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Mechanisms of Acid−Base Catalysis of β-Elimination Reactions in Systems Activated by a Pyridine Ring

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β-Elimination reactions from **1** (in quinuclidine/quinuclidinium chloride, imidazole/imidazolium, and acetate/acetic acid buffers) and from **2** (in imidazole/imidazolium and acetate/acetic acid buffers) with formation of 4-vinylpyridine and 2-vinylpyridine, respectively, were studied. The results of a kinetic study of acid−base catalysis and H/D exchange are consistent with NH^+, the protonated substrate, as the species that undergoes carbon deprotonation with an E1cb mechanism. The comparison with previously studied reactions in acetohydroxamate/acetohydroxamic acid buffer confirms this assignment. The high proton activating factor, PAF, value observed (PAF = 1.2×10^6 with isomer **1** in quinuclidine/quinuclidinium buffer) can be explained with the high stability by the resonance of the intermediate carbanion.

Introduction

The mechanism of base-induced 1,2-elimination reactions[1] has been studied owing to the various interesting mechanistic possibilities: the concerted process E2, the mechanisms involving the intermediate carbanion, or the mechanism involving the intermediate carbocation. In previous studies[2−5] of systems activated by a nitrophenyl group, the mechanism of base-induced β-elimination reactions has been shown to be E1cb ($A_{xh}D_H + D_N$)[6] with the intermediate carbanion formed with different degrees of reversibility depending on the structure of the substrate. The substrates studied were activated by *p*-nitrophenyl[2−4] or *o*-nitrophenyl[5] groups and had a tertiary amine as leaving group. Using a combination of three techniques, acid−base catalysis studies, H/D exchange, and solvent isotope effect, it was possible to demonstrate a carbanion mechanism and to evaluate the kinetic parameters of the process. An extension of these studies to systems activated by a pyridine ring has shown the importance of catalysis by protonation of the nitrogen atom of the aromatic ring.[7−10] The proposed mechanism[7,10] is shown in Scheme 1 with **1** in acetohydroxamate/acetohydroxamic acid buffer at 50 °C, μ = 1 M KCl. The pK_a^N of conjugated acid of **1**, NH^+, in the reaction condition, is 4.85 and the range of pH studied was 8.45−9.15. Under these conditions it has been demonstrated[7] that the reacting species, which undergoes carbon deprotonation, is NH^+, even if this species is present in solution at a very low concentration with respect to that of the unprotonated substrate of **1**, N. For this mechanism eq 1 is valid[7] (in the reaction conditions of the study the contribution of the elimination reaction induced by H_2O was negligible).

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

The reactivity of NH^+ was much larger than that of N; the $k_B^{NH^+}/k_B^N$ ratio ($k_B^{NH^+}$ and k_B^N are the second-order rate constants for the elimination reaction by a base B from NH^+ and N, respectively) is the proton activating factor, PAF (2.7×10^5 for isomer **1** and 5.2×10^6 for isomer **2**), and the large activation by protonation of the nitrogen atom can be explained[7] by the strong stabilization by resonance of the intermediate carbanion formed from NH^+. The PAF parameter is important in chemistry[11] and biochemistry.[12] Kinetic analysis allows the

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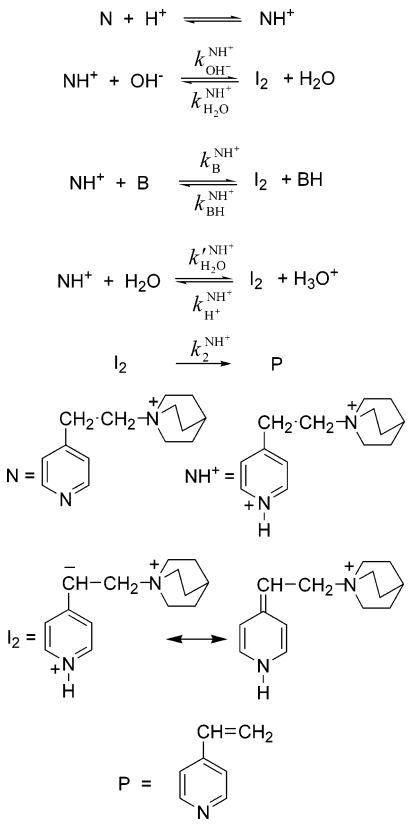
SCHEME 1



$k_B^{NH^+}$, $k_{BH}^{NH^+}/k_2^{NH^+}$, and k_∞ values to be determined; k_∞ is k_{obs} at [buffer] → ∞ (eq 10). The reacting species, NH^+, was identified using acid−base catalysis studies. The plot of k_{obs} against [B] showed curvatures indicating a stepwise mechanism with a change, induced by [BH], in the rate-determining step from carbon deprotonation to leaving group expulsion. However, the leveling-off at high [buffer] (k_∞) was constant and independent of pH, according to eq 10; this is evidence that NH^+ is the species that undergoes carbon deprotonation. H/D exchange experiments showed the incorporation of deuterium at the β-carbon during the elimination reaction in D_2O, in acetohydroxamate/acetohydroxamic acid buffer, at 50 °C and $\mu = 1$ M KCl, in agreement with a stepwise reversible mechanism, $(E1cb)_R(A_{xh}D_H + D_N*)$.[6] Further support for the proposed mechanism has come from studies of the solvent kinetic isotope effect.[10]

In this paper, we extend these studies on *N*-[2-(4-pyridyl)ethyl]quinuclidinium (**1**) and *N*-[2-(2-pyridyl)-ethyl]quinuclidinium (**2**), at 50 °C, μ = 1 M KCl, in different buffer systems and different pH ranges. The pK_a^N of **2** is 3.81 at 50 °C, μ = 1 M KCl.[7] Because the competition between N and NH^+ depends on the ratio between the rate constants of the two species and on the $[NH^+]/[N]$ ratio, we wanted to check the consistency of the previously made mechanistic assignment under different conditions of pH and buffers. The results obtained support the mechanistic assignment; in fact, by analyzing the kinetic parameters obtained and comparing them with those of the other substrates and/or different reaction conditions a significant consistency is found.

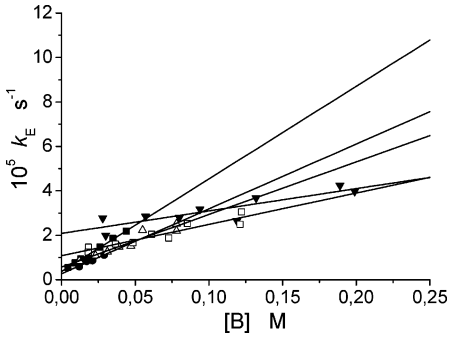


FIGURE 1. Plot of the pseudo-first-order rate constants k_E against [B] for the elimination reaction with **1** in quinuclidine/quinuclidinium buffers at 50 °C, $\mu = 1$ M KCl: (■) pH = 10.1, (●) pH = 10.24, (△) pH = 10.41, (□) pH = 10.68, (▼) pH = 11.

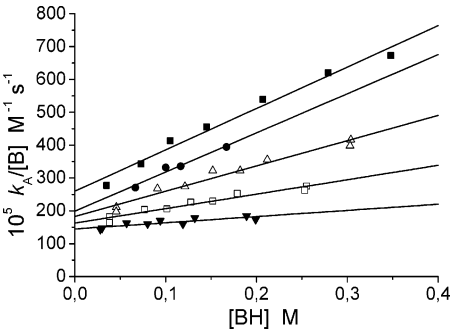


FIGURE 2. Plot of k_A/[B] against [BH] for the addition reaction with 4-vinylpyridine in quinuclidine/quinuclidinium buffers at 50 °C, $\mu = 1$ M KCl: (■) pH = 10.1, (●) pH = 10.24, (△) pH = 10.41, (□) pH = 10.68, (▼) pH = 11.

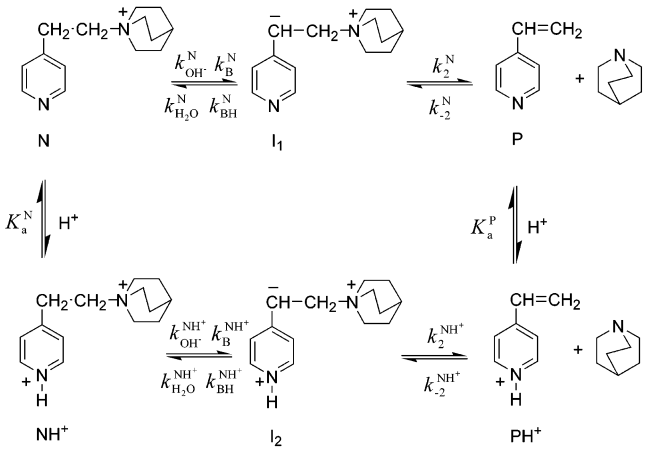
Result and Discussion

Study of Acid−Base Catalysis in Quinuclidine/Quinuclidinium (Q/QH$^+$) Buffers. Equilibration of 4-vinylpiridine in Q/QH^+ buffer, at 50 °C and μ = 1 M KCl, was followed by monitoring the decrease of absorbance of 4-vinylpiridine at 280 nm. The process of addition of quinuclidine to 4-vinylpiridine in Q/QH^+ buffer to give **1** is an equilibrium reaction involving the reverse elimination reaction from **1** to give quinuclidine and 4-vinylpyridine (P and PH^+). The observed pseudo-first-order rate constant, k_{obs}, is the sum $k_E + k_A$, where k_E and k_A are the observed pseudo-first-order rate constants for elimination and addition reactions, respectively. The two observed rate constants, k_E and k_A, were calculated as shown in the Experimental Section from the values of A_0 (absorbance at λ = 280 nm, $t = 0$), A_∞ (absorbance at λ = 280 nm, $t = \infty$, equilibrium), and A_t (absorbance at λ = 280 nm, $t = t$). In Figure 1 the plot of k_E against [B], the concentration of the basic buffer component, at various pH values is shown.

