Intramolecular Catalysis in the Enolisation of Aminoketones

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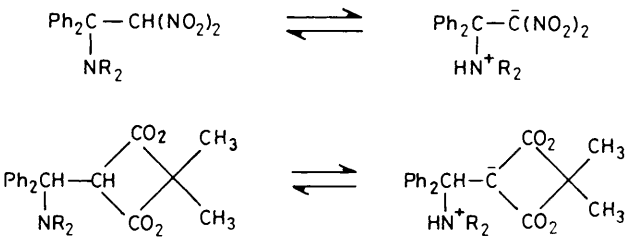
Measurements are reported on the rates of halogenation of the aminoketones $PhCO(CH_2)_nNC_5H_{10}$, with $n = 1$—3 [(**III**), (**II**), and (**IV**) respectively], and *N*-methyl-4-piperidone (**V**), and their *N*-methyl derivatives. The reactions are zero order with respect to halogen concentration, with the rate-determining step being the formation of the enol or enolate ion. Large rate accelerations relative to acetophenone and cyclohexanone were observed, and these cannot be explained entirely in terms of inductive (through-bond) effects of $>NH^+$, $>NMe^+$, or $>N$ groups. Other important factors are (i) intramolecular stabilization of the developing negative charge by the positive ammonium ion, the maximum effects being observed for (**II**); (ii) electrostatic interactions with negatively charged catalysts; (iii) direct proton transfer from the ionising C–H group to $>N$, acting as an intramolecular base catalyst. Evidence for a direct proton transfer was found only in reactions of the γ-substituted aminoketone (**IV**).

Intramolecular proton transfer between carbon and oxygen or nitrogen is well documented, and frequently plays an important role in reactions of model enzyme systems.[1] In most cases maximum effects, in terms of the effective molarities of the internal acids–bases, have been observed when cyclic transition states containing six to eight atoms (including the transferring proton) can be formed.[2-6] Recently, however, Bernasconi and his co-workers[7-9] have presented evidence for intramolecular proton transfer involving amino groups for systems in which formally only four atoms are involved (Scheme 1). It was suggested that one or more bridging water molecules may be involved in the proton-transfer reactions, and conditions under which intramolecular pathways may predominate have been discussed in some detail.[9]

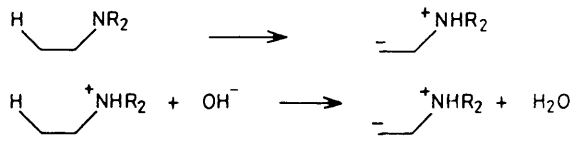
A difficulty common to studies of intramolecular catalysis is to distinguish between the intramolecular pathway and kinetically equivalent pathways involving external catalysts, as, for example, in Scheme 2. In fact, evidence for intramolecular proton transfer comes from the observation of a rate which is too high to be explained in terms of external pathways, based upon extrapolation from known related systems.[2,9]

Two examples of reactions for which the lower pathway in Scheme 2 appears to predominate have been reported recently. These are the β-elimination of 9-(dimethylaminomethyl)fluorene (**I**)[10,11] and the enolisation of β-piperidinopropiophenone (**II**).[12] In the former case the *N*-protonated substrate and the trimethylammonium iodide derivative react at similar rates, and are *ca.* 1 000 times more reactive towards hydroxide ions than the neutral form (**I**). The protonated form of (**II**) is up to 4 000 times more reactive towards various bases such as carboxylate ions and hydroxide than either (**II**) itself or acetophenone. The methiodide derivative of (**II**) displays ionisation or enolisation rates very similar to those of (**IIIH**$^+$),[12] and this suggests that the high reactivity of the protonated form is due to electrostatic stabilization of the developing negative charge, rather than to general acid catalysis by the $^+HN<$ group. It is also likely that significant inductive effects arising from the positive ammonium ion may be present.[13]

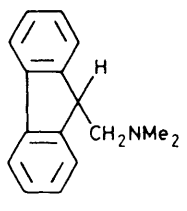
In the present paper we extend our earlier work[12] to include a study of the halogenation of the aminoketones (**III**)—(**V**) (α-piperidinoacetophenone, γ-piperidinobutyrophenone, and *N*-methyl-4-piperidone, respectively) and their methiodide derivatives, in several different buffers and dilute hydroxide solution. In these reactions the halogen (iodine or bromine) acts as a scavenger by reacting with the enol or enolate formed on proton



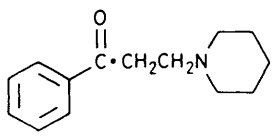
Scheme 1.



