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Mechanism and proton activating factors in the base-induced β-elimination reaction of *N*-[2-(2-quinolyl)ethyl]-quinuclidinium salt

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epoc ABSTRACT: *N*-[2-(2-Quinolyl)ethyl]quinuclidinium salt in OH^-–H_2O, 50 °C, μ = 1 M KCl undergoes an elimination reaction with formation of 2-vinylquinoline; the second-order rate constant is $k^N_{OH} = 12.8 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}. In acetohydroxamic acid–acetohydroxamate buffers at pH 8–9 the β-elimination reaction occurs by a reversible *E*1*cb* mechanism, $(E1cb)_R$. In this process, carbon deprotonation occurs from the conjugate acid, protonated at the nitrogen atom of the quinoline ring, NH^+; this species is present at a very low concentration with respect to the unprotonated substrate N, with pK_a = 3.87 at 50 °C, μ = 1 M KCl. The reason for the high reactivity of NH^+ with respect to N is related to the high stability of the intermediate carbanion formed from NH^+, which presents an enamine structure. Kinetic parameters from a study of acid–base catalysis can be calculated and compared with those of the related system activated by a pyridine ring. Studies of H/D exchange and solvent isotope effect are in agreement with the proposed mechanism. Copyright © 2001 John Wiley & Sons, Ltd.
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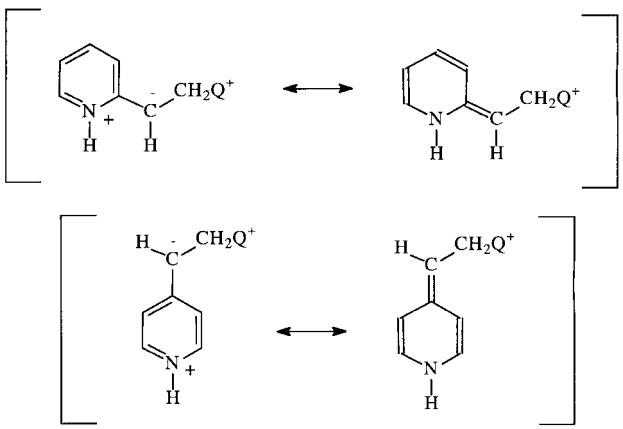
KEYWORDS: mechanism; elimination reaction; carbanion; proton activating factors; isotopes

INTRODUCTION

Studies on the base-induced β-elimination reaction with systems of high β-activation (with respect to the leaving group), such as *p*-nitrophenyl[1–3] or *o*-nitrophenyl[4] and tertiary amines as leaving group, have demonstrated an *E*1*cb* mechanism, involving an intermediate carbanion. The techniques used for these studies have been acid–base catalysis studies, H/D exchange and solvent isotope effect. Further studies with a pyridine ring[5] as the activating system have shown the importance of catalysis by protonation of the nitrogen atom of the pyridine ring for controlling the reactivity and the reaction mechanism. In fact, with *N*-[2-(4-pyridyl)ethyl]quinuclidinium and *N*-[2-(2-pyridyl)ethyl]quinuclidinium the β-elimination reaction in acetohydroxamate–acetohydroxamic acid buffer, at pH ≈9, occurs with carbon deprotonation from the substrate protonated at the nitrogen of the pyridine ring, (**NH**$^+$). In the reaction conditions, the [**NH**$^+$] is several orders of magnitude lower than that of the unprotonated substrate (**N**), with the pK_a of the 4-isomer being 4.85 and that of the 2-isomer 3.81 (50 °C, μ = 1 M KCl)[5] The reason for the high reactivity of **NH**$^+$ with respect to **N** has been explained by the high stabilization by resonance of the intermediate carbanion formed from **NH**$^+$ (see Scheme 1).



Scheme 1.

