Mechanism and proton activating factors in base-induced β-elimination reactions of *N*-[2-(4-pyridyl)ethyl]quinuclidinium and *N*-[2-(2-pyridyl)ethyl]quinuclidinium salts †

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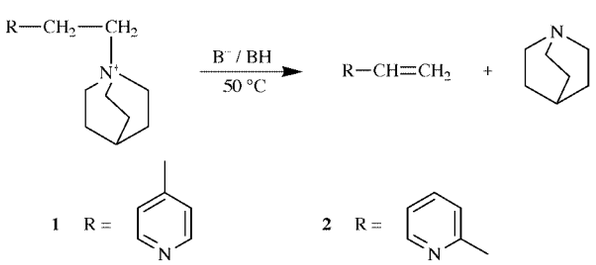
β-Elimination reactions of *N*-[2-(4-pyridyl)ethyl]quinuclidinium and *N*-[2-(2-pyridyl)ethyl]quinuclidinium salts (**N**) in acetohydroxamate–acetohydroxamic acid buffer, H_2O, $\mu = 1$ M KCl, 50 °C, with the formation of 4- or 2-vinylpyridine, respectively, proceed by an E1cb mechanism with carbon deprotonation occurring in the substrates protonated at the pyridine ring (**NH**$^+$). The formation of the intermediate carbanion has a high degree of reversibility. The systems consistently present H/D exchange. **NH**$^+$ is much more reactive than **N**; this can be attributed to the strong stabilization of the intermediate carbanion formed from **NH**$^+$ due to resonance.

Introduction

β-Elimination reactions are processes of mechanistic interest.[1–7] It has been shown[8–11] that base-induced β-elimination reactions from systems with tertiary amine leaving groups and strong β-activating groups such as *p*-nitrophenyl or *o*-nitrophenyl, proceed by an E1cb mechanism; the intermediate carbanion is formed with different degrees of reversibility depending on the structure of the leaving group and on the activating system.

As an extension of our studies on these systems, we studied the mechanism of the base-induced β-elimination reactions activated by a pyridine ring. In spite of the importance of heteroaromatic chemistry, little information is available about the elimination reactions of these systems.

The following substrates were studied: the isomeric *N*-[2-(4-pyridyl)ethyl]quinuclidinium, **1**, and *N*-[2-(2-pyridyl)ethyl]-quinuclidinium, **2** (see Scheme 1).



Scheme 1

The reactions were carried out in acetohydroxamate–acetohydroxamic acid buffer in order to be able to compare the results with those of previously studied substrates.[10,11]

An important aspect of the study of these reactions was to check for catalysis by protonation of the nitrogen atom of the pyridine ring and, if present, to compare the processes in the two isomeric substrates. The problem of measuring the effect of protonation at one reaction site upon susceptibility to an attack by a base at another site, known as proton activating factors (PAF),[12–14] is receiving attention in the literature due to its relevance in chemistry and biochemistry.

The two previously used techniques,[10,11] acid–base catalysis and H/D exchange, were adapted for the study of our substrates.

Results and discussion

Kinetic study in OH^-/H_2O

The reactions of **1** and **2** in OH^-/H_2O, 50 °C, $\mu = 1$ M KCl are complete elimination reactions with the formation of 4- and 2-vinylpyridine, respectively.

The kinetics were studied by following the formation of 4- or 2-vinylpyridine at $\lambda = 280$ nm or at $\lambda = 290$ nm, respectively. The reactions are second order, first order with respect to both the substrate and [OH^-].

In this reaction medium, the reacting species are the unprotonated substrates, **N**; the second order rate constants are $k_{OH}^{N} = 3.45 \times 10^{-3}$ dm^3 mol^{-1} s^{-1} for **1** and 0.271×10^{-3} dm^3 mol^{-1} s^{-1} for **2** (at 50 °C, $\mu = 1$ M KCl). Isomer **1** is therefore 12.7 times more reactive than **2** under these reaction conditions. These rate constants can be compared with values of $k_{OH} = 16.5 \times 10^{-3}$ dm^3 mol^{-1} s^{-1} for *N*-[2-(*p*-nitrophenyl)ethyl]quinuclidinium (measured following the formation of *p*-nitrostyrene at $\lambda = 336$ nm, OH^-/H_2O, $\mu = 1$M KCl, 50 °C) and of $k_{OH} = 1.14 \times 10^{-3}$ dm^3 mol^{-1} s^{-1} for *N*-[2-(*o*-nitrophenyl)ethyl]quinuclidinium[11] under the same reaction conditions.

