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# Catalysis of the β-Elimination of HF from Isomeric 2-Fluoroethylpyridines and 1-Methyl-2-fluoroethylpyridinium Salts. Proton-Activating Factors and Methyl-Activating Factors as a Mechanistic Test To Distinguish between Concerted E2 and E1cb Irreversible Mechanisms

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*Received September 16, 2002*

Second-order rate constants, $k_{OH}^{N}$, $M^{-1}$ $s^{-1}$, for the β-elimination reactions of HF with 2-(2-fluoroethyl)pyridine (**2**), 3-(2-fluoroethyl)pyridine (**3**), and 4-(2-fluoroethyl)pyridine (**4**) in $OH^-/H_2O$, at 50 °C and $\mu = 1$ M KCl, are $k_{OH}^{N} = 0.646 \times 10^{-4}$ $M^{-1}$ $s^{-1}$, $k_{OH}^{N} = 2.97 \times 10^{-6}$ $M^{-1}$ $s^{-1}$, and $k_{OH}^{N} = 5.28 \times 10^{-4}$ $M^{-1}$ $s^{-1}$, respectively. When compared with the second-order rate constants for the same processes with the nitrogen-methylated substrates 1-methyl-2-(2-fluoroethyl)pyridinium iodide (**5**), 1-methyl-3-(2-fluoroethyl)pyridinium iodide (**6**), and 1-methyl-4-(2-fluoroethyl)pyridinium iodide (**7**), the methyl-activating factor (MethylAF) can be calculated from the ratio $k_{OH}^{NCH_3}/k_{OH}^{N}$, and a value of $8.7 \times 10^5$ is obtained with substrates **5**/**2**, a value of $1.6 \times 10^3$ with **6**/**3**, and a value of $2.1 \times 10^4$ with **7**/**4**. The high values of MethylAF are in agreement with an irreversible E1cb mechanism ($A_ND_E^* + D_N$) for substrates **5** and **7** and with the high stability of the intermediate carbanion related to its enamine-type structure. In acetohydroxamate/acetohydroxamic acid buffers (pH 8.45−9.42) and acetate/acetic acid buffers (pH 4.13−5.13), the β-elimination reactions of HF, with substrates **2** and **4**, occur at $NH^+$, the substrates protonated at the nitrogen atom of the pyridine ring, even when the [$NH^+$] is much lower than the [N], the unprotonated substrate, due to the high proton-activating factor (PAF) value observed: $3.6 \times 10^5$ for **2** and $6.5 \times 10^4$ for **4** with acetohydroxamate base. These high PAF values are indicative of an irreversible E1cb mechanism rather than a concerted E2 ($A_ND_ED_N$) mechanism. Finally, the rate constant for carbanion formation from $NH^+$ with **2** is $k_B^{NH^+} = 0.35$ $M^{-1}$ $s^{-1}$, which is lower than when chlorine is the leaving group ($k_B^{NH^+} = 1.05$ $M^{-1}$ $s^{-1}$; Alunni, S.; Busti, A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 778). This is direct experimental evidence that some lengthening of the carbon−leaving group bond can occur in the intermediate carbanion. This is a point of interest for interpreting a heavy-atom isotope effect.

## Introduction

The mechanism of base-induced 1,2-elimination reactions has been the subject of many studies,[1] due to interest in being able to distinguish between the possible mechanisms: the concerted E2 process $A_ND_ED_N$[2] and the carbanion mechanism, irreversible $(E1cb)_I$ or $A_ND_E^* + D_N$ and reversible $(E1cb)_R$ or $A_ND_E + D_N^*$. These mechanisms are operative in systems with high β-activation with respect to the leaving group. A third mechanistic possibility involves an intermediate carbocation. Problems such as a structure-dependent mechanism and the nature of the borderline region are important aspects for this class of reactions.[3−5] It is particularly difficult to distinguish between the E2 and $(E1cb)_I$ mechanisms. While the presence of a reversibly formed carbanion can be deduced by showing a change in the rate-determining step[5−8] and by using isotopes (H/D exchange[1a,6,9] or solvent isotope effects[7,10,11]), the properties of the concerted E2 and $(E1cb)_I$ mechanisms are similar. One possible way to discriminate between these two mecha-

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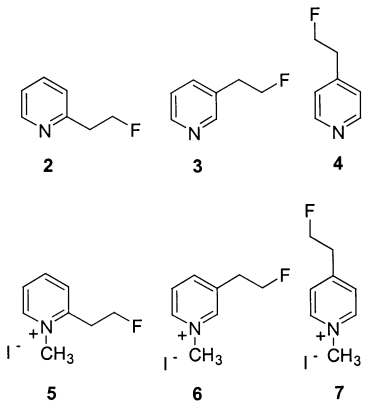
10.1021/jo020603o CCC: $25.00 
Published on Web 01/01/2003

**SCHEME 1**




nistic possibilities is to use the leaving group isotope effect.[3,12] A significant leaving group isotope effect is expected for the E2 mechanism, because in the E2 process there is the bond-breaking of the carbon−leaving group bond in the rate-determining step. However, it has been pointed out that a lengthening of the carbon−leaving group bond can occur in the transition state of the $(E1cb)_I$ mechanism by hyperconjugation,[13−19] and theoretical calculations have supported this possibility.[20−23] Another method used to confirm the presence of an intermediate carbanion is the double-isotopic fractionation technique.[24,25] In this paper we report a study of the mechanism of the base-induced *β*-elimination reactions in systems activated by a pyridine ring, with fluorine as leaving group. The substrates studied are 2-(2-fluoroethyl)pyridine (**2**), 3-(2-fluoroethyl)pyridine (**3**), 4-(2-fluoroethyl)pyridine (**4**), 1-methyl-2-(2-fluoroethyl)-pyridinium iodide (**5**), 1-methyl-3-(2-fluoroethyl)pyridinium iodide (**6**), and 1-methyl-4-(2-fluoroethyl)pyridinium iodide (**7**) (see Scheme 1).