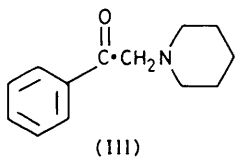
Scheme 2.



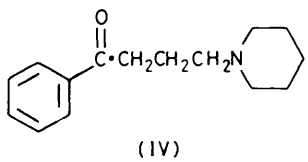
(I)



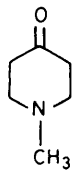
(II)



(III)



(IV)



(V)

transfer from the CH_2 group adjacent to the carbonyl group. In combination with earlier results for the aminoketone (**II**) this enables an investigation of the influence of electrostatic stabilization, inductive effects, and intramolecular proton transfer on the ionisation of aminoketones to be made.

Experimental and Results

Materials.—The hydrochlorides of the free bases (**III**) and (**IV**) were prepared by reacting the corresponding commercial halides with piperidine (1:2 mole ratio) in diethyl ether and toluene, respectively. They were purified by literature methods,[14,15] had m.p.s in good agreement with literature values, and gave satisfactory elemental analysis. Compound (**V**) was a commercial sample (Fluka). The methiodides were prepared by reaction of the free base with excess of CH_3I in anhydrous diethyl ether at room temperature [16] and purified by recrystallization from ethanol–water (1:1 v/v) in the presence of a trace of HI. The preparation of (**II**) and its methiodide derivative have been described previously [12] [note: the m.p. of the hydrochloride of (**II**) was erroneously reported in ref. 12 as 142—143 °C; the correct value is 192—193 °C]. Bromination reactions of the *N*-methylated derivatives in hydroxide solution were carried out using the *N*-methyl chloride salts rather than iodides. Solutions of the *N*-methyl chlorides were prepared from the *N*-methyl iodides by stirring with an excess of freshly prepared AgCl for at least half an hour and then filtering off the AgCl–AgI mixed precipitate. Cyclohexanone was purified by distillation under reduced pressure. The buffers used (see below) were prepared from commercial materials, purified by standard means where appropriate.

pK_a *Determinations.*—The pK_a values of the aminoketones (**III**)—(**V**) 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, were as follows: pK_a ($IIIH^+$) 8.28 (±0.03), pK_a (IVH^+) 9.65 (±0.10), and pK_a (VH^+) 9.20 (±0.05).

Kinetic Measurements.—All reactions were followed spectrophotometrically using a Gilford 2400S, a Unicam SP700, or a Durrum–Gibson stopped-flow apparatus. The rate of disapperance 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 dm^3 mol^{-1} cm^{-1}. In each series of reactions the ionic strength was made up to a constant value (0.15—0.3M) by the addition of $NaClO_4$ or KCl. Bromination rates were measured in dilute hydroxide solutions (0.02—0.2M) 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 reactions were measured at 25 (±0.2) °C.

Halogenation of α-Piperidinoacetophenone (**III**) *and its Methiodide Derivative* ($IIIMe^+$).—The rates of iodination of the protonated aminoketone ($IIIH^+$) were measured in several buffer systems and in dilute HCl solutions. Aminoketone concentrations were in the range $1 \times 10^{-3}—5 \times 10^{-3}$M. Low iodide concentrations were necessary to prevent reversibility, particularly at low pH values. 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). This is expected when the ionisation (or enolisation) of the aminoketone is rate determining.

Table 1. Rates of iodination[a] of ($IIIH^+$) in buffers at 25 °C

Base (B)	r[b]	[B]/M	10^6k_o/ s^{-1}	10^4k_B/ l mol^{-1} s^{-1}
Chloroacetate	0.5	0.025—0.1	1.1	0.325
Mandelate[c]	1.0	0.015—0.15	2.5	1.16
Acetate	0.2	0.002—0.012	1.9	8.42
Acetate	1.0	0.005—0.04	6.3	8.53
Pyridine	0.2	0.002—0.016	5.3	24.3
Pyridine	1.0	0.005—0.05	11.5	26.2

[a] $[I^-] = 0.01$M, ionic strength $I = 0.3$M. [b] r = [base]/[acid]. [c] $C_6H_5CH(OH)CO_2^-$.