The quantification of the effect of protonation at one site upon the susceptibility to an attack by a base at another site is relevant[6–8] in chemistry and biochemistry. To acquire information about the reactivity and mech-

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anism of a β-elimination reaction activated by other heteroaromatic substrates, we have studied the *N*-[2-(2-quinolyl)ethyl]quinuclidinium bromide system (**1**). The elimination reaction was studied in acetohydroxamate–acetohydroxamic acid buffers, in order to compare the results with those from previously studied systems.[5]

RESULTS AND DISCUSSION

Kinetic study in OH^-–H_2O

The β-elimination reaction of **1** in OH^-–H_2O, 50 °C, $\mu = 1$ M KCl was followed by monitoring the formation of 2-vinylquinoline at $\lambda = 322$ nm ($\varepsilon = 4932$ $dm^3\ mol^{-1}\ cm^{-1}$ in the reaction conditions). The process is a complete elimination reaction with a second-order rate constant of $k^N_{OH} = 12.8 \times 10^{-3}\ dm^3\ mol^{-1}\ s^{-1}$. The activation by a quinoline ring (2-isomer) can be compared with the activation by a pyridine ring (2-isomer) previously reported[5] for *N*-[2-(2-pyridyl)ethyl]-quinuclidinium ($k^N_{OH} = 0.271 \times 10^{-3}\ dm^3\ mol^{-1}\ s^{-1}$, 50 °C, $\mu = 1$ M KCl). Activation by quinoline is 47 times higher than that by pyridine; this higher reactivity can be related to the higher acidity of the protons in the β-position with respect to the leaving group. Owing to the high [OH^-] used (0.1–0.5 mol dm^{-3}), in this reaction medium the reacting species is the unprotonated substrate, **N**, as shown by the second-order kinetic law; the reaction with $\mathbf{NH}^+$ would be on the zero order with respect to [OH^-]. In OD^-–D_2O, 50 °C, $\mu = 1$ M KCl, the second-order rate constant for **1** is $k^N_{OD} = 23.2 \times 10^{-3}\ dm^3\ mol^{-1}\ s^{-1}$. The k^N_{OD}/k^N_{OH} ratio is 1.8 and this value is in agreement with a rate-determining proton transfer.[9] An NMR study of H/D exchange in OD^-–D_2O, 50 °C, showed the absence of deuterium in the 2-vinylquinoline formed at the end of the reaction; this result excludes the *E*1*cb* reversible mechanism in this reaction medium. The two mechanisms in OH^-–H_2O that are in agreement with the second-order kinetic law and absence of H/D exchange are the concerted *E*2 and the *E*1*cb* irreversible process, $(E1cb)_I$. The following discussion will illustrate how the experimental evidence is in agreement with a base-induced β-elimination mechanism with **1** involving a carbanion intermediate.

Acid–base catalysis

Acid–base catalysis for the β-elimination with **1** was carried out in acetohydroxamate–acetohydroxamic acid buffers, at 50 °C, $\mu = 1$ M KCl. This buffer system and these reaction conditions were chosen so that the results could be compared with those of previously studied[5] substrates. The pseudo-first-order rate constants, k'_{obs} (s^{-1}), were determined by initial rates by monitoring the formation of 2-vinylquinoline at $\lambda = 322$ nm. It was noted that 2-vinylquinoline gives a reversible addition of the buffer with the formation of *N*-(2-acetohydroxamate ethyl)quinoline. However, it was shown that this process does not alterate the kinetic study of the β-elimination reaction from **1** by initial rates, since 2-vinylquinoline is stable enough for the times used to determine the initial rate measurements under the various reaction conditions used. In fact, the values of k'_{obs} (s^{-1}) calculated up to 20% of the reaction by the $\ln[(A_\infty - A_0)/(A_\infty - A_t)] = k'_{obs}t$ (with A_∞ = [substrate]/$\varepsilon_{substrate}$) were in good agreement with those calculated by initial rates, following the reaction up to ~3%. We were not able to isolate the product of the addition of the buffer to 2-vinylquinoline, *N*-(2-acetohydroxamate ethyl)quinoline, probably because it is very unstable. However, a mixture of 2-vinylquinoline (10 mg), acetohydroxamic acid (115 mg), 0.77 ml of 1 M KOH and 4 ml of CH_3CN, kept at 50 °C for 6 h and extracted with $CHCl_3$, showed, by GC–MS analysis, the presence of a limited amount of a compound whose mass spectral data were in agreement with those of *N*-(2-acetohydroxamate ethyl)quinoline: *m/z* 230 (7), 172 (24), 156 (100), 129 (23). Consistently, a reaction mixture of **1** (8 mg) in 5 ml of acetohydroxamate–acetohydroxamic acid buffer, pH 9.15, [B] = 0.2 M, [BH] = 0.2 M kept at 50 °C for 5 h and extracted with $CHCl_3$, showed, by GC–MS analysis, the presence of a limited amount of the same compound, in addition to the two products of the elimination reaction, 2-vinylquinoline and quinuclidine. The kinetic data were treated following the same procedure as described previously[5] for the related systems activated by a pyridine ring. The contribution of the unprotonated substrate, **N**, with OH^- was subtracted from k'_{obs} to give k_{obs} (s^{-1}): $k_{obs} = k'_{obs} - k^N_{OH}[OH^-]$. The plot of k_{obs} against [acetohydroxamate] at various pH values is reported in Fig. 1.