Linearity is observed, but the slope at each pH increases by increasing the $[H^+]$, while the intercept increases by increasing the $[OH^-]$. We have observed an exponential trend in the plots of k_A against [B], while the plot of k_A/[B] against [BH] is linear (Figure 2).

Good linearity is observed in the plot of Figure 2 and both the intercept and the slope depend on $[H^+]$. As will be discussed later, these results are in agreement with an equilibrium involving the elimination-addition reac-

SCHEME 2



tion, with a competition between the unprotonated N and protonated NH^+ substrate in the elimination reaction and with the related competition between the unprotonated P and the protonated PH^+ in the addition direction. The mechanism shown in Scheme 2 is E1cb with both the unprotonated N and protonated NH^+ substrate.

Our results are in agreement with an $(E1cb)_I$ mechanism. In fact, under these conditions, $k_2^N \gg k_{H_2O}^N + k_{BH}^N$ and $k_2^{NH^+} \gg k_{H_2O}^{NH^+} + k_{BH}^{NH^+}$, the expression of k_E is given by

$$k_E = k_{OH^-}^N[OH^-] + k_{OH^-}^{NH^+}\frac{[OH^-][H^+]}{K_a^N} + \left(k_B^N + k_B^{NH^+}\frac{[H^+]}{K_a^N}\right)[B] \quad (2)$$

where $K_a^N = 1.41 \times 10^{-5}$ M is the acid dissociation constant of NH^+ at 50 °C and $\mu = 1$ M KCl.[7] It follows that the rate-determining step in the reverse direction, the addition reaction, is the protonation of the intermediate carbanions, I_1 and I_2, formed respectively from P and PH^+ by H_2O and BH. The expression of k_A for this mechanism is then given by

$$k_A = (k_{H_2O}^N + k_{BH}^N[BH])\frac{k_{-2}^N}{k_2^N}[B] + (k_{H_2O}^{NH^+} + k_{BH}^{NH^+}[BH])\frac{k_{-2}^{NH^+}}{k_2^{NH^+}}\frac{[H^+]}{K_a^P}[B] \quad (3)$$

where $K_a^P = 2.29 \times 10^{-6}$ M is the acid dissociation constant of PH^+ at 50 °C and $\mu = 1$ M KCl. It must be considered that in Scheme 2 an $(E1cb)_I$ mechanism is assumed for the elimination reaction with the unprotonated N and protonated NH^+ substrate. However, we assign the $(E1cb)_I$ mechanism with NH^+, because of the large value of PAF observed, a consistent value of k_B and analogy to the reaction in acetohydroxamate/acetohydroxamic acid[7] or imidazole/imidazolium or acetate/acetic acid buffers, where the observed change in the rate-determining step can conclusively be related to the E1cb mechanism (see the related discussion in the text). The mechanism of the elimination reaction with N can instead be E1cb or E2 concerted ($A_{xh}D_HD_N$).[6] They cannot be kinetically distinguished, and we have no specific evidence on this point. However, the value of $k_{OH^-}^N$ with isomer **1**, $k_{OH^-}^N = 3.45 \times 10^{-3}$ M^{-1} s^{-1} at 50 °C and $\mu = 1$ M KCl, is close[5] to the second-order rate constant for the OH^--induced elimination reaction at 50 °C with *N*-[2-(*o*-nitrophenyl)ethyl]quinuclidinium ion, $k_{OH^-} = 1.58 \times 10^{-3}$ M^{-1} s^{-1}. With this second substrate, an E1cb mechanism was demonstrated for the base-induced β-elimination reaction. This is an important point to be considered even if it is not clear whether the same mechanism can operate in systems with similar levels of activation. In the following kinetic treatment and related discussion, an $(E1cb)_I$ mechanism with N (Scheme 2) will be assumed. However, if the mechanism with N is E2 concerted, the same expression of k_E and k_A will be obtained, but with the rate constants $k_{OH^-}^N$, k_B^N, $k_{H_2O}^N(k_{-2}^N/k_2^N)$, and $k_{BH}^N(k_{-2}^N/k_2^N)$, which refer to the concerted process. Equation 3 explains the nonlinearity of the plot k_A against [B], owing to the significant contribution of the term containing the [B][BH] product, while it is in agreement with the linearity observed in the plot of Figure 2. From eq 2 and a plot of k_E vs [B], it is possible to evaluate the intercept, i_E, and the slope, s_E:

$$i_E = k_{OH^-}^N[OH^-] + k_{OH^-}^{NH^+}\frac{[OH^-][H^+]}{K_a^N} \quad (4)$$

$$s_E = k_B^N + k_B^{NH^+}\frac{[H^+]}{K_a^N} \quad (5)$$

From the plots i_E vs $[OH^-]$ and s_E vs $[H^+]/K_a^N$ the second-order rate constants $k_{OH^-}^N$, k_B^N, and $k_B^{NH^+}$ can be evaluated (Table 1). $k_{OH^-}^N$ and k_B^N are the rate constants for the formation of the intermediate carbanion by OH^- or quinuclidine base, if the mechanism is $(E1cb)_I$ (Scheme 2). They will represent $k_{OH^-}^N$ (*concerted*) and k_B^N (*concerted*), the rate constants for a E2 concerted process from N, if this is the operating mechanism. The $k_B^{NH^+}/k_B^N$ ratio is the proton activating factor (PAF) with the base quinuclidine, PAF $= 1.2 \times 10^6$. Again, this parameter represents the quantification of the catalysis of the elimination reaction by protonation of the nitrogen atom of the pyridine ring within an $(E1cb)_I$ mechanism as in Scheme 2; in the case of an E2 mechanism with N the PAF value is associated with a change in mechanism from E2 with N to $(E1cb)_I$ with NH^+. The kinetic analysis is, then, consistent with an E1cb irreversible mechanism from NH^+, $(E1cb)_I$ (Scheme 2), where carbon deprotonation is the rate-determining step. The alternative possibility of an $(E1cb)_R$ mechanism, with rate-determining the expulsion of the leaving group, is kinetically inconsistent with our results. The implication for the reverse reaction is that the mechanism for the addition of quinuclidine to 4-vinylpyridine (protonated and unprotonated, PH^+ and P) involves the formation of the intermediate carbanion in a reversible process, followed by rate-determining carbon protonation of the carbanion by BH and H_2O and the formation of **1**. For this mechanism (Scheme 2), eq 3 can be derived by steady-state approximation. The plots (k_A/[B] vs [BH]) are shown in Figure 2, and good linearity is observed. The intercepts

TABLE 1. Rate Constants for the Elimination Reaction with Isomer 1 According to Scheme 1 in Various Buffer Systems at 50 °C, μ = 1 M KCl

	acetate/ acetic acid	imidazole/ imidazolium	acetohydroxamate/ acetohydroxamic acid	quinuclidine/ quinuclidinium
pK_a^B [a]	4.65	6.78	9.15	11.0
$10^3 \times k_{OH^-}^N$ (M^{-1} s^{-1})				3.5[b] (3.45)[c,d]
$10^5 \times k_B^N$ (M^{-1} s^{-1})			7.8[d,e]	5.21 [f]
$k_B^{NH^+}$ (M^{-1} s^{-1})	8.8×10^{-4}	1.4×10^{-2}	20.8	63.3[f]
$k_B^{NH^+}/k_2^{NH^+}$ (M^{-1})	74.6	7.64	64	(0.53)
$10^5 \times k_\infty$ (s^{-1})	1.87	2.2	1.62	

[a] pK_a^B of the conjugated acid of the buffer at 50 °C, μ = 1 M KCl. [b] Obtained from the plot i_E vs [OH^-] (eq 4): $y = 0.3 \times 10^{-6}$ (SD = 0.6×10^{-6}) + 0.0035 (SD = 0.002)x (r = 0.9946). [c] Value directly measured in OH^-/H_2O at 50 °C, μ = 1 M KCl. [d] Reference 7. [e] Value estimated with a previously proposed LFER; the change in the rate constant $k_{OH^-}^{NH^+}$ from this work with respect to that previously reported (ref 7) does not change the parameters of the LFER. [f] Obtained from the plot s_E vs $[H^+]/K_a^N$ (eq 5): $y = 5.21 \times 10^{-5}$ (SD = 1.2×10^{-5}) + 63.3 (SD = 3.5)x (r = 0.9957).

in Figure 2, i_A, and the slopes, s_A, are both dependent on [H^+]:

$$i_A = k_{H_2O}^N \frac{k_{-2}^N}{k_2^N} + k_{H_2O}^{NH^+} \frac{k_{-2}^{NH^+}}{k_2^{NH^+}} \frac{[H^+]}{K_a^P} \quad (6)$$

$$s_A = k_{BH}^N \frac{k_{-2}^N}{k_2^N} + k_{BH}^{NH^+} \frac{k_{-2}^{NH^+}}{k_2^{NH^+}} \frac{[H^+]}{K_a^P} \quad (7)$$