Acid−base catalysis study, at different pH values, allows one to define whether the reacting species, which undergoes carbon deprotonation, is the unprotonated substrate, N, or the protonated substrate at the nitrogen atom of the pyridine ring, $NH^+$. It is important to know whether the evaluation of the reactivity ratio $k^{NH^+}/k^N$, proton-activating factor (PAF), or methyl-activating factor (MethylAF; $k^{NCH_3^+}/k^N$) can be a test for the mechanistic assignment, especially in relation to the difficult distinction between a concerted process or a stepwise process involving an intermediate carbanion. The effect of protonation at one reaction site upon the susceptibility to an attack by a base at another site, PAF, is important in chemistry[26−28] and biochemistry.[29]

**TABLE 1. Second-Order Rate Constants $k_{OH}^N$ ($M^{-1}$ $s^{-1}$) for the *β*-Elimination Reactions from Substrates 2−4 or $k_{OH}^{NCH_3}$ ($M^{-1}$ $s^{-1}$) for the *β*-Elimination Reactions from Methylated Substrates 7−7 at Various Temperatures, in $OH^-/H_2O$, at 50 °C and $\mu$ = 1 M KCl[a]**

| substrate | temp (°C) | $10^5 k_{OH}^N$ ($M^{-1}$ $s^{-1}$) | $k_{OH}^{NCH_3}$ ($M^{-1}$ $s^{-1}$) |
|---|---|---|---|
| **2** | 25 | 0.27 | |
| **2** | 33.9 | 0.90 | |
| **2** | 41.1 | 2.13 | |
| **2** | 50 | 6.46 | |
| **3** | 50 | 0.30 | |
| **4** | 14.5 | 0.73 | |
| **4** | 25 | 3.11 | |
| **4** | 34.4 | 8.68 | |
| **4** | 50 | 52.80 | |
| **5** | 18.4 | | 6.65 |
| **5** | 20.5 | | 8.24 |
| **5** | 25 | | 10.25 |
| **5** | 32 | | 18.09 |
| **5** | 50 | | 56.29[b] |
| **6** | 50 | | $4.80 \times 10^{-3}$ |
| **7** | 18.5 | | 0.69 |
| **7** | 25 | | 1.15 |
| **7** | 32 | | 2.01 |
| **7** | 50 | | 11.24 |

[a] The error is ±5%. [b] Value extrapolated from the Arrhenius plot.

## Results and Discussion

**Kinetic Study in $OH^-/H_2O$.** The reaction of **2**−**4** or the methylated substrates **5**−**7** in $OH^-/H_2O$, at 50 °C and $\mu$ = 1 M KCl, are complete elimination reactions with the formation of the corresponding vinylpyridine. The kinetics were studied by following the appearance of the related vinylpyridine at $\lambda$ = 290 nm for **2** and at $\lambda$ = 280 nm for **3** and **4** or the related 1-methylvinylpyridinium salt at $\lambda$ = 280 nm for **7** and **6** and at $\lambda$ = 287 nm for **5**. The processes were shown to be second-order, first-order with respect to both the substrates and $OH^-$. In Table 1 the second-order rate constants $k_{OH}^N$ (for substrates **2**−**4**) and $k_{OH}^{NCH_3}$ (for substrate **5**−**7**) are reported at the various temperatures studied. With substrates **2**−**4**, the reacting species is the unprotonated substrate, N, owing to the high $[OH^-]$; the reaction of the nitrogen-protonated substrates, $NH^+$, would be zero-order[6] with respect to the $[OH^-]$ ($k_0 = k_{OH}^{NH^+}(K_W/K_a^N)$, where $K_a^N$ is the acid dissociation constant of $NH^+$). The second-order rate constants are $k_{OH}^N = 0.646 \times 10^{-4}$ $M^{-1}$ $s^{-1}$ for **2**, $k_{OH}^N = 2.97 \times 10^{-6}$ $M^{-1}$ $s^{-1}$ for **3**, and $k_{OH}^N = 5.28 \times 10^{-4}$ $M^{-1}$ $s^{-1}$ for **4**. Substrate **4** is 8.17 times more reactive than **2** and 178 times more reactive than **3**. In previous works,[6,7] we studied other substrates activated by a pyridine ring with different leaving groups; in this paper we report a comparison of the behavior of all three isomers with fluorine as leaving group. The second-order kinetic law for the elimination reaction from **2**−**4** is consistent with a concerted E2 mechanism, with the irreversible E1cb mechanism $(E1cb)_I$, and with the reversible E1cb mech-

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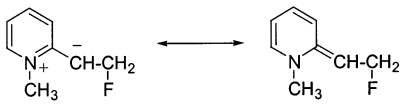
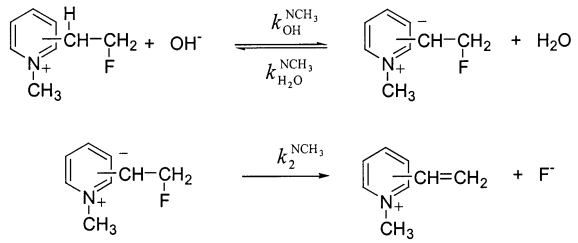
**SCHEME 2**



**SCHEME 3**



anism $(E1cb)_R$. To check for the $(E1cb)_R$ mechanism, a study of H/D exchange in $OD^-/D_2O$ at 50 °C and $\mu = 1$ M KCl was carried out with **2** and **4**. This mechanism however was excluded on the basis of the absence of deuterium incorporation into the reagent during the elimination reactions. From the data of Table 1 the MethylAF can be evaluated by comparing the second-order rate constant of isomers **2**−**4** with those of **5**−**7**, respectively (50 °C and $\mu = 1$ M KCl). A MethylAF value ($k_{OH}^{NCH_3}/k_{OH}^{N}$) of 8.7 × $10^5$ was obtained with substrates **5**/**2**, a value of 1.6 × $10^3$ with **6**/**3**, and a value of 2.1 × $10^4$ with **7**/**4**. Previously,[7b] we reported a MethylAF value of 6.88 × $10^5$ ($OH^-/H_2O$, 25 °C, and $\mu = 1$ M KCl) as the reactivity ratio of $k_{OH}^{NCH_3}/k_{OH}^{N}$ of 1-methyl-2-(2-chloroethyl)pyridinium ion and 2-(2-chloroethyl)pyridine. The high MethylAF values, obtained for **5**/**2** and **7**/**4**, are in agreement with an $(E1cb)_I$ mechanism. In fact, these values are similar to those of the PAF that were previously[6] evaluated with *N*-[2-(2-pyridyl)ethyl]quinuclidium ion (PAF = 1.5 × $10^6$; $OH^-/H_2O$, 50 °C, and $\mu = 1$ M KCl) and with *N*-[2-(4-pyridyl)ethyl]quinuclidium ion (PAF = 5.3 × $10^4$; $OH^-/H_2O$, 50 °C, and $\mu = 1$ M KCl). An $(E1cb)_R$ mechanism was demonstrated[6] with these two substrates and with acetohydroxamate base, based on a change in the rate-determining step induced by the buffer concentration, by the presence of H/D exchange and consistent results in a study of the solvent isotope effect.[11] The high MethylAF values for **5**/**2** and **7**/**4** and the similarity with the PAF values of the related[6] substrates, with quinuclidine as leaving group, are in agreement with a carbanion mechanism for the methylated substrates **5** and **7**, owing to the marked stabilization of the intermediate carbanion which has an enamine-type structure (see Scheme 2).

The MethylAF with **6**/**3** was 1.6 × $10^3$; it is only 1 order of magnitude lower than that, also high, of **7**/**4**. For the system **6**/**3**, a lower MethylAF value is expected for a carbanion mechanism because resonance, involving the positive charge of the nitrogen atom, is not possible; the significant activation of the methyl group can be interpreted as a carbanion mechanism. The general scheme of the carbanion mechanism is shown in Scheme 3.

