrations 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 mol^{-1} dm^3 cm^{-1}. In each series of reactions the ionic strength was made up to 0.3M by the addition of KCl. Bromination rates were measured in dilute hydroxide solution (0.02—0.20M) using an 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 (Gilford) or 360 nm (stopped-flow). All measurements were carried out at 25 °C.

For the iodination reactions a zero-order loss of iodine was observed (over at least 90% of reaction) and for iodide concentrations ⩽0.01M in the presence of buffers with pH ⩾ 3 there was no evidence of reversibility. This kinetic behaviour is expected when the ionisation (or enolisation) of the ketone is rate determining. Only two systems [β-morpholino, (**6**) and (**6Me**$^+$)] were studied in dilute acid solution and as with the piperidinophenones studied earlier,[5,8] the reactions showed a significant degree of reversibility. In these cases initial slopes were used to estimate the spontaneous (water-catalysed) enolisation rates.

Bromination reactions were irreversible and zero-order in OBr^- except for the δ-piperidinovalerophenone (**4**) in dilute hydroxide solutions (see below).

Halogenation of δ-Piperidinovalerophenone (**4**) *and its Methiodide Derivative* (**4Me**$^+$).—Iodination rates were measured for the protonated aminoketone (**4H**$^+$) in acetate buffers with $0.02 \leqslant [OAc^-] \leqslant 0.2$M. Aminoketone concentrations were in the range $1—4 \times 10^{-3}$M.

The observed rate law has the form (2) in which $[(\mathbf{4H}^+)]_T$

$$-d[I_2^*]/dt = k_e[\mathbf{4H}^+]_T \quad (2)$$

refers to the stoicheiometric concentration of the aminoketone hydrochloride added to the reaction mixture, and $[I_2^*]$ refers to the total concentration of iodine ($[I_2] + [I_3^-]$). The results obtained in acetate buffers were ($r = [OAc^-]/[HOAc]$): r = 1, $k_e/s^{-1} = 5.9\ (\pm 0.3) \times 10^{-7} + 7.0\ (\pm 0.8) \times 10^{-6}[OAc^-]$; r = 8, $k_e/s^{-1} = 5.8\ (\pm 0.4) \times 10^{-6} + 10.0\ (\pm 4) \times 10^{-6}[OAc^-]$.

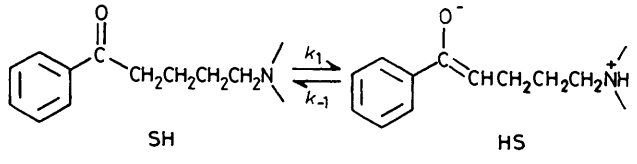
The slopes of k_e *vs.* $[OAc^-]$, especially with r = 8, are subject to quite large uncertainties because of the large intercepts, and hence the relatively small contribution from acetate catalysis.

The bromination of (**4**) and (**4Me**$^+$) was studied in dilute hydroxide solution ($0.01 \leqslant [OH^-] \leqslant 0.1$M, I = 0.1M, $NaClO_4$) under first-order conditions (an excess of Br_2).[15] The rate law for bromination of (**4Me**$^+$) is given by equations (3) and (4).

$$-d[OBr^-]/dt = k_e[(\mathbf{4Me}^+)] \quad (3)$$

where $$k_e/s^{-1} = 0.39\ (\pm 0.01)[OH^-] \quad (4)$$

The bromination of the neutral aminoketone in dilute NaOH was dominated by the intramolecular reaction, and even in 0.1M-NaOH the contribution of the OH^--catalysed bromination of the substrate was only *ca.* 15% of the total rate. Furthermore the scavenging of the enol by OBr^- was not completely efficient and the rates were slightly dependent upon $[OBr^-]$; for $[OH^-] = 0.12$M, the observed first-order rate constant decreased by *ca.* 12.5% for a 5-fold decrease in $[OBr^-]$ in the range $0.01 \geqslant [OBr^-] \geqslant 0.002$M; for $[OH^-] = 0.027$M, the corresponding decrease was 24%. This is consistent with the Scheme, in which the reprotonation of the enolate is able to



Scheme. 1

compete with the bromination step, depending upon $[OBr^-]$. This system may be analysed by plotting the reciprocal of the observed rate constant *vs.* $[OBr^-]^{-1}$ to obtain the rate constant at infinite $[OBr^-]$ concentration.[2,16] The observed rate constant is given by equation (5), but it should be noted that the

$$k_e(\mathbf{4})/s^{-1} = 0.36\ (\pm 0.01) + 0.65[OH^-] \quad (5)$$

value of $k_{OH} = 0.65$ mol^{-1} dm^3 s^{-1} is approximate only as discussed above.