The observed rate law has the form (1), in which $[(IIIH^+)]_T$

$$-d[I_2^*]/dt = k_e[(IIIH^+)]_T \quad (1)$$

refers to the stoicheiometric concentration of the aminoketone hydrochloride added to the reaction mixture, and $[I_2^*]$ refers to the total concentration of iodine ($[I_2] + [I_3^-]$). Rates were measured initially in dilute HCl solutions, with $0.01 \leqslant [H^+] \leqslant 0.1$M, and $[I^-] = 2 \times 10^{-3}$M. Even at this low iodide concentration there was a significant amount of reversibility, but from initial slopes a value for the spontaneous (water-catalysed) rate constant of $k_{H_2O} = 1.1 \times 10^{-6}$ s^{-1} was obtained.

In buffer solutions k_e was of the form (2), in which B

$$k_e = k_o + k_B[B] \quad (2)$$

represents the basic component of the buffer. Table 1 lists values of k_o and k_B obtained in different buffer solutions. Values of k_e calculated from equation (2), using k_o and k_B values from Table 1, agreed within 5% with experimental values.

Values of k_o can in principle be used to estimate k_{OH}, assuming that $k_o = k_{H_2O} + k_{OH}[OH^-]$. In practice, however, the k_o values are subject to large uncertainties, as small changes in slope of k_e *versus* [B] plots lead to large variations in k_o (*cf.* ref. 12). Taking the largest k_o value from Table 1 (pyridine, $[Py] = [PyH^+]$), together with $k_{H_2O} = 1.1 \times 10^{-6}$ s^{-1}, we may estimate $k_{OH} = 5 \times 10^3$ l mol^{-1} s^{-1} ($I = 0.3$M).

Ionisation rates in dilute hydroxide solutions were measured directly under pseudo-first-order conditions as rates of bromination, in solutions containing a slight excess of bromine.[12,17] Under these conditions the aminoketone hydrochloride is converted into the free aminoketone, and the observed rate law is shown in equation (3). In the concentration

$$-d[OBr^-]/dt = k_e[(III)] \quad (3)$$

range $0.01 \leqslant [OH^-] \leqslant 0.08$M, the observed rate constant was independent of $[OH^-]$, with a value of $k_e = 1.6 (\pm 0.3) \times 10^{-2}$ s^{-1}. This suggests that, even in dilute hydroxide solutions, the dominant reaction is between ($IIIH^+$) and OH^-. As the pH is increased, the observed rate constant for this reaction reaches a maximum value, k_e(max.), given by equation (4),[10,12] where K_a

$$k_e(\text{max.}) = k_{OH}K_w/K_a \quad (4)$$

is the acidity constant of the protonated aminoketone. Substitution of measured values into equation (4) gives $k_{OH} = 8.5 \times 10^3$ l mol^{-1} s^{-1} ($I = 0$).

Attempts were made to measure the rates of iodination of the *N*-methylated derivative of the aminoketone (**III**), ($IIIMe^+$), but these were unsuccessful due to the reversibility of the reaction. It was, however, possible to measure the ionisation

rates in dilute hydroxide solutions by stopped-flow, using the bromination reaction as described above. In this case the observed first-order rate constant, k_e [*cf.* equation (3)] was directly proportional to the hydroxide concentration and thus may be written as in equation (5). The value of k_{OH} obtained

$$-d[OBr^-]/dt = k_{OH}[OH^-][(IIIMe^+)] \quad (5)$$

from measurements in various hydroxide solutions ($0.02 \leqslant [OH^-] \leqslant 0.2$M) at a constant ionic strength of 0.2M ($NaClO_4$) was $k_{OH} = 2.7 (\pm 0.2) \times 10^2$ l mol^{-1} s^{-1}.

Halogenation of γ-Piperidinobutyrophenone (**IV**) *and its Methiodide Derivative* (**IVMe**$^+$).—The rates of iodination of the aminoketone (**IVH**$^+$) were studied in several buffers. The reactions were in all cases zero-order with respect to iodine concentration, but the rate constants obtained were not sufficiently reproducible to enable reliable catalytic constants to be obtained. The reason for this is uncertain, but it is most likely to be due to small amounts of reactive impurities. These may have a significant effect on zero-order halogenation reactions where only the consumption of the first few percent of the substrate is monitored. No such difficulties were encountered for the bromination reactions under first-order conditions[17] in dilute hydroxide solutions, and rates of bromination were measured for (**IV**) and (**IVMe**$^+$) with $0.02 \leqslant [OH^-] \leqslant 0.2$M ($I = 0.2$M, $NaClO_4$). In both cases there was a relatively fast consumption of 2 mol of OBr^-, independent of $[OBr^-]$ as expected for the enolisation reaction, followed by a much slower additional consumption of OBr^-.[12] The rate law from bromination of (**IV**) is given by equations (6) and (7) (*cf.* β-piperidinopropiophenone[12]), and that of (**IVMe**$^+$) by equations (8) and (9).