An $(E1cb)_I$ mechanism with the methylated substrates appears to be more probable than $(E1cb)_R$. In the following discussion it will be shown that an $(E1cb)_I$ mechanism can be assigned to the elimination reactions with the conjugated acid $NH^+$ of **2** and **4** when the base is an acetohydroxamate anion. In $OH^-/H_2O$ the reprotonation of the carbanion by $H_2O$ is expected to be even slower than that by acetohydroxamic acid, so the mechanism is expected to remain $(E1cb)_I$. It can be observed that the order of reactivity in $OH^-/H_2O$ is **4** > **2**, while for the corresponding methylated substrates it is **5** > **7**. Activation parameters were determined for **2** and **4** and for **5** and **7** in $OH^-/H_2O$ and are reported in Table 2. From the data of Table 2 it can be seen that $\Delta H^{\ddagger}$ values with methylated substrates **5** and **7** are lower than those with **2** and **4**, which is in agreement with the greater stabilization due to the resonance of the intermediate carbanion. The $\Delta S^{\ddagger}$ values are all negative, in agreement with an associative mechanism. It should be noted that while an $(E1cb)_I$ mechanism can be assigned to the methylated substrates **5** and **7**, as previously discussed, the mechanism could be concerted E2 or a carbanion mechanism with substrates **2**−**4** in $OH^-/H_2O$, where the reacting species is N. In this respect, the value of $k_{OH}^{N}$ with substrate **4** ($k_{OH}^{N}$ = 5.28 × $10^{-4}$ $M^{-1}$ $s^{-1}$) is very close to $k_{OH}$ for *N*-[2-(*o*-nitrophenyl)ethyl]quinuclidinium ion ($k_{OH}$ = 1.14 × $10^{-3}$ $M^{-1}$ $s^{-1}$; $H_2O$, 50 °C, and $\mu = 1$ M KCl); with this substrate an E1cb mechanism was established for the base-induced $\beta$-elimination reaction.[30] This comparison does not imply the same mechanism for the two substrates, owing to the difficult problem of the structure-dependent mechanism and nature of the borderline region, but it is a point to be considered.

**TABLE 2. Activation Parameters for the $\beta$-Elimination Reactions ($OH^-/H_2O$, $\mu = 1$ M KCl) for Substrates 2 and 4 or Methylated Substrates 5 and 7 Calculated by the Eyring Equation**

| | **2** | **4** | **5** | **7** |
|---|---|---|---|---|
| $^{\Delta}H^{\ddagger}$ (kcal mol-[1]) | 23.52 | 21.48 | 11.99 | 16.14 |
| $^{\Delta}S^{\ddagger}$ (eu) | −5.06 | −7.20 | −13.56 | −4.04 |

**Acid−Base Catalysis.** Elimination reactions in acetohydroxamate/acetohydroxamic acid buffers with **2** and **4** were followed by monitoring the formation of 2- or 4-vinylpyridine at $\lambda = 290$ nm for **2** and at $\lambda = 280$ nm for **4**. Pseudo-first-order rate constants ($k_{obs}$, $s^{-1}$; initial rates) were evaluated at different pH values ($H_2O$, 50 °C, and $\mu = 1$ M KCl). The $pK_a$ of acetohydroxamic acid is 9.15 in the reaction conditions.[30] Product analysis (see the Experimental Section) showed that the processes are complete elimination reactions. We previously reported[7b] that the reaction of 2-(2-chloroethyl)pyridine with acetohydroxamate/acetohydroxamic acid buffers involves a competition between elimination and substitution. With fluorine as leaving group, we observed a complete elimination reaction. The plots of $k_{obs}$, $s^{-1}$, vs acetohydroxamate concentration ($[B^-]$) at pH 8.45, 8.70, 8.90, 9.15, and 9.42 for **2** and **4** are shown in Figures 1 and 2. It can be seen that there is a linear dependence of $k_{obs}$ on $[B^-]$, while the slopes of the plots are directly dependent on the $[H^+]$. This is evidence that the reacting species which undergoes carbon deprotonation is the conjugated acid of **2** and **4**, $NH^+$. The $pK_a$ of $NH^+$ is 4.98 for **2** and 5.45 for **4** ($H_2O$, 50 °C, and $\mu = 1$ M KCl). The concerted E2 mechanism or the $(E1cb)_I$ mechanism would be consistent with the results of acid−base catalysis study. However, the fact that at pH ≈ 9 the reacting species is $NH^+$,

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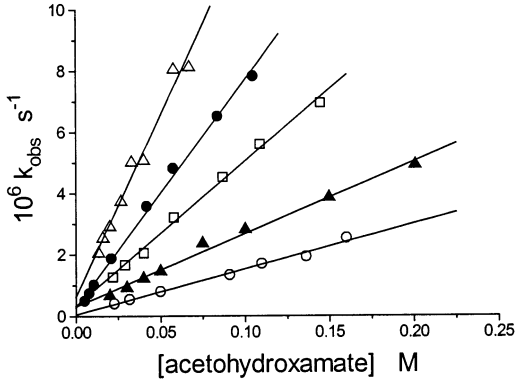



**FIGURE 1.** Dependence of $k_{obs}$ ($s^{-1}$) on acetohydroxamate concentration at different pH values for substrate **2**: open circle, pH 9.42; solid triangle, pH 9.15; open square, pH 8.90; solid circle, pH 8.70; open triangle, pH 8.45.

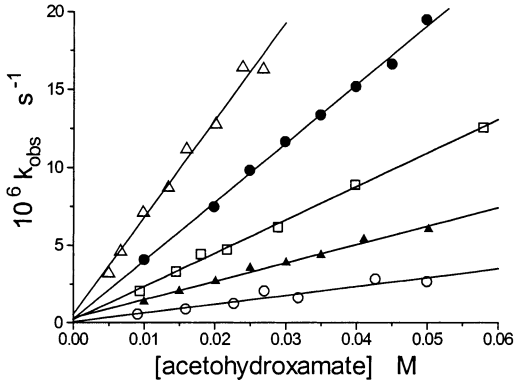



**FIGURE 2.** Dependence of $k_{obs}$ ($s^{-1}$) on acetohydroxamate concentration at different pH values for substrate **4**: open circle, pH 9.42; solid triangle, pH 9.15; open square, pH 8.90; solid circle, pH 8.70; open triangle, pH 8.45.

despite its low concentration with respect to the unprotonated substrate N, is in agreement with a carbanion mechanism,[7b] as shown in Scheme 4.