Bromination of ε-Piperidinohexanophenone (**5**) *and its Methiodide Derivative* (**5**Me$^+$).—The bromination reactions of (**5**) and (**5**Me$^+$) were carried out in dilute NaOH solutions with $0.02 \leqslant [OH^-] \leqslant 0.2$M ($I = 0.2$M, $NaClO_4$) and $0.01 \leqslant [OH^-] \leqslant 0.1$M ($I = 0.1$M, $NaClO_4$) for (**5**) and (**5**Me$^+$) respectively. The reactions were in all cases zero-order in $[OBr^-]$ and the observed rate laws are given in equations (6)—(9).

$$-d[OBr^-]/dt = k_e[(\mathbf{5})] \quad (6)$$

where
$$k_e/s^{-1} = 0.11\ (\pm 0.01) + 0.34[OH^-] \quad (7)$$

$$-d[OBr^-]/dt = k_e[(\mathbf{5}Me^+)] \quad (8)$$

where
$$k_e/s^{-1} = 0.294\ (\pm 0.014)[OH^-] \quad (9)$$

Again, for bromination of (**5**), the value $k_{OH} = 0.34$ mol^{-1} dm^3 s^{-1} is subjected to a significant uncertainty because of the large intramolecular contribution to the total rate.

Halogenation of β-Morpholinopropiophenone (**6**) *and its Methiodide Derivative* (**6**Me$^+$).—The rates of iodination of (**6**) and (**6**Me$^+$) were measured in dilute HCl and in acetate and pyridine buffers. The rate law in all cases was of the form shown in equations (10) and (11), in which $(I_2^*]$ $(= [I_2] + [I_3^-])$

$$-d[I_2^*]/dt = k_e[S] \quad (10)$$

where
$$k_e = k_0 + k_B[B] \quad (11)$$

is the total iodine concentration, $[S] = [(\mathbf{6}H^+)]_T$ (the stoicheiometric concentration of the aminoketone hydrochloride added to the solution) or $[(\mathbf{6}Me^+)]$, and B represents the basic component of the buffer. Table 1 lists the results obtained in the different solutions. Values of k_e calculated from equation (11) using k_0 and k_B values from Table 1 agree within 5% of experimental values. It should be noted that values of k_0 obtained in the buffer solutions are subject to a large uncertainty because small changes in the slopes of k_e *vs.* [B] plots lead to large variations in k_0.

Table 1. Rates of iodination[a] of β-morpholinopropiophenone (**6**H$^+$) and its methiodide derivative (**6**Me$^+$) in buffers at 25 °C

Base (B)	r[b]	[B]/M	$10^6 k_0/s^{-1}$	$10^3 k_B$/dm^3 mol^{-1} s^{-1}
(i) (**6**H$^+$)				
c			0.99 (±0.15)	
Acetate	0.1	1×10^{-3}—7×10^{-3}	1.5	1.35
Acetate	1	2×10^{-3}—2×10^{-2}	1.7	1.33
Pyridine	0.1	5×10^{-4}—5×10^{-3}	2.0	7.51
Pyridine	1	5×10^{-4}—5×10^{-3}	3.2	7.65
(ii) (**6**Me$^+$)				
d			6.2 (±0.5)	
Acetate	0.5	2×10^{-3}—6×10^{-3}	4.0	5.66
Acetate	1.0	1×10^{-3}—1×10^{-2}	5.21	5.29
Acetate	2.0	1×10^{-3}—9×10^{-3}	6.5	4.83
Pyridine	1	1×10^{-4}—6×10^{-4}	3.8	72.0

[a] $[I^-] = 0.01$M; ionic strength $I = 0.3$M (KCl). [b] r = [base]/[acid]. [c] Dilute HCl solutions. [d] Pure water and dilute HCl solutions.