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

$$k_e/s^{-1} = 2.9 (\pm 0.4) \times 10^{-3} + 0.21 (\pm 0.02)[OH^-] \quad (7)$$

$$-d[OBr^-]/dt = k_e[(IVMe^+)] \quad (8)$$

$$k_e/s^{-1} = 1.8 (\pm 0.1)[OH^-] \quad (9)$$

Halogenation of N-*Methyl-4-piperidone* (**V**) *and its Methiodide Derivative* (**VMe**$^+$).—Experimental conditions for the iodination of aminoketone (**VH**$^+$) and its methiodide (**VMe**$^+$) were the same as those for the α-piperidinoacetophenone (**III**), except for substrate concentrations which were 5×10^{-3}M $\leqslant [(V)] \leqslant 5 \times 10^{-2}$M, and 5×10^{-4}M $\leqslant [(VMe^+)] \leqslant 10^{-2}$M. The observed rate laws were analogous to those in equations (1) and (2), and values of k_o and k_B obtained in different buffers are given in Table 2.

The iodination rates were also measured in dilute acid solution. The reactions showed a significant amount of reversibility, but from initial slopes values of rate constants given by equations (10) and (11) were obtained.

$$k_e(VH^+)/s^{-1} = 1.6 \times 10^{-7} + 1.62 \times 10^{-6}[H^+] \quad (10)$$

$$k_e(VMe^+)/s^{-1} = 1.8 \times 10^{-7} + 2.72 \times 10^{-6}[H^+] \quad (11)$$

The rates of bromination of (**V**) in dilute hydroxide solutions were measured. The overall stoicheiometry of the reaction corresponded to the consumption of 4 moles Br_2 per mol (**V**), as expected for bromination on both CH_2 groups adjacent to the carbonyl group. However, the first-order rate plots showed some deviation from linearity suggesting that the first bromination step was not completely rate determining. The overall kinetic behaviour was similar to that of (**IVH**$^+$), with the (approximate) first-order rate constant given by equation (12).

$$k_{OH}/s^{-1} = 5.5 (\pm 1.5) \times 10^{-4} + 0.13 (\pm 0.01)[OH^-] \quad (12)$$

The bromination of (**VMe**$^+$) in hydroxide solutions was also investigated, but the compound was not sufficiently stable under these conditions to allow reasonable rate measurements.

Iodination of Cyclohexanone.—The iodination of cyclohexanone was studied for comparison with the aminoketone (**V**). Rates were available from previous studies in acetate buffers [$k_B = 4.7 (\pm 1.0) \times 10^{-7}$ l mol^{-1} s^{-1}][18–20] and pyridine buffers ($k_B = 1.15 \times 10^{-5}$ l mol^{-1} s^{-1}).[21] Values in pyridine buffers with several different buffer ratios were checked under the present conditions and the result obtained, $k_B = 1.26 (\pm 0.03) \times 10^{-5}$ l mol^{-1} s^{-1}, was in good agreement with that of Feather and Gold.[21]

In all cases, the results for the halogenation reactions are consistent with a simple rate-determining reaction between the substrate and the added base to form an enol (or enolate ion) which reacts rapidly with the halogen, as previously observed[12] for reactions of (**II**) and (**IIMe**$^+$). Reactions between an anion and a cation [*e.g.* (**IIIMe**$^+$) and OH^-] are subject to a large kinetic salt effect. Allowance for this may be made by correcting k_B values to zero ionic strength using the Davies equation (13),[22] in which I is the ionic strength and A is the Debye–Hückel parameter.

$$\log \gamma_\pm = -Az^2I^{1/2}/(1 + I^{1/2}) + Az^2I/3 \quad (13)$$

The catalytic constants for the carboxylate ions show a regular increase with base strength and the slopes of Brönsted plots for (**IIH**$^+$), (**IIIH**$^+$), and (**VH**$^+$) correspond to Brönsted β values of 0.64,[12] 0.75, and 0.69, respectively. In no case was there any evidence for catalysis by the acid forms of the buffer solutions.