Using linear regression analysis, the plot of intercepts i_A vs $[H^+]/K_a^P$ (eq 6) gives $y = 126.4 \times 10^{-5}$ (SD = 10×10^{-5}) + 35.14 (SD = 5)x (r = 0.9728). The new intercept of this secondary plot is $i'_A = 126.4 \times 10^{-5}$ M^{-1} s^{-1} and the new slope is $s'_A = 35.14$ M^{-1} s^{-1}. Again, using linear regression analysis, the secondary plot of s_A vs $[H^+]/K_a^P$ (eq 7) gives $y = 100 \times 10^{-5}$ (SD = 110×10^{-5}) + 371 (SD = 52)x (r = 0.9711). The value for the new intercept, i''_A, is 100×10^{-5} M^{-2} s^{-1}, the related slope value, s''_A, is 371 M^{-2} s^{-1}. The ratio i'_A/i''_A is $k_{H_2O}^N/k_{BH}^N = 1.26$ M, while the ratio s'_A/s''_A is $k_{H_2O}^{NH^+}/k_{BH}^{NH^+} = 0.095$ M. It can be seen that the protonation of I_2 by BH is faster than by H_2O, in agreement with the higher acidity of BH. The related comparison for the protonation of I_1 must take into account the large standard deviation of i''_A. However, the parameter obtained would also be consistent owing to the expected lower selectivity of I_1 with respect to I_2 and the fact that $k_{H_2O}^N$ is a first-order rate constant with standard state for [H_2O] = 55 M. In the case of an E2 mechanism with N, i'_A would be $k_{H_2O}^N$ (*concerted*) and i''_A would be k_{BH}^N (*concerted*); the ratio i'_A/i''_A is then related to the concerted addition reaction. The term $k_{BH}^{NH^+}/k_2^{NH^+}$ is an interesting parameter that can be estimated. In fact, a value of $k_{H_2O}^{NH^+}/k_2^{NH^+} = 0.05$ was previously reported,[7] so from the ratio $k_{H_2O}^{NH^+}/k_{BH}^{NH^+} = 0.095$ M, a value for $k_{BH}^{NH^+}/k_2^{NH^+} = 0.53$ M^{-1}can be calculated. As discussed in a previous paper,[7] this ratio controls the degree of curvature that can be observed in a plot of k_E vs [B] (Figure 1). The value of 0.53 M^{-1}, estimated in a Q/QH^+ buffer system, is consistent with the lack of curvature found in Figure 1.

Acid−Base Catalysis in Imidazole/Imidazolium Buffers. The pseudo-first-order rate constants (k_{obs}, initial rate) for the elimination reaction in imidazole/imidazolium buffers at different pH values (pH = 6.29, 6.71, 6.96, 7.27 for isomer **1** and pH = 6.48, 6.81, 7.07 for isomer **2**) were measured by following the formation of 4-vinylpyridine (P) in equilibrium with its conjugated acid (PH^+) from **1** at λ = 280 nm or 2-vinylpyridine (P in equilibrium with its conjugated acid PH^+) from **2** at λ = 290 nm, H_2O, μ = 1 M KCl, 50 °C. The total concentration of the product is C = [P] + [PH^+]. As will be shown by kinetic analysis of the data, the results are consistent with the mechanism of Scheme 1, with both isomers **1** and **2**. For this mechanism the kinetic expression is given by

$$C = k_2^{NH^+} \cdot \frac{k'^{NH^+}_{H_2O} + k_{OH^-}^{NH^+}[OH^-] + k_B^{NH^+}[B]}{k_{H_2O}^{NH^+} + k_2^{NH^+} + k_{H^+}^{NH^+}[H^+] + k_{BH}^{NH^+}[BH]} \cdot [NH^+] \cdot t \quad (8)$$

We have chosen to use $C = k_{obs} \cdot [N] \cdot t$, where [N] is calculated by $[N] = \{K_a^N/([H^+] + K_a^N)\} \cdot [S]_0$ and $[NH^+] = [N] \cdot [H^+]/K_a^N$. With this treatment, k_{obs} was calculated by a plot of [C] vs t (k_{obs} = slope/[N]); the expression for k_{obs} (Scheme 1) is then given by

$$k_{obs} = k_2^{NH^+} \cdot \frac{k'^{NH^+}_{H_2O} + k_{OH^-}^{NH^+}[OH^-] + k_B^{NH^+}[B]}{k_{H_2O}^{NH^+} + k_2^{NH^+} + k_{H^+}^{NH^+}[H^+] + k_{BH}^{NH^+}[BH]} \cdot \frac{[H^+]}{K_a^N} \quad (9)$$

Equation 9 is the equation of a curve for a plot of k_{obs} vs [B], and at high [buffer] it becomes

$$k_\infty = k_2^{NH^+} \cdot \frac{k_B^{NH^+}[B]}{k_{BH}^{NH^+}[BH]} \cdot \frac{[H^+]}{K_a^N} = k_2^{NH^+} \cdot \frac{k_B^{NH^+}}{k_{BH}^{NH^+}} \cdot \frac{K_a^B}{K_a^N} = k_2^{NH^+} \cdot K_{TAUT} \quad (10)$$

where K_a^B is the acid dissociation constant of the buffer BH. For the imidazolium cation $K_a^B = 1.66 \times 10^{-7}$ M (pK_a^B = 6.78) at 50 °C and μ = 1 M KCl and K_{TAUT} is the equilibrium constant for the tautomerization from N to I_2 (Scheme 1). The k_∞ value is independent of pH and is the same as that derived in a previous work[7] from eq 1 at pH ≈ 9 in acetohydroxamate/acetohydroxamic acid buffer. Our choice to calculate k_{obs} (eq 9) is related to the important point in our discussion that the term k_∞ is

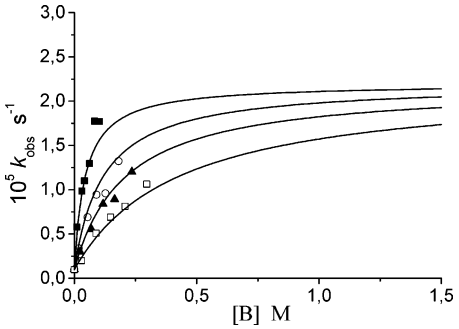


FIGURE 3. Dependence of k_{obs} on [buffer] for the elimination reaction with **1** in imidazole/imidazolium buffer at different pH values, 50 °C, μ = 1 M KCl: (■) pH = 6.29, (○) pH = 6.71, (▲) pH = 6.96, (□) pH = 7.27. Solid lines are calculated from eq 14 and rate constants from Table 1.

expected to be consistently independent of pH in several buffer systems. The plots of k_{obs} against [B] at various pH values in imidazolium/imidazole buffer for substrate **1** is shown in Figure 3. Similar behavior was observed for isomer **2**.

The parameters of the mechanism reported in Scheme 1 were calculated from eq 9 with the approximation that the term $k_{H^+}^{NH^+}$ [H$^+$] as the denominator is not significant. This term should be present conceptually for the principle of microscopic reversibility, but it is numerically not significant with respect to the others terms, so it is neglected in order to simplify the calculations. Evidence of the validity of this approximation is the consistency of the model obtained (Figure 3).

The experimental determination of the observed pseudo-first-order rate constants for the reaction of NH^+ in OH^-/H_2O, in absence of buffer (the solution was buffered by the reactants), by initial rates was done using the kinetic expression

$$C = k_2^{NH^+} \cdot \frac{k'^{NH^+}_{H_2O} + k^{NH^+}_{OH^-}[OH^-]}{k^{NH^+}_{H_2O} + k_2^{NH^+} + k^{NH^+}_{H^+}[H^+]} \cdot \frac{[H^+]}{K_a^N} \cdot [N] \cdot t \quad (11)$$

From the plot of C vs time the term slope/[N] is k_0. A study of k_0 with isomer **1** and **2** at different pH values, in the 5.2−6.35 range, showed some scatter but was consistent with a linear dependence of k_0 vs [H$^+$]/K_a^N, in agreement with an (E1cb)$_I$ mechanism, where the base H_2O competes with OH^-, and with eq 12:

$$k_0 = \frac{k_2^{NH^+}}{k^{NH^+}_{H_2O} + k_2^{NH^+}} \cdot k^{NH^+}_{OH^-} \cdot \frac{K_W}{K_a^N} + \frac{k_2^{NH^+}}{k^{NH^+}_{H_2O} + k_2^{NH^+}} \cdot k'^{NH^+}_{H_2O} \cdot \frac{[H^+]}{K_a^N} \quad (12)$$

The term $(k^{NH^+}_{H_2O} + k_2^{NH^+})/k_2^{NH^+} = 1.05$ was known from a previous work.[7] The linear regression with eq 12 of k_0 vs [H$^+$]/K_a^N is $k_0 = 0.958 \times 10^{-6}$ (SD = 0.11×10^{-6}) + 2.42×10^{-6} (SD = 0.51×10^{-6})x with isomer **1** and $k_0 = 1.05 \times 10^{-7}$ (SD = 0.08×10^{-7}) + 8.33×10^{-7} (SD = 2.6×10^{-7})x with isomer **2**. The standard deviations are reported in parentheses. A value of $k^{NH^+}_{OH^-} = 241.3$ M^{-1} s^{-1} for isomer **1** and $k^{NH^+}_{OH^-} = 290$ M^{-1} s^{-1} for isomer **2** can be calculated from eq 12. These values can be compared with those previously[7] determined by a mathematical extrapolation at [buffer] = 0 in acetohydroxamate/acetohydroxamic acid buffer pH = 8.45−9.45: $k^{NH^+}_{OH^-} = 191.1$ M^{-1} s^{-1} (isomer **1**) and $k^{NH^+}_{OH^-} = 442.05$ M^{-1} s^{-1} (isomer **2**). We consider these values in agreement, owing to the different procedures and conditions used. The calculated values of $k'^{NH^+}_{H_2O}$ are 2.54×10^{-6} s^{-1} (isomer **1**) and 8.75×10^{-7} s^{-1} (isomer **2**).