The bromination of (**6**) was carried out in dilute sodium hydroxide solutions with $0.01 \leqslant [OH^-] \leqslant 0.1$M ($I = 0.1$M, $NaClO_4$). The observed rate law is given by equations (12) and (13). Attempts to measure the rate of enolisation of the

$$-d[OBr^-]/dt = k_e[(\mathbf{6})] \quad (12)$$

where
$$k_e/s^{-1} = 4.0\ (\pm 4.0) \times 10^{-3} + 1.60\ (\pm 0.14)[OH^-] \quad (13)$$

methylated derivative (**6**Me$^+$) in dilute hydroxide solutions were unsuccessful because of the competing β-elimination reaction of the substrate.

Bromination of γ-Morpholinobutyrophenone (**7**) *and its Methiodide Derivative* (**7**Me$^+$).—The bromination reactions were carried out in dilute sodium hydroxide solutions with $0.01 \leqslant [OH^-] \leqslant 0.1$M ($I = 0.1$M, $NaClO_4$). The rate law for the neutral base (**7**) is given by equations (14) and (15).

$$-d[OBr^-]/dt = k_e[(\mathbf{7})] \quad (14)$$

where
$$k_e = 7\ (\pm 7) \times 10^{-4} + 0.21\ (\pm 0.001)[OH^-] \quad (15)$$

and for (**7**Me$^+$) by equations (16) and (17):

$$-d[OBr^-]/dt = k_e[(\mathbf{7}Me^+)] \quad (16)$$

where
$$k_e/s^{-1} = 2.36\ (\pm 0.08)[OH^-] \quad (17)$$

Bromination of δ-Morpholinovalerophenone (**8**) *and its Methiodide Derivative* (**8**Me$^+$).—Reaction conditions were the same as for the γ-derivatives and the rate laws for (**8**) and (**8**Me$^+$) are again given by equations (18)—(21).

$$-d[OBr^-]/dt = k_e[(\mathbf{8})] \quad (18)$$

Table 2. Catalytic constants for the acetate-catalysed iodination of β-morpholino- and β-piperidino-propiophenones at 25 °C (k_{OAc}/mol^{-1} dm^3 s^{-1})[a]

β-Morpholino		β-Piperidino[b]	
(**6**H$^+$)	(**6**Me$^+$)	(**2**H$^+$)	(**2**Me$^+$)
2.44×10^{-3}	9.6×10^{-3}	1.73×10^{-3}	3.80×10^{-3}

[a] Catalytic constants, corrected to $I = 0^5$. [b] Ref. 5.

where $k_e/s^{-1} = 1.69 \pm (0.08) \times 10^{-2} + 0.225\ (\pm 0.015)[OH^-]$ (19)

$$-d[OBr]/dt = k_e[(\mathbf{8}Me^+)] \quad (20)$$

where $k_e/s^{-1} = 0.535\ (\pm 0.025)[OH^-]$ (21)

In this case for the free base (**8**), a plot of k_e *vs.* [OH$^-$] gave significant intercept which could be determined with some accuracy [*cf.* β- and γ-morpholino derivatives, equations (13) and (15) respectively].

Discussion

In the discussion of the results we wish first to consider the possibility of intramolecular general acid catalysis in the enolisation reactions, especially in relation to the results for the β-morpholino derivatives and the corresponding β-piperidino derivatives.[5] Secondly a more general discussion of the influence of increasing chain length on the enolisation reactions of the aminoketones will be presented.

β-Morpholinopropiophenones (**6**H$^+$) *and* (**6**Me$^+$).—A comparison of the results for protonated β-morpholinopropiophenone (**6**H$^+$) with those of the *N*-methylated derivative (**6**Me$^+$) and the corresponding piperidino compounds (**2**H$^+$, **2**Me$^+$) shows that even for this relatively acidic aminoketone (pK_a = 6.6)[14] there is no increased reactivity attributable to intramolecular general acid catalysis *via* proton transfer to the carbonyl group or H-bond stabilisation of the (developing) enolate anion. This is illustrated, for example, by the results for the acetate-catalysed reactions summarised in Table 2. The reactivity of (**6**H$^+$) is actually lower than than of (**6**Me$^+$) and similar to that of the piperidino compound (**2**H$^+$). The higher reactivity of (**6**H$^+$) *vs.* (**2**H$^+$) and (**6**Me$^+$) *vs.* (**2**Me$^+$) is presumably due to the additional electron-withdrawing effect of the O atom in the morpholine ring as reflected in the relative pK_a values of (**6**H$^+$) and (**2**H$^+$) (pK_a = 6.6[14] and 9.2[5] respectively).