From these data it is not possible to determine if the mechanism is E2, E1cb reversible, $(E1cb)_R$, or E1cb irreversible, $(E1cb)_I$, since all three mechanisms would follow the second order kinetic law. However an NMR study of H/D exchange in OD^-/D_2O, 50 °C, showed that neither **1** nor **2** incorporated deuterium into the reacting substrate or into the vinylpyidine formed. These experimental results exclude the $(E1cb)_R$ mechanism in this reaction medium.

Acid–base catalysis

The pseudo first order rate constants (k'_{obs}, s^{-1}; initial rate) in acetohydroxamate–acetohydroxamic acid buffer at different pH values were determined by following the formation of 4- or 2-vinylpyridine from **1** and **2** at $\lambda = 280$ nm and $\lambda = 290$ nm, respectively, in H_2O, $\mu = 1$ M KCl, 50 °C.

In the following discussion we call **N** the substrate unprotonated at the basic nitrogen of the pyridine ring, and **NH**$^+$ its conjugate acid. As will be shown, the model is consistent with the substrate protonated at the basic nitrogen, **NH**$^+$, which undergoes carbon deprotonation in the β-position with respect

† Tables of kinetic data are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p2/a9/a908881d/

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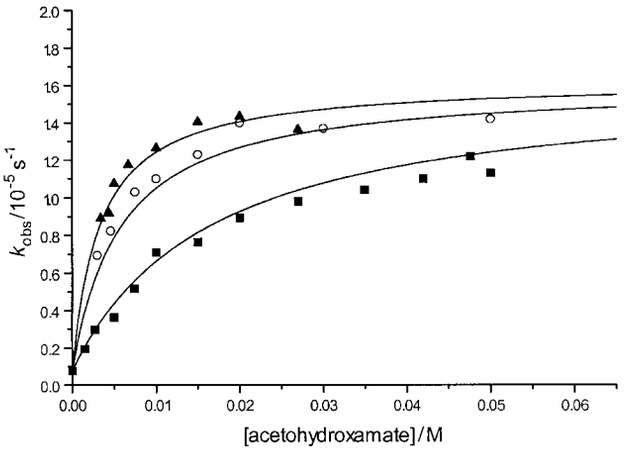


Fig. 1 Dependence of the k_{obs} (s^{-1}) on [acetohydroxamate] at various pH values for substrate **1**. Solid square pH = 9.15; open circle pH = 8.70; solid triangle pH = 8.45.

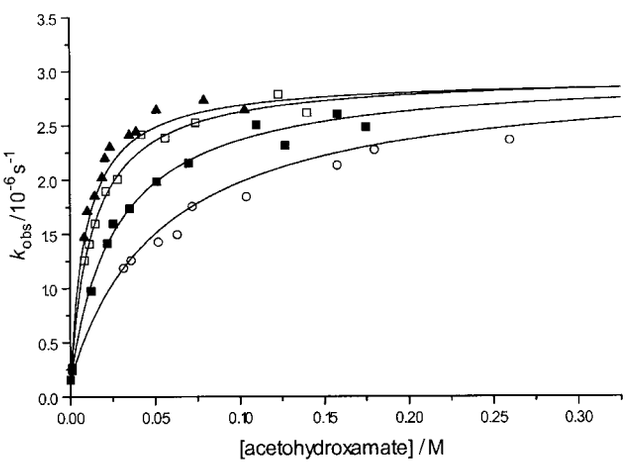


Fig. 2 Dependence of the k_{obs} (s^{-1}) on [acetohydroxamate] at various pH values for substrate **2**. Open circle pH = 9.45; solid square pH = 9.15; open square pH = 8.85; solid triangle pH = 8.70.

to the leaving group. The limited contribution (<10%) of the reaction of unprotonated substrate, **N**, with OH^- was subtracted from k'_{obs} to give k_{obs}, s^{-1}, which are then related to the mechanism (Scheme 2) of the protonated substrate: $k_{obs} = k'_{obs} - k_{OH}^{N}[OH^-]$.

The plots of k_{obs} *vs.* the [acetohydroxamate] at different pH values are shown in Fig. 1 and Fig. 2.