TABLE 2. Rate Constants for the Elimination Reaction with Isomer 2 According to Scheme 1 in Various Buffer Systems at 50 °C, μ = 1 M KCl

	acetate/ acetic acid	imidazole/ imidazolium	acetohydroxamate/ acetohydroxamic acid
pK_a^B[a]	4.65	6.78	9.15
$10^6 \times k_B^N$ (M^{-1} s^{-1})			4.8[b,c]
$k_B^{NH^+}$ (M^{-1} s^{-1})	5.97×10^{-4}	2.14×10^{-2}	24.8
$k_B^{NH^+}/k_2^{NH^+}$ (M^{-1})	27.63	9.48	38
$10^6 \times k_\infty$, (s^{-1})	3.12	2.42	2.98

[a] pK_a^B of the conjugated acid of the buffer at 50 °C, μ = 1 M KCl. [b] Value estimated with a previously proposed LFER; the change in the rate constant $k^{NH^+}_{OH^-}$ from this work with respect to that previously reported (ref 7) does not change the parameters of the LFER. [c] Reference 7.

The expression for k_{obs}, as described in the Experimental Section, is given by eq 9. This eq can be transformed into eqs 13 and 14:

$$\frac{(k_{obs} - k_0)}{[BH]} \cdot \frac{k^{NH^+}_{H_2O} + k_2^{NH^+}}{k_2^{NH^+}} = \frac{[B]}{[BH]} \cdot k_B^{NH^+} \cdot \frac{[H^+]}{K_a^N} - k_{obs}\frac{k_{BH}^{NH^+}}{k_2^{NH^+}} \quad (13)$$

$$k_{obs} = \frac{k'_0 + k_B^{NH^+} \cdot [B] \cdot \frac{[H^+]}{K_a^N}}{\frac{k^{NH^+}_{H_2O} + k_2^{NH^+}}{k_2^{NH^+}} + \frac{k_{BH}^{NH^+}}{k_2^{NH^+}} \cdot [BH]} \quad (14)$$

where $k'_0 = k_0(k^{NH^+}_{H_2O} + k_2^{NH^+})/k_2^{NH^+}$. Kinetic parameters were calculated from the intercept and from the slope of plot $\{(k_{obs} - k_0)/[BH]\} \cdot 1.05$ vs k_{obs} (eq 13). The $k_B^{NH^+}$ and $k_{BH}^{NH^+}/k_2^{NH^+}$ values found for isomers **1** and **2** are reported in Tables 1 and 2, respectively.

Figure 3 shows the fit of k_{obs} with these rate constants and eq 14 at the various pH values of work for isomer **1** and **2**, respectively. Alternatively, the $k_B^{NH^+}$ and $k_{BH}^{NH^+}/k_2^{NH^+}$ values can be calculated by eq 14 with nonlinear fitting of the data. Good agreement (±5%) between the two methods was found. The curvature at each pH is consistent[7] with a carbanion mechanism and with a change in the rate-determining step from carbon deprotonation at low [BH] ($k_2^{NH^+} > k_{BH}^{NH^+} \cdot [BH]$, mechanism (E1cb)$_I$) to leaving group expulsion at high [BH], where reprotonation of the intermediate carbanion by BH is faster than the leaving group expulsion ($k_2^{NH^+} <$

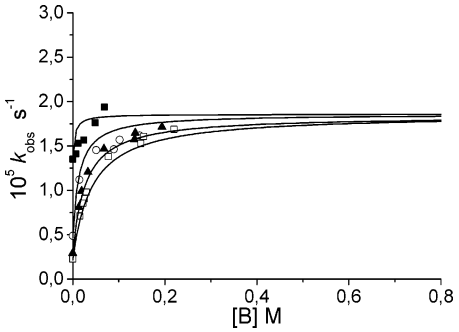
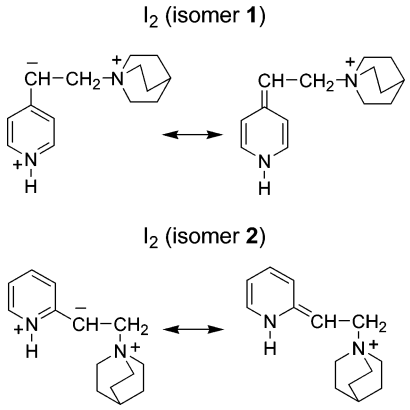


FIGURE 4. Dependence of k_{obs} on [buffer] for the elimination reaction with **1** in acetate/acetic acid buffer at different pH values, 50 °C, μ = 1 M KCl: (■) pH = 4.14, (○) pH = 4.69, (▲) pH = 4.94, (□) pH = 5.12. Solid lines are calculated from eq 14 and rate constants from Table 1.

SCHEME 3



$k_{BH}^{NH^+}$·[BH], mechanism $(E1cb)_R$). This mechanistic possibility is a partially reversible E1cb mechanism, where the two barriers for leaving group expulsion and for reprotonation of the carbanion are close enough to make possible the change in the rate-determining step within the range of [buffer] used; it will be indicated also as $(E1cb)_R$. The result that the leveling-off at high [buffer] (Figure 3) is independent of pH is in agreement with carbon deprotonation occurring from NH^+ (eq 10). The large reactivity of NH^+ with respect to N can be related to the operating E1cb mechanism and to strong stabilization by resonance of the intermediate I_2 formed from NH^+ (Scheme 3).

If the base-induced carbon deprotonation was from the unprotonated substrate, N, the value of k_∞ would be dependent on OH^- (this point is discussed later). The process (Scheme 1) from N to I_2 is a tautomerization process, and at high [BH] it will be a real equilibrium. The overall process (and k_∞) then becomes pH-independent, since both the tautomerization equilibrium and the leaving group expulsion are pH-independent.

Acid−Base Catalysis in Acetate/Acetic Acid Buffers. Pseudo-first-order rate constants (k_{obs}, initial rate) in acetate/acetic acid buffers, 50 °C and μ = 1 M KCl, were measured as previously described with imidazole/imidazolium buffers in the Experimental Section. Kinetic treatment and rate constants evaluation were also the same. The plot of k_{obs} against [B] for isomer **1** are reported in Figure 4. Similar behavior was observed with isomer **2**.

The curvatures observed are in agreement with Scheme 1 (with the two isomers) and eq 9. The calculated values of the rate constants (eq 13) are reported in Tables 1 and 2.

H/D Exchange. H/D exchange experiments confirmed the reversible E1cb mechanism at appropriate [buffer] for the β-elimination reaction from **1** or **2** in imidazole/imidazolium buffers. It was shown that **1** incorporated deuterium in the β-position with respect to the leaving group during the elimination reaction in D_2O, imidazole/imidazolium buffers. The technique used was previously described.[4,5] In an experiment with **1** in D_2O at 50 °C, μ = 1 M KCl, [B] = [BD] = 0.09 M, when the elimination reached 49% of the 4-vinylpyridine formed, H/D exchange was 38%. Similar experiments gave consistent results. With **2** in D_2O at 50 °C, μ = 1 M KCl, [B] = 0.05 M, [BD] = 0.1 M, when the elimination reached 41% of the 2-vinylpyridine formed, H/D exchange was 14%. Consistent results were also obtained with the same technique in acetate/acetic acid buffer, D_2O at 50 °C, μ = 1 M KCl. For example, with **1** (D_2O, at 50 °C, μ = 1 M KCl, [B] = [BD] = 0.05 M) the formation of ∼15% of 4-vinylpyridine corresponded to 28% H/D exchange in the substrate. With **2** (D_2O, at 50 °C, μ = 1 M KCl, [B] = 0.2 M, [BD] = 0.1 M) the formation of 22% of 2-vinylpyridine corresponded to 15% of H/D exchange in the substrate. It should be noted that the consistency of H/D exchange experiments could be qualitatively evaluated by the known term $k_{BH}^{NH^+}/k_2^{NH^+}$; in fact the ratio (% H/D exchange)/(% vinylpyridine formed) should be consistent with the term $k_{BD}^{NH^+}/k_2^{NH^+}$·[BD]. However, the lack of knowledge about the primary kinetic isotope effect, $k_{BH}^{NH^+}/k_{BD}^{NH^+}$, and, in general, the difficulty in getting quantitative results for H/D exchange experiments in our systems makes this a qualitative techniques, but it strongly supports the assigned mechanism. The presence of H/D exchange, at [BD] where some reversibility in the formation of the carbanion is expected, is evidence of the presence of the intermediate carbanion.