Furthermore we may also rule out any significant contribution from kinetic equivalent pathways for (**6**H$^+$), such as the reaction between the neutral base (**6**) and HOAc. Such an effect would also lead to an apparently higher reactivity of (**6**H$^+$) relative to (**6**Me$^+$). This alternative mechanism, which would require a proton switch from C–H to N involving a formal four-membered ring, is closely related to that proposed for the adducts of Meldrum's acid [equation (1)].[3,6,9] The reason for the different behaviour of the two systems is not apparent, although it is noticeable that the strongest evidence for an intramolecular reaction in the latter system relates to a series of secondary amino derivatives; evidence relating to tertiary derivatives (morpholino and piperidino) is much less conclusive.[9]

Influence of Chain Length on the Enolisation of Aminophenones.—It is helpful first to consider the influence of a positive charge on nitrogen using the results for the *N*-methylated aminoketones. For these systems, unlike the corresponding protonated compounds, there are no complications arising from kinetically equivalent pathways, and the results therefore serve as a useful reference point for later discussion.

Table 3. Enolisation of piperidinophenones in dilute hydroxide solution at 25 °C

Compound	*n*	k_o(calc)/s^{-1} [a]	k_o(obs)/s^{-1} [b]
(**2**)	2	12.9×10^{-3}	7.5×10^{-3}
(**3**)	3	8.0×10^{-5}	2.9×10^{-3}
(**4**)	4	3.1×10^{-5}	0.36
(**5**)	5	2.3×10^{-5}	0.12

[a] k_o(calc) = k_{OH}(RNMe$^+$)K_w/K_a(RNH$^+$). [b] k_o(obs) For reactions of RN in dilute hydroxide solution.

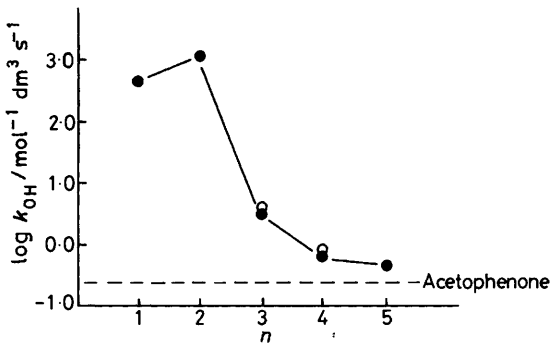


Figure 1. Enolisation of *N*-methylated aminophenones in hydroxide solutions: (●) piperidinophenones; (○) morpholinophenones

The present results extend the results obtained in earlier studies and confirm the general conclusions. This is illustrated in Figure 1 for the reactions between the various *N*-methylated aminoketones and OH$^-$. Particularly striking is the increased reactivity of the short-chain compounds relative to acetophenone, and the maximum observed for the β-derivative in the piperidino series. It is also clear that the same general trend occurs within the morpholino series. Although there will undoubtedly be significant inductive effects[17] in the α- and β-derivatives, the higher overall reactivity of the β-derivative points to a large contribution also from intramolecular electrostatic stabilisation, as in (**A**). The maximum rate acceleration (**2**Me$^+$) relative to acetophenone corresponds to a factor of *ca.* 4 000; similar effects are observed for acetate catalysis.[5]

The ionisation reactions of the free base forms of the piperidinophenones (**2**)—(**5**) in (an excess of) dilute hydroxide solutions all show pseudo-first-order rate constants of the general form in equation (22). The second-order rate constants

$$k_e = k_0 + k_{OH}[OH^-] \quad (22)$$

for reactions with hydroxide (k_{OH}) are all similar to that of acetophenone, varying between 0.3—0.6 mol^{-1} dm^3 s^{-1} compared with k_{OH} = 0.26 mol^{-1} dm^3 s^{-1} for acetophenone. Morpholino derivatives show similar behaviour except for the β-derivative which is slightly more reactive (k_{OH} = 1.6 mol^{-1} dm^3 s^{-1}), again presumably due to an additional inductive effect of the oxygen atom.