The kinetic equation for $k_{obs}$ from Scheme 4 is given as

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

where $K_a^N$ is the acid dissociation constant for $NH^+$. For an irreversible mechanism, $(E1cb)_I$, $k_2^{NH^+} > k_{BH}^{NH^+}[BH] + k_{H_2O}^{NH^+}$ and the equation for $k_{obs}$ is

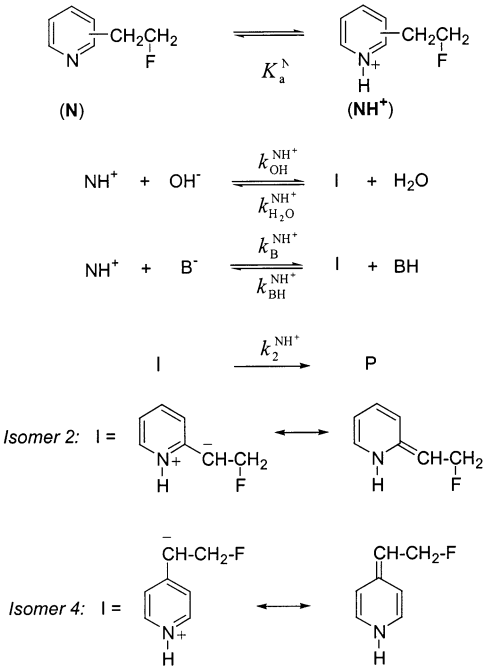
$$k_{obs} = k_0 + k_B^{NH^+}[B^-]\frac{[H^+]}{K_a^N} \qquad (2)$$

where

$$k_0 = k_{OH}^{NH^+}[OH^-]\frac{[H^+]}{K_a^N}$$

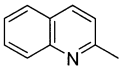
The plots of Figures 1 and 2 are in agreement with eq 2 and with carbon deprotonation from $NH^+$. If carbon deprotonation occurred from N, a different kinetic equation and different results of acid−base catalysis would

**SCHEME 4**




be obtained. In fact, for an irreversible E1cb mechanism from N, $k_{obs} = k_{OH}^N[OH^-] + k_B^N[B]$; in this case the slope of the plot $k_{obs}$ vs [B] is expected to be independent of the $[H^+]$. The $k_B^{NH^+}$ value can be calculated from a secondary plot of the slope (from the lines of Figures 1 and 2) against $[H^+]/K_a^N$, where $k_B^{NH^+}$ is the second-order rate constant for carbon deprotonation for $NH^+$ induced by the base acetohydroxamate. The values obtained are $k_B^{NH^+} = 0.35\ M^{-1}\ s^{-1}$ with **2** and $k_B^{NH^+} = 0.64\ M^{-1}\ s^{-1}$ with **4**. Isomer **4** is slightly more reactive than isomer **2**. This trend is similar to the one observed when the reacting species is N with $OH^-$ base ($k_{OH}^N$ in Table 1). However, the trend is inverted with the methylated substrates **5** and **7** in $OH^-/H_2O$ (Table 1). In Table 3 are reported the $k_B^{NH^+}$ values with acetohydroxamate base for various systems of the structure $Y-CH_2-CH_2-X$, where Y is the activating group and X is the leaving group. It can be seen that fluorides are less reactive than the corresponding chloride or quinuclidium ions. The fact that **2**, with fluorine as leaving group ($k_B^{NH^+} = 0.35\ M^{-1}\ s^{-1}$), is less reactive than 2-(2-chloroethyl)-pyridine ($k_B^{NH^+} = 1.05\ M^{-1}\ s^{-1}$) is of interest. In fact, for a carbanion mechanism, one would expect that the more electronegative fluorine would strongly stabilize the negative charge of the intermediate with respect to the chlorine, and increase the rate of the reactions. In our systems it can be seen that with a carbanion mechanism fluoride is actually less reactive than the corresponding chloride. This is clear experimental evidence that some lengthening of the carbon−leaving group bond can occur in the intermediate carbanion. This effect is expected to be larger for the C−Cl bond, with respect to the C−F bond, and can explain the greater reactivity of the chloride with respect to the fluoride. This effect was proposed in other systems[13−19] and supported by theoretical calculations with tertiary amines as leaving group.[20−23] We think that these results are important for interpreting heavy-atom isotope effects: in fact, the lengthening

**TABLE 3. Second-Order Rate Constants $k_B^{NH^+}$ ($M^{-1}$ $s^{-1}$) and $k_B^N$ ($M^{-1}$ $s^{-1}$) for the Acetohydroxamate-Promoted HX $\beta$-Elimination Reactions for the System Y−$CH_2$−$CH_2$−X in $H_2O$ at 50 °C[h]**

| Y | X | $k_B^{NH^+}$ [a] ($M^{-1}$ $s^{-1}$) | $10^6$ $k_B^N$ [b] ($M^{-1}$ $s^{-1}$) | $10^{-5}$ PAF [c] | $10^{-5}$ PAF [d] | $10^{-4}$ MethylAF [d] | ref. |
|---|---|---|---|---|---|---|---|
|  | F | 0.35 | 0.98 | 3.60 | | 87.00 | [e] |
|  | F | | | | | 0.16 | [e] |
|  | F | 0.64 | 9.88 | 0.65 | | 2.10 | [e] |
|  | Cl | 1.05 | 7.60 | 1.38 | | 68.8[f] | 7b |
|  | Q [g] | 24.80 | 4.80 | 52.00 | 15.00 | | 6 |
|  | Q [g] | 20.80 | 78.00 | 2.70 | 0.53 | | 6 |
|  | Q [g] | 935.40 | 330.00 | 28.00 | 3.44 | | 7a |

[a] In acetohydroxamate/acetohydroxamic acid buffers at 50 °C and $\mu$ = 1 M KCl. [b] Estimated by a linear free energy relationship with acetohydroxamate base.[6] [c] The PAF values are calculated as the ratio $k_B^{NH^+}/k_B^N$ in acetohydroxamate/acetohydroxamic acid buffers at 50 °C and $\mu$ = 1 M KCl. [d] Values calculated in $OH^-/H_2O$ at 50 °C and $\mu$ = 1 M KCl. [e] This work. [f] Value determined at 25 °C (ref 7b). [g] Q = quinuclidine. [h] Also reported are the corresponding calculated PAFs. For comparison, the PAF and the MethylAF values in $OH^-/H_2O$ are reported.