Table 2. Rates of iodination[a] of (**VH**$^+$) and (**VMe**$^+$) in buffers at 25 °C

Base (B)	r[b]	[B]/M	10^7k_o/ s^{-1}	10^4k_B/ l mol^{-1} s^{-1}
(i) (**VH**$^+$)				
Chloroacetate	0.2	0.02—0.20	2.1	0.160
Chloroacetate	1.0	0.022—0.20	3.2	0.130
Mandelate[c]	1.0	0.015—0.15	7.6	0.585
Acetate	0.2	0.005—0.05	3.0	2.90
Acetate	1.0	0.005—0.05	8.0	2.85
Pyridine	4.9	0.0037—0.37	3.6	4.02
(ii) (**VMe**$^+$)				
Chloroacetate	0.5	0.025—0.25	1.8	0.183
Chloroacetate	3.9	0.025—0.25	4.1	0.176
Mandelate[c]	1.0	0.015—0.15	2.4	0.701
Acetate	1.0	0.0025—0.10	3.6	2.18
Pyridine	4.0	0.004—0.04	8.6	5.00

[a] $[I^-] = 0.005$M for (**VH**$^+$), 0.01M for (**VMe**$^+$); ionic strength = 0.3M (KCl). [b] r = [base]/[acid]. [c] $C_6H_5CH(OH)CO_2^-$.

Discussion

Catalytic constants for the ionisation of α-(**IIIH**$^+$) and β-(**IIH**$^+$) and β-(**VH**$^+$) are summarised in Table 3. Large accelerations relative to acetophenone and cyclohexanone are evident, and these may be attributed to inductive effects[13] and electrostatic catalysis (*cf.* ref. 12). Values of k_B for (**VH**$^+$) and (**VMe**$^+$) are very similar to each other (Table 2) as expected from the earlier results for (**IIH**$^+$) and (**IIMe**$^+$). In addition, for

Table 3. Catalytic constants[a] for the iodination of aminoketones, acetophenone, and cyclohexanone at 25 °C

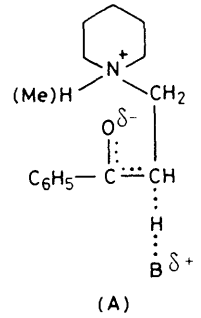
Base (B)	k_B/l mol^{-1} s^{-1} ($IIIH^+$)	(IIH^+)[b]	(VH^+)	Acetophenone[b]	Cyclohexanone
H_2O (s^{-1})	1.1×10^{-6}	1.1×10^{-6}	1.6×10^{-7}		
Chloroacetate	5.9×10^{-5}	8.4×10^{-5}	2.6×10^{-5}		
Mandelate	2.9×10^{-4}	1.1×10^{-4}			
β-Chloropropionate		7.4×10^{-4}			
Acetate	1.6×10^{-3}	1.7×10^{-3}	5.2×10^{-4}	8.4×10^{-7}	4.7×10^{-7}
Pyridine	2.5×10^{-3}	4.6×10^{-3}	4.0×10^{-4}	1.4×10^{-5}	1.3×10^{-5}
Hydroxide	8.5×10^{3}	6.2×10^{2}		0.26	

[a] Corrected to $I = 0$. [b] Ref. 12.

substrate (V), geometrical constaints would prevent direct transfer of a proton from nitrogen in any mechanism involving general acid catalysis by $^+HN<$.

In a recent study of electrostatic catalysis of proton-transfer reactions involving charged bases of the form $(CH_3)_3N^+(CH_2)_nNH_2$, Dahlberg *et al.*[23] found significant effects (up to a factor of 73) on the ionisation of chloroform, attributable to the presence of the positive charge; somewhat smaller effects were found for the ionisation of nitropropane (<5 fold). They suggested that the catalytic effects are best interpreted in terms of a field effect rather than an inductive mechanism for transmission of the polar interaction.

For the aminoketones, the greater accelerations shown for proton removal by anionic bases such as RCO_2^- and OH^- (> 10^3 fold) compared with those for the neutral base pyridine (*ca.* 10^2 fold) are also consistent with an important contribution from electrostatic catalysis, due to the attraction of the oppositely charged substrates and catalysts. This may be seen clearly from a comparison of the relative k_B values of acetate and pyridine for the neutral substrates acetophenone and cyclohexanone with those for the charged substrates ($IIIH^+$), (IIH^+), and (VH^+) (Table 3). However, in the charged substrates large inductive effects may also be involved. Thomas and Stirling[13] have shown, for example, that a β-Me_3N^+ group greatly increases the rate of ionisation of the α-CH_2 group in substrates of the type $PhSO_2CH_2CH_2Z$, and the observed rate increases could reasonably be attributed to a simple substituent effect. From the reported sensitivity of the ionisation rates of $PhCOCH_2CH_2Z$ to substituent effects in ethanol[13] (rates for $PhCOCH_2CH_2NR_3^+$ were not obtained) significant rate increases are also to be expected for $PhCOCH_2CH_2NR_3^+$ relative to the parent ketone.