The pK_a of $\mathbf{NH}^+$, determined at 50 °C, μ = 1 M KCl, is 4.85 for isomer **1** and 3.81 for isomer **2**.

As will be shown by kinetic analysis of the data, these results are consistent with the mechanism of Scheme 2.

Kinetics analysis by steady-state approximation gives the following equations:

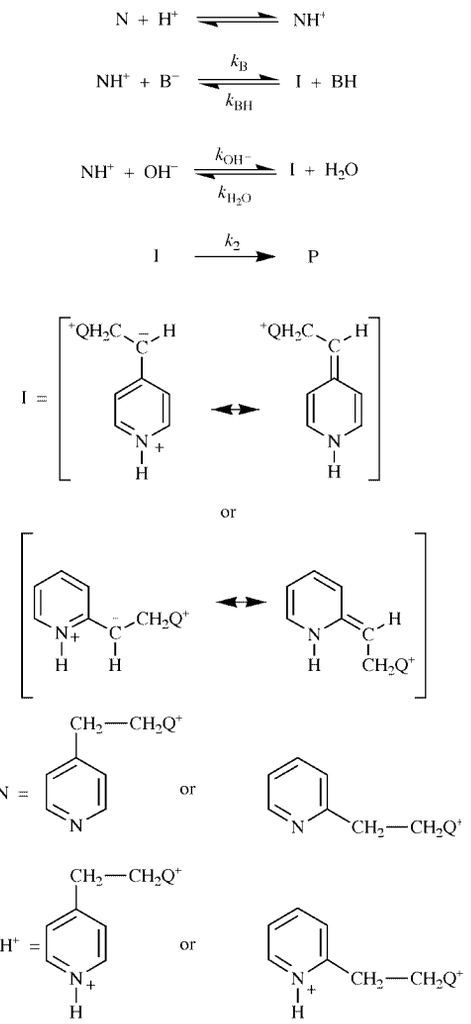
$$k_{obs} = \frac{k_2(k_{OH^-}[OH^-] + k_B[B^-])}{(k_{H_2O} + k_2 + k_{BH}[BH])} \cdot \frac{[H^+]}{K_a} \quad (1)$$

$$k_\infty = k_2 \cdot \frac{k_{OH^-}}{k_{H_2O}} \cdot \frac{K_w}{K_a} \quad (2)$$

$$k_\infty = k_2 \cdot \frac{k_B}{k_{BH}} \cdot R \cdot \frac{[H^+]}{K_a} = k_2 \cdot \frac{k_B}{k_{BH}} \cdot \frac{K_a^T}{K_a} \quad (3)$$

$$k_0 = k_{OH^-} \cdot \frac{k_2}{(k_2 + k_{H_2O})} \cdot \frac{K_w}{K_a} \quad (4)$$

$$k_0 = k_{OH} \cdot \frac{K_w}{K_a} \quad (5)$$



Scheme 2

$$k'_0 = k_{OH^-} \cdot \frac{K_w}{K_a} \quad (6)$$

$$\frac{k'_0}{k_0} = \frac{k_{H_2O} + k_2}{k_2} \quad (7)$$

$$\frac{k'_0 + k_\infty}{k_\infty} = \frac{k_{H_2O} + k_2}{k_2} \quad (8)$$

$$\frac{(k_{obs} - k_0)}{[BH]} \cdot \frac{(k_{H_2O} + k_2)}{k_2} = R \cdot k_B \cdot \frac{[H^+]}{K_a} - k_{obs} \cdot \frac{k_{BH}}{k_2} \quad (9)$$

$$k'_0 = k_{obs} \cdot \frac{(k_{H_2O} + k_2)}{k_2} + k_{obs}[BH] \cdot \frac{k_{BH}}{k_2} - k_B[B^-] \cdot \frac{[H^+]}{K_a} \quad (10)$$

$$k_{obs} = \frac{k'_0 + k_B \cdot [B^-] \cdot \frac{[H^+]}{K_a}}{\frac{(k_{H_2O} + k_2)}{k_2} + \frac{k_{BH}}{k_2} \cdot [BH]} \quad (11)$$

$R = [B^-]/[BH]$; pK_W = 13.23 (50 °C, μ = 1 M KCl); K_a^T = acidity constant of acetohydroxamic acid. $k_0 = k_{obs}$ ([buffer]→0); $k_\infty = k_{obs}$ ([buffer]→∞).