Comparison of Kinetic Parameters of the Elimination Reaction from 1 and 2 with Different Buffer Systems. The rate constants calculated for **1** and **2** in different buffer systems are reported in Table 1 and Table 2, respectively. The values of $k_B^{NH^+}$, the second-order-rate constant for carbon deprotonation from NH^+, are consistently related to the strength of the attacking base. The ratio $k_B^{NH^+}$ (**1**)/$k_B^{NH^+}$ (**2**) is 1.47 in acetate, 0.65 in imidazole, and 0.84 in acetohydroxamate. Application of the Brønsted eq[13,14] with $k_B^{NH^+}$ for isomer **1** is shown in Figure 5.

The β value obtained is 0.8. For substrate **2** there are only three $k_B^{NH^+}$ values, anyway the linear regression analysis (log $k_B^{NH^+}$ against pK_a^B + log(p/q)) gives: y = −8.2 (SD = 1.7) + 1.0 (SD = 0.2)x (r = 0.9731). However, these values are only to be considered indicative, because the set of bases used is not homogeneous, with N or O as the attacking atom and with acetohydroxamate base that could give the α effect.[14] It can be noted that the values

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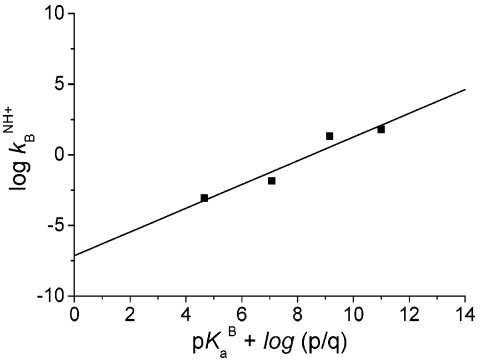
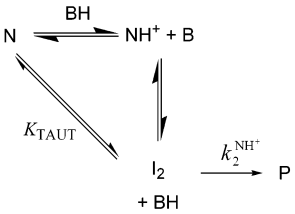


FIGURE 5. Brønsted plot of log $k_B^{NH^+}$ against $pK_a^B + \log(p/q)$ for isomer **1** (50 °C, $\mu = 1$ M KCl). pK_a^B is related to the acid of the buffer; p is the number of equivalent protons in the conjugate acid, q is the number of equivalent basic nitrogens in the base. The bases are acetate, imidazole, acetohydroxamate, and quinuclidine. Linear regression analysis gives the equation $y = -7.1(SD = 1.3) + 0.84(SD = 0.16)x$, $r = 0.9526$.

of $k_B^{NH^+}$ for isomer **1** are very close to those of isomer **2** with the same base, whereas when the reacting species is the unprotonated substrate N and the base is OH^-, $k_{OH^-}^N = 3.45 \times 10^{-3}$ M^{-1} s^{-1} (isomer **1**)[7] and $k_{OH^-}^N = 0.27 \times 10^{-3}$ M^{-1} s^{-1} (isomer **2**).[7] The $k_{OH^-}^{NH^+}$ value with isomer **1** is 241.3 M^{-1} s^{-1} and 290 M^{-1} s^{-1} with isomer **2** (this work), the ratio $k_{OH^-}^{NH^+}$(**1**)/$k_{OH^-}^{NH^+}$(**2**) is 0.83. When the reacting species is NH^+, the E1cb mechanism, involving an intermediate carbanion (Scheme 1), can be assigned, whereas with the less activated unprotonated substrate, N, it is not clear if the mechanism is $(E1cb)_I$ or E2. The different behaviors of the two isomers with respect to $k_{OH^-}^{NH^+}$ and $k_{OH^-}^N$ could be explained by the different resonance energies and different electrostatic interactions[15] if the mechanism is E1cb, or it could also be related to the different operating mechanism, if there is a change in mechanism from N to NH^+.

The ratio $k_{BH}^{NH^+}[BH]/k_2^{NH^+}$ is related to the partition of the intermediate carbanion. The E1cb mechanism with NH^+ and the presence of an intermediate carbanion were assigned in our work by focusing experiments on the minimum of the energy in the energy/reaction coordinate diagram, where the intermediate is located.[16] So the curvature observed in the studies of the acid−base catalysis is related to the competition between the two terms $k_{BH}^{NH^+}[BH]$ and $k_2^{NH^+}$, then to the presence of the carbanion intermediate in the reaction path. Even the H/D experiments (discussed in the previous section) can identify the presence of an intermediate carbanion by focusing on its partition ratio in D_2O. It was previously showed that the technique of solvent kinetic isotope effect, [3,10] focusing again on the partition ratio of the carbanion in the reaction with **1** or **2**, can be used as a quantitative support of the mechanistic model assigned. With this technique the pseudo-first-order rate constant k_{obs} for the acid−base catalysis study are compared in H_2O and D_2O. The differences observed depend on the contribution of the term $k_{BH(D)}[BH(D)]$ with respect to k_2. Apart from the Q/QH^+ buffer, all the $k_{BH}^{NH^+}/k_2^{NH^+}$ values

SCHEME 4



with the two isomer are high enough so that some reversibility in the formation of the carbanion is experimentally observed in the range of the [BH] used. The variation of $k_{BH}^{NH^+}/k_2^{NH^+}$ with the structure of BH, the protonating acid, is related to the variation of $k_{BH}^{NH^+}$, because $k_2^{NH^+}$ is independent of the buffer species. The values of $k_{BH}^{NH^+}/k_2^{NH^+}$, estimated in Q/QH^+, is 0.53 M^{-1} (Table 1); this value is related to the low acidity of QH^+ (then the low value expected for $k_{BH}^{NH^+}$) and determines the lack of curvature in the plot of k_E vs [B]. The order of $k_{BH}^{NH^+}$ (or $k_{BH}^{NH^+}/k_2^{NH^+}$) is acetate > acetohydroxamate > imidazole > quinuclidine for isomer **1** and acetohydroxamate > acetate > imidazole for isomer **2**. There is no direct relationship to the pK_a^B of the acid (BH); this could be explained by a specific interaction due to the geometry of the different structure of BH.

For the elimination reaction from NH^+ in different buffer systems and in the pH range used, an important check of the consistency of the mechanistic assignment, E1cb with some degree of reversibility, is related to the fact that k_∞, the observed first-order rate constants at high [buffer], when the leveling-off occurs, is expected to be independent of the pH and buffer (eq 10). In a condition of full reversibility, when $k_{BH}^{NH^+}[BH] \gg k_2^{NH^+}$, k_{obs} becomes $k_\infty = k_2^{NH^+}K_{TAUT}$, where K_{TAUT} is the equilibrium constant for tautomerization from N to I_2; in this condition the overall process can be written as in Scheme 4.

Because $k_2^{NH^+}$ and K_{TAUT} are independent of pH, k_∞ will be independent of pH even if other equilibrium constants and other rate constants vary with pH. In fact, the variation of the buffer system B/BH and pH implies variations in the positions of the first and second equilibrium (Scheme 4) with the related rate constants, but the ratio $[I_2]/[N] = K_{TAUT}$ remains constant. The calculated values of k_∞ for isomer **1** and **2** are reported in Tables 1 and 2. The values found with different buffer systems are in agreement, and the average value is $k_\infty = (1.9 \pm 0.3) \times 10^{-5}$ s^{-1} with isomer **1** and $(2.8 \pm 0.4) \times 10^{-6}$ s^{-1} with isomer **2**.

Another rate constant is consistent within the proposed mechanistic model, $k_{OH^-}^N$, the second-order rate constant for the reaction with **1** in Q/QH^+ buffer with OH^- base. The value extrapolated at [buffer] = 0 in the plot k_E vs [B] is $k_{OH^-}^N = 3.5 \times 10^{-3}$ M^{-1} s^{-1}, this value is in good agreement with that directly measured experimentally in OH^-/H_2O in the same reactions conditions as previously reported,[7] $k_{OH^-}^N = 3.45 \times 10^{-3}$ M^{-1} s^{-1}. The validity of the E1cb mechanistic assignment with **1** and **2** is strongly supported by the consistency of the kinetic parameters obtained: the rate constants that are expected to remain constant in different buffer systems and pH range, k_∞ and $k_{OH^-}^N$, are effectively in good ap-

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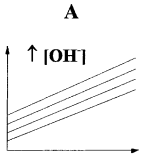
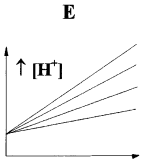
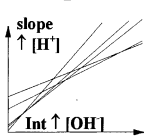
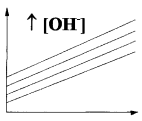
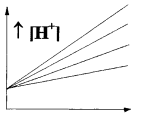
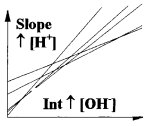
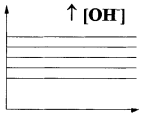
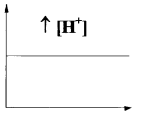
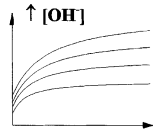
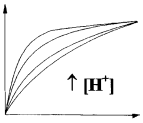
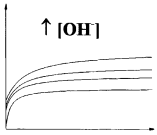
TABLE 3. Expected Plots of k_{obs} against [B] for Elimination Reaction from Substrates Activated by a Pyridine Ring[a]