(A)

In the ionisation of the aminoketones the ability of the (NH^+) or (NMe^+) group in the β-substrate (II) and γ-substrate (IV) to approach more directly the developing negative charge on the carbonyl group, as in conformation (A), does appear to play a role in the overall kinetic behaviour.

Table 4. Rates constants[a] for the hydroxide-catalysed halogenation of aminoketones and acetophenone at 25 °C

Substrate	($IIIMe^+$)	($IIMe^+$)	($IVMe^+$)	(II)[b]	(IV)	Aceto-phenone[b]
k_{OH}/ l mol^{-1} s^{-1}	4.8×10^2	1.2×10^3	3.2	0.46	0.21	0.26

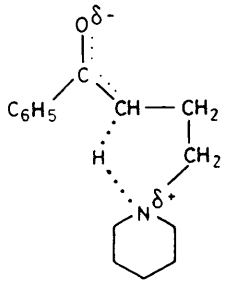
[a] Corrected to $I = 0$. [b] Ref. 12.

This may be seen in several aspects of the results. (i) Ionisation rates of (IIH^+) are normally slightly higher than those for the α-substituted substrate ($IIIH^+$), whereas a simple inductive effect would predict the opposite. (ii) Restriction of the conformational mobility of the positive charge in (VH^+) [relative to (IIH^+)] and (VMe^+) [relative to ($IIMe^+$)] leads to an average seven-fold reduction in the observed ionisation rate. (iii) Inspection of the hydroxide-catalysed ionisation rates given in Table 4 shows a clear maximum for ($IIMe^+$), but also a substantial rate acceleration for the *N*-methylated γ-substituted aminoketone ($IVMe^+$) relative to the neutral substrate (IV). Thus *N*-methylation in the γ-position, where inductive effects should be very small, gives rise to a 15-fold rate increase. This is most likely due to formation of a transition state analogous to (A), with the lower reactivity relative to that of ($IIMe^+$) being due to a combination of a much reduced inductive effect and a lower probability of intramolecular assistance *via* a transition state of the form shown in (A).

Neither of the β-substituted aminoketones (II) and (V) shows any evidence for a direct intramolecular proton switch as illustrated in the upper pathway of Scheme 2. In both cases the ionisation rates in dilute hydroxide solution contain a hydroxide-independent term, but these are best interpreted as reactions between the protonated substrate and OH^- (Scheme 2, lower pathway). Thus it was shown earlier[12] that k_{OH} (IIH^+) calculated on this basis is very similar to k_{OH} ($IIMe^+$). Furthermore, application of equation (4) to the results for (V), shown in equation (12), gives k_{OH} (VH^+) = 34.7 l mol^{-1} s^{-1}; this value, which is 17 times lower than k_{OH} (IIH^+), is quite reasonable in terms of the relative rates of ionisation of (IIH^+) and (VH^+) as discussed above, and does not suggest the need to consider additional reaction pathways.

Intramolecular base catalysis may, however, be important in the ionisation of the γ-substituted aminoketone (IV). By comparison with the results for ($IVMe^+$), the intercept of the plot of k_e *vs.* [OH^-] [2.9×10^{-3} l mol^{-1} s^{-1}, equation (7)] does appear to be too large to be attributed solely to a reaction between (IVH^+) and OH^-. Application of equation (4) to the intercept, on the assumption that it arises entirely from such an intermolecular pathways, gives k_{OH} (IVH^+) = 64.9 l mol^{-1} s^{-1}, which is 15 times larger than the measured k_{OH} ($IVMe^+$). In view of the results for the aminoketone (II),[12] such an increase

in reactivity of (IVH^+) compared with ($IVMe^+$) seems unreasonable. It is much more likely, then, that the major part of the hydroxide-independent rate arises from a direct proton transfer (*cf.* lower path, Scheme 2), with a transition state as shown in (B). It is hoped to obtain more information on this



(B)

possibility by studying the ionisation of the δ-substituted aminoketone (δ-piperidinovalerophenone). With this substrate formation of a rather more favourable transition state[2-6] containing six atoms including the transferring proton is possible.

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