The curvature at each pH is consistent with a carbanion mechanism and a change in the rate determining step from carbon deprotonation, at low [BH], when $k_{BH}[BH] < k_2$, to leaving group expulsion, at high [BH], where reprotonation of the

Table 1 Rate constants for the β-elimination reactions of *N*-[2-(4-pyridyl)ethyl]quinuclidinium, **1**, and *N*-[2-(2-pyridyl)ethyl]quinuclidinium, **2**, in acetohydroxamate–acetohydroxamic acid buffer, H_2O, μ = 1 M KCl, 50 °C. (The rate constants refer to the mechanism of Scheme 2)

Substrate	k_B/dm^3 mol^{-1} s^{-1}	(k_{BH}/k_2)/ dm^3 mol^{-1}	$k_\infty/10^{-6}$ s^{-1}	$\frac{k_{H_2O} + k_2}{k_2}$	$k_0/10^{-6}$ s^{-1}	k_{OH}/dm^3 mol^{-1} s^{-1}
1	20.8	64	16.2	1.05	0.76	182
2	24.8	38	2.98	1.05	0.16	421

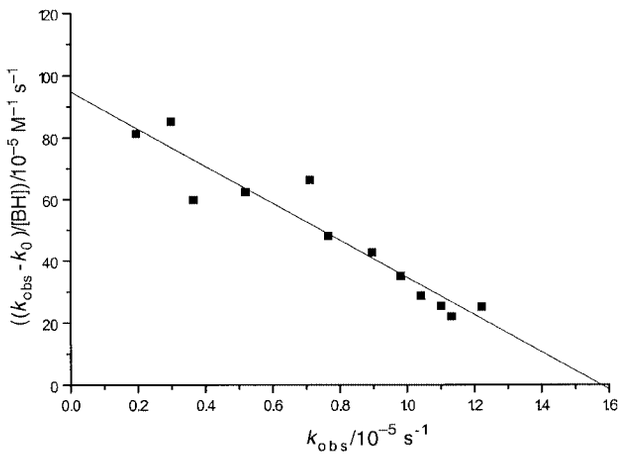


Fig. 3 Final plot with eqn. (9) for substrate **1** at pH = 9.15. Linear regression analysis gives the equation: $y = 94.8 \times 10^{-5} - 60.1x$; $r = -0.9520$.

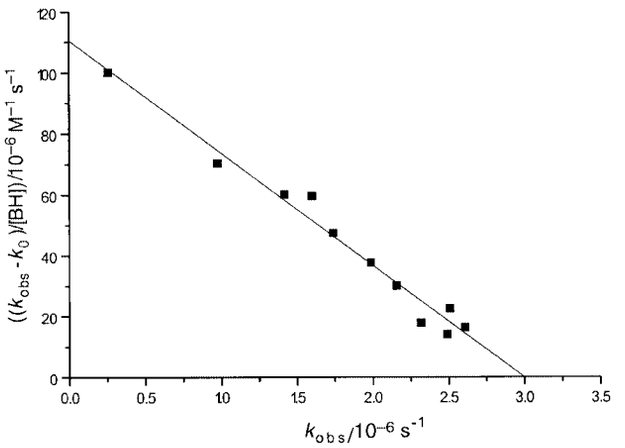


Fig. 4 Final plot with eqn. (9) for substrate **2** at pH = 9.15. Linear regression analysis gives the equation: $y = 110.5 \times 10^{-6} - 36.9x$; $r = 0.9874$.

intermediate carbanion by BH is faster than leaving group expulsion, and $k_{BH}[BH] > k_2$. It can be noted that the same levelling off occurs at different pH values (Fig. 1 and 2); this is evidence that base-induced carbon deprotonation occurs from **NH**$^+$, which is the substrate protonated at the basic nitrogen of the pyridine ring [eqn. (3)]. If the base induced carbon deprotonation occurred from the unprotonated substrate, **N**, the value of k_∞ would be dependent[11] on [OH$^-$].

The process from **N** to **I** represents an imino–enamino tautomerization and, when in real equilibrium (high [BH]), the overall process becomes pH-independent, since both tautomerization and leaving group expulsion are pH-independent.