of the C−X bond in the intermediate could simulate the breaking of the C−X bond for a concerted process. Our results give an experimental quantitative measure of this effect in systems where the E1cb mechanism can be assigned. A comparison of the reactivities of $NH^+$ and N, the proton-activating factor, requires the knowledge of $k_B^N$, the second-order rate constant for the elimination reaction from unprotonated substrate, N. This parameter cannot be directly measured since the elimination reaction of N with acetohydroxamate is too slow to be conveniently followed. We have estimated $k_B^N$ for **2** and **4** by extending a previously proposed correlation[6] for known systems between log $k_B^N$ and log $k_{OH}^N$: log $k_B^N$ = −1.4 + 1.1 log $k_{OH}^N$. The rate constants $k_{OH}^N$ were directly measured, and the values estimated for $k_B^N$ are 9.80 × $10^{-7}$ $M^{-1}$ $s^{-1}$ for **2** and 9.88 × $10^{-6}$ $M^{-1}$ $s^{-1}$ for **4**. The calculated PAF values are 3.6 × $10^5$ for **2** and 6.5 × $10^4$ for **4**. It should be noted that the reacting species is $NH^+$ in acetohydroxamate/acetohydroxamic acid buffers, and therefore, we cannot obtain information about the mechanism when the reacting species is N, the unprotonated substrate. The mechanism could be E2 or E1cb. However, with *N*-[2-(*o*-nitrophenyl)ethyl]quinuclidinium ion, a system that has a level of activation and reactivity similar to those of **4**, $k_B$ is 4.2 × $10^{-5}$ $M^{-1}$ $s^{-1}$ (acetohydroxamate/acetohydroxamic acid buffers, $H_2O$, 50 °C, and $\mu$ = 1 M KCl) and an E1cb mechanism was demonstrated.[30] The PAF values calculated in acetohydroxamate/acetohydroxamic acid buffers together with the PAF and MethylAF values calculated in $OH^-/H_2O$ for similar previously studied substrates are reported in Table 3. Support of the proposed mechanistic model for **2** and **4** comes from the comparison of the related consistent values of PAF and MethylAF. From the data of Table 3, it can be seen that when the pyridine ring is substituted in the 4 position, the PAF values are lower than those of the systems with a substitution at the 2 position. The different resonance energies are certainly important in this respect, but differences in electrostatic interactions could also play a role.[31] The elimination reactions of **2** and **4** have also been studied in acetate/acetic acid buffers at pH values of 4.13, 4.65, and 5.13. The p$K_a$ of acetic acid is 4.65 in $H_2O$, at 50 °C and $\mu$ = 1 M KCl. The reactions were followed at $\lambda$ = 290 nm with **2** and at $\lambda$ = 280 nm with **4** by the initial rate. The results are in agreement with $NH^+$ being the reacting species which undergoes carbon deprotonation by acetate base. At the pH studied, the vinylpyridine product is partially protonated (the p$K_a$ of 2-vinylpyridinium is 5.06, and the p$K_a$ of 4-vinylpyridinium is 5.64, in $H_2O$ at 50 °C and $\mu$ = 1 M KCl). If the intermediate carbanion of the mechanism depicted in Scheme 4 is formed irreversibly, $(E1cb)_I$, the rate equation is given in eq 3 and the integrated form in eq 4.

$$\frac{dC}{dt} = (k_{OH}^{NH^+}[OH^-] + k_B^{NH^+}[B^-])[NH^+] \quad (3)$$

$$C = k_{obs}[NH^+]t \quad (4)$$

where $C$ is the total concentration of the product ([P] + [$PH^+$]).

$$k_{obs} = k_{OH}^{NH^+}[OH^-] + k_B^{NH^+}[B] \quad (5)$$

(31) Tobin, J. B.; Frey, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 12253.

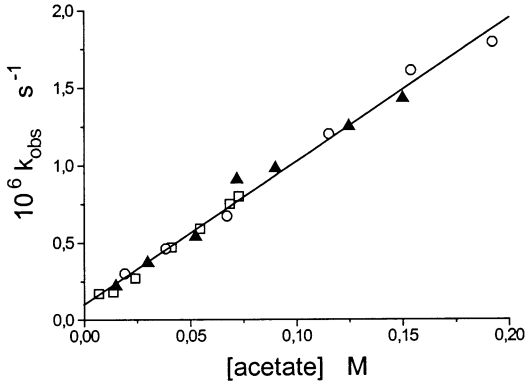



**FIGURE 3.** Dependence of $k_{obs}$ ($s^{-1}$) on acetate concentration at different pH values for substrate **2**: solid circle, pH 5.13; solid triangle, pH 4.65; solid square, pH 4.13.

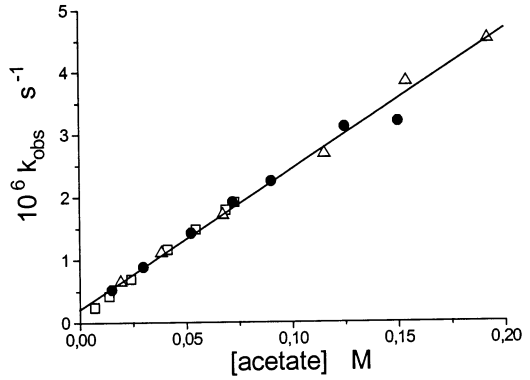
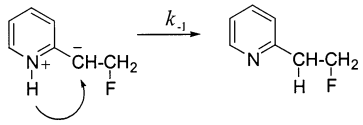



**FIGURE 4.** Dependence of $k_{obs}$ ($s^{-1}$) on acetate concentration at different pH values for substrate **4**: solid circle, pH 5.13; solid triangle, pH 4.65; solid square, pH 4.13.

**SCHEME 5**




The $k_{obs}$ values were calculated by plots of $C$ against time with the slope $s$ and $k_{obs} = s/[NH^+]$, where the $[NH^+]$ is given by $[NH^+] = \{[H^+]/([H^+] + K_a^N)\}\cdot C_T$, with $C_T$ being the total concentration of substrate. The plots of $k_{obs}$ vs [B] are shown in Figures 3 and 4. It can be seen that with this kinetic treatment there is a linear trend, independent of pH. This result is in agreement with an $(E1cb)_I$ mechanism and with the kinetic expression of eq 3, where the contribution of the term $k_{OH}^{NH^+}[OH^-]$ is negligible. The slope of the line is $k_B^{NH^+} = 9.31 \times 10^{-6}$ $M^{-1}\ s^{-1}$ with isomer **2** and $k_B^{NH^+} = 23.06 \times 10^{-6}\ M^{-1}\ s^{-1}$ with **4**. These values are significantly lower than the values calculated for the same process with acetohydroxamate base ($k_B^{NH^+} = 0.35\ M^{-1}\ s^{-1}$ with **2** and $k_B^{NH^+} = 0.64\ M^{-1}\ s^{-1}$ with **4**), and are in agreement with the lower basicity of acetate with respect to acetohydroxamate.

**H/D Exchange.** The study of H/D exchange with **2** and **4** in acetohydroxamate/acetohydroxamic acid buffer or acetate/acetic acid buffer in $D_2O$, at 50 °C and $\mu = 1$ M KCl, showed the absence of deuterium incorporation in the $\beta$-position of the substrate during the elimination reaction. These results are in agreement with the $(E1cb)_I$ mechanism assigned to **2** and **4** under these reaction conditions, as previously discussed. It is to be noted that the absence of H/D exchange with **2** and **4** allows the possibility of excluding an intramolecular proton transfer in the intermediate carbanion; a significant competition between this process and the elimination reaction would imply incorporation of deuterium in the $\beta$-position of the substrate (Scheme 5).