	N	NH^+	N + NH^+
E2	A 	E 	I 
$(E1cb)_I$	B 	F 	L 
$(E1cb)_R$	C 	G 	M 
$(E1cb)_R$ Partially reversible	D 	H 	N 

[a] k_{obs} calculated with initial rate by a plot of *C* against *t*, k_{obs} = slope/[N]. In the case of I, L, M, N plots (Q/QH^+ buffer) $k_{obs} = k_E$, calculated following the total reaction at pH ≈ 11, with isomer **1**. The E1cb mechanism from N refers to process N → I_1 → P.

proximation constant, whereas those expected to vary, $k_B^{NH^+}$ and $k_{BH}^{NH^+}/k_2^{NH^+}$, show changes that are consistent with the structure of the reactants (Tables 1 and 2). It is interesting to note that the reaction path that we have proposed for the acid−base catalysis of our reactions, represented by the sequence of steps N → NH^+ → I_2 → P, is the only path kinetically consistent with the experimentally observed acid−base catalysis. In fact, if the tautomerization process occurs by first carbon deprotonation followed by nitrogen protonation, the reaction path will be represented by the sequence of steps N → I_1 → I_2 → P. In this case, a general base catalysis would be observed, independently if the rate-determining step is the first or the second one. This discussion is valid for all studied systems except isomer **1** in quinuclidine/quinuclidinium buffer (Scheme 2).

In Table 3 is shown the expected acid−base catalysis for the various possible situations in solution, depending on if the reacting species is N, NH^+, or the competition N + NH^+ and depending on the mechanism of the reaction.

Our systems show acid−base catalysis described by plots F or H, Table 3, (k_E values in quinuclidine/quinuclidinium buffer with isomer **1** for the elimination from NH^+ are described by plot F) where the slopes increase by increasing the [H^+]; this is in agreement with the mechanism described in Scheme 1.

Mechanism Assignment for Elimination Reactions with a Series of Substrates of Different Structure and under Different Reaction Conditions. For the systems giving β-elimination reaction with structure Y-CH_2-CH_2-X, where Y is the β-activating group and X is the leaving group, the expected dependence of the plots k_{obs} vs [B] (the basic component of the buffer), for an acid−base catalysis study where Y is a pyridine ring, is shown in Table 3. In Table 4 the derived kinetic expressions of k_{obs}, related to Table 3 are reported.

TABLE 4. Expression of k_{obs} for Elimination Reaction Related to Table 3[a]

FIGURE	k_{obs} EQUATION
A	$k_{OH^-}^N[OH^-] + k_B^N[B]$ (concerted process)
B	$k_{OH^-}^N[OH^-] + k_B^N[B]$
C	$k_2^N \cdot \frac{K_a^{CH}}{K_w} \cdot [OH^-]$
D	$k_2^N \cdot \frac{k_{OH^-}^N[OH^-] + k_B^N[B]}{k_{H_2O}^N + k_{BH}^N[BH] + k_2^N}$
E	$k_0' + k_B^{NH^+}[B] \cdot \frac{[H^+]}{K_a^N}$ (concerted process)
F	$k_0' + k_B^{NH^+}[B] \cdot \frac{[H^+]}{K_a^N}$
G	$k_2^{NH^+} \cdot K_{TAUT}$
H	$k_2^{NH^+} \cdot \frac{k_{H_2O}'^{NH^+} + k_{OH^-}^{NH^+}[OH^-] + k_B^{NH^+}[B]}{k_{H_2O}^{NH^+} + k_2^{NH^+} + k_{BH}^{NH^+}[BH]} \cdot \frac{[H^+]}{K_a^N}$
I	$k_{OH^-}^N[OH^-] + k_{OH^-}^{NH^+}\frac{[OH^-][H^+]}{K_a^N} + \left(k_B^N + k_B^{NH^+}\frac{[H^+]}{K_a^N}\right)[B]$ (concerted process)
L	$k_{OH^-}^N[OH^-] + k_{OH^-}^{NH^+}\frac{[OH^-][H^+]}{K_a^N} + \left(k_B^N + k_B^{NH^+}\frac{[H^+]}{K_a^N}\right)[B]$
M	$k_2^N \cdot \frac{K_a^{CH}}{K_w} \cdot [OH^-] + k_2^{NH^+} \cdot K_{TAUT}$
N	$k_2^N \frac{k_B^N[B] + k_{OH}^N[OH^-]}{k_2^N + k_{H_2O}^N + k_{BH}^N[BH]} + k_2^{NH^+} \cdot \frac{k_B^{NH^+}[B] + k_{OH}^{NH^+}[OH^-]}{k_2^{NH^+} + k_{H_2O}^{NH^+} + k_{BH}^{NH^+}[BH]} \cdot \frac{[H^+]}{K_a^N}$

[a] k_{obs} calculated by initial rate by a plot of *C* against *t*, k_{obs} = slope/[N]. In the case of I, L, M, N plots (Q/QH^+ buffer) $k_{obs} = k_E$, calculated following the total reaction at pH ≈ 11, with isomer **1**.

Various possible situations are considered, depending on whether the reacting species is N or NH^+ or if there is competition between N and NH^+ with the possible mechanism E2, E1cb irreversible, E1cb reversible, or E1cb partially reversible. A point of mechanistic interest, in these systems, is to clarify if the reacting species undergoing carbon deprotonation is the unprotonated substrate N or the protonated substrate NH^+. It is also important to know whether the mechanism of the reaction is E2 concerted, E1cb irreversible, or E1cb reversible. It can be seen from Table 3 that there are some diagnostic differences related to the operating reaction mechanism and to the reacting species that undergoes carbon deprotonation (whether N or NH^+). Substrates **1** and **2** in acetate/acetic acid, imidazole/imidazolium, and acetohydroxamate/acetohydroxamic acid [7] buffers show acid−base catalysis as H (Table 3). This is in agreement with NH^+ as reacting species and with an E1cb partially reversible mechanism. These conclusions are confirmed by the expected presence of H/D exchange[7] and consistent

values of the solvent isotope effect.[10] The proton activating factors determined with acetohydroxamate/acetohydroxamic acid[7] buffer at 50 °C, $\mu = 1$ M KCl are 2.7×10^5 for isomer **1** and 5.2×10^6 for isomer **2**; with the base OH^- they are 0.7×10^5 for isomer **1** and 1.1×10^6 for isomer **2** (calculated with the $k_{OH^-}^{NH^+}$ values from this work). Substrate **1**, in quinuclidine/quinuclidinium buffer, shows acid−base catalysis as I or L (Table 3). So at pH 10.1−11 there is a competition between N and NH^+ as reacting species, but when NH^+ is the reacting species the consistent mechanism can be E2 or $(E1cb)_I$. A distinction between these two mechanisms can be made considering the PAF value determined, PAF $= 1.2 \times 10^6$. This value is similar to the value determined in acetohydroxamate/acetohydroxamic acid[7] buffer, where an E1cb mechanism was demonstrated with NH^+, so an E1cb irreversible mechanism can be assigned in quinuclidine/quinuclidium buffer with **1**. In agreement with this interpretation is the fact that in acetate/acetic acid and imidazole/imidazolium buffers an E1cb partially reversible mechanism can be demonstrated; the change to quinuclidine/quinuclidium buffer can be interpreted as the expected mechanistic change to $(E1cb)_I$, owing to the lower acidity of QH^+ (BH) and then to the increase in the energetic barrier for the reprotonation of the intermediate carbanion (decrease of the rate constant, $k_{BH}^{NH^+}$). We consider, also, that the fit of $k_{BH}^{NH^+}$ with isomer **1** in quinuclidine in the Brønsted plot (Figure 5) can be in agreement with an $(E1cb)_I$ mechanism in quinuclidine/quinuclidinium buffer; in fact, the Brønsted plot is related to the E1cb mechanism. A conclusion from the results of an E1cb mechanism in quinuclidine/quinuclidinium buffer is that the mechanism remains E1cb when the strength of the base increases from acetate ($pK_a = 4.65$ at 50 °C and $\mu = 1$ M KCl) to quinuclidine ($pK_a = 11$ at 50 °C and $\mu = 1$ M KCl). It has been reported in the literature a change in mechanism from E1cb to concerted E2 by increasing the strength of the base.[17]