The parameters of the mechanism were obtained by an iterative procedure,[10,11] adapted to our system. This procedure starts from eqn. (9), with a first approximation of the term $(k_{H_2O} + k_2)/k_2 = 1$; since the value of k_0 (intercept of the plots in Fig. 1 and Fig. 2 at $[B^-] = 0$) is unknown, a first approximation was made with the value of k_{obs} obtained at the lowest buffer concentration at pH = 9.15. A plot of $(k_{obs} - k_0)/[BH]$ against k_{obs} gives the first values of k_B (from the intercept), k_{BH}/k_2 (from the slope), and k_∞ [from eqn. (3)]. The term $(k_{H_2O} + k_2)/k_2$ is obtained from eqn. (8). A value for k_0' is then calculated from eqn. (10) and the new value of k_0 is determined from eqn. (7), which is used again in eqn. (9). The final parameters are obtained when the calculated values of the rate constants are stable. Once the parameters are calculated for the set of data at pH = 9.15, the values of $(k_{H_2O} + k_2)/k_2$ and k_0 are used in eqn. (9) with the sets of data for the other pH values. The average of the rate constants obtained at all the pH values is then taken. In Fig. 3 and Fig. 4 are reported the final plot with eqn. (9) with **1** and **2**.

The calculated rate constants for **1** and **2** are reported in Table 1.

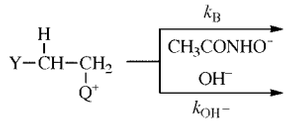
It can be noted from the data in Table 1 that the value of $k_B = 24.8$ dm^3 mol^{-1} s^{-1} for **2** is close to the value of $k_B = 20.8$ dm^3 mol^{-1} s^{-1} for **1**.

The degree of reversibility in the formation of the intermediate carbanion is greater for **1** than for **2**: the ratio k_{BH}/k_2 being 64.0 and 38 dm^3 mol^{-1}, respectively. The uncertainties in the k_B and k_{BH}/k_2 values, evaluated from the differences obtained at the different pH values, are ±10% with isomer **2** and ±20% with isomer **1**.

The uncertainties with **1** are larger, because this substrate had to be studied at $\lambda = 280$ nm, at low [buffer] and limited range of [buffer], due to the significant absorbance of the buffer system. Previously we reported[11] the rate constants for *N*-[2-(*p*-nitrophenyl)ethyl]quinuclidinium ($k_B = 19.4\times10^{-5}$ dm^3 mol^{-1} s^{-1}, $k_{BH}/k_2 = 11.5$ dm^3 mol^{-1} and $k_\infty = 1.7 \times 10^{-5}$ s^{-1}) and for *N*-[2-(*o*-nitrophenyl)ethyl]quinuclidinium ($k_B = 4.2 \times 10^{-5}$ dm^3 mol^{-1} s^{-1}, $k_{BH}/k_2 = 69.4$ dm^3 mol^{-1} and $k_\infty = 6.05 \times 10^{-7}$ s^{-1}) under the same reaction conditions.

It is of interest to compare the reactivity of **N** with that of **NH**$^+$ (proton activating factors, PAF) with the OH$^-$ base and with the acetohydroxamate base. The k_{OH}^N value is experimentally determined and the value of $k_{OH}(NH^+)$ can be calculated from k_0 and eqn. (5). The ratio $k_{OH}(NH^+)/k_{OH}^N$ is 5.3×10^4 with **1** and 1.5×10^6 with **2**.

Regarding the reaction with acetohydroxamate base, B, the values of k_B for **NH**$^+$ were calculated by an iterative procedure and are shown in Table 1. The k_B^N value (second order rate constant for carbon deprotonation of the unprotonated substrate, **N**, induced by B) can be estimated by a linear free energy relationship. For a system such as that reported in Scheme 3,



Scheme 3

with the activating system Y = *p*-nitrophenyl,[11] *o*-nitrophenyl,[11] pyridinium-2-yl and pyridinium-4-yl, a linear regression analysis of the plot of $\log(k_{OH})$ against $\log(k_B)$ gives eqn. (12).

$$\log(k_B) = -1.4 + 1.1 \log(k_{OH}) \quad (r = 0.994) \qquad (12)$$

The k_B^N values for **1** and **2** can then be calculated from the known k_{OH}^N values and eqn. (12). The calculated values are $k_B^N = 7.8 \times 10^{-5}$ dm^3 mol^{-1} s^{-1} for **1** and $k_B^N = 4.8\times10^{-6}$ dm^3

mol^{-1} s^{-1} for **2**. The k_B/k_B^N ratio (PAF with acetohydroxamate) is 2.7×10^5 for **1** and 5.2×10^6 for **2**.