## Conclusions

Methyl-activating factors have been determined in $OH^-$-induced $\beta$-elimination reactions with systems activated by a pyridine ring with fluorine as leaving group. When the pyridine ring is substituted in the 2 position, the MethylAF value is $8.7 \times 10^5$, when the substitution is in the 3 position, the MethylAF is $1.6 \times 10^3$, and when the substitution is in the 4 position, the MethylAF is $2.1 \times 10^4$. These high MethylAF values are in agreement with an irreversible E1cb mechanism involving a resonance-stabilized carbanion. $\beta$-Elimination reactions in acetohydroxamate/acetohydroxamic acid buffer (pH 8.45−9.42) or acetate/acetic acid (pH 4.13−5.13) with **2** and **4** also proceed by an irreversible E1cb mechanism. The reacting species, which undergoes carbon deprotonation, is $NH^+$, the substrates protonated at the nitrogen atom of the pyridine ring. The PAFs are $3.6 \times 10^5$ for **2** and $6.5 \times 10^4$ for **4** in acetohydroxamate/acetohydroxamic acid buffer. These values are similar to those previously reported[6,11] for *N*-[2-(4-pyridyl)ethyl]quinuclidinium and *N*-[2-(2-pyridyl)ethyl]quinuclidinium. A carbanion mechanism was demonstrated with these two substrates by a change in the rate-determining step within the E1cb mechanism, by the presence of H/D exchange, and by consistent results of the solvent isotope effect. We suggest that the PAF or MethylAF values of $10^4$−$10^6$ can be a test for assigning an E1cb mechanism to these systems; it is then possible to make the difficult diagnosis between an irreversible E1cb or concerted E2 mechanism. The comparison between the rate constants for carbon deprotonation induced by acetohydroxamate base (50 °C and $\mu = 1$ M KCl) from 2-(2-chloroethyl)pyridine,[7b] $k_B^{NH^+} = 1.05\ M^{-1}\ s^{-1}$, and 2-(2-fluoroethyl)pyridine (**2**), $k_B^{NH^+} = 0.35\ M^{-1}\ s^{-1}$, shows that with a chlorine leaving group the formation of the carbanion is faster with respect to that of the system with the more electronegative fluorine as leaving group. This is direct evidence that some lengthening of the carbon−leaving group bond occurs in the intermediate carbanion, and our results quantify this effect in systems where the E1cb mechanism can be assigned. This result is relevant for interpreting a heavy-atom isotope effect.

## Experimental Section

If not specified otherwise, $^1H$ NMR spectra were recorded at 200 MHz in $CDCl_3$ solution using tetramethylsilane as internal standard. Mass spectra were registered at 70 eV.

**Reagents and Solvents.** Reagent grade potassium chloride, potassium acetate, acetohydroxamic acid, 4-(2-hydroxyethyl)pyridine, 2-(2-hydroxyethyl)pyridine, 2-vinylpyridine, 3-pyridinecarboxaldehyde, and ethyl 3-pyridylacetate were used without further purification. 4-Vinylpyridine was purified by column chromatography on silica gel using diethyl ether as the eluent. Glass-distilled and freshly boiled water was used throughout.

**3-(2-Hydroxyethyl)pyridine (1)** was prepared by the reduction of ethyl 3-pyridylacetate with $LiAlH_4$ according to the standard procedure. Spectroscopic and analytical data were identical to those reported in the literature.[32]

**2-(2-Fluoroethyl)pyridine (2).** Diethylaminosulfur trifluoride (DAST) (2.44 g, 15.1 mmol) in dichloromethane (25 mL) was added to a solution of 2-(4-hydroxyethyl)pyridine (2.0 g, 16.2 mmol) in the same solvent (40 mL), and the mixture made to react at 10 °C for 2.5 h. Then it was poured onto ice, neutralized with $NaHCO_3$ and extracted with $CH_2Cl_2$. After solvent evaporation, chromatography of the crude product on silica gel (eluent diethyl ether) allowed **2** to be collected (0.50 g, 25%) as a pale yellow oil: $^1$H NMR $\delta$ 8.56 (d, $J$ = 4.8 Hz, 1 H), 7.63 (td, $J$ = 7.7 and 1.8 Hz, 1 H), 7.23 (d, $J$ = 7.8 Hz, 1 H), 7.17 (ddd, $J$ = 7.7, 4.9 and 0.8 Hz, 1H) 4.84 (dt, $J$ = 47.0 and 6.1 Hz, 2 H), 3.19 (dt, $J$ = 25.1 and 6.1 Hz, 2 H); MS (70 eV) $m/z$ (rel intens) 126 ($M^+ + 1$, 4), 125 ($M^+$, 49), 124 ($M^+ - 1$, 73), 105 (62), 92 (9), 79 (100), 78 (27), 65 (20), 52 (18). Anal. Calcd for $C_7H_8NF$: C, 67.18; H, 6.44; N, 11.19. Found: C, 66.91; H, 6.39; N, 11.28.

**3-(2-Fluoroethyl)pyridine (3)** was prepared from the corresponding alcohol **1** (1.0 g, 8.0 mmol) in 16% yield following the same procedure described for **2**: $^1$H NMR $\delta$ 8.5 (m, 2 H), 7.59 (dt, $J$ = 7.8 and 1.7 Hz, 1 H), 7.26 (dd, $J$ = 7.8 and 4.9 Hz, 1 H), 4.65 (dt, $J$ = 46.9 and 6.2 Hz, 2 H), 3.02 (dt, $J$ = 25.0 and 6.2 Hz, 2 H); MS (70 eV) $m/z$ (rel intens) 126 ($M^+ + 1$, 4), 125 ($M^+$, 85), 92 (100), 78 (7), 65 (47), 63 (9), 51 (16).

**4-(2-Fluoroethyl)pyridine (4)** was prepared from the corresponding alcohol (1.0 g, 8.0 mmol) as described for **2**. **4** was isolated as a pale yellow oil (0.20 g, 20%): $^1$H NMR $\delta$ 8.54 (d, AA′ portion of an AA′BB′ system, 1 H), 7.21 (d, BB′ portion of an AA′BB′ system, 1 H), 4.68 (dt, $J$ = 46.8 and 6.1 Hz, 2 H), 3.02 (dt, $J$ = 25.6 and 6.1 Hz, 2 H); MS (70 eV) $m/z$ (rel intens) 126 ($M^+ + 1$, 10), 125 ($M^+$, 100), 124 ($M^+ - 1$, 20), 92 (89), 65 (39), 51 (18). Anal. Calcd for $C_7H_8NF$: C, 67.18; H, 6.44; N, 11.19. Found: C, 67.0; H, 6.42; N, 11.16.