The intercepts, k_0, may be interpreted in two ways: (i) the hydroxide-catalysed enolisation of the protonated aminophenones (RNH$^+$ + OH$^-$), or (ii) the spontaneous reaction of the free base form (RN).

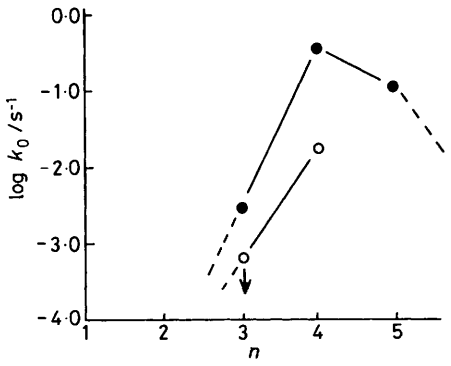


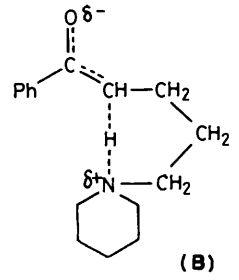
Figure 2. Effect of chain length on the intramolecular base-catalysed enolisation of aminophenones: (●) piperidinophenones; (○) morpholinophenones

In the former case the observed k_0 value is given by equation (23),[5] where k_{OH} is the rate constant for reaction between

$$k_0 = k_{OH}K_w/K_a \qquad (23)$$

$RNH^+ + OH^-$, and K_a is the acidity constant for RNH^+. In order to estimate k_0 values corresponding to (i) we have used k_{OH} values for reaction between the hydroxide and the corresponding methylated derivatives ($RNMe^+$). Table 3 shows a comparison between the calculated and observed k_0 values for compound (**2**)—(**5**).

The results in Table 3 are particularly revealing. For β-piperidinopropiophenone (**2**) the intercept can be accounted for quite satisfactorily by a reaction between ($2H^+$) and hydroxide. There is no evidence for any significant contribution from a spontaneous reaction of the free base in these solutions. For the γ-derivative (**3**), as discussed earlier,[8] although there is undoubtedly some ambiguity, the observed k_0 value is sufficiently larger than that estimated on the basis of the known reactivity of ($3Me^+$) to suggest that it represents predominately the reaction of the neutral base form. As the chain length increases further to the δ- and ε-derivatives [(**4**) and (**5**)] there can be little doubt that the k_0 values correspond to the spontaneous reaction of the neutral bases. Furthermore the absolute reactivities of (**4**) and (**5**) are some 10^8 times that of acetophenone itself[5] in keeping with a dominant intramolecular proton-transfer process (proton switch)[6,7] to give the zwitterion, as in (**B**) [and similarly for (**5**)]. The faster rate for (**4**) is in keeping with earlier studies of intramolecular catalysis



(**B**)

of proton-transfer reactions, in which a six-membered ring, including the transferring proton, was found to be most favourable.[18]

The behaviour of the morpholinophenones is qualitatively similar, although for the β- and δ-derivatives it was difficult to measure with any certainty the intercept k_0 [equation (22)]. This is not surprising as the reaction between RNH^+ and OH^- will make a very small contribution because of the relatively low pK_a of the protonated morpholino derivatives [equation (23)]. Also the reduced basicity of the bases relative to the piperidino compounds should result in a lower rate constant for intramolecular base-catalysed processes, as in (**B**). For the δ-morpholinovalerophenone (**8**), however, there is a significant intercept, which again is clearly attributable to an intramolecular proton switch. Figure 2 shows the variation in the rate constants for the intramolecular base-catalysed reaction with chain length for the two series of compounds. As discussed above the reaction is not detectable for the β-derivatives because of the dominance of the reaction between OH^- and the protonated aminoketones (*cf.* Figure 1).