The greater reactivity of $\mathbf{NH}^+$ compared with **N** can be attributed to the strong stabilization of the carbanion intermediate formed from $\mathbf{NH}^+$; this carbanion presents an enamine structure (see Scheme 2). Electrostatic interactions in the intermediate formed from the 2-isomer can also play an important role.[15]

It should be noted that the enamine intermediate from the 2-isomer can be an *E* or *Z* isomer; but this cannot be distinguished from our data. Therefore, the k_2 rate constant represents the overall process from the *E* and/or *Z* structure to products.

It can be noted that the PAF for the 2-isomer is larger than that for the 4-isomer both with the base OH^- and with acetohydroxamate, due to the different resonance energies involved in the stabilization of the two intermediates and to the differences in electrostatic interaction. This trend is similar to that reported[13] for keto-zwitterion tautomeric constants for phenacylpyridine, where log (PAF) is 7.2 for the 2-isomer and 5.7 for the 4-isomer. A value of log (PAF) = 4.83 is reported[14] for AcO^--induced carbon deprotonation from 2-phenacylpyrazine at 25 °C. PAF values for carbon deprotonation from several heteroaromatic systems have also been reported.[12]

H/D exchange

The E1cb reversible mechanism for the β-eliminations from **1** and **2** was confirmed by H/D exchange experiments. These experiments showed that **1** and **2** incorporate deuterium into the β position with respect to the leaving group during the elimination reaction in D_2O, acetohydroxamate–acetohydroxamic acid buffer. The experiments were performed using a previously described technique.[10,11]

In an experiment with substrate **1** at 50 °C, μ = 1 M KCl, $[B^-] = [BD] = 0.051$ M, when the elimination reached 36% of olefin formed, H/D exchange was 27%. With substrate **2** at 63 °C, μ = 1 M KCl, $[B^-] = 0.279$ M and $[BD] = 0.14$ M, when the elimination reached 25% of product formed, H/D exchange was 15%. Other experiments under similar conditions gave consistent results.

Conclusions

Compounds **1** and **2** react with acetohydroxamate–acetohydroxamic acid buffers in the elimination reaction by an E1cb mechanism. Carbon deprotonation occurs for the protonated substrate, $\mathbf{NH}^+$ (there is a limited concurrent reaction of **N** with OH^-). The PAF with the OH^- base are $5.3 \cdot 10^4$ for **1** and $1.5 \cdot 10^6$ for **2**. The large values of PAF are attributed to the enamine structure of the carbanion intermediate; in the reaction with **2**, electrostatic interactions can also be relevant in the intermediate carbanion.

Experimental

Materials

Glass distilled and freshly boiled water was used throughout. Reagent grade potassium chloride, acetohydroxamic acid (Aldrich) and 2-(2-hydroxyethyl)pyridine (Aldrich) were used without further purification. 4-Vinylpyridine (Aldrich) was purified by column chromatography with silica gel (Et_2O).

***N*-[2-(4-Pyridyl)ethyl]quinuclidinium bromide.** A solution of 1 g 4-vinylpyridine, 2.83 g quinuclidine, 1.47 ml HBr 48% in 14 ml CH_3OH was left to react at room temperature for 40 h. The solvent was removed under reduced pressure and the crude solid washed three times with Et_2O. The solid was crystallized with propan-2-ol at −20 °C and the mother liquor was evaporated to dryness to obtain a crude solid which was recrystallized several times from EtOH–Et_2O; 400 mg of product were obtained, mp 240 °C (decomp.) (Found: C, 56.5; N, 9.3; H, 7.3. Calc for $C_{14}H_{21}N_2Br$: C, 56.57; N, 9.42; H, 7.12%); δ_H (200 MHz, D_2O; Me_4Si) 1.8–2.0 (6H, m, CH_2), 2.2 (1H, m, CH), 3.1 (2H, m, CH_2), 3.3–3.5 (8H, m, CH_2), 7.3 (2H, d, Ar), 8.4 (2H, d, Ar).

2-(2-Pyridyl)ethyl tosylate. The products was prepared from 2-(2-hydroxyethyl)pyridine following a literature procedure,[16] mp 47–51 °C (Found: C, 60.38; N, 5.08; H, 5.49. Calc. for $C_{13}H_{15}NO_3S$: C, 60.63; N, 5.05; H, 5.45%); δ_H (80 MHz, $CDCl_3$; Me_4Si) 2.4 (3H, s, CH_3), 3.1–3.4 (2H, t, CH_2), 4.4–4.5 (2H, t, CH_2), 7.1–8.5 (8H, m, Ar).