**1-Methyl-2-(2-fluoroethyl)pyridinium Iodide (5). 2** (0.10 g, 0.80 mmol) and $CH_3I$ (2.28 g, 16.06 mmol) were made to react in acetone (2 mL) for 24 h at room temperature under stirring. The solvent was evaporated at reduced pressure, and the residual solid was washed with $Et_2O$, dried under vacuum, and recrystallized with EtOH−$Et_2O$ to obtain pure **5** (0.050 g, 23%): mp 118−120 °C; $^1$H NMR ($D_2O$) $\delta$ 8.52 (d, $J$ = 6.2 Hz, 1 H), 8.23 (t, $J$ = 7.8 Hz, 1 H), 7.81 (d, $J$ = 8.1 Hz, 1 H), 7.66 (t, $J$ = 6.8 Hz, 1 H), 4.73 (dt, $J$ = 46.7 and 5.3 Hz, 2 H), 4.08 (s, 3 H), 3.34 (dt, $J$ = 26.9 and 5.6 Hz, 2 H). Anal. Calcd for $C_8H_{11}NFI$: C, 35.98; H, 4.15; N, 5.24. Found: C, 35.85; H, 4.15; N, 5.16.

**1-Methyl-3-(2-fluoroethyl)pyridinium iodide (6)** was prepared from **3** (0.1 g 0.8 mmol) in 20% yield following the same procedure described for **5**: $^1$H NMR ($D_2O$, 400 MHz) $\delta$ 8.68 (s, 1 H), 8.61 (d, $J$ = 6.1 Hz, 1 H), 8.39 (d, $J$ = 8.1 Hz, 1 H), 7.92 (t, $J$ = 7.1 Hz, 1 H), 4.73 (dt, $J$ = 46.6 and 5.7 Hz, 2 H), 4.30 (s, 3 H), 3.20 (dt, $J$ = 28.6 and 5.7 Hz, 2 H). Anal. Calcd for $C_8H_{11}NFI$: C, 35.98; H, 4.15; N, 5.24. Found: C, 35.92; H, 4.19; N, 4.97.

**1-Methyl-4-(2-fluoroethyl)pyridinium iodide (7)** was prepared from **4** (0.1 g, 0.8 mmol) in 23% yield by the same procedure described for **5**: $^1$H NMR ($D_2O$) $\delta$ 8.43 (d, AA′ portion of an AA′BB′ system, 2 H), 7.72 (d, BB′ portion of an AA′BB′ system, 2 H), 4.62 (dt, $J$ = 46.5 and 5.6 Hz, 2 H), 4.10 (s, 3H), 3.11 (dt, $J$ = 28.8 and 5.6 Hz, 2 H). Anal. Calcd for $C_8H_{11}NFI$: C, 35.98; H, 4.15; N, 5.24. Found: C, 35.89; H, 4.16; N, 5.22.

**1-Methyl-4-vinylpyridinium Iodide (8).** 4-Vinylpiridine (0.68 mg, 6.5 mmol) and $CH_3I$ (4.56 g, 32.1 mmol) were made to react in $CH_3OH$ (10 mL) at room temperature for 36 h under stirring. The solvent was evaporated and the resulting solid washed with $Et_2O$ (4 × 20 mL) and $CH_3OH$ (50 mL), dried in a vacuum, and recrystallized with EtOH−$Et_2O$ to obtain pure **8** (1.39 g, 86.9%) as a pale yellow solid: mp 288−291 °C dec; $^1$H NMR ($D_2O$) $\delta$ 8.48 (d, AA′ portion of an AA′BB′ system, 2 H), 7.85 (d, AA′ portion of an AA′BB′ system, 2 H), 6.80 (d, $J$ = 17.6 and 10.8 Hz, 1 H), 6.28 (d, $J$ = 17.6 Hz, 1 H), 5.81 (d, $J$ = 17.6 Hz, 1 H), 5.81 (d, $J$ = 10.8 Hz, 1 H), 4.15 (s, 3 H). Anal. Calcd for $C_8H_{10}NI$: C, 38.89; N, 4.08; H, 5.67. Found: C, 38.77; N, 4.11; H, 5.63.

**1-Methyl-2-vinylpyridinium iodide (9)** was obtained as a pale yellow solid (0.18 g, 25%) from 2-vinylpyridine (0.80 g, 3.0 mmol) following the same procedure described for **8**: mp 221−226 °C dec; $^1$H NMR ($D_2O$) $\delta$ 8.47 (d, $J$ = 6.2 Hz, 1 H), 8.25 (t, $J$ = 8.0 Hz, 1 H), 7.98 (d, $J$ = 8.0 Hz, 1 H), 7.67 (t, $J$ = 7.1 Hz, 1 H), 6.95 (dd, $J$ = 17.2 and 11.3 Hz, 1 H), 6.15 (d, $J$ = 17.2 Hz, 1 H), 5.92 (d, $J$ = 11.3,1 H), 4.09 (s, 3 H). Anal. Calcd for $C_8H_{10}NI$: C, 38.89; H, 5.67; N, 4.08. Found: C, 38.77; H, 5.59; N, 4.12.

**3-Vinylpyridine (10).** Butyllithium (1.49 M in hexane, 12.5 mL, 18.6 mmol) was added to a solution of diisopropylamine (1.88 g, 18.6 mmol) in anhydrous THF at −20 °C. After 10 min, methyltriphenylphosphonium bromide (6.7 g, 18.8 mmol) was added, and the mixture was allowed to react for 30 min under stirring. After the mixture was cooled to −60 °C, 3-pyridinecarboxaldehyde (2 g, 18.6 mmol) was added in small portions. The temperature was allowed to rise to 20 °C, and the mixture was allowed to react for 1 h before it was poured into water. Aqueous HCl (10%) was added until pH 2 was reached. After extraction with diethyl ether (3 × 50 mL), the aqueous phase was basified with saturated $K_2CO_3$ and extracted again with diethyl ether (3 × 50 mL). The collected organic phases were dried with sodium sulfate. After solvent evaporation, chromatography of the crude product on silica gel (eluent diethyl ether/hexanes, 1:1 v/v) allowed pure **10** (1.5 g, 77%) to be collected as a colorless oil: $^1$H NMR (400 MHz) $\delta$ 8.62 (d, $J$ = 2.2 Hz, 1 H), 8.49 (dd, $J$ = 4.8 and 1.6 Hz, 1 H), 7.73 (dt, $J$ = 9.7 and 1.8 Hz, 1 H), 7.26 (dd, $J$ = 7.8 and 4.7 Hz, 1 H), 6.71 (dd, $J$ = 17.7 and 11.0 Hz, 1 H), 5.83 (dd, $J$ = 17.7 and 0.5 Hz, 1 H), 5.38 (dd, $J$ = 11.0 and 0.5 Hz, 1 H); MS (70 eV) $m/z$ (rel intens) 105 ($M^+$, 100), 104 (68), 78 (31), 51 (30). Anal. Calcd for $C_7H_7N$: C, 79.97; 13.32; H; N, 6.71. Found: C, 79.65; H, 13.38; N, 6.67.