We may use the results for the two δ-compounds [(**4**) and (**8**), $n = 4$] to estimate a Brönsted β-value for the process. Thus the log k_0 values for the two compounds (−0.44 and −1.77 respectively) combined with the difference in pK_a of the two amines (2.4) correspond to $\beta = 0.55$. In addition, this value, combined with the rate constant for the intermolecular reaction between pyridine and acetophenone, may be used to provide a crude estimate of the efficiency of intramolecular catalysis *via* the effective concentration $c_i = k_0/k_2^*$, where k_2^* refers to intermolecular catalysis by a (hypothetical) base of the same basic strength as that of the intramolecular group. Extrapolation of the results for pyridine ($k_{Py} = 1.43 \times 10^{-5}$ mol^{-1} dm^3 s^{-1})[5] to that for a base with p$K_a = 7.6$ (as in δ-morpholinovalerophehone (**8**) using $\beta = 0.55$ gives an estimated k_2^* value of 3×10^{-4} mol^{-1} dm^3 s^{-1} *i.e.* an effective molarity for the intramolecular catalyst of 56M. Although low compared with the enormous values sometimes observed for intramolecular nucleophilic processes (10^8M),[19] it is high for a proton-transfer reaction. For flexible ring systems involving, for example, carboxylate catalysis effective molarities are normally less than 1M, but values ~20M have been reported for 2-acetylbenzoate and related systems.[19–21]

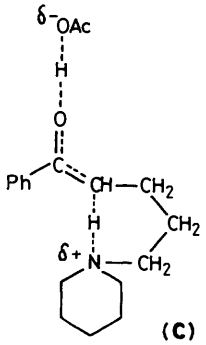
Finally, we consider the results for the δ-piperidinovalerophenone (**4**) in acetate buffers. The results are characterised by a large intercept in the plot of k_e *vs.* [OAc^-], which again may be attributed to the intramolecular base-catalysed proton-transfer reaction. The rate constant for this process may be obtained by combining the observed intercept with the fraction of the substrate in the free base form (RN) from equation (24). If

$$\frac{[RN]}{[RNH^+]_T} = \frac{[OAc^-]}{[HOAc]} \cdot \frac{K_{RNH^+}}{K_{HOAc}} \cdot \gamma_\pm^2 \qquad (24)$$

we assume a pK_a (RNH^+) of 10.0 (*cf.* values for the α, β, γ aminoketones and *N*-methylpiperidine of 8.28, 9.20, 9.65, and 10.1[22] respectively) then the intercept for $r = [OAc^-]/[HOAc]$ corresponds to a rate constant for the free base of 0.23 s^{-1}. Considering the uncertainty in the pK_a ($4H^+$) this compares favourably with the observed value in dilute hydroxide solution of 0.35 s^{-1}.

The acetate-catalysed reaction has been represented in the Results section as a reaction between RNH^+ and OAc^- ($k_{OAc} = 1.5 \times 10^{-5}$ mol^{-1} dm^3 s^{-1}, $I = 0$). However, this is kinetically equivalent to a reaction between the free base and HOAc as in (**C**), *i.e.* the dominant reactions in acetate buffers are the spontaneous (water-assisted) (**B**) and acetic acid-catalysed intramolecular proton transfer from the α-CH group to the piperidine nitrogen (**C**) (intercept and slope respectively of a plot of k_e against [HOAc]). Such a mechanism would be of some interest in relation to recently reported evidence of concerted acid–base catalysis in the keto–enol tautomerism of acetone.[23,24] It is difficult to decide between the two possibilities, but it is noticeable that if the former case is assumed, the k_{OAc} value obtained is some 20 times higher than that of OAc^- with acetophenone.[5]

This is perhaps unexpectedly large as, for example, the rate



(C)

constant for the reaction of the NMe^+ derivative (**4**Me^+) with OH^- is only a factor of two higher than that of acetophenone, suggesting that for the δ-compound the positive charge does not have a significant influence on the reactivity.

Conclusions

There are two important factors responsible for the high reactivity of aminoketones compared with simple ketones. First is the influence of the positive charge in the protonated (and *N*-methylated) derivatives, which is strong in the α- and especially the β-position. Secondly, there is intramolecular general base catalysis by the neutral amino group, which reaches a maximum for the δ-derivatives, corresponding to a six-membered transition state including the transferring proton.

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