***N*-[2-(2-Pyridyl)ethyl]quinuclidinium tosylate.** A solution of 3.02 g of 2-(2-pyridyl)ethyl tosylate and 6.09 g of quinuclidine in 20 ml of CH_3OH was left to react at room temperature for 24 h. The solution was dried by rotary evaporation and the residue washed three times with Et_2O. After two crystallizations with propan-2-ol–*n*-hexane at room temperature, 1.7 g of product were obtained, mp 147–151 °C (Found: C, 64.51; N, 7.14; H, 7.24. Calc. for $C_{21}H_{28}N_2O_3S$: C, 64.92; N, 7.21; H, 7.26%); δ_H (80 MHz, D_2O; Me_4Si) 1.8 (6H, m, CH_2), 1.9–2.1 (1H, m, CH), 2.2 (3H, s, CH_3), 2.9–3.1 (2H, m, CH_2), 3.2–3.4 (8H, m, CH_2), 7.2–8.3 (8H, m, Ar).

Kinetics measurements

The kinetic studies were carried out following the formation of 4-vinylpyridine or 2-vinylpyridine from **1** and **2** at 50 °C with aqueous potassium hydroxide and aqueous acetohydroxamate–acetohydroxamic acid buffers. The ionic strength was maintained at 1 M with potassium chloride; slight variations in pH within the buffer series required some adjustments of the pH. The appearance of 4-vinylpyridine or 2-vinylpyridine was followed spectrophotometrically at $\lambda = 280$ nm or $\lambda = 290$ nm, respectively (4-vinylpyridine, $\varepsilon = 1634$ dm^3 mol^{-1} cm^{-1} at $\lambda = 280$ nm; 2-vinylpyridine, $\varepsilon = 3584$ dm^3 mol^{-1} cm^{-1} at $\lambda = 290$ nm; both values were measured in acetohydroxamate–acetohydroxamic acid buffer, 50 °C, μ = 1 M KCl). The cuvettes with the buffer solutions were thermostatted for 2.5 h at 50 °C before injection of the substrate solution, in order to have completely stable buffer systems. The concentrations of **1** or **2** were ~3.5×10^{-3} M; the pK_a of acetohydroxamic acid[11] in H_2O, μ = 1 M KCl, 50 °C is 9.15. The pseudo-first order rate constants, k'_{obs} (s^{-1}), were obtained by initial rates (~3% of reaction) from the slopes of the A_t *vs.* time plots, divided by $(A_\infty - A_0)$. By measuring the pH of the different $[OH^-]$ solutions at μ = 1 M KCl, 50 °C, we obtained[11] a value of the term $[OH^-] \cdot 10^{-pH} = 5.89 \times 10^{-14}$, p$K_w$ = 13.23; the $[OH^-]$ was calculated from the measured pH and this K_w value. It was shown that 4-vinylpyridine and 2-vinylpyridine were stable under the experimental reaction conditions.

The reactions in OH^-/H_2O were followed in pseudo-first order conditions, with an excess of $[OH^-]$ ($[OH^-] = 0.1$–0.5 M), either by initial rates or by following the processes to completion; in this case the pseudo-first order rate constants were determined from the slopes of the plot $\ln(A_\infty - A_0)/(A_\infty - A_t)$ *vs.* time. As a control, with **1** or **2** it was confirmed that the second order rate constants obtained in OH^-/H_2O, 50 °C, μ = 1 M KCl, from the initial rates and from following the reactions to completion, were in agreement.

Product analysis

Experiments carried out with **1** or **2** in buffers showed that, after extraction with *n*-hexane and VPC analysis, the only products were the 4-vinylpyridine or 2-vinylpyridine, respectively, and quinuclidine.

H/D exchange

H/D Exchange experiments were carried out with the technique previously described[10,11] in order to determine if deuterium was incorporated in the β-position of **1** or **2** with respect to the leaving group during the elimination reactions in D_2O, acetohydroxamate–acetohydroxamic acid buffers.

pK_a Determination

The pK_a values of the conjugated acid of **1** or **2** were determined by titration of **1** or **2** at 50 °C, H_2O, μ = 1 M KCl.

Acknowledgements

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