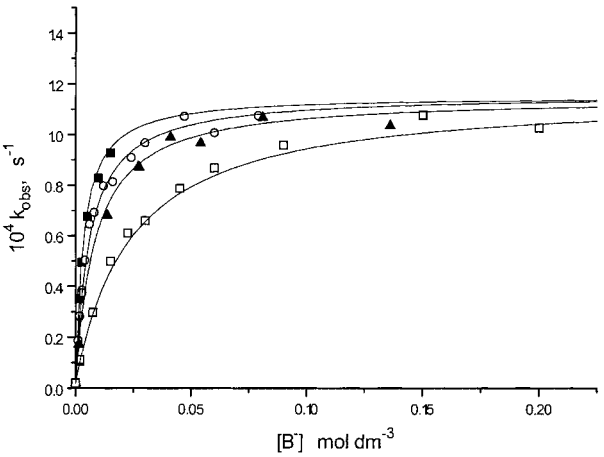

Figure 1. Dependence of k_{obs} (s^{-1}) on [acetohydroxamate] at various pH values for substrate **1**. pH = (□) 9.15, (▲) 8.70, (○) 8.55 and (■) 8.30

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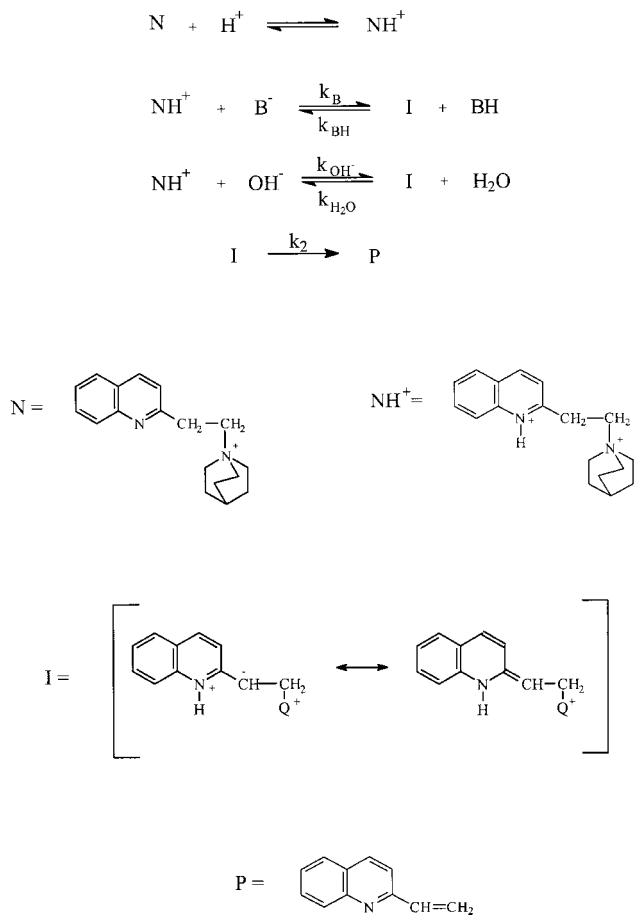
As will be shown, the model is consistent with the mechanism of Scheme 2.



Scheme 2.

The expression for k_{obs} derived[5] by steady-state approximation for the process of Scheme 2 is

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

where $K^N{}_a$ is the acid dissociation constant of $\mathbf{NH}^+$: $K^N{}_a = 1.35 \times 10^{-4}$ mol dm^{-3} [pK_a ($\mathbf{NH}^+$) = 3.87 at 50 °C, μ = 1 M KCl].