**1-Methyl-3-vinylpyridinium iodide (11)** was prepared from **10** (0.8 g, 7.6 mmol) following the same procedure described for **8**. It was collected as pale yellow needles (0.32 g, 17%) after recrystallization with EtOH−$Et_2O$: mp 115−117 °C; $^1$H NMR ($D_2O$) $\delta$ 8.64 (s, 1 H), 8.42 (d, $J$ = 6.0 Hz, 1 H), 8.35 (d, $J$ = 7.9 Hz, 1 H), 7.77 (br t, $J$ = 7.3 Hz, 1 H), 6.66 (dd, $J$ = 17.7 and 11.0 Hz, 1 H), 5.95 (dd, $J$ = 17.7 and 1.1 Hz, 1 H), 5.53 (dd, $J$ = 11.0 and 1.1 Hz, 1 H), 4.17 (s, 3 H). Anal. Calcd for $C_8H_{10}NI$: C, 38.89; H, 5.67; N, 4.08;. Found: C, 39.05; H, 5.58; N, 4.15.

**Kinetics Measurements.** The reactions in $OH^-/H_2O$ at 50 °C and $\mu$ = 1 M KCl with **2** and **4** were followed in pseudo-first-order conditions ([$OH^-$] = 0.1−0.5 M) by monitoring the formation of the vinylpyridine product, either by initial rates[6] or by following the process 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. The extinction coefficients (50 °C, $\mu$ = 1 M KCl) were $\epsilon$ = 3584 $M^{-1}$ $cm^{-1}$ at $\lambda$ = 290 nm for 2-vinylpyridine and $\epsilon$ = 1634 $M^{-1}$ $cm^{-1}$ at $\lambda$ = 280 nm for 4-vinylpyridine.[6] Good agreement was always observed between the two methods. Reactions in $OH^-/H_2O$, at 50 °C and $\mu$ = 1 M KCl, with isomer **3**, were followed by initial rates at $\lambda$ = 280 nm ($\epsilon$ of 3-vinylpyridine is 3001 $M^{-1}$ $cm^{-1}$, 50 °C, $\mu$ = 1 M KCl), and the [$OH^-$] was 0.3−0.75 M. Reactions in the same base−solvent system with **5**−**7** were followed to completion in pseudo-first-order conditions at [$OH^-$] = 0.01−0.03 M with **5** and **7**; with **6** the [$OH^-$] was 0.3−0.75 M. The extinction coefficients of the corresponding alkenes were $\epsilon$ = 14253 $M^{-1}$ $cm^{-1}$ at $\lambda$ = 280 nm, 25 °C, $\mu$ = 1 M KCl, for 1-methyl-4-vinylpyridinium iodide (**8**), $\epsilon$ = 10274 $M^{-1}$ $cm^{-1}$ at $\lambda$ = 287 nm, 25 °C, $\mu$ = 1 M KCl, for 1-methyl-2-vinylpyridinium iodide (**9**), and $\epsilon$ = 2860 $M^{-1}$ $cm^{-1}$ at $\lambda$ = 280

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nm, 50 °C, $\mu = 1$ M KCl, for 1-methyl-3-vinylpyridinium iodide (**11**). Kinetics studies in acetohydroxamate/acetohydroxamic acid buffers with **2** and **4**, at 50 °C and $\mu = 1$ M KCl, were carried out following the procedure previously described for related systems using the initial rates method.[6] Elimination reactions from **2** and **4** in $CH_3COO^-/CH_3COOH$ buffers at 50 °C and $\mu = 1$ M KCl were followed at $\lambda = 290$ nm with **2** and at $\lambda = 280$ nm with **4** by monitoring the formation of the corresponding vinylpyridine by initial rates. The concentrations of **2** and **4** were $\sim 2.5 \times 10^{-3}$ M, and the reaction was followed up to 3%. At the pH used, the 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 eq 6, where $A_t$ is the absorbance

$$C = \frac{(A_t - A_0)}{\epsilon_P + \epsilon_{PH}\dfrac{[H^+]}{K_a^P}}\left(1 + \frac{[H^+]}{K_a^P}\right) \qquad (6)$$

at time $t$, $A_0$ is the absorbance at $t = 0$, $K_a^P$ is the dissociation constant of $PH^+$ ($H_2O$, $\mu = 1$ M KCl), $\epsilon_P$ is the extinction coefficient of 2-vinylpyridine or 4-vinylpyridine, $\epsilon_{PH}$ is the extinction coefficient of 2-vinylpyridine protonated (9773 $M^{-1}$ $cm^{-1}$ at 50 °C and $\mu = 1$ M KCl) or 4-vinylpyridine protonated (8987 $M^{-1}$ $cm^{-1}$ at 50 °C and $\mu = 1$ M KCl).

**Product Analysis.** Reactions of **2**−**7** in $OH^-/H_2O$ were shown to be complete elimination reactions by the UV spectra of the corresponding vinylpyridine formed. Experiments carried out with **2**−**4** in $OH^-/H_2O$ showed, after extraction with $Et_2O$ and GLC analysis, that vinylpyridine was the only product. Reactions of **2** and **4** in acetohydroxamate/acetohydroxamic acid buffers were shown to be complete elimination reactions by GC analysis after extraction with $CHCl_3$. Reactions of **2** and **4** in $CH_3COO^-/CH_3COOH$ buffers were also shown to be complete elimination reactions by GLC analysis after the pH of the reaction mixture was adjusted to ∼7 and extraction with $Et_2O$.

**H/D Exchange.** Compounds **2** and **4** were made to react in acetohydroxamate/acetohydroxamic acid buffers, $CH_3COO^-/CH_3COOD$ buffers, or $OD^-$ in $D_2O$ at 50 °C until 30−50% of the elimination product was detected. The reaction mixture was extracted with $CDCl_3$, and the organic phase was analyzed by NMR analysis. No deuterium incorporation in the unreacted substrates was detected in any of the cases.

**p$K_a$ Determination.** The p$K_a$ values of the conjugated acid of **2** and **4** and $CH_3COO^-/CH_3COOH$ buffers at 50 °C and $\mu = 1$ M KCl were determined by potentiometric titration with 1 M HCl. The p$K_a$ values of the conjugated acid of 2-vinylpyridine and 4-vinylpyridine were determined by ultraviolet spectrophotometry at $\lambda = 290$ and 280 nm, respectively (50 °C and $\mu = 1$ M KCl) according to a standard procedure.[33]

**Acknowledgment.** Thanks are due to the CNR (Rome) and the Ministero dell'Università e della Ricerca Scientifica e Tecnologia (MURST) for financial support.

**Supporting Information Available:** Pseudo-first-order rate constants, $k_{obs}$ ($s^{-1}$), for the elimination reactions from **2** and **4** in acetohydroxamate/acetohydroxamic acid buffers or acetate/acetic acid buffers ($H_2O$, 50 °C, and $\mu = 1$ M KCl). This material is available free of charge via the Internet at http://pubs.acs.org.

JO020603O

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