Substrates 2-(2-chloroethyl)pyridine,[8] 2-(2-fluoroethyl)-pyridine,[9] and 2-(4-fluoroethyl)pyridine[9] from previous studies show acid−base catalysis in acetate/acetic acid and acetohydroxamate/acetohydroxamic acid buffers as E or F (Table 3). From these results, it can be deduced that the reacting species is NH^+, and both an E2 or $(E1cb)_I$ mechanisms are in agreement. To distinguish between these two possibilities is generally very difficult.[9,18] In our interrelated systems, however, these substrates can be put in relation with **1** or **2**. The PAF value calculated with 2-(2-chloroethyl)pyridine[8] is PAF $= 1.38 \times 10^5$ (acetohydroxamate/acetohydroxamic acid buffer, 50 °C and $\mu = 1$ M KCl), PAF $= 3.6 \times 10^5$ with 2-(2-fluoroethyl)pyridine[9] and PAF $= 0.65 \times 10^5$ with 2-(4-fluoroethyl)pyridine[9] (acetohydroxamate/acetohydroxamic acid buffer, 50 °C and $\mu = 1$ M KCl). It is to be considered that the k_B^N value in acetohydroxamate/acetohydroxamic acid with these substrates was estimated by the previously proposed LFER;[7] this value is then an approximation, but it is useful to calculate the order of magnitude of PAF. These high PAF values are similar to those determined with **1** or **2**, and they can be put in relation to the presence of a resonance stabilized intermediate carbanion, formed from NH^+, and an $(E1cb)_I$ mechanism. The change in leaving group from the tertiary amine to Cl or F shows the expected mechanistic change associated to decrease in the barrier for leaving group expulsion (increased value of $k_2^{NH^+}$) from $(E1cb)_R$ to $(E1cb)_I$ mechanism. The catalysis observed with these substrates is described by plot F (Table 3), and this is in agreement with the sequences of steps $N \rightarrow NH^+ \rightarrow I_2 \rightarrow P$, as previously described. It is relevant to report that a study of the non-steady-state kinetics of the elimination reaction of HBr from 2-(*p*-nitrophenyl)ethyl bromide in alchol/alkoxide media has been interpreted with two-steps mechanism involving an intermediate carbanion;[19] this substrate has a lower β-activation with respect to a protonated pyridine ring and Br is a better leaving group with respect to Cl or F. It is to be considered that an E2 concerted mechanism can have a transition state with partial negative charge development at the β-carbon[1] (E1cb-like transition state). However, we favor the simple interpretation that to the same values of PAF is associated the same mechanism E1cb. The substrates studied present different, but related structures, with variations of Y and X. Mechanism assignment for a single substrate is supported by applying, in most cases, the combined use of two or three techniques. As previously discussed, the interrelation between the various systems offers a further possibility of mechanism assignment.

An interesting variation in the system is represented by the variation of the buffer (consequently of the pH). This point has been previously discussed. What we would like to point out now is that, in our model, the variation of the buffer system represents a mechanistic test of self-consistency of the model. In fact, with substrates **1** and **2** we have an E1cb mechanism as mechanistic model. To check conclusively the consistency of the model, an important variation of the reaction system is made (change of the buffer and pH). The variation is selected to focalize the consistency of key parameters of the model (in our case k_∞). The analysis of the results due to the variations made in the model can be a conclusive test of the validity of the model. This situation in our systems is exemplified in Figure 6.

The consistency of the results obtained can be seen in Tables 1 and 2; the parameters that have to remain constant, with the variation of pH and buffer systems, remain constant, while those that have to change with the buffer structure change consistently.

All of the interrelated systems, where Y is a pyridyl or a quinolyl group,[7−10,20] react by an E1cb mechanism, with NH^+ being the reacting species owing to the high PAF values (a part **1** in quinuclidine/quinuclidium buffer at pH 10.1−11, where there is a competition between N

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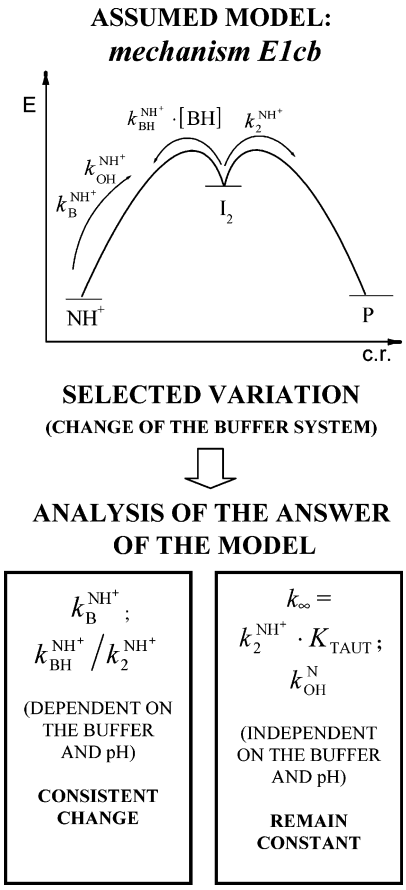

FIGURE 6. Schematic representation of the consistency of the model.

and NH^+). Systems activated by *p*-nitrophenyl or *o*-nitrophenyl groups, previously studied[3−5] react by the E1cb mechanism, and the effect of the variation of the structure of the leaving group can be understood in terms of a relief of steric strain in the expulsion of the leaving group from the intermediate carbanion. When Y = *p*-nitrophenyl in acetohydroxamate/acetohydroxamic acid buffer, 50 °C and μ = 1 M KCl at pH = 9.05, a mechanistic change from an E1cb partially reversible mechanism (X = *N*-methylpyrrolidine, pK_a = 10.77 in H_2O, at 25 °C and μ = 1 M KCl) to an E1cb irreversible mechanism (X = *N*-isopropylpyrrolidine, pK_a = 11.25 in H_2O, at 25 °C and μ = 1 M KCl) has been assigned.[4] We can conclude that the activation by *p*-nitrophenyl or *o*-nitrophenyl or protonated pyridine ring provides enough stabilization of the intermediate carbanion to make the carbanion mechanism energetically favored with respect to the concerted E2 process.[16]

Another motif of consistency of the proposed model comes from the comparison of PAF values determined with the related methyl activating factor. In fact, while the $k_B^{NH^+}$ rate constant is extracted from a mathematical model describing the E1cb mechanism from NH^+ (Scheme 1), it is possible to directly measure $k_B^{NCH_3}$ (in OH^-/H_2O, 50 °C) following the elimination reaction with 1-methyl-2-(2-chloroethyl)pyridinium iodide, 1-methyl-2-(2-fluoroethyl)pyridinium iodide, or 1-methyl-4-(2-fluoroethyl)-pyridinium iodide. The MethylAFs previously determined[8,9] with several substrates are reported in Table 5 along with the related PAF values for comparison.

TABLE 5. PAF and MethylAF Values for HX β-Elimination Reactions for the System Y-CH_2-CH_2-X in H_2O at 50 °C, μ = 1 M KCl

Y	X	10^{-5} PAF [a]	10^{-5} MethylAF [b]	Ref.
	F	3.60	8.70	9
	F		0.016	9
	F	0.65	0.21	9
	Cl	1.38	6.88[c]	8

[a] The PAF values are calculated as the ratio $k_B^{NH^+}/k_B^N$ in acetohydroxamate/acetohydroxamic acid buffers. [b] Values calculated in OH^-/H_2O. [c] Value determined at 25 °C and μ = 1 M KCl.

It can be seen that there is good agreement between the two parameters as expected within an E1cb mechanism involving the protonated or the methylated pyridine ring (activating system). A comparison of $k_B^{NH^+}$ with the same activating system (Y = 2-pyridyl) and leaving group Cl, F shows that the second-order rate constant for carbon deprotonation from NH^+ is larger (acetohydroxamate/acetohydroxamic buffer, 50 °C and μ = 1 M KCl) with the leaving group X = chlorine ($k_B^{NH^+}$ = 1.05 M^{-1} s^{-1}) than with X = fluorine ($k_B^{NH^+}$ = 0.35 M^{-1} s^{-1}). The same situation is found with the methylated substrates: when Y = 2-pyridyl and X = Cl, $k_B^{NCH_3}$ = 17.9 M^{-1} s^{-1}, whereas when X = F, $k_B^{NCH_3}$ = 10.25 M^{-1} s^{-1} (OH^-/H_2O 25 °C and μ = 1 M KCl). Because of the fact that in our interrelated model the mechanism with NH^+ or the methylated substrate can be assigned as $(E1cb)_I$, it follows that there is some lengthening of the carbon-leaving group bond in the intermediate carbanion[18d,21] (and related transition state). In fact, the higher electronegativity of F, with respect to Cl, should imply a reverse order of reactivity (even if the possible significant contribution of the enamine type structure to the delocalization of the negative charge could limit this effect). Thus the larger reactivity when the leaving group is Cl with respect to F indicates that there is a favored lengthening of the carbon−chlorine bond with respect to that of the stronger carbon−fluorine bond. This is a point of interest for interpreting a heavy atom isotope effect.[17,22]

Regarding the possibility of an E1cb ion pairs mechanism,[1a,3] where the carbanion intermediate is bonded

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with BH, in systems where the curvature in the plots k_{obs} against [B] is observed, it can be excluded. When acid−base catalysis is observed as E or F in Table 3 this mechanistic possibility would be consistent; however, the possibility of rate-determining the expulsion of the leaving group should be associated with a change from quinuclidine E1cb partially reversible mechanism to the much better leaving group fluorine or chlorine and this fact seems inconsistent. Also the PAF values, in the case of E1cb (ion pair) mechanism with the rate-determining step the expulsion of the leaving group, are related to a combination of rate constants, whereas we have found PAF values, with substrates with Cl or F as leaving group, consistent with those of substrates with quinuclidine as leaving group. The possibility of E1cb (ion pair) mechanism with rate-determining carbon deprotonation is also consistent with catalysis as E or F in Table 3. In this case the transition state for the E1cb (ion pair) or $(E1cb)_I$ mechanism would be the same, and our kinetics techniques do not allow the distinction.