The trend observed at each pH value of Fig. 1 is consistent with Eqn. (1) and the mechanism of Scheme 2. The curvature observed is related to a change in the rate-determining step from carbon deprotonation (when $k_{BH}[BH] < k_2$) to leaving group expulsion (when $k_2 < k_{BH}[BH]$) and when the levelling off occurs. It can be seen from Fig. 1 that the levelling off at high [buffer] is independent of the pH; this is in agreement with Eqn. (1) and is diagnostic proof that carbon deprotonation occurs with $\mathbf{NH}^+$, since the same process with **N** would give a levelling off that was dependent on [OH$^-$]. The set of equations related to the kinetic analysis for the mechanism of Scheme 2 is reported in Ref. 5; the iterative procedure used to calculate the kinetic parameters is also described. The procedure used in the present work is the same as in Ref. 5. The calculated rate constants for **1** are $k_B = 935.4$ dm^3 mol^{-1} s^{-1}; $k_{BH}/k_2 = 42$ dm^3 mol^{-1}; $k_\infty = 1.16 \times 10^{-4}$ s^{-1} (k_{obs} at [buffer] → ∞); $(k_{H_2O} + k_2)/k_2 = 1.02$; k_{OH} ($\mathbf{NH}^+$) = 4.4×10^3 dm^3 mol^{-1} s^{-1}. The fitting of the experimental values of k_{obs} by Eqn. (2) and the calculated rate constants are shown in Fig. 1.

$$k_{obs} = \frac{k_{OH^-}[OH^-] + k_B[B^-]}{\frac{k_{H_2O}+k_2}{k_2} + \frac{k_{BH}}{k_2}[BH]} \cdot \frac{[H^+]}{K_a^N} \qquad (2)$$

The values of the rate constants obtained with Eqn. (1) can be compared with those calculated with the related pyridine ring-activated system,[5] *N*-[2-(2-pyridyl)ethyl]-quinuclidinium. For this system we previously reported[5] a value of $k_B = 24.8$ dm^3 mol^{-1} s^{-1}, $k_{OH}(\mathbf{NH}^+) = 421$ dm^3 mol^{-1} s^{-1} and $k_{BH}/k_2 = 38$ dm^3 mol^{-1}. It can be seen that carbon deprotonation by $\mathbf{NH}^+$ with acetohydroxamate or OH$^-$ base, k_B and k_{OH} respectively, is faster with **1** with respect to *N*-[2-(2-pyridyl)ethyl]quinuclidinium: k_B(quinoline)/k_B(pyridine) = 37.7 and k_{OH}(quinoline)/k_{OH}(pyridine) = 10.5. The degree of reversibility in the formation of the intermediate carbanion from **1** is large, $k_{BH}/k_2 = 42$ dm^3 mol^{-1}, and similar to that calculated with *N*-[2-(2-pyridyl)ethyl]quinuclidinium. The effectiveness of the catalysis by protonation of the nitrogen atom of the quinoline ring can be quantified by the PAF value: $k_{OH}(\mathbf{NH}^+)/k^N{}_{OH} = 3.44 \times 10^5$ (PAF with the base OH$^-$). An estimate of the second-order rate constant for carbon deprotonation of **N** by acetohydroxamate base, $k^N{}_B$, can be made by using the known value of $k^N{}_{OH}$ for **1** and the linear free energy relationship proposed previously:[5] $\log k^N{}_B = -1.4 + 1.1 \log k^N{}_{OH}$. This relationship was derived from known values of $k^N{}_{OH}$ and related values of $k^N{}_B$ for previously[5] studied systems. A value of $k^N{}_B = 3.3 \times 10^{-4}$ dm^3 mol^{-1} s^{-1} is estimated and can be calculated $k_B(\mathbf{NH}^+)/k^N{}_B = 2.8 \times 10^6$ (PAF with the base acetohydroxamate). These PAF values are similar to those calculated[5] with *N*-[2-(2-pyridyl)ethyl]-quinuclidinium, PAF(OH$^-$) = 1.5×10^6 and PAF (acetohydroxamate) = 5.2×10^6. It can be concluded that while the activation by a quinoline ring in these reactions is larger than that of a pyridine ring, the mechanism and the catalysis by protonation of the nitrogen atom are similar, in spite of the significant difference in the heteroaromatic system. The large PAF values with **1** can be related to the high stability of the intermediate carbanion formed by $\mathbf{NH}^+$ (see Scheme 2); this intermediate has an enamine structure. However, electrostatic interactions could also play a significant role.[10]

H/D exchange

H/D exchange experiments with **1** in D_2O and acetohy-

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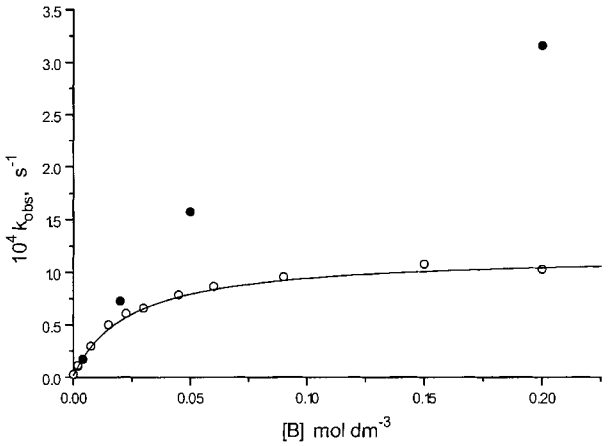


Figure 2. Dependence of k_{obs} (s^{-1}) on [acetohydroxamate] for substrate **1**. (○) k_{obs} (H_2O), $[B^-]/[BH] = 1$; (●) k_{obs} (D_2O), $[B^-]/[BD] = 1$

droxamate–acetohydroxamic acid buffers confirmed the *E*1*cb* reversible mechanism. In fact, using a previously described technique,[3,4] it was shown that **1** incorporates deuterium into the β-position with respect to the leaving group during the elimination reaction. In an experiment with **1**, at [B] = 0.2 M, [BD] = 0.2 M, when the elimination reached 36% of olefin formed, the H/D exchange was 50%. Other experiments under similar conditions gave similar results.

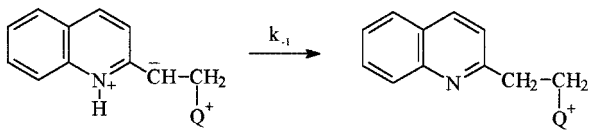
Solvent isotope effect

The observed pseudo-first-order rate constants, $k'_{obs}(D_2O)$ (s^{-1}), for the elimination reaction with **1** in acetohydroxamate–acetohydroxamic acid buffers, D_2O, pD = 9.68, [B] = [BH] = 1, 50 °C, μ = 1 M KCl, were determined by initial rates, following the same procedure[5,11] as used for the reactions in H_2O. It should be noted that following the reaction up to 3%, no appreciable exchange occurred on the substrate. The extinction coefficient of 2-vinylquinoline at λ = 322 nm, D_2O, 50 °C, μ = 1 M KCl was not significantly different from that in H_2O. The contribution of the reaction of **N** with OD^- was subtracted to give $k_{obs}(D_2O)$, which refers to the mechanism of Scheme 2.

$$k_{obs}(D_2O) = k'_{obs}(D_2O) - k^N_{OD}[OD^-] \qquad (3)$$

The $k_{obs}(D_2O)$ values at several [B] are reported in Fig. 2, together with the $k_{obs}(H_2O)$ values (solid curve), calculated for **1** with the related kinetic parameters and Eqn. (2) at pH = 9.15, [B]/[BH] = 1.