Regarding the possibility of competition E1cb/E2 it can be noted that a significant contribution of E2 can be excluded in the cases where the curvature is observed in the plots k_{obs} against [B] and the leveling-off is reached and shown to be independent of pH. In the case that the curvature is observed but the leveling-off is not reached, a large contribution by the E2 process would imply a significant distortion from the E1cb model. In the case of substrates with Cl or F as leaving group (catalysis E or F in Table 3) the assignment of the $(E1cb)_I$ mechanism with not significant contribution of E2 is related to the observed PAF values and their similarity with substrates with quinuclidine as leaving group.

Experimental Section

Materials. Glass-distilled and freshly boiled water was used throughout. Reagent-grade potassium chloride, quinuclidinium hydrochloride, potassium acetate, imidazole, and 2-vinylpyridine were used without further purification. 4-Vinylpyridine was purified by column chromatography with silica gel (Et_2O).

***N*-[2-(4-Pyridyl)ethyl]quinuclidinium bromide and *N*-[2-(2-Pyridyl)ethyl]quinuclidinium tosilate.** These compounds were prepared and characterized as previously reported.[7]

p*Ka* Determination. The pK_a of quinuclidinium chloride or imidazolium chloride, 50 °C and μ = 1 M KCl, was determined[23] by potentiometric titration with KOH 1 M or HCl 1 M, respectively. The pK_a of 4-vinylpyridine and 2-vinylpyridine were previously reported[9] as 5.64 and 5.06, respectively, measured in acetate/acetic acid buffer 0.1 M, 50 °C and μ = 1 M KCl. These values are used for the study of acid−base catalysis in the various buffer systems. However, we have found that at very low [buffer] or in the absence of buffer, the pK_a is 5.23 and 4.77, respectively. Therefore, we have found that it is more correct to use these last values to determine the rate constants in the absence of buffer ($k'^{NH^+}_{H_2O}$, $k^{NH^+}_{OH^-}$).

H/D Exchange. H/D exchange experiments in D_2O imidazole/imidazolium buffer, or D_2O, CH_3COO^-/CH_3COOD buffer, were carried out using the previously described techniques[4,5,7] 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 reaction.

Product Analysis. Reaction in Quinuclidine/Quinuclidinium (Q/QH$^+$) Buffers. Several experiments with a solution of 4-vinylpyridine in buffers, at different [buffer] and [Q]/[QH$^+$] ratios, left at 50 °C for different reaction times (6 and 20 h) showed that, after extraction with *n*-hexane and GLC analysis, the only products were 4-vinylpyridine and quinuclidine. Also, a mixture of 4-vinylpyridine and Q/QH$^+$ buffers in D_2O in a NMR tube left at 50 °C and analyzed at various intervals of time showed the formation of **1**. The same products were obtained in similar experiments following the elimination reactions from **1**.

Reactions in Imidazole/Imidazolium Buffers. A solution of **1** or **2** in several buffer solutions at different pH values were left to react at 50 °C for ∼6 or 30 h, respectively. The solution was taken to pH ≈ 10 before extraction with *n*-hexane; the GLC analysis showed the presence of only 4- or 2-vinylpyridine and quinuclidine.

Reactions in Acetate/Acetic Acid Buffers. A solution of **1** or **2** in several buffer solutions at different pH values was left to react at 50 °C for ∼3 or 25 h, respectively. The solution was taken to pH ≈ 10 before extraction with *n*-hexane; the GLC analysis showed the presence of only 4- or 2-vinylpyridine and quinuclidine.

Kinetic Measurements in Quinuclidine/Quinuclidinium Buffer. The kinetic studies in Q/QH$^+$ buffers were carried out following the decrease in absorbance at λ = 280 nm of a solution ≅ 8.6 × 10^{-4} M of 4-vinylpyridine in 2.8 mL of buffer in a thermostated cuvette at 50 °C. 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 process of the addition reaction of quinuclidine to 4-vinylpyridine in Q/QH$^+$ buffers to give **1** (substrate **1** will be indicated as S; in Q/QH$^+$ it will correspond to the unprotonated substrate N) is an equilibrium involving the reverse elimination reaction. The observed pseudo-first-order rate constants were evaluated by the equation $\ln[(A_0 - A_\infty)/(A_t - A_\infty)] = k_{obs}t$, where $k_{obs} = k_E + k_A$, where k_A is the observed pseudo-first-order rate constant for the addition reaction and k_E is the observed pseudo-first-order rate constant of the reverse elimination reaction from **1** to form 4-vinylpyridine (P). The value of k_A is calculated by $k_A = k_{obs}/[1 + ([P]_\infty/[S]_\infty)]$ and $[P]_\infty/[S]_\infty = 1/(A_0/\epsilon_P[P]_\infty - 1)$, where ϵ_P is the extinction coefficient[7] of 4-vinylpyridine at 50 °C, μ = 1 M KCl and λ = 280 nm, ϵ_P = 1634 M^{-1} cm^{-1}; A_0 is the value of absorbance at t = 0; $[S]_\infty$ is the [S] at equilibrium; $[P]_\infty$ is the [4-vinylpyridine] at equilibrium, and $[P]_\infty = [A_\infty - (\epsilon_S/\epsilon_P)A_0]/(\epsilon_P - \epsilon_S)$, where ϵ_S = 7.9 M^{-1} cm^{-1} is the extinction coefficient of **1** in the reaction condition at λ = 280 nm. The [OH$^-$] at 50 °C, μ = 1 M KCl was calculated from the measured pH and from the empirical[7] equation $[OH^-] \times 10^{-pH} = 5.89 \times 10^{-14}$, p$K_w$ = 13.23. Some equilibration experiments, starting from **1** and following the formation of 4-vinylpyridine at 280 nm, gave consistent results (in this case, $k_{obs} = k_E + k_A$, and $k_A = k_{obs}/[1 + (A_\infty - \epsilon_S[S]_0)/(\epsilon_P[S]_0 - A_\infty)]$, where A_∞ is the absorbance at $t \rightarrow \infty$ and $[S]_0$ is the concentration of **1** at t = 0).

Kinetic Measurements in Imidazole/ Imidazolium or Acetate/Acetic Acid Buffers. Elimination reactions from **1** or from **2** in imidazole/imidazolium or acetate/acetic acid buffers at 50 °C, μ = 1 M KCl were followed by monitoring the formation of 4-vinylpyridine at λ = 280 nm or 2-vinylpyridine at λ = 290 nm, by initial rates.[7] The concentration of **1** was ≅1.5 × 10^{-3} M, the concentration of **2** was ≅1.7 × 10^{-3} M, and the reactions were followed up to ≅3%. At the pH used, the 4- or 2-vinylpyridine product, P, is at equilibrium with its conjugated acid, PH$^+$. In this condition the total concentration, C, of the product ($C = [P] + [PH^+]$) was calculated from

$$C = \frac{(A_t - A_0)}{\epsilon_P + \epsilon_{PH}\dfrac{[H^+]}{K_a^P}}\left(1 + \frac{[H^+]}{K_a^P}\right) \qquad (15)$$

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where A_t is the absorbance at time t; A_0 is the absorbance at $t = 0$; K_a^P is the dissociation constant of PH^+ ($K_a^P = 2.29 \times 10^{-6}$ M for 4-vinylpyridinium,[9] $pK_a^P = 5.64$, or $K_a^P = 8.71 \times 10^{-6}$ M for 2-vinylpyridinium,[9] $pK_a^P = 5.06$, at 50 °C, $\mu = 1$ M KCl); ϵ_P is the extinction coefficient of 4-vinylpyridine[7] (1634 M^{-1} cm^{-1} at $\lambda = 280$ nm, 50 °C and $\mu = 1$ M KCl) or of 2-vinylpyridine[7] (3584 M^{-1} cm^{-1} at $\lambda = 290$ nm, 50 °C and $\mu = 1$ M KCl), and ϵ_{PH} is the extinction coefficient of 4-vinylpyridinium[9] (8987 M^{-1} cm^{-1} at $\lambda = 280$ nm, 50 °C and $\mu = 1$ M KCl) or of 2-vinylpyridinium[9] (9773 M^{-1} cm^{-1} at $\lambda = 290$ nm, 50 °C and $\mu = 1$ M KCl). A plot of C against t was linear, and the values of k_{obs} were calculated from k_{obs} = slope/[N]; the [N] was calculated from $[N] = \{K_a^N/(K_a^N + [H^+])\}[S]_0$, where $[S]_0$ is the initial concentration of **1** or **2** ($[S]_0 = [N] + [NH^+]$). 4-Vinylpyridine or 2-vinylpyridine were shown to be stable under the experimental reaction conditions.

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Supporting Information Available: Pseudo-first-order rate constants k_{obs}, k_E, and k_A, for the elimination reactions from **1** in quinuclidine/quinuclidium buffer at different pH values (H_2O, 50 °C and $\mu = 1$ M KCl); k_{obs}, for the elimination reactions from **1** and **2** in imidazole/imidazolium or acetate/acetic acid buffers at different pH values (H_2O, 50 °C and $\mu = 1$ M KCl); k_0, for the elimination reactions from **1** and **2** in absence of buffer (H_2O, 50 °C and $\mu = 1$ M KCl); and the plots for the elimination reactions from **1** and **2** in acetate/acetic acid buffers. This material is available free of charge via the Internet at http://pubs.acs.org.

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