It can be seen that at high [buffer], $k_{obs}(D_2O) > k_{obs}(H_2O)$, whereas at low [buffer], $k_{obs}(D_2O) \approx k_{obs}(H_2O)$. These results are in agreement with the *E*1*cb* mechanism of Scheme 3. In fact, the inverse solvent isotope effect at high [buffer] is explained with the presence of a primary kinetic isotope effect on the protonation of the intermediate carbanion by BH(D), $k_{BH}/k_{BD} > 1$. The magnitude of the solvent isotope effect is related to the significance of the k_{BH}[BH] term in Eqn. (1). Where this term does not compete with k_2 and an *E*1*cb* irreversible mechanism holds, it is expected that $k_{obs}(D_2O) \approx k_{obs}(H_2O)$. It should be noted, however, that possible variations between H_2O and D_2O could also be related to changes in the $[H^+]/K_a(H_2O)$ and $[D^+]/K_a(D_2O)$ terms. The value of $K_a(D_2O)$ for **1** at 50 °C, D_2O, μ = 1 M KCl is 5.25×10^{-5} mol dm^{-3}. The variation of the $[H^+]/K_a$ term between H_2O and D_2O is limited to ~25%, and is very low with respect to the observed variation in k_{obs}. Also, it is possible a cancellation between effects on pre-equilibrium ionisation of $\mathbf{NH}^+$ (D) and rate-determining attack of OH^- (or OD^-) upon the C—H bond. The results from this study on the solvent isotope effect are in agreement with the mechanism of Scheme 2 and are similar to those obtained[11] with *N*-[2-(2-pyridyl)ethyl]quinuclidinium. The lack of solvent isotope effect at low [buffer] (see Fig.2) excludes the significance of an intramolecular proton transfer in the intermediate (see Scheme 3). In fact, in this process it should be observed that $k_{obs}(D_2O) > k_{obs}(H_2O)$ even at low [buffer].



Scheme 3.

CONCLUSIONS

N-[2-(2-Quinolyl)ethyl]quinuclidinium salt, **1**, in acetohydroxamate–acetohydroxamic acid buffers at pH values ranging from 8.3 to 9.15 at 50 °C gives an elimination reaction with formation of 2-vinylquinoline by an *E*1*cb* reversible, $(E1cb)_R$, mechanism. The reacting species which undergoes carbon deprotonation is the conjugated acid of **1**, $\mathbf{NH}^+$, even if present in very low concentrations with respect to **N** under the reaction conditions (the pK_a of $\mathbf{NH}^+$ is 3.87 at 50 °C, μ = 1 M KCl). The PAF value with the base OH^- is 3.44×10^5 and the PAF with acetohydroxamate base is 2.8×10^6. The large reactivity of $\mathbf{NH}^+$ with respect to **N** is related to the high stability of the enamine structure of the intermediate carbanion.

EXPERIMENTAL

Materials. Glass-distilled and freshly boiled water was used throughout. Reagent-grade potassium chloride and acetohydroxamic acid were commercial materials (Al-

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drich); 2-vinylquinoline (Acros) was purified by column chromatography on silica gel (Et_2O–*n*-hexane, 10%).

N-[2-(2-Quinolyl)ethyl]quinuclidinium bromide, ***1****.* A solution of 800 mg (5.16 mmol) of 2-vinylquinoline, 2.58 g (23.24 mmol) of quinuclidine, 1.44 ml of 48% HBr in 10 ml of CH_3OH was left to react for 72 h at room temperature. The solvent was removed under reduced pressure and the crude solid was 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 at 0 °C; 500 mg of product were obtained, m.p. 56 °C (decomp.). Found: C, 61.98; N, 8.02; H, 6.85. Calc. for $C_{18}H_{23}N_2Br$: C, 62.25; N, 8.07; H, 6.63%. ^{1}H NMR: δ_H (200 MHz, D_2O; Me_4Si), 1.9–2.0 (6H, m, CH_2), 2.1 (1H, m, CH), 3.2–3.5 (10H, m, CH_2), 7.3–8.3 (6H, m, Ar).

Kinetic measurements. Kinetic studies were carried out following the formation of 2-vinylquinoline from **1** in OH^-–H_2O or acetohydroxamate–acetohydroxamic acid buffers, at 50 °C, μ = 1 M KCl. The procedure followed was the same as that described previously.[5] Kinetic studies in D_2O were performed with the same procedure[5,11] as used for the reaction in H_2O. The [OD^-] at 50 °C, μ = 1 M KCl was calculated from the empirical[11] relation $[D^+][OD^-] = 10^{-13.97}$ and pD = pH + 0.288.[12,13]

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

pK_a determination. The pK_a of the conjugated acid of **1** was determined by titration of **1** at 50 °C, H_2O, μ = 1 M KCl.

Acknowledgements

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